

1.01

Aziridines and Azirines: Monocyclic

WILLIAM H. PEARSON and BRIAN W. LIAN
University of Michigan, Ann Arbor, MI, USA

and

STEPHEN C. BERGMEIER
Ohio State University, Columbus, OH, USA

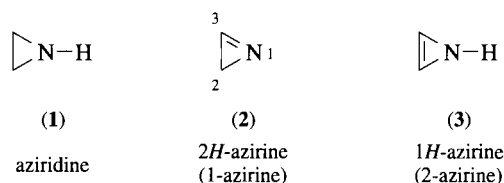
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1.01.1 INTRODUCTION

The chemistry of aziridines and azirines has been an active area of research, resulting in four to five thousand new publications since the review by Padwa and Woolhouse in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (84CHEC-I(7)47). The present review will serve primarily to update this earlier review. However, it will still provide key aspects of early work on aziridines and azirines. Due to the large number of references on these heterocycles, this review cannot be exhaustive. Instead, representative examples of the chemistry of aziridines and azirines have been selected. It should be noted that the present review will focus on the chemistry of *monocyclic* aziridines and azirines. The abundant chemistry of fused-ring aziridines and azirines will be treated in the following chapter.

The structures, names, and numbering schemes of aziridine (**1**), 2*H*-azirine (**2**), and 1*H*-azirine (**3**) are shown below. Alternate names such as ethylenimine for aziridine, 1-azirine for 2*H*-azirine, and 2-azirine for 1*H*-azirine will be encountered in the literature. The IUPAC and *Chemical Abstracts* names which use the indicated hydrogen (*H*) formality will be used in this review. Note that when 1-azirine is encountered in the literature, the numbering system is reversed, with the unsaturated carbon being numbered C(2). Hence 2-methyl-3-phenyl-2*H*-azirine (preferred) may appear as 3-methyl-2-phenyl-1-azirine.

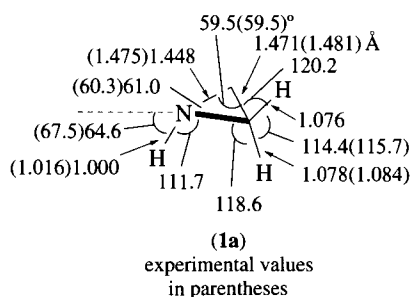


In addition to the Padwa and Woolhouse review (84CHEC-I(7)47), a number of general reviews on aziridines and azirines should be considered. Fowler reviewed the synthesis and reactions of 2*H*-azirines and the early attempts at the generation of the elusive antiaromatic 1*H*-azirines (71AHC(13)45). Two reviews by Livingstone cover the history, synthesis, reactions, and properties of aziridines and azirines (B-73MI 101-01, B-84MI 101-01). Of particular interest is coverage of the chemistry of aziridinones (α -lactams) and aziridinium salts. Amarego has reviewed the synthesis, configuration, conformation, and reactions of aziridines (B-77MI 101-01). A review of azirines by Smalley covers both 1*H*- and 2*H*-azirines, including their synthesis, physical properties, and reactions (79COC(4)565). Notably, this review covers the chemistry of benzazirines. Excellent reviews by Deyrup (B-83MI 101-01) and Nair (B-83MI 101-02) have appeared on the chemistry of aziridines and azirines, respectively. Two reviews on the chemistry of 3-amino-2*H*-azirines have appeared (90CHE719, 91AG(E)238). Padwa and co-workers have reviewed the literature of aziridines and azirines

on a yearly basis, covering the period 1988 to 1994 (89PHC82, 90PHC22, 91PHC42, 92PHC34, 93PHC54, 94PHC56). Many reviews have been published on more specific aspects of the chemistry of aziridines and azirines; these reviews will be cited in the appropriate sections below.

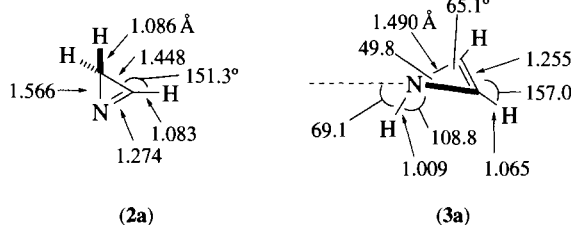
1.01.2 THEORETICAL METHODS

Aziridine (**1**) continues to be the focus of many molecular orbital calculations, particularly HF, SCF, MP2, and MP3 *ab initio* methods using a wide variety of basis sets, thus providing data on the geometry, energy, and bond order of this molecule (85JA3800, 87JA3224, 87JPC6484, 88JST(165)99, 89JCC468, 93JA11074, 93MI 101-02). Shown below are the structural parameters for aziridine (**1a**) obtained from *ab initio* calculations (87JA3224, 87JPC6484, 89JCC468), which are compared to experimental values (71JST(10)385). Extended ASED-form Hückel calculations on aziridine have also been reported (93HCA924). Complexation of aziridine with H^+ , Li^+ , and Al^+ have been simulated with *ab initio* MO calculations (84JA6579, 87JPC6484, 93JA11074, 93JPC5553). Calculated proton affinities (ca. 218.2–223.3 kcal mol⁻¹) (87JPC6484, 93JA11074) agree with experimental values (215.7 kcal mol⁻¹) (81JA486). The energy surface for the ring-opening of aziridine complexed to Al^+ has been calculated (93JPC5553). A number of studies have described *ab initio* modeling of the pyramidal inversion of the nitrogen of aziridine and other simple substituted aziridines, providing inversion barriers (12–22.3 kcal mol⁻¹, depending on method), transition structures, and calculated rate constants for inversion (87JA3224, 87JA6290, 89JCC468, B-92MI 101-01, 93CPL(204)175). The calculated inversion barrier compares favorably to the experimental value of 19 kcal mol⁻¹ determined by NMR after correcting for zero-point vibrational energy differences (74T2115, 75JA6990, 86JCP(85)4980). Speculation on the basis for the relatively high barrier to pyramidal inversion of aziridine versus simple amines has resulted from these studies (89JCC468). Aziridines bearing a chloro (93JA10267, 93JST(279)29), acyl (86JST(139)315, 92JA1616), or nitroso group (92JA8257) on the nitrogen atom have been the subject of investigations using *ab initio* methods, as have aziridines bearing a nitro group at C(2) (93MI 102-01). *N*-Acylaziridines and their *N*- and *O*-protonated forms have been studied using the MNDO semiempirical method (94JOC434). All of these *N*-substituted aziridines are pyramidal at nitrogen.

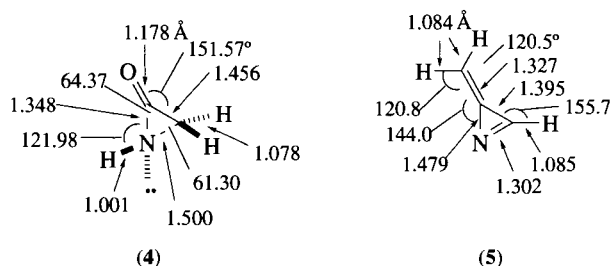


The structures of 2*H*-azirine (**2a**) (73TCC1, 82TL2339, 84JCS(P1)1401, 93JA11074) and its complexes with H^+ and Li^+ (93JA11074) have been calculated by *ab initio* methods. Semiempirical and *ab initio* MO investigations of the experimentally elusive and presumably antiaromatic compound 1*H*-azirine (**3a**) continue to appear (73TCC1, 75PAC767, 83JA396, 84JOC2971, 87JPC6484, 88JST(165)99, 89JCC468, 91JA3689, 93CB2337, 93JA11074). In an unsuccessful study aimed at matrix isolation and characterization of 1*H*-azirine, its infrared spectrum was calculated with *ab initio* methods. Absorptions at 533–691 cm⁻¹, 1183–1285 cm⁻¹, 3343–3603 cm⁻¹, and 912–1008 cm⁻¹ were predicted (93CB2337). The same study compared the calculated energies of all of the isomers of C_2H_3N , predicting that 1*H*-azirine is 32.7–33.2 kcal mol⁻¹ higher in energy than 2*H*-azirine (93CB2337). An energy difference of 37.1 kcal mol⁻¹ was obtained by other researchers (93JA11074). The barrier to pyramidal inversion of 1*H*-azirine has been calculated to be 40.0–45.6 kcal mol⁻¹ (87JA6290), 33.2–46.4 kcal mol⁻¹ (89JCC468), and 44.6 kcal mol⁻¹ (91JA3689) by different theoretical methods. These barriers are considerably higher than the values of 13.0–19.4 kcal mol⁻¹ and 12.0–22.3 kcal mol⁻¹ calculated for aziridine using the same respective MO methods, reflecting the difficulty of attaining a planar, antiaromatic conformation for 1*H*-azirine. The calculated structures of H^+ and Li^+ complexes of 1*H*-azirine have been reported (87JPC6484, 93JA11074). The relative basicities of (**1**)–(**3**) have been calculated, with 1*H*-azirine being more basic than aziridine, which was more basic than 2*H*-azirine (87JPC6484, 93JA11074). It was proposed that the antiaromaticity of 1*H*-azirine is relieved upon protonation, thus accounting for its higher basicity. Whereas 1*H*-azirine is 37.1 kcal mol⁻¹ higher in energy than

2*H*-azirine in these studies, protonated 1*H*-azirine is only 4.7 kcal mol⁻¹ higher in energy than protonated 2*H*-azirine. The trends for Li⁺ complexation to these three heterocycles is qualitatively similar <93JA11074>. The structures of the potentially aromatic aziriny cation C₂H₂N⁺ <74JOC373, 80TL4553, 82TL2339, 83JST(91)313, 91JA3689> and the aziriny radical cation <91JA3689> have also been studied by semiempirical and *ab initio* MO methods.



Aziridines and azirines with exocyclic unsaturation have also been the subject of theoretical studies. The geometry, energy, strain energy, and inversion barrier of 2-methyleneaziridine and 2,3-bis(methylene)aziridine were calculated and compared with similar information on aziridine itself <93JPC4996>. Studies of the C₂H₃NO hypersurface with *ab initio* methods included 2-aziridinone (α-lactam) (4) <92CB1249>. The *ab initio*-derived geometry and the calculated vibrational frequencies of 2-methylene-2*H*-azirine (5) agree well with data obtained on the matrix-isolated species <94JA60>. Isomers of C₂HN, including the C(2) carbene of 2*H*-azirine and the 2,3-biscarbene of aziridine were studied theoretically <93CPL(202)33>.



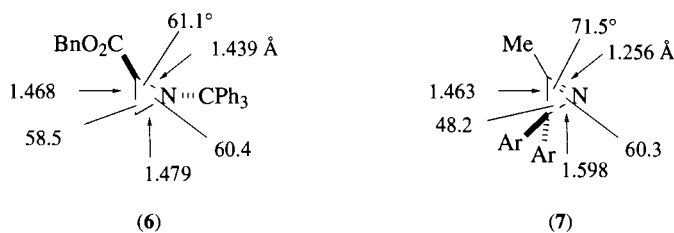
1.01.3 EXPERIMENTAL STRUCTURAL ASPECTS

Nearly every imaginable piece of data on the physical, spectroscopic, and thermodynamic properties of aziridine itself can be found in Beilstein <B-88MI 101-01>.

1.01.3.1 Determination of Geometry

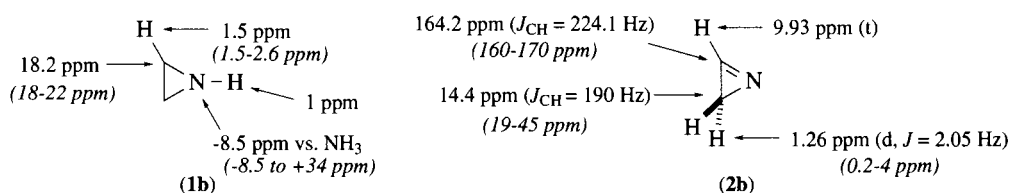
A number of x-ray crystallographic determinations of the structures of aziridines were reported in earlier reviews <72PMH(5)1, B-83MI 101-01, 84CHEC-I(7)47>. Bond lengths of 1.48 Å (C—N) and 1.46 Å (C—C) are typical values, which are shorter and longer, respectively, as compared to open-chain compounds. The endocyclic angles are all approximately 60°, and the nitrogen is pyramidal. Recent examples of x-ray structures of monocyclic (6) <93ZN(B)1146> and fused-bicyclic aziridines <91AJC1145> have been reported. Electron diffraction <61BCJ369>, microwave <55JCP(23)1966, 71JST(10)385> and photoelectron spectroscopy have been used to determine the structure of aziridine itself <74PMH(6)1, 74PMH(6)53>. X-ray crystallographic structure determinations of *N*-chloro- <92JCS(P2)959, 92JCS(P2)1541> and *N*-sulfonylaziridines <89T5015, 93AX(C)1661, 93TL3639> have been reported. The crystal structure of a rhodium complex of 2,2-dimethyl-3-phenyl-3-allylaziridine

showed that the rhodium was coordinated to both the aziridine nitrogen and the double bond in the side chain <92JOM(438)217>. Crystal structures of 2*H*-azirines have also been reported <78JOC57, 80CC98, 91AG(E)238, 92HCA1866>. Typical bond lengths and angles are shown for (7) <80CC98>.



1.01.3.2 Nuclear Magnetic Resonance and Electron Spin Resonance Spectroscopy

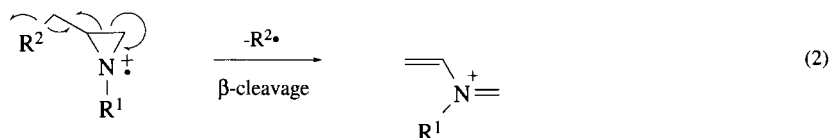
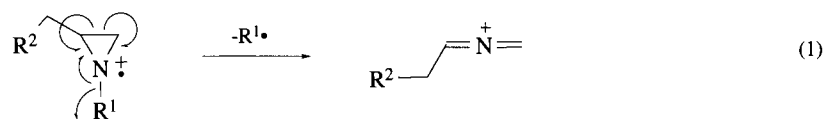
The general aspects of ^1H -, ^{13}C -, and ^{15}N -NMR spectroscopy of aziridines and 2*H*-azirines have been well reviewed <B-69MI 101-01, 71PMH(4)121, B-73MI 101-01, B-83MI 101-01, B-83MI 101-02, 84CHEC-I(7)47>. The ^1H -, ^{13}C -, and ^{15}N -NMR resonances for the parent heterocycles aziridine (1b) and 2*H*-azirine (2b) <83JA7681, 83CC238, 87CB1971, 88T4447> are shown below along with typical values (in italics) for substituted compounds. Analysis of the vicinal coupling constants in the ^1H -NMR spectra of aziridines is a useful method for determining relative stereochemistry at C(2) and C(3) <B-69MI 101-01, B-73MI 101-02, B-83MI 101-01, 84CHEC-I(7)47>. Typical values for ^1H -NMR coupling constants in aziridines are: $J_{\text{cis}} = 5\text{--}9\text{ Hz}$ (6.4 Hz average); $J_{\text{trans}} = 2\text{--}7\text{ Hz}$ (3.3 Hz average), $J_{\text{gem}} = +1.1\text{ to }-7\text{ Hz}$. An extensive listing of the chemical shifts and coupling constants for aziridine-2-carboxylic acid derivatives has appeared <85TL4439>. An analysis of the effect of *s*-character and inductive effects on geminal and vicinal coupling constants in aziridines and aziridinium salts has been reported <80OMR(13)45>. Complexation of metals to the nitrogen of aziridine has a substantial effect on the chemical shifts of the ring protons <93POL1371>. NMR spectroscopy has found wide use for the study of the pyramidal inversion of nitrogen in aziridines <B-73MI 101-02, B-83MI 101-01, 84CHEC-I(7)47, B-92MI 101-01>. The anisotropy of the aziridine ring has been studied, and may affect neighboring nuclei <66TL2921, 71CR(C)2069>. Prediction of the ^{13}C -NMR chemical shift in aziridines is possible using an empirical formula <76OMR(8)79>. The hybridization of the bonds in aziridines has been probed using $^{13}\text{C}\text{--}^1\text{H}$ and $^{13}\text{C}\text{--}^{15}\text{N}$ coupling constants <75JA4137, 79JOC2041>. A study of the effect of ring- and *N*-substitution on the ^{15}N -NMR chemical shift in aziridines has appeared <80JOC1277>. A good overview of the NMR characteristics of 2*H*-azirines, especially their ^{13}C -NMR spectra, can be found in Nair's review <B-83MI 101-02>.



The conformation of (aziridiny)methyl radical has been studied by electron spin resonance (ESR) spectroscopy <71TL2247, 74JA2447, 74PMH(6)95>. An ESR study of the radical cation of aziridine has appeared <86JPC2292>.

1.01.3.3 Mass Spectrometry

Mass spectrometry is not commonly used for the structural elucidation of aziridines and azirines. The fragmentation patterns of simple monocyclic aziridines have been reviewed <70OMS(3)1259, B-71MI 101-01, 84CHEC-I(7)47>. Aziridines generally show loss of the *N*-substituent with accompanying ring opening, as shown in Equation (1). Aziridine itself shows the loss of $\text{H}^\bullet$ by this process as the base peak. A dominant pathway for *C*-substituted aziridines is β -fragmentation, as shown in Equation (2). Fast atom bombardment (FAB) MS has been used for the analysis of aziridines <93MI 101-02>.



2*H*-Azirines show a predominant parent ion. Fragmentation of the ring to a nitrile (RCN⁺) or nitrilium ion (RCNH⁺) is often observed <70OMS(3)925, 77JA1514>. A photoionization mass spectrometer has been used to study the UV, multiphoton, and electron impact ionization of 2-phenyl-3-methyl-2*H*-azirine <92OMS(27)1105> and 2,3-diphenyl-2*H*-azirine <92IJM(115)53>.

1.01.3.4 Electronic Absorption Spectroscopy

Simple aziridines bearing alkyl groups are optically transparent in UV spectroscopy at typically useful wavelengths <84CHEC-I(7)47>. Aziridine itself absorbs at 179 nm, 145 nm, and 118 nm ($\epsilon = 4200$, 6100, and 6300 respectively) <69JCP(51)52, 72BCJ3026>. Due to such short wavelength absorptions, it has not been practical to use chiroptical methods to study the absolute configuration of simple aziridines. However, formation of the *N*-chloroaziridine provides a useful chromophore for circular dichroism studies, where Cotton effects can be observed in the range 250–300 nm <92JCS(P2)959, 93JA10267>. Another advantage of the *N*-chloro group is the 25–27 kcal mol^{−1} inversion barrier, which simplifies stereochemical analysis. Determination of the absolute configuration at the nitrogen and the carbons of aziridine is possible using this technique. The chiroptical properties of *N*-nitroso- <92JA8257> and *N*-acylaziridines <92JA1616> have also been studied. The stereoisomers of *cis*- and *trans*-2-benzoyl-3-phenylaziridines and related compounds have been distinguished by UV spectroscopy <52JOC414, 75JA2822, B-83MI 101-01, 84CHEC-I(7)47>. The $\pi \rightarrow \pi^*$ transition in the *trans*-diastereomer appears at a longer wavelength (253 nm vs. 247 nm) and is more intense ($\epsilon = 14600$ vs. 12000) than the same transition in the *cis* isomer. A similar trend is seen for the $n \rightarrow \pi^*$ transition ($\lambda = 349$ nm, $\epsilon = 297$ for *trans*; $\lambda = 327$ nm, $\epsilon = 150$ for *cis*).

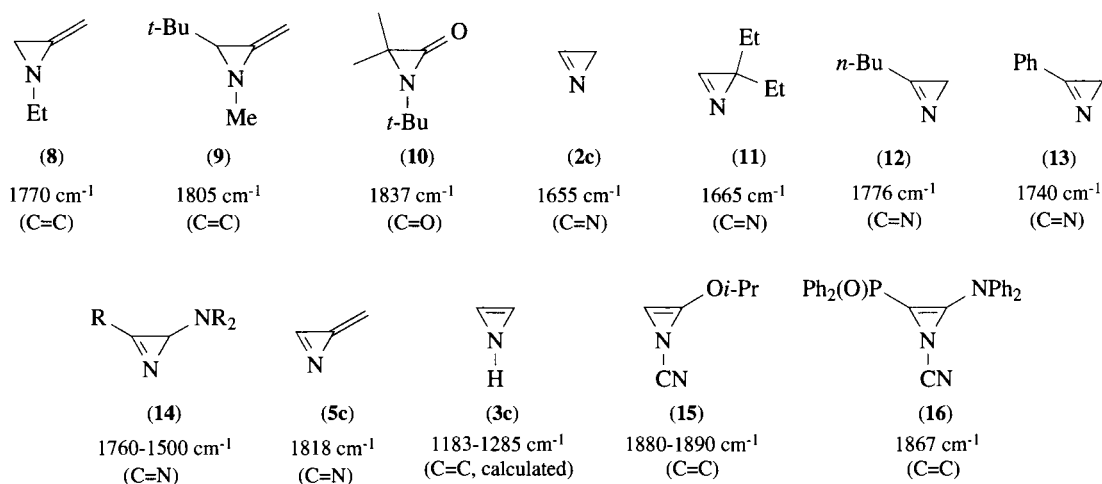
The UV absorption spectra of 3-alkyl-2*H*-azirines show a weak absorption at about 230 nm (ϵ ca. 100), while 3-aryl-2*H*-azirines exhibit a stronger absorption at about 245 nm (ϵ ca. 13000–20000) with an inflection at about 285 nm for the $n \rightarrow \pi^*$ transition (ϵ ca. 1000) <B-83MI 101-02, 84CHEC-I(7)47>. The parent compound 2*H*-azirine shows an absorption at 229 nm <88T4447>.

1.01.3.5 Infrared Spectroscopy

Infrared spectroscopy is not of particular value in assigning the structure of typical aziridines, although considerable effort has been directed at detailing the fundamental vibrations of the parent compound and simple derivatives <63PMH(2)161, 71PMH(4)265>. Aziridines with exocyclic unsaturation such as (8)–(10) show characteristic C=X stretching frequencies <80AG(E)276>. IR is more useful for the characterization of 2*H*-azirines, which show a strong C=N stretch as illustrated for (2c) <88T4447>, (11)–(13) <68JA2869, 69TL4073>, (14) <92HCA1866>, and (5c) <94JA60>. The IR spectrum of 1*H*-azirine (3c) has been calculated using MO methods (see Section 1.01.2). Regitz *et al.* reported the matrix isolation of 1*H*-azirines such as (15) and (16), which were characterized by their C=C stretching frequencies <81BSB615>.

1.01.3.6 Photoelectron Spectroscopy

The photoelectron spectra of aziridine (1) <74PMH(6)1, 74PMH(6)53> and 2*H*-azirine (2) have been measured <83JA7681, 87CB1971>. The lone-pair ionization potential was found to be 10.58 eV, while the C=N π -electron ionization potential was measured as 11.56 eV. These values compared favorably with those obtained from MNDO semiempirical MO calculations.



1.01.3.7 Dipole Moments

The dipole moments of aziridine (**1**) and 1*H*-azirine (**3**) were calculated to be 1.92–1.94 D and 2.29–2.31 D, respectively, using *ab initio* MO methods <87JPC6484, 88JST(165)99, 89JCC468>. These studies also estimated the dipole moments of the planar transition states attained during pyramidal inversion to be 0.21 D and 0.56 D, respectively, for (**1**) and (**3**). The value for aziridine compares with the known experimental value of 1.89 D. The dipole moment of 2*H*-azirine has also been estimated by theoretical methods <84CHEC-I(7)47>. Dipole moment measurements have been used to determine the preferred conformation of *N*-arylaziridines <71JCS(B)2104>.

1.01.4 THERMODYNAMIC ASPECTS

1.01.4.1 Strain, Stability, and Aromaticity

The conventional ring strain energy of aziridine (26–27 kcal mol⁻¹) is similar to that of cyclopropane (27–28 kcal mol⁻¹), reflecting high bond angle strain <74PMH(6)199>. The strain energy of 2*H*-azirine has been estimated at about 48 kcal mol⁻¹ <91AG(E)238>. The ring strain energies of 2-methyleneaziridine (39–43 kcal mol⁻¹) and 2,3-bis(methylene)aziridine (50–53 kcal mol⁻¹) have been calculated using *ab initio* MO methods <93JPC4996>.

Theoretical methods (see Section 1.01.2) have been used to estimate that 1*H*-azirine is 33–37 kcal mol⁻¹ higher in energy than 2*H*-azirine. Many theoretical studies have been carried out on the elusive heterocycle 1*H*-azirine, which is considered to be antiaromatic. These studies and calculations on the high barrier to pyramidal inversion of 1*H*-azirine were discussed in Section 1.01.2.

1.01.4.2 Pyramidal Inversion and Configuration at Nitrogen

The barrier to pyramidal inversion of the nitrogen atom of aziridines is considerably higher than in acyclic amines, making it the dominant stereodynamic process in these heterocycles <68TS97, 70AG(E)219, 70AG(E)400, B-77MI 101-01, B-83MI 101-01, 84CHEC-I(7)47, B-92MI 101-01>. An excellent review by Jennings and Boyd provides a detailed look at the dynamic NMR methods and theoretical methods that have been used to study the inversion barrier <B-92MI 101-01>. This review also provides exhaustive tabular data on the inversion barriers of many types of aziridines. It also includes coverage of aziridines that are configurationally stable at nitrogen. Theoretical methods for the estimation of inversion barriers were covered in Section 1.01.2. General trends from the Jennings and Boyd review are summarized below.

The best experimental estimate of the inversion barrier in aziridine itself is 19.5 kcal mol⁻¹ after correction for zero-point energy differences and tunneling <75JA6990>. Caution must be used when considering the inversion barrier in *N*-unsubstituted aziridines, since a net inversion may occur by a protonation–deprotonation mechanism promoted by adventitious water, thus lowering the apparent

barrier height. Typical barriers ($\Delta G^\ddagger$) for the pyramidal inversion of *N*-unsubstituted aziridines range from 15.5–17.9 kcal mol⁻¹, although values as low as 12.8 kcal mol⁻¹ have been reported. Enthalpies ($\Delta H^\ddagger$) and entropies ($\Delta S^\ddagger$) of activation for nitrogen inversion in aziridine have been determined to be 15 kcal mol⁻¹ and -6 kcal mol⁻¹, respectively. Nitrogen inversion barriers in aziridines bearing an alkyl group of low steric bulk are about 1–1.5 kcal mol⁻¹ higher than in *N*-unsubstituted aziridines. The presence of a bulky alkyl group on the nitrogen or gem dialkyl groups at C(2) lowers $\Delta G^\ddagger$ by 2–3 kcal mol⁻¹ and about 1.7 kcal mol⁻¹, respectively, as compared to *N*-methylaziridine. Electron-withdrawing groups on the α -carbon of the *N*-alkyl group lower $\Delta G^\ddagger$ by about 2 kcal mol⁻¹. *N*-Arylaziridines invert more readily than *N*-alkylaziridines by about 7 kcal mol⁻¹, presumably due to p_π - p_π conjugation of the aromatic ring with the nitrogen atom in the planar transition state. *N*-Acylaziridines have relatively low barriers to inversion. The time-scale of dynamic NMR is not short enough to measure the barriers to inversion of *N*-acetyl- and *N*-benzoylaziridine, placing an upper limit to $\Delta G^\ddagger$ of about 7 kcal mol⁻¹. The barriers for *N*-carbo-methoxy- and *N*-(*N,N*-dimethylcarbamyl)aziridine are 7.1 kcal mol⁻¹ and 9.9 kcal mol⁻¹, respectively.

Certain heteroatom substituents on nitrogen raise the barrier to pyramidal inversion when compared to *N*-alkylaziridines: NR₂ (+4 kcal mol⁻¹), Br (+5 kcal mol⁻¹), Cl (+9 kcal mol⁻¹), and OR (+15 kcal mol⁻¹). This trend correlates with increasing electronegativity, which increases the p -character in the N—X bond. Since reaching the transition state formally involves a change from sp^3 to sp^2 hybridization, the higher p -character in the N—X bond makes this change more difficult. Four-electron repulsion between the heteroatom lone pair and the nitrogen lone pair is also greatest in the trigonal transition state. The substantial barrier to inversion encountered in *N*-chloro- and *N*-alkoxyaziridines results in configurational stability of the nitrogen at room temperature. The separation of the diastereomers or enantiomers which result from this increased configurational stability has been an active area of research (B-83MI 101-01, 90TA5, 90TA865, B-92MI 101-01, 93JA10267). The inversion barriers for these aziridines have been determined by racemization or epimerization studies. For example, the inversion barrier ($\Delta G^\ddagger$) of 1-chloro-2,2-diphenylaziridine was determined to be 24.7 kcal mol⁻¹ in cyclohexane at 60°C by following the rate of racemization of optically active material (84JCS(P)2791). Aziridines which bear heteroatoms such as sulfur, phosphorus, arsenic, and silicon on the ring nitrogen have lower barriers to inversion when compared to *N*-alkylaziridines. Silicon is particularly capable of lowering the inversion barrier, resulting in values of only a few kcal mol⁻¹.

The barrier to pyramidal inversion in 1*H*-azirine (3) has been calculated to be 33–46 kcal mol⁻¹, reflecting the unfavorability of the planar transition state, which is proposed to be antiaromatic (Section 1.01.2).

1.01.4.3 Conformation of Ring Substituents

Side-chain conformational analysis of aziridines has been studied by NMR spectroscopy (B-83MI 101-01). The *s-trans* conformation of an aldehyde at C(2) is more favored than the *s-cis* form (75 : 25 ratio) as determined analysis of vicinal coupling constants (72OMR(4)703). A theoretical study of the conformation of a nitro group at C(2) of aziridine has appeared (93MI 101-01).

Theoretical methods and chiroptical studies were used to study the conformation of *N*-formyl- and *N*-acylaziridines (86JST(139)315, 92JA1616). These amides are nonplanar, showing considerable pyramidalization of the aziridine nitrogen. The lowest energy conformation about the N—(CO) bond is one in which the carbonyl group is twisted such that optimum n_N - π_{CO}^* interaction cannot be achieved. It was speculated that one of the ring N—C bonds acts as a donor to the π_{CO}^* bond. The barrier to rotation about the N—(CO) bond was estimated at about 3 kcal mol⁻¹, versus about 18 kcal mol⁻¹ for DMF.

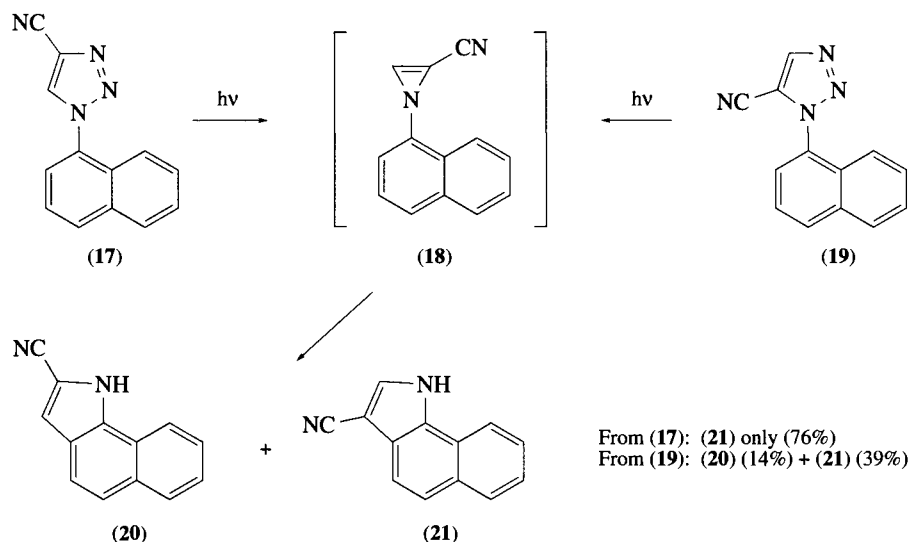
1.01.4.4 Acidity and Basicity

Aziridines are less basic than acyclic amines due to the increased s -character of the nitrogen lone pair (B-83MI 101-01). The conjugate acid of aziridine itself has a pK_a value of 7.98 (56JA4917, B-69MI 101-02), compared to a typical pK_a value of about 11 for the conjugate acid of an acyclic secondary amine. The conjugate acids of *N*-methylaziridine, 2-ethylaziridine, and 2,2-dimethylaziridine have pK_a values of 7.86, 8.31, and 8.64, respectively (56JA2159, 56JA4917). The experimental proton

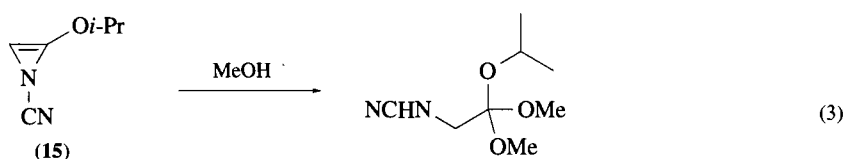
affinity of aziridine is $215.7 \text{ kcal mol}^{-1}$ <81JA486>. 2*H*-Azirines are even less basic than aziridines <71AHC(13)45>. For example, 2-methyl-3-phenyl-2*H*-azirine is insoluble in 10% hydrochloric acid, but is soluble in 37% hydrochloric acid <71AHC(13)45>. Theoretical studies have been used to investigate the complexation of H^+ and metal ions to aziridine, 1*H*-azirine, and 2*H*-azirine (see Section 1.01.2). Such studies allow a ranking of the relative basicity of these three heterocycles: 1*H*-azirine > aziridine > 2*H*-azirine <87JPC6484, 93JA11074>. The high basicity of the hypothetical species 1*H*-azirine is proposed to be due to alleviation of the antiaromatic character of the neutral heterocycle.

1.01.5 REACTIVITY OF 1*H*-AZIRINES

Little is known about the chemistry of the fully unsaturated heterocycle 1*H*-azirine (3) and its derivatives <B-83MI 101-02>. This antiaromatic heterocycle has been elusive, and thus it has been difficult to study its reactions. Circumstantial evidence for the existence of 1*H*-azirines has been obtained <B-83MI 101-02>. Typically, a rapid rearrangement occurs before the azirine can be isolated. For example, Rees and co-workers have examined the photolysis of triazoles and the addition of nitrenes to alkynes as routes to 1*H*-azirines <71CC1519, 73JCS(P1)550, 73JCS(P1)555, 75JCS(P1)1, 75JCS(P1)8, 86CC399>. Good evidence for the intermediacy of a 1*H*-azirine was obtained, although the azirine was never directly observed. Instead, further reaction to give 2*H*-azirines, indoles, and ketenimines took place (e.g., Scheme 1) <86CC399>. The formation of (21) from (19) is difficult to rationalize without the intermediacy of the 1*H*-azirine (18). A number of studies have been aimed at generating *N*-acyl-1*H*-azirines, but oxazoles are isolated instead <B-83MI 101-02>. The oxazoles may arise by rearrangement of the *N*-acyl-1*H*-azirine, or may be formed directly (e.g., by addition of an alkoxy-nitrene to an alkyne). The matrix isolation of several highly functionalized 1*H*-azirines has been reported by Regitz *et al.* <81BSB615>. Warming a matrix containing (15) and methanol causes ring-opening with the addition of two equivalents of methanol (Equation (3)). In work by Maier *et al.*, thermolysis of several likely precursors to 1*H*-azirine itself failed to allow matrix isolation of the parent heterocycle <93CB2337>. Instead, small molecules such as 2*H*-azirine and acetonitrile were produced, presumably as secondary products.



Scheme 1



1.01.6 REACTIVITY OF AZIRIDINES AND 2H-AZIRINES

Many reactions of aziridines and azirines proceed with cleavage of the highly strained three-membered ring. The π -bond of azirines is also a key reactive site, leading to nucleophilic addition as well as participation in cycloaddition reactions. Thermal and photochemical ring-opening reactions of aziridines and azirines are also common. The reactions of aziridines <B-73MI 101-01, B-77MI 101-01, B-83MI 101-01, 84CHEC-I(7)47, B-84MI 101-01, 91COS(6)65> and azirines <71AHC(13)45, B-73MI 101-01, 79COC(4)565, B-82MI 101-01, 83BSB797, B-83MI 101-02, 84CHEC-I(7)47, B-84MI 101-01, 87CHE1037, 90CHE719, 91AG(E)238> have been covered in major reviews. Padwa and co-workers have also reviewed the reactions of aziridines and azirines on a yearly basis, covering the period 1988 to 1994 <89PHC82, 90PHC22, 91PHC42, 92PHC34, 93PHC54, 94PHC56>. Kametani and Honda have reviewed the use of aziridines in the synthesis of natural products, covering many different types of aziridine reactions <86AHC(39)181>. Two reviews by Tanner cover the reactions of chiral, nonracemic aziridines, and azirines <93PAC1319, 94AG(E)599>. Heimgartner has reviewed the reactions of 3-amino-2H-azirines <91AG(E)238>.

The current review stresses the most significant reactions of aziridines and azirines published since the reviews by Padwa and Woolhouse <84CHEC-I(7)47>, Deyrup <B-83MI 101-01>, and Nair <B-83MI 101-02>. Newer examples of the more significant older reactions are also presented. The reader is referred to the above reviews for coverage of the many unique reactions of aziridines and azirines.

1.01.6.1 Thermal and Photochemical Unimolecular Reactions

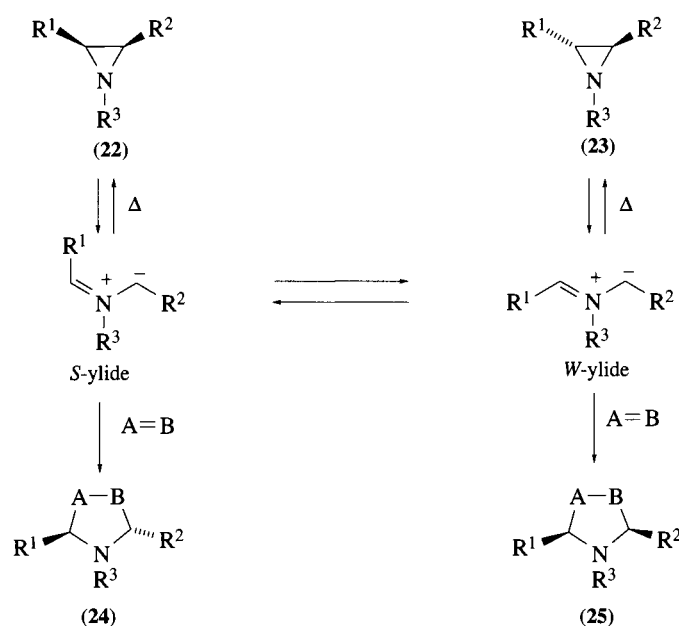
The thermal and photochemical reactions of aziridines and azirines primarily involve opening of the strained three-membered ring. Aziridines produce azomethine ylides, while 2H-azirines produce nitrile ylides or nitrenes. Typically, these intermediates react further in cycloaddition processes or other rearrangements.

1.01.6.1.1 Thermal reactions of aziridines

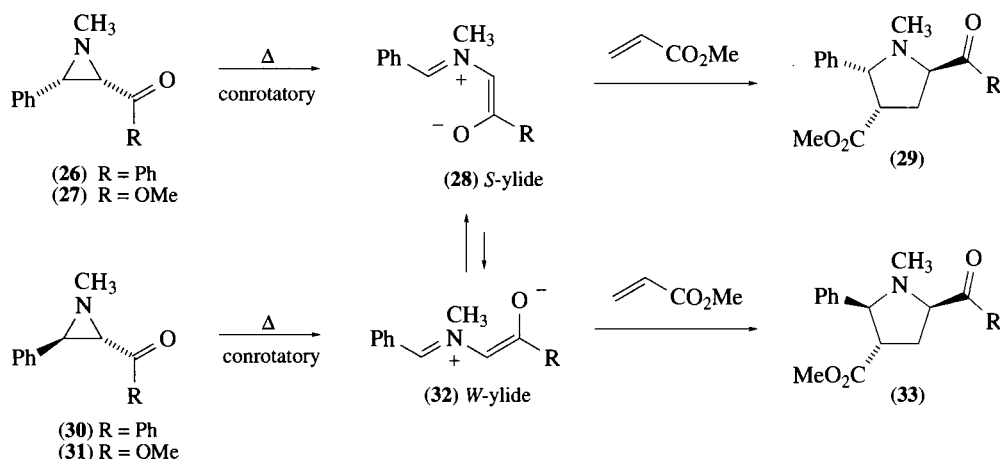
The thermal chemistry of aziridines is dominated by ring-opening to form azomethine ylides, which are often captured with appropriate dipolarophiles as shown in Scheme 2. The generation and use of azomethine ylides from aziridines has been thoroughly reviewed <B-83MI 101-01, 84CHEC-I(7)47>. Other reviews on azomethine ylide chemistry should also be consulted <B-84MI 101-02, B-88MI 101-02, B-88MI 101-03, 89AHC(45)231, 91COS(4)1111>. The thermal process involves the reversible ring-opening of the aziridine in a conrotatory fashion to provide the *S*-ylide from the *cis*-aziridine (**22**) and the *W*-ylide from the *trans*-aziridine (**23**). The expectation would be that the *W*-ylide would provide the *cis*-pyrrolidine (**25**), whereas the *S*-ylide would provide the *trans*-pyrrolidine (**24**). In practice, equilibration of the two geometric forms of the ylide can be considerably faster than cycloaddition. In the absence of a dipolarophile, this is the primary avenue for the stereochemical equilibration of aziridines. The *S*-ylide is the more stable form, and cycloadditions of the *S*-ylide are generally faster as well. Temperatures required for the conrotatory opening of the aziridine ring range from 200–310 °C. A variety of dipolarophiles have been used, including alkenes, alkynes, and carbonyl groups. A diradical intermediate rather than an azomethine ylide has been considered <92JOC6508>.

An example of the aziridine approach to azomethine ylides which illustrates the subtleties of geometry was reported by Vedejs and Grissom, and is shown in Scheme 3 <88JOC1882>. The *cis*-aziridines (**26**) and (**27**) should afford the *S*-ylide (**28**), and thus the pyrrolidine (**29**), while the *trans*-aziridines (**30**) and (**31**) should produce (**33**) through the intermediacy of the *W*-ylide (**32**). The phenyl-substituted aziridines (**26**) and (**30**) gave the same cyclization product (**29**), indicating that dipole isomerization is fast relative to cycloaddition. For the ester-substituted aziridines (**27**) and (**31**), the stereochemical outcome depended on the solvent. In hot acetonitrile, dipole isomerization was again fast relative to cycloaddition, affording (**29**) from both aziridines. In xylene, (**27**) produced (**29**) as expected, but now the *W*-ylide was competitive, affording a 2.3:1 ratio of (**33**) to (**29**). Similar results were observed in the cycloaddition reactions of azomethine ylides with aldehydes, where cycloaddition occurred through the *S*-ylide, regardless of the stereochemistry of the aziridine <70JCS(C)2383>.

Vedejs *et al.* also showed that dihydrooxazoles (**36**) may be formed upon heating *N*-Bu' aziridines (**34**), a result of electrocyclization of the *S*-dipole (**35**) (Scheme 4) <87JOC3487>. In the presence of



Scheme 2



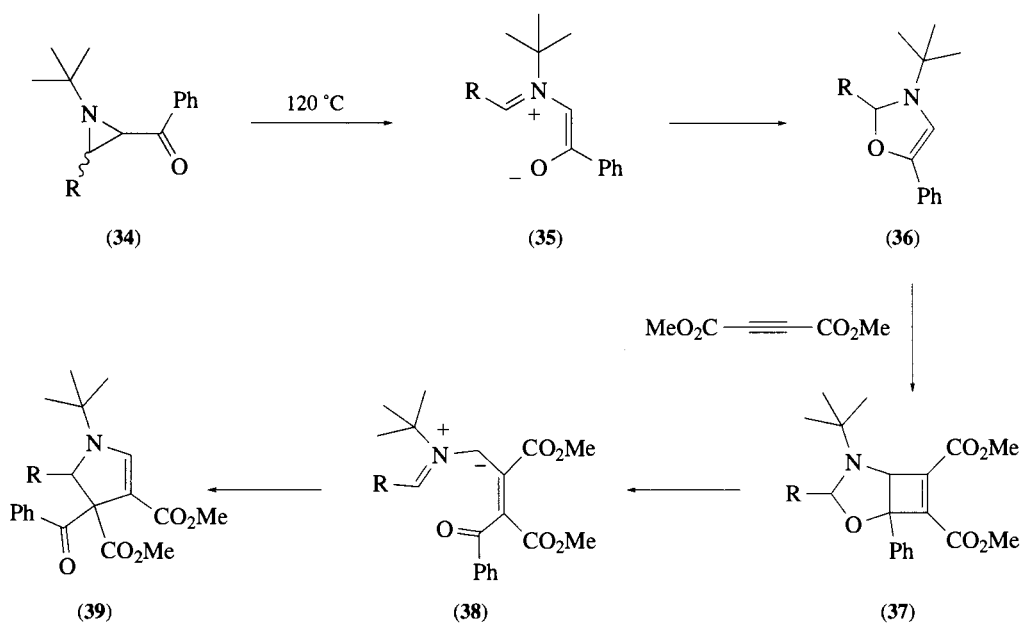
Scheme 3

dimethyl acetylenedicarboxylate (DMAD), a [2 + 2]-cycloaddition produced (37) which underwent a cycloreversion reaction to give the azomethine ylide (38). Electrocyclization of (38) gave the pyrroline (39). The bulky *t*-butyl group appears to be responsible for this novel pathway.

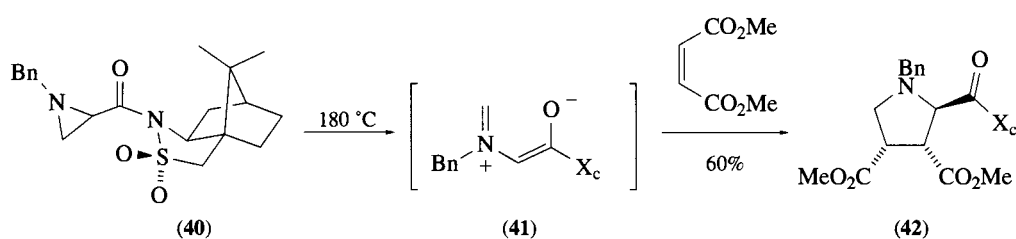
The intramolecular cycloaddition of azomethine ylides with various dipolarophiles, while outside the scope of this review (see Chapter 1.02), has been a popular approach to nitrogen-containing natural products <B-88MI 101-02>. The ring-opening of aziridines to azomethine ylides has played an important role in many cases. Syntheses of acromelic acid A, (–)-kainic acid, and the core structure of sarain A serve as representative examples for the interested reader <87JA5523, 88CC1204, 91JOC3210, 92JOC7056>. A particularly interesting report by Heathcock and co-workers showed that intramolecularity even allows cycloaddition onto a benzene ring <92JOC7056>.

Chiral azomethine ylides are produced upon heating aziridines bearing chiral auxiliaries on nitrogen <92TA681> or carbon <94JOC4, 94TL1653>. An example of the latter is shown in Scheme 5, where the thermolysis of the aziridine (40) gave the chiral azomethine ylide (41), which afforded the pyrrolidine (42) and 10% of another diastereomer.

The deprotonation of *N*-unsubstituted aziridines with *n*-butyllithium followed by heating the resultant *N*-lithioaziridines provides 2-azaallyl anions, which undergo concerted cycloaddition reactions with certain alkenes and other anionophiles as shown in Scheme 6 <74AG(E)627, B-88MI 101-02>.

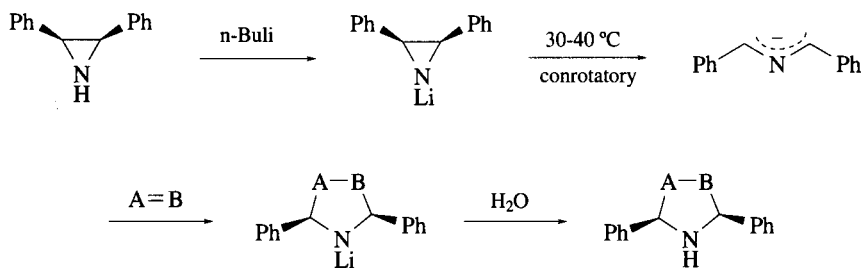


Scheme 4



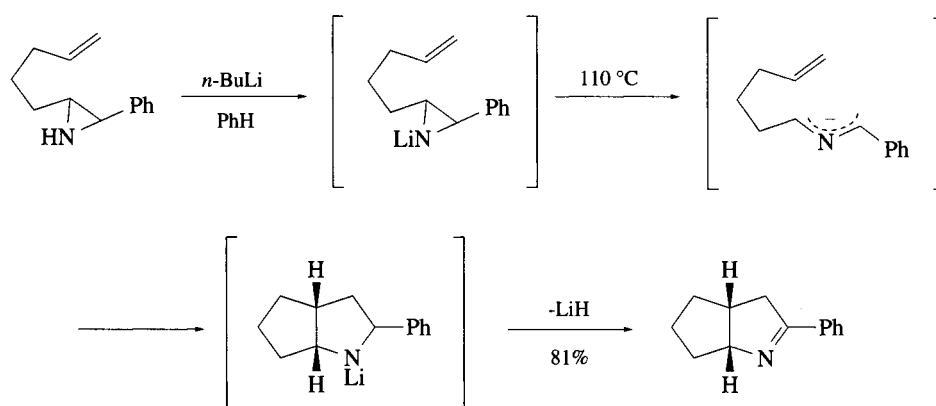
Scheme 5

The *W*-form of the anion is generally preferred, regardless of the geometry of the aziridine. The example shown in Scheme 7 illustrates the high temperatures required for ring-opening when fewer than two aryl groups are present on the aziridine <B-88MI 101-02>. At these temperatures, loss of lithium hydride from the initially formed *N*-lithiopyrrolidine occurs, producing a 1-pyrroline. Newer methods for the generation of 2-azaallyl anions that do not require the intermediacy of an *N*-metalated aziridine have proven more synthetically useful <92JA1329, 94JOC5662>.



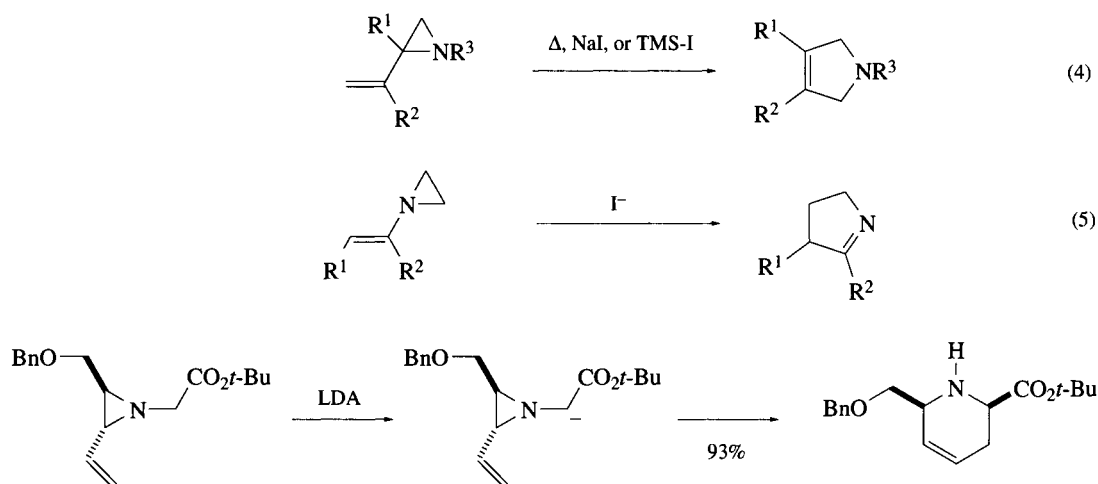
Scheme 6

Pericyclic processes which involve the aziridine ring and an unsaturated substituent on nitrogen or carbon (e.g., an alkene or carbonyl group) have been an active area of research, especially 1,3-rearrangements. Deyrup's review offers a particularly complete coverage of these reactions <B-83MI 101-01>. Aziridines bearing an alkenyl group on either the nitrogen or carbon can undergo 1,3-



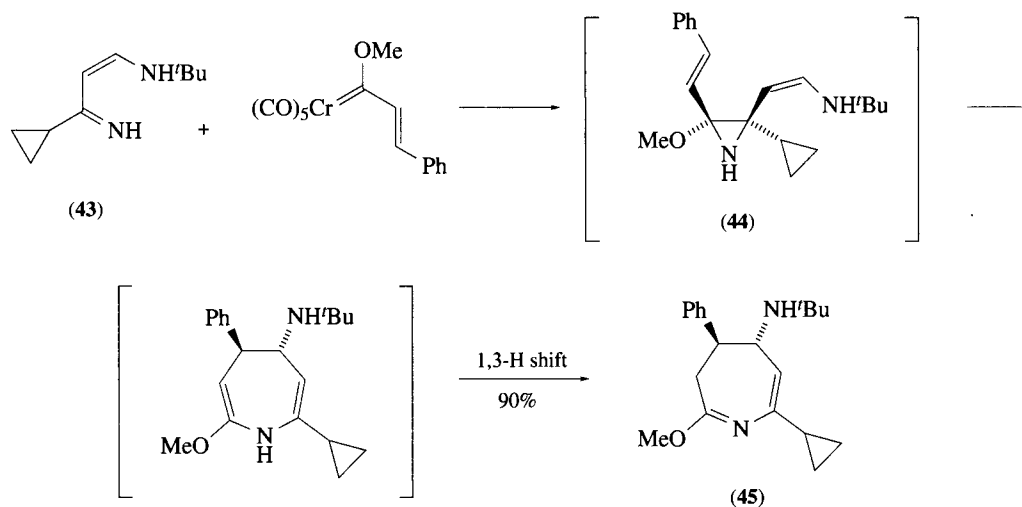
Scheme 7

rearrangements to give pyrrolines, as shown in Equations (4) and (5) (B-83MI 101-01, 84CHEC-I(7)47). Much of this work involves the formation of bicyclic pyrrolines from fused-ring aziridines. Besides Deyrup's review, a good overview of the rearrangement of *C*-(alkenyl)aziridines can be found in the work of Hudlicky *et al.* (90SL433) and Pearson *et al.* (90JOC5719). An overview of the use of *N*-(alkenyl)aziridines in the synthesis of natural products can be found in a review by Kametani and Honda (86AHC(39)181). *N*-Acylaziridines or their thiocarbonyl derivatives may also undergo a 1,3-rearrangement to produce oxazolines or thiazolines (59JA2202, B-83MI 101-01, 84CHEC-I(7)47, 94TL2039). These rearrangements are often promoted by acid or iodide ion. A number of other sigmatropic rearrangements of *N*-acylaziridines have also been reported (B-83MI 101-01, 84CHEC-I(7)47). Further work shows that *C*-(alkenyl)aziridines may also participate in aza-[2,3]-Wittig rearrangements, as shown in Scheme 8 (94JA9781). Divinylaziridines undergo a Cope rearrangement to yield dihydroazepines (B-83MI 101-01, 84CHEC-I(7)47, 89TL1789). The *cis*-divinylaziridines rearrange rapidly at or below room temperature, while the *trans* isomers require temperatures of ca. 300 °C for rearrangement. The *trans* isomer must be converted to the *cis* isomer before rearrangement is possible. This isomerization occurs via the azomethine ylide (see above). Scheme 9 shows an example of a divinylaziridine rearrangement (94CC321). Treatment of azadiene (43) with a chromium carbene complex presumably yields the divinylaziridine (44), which rearranges spontaneously. A subsequent 1,3-hydrogen shift affords the dihydroazepine (45).



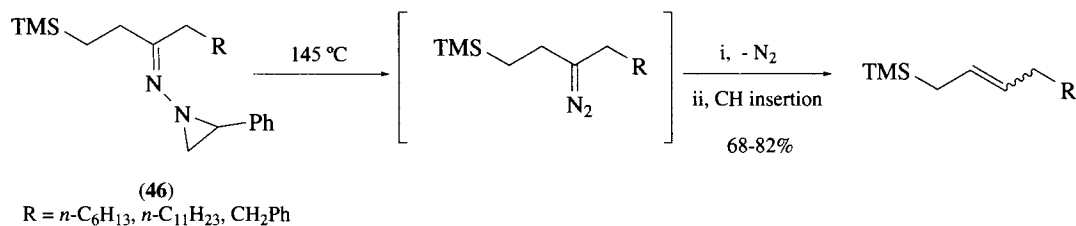
Scheme 8

Hydrazones derived from *N*-aminoaziridines such as *N*-amino-2-phenylaziridine and *trans*-*N*-amino-2,3-diphenylaziridine are converted to diazo compounds upon thermolysis (B-83MI 101-01, 84CHEC-I(7)47). For example, Scheme 10 shows that heating the hydrazone (46) yields allylsilanes by



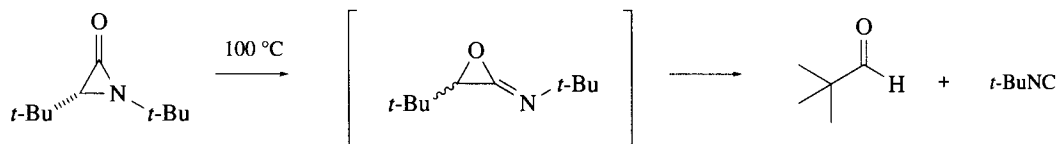
Scheme 9

selective insertion of the carbene derived from decomposition of the intermediate diazo compound into the C—H bond beta to the silyl group $\langle 92\text{CC1184} \rangle$. Intramolecular reactions of the intermediate carbenes with alkenes and alkynes have been reported $\langle 93\text{JA2637} \rangle$. The diazo compounds derived from the thermolysis of such aziridines have also been used in 1,3-dipolar cycloaddition reactions with alkenes $\langle 85\text{JOC915} \rangle$.



Scheme 10

The thermal chemistry of aziridines bearing exocyclic unsaturation such as α -lactams (aziridinones), aziridine imines, and methylene aziridines has been well reviewed $\langle \text{B-83MI 101-01, 84CHEC-I(7)47} \rangle$. A typical reaction process is shown in Scheme 11 $\langle 92\text{CB1249, 92CB2095, 92CB2749} \rangle$. Methylene aziridines and aziridine imines undergo a similar rearrangement followed by cleavage to an alkene or imine and an isonitrile $\langle 73\text{AG(E)414, 77TL1057} \rangle$.



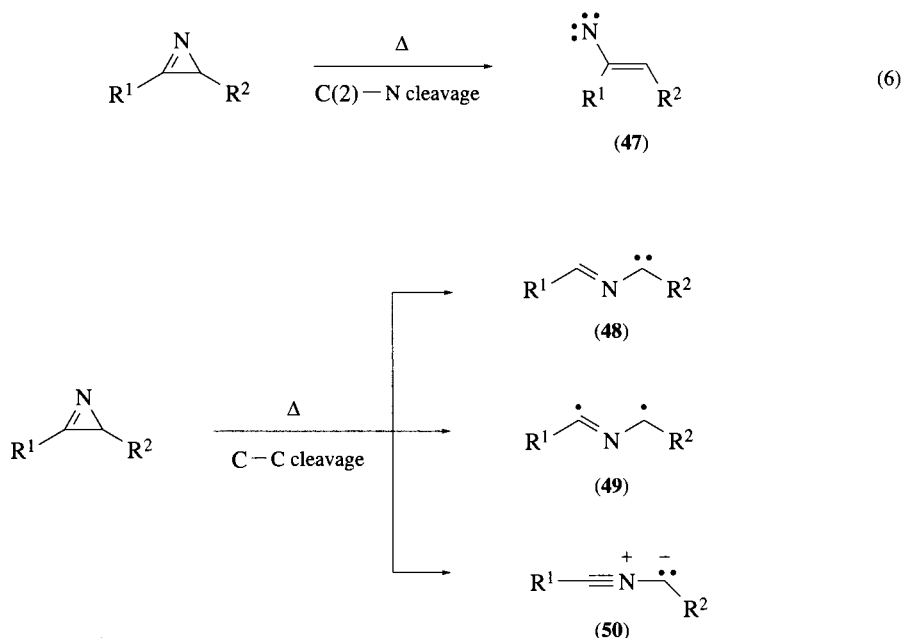
Scheme 11

Miscellaneous thermal unimolecular chemistry of aziridines such as the solvolysis of *N*-chloroaziridines and the formation of 2-azaallyl radicals has been covered in other reviews $\langle \text{B-83MI 101-01, 84CHEC-I(7)47} \rangle$.

1.01.6.1.2 Thermal reactions of 2H-azirines

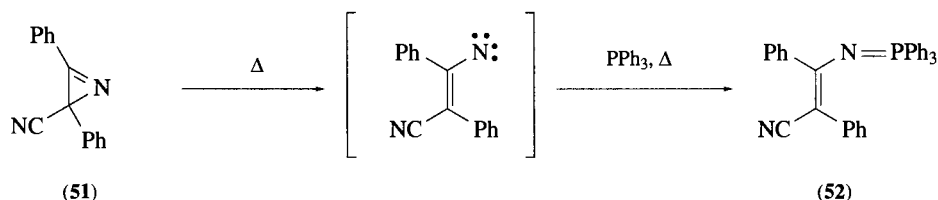
The major thermal reaction of 2H-azirines involves C(2)—N bond cleavage as shown in Equation (6) to form vinyl nitrenes (47). Cleavage of the C—C bond to produce iminocarbenes (48), diradical

species (49), or nitrile ylides (50) is possible at higher temperatures (Scheme 12). Molecular orbital calculations suggest that C—C bond cleavage occurs more readily than C(2)—N bond cleavage <78JA6575>. Excellent reviews of these processes are available <B-82MI 101-01, B-83MI 101-02, 84CHEC-1(7)47, B-84MI 101-03, 90H(30)753, 91AG(E)238>. Examples of the most general of these reactions are presented here, along with examples and advances in this area up to 1995.



Scheme 12

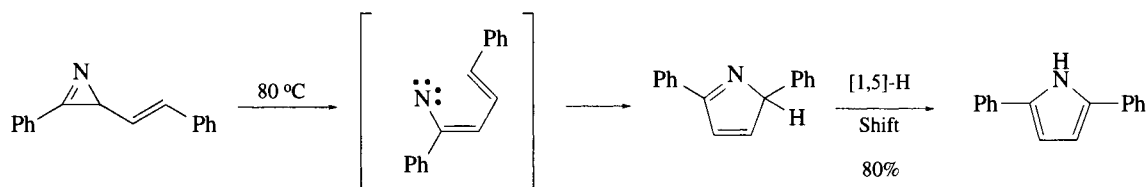
Taniguchi first described the thermally induced ring-opening of 2*H*-azirines via cleavage of the C(2)—N bond in 1968, and suggested the involvement of vinyl nitrene intermediates to explain the observed products <68TL3499>. Evidence for the presence of transient vinyl nitrenes during thermolyses of azirines has been obtained from trapping experiments using both triphenylphosphine <71JCS(C)3021, 72CC565, 72JCS(P1)1456> and tris(dimethylamino)phosphine <76JOC543>. For example, thermolysis of azirine (51) in the presence of triphenylphosphine resulted in the formation of phosphine adduct (52) (Scheme 13) <72CC565>. Taniguchi and co-workers have shown that the reactivity of 2*H*-azirines varies with the substitution pattern on the azirine ring <69TL4073>. Alkyl and aryl substituents at C(2) were found to increase the stability of the ring. Substitution at C(3) was also found to affect stability, with increasing reactivity observed in the order Ph < CH₃ < H <77H(6)1563>.



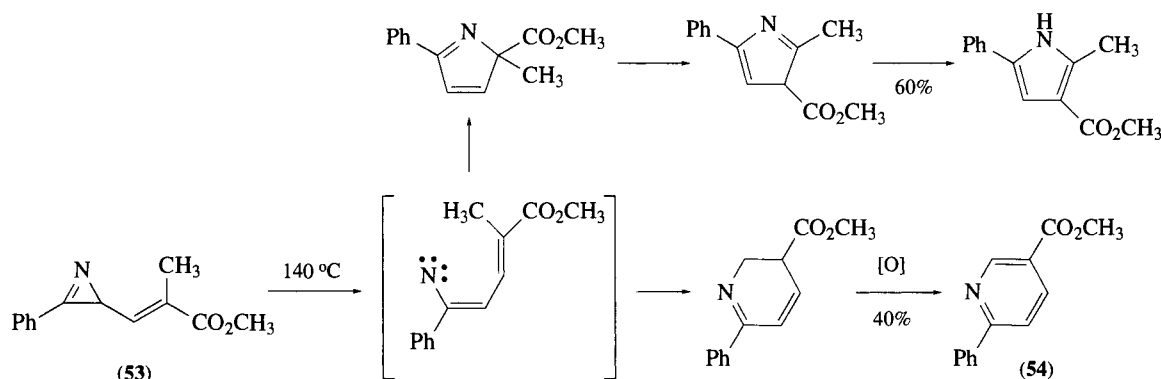
Scheme 13

Thermolysis of 2-vinyl-2*H*-azirine derivatives yields pyrroles <74TL29, 75JA4682, 76JOC543>. This can be rationalized by the formation of a vinyl nitrene intermediate which undergoes electrocyclicization followed by a [1,5]-sigmatropic hydrogen shift. An example is shown in Scheme 14 <75JA4682>. A similar reaction can occur when the vinyl substituent is conjugated with esters <72TL3479, 76JOC543>, aldehydes <75TL1067>, and nitriles <78TL3327>. With esters, alkyl substitution on the vinyl group can

lead to the formation of pyridine derivatives. For example, the formation of pyridine (**54**) from azirine (**53**) is believed to result from insertion of the intermediate vinyl nitrene into an allylic C—H bond to yield a transient dihydropyridine which is then oxidized to the pyridine (Scheme 15) <76JOC543>. In the absence of factors such as strain, pyrrole formation is generally favored over pyridine formation <90H(30)753>.

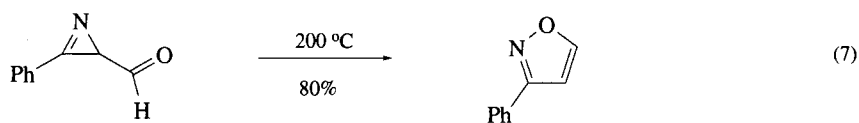


Scheme 14



Scheme 15

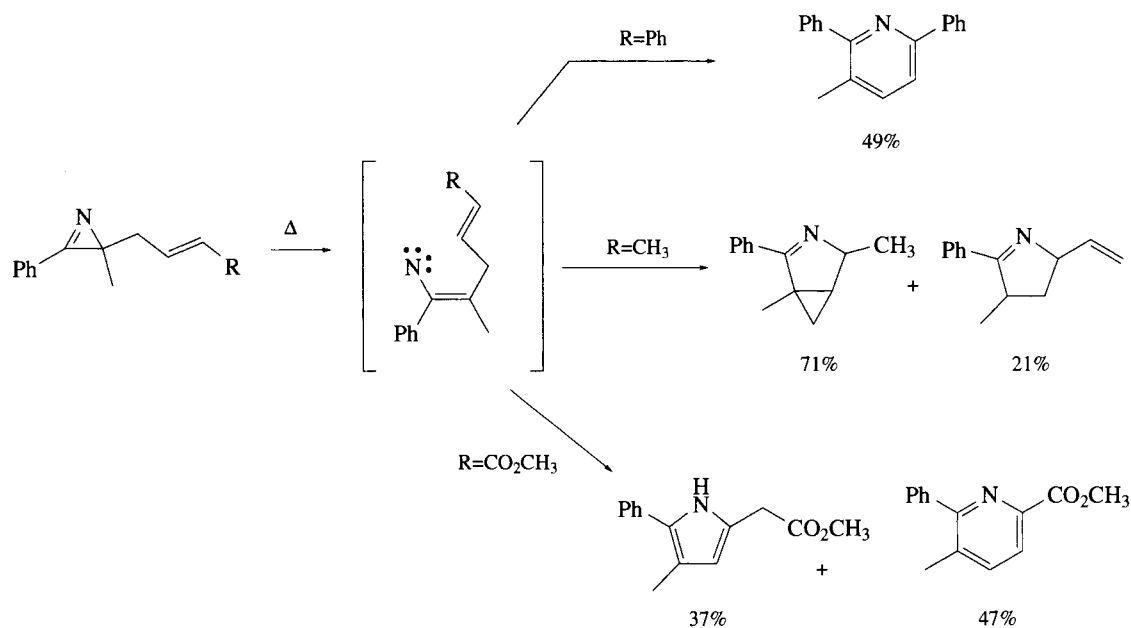
Thermolysis of 2*H*-azirines bearing an aldehyde or imine substituent at C(2) leads to the formation of isoxazoles and pyrazoles, respectively (e.g., Equation (7)) <75JA4682>. The reverse reaction, thermolysis of an isoxazole to afford an azirine, has also been reported <69TL2049>.



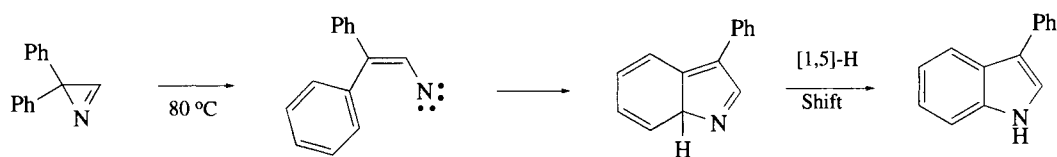
Vinyl nitrene intermediates may also be trapped intramolecularly by alkenes situated further from the azirine nucleus. A variety of products can result from these reactions, depending on the substituents present on the alkene. Scheme 16 illustrates the diverse processes that may operate <76JOC180, 78JOC2029>. 2-Propargylic 2*H*-azirines also cyclize to provide pyridine derivatives <78JOC2029>, while homoallylic substituents at C(2) allow cyclization to form pyridine and biphenyl derivatives <75CC789, 77JA1871>.

Thermolyses of 2*H*-azirines bearing aromatic substituents produce indoles by electrocyclization of the intermediate vinyl nitrene with the aromatic ring <68TL3499, 71CC1518, 77H(6)1563>, as illustrated in Scheme 17 <77H(6)1563>. When only one phenyl group is present on C(2), the intermediate vinyl nitrene can rearrange to a nitrile <68TL3499>.

Thermal cleavage of the C—C bond of 2*H*-azirines is less common than C(2)—N bond cleavage, requiring substantially higher temperatures <B-82MI 101-01>. These reactions are believed to proceed via iminocarbene intermediates which undergo a 1,4-hydrogen transfer to yield 2-aza-1,3-butadienes. The dienes which are formed often participate in subsequent intra- and intermolecular cyclization reactions <74JA308, 75JA4409, 76JOC831, 77H(7)895, 83HCA262, 86RTC456>. Scheme 18 shows an example

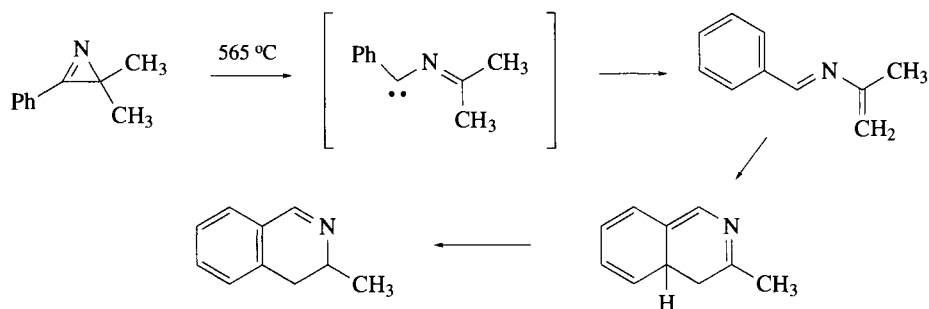


Scheme 16

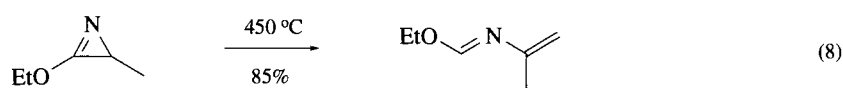


Scheme 17

where electrocyclization of the azabutadiene leads to a dihydroquinoline ^{<76JOC831>}. The thermolysis of 3-amino-2*H*-azirines affords isolable 1-amino-2-azabutadienes ^{<91AG(E)238>}. Equation (8) shows a similar process involving 3-alkoxy-2*H*-azirines ^{<86RTC456>}.



Scheme 18

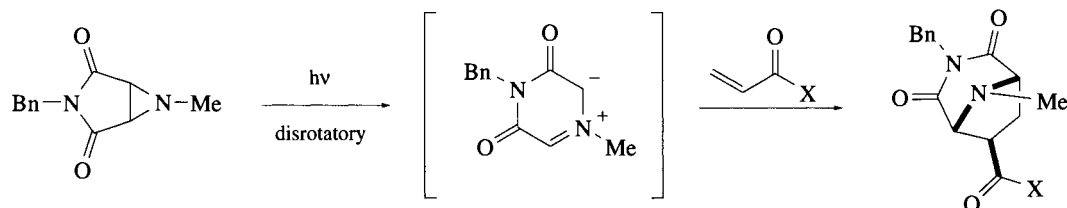


(8)

1.01.6.1.3 Photochemical reactions of aziridines

Excellent coverage of the photochemical reactions of aziridines may be found in earlier reviews ^{<73MI 101-03, B-83MI 101-01, 84CHEC-I(7)47>}. Generally, C—C bond rupture occurs, followed by a wide

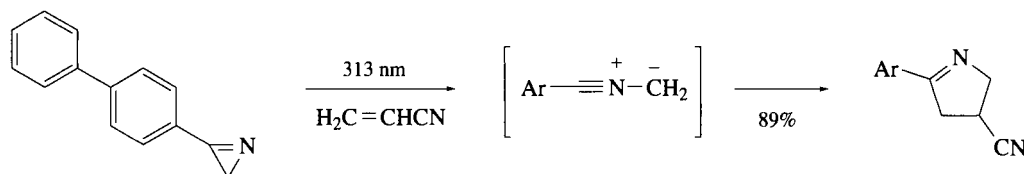
variety of subsequent steps including closure back to the aziridine (perhaps with geometrical isomerization), rearrangement, hydrogen-atom abstraction, photofragmentation, and valence isomerization. For successful photochemistry, the aziridine must bear a suitable chromophore such as an aromatic ring or carbonyl group, since simple aliphatic aziridines are transparent at typically useful wavelengths. The photochemistry of aziridines bearing a ketone at C(2) have been particularly well investigated by Padwa and co-workers. Another common process is the disrotatory ring-opening of aziridines to form azomethine ylides, providing the geometry complementary to that obtained thermally (see Section 1.01.6.1.1 above). The reader is referred to the above reviews for a complete discussion of these processes. Other examples of the formation of azomethine ylides by the photolysis of aziridines may be found in: <91JOC5893, 92CB2095, 92JOC6032>. An example is shown in Scheme 19 <91JOC5893>.



Scheme 19

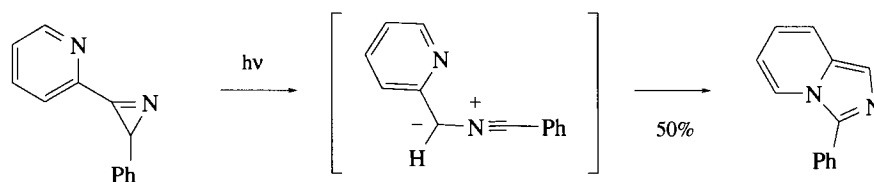
1.01.6.1.4 Photochemical reactions of 2H-azirines

The photochemistry of 2H-azirines has been a very active area of research, and represents one of the most common reactions of such azirines <71AHC(13)45, B-82MI 101-01, B-83MI 101-02, 84CHEC-I(7)47, 87CHE1037>. Photolysis generally results in ring-opening to give nitrile ylides as reactive intermediates, which subsequently undergo 1,3-dipolar cycloaddition reactions to produce five-membered-ring heterocycles <B-84MI 101-04>. The benzonitrile ylides, derived from the photolysis of 3-phenyl-2H-azirines, undergo thermal cycloaddition reactions with electron-poor alkenes and alkynes, carbonyl compounds (including aldehydes, ketones, and even carboxylic acid derivatives), imines, azo compounds, and heterocumulenes <B-83MI 101-02>. The products include 1-pyrrolines, pyrroles, imidazoles, imidazolines, imidazoles, oxazoles, oxazolidinones, and 1,2,4-triazolines. An example of the formation of a 1-pyrroline from an alkene is shown in Scheme 20 <91BCJ2757>. This paper also summarizes the available evidence for the intermediacy of nitrile ylides, including important work by Padwa, Schmid, Schuster, and others. The nitrile ylides may also undergo electrocyclization reactions with neighboring π -systems, as exemplified by Scheme 21 <93JCS(P1)675>. Protonation of the intermediate nitrile ylides can produce keteneiminium ions, which may then react with nucleophiles such as alcohols <92JCS(P2)1985>. Photoinduced electron transfer reactions of azirines have also been studied, resulting in the formation of a radical cation (a 2-azaallenyl radical cation) rather than a nitrile ylide <92AG(E)209, 93CB543, 93JOC4462>. These species still undergo cycloaddition reactions with compounds such as alkenes, alkynes, imines, and nitriles to produce five-membered-ring heterocycles, as shown in Scheme 22 <92AG(E)209>. DCN is 1,4-dicyanonaphthalene, the agent which promotes electron transfer. The advantage of this method is that the substituents on the intermediate radical cation do not have to be aryl, thus providing a method that is complementary to the traditional nitrile ylide technique. These reactions are considered to be two-step processes.

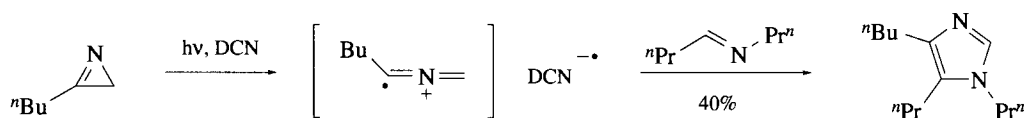


Scheme 20

Photochemically induced 1,3-rearrangements of 2-aryl-3-aryl-2H-azirines result in the formation of either oxazoles or isoxazoles, depending on the wavelength of light used <72JA1199>. Padwa and co-workers have studied the photochemical rearrangement of 2H-azirines which bear an unsaturated

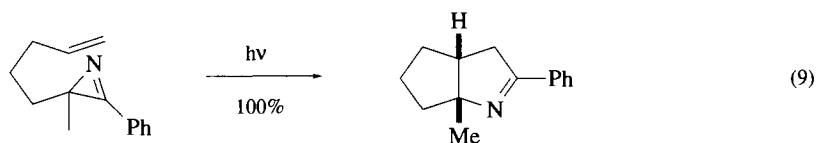


Scheme 21



Scheme 22

substituent such as an alkene or imine at C(2) (B-82MI 101-01, B-83MI 101-02, 84CHEC-I(7)47). Ring-opening to the nitrile ylide is followed by an electrocyclicization to produce pyrroles or imidazoles. Padwa and co-workers have also studied placement of an alkene further along a chain attached to C(2). Intramolecular dipolar cycloaddition or cyclopropanation results (B-82MI 101-01, B-83MI 101-02, 84CHEC-I(7)47). An example is shown in Equation (9) (77JA1871).

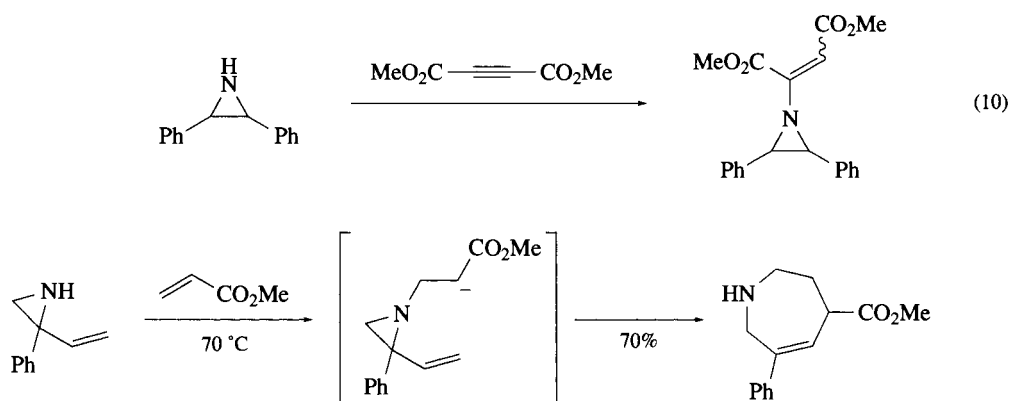


1.01.6.2 Electrophilic Attack on Nitrogen

Electrophilic attack on the nitrogen atom of aziridines and azirines results in either derivatization or a subsequent ring-opening reaction. Reactions involving nucleophilic attack at carbon promoted by protonation or Lewis acid complexation at nitrogen are covered in Section 1.01.6.3.2.

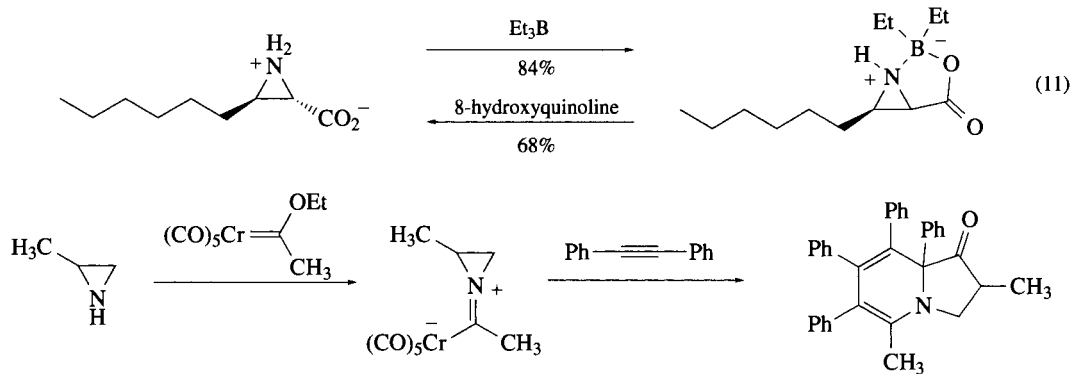
The nucleophilicity, basicity, and π -donating ability of the nitrogen of aziridines and azirines are decreased as compared to simple amines and imines due to the increased s -character of the nitrogen lone pair. The basicity of these heterocycles was discussed in Section 1.01.4.4. Despite this lowered nucleophilicity, examples of alkylation (90JOC1144, 93JOC7848), acylation (87CC153, 93JA6094, 93T4627), sulfonylation (92T6079, 93TL3639), halogenation (92RTC75, 92JCS(P2)1541, 93JA10267), silylation, and phosphorylation of aziridines at nitrogen abound in the literature (B-83MI 101-01). However, *N*-substituted aziridines are most often synthesized by formation of the ring from a precursor which already has the desired substituent in place (see Section 1.01.9). Aziridinium salts may be prepared by further alkylation of the aziridine nitrogen (B-83MI 101-01). Aziridines can be alkylated on nitrogen with epoxides, producing β -hydroxyamines (92JMC3573). The conjugate bases of aziridines have also been used to open epoxides (93JMC2232).

Michael additions of aziridines to α,β -unsaturated carbonyl compounds have been studied (B-83MI 101-01). Equation (10) shows a recent example (92JOC6032). Of interest is the application of such a process to the synthesis of the unique enamido aziridine portion of azinomycin (see Section 1.01.10.1), where an intramolecular Michael reaction of an aziridine onto a β -bromoacrylate produces a bicyclic aziridine (93JOC7848, 92JOC5813). Anticancer bisaziridinyl benzoquinones have been prepared via Michael reactions of aziridines with benzoquinones (93JMC1797). The conjugate addition of vinyl aziridines to acrylates produces the azepine ring system after an intramolecular S_N2' reaction, as shown in Scheme 23 (81TL3691, 82TL1989).

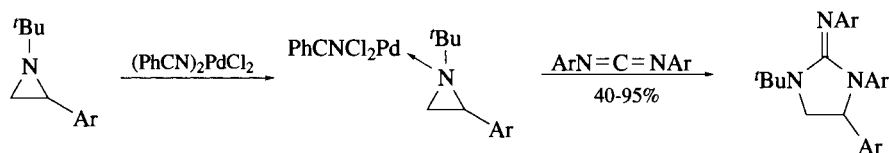


Scheme 23

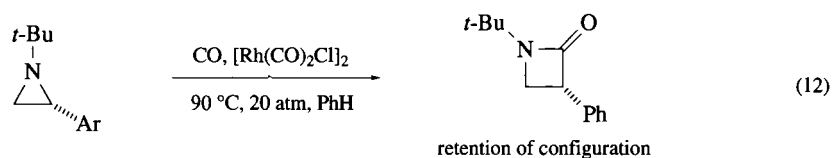
Aziridine-2-carboxylates can be converted to the boroxazolidone derivatives by treatment with BEt_3 , as shown in Equation (11) (92RTC211). The boron can be removed using acid, refluxing methanol, or 8-hydroxyquinoline with no loss of optical activity. Chromium carbene complexes react with aziridines to provide the ylide-like intermediate shown in Scheme 24 which reacts with alkynes to provide the indolizidine skeleton (88CC1303). Other metals have been used as electrophiles as well. The cobalt complex (55) was prepared via a displacement of a sulfide from a cobalt complex (93POL1371). Palladium (92JOC157) and rhodium (92JOM(438)217) also form complexes with the nitrogen of the aziridine ring. This initial complexation is often followed by an insertion reaction. An example of such a process is shown in Scheme 25 (92JOC157, 94JA1220). This general type of reaction has also been used in the synthesis of β -lactams from aziridines using rhodium or palladium catalysts (83JA6737, 89JA931, 91SL91, 93BMC2415), for example, Equation (12) (89JA931).

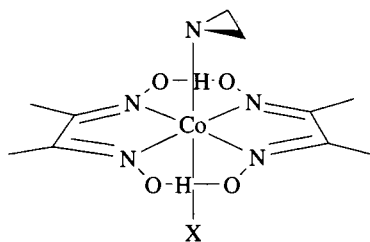


Scheme 24



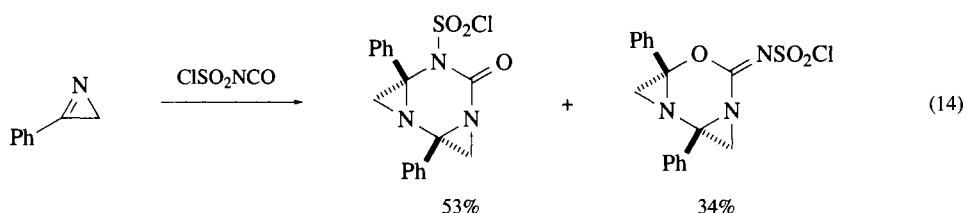
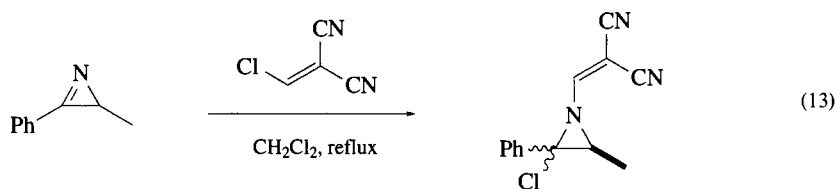
Scheme 25



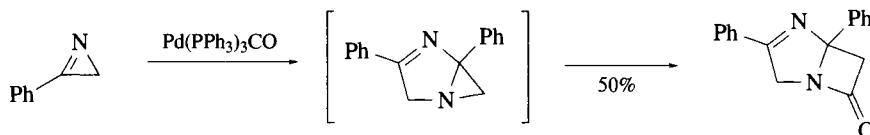


(55) X = Cl, Br, I, SeCN

The nitrogen of azirines can enter into Michael additions, with the resultant iminium ion being captured by a nucleophile, as shown in Equation (13) <92JCR(S)266>. The reaction of azirines with acylating agents also results in subsequent nucleophilic attack at carbon, for example, Equation (14) <93SC2151>. Similar reactions of azirines which result in ring cleavage will be covered in Section 1.01.6.3.2.



The metal complexes and metal-induced reactions of azirines have been reviewed <B-83MI 101-01>. Stable complexes of silver, platinum, palladium, and zinc are known. The reaction of azirines with tungsten or molybdenum complexes provides ring-opened compounds via initial complexation of the azirine nitrogen with the metal <92OM2884>. The products, metal imido complexes, are essentially a result of the complexation of a vinyl nitrene to the metal. The reaction of a 2,2-dimethyl-3-phenyl-2*H*-azirine with molybdenum carbonyl in the presence of an alkyne produces 2*H*-pyrroles <82HCA1489>. Dimerization of azirines is possible with a palladium catalyst, as shown in Scheme 26 <81JA1289>. A variety of other insertion reactions, dimerizations, intramolecular cyclizations, and intermolecular addition reactions of azirines are known to be promoted by transition metals <B-83MI 101-02>.



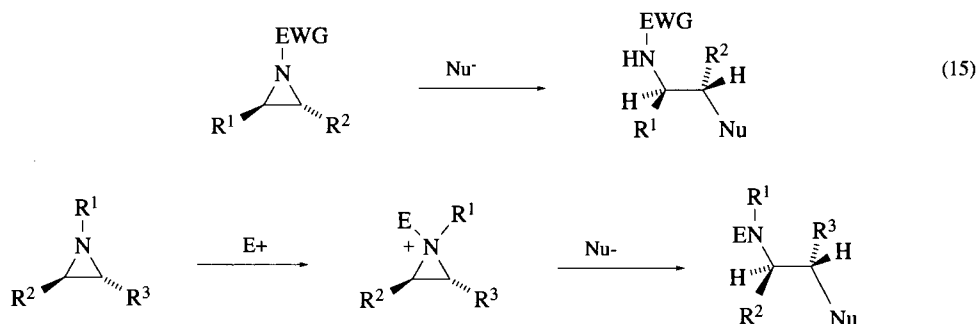
Scheme 26

1.01.6.3 Nucleophilic Attack on Carbon

The most common reactions of aziridines and azirines involve their reactions with nucleophiles at the ring carbons. Aziridines undergo ring-opening to produce amines and their derivatives, acting as β -amino carbocation equivalents. Azirines react with nucleophiles at the C(3)—N double bond, producing aziridines (which may undergo reaction by ring-opening). These processes have been well reviewed <71AHC(13)45, B-77MI 101-01, B-83MI 101-01, B-83MI 101-02, 84CHEC-I(7)47, 86AHC(39)181, 91AG(E)238,

91COS(6)65, 93PAC1319, 94AG(E)599). New reactions as well as new examples of older reactions will be presented in this section.

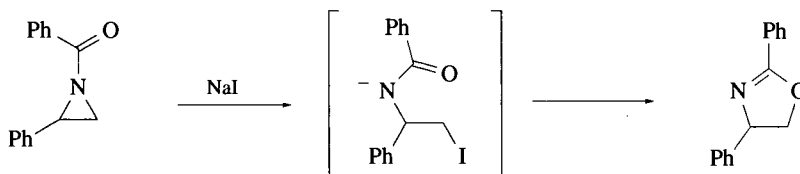
The ring-opening reactions of aziridines can be divided into two categories (64JOC3052, 91COS(6)65): (i) the reaction of nonactivated aziridines with nucleophiles, which generally requires activation by protonation of the nitrogen or complexation of the nitrogen with a Lewis acid; and (ii) the reaction of activated aziridines (i.e., those bearing an electron-withdrawing group, EWG) with nucleophiles, a process that can proceed without further activation, although sometimes even these processes are promoted by protonation or Lewis acid complexation. The following sections are organized according to whether simple nucleophilic attack (i.e., with activated aziridines) or acid-catalyzed attack is observed as shown in Equation (15) and Scheme 27. The addition of strong nucleophiles to azirines is considered in Section 1.01.6.3.1, while nucleophilic additions to azirines, which proceed by acid catalysis, are presented in Section 1.01.6.3.2.



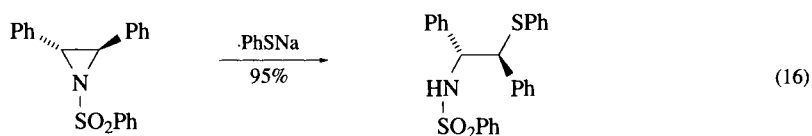
Scheme 27

1.01.6.3.1 Simple nucleophilic attack at carbon

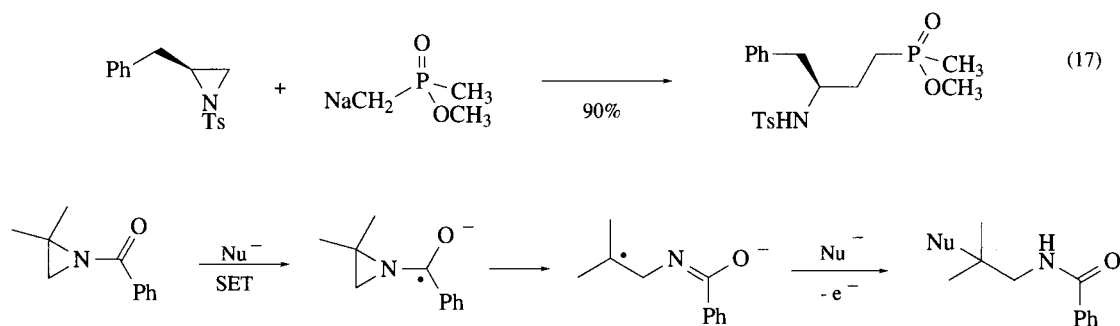
Direct nucleophilic attack at a ring carbon atom of an aziridine is best accomplished when an electron-withdrawing group is present on the nitrogen atom. Typical *N*-substituents include acyl, carboalkoxy, and sulfonyl. More recently, the diphenylphosphinyl group has proven to be useful (94SL145). The use of *N*-acyl and *N*-carboalkoxy activating groups can be complicated by attack of the nucleophile at the carbonyl group of the activating group rather than attack at the ring (84TL811, 87CC153, 93SL764). Further participation by the *N*-carbonyl group can also result, as shown in Scheme 28 (94TL2039). The arenesulfonyl group would appear to be an ideal activating group in that it does not undergo undesired reactions with the nucleophile and is relatively inert toward other subsequent reaction processes. However, it is often difficult to deprotect the resultant sulfonamide to the amine after ring-opening. Nonetheless, the *N*-arenesulfonylaziridines are the most popular activated aziridines in the literature. An example which also illustrates the clean inversion of stereochemistry in the reaction of nucleophiles with activated aziridines is shown in Equation (16) (88CB1353). Inversion is generally observed in the reactions encountered in this section.



Scheme 28

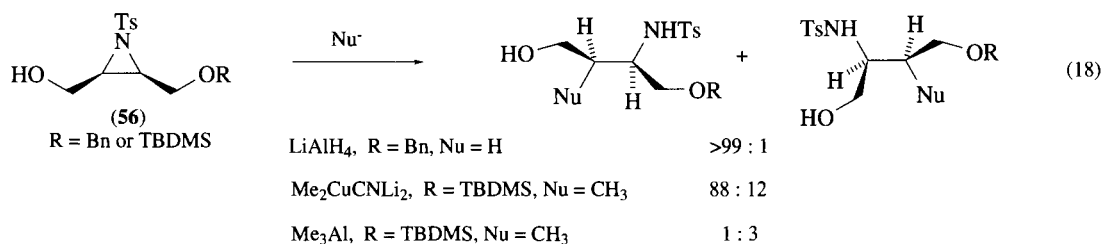


Regarding the regiochemistry of ring-opening, nucleophilic attack on the aziridine ring occurs primarily at the least substituted carbon, as illustrated by Equation (17) <83TL2935>. However, nucleophilic attack at the more substituted carbon is sometimes observed. Stamm and co-workers have studied this abnormal addition and found that a single electron transfer (SET) mechanism may be operational, shown in Scheme 29 <93JOC7377>. Initial electron transfer to the carbonyl group produces an intermediate ketyl. With *N*-aroylaziridines, the ketyl has a measurable lifetime <84CC753, 89BSF537>. Ring-opening of the ketyl produces the more substituted radical, which combines with the nucleophile to provide the abnormal addition product. Through the work of Stamm and co-workers, some guidelines have emerged regarding operation of the SET mechanism. When the activating group is a sulfonyl or carboalkoxy group, little SET is operational. The SET mechanism is mainly observed when *N*-acylaziridines are used. In addition, increasing the steric hindrance to nucleophilic attack increases the propensity for an SET reaction.



Scheme 29

A number of generalizations can be used to predict the regiochemistry of the ring-opening of 2,3-disubstituted aziridines. Aziridines fused to a cyclohexane ring give products resulting from *trans*-diaxial attack <76JCS(P1)801>. Ring-opening of monoprotected bis(hydroxymethyl)-substituted aziridines (**56**) can be regioselective, as shown in Equation (18) <92T6069, 92T6079, 94AG(E)599>. When the nucleophile is a hydride (RedAl or LiAlH₄) or Me₂CuCNLi₂, products arising from attack upon the carbon nearest the free hydroxyl group are seen, presumably as a result of internal delivery <88T619>. (See, however <93TL7421>.) The use of Me₃Al leads to the opposite regiochemical result.

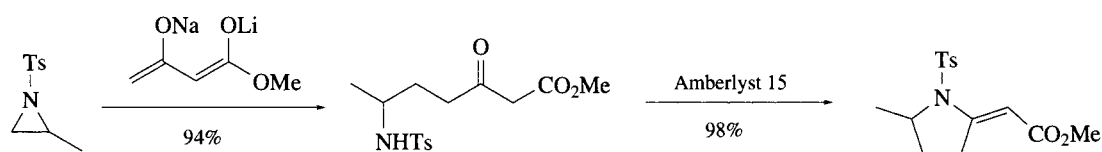
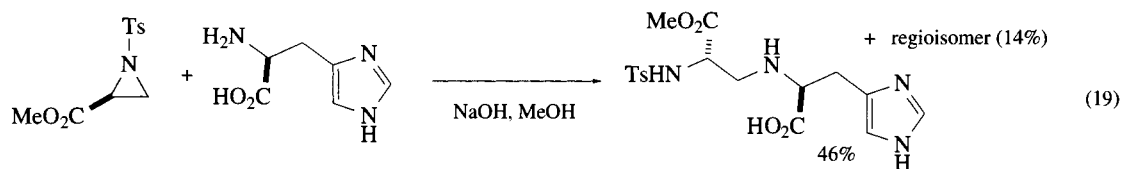


The reactions of C(2)-ester-substituted aziridines with organocuprates proceed with variable regioselectivity <87CC153, 93T6309>. Methyl cuprates show a preference for attack at the α -carbon, while larger nucleophiles such as *n*-butyl cuprates show a preference for attack at the β -carbon. Tanner has reviewed the use of these and other types of nucleophiles for the ring-opening of aziridine-2-carboxylates <94AG(E)599>.

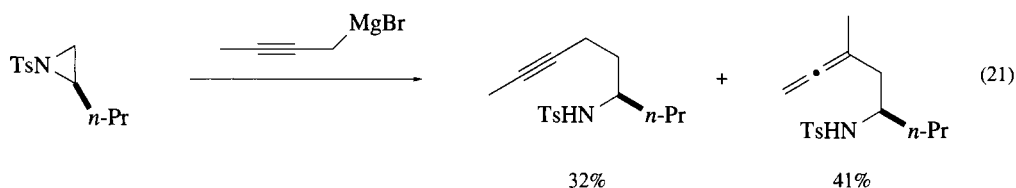
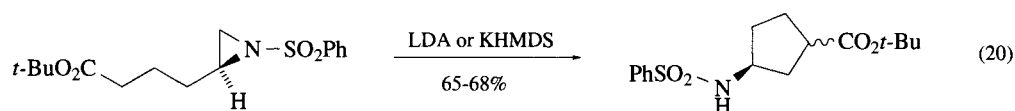
Particularly useful reviews on the ring-opening of aziridines with nucleophiles have been written by Mitsunobu <91COS(6)65> and Tanner <94AG(E)599>. Examples of the direct ring-opening of activated aziridines with thiols and thiolates <92CHE704, 92SL527, 92T2359, 93TL4953, 94SL145> (including the use of the thiol group of cysteine to open *N*-unsubstituted aziridine-2-carboxylates <87T3881>), amines and their conjugate bases <64JOC3052, 70TL4623, 88S335, 91JAN76, 92TL6287>, azide ion <89JOC5324, 90TL1903, 94SL145>, iodide <90TL1903, 92TL7949, 94SL145>, bromide <89JOC5324, 90TL1903>, cyanide <90TL6379, 94SL145>, phosphines <90TL2661>, enolates <86S392, 86S395, 89JOC1940, 93JOC5019, 93SL764>, cuprates <79JOC2788, 85TL1153, 87TL1211, 89CC1852, 89JOC5324, 90TL1903, 91TL1897, 92T6069, 93TL7421, 94JA5108, 94JOC4875, 94SL145>, organomagnesium and organolithium reagents <70TL4623, 77HCA204, 79JOC2788, 84TL811, 89JOC1940>, dithiane anions <93SL675>, α -lithiosulfones <93SL513>, phosphorus

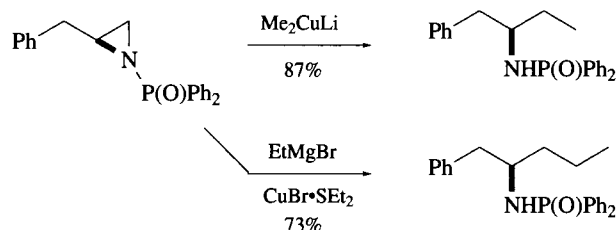
ylides <87CC153>, sulfur ylides <89T1851>, and hydride reagents <87TL1211, 92T6069> may be found in the references cited. While alcohols are not generally nucleophilic enough to open an aziridine without additional activation (see Section 1.01.6.3.2), they have been used for the intramolecular ring-opening of aziridines under basic conditions <93TL5127>. Further discussion of specific ring-opening reactions accompanied by additional examples are presented below.

Equation (19) shows the ring-opening of an aziridine-2-carboxylate with the amino group of L-histidine <91JAN76>. In Scheme 30, the dianion of methyl acetoacetate produces a γ -aminoketone which may be cyclized to a pyrrolidine derivative <93SL764>. Use of an *N*-tosyl activating group was crucial, since *N*-acyl groups (e.g., benzoyl) led to acyl transfer rather than ring-opening. An intramolecular reaction of an enolate with an aziridine has been reported, as shown in Equation (20) <93JOC5019>. Equation (21) illustrates the use of an organomagnesium reagent for an aziridine ring-opening reaction <77HCA204>. More commonly, organocopper reagents are used. Scheme 31 illustrates the use of Gilman reagents as well as copper catalyzed organomagnesium reagents <94SL145, 94TL2739>. Aryl cuprates are also useful, as shown in Equation (22) <91TL1897, 94JA5108>. Nucleophilic attack by cuprates on allylic aziridines can proceed by direct substitution at either ring carbon (S_N2 attack) or by allylic substitution (S_N2' attack), depending on the substrate and the conditions <94AG(E)652, 94JA5108, 94JOC4875>. The ring-opening of aziridine-2-carboxylates with cuprates have been reported, leading to α -amino acid derivatives <89CC1852, 90TL1903>. Thus, aziridine-2-carboxylates are β -glycine carbocation equivalents. Eis and Ganem have reported that cuprates may open unactivated aziridines if $BF_3 \cdot OEt_2$ is present <85TL1153>. An example is shown in Equation (23) <87TL1211>. In addition to the chemistry shown, when carbobenzyloxy or tosyl activating groups were used with cuprates without $BF_3 \cdot OEt_2$, both aziridine rings were opened and none of the piperidine was formed. Phosphorus ylides may be used in ring-opening reactions, forming new ylides after a proton transfer. Such chemistry was used by Baldwin and co-workers in a synthesis of γ -methyleneglutamate (Scheme 32) <87CC153>. Nucleophilic attack of triphenylphosphine on an aziridine ring was shown to produce a different type of ylide, again used for a subsequent Wittig reaction (Scheme 33) <90TL2661>. The nucleophilic attack of cobalt(III) on an aziridine ring has been observed <93HCA2602>. Several reactions involving S_N2' attack of a transition metal on an allylic aziridine are known and are discussed in Section 1.01.7.2.

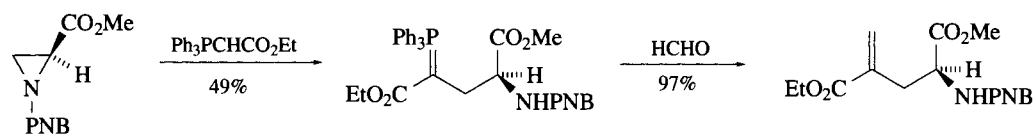
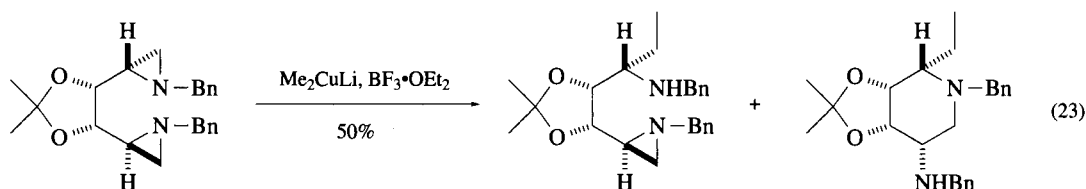
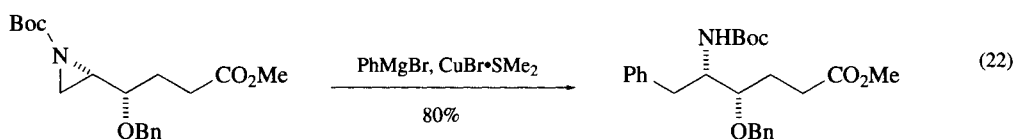


Scheme 30

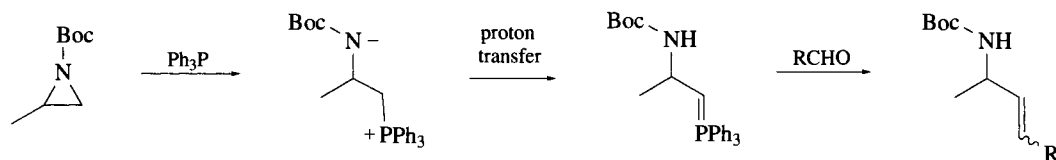




Scheme 31



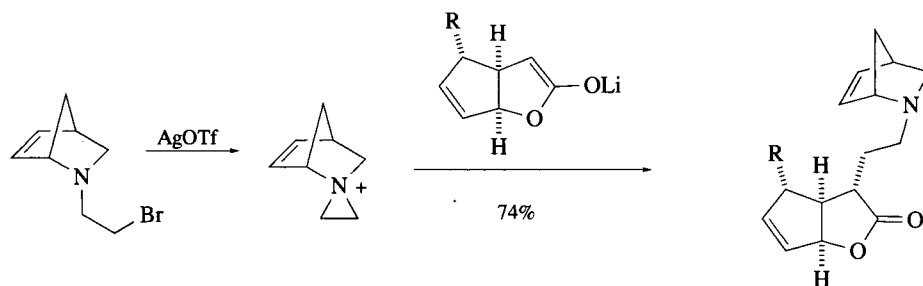
Scheme 32



Scheme 33

Nucleophilic attack on aziridinium ions is also well known (B-83MI 101-01, 86AHC(39)181). For example, ring-opening of aziridinium ions by enolates have been reported, as shown in Scheme 34 (92TL4401). The kinetics of ring-opening of aziridinium compounds have also been studied (88JOC1733, 93JPO187). Aziridinium ions have been used extensively in the synthesis of alkaloids (86AHC(39)181).

Nucleophilic attack on azirines at the C(3)—N double bond has proven to be a useful method

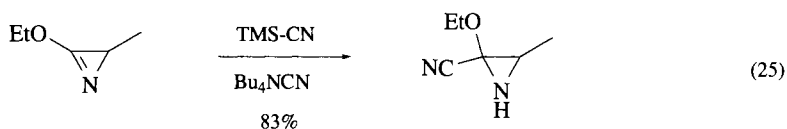
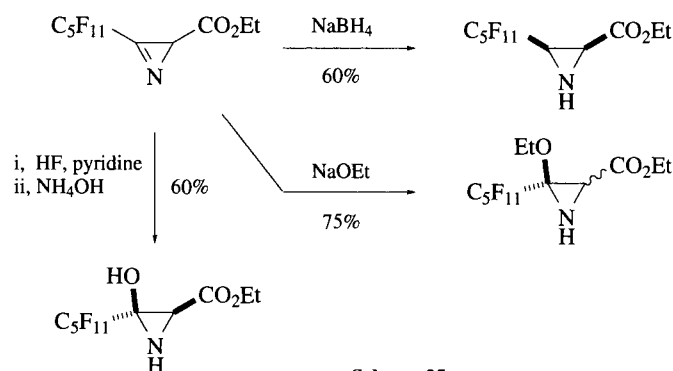
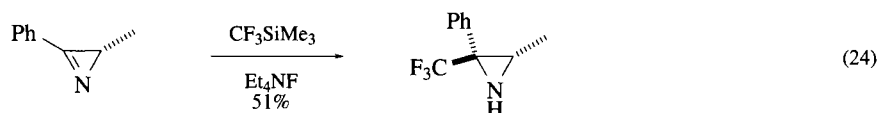


Scheme 34

for the preparation of substituted aziridines <B-83MI 101-02, 84CHEC-I(7)47>. The C=N bond is more electrophilic than a normal imine due to the strain of the three-membered ring. The following overview summarizes the material reviewed by Nair <B-83MI 101-02> and Padwa and Woolhouse <84CHEC-I(7)47>.

Direct additions (i.e., those not requiring an acidic catalyst) have been reported with a number of strong nucleophiles, including LiAlH_4 , NaBH_4 , organomagnesium reagents, sulfur ylides, alkoxides, amines and their derivatives, nitrones, and enolates. The addition of the nucleophile to the face of the azirine opposite to the substituent at C(2) can be highly stereoselective. The reactions of azirines with enolates, enamines, and Wittig reagents can provide trisubstituted pyrroles by cyclization after addition to the double bond <82CC784, 84JCS(P1)111>. More examples of nucleophilic additions to azirines are shown below.

Trifluoromethylaziridines may be prepared by the reaction of trifluoromethyl anion to azirines as shown in Equation (24) <94TL3303>. Two of the reactions of a highly electrophilic 3-(perfluoroalkyl)-2*H*-azirine are shown in Scheme 35 <93T4627>. Interestingly, the addition of water led to a stable 2-hydroxyaziridine, presumably due to the electron-withdrawing perfluoroalkyl group. Normally, ring-opening to an aminoketone would be observed. Nucleophilic additions to 3-alkoxy- <86RTC456> and 3-amino-2*H*-azirines <91AG(E)238> are especially well studied. Many of these reactions involve assistance by protonation of the nitrogen and will thus be covered in Section 1.01.6.3.2, but an example of the addition of cyanide to a 3-alkoxy-2*H*-azirine is shown in Equation (25) <86RTC456>.



1.01.6.3.2 Acid-catalyzed nucleophilic attack at carbon

The acid-catalyzed addition of nucleophiles to aziridines has also been used extensively for synthetic transformations <B-83MI 101-01, 84CHEC-I(7)47>. The acid-promoted addition of nucleophiles to azirines has also been studied <B-83MI 102-02, 84CHEC-I(7)47>. While earlier reviews should be consulted for much of this literature, citations up to 1995 have been included here.

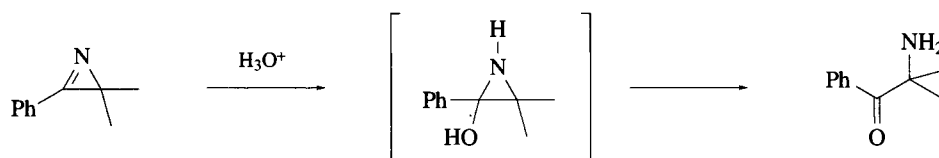
For the acid-catalyzed ring-opening of aziridines with nucleophiles, the nitrogen substituent can be almost any group (e.g., hydrogen, alkyl, aryl, acyl, sulfonyl, etc.). Inversion of stereochemistry is most commonly observed, presumably the result of an $\text{S}_{\text{N}}2$ mechanism rather than an $\text{S}_{\text{N}}1$ -like

Heteroatom nucleophiles are the most commonly used. Water ^{<93JA5328, 94JOC3243>}, alcohols ^{<87BCJ2963, 89AP(322)277, 92BMC1489, 93TL6513>}, ethers ^{<92TL3607>}, carboxylic acids ^{<81JCS(P2)121, 89JOC1940, 92RTC59, 94JOC3243, 94TL3489>}, esters and amides ^{<93TL6513>}, thioamides, acid chlorides, azidoformates, and sulfonyl halides ^{<92RTC16>}, hydrazoic acid (or azide ion ^{<89JOC5324>} or TMS-N₃ ^{<92RTC59>}), thiols ^{<83TL1133, 92RTC16, 92RTC59>}, HF ^{<80JOC5328>}, HCl ^{<89JOC1940, 92RTC16, 92RTC59>} or ZnCl₂ ^{<93TL6513>}, HBr or bromide ion ^{<89JOC5324>}, heterocumulenes, and the nitrogen atom of nitriles ^{<92RTC16>} have been observed to open aziridines in the presence of protic acid or Lewis acids (especially BF₃). Ethylenimine and derivatives are polymerized with acid (see Section 1.01.10).

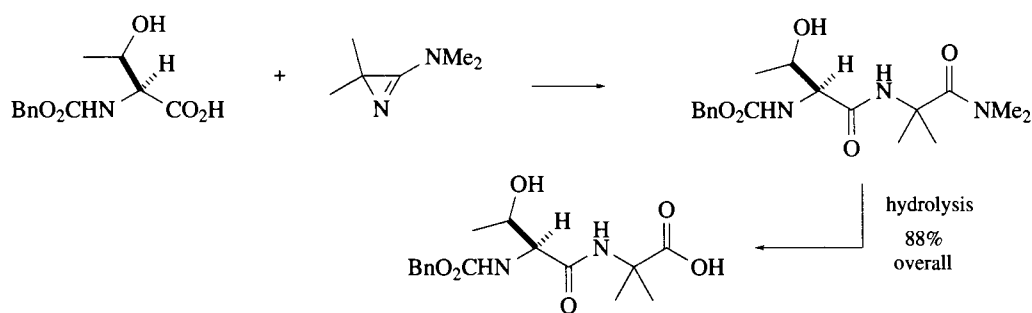
〈87BCJ2963, 89TL4073, 92RTC16〉.



The acid-catalyzed reactions of 2*H*-azirines often result in subsequent ring-opening to an amino ketone as shown in Scheme 36 [\(67JA4456, B-83MI 101-02, 84CHEC-1\(7\)47\)](#). The initially formed aziridines can sometimes be isolated (see Equation (25)). The addition of carboxylic acids, phenols, ketones, ammonium salts, acid chlorides, sulfonic acids, anhydrides, and many other electrophilic reagents have been studied, leading to a variety of products [\(B-83MI 101-02, 84CHEC-1\(7\)47\)](#). 3-Amino-2*H*-azirines have proven to be exceptionally useful in addition reactions, producing a variety of heterocycles and other interesting compounds after subsequent ring-opening of the intermediate aziridine [\(91AG\(E\)238\)](#). One of the most useful reactions of 3-amino-2*H*-azirines is the synthesis of peptides containing an α,α -disubstituted amino acid, as shown in Scheme 37 [\(89T2999\)](#). Similar reactions have been reported with 3-ethoxy-2*H*-azirines [\(86RTC456\)](#).



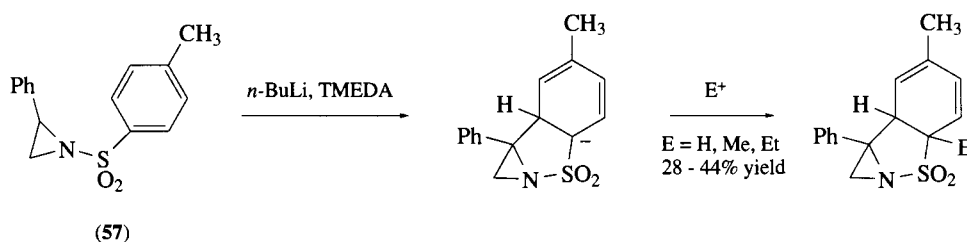
Scheme 36



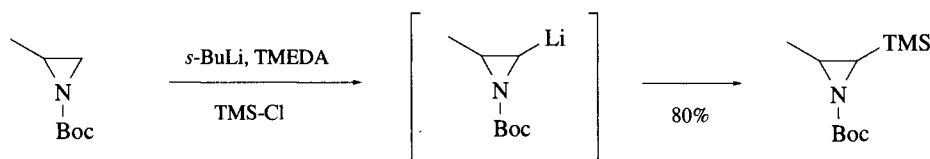
Scheme 37

1.01.6.4 Ring Metalated Aziridines

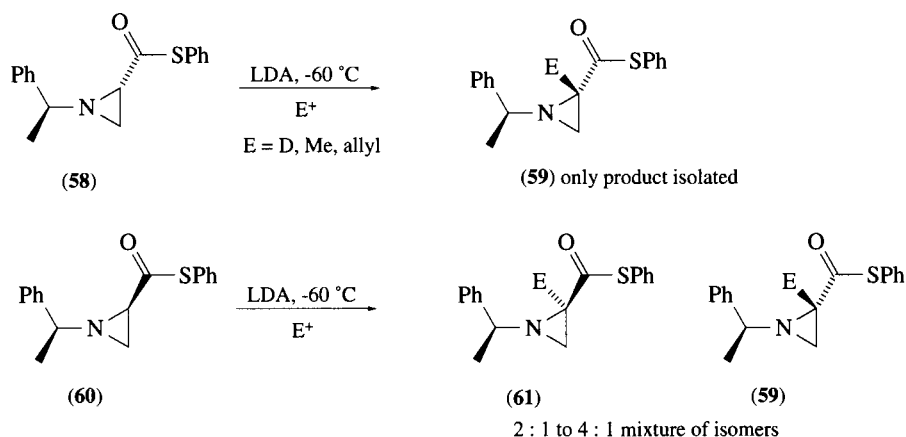
Carbanions at C(2) of the aziridine ring may be generated by deprotonation, tin–lithium exchange, or related processes. A major problem with the deprotonation approach is the necessity for a strong base which may also react by a nucleophilic ring-opening process. Few examples of such reactions have been reported. Deprotonation of the *N*-tosylaziridine (**57**) gave a 2-lithioaziridine which cyclized onto the tosyl group (Scheme 38) <91TL1299>. Treatment of optically pure aziridine (**57**) with lithiodithiane led to its racemization, indicating deprotonation of the ring <93SL675>. Beak *et al.* have shown that *N*-(*t*-butoxycarbonyl)aziridines may be deprotonated with Bu^sLi/TMEDA, as shown in Scheme 39 <94JOC276>. For a successful reaction, trimethylsilyl chloride must be present during the metalation, perhaps implying that the anion has a short lifetime. Deprotonation of the thioesters (**58**) or (**60**) followed by quenching with an electrophile gave (**59**) and (**61**), providing evidence that the intermediate “enolate” is pyramidalized and has significant configurational stability (Scheme 40) <87HCA1676>. Other groups on the aziridine ring including ketones <65JA1050>, sulfones, and phosphonates <89H(28)1179> have been used to aid in similar deprotonation reactions. A new method for the preparation of 2-lithioaziridines involves the tin–lithium exchange of 2-(tri-*n*-butylstannyl)aziridines (Scheme 41) <93JA1607>. Transmetalation and quenching at -78°C gave excellent yields of products with retention of stereochemistry. Warming the lithiated aziridine above -10°C resulted in carbon-to-nitrogen migration of the trityl group. Desulfinylation of 2-sulfinylaziridines is presumed to involve a 2-metalloaziridine intermediate, as shown in Equation (29) <88TL4093, 89JOC3973>. Treatment of the aziridine (**62**) with EtMgBr followed by quenching with H₂O or D₂O gave the *cis*-aziridine (**63**). Quenching with other electrophiles was also possible, although mixtures of diastereomers resulted.



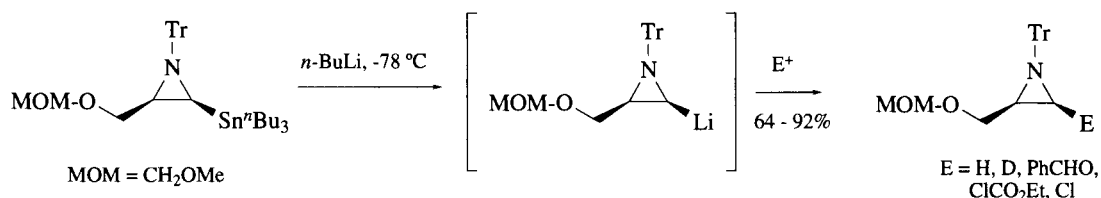
Scheme 38



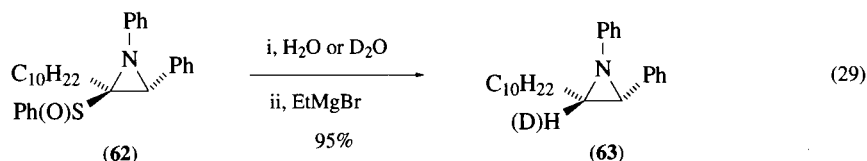
Scheme 39



Scheme 40

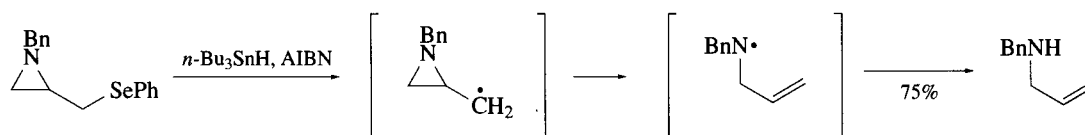


Scheme 41

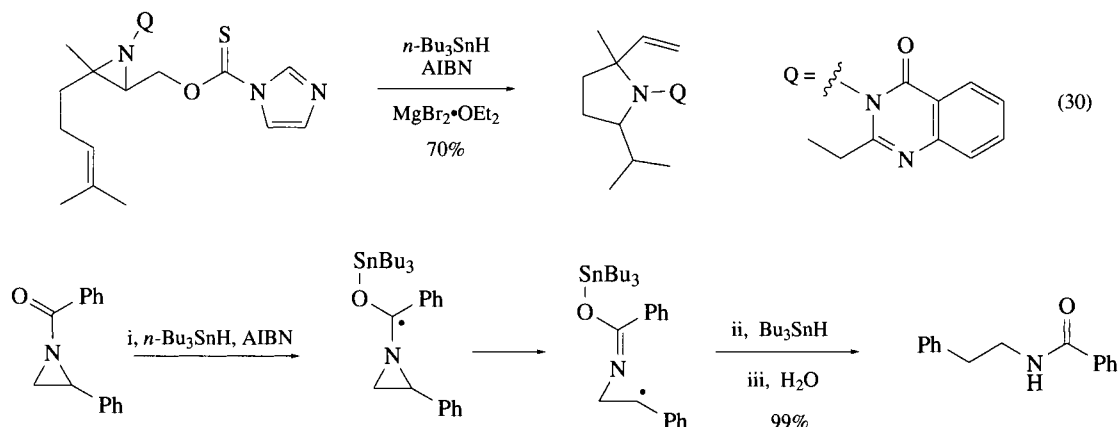


1.01.6.5 Reactions with Radicals and Electron-deficient Species, Heterogeneous Surface Reactions, and Reductions

The formation of a radical on a carbon adjacent the aziridine ring causes ring-opening in much the same fashion as a cyclopropylcarbinyl radical. Cleavage of a carbon–bromine ^[94SL287] or carbon–selenium bond ^[90CC434, 93TL4901] with Bu₃SnH/AIBN has been used to initiate this reaction, as shown in Scheme 42. When the aziridine ring is substituted with an aromatic ring, C–C bond homolysis becomes competitive. Capture of the intermediate aminyl radical by a suitable trap is possible, as shown in Equation (30) ^[92T1317]. Aziridines bearing a dienyl substituent at C(2) undergo a similar reaction to yield pyrrolines (see Scheme 47 in Section 1.01.7.2 below) ^[88TL1543]. Generation of a radical at a carbon atom directly attached to the aziridine nitrogen atom also leads to ring cleavage. For example, *N*-acylaziridines may be reduced to ketyls which undergo ring-opening ^[87TL2511, 89TL2271]. Such a process may operate in nucleophilic substitution reactions using *N*-acylaziridines, where the nucleophile reacts via an SET reaction (see Scheme 29 above) ^[93JOC7377]. The addition of tributyltin radical to the carbonyl group of *N*-acylaziridines causes a similar opening as illustrated in Scheme 43 ^[89T5015]. The addition of radicals to the C=N bond of *N*-aziridinylhydrazones results in an intermediate aziridine bearing an aminyl radical on the aziridine nitrogen atom, resulting in fragmentation ^[93TL4213].

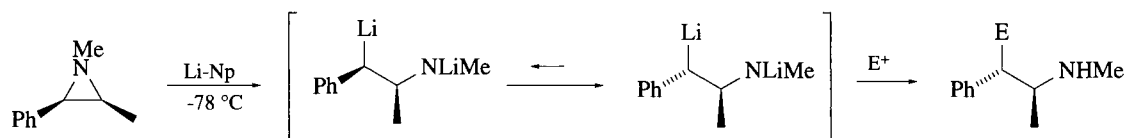


Scheme 42



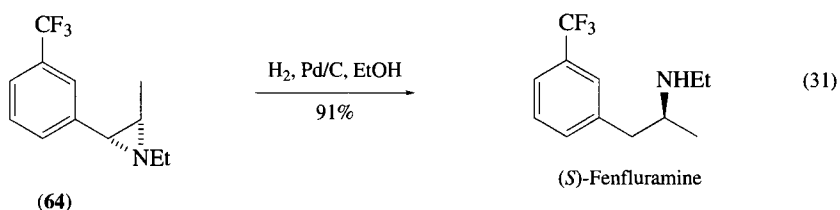
Scheme 43

Aziridine rings have been reductively cleaved with Na/NH₃ and Li/EtNH₂, resulting in scission of a C—N ring bond (71JOC330). The cleavage of aziridines with lithium naphthalenide provides synthetically useful dianions as shown in Scheme 44 (93TL1649, 94JOC3210).



Scheme 44

While the hydrogenolysis of aziridine ring bonds is normally difficult, examples of the hydrogenolysis of strained aziridines (67JOC2388, 76HCA2114) and aziridines with benzylic C—N bonds are known (93BSF459, 93JA5328, 93SL35, 94JOC3243). For example, (*S*)-fenfluramine was prepared by the hydrogenolysis of the *cis*-aziridine (64) in Equation (31) (93BSF459). Aziridinium ions can be reduced to the tertiary amine, even when the C—N bond being reduced is not benzylic (62JA4806, 63JOC1499). The least substituted C—N bond is normally reduced. The C=N of azirine rings can be hydrogenated to provide aziridines (B-83MI 101-01). Platinum-catalyzed hydrosilylation of the C(2)—N σ -bond of azirines provides *N*-silylenamines (92CL45).

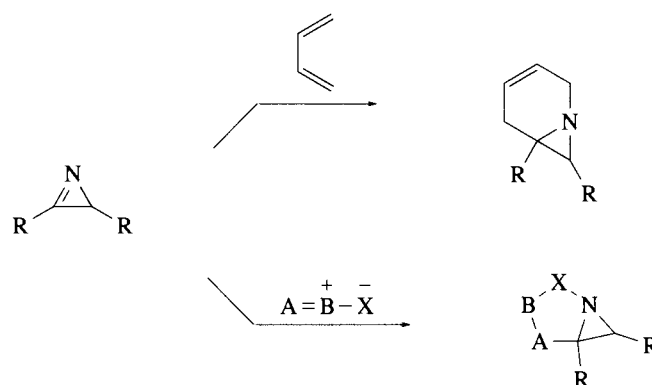


1.01.6.6 Bimolecular Reactions Involving a Cyclic Transition State

Cycloaddition reactions of the C(3)=N bond of azirines are common (Scheme 45) (71AHC(13)45, B-83MI 101-03, 84CHEC-I(7)47). Azirines can participate in [4 + 2] cycloadditions with dienes including cyclopentadienones, isobenzofurans, triazines, and tetrazines. They also participate in 1,3-dipolar cycloadditions with azomethine ylides, nitrile oxides, mesoionic compounds, and diazomethane. Cycloadditions with heterocumulenes, benzyne, and carbenes are known. Azirines also participate in other pericyclic reactions, such as ene reactions.

1.01.7 REACTIVITY AT SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Reactions of substituents attached to the ring carbon atoms of aziridines and azirines have been reviewed (B-83MI 101-01, B-83MI 101-02, 84CHEC-I(7)47). Many of the reactions involving substituents

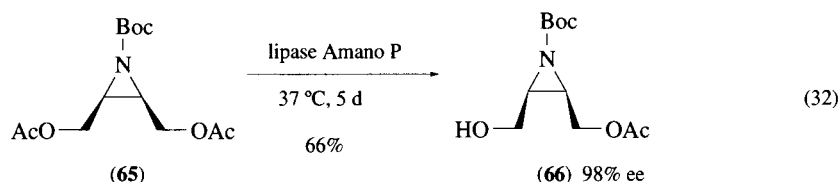


Scheme 45

attached to ring carbon atoms are discussed elsewhere in this chapter (see Section 1.01.6), particularly those reactions in which the aziridine or azirine ring participates in a pericyclic process or is transformed into a reactive intermediate (e.g., azomethine ylide, nitrile ylide, vinyl nitrene).

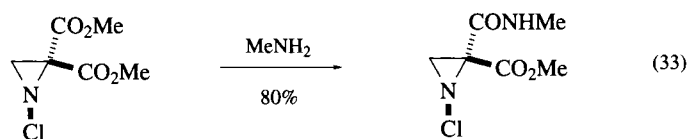
1.01.7.1 Reactions at Carboxylic Acids and Their Derivatives

Optically active aziridines have been prepared in high enantiomeric excess by the enzymatic resolution of *meso* diesters $\langle 94\text{AG(E)599} \rangle$. For example, when the *meso*-bis(acetoxymethyl)aziridine (**65**) was subjected to enzymatic hydrolysis with lipase Amano P, the aziridine (**66**) was obtained in 98% *ee* (Equation (32)) $\langle 90\text{TL6663} \rangle$. The structure of (**66**) was verified by x-ray crystallographic analysis. Similar enzymatic resolutions have employed pig liver esterase $\langle 93\text{TA2295} \rangle$, lipase from *Candida cylindracea* $\langle 93\text{TA903} \rangle$, lipase from *Rhizopus delemar* $\langle 90\text{TA5} \rangle$, and α -chymotrypsin $\langle 90\text{TA5, 92JCS(P2)959} \rangle$. The resolution of ester-substituted aziridines based on selective complexation with optically active host compounds has also been reported $\langle 90\text{TA281} \rangle$.



Aziridine-2-carboxylates can be converted to bicyclic boroxazolidones in one step with triethylborane, as shown in Equation (11) in Section 1.01.6.2 $\langle 92\text{RTC211} \rangle$. These can be considered doubly protected α -amino acids, and can be converted back to the parent aziridine-2-carboxylates using a variety of conditions.

Deyrup's review provides good coverage of some of the conventional reactions that one might expect to find on aziridine-2-carboxylic acids and their derivatives $\langle \text{B-83MI 101-01} \rangle$. The following summary is from that review. Metal hydride reduction of aziridine esters to the corresponding alcohol or aldehyde can be accomplished without ring-opening. Reduction of aziridine amides to amines with LiAlH_4 has been reported. A nitrile substituent on an aziridine can be reduced to an aminomethyl group. Addition of Grignard reagents to such esters affords the tertiary alcohol, as expected. Aziridine esters are easily hydrolyzed to carboxylate salts, which may be converted to trityl esters using trityl bromide. The salts may also be treated with organolithium reagents to form ketones. The free acid is relatively stable in cases where an electron-withdrawing group is present on the aziridine nitrogen. Such acids have been esterified with diazomethane. The formation of thioesters from the carboxylate salt $\langle 74\text{S811} \rangle$ or from the ester with Et_2AlSPh $\langle 87\text{HCA1676} \rangle$ has been reported. An example of the aminolysis of an ester is shown in Equation (33) $\langle 91\text{CC538} \rangle$. The reaction proceeds with complete stereoselectivity, and neither the ring nor the *N*-chloro group are harmed.



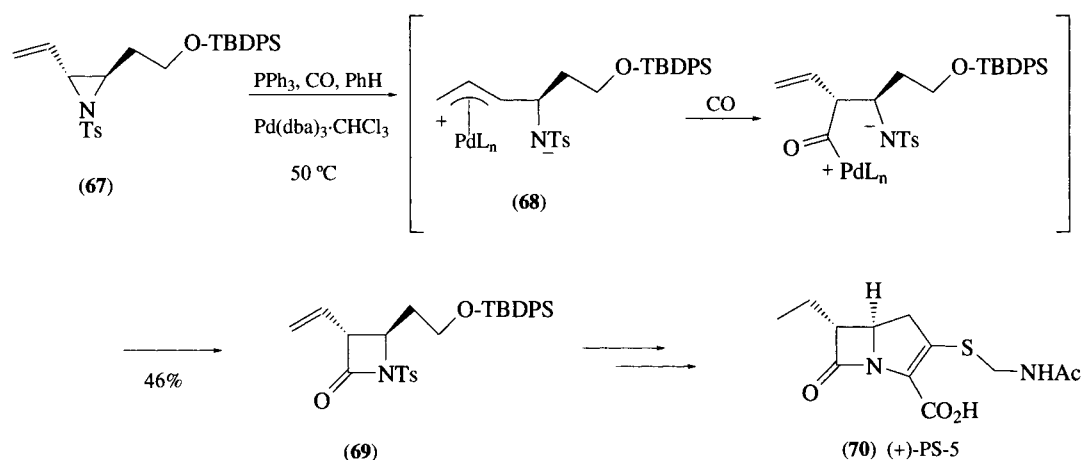
Ester enolates on the side chain of aziridine have been used for intramolecular nucleophilic ring-opening of the aziridine, as shown in Equation (20) in Section 1.01.6.3.1 <93JOC5019>.

Reactions at carboxyl groups in azirines are rare, perhaps due to competing reactivity at the C=N bond of the ring.

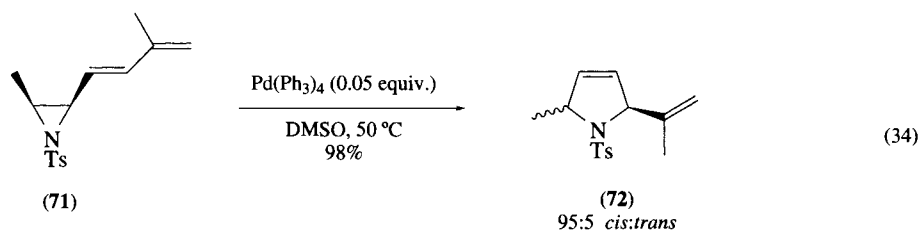
1.01.7.2 Reactions at Vinyl or Alkenyl Groups

The most common reactions of a vinyl or alkenyl group attached to a ring carbon atom are pericyclic processes involving the aziridine or azirine ring <B-83MI 101-01>. These reactions were covered in Section 1.01.6.

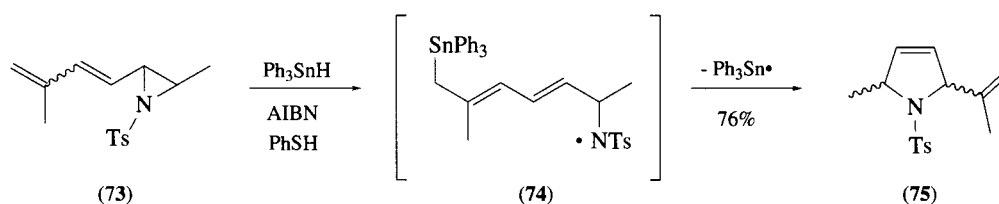
Alkenyl substituents attached to aziridine ring carbons allow a palladium-catalyzed carbonyl-insertion reaction to occur, producing a β -lactam (Scheme 46) <91SL91>. The proposed mechanism <93BMC2415> is based on an analogous reaction of vinyl epoxides <85JA6123>. Initial attack of palladium(0) on the optically active *trans*-vinylaziridine (**67**) leads to the π -allyl palladium complex (**68**). Insertion of CO followed by rapid recyclization leads to formation of optically active β -lactam (**69**). The utility of this reaction was illustrated by the conversion of (**69**) to the β -lactam antibiotic (+)-PS-5 (**70**) <93BMC2415>. The palladium(0)-catalyzed conversion of 2-dienylaziridines such as (**71**) to 3-pyrrolines (**72**) is believed to proceed by the same mechanism (Equation (34)) <85TL857>.



Scheme 46



Addition of a tin radical to the diene (**73**) causes cleavage of the aziridine ring to the nitrogen-centered radical (**74**), which undergoes readdition to the dienyl stannane with loss of tin radical to produce the 3-pyrroline (**75**) (Scheme 47) <88TL1543>.



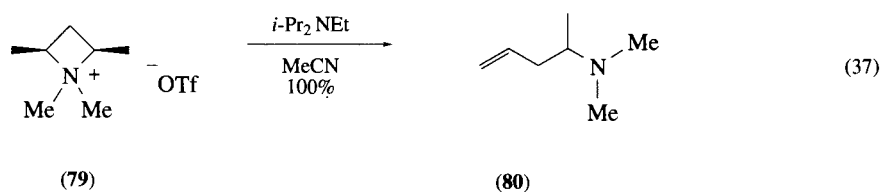
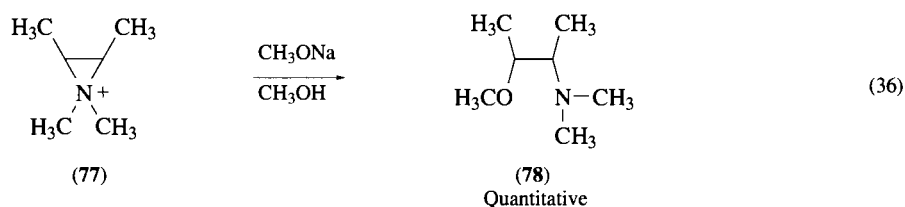
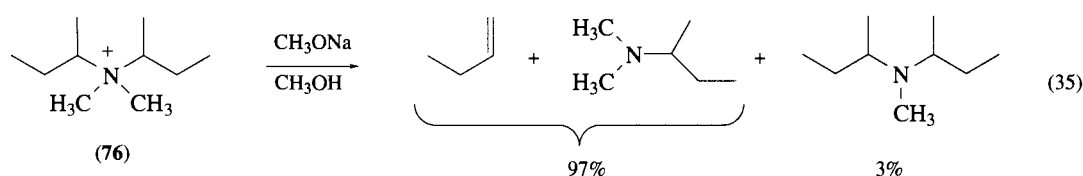
Scheme 47

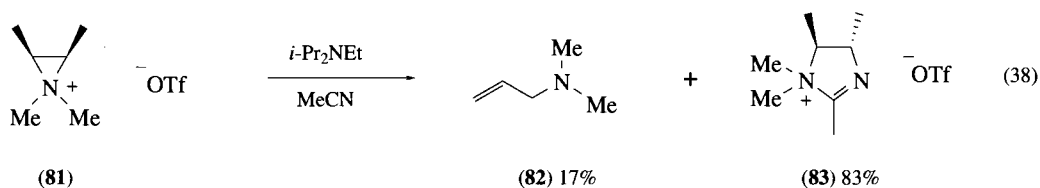
Diimide reduction of a side-chain alkene in an aziridine has been reported, which proceeds without destroying the aziridine ring $\langle 68\text{JOC}481 \rangle$.

The reactions of 2-alkylideneaziridines have been reviewed $\langle \text{B-83MI } 101\text{-}01, 84\text{CHEC-I}(7)47 \rangle$. Ring-expansion, ring transformation to cyclopropylimines, and cycloaddition reactions at the exocyclic double bond are the common reactions observed.

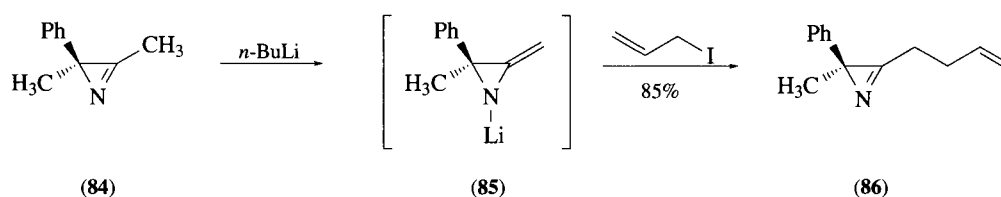
1.01.7.3 Reactions at Alkyl Groups

Studies of deprotonation reactions at carbon atoms adjacent to aziridinium ions have led to the discovery that aziridinium ions are much less prone to eliminative ring cleavage than would be expected by comparison with their acyclic analogues $\langle 88\text{JOC}1733 \rangle$. As shown in Equations (35) and (36), when the acyclic ammonium ion (76) was treated with sodium methoxide, a nearly quantitative yield of elimination products was obtained. However, when the aziridinium ion (77) was subjected to these conditions, the ring-opened aminoether (78) was the sole product, a result of nucleophilic ring-opening. A comparison of aziridinium and azetidinium triflates in eliminative ring-opening reactions led to similar findings, as shown in Equations (37) and (38) $\langle 93\text{JPO}187 \rangle$. Treatment of azetidinium triflate (79) with diisopropylethylamine in acetonitrile produced a quantitative yield of the elimination product (80). The corresponding aziridinium salt (81) provided only a 17% yield of the elimination product (82) and an 83% yield of compound (83), the result of nucleophilic addition of solvent to the aziridinium ring. The reluctance of aziridinium ions to open via elimination, while being especially prone to nucleophilic ring-opening, is believed to be due to the steric environment around the ring carbons. The small ring geometry orients substituents such that backside approach to the reaction center is more accessible to nucleophiles than in open-chain or larger ring analogues $\langle 85\text{CC}380 \rangle$. Hence deprotonation reactions leading to eliminative ring-opening of aziridines are rarely observed in the literature $\langle 77\text{H}(6)1861 \rangle$. This is in contrast to the relatively common base-promoted elimination of epoxides to allylic alcohols.





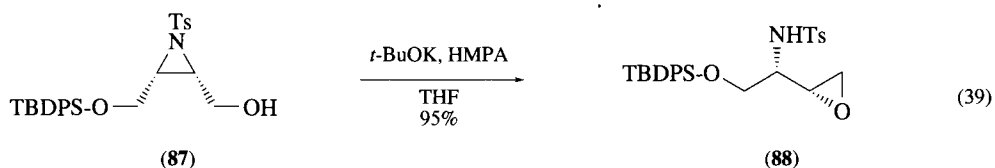
Deprotonation of alkyl groups attached to C(3) of 2*H*-azirines leads to formation of metallo-enamines. As shown in Scheme 48, the 3-methyl-2*H*-azirine derivative (**84**) can be deprotonated to give the *N*-lithioenamine (**85**), which can react with a variety of electrophiles to yield *C*-alkylated products such as (**86**) <85TL2637>.



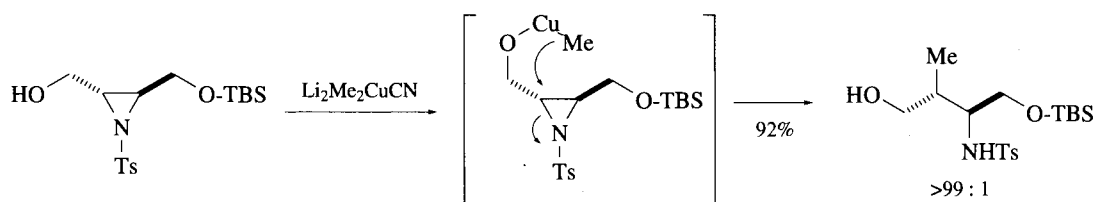
Scheme 48

1.01.7.4 Reactions at Hydroxy, Oxo, and Other Oxygen-linked Groups

Treatment of certain 2-(hydroxymethyl)aziridines with base can lead to an intramolecular ring-opening reaction to yield an α -amino epoxide, a reaction analogous to the Payne rearrangement of (hydroxymethyl)epoxides. For example, treatment of the aziridine (**87**) with potassium *t*-butoxide provided the epoxide (**88**) in good yield (Equation (39)) <93TL5127>. This type of rearrangement is also believed to occur during the reaction of similar 2-(hydroxymethyl)aziridines with organocuprate reagents <93TL7421>. The base-promoted conversion of (aminomethyl)epoxides to (hydroxymethyl)-aziridines, the reverse of the process shown in Equation (39), is also known, and will be covered in Section 1.01.9.



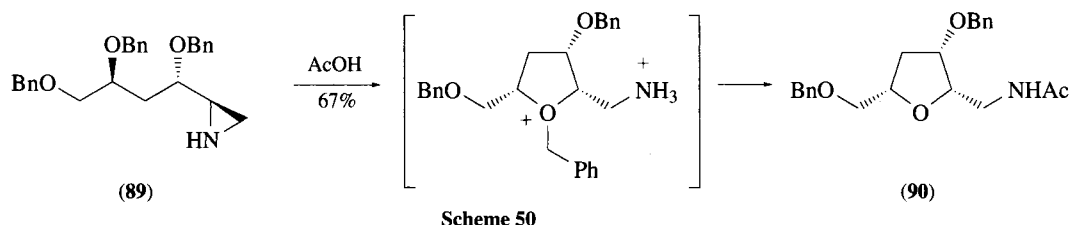
In related work, the hydroxymethyl substituent of 2-(hydroxymethyl)aziridines has been used to direct the addition of nucleophiles to the adjacent aziridine carbon for regioselective ring-opening reactions <94AG(E)599>. As shown in Scheme 49, opening of such an aziridine with an organocupper reagent is highly regioselective. Hydride reagents such as Red-Al, dibal, and LiAlH_4 undergo similar regioselective ring-opening reactions. Trimethylaluminum was reported to cause attack at the distal carbon of the aziridine. An advantage of this chemistry is that either diastereomer of the starting materials is available in optically active form.



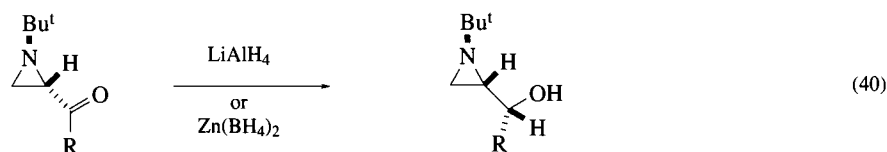
Scheme 49

Another reaction of 2-(hydroxymethyl)aziridines involves radical deoxygenation with concomitant aziridine ring-opening, as shown in Equation (30) in Section 1.01.6.5.

Tetrahydrofurans are formed from the intramolecular ring-opening of aziridines by a δ -oxygen substituent. As shown in Scheme 50, aziridine (**89**) undergoes an acid-catalyzed ring-opening to provide the tetrahydrofuran (**90**) <92TL3607>.



Deyrup has provided excellent coverage of some of the more conventional reactions of oxygen-containing functional groups attached to aziridines, including the addition of hydride and organometallic reagents to ketones and aldehydes, Wittig reactions, carbonyl group reductions, imine and enamine formation from aldehydes and ketones, halide formation from alcohols, and substitution reactions of sulfonates and halides <B-83MI 101-01>. The diastereoselectivity of the addition of organometallic reagents and hydride reagents to carbonyl groups attached to aziridine rings has been studied <57HCA1652, 73BSF2466, 75T997, B-77MI 101-01, 82JCR(S)287, 82JCS(P2)1483>. An example is shown in Equation (40), where chelation-controlled hydride reductions proceeded with high diastereoselectivity <57HCA1652, 82JCS(P2)1483>.

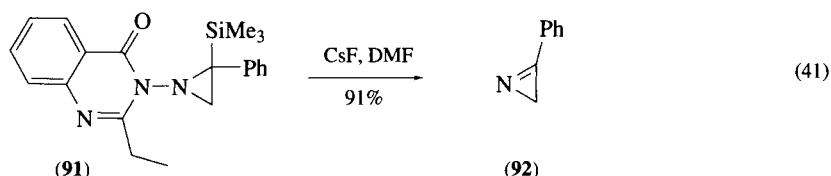


The reactions of α -lactams have been reviewed <B-83MI 101-01, 84CHEC-I(7)47>.

1.01.7.5 Miscellaneous Reactions of Substituents Attached to Ring Carbon Atoms

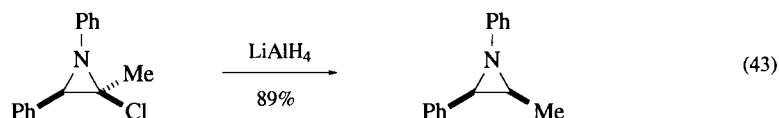
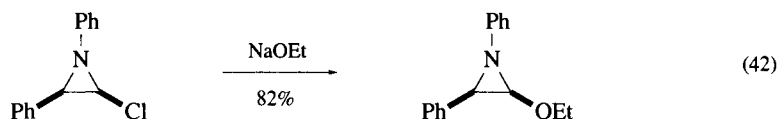
Aziridines which have a sulfinyl group attached to a ring carbon can be stereospecifically desulfinylated with organometallic reagents, as shown in Equation (29) in Section 1.01.6.4 above <88TL4093, 89JOC3973>.

Desilylation of the *C*-silylaziridine (**91**) with caesium fluoride produced the 2*H*-azirine (**92**) in good yield by an elimination reaction (Equation (41)) <89CC836>. The aziridine (**91**) was prepared by addition of a nitrene to a vinyl silane (see Section 1.01.9.2).



Aziridines bearing a halogen at C(2) are stable relative to their acyclic counterparts, and thus substitution reactions have been investigated <B-83MI 101-01>. The nitrogen substituent can be aryl, alkyl, or an electron-withdrawing group, although the latter is limited by the possibility of ring-opening. Reaction of 2-chloroaziridines with organolithium reagents, organomagnesium reagents, sodium alkoxides, sodium thiolates, potassium cyanide, and LiAlH_4 results in substitution. The stereochemistry of the displacement is variable, since an $\text{S}_{\text{N}}1$ mechanism is proposed to be operational <B-83MI 101-01>. Examples of substitution reactions at C(2) are shown in Equations (42) and

(43) <65JA4538>. Free-radical reduction of 2-bromoaziridines is possible with Bu_3SnH <B-83MI 101-01>.



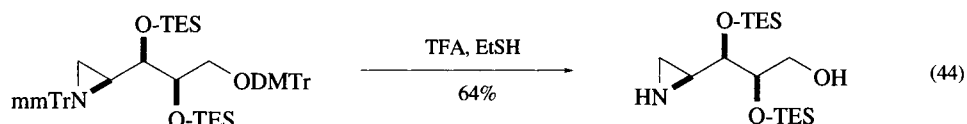
The reactions of aziridine bearing an imino group at C(2) (aziridine imines) have been reviewed <B-83MI 101-01, 84CHEC-I(7)47>.

1.01.8 REACTIVITY AT SUBSTITUENTS ATTACHED TO THE AZIRIDINE RING NITROGEN ATOM

Reactions of substituents attached to the nitrogen atom of aziridines have been reviewed <B-83MI 101-01, 84CHEC-I(7)47>. Many of these reactions also result in cleavage of the aziridine ring. Only those reactions of *N*-substituents which do not result in ring-opening will be covered below.

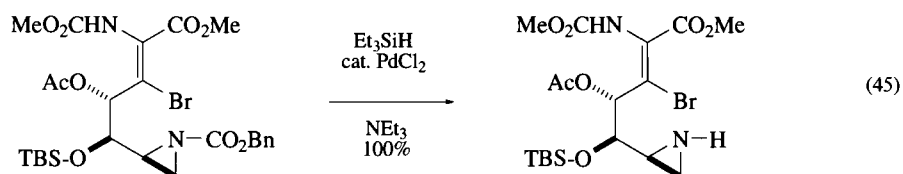
1.01.8.1 Reactions at Alkyl Groups

The removal of benzyl groups from the nitrogen atom of an aziridine is a potentially useful component of protecting group chemistry. However, there are few examples of such a process. An example involving the removal of a monomethoxytrityl (mmTr) group under acidic conditions is shown in Equation (44) <93JOC7848>. *N*-Trityl groups can also be removed with TFA <78BCJ1577>. Hydrogenolytic removal of *N*-benzyl groups is often complicated by the ease of hydrogenolytic ring-opening of the aziridine (e.g., <83JCS(P1)2277>).



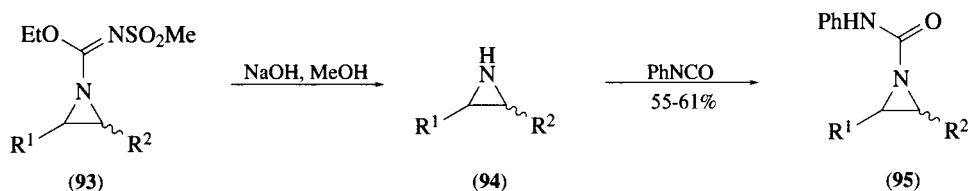
1.01.8.2 Reactions at Other Carbon-linked Groups

Deprotection of an *N*-(benzyloxycarbonyl)aziridine to the free aziridine was accomplished using a nonhydrogenolytic technique, as shown in Equation (45) <92JOC5813>.

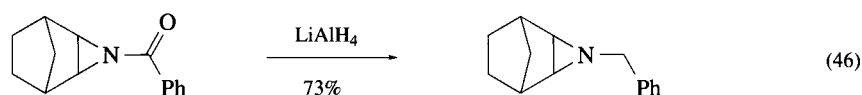


Hydrolysis of *N*-acyl- and *N*-(carboalkoxy)aziridines to provide the free aziridines is not commonly reported, presumably due to ring-opening under the acidic or basic conditions necessary for hydrolysis (e.g., <B-83MI 101-01, 84CAR(129)267, 84CHEC-I(7)47>). Scheme 51 shows one example,

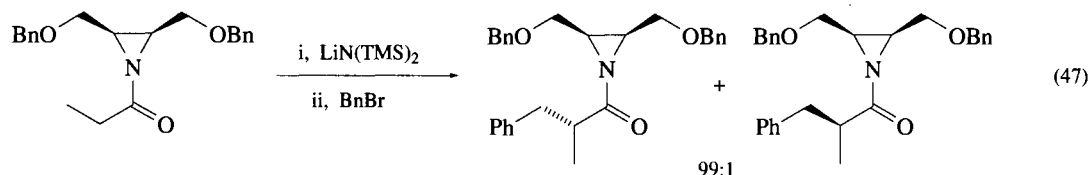
where the imidoylester (**93**) was hydrolyzed to aziridine (**94**). The free aziridine was not isolated but was immediately converted to the phenyl urea (**95**) (Scheme 51) <89JOC3945>. *N*-Acylaziridines have been used as acyl-transfer reagents. For example, the dianion of a β -ketoester was reported to react exclusively at the acyl carbon of an *N*-benzoylaziridine to yield the benzoylated β -ketoester <93SL764>. The fate of the deprotected aziridine was not discussed. The reduction of *N*-acylaziridines with LiAlH_4 produces either unsubstituted aziridines (with the aldehyde as the by-product), or *N*-alkylaziridines (e.g., Equation (46)), depending on the level of substitution on the aziridine ring carbons <61JA4549, 68JA2875, 75JA4692, B-83MI 101-01>. Deacylation of *N*-acylaziridines can also be accomplished with PhMgBr .



Scheme 51



N-Acylaziridines can be deprotonated to yield enolates, which can participate in alkylations and aldol condensations <91TL2533, 94AG(E)599>. The aziridine ring was used as a chiral auxiliary, and good to excellent diastereoselectivity was obtained. Equation (47) shows an example of such an enolate alkylation. Quenching the enolate with an aldehyde produced a single *syn* aldol adduct.



A Wittig reaction of the carbonyl group of an *N*-trifluoroacetylaziridine has been reported <87CC153>. The reaction of a series of *N*-acylaziridines with Wittig reagents gave primarily aziridine ring-opened products. Reaction at the carbonyl group without ring-opening occurred only when the acyl group was trifluoroacetyl or *p*-nitrobenzoyl.

N-Phenylaziridines may be cleaved to the *N*-unsubstituted aziridines in good yield with ozone <78TL3119>. The stable hemiaminal adducts of aziridines with aldehydes may react with amines to give aminals (*N*-(1-aminoalkyl)aziridines) <B-83MI 101-01>.

1.01.8.3 Reactions at Oxygen-linked Groups

N-Alkoxyaziridines, available from the addition of alkoxy nitrenes <90CHE245> or their equivalents <92TL3261> to alkenes, may be cleaved reductively to the *N*-unsubstituted aziridines, e.g., Equation (48) <92TL3261>. This would seem to suggest that dissolving metal reductions might be an appropriate method for the removal of other groups (for example, tosyl) from the nitrogen of an aziridine.

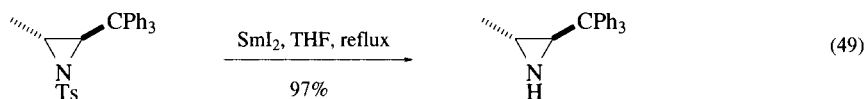


1.01.8.4 Reactions at Other Substituents

The alkylation, acylation, and chlorination of *N*-unsubstituted aziridines has been reviewed (B-83MI 101-01, 84CHEC-I(7)47), and was covered in Section 1.01.6.

Removal of an *N*-phthalimido group may be accomplished with hydrazine without destruction of the aziridine ring (70HCA1479, 70JA1784). Reduction of the *N*-phthalimido group with LiAlH_4 produces *N*-(isoindolino)aziridines (71JCS(C)988). *N*-Aminoaziridines form hydrazones readily (B-83MI 101-01). Iminophosphoranes bearing an *N*-aziridinyl group have been used to carry out aza-Wittig reactions with carbonyl compounds, resulting in the formation of cumulenes (B-83MI 101-01).

The reductive removal of phosphoryl groups and chloro groups from aziridine nitrogen atoms can be accomplished with LiAlH_4 and NaBH_4 , respectively (B-83MI 101-01). *N*-Chlorosulfonyl aziridines have been dimerized to the disulfides with mercury (92CC898). Desulfurization of an *N*-(methylthio)methyl group to produce an *N*-methylaziridine has been reported (see Scheme 86 in Section 1.01.9.6) (92AG(E)915, 93JA12305). The deprotection of *N*-(arenesulfonyl)aziridines has seen limited success, since the reductive conditions normally employed for the cleavage of the $\text{N}-\text{SO}_2$ bond often cause cleavage of the aziridine ring. However, single electron transfer reducing agents have been shown to be capable of selectively cleaving the $\text{N}-\text{S}$ bond faster than a ring $\text{C}-\text{N}$ bond (91JOC6846). A recent example using SmI_2 to remove an *N*-tosyl group from an aziridine is shown in Equation (49) (94JOC1602). The trityl substituent was important, since aziridines bearing only a phenyl substituent produced the styrene as the major product. Other examples of the cleavage of *N*-(arenesulfonyl)aziridines with single electron reductants have appeared (90CC468, 91JOC6846).



1.01.9 SYNTHESIS OF MONOCYCLIC AZIRIDINES AND AZIRINES

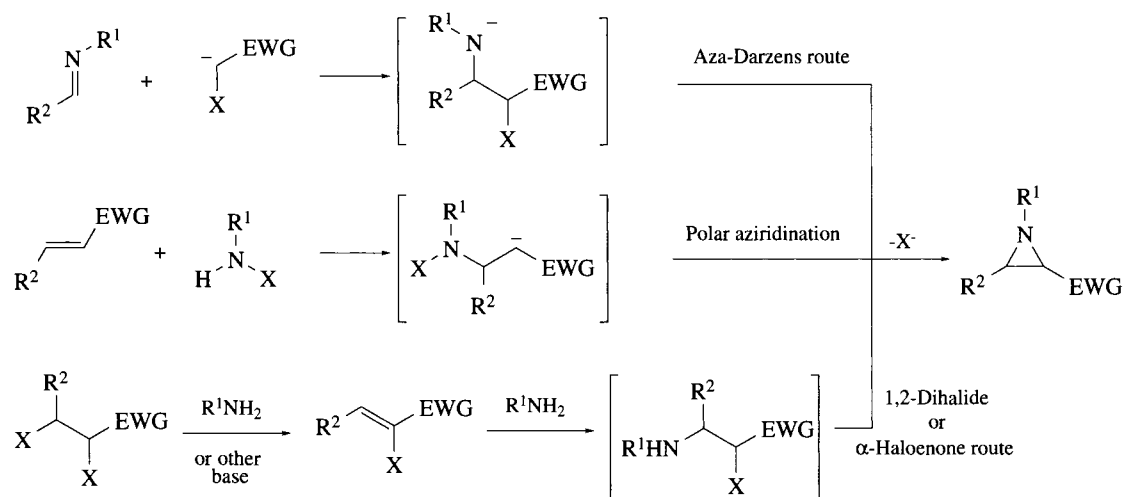
The syntheses of aziridines (B-83MI 101-01, 84CHEC-I(7)47) and azirines (B-83MI 101-02) have been covered in major review chapters. Padwa and co-workers have reviewed the literature of aziridine and azirine syntheses on a yearly basis, covering the period 1988 to 1994 (89PHC82, 90PHC22, 91PHC42, 92PHC34, 93PHC54, 94PHC56). Kametani and Honda have reviewed the use of aziridines in the synthesis of natural products, covering many different methods for aziridine synthesis (86AHC(39)181). Two reviews by Tanner cover the synthesis of chiral, nonracemic aziridines (93PAC1319, 94AG(E)599). Heimgartner has reviewed the synthesis and uses of 3-amino-2*H*-azirines (91AG(E)238). A book on azides and nitrenes covers various aspects of aziridine and azirine synthesis (B-84MI 101-05). Representative examples of all of the useful methods for monocyclic aziridine and azirine synthesis will be presented below. In addition to coverage of new methods published since CHEC-I, later examples of older methods will be reported. The material below is organized into three fundamental categories: (i) synthesis from two components, (ii) synthesis from one component, and (iii) synthesis from other rings. It is sometimes difficult to categorize reactions based on the number of components used. For example, two components are often combined, but the crucial ring-forming step is actually a cyclization of a single component. To avoid confusion, syntheses will be organized by the number of reactants that are combined, not by the number of components that are mechanistically involved in the actual cyclization step.

1.01.9.1 From Two Components: Intermolecular Reaction of Electrophiles and Nucleophiles

The most common polar processes that form aziridines from two components may be classified into three groups as shown in Scheme 52. In every case, each of the two reactants must be capable of acting formally as either a bis-nucleophile or a bis-electrophile, or they must each have both nucleophilic and electrophilic character. In the aza-Darzens route (B-83MI 101-01, 84CHEC-I(7)47), the imine acts as an electrophile at carbon and later as a nucleophile at nitrogen, while the α -halo-

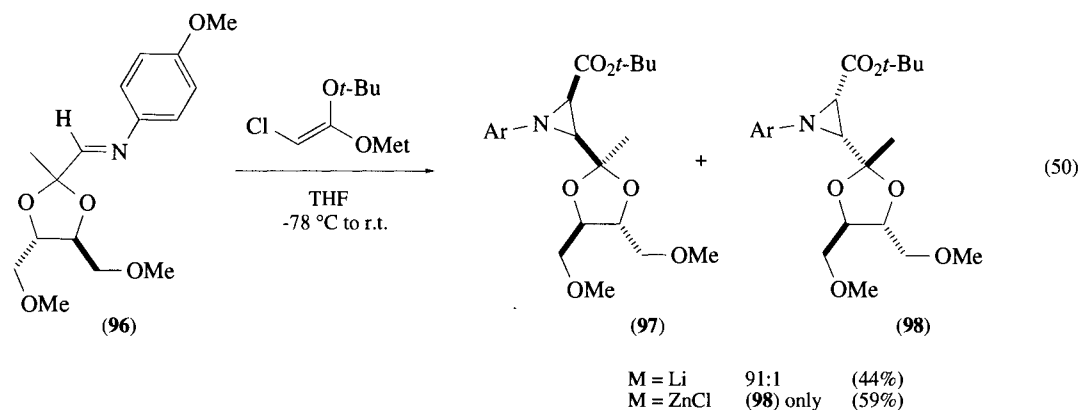
enolate acts initially as a nucleophile at carbon and later as an electrophile at the same carbon. The roles of the two components are reversed for the polar aziridination route, which is related to the epoxidation reaction. In the last route, the 1,2-dihalide or α -haloenone acts formally as a bis-electrophile while the amine acts as a bis-nucleophile.

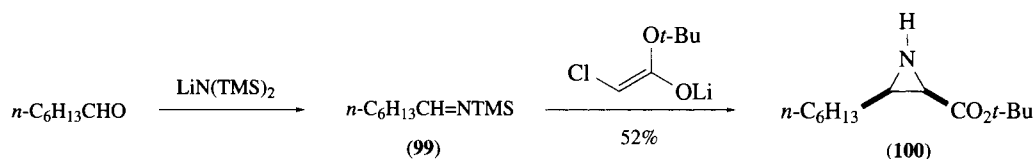
The aza-Darzens route to aziridines <B-83MI 101-01, 84CHEC-I(7)47> is analogous to the Darzens reaction of α -haloenolates with carbonyl compounds to produce oxiranes. It continues to be the most popular of the three pathways shown in Scheme 52 as judged by the diversity of examples reported. Selected examples which illustrate primarily the variation of the electron-withdrawing group are shown below.



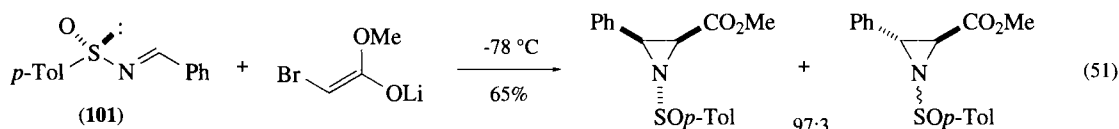
Scheme 52

α -Haloester enolates are the most commonly observed anions for the aza-Darzens reaction. These reactions produce aziridine-2-carboxylic acid derivatives. Fujisawa *et al.* have reported the reaction of various metal enolates of α -chloroesters with the chiral, nonracemic imine (**96**) <92TL7903> as shown in Equation (50). The ratio of the diastereomeric aziridines (**97**) and (**98**) varied dramatically as a function of the metal used. The titanium enolate led not to the aziridine, but to the 3-chloroazetidin-2-one by a Staudinger reaction. Scheme 53 illustrates the preparation of *N*-unsubstituted aziridines (**100**) from *N*-trimethylsilyl imines (**99**) and α -chloroester enolates <91TL121>. Davis *et al.* have reported the reaction of α -bromoester enolates with chiral, nonracemic *N*-(*p*-toluenesulfinyl)imines (**101**) as shown in Equation (51) <94JOC3243>. TFA hydrolysis of the major product gave the *N*-unsubstituted aziridine in optically pure form. The sulfinyl group could also be oxidized to the sulfonamide with mcpba.

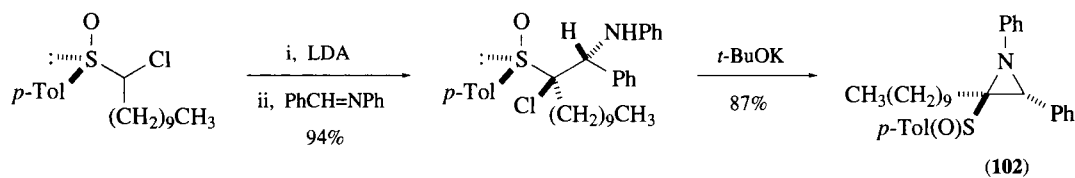




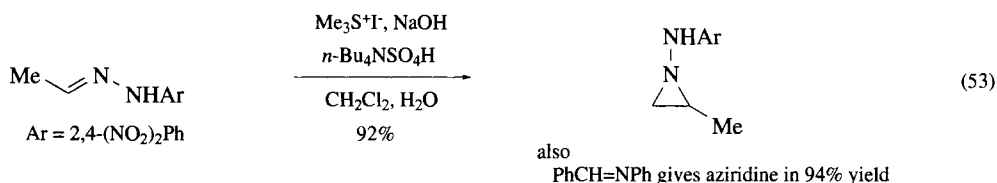
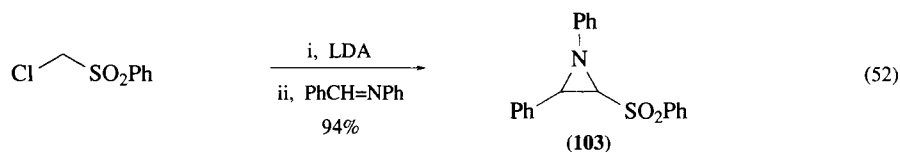
Scheme 53



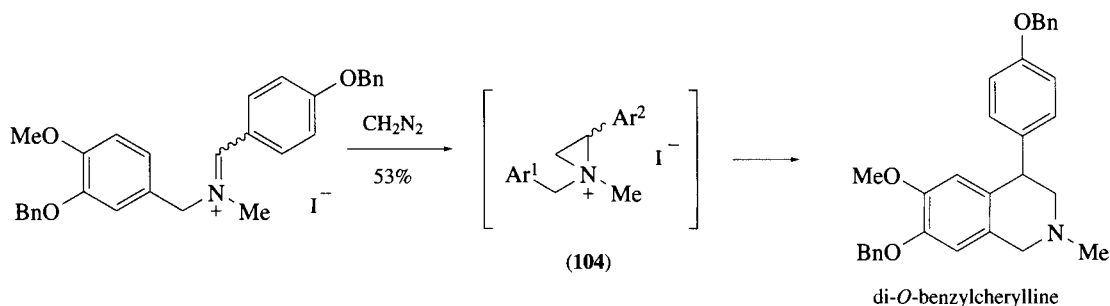
Anions of α -halosulfoxides $\langle 84\text{CL}969, 89\text{JOC}3973 \rangle$ and α -halosulfones $\langle 84\text{TL}1949 \rangle$ have been used in the aza-Darzens reaction, as shown in Scheme 54 and Equation (52). Desulfinylation of (102) with ethylmagnesium bromide gave the optically pure 2,3-*cis*-disubstituted *N*-arylaziridine in 95% yield with complete retention of configuration during the replacement of the sulfinyl group with hydrogen $\langle 89\text{JOC}3973 \rangle$. The stereochemistry of (103) was not reported $\langle 84\text{TL}1949 \rangle$. Both α -chlorosulfoxide and α -chlorosulfone anions have been reacted with 2*H*-azirines to give bicyclic diaziridines $\langle 86\text{TL}2739 \rangle$. Johnson *et al.* have described the reaction of optically enriched $\text{PhS}(\text{O})(=\text{NTs})\text{CH}_2\text{Na}$ with *N*-phenylbenzalimine to give an optically active aziridine $\langle 73\text{JA}4287 \rangle$. Other sulfur-stabilized nucleophiles which have been used to make aziridines via the aza-Darzens route include sulfur ylides and sulfoxonium ylides $\langle \text{B-}83\text{MI } 101\text{-}01, 84\text{CHEC-I}(7)47 \rangle$. For example, methylenation of imines and hydrazones with dimethylsulfonium methylide gave aziridines and *N*-aminoaziridines, as shown in Equation (53) $\langle 83\text{S}330 \rangle$.



Scheme 54

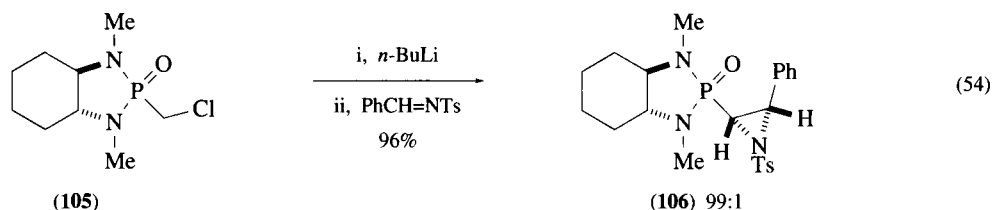


While diazoalkanes do not generally react with imines to produce aziridines, the more electrophilic iminium ions are smoothly alkylidenated to produce aziridinium ions $\langle 86\text{AHC}(39)181 \rangle$. An example is shown in Scheme 55, where the aziridinium ion (104) is a presumed intermediate $\langle 82\text{JCS}(P1)2935 \rangle$.



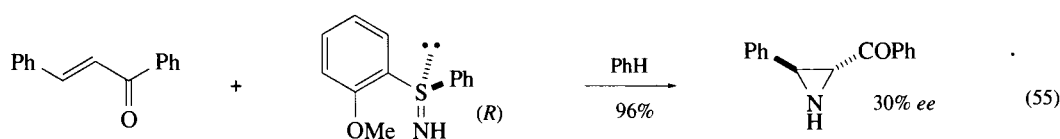
Scheme 55

Hanessian *et al.* have described the reaction of chiral, nonracemic *P*-chloromethylphosphonamide anions derived from (105) with imines to give chiral aziridines (106) as shown in Equation (54) <93SL35>.

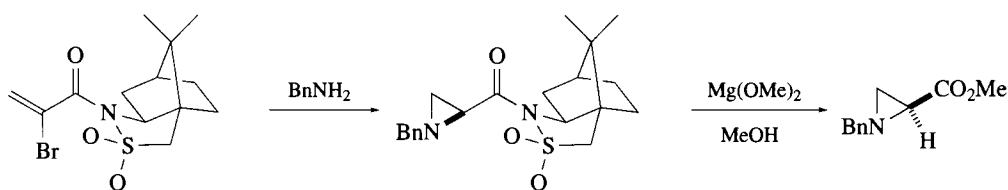
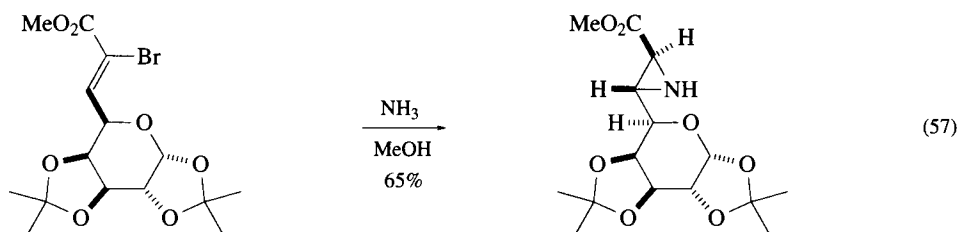
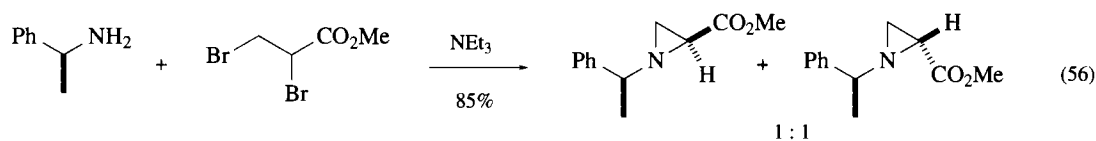


Mauzé has examined the reactions of chlorine-bearing allyllithium reagents with imines to produce 2-alkenylaziridines <80JOM(202)233, 84TL843>.

Polar aziridinations of alkenes (see Scheme 52) are mechanistically related to the aza-Darzens reaction except that the nitrogen atom, which bears a leaving group, is both the initial nucleophile and the subsequent electrophile <B-83MI 101-01>. For example, the reaction of diphenylsulfimine ($\text{Ph}_2\text{S=NH}$) with electron-poor alkenes gives aziridines by Michael-type nucleophilic attack of nitrogen on the alkene followed by displacement of Ph_2S by the resultant stabilized carbanion <82S509, B-83MI 101-01>. An example using a chiral sulfimine is shown in Equation (55) <80T73>. Sulfonamides react with enoates in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ to give aziridine-2-carboxylates <80CC1038>. The sodium salts of phosphonates exhibit similar behavior <B-83MI 101-01>.



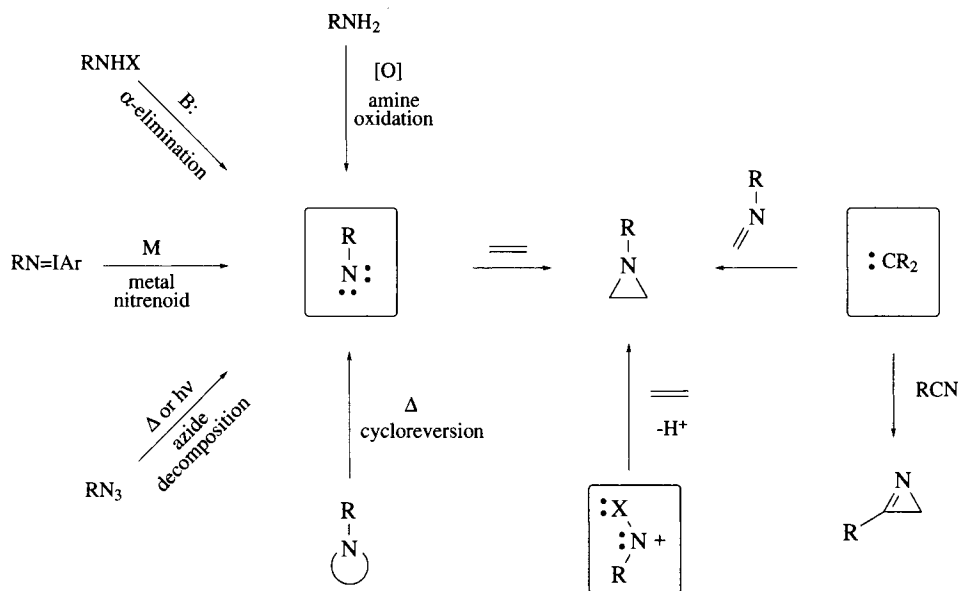
Both 1,2-dihalides and α -halo- α,β -unsaturated carbonyl compounds react with primary amines to give aziridines as shown in Scheme 52. Good coverage of this method may be found in Deyrup's review, which includes a discussion of the scope and stereochemistry of the reaction <B-83MI 101-01>. The dihalide is dehydrohalogenated by excess amine to provide the α -halo- α,β -unsaturated carbonyl compound which participates in a Michael-type reaction with the amine. The resultant intermediate undergoes an intramolecular *N*-alkylation to produce the aziridine. Alternatively, one may start with a pre-formed α -halo- α,β -unsaturated carbonyl compound. Unsaturated ketones, aldehydes, esters, amides, nitriles, nitro compounds, phosphonates, and sulfones are all successful in this route to aziridines <B-83MI 101-01>. Examples include the use of ethyl 2-carboethoxy-2,3-dibromopropionate with butylamine <92JOC7056> or ammonia <92JCS(P2)1541>, the reaction of 2,3-dibromoacryloyl chloride first with alcohols (to form the ester) and then amines <87JA5523, 89H(29)1473, 92TA681>, and the use of *p*-toluenesulfonamide with methyl 2,3-dibromopropionate <92G7>. The reaction of 2-chloroacrylic amides, thioamides, and amidines with primary amines has also been described <85BSB457>. Specific examples of the use of dihalides or α -bromocarbonyl compounds to make aziridines are shown in Equations (56) and (57) and Scheme (56) <87HCA1676, 89H(29)419, 94TL1653>. Note that optically active aziridine-2-carboxylates are produced in each case.



Scheme 56

1.01.9.2 From Two Components: Intermolecular Cycloaddition Reactions

The intermolecular cycloaddition of an electron-deficient species such as a nitrene, a nitrenium ion, or a carbene (or their formal equivalents) to the π -bond of an alkene, alkyne, imine, or nitrile is a significant approach to aziridines and azirines (Scheme 57).

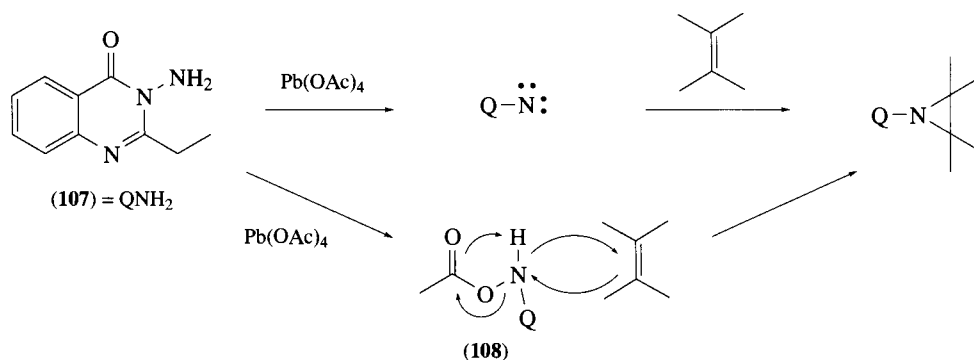


Scheme 57

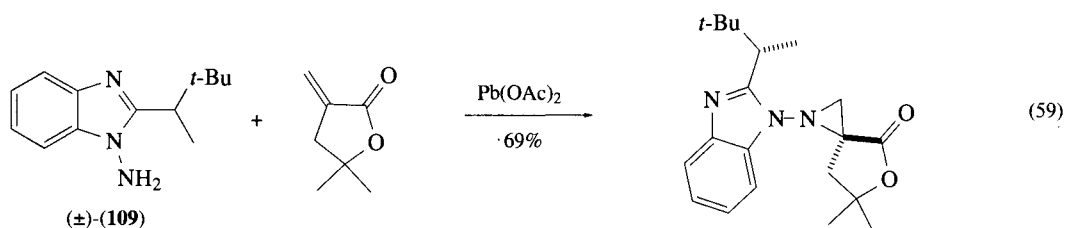
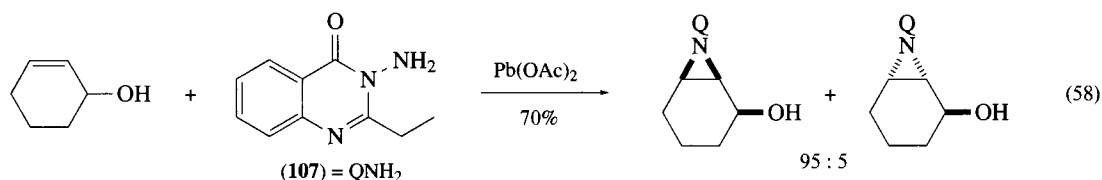
The oxidation of primary amines to nitrenes for the purpose of intermolecular aziridination is best accomplished using 1,1-disubstituted hydrazine derivatives, which result in the formation of *N*-aminonitrenes (B-84MI 101-06). Oxynitrenes derived from the oxidation of alkoxyamines are known, but are generally less efficient in aziridination reactions (B-83MI 101-01, B-84MI 101-06, 90CHE245). Sulfur-substituted nitrenes are also known to aziridinate alkenes (B-84MI 101-06). Simple

primary amines have been oxidized to nitrenes, but capture of the nitrenes by alkenes has only been observed in intramolecular reactions (B-83MI 101-01, 84CHEC-I(7)47, B-84MI 101-07, 86AHC(39)181).

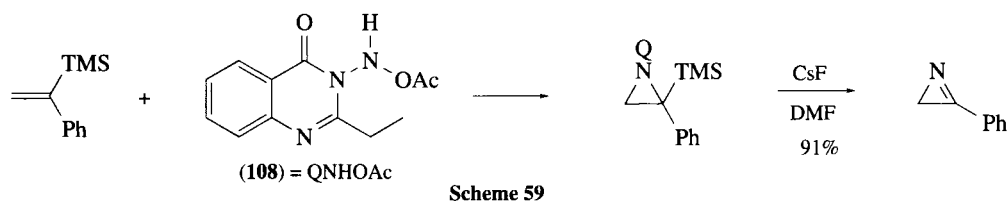
Aminonitrenes are relatively well behaved nitrenes (B-83MI 101-01, 84CHEC-I(7)47, B-84MI 101-06). They are commonly generated by the lead tetraacetate oxidation of various *N*-aminoheterocycles such as *N*-aminophthalimide (69C405, 69CC146) and *N*-amino-2-ethylquinazolinone (**107**) (70JCS(C)576) as shown in Scheme 58. Deyrup's review has a good overview of these reactions (B-83MI 101-01). Aminonitrenes may also be generated by the cycloreversion of certain heterocycles. Atkinson, Kelly, and co-workers have contributed considerably to the understanding of the mechanism, stereoselectivity, and regioselectivity of the use of *N*-aminoquinazolones for the aziridination of alkenes. They have found evidence that the lead tetraacetate oxidation of *N*-aminophthalimide and *N*-aminoquinazolones proceeds through an *N*-acetoxyamino heterocycle rather than a nitrene, as shown in Scheme 58 (87CC1362, 89T2875). Thus, the aziridination reaction may be more related to the peracid oxidation of alkenes to oxiranes than to nitrene chemistry. In fact, the *N*-acetoxyaminoquinazolinone (**108**), the nitrogen analogue of a peracid, has been used directly in aziridination reactions. The analogy to a peracid is strengthened by studies on the aziridination of allylic alcohols with either (**107**) or (**108**) (88CC624, 89JCS(P1)1515, 92T1317). As shown in Equation (58), aziridination *cis* to the allylic hydroxy group is observed. The magnitude of this stereoselectivity is higher than that for the corresponding peracid oxidation to the *syn*-oxirane. Protection of the hydroxy group as an acetate led to the *trans* aziridine in low yield, thus enforcing the idea that hydrogen bonding to the hydroxy group is important in the transition state. Further evidence for the directing effect of an allylic alcohol was found in the aziridination of geraniol using this method (88CC624). The 2,3- and 6,7-aziridinated products were isolated in an 11 : 1 ratio, whereas aziridination of geranyl chloride gave a 1 : 6 ratio of 2,3- to 6,7-aziridinated products. Homoallylic alcohols were also examined (89CC562). Aziridination of 3-cyclohexene-1-ol with the *N*-acetoxyaminoquinazolinone (**108**) was highly *syn*-selective, while peracid oxidation proceeded with low stereoselectivity. Again, protection of the alcohol as an acetate caused an inefficient aziridination reaction with low stereoselectivity. With the aim of designing an asymmetric aziridination reagent, Atkinson examined the chiral (but racemic) *N*-aminobenzimidazole (**109**), which gave complete stereoinduction in the aziridination reaction as shown in Equation (59) (86CC832).



Scheme 58

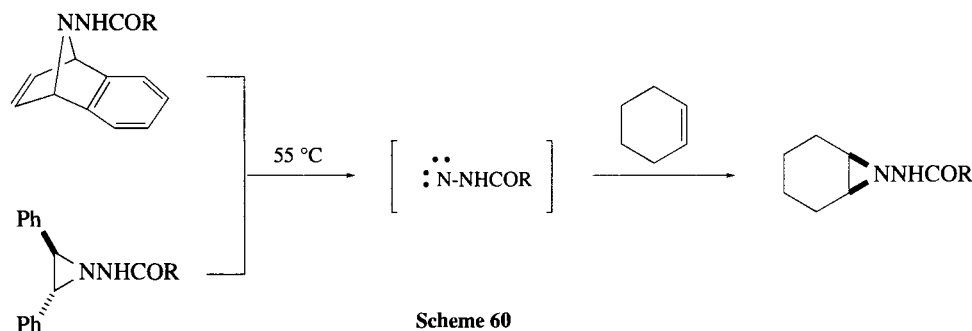


Aziridinations of vinylsilanes <89TL2703> and vinylstannanes <89CC836> have been reported. Treatment of the resultant aziridines with caesium fluoride caused elimination to the 2*H*-azirine, as shown in Scheme 59.

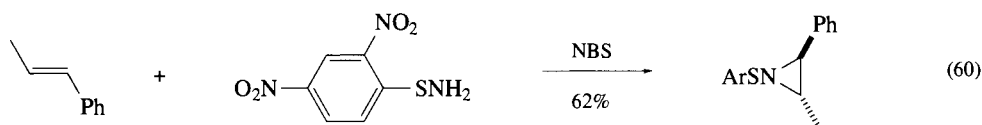


Attempts to prepare 1*H*-azirines by the reaction of *N*-aminonitrenes with alkynes have been unsuccessful, although convincing evidence for the intermediacy of 1*H*-azirines has been obtained by analysis of the products from such reactions <69CC147, 71AHC(13)45, B-83MI 101-02, 84CHEC-I(7)47>.

Aminonitrenes may also be generated by the thermal or photochemical cycloreversion of certain heterocycles. *N*-Aminoaziridines have been photochemically transformed into *N*-aminonitrenes, which have been used to form a new aziridine from a different alkene <71JCS(C)988>. The thermal cycloreversion of 7-azabicyclo[2.2.1]heptadiene derivatives and of certain aziridines also leads to the formation of *N*-aminonitrenes suitable for aziridination reactions, as shown in Scheme 60 <72HCA1276, 86CC747, 88JOC6047>. While the photochemical cycloreversion reactions do not appear to offer any advantage over the oxidative route to *N*-aminonitrenes, Carpino's thermal cycloreversion chemistry (Scheme 60) allows the generation of monosubstituted aminonitrenes <86CC747, 88JOC6047>. Such nitrenes are not accessible by the oxidative method described above.

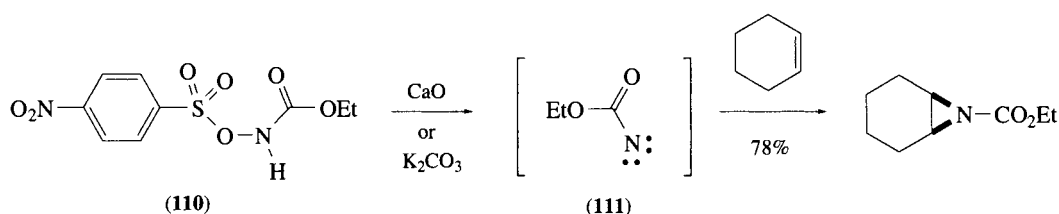


Sulfur stabilized nitrenes have been implicated in aziridination reactions <B-84MI 101-6, 92CC898, 94CPB27>. An example using oxidative conditions is shown in Equation (60) <94CPB27>. The authors favor an (arenesulfonyl)nitrene intermediate.



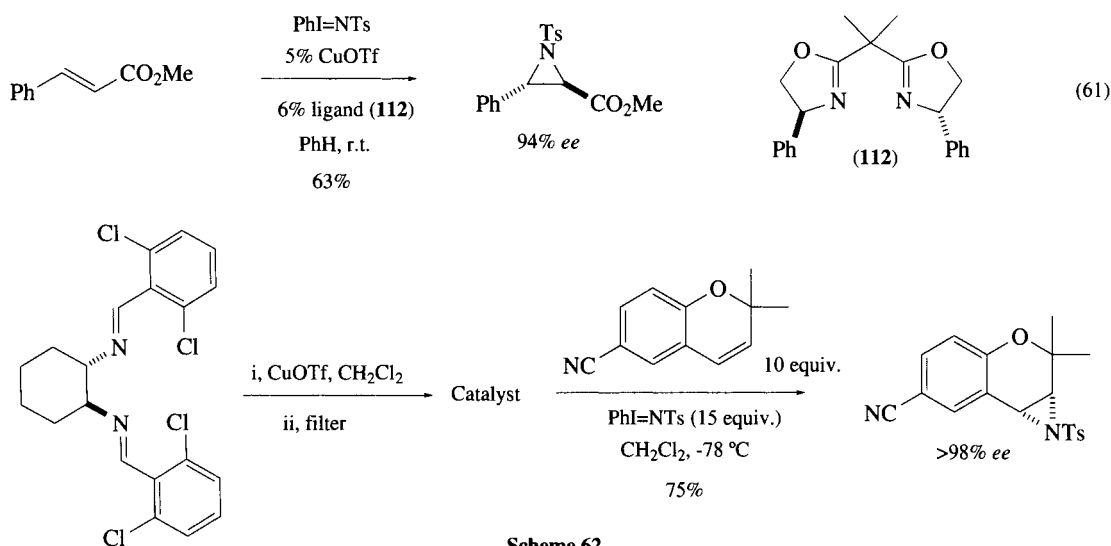
α -Elimination continues to be a popular approach to carbonyl-substituted nitrenes for aziridination reactions <B-83MI 101-01, 84CHEC-I(7)47, B-84MI 101-08>. Most common is the use of (ethoxycarbonyl)nitrene (**111**), generated from ethyl *N*-[(4-nitrophenyl)sulfonyl]oxycarbamate (also known as 4-nitrobenzenesulfonyloxycarbonyurethane) (**110**) and a base such as triethylamine <65JA3630, 67JA2357>. An example is shown in Scheme 61 <94T3829>. As is often the case with (ethoxycarbonyl)nitrene, insertion into an allylic C—H bond is a competing process, leading to a 7% yield of the allylic carbamate (not shown). Inorganic oxides and carbonates appear to offer some advantage over bases such as triethylamine <94T3829>. The development of procedures to generate (ethoxycarbonyl)nitrene under phase-transfer conditions has enhanced the utility of (**111**) <79BCJ2975, 85T1329>. Evidence is growing that intramolecular coordination to an oxygen atom can increase the efficiency of aziridinations with this (ethoxycarbonyl)nitrene. For example, allylic ethers <84TL4271> and homoallylic ketals <93TL4353> are particularly good substrates for aziridination, although geranyl methyl ether is selectively aziridinated at the distal alkene rather than the alkene of the allylic ether <92T2495>. Aziridinations of allylic silanes <93TL4101>, vinyl silanes <86JOM(316)249>, and electron-rich dienes

<89TL5025> with (ethoxycarbonyl)nitrene have been reported. An attempt at asymmetric aziridination using a chiral *N*-nosylcarbamate was reported, but a low yield and low stereoselection were observed <92T7979>. The α -elimination approach to (ethoxycarbonyl)nitrene is a generally milder and more efficient route to *N*-(ethoxycarbonyl)aziridines than the use of ethyl azidoformate.



Scheme 61

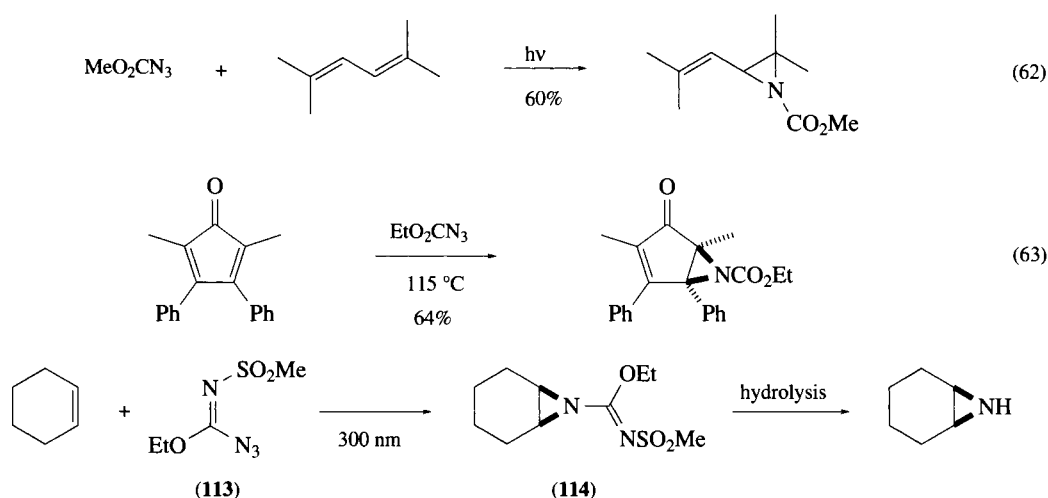
Transition metal nitrenoids suitable for aziridination of alkenes have been developed by several groups. The early work involved the reaction of a catalytic amount of an iron or manganese porphyrin with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs) or other nitrogen transfer agents to produce the intermediate metal nitrenoids $M=NTs$ which then react with alkenes to produce *N*-tosylaziridines <80CC560, 83JA2073, 88JCS(P2)1517>. Copper(I) or copper(II) salts are also capable of catalyzing the transfer of the *N*-tosylamino group to alkenes <91JOC6744, 93OM261, 94JA2742>. The most significant aspect of this method is the recent advent of asymmetric aziridinations using chiral copper ligands <91JA726, 91TL7373, 92TL1001, 93JA5326, 93JA5328, 93SL469>. The magnitude of asymmetric induction varies widely with the exact metal ligand. The most successful ligands are those developed by Evans <91JA726, 93JA5328> and Jacobsen <93JA5326> as shown in Equation (61) and Scheme 62, respectively. Evidence for a stepwise mechanism involving radical intermediates has been obtained as indicated by nonstereospecific aziridination in some cases <94JA425>.



Scheme 62

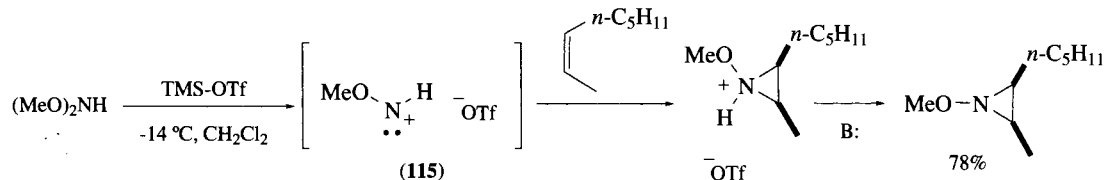
The thermal or photochemical decomposition of azides to nitrenes for the intermolecular aziridination of alkenes is still a rather limited approach to aziridines <B-70MI 101-01, B-83MI 101-01, 84CHEC-I(7)47, B-84MI 101-05>. Section 1.01.9.6 covers a more general method for the use of azides for aziridination, namely the 1,3-dipolar cycloaddition of an azide onto an alkene followed by thermal or photochemical transformation of the resultant triazoline into an aziridine. Nitrenes derived from aliphatic and aromatic azides are not generally useful for aziridination due to competing decomposition and intramolecular reaction processes. The most useful type of nitrenes that are available by azide decomposition are the carbonylnitrenes, especially the (alkoxycarbonyl)nitrenes <B-84MI 101-08>. Thermal decomposition of azidoformates RO_2CN_3 at temperatures above about 60 °C leads to (alkoxycarbonyl)nitrene formation. However, heating azidoformates with alkenes may not lead to aziridines by a nitrene mechanism, since 1,3-dipolar cycloaddition followed by

thermal conversion of the resultant triazoline to an aziridine is also a favorable process (see Section 1.01.9.6). On the other hand, photochemical decomposition of azidoformates in the presence of alkenes clearly proceeds through the (alkoxycarbonyl)nitrene. Ethyl azidoformate and methyl azidoformate are the most popular azides for photochemical aziridination reactions. Deyrup's review has a good overview of the use of these reagents for aziridination <B-83MI 101-01>. Examples of the use of azidoformates in photochemical <72JCS(P1)344> and thermal <77TL2463> aziridinations are shown in Equations (62) and (63). The use of acyl azides $RCON_3$ for nitrene-based aziridinations, whether aliphatic or aryl, are very limited due to competing rearrangement reactions of the carbonylnitrene. Lwowski and co-workers have reported the use of (alkoxycarbimidoyl)nitrenes for aziridinations <89JOC3945>. Photolysis of alkoxycarbimidoylazides bearing an *N*-cyano or *N*-(methylsulfonyl) group (e.g., (113)) in the presence of a wide variety of alkenes leads smoothly to the aziridines as shown in Scheme 63. The nitrogen substituent of (114) may be removed by hydrolysis to leave the *N*-unsubstituted aziridine. Thus, the azide (113) is the synthetic equivalent of the parent nitrene HN.



Scheme 63

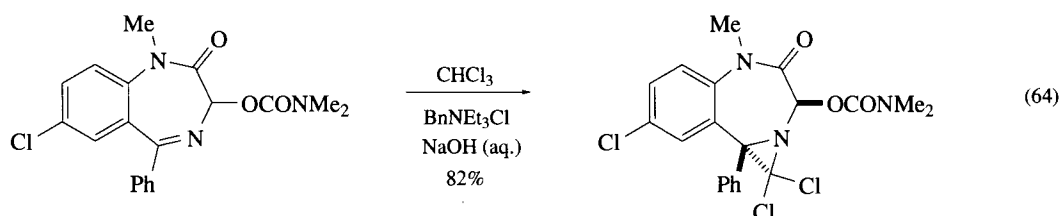
Electrophilic aziridinations using nitrenium ion intermediates or their equivalents have been reported. Rudchenko <90CC261> and Vedejs <92TL3261> have reported the generation of the *N*-methoxynitrenium ion (115) by treatment of dimethoxyamine with either BF_3 or TMS-OTf. The use of these reagents to aziridinate an alkene in a stereospecific fashion is shown in Scheme 64. The N—O bond may be cleaved with sodium and ammonia to leave the *N*-unsubstituted aziridine <92TL3261>. Takeuchi has reported an electrophilic aziridination using PhN_3 and $AlCl_3$, which promotes aziridination of cycloheptene and cyclooctene <85CC1251, 90JCS(P1)321>.



Scheme 64

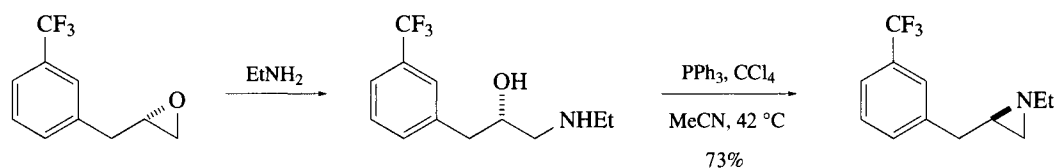
The addition of carbenes and carbenoids to imines and nitriles continues to be a popular approach to aziridines and 2*H*-azirines. These processes have been well reviewed by Deyrup <B-83MI 101-01>. Dichlorocarbene and other dihalocarbenes have been added to a wide variety of imines to provide dihaloaziridines. A recent example is shown in Equation (64), illustrating the use of phase-transfer conditions <93H(36)691>. The treatment of azides with excess dichlorocarbene results in the formation of the 2,2,3,3-tetrachloroaziridines <92TL2339>. Presumably, the azide is converted by dichlorocarbene to the imido dihalide $RN=CCl_2$ which reacts further with dichlorocarbene. Transition metal-promoted reaction of α -diazooesters with imines provides 2-(alkoxycarbonyl)aziridines <B-

83MI 101-01). Thermal reactions of less stabilized diazoalkanes with imines are possible when the reaction is intramolecular (88CC1009). The mechanism may involve formation of an azomethine ylide followed by electrocyclic ring-closure to the aziridine (84T2569). Simmons-Smith-type methylations of electron-poor imines are possible (72BSF825). Diazoalkanes do not normally react with simple imines to give aziridines, but iminium ions are useful reaction partners, providing aziridinium ions (*vide supra*) (86AHC(39)181). The use of chromium carbene complexes to convert imines to aziridines has been reported (94CC321). Sulfur ylides and related compounds, while not carbene reactions, also convert imines to aziridines (*vide supra*).

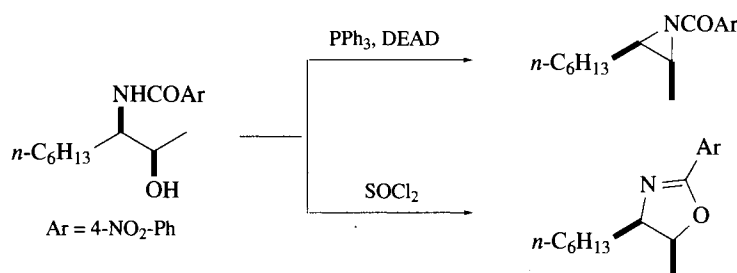


1.01.9.3 From One Component: Intramolecular Reaction between Electrophilic and Nucleophilic Sites

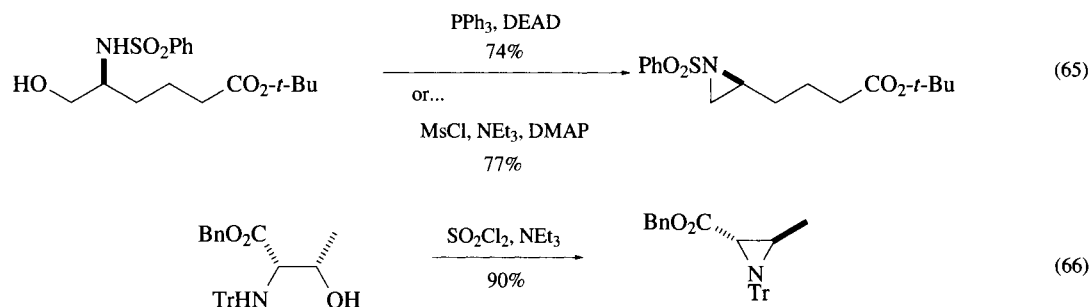
The cyclization of β -aminoalcohols and their derivatives is a common way to prepare aziridines. Examples of the conditions required to carry out such reactions are shown in Table 1. Selected specific examples are shown in Schemes 65 and 66 (88SC1391, 93BSF459) and Equations (65) and (66) (92TL3013, 93JOC5019). In one approach (Table 1 and Equations (66) and (67)), the alcohol is first converted to a leaving group such as a tosylate, mesylate, or halide. Cyclization may occur spontaneously, or may be induced by a subsequent treatment with base. Such derivatization reactions are generally carried out on derivatives of β -aminoalcohols having an electron-withdrawing group on the nitrogen atom (e.g., sulfonyl, acyl, phosphoryl) to avoid *N*-tosylation, *N*-mesylation, etc., which often occurs rapidly with simple secondary and primary amines. Benzylic amines, especially *N*-trityl- and *N*-benzhydrylamines are less prone to sulfonylation, hence the β -hydroxy group may often be converted to a leaving group without *N*-protection (Table 1, entries 7, 8, 10, and Equation (66)). The other approach to the cyclization of β -aminoalcohols is a one-step procedure using organophosphorus chemistry (Table 1, Schemes 65 and 66, and Equation (65)) (81S1, 83OR(29)1, 92OR(42)335). This approach can be successful on simple amines as well as other *N*-derivatives. Reagents such as thionyl chloride, sulfonyl chloride (e.g., Equation (66)), and Et_2NSF_3 (DAST; Table 1, entry 17) have also been used for the direct cyclization of β -aminoalcohols. While these reactions may, in principle, proceed through the β -haloamine, other intermediates which may lead to cyclization have also been proposed (92TL3013). Scheme 66 shows a potential side-reaction in the cyclization of *N*-acyl- β -aminoalcohols, namely oxazoline formation (88SC1391, 92TL6267).



Scheme 65

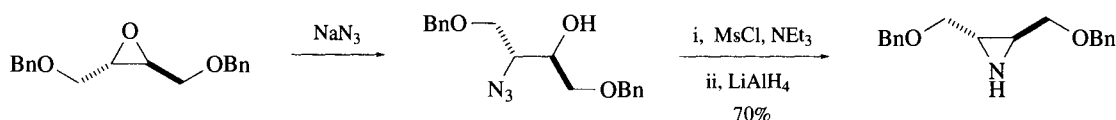


Scheme 66

**Table 1** Cyclization of β -aminoalcohols and their *N*-derivatives to aziridines.

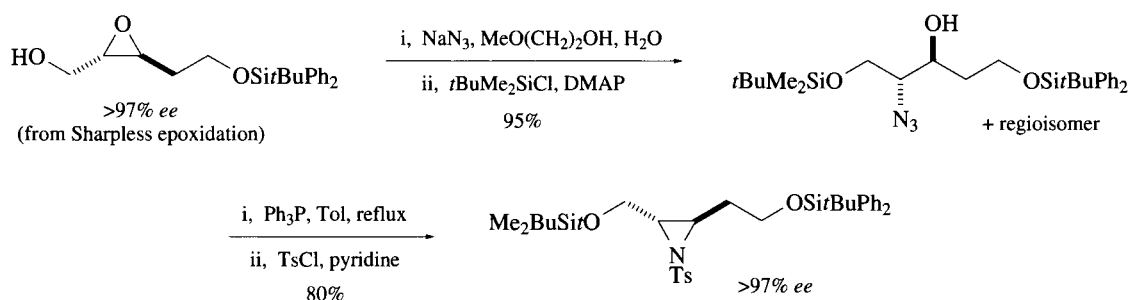
No.	N-Substituent	Conditions	Ref.
1	H	$\text{Ph}_3\text{P}(\text{OR})_2$	86JOC95
2	Me	i, SOCl_2 ; ii, NaOH	94JOC3210
3	Et	Ph_3P , CCl_4	93BSF459
4	Bu ^t	Br_2 , PPh_3 , NEt_3 , MeCN	94JA1220
5	Aliphatic	Ph_3P , dead	94TL4631
6	Bn	Ph_3P , CX_4 , NEt_3	85JOC4515, 87HCA1676
7	Bn	Ph_3P , dead	84S969
8	Tr	TsCl, pyridine	78BCJ1577
9	Tr	SO_2Cl_2 , NEt_3	92TL3013, 93CC1857
10	Tr	Ph_3P , dead	93JA1607
11	CHPh_2	MsCl, NEt_3	91TL6931, 91TL6935
12	Hetaryl	i, SOCl_2 ; ii, KOH	92ZOR422
13	COR	Ph_3P , dead	92TL6267
14	COAr	Ph_3P , dead	81JOC1229, 83JOC24, 88SC1391
15	$\text{CO}_2\text{-Bu}^t$	i, MsCl; ii, $\text{LiN}(\text{TMS})_2$	90TL2661
16	$\text{CO}_2\text{-Bu}^t$	Ph_3P , dead	93TL6513
17	$\text{CO}_2\text{-Bu}^t$	DAST (Et_2NSF_3)	92TL4487
18	CO_2Bn	Ph_3P , dead	92JOC5813
19	$\text{P}(\text{O})\text{Ph}_2$	i, $\text{Ph}_2\text{P}(\text{O})\text{Cl}$, NEt_3 ; ii, NaH, THF	94TL3159
20	$\text{P}(\text{O})\text{Ph}_2$	i, TsCl, NEt_3 , dmap; ii, NaH	94SL145
21	Ms	i, MsCl, NEt_3 ; ii, K_2CO_3 , MeOH	85TL857
22	SO_2Ph	MsCl, NEt_3 , dmap	93JOC5019
23	SO_2Ph	Ph_3P , dead	93JOC5019
24	Ts	TsCl, pyridine, K_2CO_3 , MeOH	88T3919
25	Ts	i, TsCl, pyridine, dmap; ii, Amberlite IRA-400 (OH^- form)	92SL41
26	Ts	Ph_3P , dead	90TL1903

β -Aminoalcohols may be generated from β -azidoalcohols, which are commonly made from the opening of epoxides with azide ion as shown in Scheme 67 <91TL2533>. After conversion of the alcohol into a leaving group, the azide may be reduced to an amine which cyclizes to the *N*-unsubstituted aziridine <81LA1633, 83CAR(113)C6, 91TL2533>.

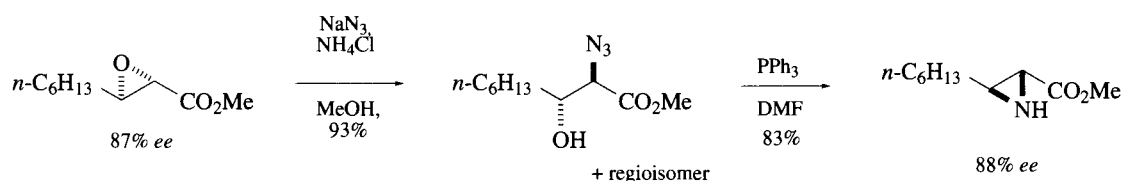
**Scheme 67**

Another route to aziridines from β -azidoalcohols is direct ring closure using triphenylphosphine <76CB814, 78JOC4271, 82HCA1617, 83HCA2467>. The mechanism of this process has been studied <84HCA1238>. Typically, the β -azidoalcohols are prepared by the reaction of epoxides with azide ion <78JOC4271, 90TL6663, 92TL3567>. The overall transformation of an epoxide into an aziridine using this two-step method results in inversion of configuration at both carbon atoms. It is important that the reaction of the β -azidoalcohol with triphenylphosphine be carried out under anhydrous conditions to avoid reduction of the azide to the amine <85BSF815>. Tanner and co-workers have reported the use of optically active 2,3-epoxyalcohols prepared by the Sharpless epoxidation for the synthesis of optically active aziridines <87TL1211, 88T619, 92T6079>, for example, Scheme 68 <88T619>.

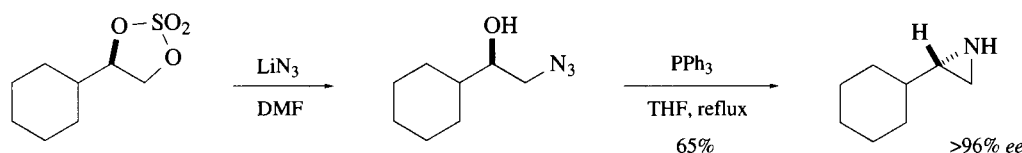
Glycidates prepared from the oxidation of Sharpless epoxyalcohols have been used to prepare optically pure aziridine-2-carboxylates <89TL4881, 92RTC1> as shown in Scheme 69 <92RTC1>. Optically active 1,2-diols derived from the Sharpless asymmetric dihydroxylation of alkenes have been used to prepare optically pure aziridines via the cyclic sulfates, as shown in Scheme 70 <91CC95> (see also <88JA7538, 89TL2623, 93JA10267> and Scheme 72). Optically active aziridines derived from carbohydrates <86TL4157, 87H(25)541, 92SL527, 93JOC7848> and tartrates <90TL1903, 93JA10267> have been prepared from β -hydroxyazides using the triphenylphosphine method.



Scheme 68

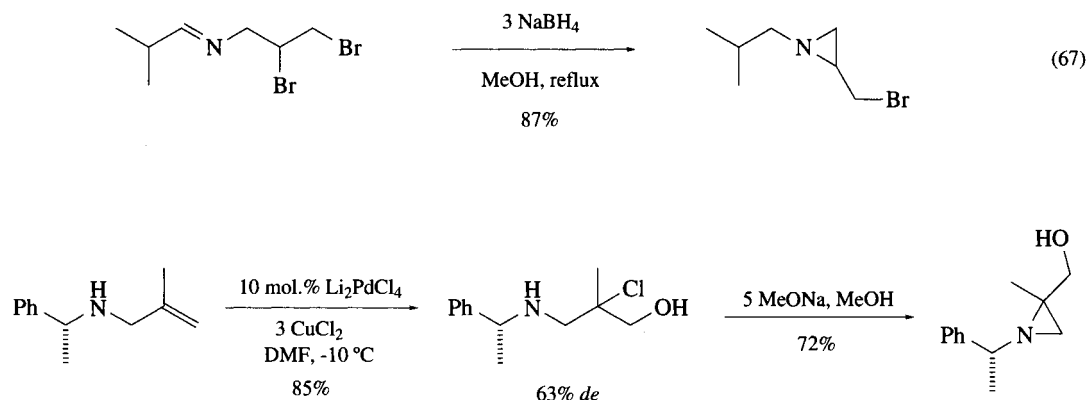


Scheme 69

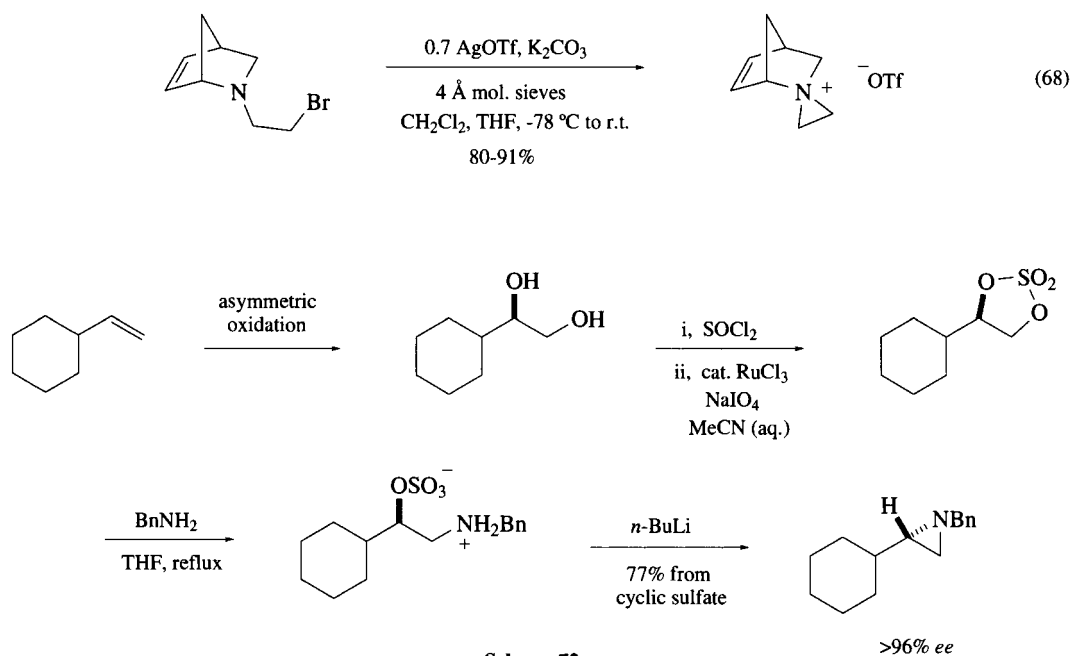


Scheme 70

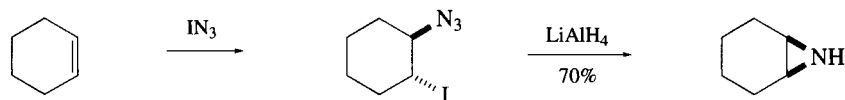
The cyclization of β -haloamines and their derivatives to aziridines is known as the Gabriel synthesis of aziridines <B-83MI 101-01, 84CHEC-I(7)47>. Reduction of imines with halogen-containing side chains on the nitrogen atom have been reductively cyclized via the β -haloamines, as shown in Equation (67) <94SL287>. The reduction of α -haloimines is also a productive route to aziridines <90T2965>. An interesting route to β -haloamines involves the heteroatom-directed chlorohydroxylation of allylic amines. Base-promoted cyclization produces the aziridine, as shown in Scheme 71 <93JOC6944>. Equation (68) shows the formation of aziridinium ions by the silver-assisted internal substitution reaction of a β -bromoethyl tertiary amine <92TL4401>. Derivatives of β -haloamines which bear an electron-withdrawing group on the nitrogen atom may also be cyclized to aziridines with base <93JCR(S)372>. The Wenkert modification of the Gabriel aziridine synthesis involves the cyclization of β -aminoethyl sulfonates <B-83MI 101-01, 84CHEC-I(7)47>. Scheme 72 shows a related method involving cyclic sulfates <88JA7538, 89TL2623>. Another route to β -haloamines is Hassner's method, which involves the reduction of β -iodoazides which are in turn prepared from the addition of IN_3 to alkenes <71ACR9, B-83MI 101-01, 84CHEC-I(7)47>. The example shown in Scheme 73 compared favorably with the method described above involving the triphenylphosphine mediated closure of the β -hydroxyazide, where triphenylphosphine oxide hampered product isolation <93HCA2602>.



Scheme 71

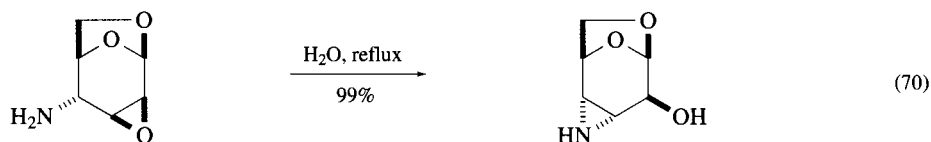
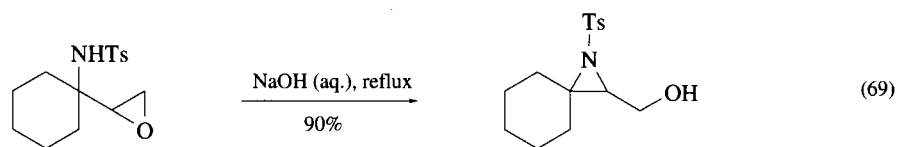


Scheme 72

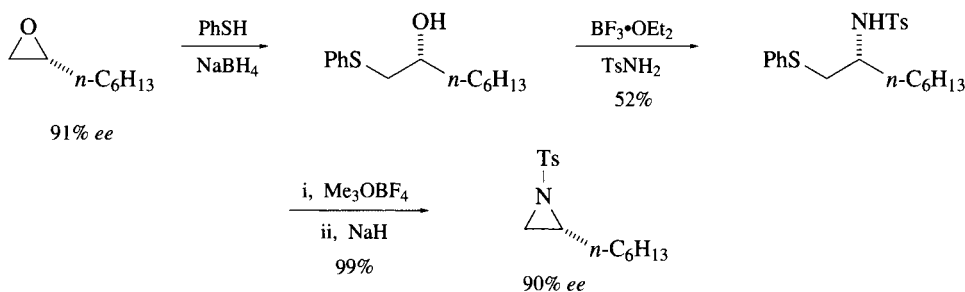


Scheme 73

Aziridines may be prepared by the intramolecular nucleophilic opening of epoxides by amines and their derivatives (84CAR(130)103, 92T5639, 92TL487, 92TL5351). This process is analogous to the Payne rearrangement of 1,2-epoxyalcohols. Sulfonamide anions cyclize smoothly to aziridines as shown in Equation (69), although the success of the reaction depends significantly on the epoxide substituents (92TL487). Amines may cyclize with epoxides simply upon heating, as shown in Equation (70) (84CAR(130)103). However, other epoxyamines are thermally stable and require the presence of Lewis acid promoters such as titanium(IV)isopropoxide (92T5639) or Bu^nLi /trimethylaluminum (92TL5351) for cyclization.

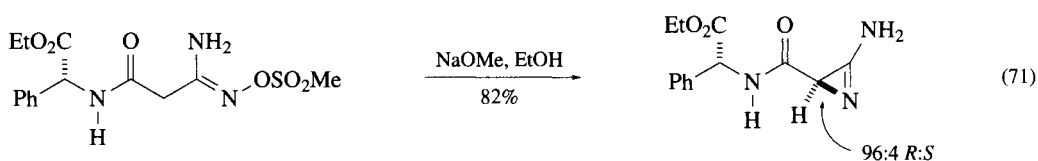


Epoxides may be converted to aziridines with retention of configuration using a three-step procedure involving sulfur chemistry, as shown in Scheme 74 <92CC284>. Compare this stereochemical outcome with that observed above in the conversion of epoxides to aziridines via the β -azidoalcohol and triphenylphosphine, where both epoxide carbons undergo inversion of configuration.



Scheme 74

The Neber reaction continues to be a useful route to 2*H*-azirines, and has been reviewed <B-83MI 101-02, 84CHEC-1(7)47>. Imines bearing a leaving group on the nitrogen atom (e.g., oxime sulfonates, hydrazone methiodides, etc.) as well as at least one α -hydrogen next to the imine are converted to 2*H*-azirines upon treatment with base. Mechanisms involving base-promoted cyclodehydration or the intermediacy of a vinylnitrene have been considered (see Section 1.01.9.5). An example is shown in Equation (71), where a peptide containing a 3-amino-2*H*-azirine was prepared in good yield <93T4671>. In a mechanistically related reaction, amides bearing a leaving group on nitrogen have been shown to produce aziridinones (α -lactams) as intermediates in α -substitution reactions upon treatment with base <93JA5031, 93JA6557>.

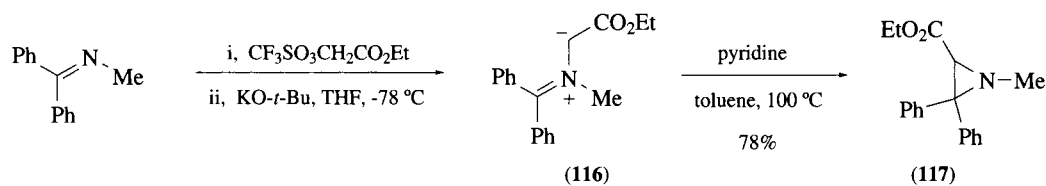


Miscellaneous reactions which involve the cyclization of one component to an aziridine by a polar reaction include the electrochemical oxidative cyclization of β -(*p*-toluenesulfonyl) aminomalonates to 2,2-bis(carbomethoxy)-*N*-(*p*-toluenesulfonyl)aziridines <88CL1065> and the bromonium ion-mediated cyclization of *N*-propargyl acetamides to 2-(2-bromoalkylidene)aziridines <92JOC5023>.

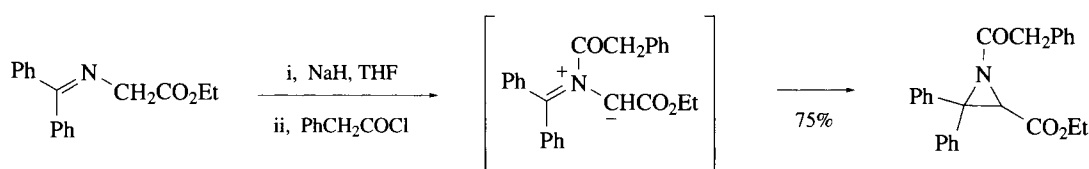
1.01.9.4 From One Component: Electrocyclic Processes

While the electrocyclic ring-opening of aziridines to azomethine ylides is well known, the reverse reaction has also been studied as a route to aziridines <B-83MI 101-01>. This process is implicit in the *cis*–*trans* equilibration of substituted aziridines <67JA1753, 71JA1779>, and may be involved in the reaction of diazoalkanes with imines <84T2569>. Convincing evidence for the electrocyclization of

azomethine ylides to aziridines was found when the azomethine ylide (**116**) was generated as a relatively stable species at low temperature and then added to hot toluene to produce the aziridine (**117**) in good yield, as shown in Scheme 75 <87JOC3470>. *N*-Acylation of a 2-azaallyl anion was proposed to generate an azomethine ylide, which underwent electrocyclicization to produce an aziridine in good yield (Scheme 76) <89TL4717>. The thermolysis of oxazolidines may lead to aziridines via an azomethine ylide intermediate <90TL6017>. Other routes to azomethine ylides which may result in aziridine formation include the deprotonation of *N*-oxides <82CC408, 85CJC725> and the deprotonation of iminium ions <75JOC2048>. Photochemical electrocyclicization reactions of pyridinium salts and cyclic azomethine ylides produce fused bicyclic aziridines <B-83MI 101-01, 86AHC(39)181>.



Scheme 75



Scheme 76

Attempts to isolate or observe 1*H*-azirine by a cycloreversion approach were unsuccessful (e.g., Scheme 77 <93CB2337>). Pyrolysis or photolysis of a wide variety of precursors failed to generate 1*H*-azirine in observable quantities. Products which may be the result of further transformation of this elusive heterocycle were isolated, such as 2*H*-azirine, calculated to be 33.2 kcal mol⁻¹ more stable.



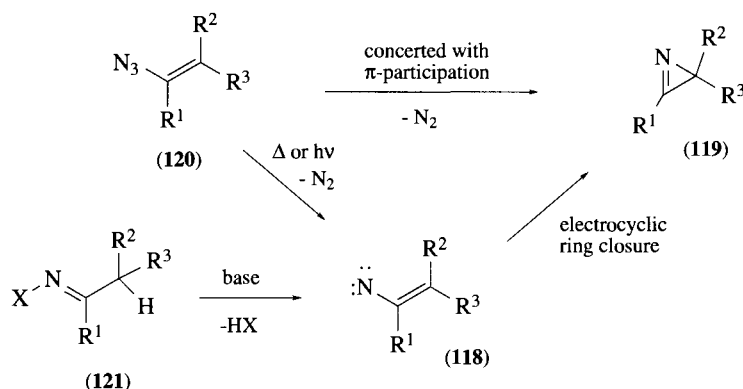
Scheme 77

Sigmatropic rearrangements of cyclopropylimines <91TL7127> and cyclobutylimines <88H(27)1665> to generate fused bicyclic aziridines have been reported <84CHEC-I(7)47>. The sigmatropic rearrangement of isoxazoles to azirines will be covered in Section 1.01.9.6. Electrocyclic closure of vinyl nitrenes to azirines will be discussed in Section 1.01.9.5.

1.01.9.5 From One Component: Cyclization of Reactive Intermediates

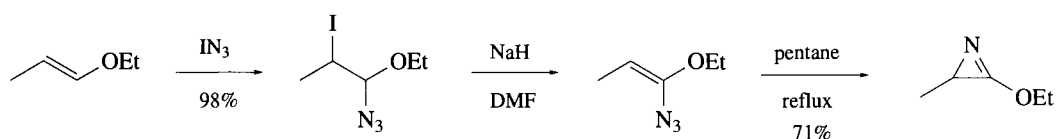
Reactive intermediates such as nitrenes, carbenes, and radicals have been used in cyclization reactions which produce aziridines and azirines. Intermolecular aziridination reactions with nitrenes were covered in Section 1.01.9.2. Vinyl nitrenes (**118**) may undergo cyclization to 2*H*-azirines (**119**), as shown in Scheme 78. This reaction has been covered in several reviews <B-82MI 101-01, B-83MI 101-02, 84CHEC-I(7)47, B-84MI 101-03, 87CHE1037>. Vinyl nitrenes (**118**) may be generated by the thermolysis or photolysis of vinyl azides (**120**), or by the base-promoted loss of HX from oxime *O*-sulfonates (**121**) (X = SO₂Ar) or hydrazonium salts (**121**) (X = N(+)Me₃ I(-)). The latter process is known as the Neber reaction (see also Section 1.01.9.3). While there has been considerable debate about

the intermediacy of vinylnitrenes in both processes, these reactions are conveniently discussed in this Section.

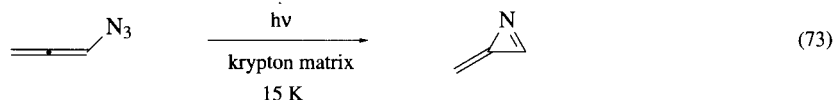
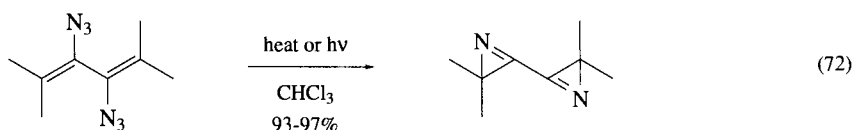


Scheme 78

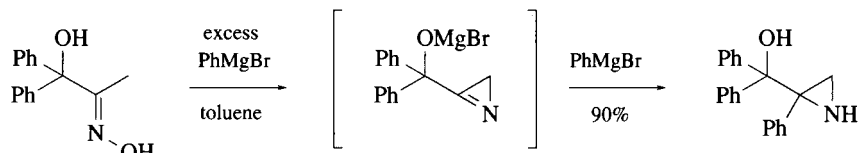
Vinyl azides are easily prepared by the Hassner reaction $\langle 68\text{JOC}2686, 71\text{ACR}9 \rangle$, where iodine azide is first added to an alkene and the resultant β -iodoazide is dehydrohalogenated with base. Thermolysis or photolysis of the vinyl azide produces a $2H$ -azirine $\langle \text{B-83MI } 101\text{-}02, \text{B-83MI } 101\text{-}03, 84\text{CHEC-I(7)47, B-84MI } 101\text{-}03 \rangle$. An example of the use of the Hassner reaction followed by thermolysis of a vinyl azide is shown in Scheme 79 $\langle 86\text{RTC}456 \rangle$. Other examples of both thermolysis and photolysis reactions of vinyl azides are shown in Equations (72) and (73) $\langle 85\text{TL}5261, 94\text{JA}60 \rangle$. Two groups have successfully isolated and characterized the parent compound $2H$ -azirine by flash vacuum thermolysis of vinyl azide at $397\text{--}500^\circ\text{C}$ $\langle 83\text{CC}238, 83\text{JA}7681, 87\text{CB}1971, 88\text{T}4447 \rangle$. Hassner and co-workers have nicely summarized the understanding of the mechanism of the thermolysis of vinyl azides and have made some generalizations about the probability of $2H$ -azirine formation based on the structure of the vinyl azide $\langle 86\text{JOC}3176 \rangle$. Thermolyses of vinyl azides lead most often to isolable $2H$ -azirines when R^1 is an aryl, alkyl, alkoxy, amino, or carboethoxy group (see Scheme 78). Azirines are rarely isolated when R^1 is hydrogen, a keto-carbonyl group, or a group which destabilizes positive charge. In these cases, nitriles or other heterocycles may form. If R^2 or R^3 are aryl or vinyl groups, indoles or other heterocycles are usually formed. Isoxazoles result when R^2 is a carbonyl group. Of the possible mechanisms for the conversion of the vinyl azide to the azirine, a concerted loss of nitrogen involving participation by the π -bond of the alkene is often proposed as the most favored pathway $\langle 86\text{JOC}3176 \rangle$, although vinylnitrene formation is a reasonable alternative explanation in certain cases. The cyclization of vinylnitrenes to $2H$ -azirines is often reversible. Hence, while the initial cyclization of the vinyl azide may (or may not) involve a vinylnitrene, a vinylnitrene may be formed from the azirine after the fact and may lead to other products resulting from nitrene chemistry $\langle \text{B-82MI } 101\text{-}01 \rangle$. Low temperature photolysis of vinyl azides is a useful alternative to thermolysis for the formation of $2H$ -azirines.



Scheme 79

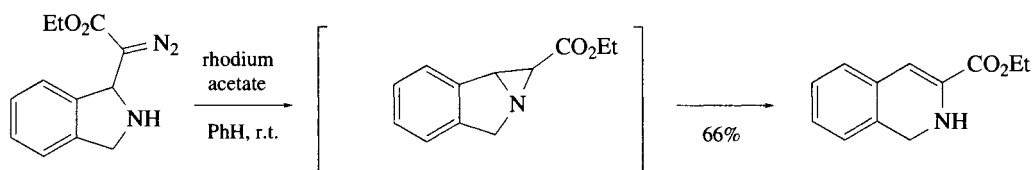


The Neber reaction ((121) to (119) in Scheme 78) may also involve vinylnitrenes, although an internal nucleophilic displacement cannot be ruled out <B-83MI 101-02, 84CHEC-I(7)47, B-84MI 101-03>. The Neber reaction of oxime *O*-sulfonates with base normally results in hydrolysis of the 2*H*-azirine to an α -aminoketone, but there are examples of this process which lead to isolation of the 2*H*-azirine in good yield (e.g., Equation (71) in Section 1.01.9.3). The treatment of ketone dimethylhydrazone methiodides with base is a milder method and is often useful for 2*H*-azirine formation <B-83MI 101-02, 84CHEC-I(7)47>. The reduction of ketoximes with LAH produces aziridines, presumably through the 2*H*-azirine. This process is considered to be related to the Neber reaction and may also proceed through a vinylnitrene <B-84MI 101-03>. A similar reaction involving the treatment of ketoximes with Grignard reagents is shown in Scheme 80 <77T1279>.



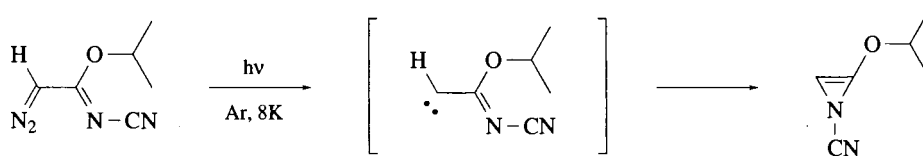
Scheme 80

The intramolecular insertion of carbenoids into NH bonds is a potential route to aziridines. Scheme 81 shows an example of such a process <86JOC1120>. The starting material was prepared by the intramolecular cycloaddition of an azide with an acrylate followed by ring-opening of the resultant triazoline.



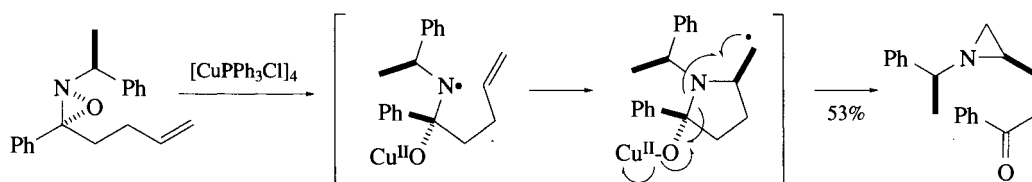
Scheme 81

Regitz and co-workers have reported the matrix isolation of 1*H*-azirines generated by the photolysis of diazo compounds, as shown in Scheme 82 <81BSB615>.



Scheme 82

Aubé and co-workers have reported an aziridine synthesis which involves a radical cyclization (Scheme 83) <92JA5466>.



Scheme 83

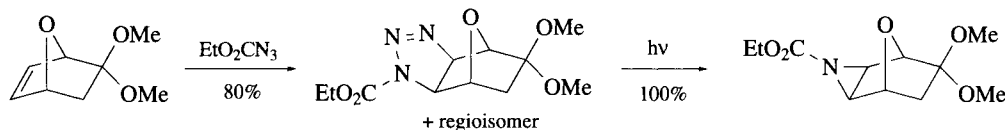
The conversion of epoxides to aziridines by nucleophilic ring-opening with azide ion or amines followed by cyclization was covered in Section 1.01.9.3. The conversion of azirines to aziridines by nucleophilic addition and the conversion of aziridines to azirines by elimination were covered in Sections 1.01.6 and 1.01.7, respectively.

The thermal or photochemical extrusion of nitrogen from 4,5-dihydro-1,2,3-triazoles (henceforth referred to as triazolines) continues to be one of the most popular routes to aziridines (B-70MI 101-02, B-83MI 101-01, 84AHC(37)219, 84CHEC-I(7)47). The triazolines are generally prepared by the 1,3-dipolar cycloaddition of azides with alkenes (B-70MI 101-02, B-83MI 101-01, B-83MI 101-04, 84AHC(37)219, 84CHEC-I(7)47, B-84MI 101-05, B-84MI 101-09). Scheme 84 summarizes the pathways that are generally considered to be in operation for this transformation. Fragmentation of the triazoline (**122**) by either a homolytic or ionic pathway leads to either the diradical (**124**) or the zwitterion (**125**), respectively, each of which may close to the aziridine (**126**). In the case of the zwitterion, a 1,2-shift leading to an imine (**127**) is often a competing pathway. It is generally considered that photolysis of triazolines is the cleaner route to aziridines, but it is not always possible to isolate and manipulate the triazoline, since it is often thermally sensitive. In such cases, the triazoline derived from a 1,3-dipolar cycloaddition of an azide with an alkene may not be observed, but may be transformed thermally to the aziridine. The facility of the 1,3-dipolar cycloaddition, the lability of the triazoline, and the success of the photochemical or thermal conversion of the triazoline to the aziridine are all dependent on the nature of the substituents present. Kadaba and co-workers' discussion of triazoline decomposition to aziridines is organized by the type of alkene (simple alkenes, strained alkenes, electron-poor alkenes, electron-rich alkenes) (84AHC(37)219). Deyrup's review provides a tabular survey of the decomposition of many triazolines to aziridines (B-83MI 101-01). Reviews covering the specifics of the decomposition of triazolines derived from alkyl azides (B-84MI 101-01), vinyl azides (B-84MI 101-03), aryl and heteroaryl azides (B-84MI 101-10), acyl azides (B-84MI 101-08), and heteroazides (i.e., HN₃, silyl azides, and stannyl azides) (B-84MI 101-06) have been published. Generalizations regarding the mechanism and stereochemistry of the formation of aziridines from triazolines have been made (B-70MI 101-02, 84AHC(37)219, 84CHEC-I(7)47). The photochemical process is considered to produce a singlet diradical which closes to the aziridine faster than bond rotation can occur. Hence, the geometry of the triazoline (and thus the alkene before it) is translated selectively (but not exclusively) into the stereochemistry of the aziridine with retention of configuration.

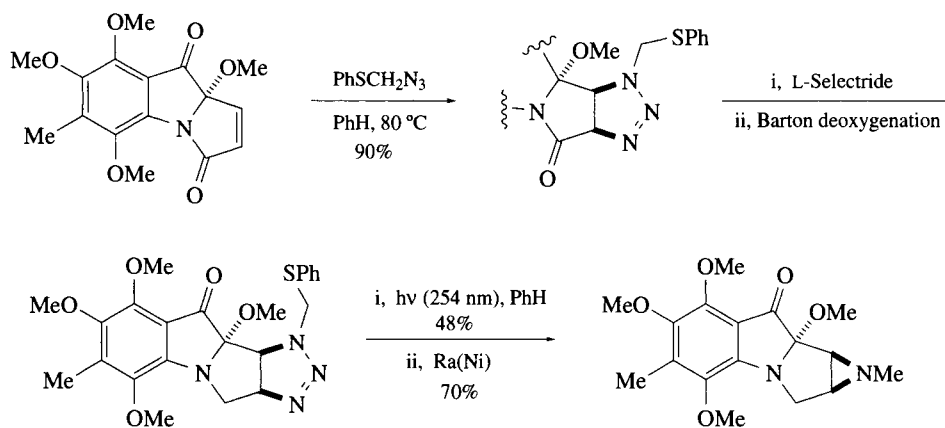


A selection of examples of the formation of aziridines from triazolines derived from intermolecular cycloadditions of azides with alkenes are shown in Schemes 85–89. A large body of literature exists on the intramolecular cycloaddition of azides to give fused-ring triazolines and aziridines (<B-84MI 101-09, B-84MI 101-10, 90JOC5719, 90SL433, 91COS(6)65, 94TL3489>), but this work is outside the scope of this chapter and will be covered in the following chapter. Aziridines bearing simple alkyl groups are not easily prepared by the triazoline route since imines (**127**) are also produced, often as the major

products <65JA749, B-70MI 101-02, 94T12293>. Triazolines bearing an electron-withdrawing group at N(1) may be prepared from aliphatic alkenes, and generally give aziridines, as shown in Scheme 85 <88TL3695, 90SL173>. This type of triazoline is often thermally labile. Aliphatic azides may be used with electron-poor alkenes to prepare aziridines, generally proceeding through a 4-substituted triazoline. Such triazolines are often thermally sensitive and produce aziridines under the conditions of the cycloaddition, but in some cases they are relatively stable. The example shown in Scheme 86 is illustrative, since the triazoline is untouched under the conditions necessary to remove a lactam carbonyl group <92AG(E)915, 93JA12305>. The use of azidomethyl phenyl sulfide in this process provides an alternative to the use of the hazardous methyl azide, although methyl azide itself can be used effectively in a similar process <88TL3525>. The intramolecular cycloaddition of azides with electron-poor alkenes is a particularly popular reaction, producing synthetically useful bicyclic aziridines <90JOC5719, 90SL433, 94TL3489>. Electron-rich alkenes may be used in cycloaddition reactions with azides, as shown in Scheme 87 <85TL5407>. The electron-donating group directs the cycloaddition such that a 5-substituted triazoline is formed <88TL6475>. A potential side-reaction is the loss of the heteroatom to give an aromatic triazole. Intramolecular cycloadditions of azides with electron-rich alkenes may force the formation of 4-substituted triazolines, which are not usually observable and do not produce isolable aziridines <90CC51, 90JOC5719>. Aryl and heteroaryl azides have commonly been used to prepare *N*-aryl aziridines <B-84MI 101-11, 89JA8303>. Vinyl silanes appear to be very useful for the formation of 2-(trialkylsilyl)aziridines, as shown in Scheme 88 <91JCS(P1)2789, 93JCS(P2)1129>. Note that the decomposition of the triazoline was accomplished with silica gel. Protic acids may also promote the decomposition of triazolines, although the resultant aziridines may undergo further transformations under such conditions <93JOC2097>. Scheme 89 illustrates another approach to triazolines, the reaction of azides with sulfoxonium ylides <81TL1863, 93JOC2097>. Note the smooth formation of the aziridine under thermal rather than photochemical conditions. Triazolines may also be prepared by the cycloaddition of diazo compounds with imines, thus providing another route to aziridines <88CC1009>.



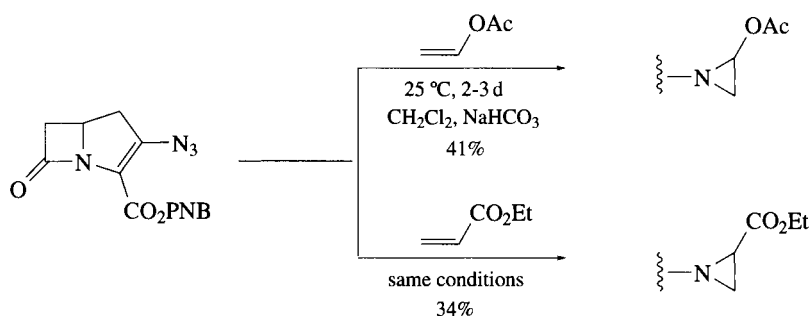
Scheme 85



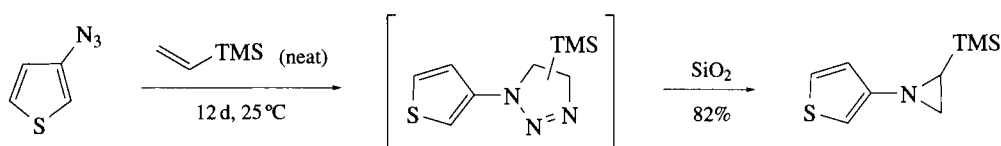
Scheme 86

The photolysis of 1,2,3-triazoles continues to be studied as a possible route to the highly elusive 1*H*-azirines <73JCS(P1)550, 73JCS(P1)555, 75JCS(P1)1, 75JCS(P1)8, 86CC399>. Although not directly observed, a 1*H*-azirine was implicated in the photolysis of the two regioisomeric triazoles shown in Scheme 90 <86CC399>. The azirine subsequently underwent ring-opening and cyclization onto the naphthalene core to give a pyrrole ring. Similar studies involving ¹³C-labeled triazoles provide convincing evidence for the intermediacy of 1*H*-azirines <75JCS(P1)8>.

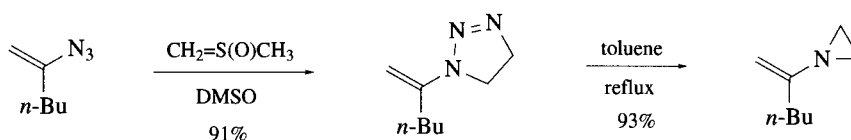
Photolysis or thermolysis of 2,3-dihydroisoxazoles produces azomethine ylides, and aziridines



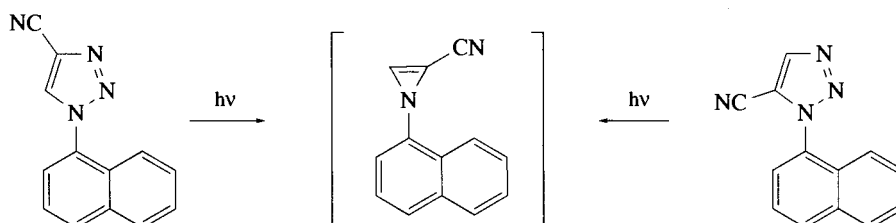
Scheme 87



Scheme 88



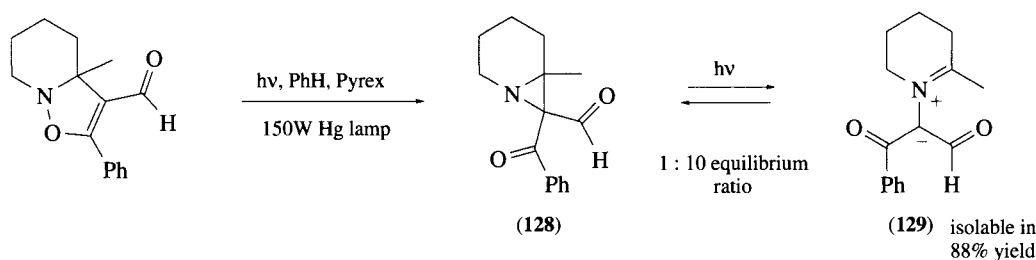
Scheme 89



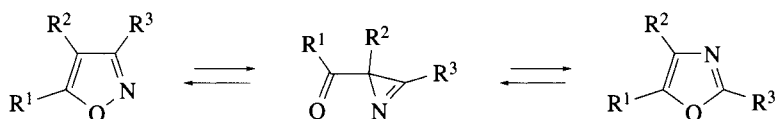
Scheme 90

have been implicated as intermediates in this transformation $\langle 84\text{CL}797, 93\text{TL}5047 \rangle$. This method does not appear to be useful as a preparative route to aziridines, since the aziridine is not observed in most cases. It is more useful as a route to azomethine ylides. An aziridine was observed in the example shown in Scheme 91, where photolysis of a 2,3-dihydroisoxazole produced the aziridine (**128**) and the isolable azomethine ylide (**129**) in a 1 : 10 equilibrium ratio $\langle 94\text{CC}301 \rangle$. In a somewhat related process, photolysis $\langle 81\text{CL}1585 \rangle$ or flash vacuum thermolysis $\langle 90\text{TL}6017 \rangle$ of oxazolidines (i.e., tetrahydrooxazoles) may produce aziridines in equilibrium with azomethine ylides. Again, this does not appear to be a preparatively useful route to aziridines.

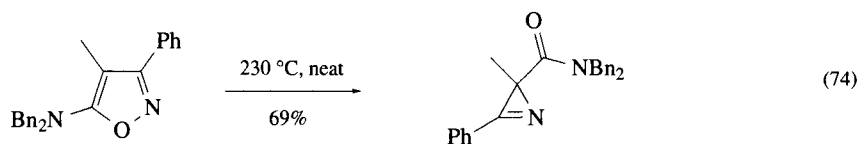
Photolysis and thermolysis of isoxazoles and oxazoles causes ring-contraction to 2-acyl-2*H*-azirines, as shown in Scheme 92 $\langle \text{B-82MI } 101\text{-}01, \text{B-83MI } 101\text{-}02, 84\text{CHEC-I(7)47} \rangle$. The azirines may be observed in some cases, or may be transformed without observation to other heterocycles. Equation (74) shows an example where the azirine was isolated in good yield $\langle 88\text{TL}6067 \rangle$. An isolable azirine was also formed in the photolysis of a 4-acylisoxazole $\langle 90\text{JOC}4011 \rangle$.



Scheme 91



Scheme 92



Alkylidenetetrazolines may be converted to iminoaziridines by photolysis with loss of nitrogen <92CB2095, 92CB2749> as shown in Equation (75).



1.01.10 IMPORTANT COMPOUNDS AND APPLICATIONS

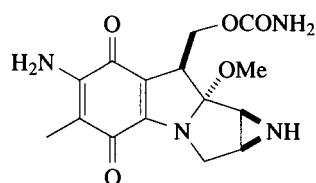
A majority of the literature on aziridines and azirines concerns their use as synthetic intermediates, since their ring strain can be harnessed to carry out other reactions. For example, aziridines have found wide use in the synthesis of natural products <86AHC(39)181>. However, other aspects of the chemistry of these heterocycles are finding an increasing amount of interest. Naturally occurring bio-active aziridines and azirines have generated a substantial amount of excitement. The use of aziridines as chiral auxiliaries, reagents, and ligands has begun to attract attention. Finally, a large body of work exists on the use of aziridines as monomers for polymer synthesis.

1.01.10.1 Natural Products and Medicinal Agents

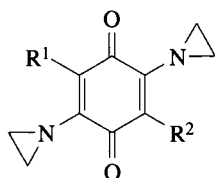
Natural products containing an intact aziridine ring continue to be discovered <B-83MI 101-01>. The biological activity of some of these compounds is often attributed to the chemistry of the aziridine ring, prompting the synthesis of simpler, nonnatural, aziridine-containing analogues. Aziridines are used as alkylating agents, both for the treatment of cancer and as affinity probes of receptors and peptides. There are several distinct classes of aziridine alkylating agents <B-79MI 101-01, B-85MI 101-01>. These include the bioreductively activated aziridines, simple aryl aziridines, and the nitrogen mustards.

The mitomycin family of antitumor antibiotics, represented below by Mitomycin C (130), is perhaps the most well known class of natural products containing the aziridine ring. Bioreductive activation of the quinone ring is proposed to initiate a cascade of events leading to activation of the aziridine ring toward attack by DNA <90JA3637, 92SL778, 93JA10497>. A number of simpler aziridines

which alkylate DNA have been reported, such as (131), which is relatively selective for alkylation of DNA at G-C base pairs <92MI 101-02, 93B3306>, thio-TEPA (132), and TEM (133) <93JCR(S)372>.



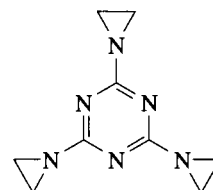
Mitomycin C (130)



(131)

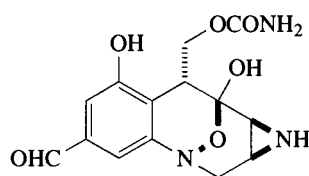


(132)

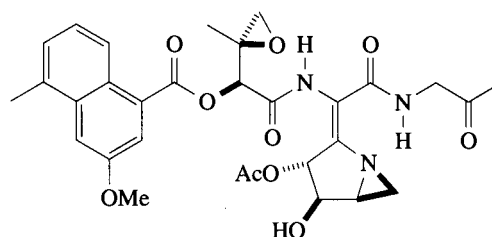


(133)

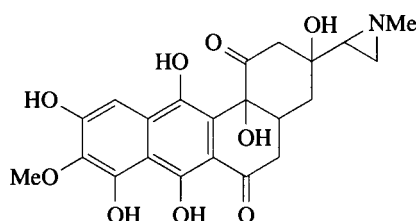
Other examples of aziridine-containing natural products are FR-900482 (134) <92JA383, 94JOC355> and Azinomycin A (135) <92JOC5813, 93JOC7848>. The new antibacterial compound Azicemicin A (136) is the first example of a natural product containing an aziridine ring that is not fused to another ring <93JAN1772>.



FR-900482 (134)

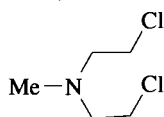


Azinomycin A (135)

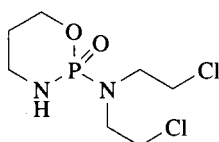


Azicemicin A (136)

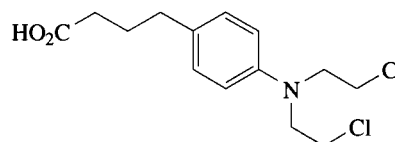
The nitrogen mustards were among the first anticancer drugs developed. An intermediate aziridinium ion is proposed as the active alkylating agent. Mechlorethamine (137) was first used in 1942. Some other examples include cyclophosphamide (138) and chlorambucil (139). Mustards linked to steroids have also seen use as anticancer agents <B-92MI 101-03>. These compounds are bisalkylating agents, inhibiting DNA replication by acting primarily at guanine residues. Aziridines have also been used to label receptors and proteins. For example, aziridines and mustards have been used to label muscarinic receptors <B-90MI 101-01, 92MI 101-04>.



(137)

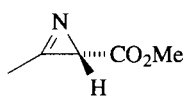


(138)

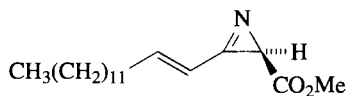


(139)

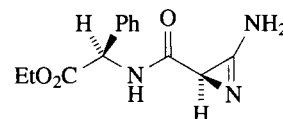
The azirine ring has also been found in several natural products. The first azirine-containing natural product isolated was Azirinomycin (140) <71JAN48>. More recently, the similar azirine-containing antibiotic Dysidazirine (141) was isolated and shown to possess cytotoxic and antibacterial activity <88JOC2103>. The synthesis of an aminoazirine-containing peptide (142) has been reported <93T4671>.



Azirinomycin (140)



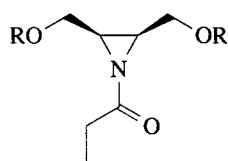
Dysidazirine (141)



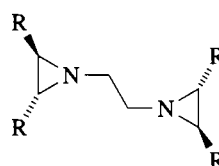
(142)

1.01.10.2 As Chiral Auxiliaries and Ligands

The use of C_2 -symmetric aziridines as chiral auxiliaries has been reviewed by Tanner <94AG(E)599>. Chiral *N*-acylaziridines such as (143) have been used in enolate chemistry (see Section 1.01.8.2). Aziridine-containing ligands such as (144) have been used for a variety of metal-catalyzed reactions such as the asymmetric dihydroxylation of alkenes, the palladium-catalyzed allylation of nucleophiles, asymmetric cyclopropanation, and aziridination <94AG(E)599, 94TL4631>.



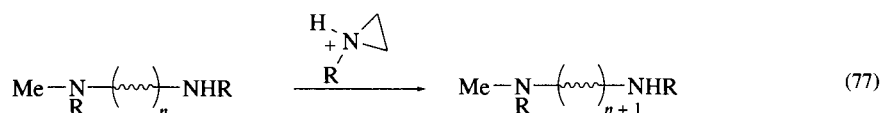
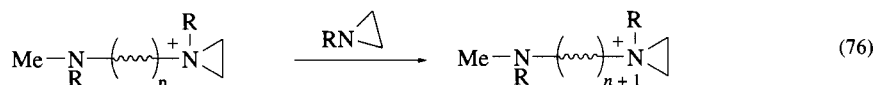
(143)



(144)

1.01.10.3 Polymers

Aziridines are used extensively as monomers for the preparation of polymers. This area has been well reviewed <B-89MI 101-01, B-89MI 101-02, B-89MI 101-03>. Aziridine is polymerized under acidic conditions to provide poly(ethylenimine) or PEI. Two general modes of polymerization have been noted with aziridines. The first is the activated chain end mode, shown in Equation (76). The aziridine end of the growing polymer is protonated and attacked with a molecule of the monomer. The second mode is the activated monomer mechanism shown in Equation (77), where the terminal amine attacks a protonated aziridine monomer. In the polymerization of substituted aziridines, substitution generally occurs at the least substituted carbon of the ring. A wide variety of substitution patterns on both the carbon and nitrogen of the aziridine monomer has been used. The polymerization of *N*-alkylaziridines can be initiated by either acid or alkyl halides.



1.02

Aziridines and Azirines: Fused-ring Derivatives

KURIYA MADAVU LOKANATHA RAI
Mysore University, India

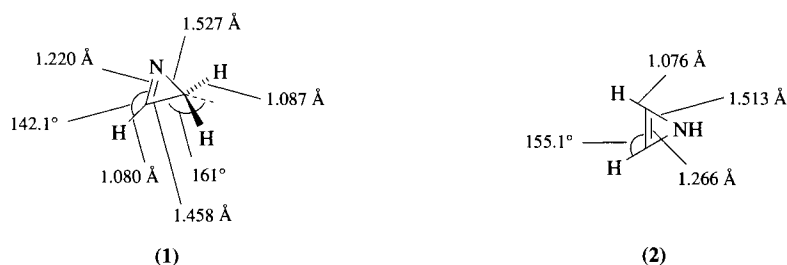
and

ALFRED HASSNER
Bar-Ilan University, Ramat Gan, Israel

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1.02.1 INTRODUCTION

Azirine and its dihydro derivative, aziridine, can be regarded as representative of the first and most simple of all heterocyclic systems, one which is characterized by the presence of two carbon atoms and one nitrogen in a three-membered ring. Throughout this chapter the nomenclature of 1-azirine for (1) and 2-azirine for (2) is used. The chemistry of these heterocycles has flourished with considerable intensity since the mid-1960s because of its theoretical, mechanistic, synthetic, and biological applications. A number of reviews on azirines have appeared during this period <B-64MI 102-01, 66RCR105, B-67MI 102-01, 70RCR118, B-71MI 102-01, B-76MI 102-01, B-79MI 102-01, B-83MI 102-01, B-83MI 102-02, 84CHEC-I(7)47, 86AHC(39)181, 91COS(7)469>. The theoretical and mechanistic interests are associated with the structure, stability, and inherent strain energy of azirines and the ability of the system to direct the course of many mechanistically significant reactions in several distinct ways. The outstanding characteristic of aziridines is their high reactivity to a wide variety of both electrophilic and nucleophilic reagents to afford the more stable ring-opened or ring-expanded amines, a property that stems from the release of the strain energy inherent in a small ring. The strain and reactivity of the aziridine ring has led to the hope that these properties might be translated into useful biological activity. Synthetic approaches to the aziridine ring, modifications of functionalized aziridines and the reactions of aziridines have received particular attention. As a result, there have been many applications of aziridine chemistry to synthesis, mechanistic studies, and biological investigations.

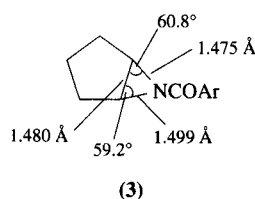


1.02.2 STRUCTURE

1.02.2.1 Theoretical Considerations

The structure and relative stability of the parent heterocycles have been the subject of considerable theoretical attention. *Ab initio* MO calculations <B-83MI 102-02, 84CHEC-I(7)47> predict for 1-azirine (1), in which an overall C_s symmetry is assumed, a C—C bond shorter and a C—N bond longer than those commonly encountered in acyclic molecules. Experimentally these predictions have been substantiated from an x-ray crystallographic structure determination reported for highly substituted derivatives. An exploration of the $C_2H_5NAl^+$ potential energy surface has been carried out by means of *ab initio* MO theory at the SCF-6-31 G^* level. The relative stabilities of the corresponding stationary points were calculated at the MP4/6-31 + G(d,p) level. The results <93JPC5553> show that most stable $C_2H_5NAl^+$ cations in the gas phase correspond to the nitrogen adducts of C-methylmethylene, *N*-methylmethylene, vinylamine, and aziridine. Another stable species corresponds to the carbon association to the carbene CH_3CNH_2 , which has been identified as a minimum of the C_2H_5N potential energy surface. The Al^{3+} -carbon adduct of vinylamine and the CH_4Al^+ -NCH complex are more stable than the nitrogen adduct of aziridine. Cationization of aziridine and C-methylmethyleimine by aluminum ions parallels their gas phase protonations. There are significant differences between the general features of the $C_2H_5NAl^+$ potential energy surface and that of the analogous oxygen-containing system $[C_2H_4OAl]^+$ due to the fact that while O- Al^+ association is clearly preferred to C- Al^+ association, C- Al^+ adducts are only slightly less stable than the N- Al^+ ones. Another main difference is related to the low stability of the transition state corresponding to the opening of the aziridine ring, which is much higher in energy than the transition state corresponding to the opening of oxirane. Bicyclic aziridines with a common C—C bond, for example (3), follow the general C—C and C—N bond lengthening trends to 1.54 Å and

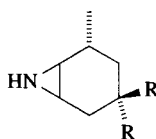
1.50 Å respectively as the fused carbocyclic ring increases from cyclopentyl to cyclotridecyl. The total strain energy of course may be somewhat higher than that of the unsubstituted ring because of the contribution from interaction of substituents with the ring and with other substituents. The replacement of the methylene residue of cyclopropane by a nitrogen atom causes an insignificant change in the conventional ring strain energy. For the 2-azirine (2), in which both C_s symmetry and nonplanarity of the nitrogen substituents were considered, calculations show the C—N bond in (2) to be slightly longer and the C=C bond shorter than that in cyclopropane (1.28 Å). The degree of nonplanarity about nitrogen is predicted to be ca. 72°, a value which is significantly larger than that calculated for the 1-azirine ring. It has been suggested that as a planar species, the 2-azirine ring is unstable because of the antiaromatic character which will result from complete delocalization of its π -electrons.



The presence of ring strain within small-ring compounds results in the formation of bent bonds which are high in p -character. This phenomenon can be determined quantitatively from measurements of NMR coupling constants.

1.02.2.2 Conformational Analysis

On the basis of NMR spectra and crystal structure determination it was found that five-membered rings of spiro fused azirines are commonly locked in the envelope conformation and are stabilized by the interaction between a quinazalone nitrogen (N-3) p -orbital and a bonded p -orbital of the adjacent azirine carbon atom (85TL4399). The dynamic conformational analysis of the cleavage of methyl substituted 7-azabicyclo[4.1.0]heptanes (4) by Olah's reagent (30 wt of pyridine in hydrogen fluoride), using the torsion angle notation, permits structural and conformational prediction for 2-fluoro cyclohexylamine products (87T2485). In many cases the presence of methyl groups on the cyclohexane ring prevents the interconversion of the primary forms with the diaxial orientation of the C—N bond and the newly formed C—F bond to the more stable diequatorial conformer.



(4) R = H, Me

1.02.2.3 Electron Absorption Spectroscopy

Simple aziridines are optically transparent in the UV region of the electromagnetic spectrum. In more highly substituted aziridines, such as the 2-aryl-3-arylaziridine (5) there is an interaction between the carbonyl and aryl ring substituents which is transmitted through the ring and which manifests itself in the appearance of longer wavelength absorption maxima and greater molar absorptivity for the *trans* isomers than for the *cis* isomers. These differences, depicted for *cis*- and *trans*-aziridine (5) in Figure 1, are useful for distinguishing pairs of stereoisomers and are, in fact,

observable in both the $\pi-\pi^*$ (3–5 nm) and $n-\pi^*$ (ca. 25 nm) transitions. This interaction has been attributed to the existence of more favorable orbital overlap between the carbonyl π -bond and the bent p-type σ -bonds in the *trans* rather than in the *cis* isomer <84CHEC-I(7)47>.

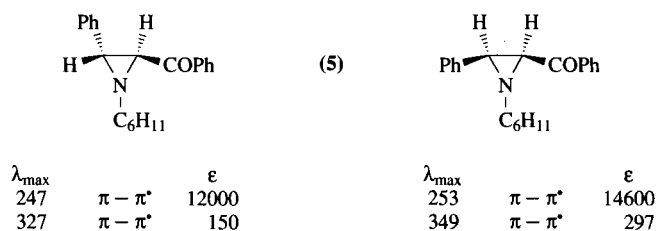


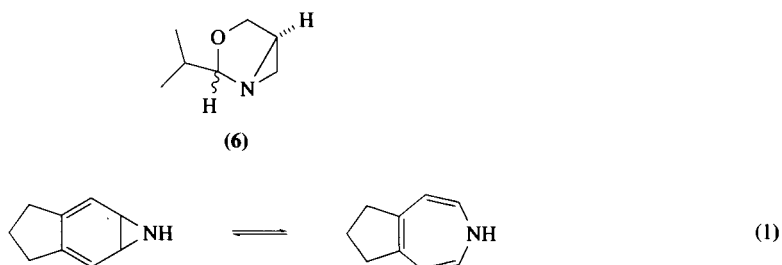
Figure 1

1.02.2.4 Infrared Absorption Spectroscopy

More attention has been devoted to the assignment of the fundamental vibrations of simple, low molecular weight aziridines <84CHEC-I(7)47>. Absorptions specifically attributable to the various modes of ring deformation have been assigned in the 1230–1250 cm^{-1} regions. On the other hand, 1-azirines exhibit absorptions very characteristic of the unsaturated ring. Alkyl and aryl substitution at C-2 gives rise to intense absorption (C=N stretching) at 1740 cm^{-1} and 1770 cm^{-1} . The fused-ring 2,3-hexamethylene-1-azirine shows the C=N stretching at 1760 cm^{-1} <67TL1545>.

1.02.2.5 NMR Spectroscopy

NMR spectroscopy is applied to the determination of the structure and stereochemistry of aziridines <84CHEC-I(7)47>. Protons attached to the parent aziridine ring carbon resonate at ca. δ 1.5 ppm and substituents almost invariably have a deshielding influence upon them. Hydrogen atoms attached to nitrogen tend to exhibit low δ values (ca. 1.0 ppm). It is frequently possible to assign ring stereochemistry on the basis of chemical shift data. Proton resonances in *cis* isomers appear at higher fields than do those of the *trans* isomers. For instance, the aziridine methylene protons have characteristic absorption at δ 1.76 (dd) ppm and 1.37 (d) ppm in *trans* (6) and at 1.48 (dd) ppm and 1.52 (d) ppm in *cis* (6). In each case both hydrogens exhibit a small coupling (3.5 Hz) to the vicinal methine proton while one of the hydrogens shows long-range coupling to one C_5 proton <88JOC27>. Low-temperature ^1H and ^{13}C NMR experiments on the rearrangement of tetrahydrocyclopentabenzene imine to cyclopentaazepine (Equation (1)) demonstrates that the free activation enthalpy of the valence tautomerization must be below 5 kcal mol^{-1} (21 kJ mol^{-1}) but that the nitrogen inversion can be frozen, with the *syn* isomer, that is H on N *syn* relative to the C—C bonds, predominating. *N*-Me and *N*-Cl substitution favors the closed valence tautomer while the *N*- CO_2Me group shifts the equilibrium towards the open isomer <89CB1765>.



1.02.2.6 Mass Spectroscopy

A systematic study of the behavior of simple monocyclic and fused aziridines towards electron impact shows strong parent mass peaks (usually more than 10% of the base peak intensity) and

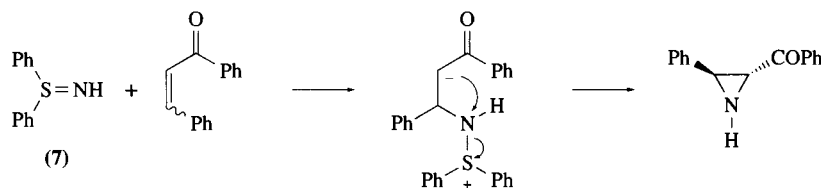
straightforward fragmentation patterns <89JOC3945>. The base peaks correspond to the mass of the *N*-substituted aziridines minus 1, perhaps due to the ring-opened imine radical cations. The parent alkene mass is always prominent, but for the parent nitrene mass a strong peak is not seen. Instead, the *N*-substituent of the aziridine breaks up in a fashion depending on its structure. If the substituent *Z* on the imine function ($C=NZ$) is methylsulphonyl, masses of 79 and 121 are observed, perhaps due to methylsulfonyl and methylsulfonyl isocyanate fragments. When *Z* is CN and RO is ethoxy, mass 70, corresponding to EtNHCN, is strong. The aziridine derived from cyclohexene also shows a strong peak at mass 69, which might be due to the cyclopentyl radical cation.

1.02.3 SYNTHESIS

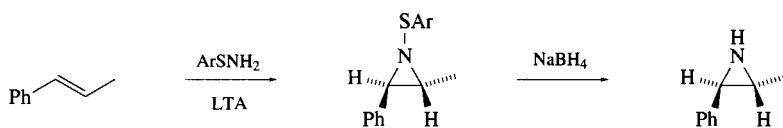
Extensive reviews covering many synthetic and mechanistic aspects of reactions leading to the synthesis of aziridines and azirine have been published <B-69MI 102-01, 84CHEC-I(7)47, 91COS(7)469>. Only those reactions to which a measure of generality and/or uniqueness can be assigned will be outlined in the following discussion.

1.02.3.1 Aziridine Formation from Alkenes

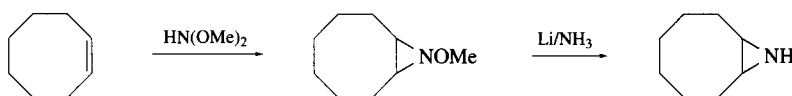
Several reagents effect the aziridination of alkenes directly <91COS(7)469>, for example, electrophilic alkenes react with diphenylsulfilimine (7) in good yield with the elimination of diphenylsulfide (Scheme 1) <88JCR(S)349>. *NS*-Aziridines are available by the oxidation of 2,4-dinitrobenzenesulfenamide in the presence of alkenes (Scheme 2) <79CC832>. Electron-rich alkenes are converted into *N*-methoxy aziridines by treatment with $HN(OMe)_2$ and trimethylsilyl triflate. The process is believed to generate *N*-methoxynitrenium ion $CH_3ONH^+F_3CSO_3^-$ *in situ* and allows stereospecific aziridination of electron-rich alkenes. Reduction with Li/NH_3 affords the *NH*-aziridine (Scheme 3) <90CC261>.



Scheme 1



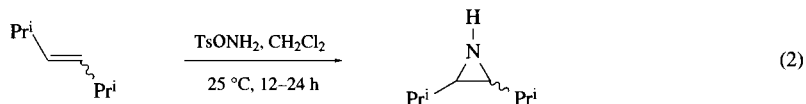
Scheme 2



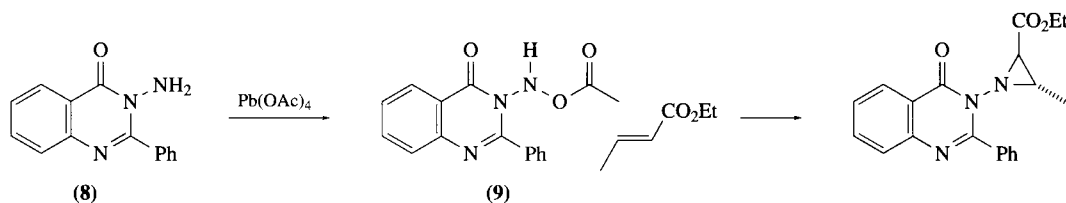
Scheme 3

Electron-deficient alkenes (e.g., $NCHC=C(COOMe)_2$) can be aziridinated with *O*-(aryl-sulfonyl)hydroxylamines <91COS(7)469>. The reaction is believed to involve a Michael addition followed by cyclization with expulsion of a sulfonate anion. Less electrophilic alkenes react in lower yield but with high stereoselectivity (Equation (2)). The chiral catalyst prepared from an optically active bisoxazoline and $Cu(I)$ triflate is effective in promoting the enantioselective aziridination of alkenes <93JA5328>. The addition of nitrosyl chloride to alkenes, which are especially susceptible to

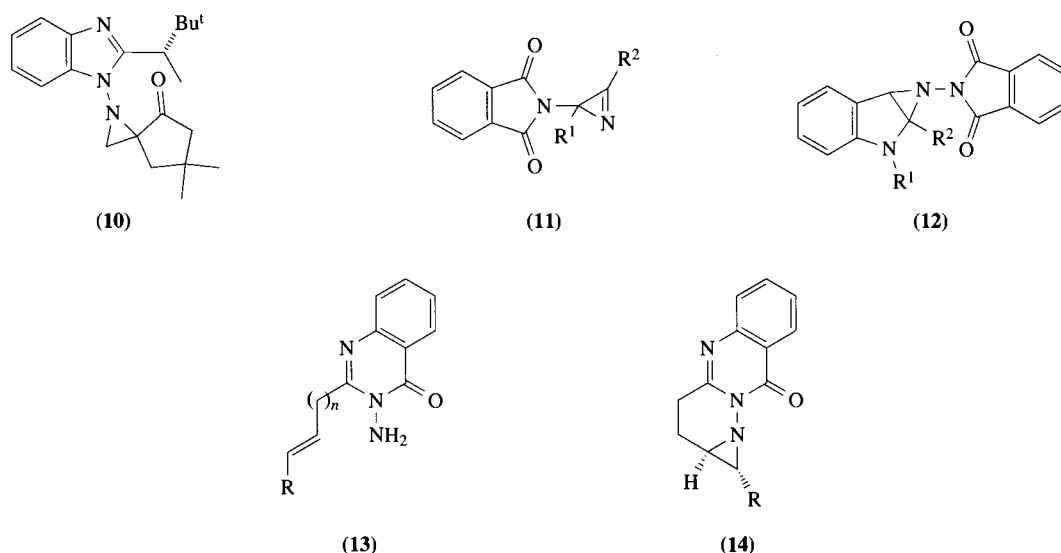
electrophilic attack (e.g., tetraalkyl-substituted alkenes) proceeds in the reverse regiochemical sense to give the vicinal chloronitroso alkanes which, after reduction with tin(II)chloride or LAH, can be cyclized to the aziridine $\langle 64\text{AG(E)}642 \rangle$.



Electron-deficient alkenes (i.e., α,β -unsaturated esters or ketones) can be aziridinated in good yields by oxidation of various *N*-aminoheterocycles $\langle 89\text{HCA}1095, 92\text{T}7713, 93\text{IJC(B)}1055 \rangle$. For example, LTA oxidation of *N*-aminoquinazolinone (**8**) brings about aziridination of alkenes via *N*-acetoxyaminoquinazolinone (**9**) and not through a nitrene intermediate (Scheme 4) $\langle 92\text{IJC(B)}456 \rangle$. Strong evidence for an *N*-acetoxy intermediate has been obtained for the *N*-aminophthalimide/ $\text{Pb}(\text{OAc})_4$ reactions $\langle 89\text{T}2875 \rangle$. Prior to 1987, these reactions were all assumed to occur via singlet nitrenes and indeed all the early evidence was consistent with this suggestion, except perhaps, in retrospect, the absence of products of C—H insertion. A promising start has been made in applying the LTA oxidation to chiral aminoheterocycles in the presence of achiral alkenes, leading to chiral aziridines via asymmetric induction, with compound (**10**) being obtained in 100% yield from the appropriate precursor $\langle 87\text{JCS(P1)}2787 \rangle$. Geraniol [$\text{Me}_2\text{C}=\text{CHCH}_2\text{CH}_2\text{C}(\text{Me})=\text{CHCH}_2\text{OH}$] is aziridinated at the 2,3-position due to hydrogen bonding while 2-geranyl chloride reacts preferentially at the 6,7-position $\langle 88\text{JCS(P2)}1517 \rangle$.



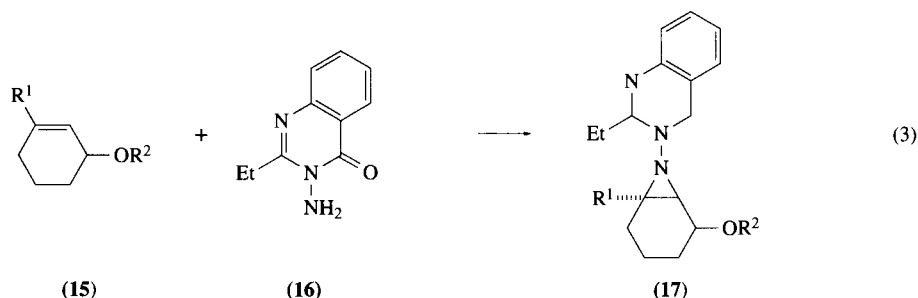
Scheme 4



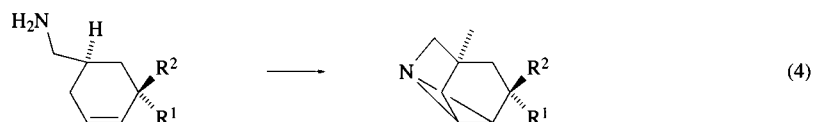
Oxidation of *N*-aminophthalimide with LTA in the presence of $\text{R}^1\text{C}\equiv\text{CR}^2$ gave 1-azirines (**11**) $\langle 86\text{MI } 102-01, 86\text{USP}4617398 \rangle$ as inseparable regioisomers. Phthalimidonitrene ($:\text{NPhth}$) generated from *N*-aminophthalimide and LTA in chlorobenzene was found to add to C_{60} , affording $\text{C}_{60}(\text{NPhth})_n$ ($n = 1-4$) $\langle 94\text{TL}4371 \rangle$. Reaction with indole gave fused aziridine (**12**) $\langle 87\text{H(26)}1257 \rangle$ while with tropone 8-azabicyclo[5.1.0]octa-3,5-dien-2-one was produced. Preferred nitrene addition to the 4,5 rather than the 2,3 double bond of tropone can be rationalized in terms of secondary MO interaction, which explains the differing effectiveness of various nitrene traps as well as the *syn* selectivity

observed in the addition of amino nitrene to the conjugated double bond. The tropone HOMO overlaps favorably at C-2 and C-7 with the nitrene LUMO giving two favorable secondary interactions which support the primary bond forming interaction at C-4 and C-5 of tropone <78CC404>. Oxidation of quinazolinones (**13**; R = H, Ph) with LTA in CH₂Cl₂ gave the corresponding aziridines (**14**) in 50% and 76% yield respectively, presumably via intramolecular trapping of *N*-nitrenes by the double bond <84JCS(P1)1905>. Competitive intramolecular trapping of the nitrene in 3-aminoquinazolinones with a bifurcated chain at position 2 showed that these reactions are non-concerted and occur via seven-membered transition states with the nitrene functioning as an electrophile.

Aziridination of cyclohexen-2-ol (**15**; R² = H) with 2-ethyl quinazoline-4-one (**16**) and LTA proceeds with high stereoselectivity *syn* to the OH group to give aziridine (**17**) (Equation (3)) <89CC562, 89JCS(P1)1515>. These results are analogous to epoxidation of alkenes using peracids. Aziridination of cyclohex-2-enyl acetate (or Me ether) proceeds stereospecifically *anti* to the AcO or MeO group to give aziridines. 3-Acetylamino-2-trifluoromethyl quinazoline-4(3*H*)-ones, prepared by LTA oxidation of corresponding *N*-amino-quinazoline, aziridinate cyclohexene in better yield with higher diastereoselectivity than the 2-ethyl derivatives <93CC1215>.

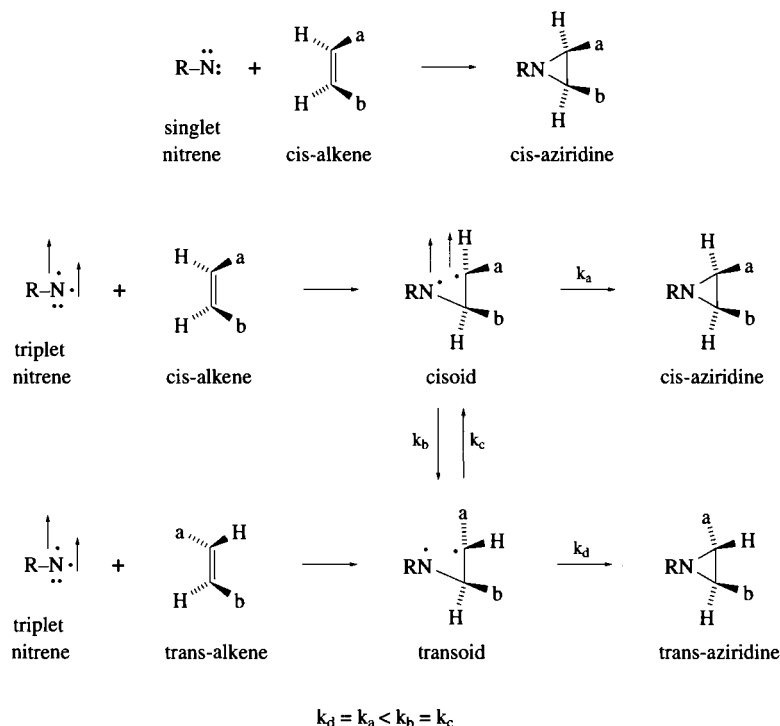


The electrophilic addition of singlet nitrenes, generated from organic azides, or from the 1,1-elimination from arylsulfonyl urethanes or from the oxidation of certain primary amines by NCS or LTA or mercury(II)oxide, to suitably substituted alkenes has been employed as a stereospecific entry to the aziridine ring system <B-70MI 102-01, 84CHEC-I(7)47>. For instance, intramolecular alkyl-nitrene addition to an alkenoic moiety situated δ,ϵ to the electron-deficient center has been utilized for the preparation of bi- and tricyclic aziridines (Equation (4)). The facility with which the initially formed singlet nitrenes undergo intersystem crossing to the triplet species (and therefore to nonstereospecific addition and competing abstraction and insertion processes) is dependent upon the nitrene substituent. Results from *cis* and *trans* alkenes show that all the nitrene is generated in the singlet state (which adds stereospecifically) but concurrent decay to the triplet state (1/30 as fast as addition) leads to loss of stereospecificity (Scheme 5) <91COS(7)469>. Thermolysis of ethoxycarbonyl azide also produces a singlet nitrene, however photolysis produces two-thirds singlet and one-third triplet, which sets an upper limit to the stereospecificity of the addition <91COS(7)469>. A fullerene urethan, C₆₀NCO₂Et was obtained by a one-pot reaction from C₆₀, NaN₃, ClCO₂Et, and 15-crown-5 ether in refluxing toluene <94CL561>.

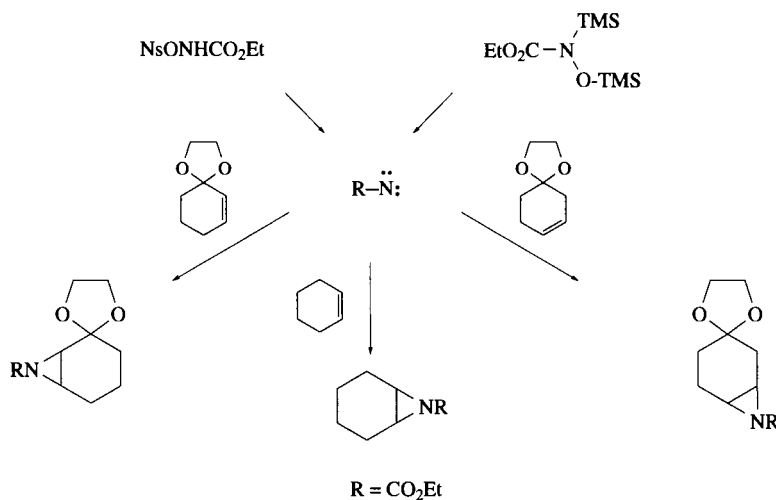


Ethoxycarbonyl nitrene (:NCO₂Et) is known to show good reactivity towards α,β -unsaturated esters, electron-rich alkenes especially enamines, enols, silyl enol ethers, and silyl ketone acetals <91T5877>, while with allylic ethers it reacts sluggishly <84TL4271>. Ethoxycarbonyl nitrene can also be generated and trapped as an aziridine by thermolysis of a bisilylated hydroxylamine <81JOC342> or by *N*-[(4-nitrophenyl)sulfonyl]oxy-carbamate (NsONHCO₂Et) in the presence of solid K₂CO₃ (Scheme 6) <93TL4353>.

N-Cyanoaziridines can be made from alkenes via either cyanogen azide or cyanonitrene <91COS(7)469>. Cyanogen azide adds to alkenes at 0–35°C giving transient triazolines, which decompose to alkylidenecyanamides, often with rearrangement (from simple alkenes) or to aziridines (clearly from polycyclic, strained or more highly alkylated alkenes) (Scheme 7) <72JOC2969>.



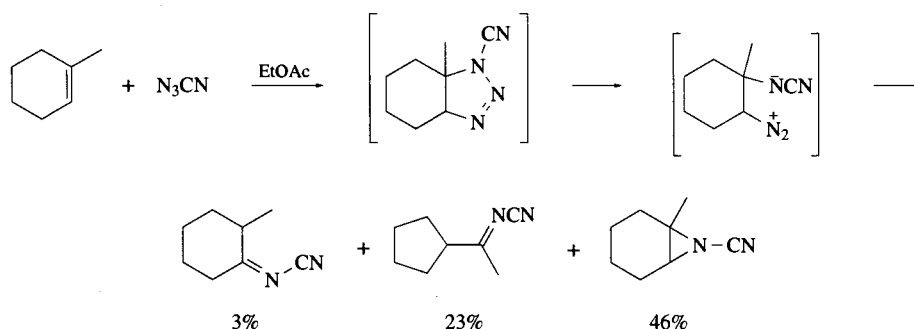
Scheme 5



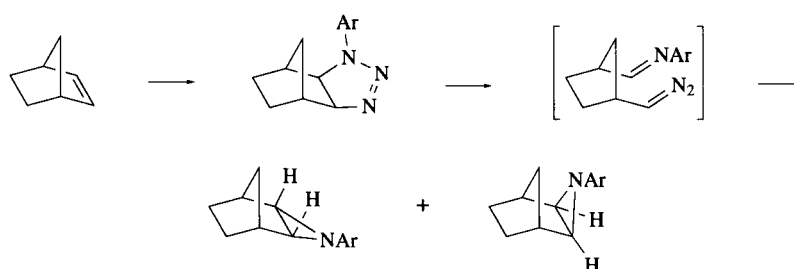
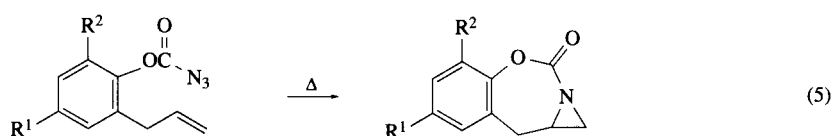
Scheme 6

[*N*-cyano]- and [*N*-(methylsulfonyl)alkoxy-carbimidoyl]nitrenes, generated *in situ* from the corresponding azides by 300 nm UV light, convert a variety of alkenes cleanly and stereospecifically to the corresponding aziridines (89JOC3945).

Thermolysis of an aryl azidoformate in tetrachloroethylene gave an aziridine while the same azide when decomposed in toluene gave a phenoxycarbonyl azepine (Equation (5)) (89CC730). Thermolysis of azidocinnamate with alkenic *ortho* substituents gave products such as isoquinolines, azepines, and aziridines formed by selective interaction of the nitrene derived from the azide with the alkenic substituent (86JCS(P1)1113). Norbornene-type systems form overwhelmingly the *exo*-triazolines with aryl azides, which on photolysis give *exo*-aziridines. Thermolysis of these triazolines occurs via a ring-opened intermediate and hence is not stereospecific (Scheme 8) (84AHC(37)217).

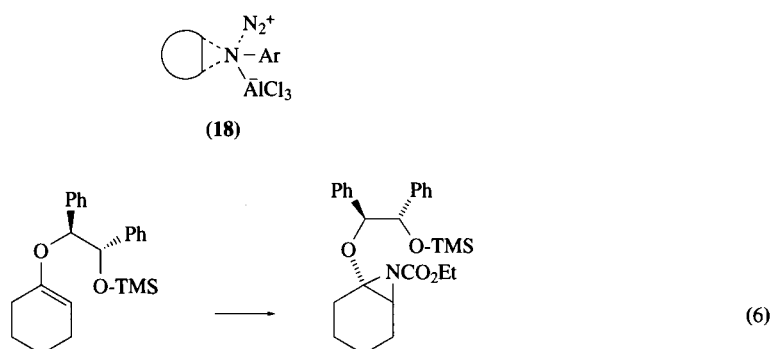


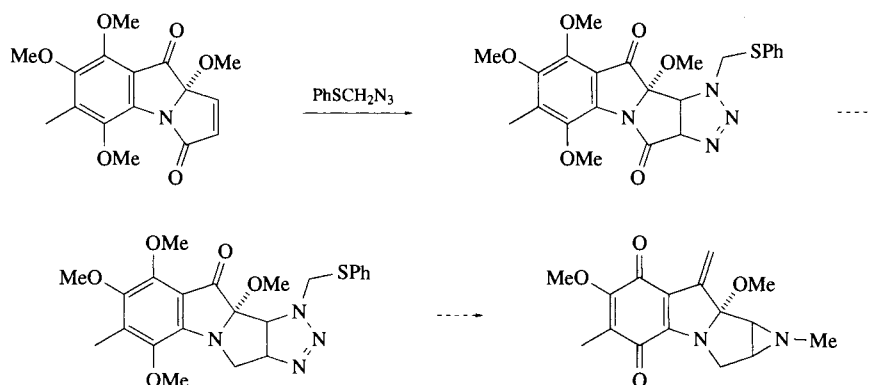
Scheme 7



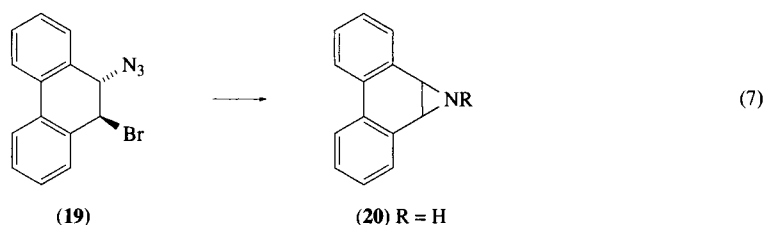
Scheme 8

Reaction of an aryl azide with cycloheptene or *cis*-cyclooctene in the presence of AlCl_3 gave the novel aziridine derivative 8-aryl-8-azabicyclo[5.1.0]octane or 9-aryl-9-azabicyclo[6.1.0]nonane respectively. The formation of aziridine or of ring-opened products was explained by a mechanism involving an aziridino- AlCl_3 complex (18) <90JCS(P1)321>. Attack of azidoformate on an enol ether carrying (*S,S*)-hydrobenzoin as a chiral auxiliary gave diastereomeric aziridination with a diastereomeric excess of 90% (Equation (6)) <91T5877>. The use of (benzenethio)methyl azide to build the *N*-methylaziridine unit is one of the crucial steps in the total synthesis of ($\pm$)-mitomycin K (Scheme 9) <92AG(E)915>. The bromo azide (19) formed via stereospecific addition of BrN_3 (Hassner reaction) to phenanthrene can be converted to aziridine (20; $\text{R} = \text{H}$) by treatment with LAH (Equation (7)) <71ACR9, 79T2901>. Similarly treatment of the isopentenoids geraniol, farnesol, and lanosterol with an excess of iodine azide and LAH results in the selective introduction of the aziridine function at the terminal and least hindered isopentenoid unit. Treatment of squalene in an analogous manner resulted in the formation of diepiminosqualene <88SC221>.



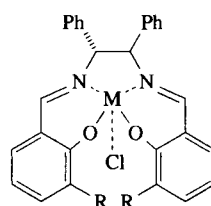
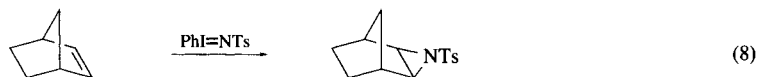


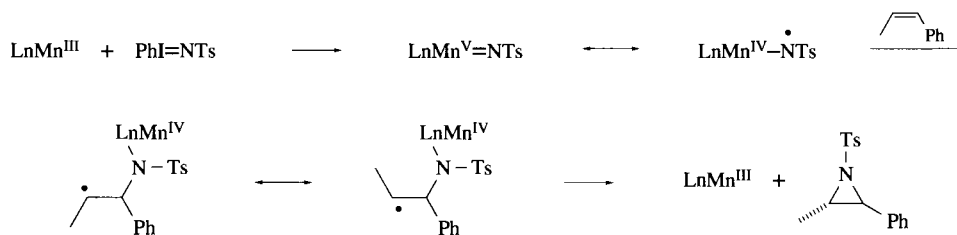
Scheme 9



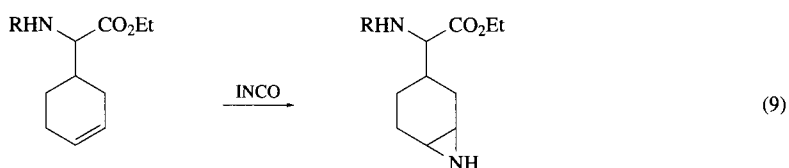
The β -iodoisocyanate obtained by addition of iodine isocyanate to alkenes can be transformed into aziridines via carbamates, amine salts, or bisulfite addition compounds $\langle 67\text{JOC}540 \rangle$.

Copper is superior to other metal complexes such as $\text{Mn}(\text{tpp})\text{Cl}$, $\text{Fe}(\text{tpp})\text{Cl}$, $\text{Rh}_2(\text{OAc})_4$, and $\text{Co}(\text{AcAc})_2$ in effecting the metal-catalyzed aziridination of both electron-rich and electron-deficient alkenes employing $[(N\text{-}p\text{-toluenesulfonyl})\text{-imino}]\text{phenyl iodine}$, $\text{PhI}=\text{NTs}$, as the nitrene precursor. This affords *N*-tosylaziridines in yields ranging from 55% to 95% (Equation (8)) $\langle 91\text{JOC}6744 \rangle$. Mansuy *et al.* disclosed that aziridination of a number of alkenes can be achieved with $\text{PhI}=\text{NTs}$ using $\text{Fe}(\text{III})$ - and $\text{Mn}(\text{III})$ -porphyrin as catalyst $\langle 84\text{CC}1161, 88\text{JCS}(\text{P}2)1517, 88\text{TL}1927 \rangle$. The copper(I) complex $\text{Tp}'\text{Cu}(\text{C}_2\text{H}_4)$ ($\text{Tp}' = \text{hydrotris}(3,5\text{-dimethyl-1-pyrazolyl})\text{borate}$) catalyzes nitrene transfer from $\text{PhI}=\text{NTs}$ to $\text{R}^1\text{-CH}=\text{CHR}^2$ [$\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Ph}$, Bu ; $\text{R}^1\text{R}^2 = (\text{CH}_2)_6$] to produce aziridines in high yield $\langle 93\text{OM}261 \rangle$. A photochemical reaction involves formation of a *N*-tosylaziridine from styrene or other alkenes with $\text{PhI}=\text{NTs}$ in the presence of 5 mol% metal(salen) complex (**21**). The reaction proceeds stepwise via the initial formation of a $\text{LnMn}(\text{V})=\text{NTs}$ species (Scheme 10) $\langle 92\text{TL}1001, 93\text{SL}469 \rangle$. Bis(oxazoline)copper complex is used as chiral catalyst for the enantioselective aziridination of alkenes $\langle 93\text{MI} 102\text{-}02 \rangle$. The compound (**20**; $\text{R} = \text{Ts}$) was prepared in 74% yield by treating phenanthrene with RSO_2NCl_2 in benzene containing CuCl and then with NaOH in dioxane $\langle 86\text{UKZ}1212 \rangle$. The synthesis of 3,4-(iminocyclohexyl)glycine and its *N*-benzyloxycarbonyl derivatives (an inhibitor for glucosamine synthetase) from cyclohexenylglycine was carried out via an addition reaction with iodine isocyanate (Equation 9) $\langle 85\text{MI} 102\text{-}01 \rangle$.

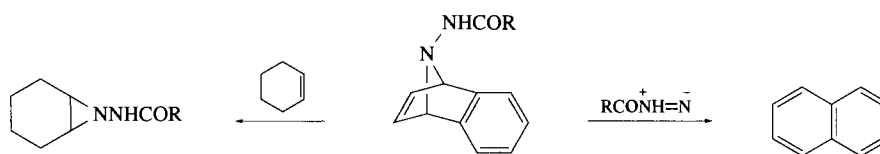
(21) $\text{R} = \text{TMS}$



Scheme 10



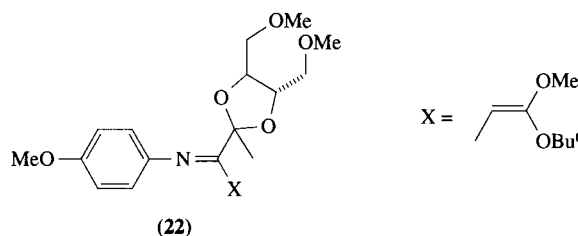
Thermolysis of azabenzonorbornadiene at 55°C generated $(\text{RCONH}=\text{N}^-)$ species, which were trapped by cyclohexene as azabicycloheptanes (Scheme 11) <88JOC6047>.



Scheme 11

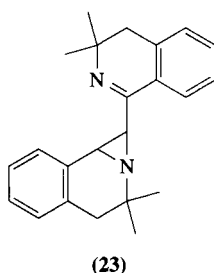
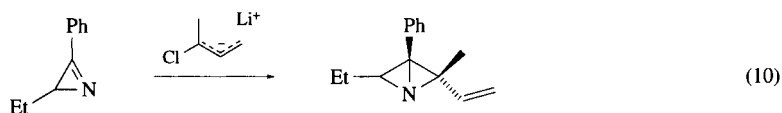
1.02.3.2 Aziridine Formation from Imines

A procedure has been developed which extends the Darzen synthesis to the preparation of aziridine esters and amides <69JOC2724>. Reaction of *N*-phenylbenzimine with ethyl chloroacetate in $\text{KO}^\text{t}\text{Bu}/\text{DMSO}$ results in the formation of a *trans*-aziridine in 29% yield <69JOC2724>, while with ethyl dichloroacetate in a protic media the reaction affords highly functionalized 1,3-diarylaziridines <85JOM(280)C11>. Addition of the lithium enolate of 2-halocarboxylic esters to *N*-trimethylsilylimines results in high *cis* selectivity in the formation of 2-aziridine derivatives in the Darzen fashion <91TL121>. The reactions of *gem*-chloro(methyl)alkyl lithium with aldimines and ketimines are efficient methods for the synthesis of 2-vinylaziridines <80JOM(202)233>. Optically active aziridines were prepared by the condensation of lithium or zinc enolate of α -haloacetate with a chiral imine (22) <92TL7903>.

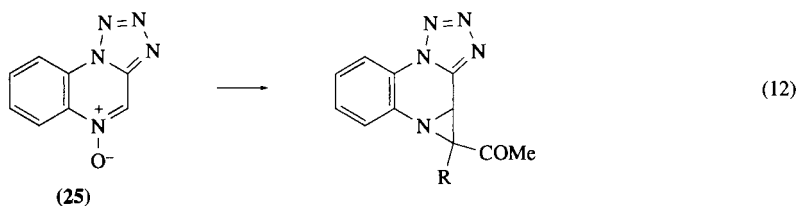
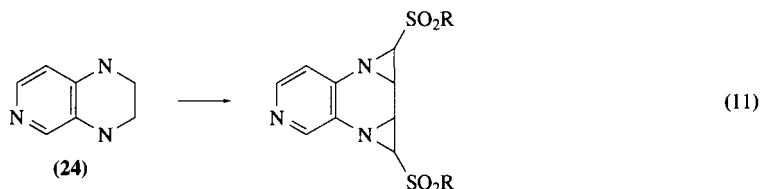


A method for the synthesis of *cis*-arylaziridines involves sequential condensation of substituted 1-chloroalkyl-*p*-tolyl sulfoxide and an aromatic imine, cyclization with $\text{KO}^\text{t}\text{Bu}$ and desulfenization with EtMgBr <88TL4093>. The reaction of $:\text{CCl}_2$ with dihydrobenzothiazepines affords azirino-benzothiazepines <92MI 102-01> while with dihydroisoquinoline, *gem*-dichloro-aziridino[2,1-*a*]isoquinoline is obtained in 81–100% yield <90KGS1086>. Addition of dihalocarbenes, generated from haloform using a phase-transfer catalyst, to 3*H*-1,5-benzodiazepine gives 2*H*-bisaziridino[1,2-

$\alpha:2',1'-d$ [(1,5)-benzodiazepines <87JHC797>, while a *N*-alkyl-1,4-benzodiazepine derivative gave 3*H*-aziridino-[1,2-*d*](1,4)-benzodiazepin-4(5*H*)-ones <93H(36)691>. Dihydro-1-benzoyl-1,5-benzodiazepines react with ethoxycarbonyl carbene to give 4*H*-azirino-[1,2-*a*](1,5)-benzodiazepine and an unexpected new ring system 1*H*-pyrrolo-[1,2-*a*](1,5)-benzoazepine <91MI 102-01>. Reaction of halogen-stabilized carbenoids with imines have been carried out using preformed lithium species (Equation (10)) <84TL843> or via a carbenoid generated from diiodomethane using zinc-copper (Simmons-Smith conditions) <72BSF825>. Carbenoid reaction of 1-(chloromethyl)-3,3-dimethyl-3,4-dihydroisoquinoline with ethyl magnesium bromide gave 66% of an aziridino[2,1-*a*]isoquinoline derivative (**23**) <92MI 102-02>.



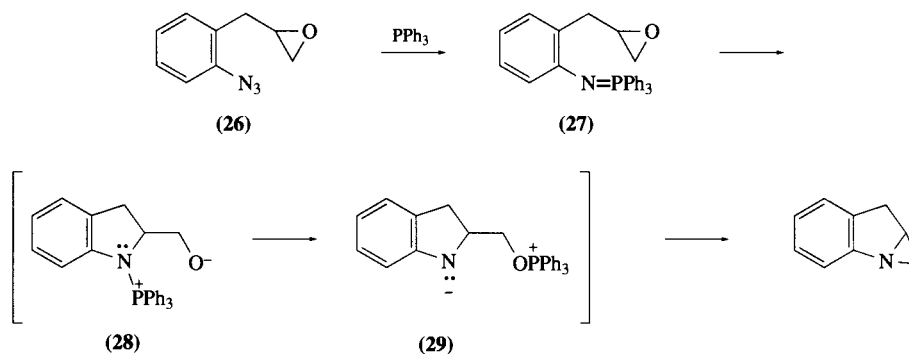
Carbanions of $R^1R^2CHSO_2R^3$ ($R^1 = H$, $R^2 = Cl$, Br , Ph , SPh , etc., $R^3 = Ph$, 4-Me- C_6H_4 -) react with 6-azaquinoxaline (**24**) to give bisaziridinoquinoxaline (Equation (11)) <88T1721, 91CB577>. Substituted aziridines were conveniently prepared by the addition of α -halosulfonyl carbanions to imines <84TL1949>. Reaction of diphenylsulfonium cyclopropanide with $R^1CH=NR^2$ gave azaspiropentanes <88MI 102-01>. Tetrazolo[1,5-*a*]quinoxaline-5-oxide (**25**) reacts with carbanions of 3-methyl- and 3-ethylpentane-2,4-dione to give a racemic mixture of the derivatives of the aziridinotetrazoloquinoxaline (Equation (12)) <90JCS(P1)3049>.



1.02.3.3 Aziridines via Intramolecular Cyclization

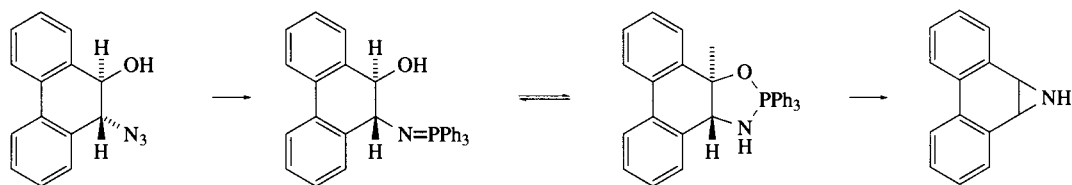
On treatment with Ph_3P , the epoxy azide (**26**) forms aziridino[1,2-*a*]indole via a Staudinger-type aminocyclization reaction <92TL2387>. A reasonable mechanism for the conversion of (**26**) to the final product involves the formation of the iminophosphorane (**27**) via a Staudinger reaction <81T437> as the first step. The strongly nucleophilic nitrogen atom opens the epoxide in a 5-*exo* fashion to generate the betaine (**28**) which undergoes a *N*-*O*-migration of the phosphorane to give (**29**). $Ph_3P=O$ is eliminated from (**29**) and the 1-azabicyclo[3.1.0]hexane ring system is formed via a S_N2 type cyclization (Scheme 12). The combination of epoxidation/Staudinger reaction on *o*-alkyl

phenyl azide provides a new entry for the preparation of aziridino[1,2-*a*]indole derivatives under mild conditions (92TL3261) and compares favorably with other synthetic methods.

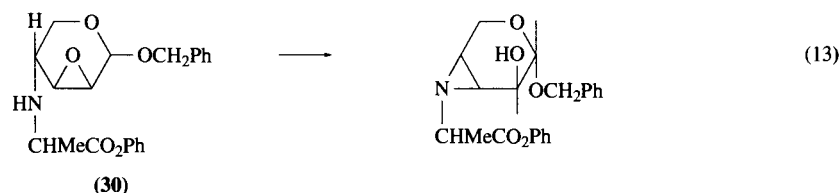


Scheme 12

Epoxides can be converted into aziridines with overall retention of configuration by using NaN_3 to form an azidoalcohol (inversion), which is converted into an aziridine by reaction with a tertiary phosphine (inversion) (78JOC4271) or with trialkyl phosphite (Blum synthesis) (91JHC473). It was shown that the formation of aziridine from 2-azido alcohols proceeds via 1,3,2-oxazaphospholidines (Scheme 13). On similar lines, the 1*a*,9*b*-dihydrobenz[*h*]azirino[*f*](1,10)-phenanthrolines were synthesized from the corresponding 2-azidoalcohol (90JHC1197). The reaction of *N*-tosyloxirane methylamines either with aqueous NaOH (92TL487) or with trimethylaluminum (92TL5351) affords aziridine methanols in excellent yields, through an intramolecular ring opening by the nitrogen atom of the tosylamino group (Payne-like rearrangement). Thus anhydrosugar (30) was isomerized to epiminopyranoside in 75% yield by passage of an ether solution of (30) through a column of SiO_2 (Equation (13)) (85GEP(O)3531102). The reaction of azido alcohols, their pivalate and methanesulfonates with triphenylphosphine (84HCA1238) or trialkyl phosphites (83HCA2467) gave aziridine derivatives (20; $\text{R} = \text{Ts}$).

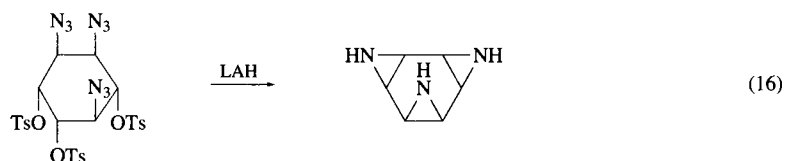
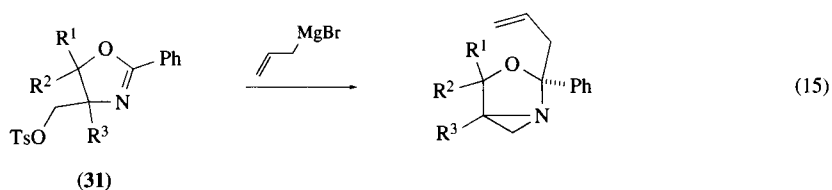
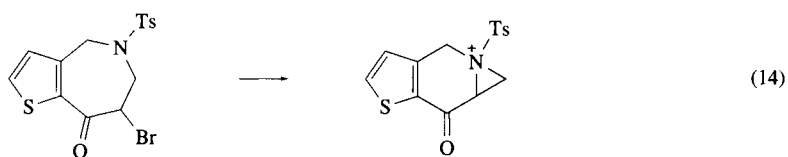


Scheme 13



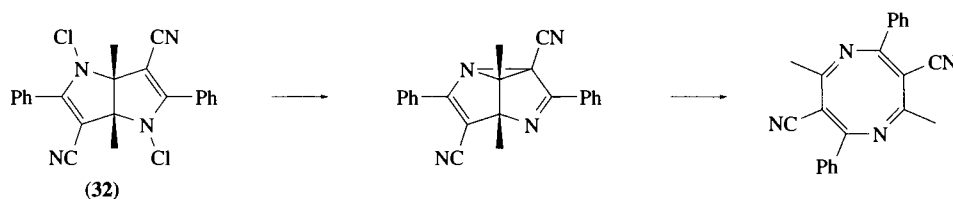
The most obvious and oldest approach to aziridine synthesis involves internal (neighboring group) cyclization of an amino group situated β to a leaving group. Amino alcohols suitable for aziridine synthesis are readily available from epoxides and occasionally from the reduction of α -aminoketones. Aziridine derivatives are prepared in high yield by intramolecular dehydration of an alkanolamine either in the gas phase (92JAP(K)04217659) or on treatment with diethoxy triphenyl phosphorane (86JOC95) or under Mitsunobu conditions (86H(24)2099, 94H(37)461). It is possible to convert an aminoalcohol to the corresponding tosylate or methanesulfonate ester. This variation has most often been applied to compounds that have bulky or electron-attracting groups on nitrogen because such groups inhibit reaction on nitrogen. Treatment of the mono- and dimesylate derived from *N*-diphenylmethyl-3-aminopropane-1,2-diols of high enantiomeric purity with Et_3N affords the

aziridines in a stereospecific fashion <91TL6935>. Neighboring group participation prevents nucleophilic substitution of a 2-amino-2-deoxy-3-*O*-mesyl- β -D-glucopyranoside with azide ions; instead they form aziridine derivatives (epiminoglucofuranosides) <85LA477>. During an attempted desotylation of a cyclic tosylamino α -bromoketone with ppa at 80°C for 30 h, a tricyclic aziridino compound was obtained in 63% yield instead of the expected free amine (Equation (14)) <80CL1389>. Treatment of the oxazoline (31) with allyl magnesium chloride in THF or ether gave an oxazabicyclo-[3.1.0]hexane as the only isolated product (Equation (15)) <90JOC6216>. The 1,2-cyclic sulfate of chiral diols reacts with RNH₂ or LiN₃ to form a β -aminosulfonate or β -azidosulfate respectively. These on reduction with LAH afford aziridine derivatives <89TL2623>. The reductive cyclization of a β -azidosulfate by LAH has been employed successfully for the preparation of the novel trishomoaromatic benzene triimine (Equation (16)) <73AG(E)989>.



The synthesis of aziridines from β -haloamines (Gabriel synthesis) is very general and has been used extensively.

Reductive dehalogenation of the dichloride (32) with magnesium affords the new stable diazoctatetraene (1,5-diazocine) via an aziridine intermediate (Scheme 14) <92TL8047>.

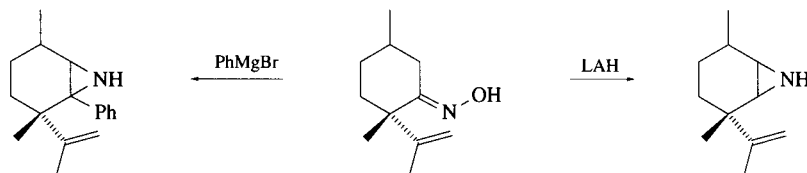


Scheme 14

1.02.3.4 Aziridines from Oximes

The reduction of oximes with LAH yields, in certain cases, aziridines instead of the expected amine. The reaction is stereoselective in that only the *cis*-aziridine is formed by reduction of the azirine intermediate <67TL1545, B-83MI 102-01>. The reaction of ketoximes with Grignard reagents has been extensively investigated and provides aziridines in low to moderate yields <73BSF2680>. The stereochemical preference for substituted aziridines is consistent with the formation of an azirine intermediate followed by addition from the less-hindered side of the ring. Azirine ring formation in turn occurs predominantly *syn* to the oxime hydroxyl group. Azabicyclo[4.1.0]heptanes related to pulegone were prepared by treating pulegone oxime with PhMgBr in refluxing THF or by LAH reduction (Scheme 15) <B-85MI 102-02>. Replacement of the oxime functionality with dimethyl

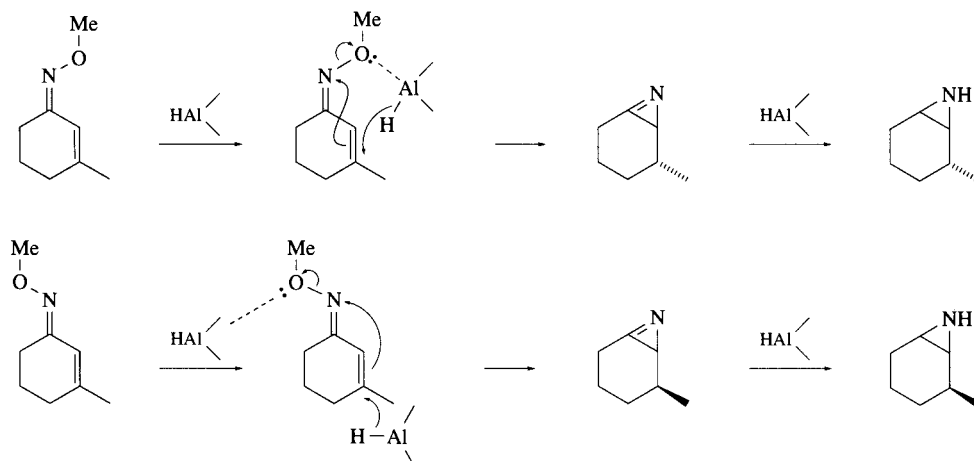
hydrazone methiodide provides in many instances superior yields of substituted aziridines <75TL355>. The reduction of representative conjugated cyclohexenone oximes with aluminum hydride in THF yields 2-cyclohexylamines and saturated aziridine-7-azabicyclo[4.1.0]heptane derivatives as the main reaction products <88PJC143>.



Scheme 15

The reaction of diborane with *O*-acetyl-3,5,5-trimethyl-2-cyclohexane-1-oxime depends on the configuration of the *O*-acetyl oxime as well as the reaction conditions <90PJC577>. It proceeds in two directions, the main reaction products being aziridines, amines, and amino alcohols. Regioselectivity of the reaction of diborane with α,β -unsaturated nitrogen derivatives in the cyclohexane system depends on electronic effects of the conjugated double bond system $\text{C}=\text{C}-\text{C}=\text{N}-$, as well as the inductive effect of the nitrogen atom. The stereochemistry of the reaction is influenced by steric factors <90PJC577>. The reduction of *O*-methyl oxime ethers with aluminum hydride in THF is superior to the reduction of their parent oximes with the same reagent or with LAH .

In contrast to the oximes which were reduced to a mixture of several products, *O*-methyl ethers gave two main products: alkyl amines and saturated aziridines. The reduction to aziridine-7-azabicyclo[4.1.0]heptane is highly stereoselective, depending on the oxime ether configuration (Scheme 16) <93HAC73>.

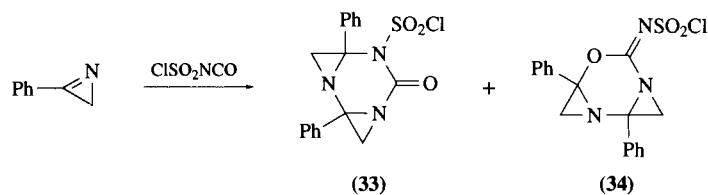


Scheme 16

1.02.3.5 Miscellaneous Syntheses

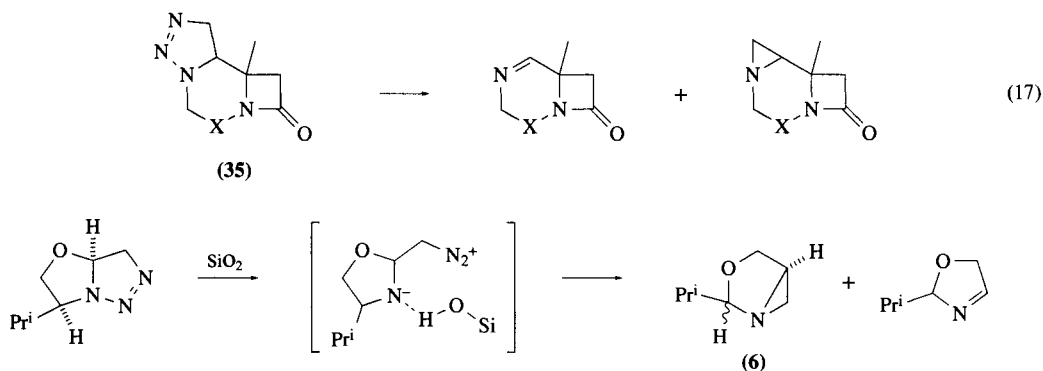
Methyl-2,3-dibromohexadecanoate on treatment with RNH_2 gave a mixture of *cis* and *trans* aziridine carboxylates <86IJC(B)536>. Chlorosulfonyl isocyanide reacts with azirines at -78°C to give tricyclic aziridines (33) and (34) (Scheme 17). *N,N*-Diaryl-*N'*-(2-chloroethyl)-phosphorotriamidate undergoes base promoted 1,3 and 1,5 cyclization yielding *N*-phosphorylated aziridines and 1,3,2-diazaphosphorolidines respectively. The former products are less stable toward bases while the latter undergo base-promoted ring contraction resulting in the isomeric aziridine derivatives <89TL2141>.

Logothetis studied the thermal intramolecular azide-alkene cycloaddition (IAAC) of 5-azido-5-methyl-1-hexene and observed the formation of a mixture of imines and aziridines <65JA749>. The first case of utilization of silica gel in the selective decomposition of triazoline (35) to pyridines and aziridines ($\text{X} = \text{CH}_2-\text{CH}_2, (\text{CH}_2)_3$) was reported by Murthy and Hassner (Equation (17)) <87TL97>. The role of silica gel in the chemoselective reaction is still obscure, but it is likely that acidic surface



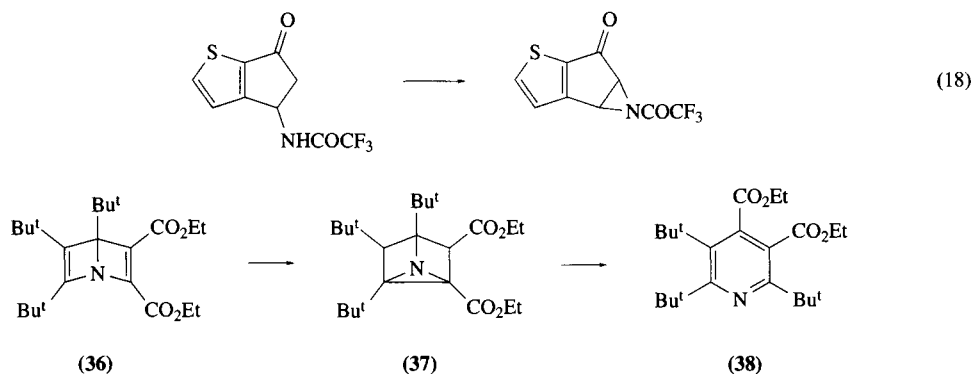
Scheme 17

sites catalyze the triazoline decomposition via an intermediate which prefers to close to an aziridine (6) (Scheme 18) <88JOC27>. Thermolysis of oxazolidines leads to azomethine ylides via a cycloreversion mechanism involving aziridine–azomethine ylide–enamine tautomerism <93BSF584>.



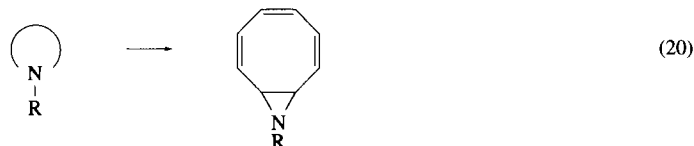
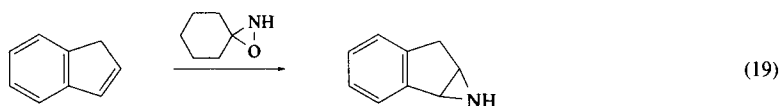
Scheme 18

A tetrahydrothieno(2',3':5,4)cyclopenta[2,3-*b*]-aziridine derivative was prepared by chlorination of thienocyclopentanone followed by ring closure (Equation (18)) <87H(26)1449>. When Dewar pyridine (36) is subjected to irradiation in deuteriohaloform, the azaprismane (37) is formed (92% yield) in a highly selective intramolecular [2 + 2] cycloaddition. The azaprismane (37) undergoes selective isomerization to the pyridine (38) in 1,2-dideuteriotetrachloroethane under both thermal (140°C) and photochemical conditions (Scheme 19) <89T3115>. Irradiation of 8-azatricycl[3.2.1.0 2,4]oct-6-enes in dry ether with a low-pressure mercury lamp gave azabishomobenzenes through a $(2\pi + 2\sigma)$ -type migration reaction between C—N bonds and alkene moieties <93CL757>.



Scheme 19

Oxaziridine unsubstituted at nitrogen as well as some *N*-acylated oxaziridines offer synthetic potentialities owing to their ability to transfer the nitrogen function to nucleophiles. For instance a tricyclic aziridine is obtained by simply heating indene with spirooxaziridine in toluene (Equation (19)) <74KGS1629>. The presence of continuous 8π -electron ribbon linked through the heteroatom renders the polyenic azonines with their tight undelocalized lone pairs, amenable to rapid 8π photochemical pericyclization to the *cis* (6.1.0) frame (Equation (20)) <72ACR281>.



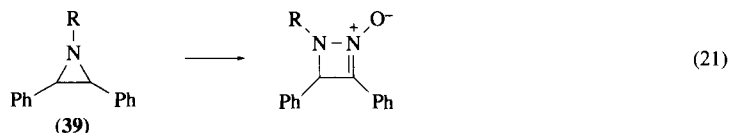
1.02.4 REACTIONS OF AZIRIDINES

The outstanding characteristic reactions of aziridines are their high reactivity to a wide variety of both electrophilic and nucleophilic reagents to give the more stable ring-opened or ring-expanded amines, a property that stems from the release of the strain energy inherent in a small ring. Aziridines may be classified into two groups: activated and simple aziridines. The former contain substituents capable of stabilizing a negative charge that is developed in the transition state during nucleophilic ring opening. The activated aziridines undergo ring-opening reactions with nucleophiles in the absence of catalysts while unactivated aziridines generally require acidic catalysts to promote the reaction.

1.02.4.1 Ring Expansion

Aziridines can be carbonylated to bicyclic β -lactams by exposing them to CO in the presence of a catalytic amount of $[\text{Pd}(\text{PPh}_3)_4]$ $\langle 82\text{OM}70 \rangle$. Depending on the organometallic reagents used, two different products can be obtained. Using a catalytic quantity of the rhodium complex (chlorodicarbonyl rhodium(I) dimer ($\text{Rh}_2(\text{CO})_2\text{Cl}_2$)), CO insertion occurs selectively into the more substituted C—N bond $\langle 83\text{JA}6737 \rangle$, whereas with stoichiometric amounts of $\text{Ni}(\text{CO})_4$, the less substituted C—N bond is carbonylated $\langle 88\text{CC}710, 90\text{JOC}2943 \rangle$.

Nitrosation of 2,3-diphenyl aziridine (**39**; $\text{R} = \text{Bu}, \text{CH}_2\text{Ph}$) in AcOH at 25°C gave the corresponding 1-alkyl-1,4-dihydro-3,4-diphenyl-1,2-diazete-2-oxide in 57% yield (Equation (21)) $\langle 91\text{JA}2308 \rangle$. Regioselective ring opening of *N*-tosylaziridines by $\text{Li}_2\text{Me}_2\text{Cu}$ followed by cyclization under mild conditions gives *N*-tosylazetidines $\langle 90\text{TL}1903 \rangle$. The zerovalent palladium complex $[\text{Pd}(\text{PPh}_3)_4]$ catalyzes the cycloaddition of trimethylenemethane to activated aziridines to afford 5-methylenepiperidines in high yield $\langle 89\text{JOM}(362)\text{C}18 \rangle$. Chiroselective synthesis of (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentane, a precursor for carbocyclic nucleosides involves the intramolecular cyclization of an ester enolate onto an activated aziridine $\langle 93\text{JOC}5019 \rangle$. Ring enlargement of *N*-acylaziridines followed by nickel peroxide oxidation provides a variety of 2,4-disubstituted 1,3-oxazoles suitable for *cis* and *trans* tris oxazole synthesis $\langle 94\text{TL}2039 \rangle$. Bis(benzonitrile)palladium dichloride is an effective catalyst for the cyclization reaction of aziridine and sulfur diimides in toluene affording imidazolidinethione in 52–70% yield $\langle 94\text{JA}1220 \rangle$.

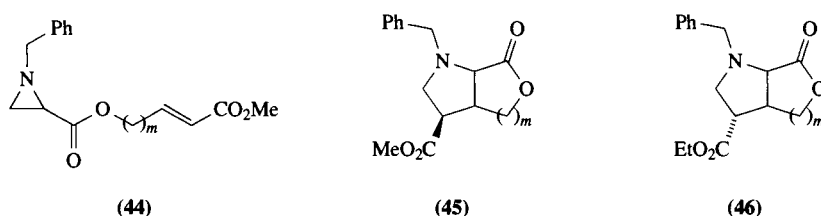
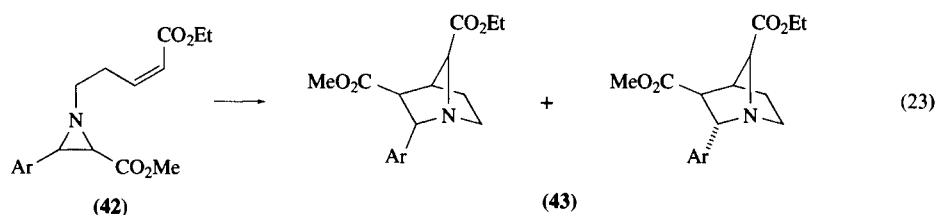
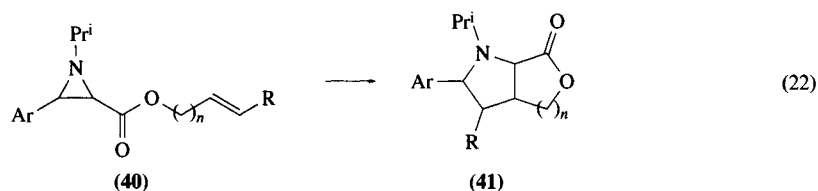


1.02.4.2 Dipolar Cycloadditions

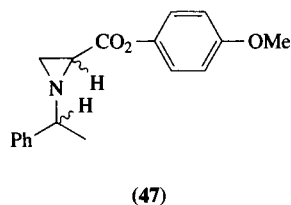
Cycloaddition reactions of aziridines have also been of considerable interest since the early 1980s, and the synthetic applications of these reactions have attracted a great deal of attention. Conclusive evidence has been presented that the reactions proceed via intermediate azomethine ylides, formed

from aziridines by conrotatory ring opening in a thermal process and disrotatory ring opening when photochemically generated.

An example of intramolecular cycloaddition involving an azomethine ylide utilizes aziridine derivatives bearing an ester-activated alkene as a dipole trap <89AHC(45)231>. Thus heating either *cis*- or *trans*-aziridine (**40**; R = CO₂Me, *n* = 1) in benzene produces a high yield of *cis*-fused bicyclo[3.3.0]octanelactone (**41**; R = CO₂Me, *n* = 1) as a sole product (Equation (22)) <79JOC255>. Exclusive formation of (**41**) indicates the selective participation of an antidipole in the stereospecific cycloaddition. This intramolecular cycloaddition is somewhat slower than expected. The slow rate is evidenced by the competitive intermolecular cycloaddition using DMAD. When an alkene chain is on the aziridine nitrogen (**42**), the bicyclic system (**43**) with a bridgehead nitrogen is formed (Equation (23)). Aziridine (**40**; R = CO₂Me, *n* = 2) having an activated alkene chain longer by one carbon gives the *cis*-fused bicyclo[4.3.0]nonane (**41**; R = CO₂Me, *n* = 2) and again an antiylide has been selectively formed from either *cis* (**40**) or *trans* (**40**). Ring opening of the aziridine (**44**) in which the aryl substituent on the ring is missing is very difficult under the usual thermal conditions, and a flash vapor pyrolysis had to be applied <85JOC2309>. Mostly *cis*-fused bicyclic lactones (**45**; *m* = 2) and (**46**; *m* = 1) were obtained from (*E*)-(**44**) and (*Z*)-(**44**) respectively, regardless of the presence of an activating substituent.

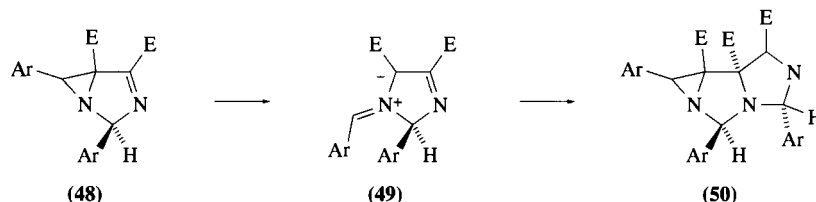


Both diastereomeric aziridines (**47**), upon heating with vinylene carbonate, furnished four readily separable diastereomeric pyrrolidine esters which were transformed into both enantiomers of 1,4-dideoxy-1,4-iminoxylitol and 1,4-dideoxy-1,4-iminoribitol <92TA681>. 3-Phenyl and 3-unsubstituted 2-alkenoyl-methylaziridines synthesized via Grignard reaction from the corresponding cyanoaziridines have been thermally transformed into ring-fused pyrrolidine compounds via azomethine ylide intermediates <85JOC4114>.

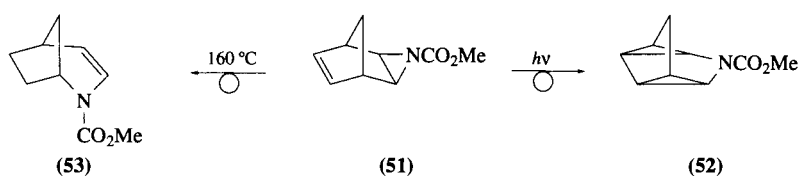


A ring-fused aziridine (**48**), in which the Ar and ester groups are *cis*, undergoes a stereospecific conrotatory ring opening leading to (*E*),(*Z*)-azomethine ylide (**49**), which is trapped with an aziridine

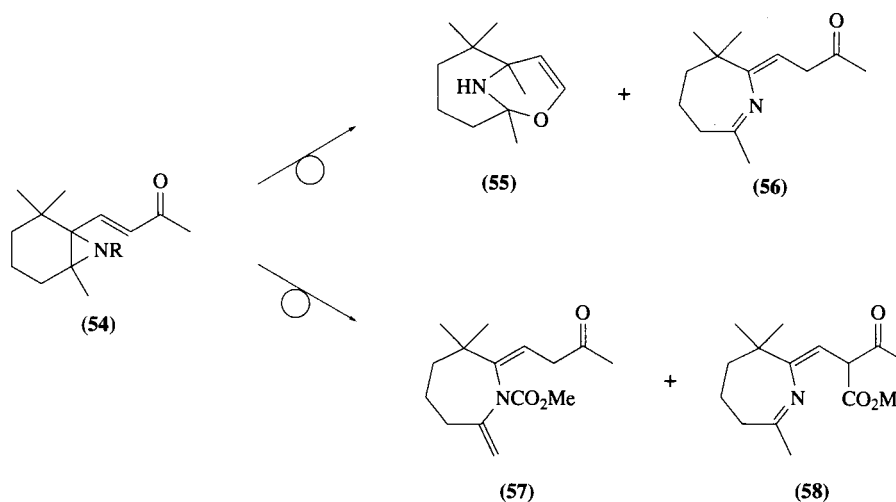
in a stereo and face selective fashion providing the tricyclic product (**50**) (Scheme 20) <86JCS(P1)1119>. Photolysis of aziridine (**51**) leads to the fused ring system (**52**) via an intramolecular 1,3-cycloaddition reaction <71AG(E)273>. Conrotatory ring opening is obviously restricted by the ring system and in contrast to photolysis, heating (**51**) at 160°C gives the rearranged product (**53**) (Scheme 21). On irradiation at -20°C , 5,6-epimino-5,6-dihydro- β -ionone (**54**; R = H) rearranges to the products (**55**) and (**56**) while (**54**; R = CO₂Me) undergoes rapid (*E*)/(*Z*) isomerization and slow rearrangement to azepine (**57**) and (**58**) (Scheme 22) <86HCA692>.



Scheme 20



Scheme 21

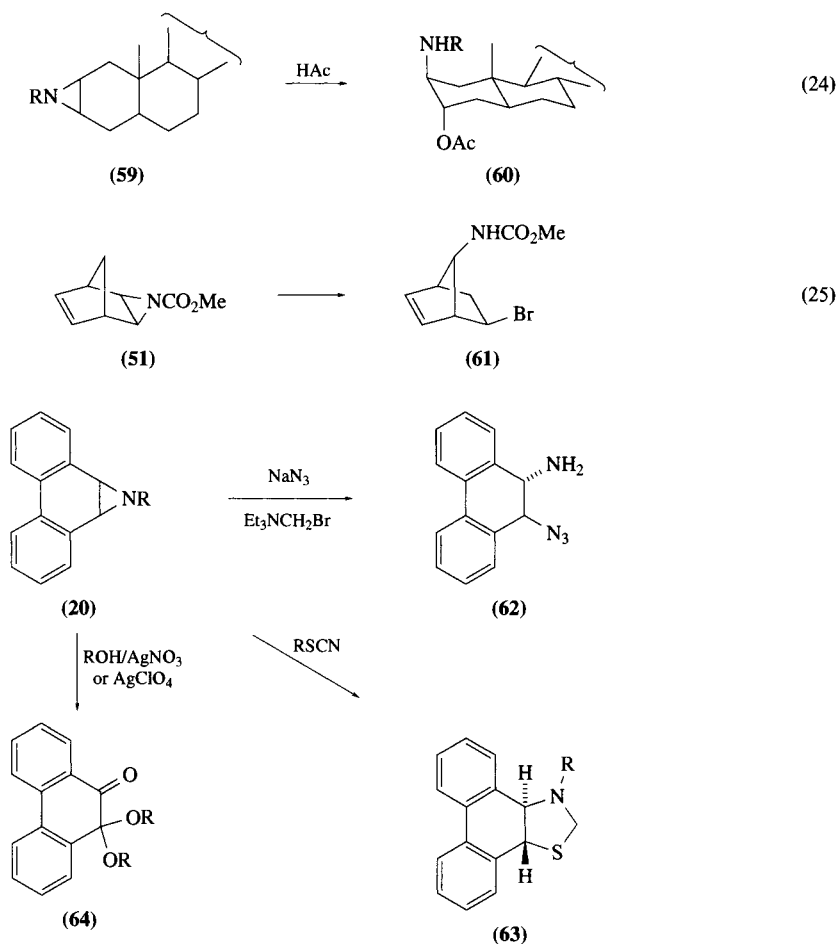


Scheme 22

1.02.4.3 Ring-opening Reactions

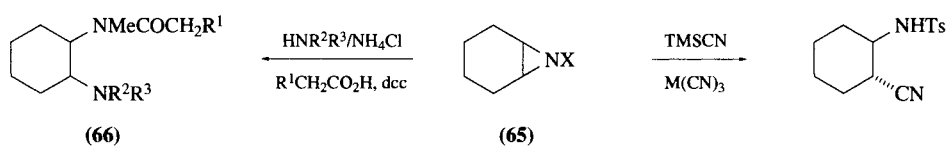
Ring-opening reactions of aziridines, which are initiated either by electrophilic reagents or by nucleophilic reagents generally occur stereospecifically with inversion of configuration at the point of attack. The reductive opening of aziridine with lithium in the presence of a catalytic amount of naphthalene at -78°C leads to the corresponding dianionic intermediate. This is stable under these conditions and reacts with a variety of electrophilic reagents to give the corresponding difunctionalized compounds <94JOC3210>. Acid-catalyzed ring opening of rigid steroidal aziridine (**59**) results in *trans*-diaxial ring opening to give (**60**) (Equation (24)) <84CHEC-I(7)47>. In some cases, for instance (**51**), the intermediate carbocation undergoes rearrangement to give (**61**) (Equation

(25)) <87S1097>. Reactions of phenanthrene-9,10-imine (**20**; R = H) with nucleophiles like NaN_3 or RSCN under phase-transfer conditions gives compounds (**62**) and (**63**) respectively <84JHC1597>, while (**20**; R = Cl) undergoes an unusual transformation to 9,10-phenanthroquinone dialkyl monoacetal (**64**) in a silver-promoted reaction (Scheme 23) <84JHC1593>.



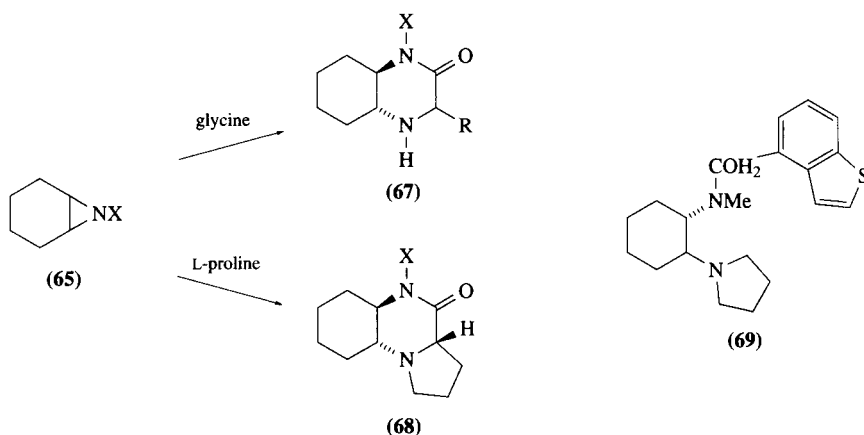
Scheme 23

Analgesic opiate kappa-agonist (**66**; R = Ph, 2- or 4- ClC_6H_4 -, 3,4- $\text{Cl}_2\text{C}_6\text{H}_3$ -; NR^2R^3 = pyrrolidino, piperidino, morpholino, piperazino) was prepared in 60–82% yield by treating aziridine (**65**; X = Me) with HNR^2R^3 in water containing NH_4Cl followed by reaction with $\text{R}^1\text{CH}_2\text{CO}_2\text{H}$ in THF containing dcc (Scheme 24) <89JMC1620, 91MI 102-02>. Reaction of *N*-tosyl aziridine (**65**; X = Ts) with cyanotrimethylsilane in the presence of lanthanide tricyanide gives *N*-tosyl- β -aminonitrile by attack of cyanide at the less-substituted ring carbon. An optically pure 2-substituted aziridine affords the corresponding aminonitrile with complete retention of the stereochemistry at the stereogenic center <90TL6379>. Since optically pure aziridine derivatives can be derived from α -aminoacids, stereoselective ring-opening reactions have been reported to give important chiral intermediates in organic synthesis <90TL1903>.



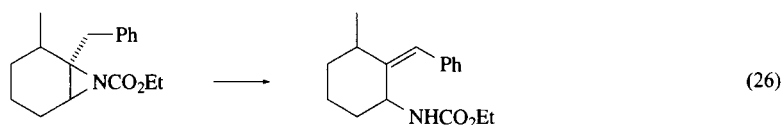
Scheme 24

The *trans* perhydroquinoxalinones (**67**; X = H, Me; R = H, Me, PhCH₂) and the perhydropyrroloquinoxalin-4-ones (**68**; X = H, Me) are prepared via a ring-opening and spontaneous ring-closure reaction of the bicyclic aziridine (**65**; X = H, Me) with α -aminoacids (glycine, L-alanine, L-proline and L-phenylalanine) <87JHC1297>. This method was used to prepare the rigid kappa-opioid compound analogue (**69**) (Scheme 25).



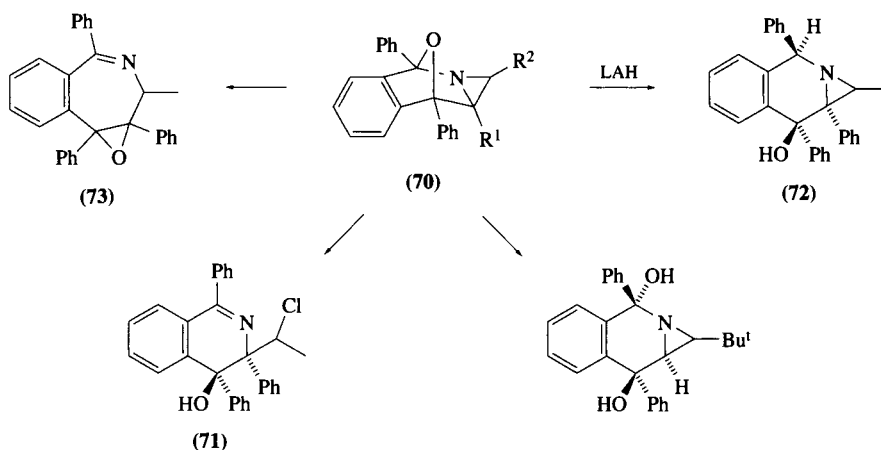
Scheme 25

N-Carbethoxyaziridines can be converted into vinyl urethanes by thermolysis in benzene at 200–250 °C <88MI 102-02>. Thermal rearrangement of a trisubstituted cyclic *N*-carbethoxyaziridine is regiospecific (Equation (26)) <84JCR(M)354> and afforded an allylcarbamate, which was then hydrolyzed to a primary allylic amine. The isomerization of achiral aziridines to optically active allylic amines was achieved by vitamin B₁₂ <93HCA2602>. 1-Alkyl and 1-arylmethyl-2-(bromomethyl) aziridines are readily cleaved to allylamine by the sonochemical zinc–copper couple in aqueous methanol at room temperature <94CC1221>. Radical-induced cleavage of substituted aziridines proceeds well to form the aminyl radicals selectively. Such aminyl radicals cyclize to give pyrrolidines <90CC434, 92T1317>. The cycloadduct (**70**) undergoes a number of interesting reactions involving both the oxide bridge and the aziridine C—N bonds. Thus when (**70a**; R¹ = Ph, R² = CH₃) was treated with anhydrous HCl in benzene the hydrochloride salt (**71**) was isolated, while reductive cleavage of adduct (**70a**) with LAH gave the benzoazanorbornane (**72**). An unusual isomerization reaction, reported by Hassner and Anderson <74JOC2031>, took place when (**70a**) was stirred in benzene with Woelm neutral alumina, to be converted in good yield to azepine (**73**) (Scheme 26). Tris-X, a new high-energy polynitramine explosive was prepared via the ring-opening product nitramine-nitrate from an aziridine by treatment with dinitrogen pentoxide <93MI 102-01>.



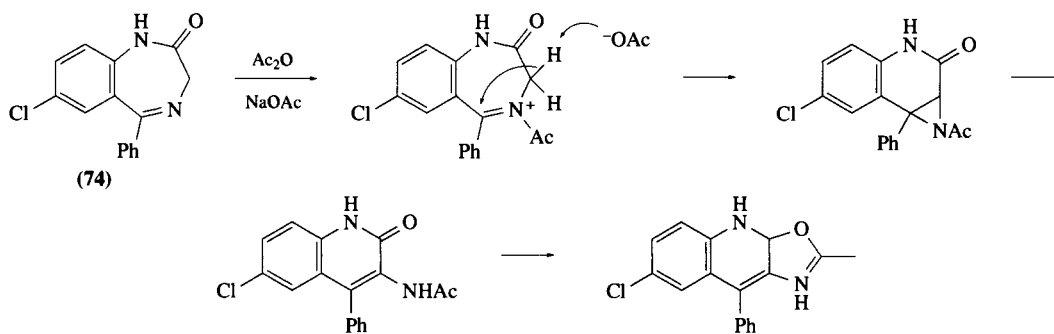
1.02.4.4 Rearrangements

Reaction of *N*-carbethoxy-8-azabicyclo[5.1.0]oct-3-ene with dichlorobis(benzonitrile)palladium(II) results in essentially quantitative rearrangement to *N*-carbethoxynortropidine. The rearrangement is catalytic and is believed to proceed in four steps: (i) formation of palladium π -complex with aziridine, (ii) attack of chloride on the aziridine ring to cleave one C—N bond regioselectively, (iii) regioselective intramolecular attack of N—CO₂R on the alkene coordinated to palladium, and (iv) 1,3 Pd—Cl elimination or 1,2 Pd— π elimination/addition or 1,2 Pd—Cl elimination <76JA4168>. 1,3-Butadienyl aziridines activated by an *N*-tosyl group smoothly rearrange to vinyl pyrrolidine derivatives in the presence of Pd(PPh₃)₄ <85TL857>.

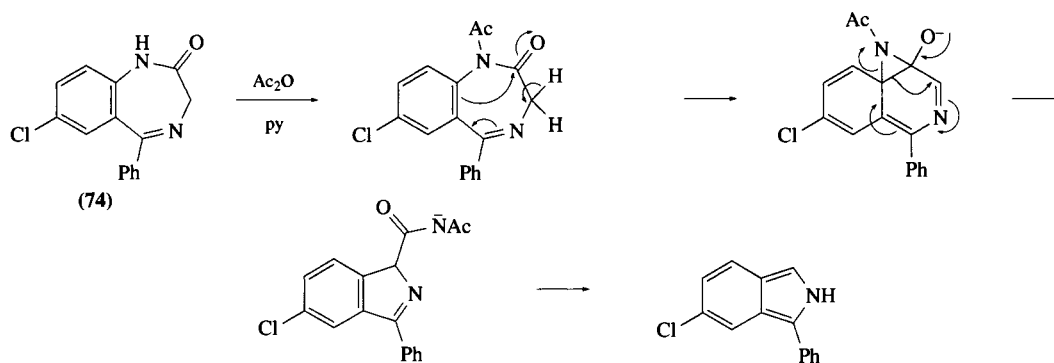


Scheme 26

The reaction of (74) with acetic anhydride leads to two types of rearrangement, both via an aziridine intermediate. In the presence of sodium acetate the oxazoloquinoline is formed (Scheme 27) but in pyridine a different ring contraction gives the isoindole (Scheme 28) <76JHC1165>.

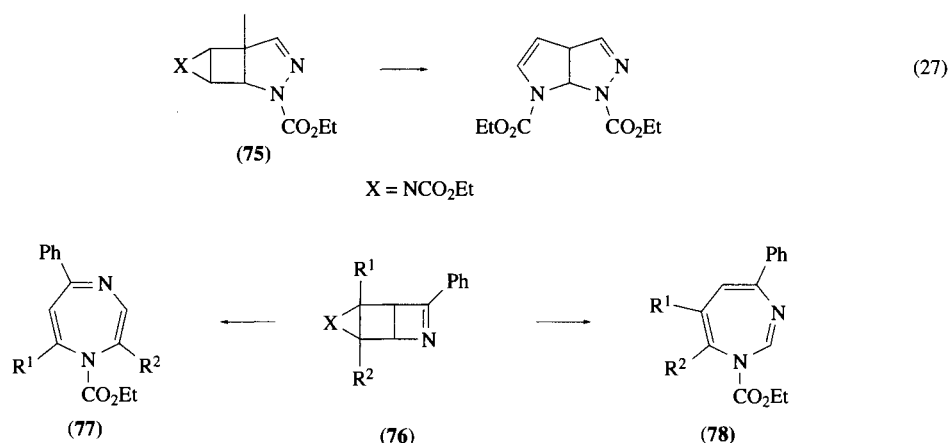


Scheme 27

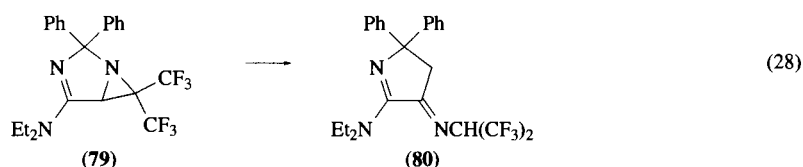


Scheme 28

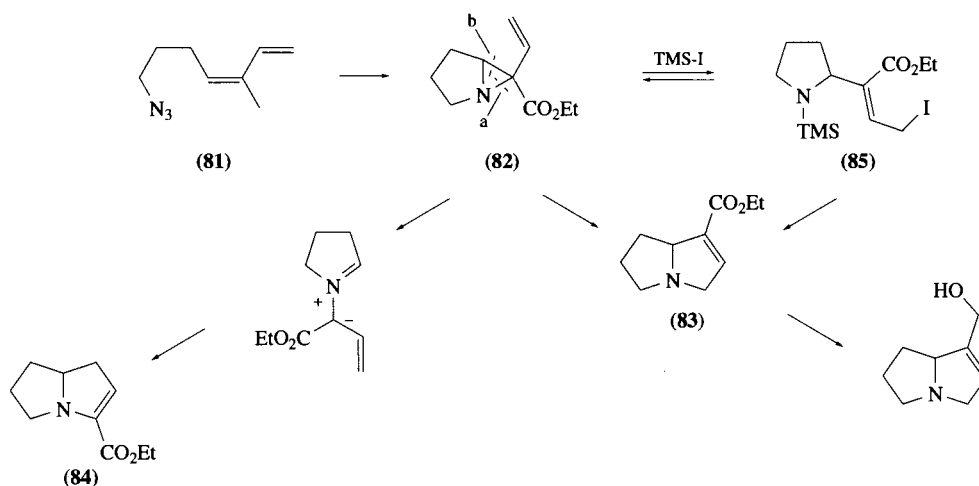
On flash vacuum pyrolysis (FVP) 8-aza-analogues of oxadiazatricycloenes (75) undergo rearrangement to give a dihydropyrrolopyrrazine (Equation (27)) <87H(26)2861>, while photochemical ring opening of diazatricycloheptanes (76; X = NCO₂Et, R¹ = R² = H, Me; R¹ = Me, R² = H) gave diazepine (77) in 65–95% yield <87CPB3166>. Thermolysis of (76; R¹ = R² = Me) gave rearranged diazepine (78) in 49% yield (Scheme 29). Diazabicyclohexene (79) on thermolysis undergoes rearrangement to give pyrroline (80) (Equation (28)) <86CZ265>. It was known that pyrrolytic elimination of CO₂ from 5-substituted 4,4-diphenyl-3-oxa-1-azabicyclo[3.1.0]hexan-2-ones (bicyclic carbamate) leads to azabicyclobutanes. Rearrangement of this compound under FVP conditions gave 3-substituted-4-phenyl quinazoline <93TL3471>.



Scheme 29



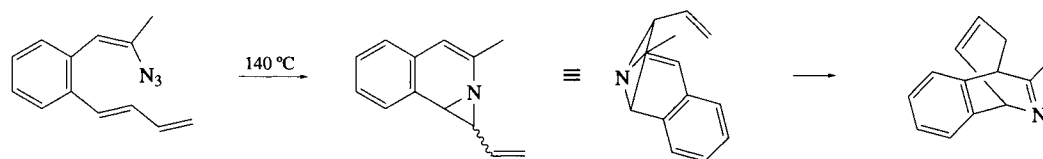
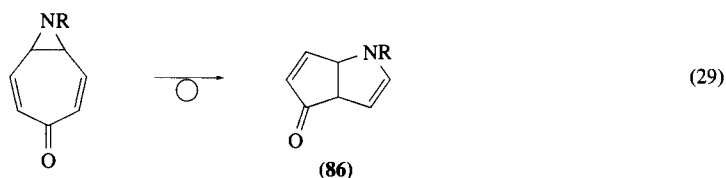
Intramolecular 1,3-dipolar cycloaddition of azide **(81)** proceeds through a triazoline and vinylaziridine **(82)** and results in the formation of tetrahydropyrrolizidine **(83)** and **(84)**. This represents a formal total synthesis of supinidine. Thermolysis of vinyl aziridine **(82)** leads to pyrrolizidine **(84)** probably via azomethine ylides, while the nucleophilic opening leads exclusively to **(83)** through an intermediate allylic iodide **(85)**. The latter is produced as a mixture of (*E*) and (*Z*) isomers but is converted to **(83)** via an equilibrium and recyclization of the (*Z*)-isomer (Scheme 30) <85TL3523, 85TL3527>.



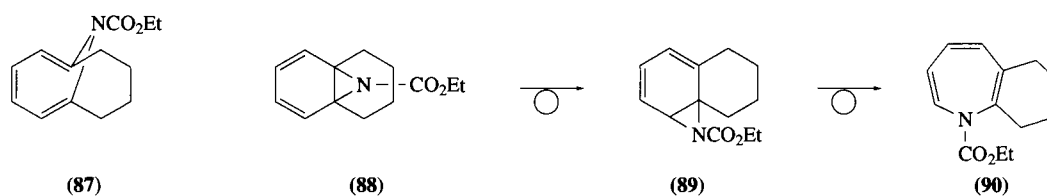
Scheme 30

Thermal and photochemical rearrangements of the 8-azabicyclo[5.1.0]octadienone derivatives at 80°C proceed through C—C bond cleavage to give **(86)** (Equation (29)) <78CC404>. The thermal decomposition of vinyl azides, notably α -azidocinnamate (3-aryl-2-azidopropionate ester), has been used for the construction of *N*-heterocycles such as indole, isoquinolines, and benzazepines <88CRV297>. The actual decomposition process, with loss of N_2 , was shown to involve the intermediacy of an aziridine which is in equilibrium with the corresponding vinyl nitrene, for instance the construction of the 6-aza-bicyclo[7.2.2]nonane skeleton was achieved by a new tandem aziridination/3-aza-Cope rearrangement sequence employing the intramolecular reaction of a vinyl azide with a 1,3-diene (Scheme 31) <89TL1789>. Thermolysis of the bridged azepine **(87)** and the

structurally related benzeneimine (**88**) results in isomerization in high yields to the new bicyclic azepine (**90**) (Scheme 32) <81H(15)1569>. A mechanistic rationale involving either a concerted suprafacial sigmatropic or diradical-1,5-nitrogen shift of benzeneimine (**88**) followed by electrocyclic ring opening of the new isomeric benzeneimine (**89**) is proposed.

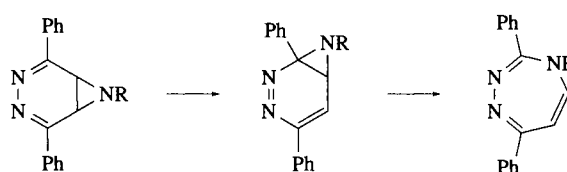
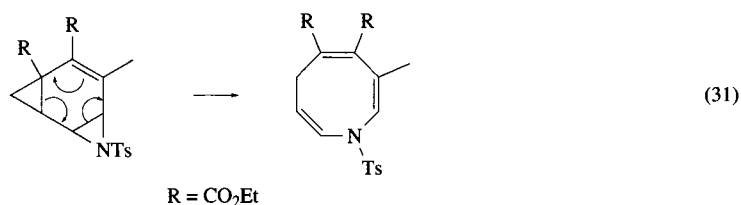
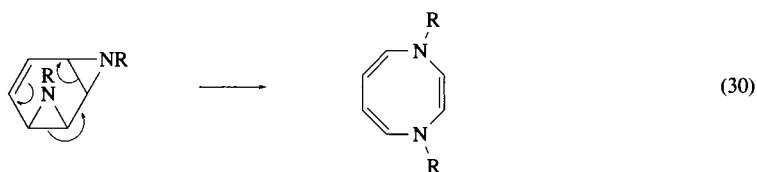


Scheme 31



Scheme 32

A general approach to 1,4-diazocine is provided by the valence isomerization of benzene diimines via retro Diels–Alder conversion (Equation (30)) <78AHC(23)55> while *cis*-azabishomobenzene at 125 °C gave 1-sulfonyl-1,6-dehydroazocine dicarboxylates (Equation (31)) <76CB3505>. The 4*H*-1,2,4-triazepine system can be prepared via a photochemical walk rearrangement of 3,4,7-triaza-2,6-norcaradiene (Scheme 33) <76TL2459>.



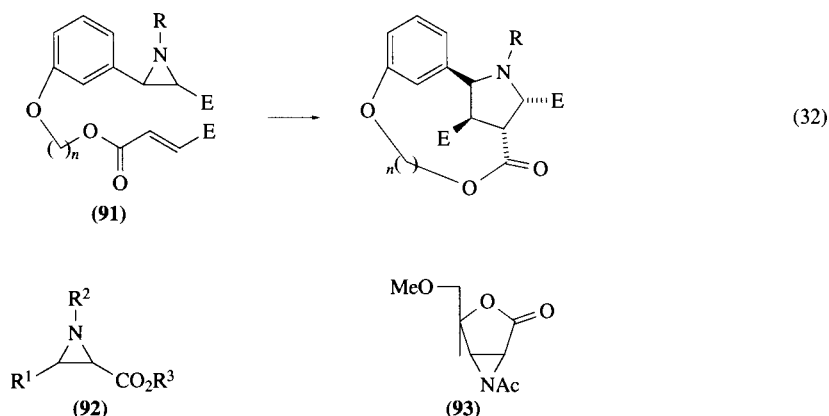
Scheme 33

1.02.5 AZIRIDINE-2-CARBOXYLATES

Stereochemically well-defined aziridine-2-carboxylates are proving to be useful intermediates for the synthesis of modified optically active aminoacids. Either substituted α -aminoacids <82BCJ3049, 89TL4073, 90CPB564> or β -aminoacids <87CC153, 89CC1852> may be prepared by nucleophilic attack on the aziridine ring at C-3 or C-2 respectively. Ring opening is promoted by Lewis acids and the presence of an electron-withdrawing group on the nitrogen atom. The large number of nucleophiles which have been employed for this reaction (viz. alcohols <92BMC1489, 92S288>, Wittig reagent <87CC153>, organocuprate <89CC1852>, halides <82BCJ174, 92RTC59>, amines <80BCJ283>, thiols <83TL1133, 92RTC59>, phosphite <79BSF(2)343>, malonate <91JHC1757>, indole <89TL4073>, and azide <92RTC59>) give access to a great variety of optically pure functionalized aminoacids.

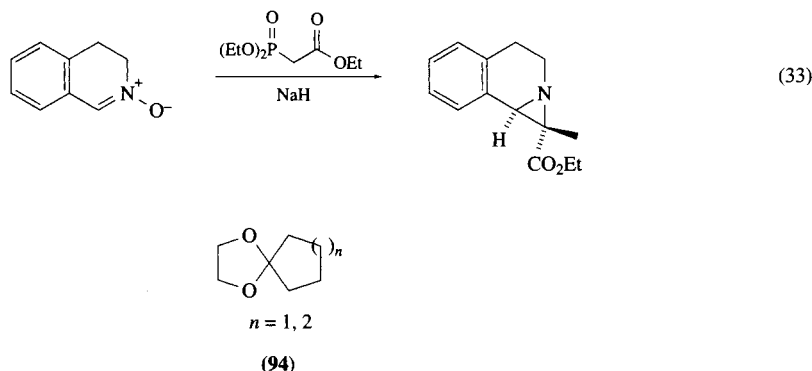
1.02.5.1 Reactions

Reaction of activated aziridines with acetonitrile in the presence of boron trifluoride etherate takes place via ring expansion leading to imidazolines <92RTC59>. Treatment of zwitterionic aziridine-2-carboxylic acid prepared from the ester, with triethylborane in hexane gave boraxazolidones <92RTC211> via 1,3-dipolar cycloaddition. Aziridine-2-carboxylates react with 2-methyl- β -nitrostyrene to yield substituted pyrrole derivatives <89BSF409>. 2-Pyrrolidone is the product in the reaction with dimethyl malonate anion <91JHC1757>. On thermolysis aziridine (**91**) undergoes intramolecular cycloaddition via an intermediate azomethine ylide to yield metacyclophane (Equation (32)) <86TL4003>. Alkylation of a triazole with an aziridine using boron trifluoride etherate as catalyst gave a bicyclic amino ester <92TA51>. Studies show that *N*-methylindole reacts at the C-3 position of aziridine-2-carboxylates (**92**) and reacts exclusively at the C-2 position of aziridine-2-lactone (**93**). This unexpected regioselectivity can moreover be rationalized by consideration of the LUMO coefficients of the reaction centers of the substrates <94JOC434>.

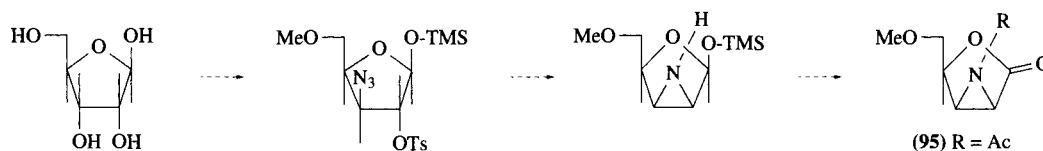


1.02.5.2 Synthesis

A few reported syntheses of aziridine-2-carboxylic acids <B-69MI 102-01, 92RTC1> are nonstereoselective and in most cases are applicable only to *N*-substituted derivatives. The stereospecific synthesis of ethyl aziridine-2-carboxylate was achieved by a number of methods starting from glycidic ester via NaN_3 attack and Staudinger reaction <92RTC1>, or by addition of phthalimidonitrene to α,β -unsaturated esters <89HCA1095>, or by the reaction of a chiral imine with ethyl chloroacetate via Darzen's reaction <85JOM(280)C11, 92TL7903>, or starting from an α -hydroxy- β -aminoester via the Mitsunobu reaction <92SC1487, 92TL2387>. Nitrones react with stabilized phosphonate esters to give fused aziridine carboxylate derivatives in good yield (Equation (33)) <82JOC1073>. Mori and Toda developed a method for optical resolution of aziridines by complexation with an optically active host compound (**94**) <90TA281>.



An optically pure cyclic analogue of aziridine-2-carboxylate ester was prepared from ribose via a Ph_3P -promoted conversion of 3-azido-2-tosyl-D-xylofuranoside to its corresponding 2,3-aziridine (95) (Scheme 34) <93T901>. The procedure is directly applicable to the synthesis of enantiomerically pure 2,3-aziridine carboxylate isomers from D-lyxose.



Scheme 34

1.02.6 AZIRINES

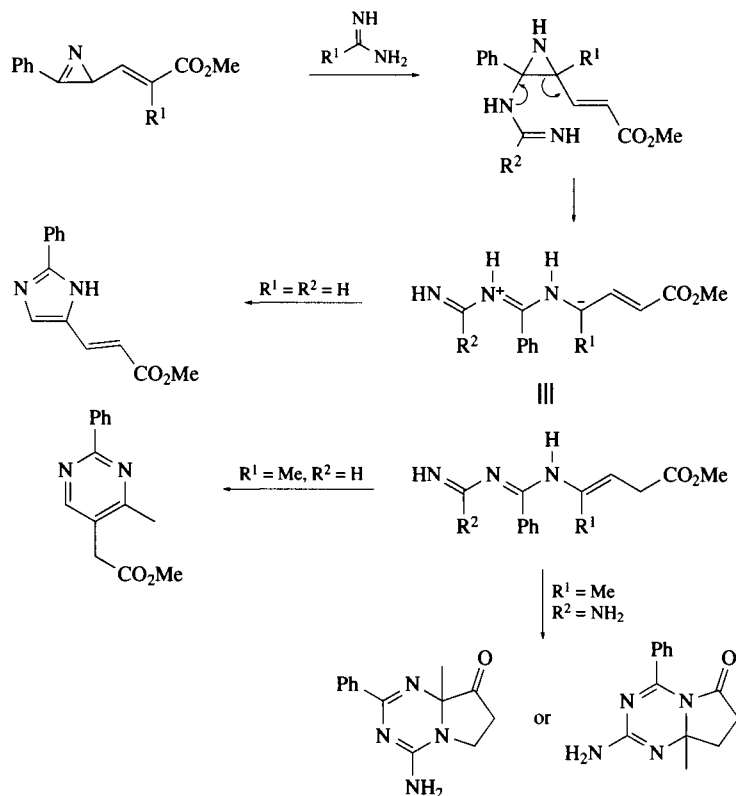
1-Azirines are reactive and versatile substrates because of certain inherent features within their structure. These include high ring strain, a reactive π -bond, a lone pair of electrons on the nitrogen and the ability to undergo ring cleavage on thermal or photochemical excitation to give such reactive fugative species as vinyl nitrene, iminocarbene and nitrile ylide. 1-Azirines are capable of acting in reactions as nucleophiles and electrophiles <B-83MI 102-02>. Azirines have been shown to be discrete intermediates in the Hoch–Campbell synthesis of *N*-unsubstituted aziridines <B-83MI 102-01>. Stable 2-azirines have not been isolated.

1.02.6.1 Synthesis of Small-ring Heterocycles

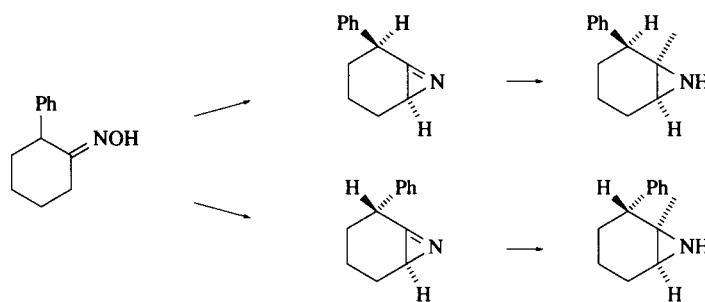
Simple alkyl and aryl azirines react with cyclopentadienones to afford azeepines as the ultimate products. Azirines have also been shown to react stereoselectively in a [4 + 2] fashion with triazines and benzofurans <80H(14)1517>. Exposure of azirines to CO in the presence of a catalytic amount of $[\text{Pd}(\text{PPh}_3)_4]$ gives the bicyclic β -lactam in reasonable yield <82OM70>.

3-Monosubstituted-2-amino-2-azirines react with several heterocycles containing acidic NH groups via ring expansion leading to benzo[*g*][1,2,5]thiadiazocine-1,1-dioxin derivatives and imidazoles <92HCA2270>. Reaction of 1-azirine-3-carboxamide with hydrazine has been suggested to proceed through a bicyclic aziridine intermediate with subsequent C—C or C—N bond cleavage to afford tetrahydro-1,2,4-triazolin-6-ones or unstable 4-amino-2-pyrazoline-5-ones depending upon the nature of the 3-substituent. In DMSO on the other hand, reaction with formamidine, guanidine, and hydrazines affords imidazole, pyrimidine, amino-5-triazine, or triazole derivatives respectively (Scheme 35) <91JOC7>. Ketoximes possessing an α -hydrogen atom, when treated with an excess of a Grignard reagent, initially give the 1-azirine via a nitrene intermediate which undergoes subsequent

nucleophilic attack by an additional equivalence of Grignard reagent to give the corresponding aziridine (Scheme 36). Hassner and Fowler reported the first synthesis of a ring-fused azirine, 9-azabicyclo[6.1.0]non-1(9)-ene in 93% yield by the photolysis of 1-azidocyclooctene <68JA2869>.



Scheme 35

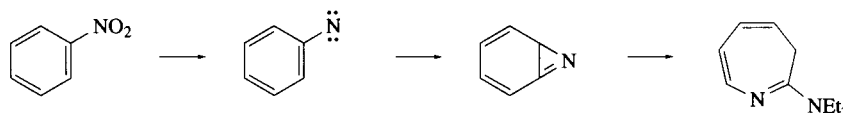


Scheme 36

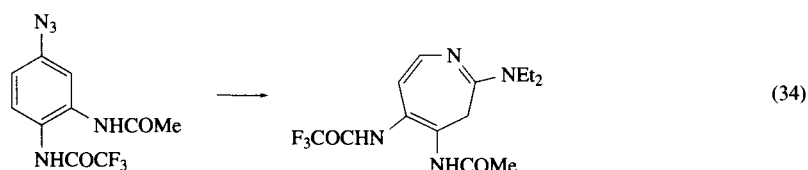
1.02.6.2 Synthesis of Azepines and Azocines

An alternative and major method for preparing 2-amino-3*H*-azepine utilizes the deoxygenation of nitroso and nitro arenes (Scheme 37) <B-79MI 102-02> or photolysis of aryl azides (Equation (34)) <92CC1359> or 1-naphthyl azide in the presence of diethylamine (Scheme 38) <87TL11>. The reaction pathway for the ring expansion as proposed by Huisgen and co-workers is outlined *in situ* and involves generation of the electron-deficient nitrene, which is held to be in dynamic equilibrium with the benzazirine. Nucleophilic addition of amine to the reactive imine bond followed by electrocyclic

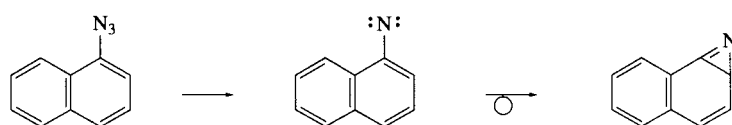
ring opening of the azanorcaradiene is thought to give initially 1*H*-azepine which subsequently rearranges to the more stable 3*H*-tautomer. A facile synthesis of 4,7-diphenyl-1,3,6-trihydro-1,3,6-triazocine-2-ones (**96**), 5,8-diphenyl-3,6-dihydro-1,3,6-oxadiazocine-2-ones (**97**) and 2,5-diphenylpyrazines (**98**) was reported by the interaction of chlorosulfonyl isocyanate with 1-azirine followed by alkaline hydrolysis in 47.5%, 25% and 10% yield respectively <93SC2151>.



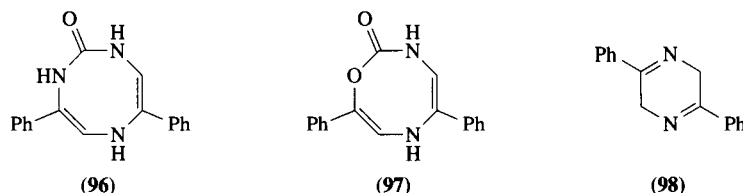
Scheme 37



(34)



Scheme 38



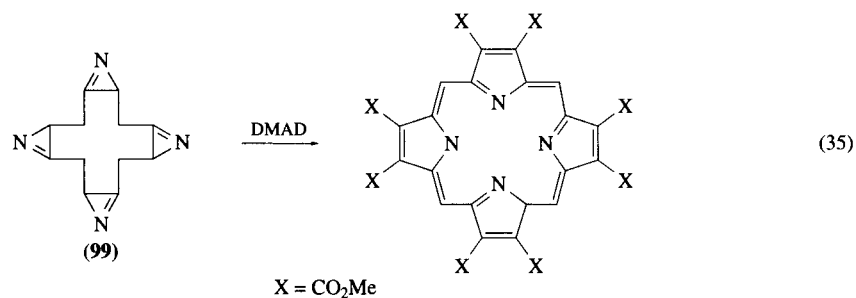
(96)

(97)

(98)

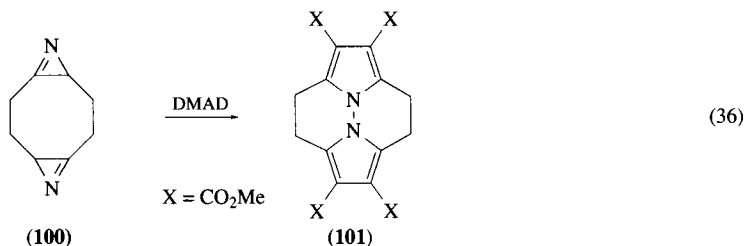
1.02.6.3 Synthesis of Macrocycles

A new approach to the synthesis of porphyrin systems by four consecutive (3 + 2) cycloadditions between tetraazapentacyclohexadecatetraene (**99**) and DMAD involves the opening of an azirine ring by a photochemical electrocyclic process (Equation (35)) <92JOC6080>. This approach has also been used to synthesize pyrrolophane and imidazolophane from bicyclic 1-azirines. Similarly diazacyclopentacenetetra-carboxylate (**101**) was prepared from DMAD and bisazirine (**100**) (Equation (36)) <93CB543>.



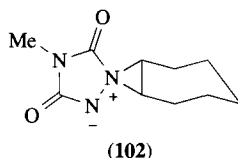
(35)

X = CO₂Me



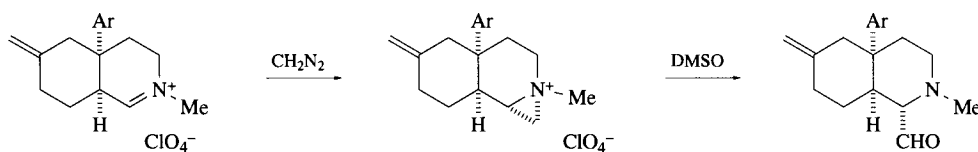
1.02.7 AZIRIDIUM SALTS

The great lability of aziridinium ions towards ring opening does not preclude isolation of aziridinium salts under proper conditions. Aziridinium salts can be distinguished from ring-opened and dimeric salts by NMR spectroscopy and then reaction with $\text{Na}_2\text{S}_2\text{O}_3$. The latter reagent is specific for aziridinium salts and forms the basis for quantitative analysis of the aziridine ring (B-83MI 102-01). Results of isotope effect studies have indicated that an aziridinium ion intermediate (102) is involved in the ene reaction of *trans*-cycloheptene with *N*-methyl-1,2,4-triazoline-3,5-dione; furthermore, the intermediate must be in prior equilibrium with another isomer (90JA5364).



1.02.7.1 Synthesis and Reactions

A simple and versatile method for the synthesis of aziridinium salts involves the reaction of a diazoalkane with an iminium salt (82TL285, B-83MI 102-01). The aziridinium salt thus formed was oxidized to an aminoaldehyde by DMSO (Scheme 39). A key step in the preparation of the oxindole alkaloid gelsemine (104) involves the carbonylation of the unsaturated aziridinium ion (103) with disodiumtetracarbonyl picrate-dioxane complex under a CO atmosphere followed by base-promoted epimerization and deprotonation (Scheme 40) (92JOC1035).



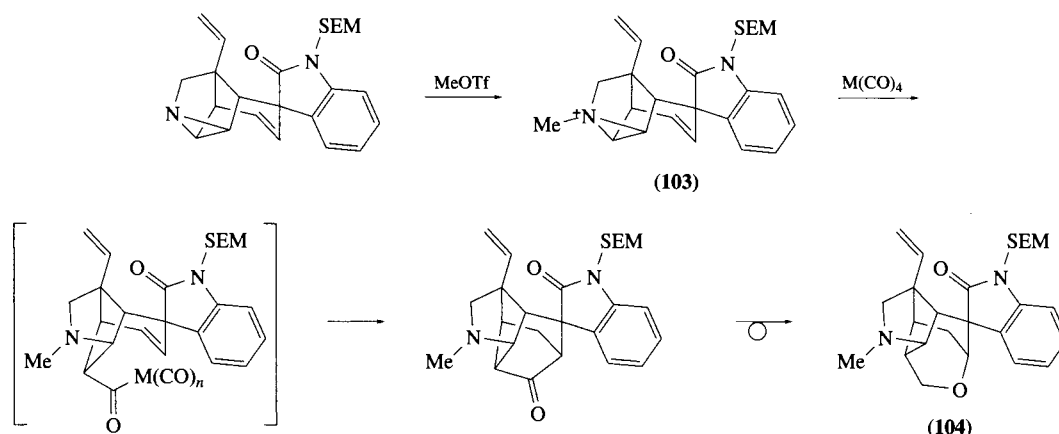
Scheme 39

The direct synthesis of the morphinan skeleton (107) from (105) involves the intramolecular ring opening by the enolate anion of the *in situ* generated aziridine cation (106) (Scheme 41) (88JOC2144). Compound (108) was found to rearrange thermally to the thermodynamically favored azabicyclo-[3.3.1]octane (110) via the aziridinium ion (109) (Scheme 42) (93CC758).

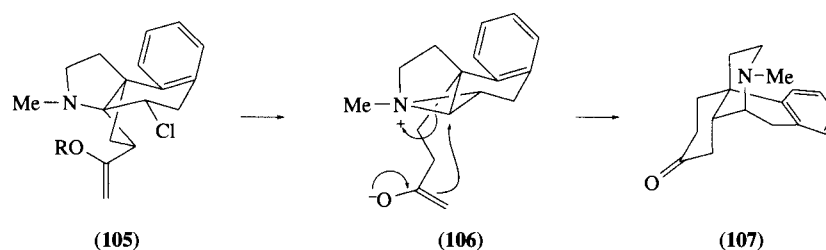
1.02.8 APPLICATION OF AZIRIDINES TO THE SYNTHESIS OF NATURAL PRODUCTS

A spirobenzylisoquinoline alkaloid, ochrobirine (112) has been synthesized from its biogenetic precursor, coptisine (111) (Scheme 43). The key reaction presented in this biomimetic and stereoselective conversion involves a regioselective $\text{C}_8\text{—N}$ bond fission of the aziridine (113), which is formed from the betaine by photochemical valence tautomerization (79TL3749).

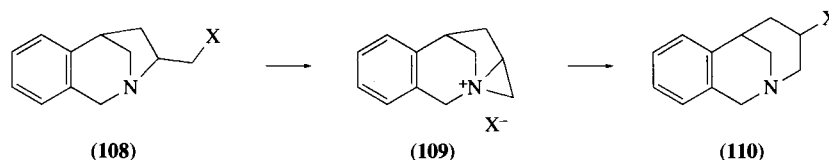
A novel synthesis of (±)-fumaricine (114), (±)-*cis*-alpinigenine (115a), (±)-*cis*-alpinine (115b), (±)-fumaritrine (116), lahorine (117a), lahoramine (117b), raddeanine (118), yenusomine (119),



Scheme 40



Scheme 41

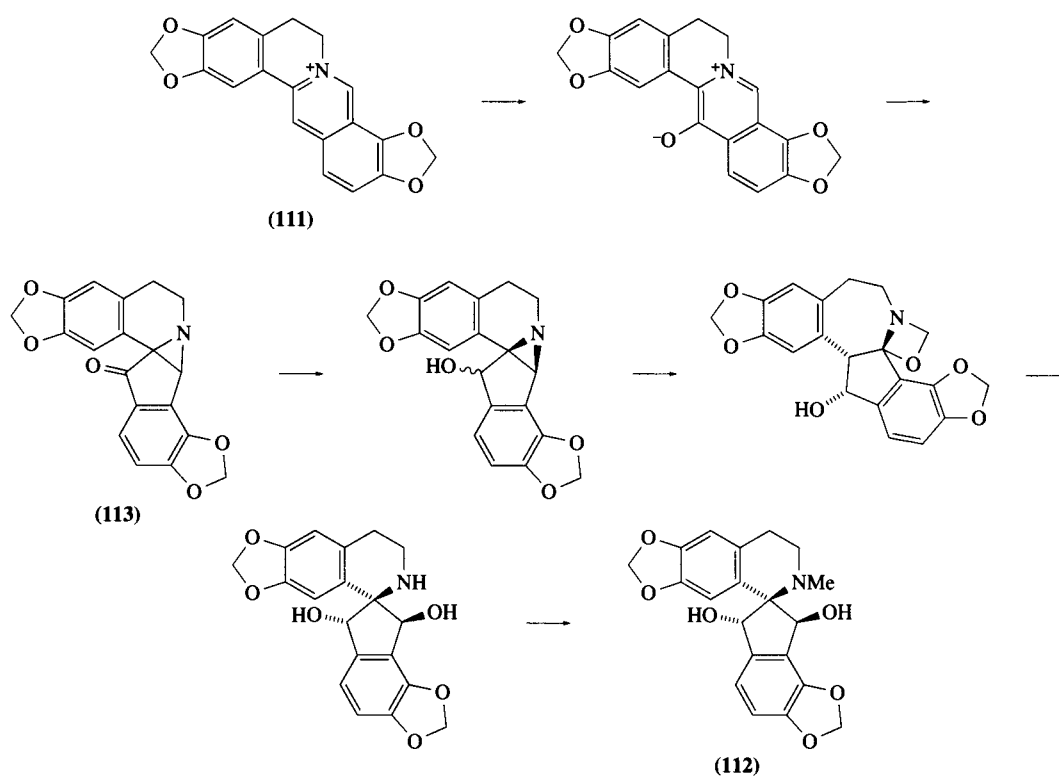


Scheme 42

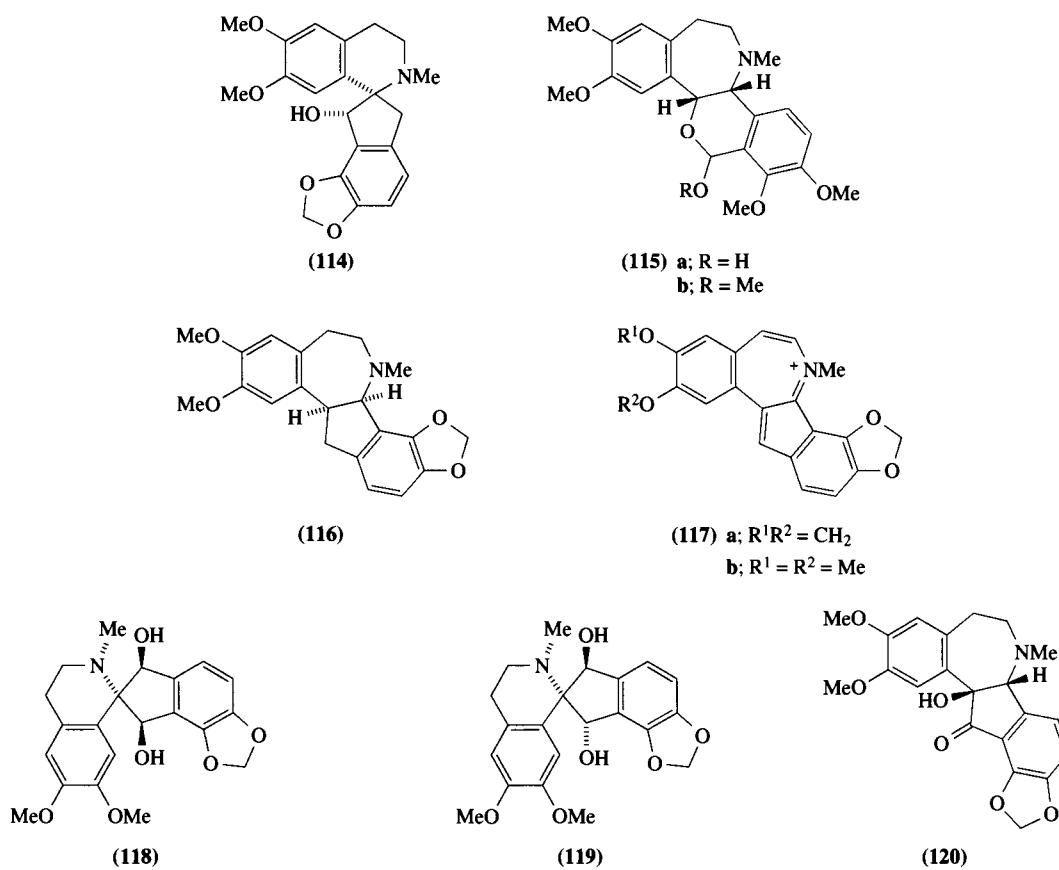
and fumarofine (**120**) was also achieved by a similar strategy, which involves an aziridine analogue of (**113**) as a key intermediate ^[86AHC(39)181]. An efficient and stereospecific synthesis of the tetrahydroquinone ring system of the structurally unique alkaloid vivanatmycin (**121**) has been achieved using a nitrene-alkene intramolecular addition reaction as the key step (Scheme 44) ^[90TL6031].

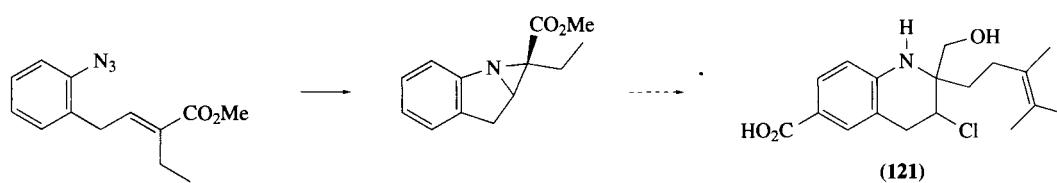
A conversion of chlorobenzenediol (**122**) to lactone (**123**) and elaboration of this material to either enantiomer of trihydroxyheliotridane (**124**) constituted a fully enantiocontrolled approach to both enantiomeric series of highly oxygenated pyrrolizidine alkaloids via vinylaziridines (Scheme 45) ^[90JOC4683]. Construction of an isoquinuclidine ring system employing intramolecular aziridine formation of alkenic amines and subsequent ring opening has been reported by Nagata and co-workers (Scheme 46) ^[67JA5046, 73T2253]. These reactions were successfully applied to the synthesis of indole alkaloids ($\pm$)-ibogamine (**126**; R = H), ($\pm$)-epiibogamine (**127**), and coronaridine (**126**; R = CO₂Me) where an analogue of the aziridine (**125**) serves as the key intermediate ^[86AHC(39)181].

An intramolecular oxidative aziridine formation (**128**) and its subsequent ring-opening reaction has been utilized to construct the indolizidine ring system present in lycopodium alkaloid ($\pm$)-serratinine (**129**) (Scheme 47) ^[75CPB1511]. A fascinating rearrangement of aziridines (Equation (37)) ^[73CJC1448] as a key reaction has been applied to the synthesis of diterpene alkaloids like songorine (**130**), chasmanine (**131**) and 13-deoxydelphonine (**132**) ^[86AHC(39)181]. Tungsten hexacarbonyl on rhodium(II) acetate mediated reductive coupling of a dithione or of 2,3-diphenyl-*N*-aziridinohydrazone respectively with a regioselectively activated unsymmetrical dimethiyl-

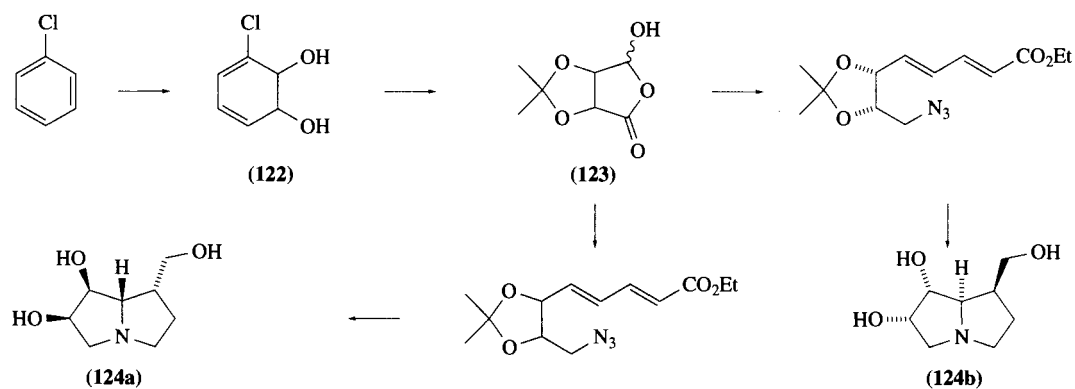


Scheme 43

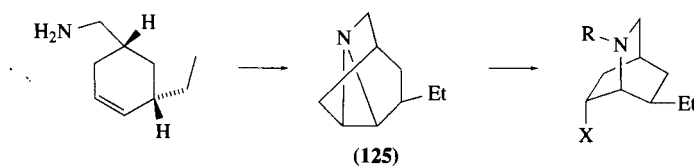




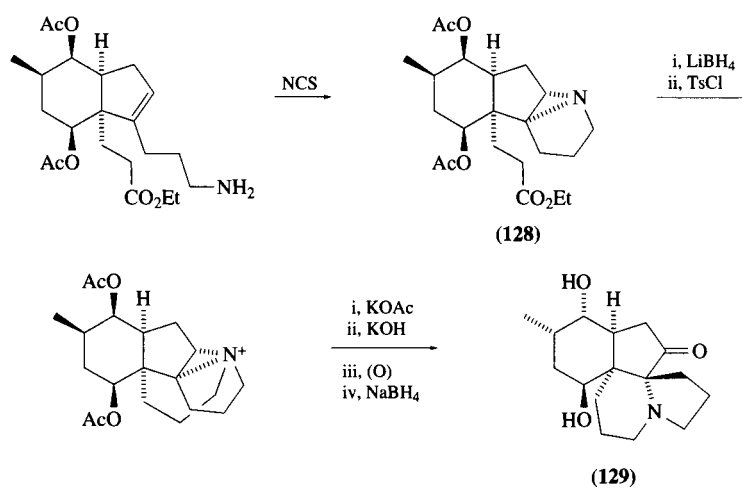
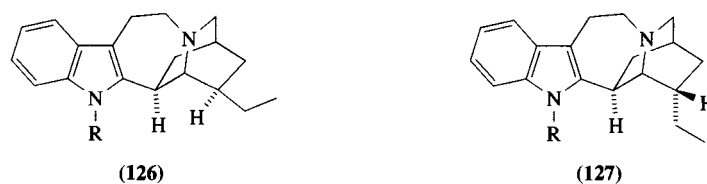
Scheme 44



Scheme 45

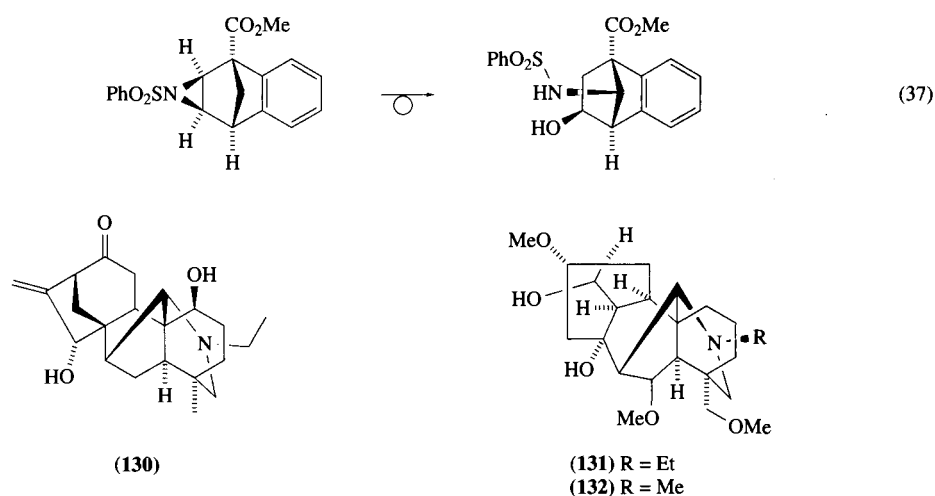


Scheme 46

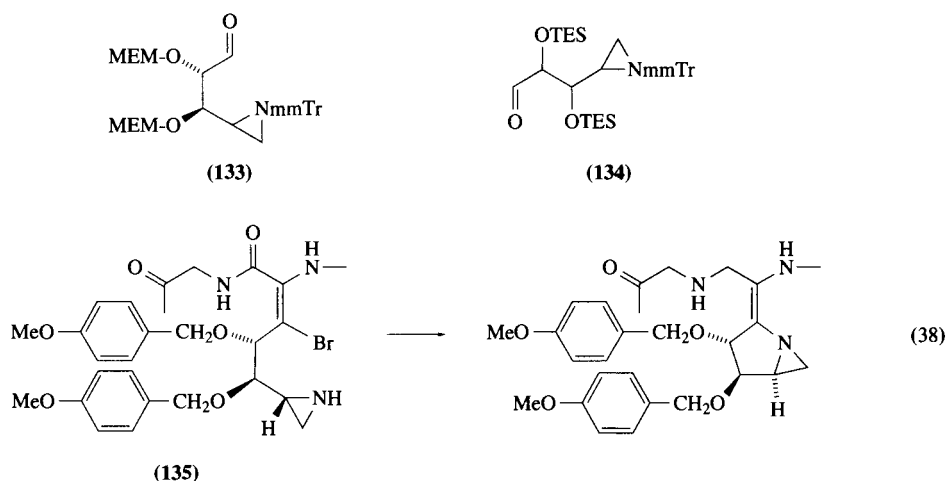


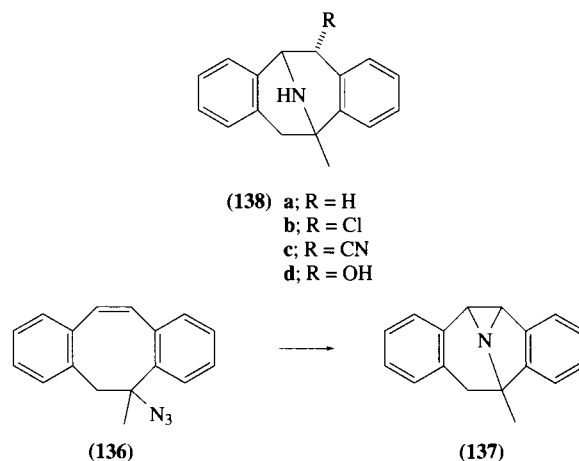
Scheme 47

phthalimide provides a key step in the total synthesis of isoindoloazepine alkaloid chelenine <89TL2747>.

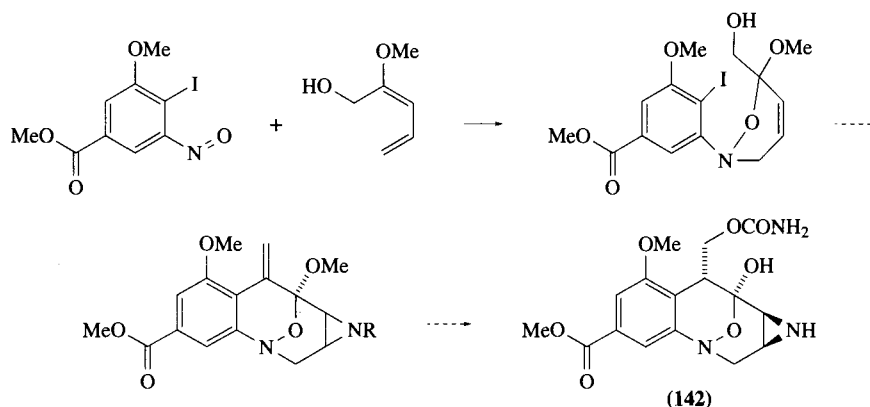
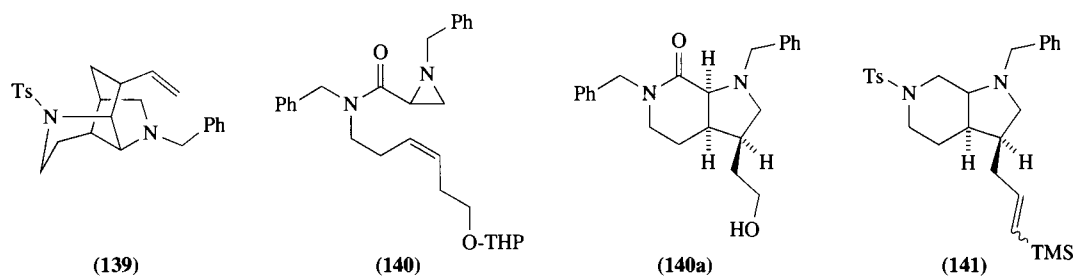


Synthesis of aldehydes (133) from D-arabinose and (134) from L-serine provided key precursors for the generation of highly functionalized dehydroamino acid derivative upon condensation with glycyl phosphonate. Subsequent bromination and intramolecular addition/elimination afforded the 1-azabicyclo[3.1.0]hex-2-ylidene ring systems, postulated to exist in the azinomycin antitumor antibiotics <93JOC7848>. The same system was synthesized by a different route via an intramolecular cyclization of an aziridine to a vinyl bromide in (135) (Equation (38)) <92JA371>. Synthesis of carzinophillin (azinomycin B) congeners carrying a 8-(1-arylamino-1-alkoxycarbonyl)methylidene-1-azabicyclo[3.1.0]hexane system were achieved by employing condensation of the 2-methoxy-1-pyrroline with ethyl nitroacetate and construction of 1-azabicyclo[3.1.0]hexane systems from 5-mesyloxymethylpyrrolidine as a key step. Some of these congeners which carry a C₆—C₁₁ unit involving the naphthalene part, were found to exhibit prominent cytotoxicity and effectively alkylate nucleophiles at both the aziridine and epoxide moieties <94TL2207>. Controlled thermolysis of the 5-azidodibenzo[*a,e*]cyclooctene derivative (136) yields the pentacyclic aziridine (137). Aziridine ring opening of (137) provides a regioselective route to 12-*endo*-substituted pavine alkaloid analogues (138a–d) (Scheme 48) <90JOC2103>. Pivotal steps in the construction of the tricyclic compound (139), which contains the alkaloidal nucleus of the marine natural product sarain A, include stereospecific intramolecular dipolar (3 + 2) cycloaddition of azomethine ylide generated from aziridine (140) to afford bicyclic lactam (140a), followed by a novel intramolecular allylsilane/*N*-tosylaminium ion cyclization of (141) <93JOC4945>. The key reaction involved in the total synthesis of a dimethyl ester analogue of FR900482 (142) was a Diels–Alder reaction of an aryl nitroso dienophile and the oxygenated diene (Scheme 49) <93JA6094>.





Scheme 48

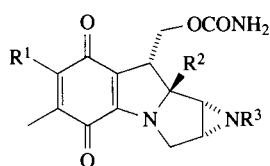


Scheme 49

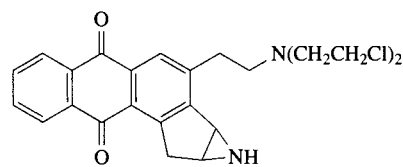
1.02.9 NATURAL OCCURRENCE AND BIOLOGICAL PROPERTIES

Only a few fused derivatives of the saturated aziridine ring system have been found to occur in nature (84CHEC-I(7)47). A group of structurally related substances (143) possessing wide-ranging antibiotic and antitumor activity have been isolated as metabolites of several strains of *Streptomyces*. From *S. caespitosus* and *S. verticillatus*, for example, mitomycin A, B, and C have been isolated. It has been demonstrated that in cyclopentantraquinone analogues (144) of mitomycin, both the aziridine group and the mustard side chain play a significant role in their cytotoxicity against leukemia L-210 and HL-60 cell growth in culture (93JOC1680).

The antitumor activity displayed by the mitosans and many synthetic aziridines stems from their ability to act as alkylating agents which chemically modify (crosslink) DNA. For this reason, a



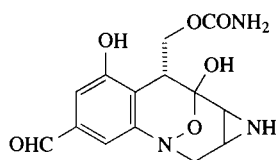
- (143) a; $R^1 = R^2 = \text{OMe}$, $R^3 = \text{H}$ (Mitomycin-A)
 b; $R^1 = \text{OMe}$, $R^2 = \text{OH}$, $R^3 = \text{Me}$ (Mitomycin B)
 c; $R^1 = \text{NH}_2$, $R^2 = \text{OMe}$, $R^3 = \text{H}$ (Mitomycin-C)
 d; $R^1 = \text{NH}_2$, $R^2 = \text{OMe}$, $R^3 = \text{Me}$
 e; $R^1 = R^2 = \text{OMe}$, $R^3 = \text{Me}$



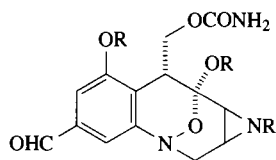
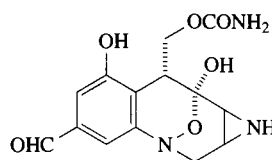
(144)

large number of such compounds have been screened for antitumor activity, the mechanism of which has been the subject of considerable research efforts.

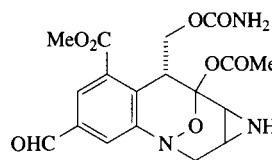
Isolated from a culture broth of *Streptomyces sandaensis* FR900482 (145) is a mixture of two hydroxylamine hemiketal isomers I and II and was shown to exhibit exceptionally potent antitumor activity <87JA4108, 89TL6491, 90TL6663>. Biological testing against experimental tumors has revealed that FR900482 is at least as active as mitomycin and is also active against mitomycin C and vincristin resistant P-388 cells. The triacetate FK973 (146) has displayed very promising biological properties showing activity against various transplanted human and murine tumors. FK973 is three times more potent than mitomycin C and significantly less toxic. It has been proposed that FK973 is gradually activated in cytoplasm cells and that activated FK973 forms intestinal DNA-DNA and DNA-protein crosslinks <90JOC1144>. The close resemblance of FR900482 to mitomycin suggests the involvement of aziridine-mitosane-like compounds in the mode of action. Analogue (147) also showed antitumor and antimicrobial activity <90USP4973693> while (148) and its salts are useful as medicinal bactericides and neoplasm inhibitors <89JAP(K)01146883>. Antitumor antibiotics azinomycin A and B (149) were isolated from the fermentation broth of *Streptomyces griseofuseus* <86JAN1527>. An *in vitro* assay has established that azinomycin B induces innerstrand crosslinks in duplexed DNA between G and purine residues two base pairs removed <92JA3144>. Azinomycin also monoalkylates single-stranded DNA and duplex DNA exclusively at G residue. Piperidine treatment of monoalkylate intermediates results in depurination and strand scission has been observed for adducts of DNA with synthetic aziridines. It was postulated that a bicyclic and vinylic aziridine proposed to exist in the natural products is responsible for monoalkylation of G residues <92TL3711, 93JOC7848>.



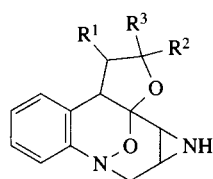
(145)



(146)

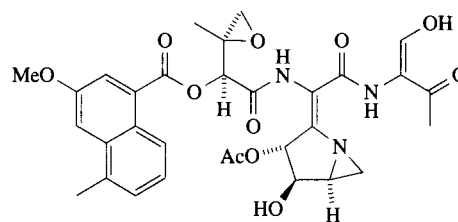


(147)



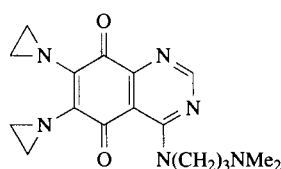
(148)

$R^1 = \text{aryl, heteroaryl}$
 $R^3 = \text{C}_{1-6} \text{ alkoxy}$
 $R^2R^3 = \text{a bond}$

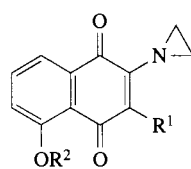


(149)

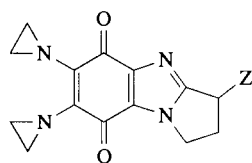
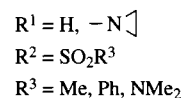
Aziridinyl quinazolinone (150) was tested in a cell image process on human mammary and melanoma cell lines. The results show that (150) influences cell proliferation and blocks both cell lines in the S phase. *In vitro* antineoplastic activity was demonstrated as a broad spectrum of marine experimental models, but was found to be highly toxic and produced long-delayed death (91JMC38). A series of 2-aziridinyl and 2,3-(bisaziridinyl)-1,4-naphthoquinonyl sulfonates and acylates (151) possess antimalarial activity against the human malaria parasite, *Plasmodium* (Vietnam Smith strain, chloroquine-resistant at the R₃ level) (91JMC1634). Three pyrallo[1,2-*a*]benzimidazole-based aziridinyl quinones (152; Z = OAc, carbamate or H) cleaved DNA under reducing conditions specifically at G + A bases without any significant cleavage at C + T bases. The postulated mechanism involves phosphate alkylation by the reductively activated aziridine to afford a hydrolytically labile phosphate triester as well as the classic *N*(7) purine alkylation followed by depurination and backbone cleavage. Compound (152) possesses a unique spectrum of cytotoxicity *in vitro* against cancer (93JMC3050). *N*-Isoalkyl, α -aziridine- β -(*p*-chlorobenzoyl) propionamide (153) showed immunosuppressant activity in several tests (90MIP150095). Phosphaaziridine (154) proved effective *in vitro* against lymphocytic leukemia P-388 in mice at 8–256 mg kg⁻¹, whereas (155) showed antimicrobial activity against *Staphylococcus aureus* (86USP4617398). Tetrakis(aziridinyl)spiro (alkylenediamino)cyclotriphosphorazines are antineoplastics, capable of biodegradation *in vivo* and having reduced cumulative toxicity (87MIP143882).



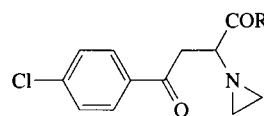
(150)



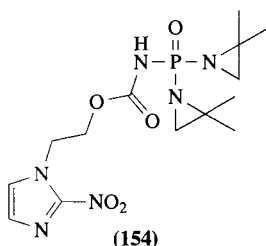
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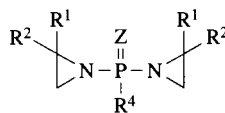
(152)



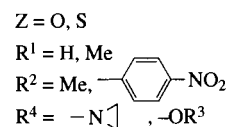
(153)



(154)



(155)



α -[(1-Aziridinyl)methyl]-2-nitro-1*H*-imidazo-1-ethanol (RSU-1069) is one of the most effective radiosensitizers and bioreductively-activated cytotoxins. Compounds of this type owe their selective cytotoxicity towards hypoxic cells within tumors to their bioreductive process (87MI 102-01, 92JMC3573). Replacement of aziridine in RSU-1069 by a number of other potential alkylating groups, including cycloalkyl aziridines, also acts as selective hypoxic cell cytotoxic agents and as radiosensitizers (91JMC2484). The data indicated that modification of the aziridine in RSU-1069 resulted in a substantial decrease in the ability of the compounds to selectively kill hypoxic cells. RSV-1131 has strong affinity to B-16 melanoma cells; its biological activity is considered to be due to the very reactive aziridine ring which irreversibly forms a light covalent bond with DNA (89MI 102-01). 1-Carboranyl-3-(2-methylaziridino)-2-propanol (MACB) was prepared from the reaction of 1-carboranyl-2,3-epoxypropane with metallated methyl aziridine having copper [Cu(CN)Li]_{1/2} or lead (PbBu₃) as the metal. MACB exhibited relatively high growth inhibition towards some cancer cells (93JMC2232). Acenaphthalene-1,2-imine efficiently inhibits various strains of *Salmonella typhimurium*, and demonstrates that not only *k*-region arene-imines, but also other aziridines substituted at the 2 carbon with aromatic moieties are mutagenic (86MI 102-02).

1.03

Oxiranes and Oxirenes: Monocyclic

IHSAN ERDEN

San Francisco State University, CA, USA

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1.03.1 INTRODUCTION TO OXIRANES AND OXIRENES

Oxiranes are among the most intensely studied group of compounds. Owing to the considerable ring strain (~ 27 kcal mol⁻¹), as well as the polarization of the C—O bonds in the three-membered ring system, oxiranes exhibit such varied modes of reactions that it is impossible to cover all of the work reported in literature in this area since 1982. The synthesis of oxiranes can be accomplished from a very large number of substrates, using a plethora of reagents and reagent systems by direct or indirect oxygenation methodologies. This area, in particular the field of enantioselective epoxidations, has burgeoned in the past decade to the extent that the discussion of every method here is beyond the scope of this chapter.

The nomenclature of oxiranes is discussed in <B-79MI 103-01, 84CHEC-I(7)95>. The generic name of the three-membered oxygen heterocycle is *oxirane*, according to the Hantzsch–Widman system <B-74MI 103-01, 83PAC409>. A search of current literature in this area reveals that the names oxirane and 1,2-epoxide are used interchangeably, as well as additive nomenclature (e.g., ethylene oxide). The most systematic method of naming heterocyclic compounds, including oxiranes, is the replacement nomenclature <B-79MI 103-01>, according to which an oxygen-containing three-membered ring is named oxacyclopropane. However, this nomenclature system is more frequently used for heterocycles containing unusual heteroatoms, as well as bridged and spiro systems. There have been a large number of excellent review articles on oxiranes published since 1982; these are mentioned in each of the sections below.

1.03.2 OXIRANES: STRUCTURE AND PROPERTIES, INCLUDING SPECTRA

1.03.2.1 Molecular Geometry and Energetics

The microwave structure of oxirane has been determined by Hirose <74BCJ1311>. Molecular geometries of oxirane have been determined by *ab initio* calculations at various levels with remarkable agreement with the experimental values (Figure 1) <85JA3800, 89JA6957, 89JPC3025>. The conventional ring strain energy of oxirane is 27.2 kcal mol⁻¹ <B-74MI 103-02>.

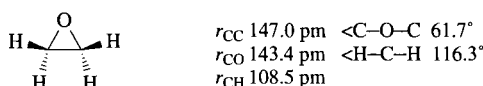


Figure 1

1.03.2.2 NMR Spectra

Proton and carbon-13 NMR chemical shifts, geminal, and vicinal proton–proton coupling constants for oxirane and derivatives have been discussed in the first edition of *Comprehensive Heterocyclic Chemistry* <84CHEC-I(7)95>. The stereochemical assignment of several epoxy alcohols has been achieved by a combination of H—H and C—H coupling constants and nuclear Overhauser effect (NOE) data <92JOC6025>. The NMR arguments have been supported by molecular modeling (MMX force field) and semiempirical quantum mechanical (AM1) calculations. A report in 1986

on ^{13}C NMR and ^{17}O chemical shifts of a large number of mono- and disubstituted oxiranes has been used to determine the direct additivity parameters for calculating chemical shifts of oxiranes $\langle 86\text{MRC}15 \rangle$. A comparison of ^{13}C experimental shifts and calculated values for di- and trisubstituted oxiranes indicates good agreement in most cases. Discrepancies between experimental and calculated ^{17}O shift values fall in the range 0 ± 14 ppm. A striking feature of the ^{17}O NMR shift data is the possibility of distinguishing between different molecular configuration for isomeric compounds by ^{17}O NMR. Oxygen-17 NMR data of 17 variously substituted oxiranes have been reported by the same authors $\langle 83\text{OMR}(21)403 \rangle$. Table 1 depicts some characteristic ^{17}O NMR shifts for selected oxiranes. An excellent discussion of ^{17}O NMR spectroscopy of epoxides can be found in $\langle \text{B-91MI } 103-01 \rangle$.

Table 1 Oxygen-17 NMR shift values of some oxiranes.

					
	(1)	(2)	(3)	(4)	(5)
$\delta(^{17}\text{O})$ (ppm)	-49	-16	-18	-9.5	-8

The ^{13}C NMR data of 42 ring-halogenated oxiranes containing F, Cl, Br (and I in one case) as substituents have been reported and discussed with respect to the influence of the halogen and other substituents on the chemical shifts of the ring carbons $\langle 85\text{MRC}524 \rangle$. For monocyclic mono- and dichlorooxiranes, increments have been determined which allow the calculation of the chemical shifts of the ring carbon atoms. Comparison of the ^{13}C NMR data of substituted 1,2-dihaloethylenes (C(1)—C(2) ca. 111–158 ppm) with those of the corresponding oxiranes (C(1)—C(2) ca. 60–90 ppm) shows that the signals of the ring carbons of the halogenated oxiranes invariably appear at considerably higher field than the vinylic carbons in the alkene precursors.

1.03.2.3 Mass Spectra

The mass spectra of oxiranes are discussed in $\langle \text{B-71MI } 103-01 \rangle$. Ionized oxiranes undergo unimolecular decomposition in the mass spectrometer; the fragment ions observed are in general due to rearrangements, transannular hydrogen transfer, and α - and β -cleavage $\langle 89\text{MI } 103-01 \rangle$. Mass spectroscopic studies on *trans*-chalcone epoxides reveal that the most stable fragments are formed by bond cleavage to the oxirane ring carbons (onium cleavage and aryl fragmentation) $\langle 89\text{JPR}37 \rangle$.

1.03.2.4 UV Spectra

Oxiranes do not have an absorption in the UV spectrum above 200 nm to be of diagnostic value for structural characterization. The λ_{max} values of substituted oxiranes are surveyed in $\langle 64\text{CHE}17 \rangle$. Unsubstituted oxirane has an absorption at 171 nm (gas phase, ϵ -5600) $\langle 63\text{PMH}(2)1 \rangle$.

1.03.2.5 IR Spectra

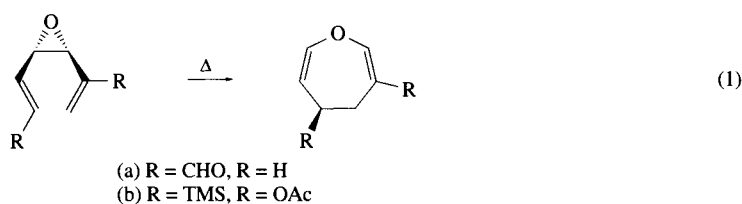
The routine employment of high-resolution FT-IR spectroscopy in organic chemistry has allowed the assignment of IR signals of oxiranes to the corresponding vibrational modes with greater confidence. The controversy around the assignment of the B_1 (asymmetric) ring deformation in oxirane has been resolved by high-resolution (0.04 cm^{-1}) FT-IR techniques $\langle 86\text{MI } 103-01 \rangle$. The peak at 897 cm^{-1} in the vapor-phase FT-IR spectrum of oxirane has now been assigned as the Q-branch of the expected type-A band, and results from the B_1 ring deformation. The IR group frequencies complementing the existing data $\langle \text{B-75MI } 103-01 \rangle$ have been reported in an attempt to confirm and expand previous IR spectra-structure correlations of oxiranes $\langle 86\text{MI } 103-02 \rangle$. In all cases studied, the symmetric ring deformation has the highest IR band intensity (830 – 877 cm^{-1}). The absorbance ratio for ring-breathing (1248 – 1268 cm^{-1})/symmetric ring deformation varies between 0.22 and 0.43, and the absorbance ratio for antisymmetric in-plane deformation (883 – 932 cm^{-1})/symmetric in-plane ring deformation varies between 0.009 and 0.96. The band intensity ratios are of diagnostic

value in specific spectra—structure identifications of oxiranes. The 1,2-epoxyalkanes exhibit IR bands in the $3038\text{--}3065\text{ cm}^{-1}$ and $2990\text{--}3001\text{ cm}^{-1}$ regions, respectively. The higher and lower frequency bands in this set have been assigned to the antisymmetric and symmetric oxirane CH_2 stretching vibrations, respectively. The IR bands in the regions $1478\text{--}1501$, $1404\text{--}1412$, $1125\text{--}1130\text{ cm}^{-1}$ are assigned to oxirane CH_2 bending, twisting, and swagging vibrations, respectively, based on comparable assignments for ethylene oxide at 1497.5 , 1412 , and $1130\text{--}1151\text{ cm}^{-1}$, respectively.

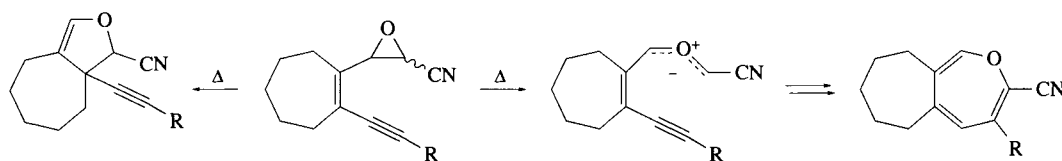
1.03.3 OXIRANES: REACTIVITY

1.03.3.1 Thermal Reactions

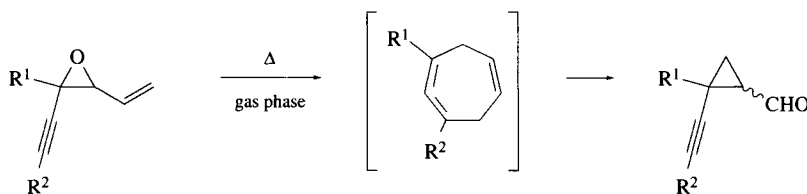
In most cases, the preferred mode of cleavage is the oxirane C—C bond. Thermal rearrangements of vinyl oxiranes generally proceed at relatively high temperatures (ca. $200\text{--}400^\circ\text{C}$) via carbonyl ylides to give dihydrofurans in a stereospecific manner $\langle 85\text{HCA}1089, 87\text{TL}2685, 89\text{T}3021 \rangle$. *cis*-2,3-Divinyl oxiranes undergo [3,3] sigmatropic (Cope) rearrangements at $100\text{--}150^\circ\text{C}$ to afford 4,5-dihydrooxepins (Equation (1)) $\langle 83\text{TL}4135, 88\text{JOC}2312, 90\text{JOC}3975, 91\text{TL}157, 92\text{JA}4658 \rangle$.



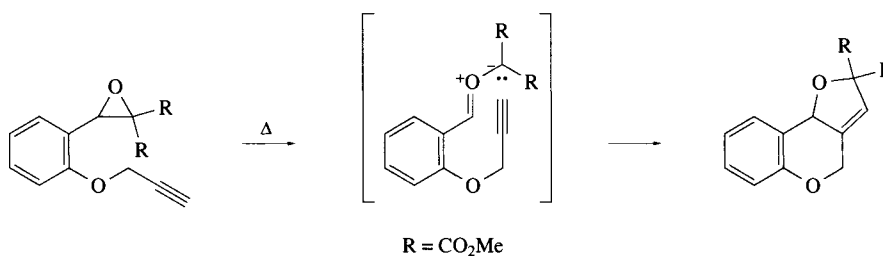
These rearrangements have been reviewed $\langle 91\text{COS}(5)899 \rangle$. Some interesting examples of thermal rearrangements of oxiranes with concomitant intramolecular cyclizations are shown in Schemes 1, 2, and 3 $\langle 80\text{JOC}428, 85\text{H}(23)2797, 86\text{T}2221, 87\text{TL}2685, 88\text{AG}(\text{E})568, 91\text{JOC}4598, 91\text{T}7713 \rangle$.



Scheme 1



Scheme 2

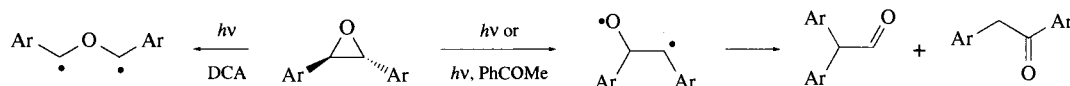


Scheme 3

Thermal rearrangements of γ,δ -epoxyenones and related compounds have been reviewed $\langle 85\text{YGK}55 \rangle$. On vapor phase thermolysis, in general, epoxyenones suffer 1,5-homosigmatropic H-shift with cleavage of the $\text{C}_\gamma\text{—C}_\delta$ bond of the oxirane ring, leading to divinyl ethers in high yields.

1.03.3.2 Photochemical Reactions

Photoisomerizations of 2,3-diaryloxiranes have been reviewed <B-79MI 103-02, 83CRV535, 92CR741>. *Cis*- and *trans*-2,3-diaryloxiranes undergo photoisomerization by C—C cleavage via an electron transfer process <78CJC2985, 83CL1059, 84JA8077, 84JCC1107, 85CL455, 85T2207, 87CJC976, 87JA2780, 93JOC1785>. Whereas direct or benzophenone-sensitized photolysis of stilbene oxides results in C—O cleavage, yielding carbonyl compounds, electron transfer photolysis with 1,4-dicyanoanthracene (DCA) results in C—C cleavage, leading to the corresponding diradical (or the carbonyl ylide), which can be trapped by a variety of cycloaddends (Scheme 4) <90JCS(P1)153>.

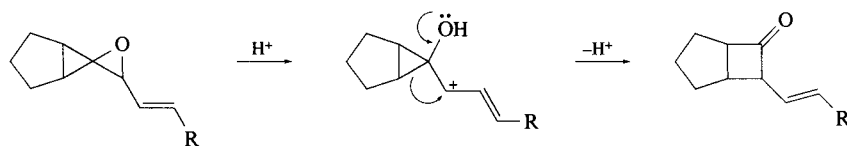


Scheme 4

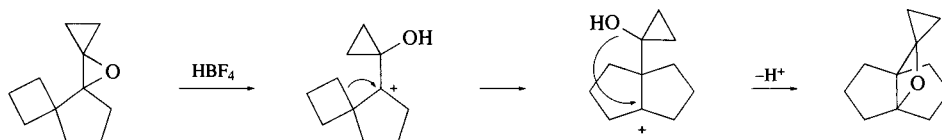
Also, fragmentations have been observed during the photolysis of certain oxiranes <84IJC940, 90JCS(P1)159, 90JCS(P1)1193>. A carbonyl ylide intermediate has been observed by UV spectroscopy during the photoextrusion of diphenylcarbene from 1,1,4,4-diphenylbutadiene monoepoxide <85JOC4899>. Photoinduced single electron transfer (SET) reactions of substituted α,β -epoxy ketones using triethylamine as electron donor have been studied <82CL1, 91JOC1631, 91T7775>. These reactions generate the corresponding anion radicals, which undergo selective C α —O bond cleavage leading to β -diketones and/or β -hydroxy ketones in varying ratios, depending on the solvent used and the nature of β -substituents. Photolysis of α,β -epoxy ketones in the presence of azobisisobutyronitrile (AIBN) and Bu₃SnH affords β -hydroxy ketones <90CC550>. Photochemical reaction of aryl-substituted oxiranes sensitized by 2,4,6-triphenylpyrilium tetrafluoroborate results in C—O bond cleavage, affording carbonyl compounds <83CL305, 90TL4045>.

1.03.3.3 Electrophilic Ring Opening

Acid- and Lewis acid-catalyzed ring opening of epoxides has been studied extensively in the past <B-80MI 103-01, 85CHE1>. Catalytic rearrangements of oxiranes have been reviewed <83MI 103-01>. Of considerable interest are the acid-catalyzed rearrangements in the absence of a nucleophile. The common pathway observed in most of these reactions involves initial attack of the electrophilic reagent by the oxirane oxygen followed by ring opening giving a carbocation. A 1,2-shift usually ensues, leading to a carbonyl compound. When small rings are in close proximity of the reactive center, rearrangements are very common. Two interesting examples are shown in Schemes 5 and 6 <88TL27, 94T10879>.

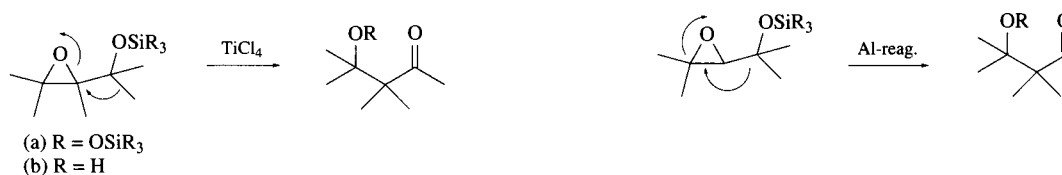


Scheme 5



Scheme 6

An efficient AlL₃ [L¹ = Me, L², L³ = *o*-C₆H₂-*p*-Br(*o*-Bu^t)₂] catalyst has successfully been employed in ring opening reactions of epoxides to carbonyl compounds <89TL5607>. The same aluminum-based Lewis acid, when applied to SiR₃ or SiR¹R₂² (R² = Me, R¹ = Bu^t) ethers of 2,3-epoxy alcohols, gives rise to β -siloxy aldehydes <89JA6431>. In the presence of TiCl₄, the epoxy alcohol precursors suffer a different type of rearrangement resulting in the formation of β -siloxy carbonyl compounds (Scheme 7) <86JA3827, 87TL3515, 87TL5891>.

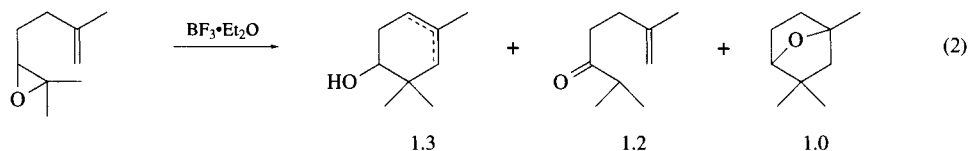


Scheme 7

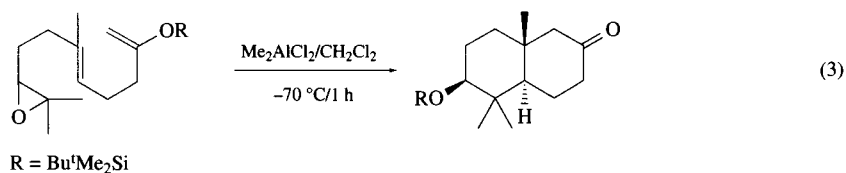
In SbF_5 -mediated rearrangements of ordinary oxiranes 1,2-alkyl shifts are dominant, in methylaluminum bis(4-bromo-2,6-di-*t*-butylphenoxide, MABR)-catalyzed cases only 1,2-hydride shifts are observed (89JA6431, 91JA5449, 91SL491, 92T3303). This remarkable selectivity in the latter reactions has been attributed to the Al reagent's extreme steric bulk and affinity to oxygen. Highly selective aluminum- and antimony-catalyzed isomerizations of oxiranes have been reported (94T3663).

Facile oxirane rearrangements in the presence of Cp_2ZrCl_2 and catalytic AgClO_4 have been observed (93JOC825).

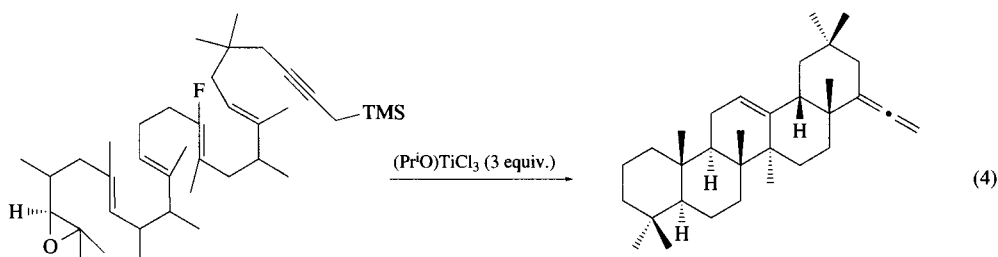
Certain oxiranes undergo intramolecular epoxy-ene cyclizations under the action of acids or Lewis acids (Equation (2)) (92OPP245).



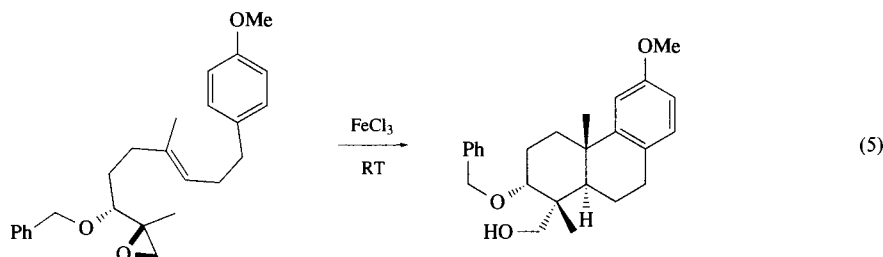
In a variety of cases of epoxide-alkene cyclizations, undesired side reactions such as pinacol rearrangement to carbonyl compounds, or 1,2-diol formation can occur, precluding the cyclization. Corey and Sodeoka have recommended the use of methylaluminum dichloride (MeAlCl_2) as catalyst to alleviate such problems (91TL7005). Equation (3) illustrates the efficacy of this method in effecting optimal yields of cyclization products.



The first examples of high-yielding epoxide-initiated tri- and pentacarbocyclizations (Equation (4)) utilizing (2-propoxy)titanium trichloride ($(\text{Pr}^i\text{O})\text{TiCl}_3$) have been reported (93TL7849).

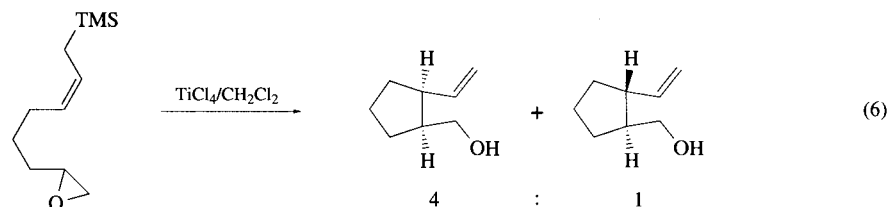


An intramolecular epoxide-ene cyclization has been used in the synthesis of ($\pm$) aphidicolin (Equation (5)) (83JA142).

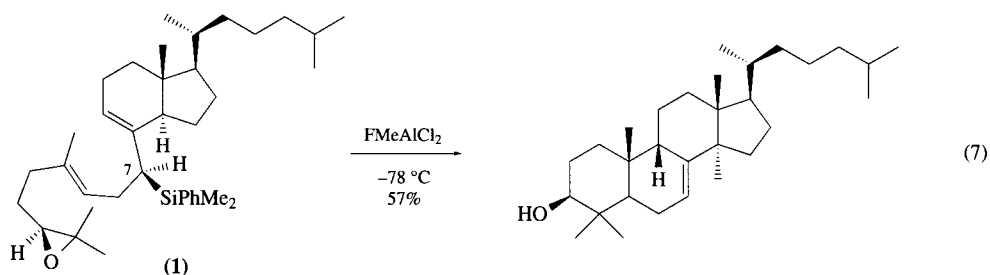


The enantioselective total synthesis of triterpenes of the β -amyrin series has been described by Corey and co-workers who utilized a MeAlCl_2 -catalyzed tricarbocyclization of a chiral oxirane $\langle 93\text{JA}8873 \rangle$, see also $\langle 91\text{TL}7005 \rangle$.

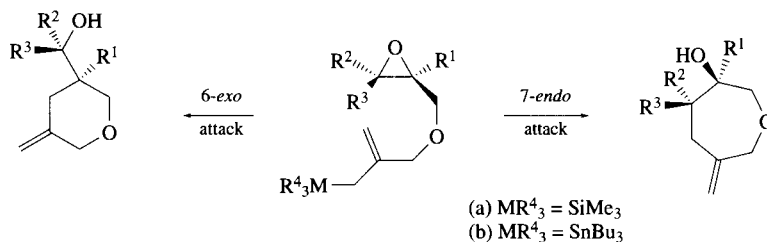
The remarkable ability of silicon to stabilize a positive charge at the β -position has been utilized in highly regio- and stereoselective cyclization reactions. $\langle 84\text{JCC}1273, 86\text{CJC}584, 88\text{JOC}4869, 88\text{T}3953 \rangle$. In these reactions carbon-carbon bond formation takes place at the most highly substituted epoxide center under Lewis acid catalysis (Equation (6)).



The first demonstration of a carbocation-alkene cyclization route to the lanesterol series has been described by Corey *et al.* $\langle 94\text{TL}9149 \rangle$ (Equation (7)). The failure of the analogue of (1) lacking the 7α -silyl substituent to cyclize underscores the crucial role of silyl assistance in alkene-oxirane cyclizations.



Intramolecular addition of allylstannanes and allylsilanes to 2,3-epoxy ethers has also been reported $\langle 89\text{JOC}3114 \rangle$. These reactions give rise to mixtures of products, resulting from 6-*exo* and 7-*endo* attack, respectively (Scheme 8).

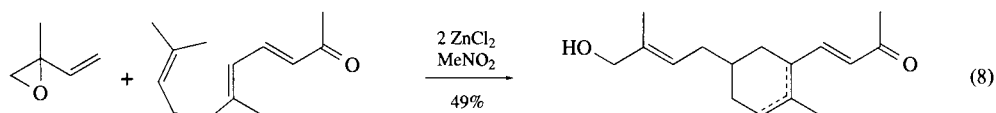


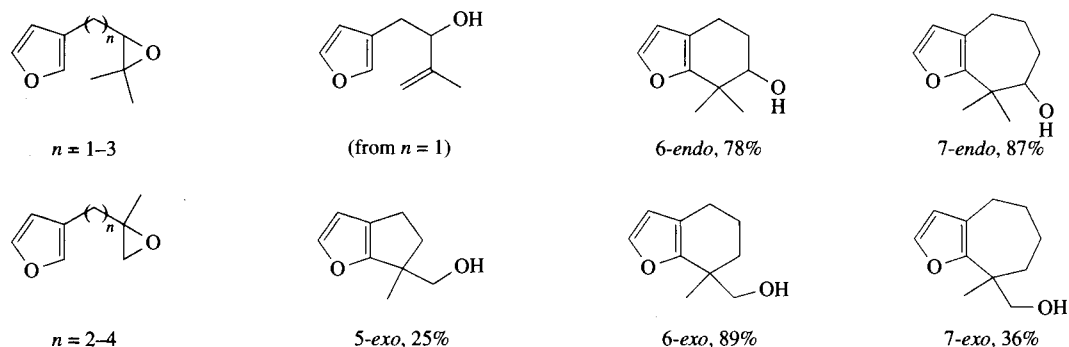
Scheme 8

These types of intramolecular cyclizations offer an excellent opportunity to test the Baldwin rules $\langle 76\text{CC}734 \rangle$ for ring closure. Such studies have been undertaken on furans and pyrroles carrying a $(\text{CH}_2)_n$ -epoxyalkyl tether at the 3-position of the furan and 1-position of the pyrrole, respectively (Scheme 9) $\langle 83\text{JOC}4572, 87\text{JOC}819 \rangle$.

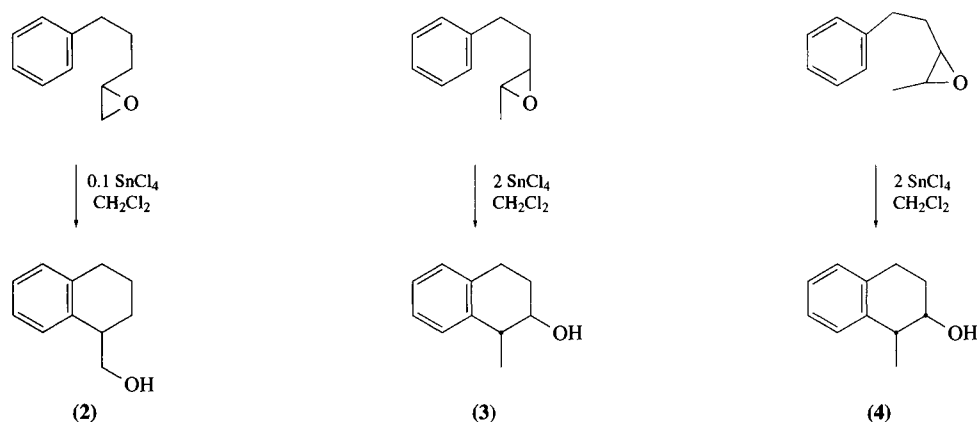
Epoxy-arene cyclizations have been studied extensively by Taylor *et al.* $\langle 87\text{JOC}425 \rangle$. The reaction to give six-membered rings can be specific (Scheme 10). The yields for (3) and (4) are lower than for (2), and this is in accord with the Baldwin rules: the former reaction is *exo*, whereas the latter reactions are *endo*.

An intermolecular variant of the epoxide-alkene cyclizations has been realized (Equation (8)) $\langle 85\text{T}1277 \rangle$.



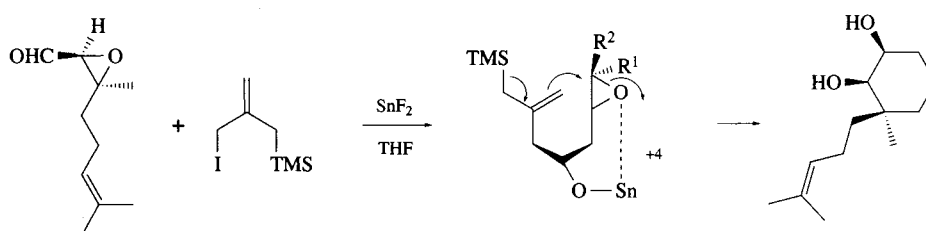


Scheme 9



Scheme 10

In another example, α,β -epoxy aldehydes have been coupled with 3-iodo-2[(trimethylsilyl)methyl]propene in the presence of stannous fluoride (SnF_2) $\langle 87\text{JA}576 \rangle$. This reaction constitutes a [3 + 3] annulation method and proceeds with good to excellent stereocontrol, and the products can be accessed in chiral, nonracemic form when optically active epoxy aldehydes are employed (Scheme 11).



Scheme 11

Epoxy-ene cyclizations have been used as key steps in natural products synthesis. The preparations of pseudopterosin, a potent antiinflammatory agent and analgesic $\langle 88\text{JOC}1584 \rangle$, and (+)-aphidicolin $\langle 85\text{TL}6147, 88\text{JOC}4929 \rangle$, (+)-9,10-*syn*- and (+)-9,10-*anti*-copalol $\langle 92\text{JOC}4598 \rangle$ are representative examples of the synthetic utility of Lewis acid-catalyzed epoxide cyclizations.

1,3-Eliminations of (3,4-epoxybutyl)stannanes under the action of EtAlCl_2 give rise to cyclopropylmethyl alcohols $\langle 87\text{SC}781, 91\text{JOC}2066, 91\text{JOC}2076 \rangle$. This method can be used reliably to prepare bicyclo[3.1.0]hexanes from the corresponding spirocyclic epoxy stannanes (Equation (9)). These eliminations appear to be concerted when inversion can take place at both centers. In other cases, the 1,3-eliminations are stepwise and must compete with 1,2-hydride shifts.



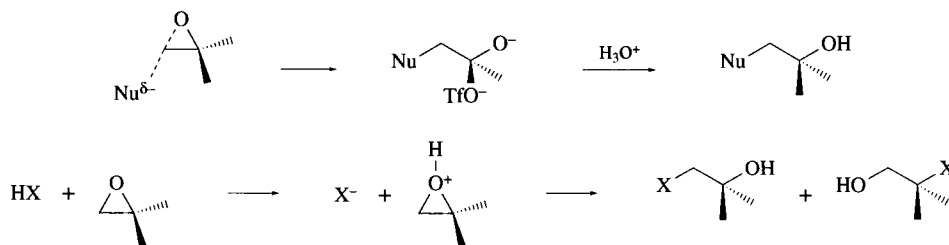
1.03.3.4 Reactions with Carbonyl Compounds

Oxiranes undergo regioselective ring-opening reactions with benzoyl chloride in the presence of CoCl_2 <88TL4985>. Similar results are obtained when TMS-Cl is used in the presence of CoCl_2 <88CL1157>. Epoxyketones likewise suffer regioselective acylative cleavage with benzoyl chloride in the presence of tin halide–Lewis base complexes ($\text{Bu}_2\text{SnCl}_2\text{-Ph}_3\text{P}$ or $\text{SnCl}_2\text{-PPh}_3$) <86TL3021, 92TL7149>. Treatment of oxiranes with acid chlorides in the presence of hexaalkylguanidinium chloride, as well as the silica-supported analogues, results in regioselective formation of 2-chloroalkyl alkanoates or benzoates <94JOC4925>. Moreover, an *N*-arylmethylpyridinium $\cdot \text{SbF}_6^-$ based catalyst converts oxiranes in the presence of carbonyl compounds to 1,3-dioxolanes <90CL2019>. There are a series of reports on ring openings of oxiranes via acid-catalyzed reactions with anhydrides <83KGS125, 89KGS269, 89KGS309>. From these reactions, isomerization products (allylic acetates) are usually obtained at high temperatures, and diesters of 1,2-diols at lower temperatures. The same authors <90KGS174> have described a noncatalytic substitutive *O*-acylation of oxiranes with trifluoroacetic anhydride (TFAA). The authors concluded that the mechanism of ring opening involves initial attack of TFAA by the oxirane oxygen, followed by either capture of the more stable carbocation intermediate by CF_3COO^- , or E1 elimination to the corresponding allylic acetate. Noncatalyzed regioselective and stereospecific ring opening of oxiranes with trichloroacetyl chloride and dichloroacetyl chloride have also been observed. These latter reactions invariably give trichloro- or dichloroacetates of chlorohydrins <86UP 103-01>; depending on the nature of the substituent, the “normal” and/or “abnormal” products are formed.

1.03.3.5 Nucleophilic Attack on Ring Carbon

1.03.3.5.1 Introduction and mechanistic aspects

Nucleophilic ring opening reactions of oxiranes are among the most important reactions of these small ring systems <83T2323, 84S629, 92AG(E)1179, 93JOC1221>. The driving forces for the ease of ring opening of an oxirane are (a) the ring strain, (b) the polarization of the C—O bonds in the small ring system, and (c) the basicity of the oxirane oxygen. The stereoselectivity of the ring opening of oxiranes is usually completely *anti* <71G300, B-72MI 103-01>. A theoretical study <84TL5339> corroborates the experimentally observed preference for the *anti* attack, i.e., the transition state for the rear-side attack is lower in energy than that for the front-side attack. The higher energy of the latter mode of attack has been ascribed to a strong repulsive electronic interaction between the nucleophile and the epoxide oxygen on which a negative charge is developing. However, control of regioselectivity is not always simple, especially when acids or Lewis acids are used as catalysts. The ring opening can, therefore, proceed by more than one mechanism. When strong nucleophiles are used, the preferred site of attack is the least-substituted carbon ($\text{S}_{\text{N}}2$) for steric reasons. When acids or Lewis acids are used, protonation (or metallation) of the oxirane oxygen weakens the C—O bond and increases the positive charge on the carbon atoms, and the mechanism shifts to a “borderline $\text{S}_{\text{N}}2$ ”, with considerable $\text{S}_{\text{N}}1$ character in the transition state <86JA1594, 88JA2508, 88JA6492, 90OM511>. An intermediate hydrogen-bonded complex of ethylene oxide and HCl (isolated in a pulsed jet) has been characterized in the gas phase by microwave spectroscopy (Scheme 12) <90AG(E)72>.

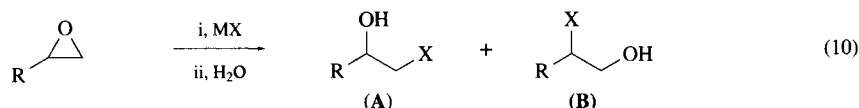


Scheme 12

1.03.3.5.2 H^+ - or Lewis acid-assisted ring opening

Acid-catalyzed hydrolysis of oxiranes has been reviewed extensively <59CRV737, 60QR317, B-64MI 103-01, B-72MI 104-01>. The kinetics and mechanism of the acid-catalyzed hydrolysis of styrene oxides

<93JOC924> and *cis*- and *trans*-anethole oxides has been investigated by Whalen and co-workers <93JOC2663>. Regio- and chemoselective synthesis of halohydrins by cleavage of oxiranes with metal halides has been reviewed <94S225>. In a study, the effects of a number of Li-, Mg-, Al-, and Ti-based Lewis acids on the regioselectivity of oxirane ring opening were reported <92JOC5140>. The use of Mg(TMP)Br, AlCl₃, AlI₃, and Buⁱ₃AlCl favored exclusively the formation of type (A) products (Equation (10)), whereas Ti(NEt)₃ and TiCl₄, strongly favored type (B) products (91% and 89%, respectively).



The methanolysis, azidolysis, and aminolysis of epoxy benzyl ethers and epoxy alcohols have been reported <93JOC1221>. All the epoxides studied showed a tendency toward C-3 selectivity when a Lewis-acidic metal cation (Li⁺, Mg²⁺, or Zn²⁺) was added to the reaction mixture, suggesting that the nucleophilic attack in these instances is chelation-controlled (Equation (11), and see Table 2).

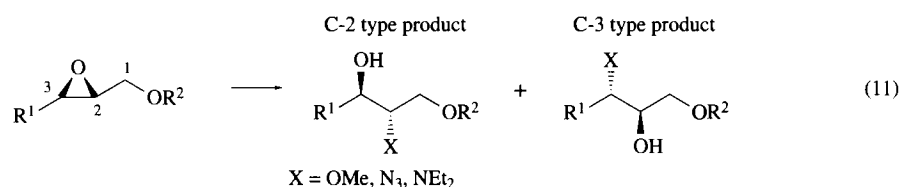


Table 2 Regioselectivity (%) of ring-opening reactions of *trans*-oxiranes.

Reagent	C-2 type product (%)	C-3 type product (%)
MeOH/H ⁺	19	81
MeOH/LiClO ₄	11	89
NaN ₃ /LiClO ₄	6	94
NHEt ₂	13	87
NHEt ₂ /LiClO ₄	<1	>99

Aluminum and titanium catalysts mediate azidotrimethylsilane (TMS-N₃) additions to oxiranes <91T1435>. TMS-N₃ adds to oxiranes in the presence of dimethyl tartrate and stoichiometric amounts of Ti(OPrⁱ)₄ in modest enantiomeric excess; and in the presence of catalytic amounts of Ti(OPrⁱ)₄, racemic *trans*-2-azido-1-trimethylsilyl ethers are formed <88BCJ1213, 88JOM(346)C7, 88S541, 91SL774>. Nugent utilized an optically active zirconium catalyst in conjunction with PrⁱMe₂SiN₃ or TMS-N₃, and trimethylsilyl triflate (TMS-OCOCF₃) to affect enantioselective ring opening of *meso* oxiranes in 83–93% enantiomeric excess <92JA2768>. Also, organoimido complexes catalyze regioselective TMS-N₃ additions to oxiranes, with the catalyst activity decreasing in the order Cr(IV) > Cr(IV) ≈ Mo(VI) >> W(VI) <95TL107>. SmI₂(THF)₂ has been found to catalyze regioselective ring opening of oxiranes by TMS-N₃, TMS-CN, and primary and secondary amines <95TL1649>.

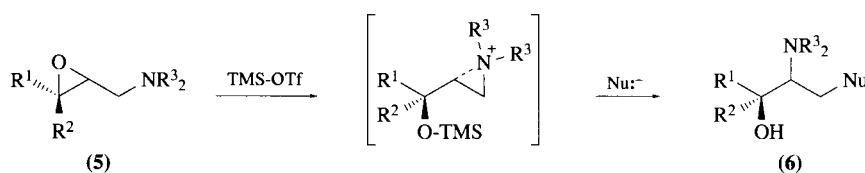
A mild and efficient method for the aminolysis of oxiranes in aprotic solvents using metal ion salts of Li⁺, Na⁺, Mg²⁺, Ca²⁺, and Zn²⁺ as Lewis acid has been reported <90TL4661>. The reaction rates depend, in addition to the nature of the amine and epoxide, also on the type of the metal ion of the catalyst salt. The stereoselectivity observed in these reactions is complete inversion of configuration. Epoxy carboxylic acids are cleanly ring-opened by primary amines at C-2 to provide α-amino-β-hydroxy acids <92TL2497>.

The metal-assisted aminolysis of epoxides proceeds through an A1-type mechanism <87JA1463, B-87MI 103-01>. The regioselectivity of the ring opening can be altered by the choice of the amine, as well as the metal ion. For instance, styrene oxide combines with aniline in the presence of LiClO₄ to give the 2-amino-2-phenylethanol (C-1 attack) as the overwhelming product (95% relative yield), whereas the more bulky amine (Prⁱ)₂NH (LiClO₄ catalyst) almost exclusively attacks the less highly substituted epoxide carbon (C-2 attack, 99% relative yield) <91JOC5939>. The metal ion is also able to modulate the regioselectivity of ring opening: weaker Lewis acid cations like Na⁺ promote more

S_N2 -type nucleophilic attack on the less highly substituted carbon; better Lewis acids cations, e.g., Zn^{2+} , Li^+ , and Mg^{2+} , are more effective in directing the attack of the amine to the benzylic carbon.

The role of lanthanides in oxirane ring openings had been recognized $\langle 87TL6065 \rangle$, and lanthanide(III) trifluoromethanesulfonates have been shown to effectively catalyze oxirane ring opening by nucleophiles $\langle 94JCS(P1)2597, 94TL6537 \rangle$; for aminolysis reactions even sterically hindered amines and/or oxiranes can be used in this process $\langle 94TL433 \rangle$.

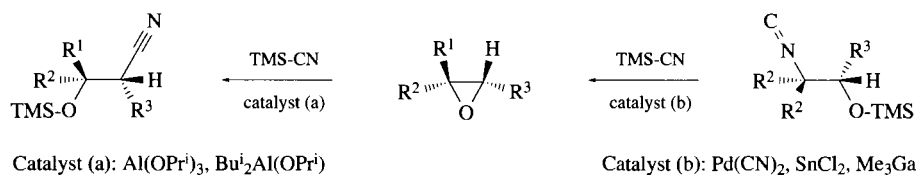
2,3-Epoxy sulfides isomerize in the presence of Lewis acids into the corresponding 2-trimethylsiloxythiiranium trifluoromethanesulfonates, which are regioselectively trapped at the least-hindered position (C-1) with a variety of nucleophiles $\langle 93JCS(P1)1371 \rangle$. The analogous reaction of 2,3-epoxy amines likewise gives with trifluoromethylsulfonic acid (TMS-OTf) the corresponding 2-trimethylsiloxyaziridinium trifluoromethanesulfonates which, when treated with nucleophiles, give 1-substituted 2,3-diamino alcohols in enantiometrically and diastereometrically pure form $\langle 94JCS(P1)1363 \rangle$. The intermediate aziridinium salt is stable at room temperature and has been characterized by NMR spectroscopy. Quenching with various nitrogen-based nucleophiles leads to the corresponding amino alcohols (Scheme 13).



Scheme 13

The isomerization of (5) to (6) is related to the known Payne rearrangement of 2,3-epoxy alcohols $\langle 62JOC3819, 82JOC1373, 83JOC3761, 93JOC5153 \rangle$. A related isomerization of a primary 2,3-epoxy amine to the corresponding aziridin-2-yl-methanol using trimethylaluminum as catalyst has been described $\langle 92TL5351 \rangle$. Also, 2,3-epoxy sulfonamides rearrange to *N*-tosylaziridin-2-ylmethanols under basic conditions $\langle 92TL487 \rangle$.

Ambident nucleophiles such as cyanotrimethylsilane can, in principle, give either nitriles or isonitriles with oxiranes, depending on the nature of the Lewis acid catalyst. In the presence of Et_2AlCl $\langle 82JOC2873 \rangle$, trimethylsilyl ethers of β -hydroxy nitriles are obtained. Gassman and co-workers $\langle 82JA5849, 84TL3259, 86JOC5010 \rangle$ found that with ZnI_2 catalyst, trimethylsilyl ethers of β -hydroxy isonitriles are isolated instead. These latter compounds serve as important precursors of β -amino alcohols and oxazolines. In 1987, Utimoto *et al.* $\langle 87JOC1013 \rangle$ described controlled utilization of the ambident reactivity of TMS-CN to affect either isocyanosilylation or cyanosilylation of oxiranes. In general, soft Lewis acids ($Pd(CN)_2$, $SnCl_2$, Me_2Ga , ZnI_2) favor the formation of isocyanides, while harder ones ($Al(OPr)_3$, or $Bu_2Al(OPr^i)$) favor trimethylsiloxy nitriles. In isonitrile formations the nucleophile attacks the most highly substituted carbon, with the exception of propylene oxide which gives a $\approx 1:1$ mixture of regioisomers with $Pd(CN)_2$, $SnCl_2$, and Me_3Ga (Scheme 14).

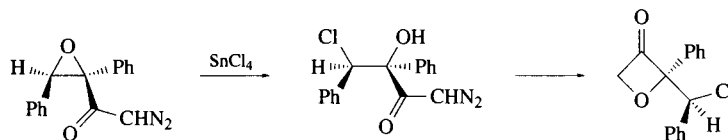


Scheme 14

The researchers found that the Et_2AlCl -mediated reactions lead to mixtures of both types of products. Control over the ambident nucleophilicity of TMS-CN as a function of Lewis acid has been rationalized in terms of the HSAB (hard-soft-acid-base) theory $\langle 83TL655 \rangle$. Olah *et al.* recommend the use of TMS-CN in the presence of catalytic potassium cyanide/18-crown-6 complex for the regiospecific synthesis of 3-[(trimethylsilyl)oxy] nitriles from terminal oxiranes $\langle 90JOC2016 \rangle$. In the nitrile formation, general Lewis acid catalysis has been invoked to explain the observed regioselectivity (S_N1 character). In the isonitrile formation, TMS-CN is believed to transfer CN^- to the Al-catalyst to give R_2AlCN which attacks the less highly substituted epoxide carbon in an S_N2 -type reaction. The first examples of base-catalyzed ring opening of oxiranes with TMS-CN were reported to produce β -trimethylsiloxy nitriles exclusively in a regioselective fashion $\langle 90CL481 \rangle$. As

catalysts, solid bases such as CaO, MgO, hydroxyapatite (HAp, $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH}_2)$), and CaF_2 have been employed. The catalytic activity of solid base correlates well with the respective intrinsic base strengths ($\text{CaO} \sim \text{MgO} > \text{HAp} \gg \text{CaF}_2$). Also, acetone cyanohydrin in THF has been used to convert terminal oxiranes to 1-cyano-2-hydroxyalkanes $\langle 92\text{TL}3281 \rangle$.

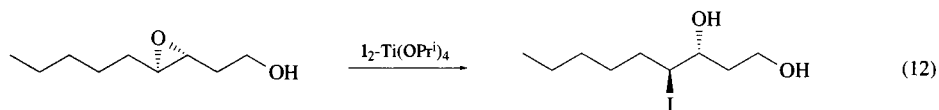
In an interesting application of Lewis acid-mediated oxirane ring openings, diazomethylchlorohydrins, formed from α,β -epoxy diazomethylketones with SnCl_4 , cyclize to 3-oxetanones (Scheme 15) $\langle 92\text{T}9985 \rangle$.



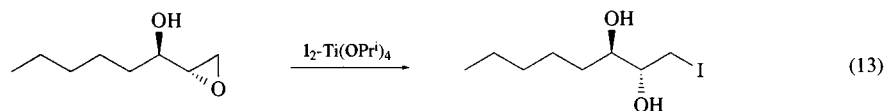
Scheme 15

1.03.3.6 Reactions with Halogens

Treatment of allylic and homoallylic epoxy alcohols with a halogen (Br_2 , I_2) in the presence of a stoichiometric amount of $\text{Ti}(\text{OPr}^i)_4$ provides halohydrins in a highly regioselective manner $\langle 90\text{JOC}3429 \rangle$. The method is not applicable when acid-sensitive groups are present. Halogenations of oxiranes with elemental bromine and iodine have been found to give halohydrins in a regioselective manner. The halide predominantly attacks the least-substituted carbon in benzene; however, the opposite regioisomer is favored in nitromethane (Equations (12) and (13)) $\langle 92\text{TL}7093 \rangle$.



(12)



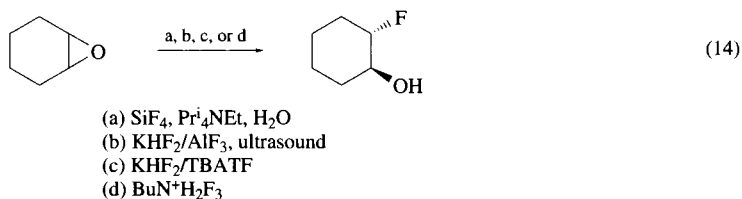
(13)

1.03.3.7 Ring Opening with Neutral or Basic Nucleophiles

1.03.3.7.1 Halides

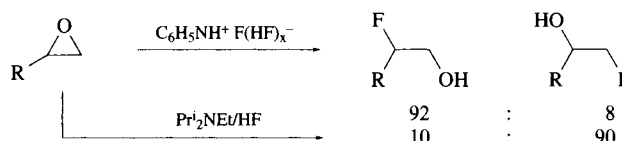
Ring opening of oxiranes with iodotrimethylsilane provides silylated halohydrins $\langle 84\text{CHEC-}1(7)111 \rangle$. An exception to this reaction mode has been reported $\langle 91\text{JOC}4598 \rangle$. Silyl enol ether-terminated oxiranes, when treated with TMS-I in the presence of hexamethyldisilazide (HMDS) at low temperatures suffer C—C cleavage and cyclization to dihydrofurans.

Cleavage of oxiranes with metal halides as a means for regio- and stereoselective synthesis of halohydrins has been reviewed $\langle 94\text{S}225 \rangle$. Metal halides (CuCl_2 , CuBr_2 , ZnBr_2 , CoCl_2 , FeCl_3) and SiO_2 -supported metal halides have been applied to regioselective ring opening of aryloxiranes carrying electron-withdrawing groups (CN , CO_2Me) $\langle 93\text{BSF}620 \rangle$. Organotin halides have been employed as effective reagents for the conversion of oxiranes to halohydrins $\langle 83\text{S}640$, $86\text{JOC}2177$, $92\text{TL}7149 \rangle$. Benzyl ether derivatives of simple aliphatic epoxides are converted to mixtures of the corresponding fluorohydrins in good yields $\langle 88\text{JOC}1026 \rangle$. Alternatively, SiF_4 in conjunction with Hünig's base (diisopropylethylamine) or SiF_4 /tetrabutylammoniumfluoride (tbaF), or $\text{SiF}_4/\text{H}_2\text{O}$ can be used for the transformation of oxiranes to fluorohydrins $\langle 88\text{TL}4101 \rangle$. In the case of 1-methylcyclohexene oxide, the presence of H_2O is essential. Other reagent systems, such as KHF_2 /porous AlF_3 $\langle 89\text{JCC}1848 \rangle$, KHF_2 /cat. tbaF (phase-transfer conditions) $\langle 90\text{TL}7209 \rangle$, and finally, pyridine/HF in toluene $\langle 90\text{T}4247$, $93\text{SC}2389 \rangle$ have also been successfully applied to regioselective fluorohydrin synthesis from oxiranes (Equation (14)).



With the latter reagent terminal oxiranes preferentially give 2-fluoro-1-alkanols with pyridine/HF in toluene. In contrast, 1-fluoro-2-alkanols are the major products of the reaction with HF/*N*-ethyldiisopropylamine adduct (Scheme 16).

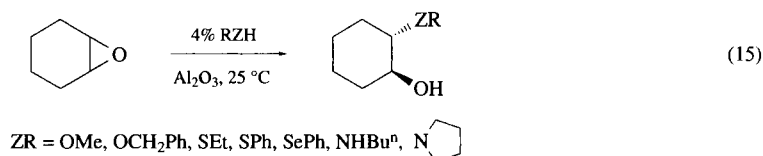
2,3-Epoxytosylates are converted to the corresponding halohydrins with lithium halides (LiCl , LiBr , LiI) in the presence of Amberlyst 15 resin as catalyst <94TL797>.



Scheme 16

1.03.3.7.2 *N*-, *P*-, *O*-, *S*-, and *Se*-based nucleophiles

Addition of strong bases to oxiranes usually gives poor yields of nucleophile incorporation, sometimes resulting in products derived from transannular interactions. To ameliorate these problems, Posner and Rogers introduced a mild and selective method for oxirane ring opening by alcohols, thiols, benzeneselenol, amines, and acetic acid in the presence of unactivated, commercially available neutral chromatographic alumina as catalyst <77JA8208, 77JA8214>. The use of this “nucleophile-doped” alumina (4% by weight of alumina) catalyzes smooth ring opening of oxiranes. Whereas the regioselectivity in alcohol-doped ring opening of trisubstituted oxiranes is relatively poor (1.5:1 to 6:1—obviously $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms intervene), all other nucleophile-doped alumina reactions involve introduction of the nucleophile *regiospecifically* at the less-substituted center (Equation (15)).

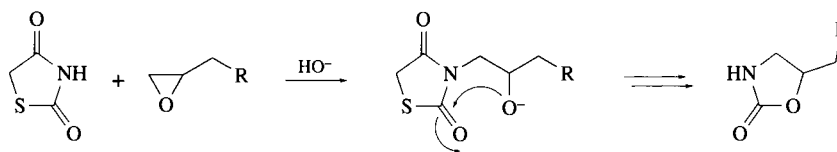


Ring opening of 2,3-epoxy alcohols under the action of a wide variety of nucleophiles under neutral, basic (Payne rearrangements), or acidic conditions has thoroughly been reviewed by Sharpless and Behrens <82JOC1373, 83JOC3761, 83MI 103-02>, see also <83PAC589>.

The azide anion has frequently been used in epoxide ring openings. <83TL4189, 86TL4423, 86CL1327, 89TL4153>. Excellent discussions of factors affecting regiochemistry of azide ring openings of oxiranes are available <83MI 103-02, 85JOC1560>. $[\text{Ti}(\text{O}-\text{Pr}^i)_2(\text{N}_3)_2]$ has been utilized as a safe, mild reagent for azide ring opening of 2,3-epoxy alcohols <88JOC5185>. An application of azide-induced ring opening of 1,1-dichloro-1,2-epoxides to enantioselective synthesis of α -amino acids has been reported by Corey and Link <92JA1906>.

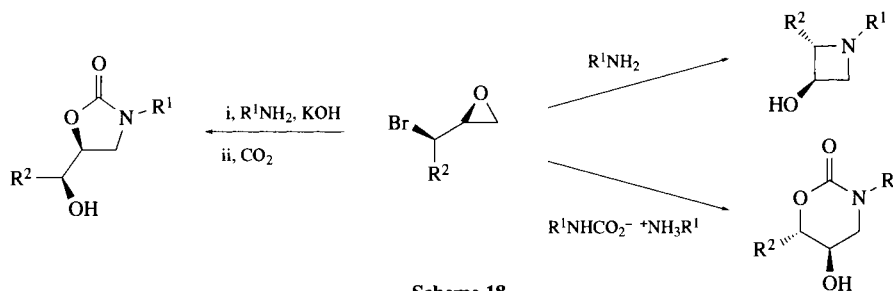
In cases where electrophiles are suitably located in the primary adduct to an oxirane, tandem cyclizations may ensue, leading to cyclic products. The reaction of thiazolidine-2,4-dione in the presence of base is a representative example (Scheme 17) <91KGS1137>.

2-(1-Haloalkyl)oxiranes undergo with amines a multitude of reactions, depending on the reaction conditions: (a) with primary amines one obtains 3-hydroxyazetidines (four-membered ring formation) <92H(33)511>; (b) with primary amines in the presence of base (Cs_2CO_3) oxazolidin-2-ones form (five-membered ring formation) <93H(35)623>; and (c) with a carbamate salt (RNHCO_2^-)



Scheme 17

$^+\text{NH}_3\text{R}$ derived from a primary amine, in the presence of CO_2 , perhydrooxazin-2-ones (six-membered cyclic carbamates) are isolated (Scheme 18) $\langle 93\text{H}(35)623 \rangle$.

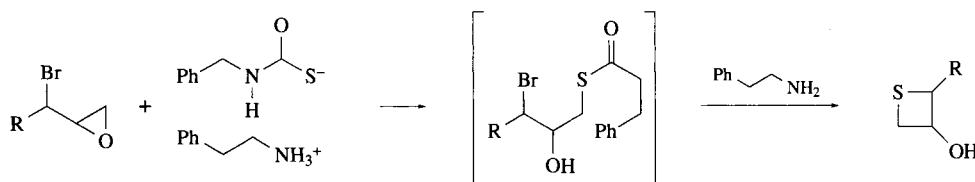


Scheme 18

Intramolecular amine-oxirane cyclizations give mainly quinolizidine derivatives by a 6-*exo-tet* ring closure $\langle 88\text{JOC}4452 \rangle$.

Vinyloxiranes have been ring-opened regioselectively by indoles $\langle 90\text{JOC}2969 \rangle$ under neutral conditions at high pressures (acetonitrile, 10 kbar). The reactions result in C-3 substitution of the indole by the C-1 of the vinyloxirane.

Thiolate (RS^-) $\langle 78\text{JOC}3803, 94\text{S}34 \rangle$, selenide (RSe^-) $\langle 78\text{T}1049, 86\text{TL}5579, 88\text{CC}1283, 92\text{S}377 \rangle$ and telluride (RTe^- or Te^{2-}) $\langle 80\text{JA}4438, 86\text{TL}5579, 93\text{JOC}718 \rangle$ ions convert oxiranes into the corresponding β -alkyl- or arylthio-, seleneno- or tellurio- substituted alcohols, respectively. LiClO_4 -assisted nucleophilic attack by thiols has been reported to afford 2-thioalkyl alcohols, with the dominant site of attack being the least-substituted oxirane carbon $\langle 92\text{SL}303 \rangle$. 2,3-Epoxy alcohols give with thiourea 2,3-epithio alcohols in the presence of $\text{Ti}(\text{OPr}^i)_4$ $\langle 88\text{JOC}4114 \rangle$. Upon treatment of oxiranes with *p*-toluene sulfinate or benzenethiolate salts in the presence of polyethylene glycol 4000 (PEG 4000; a phase transfer catalyst), β -hydroxy sulfones and sulfides form, respectively, in 60–90% yields $\langle 94\text{TL}10483 \rangle$. The reactions are regioselective and *anti*-stereoselective. The dialkylammonium salt of monothiocarbamic acid can act as a S^{2-} equivalent when reacted with 2-(1-haloalkyl)oxiranes $\langle 92\text{CL}1655 \rangle$. The initially formed thiocarbamate derivative suffers S—CO cleavage with a secondary or primary amine to deliver 3-thietanols (Scheme 19).



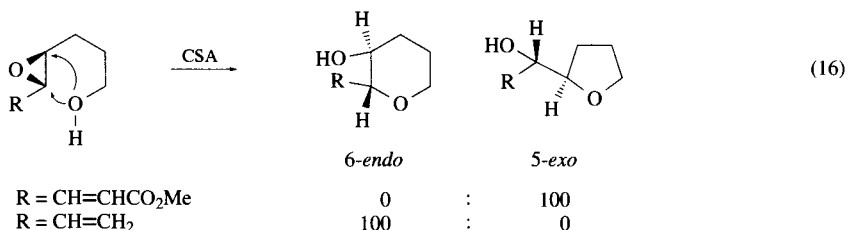
Scheme 19

Dialkylphosphite anions $[(\text{RO})_2\text{P}(\text{O})^-]$, generated from dialkyl phosphites with KF , have been shown to combine with oxiranes to afford α -hydroxyphosphonates $\langle 82\text{S}165, 84\text{ZOB}1205, 88\text{ZOB}2612, 90\text{DOK}(314)868 \rangle$.

1.03.3.7.3 Intramolecular nucleophilic attack

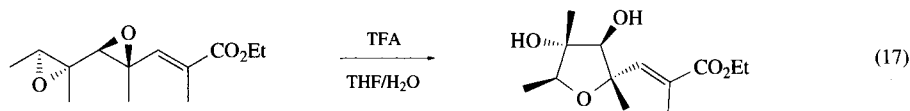
Nicolaou and co-workers undertook careful and extensive studies in this area, particularly paying attention to the stereoselectivities and ring selectivities of intramolecular epoxide ring-opening reactions $\langle 89\text{JA}5321, 89\text{JA}5330, 89\text{JA}6666, 89\text{JA}6676, 89\text{JA}6682 \rangle$. They determined that acid catalysis is

superior to base catalysis, and the most efficient catalyst was found to be camphorsulfonic acid (CSA) (Equation (16)).

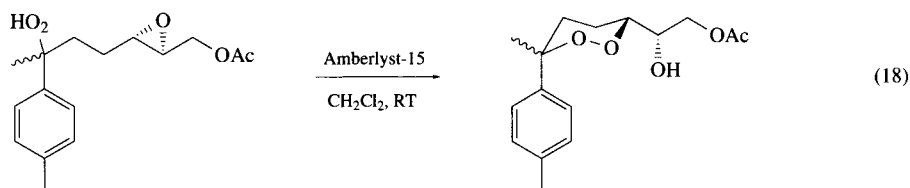


Their results show that, depending on the substituents on the starting oxirane and whether it is *cis*- or *trans*-1,2-disubstituted, tetrahydrofuran (via 5-*exo* ring closure), or tetrahydropyran (via 6-*endo* ring closure) formation dominated. *trans*-Hydroxy epoxides carrying an alkyl or vinyl group on C-1 preferentially cyclize to five-membered rings, while electron-withdrawing alkenyl groups at C-1 (CH=CHCO₂Me, CH=CHBr) favor six-membered oxaring formation. Under the same conditions, hydroxy oxiranes derived from *cis*-alkenes favor tetrahydrofuran formation to a greater extent than the *trans* counterparts; evidently the *cis*-oxirane stereochemistry disfavors the 6-*endo* ring closure owing to steric hindrance in the transition-state structure of cyclization. Along similar lines <89JA5335>, activation of 7-*endo* over 6-*exo* hydroxy epoxide opening has been achieved by placing an electron-rich double bond on C-1 of the oxirane. *cis*-Hydroxy epoxides exhibit lower selectivity. Attempts to prepare fused ring systems containing the oxepane framework lead to clean formation of fused tetrahydropyrans instead.

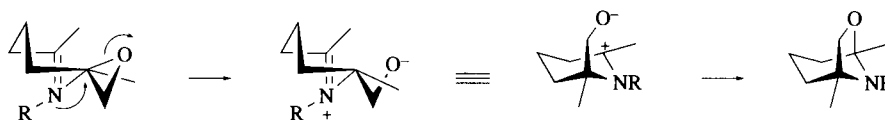
An acid-catalyzed hydrolysis of bis-(1,2,3,4-)epoxides with concomitant intramolecular cyclization leads to tetrahydrofuran derivatives (Equation (17)) <92TL4053>.



The OH group of a hydroperoxide can function as nucleophile as well, the result being a cyclic peroxide. This methodology has been applied to the total synthesis of all four stereoisomers of the natural product Yingzhaosu C (Equation (18)) <94TL9429>.



Wasserman *et al.* utilized an intramolecular imine-epoxide ring opening/cyclization process <88TL4973> to synthesize heterotropanes and substituted piperidines (Scheme 20). This methodology has been applied to the total syntheses of piperidine-based alkaloids (±)-teneraic acid <89TL6077> and (±)-solenopsin-A <88TL4977>.



Scheme 20

1.03.3.7.4 Organometallic reagents

This subject has been reviewed <91COS(3)223, 91COS(3)342>. The reactions of Grignard reagents with oxiranes can yield “normal” and/or “abnormal” alcohols <84CHEC-I(7)112>. Schleyer and co-workers

A theoretical interpretation of regioselectivities observed in additions of organometallic reagents to conjugated oxiranes has been reported ^[88JOC139].

Chamberlain and co-workers investigated the factors affecting the stereochemical control in Lewis acid-catalyzed cyclizations of various epoxy ketones in the presence of organoaluminum and silyl nucleophiles (88JOC1082, 91JOC4141).

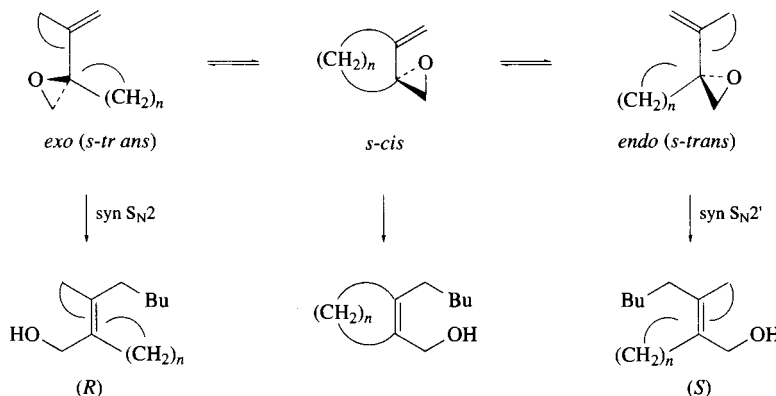
Reactions of homocuprates (R_2CuLi) with monosubstituted oxiranes proceed stereoselectively to give alcohols, and the alkylation occurs at the unsubstituted carbon of the ring [\(70JA3813, 73JOC4263, 73JOC4346, 75OR\(22\)353\)](#). 1,2-Disubstituted cases often lead to mixtures of products resulting from rearrangement or elimination in addition to substitution. Using higher-order mixed cuprates ($R_2Cu(CN)Li_2$), Lipschutz and co-workers achieved excellent yields on nucleophilic ring opening of oxiranes with a high degree of regioselectivity (Scheme 21) [\(82JA2305, 84JOC3928, 86TL4825, 88JOC4495, 92OR\(41\)135\)](#). The cleavage occurs at the less sterically encumbered position of the oxirane with a net inversion of configuration. It is interesting to note that in the case of styrene oxide a complete reversal of regioselectivity is observed when $RCu(CN)Li$ instead of $R_2Cu(CN)Li_2$ is used [\(77TL3407, 78TL2399\)](#). For examples of organocuprate additions to oxiranes, see [\(85TL4683, 86T5607, 87JOC4412, 87TL5631, 89TL5693, 90T5085, 91JOC5161\)](#).



Even though epoxysilanes are attacked by nucleophiles $\langle 90\text{JCS(P1)419, } 91\text{CC297, B-93MI } 103\text{-01} \rangle$ and in particular cuprate reagents $\langle 92\text{OR(41)135} \rangle$ predominantly at the carbon bearing the silicon atom $\langle 89\text{S647, } 90\text{CSR147, } 92\text{OPP553} \rangle$, the triisopropyl (TIPS) group reverses the regiochemistry of addition $\langle 93\text{TL3695} \rangle$. Epoxy organostannanes, like epoxy silanes, react with Me_2CuLi exclusively at the carbon bearing the stannyl group, irrespective of the nature of the substituent on the other oxirane carbon (alkyl or carboethoxy) $\langle 92\text{JOC46} \rangle$. The corresponding reaction of sulfinyloxiranes with R_2CuLi results in electron transfer to the oxirane carbon, rather than alkylation, followed by desulfinylation $\langle 89\text{TL1083} \rangle$. Lipshutz *et al.* described a two-step preparation of acyl silanes based on cyanocuprate additions to TIPS-substituted oxiranes followed by oxidation of the resulting alcohols

<94TL8999>. Triisopropyl (TIPS) acyl silanes have been prepared by a regiospecific ring opening of TIPS-substituted oxiranes with cyanocuprates and subsequent oxidation of the resulting alcohols.

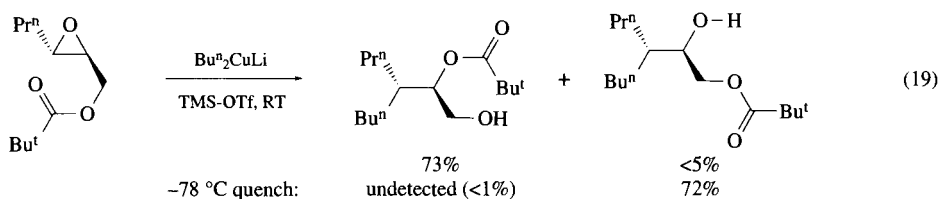
Additions of organocopper reagents to α -methylenecycloalkylidene epoxides have been found to proceed via S_N2' displacement to yield predominantly (Z)-cycloalkylcarbinols <83JA3360, 83JA6515, 84JA723, 84JA6006, 85JOC1607, 86T1703, 86TL2211, 89CRV1503, B-89MI 103-02>. The stereoselectivity of these reactions was studied using optically active starting materials. In all cases the cuprate additions have been found to proceed via the *syn* S_N2' pathway with high stereoselectivity <87JOC1106>. This study delineates the first route to optically active *trans*-cycloalkenes not requiring optical resolution. It also provides a third example of jump-rope racemization that occurs on a measurable time and temperature scale (Scheme 22).



Scheme 22

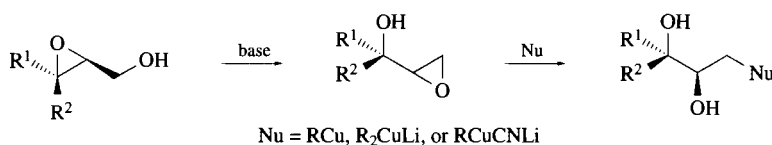
A stereoselective synthesis of 2,5-dihydrofurans has been accomplished by sequential S_N2' cleavage of alkynyloxiranes (mainly *anti* S_N2' product) with Me_2CuLi and silver(I)-catalyzed cyclization of the allenylcarbinol products <93JOC7180>.

By highly *anti*-selective conjugate addition of $\text{MeCu}(\text{CN})\text{Li}$, as well as Me_2CuLi <88TL913> to vinyloxiranes, nonracemic allylic alcohols are obtained in excellent yields <90JOC1540, 91JOC2225>. These latter compounds are suitable intermediates for the synthesis of differentially protected triol and tetrol subunits of macrolides. An unusual intramolecular transesterification process has been discovered following the trimethylsilyl trifluoromethanesulfonate (TMS-OTf)-mediated dialkylcuprate addition to 2,3-epoxyol pivaloylates (Equation (19)) <92JOC5031>. This protocol has been shown to be a useful method for the synthesis of an important class of 1,2-monoprotected 1,2-diols that are difficult to access by more traditional means.



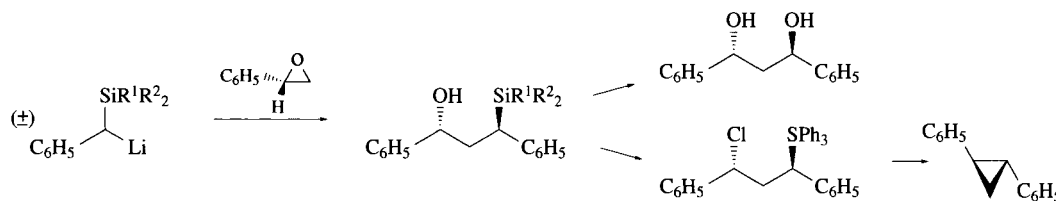
Payne rearrangement of 2,3-epoxyols followed by alkylation with organometallic reagents has now become possible since the reactions can be carried out in an aprotic solvent (THF) containing LiCl <90JCS(P1)1375>. The more reactive (usually terminal) oxirane isomer undergoes *in situ* nucleophilic attack by a variety of organocopper reagents (RCu , R_2CuLi or RCuCNLi) (Scheme 23).

Corey and Chen described methods for the synthesis of γ -hydroxysilanes, 1,3-diols, and cyclo-



Scheme 23

propanes by the reaction of a chiral epoxide with a racemic α -silyl organolithium reagent (Scheme 24) <94TL8831>.



Scheme 24

Epoxysilanes, upon ring opening with organometals containing lithium and copper, give rise to adducts which either under the reaction conditions or upon treatment with KH can be stereospecifically converted to the corresponding (*E*)- and (*Z*)-alkenes, respectively <89JOC2043>.

Regioselective oxirane opening with alkynyllithium in the presence of $\text{BF}_3/\text{Et}_2\text{O}$ (Yamaguchi method) <83TL391, 84JA3693, 92S191> or ethylene diamine has been described <83JOC3548, 85CJC651, 91JOC3449>. The attack by the nucleophile occurs at the less-hindered carbon in these cases.

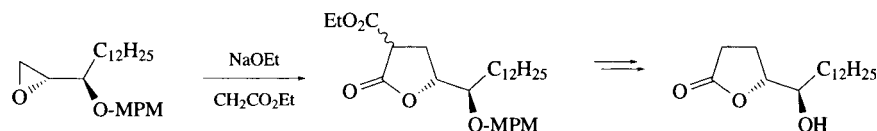
Other examples of regioselective ring openings of chiral 2,3-epoxy alcohols with various nucleophiles, carbanions, and organocuprates have been reviewed <83PAC589>. Diethylaluminum amides <81TL195> and lithium aluminum amides <92JOC5831> have been found to give 2-amino alcohols in regioselective manner. Reactions of 2-(trialkylsilyl)allyl organometallic reagents (Li, Si, Sn) with terminal oxiranes have been reported <94JOC4138>.

Alkyl- and alkenylzirconocenes react with oxiranes in the presence of catalytic AgClO_4 in a tandem oxirane rearrangement-carbonyl addition to give chain-extended secondary alcohols <93JOC825>. The regioselectivity of alkyl or alkenyl transfer by the organozirconocene in these reactions is the opposite of that observed in reactions of oxiranes with organometallics <84JA3693, 88MI 103-01, 91TL5647>.

Finally, (trialkylsilyl)manganese pentacarbonyl complexes ($\text{TMS-Mn}(\text{CO})_5$) react with oxiranes in a regioselective manner to furnish functionalized alkylmanganese pentacarbonyl complexes, which have been converted to spiroketal lactones or cyclopentenone derivatives <88JOC4892>.

1.03.3.7.5 Carbanions

This subject has been reviewed by Rao *et al.* <83T2323> with special attention given to intramolecular substitution reactions, and Smith <84S629>. Cyanide (CN^-) regioselectively attacks the less-substituted oxirane carbon to furnish β -hydroxy nitriles <92JOC4441, 92TL1431, 92TL3281>. As mentioned in <84CHEC-I(7)112>, relatively strong C—H acids induce oxirane ring opening in the presence of base <89OPP241>. In an application reported in 1994, the sodium salt of diethyl malonate was condensed with an appropriately substituted oxirane to give a γ -butyrolactone which was converted to the naturally occurring muricatacin (Scheme 25, MPM = *p*-methoxyphenylmethyl) <94TL115>.

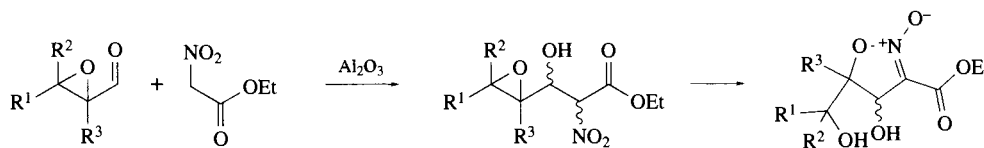


Scheme 25

2-(1-Ethoxyvinyl)oxiranes are attacked by the diethyl malonate anion regioselectively, rather than regiospecifically <85IZV6825>, giving rise to mixtures of isomeric γ -lactones <92KGS22>.

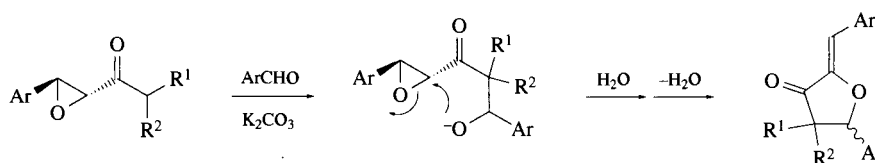
Also, dianions derived from γ -substituted β -ketoesters engage in condensations with oxiranes, to afford 2-carbomethoxyethylidene-tetrahydrofurans in a stereospecific manner <92SL529>. In certain cases these types of reactions can be effected on an alumina surface without solvent. In a base-catalyzed tandem nitroaldol cyclization process <90JOC781>, 2-isoxazoline-2-oxides are formed in

ambido- and regiospecific fashion; only the 5-*exo* cyclization mode is observed in these examples (Scheme 26).



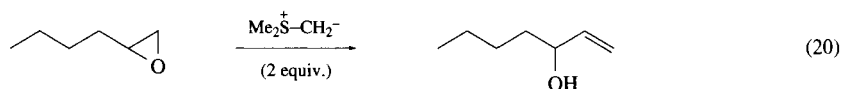
Scheme 26

An intramolecular analogue of the aforementioned reaction has been encountered during the Darzens condensation of α -bromoketones with two equivalents of an aryl aldehyde (94TL9367). The intermediate α -keto oxiranes engage in aldol additions to the second aldehyde equivalent before cyclizing to the five-membered heterocyclic ring (Scheme 27).



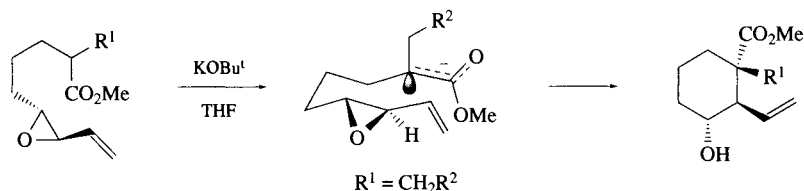
Scheme 27

The well-known Wadsworth–Emmons α -phosphono ester/epoxide condensation methodology has now been extended to β -keto phosphonates for the preparation of spirocyclopropyl ketones (93JOC4584). α -Phenylsulfonyl carbanions, when condensed with triphenylsilyloxiranes, afford 3-phenylsulfonyl alcohols, which serve as precursors of silylcyclopropenes (92CC802). Terminal, allylic, and benzylic oxiranes are smoothly converted directly to one-carbon homologated allylic alcohols with an excess of dimethylsulfonium methylide in excellent yields (Equation (20)) (94TL2009, 94TL5449).



N-Tosylsulfonimidoyl-stabilized carbanions convert oxiranes to oxetanes (83JA252). Additions of selenium-stabilized carbanions to oxiranes have found use in the synthesis of δ -acetoxy α,β -unsaturated aldehydes (82JOC1618).

Stork's intramolecular "allylic epoxide cyclizations" proceed stereospecifically to give cyclohexanone derivatives (90JA1661). The reason for the observed stereospecificity (OH, CO₂Me *cis*) can be traced to the energetically more favorable transition-state conformation. This methodology has been applied to enantioselective total syntheses of (–)-histrionicotoxins (Scheme 28) (90JA5875).

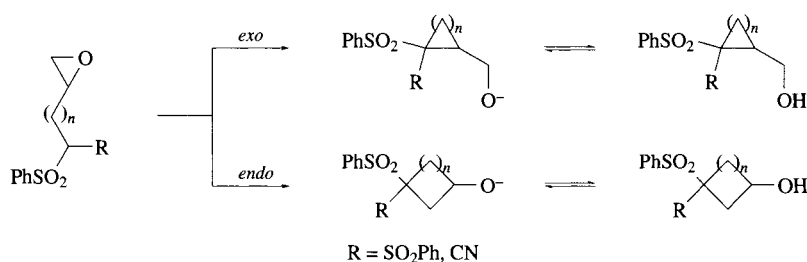


Scheme 28

The intermolecular variants of the above-mentioned enolate/epoxide condensations are much less common in organic synthesis. Nitrogen-containing enolates (e.g., of amides (77JOC1688, 81JOC2833, 88SC1159), enamines (69T3157), and ketimines (75S256) do open oxiranes; however, enolates of ketones and esters do not react with epoxides which favor selectivity (89JOC2039). Taylor and co-workers have employed aluminum enolates of *t*-butyl esters (89JOC2039, 91JOC5951), encouraged by an earlier report (76JOC1669) on epoxide ring openings. These reactions give γ -hydroxy esters in a diastereoselective fashion. Crotti and co-workers found that LiClO₄ promotes the addition of certain enolates to oxiranes in excellent yields to give γ -hydroxyketones (91TL7583). The same research

group discovered a more efficient catalyst, yttrium triflate [$\text{Y}(\text{OTf})_3$], which allows for lower reaction temperatures, shorter times, and smaller amounts of catalyst (10 mol%) (94TL6537). The authors ascribe the greater catalytic effect of Y^{3+} to its ability for tighter coordination to oxygen.

Diastereoface differentiation in the addition of lithium enolates to chiral α,β -epoxy aldehydes has been investigated (93T5253). A Reformatsky-type reaction of styrene oxide with ethyl 3-bromo-2-methylenepropanoate has been reported to yield an α -methylene- γ -butyrolactone (81JPS84). Carbanions derived from γ - and δ -epoxy sulfones preferentially cyclize to five-membered rings (81CJC1415, 85TL3643, 85JOC3674, 87JOC4614). However, steric hindrance at the oxirane carbon closer to the enolate results in 6-*endo-trig* cyclization in favor of formation of the cyclopentanol (90JOC3962). The effects of ring size on regioselectivity and reaction rates have been studied for intramolecular epoxy carbanion cyclizations of several epoxy bis(sulfones) and cyano sulfones (94JOC1518) (Scheme 29).



Scheme 29

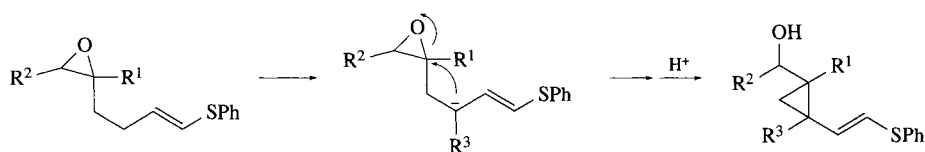
Cyano sulfonyl carbanions have been found to be more reactive than their bis(sulfonyl) counterparts by a factor of 2 to 100, the reactivity difference being larger for the longer chains. The authors suggest steric, rather than electronic factors, for the slower rates observed for bis(sulfones). The regioselectivities for the ring closure are shown in Table 3.

Table 3 Regioselectivities in epoxysulfone cyclizations.

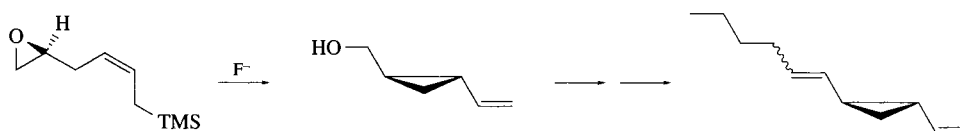
<i>R</i>	<i>n</i>	<i>Exo/endo</i> ratio
$\text{C}_6\text{H}_5\text{SO}_2$	1	100:0
$\text{C}_6\text{H}_5\text{SO}_2$	2	0:100
$\text{C}_6\text{H}_5\text{SO}_2$	3	64:36
$\text{C}_6\text{H}_5\text{SO}_2$	4	0:100
CN	1	100:0
CN	2	0:100
CN	3	53:47
CN	4	55:45

Like sulfones and/or bis(sulfones) (91JOC3530), thio (82OR(27)1, 91S1168, 93JOC626) and 1,3-dithianyl groups (91JOC6038), nitriles (91TL2637) (see also Stork's epoxy nitrile cyclizations, (74JA5268, 74JA5270), as well as 1,3-bis(silyl) substituents (93JOC626) facilitate carbanion formation and promote inter- and intramolecular ring opening of oxiranes. Three-membered rings form with ease (91LA1101, 91JOC717, 91T3281, 91TL2637, 92JOC5360, 93TL6443, 93JOC1496); four-membered carbocyclic rings may also arise in certain cases to a lesser extent. Even allylic carbanions have been employed in these types of reactions (90TL3609, 93JOC626) (Schemes 30 and 31).

Also, NaOMe-promoted cyclization of γ,δ -epoxy ketones results in cyclopropane formation,



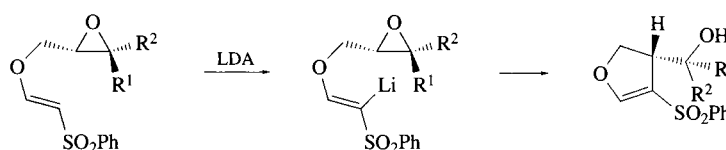
Scheme 30



Scheme 31

affording exclusively *cis*-1-acyl-2-hydroxymethyl derivatives, suggesting that a chelated intermediate ($\text{C}=\text{C}-\text{O} \rightarrow \text{Na} \leftarrow \text{O}$ -oxirane) is involved in the process $\langle 94\text{TL}5633 \rangle$.

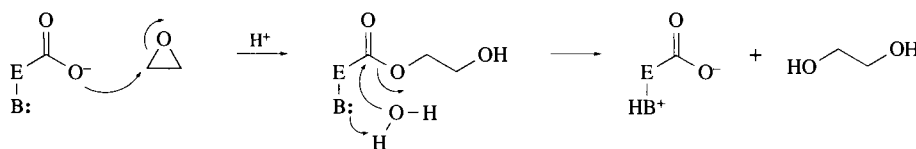
Finally, vinylsulfonyl carbanions, generated from (*E*)-2-(phenylsulfonyl)vinyl ethers of 2,3-alcohols with LDA, cyclize to dihydrofurans $\langle 91\text{JOC}3556 \rangle$; see also $\langle 85\text{TL}6301, 89\text{TL}7029 \rangle$ (Scheme 32).



Scheme 32

1.03.3.7.6 Enzyme-catalyzed reactions

Enzyme-catalyzed hydrolysis of oxiranes has been known since the 1970s $\langle 71\text{B}4858, 87\text{MI} 103-02 \rangle$. Microsomal epoxide hydrolase (MEH) $\langle 83\text{BBA}(695)251, 93\text{B}2610 \rangle$ catalyzes the *trans*-antiperiplanar addition of water to oxiranes and arene oxides to afford vicinal diols. It has been demonstrated by isotope labeling experiments that the catalytic mechanism of MEH involves an ester intermediate $\langle 93\text{JA}10466 \rangle$. In this mechanism an oxygen atom is transferred from the enzyme to the product (Scheme 33).

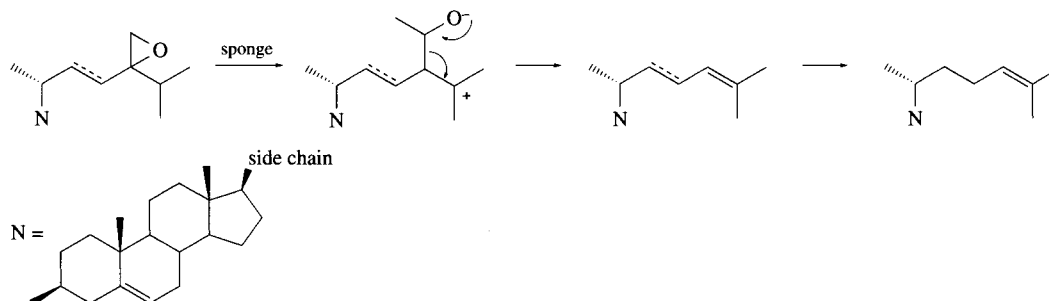


Scheme 33

Selective epoxide ring openings in natural processes can also be accomplished by a number of enzymes. While a variety of epoxy hydrolases convert oxiranes to 1,2-diols or other 1-hydroxy-2-Nu (Nu = nucleophile, e.g., amines, azide, CN^-) compounds $\langle 82\text{JBC}3771, 83\text{BBA}(695)251, 84\text{ACR}9, 86\text{AG}(\text{E})1032, 86\text{CC}7, \text{B}-86\text{MI} 103-03, 87\text{MI} 103-03, 88\text{MI} 103-02, 89\text{CC}1170, 89\text{JCS}(\text{P}1)2369, 89\text{JOC}5978, 90\text{ABC}1819, 92\text{IJC}(\text{B})828, 92\text{TA}1361, 92\text{TL}4077, 93\text{TA}1161, 93\text{TA}1331, 94\text{TL}81, 94\text{TL}331, 94\text{TL}4219, 94\text{T}11821 \rangle$, leukotriene A4 hydrolase $\langle 91\text{BMC}551 \rangle$ forms 1,8-diols. Squalene epoxide cyclase induces formation of new C—C bonds with skeletal rearrangement $\langle 82\text{MI} 103-01 \rangle$. Also, baker's yeast has been shown to mediate conversion of α -keto epoxides to 1,2-diols $\langle 95\text{TL}1541 \rangle$ and 1,2,3-triols $\langle 93\text{CC}119, 94\text{JCS}(\text{P}1)1517 \rangle$. The first example of an antibody-catalyzed enantioselective epoxide hydrolysis has been reported $\langle 93\text{JA}4893 \rangle$. The enantioselectivity of this reaction appears to depend on the structure of the substrate; substrate-antibody interactions are necessary in order to obtain efficient, enantioselective antibody catalysis. In a related study $\langle 93\text{SCI}490 \rangle$, antibodies were generated capable of selectively catalyzing the 6-*endo-tet* cyclization, in violation of Baldwin's rules for ring-forming reactions $\langle 82\text{T}2939 \rangle$. This was achieved through designed interactions between the catalyst and the substrate. *Ab initio* calculations indicate that the antibody provides a 3–4 kcal mol $^{-1}$ differential stabilization of the intrinsically disfavored 6-*endo* transition state $\langle 93\text{JA}8453 \rangle$. The origin of stabilization is suggested to arise from the more $\text{S}_{\text{N}}1$ -like charge distribution for the 6-*endo* transition state rather than from the difference in ring sizes.

Djerassi and co-workers reported the first documentation by radiolabeling studies that cholesterol can be produced in sponges by dealkylation of 24(28)-unsaturated precursors, that the reaction

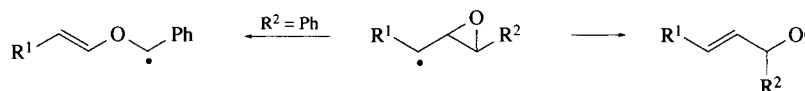
proceeds through the same oxirane intermediate operative in insects, and most strikingly, that this dealkylation can occur in sponges that are capable of *de novo* sterol biosynthesis and side chain dealkylation (at C-24) and C-24 side chain alkylation (Scheme 34) <88JA6895>.



Scheme 34

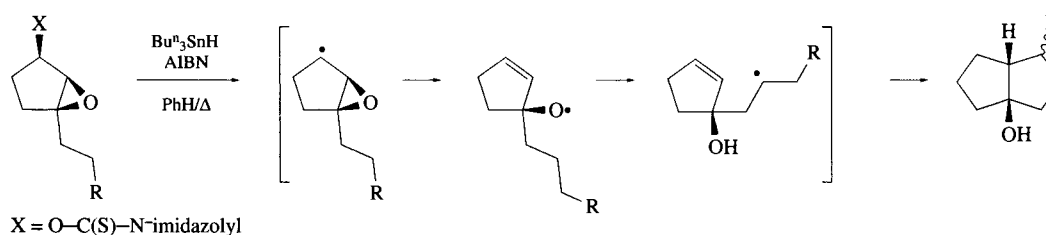
1.03.3.8 Free Radical Reactions

The first example of an epoxide cleavage reaction brought about by an adjacent radical was reported in the early 1960s <63JOC3437>. A computer-assisted mechanistic evaluation of free radical chain reactions, including those of α -epoxy radicals, has been performed by Laird and Jorgensen <90JOC9>. In the 1980s and 1990s a number of studies were reported in this area <81JCS(P1)2363, 87CC1238, 88CC294, 88TL955, 89T7835, 89TL3343, 90CC1629, 91JA5106, 91T8417>. It has been shown that when a radical center is placed adjacent to an epoxide, the C—O bond cleaves in preference to the C—C bond unless the latter is stabilized by aryl or vinyl groups (Scheme 35).



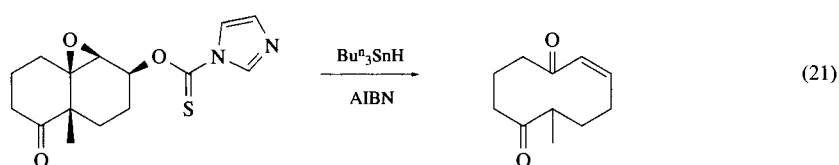
Scheme 35

The first examples of radical cyclizations to afford medium-sized carbocycles via radical-initiated oxirane cleavage have been described <93JOC1215>. Rawal and co-workers have made contributions to this area in a series of synthetically useful examples featuring intramolecular cyclizations <90JOC5181, 92TL3439, 92TL4687, 93TL2899> (Scheme 36).



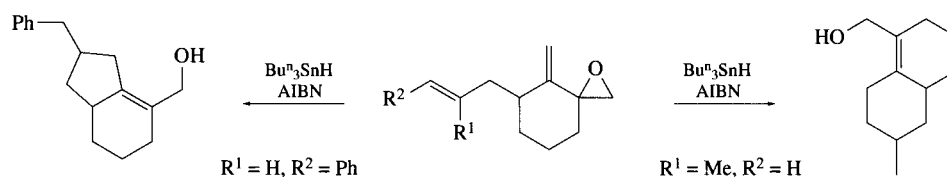
Scheme 36

In certain cases ring expansions have also been observed (Equation (21)) <93TL5197>.



(21)

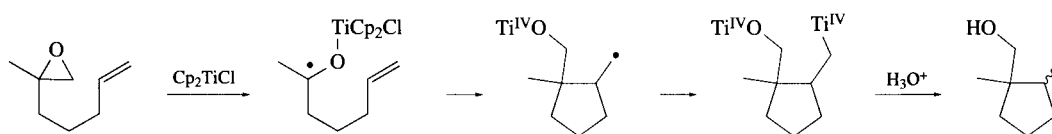
Vinyl oxiranes have been shown to undergo radical translocations by a 1,5 Bu^n_3Sn or a 1,5 hydrogen atom transfer (Scheme 37) <91JA5106>.



Scheme 37

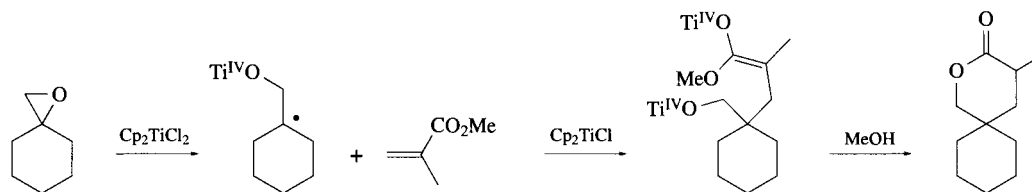
α -Halo oxiranes suffer reductive ring opening with Zn/Cu under ultrasonication to furnish allylic alcohols <91CC818>. This methodology has been applied to the total synthesis of α - and β -damascone from ionones <92JOC2757>.

Bis(cyclopentadienyl)titanium(III) chloride, Cp_2TiCl , has been employed in epoxyalkene cyclizations <88JA8561, 89CS439, 89JA4525, 90JA6408, 94JA986> (Scheme 38).



Scheme 38

These reactions can also proceed intermolecularly. γ -Lactones are obtained from these reactions in the presence of methyl methacrylate (Scheme 39).

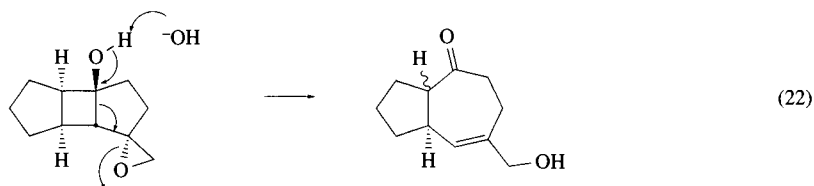


Scheme 39

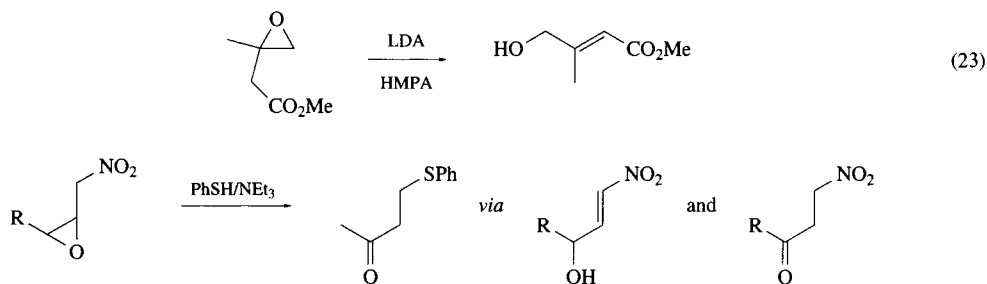
Merlic *et al.* showed that radical coupling reactions between unsaturated carbene tungsten or chromium carbene complexes and epoxides in the presence of Cp_2TiCl lead to tetrahydropyranylidene carbene complexes with high diastereoselectivity <91JA9855, 93TL227>.

1.03.3.9 Base-catalyzed Isomerizations

These reactions are discussed in <B-80MI 103-02, 83MI 103-01, 83OR(29)345, 85CHE62>. Enantioselective rearrangements of oxiranes to allylic alcohols have been reviewed <91TA1>. When an oxirane carrying a β -hydrogen is treated with a strong, nonnucleophilic base, allylic alcohols form. Crandall <64JOC2830, 67JA4526, 67JA4527, 67JOC435, 67JOC532> and Rickborn <69JOC3583, 70JA2064, 71JOC1365, 72JOC2060, 72JOC4250> developed procedures for base-catalyzed isomerization of oxiranes using lithium diethylamide and lithium diisopropylamide (LDA). A base system comprised of LDA and KO^tBu ('LIDAKOR reagent') has been used successfully in regio- and stereoselective isomerizations of protected Sharpless oxiranes (2,3-epoxy alcohols) to the corresponding allylic alcohols <90T2401>. Base-promoted fragmentations can also take place when the oxirane ring is properly situated in the molecule (Equation (22)) <92JOC5370>.

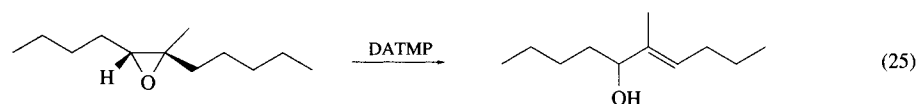
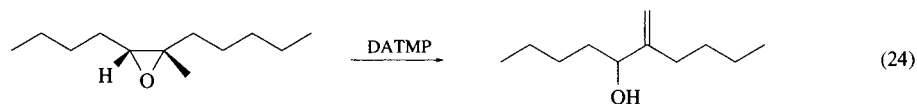


In certain oxiranes where the β -hydrogen is rendered acidic by an electron-withdrawing group, such as CO_2Et [\(90TL6789\)](#) or NO_2 [\(90JOC595\)](#), useful functional group transformations can result (Equation (23), Scheme 40).



Scheme 40

Regioselectivities in isomerizations of oxaspiropentane-type oxiranes with a variety of bases have been examined by Trost and co-workers [\(73JA5311, 73JA5321, 74TL1929\)](#). Diehyaluminum 2,2,6,6-tetramethylpiperidine (DATMP), a strong nonnucleophilic base with a high affinity for the oxirane oxygen, has been recommended as a reagent for regioselective isomerization of unsymmetrical oxiranes by Yamamoto and co-workers [\(74JA6513\)](#). The two examples shown below attest to the high regio- and stereoselectivities achieved with DATMP (Equations (24) and (25)).



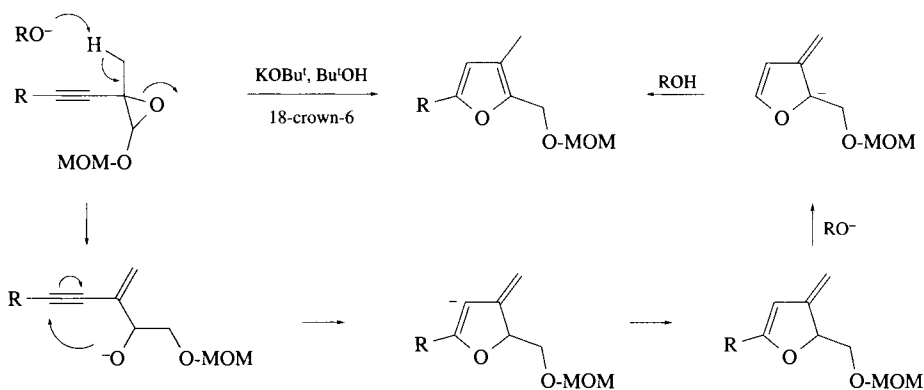
Chiral lithium amides have been developed for enantioselective deprotonation of various oxiranes [\(80JOC755, 84CL829, 85TL5803, 87T2249, 89TL2125, 90BCJ1402, 90BCJ721, 94TA337, 94TA1649\)](#). Corey *et al.* observed in one case that the magnesium derivative of cyclohexylisopropylamine is superior to LiNEt_2 , $\text{LiN}(\text{Pr})_2$ (LDA), and DATMP for the oxirane-allyl alcohol conversion [\(80JA1433\)](#). A systematic study by Falck *et al.* confirmed that methylmagnesium *N*-cyclohexylisopropylamide (MMA) is an excellent reagent for regioselective isomerizations of oxiranes to allylic alcohols. Proton abstraction by MMA from a methyl group is greatly preferred over that from a methylene group in acyclic and cyclic systems; transannular insertion reactions are suppressed with MMA in contrast to LiNEt_2 or LDA. In a few cases, however, nucleophilic methyl attack from MMA dominates [\(86TL299\)](#).

In certain cases *n*-butyllithium can also be used for isomerizations of oxiranes [\(91TL2861, 92SL668\)](#), in particular when thio groups are present on the β -carbon.

Marshall and DuBay observed a marvelous cascade of events during the base-catalyzed isomerizations of alkynyloxiranes to produce furans (Scheme 41) [\(91JOC1685, 92JA1450\)](#).

Nucleophilic oxirane ring opening with sodium phenyltellurate ($\text{Na}^+ \text{C}_6\text{H}_5\text{Te}^-$), followed by telluroxide elimination with base, has been employed as a two-step protocol for isomerizations to allyl alcohols [\(82TL1177, 83JOM\(250\)203\)](#).

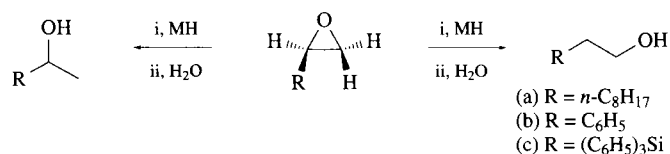
Base-promoted isomerizations of oxiranes by way of oxirane C—H abstraction are less common. Lithium tetramethylpiperidine (LiTMP) has successfully been used for this purpose [\(94CC2103\)](#). Monosubstituted oxiranes are isomerized with LiTMP to aldehydes.



Scheme 41

1.03.3.10 Reductions

Earlier work in this area (up to the end of 1982) has been thoroughly reviewed by Bartók and Láng in <85CHE1>. Results of extensive research activity on reductions with metal hydrides have been reviewed by Brown and Krishnamurthy <79T567>. Of the complex metal hydrides, lithium triethylborohydride (Super Hydride) has been advocated as the reagent of choice for reduction of oxiranes <73JA8486, 84CHEC-1(7)112>. In the 1980s and 1990s the reductive cleavage of terminal oxiranes has been examined in studies that have employed LiAlH_4 <86T5985, 92TL33>, $\text{LiAlH}_4\text{-AlCl}_3$ <85HCA2030>, $\text{LiBH}_4\text{-MeOH}$ <86JOC4000>, NaBH_3CN <81JOC5214>, NaBH_4 <88H(27)213>, $\text{LiBH}_4\text{-Ti(OR)}_4$ <86TL4343>, $\text{K(Pr}^i\text{O)}_3\text{AlH}$ <82H(19)1371>, $\text{Bu}^i_2\text{AlH}_2$ (dibal-H) <92JOC5056, 92TL33, 94TL7197>, $\text{Bu}^n_3\text{SnH-NaI}$ <88TL819>. $\text{Zn(BH}_4)_2$ on SiO_2 has successfully been employed to reduce terminal oxiranes to primary alcohols <90CC1334, 92JCS(P1)1881>. The reductions of Sharpless oxiranes (2,3-epoxy alcohols) using LiAlH_4 , dibal-H and Red-Al (sodium bis(2-carbomethoxyethoxy)aluminum hydride) have been reported to give 1,2- and 1,3-diols, respectively <82TL2719, 82TL4541, 85JOC1557, 86TL3535, see also 90CC906>. The use of Red-Al in most cases allows regioselective formation of 1,3-diols, i.e., the hydride ion preferentially attacks the oxirane carbon bearing the hydroxymethyl group <82JOC1378>. Sharpless and Gao found that the solvent and concentration of reagents have a profound effect on the products ratios <88JOC4081>. Thus, epoxycinnamyl alcohol, when treated with Red-Al in THF gives a 4.5 : 1 mixture of the 1,3-diol and 1,2-diol; in dimethoxyethane (DME), this ratio rises to 22 : 1. Eisch *et al.* <92JOC1618> have tested several aluminum reagents under different reaction conditions. They observed that by rational choice of experimental conditions (e.g., by varying the solvent or the Lewis base) the regiochemistry of these reductive cleavages of oxiranes can be advantageously steered. The authors found that with alkyl-substituted oxiranes, the use of dibal-H, with or without strong donors, favors the formation of the secondary alcohol, whereas the use of Bu^i_3Al favors the formation of the primary alcohol only with a strong donor (THF); with phenyl-substituted oxiranes, Bu^i_3Al , with or without strong donors always favors the formation of primary alcohols, while an aluminum hydride source favors the secondary alcohol only with the strongest donors (R_3N with dibal-H, and H^- with LiAlH_4) (Scheme 42).

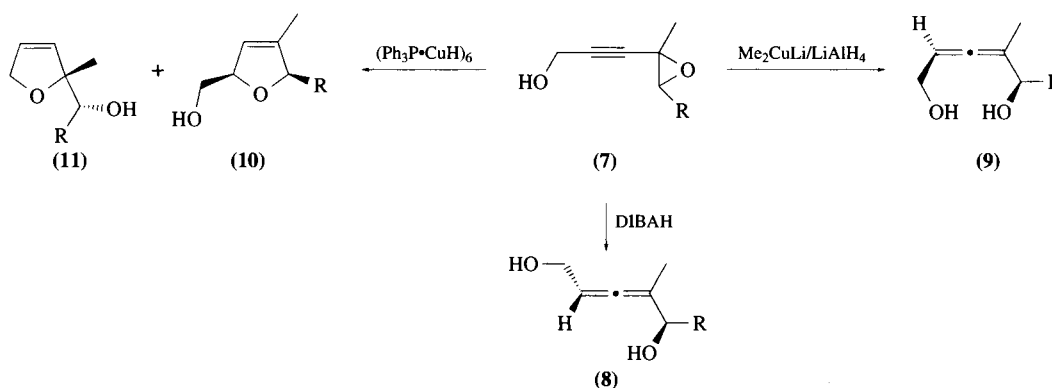


Scheme 42

With silyl-substituted oxiranes, dibal-H favors the primary alcohol and Bu^i_3AlH favors the secondary alcohol. These observations have been interpreted in terms of the timing of the hydride transfer to one of the oxirane carbons. dibal-H, which exists as a Lewis complex in donor media ($\text{R}_3\text{N-AlH(Bu}^i)_2$, or $\text{R}_2\text{O-AlH(Bu}^i)_2$) acts as a nucleophilic hydride source, which preferentially attacks the least-hindered carbon. With Bu^i_3Al , complexation with the oxirane oxygen precedes isobutene elimination and the generation of the Al-H bond. A considerable carbocation character is acquired in the transition state, hence formation of the primary alcohol is favored. It is worthy of note that trialkylstannyl-substituted oxiranes are reduced with Red-Al invariably at the oxirane

carbon bearing the tin atom <92JOC46>, in analogy to the α -epoxysilane analogues <B-88MI 103-03>. Enantioselective reductive ring cleavage of *meso*-epoxides has been reported by Brown and colleagues <88JA6246, 89IJ229>, using β -halodiisocampheyl-boranes (Ipc_2BX , derived from (+)- α -pinene; X = Cl, Br, I). Optical induction was achieved to the extent of 22–100% enantiometric excess, depending on the substrate structure.

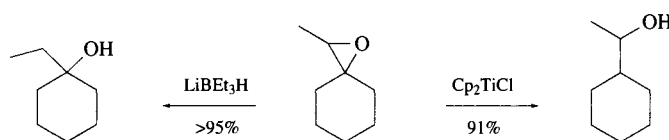
Chemoselective reduction of oxiranes in the presence of reducible groups (e.g., carbonyl) is difficult. NaBH_4 in a mixed solvent containing methanol has been used with some success for this purpose to reduce carboxyl- and carbamoyl-containing oxiranes <87BCJ1813>. A reduction method specific for oxiranes in the presence of carbonyl groups features organometallic reagents (RMgI or RLi) in the presence of CuBr/PBu_3 <90JA1286>. Interesting results are obtained when alkynylloxiranes are used as substrates (Scheme 43) <94JOC324>. dibal-H reduction of oxirane (7) proceeds with $\text{S}_{\text{N}}2'$ attack of the hydride ion at the alkynyl carbon to give (8) exclusively. With $\text{Me}_2\text{CuLi/LiAlH}_4$, a 94:6 mixture of (8) and (9) was obtained. When the Ph_3CuH hexamer was employed for the reduction, the same oxirane (7) afforded a nearly 1:1 mixture of the dihydrofurans (10) and (11). These products evidently arise from anti $\text{S}_{\text{N}}2'$ addition of the hydride followed by copper(I)-promoted cyclization of the resulting allenyl alcohol.



Scheme 43

Opposite regioselectivity to that of regular metal hydride reductions has been observed in the NaBH_4 reductions of oxiranes in the presence of triethylamine under photochemical conditions (hydride attacks the more highly substituted carbon) <92CC1133>. Diborane (B_2H_6) likewise tends to reduce oxiranes at the sterically more hindered oxirane carbon; the mechanism and stereochemistry of the diborane reduction in connection with aliphatic oxiranes has been studied <82H(18)281>.

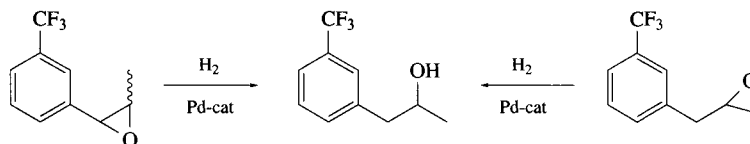
A selective, radical-mediated reduction method utilizing Cp_2TiCl (Cp = cyclopentadienyl) has been introduced by Nugent and RajanBabu <88JA8561, 89JA4525, 90JA6408, 94JA986>. The observed regiochemistry using Cp_2TiCl is opposite to that expected for an $\text{S}_{\text{N}}2$ -type reduction process with a hydride reagent (Scheme 44). An application of the aforementioned reagent to the reduction of carboethoxyvinyl oxiranes results in a regioselective reduction at the allylic carbon <92TL7973>; epoxy alcohols undergo 1,3-rearrangements <90CC843>, and 4,5-epoxy-2-alken-1-ols give rise to butadienyl alcohols with the same reagent <94TL3625>.



Scheme 44

Reductive cleavage of oxiranes <B-80MI 103-02, 85CHE83> by catalytic hydrogenation finds occasional use; hydride reagents have been found to be much more effective for this purpose. The hydrogenation of 1-methyl-2,3-epoxycyclohexene, for instance, upon hydrogenation over Pd gives 1-methylcyclohexanol (19%), *trans*-2-methylcyclohexanol (31%) and *cis*-2-methylcyclohexanol (13%) <80JOC4139>. The hydrogenation of 4-*t*-butylmethylenecyclohexane oxiranes using Pd, Pt, Rh, and Ni catalysts has been studied <81BSF19>, as well as that of C-5–10 1,2-epoxyalkanes on Co, Ni, and Pt catalysts <82CA144282u>. In one application, catalytic hydrogenation over Pd was the

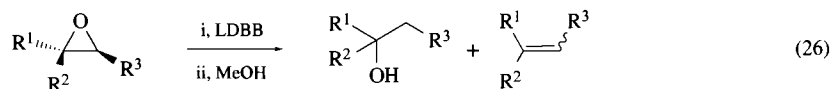
preferred method for the selective reduction of the oxirane ring <90JOC2797, 94TL8927>. The effect of the Pd-based catalysts, Pd-C (5% and 15%) and Pd-CaCO₃ (5%) on the regioselectivity of the reductions of some oxiranes has been studied (Scheme 45) <93BSF459>.



Scheme 45

Reduction of certain oxiranes with hydrogen in the presence of a chiral Rh catalyst has been reported to proceed in 6–62% enantiomeric excess, depending on the substrate <92CC535>.

The reductive ring opening of oxiranes with lithium 4,4'-di-*t*-butylbiphenylide (LDBB) yields β -lithioalkoxides <86AG(E)653>. Based on this methodology, Cohen *et al.* <90JOC1528> reported a general reduction method for oxiranes. Substituted oxiranes, when treated with LDBB, give rise to alcohols which are in most cases accompanied by deoxygenation products (Equation (26)). The latter presumably arise from dilithiation followed by loss of Li₂O. When the lithiated species are treated with aldehydes or ketones, condensation products (1,3-diols and alcohols) are isolated.

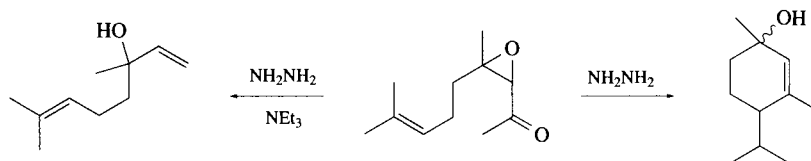


Shimizu *et al.* reported selective reduction of oxiranes using a palladium catalyst (Pd(dba)₃) in the presence of Ph₃P, HCO₂H, and NEt₃ <91T2991>. Alkenyloxiranes are selectively reduced with Pd₂(dba)₃-CHCl₃-Buⁿ₃P/HCO₂H-NEt₃ <84CL1017, 89JA6280>. The reduction of α,β -epoxy ketones to the corresponding aldols can be accomplished by a variety of reagents: with Pd(0)/HCO₂H/NEt₃ <89CL1975> (41–96% yield), NaTeH <84CL271> (72–96%), SmI₂ <86JOC2596> (74–96%), aluminum amalgam <78JA4618, 78JOC3942> (76–85%), lithium–liquid ammonia <85JOC3473> (35%), and selenium borate complex [Na(PhSeB(OEt)₃)] <87TL4293> (41–96%). PhSe⁻-catalyzed reductive ring opening of α,β -epoxyketones affords β -hydroxyketones <94JOC5179>. A nucleophilic reduction involving telluride ion converts tosylates of epoxy alcohols to allylic alcohols <93JOC718>. A variant of this reaction using catalytic amounts of Te²⁻, formed from elemental Te and rongalite (HOCH₂SO₂Na·2H₂O), has been described <94TL5583>. An electroreductive ring opening of α,β -epoxy carbonyl ketones, esters, and nitriles through recyclable use of (PhSe)₂ or (PhTe)₂ as mediator has been reported <90JOC1548>. The electrogenerated phenyl selenide and telluride anions behave as highly chemo- and regioselective nucleophiles at the α -position of an α,β -epoxy ketone. Direct electrochemical opening of α,β -epoxy ketones has also been reported and the hydrogen is often delivered to the more highly substituted oxirane carbon in this process <84IZV1901>.

Reductive cleavage of oxiranes with tin hydrides <81JCS(P1)2363, 88TL837, 90JOC5181, 91JA5106, 93JOC7608> are of particular interest when the oxirane is in close proximity to certain groups. α -Chloro oxiranes are reduced by Ph₃SnH to give carbonyl compounds <92JOC840>. The latter arise from rearrangement of the labile starting material to the α -chloro ketone prior to reduction of the halogen <91JCR(S)1101>. β -Chloro oxiranes react faster than the α -chloro analogues, and give rise to allylic alcohols in very good yields. On the other hand, 1-aryl-3-halo-1,2-epoxypropanes invariably suffer oxirane C—C cleavage under the same conditions <90JCS(P1)1179>, presumably owing to the greater stability of the benzylic radical. α,β -Epoxyketones undergo oxirane C—O cleavage with Buⁿ₃SnH either photochemically, or thermally <90JCC550, 91T7775, 92JOC5352, 90TL4045> in the presence of AIBN to give β -hydroxy carbonyl compounds (aldols). Similar results have been obtained with Bu₂SnIH-HMPA or Ph₃PO <92MI 103-01, 95PC 103-01>. Trimethylsilyl oxiranes upon treatment with Buⁿ₃SnH in the presence of BEt₃ and O₂ give α,β -unsaturated aldehydes <93MI 103-02>.

Since it represents a reductive transformation of an α,β -epoxyhydrazone, the Wharton reaction <61JOC3615, 61TL666> is mentioned here. The normal course of the Wharton reaction leads to allylic alcohols <84JA4558, 87TL2099>. In certain cases where there is a remote double bond within the molecule, cyclizations can occur <70HCA531, 71HCA1805>. Stork's studies have indicated that these cyclization products may stem from a radical pathway <77JA7067>. In order to minimize the extent of this side reaction, Luche and Dupuy have carried out the Wharton transposition in the presence of base (Scheme 46) <89T3437>.

Finally, dissolving-metal reductions (e.g., Li in liquid NH₃) of oxiranes proceed with good



Scheme 46

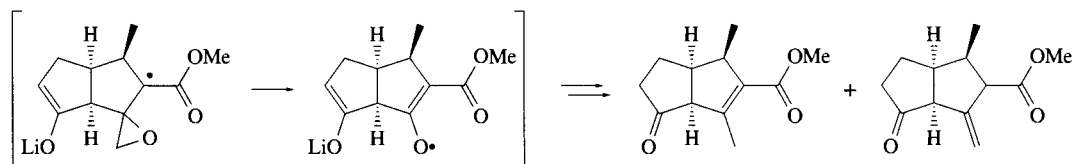
regio- and stereoselectivity, favoring the formation of the less highly substituted alcohols <70JOC3243, 76JA1612, 77JA5773, 84JOC1875>. The Benkeser reduction, using Ca in ethylenediamine is the preferred method of reduction in cases where LiAlH_4 fails or the reaction is very slow <86JOC3391>.

1.03.3.11 Deoxygenations

Deoxygenations of oxiranes have been reviewed <87H(26)1345>. Of the later methods for deoxygenation, those utilizing P_2I_4 <84TL2601, 85S65>, Nb-NaAlH_4 in $\text{THF-C}_6\text{H}_6$ <82CL157> and Zn/TMSiCl <92TL3367> are one-step processes. A mild deoxygenation method under neutral conditions using dimethyl diazomalonate and a catalytic amount of $\text{Rh}_2(\text{OAc})_4$ has been described <84TL251>. The reaction proceeds with retention of configuration. Alkyl and homoalkylmanganese complexes have also been used for oxirane deoxygenations <84TL293>. It appears that Bu_3MnLi is more effective than MeMnCl for this purpose.

Aryl selenenocarboxamide can be used for the conversion of mono-, di-, and trisubstituted oxiranes to alkenes with retention of configuration <85TL669>. Trifluoroacetic acid in the presence of sodium iodide likewise furnishes alkenes from oxiranes in a stereospecific manner <84CI(L)712>. Tungsten $[\text{WCl}_2(\text{CH}_2\text{CH}_2)_2(\text{PMePh}_2)_2]$ <91JA870> and vanadium $[\text{V}_2\text{Cl}_3(\text{THF})_6]_2[\text{Zn}_2\text{Cl}_6]$ <92SL510> complexes have been reported to effect deoxygenations successfully with predominant retention of configuration. Silyl oxiranes, upon treatment with excess organolithium reagents, form vinyl silanes <91TL2783, 91TL3457>.

A fragmentation reaction, triggered by the formation of an oxiranylcarbinyl radical resulted in the deoxygenation of a spirocyclic oxirane (Scheme 47) <95TL19>.

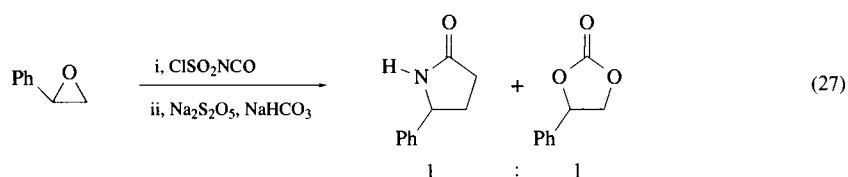


Scheme 47

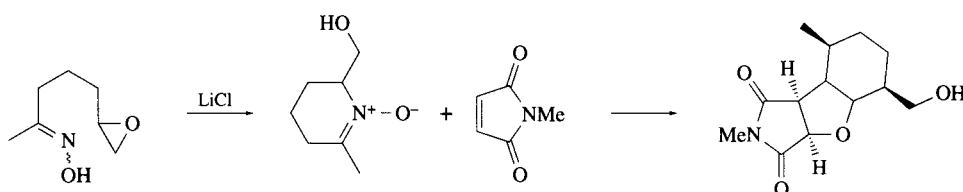
Low-valent titanium species generated from titanocene dichloride/Mg can be used for deoxygenation of oxiranes with high selectivity and retention of configuration in high yields <88AG(E)855>. For other oxirane deoxygenations, see <90JCR(S)192, 90OPP534, 90SL465, 92SL510>.

1.03.3.12 Cycloaddition Reactions

Two groups have independently explored dipolar cycloadditions of oxiranes with chlorosulfonyl isocyanate. Treatment of oxiranes with $\text{ClSO}_2\text{N}=\text{C}=\text{O}$ in benzene <84JHC1721, 84SC687> or in CH_2Cl_2 <86SC123> gives rise to either cyclic carbonates or 2-oxazolidones, or both after hydrolytic workup (Equation (27)).



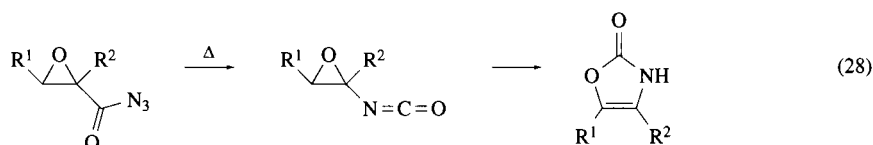
Similar results have been obtained with less-reactive heterocumulenes, such as RNCO , RNCS , and $\text{RN}=\text{C}=\text{NR}$, in the presence of organotin iodide–Lewis base complexes ($\text{Bu}^n_3\text{SnI}-\text{Ph}_3\text{PO}$ or $\text{Me}_2\text{SnI}_2-\text{HMPA}$) (85S1144, 86JOC2177). Oximes undergo a tandem nucleophilic substitution–1,3-dipolar cycloaddition with oxiranes (89TL5489) (Scheme 48).



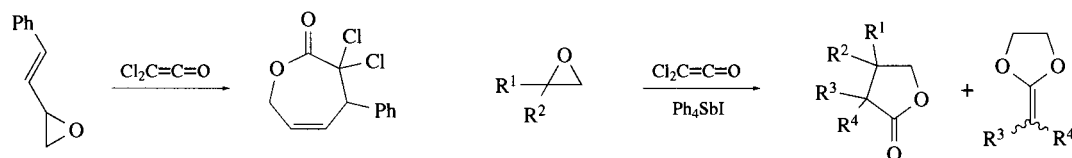
Scheme 48

Oxiranes carrying an oximino group give isoxazoles in the presence of BF_3 -etherate (90CJC1271).

Vinyl oxiranes have been shown to give oxazepinones with CSI (92CL1575). An intramolecular version of the isocyanate–oxirane cycloadditions has been described. The isocyanate functionality is obtained by thermal rearrangement of epoxyacyl azides (Equation (28)) (84JOC2231).



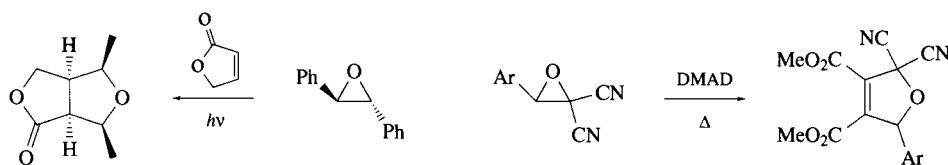
Dichloroketene has also been reported to undergo cycloadditions with various aryl-substituted vinyl oxiranes to give seven-membered cyclic lactones (89S562). Similar compounds have been postulated as intermediates in dichloroketene additions to steroidal vinyl oxiranes (88JOC3469). Simple oxiranes cycloadd to dichloroketene in the presence of Ph_4SbI to give γ -lactones and/or ketene acetals (88JOC5974). In the presence of conventional catalysts (e.g., LiX) only cyclic ketene acetals are formed (Scheme 49) (86BJC4000).



Scheme 49

Aryl-substituted oxiranes are converted to ozonides by co-sensitized electron transfer photo-oxygenation with 9,10-dicyanoanthracene (DCA) and biphenyl (82CC1223, 83JA663, 83JA5149, 83JCS596, 84JCS(P1)15).

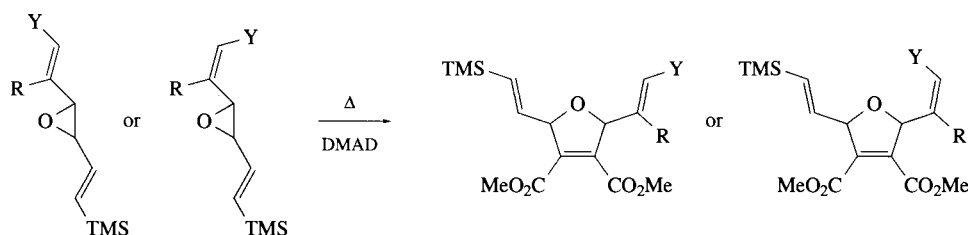
Thermal and photochemical cycloadditions of a variety of aryl oxiranes with electron-deficient cycloaddends have been described (90JCS(P1)153, 90JCS(P1)159, 90JCS(P1)1193). These reactions give five-membered cycloadducts by way of cycloaddition across the oxirane C—C bond, presumably via a carbonyl ylide (Scheme 50).



Scheme 50

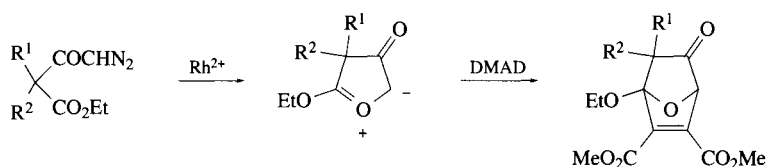
White and Chou reported that when certain 1,2-divinyl oxiranes are thermolyzed in the presence of cycloaddends, e.g., dimethyl acetylenedicarboxylate (DMAD), cycloaddition via carbonyl ylide

intermediates occur to give dihydrofuran derivatives (Scheme 51) <91TL7637>. Similar cycloadditions have been reported by others <84CB2157, 91T7713>.



Scheme 51

Carbonyl ylides have also been generated by Padwa and co-workers by rhodium carbenoid-induced cyclization of diazobutanedione and hexanedione. The aforementioned reactive intermediates are trapped with dimethyl acetylenedicarboxylate or methyl propiolate to afford unique oxabicyclic ring systems (Scheme 52) <86JOC1157, 88JA2894, 88JOC2875, 90JA3100, 90JOC4144, 91JOC3271, 95JOC53>. Related reactions involving 1,3-dipolar cycloadditions to carbonyl ylides have been described by others <82T1477, 88TL1677>. This method has been employed by Padwa and colleagues in the synthesis of the core skeleton of natural products of the illudin and ptaquilosin family <94JA2667>.



Scheme 52

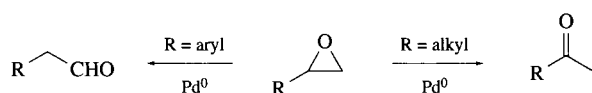
Cycloadditions of carbonyl ylides, generated from the reaction of carbenes with heteroatom lone pairs have been reviewed <91ACR22, 91CRV263>.

Aryl vinyloxiranes cycloadd to electron-deficient alkenes photolytically in the presence of Ph_2S_2 and AIBN to afford *cis*-2-aryl-5-vinyl tetrahydrofuran derivatives via a radical mechanism <89T2969>.

The photochemical reaction of $\text{Cp}(\text{L})\text{RhH}_2$ ($\text{L} = \text{PMe}_3$) with oxiranes involves initial oxidative addition of rhodium into the three-membered ring C—H bond; the resulting epoxyrhodium complex rearranges to an enolate by a hydrogen shift <89JA7628>.

1.03.3.13 Palladium-mediated Reactions

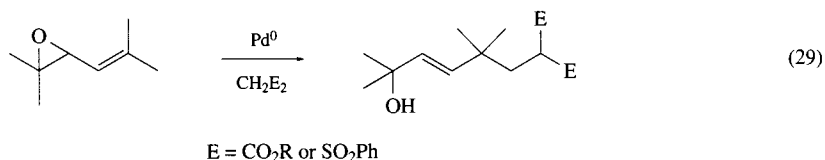
This subject has been reviewed <82COMC-I(8)799, 86T4361, 89AG(E)1173>. Vinyl oxiranes are converted to dienols in high yields with a $\text{Pd}(0)$ catalyst <79JA1623>. Silicon-substituted vinyl oxiranes undergo rearrangements with $\text{Pd}(0)$ catalysts by a 1,2 silicon shift, either from carbon to carbon or from carbon to oxygen (Brook rearrangement) depending on the nature of the substituents on silicon <92TL3859, 95TL1641>. Low-valent palladium complexes catalyze isomerization of α,β -epoxyketones to 1,3-diones <80JA2095> and of aryl oxiranes to benzyl ketones <86SC1621>. Alkyl-substituted oxiranes are isomerized by $\text{Pd}(0)$ -tertiary phosphine complexes to methyl ketones, and aryl-substituted oxiranes form aldehydes or ketones via cleavage of the benzylic C—O bond (Scheme 53) <94PC 103-01>.



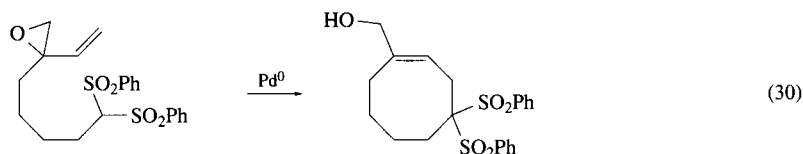
Scheme 53

In one case a spirocyclobutyl-substituted vinyl oxirane has been converted to an α -ethylidenecyclopentanone <91TL3395>. Vinyl oxiranes are coupled with organostannanes in the presence of $(\text{CH}_3\text{CN})_2\text{PdCl}_2$ to furnish allylic alcohols in good yields <88JA4039, 89T979>. Heteroatom nucleophile

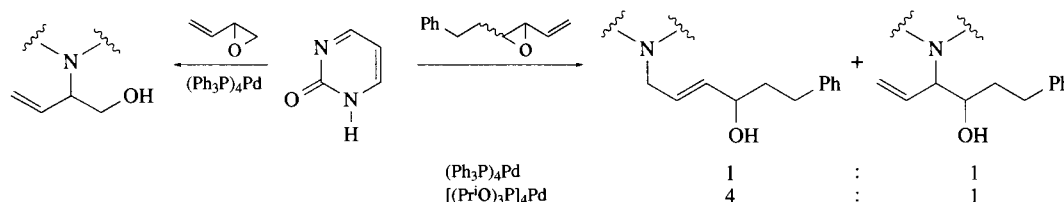
addition to Pd(II)–alkene complexes are discussed in <82ACS(B)577, 84T2415, 89AG(E)1173, 89JOC977, 91COS(7)449, 91COS(7)551>. Vinyl oxiranes form with Pd(0) π -allylpalladium species which can be attacked by various nucleophiles under neutral conditions <81JA5969, 81TL2575, 83CC985, 84TL1921, 85T5747, 85TL5615, 86JOC5216, 86TL4141, 88JA8239, 88JOC189, 88TL2931, 88TL4851, 91TL2193>. Also, aryl and vinyl halides have been coupled by Pd(0) catalysis with oxiranes in which the C—C double bond and the oxirane are separated by one or more carbons (Equation (29)) <86TL2211, 90JOC6244, 93JOC804>.



Oxiranes derived from nitroalkenes can suffer Pd(0)-catalyzed cleavage by two different mechanisms, yielding 1,2-dicarbonyl compounds and/or α -nitroketones <86CL1939, 91T8883>. Intramolecular variants of this reaction have proven very useful for the synthesis of functionalized carbo- and heterocyclic ring systems <83JA147, 83JA5940, 86JOC2332, 86TL3881, 86TL5695, 89JA4988, 90TL4747, 92TL717, 95TL2487>. The reaction shown in Equation (30) is representative of Pd(0)-mediated intramolecular vinyl oxirane alkylations <92TL717>.



Palladium(0)-mediated ring opening of vinyl oxiranes with nitrogen-based nucleophiles can result in either S_N2' or 1,2-attack at the oxirane carbon bearing the vinyl group <86JOC2332, 88JA621, 88TL4851>. The oxirane structure, as well as the catalyst ligand, have been found to affect the product distribution (Scheme 54) <88JA621>.



Scheme 54

Vinyl oxiranes form cyclic carbonates in a regio- and stereoselective fashion when treated with CO₂ in the presence of a Pd(0) complex <85JA6123>, see also <85CL199>.

Along similar lines, Pd(0)-catalyzed cycloadditions of isocyanates to vinyl oxiranes invariably give rise to *cis*-oxazolidin-2-ones, irrespective of the stereochemistry of the starting oxirane <87JA3792, 89TL3893>, see also <88TL99>.

1.03.4 OXIRANES: SYNTHESIS

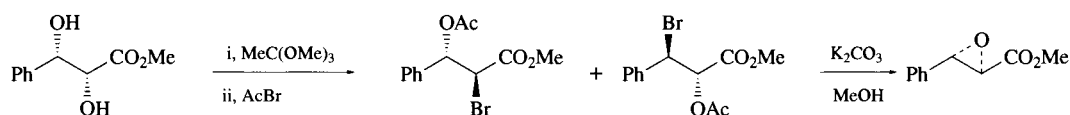
1.03.4.1 General Survey of Synthesis

The most common method of oxirane synthesis involves oxygen atom transfer to a double bond. Transfer of a methylene equivalent to a carbonyl group is also frequently used. Of some importance is the intramolecular nucleophilic displacement of a nucleofuge by an oxide, as in a halohydrin. Thermal, photochemical, as well as Co-TPP (cobalt tetraphenylporphyrin) isomerization of unsaturated endoperoxides leads to bisepoxides (see Chapter 1.06). Deoxygenation of cyclic endoperoxides with R₃P gives rise to vinyl oxiranes. Oxiranes can also be prepared from 1,2-diols with certain reagents; Darzens-type condensations of carbonyl compounds with enolates give rise to func-

tionalized oxiranes; enzymatic epoxidations are gaining importance in regio- and stereoselective synthesis of organic molecules. Oxirane syntheses have been reviewed (83T2323, 85CHE197, 85MI 103-01, 85UK 1674, B-86MI 103-03, 91AG(E)403, 91COS(7)357, 92T2803, 93PHC(5)54).

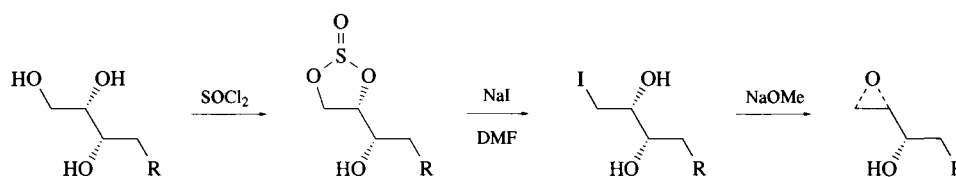
1.03.4.2 Oxiranes by Intramolecular Substitution

This classical example of oxirane synthesis involves treatment of a halohydrin with base (84CHEC-I(7)115, 85CHE1, 85MI 103-01). Kolb and Sharpless introduced a three-step protocol (92T10515, 92TL2095) whereby chiral diols, available by Sharpless' asymmetric dihydroxylation (92JOC2768), are efficiently converted into chiral oxiranes (Scheme 55).



Scheme 55

Similar procedures involving selective monoactivation of a vicinal diol and subsequent oxirane formation have been reported: TsCl, NaH (93SC285), Tf₂O/pyridine (93JOC1762). In certain cases chemical differentiation of the hydroxy groups by selective activation (e.g., tosylation) is difficult to achieve. A general solution to this problem has been found (94TA2485): the diol is first treated with SOCl₂, then treated with NaI which regioselectively attacks the terminal carbon (Scheme 56).



Scheme 56

A highly stereoselective preparation of iodovinyl-substituted oxiranes is accomplished by iodine addition to α -allenic alcohols followed by treatment of the resulting 3,4-diiodo-2-en-1-ols with strong base (93JOC1653).

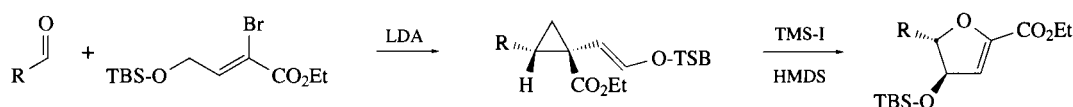
1,2-Diols can be directly converted to oxiranes with Ph₃P in the presence of diisopropyl azodicarboxylate (Mitsunobu reaction) (81S1).

In various cases, protocols involving enantioselective reduction of an α -halocarbonyl compound and subsequent cyclization of the halohydrin with base have been employed for the preparation of optically active oxiranes. Representative examples include Corey's chiral oxazaborolidine catalyst using borane as stoichiometric reductant (87JA5551, 87JA7925, 88JOC2861, 92JOC7115, 92JOC7372, 93TL5227), or asymmetric reduction of 3-chloroalkanoates with baker's yeast and cyclization of the resulting chiral chlorohydrins with base (87BCJ833, 87TL2709, 91JOC7177, 93JOC486). Other bromohydrin derivatives, available in enantiometrically pure form by chemoenzymatic processes, have been converted to optically pure oxiranes by a similar protocol (91CC1064). PhSeO may also serve as a leaving group in intramolecular displacements forming oxiranes (88CC111). A mild, cost-efficient synthesis of ¹⁸O-labeled oxiranes using H₂/¹⁸O as the isotope source has been described (94JOC4316). In this process, alkenes are converted to iodohydrins with Ag₂O/I₂, followed by treatment with base (dbu), with >90% ¹⁸O incorporation.

Also, condensations of carbonyl compounds with enolates (Darzens type) lend themselves to oxirane synthesis (82AP(315)284, 84OR(31)1, 85MI 103-01, 86JA4595, 87BCJ2475, 87CC762, 88BCJ2109, 91TL2857, 93JOC486, 93JOC5107, 93JOC5153, 94TL9367). Maryanoff *et al.* found that in Darzens condensations with α -halo esters a ketene-enolate-carbenoid manifold exists, and the success of glycidic ester formation largely depends on the stability of the α -halo ester enolate (94JOC237). Whereas sodium enolates of α -bromo esters decompose faster than they react with formaldehyde, lithium enolates of α -chloro esters are stable at room temperature and react smoothly with HCHO to furnish the glycidic esters. Certain α -halo ketones do not serve as suitable substrates in Darzens condensations because of competing reactions in basic medium (e.g., Favorskii rearrangement, nucleophilic addition to the

carbonyl group, and nucleophilic substitution of the halide). Enolate-generating agents, such as $\text{Sn}(\text{OTf})_2\text{R}_3\text{N}$ <82CL1601> or $\text{Zr}(\text{OBu}^t)_4$ <90JOC5306> do avoid undesired side reactions; however, subsequent cyclization of the halohydrins must still be effected by the use of KF -crown ether or BuLi . The use of *N*-alkyl α -haloimines avoids the intervention of carbanions and allows the preparation of 2-imidoyloxiranes which can be hydrolyzed to the corresponding α,β -epoxyketones <88JOC4457>. *N*-Tri-*n*-butylstannyl carbamate has been identified as an effective reagent for one-pot Darzens condensations which proceed under mild, neutral conditions with high regio- and chemoselectivity <92JOC6909>.

Other substrates employed in related oxirane-forming condensations of carbonyl compounds include α -halosulfoxides <85BCJ2849, 86BCJ457, 86BCJ2463, 86TL2379, 87BCJ1839, 89JOC3130, 89TL1083>, and α -halosulfones <84JOC1378>. The synthesis and chemistry of sulfinyl- and sulfonyloxiranes have been reviewed <92RHA218>. Dienolate anions can be condensed with aldehydes to give suitably substituted vinyl oxiranes which undergo a remarkably facile rearrangement to functionalized dihydrofurans with TMS-I and hexamethyldisilazane (HMDS) at -78°C (Scheme 57) <91JOC4598>.

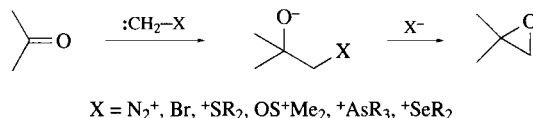


Scheme 57

For some examples of related oxirane-forming reactions, see <83S462, 84T2935, 85H(23)2347, 87IJC(B)605, 89TL3923, 92JCC986, 92S693, 93TL3145>.

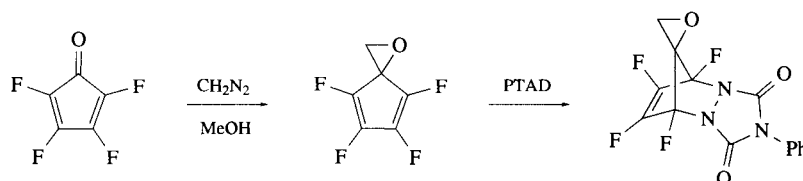
1.03.4.3 Oxiranes from Carbonyl Compounds with CH_2 -equivalents (CH_2N_2 , LiCH_2X , S, Se, and As Ylides)

Reactions of carbonyl compounds with methylene equivalents leading to oxiranes (see Scheme 58) have been described <B-80MI 103-02, 83T2323, 85CHE51, 85MI 103-01, 86MI 103-04>.



Scheme 58

Transfer of methylene from diazomethane to the carbonyl group of 1-fluoro-3-*p*-tolylsulphinyllacetone has been observed to proceed with high chemo- and enantioselectivity <92TL5609, 93TL7771, 94T13485>. Also, esters have been converted to the corresponding oxiranes with diazomethane <88JOC3321>. A very interesting example of carbonyl to oxirane transformation was observed by Lemal *et al.* when tetrafluorocyclopentadiene was treated with diazomethane (Scheme 59, PTAD = 4-phenyl-1,2,4-triazolin-3,5-dione) <91JOC157>.



Scheme 59

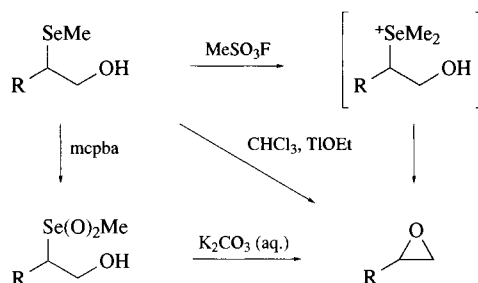
Treatment of carbonyl compounds with LiCH_2X ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) at low temperatures results in oxirane formation <71T6109, 85BSF825, 87T2609>. Deprotonation of α -chloromethyltrimethylsilane with *s*-butyllithium generates MeSiCHClLi , which adds to aldehydes or ketones to give α,β -epoxysilanes via the chlorohydrin intermediates <B-80MI 103-03, 83T867>.

Methylene transfer to carbonyl compounds by sulfur ylides has been reviewed <B-75MI 103-02, B-78MI 103-01, 79COC(3)247, 83T2323, 86MI 103-04>. Dimethylsulfonium methylide, $\text{Me}_2\text{S}=\text{CH}_2$ and dimethyloxosulfonium methylide, $\text{Me}_2\text{S}(\text{O})=\text{CH}_2$ (Corey's reagent), are efficient methylene transfer agents, but have some limitations in certain cases, in particular when hindered, or highly

enolizable ketones are used, or when the sulfur ylides bear alkyl substituents. Generation of the $\text{Me}_2\text{S}(\text{O})=\text{CH}_2$ under phase transfer conditions in $\text{CH}_2\text{Cl}_2/\text{NaOH}$ mixtures provides a convenient variant of oxirane synthesis with sulfur ylides $\langle 85\text{SC}749 \rangle$. By applying this procedure to 2-thiomethylene ketones, Price and Schore improved the existing furan annulation methodology $\langle 89\text{JOC}2777, 89\text{TL}5865 \rangle$. Reaction of polyene sulfonium salts with carbonyl compounds under aqueous conditions has been shown to provide a convenient route to a variety of vinyl, dienyl, and divinyl oxiranes $\langle 82\text{JOC}1698, 83\text{JA}3656 \rangle$.

N-Tosylsulfoximines and sulfilimines have successfully been used as sulfur ylide precursors in oxirane synthesis $\langle 85\text{MI} 103-02, 85\text{PS}(24)531, 92\text{SR}57 \rangle$. Using a chiral sulfoximine (*S*-neomenthyl-*N*-tosyl oxosulfonium methylide), various aromatic aldehydes and ketones have been converted to oxiranes in relatively high enantiomeric excess (56–86% *ee*) $\langle 94\text{TA}1513 \rangle$.

Krief *et al.* have shown that selenium ylides behave as their sulfur analogues and convert a variety of carbonyl compounds to oxiranes $\langle 89\text{H}(28)1203 \rangle$. The latter compounds can be directly obtained by using $\text{R}^2\text{Se}=\text{CHR}^1$; β -hydroxyalkylselenides (available from carbonyl compounds by addition of RSeCH_2Li) may serve as suitable precursors as well, either in a two-step protocol, via the selenonium salt by alkylation with magic methyl (MeSO_3F), or directly by treatment with thallos ethoxide in chloroform. Oxidation of the β -hydroxyalkylselenides with peracid, followed by treatment of the resulting selenone with base, results in oxirane formation (Scheme 60).



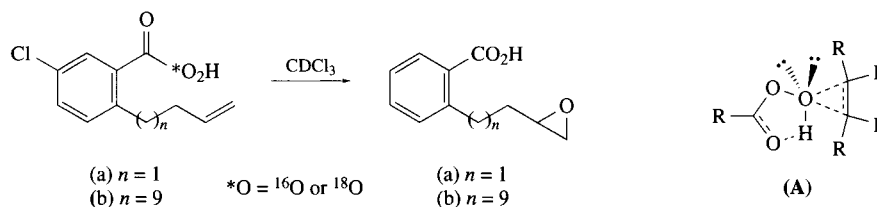
Scheme 60

Arsonium semistabilized or nonstabilized ylides have been shown to react with aldehydes and ketones in a similar fashion to afford oxiranes in high yields $\langle 81\text{JA}1283 \rangle$; see also $\langle 83\text{SC}1193, 83\text{TL}4419, 88\text{BSB}271, 89\text{JOC}3229, 89\text{TL}6023, 91\text{TL}3999 \rangle$.

1.03.4.4 Oxirane Synthesis from [2 + 1] Fragments

1.03.4.4.1 Peroxy acid epoxidation

Alkenes can be epoxidized with a variety of peroxy acids $\langle \text{B-}71\text{MI} 103-03, 76\text{T}2855, 81\text{H}(15)517, \text{B-}83\text{MI} 103-03, 87\text{MI} 103-04 \rangle$, of which *m*-chloroperoxybenzoic acid (MCPBA) is the most commonly used. Woods and Beak have provided experimental evidence for the “butterfly transition state” (A) in Scheme 61 (Bartlett mechanism $\langle 50\text{RCP}47 \rangle$) involved in peroxy acid epoxidations $\langle 91\text{JA}6281 \rangle$.



Scheme 61

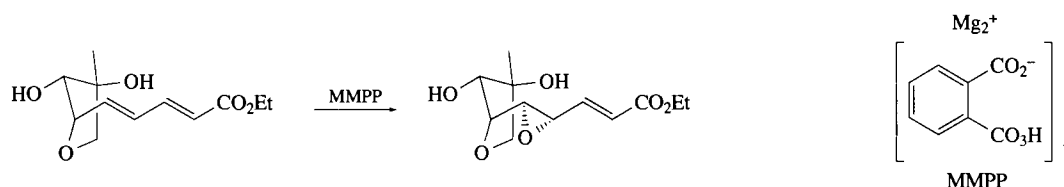
Kinetic and computational studies by Shea and Kim on MCPBA epoxidations of a series of cyclic alkenes including bridgehead alkenes and *trans*-cycloalkenes have shown that the reactivity depends primarily on the strain energy relief in the transition state $\langle 92\text{JA}3044 \rangle$.

Directing effects of various functional groups on the stereoselectivities of peroxy acid epoxidations have been studied in detail. In the case of allylic alcohols, the weak directing effect of the hydroxy

group has been attributed to complex formation between the peroxy acid and the hydroxy group during the oxygen atom transfer. Thus, a conformation is preferred in which the dihedral angle is 120° between the π -system and the OH group <57JCS1958, 73TS93, 76T549, 79TL4729, 79TL4733, B-79MI 103-03, 80MI 103-04, 80TL4229, 82TL3387, 83T2323, 84S834, 85S89, 87JA5765, 93TA5>. The directing effects of other neighboring groups in related studies have been reported: $-\text{CR}=\text{O}$ <87JOC1487, 87JOC5127, 88CCC1549, 88JOC3886, 88TL2475, 89TL1913, 89TL1993, 90JOC3236, 94JOC653, 94TL6155> and amino groups <84TL1587, 85JOC4515, 86JOC50, 87JOC1487, 91JMC1222, 93TL7187, 94TL4939, 94JOC653>.

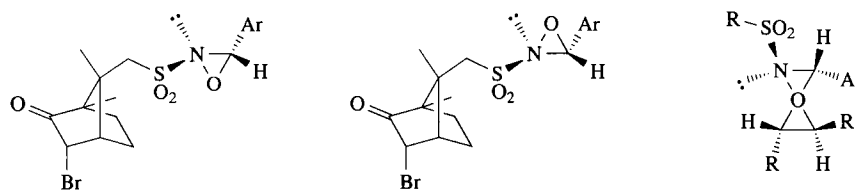
In the absence of substituents with directive abilities, the peroxy acid usually approaches the alkene from the least-hindered face <86JOC793>, and such reactions are diastereoselective. Simple alkenes are relatively insensitive to steric effects; *cis*-, *trans*- and 1,1-disubstituted alkenes react at nearly the same rate <B-71MI 103-02>. Facial selectivity with simple alkenes is difficult to achieve; however, progress has been made in this area <84JA1170>. By using bulky peroxy acids, *cis/trans* selectivity has been achieved to a considerable extent.

The requirement for concentrated H_2O_2 for the preparation of MCPBA and other peroxy acids and regulations on transportation of pure MCPBA (shock-sensitive and potentially explosive) have impelled the search for safe alternative reagents. Heaney and Brougham developed a useful MCPBA substitute, magnesium monoperoxyphthalate hexahydrate (MMPP) <87S1015, 93MI 103-03>. This reagent is used in a protic solvent, e.g., methanol or *i*-propanol, as well as water/ CH_2Cl_2 or $\text{H}_2\text{O}/\text{CHCl}_3$ together with a phase transfer catalyst. In certain cases where epoxidation with MCPBA is unsuccessful, the use of MMPP has proved beneficial (Scheme 62) <91JCS(P1)1967>.



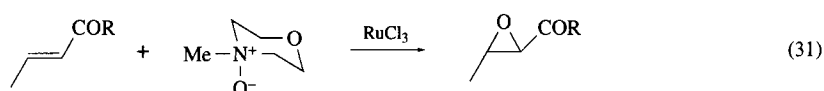
1.03.4.4.2 Oxaziridine epoxidations

Davis and co-workers described the synthesis of chiral 2-sulfonyloxaziridine diastereomers (Figure 2) <81TL917, 89T5703>. These reagents give much better results for the asymmetric epoxidation of unfunctionalized alkenes than do chiral peroxy acids; the epoxidation transition state can be considered as planar, with steric factors responsible for chiral recognition <83JA3123, 84JOC3241, 86JOC4240, 86TL5079>.

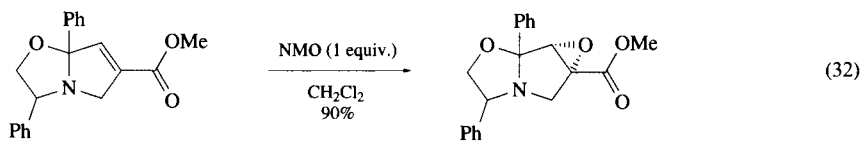


1.03.4.4.3 Epoxidations with tertiary amine N-oxides

Enones are epoxidized by *N*-methylmorpholine *N*-oxide (NMO)–ruthenium trichloride (Equation (31)) <88IJC(A)873>.



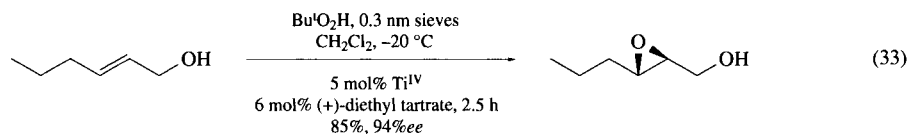
Meyers and co-workers found that bicyclic lactams carrying a carboxyl group on the double bond are efficiently epoxidized with NMO in the absence of RuCl_3 (Equation (32)) <95TL1613>.



1.03.4.5 Metal-mediated Epoxidations

1.03.4.5.1 *t*-Butylhydroperoxide (tbhp) epoxidations catalyzed by titanium tartrate systems (Sharpless epoxidation)

In 1980 Katsuki and Sharpless discovered a powerful method for enantioselective epoxidation of allylic alcohols, using a mixture of $\text{Ti}(\text{OPr}^i)_4$, $\text{Bu}^t\text{O}_2\text{H}$ and (*R,R*)-(+)-diethyl tartrate <80JA5974>. This method is of extraordinary importance in organic synthesis since it provides functionalized oxiranes in good chemical yields with high enantiomeric excess. The original procedure, which called for a stoichiometric amount of the $\text{Ti}(\text{OPr}^i)_4$ /dialkyl tartrate complex has been significantly improved by carrying out the asymmetric epoxidation in the presence of zeolites with a catalytic amount of the $\text{Ti}(\text{IV})$ /tartrate complex (Equation (33)) <86JOC1922, 87JA5765>. Using the modified procedure, the enantiomeric excesses are high (90–95%), *in situ* derivatization (e.g., as *p*-nitrobenzoate) is possible, and isolation of products is simplified; moreover, low-molecular mass allylic alcohols are epoxidized efficiently by this variant.



For excellent reviews and discussions of the mechanistic and synthetic aspects of the Sharpless asymmetric epoxidation methodology, see <83MI 103-04, B-85MI 103-03, B-85MI 103-04, 86CBR38, 87MI 103-04, 89CRV431, 92T2803, B-94MI 103-01>. A logical explanation for the enantioselectivity observed in the Katsuki–Sharpless epoxidations, consistent with the experimental data, has been advanced by Corey <90JOC1693>. In a mechanistic study of the Sharpless epoxidation, the kinetics of the reaction was shown to be first order with respect to substrate and oxidant <91JA106>. Schreiber and co-workers have studied the Sharpless epoxidation of divinylcarbinols; they showed that the enantiomeric purity of the epoxy alcohol products increased as the reactions proceeded toward completion <87JA1525, 90T4793>. These results are in accord with the mathematical model the researchers have developed; moreover, it can be used to estimate qualitatively the effect of substrate and reagent concentration on the outcome of addition reactions which employ chiral nonracemic reagents with substrates that are equipped with unsaturated and enantiotopic ligands.

1.03.4.5.2 Metal-catalyzed epoxidations of alkenes

These are discussed in <B-81MI 103-01> and <B-87MI 103-05>. A number of transition metal complexes have been used in conjunction with oxidants such as iodosylbenzene, NaIO_4 , H_2O_2 , alkylhydroperoxides, peracid esters, or molecular oxygen for oxygen transfer to alkenes. Molybdenum and vanadium catalysts are well established as effective catalysts for alkene epoxidations <B-79MI 103-03, 85CHE29, 85MI 103-05, 93AG(E)1144, 94AG(E)497>. The Mimoun reagent (Figure 3: (A), $\text{L} = \text{HMPA}$, DMF , etc.) has long been known and has been successfully employed in epoxidations <82AG(E)734, 90CRV1483>. Other molybdenum complexes (e.g., (B) <91OM1172>, or $\text{MoO}_2(\text{acac})_2$ <88TL2843>) also activate hydroperoxides in alkene epoxidations. Moreover, rhenium oxo complexes

(E) have been shown to exhibit catalytic activity in oxygen-transfer reactions <91AG(E)1638, 93AG(E)1157>.

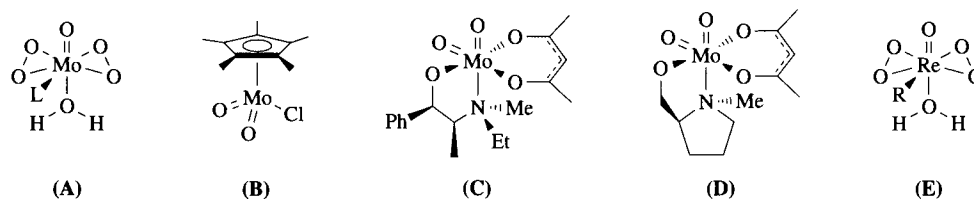
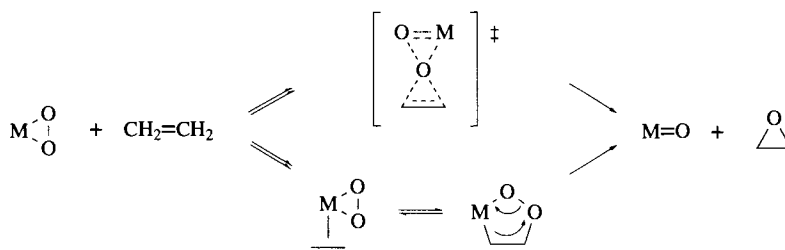


Figure 3

Two mechanisms have been advanced whereby the metal–peroxo complexes transfer oxygen to alkenes, either by a “butterfly mechanism” <77JOC1587>, or via alkene coordination and subsequent 1,3-dipolar cycloinsertion, followed by cycloreversion of the resulting metallodioxacyclopentane species (Scheme 63) <82AG(E)734>. With dioxomolybdenum complexes carrying chiral ligands of the type (C) or (D) <77JA1988, 83JOM(246)53>, modest to good enantioselectivities (up to 50% *ee*) have been achieved; see also <79AG(E)485, 79TL3017>. In some cases, very high enantiomeric excesses have been achieved <89JOM(370)81>.



Scheme 63

Achiral Mn(III) and Cr(III) complexes containing salen-type ligands (salen = *N,N'*-bis(salicylidene)ethylenediamine) have been shown to catalyze epoxidation of simple alkenes <85JA7606, 86JA2309, 86JOC297>. Mechanistic studies suggest that these reactions proceed via discrete manganese(V)-oxo intermediates; unfunctionalized alkyl-substituted alkenes presumably react via a concerted process, whereas a stepwise mechanism has been proposed for aryl-substituted alkenes <91JOC6497>. Kochi's research effort in this area laid the groundwork for the development of chiral derivatives of the [Mn(salen)]⁺ complexes (e.g., (12) and (13), Figure 4) by mainly two research groups, Jacobsen and colleagues <90JA2801, 91JA7063, 91JOC2296, 91JOC6497, 91TL5055, 91TL6533, 92CC1072, 92JOC4320, 93JOC6939, 94JOC4378>, and Katsuki and colleagues <90TL7345, 91SL265, 91TA481, 91TL1055, 92SL407, 94T4311, 94T11827>. In conjunction with these chiral complexes, stoichiometric oxidants such as PhIO, or aqueous NaOCl under phase transfer conditions are used; the enantiomeric excess achieved in catalytic epoxidation of simple olefins exceeds 90% in some cases. Periodates have also been used as oxidants in these types of reactions <95TL319>.

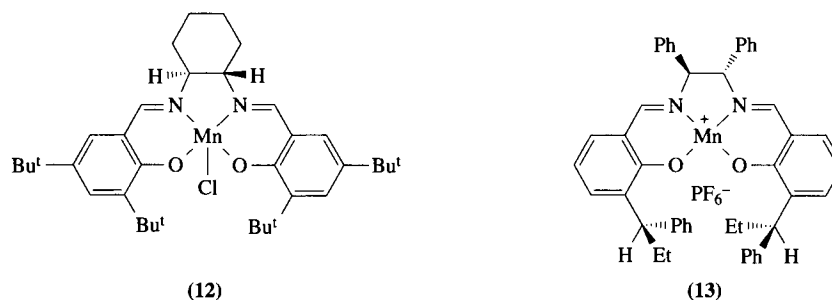


Figure 4

A highly enantioselective, low-temperature epoxidation of styrene has been disclosed by Jacobsen and co-workers using a chiral manganese salen catalyst and MCPBA as oxidant in the presence of NMO <94JA9333>.

Mukaiyama and co-workers showed that chiral salen–manganese complexes can catalyze epoxidation of simple alkenes with molecular oxygen in the presence of pivalaldehyde <92CL2231, 93CL327>. The actual oxidant in this reaction is presumably peroxopivalic acid. H_2O_2 has also successfully been employed in Mn–salen-catalyzed epoxidation <94TL941>; see also <93TL4785, 94SL255>. This latter method is of particular interest since it can be applied to both *cis*- and *trans*-alkenes.

Synthetic metal(III) porphyrins have found frequent use as catalysts in alkene epoxidations in the presence of oxygen donors (e.g. PhIO, NaOCl) <79JA1032, B-80MI 103-05, 83JA5786, 89JOC1850, 90JA2977, 92JA1308>. These reagents provide an opportunity for modeling the oxygen transfer reaction of cytochrome P450 <B-86MI 103-03>. Whereas metalloporphyrin-catalyzed epoxidations with PhIO proceed with high turnovers, H_2O_2 , $\text{Bu}^t\text{O}_2\text{H}$, or dioxygen have been employed with limited success in these types of epoxidations. Traylor *et al.* have achieved high-yield, high-turnover, regiospecific hemin-catalyzed epoxidations using H_2O_2 (or $\text{Bu}^t\text{O}_2\text{H}$) and electron-deficient porphyrins <93JA2775>. An efficient catalytic system composed of Mn(III)(TPP)Cl in homogeneous solution (CH_2Cl_2 , imidazole) <94TL945>, or biphasic medium <93CC240> using $\text{Bu}^n_4\text{NIO}_4$ affords oxiranes in high yields under mild conditions. Research activity in this area has been reviewed <86BSF578, 88CCR1, 88G485, 88MI 103-4, 92ACR314, 94AG(E)497>. Regioselective epoxidations with membrane-spanning metalloporphyrins encapsulated in synthetic vesicles have been achieved <87JA5045>. Cr(III), Fe(III), as well as Mn(III) complexes of porphyrins bearing stereogenic binaphthyl, amino acid, and threitol units have been developed for asymmetric epoxidation of simple alkenes <83JA5791, 85CC155, 85NJC216, 86JA2782, 87JA3625, 87NJC270, 89JA7443, 89JA9116, 90JOC3628, 93JA3834, 93SCI1404>. When used in combination with either PhIO or NaOCl as oxidants, enantioselectivities in the range 16–88% have been achieved with these catalysts. Other related epoxidizing agents include Co(III) complexes using $\text{Bu}^t\text{O}_2\text{H}$ as oxidant <87JOC4545>, or Co(II) complexes derived from Schiff base in the presence of molecular O_2 and 2-methylpropanal <93SC2285, 93TL4657, 93T6101, 94JOC850, 94TL4003, 94TL4007, 94TL4847, 95TL159>, porphyrin and other sterically hindered complexes of ruthenium in the presence of oxygen or H_2O_2 <85JA5790, 87CC179, 88CC298, 91CC21, 94JA2424> (see <89S389> for some applications in stereoselective steroid epoxidations), Ni(II) cyclam or salen complexes (NaOCl oxidant) <87IC908, 88JA4087, 88JA6124, 88TL877, 88TL5091, 89JOC1584>. A polymer-bound Fe(III) porphyrin complex has been employed as a catalyst in alkene epoxidations with a catalyst turnover of 7900 <92TL2737>.

Zinc(II) and Al(III) porphyrin complexes <90JA4977> and Fe(III) and Al(III) nonporphyrin complexes <90JA7826> have been shown to catalyze epoxidations of alkenes with iodosylbenzene.

1.03.4.6 Epoxidations with Dioxiranes

Activity in this area has flourished since Murray and Jerayaman reported a convenient method for the preparation, isolation, and characterization of a number of low-molecular-mass, volatile dioxiranes <85JOC2847, 86TL2335, 92JA1346>. In particular, acetone solutions of dimethyl dioxirane (DMDO, Figure 5), generated by Murray's method, as well as modifications thereof by Adam <87JOC2800, 91CB227, 91CB2377>, and Curci <87JOC699>, have been employed extensively in alkene epoxidations. A large variety of simple alkenes or those carrying diverse functionalities have successfully been epoxidized with dimethyl dioxirane <B-85MI 103-06, 87TL3311, 88JOC3007, 88JOC3437, 89JA6661, 89TL4223, 89TL6497, 90CAR(206)361, 90CB2077, 90JCS(P2)349, 90JOC4211, 90TL331, 90TL6517, 91AG(E)200, 91CB227, 91CB2361, 91JA8005, 91JOC3677, 91JOC7292, 91LA445, 91T1291, 91TL1041, 91TL1295, 91TL6697, 92CB231, 92CB2719, 92JA3471, 93AG(E)735, 93JA8603, 93JA8867, 93JCS(P2)2203, 93JOC5076, 93JOC7615, 93T6299, 93TL5247, 94CB433, 94CB941, 94CB1115, 94JOC1892, 94LA689, 94LA795, 94S111, 94T8393, 94TL5625, 94TL6063, 94TL6155, 95TL2437>. The *in situ* preparation of dimethyldioxirane by the caroate/acetone system has also been applied to alkene epoxidations, mainly by Curci and colleagues and by Edwards and colleagues <80JOC4758, 82JOC2670, 83JCS(P2)769, 84CC155, 91TL533, 94TL1577>.



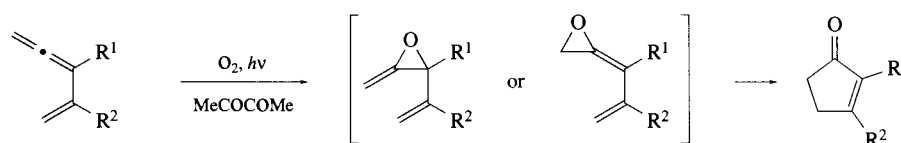
Figure 5

Denmark and co-workers have introduced a convenient protocol for the catalytic epoxidation of alkenes with *in situ*-generated dioxiranes under biphasic conditions using phase-transfer catalysts bearing a carbonyl group <B-94MI 103-02, 95JOC1391>. Curci and co-workers described the isolation

and characterization of methyl(trifluoromethyl)dioxirane (TFMD, Figure 5) <88JOC3890, 89JA6749> and showed that the latter reagent is a much more powerful (~ 1000 -fold) oxidant than DMDO <88JOC3890, 89JA6749>. Various reports describing the utility of TFMD in epoxidations have appeared in the literature since its discovery <90TL3067, 90TL6097, 93T6299, 94JA8112, 94LA689>. Several excellent review articles on dioxirane epoxidations have been published <89ACR205, 89CRV1187, B-90MI 103-01, B-92MI 103-02, 93TCC45>.

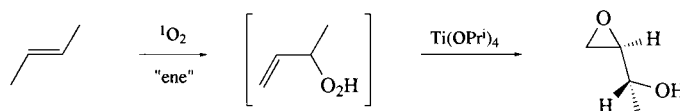
1.03.4.7 Epoxidations with Molecular Oxygen

Shimizu and Bartlett found that irradiation of an alkene in the presence of molecular oxygen and an α -diketone as sensitizer gives rise to oxiranes <76JA4193> (see also <81JA2049> and <82JA544>). This method is also applicable to deactivated alkenes. Under the same conditions, vinylallenes afford cyclopentenones, presumably via the allene oxide(s) (Scheme 64) <79JOC885>.

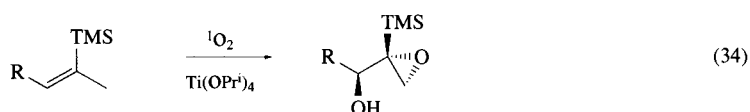


Scheme 64

Kaneda *et al.* have described an efficient method for epoxidation of alkenes using a combination of molecular oxygen and pivalaldehyde <92TL6827>. Adam and co-workers developed a method whereby 2,3-epoxy alcohols can be obtained directly from alkenes via sensitized photooxygenation in the presence of $Ti(OPr^i)_4$ and in some cases $VO(acac)_2$ <86AG(E)269, 86TL2839, 87TL311, 88CB21, 88CB2151, 88LA757, 88TL531, 89JA203, 93AG(E)733, 93JA7226, 93TL611, 94AG(E)1107>. Also, vinyl silanes and vinyl stannanes have been epoxidized regio- and diastereoselectively by this method, taking advantage of the *gem*-directing effect of the silyl and stannyl groups <94CB1441, 94JOC3335, 94JOC3341>. The metal-catalyzed direct hydroxy-epoxidation methodology has been reviewed <94ACR57, B-94MI 103-03> (Scheme 65, Equation (34)).

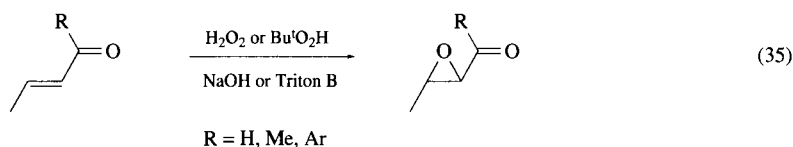


Scheme 65

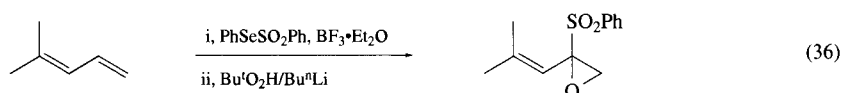


1.03.4.8 Nucleophilic Epoxidations

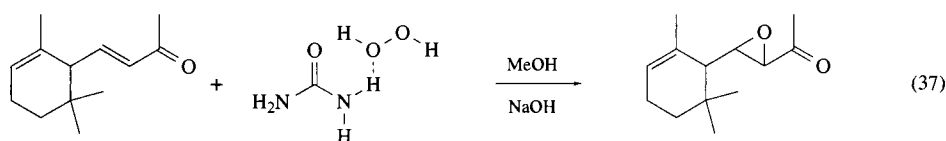
Alkenes carrying strongly electron-withdrawing groups exhibit low reactivity towards most peroxyacids (except for CF_3CO_3H , <55JA89, 61JOC651>). α,β -Unsaturated aldehydes, ketones, and sulfones are readily epoxidized with alkaline H_2O_2 <49JCS665, 59JOC284, 59JOC2048, 61JOC651, 70TL935> or Bu^tO_2H <78JA5946, 78CC76>; the mechanism involves a Michael-type nucleophilic attack of HO_2^- or $Bu^tO_2^-$ at the β -carbon (Equation (35)).



The epoxidation by this method is stereoselective and in certain cases stereospecific <58JA2428, 76TL1769>. Epoxidation with $\text{H}_2\text{O}_2/\text{OH}^-$ is applicable to alkylidene malonate derivatives but not to simple α,β -unsaturated esters; the latter compounds and the corresponding amides and sulfones are best epoxidized with $\text{Bu}^t\text{O}_2\text{H}$ in basic solution (NaOH or Triton B base) <61JOC651, 63OSC(4)552> or in the presence of an alkyllithium <83JOC3607, 86CC1378, 88JCS(P1)2663, 90JCS(P1)200, 93JCS(P1)343>. α,β -Unsaturated nitriles are converted to epoxy amides with $\text{H}_2\text{O}_2/\text{NaOH}$ via initial attack of HO_2^- at the nitrile carbon; epoxynitriles are obtained in good yields with $\text{Bu}^t\text{O}_2\text{H}/\text{NaOH}$ <62T763>. α,β -Unsaturated acids can be epoxidized with H_2O_2 and heteropoly acids at pH 6–7 <89CL2053>. Simple alkenes and allylic alcohols are epoxidized with heteropoly acids under phase transfer conditions <84SC865, B-88MI 103-05, 92T5099>. Al_2O_3 -supported KF has also been used to promote epoxidation of electron-deficient alkenes with $\text{Bu}^t\text{O}_2\text{H}$ <94TL9481>. A highly enantioselective method for epoxidizing electron-poor alkenes in a triphase system (poly-L-amino acid/aqueous phase/organic phase) proceeds with 84–96% enantiomeric excesses <82JCS(P1)1317, 83T1635>, whereas the NaOH/ H_2O_2 method utilizing a chiral phase transfer catalyst affords only 25% *ee* <76TL1831>. Saturated solutions of sodium perborate (NaBO_3) in the presence of NaOH and a phase transfer catalyst epoxidize enones in high yields <95TL663>, see also <89MI 103-03, 89SC3579>. A one-pot procedure for regioselective preparations of 2-(phenylsulfonyl)-1,3-diene monoepoxides from 1,3-dienes has been described (Equation (36)) <88JOC2398, 93JOC5221>.

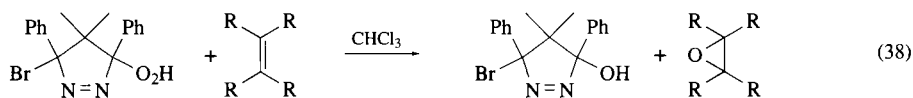


Urea–hydrogen peroxide (UHP) has been found to epoxidize electron-deficient alkenes under various conditions <90SL533, 93MI 103-03>; for example, methyl methacrylate is epoxidized with UHP– Na_2HPO_4 in the presence of $(\text{CF}_3\text{CO})_2\text{O}$; α,β -unsaturated ketones and nitroalkenes are cleanly transformed into the corresponding oxiranes with UHP–NaOH in methanol (Equation (37)).



1.03.4.9 Epoxidations with α -Azohydroperoxides

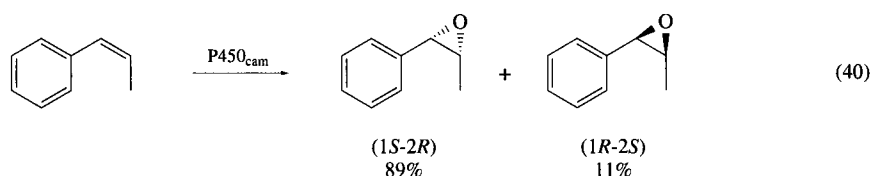
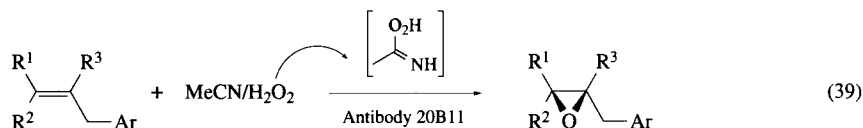
Alkenes are essentially inert to most alkyl hydroperoxides in the absence of certain reagents such as Mo or V catalysts, or basic alumina. Direct epoxidations with a number of unusual hydroperoxides have been observed. The most notable of these are triphenylsilyl hydroperoxide <79TL4337>, 2-hydroperoxyhexafluoro-2-propanol <79JA2485>, α -hydroperoxy esters, and α -hydroperoxynitriles <80CC705, 80JA5602>. Baumstark and co-workers have shown that α -azohydroperoxides, in particular cyclic derivatives thereof, convert alkenes to oxiranes in good yield under mild conditions without added catalysts (Equation (38)) <81JOC1964, 82JOC1141, 86MI 103-05>.



1.03.4.10 Enzyme-catalyzed Epoxidations

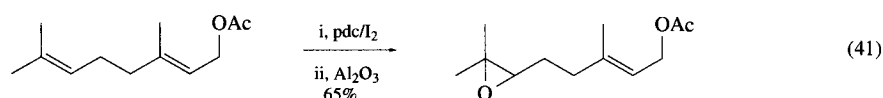
Enzymatic epoxidations of alkenes proceed with high stereoselectivity. Several such epoxidations, catalyzed by enzymes, can be carried out on a multigram scale; most of these methods employ purified enzymes or whole cells <71MI 103-02, 74JA4031, 76JA7856, 78CC849, 81JOC3128, 81MI 103-02, 82JCS(P1)2767, 84AG(E)796, 84JA7928, 86MI 103-06, 89TL1583, 90JA3993, 91JA684, 91JA3195, 91JA5878, 94TL279> and useful levels of enantioselectivity have been obtained in a few cases using purified enzymes. Chloroperoxidase (CPO) is among the best known and most readily available enzymes for catalysis of alkene epoxidations <83BBR(116)82, 83JBC(258)9153, 87JBC(262)11641, 88MI 103-06, 89MI 103-04>. CPO has

been shown to effectively catalyze enantioselective (66–97% *ee*) alkene epoxidations with H_2O_2 in high chemical yields (93JA4415). The first antibody-catalyzed epoxidations of unfunctionalized alkenes with H_2O_2 have been reported to proceed in highly enantioselective (67–100% *ee*) manner (Equation (39)) (94JA803). Cytochrome P450 enzymes catalyze epoxidations by utilizing molecular oxygen and a catalyst, usually NADH. Cytochrome P450 reactions are the subject of reviews (B-86MI 103-03, 88SCI433, B-92MI 103-03). The camphor-specific cytochrome P450_{cam} enzyme epoxidizes simple alkenes unrelated to camphor with high stereoselectivity (Equation (40)) (91JA3195).

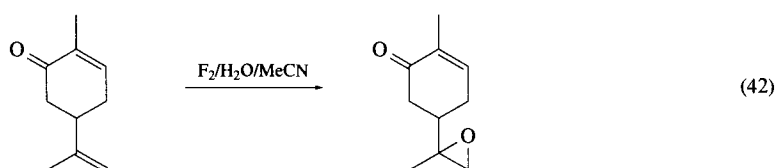


1.03.4.11 Miscellaneous Methods

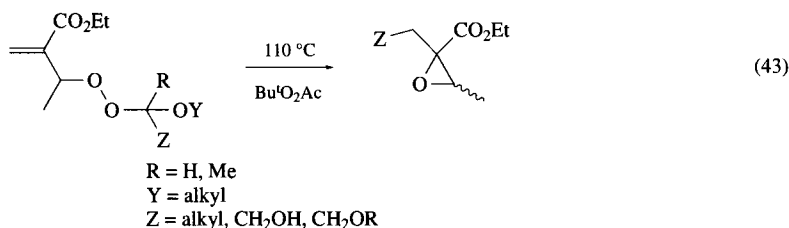
Alkenes are converted to oxiranes upon treatment with I_2 and pyridinium dichromate (pdc) in CH_2Cl_2 (Equation (41)) (83T1765). The respective iodohydrins have been shown to be the precursors of the oxiranes formed in these reactions.



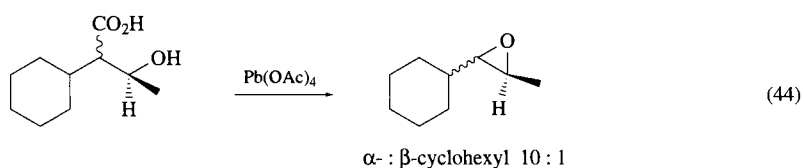
Ozone has also been employed in alkene epoxidations using metalloporphyrins (91JOC3725). Elemental fluorine in aqueous acetonitrile epoxidizes alkenes in good to excellent yields (Equation (42)). It has been suggested that the actual oxygen transfer agent is HOF (90JOC5155).



The same research group has demonstrated the high reactivity of the aforementioned reagent system by epoxidizing strongly electron-deficient alkenes, such as fluoroalkenes (91JOC3187). Glycidic esters have been prepared by induced decomposition of peroxy ketals (Equation (43)) (94JOC4765). The decrease in the yield of epoxide with increasing bulk of the alkyl group of the aldehyde precursor was attributed to a side reaction involving hydrogen elimination. In those instances, improved yields were obtained at lower temperatures by using BF_3 in the presence of O_2 , instead of the *t*-butyl peracetate in the initiation step.



Oxidative decarboxylation of β -hydroxy acids with $\text{Pb}(\text{OAc})_4$ results in oxirane formation with good stereoselectivity (Equation (44)) <90JOC1965>.



A method employing KMnO_4 - CuSO_4 has been found to proceed in a highly β -selective manner in the epoxidation of Δ^5 -unsaturated steroids <92JOC1928>.

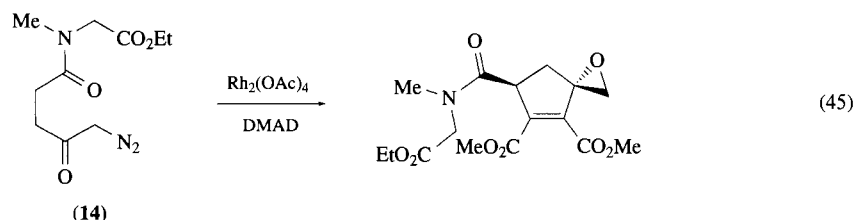
Electrolytic oxidation of ketones in methanolic solutions of NaCN in the presence of catalytic amounts of KI affords oxiranecarbonitriles along with small amounts of oxiranecarboximidates; aryl ketones, however, lead to benzoylpropanedinitriles <93JOC6194>.

2-Nitrobenzenesulfonyl peroxy (A) or sulfinylperoxy (B) intermediates (Figure 6), generated at low temperature from 2-nitrobenzenesulfonyl- or -sulfinyl chloride with KO_2 , serve as excellent oxidizing agents and preferentially epoxidize isolated double bonds rather than enones <B-88MI 103-05>.



Figure 6

A remarkable oxirane synthesis has evolved from Padwa's *dipole cascade* reactions: treatment of diazoketone (14) with $\text{Rh}_2(\text{OAc})_4$ in the presence of dimethyl acetylenedicarboxylate (ADM) affords uniquely functionalized oxiranes (Equation (45)) <90JA2037>.



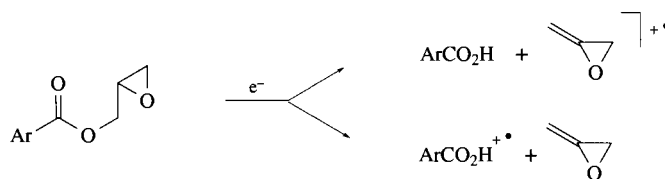
Finally, unfunctionalized alkenes are epoxidized using chiral borates and an alkyl hydroperoxide with enantiomeric excesses up to 51% <93TA2339>.

1.03.5 ALLENE MONO- AND BISOXIRANES

Allene oxides have been proposed as biogenic precursors to prostanooids in the "lipoxygenase pathway" <80MI 103-07, 83BBR(111)470>. Several research groups have presented strong evidence for such a biogenic pathway <87JA289, 87JBC(262)15829, 87TL3547, 88B18, 88MI 103-07, 88TL2555>, and Brash *et al.* have actually isolated and spectroscopically characterized the proposed allene oxide intermediate <88PNA(86)3382>. Allene oxides have been reviewed <80AG277, B-80MI 103-06, 80T2269, 83CRV263, B-83MI 103-05>. Ample theoretical work on allene oxides has been published in <81JOC1909, 83JOC4744, 84JA5112, 85JA2273, 87PAC1571, 90JA1751>. The elusive parent compound, methylenecyclopropane, and its radical cation have been prepared by flash vacuum pyrolysis of glycidol benzoates <91JA5950, 90JA5892> and characterized by neutralization-reionization spectroscopy (Scheme 66).

In a similar study, formation of allene oxides has been inferred from the collisional activation (CA) mass spectra of the products from rearrangements of α -methoxy- or thiomethoxyketones in the gas phase <93JCS(P1)2235>.

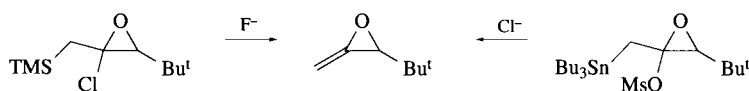
Synthetic activity in this area has increased mainly owing to the implementation of convenient procedures for generating dimethyldioxirane (DMDO), a powerful oxygen atom transfer agent <85JOC2847, 87JOC699, 87JOC2800, 91CB227, 91CB2377>. The use of DMDO as an acetone solution under



Scheme 66

neutral conditions permits the isolation of highly reactive acid- and nucleophile-sensitive oxiranes derived from allenes. However, only sterically encumbered monooxiranes can be isolated under these conditions, the major pathway being bisoxirane formation. There are mainly three different approaches to allene monooxiranes.

(i) Chan's dehalosilylation of 1-halo-1-trimethylsilylmethyleneoxiranes with fluoride ion (Scheme 67) <78JOC2994>. In one instance a sterically hindered allene oxide (1-*t*-butyl allene oxide) has been isolated and characterized. In most cases, however, the halide causes ring opening. A similar strategy has been used to prepare chiral α -substituted ketones via the intermediate allene oxides <93TA1417, 93TL8543>. Optically active 2-*t*-butyl-3-methylene oxirane has been prepared from chiral 2,3-epoxy-4,4-dimethyl-2-tributylstannylpentan-1-ol by first activating the hydroxy group then inducing deoxystannylation with chloride ion in low yield <92TL5093, 94TA1559>. The (*S*)-(-)-allene oxide so obtained undergoes hydroboration to give the corresponding optically active (*R*)-1,3-diol.

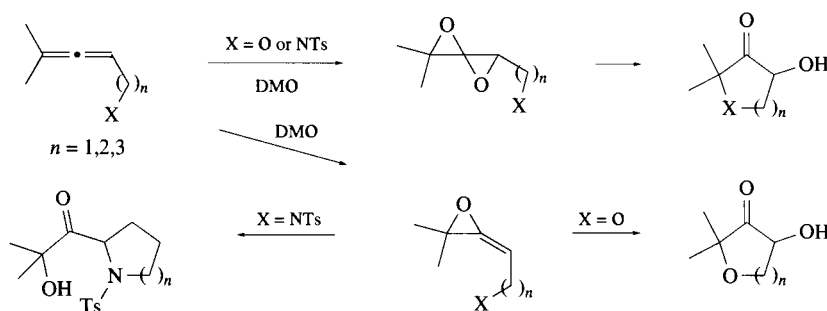


Scheme 67

(ii) Crandall's epoxidation of allenes and cumulenes with *m*-chloroperoxybenzoic acid (MCPBA) and dimethyldioxirane (DMDO). The per-*t*-butyl substituted 1,2,3-butatriene is epoxidized <87JA4338> with MCPBA at the terminal double bond, to give an unstable yet spectroscopically detectable monooxirane which continues on to several products, e.g., the corresponding methylenecyclopropanone, a benzoic acid addition product, and the methyleneoxetanone derivative via the transient 1,2:3,4-dioxirane. Ando *et al.* reported a similar study <86TL6357> corroborating Crandall's results; see also <89BCJ1367>. Crandall *et al.* also studied the oxygenation of hindered [4]- and [5]-cumulenes, but were able to detect only the cyclopropanones, rather than their allene oxide precursors from these reactions <92JA5998>.

Unable to isolate the postulated bisoxiranes in earlier studies owing to their lability toward the benzoic acid by-product, Crandall and co-workers have now been able to prepare them with dimethyldioxirane (DMDO) and study their spectroscopic and chemical properties <88JOC1338>. Moreover, the same research group trapped the intermediate allene oxides and bisoxiranes intermolecularly with a large number of nucleophiles <91JOC1153>, and intramolecularly with hydroxyl <88TL4791, 92T1427>, formyl <94TL1489>, and carboxylic acid groups <90JOC5929>, as well as nitrogen-based nucleophiles <94TL2513>. The intramolecular variants of these trapping reactions have allowed the preparation of a number of highly functionalized heterocyclic systems (Scheme 68).

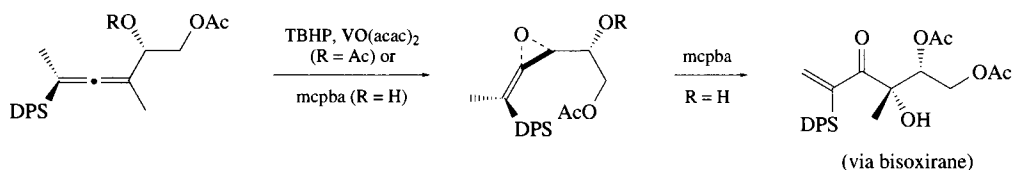
In a similar vein, Kim and Cha reported the regioselective monoepoxidation of vinyl allenes



Scheme 68

with $\text{Bu}^t\text{O}_2\text{H}$ (TBHP)/ $\text{VO}(\text{acac})_2$ $\langle 88\text{TL}5613 \rangle$. The resulting allene oxides undergo intramolecular cycloaddition to the vinyl group, leading to cyclopentenones, in analogy to the previous work in this area by Bertrand and co-workers. $\langle 76\text{S}755, 76\text{TL}1507, 76\text{TL}3305, 77\text{TL}4403, 79\text{TL}1845, 81\text{TL}3179 \rangle$. Substituted bisallenes have been oxygenated by Pasto *et al.* with O_2 , dimethyldioxirane, and MCPBA $\langle 92\text{JOC}2976 \rangle$. The products from these reactions are mostly 4-alkylenecyclopentenones via intramolecular Nazarov-type cyclization of the transient allene oxide species.

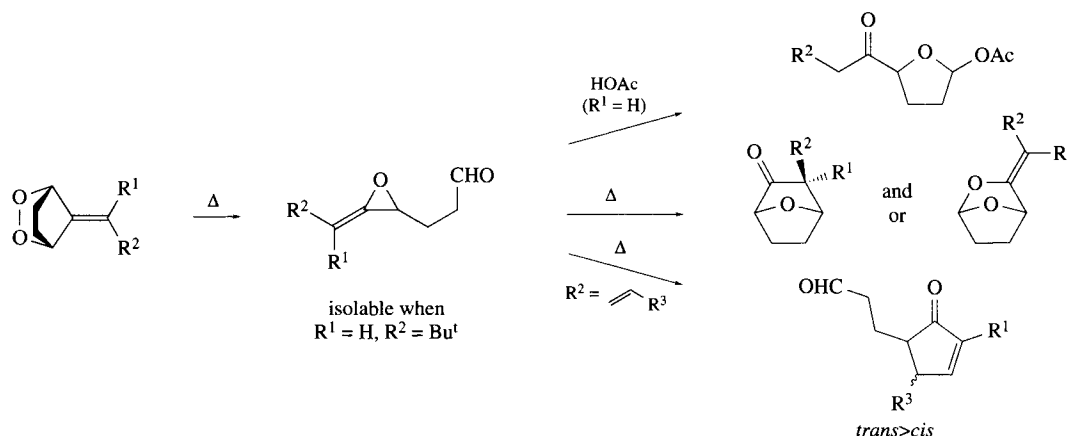
Marshall and Tang have isolated stable allene oxides from regioselective epoxidation of functionalized allenes with either MCPBA (buffered with NaH_2PO_4) or TBHP/ $\text{VO}(\text{acac})_2$ $\langle 93\text{JOC}3233, 94\text{JOC}1457 \rangle$. Further epoxidation of the allene oxides gives rise to enones bearing three hydroxy functionalities on the alkyl chain (Scheme 69, DPS = diphenyl-*t*-butysilyl). The intermediate bisoxiranes have not been detected. The researchers employed this methodology for the construction of chiral carbohydrate precursors.



Scheme 69

Finally, Wolff and Agosta isolated a stable keto allene oxide which upon thermolysis at 125°C leads to the respective 3(2*H*)-furanone; further oxidation of the former furnishes a stable acyl dioxaspiropentane $\langle 84\text{CJC}2429 \rangle$.

(iii) Thermal decomposition of saturated fulvene endoperoxides $\langle 87\text{TL}3779 \rangle$. This is an unconventional method for the generation of functionalized allene oxides (Scheme 70). In the absence of trapping agents, the intermediates undergo intramolecular 1,3-dipolar cycloaddition with the formyl group to give 7-oxabicyclo[2.2.1]heptanones and/or the corresponding bicyclic acetals $\langle 94\text{UP} 103-01 \rangle$. When R^2 is a vinyl group, cyclization to a cyclopentenone takes place $\langle 93\text{JOC}3611 \rangle$. In the presence of trapping agents, e.g., 1,3-dienes or acetic acid, the allene oxide intermediates exhibit reactivity characteristic of their cyclopropanone valence tautomers $\langle 93\text{TL}2291 \rangle$. In one case ($\text{R}^1 = \text{H}$, $\text{R}^2 = \text{Bu}^t$), a very stable allene oxide was isolated and characterized $\langle 93\text{TL}1255 \rangle$.



Scheme 70

1.03.6 OXIRANES: BIOLOGICAL ASPECTS, OCCURRENCE

1.03.6.1 Biological Aspects

Oxiranes figure prominently in the biosynthesis of a large family of biologically important substances. The enzyme 5-lipoxygenase catalyzes the conversion of arachidonic acid, the predecessor of the members of the "arachidonic cascade" $\langle 77\text{MI} 103-01, 86\text{MI} 103-07, 90\text{MI} 103-02 \rangle$, into leukotriene (LT) A_4 by way of a hydroperoxide intermediate $\langle 87\text{JA}8107, 89\text{MI} 103-05 \rangle$. Leukotriene A_4 is a known precursor of another biologically active leukotriene, LTB_4 , and its conjugates with various peptides

(LTC₄ and LTD₄) or cysteine (LTE₄) <80JA1433, 80JA1436>. These conjugates are implicated in many inflammatory and allergic conditions <B-80MI 103-08>. An allene oxide ((15), Figure 7) has been identified as the possible precursor of prostaglandins of the A and E series in the gorgonian coral *Plexaura homomalla* <87JBC(262)15829, 88PNA(85)3382, 89JA1891> and other arachidonic acid metabolites such as preclavulone A. This epoxide is formed via an (8(*R*))-lipoxygenase pathway from (8(*R*))-8-hydroperoxyeicosatetraenoic acid (8(*R*))-HPETE <85TL4171, 87JA289, 87TL4247, 88TL2555>.

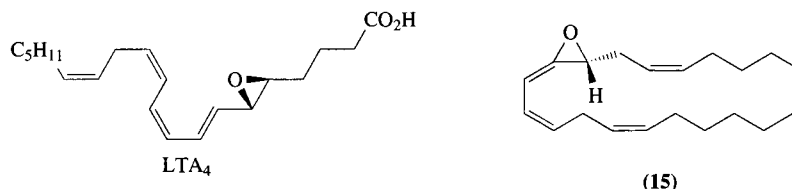
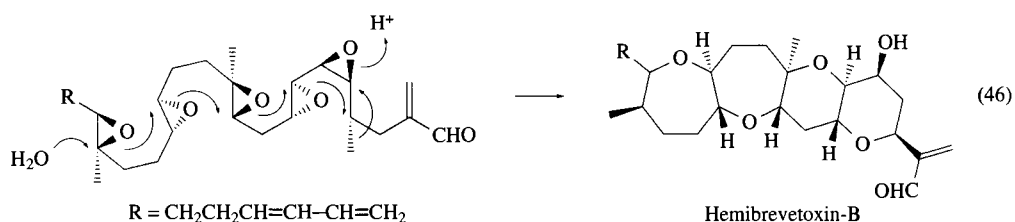


Figure 7

The synthesis and chemistry of arachidonate metabolites from the hepoxilin/trioxilin pathway have been reviewed <93MI 103-04>. A bisepoxide has been implicated in the biosynthesis of the antibiotic furanomycin <88JA4035>. Numerous epoxyquinones have been found in many metabolic pathways, including the shikimate pathway <89JA7932, 91JA684>. Arene oxides are intermediates in the biosynthesis of various metabolically important phenols and proven causative agents of necrosis, mutagenesis, and carcinogenesis as a result of covalent binding to cellular macromolecules <85CHE197>. Numerous reports indicate that the most important ultimate carcinogens formed upon metabolism of carcinogenic alternant polycyclic hydrocarbons (PAH) are benzo-ring diol epoxides in which the epoxide group forms part of a bay region <B-84MI 103-01, B-85MI 103-07, 88ACR66, B-88MI 103-08>. The mechanism of the catalytic function of vitamin K, the blood clotting factor, in the carboxylation of glutamate has been studied extensively <94MI 103-04, 94MI 103-05>. ¹⁸O Labeling experiments carried out by Dowd and co-workers indicate that intramolecular epoxidation of vitamin K proceeds through a 1,2-dioxetane intermediate leading to vitamin K oxide <93JA5839, 94JA9831>. Aflatoxin B1 epoxide has been recognized as the ultimate carcinogenic form of aflatoxin B1 <88JA7929, 89MI 103-05, 94JA8863>. It has been proposed that 1,2-dioxetanes derived from polycyclic arenes such as benz[a]pyrene or polycyclic heteroarenes such as furacoumarins may be transformed into their reactive epoxides, the ultimate mutagens, by deoxygenation of the corresponding dioxetanes <91JA8005>. The intramolecular cyclization of (3*S*)-2,3-oxidosqualene to lanosterol, mediated by 2,3-oxidosqualene-lanesterol cyclase, represents one of the most fascinating biosynthetic processes in nature <75ACR152, 82MI 103-01, 91T5925>. Corey and Matsuda succeeded in purifying the enzyme 2,3-oxidosqualene-lanesterol cyclase from yeast (*Saccharomyces cerevisiae*) <91JA8172>. It has been speculated that brevetoxins, the potent neurotoxins responsible for the massive fish kills and human intoxication known as neurotoxic shellfish poisoning, are biosynthesized through a similar cascade of epoxide ring openings (Equation (46)) <82PAC1973, 85MI 103-09, 86JA7855, B-86MI 103-08, 89JA6476, 94JA9371>.



1.03.6.2 Occurrence (Natural Products)

Compounds containing the oxirane ring are ubiquitous in nature. A large number of oxirane-containing compounds have been isolated from various sources and some of them exhibit wide-ranging biological activities. These include insect juvenile hormones (e.g., juvenile hormone bis-epoxide, JHB₃ (Figure 8) <89PNA(86)1421>), pheromones <85MI 103-08, 86T3479, 89ABC801, 89LA453, 89T3233, 89TL3405, B-92MI 103-04, 92S1007, 93JOC5153, 95TL1477>, and marine natural products <88JOC3642, 88JOC3644, B-93MI 103-05, 94MI 103-06, 94P835, 94TL7969, 94T9893, 95TL1763> (e.g., spatol) (Figure 8)

<80JA7991, 80TL2249, 81JOC2233, 82AJC129, 83JOC3325, 86T3789, 91JA3096>. A number of oxiranes have been isolated from fungi <84G163, 85JAN1040, 85MI 103-10, 85TL3163, 88JA4043, 90JOC4916, B-91MI 103-02, 93T811, 94T9989, 94TL1043, 94TL1343, 94TL6009, 95JA2421, 95TL1469>. The (–)-ovalicin (Figure 8) has been isolated from cultures of the fungus *Pseudorotium ovalis*; it is an angiogenesis inhibitor and has potential for inhibiting development of solid tumors by cutting off their blood supply <85JA256, 94JA12109>.

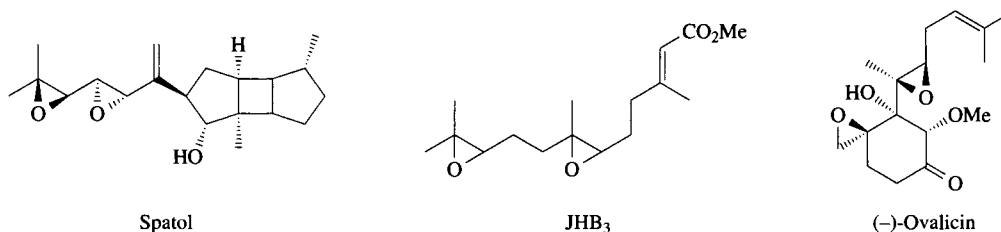


Figure 8

1.03.7 OXIRENES

1.03.7.1 Background and Theoretical Studies

Considerable research effort has been directed towards the generation, detection, and isolation of oxirenes, a highly strained class of antiaromatic heterocycles <83CRV519>. Although the unsaturated oxiranes are called oxirenes, much confusion is generated by the fact that *Chemical Abstracts* denotes oxiranes fused onto a polycyclic aromatic compound as oxirenes also (e.g., compound (16), Figure 9 <91JHC473>).

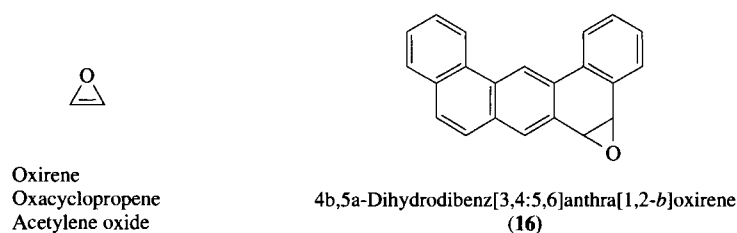


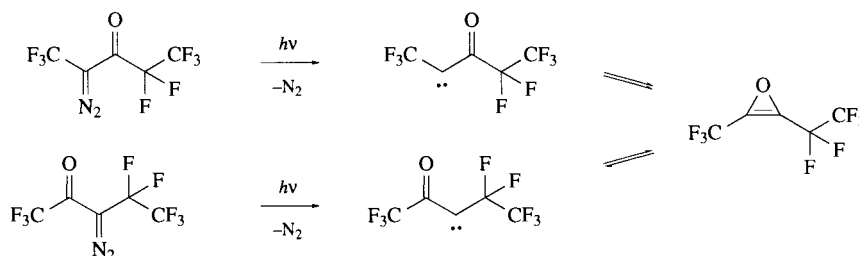
Figure 9

The parent oxirene has never been observed, despite efforts by several research groups <89JA441, 90AG(E)411>. A number of theoretical studies of oxirene have been reported <80JA7655, 82JOC1869, 83CJC2596, 83JA396, 87JA5883, 89JCP(90)378, 91CPL(177)468>. Tanaka's and Yoshimine's calculations on oxirene <80JA7655> suggest a barrier to isomerization as low as 2 kcal mol^{–1}. In a later study, Schaefer and co-workers disclosed their results on the molecular structure and harmonic vibrational frequencies of oxirene at the DZP SCF, DZP CISD, and DZP CCSD levels of theory, the latter two being the highest levels at which the structure of oxirene has been examined <91CPL(177)468>. Schaefer's latest *ab initio* study of substituted oxirenes predicts that of all the oxirenes with the formula X₂C₂O, where X = BH₂, CH₃, NH₂, OH, F, only dimethyloxirene will be a true minimum on the potential energy surface <94JA9311>. This prediction has been borne out by experiment (see below).

1.03.7.2 Synthetic Approaches to Oxirenes

The photochemical and thermal denitrogenation of α -diazoketones (the Wolff rearrangement) has been one of the most commonly used methods to generate oxirenes. Extensive matrix-isolation experiments with diazoketones failed to provide evidence for oxirene formation <82CB2192>. Strausz and co-workers reported an unstable intermediate formed during the low-temperature argon matrix photolysis of hexafluoro-3-diazo-2-butanone at 270 nm <83JA1698>. They assigned the FT-IR spectrum of this intermediate to bis(trifluoromethyl)oxirene. This result could not be confirmed in a

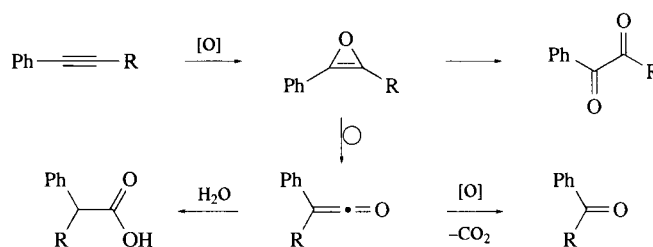
similar study by Lemal and co-workers, obviously because of the wavelength dependence of the photolysis $\langle 83JA7457 \rangle$. A later report by Strausz and colleagues confirmed the original assignment $\langle 87JOC2680 \rangle$. The intermediacy of the oxirene was further supported by trapping experiments with hexafluoro-2-butyne. The authors tentatively ascribed the formation of the trapped products from two different diazoketone precursors in essentially the same ratio to a common intermediate, possibly an oxirene (Scheme 71).



Scheme 71

Bodot and colleagues reported the trapping of dimethyloxirene, generated by photolysis of 3-diazo-2-butanone, in rare gas matrices $\langle 86MI\ 103-09, 90JA7488 \rangle$; the reactions were monitored by FT-IR spectroscopy; the oxirene intermediates were identified as minor products which were stable at temperatures lower than 25 K, isomerizing with an activation energy of $\approx 4.5\text{ kcal mol}^{-1}$. In other studies the intermediacy of an oxirene in the ketocarbene–oxirene–ketocarbene equilibrium has been inferred from product studies $\langle 86ZN(B)772, 89CPB573, 94TL2929 \rangle$. Turecek, Drinkwater, and McLafferty studied the gas-phase dissociative ionization of diazoacetone, and detected the stable methyloxirene cation radical by collisionally activated dissociation (CAD) and charge-inversion mass spectroscopy and isotopic labeling $\langle 91JA5958 \rangle$. Neutral methyloxirene is formed from its radical cation by charge exchange with mercury atoms, and characterized by neutralization–reionization mass spectrometry (NRMS). The oxirene thus generated is unstable and rearranges rapidly to methylformyl carbene and further to methylketene and 2-propenal or 1-hydroxypropyne.

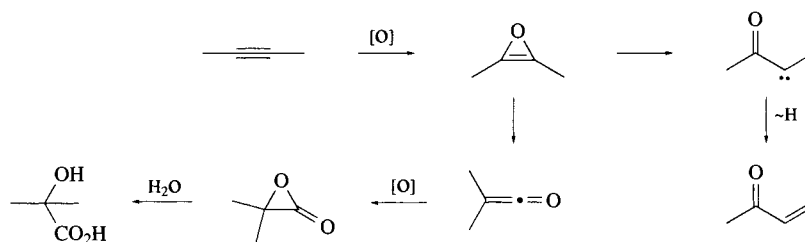
Oxirenes can in principle be obtained by oxygen atom transfer to alkynes. Mainly three groups have studied the epoxidation of alkynes by various reagents, in particular, molecular oxygen $\langle 84JPR73 \rangle$, peroxy acids $\langle B-83MI\ 103-03, B-92MI\ 103-05 \rangle$, *in situ*-generated dioxiranes $\langle 79MI\ 103-03, 92TL7929 \rangle$, and isolated dioxiranes $\langle 92TL7929, 93JOC5076 \rangle$. The peroxyacid oxidations of alkynes have been shown to be rarely selective, yielding complex mixtures the composition of which is highly particular to substrate structure, peroxyacid used, and reaction conditions. The products observed by Curci *et al.* in the dioxirane epoxidations of aryl-substituted alkynes are shown in Scheme 72. The formation of all products can be rationalized by way of an oxirene intermediate $\langle 92TL7929 \rangle$. The authors did not observe products arising from an oxocarbene, an intermediate often postulated as a valence tautomer of an oxirene, both species being of similar energy content according to theoretical calculations $\langle 87JA5883, 90JA7488 \rangle$.



Scheme 72

Murray's and Singh's studies on dialkylalkynes and alkyltrimethylsilyl-substituted alkynes likewise lead to products arising from oxirene and oxocarbene intermediates. The latter serve as precursors of products arising from hydrogen- or CH_3 -shifts, as well as cyclopropane insertion in some cases (Scheme 73). The enones derived from some of these carbene reactions are partially converted to 2,3-epoxyketones $\langle 93JOC5076 \rangle$.

Other attempts to generate oxirenes include photochemical cycloreversion of suitably constructed polycyclic oxirenes. These experiments, however, did not yield evidence for oxirene intermediates $\langle 82CB2202 \rangle$.

**Scheme 73**

An elegant study by Ortiz de Montellano and Kunze strongly suggests that oxirenes are formed as intermediates in the oxidation of alkynes by microsomes $\langle 80JA7373 \rangle$. 5-Ethynyluracil has been shown to act as a potent mechanism-based inhibitor of thymine 7-hydroxylase, an α -ketoglutarate dioxygenase; the intermediacy of an oxirene has been proposed for the inactivation mechanism $\langle 89JA7632 \rangle$.

1.03.7.3 Conclusions

Oxirenes, a unique class of strained heterocycles which have long been elusive, are now emerging as species that can be generated at low temperatures and detected by spectroscopy. It appears that the most promising method of generation of a "stable" oxirene still remains the photochemical decomposition of α -diazoketones at low temperatures.

1.04

Oxiranes and Oxirenes: Fused-ring Derivatives

IHSAN ERDEN

San Francisco State University, CA, USA

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1.04.1 INTRODUCTION

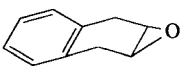
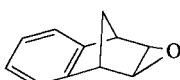
There are a large number of methods for preparing oxiranes (see Chapter 1.03). Practically all of these can be applied to the synthesis of fused-ring oxiranes. Emphasis is placed on oxiranes fused onto small rings or other systems with unusual structural features and reactivity not exhibited by their acyclic counterparts. Since 1985 the implementation of isolated and *in situ* dioxiranes in oxygen transfer reactions has revolutionized the field of selective epoxidations under conditions mild enough (e.g., neutral medium, nonnucleophilic by-products, and low reaction temperatures) to permit isolation of even the most labile fused-ring oxiranes, therefore a large section of this chapter has

been devoted to this area. The epoxidation methods mentioned in this chapter are meant to be complementary to those discussed in Chapter 1.03 and have been selected based on their relevance to factors encountered in cyclic systems, such as strain and stereochemistry.

1.04.2 NMR SPECTROSCOPY

Oxygen-17 NMR spectroscopy has been employed extensively in oxirane-containing compounds (B-91MI 104-01). Valuable information about structures of fused-ring oxiranes can be garnered from a comparative study of ^{17}O NMR absorptions (79TL3449). For instance, the oxirane oxygen in norbornane *exo*-oxirane is considerably shielded as compared to that in cyclohexene oxide (Table 1). This shift is attributable to a γ -effect brought on by the methano bridge in (2). This effect is reversed in the corresponding norbornadiene oxide as well as the benzo annelated counterpart, with the oxirane oxygen experiencing a large deshielding effect caused by the remote π -systems in (4) and (6).

Table 1 Oxygen-17 NMR data of fused-ring oxiranes.

			
	(1)	(2)	
$\delta (^{17}\text{O})$ ppm	3.0	-15.0	$\Delta\delta = -18.0$
			
	(3)	(4)	
$\delta (^{17}\text{O})$ ppm	1.0	53.0	$\Delta\delta = 52.0$
			
	(5)	(6)	
$\delta (^{17}\text{O})$ ppm	-8.0	37.0	$\Delta\delta = 45.0$

Others have noted a modest correlation between the oxirane ^{17}O chemical shifts and the $^1J_{\text{C-H}}$, the latter being a measure for the s-character for the C—H bond and oxirane ring strain (Figure 1) (86ZOR215).

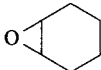
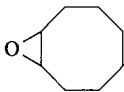
				
$\delta (^{17}\text{O})$ ppm	-6.0	3.0	4.0	9.0
$^1J_{\text{C-H}}$ (Hz)	162.0	171.9	168.0	170.0

Figure 1

A remarkable correlation of the $^{13}\text{CH}_2$ shifts between the oxiranes (7a)–(12a) and the carbocyclic analogues (7b)–(8b) has been reported (Figure 2) (82CB2287). Assuming similar anisotropy effects (64TL559, 74OMR(6)492, 75CB2781, 75JCS(P2)861, 76CJC231) of the cyclopropane and oxirane series as the principal cause of the order of the observed $^{13}\text{CH}_2$ chemical shifts in both series the authors concluded that in both series the analogous members prefer similar conformations (Table 2).

The shielding of the methano bridge hydrogens in the [2.2.1]heptyl and the ethano bridge hydrogens in the bicyclo[2.2.2]octyl system *syn* to the oxirane ring (83MI 104-01), as well as the corresponding etheno bridge hydrogens in the unsaturated analogues (76MI 104-01), is ascribed to a ring-current effect of the oxirane ring; 1,3-diaxial interactions between oxygen and hydrogen deshields the proton predominantly (Figure 3); presumably the lone-pair of electrons on oxygen plays a role in

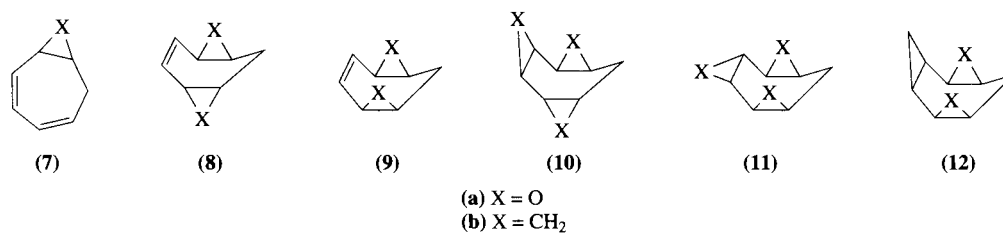


Figure 2

Table 2 ¹³CH₂-shifts (CDCl₃, δ) of epoxidized and cyclopropanated cycloheptatrienes.

	(7)	(8)	(9)	(10)	(11)	(12)
X = O	29.8	27.8	32.3	27.4	32.5	28.3
X = CH ₂	29.1	27.5				

deshielding. The significant shielding caused by the oxirane magnetic anisotropy also manifests itself in the strong upfield shift of the apical carbons in the propellanes (13) and (14) (Figure 4) <80JA7553, 83JA7364, 84JA8232>. The anisotropy effect discussed above, however, does not explain the unusually high shift caused ($\Delta\delta = 29.0$ ppm) by the oxirane ring in (15b) (Figure 5) <82CB1835>. This phenomenon has been ascribed to a polarization of the central C=C bond in (15b).

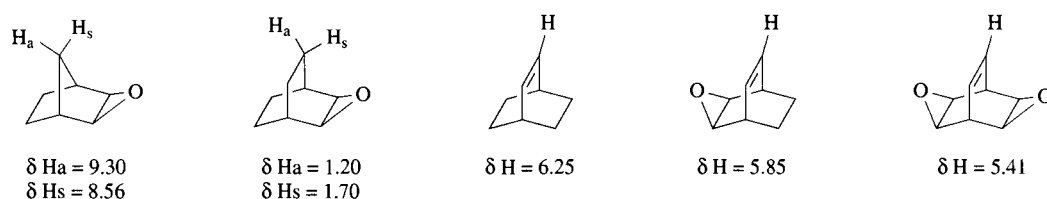


Figure 3

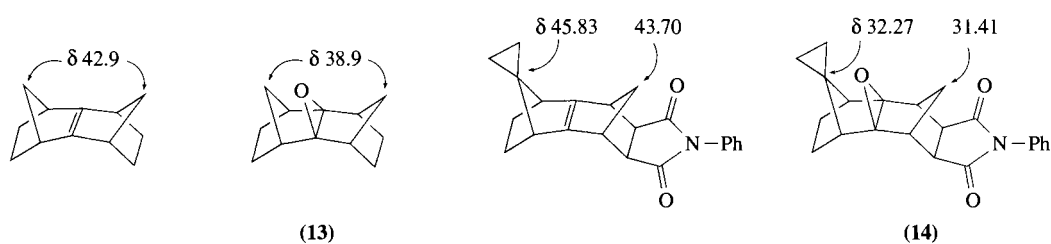


Figure 4

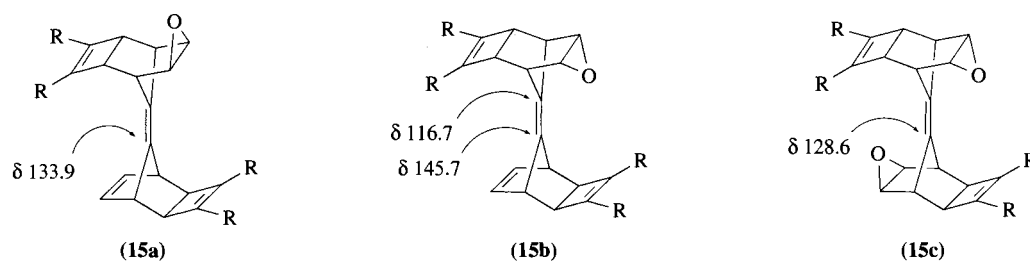
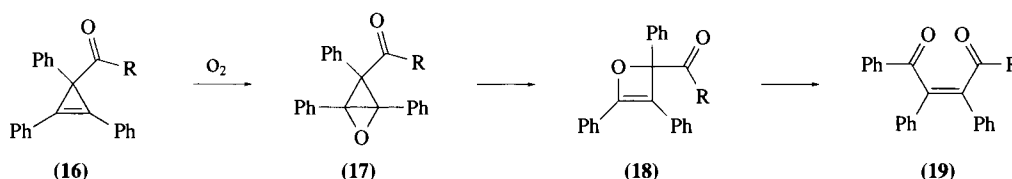


Figure 5

1.04.3 FUSION TO THREE-MEMBERED RINGS

Fusion to three-membered rings is formally derived from a cyclopropene by oxygen atom transfer. To date, no member of this class of bicyclic rings has been characterized, presumably due to the significant strain present in this framework, as well as the facile rearrangement pathway available under the conditions in which it is usually generated. Treatment of cyclopropenes with peracids is believed to proceed via oxabicyclobutane intermediates which give rise to α,β -unsaturated carbonyl compounds <67HCA1669, 69ACR25, 69JA6534, 70JOC450, 71JA4902, 71TL4761, 74JA5783, 74JOC388, 74JOC416, 86TL5143>. The use of dimethyldioxirane (DMD), the neutral and very reactive alternative epoxidizing agent, has been reported to result in the oxidation of a 3-methyl substituent, rather than addition to the cyclopropene double bond <91JOC5480>. The same substrate (1,2-bis(trimethylsilyl)-3,3-dimethylcyclopropene) gives with MCPBA an α,β -epoxyketone, presumably via the 2-oxabicyclo[1.1.0]butane intermediate. Similar products are formed when cyclopropenes are treated with oxygen (^3P) atoms <74JA632>. Padwa *et al.* observed a similar reaction during the air oxidation of cyclopropene (16) to (19) <82JOC183>. Intervention of an oxetene intermediate (18) prior to isomerization to (19) was proposed (Scheme 1).

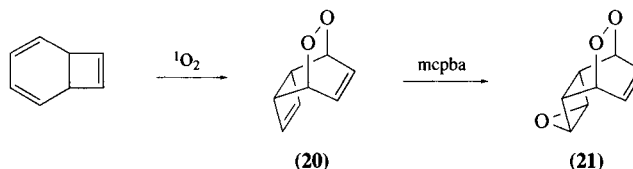


Scheme 1

2,4-Dioxabicyclo[1.1.0]butanes have been postulated as intermediates in the epoxidation of phenylalkynes with H_3PO_5 <82JA216>. The initially formed oxirenes are believed to undergo a second epoxidation leading to the oxygen analogues of (17) which spontaneously rearrange to 1,2-diones.

1.04.4 FUSION TO FOUR-MEMBERED RINGS

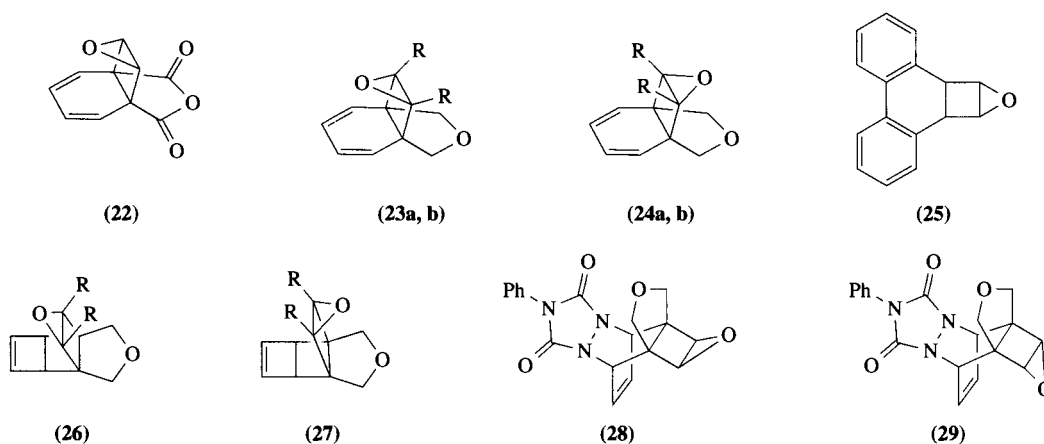
A number of 5-oxabicyclo[2.1.0]pentane derivatives have been prepared by several groups. Adam *et al.* obtained (21) from the endoperoxide precursor (20) with MCPBA as a single isomer (Scheme 2) <81AG(E)580, 85T2045>.



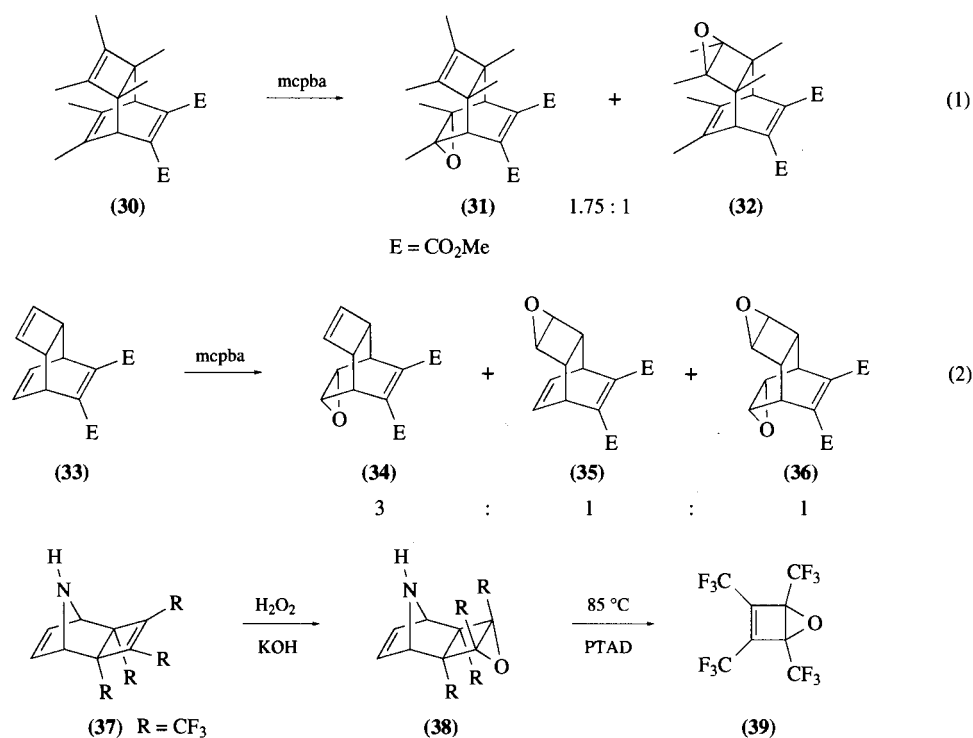
Scheme 2

Maier *et al.* prepared the interesting propellanes (22)–(24), as well as the oxirane (25). These oxiranes were prepared in hopes of affecting thermal or photochemical cycloreversion to the corresponding oxirenes, however, in none of the cases studied did evidence indicate the formation of an oxirene <82CB2202>. Propellane epoxide (23a) gave with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) the cycloadducts (28) and (29) exclusively, with the urazole ring *syn* to the tetrahydrofuran moiety and *anti* to the oxirane ring in both cases <83HCA2709>. These facial selectivities have been attributed to the greater steric interference between the dienophile and the oxirane ring hydrogens in (28) and/or the oxirane oxygen in (29). In the latter case, electronic repulsion of the oxirane oxygen may operate as well.

The research of Warrenner *et al.* in this area has yielded a number of interesting oxabicyclopentane derivatives. In their epoxidation of the Cookson ester (30) a mixture of the two monoepoxides (31) and (32) was isolated (Equation (1)) <94TL1075>. Epoxidation of Nenitzescu's ester (33) with MCPBA, contrary to an earlier report <83JOU1390, 83ZOR1543>, delivers a mixture of the three epoxides (34), (35), and (36) (Equation (2)). Several research groups have directed interest toward the synthesis of Dewar furan (5-oxabicyclo[2.1.0]pent-2-ene) and its derivatives; these have been



reviewed by Warrener *et al.* <86PAC161, B-92MI 104-01>. Lemal and Wirth prepared the first stable Dewar furan (**39**) by a retro-Diels–Alder reaction from (**38**) (Scheme 3 and Table 3) <82JA847>.



Scheme 3

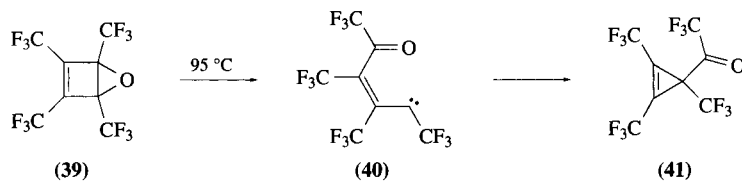
Table 3 Spectroscopic data of Dewar benzene (**39**).

IR (vapor) (cm^{-1})	^{19}F NMR (CDCl_3) (ppm)	Mass spectrum (m/e)
1695 ($\nu_{\text{C}=\text{C}}$)	64.35, 66.80	321 ($\text{M}^+ - \text{F}$), 290 ($\text{M}^+ - \text{CF}_2$), 271 ($\text{M}^+ - \text{CF}_3$), 243 ($\text{M}^+ - \text{COCF}_3$), 69 (base, CF_3)

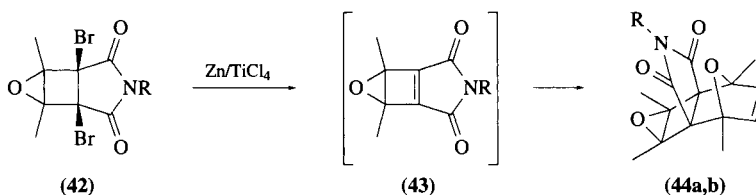
The formation of (**39**) was further confirmed by its cycloadditions with furan and pyrrole to give the corresponding Diels–Alder adducts. When heated, (**39**) suffers valence isomerization, yielding the cyclopropenyl ketone (**41**), presumably via the vinylcarbene (**40**) (Scheme 4).

The Dewar furan (**43**), prepared by debromination of (**42**), proved to be too unstable <84CC1466>. Its formation was inferred from the trapping products (**44a,b**) with 2,5-dimethylfuran (Scheme 5).

Initial attempts to generate alkyl substituted Dewar furans by photochemical breakdown of

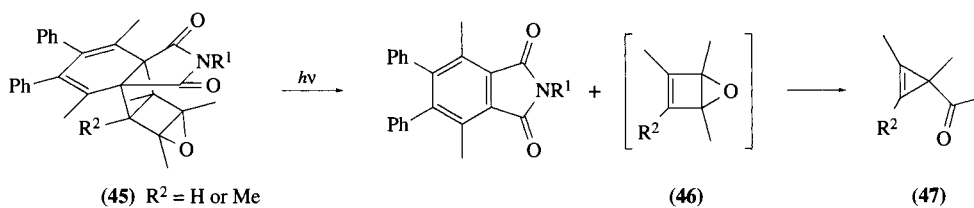


Scheme 4



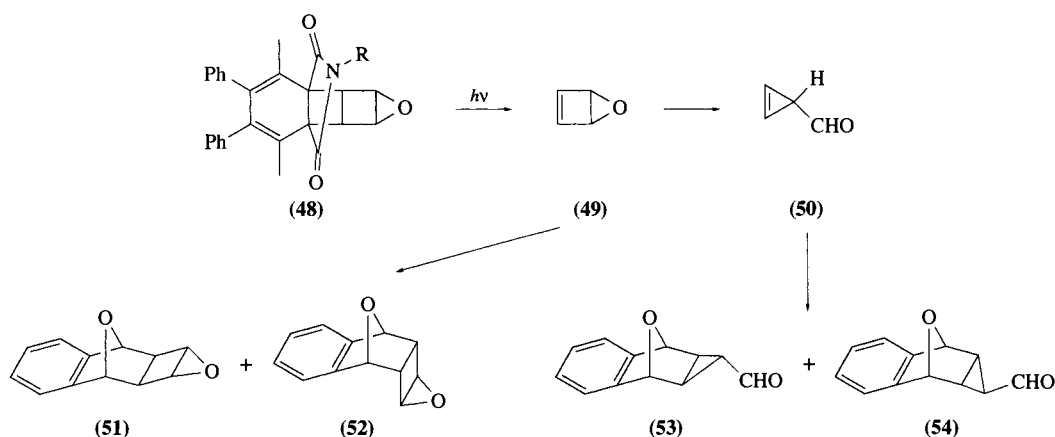
Scheme 5

propellane precursors of the type (45) afforded secondary products (47) believed to derive from (46) via a carbene intermediate (Scheme 6) [84CC1464, 86PAC161].



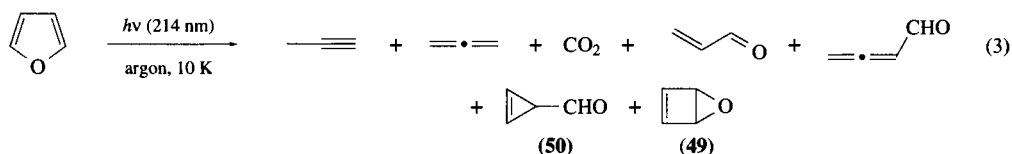
Scheme 6

The parent Dewar furan (49) was generated in a similar fashion from the corresponding propellane precursor (48) and trapped with isobenzofuran to give the cycloadducts (51) and (52) (Scheme 7) [85JA7176, 86PAC161]. The proportion of isobenzofuran–Dewar furan adducts (51) and (52) was increased at the cost of the cyclopropene aldehyde adducts (53) and (54) as the photolysis temperature was lowered, indicating that (49) is indeed the primary photolysis product.

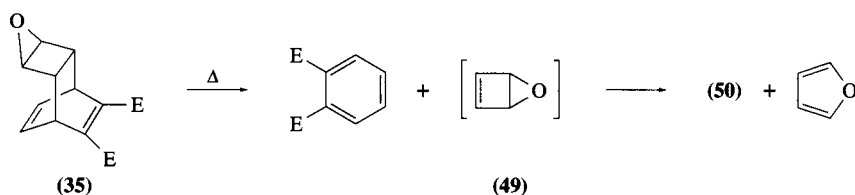


Scheme 7

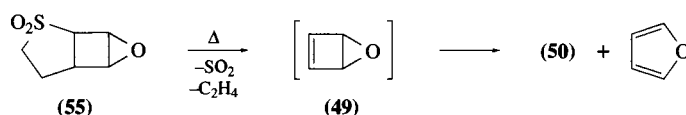
Strausz and co-workers reported formation and spectroscopic detection of (49) in argon matrices at 10 K (Equation (3)) [86JA1691]. The structure of (49) was assigned to the photoproduct based on characteristic IR-absorptions at 890 cm^{-1} and 760 cm^{-1} .



Thermal decomposition of suitable precursors can afford Dewar furan as well (Schemes 8 <83ZOR1543> and 9 <94JCS(P1)1983>). Under these conditions, however, (34) is too unstable for detection and gives rise to (50) and/or furan.



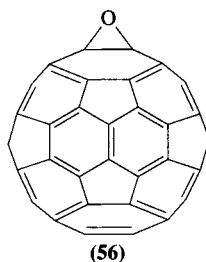
Scheme 8



Scheme 9

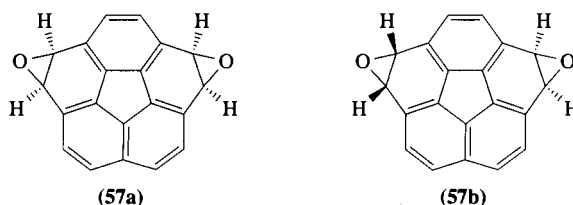
1.04.5 FUSION TO ORDINARY AND LARGE RINGS

Among the most prominent fused-ring oxiranes reported since the early 1980s is the fullerene epoxide. It has been prepared mainly by two different methods. Cox, Smith, and co-workers obtained (56) during the photooxygenation of C_{60} as the sole isolable product in 7% yield <92JA1103>. The addition of benzil significantly enhances both the yield (16%) and the rate of oxidation. The same oxirane (56) was independently prepared from C_{60} by epoxidation with dimethyldioxirane along with the corresponding dioxolane <92AG(E)351>. Others have detected C_{60}O by mass spectrometry in C_{60} and C_{70} carbon clusters derived from mixtures of fullerenes from soot <91JA5907>. Two oxidized products from treatment of C_{60} with MCPBA, C_{60}O and C_{60}O_2 , have been isolated and identified by mass spectrometry <93MI 104-01>. During the chromatographic separation of fullerene extracts, C_{60}O was isolated and subjected to extensive spectroscopic scrutiny <93MI 104-02>. Oxides of C_{60} have also been detected in the ozonolysis mixtures <93CPL(207)339, 93RTC639>. The corresponding monooxidation product derived from C_{70} , however, appears to be the oxidoannulene isomer rather than the epoxide <91SCI548, 92AG(E)223>.

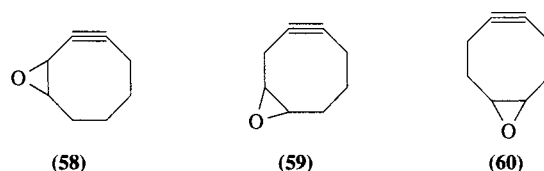


The epoxidation studies by Cheng and Scott on another fascinating hydrocarbon, corannulene, should also be mentioned here <94MI 104-01>. The initial formation of corannulene monoepoxide can be observed spectroscopically; however, the second epoxidation is about as fast as the first,

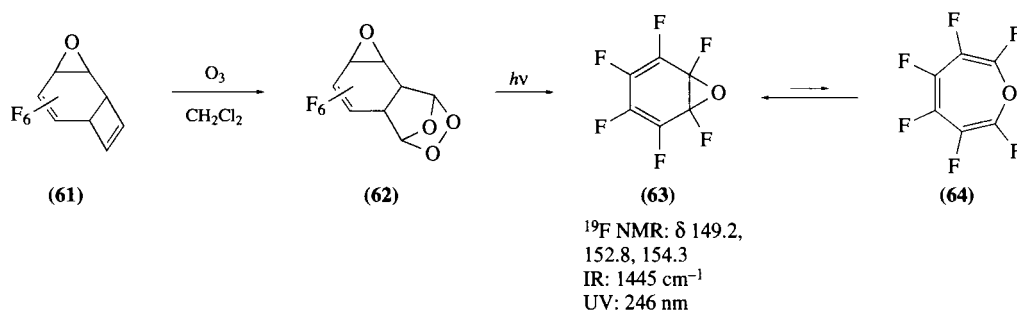
leading to a ca. 1 : 1 mixture of **(57a)** and **(57b)** <95PC 104-01>. Remarkably, only a single regioisomer is formed in this process, and further oxidation with excess peroxy acid does not produce a trisepoxide.



All three isomers of the highly strained 9-oxabicyclo[6.1.0]nonyne family, **(58)**–**(60)**, have been synthesized <89CB509>. These compounds, as expected, readily participate in cycloadditions with tetracyclone to afford tetraphenylbenzene annulated cyclooctenes.



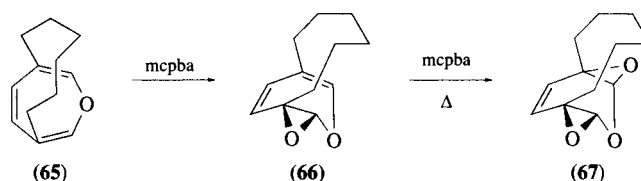
Oxepins and their bicyclic valence tautomers, arene oxides are discussed in <95CHE(42)197>. Particularly noteworthy is the synthesis of a stable benzene oxide **(63)** which surprisingly shows little tendency to isomerize to the corresponding oxepin **(64)** in spite of the expectation that the fluorines would greatly destabilize the three-membered ring in the bicyclic structure **(63)** (Scheme 10) <90JA6715>.



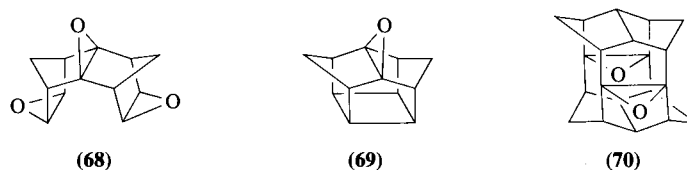
Scheme 10

Sequential epoxidation of a β,β -hexano-bridged oxepin **(65)** leads to the interesting mono- and bis-epoxides **(66)** and **(67)**, respectively (Scheme 11) <82CB1162>. The double bonds adjacent to the oxepin oxygen proved to be the preferred sites of attack in both cases.

Some examples of highly strained and symmetrical fused-ring oxiranes are **(68)**, **(69)** <83JA4113, 86JA3453>, and **(70)** <92CB1719>.

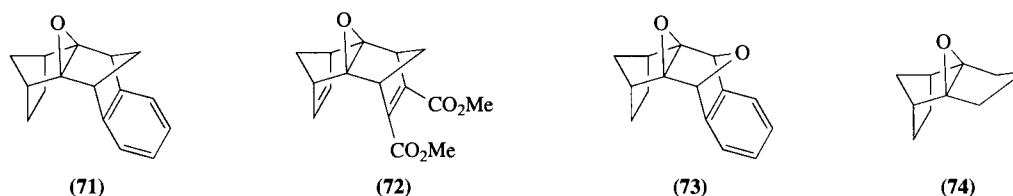


Scheme 11

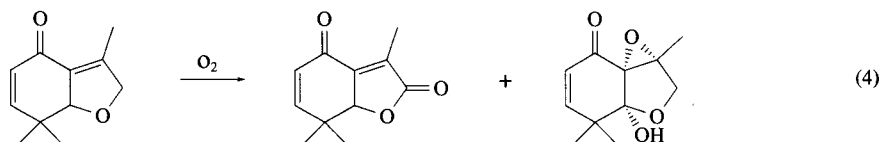


1.04.6 FUSED-RING OXIRANES BY SPONTANEOUS OXYGENATION OF CYCLIC ALKENES

Ground-state molecular oxygen ($^3\text{O}_2$) is capable of epoxidizing cyclic alkenes. Of the earlier examples of thermal epoxidations with molecular oxygen, the ones involving a nonfunctionalized cycloalkene by Padwa and Brodsky $\langle 73\text{TL}1045 \rangle$ and Jefford *et al.* $\langle 76\text{HCA}2542 \rangle$ and a cyclohexadienone derivative by Hart and Lavrik $\langle 74\text{JOC}1793 \rangle$ are particularly noteworthy. Certain strained alkenes are exceptionally reactive toward $^3\text{O}_2$, the epoxidations not requiring the aid of an initiator. Oxiranes **(71)**, **(72)** $\langle 80\text{JA}7553 \rangle$, **(73)**, and **(74)** $\langle 82\text{TH} 104-01, 91\text{JOC}6043 \rangle$, for example, are formed from the corresponding alkene precursors by spontaneous oxidation with molecular oxygen. In these reactions free radical intermediates have been advanced as possible precursors of the observed products.



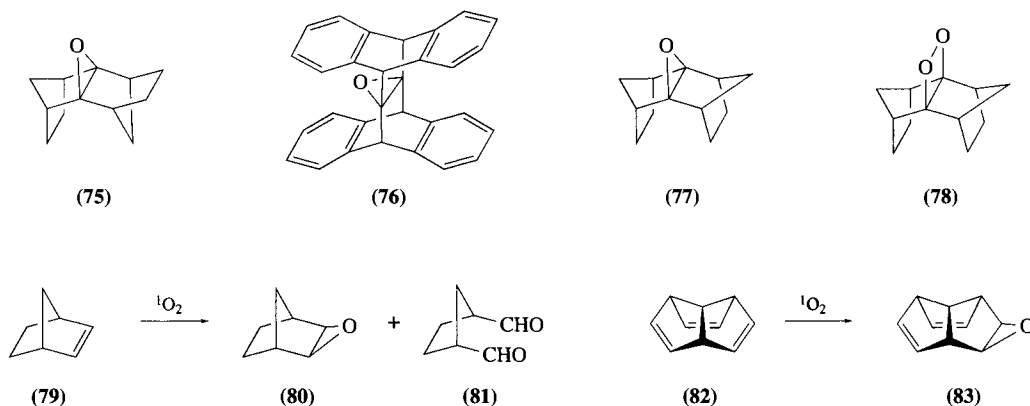
An example from 1992 of epoxidation of a strained dihydrofuran derivative by molecular oxygen is shown in Equation (4) $\langle 92\text{JOC}2467 \rangle$. It is believed that an initially formed hydroperoxide at the ring junction adjacent to the furan oxygen is responsible for oxirane formation.



1.04.7 OXIRANES VIA PHOTOOXYGENATION

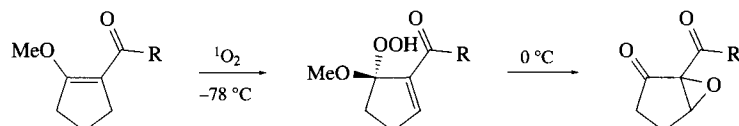
Certain substrates, in particular strained alkenes, undergo photooxidations leading to oxiranes. Well-known examples of this phenomenon are *anti*-sesquiorbornane and dehydrojansuene which upon irradiation in the presence of oxygen and a sensitizer (e.g., tetraphenylporphyrin (TPP), rose bengal (RB), or biacetyl) give rise to the corresponding oxiranes **(75)** $\langle 80\text{JA}1383, \text{B-}83\text{MI} 104-02 \rangle$ and **(76)** $\langle 79\text{JA}6332 \rangle$. In both cases photosensitization for oxygen transfer was necessary, and biacetyl- or benzil-sensitized reactions proceeded much more rapidly than the TPP-sensitized photo-oxygenations. The absence of 1,2-dioxetanes or cleavage products derived therefrom, and other unusual characteristics of these reactions indicate that singlet oxygen ($^1\text{O}_2$) is not the epoxidizing agent. Photooxygenation of *syn*-sesquiorbornene, on the other hand, also gives rise to the cleavage product (from **(78)**) in addition to **(77)** $\langle 80\text{JA}7553 \rangle$. Jefford proposes peroxy diradical intermediates to be responsible for epoxide formation $\langle 93\text{CSR}59 \rangle$. The fact that the use of RB as sensitizer favors the epoxidation pathway points to an electron transfer mechanism from the sensitizer to singlet oxygen, the resulting superoxide radical anion acting as the oxygen atom transfer agent. Two additional examples of epoxidation of norbornene $\langle 74\text{HCA}2257 \rangle$ and triquinacene $\langle 95\text{UP} 104-01 \rangle$, affected by photooxygenation, are shown in Scheme 12.

In another example of singlet oxygen oxidation, β -methoxy enones of the type undergo ene-reaction with singlet oxygen $\langle 83\text{TL}5189 \rangle$. The resulting hydroperoxides rearrange to the cor-



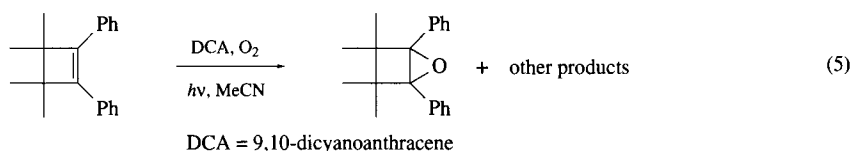
Scheme 12

responding α,β -epoxycyclopentanone derivatives (Scheme 13). The corresponding six-membered ring analogues do not react under the same conditions.



Scheme 13

Photooxidation of strained alkenes under electron-transfer conditions can also result in oxirane annelation (Equation (5)) <85T2069>.

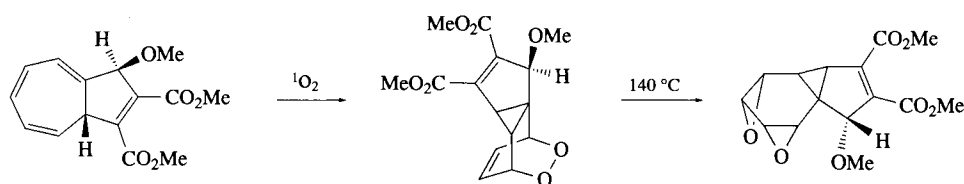


For other examples of oxirane formation from various alkenes by photooxygenation, see <80TL4327, 86JA2775, 89JA203, 89TL4481, 90JCS(P1)1097>. This subject has been reviewed by Bartlett <76CSR149>.

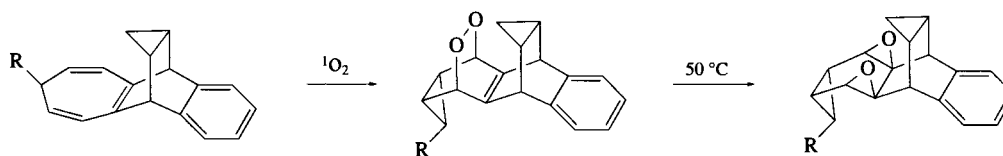
1.04.8 OXIRANES FROM ENDOPEROXIDES

The thermal and photochemical isomerizations of endoperoxides to bisepoxides are well documented <B-79MI 104-01, B-79MI 104-02, 80T833, 81CRV91>. Foote's catalytic rearrangement method using cobalt meso-tetraphenylporphine (CoTPP) constitutes a major breakthrough in 1,2:3,4-diepoxy synthesis from endoperoxides <80JA3641>. In some cases the thermal isomerization proceeds without side reactions (Schemes 14 <82CC337> and 15 <91JOC6755>).

In various other cases, however, thermal or photochemical isomerizations of endoperoxides

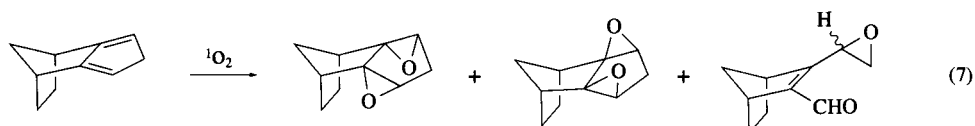
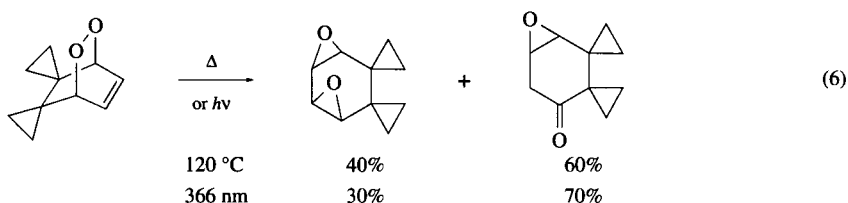


Scheme 14

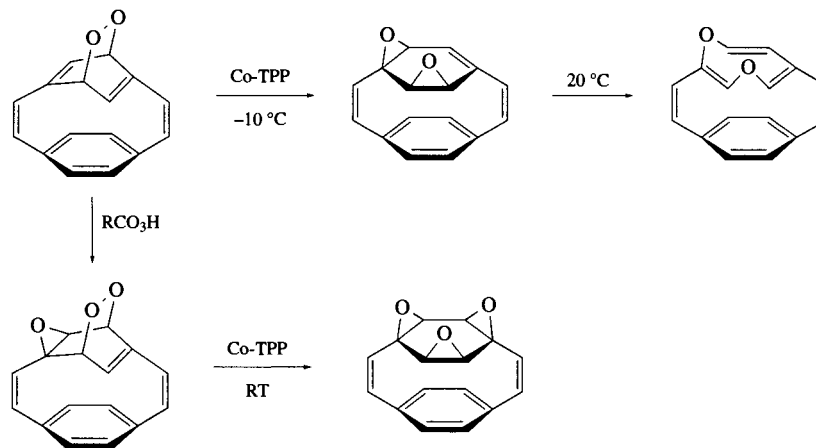


Scheme 15

afford, along with the bisepoxides, epoxy ketones (or aldehydes) (e.g., Equations (6) <86T6487> and (7) <80JOC4907, 85T2037>).

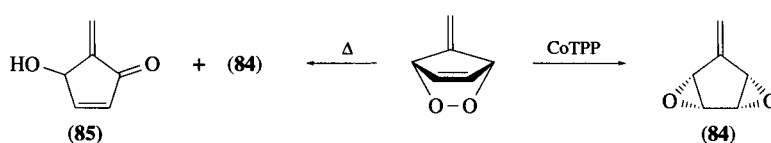


The use of CoTPP allows for low reaction temperatures for isomerizations and only in very rare cases are side reactions observed <86T6487>. Two applications of Foote's CoTPP methodology leading exclusively to some highly interesting bis- and trisepoxides of paracyclophane diene are shown in Scheme 16 <81AG(E)583>.

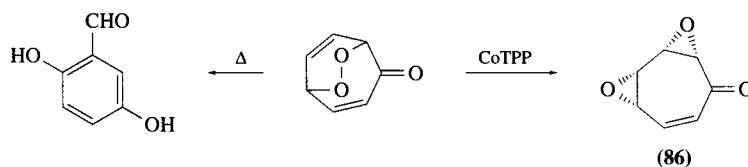


Scheme 16

Two other bisepoxides derived from fulvene (**84**) (Scheme 17) <87TL3779> and tropone (**86**) (Scheme 18) <83TL311> have been prepared from the respective endoperoxide precursors with CoTPP under mild conditions without any by-products.

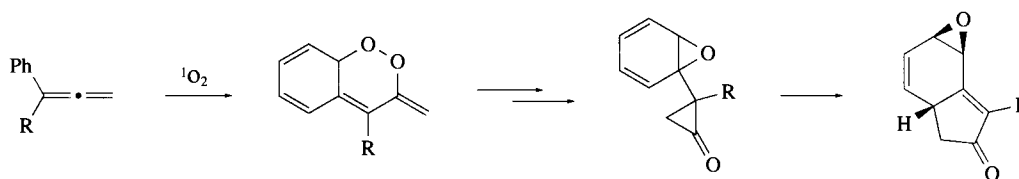


Scheme 17



Scheme 18

Photooxygenation of arylallenes results in the formation of epoxy-fused dihydroindanone derivatives (Scheme 19) <91TL1859>. For other examples of CoTPP catalyzed conversions of bicyclic peroxides to bisepoxides, see <83TL4135, 85MI 104-01, 85T1315, 87TL555, 88JOC2312>.

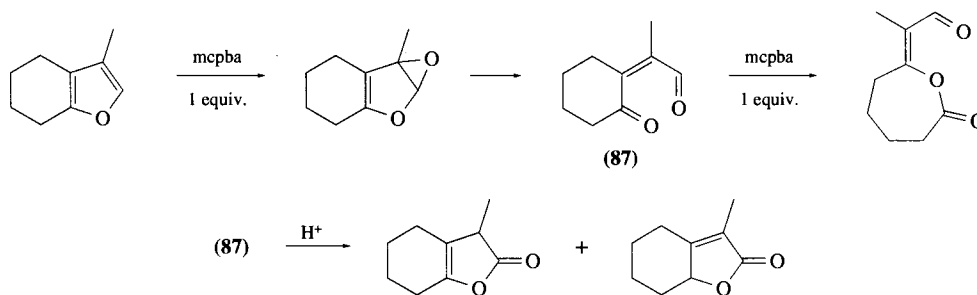


Scheme 19

1.04.9 EPOXIDATIONS OF HETEROCYCLIC COMPOUNDS

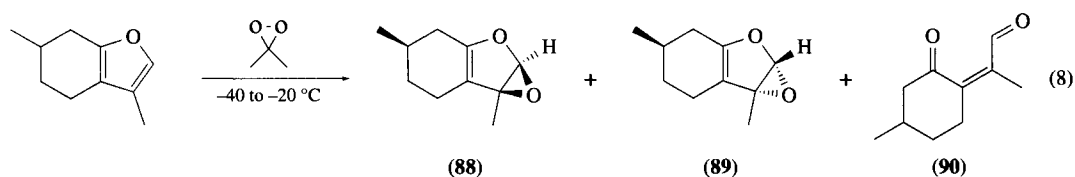
1.04.9.1 Oxygen Heterocycles

Epoxides have been proposed in furan metabolism as reactive intermediates <B-85MI 104-02>. Earlier work on furan epoxidations with peroxy acids did not provide unequivocal proof for the intervention of furan epoxides. Jennings and co-workers showed by means of mechanistic studies that bicyclic furans undergo epoxidation with peroxy acids to initially afford oxiranes, which isomerize to ene diones thermally, which undergo Baeyer–Villiger oxidation with excess peroxy acid; in the presence of trace acids ene lactones are formed (Scheme 20) <83JOC2606, 84JOC1284, 85MI 104-03, 89JOC5186, B-90MI 104-01>, see also <84SCI884, 85CC1642>.

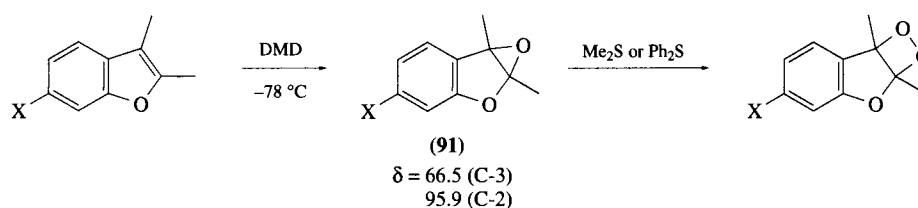


Scheme 20

The 4,5-epoxyfuran intermediate in the oxidation of the tetrasubstituted fungicidal furan, methfuroxam, by MCPBA has also been characterized by NMR spectroscopy <85JCS1642>. Since the implementation of dimethyldioxirane (DMD) <80JOC4758, 85JOC2847> and its trifluoromethyl analogue <89JA6749, 91JA2205> as a mild and efficient oxygen transfer agent in organic chemistry <89ACR205, 89CRV1187, B-90MI 104-02, B-92MI 104-02, 93TCC45> studies on epoxidations of oxygen- and nitrogen-containing heterocycles have intensified. Oishi and Nelson employed DMD as the epoxidizing agent at low temperatures in the epoxidation of the natural product menthofuran <92JOC2744>. Low-temperature NMR spectroscopy of the product mixture revealed the formation of the two oxiranes (88) and (89) along with the γ -keto enal (90) (Equation (8)).

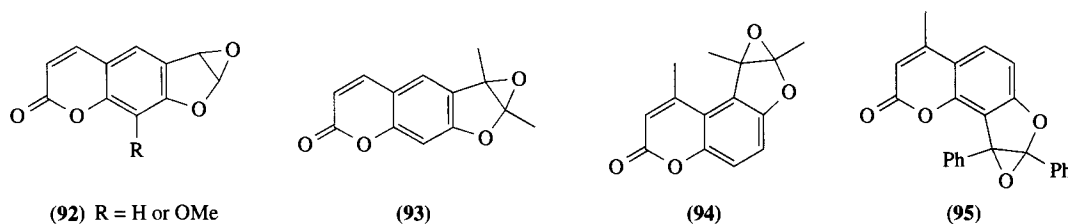


The 8,9-epoxide of the mycotoxin aflatoxin B₁ was prepared with DMD and characterized by spectroscopic and chemical means <88JA7929, 89MI 104-01>. Benzofuran epoxide (**91**) and some derivatives thereof have been prepared by Adam *et al.* by epoxidation of the benzofuran precursors with DMD and alternatively by singlet oxygen addition followed by deoxygenation of the resulting 1,2-dioxetanes with Me₂S or Ph₂S (Scheme 21) <91AG(E)200, 92CB231, 93AG(E)735, 93AG(E)737, 93JA8603, 94CB433, 94CB1115, 94SI111, 94T8393, 94T11441, 94TL6063>. The same research group demonstrated that contrary to earlier reports <56BSF1817, 62BSF925> claiming the isolation of benzofuran epoxides, the most labile and reactive epoxides known to date, from MCPBA oxidations of the alkene precursors cannot be prepared under these conditions <94CB941>.

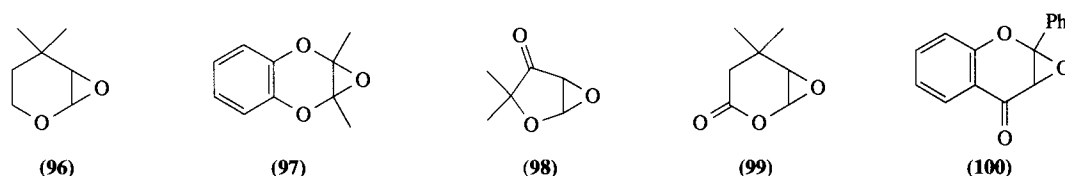


Scheme 21

Furocoumarins not carrying aryl or alkyl groups on the furan moiety, such as psoralen and 8-methoxypsoralen, do not react with DMD below -20°C and give at room temperature intractable high-molecular weight material <91CB2377>; the epoxide intermediates from these reactions can, however, be trapped with methanol to afford MeOH addition products <92LA1095>. The use of the more powerful oxidant methyl(trifluoromethyl)dioxirane (TFD) <89JA6749> at -78°C to -40°C does afford the corresponding oxiranes in high purity, as established by NMR spectroscopy <94LA689>. In contrast to the natural psoralens, the 2,3-disubstituted analogues, as well as substituted naphtofurans are reactive toward DMD and yield the corresponding oxiranes (**93**)–(**95**). In all the cases studied the epoxidation occurs at the furan ring rather than the electron-poor α -pyrone double bond. All the oxiranes derived from furocoumarins and naphtofurans, except for (**95**), proved to be unstable at room temperature and were, therefore, characterized by low-temperature NMR spectroscopy.

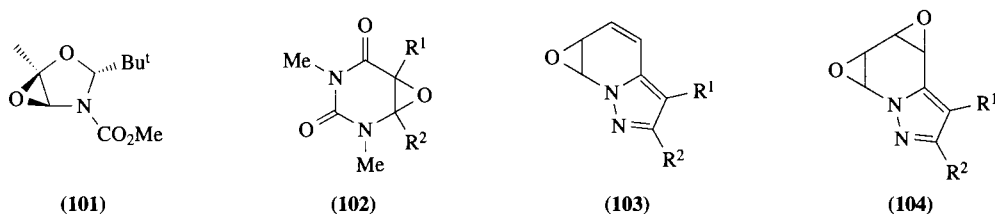


A number of labile oxiranes derived from heterocyclic compounds have been prepared with dioxiranes and characterized at low temperatures by spectroscopic techniques. Some of these epoxides are: (**96**) <91JOC3677>, (**97**) <91TL1295>, (**98**) <90CB2077>, (**99**) <89TL4223, 91CB2361>, and (**100**) <91JOC7292, 91TL1041> see also <94LA795>. Acronycine epoxide, a natural product of pharmacological interest, has also been prepared by this methodology <94LA317>.

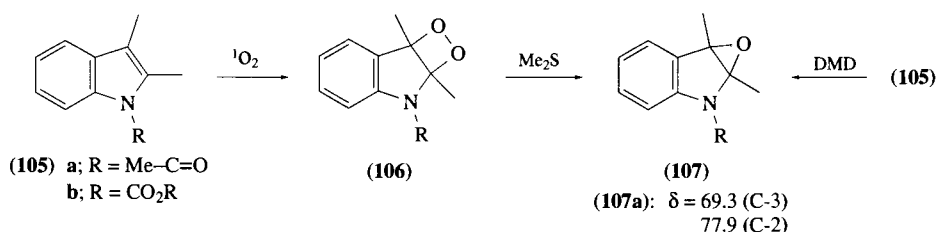


1.04.9.2 Nitrogen Heterocycles

The epoxidation of oxazolines with DMD by Adam and Hadjirapoglou has been mentioned in <93TCC45> (Structure (101)). Epoxidations of pyrimidine and purine derivatives with DMD <93TL6313, 95T7561> as well as pyrazolo[1,5-*a*]pyridine derivatives with Mn-TPP and Fe-TPP complexes using NaOCl as oxidant have also been reported (102)–(104) <89CPB1410>.



In analogy to their work on benzofurans, Adam *et al.* prepared thermally labile oxiranes from indoles either directly by DMD epoxidation at low temperatures, or by photooxidation followed by deoxygenation of the resulting $^1\text{O}_2$ adducts with Me_2S (Scheme 22) <93TL5247, 94JCS(P1)1503, 94JOC2733>. The presence of electron-attracting groups on the nitrogen atom in indoles enables the isolation of the unstable indole epoxides.

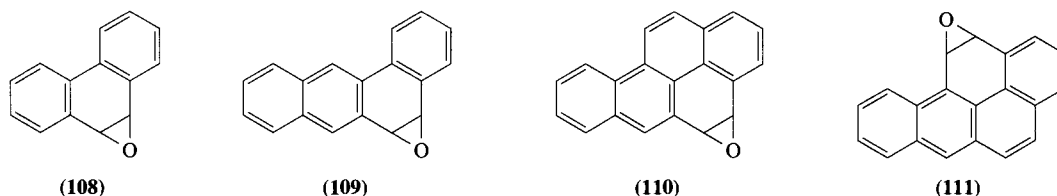


Scheme 22

Zhang and Foote also prepared and characterized oxiranes derived from *N*-acylindoles using dimethyldioxirane <93JA8867>.

1.04.10 FUSED-RING OXIRANES BY DIOXIRANE EPOXIDATIONS

Dimethyldioxirane generated *in situ* by the caroate-acetone system has been employed by Jeyaraman and Murray for the epoxidation of arenes to arene oxides <84JA2462>. The yields reported for these reactions range from 5% (naphthalene) to 60% (phenanthrene). In a subsequent study the same authors reported the use of isolated DMD for the epoxidation of several other polycyclic aromatic hydrocarbons (PAH) with similar success <B-85MI 104-04, B-91MI 104-02, 94MI 104-02>. Under these conditions phenanthrene (108), pyrene, and benz[a]anthracene (109) all gave their K-region oxides, whereas benz[e]pyrene showed no oxide in the product mixture. Benz[a]pyrene, on the other hand, was converted to two monooxides which are presumably the K-region oxides (110) and (111).



Boyd and co-workers have also shown that DMD can convert PAH to arene oxides and dioxides <89TL123, 90JCS(P1)3073>. Curci and co-workers used the more reactive TFD instead of DMD to oxidize PAH, and isolated the corresponding oxiranes in excellent yields in most cases (Structures (112) and (113)) <90TL6097>. Only in the case of pyrene does the yield drop to 10% (Structure (114)). As ESR studies have confirmed, in cases where the arene possesses an accessible oxidation potential,

(112) 98%

(113) 96%

(114) 10%

The figure displays five chemical structures. On the left, four structures represent precursors: a bicyclic epoxide with an OH group (1%), a bicyclic epoxide with an OH group and a dashed bond (99%), a bicyclic epoxide with an OH group and a wedged bond (29%), and a bicyclic epoxide with an OH group and a dashed bond (71%). On the right, two structures represent products: compound 115, a tricyclic molecule with two OH groups and a wedged bond (78%), and compound 116, a tricyclic molecule with two OH groups and a dashed bond (22%).

Figure 6

Chemical reaction scheme showing the conversion of 1,2:5,6-di-O-isopropylidene-3-O-alkyl- α -D-glucopyranosides (117-119) to 1,2:3,4-di-O-isopropylidene-6-O-alkyl- α -D-glucopyranosides (120-122) using DMO.

Structure 117: 1,2:5,6-di-O-isopropylidene-3-O-alkyl- α -D-glucopyranoside (General structure).

Structure 118: 1,2:5,6-di-O-isopropylidene-3-O-alkyl- α -D-glucopyranoside (Specific structure).

Structure 119: 1,2:5,6-di-O-isopropylidene-3-O-alkyl- α -D-glucopyranoside (Specific structure with Ph and O-TBS groups).

Structure 120: 1,2:3,4-di-O-isopropylidene-6-O-alkyl- α -D-glucopyranoside (General structure).

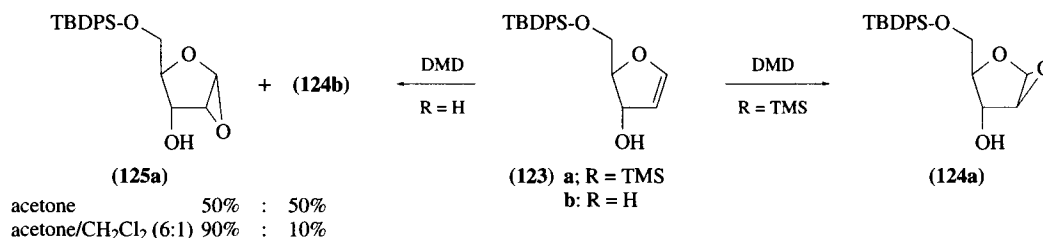
Structure 121: 1,2:3,4-di-O-isopropylidene-6-O-alkyl- α -D-glucopyranoside (Specific structure).

Structure 122: 1,2:3,4-di-O-isopropylidene-6-O-alkyl- α -D-glucopyranoside (Specific structure with Ph and O-TBS groups).

Scheme 23

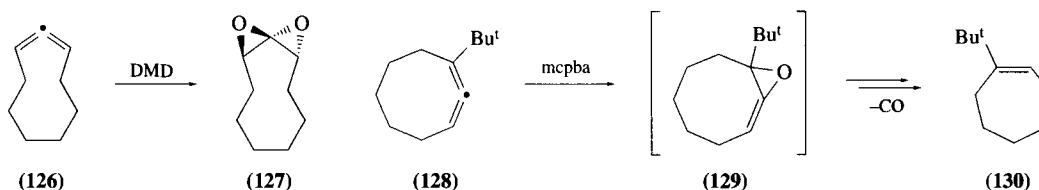
Furanose derivatives undergo facile epoxidations with DMD [\[90JOC4211\]](#). A remarkable solvent effect was observed in these epoxidations. In acetone solvent the hydroxyl group in (**124**) did not exert a directive effect on the stereochemical course of the epoxidation, as it does with MCPBA or

metal-catalyzed reactions in the presence of hydroperoxides (Scheme 24). It was argued that in acetone solvent, diluted with CH_2Cl_2 , directivity of the free hydroxyl group at C_3 via hydrogen bonding would be increased. This expectation was borne out when the epoxidation was conducted in a 6:1 mixture of acetone- CH_2Cl_2 ; significant *syn* stereoselectivity (9:1) was achieved under these conditions. For other reports by Danishefsky and co-workers in this series, see <91JOC3713, 93JA8473, 94JOC1892, 94JOC1895>.



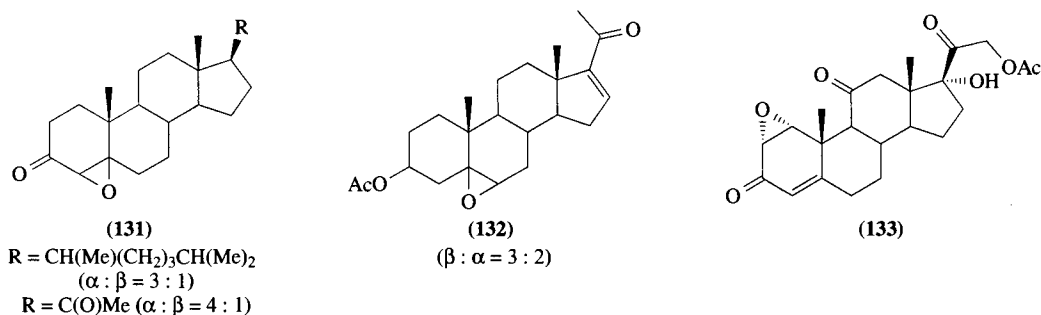
Scheme 24

Cyclic allenes have also been subjected to DMD oxidations (Scheme 25). Treatment of 1,2-cyclononadiene (**126**) with DMD affords the corresponding stable dioxide (**127**) exclusively <91JOC1153>; on the other hand, MCPBA oxidation of (**128**) leads to an unstable monooxide (**129**) which gives (**130**) via rearrangement to the corresponding cyclopropanone and CO loss <91JOC6372>.

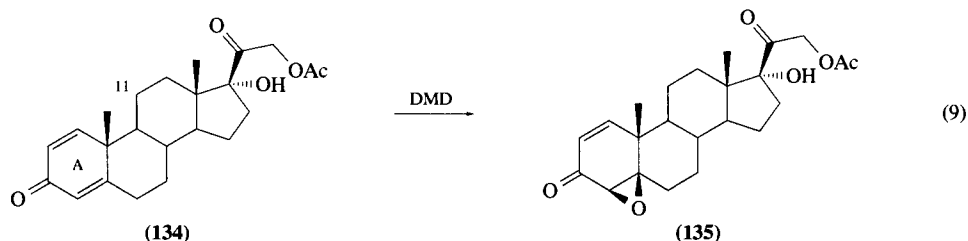


Scheme 25

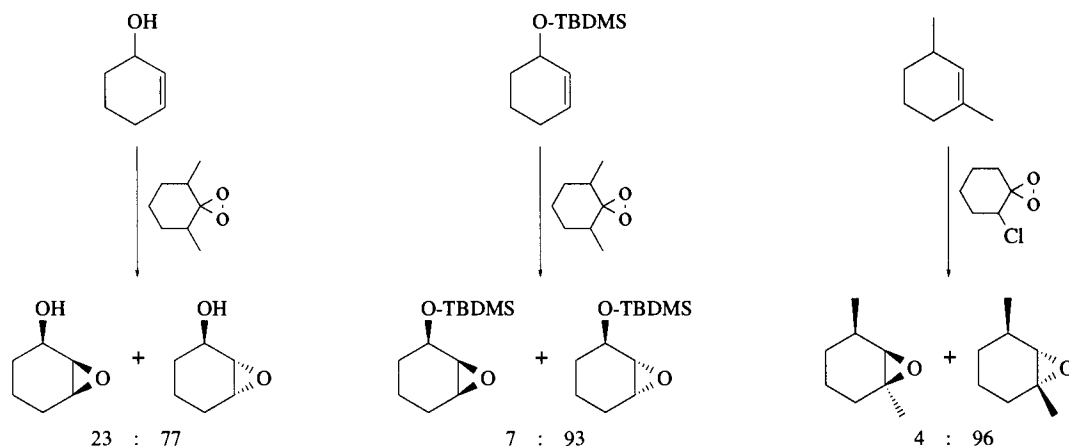
Steroids have been epoxidized with *in situ* generated DMD <91TL2667> as well as the isolated variant and TFD <92JOC2182>. In the latter report some *cis/trans* selectivity was observed with substrates (**131**) and (**132**), and remarkable regio- and stereoselectivity was attained in the case of (**133**).



When there is no $\text{C}=\text{O}$ present at C_{11} in the 1,4-diene-3-one precursor, as in (**134**), the more nucleophilic 4,5-double bond is epoxidized with DMD affording (**135**) exclusively (Equation (9)) <94JOC4304>. The observed regioselectivities have been ascribed to the directing effect of the C_{11} -carbonyl favoring the approach of DMD from the α -face of the dienoid A-ring.

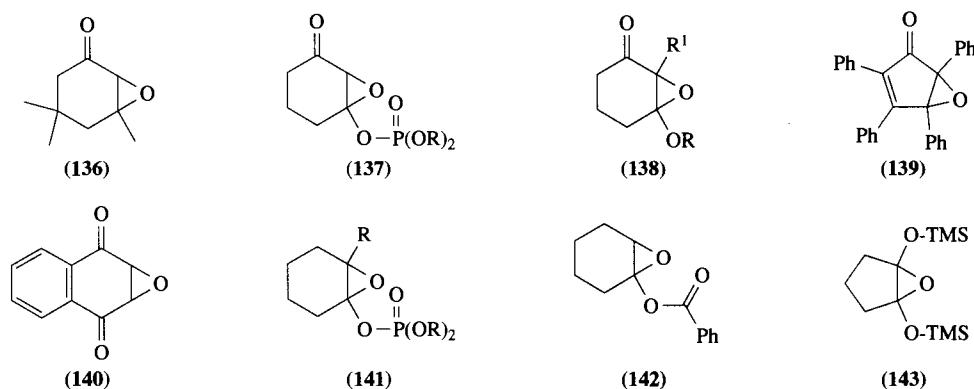


Stereoselective epoxidations of substituted cyclohexenes with *in situ* generated dioxiranes have been studied $\langle 94\text{TL}1577 \rangle$. The most favorable *trans/cis* selectivities have been achieved using dioxiranes derived from sterically hindered ketones (Scheme 26).

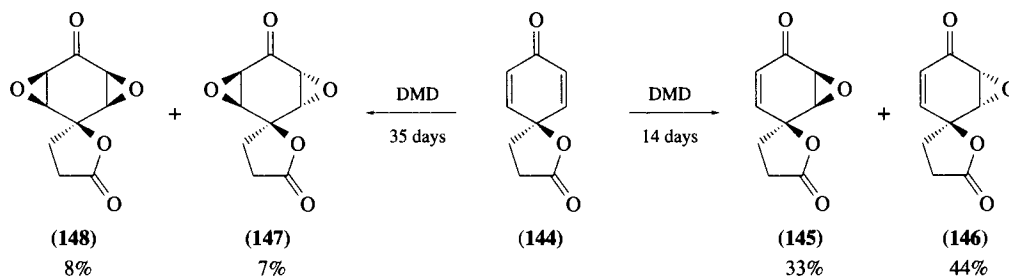


Scheme 26

Alkenes and cycloalkenes with electron acceptors require longer reaction times and excess dioxirane for complete conversion into their corresponding oxiranes, for example **(136)** $\langle 90\text{TL}331, 91\text{CB}2077 \rangle$, **(137)** $\langle 90\text{TL}6517 \rangle$, **(138)** $\langle 90\text{CB}2077 \rangle$, **(139)** $\langle 93\text{TCC}45 \rangle$, and **(140)** (from the corresponding diazoquinone) $\langle 94\text{TL}5625 \rangle$. Electron-rich substrates, such as enol phosphates, enol esters, and 1,2-bis(trimethylsilyloxy) cycloalkenes afford in most cases labile oxiranes (e.g., **(141)** $\langle 90\text{TL}6517, 91\text{CB}2361 \rangle$, **(142)** $\langle 89\text{TL}4223 \rangle$, and **(143)** $\langle 91\text{TL}1295 \rangle$, respectively) which are obtained in essentially quantitative yields and spectrally characterized.



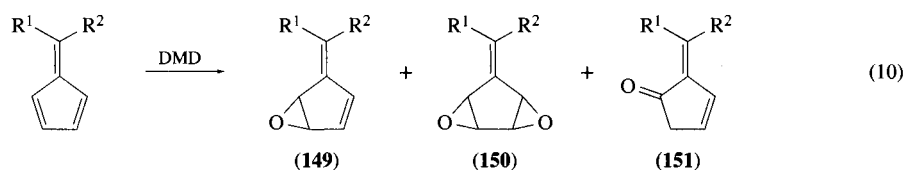
In various cases the use of conventional epoxidizing agents, such as alkaline hydrogen peroxide and organic peroxides do give satisfactory results due to the sensitivity of the resulting epoxides (or the groups already present) to basic conditions. The use of DMD in such a case (Scheme 27) dramatically ameliorates similar problems $\langle 92\text{SL}2011 \rangle$.



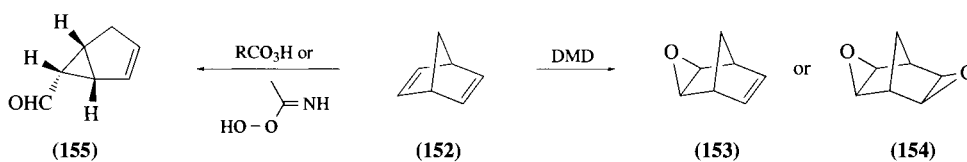
Scheme 27

2,2-Dimethyl-2*H*-chromenes have been epoxidized enantioselectively with DMD in the presence of chiral Mn(III)salen catalysts <95TL3669>.

The DMD epoxidation of fulvenes is worthy of note since the endocyclic fulvene epoxides have been obtained only via photochemical oxidation followed by thermal isomerization in a few cases <59CR(248)700, 61AC(P)1131, 87TL3779, 93TL1255> as well as CoTPP-catalyzed rearrangement (Scheme 16) <87TL3779>. Nucleophilic epoxidation using the Weitz–Scheffer method of pentafulvenes with H₂O₂/base affords endocyclic epoxides exclusively which dimerize upon formation <57CB1709>. By contrast, the highly electrophilic DMD attacks the endocyclic fulvene double bond(s) giving the corresponding epoxide (**149**) or bisepoxide (**150**), depending on the dose of the epoxidizing agent (Equation (10)). Compounds (**151**) have been shown to arise by isomerization of the labile monooxides (**149**) <91TL6697>.



The epoxidation of norbornadiene and quadricyclane with peroxy acids or CH₃CN/H₂O₂ gives rise to the rearrangement product (**155**), presumably formed via the monooxide (**153**) (Scheme 28) <63JA582, 65HCA1985, 65TL1789>. DMD oxidation of (**152**) furnishes bisepoxide (**154**) as the sole product when norbornadiene is added dropwise to excess DMD solutions <88JOC3007>. The use of a less than stoichiometric amount of DMD leads to a product mixture that is largely monooxide (**153**) contaminated by a small amount of (**155**). Moreover, quadricyclane gives with DMD exclusively bisepoxide (**154**). It has been argued that DMD causes isomerization of quadricyclane to norbornadiene before the latter is epoxidized.



Scheme 28

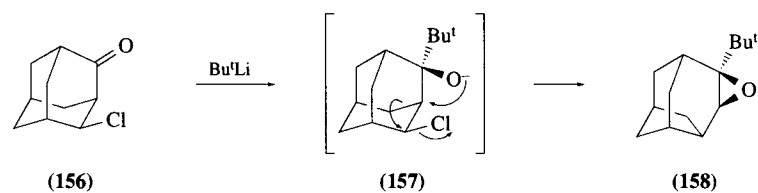
Dioxiranes have been implicated in the epoxidations of alkenes with ozone <93JOC315>. Murray *et al.* have used ozone in the presence of tetramethyl ethylene as an effective oxygen transfer agent and employed this methodology to the preparation of oxiranes from polycyclic aromatic hydrocarbons <B-90MI 104-03, 94MI 104-02>. Cyclic thioenol ethers are ozonized at low temperatures to give epoxy sulfoxides <86JOC2276>. Dry ozonolysis of steroids on silica gel results in selective epoxidations <82CC306>.

1.04.11 MISCELLANEOUS METHODS

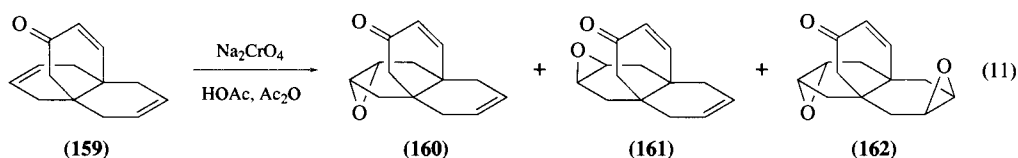
The reader is referred to Chapter 1.03.4, and the reviews cited there, for methods used for the synthesis of oxiranes, since most of those are also applicable to fused rings. In this section the emphasis will be on epoxidations which are highly particular to ring structures, especially with respect to stereoselectivities and certain other factors, including strain.

Oxirane formation by intramolecular displacement reactions of halohydrins (2-halo-1-ols) is a general and useful reaction, as discussed in Chapter 1.03.4.2. A unique example of an intramolecular substitution is observed during *t*-butyllithium addition to (**156**): the reaction involves 1,2-attack of the resulting alkoxide ion in (**157**) with concomitant 1,2-alkyl shift to give the protoadamantane derivative (**158**), reminiscent of a fragmentation reaction (Scheme 29) <91JOC1700>.

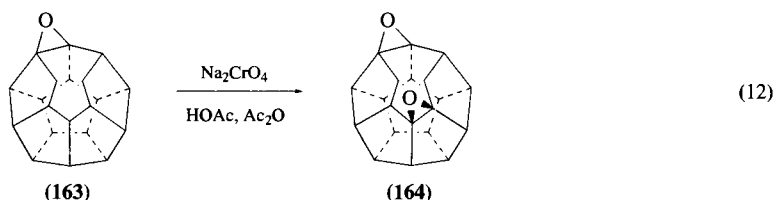
The reagent system Na₂CrO₄/HOAc/Ac₂O is frequently used in allylic oxidations. In certain cases, however, oxiranes can also form in addition to the expected enones (Equation (11)) <90JOC1598>.



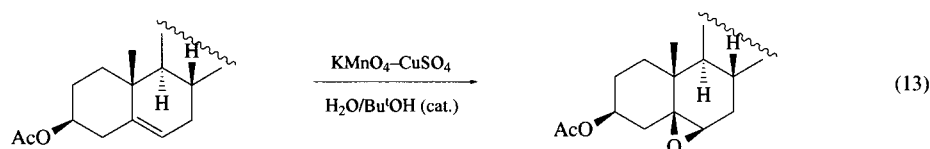
Scheme 29



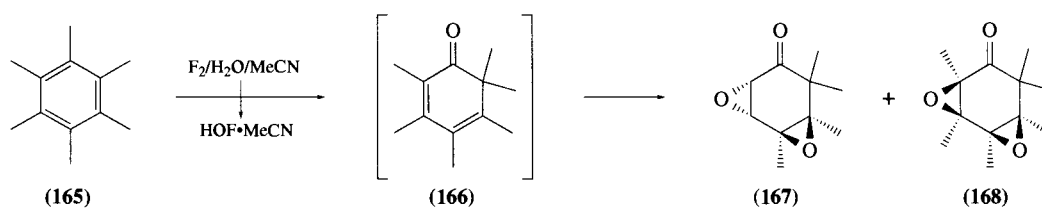
Perhaps one of the most intriguing examples of oxirane formation with the sodium dichromate reagent is the conversion of **(163)** to the bisoxirane **(164)** (Equation (12)). The high degree of strain in this system seems to be at least partially responsible for the formation of **(164)** from its nonalkenic precursor <87TL3531>.



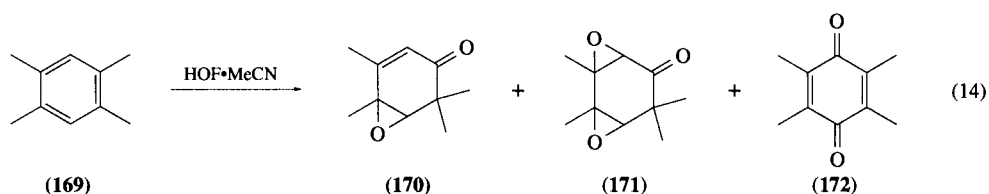
Permanganate oxidations of alkenes do not ordinarily lead to oxiranes, however, a mixture of $\text{KMnO}_4\text{-CuSO}_4\cdot 5\text{H}_2\text{O}$ in CH_2Cl_2 in the presence of a catalytic amount of water and *t*-butyl alcohol has been found to be an effective epoxidizing agent <92JOC1928>. It is believed that Bu^tOH acts as a phase-transfer catalyst and that H_2O and Bu^tOH form the third phase (i.e. the omega phase) in which the reaction takes place. Using this reagent system a number of Δ^5 -unsaturated steroids were epoxidized to give the corresponding $5\beta,6\beta$ -oxiranes in excellent yields in a highly stereoselective manner (Equation (13)).



Selective epoxidations of cycloalkenes have been achieved using $\text{F}_2/\text{H}_2\text{O}/\text{CH}_3\text{CN}$, a very electrophilic and powerful oxygen transfer agent <90JOC5155>. Limonene, for instance, is attacked by this reagent system at the more electron-rich endocyclic double bond. The oxidizing agent here is the $\text{HO}\cdot\text{F}\cdot\text{CH}_3\text{CN}$ complex which has also been used to epoxidize aromatic hydrocarbons (Scheme 30) <93JOC1593>. Bisepoxides **(167)** and **(168)** are believed to have been formed via the dienone intermediate **(166)**. When **(169)** was subjected to the same conditions a mixture of **(170)**, **(171)**, and the quinone **(172)** was obtained (Equation (14)).

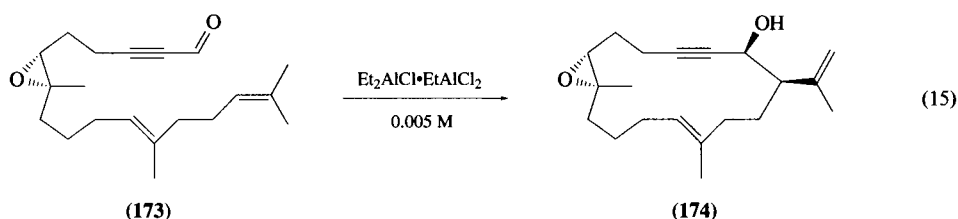


Scheme 30

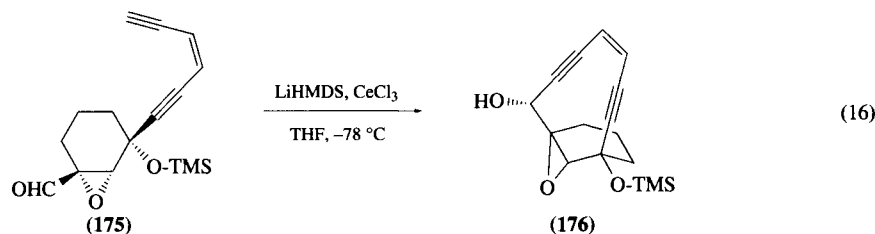


In ketone-directed peroxy acid epoxidations of cyclic alkenes the actual epoxidizing agent has been shown by ^{18}O -labeling not to involve a dioxirane <94TL6155>. Instead, an α -hydroxybenzoylperoxide or a carbonyl oxide is believed to be responsible for observed stereoselectivities in the intramolecular epoxidations. The extent of *syn*-selectivity is greater for ketones than with esters; the *syn/anti* ratios increase when ether is used as solvent rather than CH_2Cl_2 , the reverse situation for hydroxyl-directed epoxidations. Fused-ring oxiranes can also be prepared from acyclic precursors. Four different approaches are discussed below.

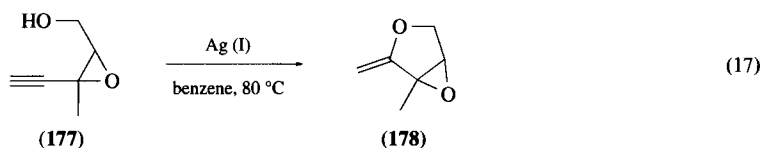
(i) Marshall's intramolecular Lewis acid-promoted ene cyclizations of epoxy ynals using a 1 : 1 mixture of EtAlCl_2 and Et_2AlCl give in excellent diastereoselectivity and yields large ring propargylic alcohols (Equation (15)) <93JOC3912>.



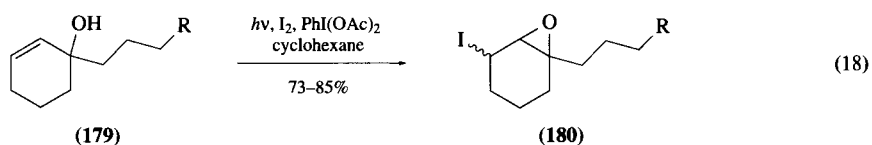
(ii) In another example the cyclization is affected by intramolecular nucleophilic attack by an acetylide ion at an aldehyde functionality (Equation (16)) <92SL393>.



(iii) Lewis acid-catalyzed cyclization of (177) gives the isomeric exocyclic enol ether (178) arising from addition to the internal carbon of the alkyne (Equation (17)) <87TL6447>.



(iv) Finally, free radical cyclization of (179) in the presence of I_2 and $\text{PhI}(\text{OAc})_2$ under photochemical conditions results in the formation of oxiranes of the type (180) (Equation (18)) <92TL4687>.



The approach of Tanner *et al.* to 3,4-epoxytetrahydroazepine derivatives from acyclic precursors involves a two-fold displacement reaction using a primary amine <95T6061>.

1.04.12 RING OPENING REACTIONS

The discussion of ring opening reactions will be limited to cases where the bicyclic nature of the oxirane ring plays a central role in the course of the rearrangement.

Flippin, Crotti, and co-workers studied a number of systems in which the regioselectivity of nucleophilic attack is dictated by intramolecular chelating effects, brought on by OBn, CH₂OBn, CH₂OH, CO₂CH₃, and CO₂H groups within the same molecule (Figure 7) <91JOC7043, 92JOC1405, 92JOC1713, 94T12999>.

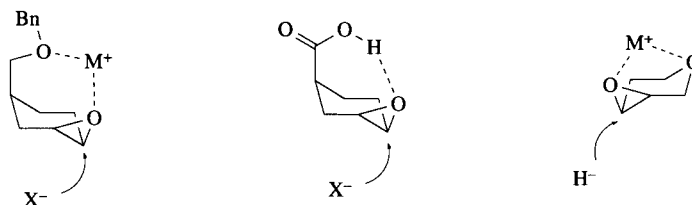
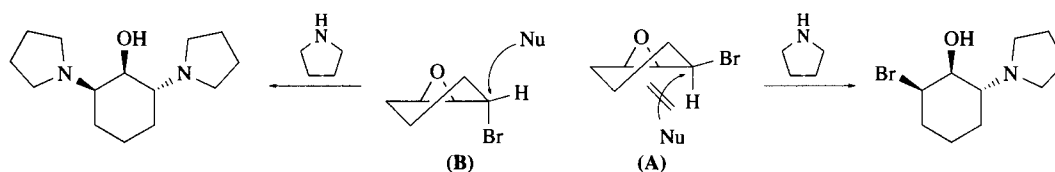


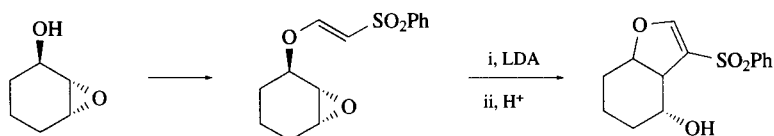
Figure 7

When a 3-halo-1,2-epoxycyclohexane is reacted with a nitrogen nucleophile (e.g., pyrrolidine) the stereochemistry of the halogen determines whether or not it is going to be displaced. The *cis* isomer (A) reacts with only one equivalent of nucleophile at the epoxide carbon, due to the equatorial placement of the Br atom in (A) being unfavorable for an *anti*-periplanar displacement. The *trans* isomer (B) undergoes epoxide ring opening as well as displacement of the halide since the latter is positioned axially (Scheme 31) <93JOC4043>.



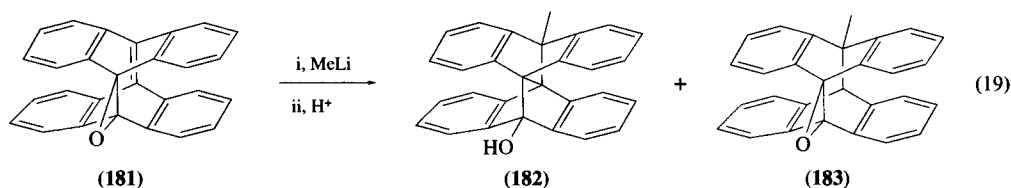
Scheme 31

Cyclic oxiranes containing sulfonyl groups undergo a variety of interesting and synthetically useful ring opening reactions. One example is shown in Scheme 32 <91JOC3556>.



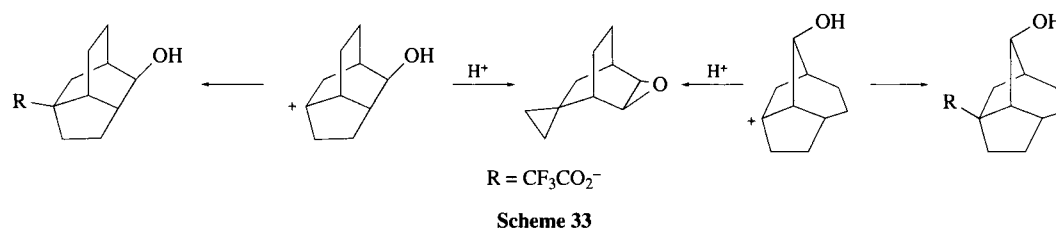
Scheme 32

Compound (181) derived from the corresponding bridgehead diene by epoxidation, reacts with MeLi at -5°C to give the transannular addition product (182) and the *syn* addition product (183) (Equation (19)) <94AG(E)993>. The pathway could be shifted away from the transannular reaction through addition of lithium complexing ligands to the mixture (in ether, no ligands, (182)/(183): 45/6, with 12-crown-4: 18/22). The unusual transannular addition to (181) is favored by the exact coplanarity and closeness of the π -orbital of the double bond and the Walsh orbitals of the epoxide.

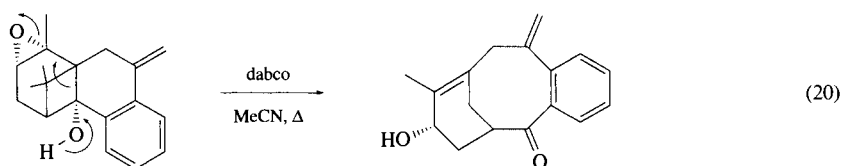
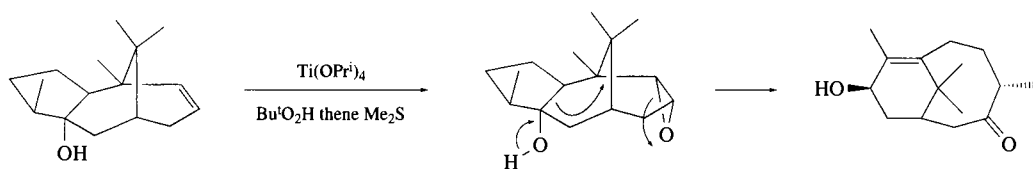


Transannular reactions involving oxiranes are more common in acid-catalyzed ring openings. A representative example of these types of reactions is shown in Scheme 33 <87CB705>. Similar

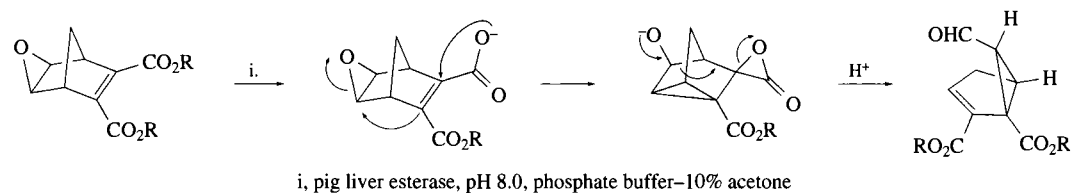
rearrangements in the norbornyl and bicyclo[3.2.1]octyl systems have also been reported (<86TL3361, 87CB521, 87CB1719>).



Among other types of oxirane ring opening reactions involving skeletal rearrangements, Holton's elegant approach to advanced intermediates of the antitumor agent taxol and related compounds is particularly noteworthy (Scheme 34) (<84JA5731, 84TL4455, 88JA6558, B-91MI 104-03>). Wender and Mucciari's ring expansion to a benzoannulated taxane system is also quite remarkable (Equation (20)) (<92JA5878>).

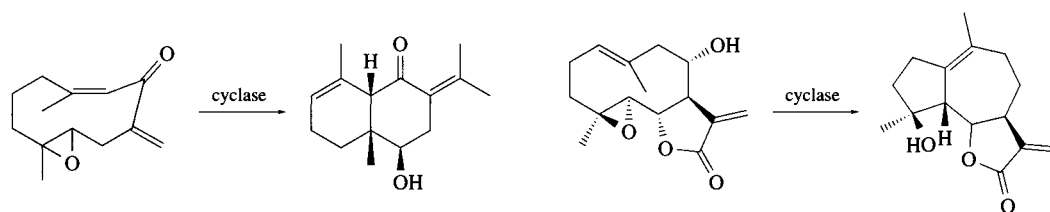


An intriguing oxirane rearrangement in a tricyclic system is the Meinwald rearrangement which has been observed during the epoxidation of norbornadiene with peroxy acids (<94JA3290>). In a chemicoenzymatic analogue of this isomerization the 2,3-dicarboxylic ester derivative of norbornadiene monoepoxide has been treated with pig liver esterase in a buffered medium to give the analogous rearrangement. The mechanism involving an α -lactone intermediate shown in Scheme 35 has been advanced by the authors. This reaction appears to be the first facile, completely regio- and stereospecific asymmetric rearrangement caused by chemicoenzymatic hydrolysis. By contrast to the classical Meinwald rearrangement which occurs by acid-catalysis, the present reaction takes place in slightly basic medium, even with the electron-deficient norbornadiene oxide.

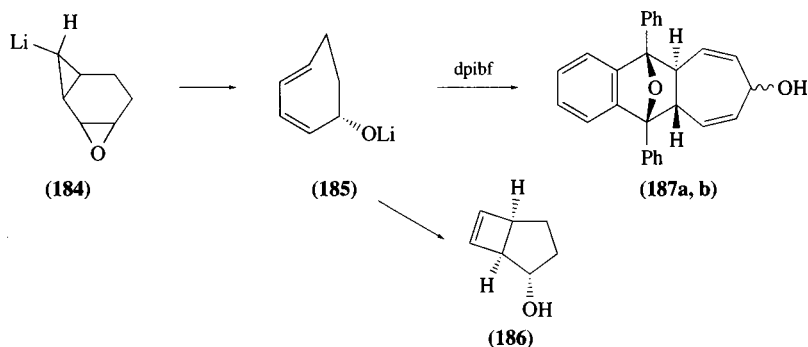


Biotransformations of germacrane epoxides by *Cichorium intybus* have been studied (<95T6303>). The enzyme-catalyzed cyclizations of the oxirane precursors towards substituted guaianes and eudesmanes were observed. Two examples of these transformations are shown in Scheme 36.

An electrocyclic ring opening of a β -lithiocyclopropyl oxirane has been reported by Coates and Last (<83JA7322>). Conrotatory opening of (**184**) with concomitant oxirane cleavage leads to a (*Z,E*)- or (*E,Z*)-cyclohepta-2,4-dienyl oxide (**185**) which undergoes rapid conrotatory closure to (**186**), or is trapped with diphenylisobenzofuran (DPIBF) to afford the cycloadducts (both isomers) (**187a,b**) (Scheme 37).

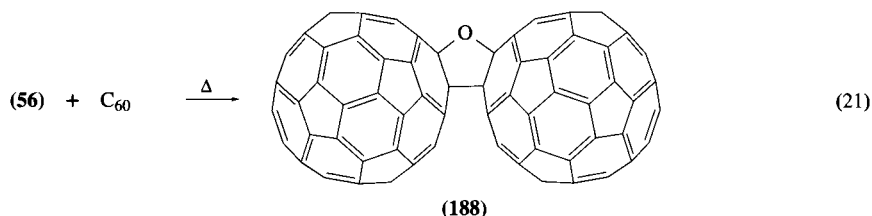


Scheme 36



Scheme 37

Finally, an oxirane ring opening via an intermolecular attack has been observed in the [60]fullerene series. Upon heating a mixture of C_{60} and the aforementioned C_{60} epoxide (**56**) (Section 1.04.5) in solution of solid state (higher yields in the latter) a dimerization occurs giving rise to (**188**) the structure of which was tentatively assigned based on spectroscopic data (Equation (21)) <95TL4971>.



1.04.13 OXIRANE AS A NEIGHBORING GROUP

The neighboring group participation of the oxirane ring has been studied in various systems. Gassman *et al.* investigated the effect of an *endo*-oxirane ring on the solvolysis rates of norbornyl systems carrying a 7-tosylate group <82JA6408>. Their solvolysis studies indicate that the C—C bond of an oxirane is a powerful neighboring group in terms of stabilizing the carbocation at C-7 (Figure 8).

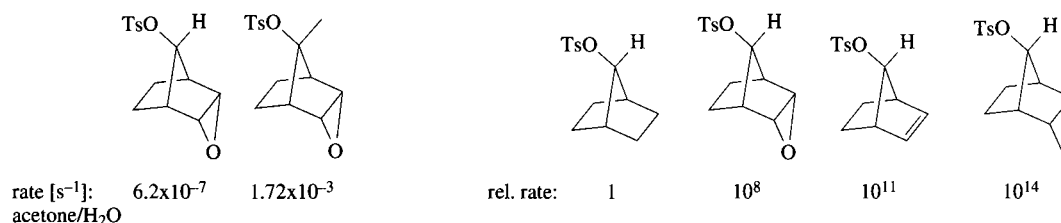


Figure 8

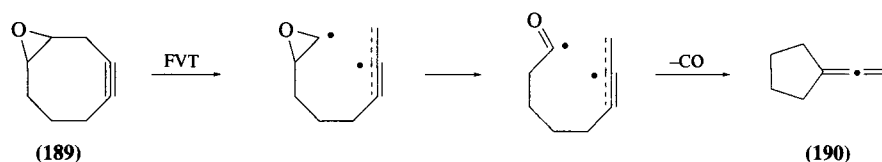
A study by Whalen indicates that the solvolytic reactivity of the 9-oxabicyclo[6.1.0]non-2-yl system can be estimated to be a factor of around 10^6 – 10^7 less than the corresponding bicyclo[6.1.0]non-2-

yl system <70JA7619>. These data indicate that oxirane rings, in the absence of participation by the nonbonding electrons on oxygen, do not stabilize a developing positive charge on adjacent carbon atoms.

A study by Santelli and Viala on hydrolysis reactions of oxirymethyl tosylates shows that the reactions proceed via 2-oxocyclobutyl cations with ring opening to β -ketol derivatives <78T2327>. A Taft–Streitwieser treatment of the solvolysis data shows an anchimeric assistance by the oxiranyl group of small magnitude (<15). Weitemeyer showed that when annelated onto the bicyclo-[2.2.2]octyl system, in which the ring expansion pathway is precluded due to strain reasons, the oxirane ring destabilizes the adjacent bridgehead carbocation by a factor of around 400 <76MI 104-01>.

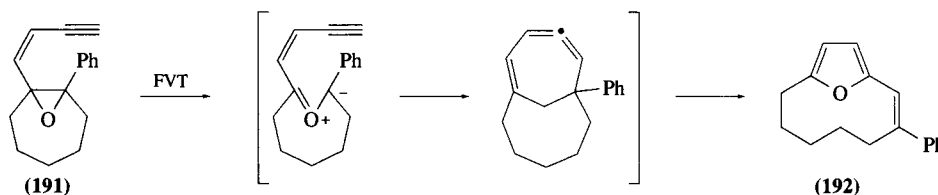
1.04.14 THERMAL REACTIONS

Thermal reactions are discussed in Chapter 1.03.3.1. The discussion here is limited to the fused-ring analogues. Isolated oxiranes exhibit greater thermal stability than the analogues which are adjacent to π -systems of heteroatoms. The bicyclic oxirane (**189**), for instance, undergoes decomposition at temperatures $> 500^\circ\text{C}$ in the gas phase, to afford the product (**190**) (Scheme 38) <89TL5873>.



Scheme 38

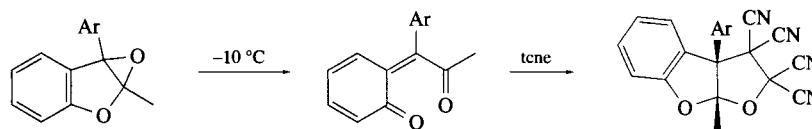
The bicyclic oxirane (**191**) suffers C—C cleavage to a carbonyl ylide before undergoing an intramolecular cyclization, affording (**192**) as the major product (Scheme 39) <92TL57>.



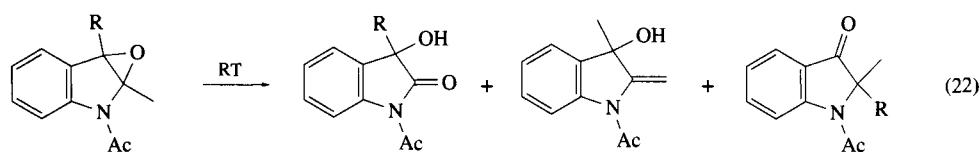
Scheme 39

Thermal fragmentations have also been observed with hydrazones <75JOC579> and diazo compounds <78CJC308>.

A large number of oxiranes fused to heterocycles are very labile and undergo facile isomerizations. Two examples are shown in Scheme 40 <94CB1115, 94S111> and Equation (22) <93JA8867, 93TL5247, 94JOC2733>.

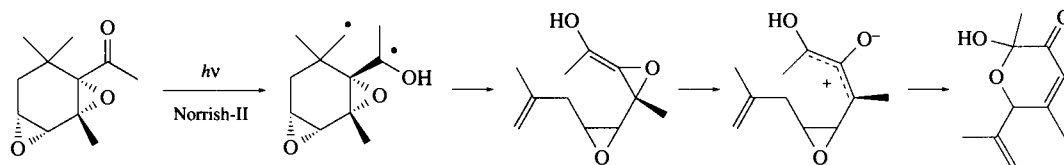


Scheme 40

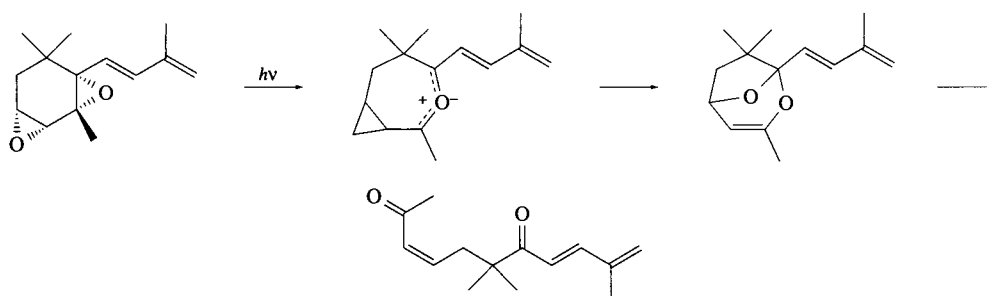


1.04.15 PHOTOCHEMICAL REACTIONS

Frei *et al.* have studied the photochemistry of a large number of fused-ring epoxyenones in a series of publications which they have reviewed in <85YK55>. Two interesting examples involving different pathways are shown in Schemes 41 and 42 <83HCA1638, 85HCA207>.

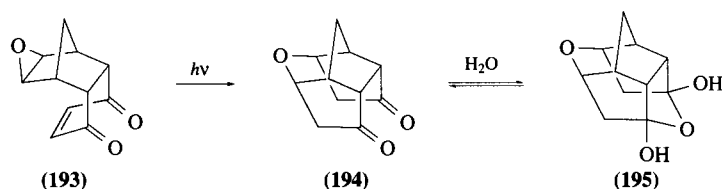


Scheme 41



Scheme 42

A photochemical intramolecular alkene-oxirane cycloaddition can occur when the C—C bond of the oxirane and the alkene π -system are properly aligned, as in compound (193) (Scheme 43) <90T3409>.

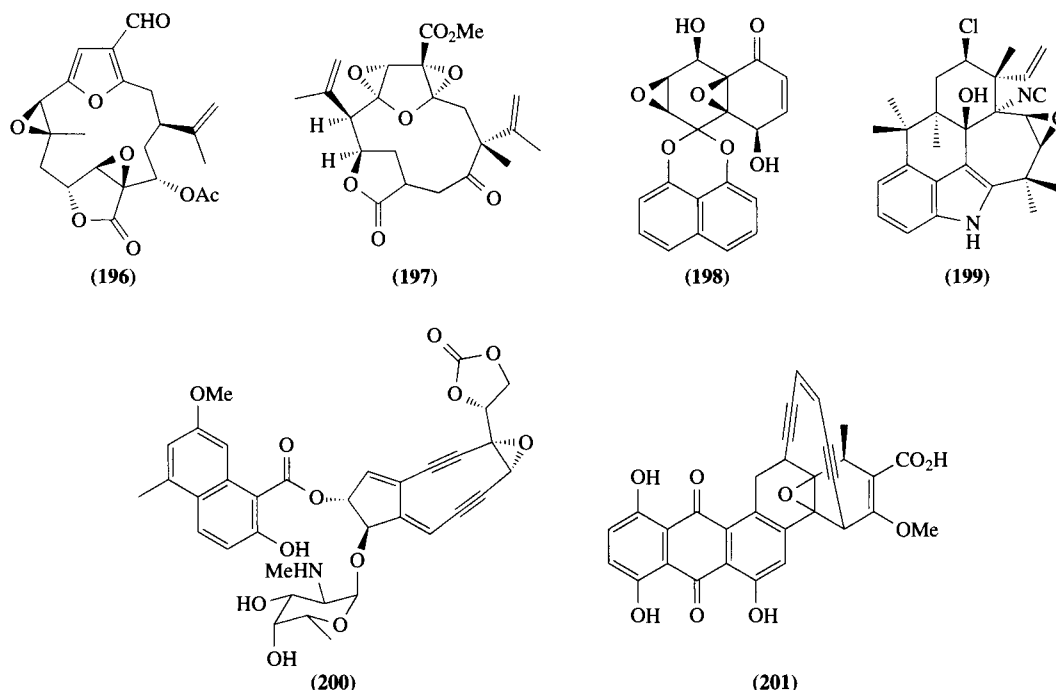


Scheme 43

1.04.16 NATURAL PRODUCTS

Natural products containing one or more fused oxirane rings are abundant. A large number of marine natural products, in particular the structures, occurrence, chemistry, and biological activity of West Indian Gorgonian octocorals containing fused oxiranes are discussed in <95T4571>. Lophotoxin (196), for instance, is a potent neurotoxic substance that binds selectively and irreversibly to acetylcholine recognition sites in nicotinic acetylcholine receptors <81SCI1512>. Diepoxygorgiacerone (197), isolated from *Pseudopterogorgia acerosa* was collected in the Florida Keys and contains an unusually stable diepoxifyran moiety <91TL4661>. Cladospiron bisepoxide (198) is a metabolite isolated from cultures of a saprophytic fungus identified as *Cladosporium chlorocephalum* Fresen <94TL1043>, as well as several structurally related antitumor agents produced in the fermentation broth of a culture identified as *Natrasia mangifera* <94TL1343>. Some ambiguine isonitriles, fungicidal hapalindole-type alkaloids which have been isolated from the genera of blue-green algae contain oxirane rings annulated to a seven-membered ring <92JOC857>; ambiguine isonitrile E (199) is one of these. New classes of DNA-cleaving molecules with potent and selective anticancer activity have emerged since the early 1990s <91AG(E)1387, 92SCI1172>; these compounds include

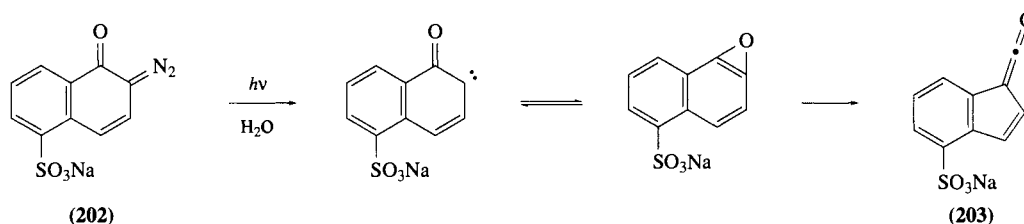
neocarzinostatin chromophore (**200**) and dynemycin A (**201**), both of which contain the enediyne and oxirane moieties. The antibiotic and antitumor activities of these compounds stem from their ability to generate, upon *in vivo* activation, benzenoid diradicals that damage DNA.



1.04.17 FUSED-RING OXIRENES

Background information and theoretical studies on oxirenes are presented in Chapter 1.03.7. Oxirenes have been reviewed by Lewars <83CRV519>.

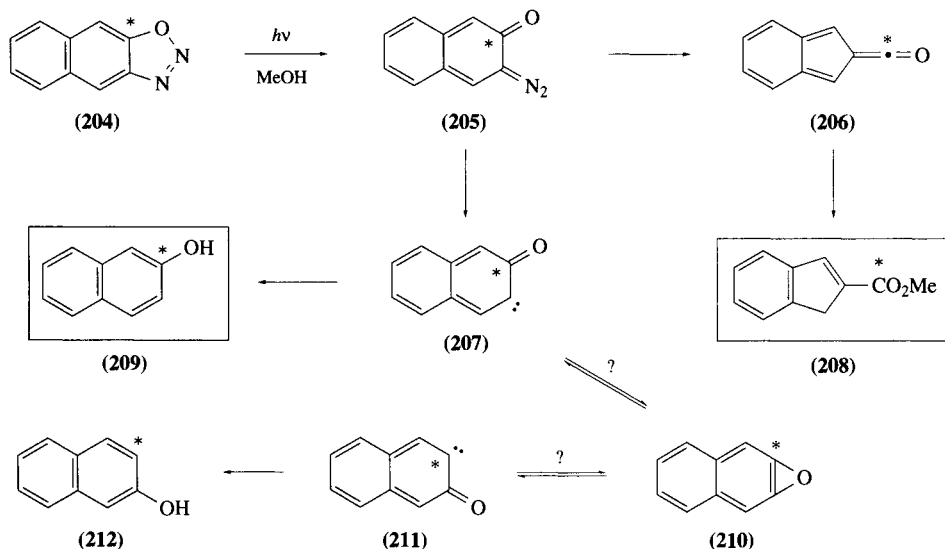
The Wolff rearrangement, involving the decomposition of an α -diazoketone has frequently been applied for generating and detecting oxirene intermediates. Tanigaki and Ebbesen have obtained spectroscopic evidence for such an oxirene intermediate <87JA5883, 89JPC4531>. The researchers have observed the dynamics of the photochemical Wolff rearrangement of (**202**) by laser spectroscopy in water at room temperature. The primary precursor to a ketene has been spectrally detected. Based on its reactivity this entity has been assigned to be the oxirene (**203**) (Scheme 44).



Scheme 44

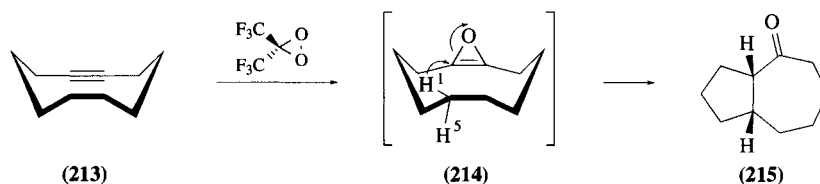
Zeller and co-workers' studies on Wolff rearrangements <75CB3566> with 1-¹³C-labeled regioisomers of diazonaphthalenone, (**206**; 1-¹³C) and its regioisomer (2-¹³C), however, indicate that the Wolff rearrangement in these systems does not involve the intermediacy of naphth[1,2-*b*]oxirene (**207**), due to lack of ¹³C distribution in the product. Studies by others <90MI 104-04, 92JA2630> employing the time-resolved laser flash photolysis technique in the nanosecond time-scale lend further support to Zeller's conclusion. Photochemical studies on the ¹³C-labeled naphthoxadiazole (**208**) by Blocher and Zeller further corroborate the earlier results and preclude the possibility of the intermediacy of an oxirene <94CB551>.

Photolysis of (204) in methanol gives rise to (208) and (209), products from Wolff rearrangement and hydrogen-abstraction, respectively. No traces of (212) were detected, implying that a symmetrical intermediate such as (210) could not have intervened (Scheme 45). It appears that fused-ring oxirenes are still elusive species and further research in this area is warranted.



Scheme 45

An alternative method whereby a fused-ring oxirene may be generated is the epoxidation of a cycloalkyne. Curci *et al.* have employed methyl(trifluoromethyl)dioxirane (TFD) toward that end, and obtained (215) and *cis*-bicyclo[4.4.0]decan-2-one in ca. 7:1 ratio from cyclodecayne (213) <92TL7929>. These products obviously stem from stereoselective 1,5- and 1,6-transannular insertion pathways. The authors conclude that the products of cycloalkyne oxidations may arise directly from trapping of the oxirene intermediates by transannular hydrogen transfer, as shown in Scheme 46.



Scheme 46

1.05

Thiiranes and Thiirenes: Monocyclic

WATARU ANDO and NAMI CHOI
University of Tsukuba, Japan

and

NORIHIRO TOKITOH
University of Tokyo, Japan

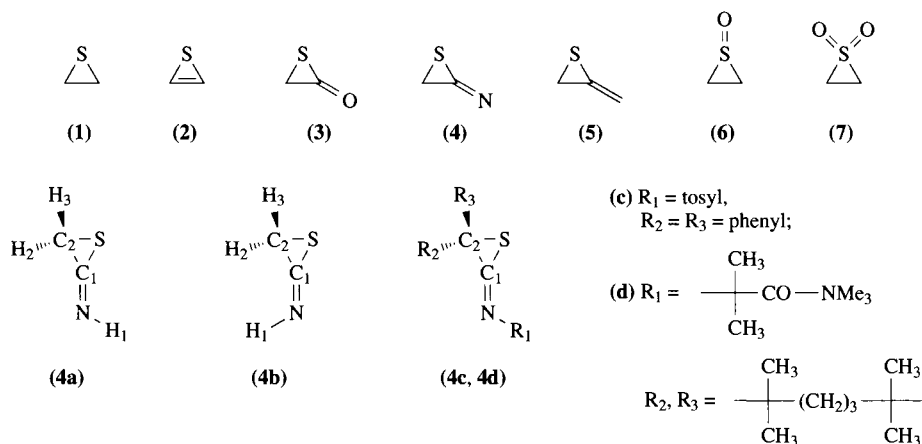
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1.05.1 INTRODUCTION

Three-membered rings containing one sulfur atom are known as thiiranes (1) or thiirenes (2), with ring numbering starting at the sulfur atom. Other systems of nomenclature which have been used are: (i) name of alkene + sulfide; and (ii) name of alkene + episulfide. Other substituted thiiranes are called “thiirane + functional name”: for example, thiiranone (3) and thiiranimine (4). The thiirane, thiirene, or substitution system of nomenclature is preferred, although the episulfide terminology is often useful in general discussion of complex systems. For instance, compound (5)

is called allene episulfide or alkylidene thiirane. Thiirane 1-oxides (6) and 1,1-dioxides (7) are sometimes called episulfoxides and episulfones, respectively, and the simplest examples are often referred to as ethylene sulfoxide and ethylene sulfone.



1.05.2 THEORETICAL METHODS

1.05.2.1 Introduction

The valence electron shells of sulfur are of $3s^2 3p^4$ configuration. The trends found in the physical and chemical properties of the group 16 elements (O, S, Se, Te) and their compounds justify the notion that these elements constitute a family.

Theoretically calculated values of a number of components of the experimentally derived electronic energy of the group 16 elements are shown in Table 1 <70MP697, 76MI 105-01>; these components are: the Hartree–Fock energy (E_{HF}), the correlation energy (E_{cor}), and the relativistic energy (E_{rel}). Table 2 <B-49MI 105-01> shows that E_{cor} and E_{rel} increase rapidly as one goes from oxygen to tellurium. A consequence is that experimental quantities such as ionization potential (IP) are insignificant with respect to E_{cor} and E_{rel} . However, it should be noted that relativistic effects will be much more important for the core electrons than for the valence electrons, and therefore, the relativistic contribution to the first IP is not expected to increase significantly from oxygen to tellurium. Consequently, certain atomic and molecular quantities cannot be determined to any useful level of accuracy with the theoretical methods available up to 1995. However, it should be pointed out that for certain non-energy-related properties the correlation and relativistic contributions are very small and that for certain energy-related properties (ΔE s), the correlation (ΔE_{cor}) and relativistic (ΔE_{rel}) contributions effectively cancel; that is, $\Delta E_{\text{cor}} \cong 0$ and $\Delta E_{\text{rel}} \cong 0$.

Table 1 Experimentally derived electronic energy of group 16 elements and theoretically calculated components.

Component	Energy (hartree) ^a			
	O	S	Se	Te
E_{HF}	−74.8095	−397.5050	−2399.8669	−6611.785
E_{cor}	−0.2575	−0.6400	—	—
R_{rel}	−0.0490	−1.0335	−26.9247	−165.6293
E_{total}	−75.1160	−399.1785	—	—

Sources: Fraga *et al.* <B-76MI 105-01>, Mackrodt <70MP697>.

^aThe energies are quoted in Hartree atomic units (1 hartree = 2625.5 kJ mol^{−1} = 627.51 kcal mol^{−1} = 27.232 eV particle^{−1}).

1.05.2.2 Structure

Thiirane and thiirene have been subject to heavy theoretical investigation from the mid-1970s to the mid-1990s. Parent thiirene has been prepared in a glass matrix and its physical and chemical

Table 2 Experimental first ionization potentials (eV) of group 16 elements.

Species	X = O	S	Se	Te
X	13.614	10.357	9.750	9.01

Source: Moore (B-49MI 105-01).

properties have been partly disclosed (77JA4842). Theoretical investigations of thiirane and thiirene reported in the literature used basis sets of different quality, which would not lend themselves to easy comparison, and the majority of the studies involved fixed geometries. Six basis sets are available for sulfur compounds: STO-3G, MINI-1, 3-21G/LWD (Lehn *et al.*) (77HCA1239), UMNDO, 4-31G, and 6-31G**. The total molecular energies for thiirane and thiirene that have been studied with the STO-3G (69JCP(51)2657, 83CJC2596), MINI-1 (80MI 105-01, 81MI 105-01, 82MI 105-01), 3-21G/LWD (80JA939, 82JA2797), 4-31G (80JA2507, 83JA396), UMNDO (86JA5059) and 6-31G**, (87JPC6484) basis sets are summarized in Table 3. The corresponding geometries obtained from these six basis sets are given in Table 4, together with the corresponding microwave-derived structures where available. The STO-3G minimal basis set yields optimized structures in surprisingly good agreement with those obtained at the 6-31G** level. However, this is not the case for split-valence basis sets (3-21G, MINI-1); they overestimate the C—S bond lengths from 0.10 Å to 0.15 Å.

Table 3 Total molecular energies (hartree)^a thiirane and thiirene.

	STO-3G	MINI-1 or 4-31G	3-21G/LWD	6-31G** (SCF)
	−470.276760	−473.024873	−473.157121	−475.55349
	−468.996100 ^b	−473.725975 ^c	−471.915088 ^d	−474.30196

Source: Lehn *et al.* (77HCA1239).^a 1 hartree = 2625.5 kJ mol^{−1}. ^b (83CJC2596). ^c 4-31G (80JA2507). ^d (83JA396).**Table 4** Geometries^a of thiirane and thiirene.

Molecule	Parameter	STO-3G	MINI-1 or 4-31G	3-21G/LWD	UMNDO ^b	6-31G**
	C—H	1.0833	1.1140	1.0697	—	1.075 (1.083) ^c
	C—C	1.5067	1.5244	1.4633	1.501	1.472 (1.484)
	C—S	1.7736	1.9521	1.9337	1.752	1.811 (1.815)
	∠CCH	117.59	118.30	118.65	119.8	—
	∠CCS	64.86	67.02	67.77	—	66.0 (65.9)
	∠CSC	50.27	45.97	44.47	—	48.0 (48.3)
	∠HCCS	110.00	106.12	104.30	—	115.2
	C—H	1.0761 ^d	1.056 ^e	1.055 ^f	—	1.065 ^g (1.071) ^c
	C—C	1.2668	1.251	1.247	1.323	1.256 (1.258)
	C—S	1.8119	1.978	1.993	1.748	1.840 (1.830)
	∠CCH	149.31	154.9	155.1	154.4	—
	∠CCS	—	—	—	—	70.0 (69.9)
	∠CSC	—	—	—	—	39.9 (40.2)
	∠HCCS	—	—	—	—	137.0 (140.7)

Source: Lehn *et al.* (77HCA1239).^a Bond lengths in angstrom, bond angles in degree. 1 Å = 100 pm. ^b (86JA5059). ^c Experimental values taken from (51JCP(19)676) and (74CPL111). ^d (83CJC2596). ^e 4-31G (83JA396). ^f 3-21G (83JA396). ^g DZ + P optimized values taken from (83JCP(78)1384).

The structural details of thiiranium ions are shown in Figure 1.

Special interest has been focused on the structure and reactivity of thiirane derivatives bearing exocyclic double bonds, methylenethiirane (or allene episulfide), thiiranone, and thiiranimine. The molecular structure of allene episulfide has been optimized by Closed-Shell SCF (CS-SCF) calculation using restricted Hartree–Fock (RHF) built into the GAUSSIAN 80 program, with the



Figure 1 Structural details of thiiranium ions from 6-31G* calculations. The dimethylthiiranium ion is optimized with the 3-21G* basis set. Bond lengths are in angstroms, angles are in degrees <87JST(152)69>.

STO-3G minimal basis set <88RHA235>. The calculated structure of allene episulfide is similar to the values obtained by microwave analysis <78JA7436>, as shown in Figure 2.

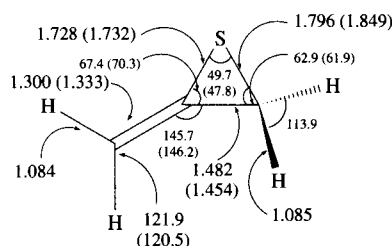


Figure 2 Optimized geometries of parent allene episulfide. Bond lengths are in angstroms, angles are in degrees. Values in parentheses were obtained from microwave studies <78JA7436>. The total energy of allene episulfide is $-318\,547.888\text{ kcal mol}^{-1}$ <88RHA235>.

The geometry of thiiranimines obtained at the RHF/6-31G*-level is used as a stationary point for the MP2/6-31G** optimization and x-ray analyses, as shown in Figure 3 <82AG(E)694, 90JPC1335, 91JOC5651>. Table 5 shows the total energy of *syn*- and *anti*-thiiranimine and of the transition state connecting both species. At all levels of theory, the *syn* structure (4a) is found at the deepest minimum and corresponds to the ground state of the molecule. Whereas the stability of the experimentally observed *syn* structures (4c, 4d) might be due to the rather bulky substituents to some extent, Table 5 shows that even the simplest unsubstituted thiiranimine has a small but definite *syn* preference. Apparently, it is energetically favorable to maximize the distance between the lone pairs on sulfur and nitrogen, as well as the distance between H₁ and (H₂, H₃). The *syn-anti* energy difference varies from 2.1 kcal mol^{-1} (8.8 kJ mol^{-1}) at the RHF level to 2.6 kcal mol^{-1} (10.9 kJ mol^{-1}) in the MP4 calculations. The *syn* species is separated from the *anti* species by an energy barrier of approximately 26 kcal mol^{-1} (109 kJ mol^{-1}) <90JPC1335>. Table 6 shows the calculated bond lengths and bond angles, as compared with the available experimental data. First of all, it should be stressed that the differences between the two sets of experiments are significant. Apparently, the effect of the substituents induces variations of up to 0.06 Å in some of the ring bond lengths.

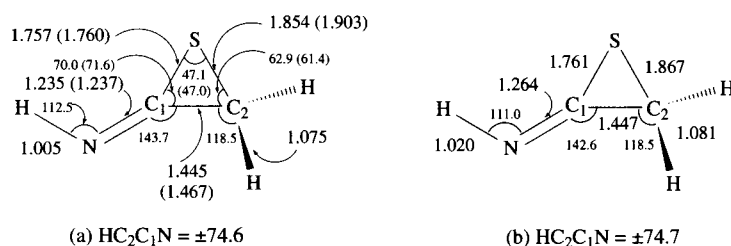


Figure 3 Optimized geometries of thiiranimine for the stationary points along the fragmentation reaction at the RHF/6-31G* (a), and MP2/6-31G** (b) levels. Bond lengths are in angstroms, bond angles in degrees. The total energies (hartree) of thiiranimines (a) and (b) are $-529.38137(0)$ and $-529.94858(0)$, respectively <90JPC1335, 91JOC5651>. Values in parentheses were obtained from x-ray analyses of substituted thiiranimine <82AG(E)694>.

1.05.2.3 Ring Strain

The strain energies and enthalpies for thiirane are listed in Table 7. The stability of thiiranimine can be analyzed by using the isodesmic reaction technique. Isodesmic reactions <B-86MI 105-01> are,

Table 5 Total energies (in hartree^a, with respect to -529.000 00 au) of syn- and anti-thiiranimines, as well as the transition state between the species.

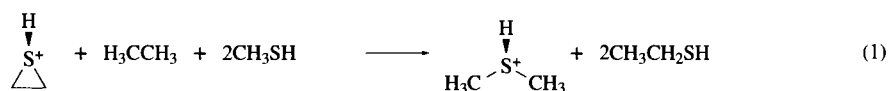
	syn (4a)	anti (4b)	Transition state
RHF/6-31G*	-0.381 37	-0.378 04	-0.338 87
MP2 ^b /6-31G**/6-31G*	-0.921 17	-0.917 06	-0.881 70
MP3 ^b /6-31G**/6-31G*	-0.942 35	-0.938 87	-0.900 70
MP4 ^b /6-31G**/6-31G*	-0.974 58	-0.970 49	-0.933 80

Source: Vanquickenborne *et al.* <90JPC1335>.^a 1 hartree = 2625.5 kJ mol⁻¹. ^b Møller–Plesset perturbation theory at the 2nd, 3rd, and 4th orders.**Table 6** Geometrical parameters^a of experimental and 6-31G* theoretical structures of thiiranimine^b and thiirane.

	Expt (4c) ^c (syn)	Expt (4d) ^d (syn)	Calc (4a) (syn)	Calc (4b) (anti)	Calc transition structure	Thiirane
C ₁ —C ₂	1.47	1.467	1.445	1.455	1.448	1.473
C ₁ —S	1.70	1.760	1.757	1.740	1.832	1.811
C ₂ —S	1.94	1.903	1.854	1.847	1.850	1.811
C ₁ —N	1.27	1.237	1.235	1.237	1.188	—
N—H ₁	—	—	1.005	1.007	0.979	—
C ₂ —H	—	—	1.075	1.076	1.077	—
∠ C ₂ C ₁ S	74.7	71.6	70.0	70.0	67.5	66.0
∠ C ₁ C ₂ S	58.1	61.4	62.9	62.3	66.2	66.0
∠ C ₁ SC ₂	47.2	47.0	47.1	47.8	46.3	48.0
∠ NC ₁ S	—	—	146.3	140.8	141.8	—
∠ H ₁ NC ₁	—	—	112.5	111.1	177.2	—
∠ H ₂ C ₂ H ₃	—	—	115.8	115.5	115.0	—
∠ HC ₂ C ₁	—	—	118.5	118.6	117.9	—
∠ H ₁ NC ₁ S	—	—	0.0	180.0	181.5	—
∠ H ₂ C ₂ C ₁ S	—	—	74.6	74.5	72.3	—
∠ H ₃ C ₂ C ₁ S	—	—	-74.6	-74.5	-73.0	—
∠ NC ₁ SC ₂	—	—	180.0	180.0	180.3	—

Source: Vanquickenborne *et al.* <90JPC(94)1335>.^a Bond lengths in angstrom, bond angles in degree. 1 Å = 100 pm. ^b The atom numbering is shown in Structures (**4a**), (**4b**), (**4c**), and (**4d**) (C₁ is the imine carbon). ^c <78AG(E)195>. ^d <82AG(E)694>.

in general, reactions where the number of any kind of bond is conserved. The intrinsic ring strain is definitely larger in thiiranimine than in thiirane (compare (c) and (d) in Scheme 1 and Table 8), but the stabilizing interaction between the exocyclic imine function and the ring exceeds the destabilizing effect due to the ring strain (compare (a) and (c) in Scheme 1 and Table 8) <91JOC5651>. In conclusion, evaluation of a number of isodesmic reactions indicates that thiiranimine is at least as stable as thiirane, the unexpected stability of thiiranimine being due to the ring–imine interaction <91JOC5651>. The strain energy of the thiiranium ion may be calculated using the homodesmotic reaction given in Equation (1) <87JST(152)69>. Here it must be pointed out that the strain energy is not the only factor determining the relative energy of the cyclic and β -substituted ion as shown in Table 9. Formally, the driving force for formation of the cyclic compound is formation of an additional bond. The longer C—S bond indicates a weaker C—S bond than in the unstrained ion, and the relative energies of structures (**8a**) and (**9**) are determined largely by the energy gained by formation of an extra partial bond minus the strain energy of the cyclic system.



1.05.2.4 Proton Affinity

The protonation of thiirane and thiirene was studied systematically by using basis sets ranging from minimal to split valence plus polarization quality. The 6-31G** optimized geometries for

Table 7 Strain energies and enthalpies for thiirane^a (kcal mol⁻¹)^b.

$-\Delta E$		$-\Delta H_{r,0}$		
SCF	MP2	SCF	MP2	Observed ^c
18.5	17.7	16.3	15.5	17.1

^a Computed values determined at the SCF (HF/6-31G(d))/HF/6-31G(d)) and MP2 (MP2/6-31G(d))/HF/6-31G(d)) level. ^b 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹. ^c The observed value is obtained from experimental heats of formation <82MI 105-01>.

Table 8 Isodesmic reaction energies calculated using the 6-31G* basis set^a.

Reaction	Energy ^b (kJ mol ⁻¹) ^c			
	HF	MP2	MP3	MP4
(a)	-62	-14	-11	-20
(b)	-65	-45	-55	-49
(c)	-110	-95	-107	-98
(d)	-70	-58	-64	-60

Source: Nguyen *et al.* <91JOC5651>.

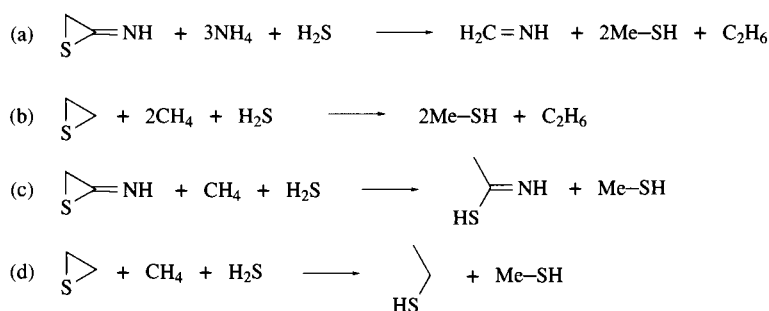
^a The reactions are listed in Scheme 1; the negative values of the different reaction energies correspond to a stabilization on going to the separated products. ^b At the indicated level with the geometry fully optimized at the HF/6-31G* level. ^c 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹.

Table 9 Strain energies (kcal mol⁻¹)^a for thiiranium ion as calculated from Equation (1).

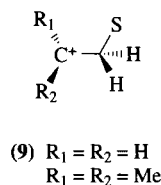
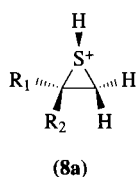
3-21G//3-21G	6-31G*//3-21G
28.4	25.5

Source: Rodriguez and Hopkinson <87JSJ(152)69>.

^a Strain energies are $-\Delta E$ for Equation (1). 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹.

**Scheme 1**

thiiraneH⁺ (**8b**) and thiireneH⁺ (**10**) are shown in Tables 10 and 11. The protonation energies of thiirane and thiirene are listed in Table 12. The STO-3G minimal basis substantially overestimates the basicity of thiirane, whose gas-phase proton affinities have been measured <80JA5151>, and therefore, one should expect a similar overestimation for thiirene. Table 13 presents the relative protonation energies for thiirane–thiirene. One of the most significant features of Table 13 is that



split-valence basis sets yield relative protonation energies much lower than those obtained when polarization functions are included in the basis. For thiirane and thiirene, relative protonation energies illustrate again the anomalous behavior of split-valence bases, which predict the same basicity for both compounds in contrast with the 6-31G* and 6-31G** results. These results indicate that thiirene is clearly more basic than thiirane. These results are supported by some experimental findings $\langle 80PAC1623 \rangle$ which suggested that thiirene must have a significant basic character.

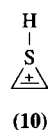
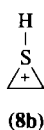


Table 10 6-31G** optimized geometries^a for thiirane H⁺ and thiirene H⁺.

Parameter	ThiiraneH ⁺	ThiireneH ⁺
C—H	1.076	1.070
C—C	1.450	1.256
C—S	1.866	1.828
S—H	1.328	1.335
$\angle CCS$	67.2	69.9
$\angle CSC$	45.7	40.2
$\angle SCH$	110.2	133.2
$\angle SCH'$	112.7	—
$\angle HCH$	116.2	—
γ^b	80.8	60.0

Source: Mo *et al.* $\langle 87JPC6484 \rangle$.

^a Bond lengths in angstrom, bond angles in degree. 1 Å = 100 pm. ^b γ is the angle between the S—H bond and the plane of the ring.

Table 11 Total energies and structural parameters for thiiranium ions.

	Total energy (hartree) ^a		Bond length (Å) ^b			Bond angle (°) ^c
	3-21G//3-21G	6-31G**//3-21G	C—C	C ₂ —S	C ₁ —S	$\angle C_1SC_2$
$R_1 = R_2 = H$	−473.45153	−475.85390	1.442	2.026 (1.917) ^c	2.026	41.7
$R_1 = H, R_2 = CH_3$	−512.28772	−514.90146	1.442	1.995	2.115	41.0
$R_1 = R_2 = CH_3$	−551.12401	−553.94667	1.451	1.949	2.416	36.9

^a 1 hartree = 2625.5 kJ mol^{−1}. ^b 1 Å = 100 pm. ^c Bond lengths in unstrained H₃CS⁺CH₃ $\langle 87JST(152)69 \rangle$.

The proton affinities of the imine nitrogen and sulfur atom in thiiranimine, listed in Table 14, are obtained as the difference of the total energies of the neutral and protonated forms at the indicated level. Protonation can take place at two sites. On the sulfur atom it induces a ring opening at the C—S bond; on nitrogen, it leads to a thioamide-like structure. The nitrogen protonation is favored, and the corresponding proton affinity is larger than that of methylenamine $\langle 91JOC5651 \rangle$.

Table 12 Protonation energies (kcal mol⁻¹)^a of thiirane and thiirene.

Basis set (SCF)	Thiirane	Thiirene
STO-3G	243.2	253.6
3-21G	184.8	184.3
6-31G	186.7	187.2
6-31G*	199.4 (200.0) ^c	205.2 (208.1) ^c
6-31G**	200.6	207.5
expt ^b	195.8	—

Source: Mo *et al.* <87JPC6484>.^a 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹. ^b Value taken from <80JA5151>.^c Value obtained by using a 6-31G* + d_s basis set with exponents of the two d functions on sulfur equal to 1.18 and 0.39, respectively.**Table 13** Relative protonation energies^a of thiirane and thiirene (kcal mol⁻¹)^b.

	STO-3G	3-21G	6-31G	6-31G*	6-31G**
thiirane-thiirene	11.1	-0.5	0.5	5.8 (8.1) ^c	6.9

Source: Mo *et al.* <87JPC6484>.^a Values referred to the corresponding saturated system. ^b 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹. ^c Value obtained using a 6-31G* + d_s basis set with exponents of the two d functions on sulfur equal to 1.18 and 0.39, respectively.**Table 14** Proton affinities and C—N and C—S bond length changes in thiiranimine (**4**).

	Proton affinities, P ^a (kcal mol ⁻¹) ^b		Δr (Å) ^c	
	HF/6-31G*	MP2/6-31G*	C—N ^d	C—S ^d
On N	225	220	0.038	-0.097
On S	218	203	^e	^e

Source: Nguyen *et al.* <91JOC5651>.^a At the indicated level with the geometry fully optimized at the HF/6-31G* level.^b 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹. ^c 1 Å = 100 pm. ^d At the HF/6-31G* level; positive value indicates an increase, and negative value a shortening, of the bond distance upon protonation. ^e Ring opening.

1.05.2.5 Energies of Hydrogenation, Ionization Potential, Net Charge, and Dipole Moment

Tables 15 to 18 summarize four properties of thiirane and thiirene: energies of hydrogenation, the ionization potentials (IP), net charges, and dipole moments. The calculated dipole moment of 2.32 debye (D) by 6-31G** <87JCP(87)6468> is similar to the value of 2.34 D calculated by the 6-31G* basis set <90JA8670>, and is 26% higher than the experimental value of 1.84 D <74CPL111>. Calculated dipole moment of allene episulfide is 0.5346 D <88RHA235>, which is smaller than the value 1.36 D experimentally obtained by microwave analysis <78JA7436>.

A Mulliken population analysis of thiiranimine (Table 19) confirms the expectation of a positive charge of the sulfur atom, when the imine function is introduced: the sulfur atom acquires a slightly positive charge in thiiranimine, whereas it has a slight electron excess ($q = -0.014$) in thiirane. The strongly negatively charged nitrogen atom has withdrawn an electron from C₁ ($\Delta q = 0.661$ electron) of the CH₂ group, and also from the more exposed sulfur atom, which becomes very slightly positive <90JPC1335>. The overlap populations of the ring bonds are very small, which is characteristic of bent bonds <69TCA281>. Especially noteworthy is the extremely small value for the facile ring opening at the C₂S side of (**4a**) and (**4b**) in addition reactions <90JPC1335>.

The ionization potentials of methylene thiirane (**5**) and its tetramethyl derivative (**5a**) are given in Table 20. MNDO <77JA4899, 77JA4907>, AM1 <85JA3902> and PM3 <89MI 105-01> calculations also reveal four high-lying occupied molecular orbitals above the various σ levels.

Table 15 Energies of hydrogenation for a series of isodesmic reactions of thiirane.

Reaction ^a	Energy of hydrogenation (kJ mol ⁻¹)		
	STO-3G	MINI-1	3-21G/LWD
C ₂ H ₄ S + 3H ₂ → 2CH ₄ + H ₂ S	-357	-372	-348

Source: Lehn *et al.* <77HCA1239>.^a Energies (hartree) for H₂ and CH₄ are: -1.117506 and -39.726864 for STO-3G, -1.122073 and -39.928559 for MINI-1 and -1.122960 and -39.976878 for 3-21G/LWD, respectively. 1 hartree = 2625.5 kJ mol⁻¹.**Table 16** First ionization potentials (eV) (Koopman's theorem) for thiirane.

STO-3G	MINI-1	3-21G/LWD	STO-431G ^a
6.94	9.73	9.51	6.94

Source: Lehn *et al.* <77HCA1239>.^a <80JA5151>.**Table 17** Net charges (from Mulliken populations) of thiirane and thiirene.

Molecule		STO-3G	MINI-1	3-21G/LWD	6-31G*
	S	+0.127	-0.089	+0.086	-0.015
	C	-0.205	-0.313	-0.604	-0.334
	H	+0.071	+0.179	+0.280	+0.171
	S	—	—	—	-0.199
	C	—	—	—	-0.022
	H	—	—	—	+0.210

Sources: Lehn *et al.* <77HCA1239>, Mó *et al.* <87JPC(91)6484>.**Table 18** Dipole moments (D)^a for thiirane and thiirene calculated with the STO-3G, MINI-1, 3-21G/LWD and 6-31G** basis sets.

Molecule	STO-3G	MINI-1	3-21G/LWD ^b	6-31G**
	0.75	2.54	2.81	2.32 (1.84) ^c
	—	—	—	2.65

Source: Mó *et al.* <87JPC(91)6484>.^a 1 hartree / angstrom² = 2.5417655 D. ^b <77HCA1239>. ^c Experimental values taken from <51JCP(19)676> and <74CPL111>.

1.05.2.6 Energies of Isomers

From consideration of resonance energy, thiirenes should be antiaromatic, and their existence consequently highly unfavored. Nevertheless, their formation in chemical or photochemical reactions has been discussed <72MI 105-01>.

Using the MNDO/3 approach with SIMPLEX energy optimization, Dewar and Ramsden have computed the isomeric structures: i.e., the carbenes (**11a**), the zwitterions (**11b**), the heterocumulenes (**11c**), and the cyclic carbenes (Equation (2)). Structure (**11**) is calculated to lie in local energy minima, implying that if generated in a chemical reaction, it should be a stable intermediate. The

Table 19 Mulliken population analysis of thiiranimine ((4a) and (4b)) Hartree-Fock 6-31G* level.

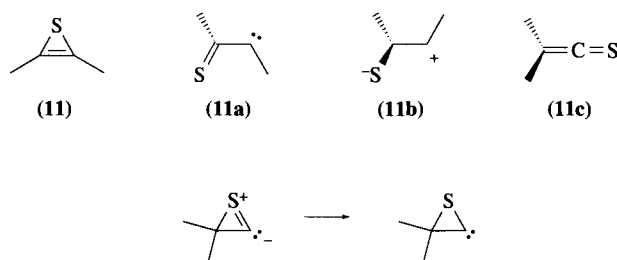
	Thiirane	Syn-thiiranimine	Anti-thiiranimine
Atomic charge			
S	-0.014	0.019	0.071
C ₂	-0.431	-0.466	-0.496
C ₁	-0.431	0.230	0.221
N	—	-0.626	-0.618
H ₁	—	0.356	0.346
Overlap population			
H ₂ H ₃	0.219	0.243	0.238
C ₂ S	0.351	0.274	0.272
C ₁ S	0.351	0.460	0.457
C ₁ C ₂	0.439	0.470	0.405
C ₁ N	—	1.131	1.229
NH ₁	—	0.620	0.638
C ₂ H	0.774	0.754	0.745

Source: Vanquickenborne *et al.* <90JPC1335>.**Table 20** Vertical Ionization potentials, I_v and calculated orbital energies, ϵ , of the methylenethiirane (5) and its tetramethyl derivative (5a).

Band	I_v (eV)	Assignment	ϵ (eV)		
			$-\omega$ (MNDO)	$-\omega$ (AM1)	$-\omega$ (PM3)
1	7.87 ^a	$\pi_{ns/C=C}^-$	9.38	9.00	8.68
2	9.84	$\pi_{ns/C=C}^+$	11.20	10.92	11.00
3	10.21	ω_s	11.38	10.84	10.90
4	10.74	ω_a	12.00	11.58	11.93

Source: Kindermann *et al.* <90CB1161>. ^a Vibrational splitting: 640 cm⁻¹.

carbene (11a) was found to be considerably less stable than the corresponding heterocycles. SCF-gradient and configuration interaction (CI) methods have been used in a study of the lowest singlet and triplet states of various isomers on the C₂H₂S energy surface as shown in Figure 4 <83JCP(78)1384>. The main conclusions are as follows: the single isomer with the lowest energy is thioketene, with mercaptoacetylene higher in energy by 17.4 kcal mol⁻¹ (72.8 kJ mol⁻¹). The much-debated anti-aromatic isomer thiirene is found to be 37.5 kcal mol⁻¹ (157 kJ mol⁻¹) more energetic than thioketene and is found to be considerably lower in energy than thioformylmethylene carbene (by 32 kcal mol⁻¹ (134 kJ mol⁻¹)) or the 1,3-diradical (by approximately 22 kcal mol⁻¹ (92 kJ mol⁻¹)) formed by scission of a C—S bond. Consequently, thiirene has some stability towards thermal rearrangement by this route <83JCP(78)1384>. The calculated heat of hydrogenation for thiirene may be considered, if compared with that of cyclopropene, as a measure of the antiaromatic destabilization. Since the heats of hydrogenation of both compounds are nearly equal, the antiaromatic destabilization should be small if not zero. Derivatives of the thiirenium ion (10) may also be intermediates of chemical reactions; nonempirical SCF-MO calculations showed that the thiirenium form is more stable than the HSCH=CH⁺ form <72CC8>.



The role of the sulfur *d*-orbitals in bonding has been discussed for (10) and (11). If an appropriate

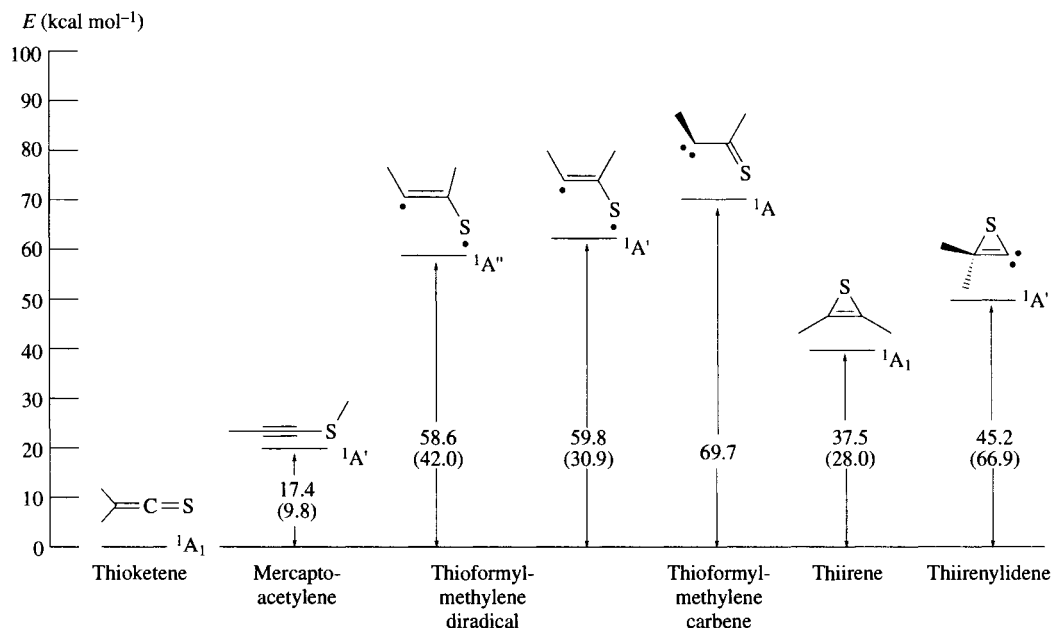
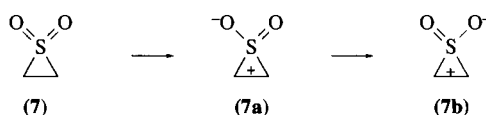


Figure 4 Relative energies of the C_2H_2S singlet isomers calculated in the SDCI (DZ + P) approximation at SCF (DZ + P) optimized geometries. The $^1A_1$ state of thioketene is the reference. Values in parentheses are calculated by UMNDO with the same reference <86JA5059, 83JCP(78)1384>.

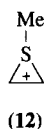
$d\pi$ orbital participated, a Möbius-type system could arise and a 4π -electronic system would be energetically preferred in this case. The relevance of the Möbius-type overlap was recently discussed by Janssen *et al.* in an elucidation of the bonding in thiirene dioxide (7) <74TL1209>. CNDO/2 calculations revealed that the dipolar structures (7a) and (7b) (Scheme 2) were not important for the description of the electronic structure (as in the case of cyclopropanone). In good agreement with experimental finding the SO_2 group of structure (7) was calculated to barely differ from that in aliphatic sulfones.



Scheme 2

The barrier to pyramidal inversion of methyl-substituted structure (12) is calculated to be high, relative to the barrier for thiophene dioxide, and this has been interpreted in terms of the energetically unfavored planar 4π Hückel-type system <71MI 105-03, 72MI 105-02>.

The theoretical studies suggest allene oxide is about 23 kcal mol⁻¹ (96 kJ mol⁻¹) less stable than cyclopropanone, while methylene thiirane is 7 kcal mol⁻¹ (29 kJ mol⁻¹) more stable than cyclopropanethione <91PS(58)179>.



1.05.3 EXPERIMENTAL STRUCTURAL METHODS

1.05.3.1 Bond Length and Bond Angles

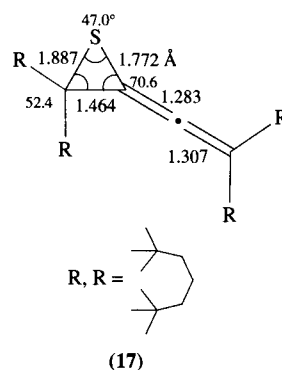
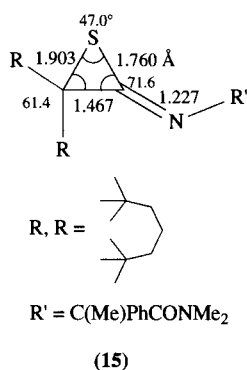
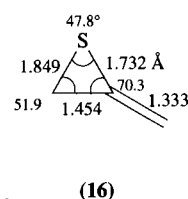
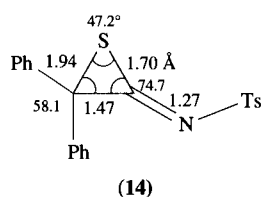
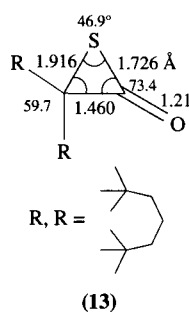
Theoretical geometries of thiirane, thiirene, and their related compounds are given in Section 1.05.2.2. Experimental data of geometries in thiirane, thiirene, and their related compounds are

listed in Table 21. In α -thiolactone (**13**) $\langle 77\text{AG(E)722} \rangle$, thiiranimine ((**14**) and (**15**)) $\langle 78\text{AG(E)195}$, $82\text{AG(E)694} \rangle$, or 2-methylenethiirane ((**16**) and (**17**)) $\langle 78\text{JA7436}$, $88\text{CL961} \rangle$, the C—S bonds which are on the opposite side to carbonyl, imine, or exomethylene are unusually long, because of the large C $\hat{\text{C}}$ S angle associated with the sp^2 -hybridized carbon atoms. Though this is also observed with other heteroatom analogues, methylenethiiranes have a long S—C bond, which markedly exceeds the sum of the covalent radii, and a particularly small bond angle at the sulfur. The exocyclic C=N bonds in thiiranimines are somewhat shorter than those in cyclic thioimidic esters $\langle 78\text{BSB893}$, $79\text{CC160} \rangle$.

Table 21 Experimentally derived bond lengths and angles for some thiiranes and thiirenes.

Compound	Bond length (Å) ^a			Bond angle (°)		Reference
	C—C	C—S	S—O	$\angle \text{C—S—C}$	$\angle \text{O—S—O}$	
	1.484	1.815	—	48.3	—	74CPL111
	1.504	1.822	1.483	48.8	133.6 ^b	76AX(B)2171
	1.590	1.731	1.439	54.7	121.4	76AX(B)2171
	1.305	1.784	1.467	42.9	126.0	76AX(B)2171
	1.354	1.716 1.703	1.444 1.453	46.7	116.1	76AX(B)2171
	1.277	1.820	1.802 ^c	41.1	—	79MI 105-01

^a 1 Å = 100 pm. ^b Twice the angle between the S—O bond and the ring. ^c S—Me.



1.05.3.2 NMR Spectra

Chemical shifts (^1H , ^{13}C) and coupling constants for thiirane and its derivatives are listed in Table 22. Vicinal H—H coupling constants ($J_{\text{H—H}}^{\text{vic}}$) are larger and geminal H—H coupling constants ($J_{\text{H—H}}^{\text{gem}}$) are smaller for thiiranes than those for oxiranes. Three-bond C—H and H—H coupling constants ($^3J_{\text{C—H}}$, $^3J_{\text{H—H}}$) are larger in thiiranes than in oxiranes (see Figure 5) <78JOC4696>. Solkan and Sergeyev and others have given a mathematical relationship that predicts a decrease in spin coupling magnitude as bond length increases:

$$^3J_{\text{H—H}} = ^3J_0 [1 - 2.9 (r_{\text{C—C}} - 1.350)] \text{ for HC=CH}$$

This idea seems to be well established in NMR <72JA6021>, but it is clearly not obeyed for the three-membered rings; in the latter case the increase in $^3J_{\text{C—H}}$ in the order O, N and S parallels the increase in bond length of the ring C—C bond.

Regarding thiirane 1,1-dioxides, Hoffmann *et al.* have interpreted the increase in bond length in terms of a weakening of the C—C bond across the ring from SO_2 due to a back-donation of electrons from SO_2 into the C—C antibonding orbital <73JA7644>. The reason for the increased magnitudes of spin coupling (X = O, N, S) may be sought in the lower excitation energies likely to be present in the molecules having weak bonds <66JCP(44)1836>.

The methine protons and ring carbons in *S*-methyl or *S*-protonated thiiranium ions appear at lower field (^1H , 4.0–5.0 ppm; ^{13}C , 74.0–78.0 ppm) as shown in Table 22. The methine hydrogens of the ring are coupled to the S—H proton, $^3J_{\text{H—H}} = 6\text{--}8\text{ Hz}$ —of the same magnitude as observed in acyclic protonated sulfides.

The chemical shift of the vinylic carbon of 2,3-diphenylthiirene 1-oxide (**18**) is found to be 137.3 ppm (downfield from SiMe_4) and those of the corresponding 2,3-diphenyl- and 2,3-dimethylsulfone dioxides to be 158.9 ppm and 167.4 ppm, respectively, which correspond to the reported values of 148.5 ppm and 157.9 ppm for the 2,3-diphenyl- and 2,3-dimethylcyclopropenones, the analogous cycloketone Hückel systems <85JOC1107>. In comparing the degree of possible aromaticity of thiirene 1-oxides and thiirene 1,1-dioxides, the degree of π -electron delocalization is expected to be proportional to the oxidation state of sulfur, and the thiirene 1,1-dioxide (**19**) would have a higher C—S π -bond order than the thiirene 1-oxide. The former molecule is also stabilized by spiroconjugative interaction. On the other hand, the thiirene 1-oxide suffers homoconjugative destabilization as is illustrated in the interaction diagram (Figure 6) <85JOC1107>.

Chemical shifts (^1H and ^{13}C NMR) in *S*-phenyl thiiranium ions are observed at 3.6–3.8 ppm in ^1H NMR and 55.0–92.0 ppm in ^{13}C NMR as shown in Table 23 <75TL2603, 78CC630, 79IZV510, 87JOC2403>. ^1H , ^{13}C , and ^{19}F NMR parameters of *S*-fluoro-*S*-methyl episulfuranes (**20**) and (**21**) are shown in Table 24 <87TL4593>.

Sulfur-33 NMR data of thiirane, thiirane 1-oxide, and thiirane 1,1-dioxide are reported by Barbarella *et al.* <87JOC3857>. Chemical shifts of ^{33}S NMR (in ppm with respect to CS_2 as external reference) in thiirane, thiirane 1-oxide, and thiirane 1,1-dioxide were observed at –240, 120 and 245 ppm, respectively.

1.05.3.3 Mass Spectra and Photoelectron Spectra

Mass spectra of sulfur compounds show a cluster of peaks around the molecular ion peak ($M + 2$, $M + 1$ and M ; the ratio is 4:11:100), which are derived from ^{34}S , ^{33}S and ^{32}S . The fragments observed in electron ionization (EI) mass spectra of thiiranes are due to loss of a hydrogen atom or alkyl group or to ionization to a thioaldehyde or thioketone followed by loss of a neutral alkyl group or hydrogen. 2,3-Diphenylthiirane 1-oxide and several thiirane 1,1-dioxides show very weak molecular ions by EI mass spectrometry, but much more abundant molecular ions are given in chemical ionization (CI) mass spectrometry <75JHC21>. The major fragments are sulfur monoxide or sulfur dioxide and alkynic ions. The EI mass spectrum of methylene thiirane $\text{C}_3\text{H}_4\text{S}$ ($M = 72$) shows a molecular ion peak and fragments at m/e 72 (61%), 71 (100%), 45 (30%), 40 (22%) and 39 (46%), of which the first two have elemental compositions $^{12}\text{C}_3\text{H}_4^{32}\text{S}$ and $^{12}\text{C}_3\text{H}_3^{32}\text{S}$, respectively <78RTC214>. A meta-stable peak at m/e 28.52 points to the fragmentation $\text{C}_3\text{H}_3\text{S}^+ (m/e 71) \rightarrow \text{CHS}^+ (m/e 45) + \text{C}_2\text{H}_2$.

The photoelectron (PE) spectroscopic data for thiirane assigned from the *ab initio* STO-431G (double ζ) calculation are summarized in Table 25. This calculation agrees reasonably well with experiment and leads to a clear assignment of the highest energy bands <80JA5151>. The lone-pair ionization potentials of the thiirane are higher than those of dimethyl sulfide because of charge

Table 22 Chemical shifts of ^1H and ^{13}C NMR in thiirane derivatives.

Compound	Solvent	$\delta(^1\text{H})$	$\delta(^{13}\text{C})$	$^2J_{\text{H-H}}$	$^3J_{\text{H-H}}$	$^1J_{\text{C-H}}$	References
	Nematic solvent	2.27	1.81	0	7.15 5.65	170.26	75JST(24)85
	CCl_4	2.42 1.92	33.8	-6.4	11.7 11.5 10.5	171.8 171.9	70TL2877
	CDCl_3	3.15	31.6	-9.8	11.87 6.89	170.4	72OMR(4)441
	CDCl_3		55.6	—	—	155	72JOC4045
	CDCl_3	3.07 1.18	71.4	—	—	157	74JA3146
	CDCl_3		50.7	—	—	160	72JOC4045
	CDCl_3	3.11 1.87 1.28 0.92	63.8 58.3	—	12.0 12.0	155 (ring CH) 157 (Me)	74JA3146
	CDCl_3	4.40 (ring CH) 2.80 (SMe)	76.2 (ring C) 27.6 (SMe)	—	0	165 (ring CH) 128 (SMe)	74JA3146
	CDCl_3	4.96 (H) 4.90 (H) 3.01 (SH) 1.52 (Bu^t) 1.49 (Bu^t)	75.1 (ring C) 74.5 (ring C) 37.2 (CMe) 37.7 (CMe) 30.2 (Me)	—	6 8 6, 8	167 (ring CH) 167 (ring CH) 120 (Me)	74JA3146
	CDCl_3	4.95 (H) 3.54 (SH) 1.70 (Bu^t)	78.3 (ring C) (Me) 34.0 (CMe)	38.3 —	8 8	127 (ring CH) 125 (Me)	74JA3146
	SO_2	2.77 (CMe) 2.50 (SMe)	107.0 (ring C) 25.6 (SMe) 9.0 (CMe)	—	—	—	79MI 105-01
	CDCl_3	9.04 (H) 2.50 (Me)	—	—	—	230	71JA476
	CDCl_3	5.71 5.34 2.68	130.1 99.5 18.5	± 1.55	—	174 166	78RTC214

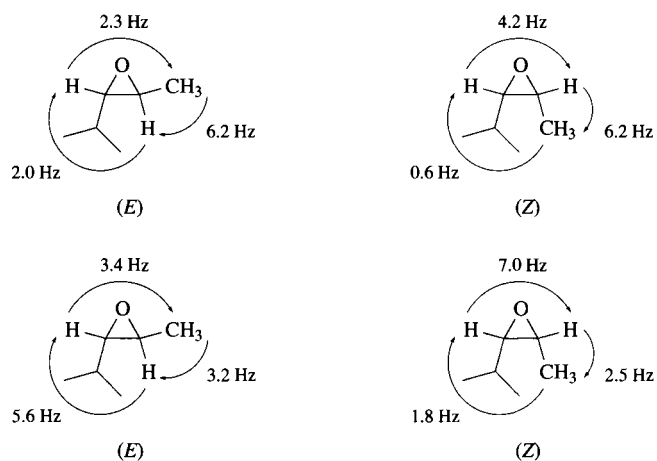


Figure 5 Three-bond C—H and H—H NMR coupling constants in thiiranes and oxiranes.

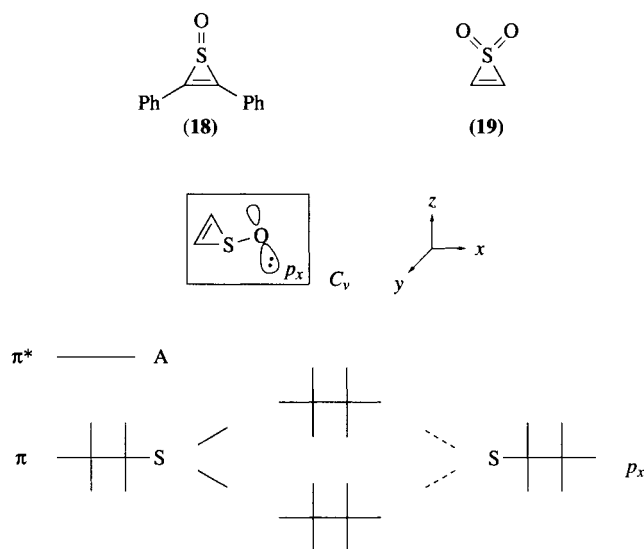
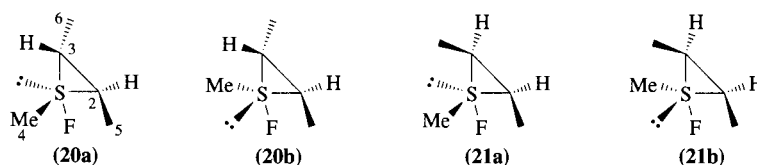


Figure 6 The interactive diagram of thiirane 1-oxide.

Table 23 Observed NMR spectra of thiiranium ions.

¹ H spectra Chemical shifts (ppm)						
	H ^a	H ^b	H ^c , H ^d	X ⁻	R	References
	1.58	1.82	3.62	SbCl ₆ ⁻	4-ClC ₆ H ₄	79IZV510
	1.58	1.82	3.80	CF ₃ SO ₃ ⁻	4-ClC ₆ H ₄	87JOC2403
¹³ C spectra Chemical shifts (ppm)						
	C ₁ C ₂	C ₃	C ₄	X ⁻	R	References
	15.0	62.4	49.5	SbCl ₆ ⁻	4-ClC ₆ H ₄	78CC630
	19.0	91.7	54.9	SbCl ₆ ⁻	2,4,6-(CH ₃) ₃ C ₆ H ₂	75TL2603
	21.9	88.0	55.0	CF ₃ SO ₃ ⁻	4-ClC ₆ H ₄	87JOC2403

**Table 24** NMR parameters of mixtures (20a) + (20b) and (21a) + (21b).

¹ H NMR	Chemical shifts (ppm)					Coupling constants (Hz)			¹⁹ F-NMR ^a Chemical shifts	
	H(2)	H(3)	H(4)	H(5)	H(6)	³ J _{2,3}	³ J _{2,5}	³ J _{3,6}		
(20a) + (20b)	3.59	2.74	2.13	1.22	1.30	4.7	6.2	6.9	(8a) + (8b) 71.5 (s, br)	
	3.56	2.67	2.13	1.22	1.27	5.0	6.2	7.1		
(21a) + (21b)	3.61	2.77	2.13	1.17	1.25	4.2	6.3	6.9	(9a) + (9b) 71.4 (s)	
	3.58	2.79	2.13	1.17	1.25	4.4	6.3	5.9		
¹³ C NMR	Chemical shifts (ppm)					Coupling constants (Hz)				
	C(2)	C(3)	C(4)	C(5)	C(6)	¹ J _{2,H}	¹ J _{3,H}	¹ J _{4,H}	¹ J _{5,H}	¹ J _{6,H}
(20a) + (20b)	78.03	47.67	14.55	18.32	16.90	140.6	136.9	138.0	126.0	127.4
	86.40	47.43	14.37	17.24	16.57	140.0	136.9	138.0	126.0	127.4
(21a) + (21b)	75.98	45.88	14.56	16.08	15.19	140.5	136.4	138.1	126.2	127.4
	75.82	45.54	14.43	15.70	15.19	140.5	136.4	138.1	126.1	127.4

Source: Carretero *et al.* <87TL4593>.^a CFC1₃ as internal reference.

redistribution effect in the C—S bonds and an increase in lone-pair *s* character. The proton affinity is lower in thiirane than in dimethyl sulfide as a result of an increase in lone-pair *s* character and an increase in the CŜC angle strain on protonation (Table 26). According to the PE spectrum of thiirane, no correlation is found between the first ionization potential of thiirane and rate constants for ring cleavage by phenols <85MI 105-01>.

Table 25 Vertical ionization potentials and orbital energies of thiirane.

Orbital	<i>b</i> ₁ (<i>n</i>)	<i>b</i> ₂ (<i>σ</i> _a)	<i>a</i> ₁ (<i>σ</i> _s)	<i>a</i> ₂ (<i>π</i> _{CH2})	<i>a</i> ₁ (<i>n</i>)	<i>b</i> ₂ (<i>π</i> _{CH2})
Expt.	9.03	11.37	11.93	13.51	15.33	16.58
Calc. ^a	9.36	11.51	11.71	14.91	16.43	18.5

Source: Aue *et al.* <80JA5151>.^a STO-431G calculations.**Table 26** Comparisons of experimental and STO-431G calculated proton affinity and ionization potential charges in thiirane^a.

ΔPA _{expt} (kcal mol ⁻¹) ^b	4.9	ΔIP(<i>n</i> , <i>a</i> ₁) _{expt} (eV)	4.0
ΔPA _{calc} (HSH) (kcal mol ⁻¹) ^b	5.7	ΔIP(<i>n</i> , <i>a</i> ₁) _{calc} (eV)	5.13
Δ∠RSR (°)	4–5	ΔIP(<i>n</i> , <i>a</i> ₁)(HSH) _{calc} (eV)	0.05
		ΔIP(<i>σ</i> _a) (eV)	–1.38
ΔIP(<i>n</i>) _{expt} (eV)	0.35	ΔIP(<i>σ</i> _a) _{calc} (eV)	–1.78
ΔIP(<i>n</i>) _{calc} (eV)	0.33	ΔIP(<i>π</i> _{CH2}) (eV)	–0.74
ΔIP(<i>n</i>)(HSH) _{calc} (eV)	0.11	ΔIP(<i>π</i> _{CH2}) _{calc} (eV)	–0.48
		ΔIP(<i>π</i> _{SCH2}) (eV)	1.1
		ΔIP(<i>π</i> _{SCH2}) _{calc} (eV)	2.1

Source: Aue *et al.* <80JA5151>.^a ΔPA and ΔIP refer to changes in proton affinities and ionization potentials between the three-membered heterocycles and corresponding dimethyl compounds and between HSH compounds of different bond angles. ^b 1 kcal mol⁻¹ = 4.186 kJ mol⁻¹.

The photoabsorption cross-section of thiirane has been studied in the 110–240 nm region using synchrotron radiation <89JCP(91)2808>. A number of peaks from thiirane can be arranged into four Rydberg series, converging to the first ionization potential. Many Rydberg peaks from thiirane are observed to possess vibronic structures. The vibronic frequency intervals and their assignments are listed in Table 27. The four Rydberg series constructed for thiirane are:

$$\begin{aligned} s \text{ series: } v_n &= 73076 - R/(n - 1.907)^2, n = 4-8, \\ p \text{ series: } v_n &= 73144 - R/(n - 1.663)^2, n = 4-9, \\ d \text{ series: } v_n &= 73048 - R/(n - 0.351)^2, n = 3-10, \\ d' \text{ series: } v_n &= 73117 - R/(n - 0.072)^2, n = 3-11. \end{aligned}$$

Many of the lower members of the four Rydberg series possess vibrational progressions. Following the notation of Wang *et al.* <77JCP(67)2614>, the Rydberg orbitals under C_{2v} symmetry where the Z axis is the C_2 symmetry axis are:

$$\begin{aligned} ns: & a_1 (\sigma_g) \text{ for } n \geq 4, \\ np: & b_2 (\sigma_u), a_1 (\pi_u), b_1 (\pi_u) \text{ for } n \geq 4, \\ nd: & a_1 (\sigma_g), a_2 (\pi_g), b_2 (\pi_g), a_1' (\delta_g), b_1 (\delta_g) \text{ for } n \geq 3, \end{aligned}$$

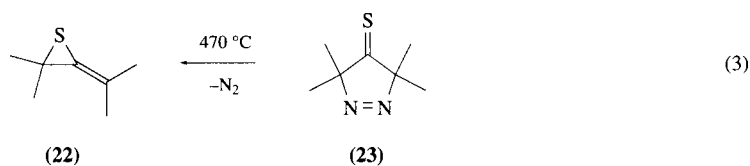
where the notations in parentheses correspond to $D_{\infty h}$; the y axis is the C_∞ symmetry axis. Two of the five a_1 vibrational modes are seen to be active in the Rydberg transition. Molecular geometries of the $(3b_1)^{-1}$ ion state evaluated by the MO calculations are partly changed from those of the ground state: $r_{(C-S)}$ is lengthened by about 0.05 Å and ϕ enlarged by about 10°. This change in geometry is caused by the change in the character of the $4b_2$ orbital upon ionization. The $4b_2$ orbital in the ground state is composed of the $3p_y$ orbital of sulfur (52%) and the $2p_z$ orbital of two carbon atoms ($2 \times 24\%$) and then its character is $\sigma_{cs} + \sigma_{cc}^*$. When the $3b_1$ electron ionizes, the C—S bond weakens and the C—C bond strengthens since the $3p_y$ component increases by about 10% and the $2p_z$ component decreases. Thus, the vibrational analysis together with the calculated molecular geometries for thiirane gives rise to partly changed structure of the excited states with respect to the ground state: that is, the lengthened C—S bond and enlarged angle between the HCH bisector and the C—C bond.

Table 27 Observed vibronic frequency intervals in the Rydberg states of thiirane (cm^{-1}).

Thiirane state	v_4	v_5
X A_1		626
4s	1048	
4p	1081	634
3d	1060	562
3d'	1060	
5s	1081	620
5p	1047	
4d	1037	614
4d'		
6s	1054	586
5d	1057	
X B_1	1041	
	1088	526

Source: Tokue *et al.* <89JCP(91)2808>.

The photoelectron spectrum of 3-isopropylidene-2,2-dimethylthiirane (**22**) has been recorded, and the same spectrum as in the pyrolysis of the tetramethylpyrazolinethione (**23**) is obtained without the bands of molecular nitrogen (Equation (3)). The PE spectrum recorded during the pyrolysis of (**23**) at 470°C provides unequivocal evidence for the occurrence of the methylenethiirane (**22**) by the signals at 7.87 eV and 9.84 eV, which are assigned to $\pi_{ns/C=C}^-$ and $\pi_{ns/C=C}^+$, respectively. The third and the fourth ionization potentials are recorded at 10.21 eV and 10.74 eV, which are assigned to ω_s and ω_A , respectively (see Section 1.05.2.5 and Table 16) <90CB1161>.



1.05.3.4 Electronic Spectra and Optical Rotatory Dispersion (Circular Dichroism)

The UV absorption spectrum of thiirane reveals two broad and diffuse bands in the region of 230–260 nm and a sharp and structured spectrum below 210 nm. The two weak bands centered at 259 nm and 243 nm ($\epsilon \cong 30$) are assigned as $n \rightarrow \sigma^*$ valence transitions, the n orbital being the nonbonding $3p$ orbital of the sulfur atom $\langle 65JCP(43)3666 \rangle$. The UV absorption spectrum of propylene sulfide in cyclohexane solution reveals only one band around 250 nm $\langle 65JCP(43)3666 \rangle$, while the gas-phase measurements identified two transitions. The possibility of assigning the 244 nm as a $4s$ Rydberg transition, thus explaining its disappearance in the solution spectrum, is ruled out, the reasons being that such an assignment would yield a very high ($\approx 3 \times 10^4 \text{ cm}^{-1}$) term value for the $4s$ Rydberg and that, for an allowed transition such as the $n \rightarrow 4s$, one expects a higher ϵ value than that observed ($\epsilon \cong 30$).

The structured spectrum below 210 nm is assigned as being composed of various Rydberg transitions. The CD of the (+)-propylene sulfide around 250 nm is dominated by the $n \rightarrow \sigma^*$, $3b_2 \rightarrow 5b_1$ transition which is magnetic dipole allowed and electric dipole forbidden and therefore is expected to yield a large CD signal $\langle 83JPC(87)4585 \rangle$. Thiirane and oxirane groups behave as electron-withdrawing substituents when attached to an aromatic ring, as indicated by the UV spectra of 2-arylthiiranes. The 260 nm band of chiral thiiranes is optically active, and a Cotton effect is observed; (*R*)-(+)-methylthiirane shows a negative Cotton effect at ≈ 250 nm, followed by a positive effect below 200 nm. An MO analysis indicates that charge transfer contributions are most important in determining the optical activity of the $n \rightarrow \sigma^*$ transition $\langle 81JCS(F2)503 \rangle$. The UV spectra of thiirane 1-oxide and (1*S*, 2*S*)-(+)-2-methylthiirane 1-oxide show a broad maximum at about 205 nm ($\epsilon \approx 23 \times 10^3$). The latter shows a positive Cotton effect at low energy followed by a negative effect at high energy. The lowest excited states of thiirane 1-oxide involve excitations from the two lone pairs of the oxygen atom $\langle 79G19 \rangle$. 2,3-Diphenylthiirane 1-oxide and 1,1-dioxide show absorption due to the 1,2-diphenylethylene chromophore.

1.05.3.5 Infrared, Raman, and Microwave Spectra

Infrared spectra of gaseous C_2H_4S , and its Raman spectra in the liquid phase, are listed in Table 28 $\langle 86JCP(84)4211 \rangle$; the data are in good agreement with other reports $\langle 68CR(B)283, 71MI\ 105-02, 73MI\ 105-01, 74MI\ 105-01, 86JCP(84)4211 \rangle$. The ring deformation frequencies of thiirane are reported at 627.3 cm^{-1} and 623.0 cm^{-1} . IR spectra of the S—O bond in thiirane 1-oxides and their derivatives are summarized in Table 29. The sulfonyl group in thiirane 1,1-dioxide exhibits symmetric and antisymmetric bending frequencies at 1159 cm^{-1} and 1308 cm^{-1} , respectively, and a bending frequency at 446 cm^{-1} . The frequency of the methylene scissoring vibrations decreases in the order thiirane (1450 cm^{-1}) > thiirane 1-oxide (1418 cm^{-1}) > thiirane 1,1-dioxide (1388 cm^{-1}). The C=C stretching frequency in methylenethiirane is tentatively assigned to a weak absorption at 1717 cm^{-1} $\langle 90CB1161 \rangle$. IR data for other methylenethiirane $\langle 78JA7436, 77AG(E)722 \rangle$, thiiranone $\langle 78AG(E)195 \rangle$ and thiiranimine $\langle 82AG(E)694 \rangle$ derivatives are given in Table 30. The high C=C, C=O, C=N stretching wave numbers in the IR spectrum of these systems are especially due to the presence of the three-membered ring, which causes a remarkable upfield shift.

The photolysis of 1,2,3-thiadiazole with a light of wavelength = 215 nm yielded a product isolated in an argon matrix at 8 K with an IR spectrum displaying increase absorption of the bands attributable to thiirene and ethynylthiol as compared with the absorption of thioketene $\langle 78JOC2487 \rangle$. This enhancement in the spectral intensity made it possible to identify the bands which could be assigned to the thiirene molecule. On this basis, seven of the eight bands (3208 (w), 3170 (m), 1660, 912 (s), 660 (m), 563 (m), and 425 (m) cm^{-1}) expected for thiirene could be located, and only two of these lie in the C—H stretching region. Based on the similarity between the fully optimized *ab initio* molecular orbital geometry of thiirene $\langle 78CPL211 \rangle$ and those of cyclopropene $\langle 59JCP(30)512 \rangle$

Table 28 Infrared and Raman spectral features of C₂H₄S.

Infrared (gas)			Raman (liquid)		Qualitative assignment
ν^a (cm ⁻¹)	RIA ^b	Type ^c	$\Delta\nu^a$ (cm ⁻¹)	Type ^c	
3088.0	18	m, PQR	3071.7	m	$\nu_9(B_1)$ C—H stretch
3084.2		w, Q			hot band
3013.5	100	vs, PQR	2994.7	vs, P	$\nu_1(A_1)$ C—H stretch
					$\nu_{12}(B_2)$ C—H stretch
2903.6		w, PQR			$2\nu_2$
2863.5		w, PQR			$2\nu_{13}$
1456.8	$\approx 7 \left. \begin{matrix} \approx 5 \end{matrix} \right\} 12$	m, PQR	1450	m, P	$\nu_2(A_1)$ CH ₂ scissor
1435.9		m, PR	1431	m	$\nu_{13}(B_2)$ CH ₂ scissor
1255		vw, PQR	1230	vw	$2\nu_5$
1173.3		vw, Q			
1109.9	4	m, PQR	1112	s, P	$\nu_3(A_1)$ C—C stretch
1050.8	80	s, PR			$\nu_{14}(B_2)$ CH ₂ wag
1024.0	1	m, PQR	1025	s, P	$\nu_4(A_1)$ CH ₂ wag
945.2	8	m, PQR	944	w	$\nu_{10}(B_1)$ CH ₂ twist
824.3	<1	w, PQR	895	vw	$\nu_8(A_2)$
688		m, bd	822	w	$\nu_{11}(B_1)$ CH ₂ rock
627.3		vs, PQR	650.8	m	$\nu_{15}(B_2)$ C—S stretch
623.0	75	w	611.3	vs, P	$\nu_5(A_1)$ C—S stretch hot band

Source: Allen *et al.* <86JCP(84)4211>.^a Accuracy $\cong \pm 1$ cm⁻¹. ^b Relative integrated absorbance. ^c Abbreviations: w = weak; m = medium; s = strong; v = very; bd = broad; P = polarized; Q = Q branch; PQR = P, Q and R branches were visible; PR = only P and R branches were visible.**Table 29** IR spectra of thiirane 1-oxides.

Compound	ir ν (cm ⁻¹)	Compound	IR ν (cm ⁻¹)
	1060 (S—O) ^a (in solution) 1050, 1065 (sh) (vapor phase)		1035 ^b (KBr)
	1072 ^c (neat)		1062 ^c (KBr)
	1080 ^d (CHCl ₃)		1050 ^d (CHCl ₃)
	1085 ^d (CCl ₄)		1080 ^d (CCl ₄)

^a <68TL959>. ^b <86JOC2122>. ^c <74JA3146>. ^d <88CL1501>.

and thiirane <51JCP(19)676> (Table 31), it is possible to make the following tentative assignments of the observed bands.

Irradiation ($\lambda = 235.0$ – 280.0 nm) of either [4-¹³C]-1,2,3-thiadiazole or [5-¹³C]-1,2,3-thiadiazole gives [¹³C]-thiirene with bands shifted to 3198 cm⁻¹, 3163 cm⁻¹, 3158 cm⁻¹, 1634 cm⁻¹, 910 cm⁻¹ and 558 cm⁻¹. [¹³C]-Thiirene is transformed with light of wavelength = 33–37 nm to ethynyl mercaptane and thioketene, with the C-13 label scrambled in both products (Equation (4)). Irradiation of either 4-methyl-5-carboethoxy- or 5-methyl-4-carboethoxy-1,2,3-thiadiazole using a 265 nm interference filter resulted in the appearance of a spectrum with significant absorptions at

Table 30 IR spectra of methylene thiirane, thiiranone and thiiranimine.

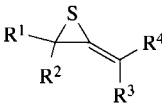
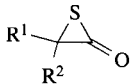
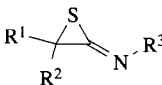
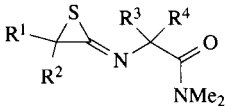
Compounds	Substitution	IR ν (cm^{-1})	References
	$R^1 = R^2 = R^3 = R^4 = \text{H}$	C=C 1717	78RTC214
	$R^1 = R^2 = R^3 = R^4 = \text{CH}_3$	1738	76JA7081
	$R^1 = R^2 = R^3 = R^4 = \text{CF}_3$	1740	69JOC3201
	$R^1 = \text{Pr}^i, R^2 = \text{Bu}^i, R^3 = R^4 = \text{CN}$	1620	93JCS(P1)2385
	$R^1 = R^2 = \text{Bu}^i, R^3 = R^4 = \text{CN}$	1610	
	$R^1, R^2 = -\text{C}(\text{CH}_3)_2(\text{CH}_2)_3\text{C}(\text{CH}_3)_2-, R^3 = R^4 = \text{CN}$	1630	
	$R^1 + R^2 = -\text{C}(\text{CH}_3)_2(\text{CH}_2)_3\text{C}(\text{CH}_3)_2-$	C=O 1785	77AG(E)722
	$R^1 = \text{Pr}^i, R^2 = \text{Bu}^i$	1800	
	$R^1 = R^2 = \text{Bu}^i$	1810, 1785	
	$R^1 = R^2 = \text{Ph}, R^3 = -\text{SO}_2-\text{C}_6\text{H}_4-\text{CF}_3$	C=N 1700 (m) 1630 (s)	78AG(E)195
	$R^1 = \text{Pr}^i, R^2 = \text{Bu}^i, R^3 = R^4 = \text{CH}_3$	1730	82AG(E)694
	$R^1, R^2 = -\text{C}(\text{CH}_3)_2(\text{CH}_2)_3\text{C}(\text{CH}_3)_2-, R^3 = R^4 = \text{CH}_3$	1735	
	$R^1 = R^2 = \text{Bu}^i, R^3 = R^4 = \text{CH}_3$	1715	
	$R^1, R^2 = -\text{C}(\text{CH}_3)_2(\text{CH}_2)_3\text{C}(\text{CH}_3)_2-, R^3 = \text{CON}(\text{CH}_3)_2, R^4 = \text{H}$	1745, 1725	
	$R^1 = R^2 = \text{Bu}^i, R^3 = \text{CON}(\text{CH}_3)_2, R^4 = \text{H}$	1730	
	$R^1, R^2 = -\text{C}(\text{CH}_3)_2(\text{CH}_2)_3\text{C}(\text{CH}_3)_2-, R^3 = \text{CH}_3, R^4 = \text{C}_6\text{H}_5$	1730	

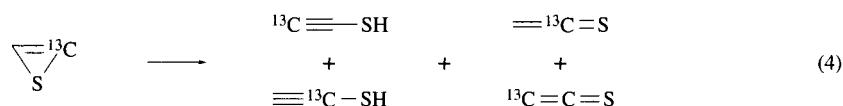
Table 31 Tentative assignment of the observed IR bands of thiirene (cm^{-1}).

	Thiirene	Reference compd
C—H stretch	3208 3170	3124 ^a 3158 ^a
C=C stretch	1660	1656 ^a
C—H in-plane bend		1010 ^a
	912	905 ^a
C—H out-of-plane bend	425	570 ^a
Ring deformation	660	633 ^b
	563	646 ^b

 Source: Straus *et al.* <78CPL211>.

^a Cyclopropene <59JCP(30)512>. ^b Thiirane <51JCP(19)676>.

3205 (vw), 3000 (w), 1875 (m), 1715 (s), 1440 (w), 1400 (w), 1370 (m), 1270 (s), 1070 (m), 1040 (m), 1020 (w), 760 (w), 730 (w), and 490 (w) cm^{-1} <B-66MI 105-01>.



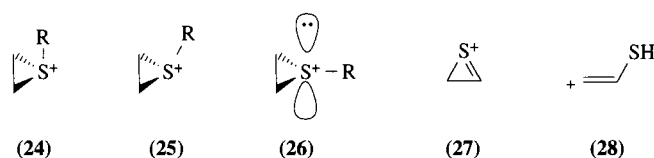
The presence of an absorption at 1875 cm^{-1} for a C=C stretching indicates an unusually large shift from the value of 1660 cm^{-1} for the parent compound; however, this again parallels the behavior of cyclopropenes, since similarly substituted cyclopropenes exhibit an absorption at 1840 cm^{-1} which was assigned to the C=C stretching <B-66MI 105-01>.

The IR spectra of episulfuranes (**20**) and (**21**) are observed at 1150, 1080, 1045 and 800 cm^{-1} for (**20**) and 1150, 1090, 1070, 980 and 800 cm^{-1} for (**21**) <87TL4593>.

1.05.3.6 Thermodynamic Properties

The heat of formation ($\Delta H_{f,0}$) for thiirane is $22.4 \text{ kcal mol}^{-1}$ (93.8 kJ mol^{-1}), the value of which is in good agreement with the theoretical values $21.6 \text{ kcal mol}^{-1}$ (90.4 kJ mol^{-1}) for SCF (HF/6-

31G(d)//HF(6-31G(d)) level and 20.8 kcal mol⁻¹ (87.1 kJ mol⁻¹) for MP2 (MP2/6-31G(d)//HF/6-31G(d)) level) <89JPC3025>. The strain energy of thiirane is 17.1 kcal mol⁻¹ (71.6 kJ mol⁻¹) <82MI 105-02>. The stability of thiiranium ions is calculated to decrease in the order: pyramidal ion (**24**), *sp*³-hybridized ion (**25**) and *sp*²-hybridized ion (**26**) <74T2197>. Ion (**27**) is calculated to be more stable than (**28**) by 66.0 kcal mol⁻¹ (276.3 kJ mol⁻¹). The energetic consideration of thiirene have been shown in Section 1.05.2.6 (Figure 3). The *syn* thiiranimine is more stable than the *anti* form, which has already been mentioned in Section 1.05.2.2. The interaction of the sulfur atom with the imine π -bond is shown to be responsible for several interesting effects. The first electronic transition is expected to correspond essentially to an intraatomic sulfur excitation, in contrast with methylenamine where one observes an *n*- π^* transition. Evaluation of a number of isodesmic reactions indicates that thiiranimine is at least as stable as thiirane, the unexpected stability of thiiranimine being due to the ring imine interaction. Frontier orbital considerations can partly explain the regioselectivity of the observed cycloaddition reactions. The results of *ab initio* calculation also confirm that thiiranimine is stable toward fragmentation (into an isocyanide plus a thioketone), and they are in agreement with experimental findings for substituted thiiranimines <91JOC5651>. The theoretical studies suggest allene oxide is about 23 kcal mol⁻¹ (96 kJ mol⁻¹) less stable than cyclopropanone, while methylene thiirane is 7 kcal mol⁻¹ (29 kJ mol⁻¹) more stable than cyclopropanethione <91PS(58)179>.



1.05.3.7 Miscellaneous Properties: Dipole Moments

Dipole moments of thiirane and methylene thiirane are 1.84 D <51JCP(19)676> and 1.36 D <78JA7436>, respectively. The dipole moments of thiirane 1-oxide, thiirane 1,1-dioxide and oxirane are 3.72 D, 4.41 D and 1.88 D, respectively. The C—S and S—O bond moments in thiirane 1-oxide are 1.06 D and 2.53 D. The calculated values of dipole moment for thiirane and thiirene are mentioned in Section 1.05.2.5 (Table 18).

1.05.4 THERMODYNAMIC ASPECTS

1.05.4.1 Physical Properties

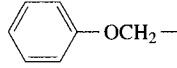
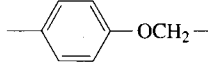
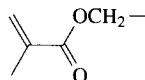
Some thiiranes are distillable under reduced pressure, as shown in Table 32, or can be purified by silica-gel column chromatography <86S779>. Sterically crowded methylene thiiranes and thiiranimines can be purified by silica-gel column chromatography or high performance liquid chromatography.

The aromaticity of the thiirene oxide system is mentioned in Section 1.05.5.1.

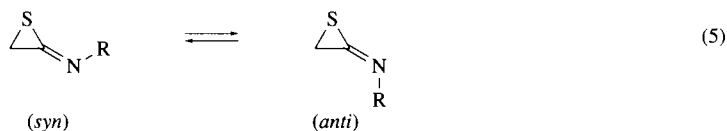
1.05.4.2 Tautomerism

The calculated relative energies of C₂H₂S singlet isomers are mentioned in Section 1.05.2.6. The energy difference between *syn*- and *anti*-thiiranimines is 2.1–2.6 kcal mol⁻¹ (8.8–10.9 kJ mol⁻¹) (see Section 1.05.2.2) <90JPC(94)1335>. The *syn* species is separated from the *anti* species by an energy barrier of approximately 26 kcal mol⁻¹ (109 kJ mol⁻¹) (Equation (5)) <90JPC1335>.

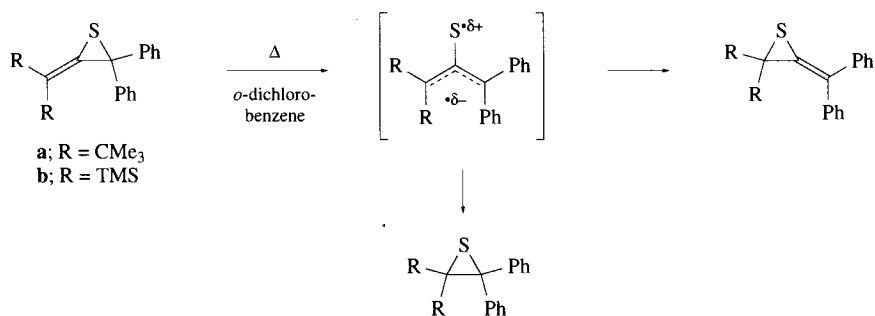
Table 32 Boiling points of thiirane derivatives.

 R	<i>b.p.</i> (°C)	<i>Pressure</i> (torr)
Ph—	86 (87–88) ^a	5 (4) ^a
<i>n</i> -C ₆ H ₁₃ —	81–82 (83) ^b	5 (5) ^b
 —OCH ₂ —	103–104 (113) ^c	7 (13) ^c
 —OCH ₂ —	137–139	6
<i>n</i> -C ₄ H ₉ —OCH ₂ —	74–75 (92–94) ^c	7 (22) ^c
 —OCH ₂ —	77–80	7.5
H ₂ C=CH-CH ₂ -OCH ₂ —	78–79	8

 Source: Takido *et al.* <86S779>.

^a <52JA1342>. ^b <58JCS2062>. ^c <56NKZ198>.


In the tautomerism of allene episulfide with cyclopropanethione, thioallyl intermediate has played a well-known and very important role. But aryl-substituted allene episulfides isomerize allyl conjugated allene episulfides on thermolysis (Scheme 3). The activation energy of thermal isomerization of *t*-butyl-substituted allene episulfide is 24.3 kcal mol⁻¹ (101.7 kJ mol⁻¹) <87TL1787>. Replacing two *t*-butyl groups by more electropositive trimethylsilyl groups resulted in a noticeable decrease of activation energy (19.2 kcal mol⁻¹ (80.4 kJ mol⁻¹)) <87CL2177>. This substituent effect reveals that thioallyl is a biradical with partial ionic character—i.e., with a positive charge on sulfur and a negative charge on allylic parts—which is also supported by MCSCF calculation with STO-3G minimal basis set <87NKK1293>.



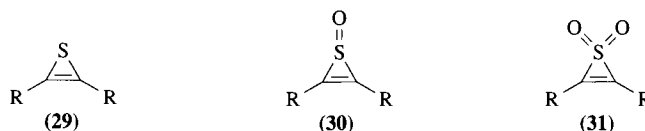
Scheme 3

1.05.5 REACTIVITY OF FULLY CONJUGATED RINGS—THIIRENE, THIIRENE 1-OXIDE, AND THIIRENE 1,1-DIOXIDE

1.05.5.1 Introduction

Thiirene (**29**) is a very unstable species, because it has a 4π electronic system. Only one example, bis(trifluoromethyl)thiirene, has been found (during the period from the mid-1970s to the mid-1990s) to be isolable.

Thiirene oxide systems ((**30**) and (**31**)) are of particular interest due to their being simultaneously both a potentially nonbenzenoid aromatic ($4n + 2$) π and antiaromatic $4n\pi$ Hückel system.

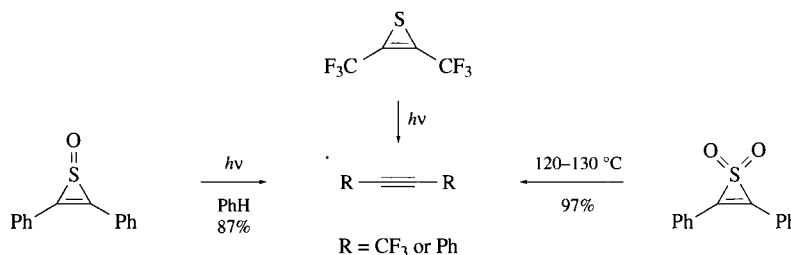


The isolation and the characterization of the first diaryl-substituted derivative (i.e., (**30**), R = Ph) <79JA390> enables one to carry out 'bench scale' chemistry on this class of compounds under ordinary laboratory conditions.

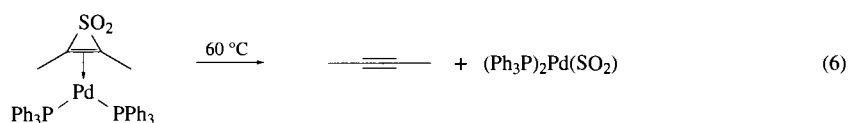
On the basis of the available experimental data as well as extensive theoretical studies of the thiirene 1-oxide system <76AX(B)2171>, the following conclusions concerning its structure, properties and reactivity emerge: (i) Conjugative interactions and/or cyclic π -delocalizations are small compared with closely related systems <78T2983>; (ii) No significant antiaromatic destabilizing effects can be ascribed to the sulfur unshared pair of electrons; (iii) The oxygen moiety in the sulfoxide function is not and probably should not be expected to be highly reactive. Thus, theoretical calculations predict <78T2983> possible spiroconjugative-type <67JA5208, 73AG(E)310> interaction between the $\pi^*_{C=C}$ orbital of the ring and the π orbitals of the SO (which leads to aromatic stabilization of the $\pi^*_{SO}(d_{xy})$ orbital <78T2983>). Experimentally, the ring carbon-carbon double bond of thiirene 1-oxides was shown to be the primary active site towards chemical attack, rather than its sulfoxide function <79JA390>.

1.05.5.2 Thermal and Photochemical Reactions

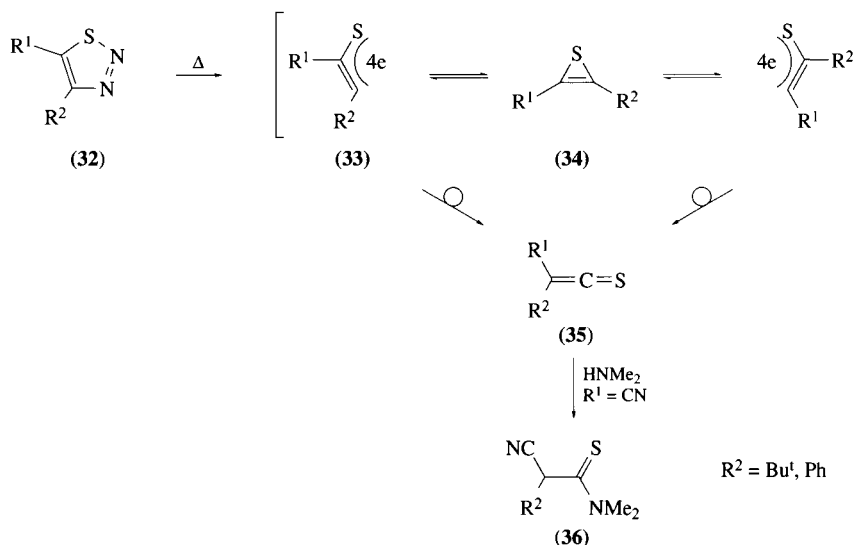
Some thiirene derivatives undergo thermal and photochemical extrusion reactions of the sulfur atom to give alkynes. Most of the relatively few known thiirenes rearrange thermally or photochemically to thioketenes via thioketocarbenes, but 2,3-bis(trifluoromethyl)thiirene photochemically extrudes sulfur to give hexafluoro-2-butyne <80PAC1623>. Photolysis of 2,3-diphenylthiirene 1-oxide gives diphenylacetylene (87%); thermolysis in air gives benzil via a rearrangement. Thiirene 1,1-dioxides readily lose sulfur dioxide (at about 100°C) to give alkynes <79JA390>. Examples of these extrusion reactions for thiirenes are given in Scheme 4. In the thermolysis of 2,3-diarylthiirene 1,1-dioxides the rate of loss of sulfur dioxide correlates best with the sum of σ_p^+ substituents ($\rho = -0.86$) and a stepwise homolytic cleavage of the C—S bonds is inferred <77CC713>. 2,3-Diphenylthiirene 1,1-dioxide decomposes about 10^3 times slower than the saturated *cis*-2,3-diphenyl episulfone. The thermal stability of 2,3-dimethylthiirene 1,1-dioxide is similar to that of the diphenyl derivative. Derivatives of Pd(0), Pt(0) and Ir(I) catalyze the thermal extrusion of SO₂ from thiirene 1,1-dioxides via complexes of the C=C double bond with the transition metals, the latter acting as electron donors to decrease the bond order of the C=C double bonds. As a result, the thermal reactivity of the complex approaches that of the less stable, saturated thiirane dioxides (Equation (6)) <73JOM(57)403>.



Scheme 4



Thiadiazole (32) is a good precursor of thioketene via a thiirene intermediate (34). Flash thermolysis of the thiadiazoles (32) ($\text{R}^1 = \text{Me}, \text{Pr}^i, \text{Bu}^i, \text{Ph}$; $\text{R}^2 = \text{Me}, \text{Pr}^i, \text{Bu}^i, \text{Ph}, \text{Cl}, \text{CN}$) gives thioketenes (35) ($\text{R}^2 = \text{Ph}, \text{Bu}^i$) (Scheme 5). The cyanothiadiazolines ($\text{R}^2 = \text{CN}$) can be detected by the trapping reaction to give thioamides (36). Irregularities in the migratory aptitudes of R^2 in the Wolff-type rearrangement of the primary fragments (33) indicate that thiirenes (34) participate in the formation of the thioketenes (35) <79LA1734>.

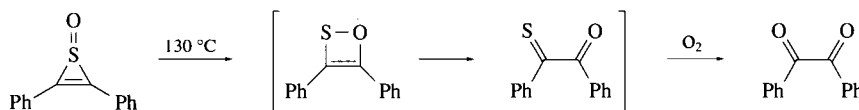


Scheme 5

Thiirenes are photochemically converted to thioketenes or alkynylthiols (Scheme 6) <80PAC1623>. On irradiation with a light of $\lambda = 310 \text{ nm}$, 2-acetyl-3-methylthiirene rearranges to a mixture of acetylmethylthioketene and thioacetylmethylketene, identified by their IR spectra <80NJC703>. 2,3-Diphenylthiirene 1-oxide is isomerized at 130°C to monothiobenzil, which is air-oxidized to benzil (Scheme 7) <79JA390>.



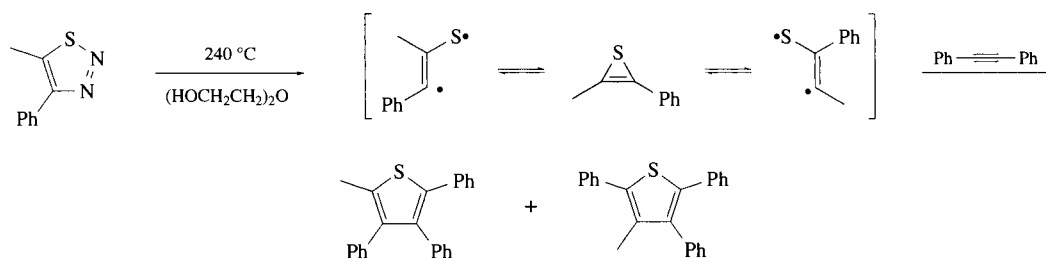
Scheme 6



Scheme 7

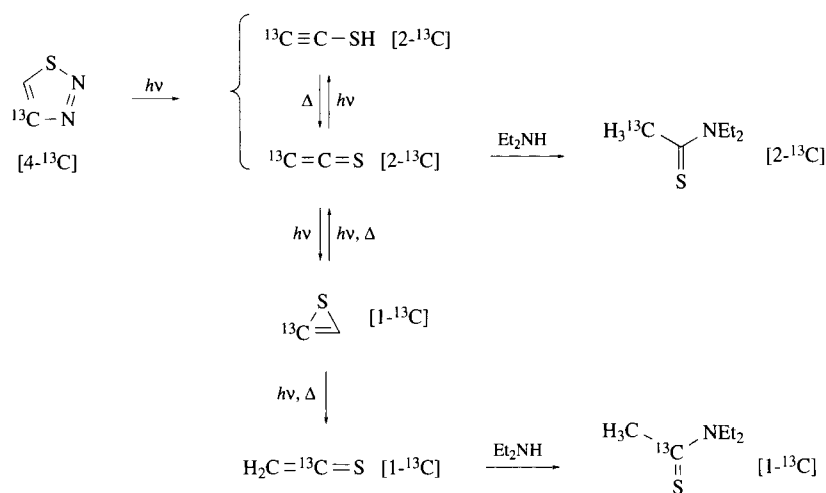
Thiirene intermediates in the photolysis of 1,2,3-thiadiazoles readily undergo ring opening to a diradical which can be trapped by reaction with an alkyne (Scheme 8) <79CB1769>.

A formation of thiirene by secondary photolysis of thioketene, which is generated by photolysis of 1,2,3-thiadiazole, has been reported <92ACS482>. Irradiation of $[4\text{-}^{13}\text{C}]$ -1,2,3-thiadiazole together with diethylamine in an EPA glass (diethyl ether–isopentane–ethanol (5:5:2)) at 77 K gave *N,N*-diethylthioacetamide with 37% carbon randomization in the thioketene (Scheme 9). Experiments with $[4\text{-}^{13}\text{C}]$ -1,2,3-thiadiazole at room temperature demonstrate lack of carbon randomization in the thioacetyl group of the trapping product. Therefore, the reaction mechanism of photolysis of



Scheme 8

the thioketene in solid solution includes the formation of thiirane and rapidly reverts to thioketene, resulting in the observed carbon randomization. This process does not occur in liquid solution owing to the extremely small steady-state concentration of thioketene during photolysis.



Scheme 9

1.05.5.3 Nucleophilic Attack on Sulfur

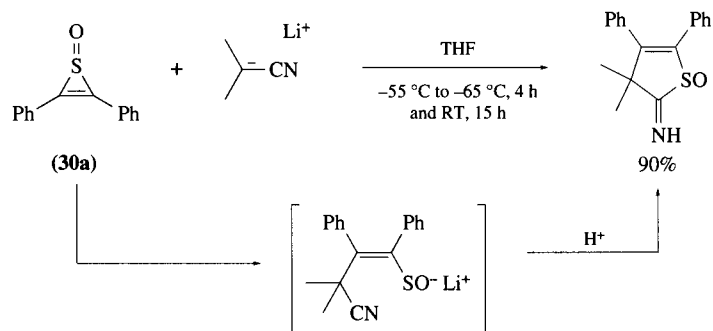
Fluoride ion attacks the sulfur atom in 2,3-diphenylthiirene 1,1-dioxide to give *cis*-1,2-diphenyl-ethylenesulfonyl fluoride (23%) and diphenylacetylene (35%), whereas bromide or iodide ion does not react <80JOC2604>.

1.05.5.4 Nucleophilic Attack on Carbon

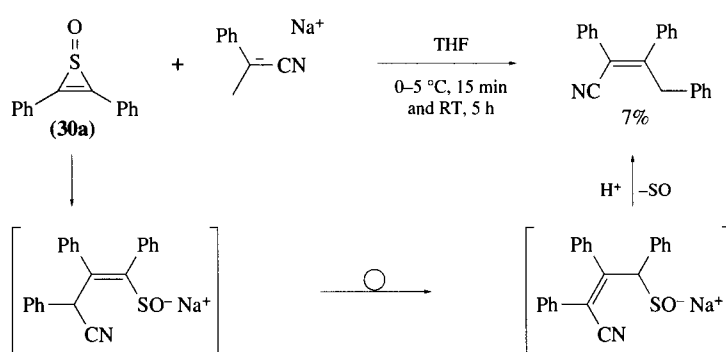
2,3-Diphenylthiirene 1-oxide (**29**) reacts with α-lithioisobutyronitrile to yield 5-imino-4,4-dimethyl-2,3-diphenyl-2-thiolen-1-oxide in 90% yield via nucleophilic attack of the carbanion to the ring carbon of (**29**) followed by recrystallization of the resulting sulfenic acid intermediate (Scheme 10) <87NKK1393>.

When a nitrile bearing an α-hydrogen such as α-sodiobenzyl cyanide reacts, an acyclic product, 2,3,4-triphenyl-2-butenenitrile, is obtained through rearrangement of a sulfenic acid intermediate to an alkene with extrusion of SO (Scheme 11).

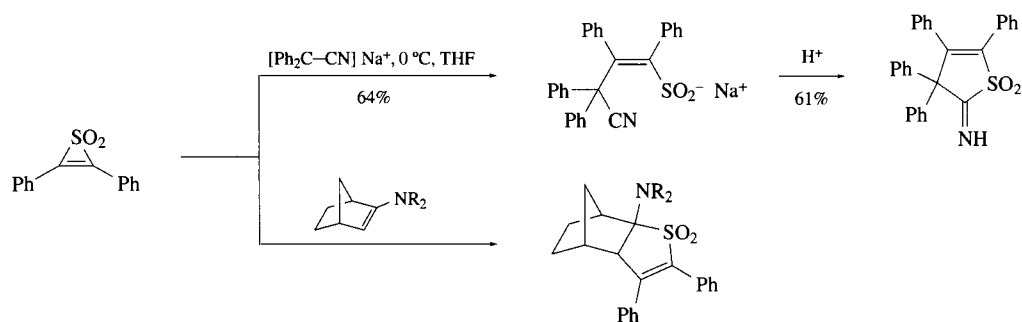
α-Metalated nitriles and enamines attack the carbon atoms of thiirene 1,1-dioxides to give products derived from ring opening followed by recyclization to five-membered cyclic sulfones (Scheme 12). A sulfur ylide of acetophenone reacts with 2,3-diarylthiirene 1,1-dioxides to give four- and six-membered cyclic sulfones by cleavage of the carbon-carbon bond in the thiirene sulfone (Scheme 13). Reaction of a pyridinium ylide of acetophenone is similar, but sulfur dioxide is lost from the intermediate adduct <73BCJ667>. Thiiranium ions may be attacked at carbon or sulfur by the anion of diethyl malonate.



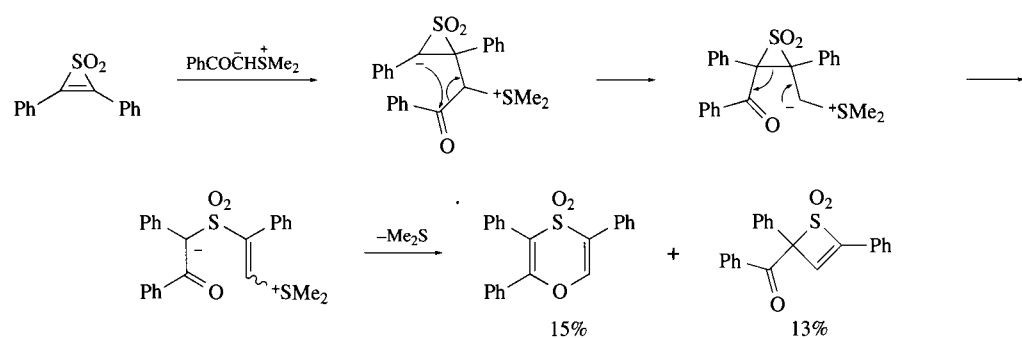
Scheme 10



Scheme 11



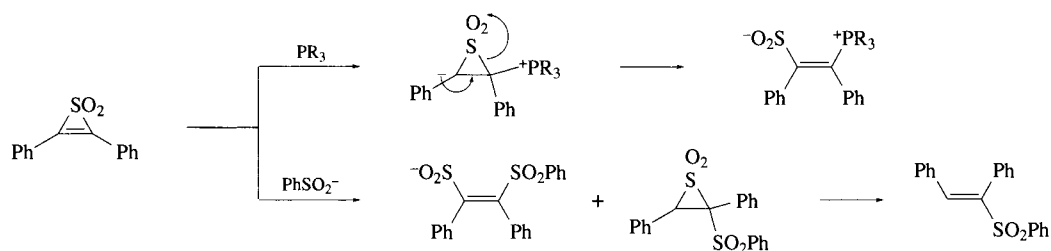
Scheme 12



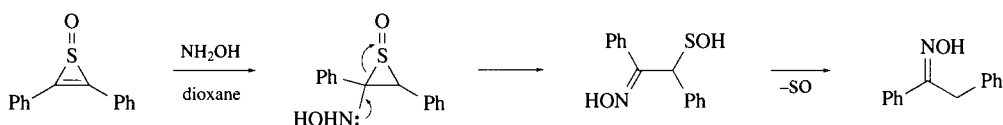
Scheme 13

Addition–elimination reactions occur on treatment of 2,3-diphenylthiirene 1,1-dioxide with benzenesulfonate ion or with trisubstituted phosphines (Scheme 14).

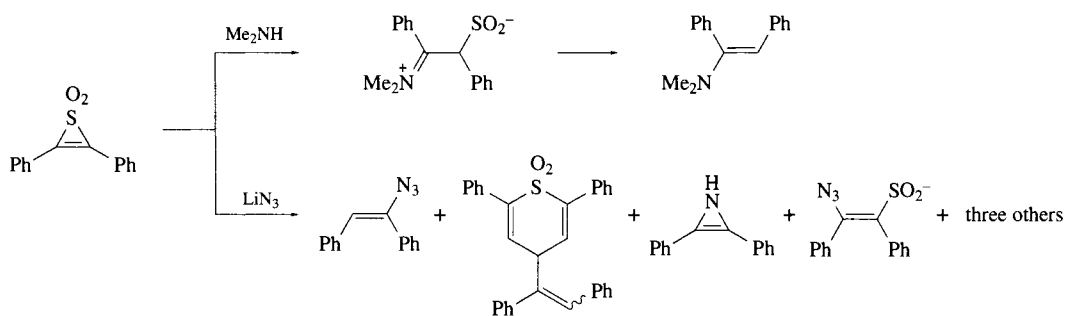
2,3-Diphenylthiirene 1-oxide reacts with hydroxylamine to give the oxime of benzyl phenyl ketone <79JA390>. The reaction probably occurs by addition to the carbon–carbon double bond followed by loss of sulfur monoxide (Scheme 15). Dimethylamine adds to the double bond of 2,3-diphenylthiirene 1,1-dioxide with loss of sulfur dioxide (Scheme 16) <75JOC3189>. Reaction of 2,3-diphenylthiirene 1,1-dioxide with azide ion gives seven products, one of which involves cleavage of the carbon–carbon bond of an intermediate cycloadduct (Scheme 16) <80JOC2604>.



Scheme 14



Scheme 15



Scheme 16

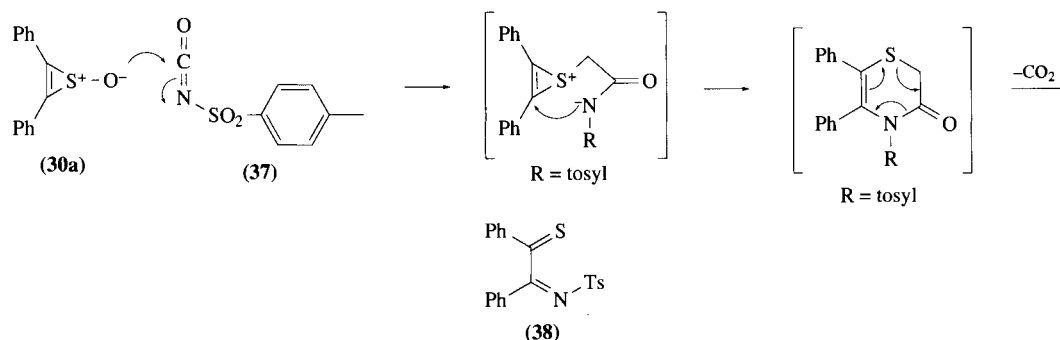
1.05.5.5 Electrophilic Attack on Carbon

The sulfoxide function in the thiirene 1-oxide did not react with the particularly electrophilic <76CRV389, 68AG(E)172> *p*-toluene sulfonyl and chlorosulfonyl isocyanates.

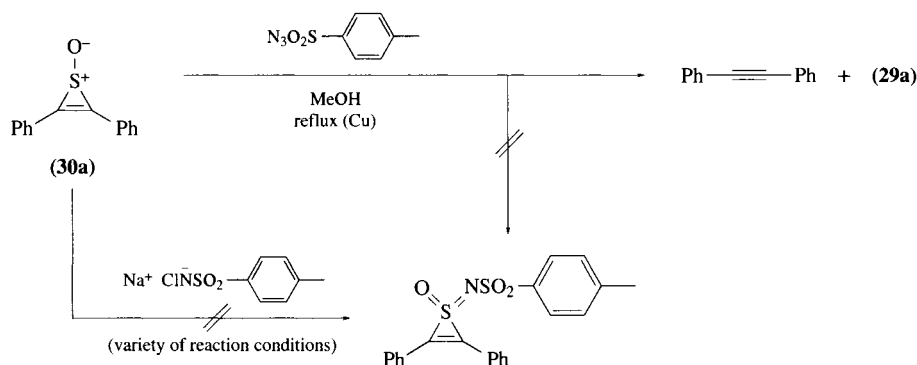
The sulfoxide (**30a**) reacted with isocyanate (**37**) to give the deep-blue, “glassy” *N*-tosylmonothiobenzilimine (**38**) (Scheme 17) <85JOC1107>.

Numerous attempts to prepare the corresponding sulfilimine (or sulfoximine) from the sulfoxide

(30a) by using well-established methods applicable to other sulfoxides <65JA4398, 67JA1950, 75JOC2758, 77CRV409> failed. By using *p*-toluenesulfonyl azide, only diphenyl acetylene could be obtained in 22% yield apart from the recovered starting material (30a) (Scheme 18).



Scheme 17



Scheme 18

1.05.5.6 Reactions Involving Cyclic Transition States—Dipolar Addition to Thiirene 1-Oxides and 1,1-Dioxides

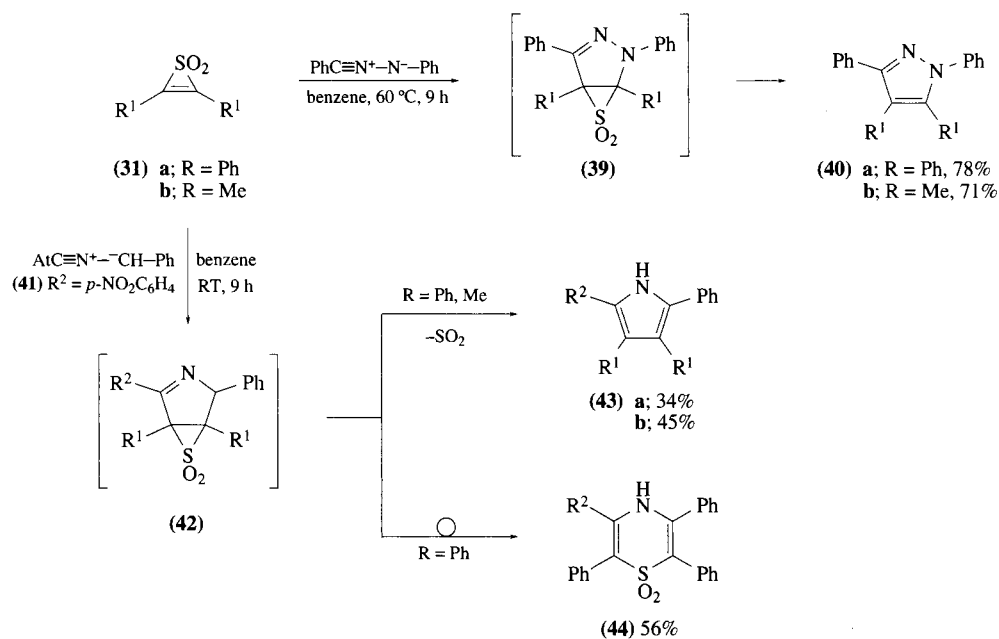
Enophiles such as 1,3-dipoles and dienamines add to the carbon-carbon double bonds of thiirene 1-oxide and 1,1-dioxide. The adducts (39), (42), and (45) lose SO₂ to give, respectively (40), (43) and (46) and related compounds (44) and (47) (Schemes 19 and 20) <80CB1632, 84JOC1300>.

The thiirene 1,1-dioxide (31a) gives two products when it is treated with the nitrile ylide (41) *in situ* generated in benzene at room temperature. The major product is 3-(*p*-nitrophenyl)-2,5,6-triphenyl-1,4-thiazine 1,1-dioxide (44); the minor product is 2-(*p*-nitrophenyl)-3,4,5-triphenylpyrrole (43a) (Scheme 19) <84JOC1300>.

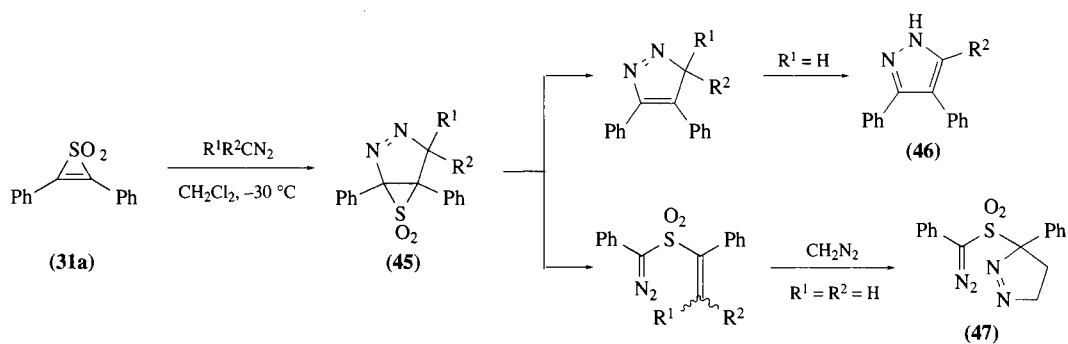
In contrast to the 1,3-dipoles mentioned above, benzonitrile oxide did not react with the thiirene dioxide (31) even in refluxing benzene.

The electron-rich diene, 1-piperidino-2-methyl-1,3-pentadiene (48), reacted with the thiirene 1,1-dioxide (31a) in boiling benzene to afford 61% of the dihydrobenzene derivative (50) via (49) (Scheme 21) <84JOC1300>.

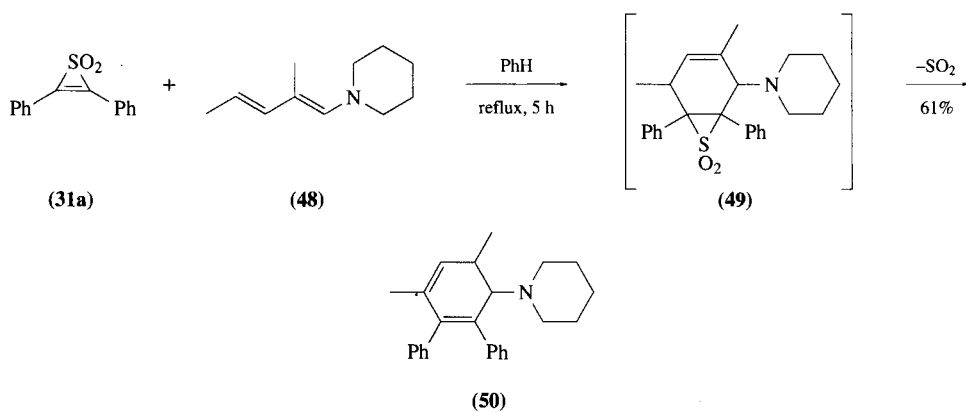
Similarly, mesoionic oxazolones <75CL1153>, 4-methyl-5-phenyl-1,2-dithiolene-3-thione <80JOU395> and pyrylium betaines <72JOC3838> react with diphenylthiirene 1,1-dioxide via intermediary adducts (Scheme 22). Enamines and ynamines add to the double bond of 2,3-diarylthiirene 1,1-dioxides to give acyclic and cyclic sulfones by a thermal, two-step [2 + 2] cycloaddition mechanism. The reaction is faster than that of diphenylcyclopropenone. The initially formed cyclobutane derivative may undergo a bond cleavage leading to an acyclic β -amino- α,β -unsaturated sulfone or may eliminate the amine to give a cyclic sulfone (Scheme 23) <72USP3706769, 74JOC3805>.



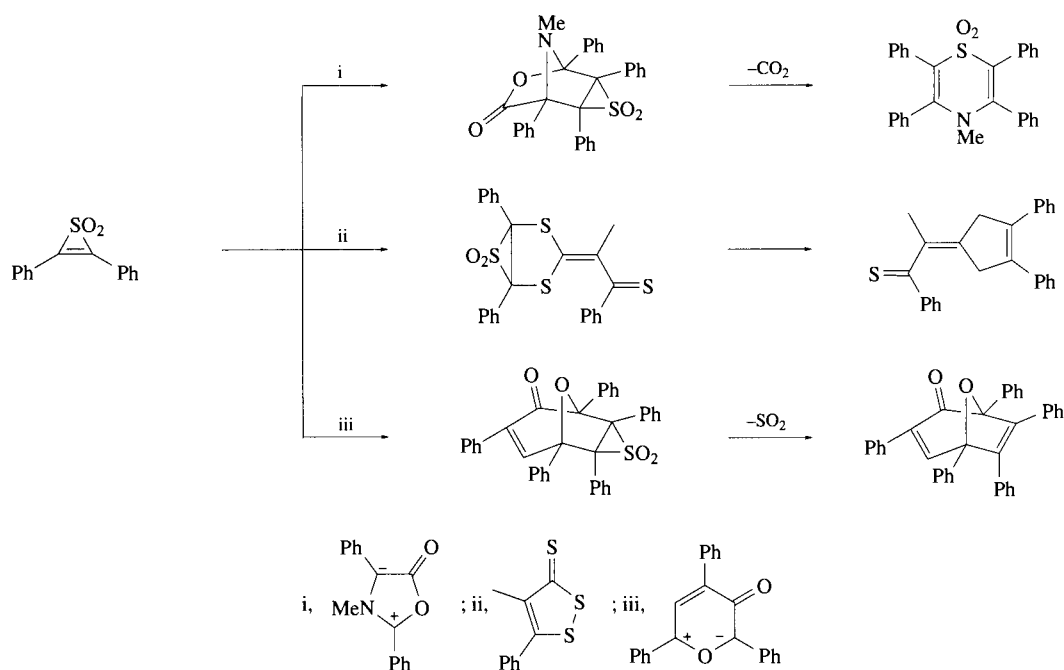
Scheme 19



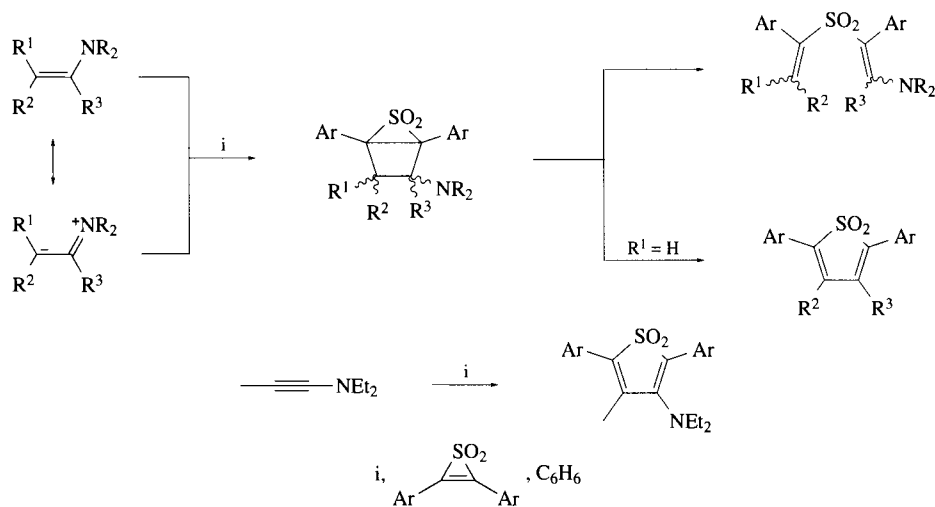
Scheme 20



Scheme 21



Scheme 22



Scheme 23

1.05.6 REACTIVITY OF NONCONJUGATED RINGS—THIIRANE, THIIRANE 1-OXIDE, AND THIIRANE 1,1-DIOXIDE

1.05.6.1 Introduction

Thermal and photochemical reactions of thiiranes, thiirane 1-oxides, and thiirane 1,1-dioxides may result in a cleavage of a carbon-sulfur bond and further extrusion of sulfur, sulfur monoxide or sulfur dioxide, respectively.

Electrophilic reagents attack the sulfur atom of the sulfides. Nucleophiles attack at sulfur or carbon to cleave the rings.

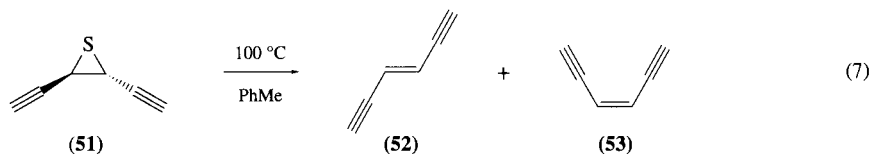
Most of the fundamental reactions of thiiranes, thiirane 1-oxides, and thiirane 1,1-dioxides are

discussed in detail in the first edition of *Comprehensive Heterocyclic Chemistry*, <84CHEC-I(7)131>. This section mainly contains a survey of thiiranes, thiirane 1-oxides, and thiirane 1,1-dioxides during the 10 years from 1984 to 1994.

1.05.6.2 Thermal and Photochemical Reactions

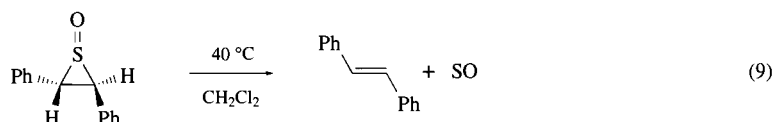
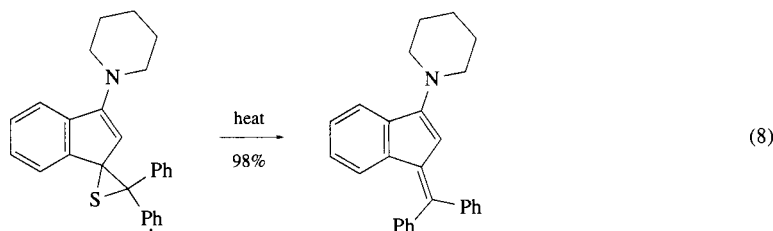
Thermolysis of thiiranes causes extrusion of elemental sulfur, with the formation of alkenes <64HC(19/1)576, 66CRV297, 76RCR25>; however, the desulfurization mechanism by thermolysis is not clear at present. It cannot be explained by a simple cheletropic extrusion, but involving a more complex reaction scheme <85TL2789>.

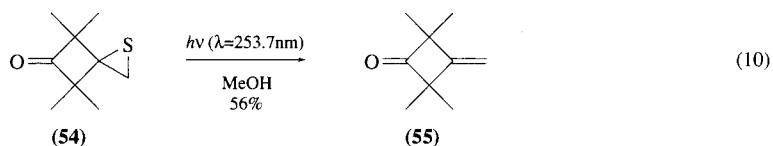
Other reactions may occur with cleavage of only one C—S bond, leading to products of rearrangement, isomerization, or polymerization. Thiiranes which are highly substituted or which are substituted with groups, which can stabilize free radicals such as phenyl, vinyl, acetyl, or chloro, are more prone to lose sulfur. Thermolysis at 100 °C of *trans*-2,3-diethynylthiirane (**51**) gives a good yield of *trans* alkenes (**52**) with only a small amount of the *cis* alkene (**53**) (Equation (7)). The *cis* diethynylthiirane gives *cis* alkene (**53**). At 395 °C (gas phase) the stereospecificity is lowered, a 4 : 3 ratio of (**52**) to (**53**) being obtained from the *trans* thiirane and a 1 : 2 ratio from the *cis* thiirane <73JA7538>. The retention of stereochemistry may be explained by a simple cheletropic extrusion of a sulfur atom in which both C—S bonds break simultaneously. In cases of nonstereospecific reactions, a mechanism involving stepwise cleavage of C—S bonds is probable; and the kinetic study on the desulfurization of (**51**) indicates a bimolecular process may occur under some conditions. The thermal decomposition of thiirane to alkene is not a first order reaction, and, therefore, is not a simple cheletropic process <85TL2789>. A more complex reaction scheme is involved.



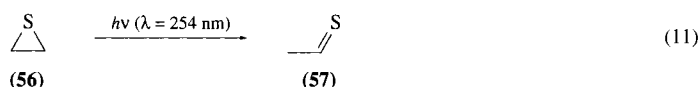
On the other hand, a low-pressure (10^{-2} Pa) pyrolysis technique has been used to study the thermal decomposition of thiirane. Thiirane decomposed above 900 K to yield ethylene stoichiometrically. The estimation of thermodynamic properties of the 2-thioethyl biradical indicated that the obtained activation energy is too low to form the biradical as an intermediate. The unusually low activation energy is characteristic to thiirane. That is not observed in other cyclic thioethers such as thiolane <87NKK1377>. An alternative mechanism in which thiirane decomposes through a triplet state rather than biradical formation is as mentioned above <68JA7164>. The extrusion reaction in other favorable cases, in which competing reactions are minimized, can give good yields of alkenes (Equations (8) and (9)) <74CHE623>.

Irradiation ($\lambda = 253.7$ nm) of thiirane (**54**) gives alkene (**55**) by extrusion of sulfur (Equation (10)).

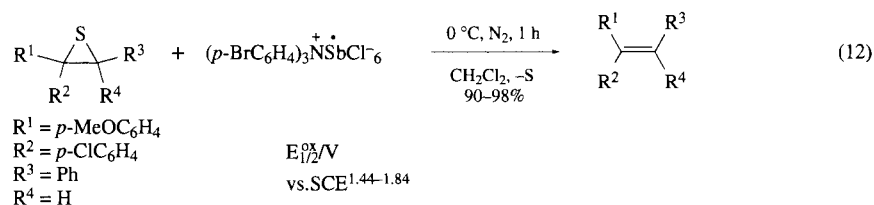




Matrix irradiation ($\lambda = 254 \text{ nm}$) of thiirane (**56**) gives thioacetaldehyde (**57**) (Equation (11)) <91CB2609>. The 193 nm photodissociation of thiirane is carried out using the time-of-flight crossed laser-molecular beam technique. Following excitation of the transition with $4p \leftarrow n$ Rydberg character at 192.2 nm, the dominant primary decay ($\sim 80\%$) is hydrogen abstraction yielding the fragments $\text{H} + \text{SC}_2\text{H}_3$. In competition with this decay are two primary dissociation processes about equally efficient ($\sim 10\%$ each), which form $\text{S} + \text{C}_2\text{H}_4$ and $\text{HS} + \text{C}_2\text{H}_3$, respectively. Furthermore, the same 15 ns photolysis pulse, which induces the three primary processes, also gives rise to three secondary dissociation reactions identified as $\text{SC}_2\text{H}_3 \rightarrow \text{S} + \text{C}_2\text{H}_3$, $\text{C}_2\text{H}_3 \rightarrow \text{H} + \text{C}_2\text{H}_2$ and $\text{HS} \rightarrow \text{H} + \text{S}$ <92JPC4470>.



Upon irradiation of the electron donor-acceptor complexes of 2,2,3,3-tetraarylthiiranes and tetracyanoethene (TCNE), [3 + 2] cycloadditions occurred efficiently without the desulfurization of thiiranes <89CC557>. When thiirane (**58**) and 5 equiv. of fumaronitrile (FN) are irradiated with light of wavelength longer than 360 nm in CH_2Cl_2 , no photoreaction takes place, whereas irradiation through a Pyrex filter ($> 290 \text{ nm}$), with FN, results in desulfurization to give the corresponding alkene instead of a [3 + 2] cycloadduct (Scheme 24). The first step of the reaction of thiiranes with TCNE may be the formation of radical ion pairs initiated by the photoexcitation of EDA complexes (Scheme 24). After selective C—C bond cleavage of thiirane, products are formed via thiocarbonyl ylide. This reaction is similar to the oxirane-TCNE systems <86CC1577, 86JA2755, 87JA2780>. Aryl-substituted alkenes are obtained from the corresponding thiiranes in high yields under mild conditions by using a catalytic amount of tris (*p*-bromophenyl)aminium hexachloroantimonate as a single electron transfer oxidant (Equation (12)) <89TL4129>. The reaction of Cl atoms with ethylene sulfide, $\text{C}_2\text{H}_4\text{S}$, has been used as a source of SCl radicals in a discharge-flow system with detection of free-radical and molecular species by molecular-beam-sampling mass spectrometry <88JCS(F2)67>.

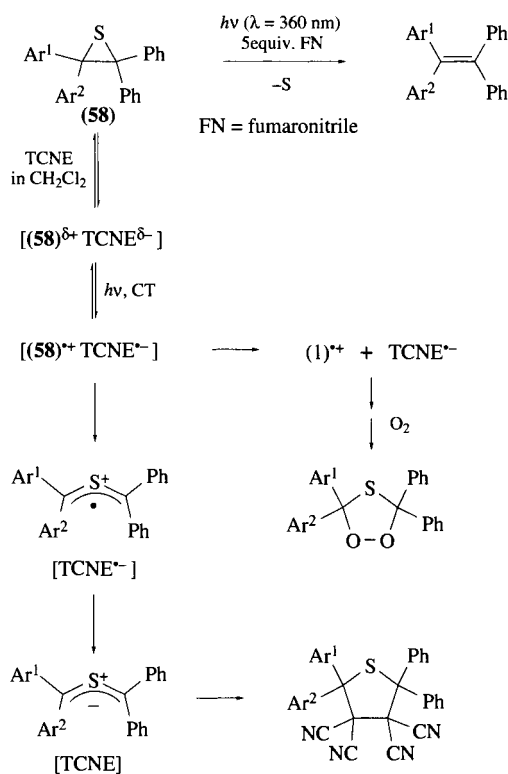


Thioepichlorohydrine reacted with Ce(IV) oxidants in different alcohols under refluxing conditions to produce bis(2-chloro-2'-alkoxy-isopropyl)disulfides in 40–70% yields (Scheme 25). By comparison of the results obtained from the reactions of thiiranes with Ce(IV) oxidants, the order of reactivity of these reagents was found to be as follows: ceric ammonium nitrate > ceric triethyl ammonium nitrate > ceric pyridinium nitrate and ceric sulphate. The assumption that the radical cations (**59**) and (**60**) are intermediates may account for the mechanism of this reaction <91T149>.

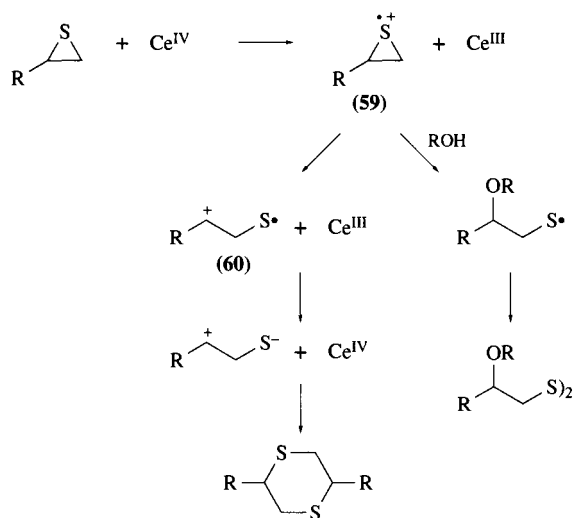
1.05.6.3 Electrophilic Attack on Sulfur

1.05.6.3.1 Lewis acids

Treatment of 2-methylthiirane (**61**) with TMS-CN (**62**) in the presence of AlCl_3 as Lewis acid catalyst resulted in a regioselective opening of the heterocyclic ring, giving rise to 2-trimethylsilylthiopropionitrile (**63**) (Scheme 26) <83TL2311>. Trimethylsilylthioisothiocyanate (**64**) was obtained together with propylene derived from desulfurization of the cyclic thioether. A similar behavior is



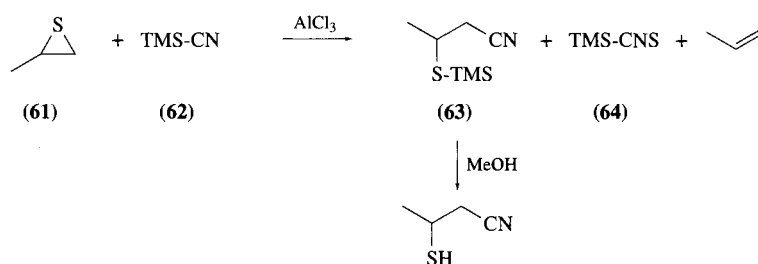
Scheme 24



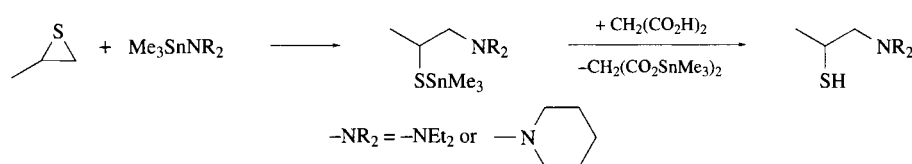
Scheme 25

observed in the reaction of the thiirane ring with different organosilicon compounds such as TMS-X (X = Br, I, NEt₂, SPh, N₃), all with AlCl₃, and although regioselective ring opening of (61) failed with AlCl₃ and aminosilane, the insertion of an amino group is possible using Me₃SnNR₂ without catalyst (Scheme 27) <83TL2311>.

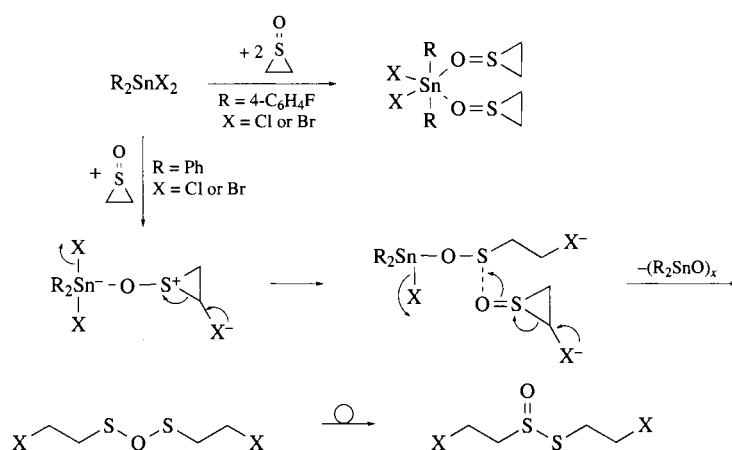
Thiirane 1-oxide reacted with (4-FC₆H₄)₂SnCl₂ to yield the corresponding 2:1 adduct in 96% yield. Dichlorodiphenylstannane reacted with thiirane 1-oxide in the presence of tetraethylammonium chloride to give a polymer (Ph₂SnO)_x and the thiolsulfinate in 83% yield (Scheme 28). In the case of dibromodiphenylstannane, this reaction proceeded without ammonium salts to give the corresponding thiolsulfinate in 94% yield <90JOM(396)C4>.



Scheme 26



Scheme 27



Scheme 28

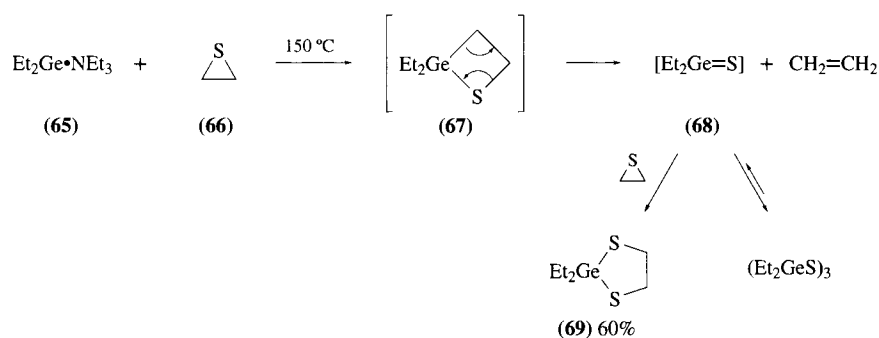
1.05.6.3.2 Carbenes and related species

Treatment of several thiiranes with substituted carbene gives the corresponding alkenes in good yields. The mechanism is considered to involve electrophilic attack by carbene on the sulfur atom <75JA2553>.

Condensation of complexed dialkylgermylenes $\text{R}_2\text{Ge} \cdot \text{NEt}_3$ (**65**) with thiirane (**66**) gave the corresponding thiagermacyclobutane (**67**) by insertion and ring expansion (Scheme 29). This thermally unstable heterocycle (**67**) undergoes β -elimination to give a transient dialkylgermanethione (**68**), which can be trapped by another thiirane to give 1,3,2-dithiagermolane (**69**) or undergo trimerization <83JOM(243)281>.

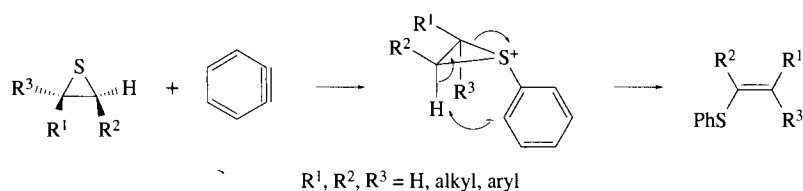
1.05.6.3.3 Benzyne

A series of thiiranes react with benzyne to provide an efficient synthesis of phenyl vinyl sulfides. The reaction is stereospecific, thus producing *cis*-(phenylthio)stilbene from *cis*-2,3-diphenylthiirane and *trans*-(phenylthio)stilbene from *trans*-2,3-diphenylthiirane (Scheme 30) <84TL2679>. 2-Carboxybenzenediazonium chloride and benzenediazonium-2-carboxylate provide a clean source of benzyne. A mixture of 2-carboxybenzenediazonium chloride (a source of benzyne), a thiirane, and



Scheme 29

propyleneoxide (hydrogen chloride scavenger) is heated in 1,2-dichloroethane at reflux temperature until all the benzyne precursor disappeared to yield the corresponding vinyl sulfide. Results are summarized in Table 33.



Scheme 30

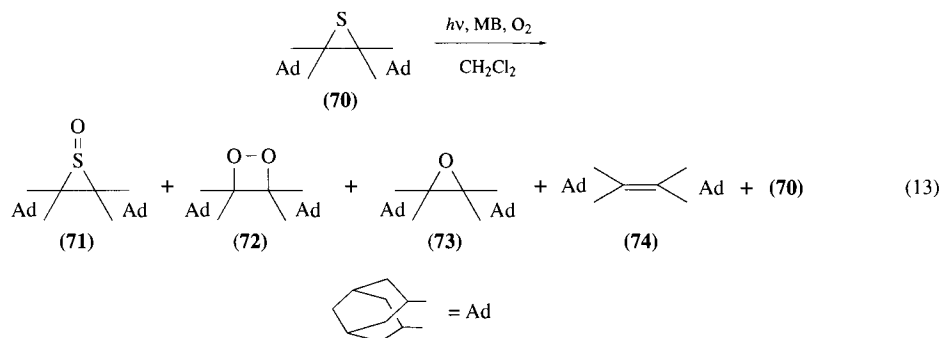
Table 33 Yields of vinylsulfides (in Scheme 30).

(a): $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$	74%
(b): $\text{R}^1 = \text{Me}, \text{R}^2 = \text{R}^3 = \text{H}$	77% (<i>cis</i> + <i>trans</i>)
	58%
(c): $\text{R}^1 = \text{Ph}, \text{R}^2 = \text{R}^3 = \text{H}$	15%
(d): $\text{R}^1 = \text{C}_6\text{H}_{13}, \text{R}^2 = \text{R}^3 = \text{H}$	90% (<i>cis</i> + <i>trans</i>)
(e): $\text{R}^1 = \text{R}^3 = \text{Me}, \text{R}^2 = \text{H}$	79%
(f): $\text{R}^1 = \text{R}^2 = \text{Ph}, \text{R}^3 = \text{H}$	79%
(g): $\text{R}^1 = \text{H}, \text{R}^2 = \text{R}^3 = \text{Ph}$	71%

1.05.6.3.4 Singlet oxygen

Photosensitized oxygenation of thiirane (70) (3.3×10^{-2} M) as carried out at 15°C for 6 h in methylene chloride in the presence of methylene blue (MB, 1.1×10^{-3} M) as a sensitizer and with

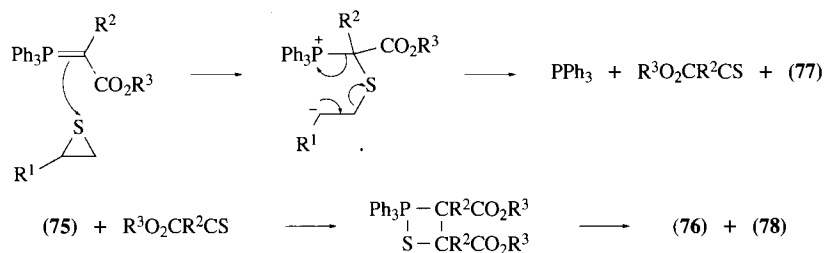
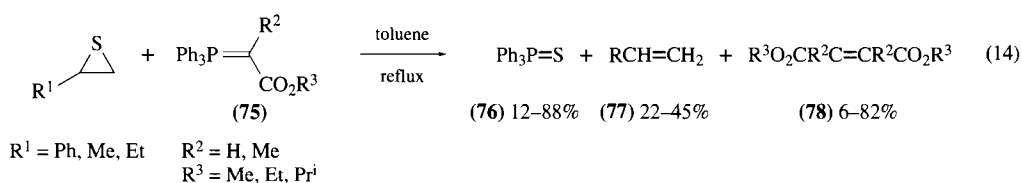
the use of two 500 W halogen lamps. When the reaction mixture was chromatographed on silica gel, the corresponding thiirane oxide (**71**), biadamantylidene dioxetane (**72**) and biadamantylidene oxirane (**73**) with a trace amount of biadamantylidene (**74**) were obtained together with unreacted thiirane (**70**) (Equation (13)) <86TL4473>. According to several control experiments, this reaction incorporates singlet oxygen. This reaction depends on temperature or solvent.



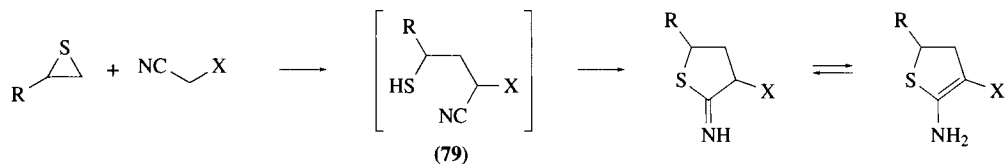
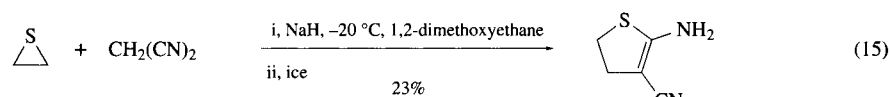
Regioselective opening of the thiirane ring occurs spontaneously by the action of group 14 organometallics such as Me_3SnNR_2 or under the catalytic action of AlCl_3 with TMS-CN , affording difunctional thiols <83TL2311>.

1.05.6.4 Nucleophilic Attack on Sulfur

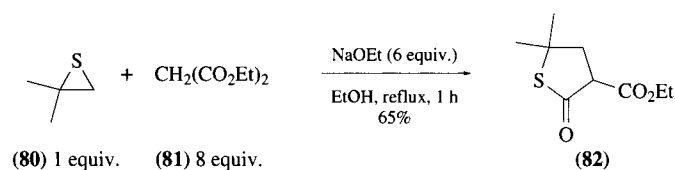
Stable Wittig reagents react with episulfides to afford corresponding alkenes (Equation (14)). This reaction can proceed via a thiocarbonyl intermediate (Scheme 31) <87CL357>. A thiirane reacted with a malonodinitrile gives 2-amino-4,5-dihydro-3-thiophen nitrile <85CB4437> (Equation (15)). Reactions of thiiranes with ethyl cyanoacetate <48JA217> or malononitrile <74JAP13164> in the presence of a base catalyst gave dihydrothiophene derivatives. These reactions are considered to proceed via thiol (**79**) and a following ring closure by the reaction of (**79**) with a cyano group (Scheme 32). This ring closure is considered to inhibit the polymerization of (**79**) with thiirane. The reaction of 2,2-dimethylthiirane (**80**) with diethyl malonate (**81**) in the presence of sodium ethoxide or sodium hydride gave 3-ethoxycarbonyl-5,5-dimethyldihydro-2-(3H)-thiophenone (**82**) and a polymer (Scheme 33) <86BCJ2321>. Reactions of thiirane, 2-methylthiirane, 2-butylthiirane, 2-hexylthiirane, 1,2-epithiocyclohexane, and 2-phenylthiirane with (**81**) also gave the corresponding dihydro-2(3H)-thiophenone derivatives. The reaction of 2,2-dimethylthiirane with carbon disulfide in the presence of triethylamine is accelerated under high pressure ($\approx 8000 \text{ kg cm}^{-2}$) to give 4,4-dimethyl-1,3-dithiolane-2-thione nearly quantitatively (Equation (16)) <87BCJ727>. Thiirane reacts with germanethione generated from cyclogermathiane to give a germaheterocycle (**69**) in 90% yield (Scheme 34) <83JOM(246)227>.



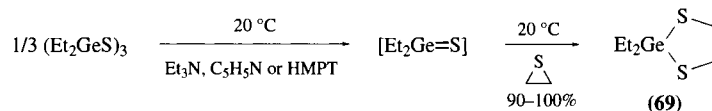
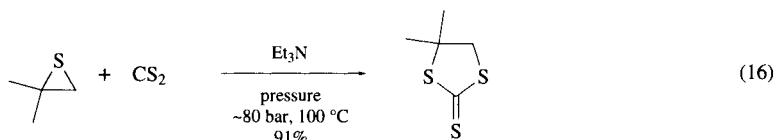
Scheme 31



Scheme 32

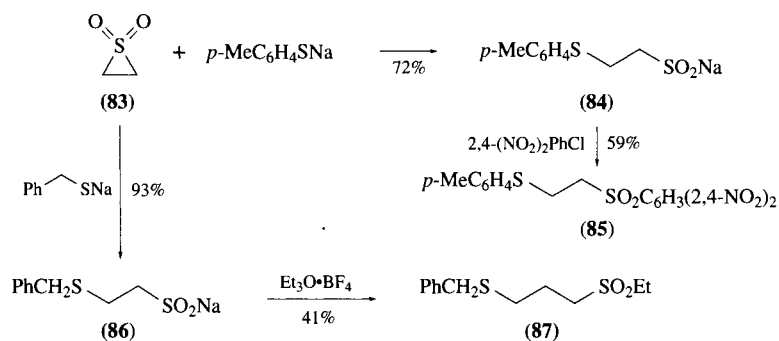


Scheme 33



Scheme 34

Use of thiirane 1,1-dioxide affords a useful synthesis of ethanesulfonates with the following functions in the 2-position: thiol, disulfide, trisulfide, thiosulfate, thiosulfonate, and phosphorothioate. Reaction of episulfone (**83**) with sodium *p*-toluenethiolate gives the sulfinate (**84**), which can be converted to the sulfone (**85**) (Scheme 35). Similarly, (**83**) is converted to the benzyl counterpart (**86**), which is desired for possible debenzoylation to the thiol; since the salt (**86**) is difficult to purify, it is converted to the ethyl ester (**87**) <86JOC5235>.



Scheme 35

Scheme 36

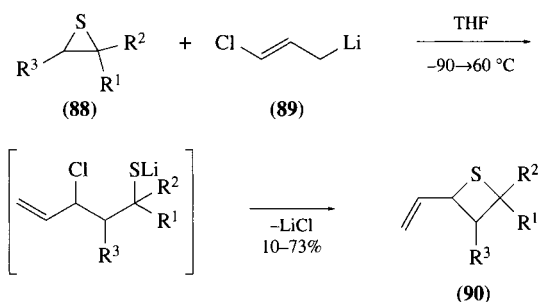
Table 34 $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ catalyzed desulfurization of thiiranes.

<i>Thiirane</i>	<i>Product</i>	<i>Yield</i> (%)
2-phenylthiirane	stylene	91
<i>cis</i> -2,3-diphenylthiirane	<i>cis</i> -stilbene	71
<i>trans</i> -2,3-diphenylthiirane	<i>trans</i> -stilbene	99
<i>trans</i> -2-methyl-3-phenylthiirane	<i>trans</i> - β -methylstyrene	64
<i>trans</i> -2,3-di-n-butylthiirane	<i>trans</i> -5-decene	66
ethyl <i>trans</i> -2-methylthiirane carboxylate	ethyl <i>trans</i> -crotonate	97
$\begin{array}{c} \text{p-CH}_3\text{OC}_6\text{H}_4\text{OCH}_2\text{CH} \text{---} \text{CH}_2 \\ \quad \quad \quad \diagdown \quad \diagup \\ \quad \quad \quad \text{S} \end{array}$	$\text{p-CH}_3\text{OC}_6\text{H}_4\text{OCH}_2\text{CH}=\text{CH}_2$	98

Reaction conditions: CO, C₆H₆, 28 bar, RT, 2 mol% [Rh(CO)₂Cl]₂.

1.05.6.5 Nucleophilic Attack on Carbon

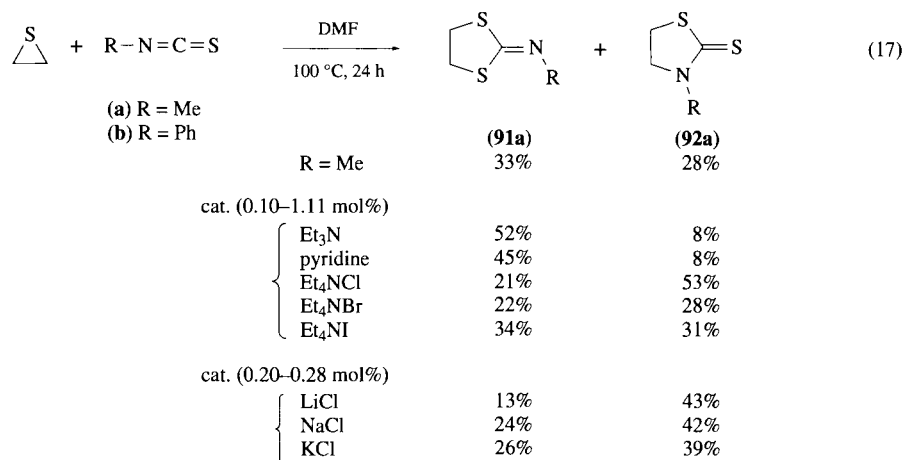
3-Chloroalkyllithium (**89**) reacts with alkyl-substituted thiiranes (**88**) to give pure 2-vinylthietanes (**90**) in good yields (Scheme 37 and Table 35) <85S1069>. The reaction of thiirane with methylisothiocyanate in DMF gives *N*-methyl-1,3-thiazolidine-2-thione (**92**) (Equation (17)). The ratio of (**91**) to (**92**) is remarkably increased by the addition of tertiary amine such as triethylamine, and decreased by addition of salts such as tetraethylammonium bromide or lithium chloride. In the reaction of thiirane with phenyl isothiocyanate the main product is *N*-phenyl-1,3-dithiolane-2-imine, even using lithium chloride catalyst at 120°C, though 3-phenyl-1,3-thiazolidine-2-thione is formed in 12% yield. Reaction of substituted thiiranes such as methylthiirane with methyl isothiocyanate gives 1,3-dithiolane-2-thiones (**95**) in addition to the compounds corresponding to (**93**) and (**94**) (Scheme 38). The mechanism is presumed as follows: the first step is the formation of 1,3-dithiolanes, followed by the reaction of 1,3-dithiolanes with thiirane to give 1,3-thiazolidene-2-thiones (Schemes 38 and 39).



Scheme 37

Table 35 Yields of thietanes (90).

(88), (90)	R ¹	R ²	Yield of (90) (%)
(a)	H	C ₂ H ₅	73
(b)	H	—CH ₂ —O—C ₂ H ₅	48
(c)	H	—CH— <i>n</i> -C ₄ H ₉	21 ^a
(d)	CH ₃	CH ₃	56
(e)	<i>n</i> -C ₃ H ₇	<i>n</i> -C ₃ H ₇	63
(f)	—CH ₂ —CH=CH ₂	—CH ₂ —CH=CH ₂	67
(g)	H	—(CH ₂) ₄ —	28 ^a
(h)	CH ₃	CH ₃	10 ^a

^aIn these cases, 65–80% of thiirane (88) is recovered unchanged.

1.05.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS—ALLENE EPISULFIDES, THIIRANONES, AND THIIRANIMINES

1.05.7.1 Introduction

Considerable interest has long been focused on the synthesis of three-membered sulfur-containing ring systems bearing exocyclic double bonds: i.e., allene episulfides, thiiranones and thiiranimines.

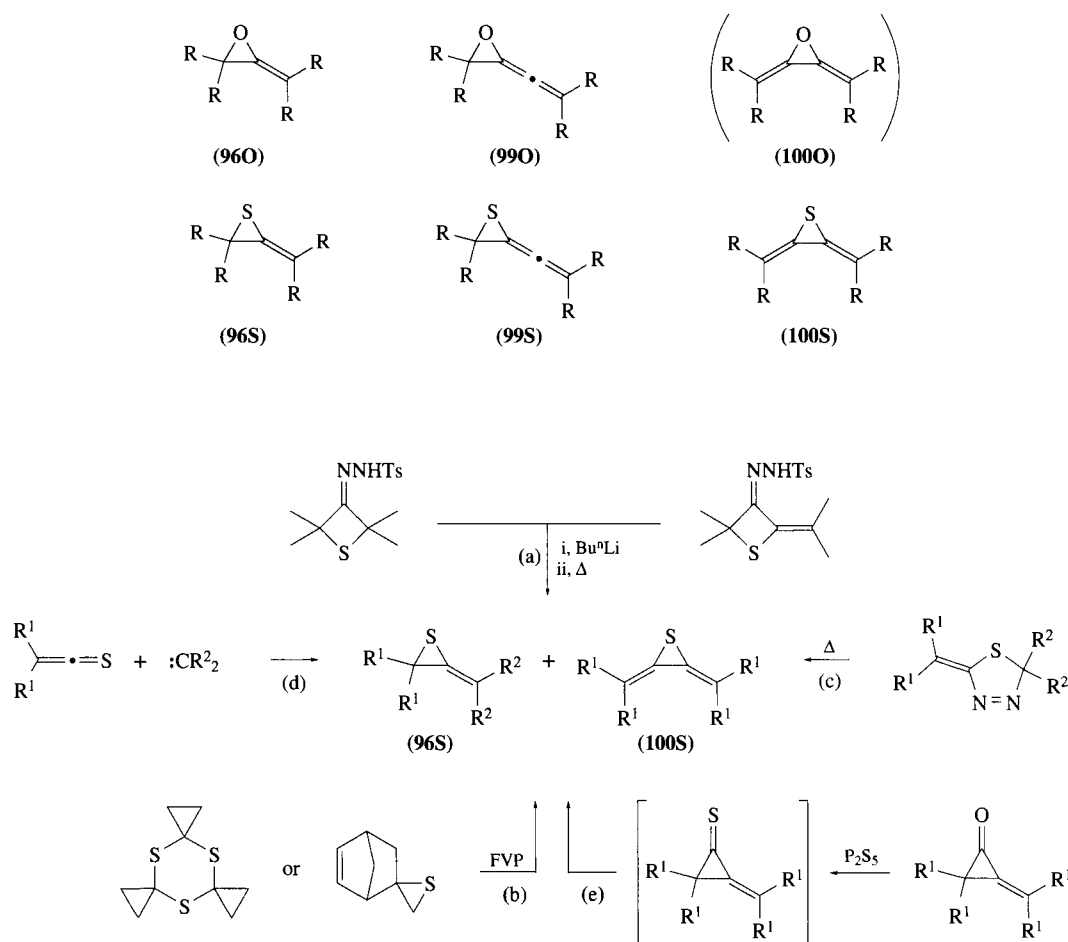
1.05.7.1.1 Allene episulfide (methylene thiirane)

Methylenecyclopropane (**96CH₂**), allene oxides (**96O**) and allene episulfide (**96S**) are shown in Scheme 40. These systems undergo interconversion (**96**)–(**97**)–(**98**) and have always intrigued chemists from both theoretical and synthetic points of view. Trimethylenemethane (**97CH₂**), oxyallyl


$$\begin{array}{ccccc}
 \text{X} & & \left[\begin{array}{c} \text{X}^* \\ \text{C} \\ \text{C} \end{array} \right] & & \text{X} \\
 \diagup \quad \diagdown & \xrightleftharpoons{\Delta \text{ or } h\nu} & & \xrightleftharpoons{\Delta \text{ or } h\nu} & \diagup \quad \diagdown \\
 \text{(96X)} & & \text{(97X)} & & \text{(98X)} \\
 \text{X = CH}_2, \text{O, S} & & * = \text{radical or ions} & &
 \end{array}$$

Scheme 40

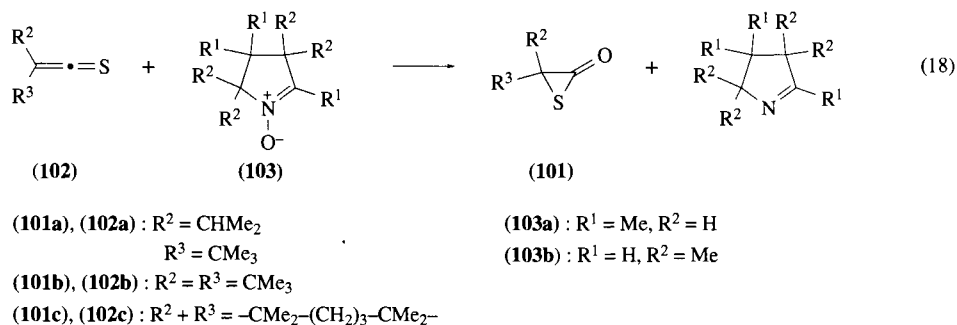
The discovery of this carbene route laid Ando's foundation for the project aimed at developing the chemistry of strained alkylidene thiirane, which involves not only (**96S**) but also (**99S**) and (**100S**). In contrast to (**99S**) and (**100S**), oxygen analog (**99O**) is only observed by NMR at -50°C , and (**100O**) is unknown so far. Meanwhile, there have been no attempts on the direct sulfurization of cumulene and cyclopropanone, which is expected to provide a new synthetic route for alkylidene thiirane. Although thionation of cyclopropanone (route e) yielded alkylidene thiirane $\langle 87\text{TL1803} \rangle$, the direct sulfurization of 1,2,3-butatrienes resulted in a novel formation of 6,7-bis(alkylidene)-1,2,3,4,5-pentathiepanes $\langle 88\text{TL1935} \rangle$.



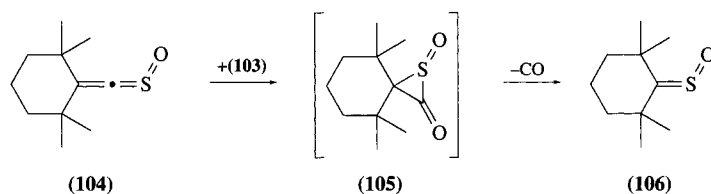
Scheme 41

1.05.7.1.2 Thiiranone (α -thiolactones)

α -Thiolactones (thiiranones) (**101**) were first isolated by the oxidation of thioketenes (**102**) bearing bulky substituents with nitrones of the 1-pyrroline 1-oxide type (**103**) (Equation (18)) <77AG(E)722>. Oxidation of stable thioketenes by peracid and hydrogen peroxide gives only thioketene *S*-oxides without α -thiolactones (thiiranones) <68JOC2738, 77TL3457>. The reaction of the thioketene *S*-oxide (**104**) with (**103**) gives the thioketone *S*-oxide (**106**) via the α -thiolactone *S*-oxide (thiiranone *S*-oxide) (**105**) (Scheme 42) <77AG(E)722>.

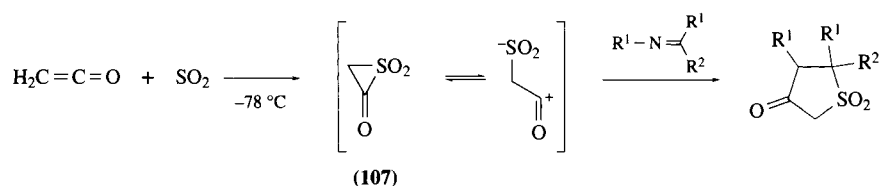


On the other hand, α -thiolactones *S,S*-dioxide is formed *in situ* when ketene is dissolved in liquid SO_2 at -78°C , and it can be trapped with imines (Scheme 43) <76JOC3925>. This supposed



Scheme 42

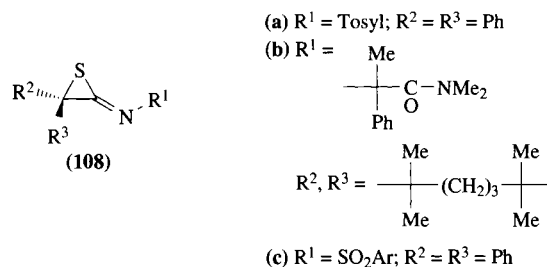
intermediate (107) undergoes sp^2C-S bond cleavage as expected, rather than sp^3C-S bond cleavage.



Scheme 43

1.05.7.1.3 Thiiranimine

Stable thiiranimines have been isolated $\langle 78AG(E)195, 79TL1819, 82AG(E)694 \rangle$, and in two specific cases (108a) and (108b) these products have been crystallographically characterized to give their experimental geometries $\langle 78AG(E)195, 82AG(E)694 \rangle$.



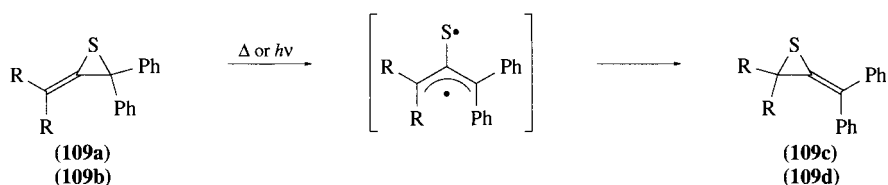
The electron-withdrawing imine function might be expected to induce electrophilic character for the sulfur atom. However, the observed reactions of the thiiranimines are only partly compatible with this view. In order to rationalize the observed reactivity pattern, it may be necessary to postulate the existence of a noncyclic isomer $\langle 79TL1819 \rangle$, and it might be interesting to investigate the two alternative ring systems characterized by an exocyclic $C=C$ or $C=S$ bond.

1.05.7.2 Thermal and Photochemical Reactions

1.05.7.2.1 Allene episulfide

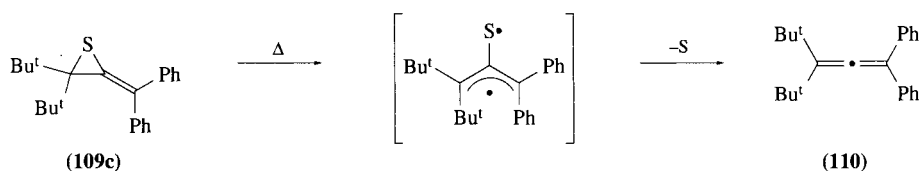
In the tautomerism of allene episulfide with cyclopropanethione, thioallyl intermediate has played well-fitting and very important roles. Thermal isomerization reactions of different types of substituted allene episulfides ((109a) and (109b)) were investigated by Ando and co-workers (Scheme 44) $\langle 87CL2177 \rangle$. Since the thermolysis of (109c) gave only the corresponding allene (110) without any isomerization backward into the original allene episulfide (109a), the isomerization between (109a) and (109c) was an irreversible process (Scheme 45). Replacing of two *t*-butyl groups by more electropositive trimethylsilyl groups resulted in a noticeable decrease of activation energy. This substituent effect reveals that thioallyl is a biradical with partial ionic character—i.e., with a positive

charge on sulfur and a negative charge on the allylic part—which is also supported by MCSCF calculation. Photochemically, both 1,2,3-butatriene 1-episulfides (**111a–d**) and 2-episulfides (**112a–d**) were easily desulfurized into the corresponding 1,2,3-butatriene (**113a–d**) (Scheme 46). On the other hand, thermal isomerization was found between the two types of 1,2,3-butatriene episulfides, such as (**111d**) and (**112d**) <88TL5161>. Heating of (**111d**) or (**112d**) resulted in the same equilibrated mixture, the equilibrium ratio of (**112d**) to (**111d**) being 1.52 (90°C) and 1.16 (120°C), respectively. This thermal instability of (**112d**) might be attributable to the increasing steric repulsion of inner methyl groups on the cisoid butadiene unit of (**112d**), caused by augmentative molecular vibration at high temperature. The thermal interconversion between (**111d**) and (**112d**) is worthy of attention as the first example of the sulfur-analogous tautomeric system of alkylidene cyclopropane and bisalkylidene cyclopropane. Pentatetraene 2-episulfides ((**114a**) and (**114b**)) readily underwent a thermal C—S bond cleavage (at a-bond) in refluxing benzene to give the corresponding 2-alkylidene thietane-3-thiones ((**116a**) and (**116b**)) in addition to the isomerized 1-episulfides ((**115a**) and (**115b**)) and desulfurized tetraenes ((**117a**) and (**117b**)) (Equation (19)) <89TL4271>. Once isolated, 1-episulfides ((**115a**) and (**115b**)) were also converted into (**116a**), (**116b**), (**117a**) and (**117b**) slowly in refluxing benzene. Meanwhile, similar formation of thietanethiones (**116a**) and (**116b**) was attained by the irradiation of (**114a**) and (**114b**) with light of wavelength > 300 nm in chloroform at room temperature. The C—S bond cleavage of (**114**) exclusively occurred along path *a*, resulting in the formation of thioallyl (**118**), because of cumulenenic stability of the π -conjugated systems of (**118**) compared with (**119**) (Scheme 47). The formation of (**116a**) and (**116b**) might be rationalized by an intramolecular sulfur transfer reaction mechanism with intermediacy of (**118**), which is also a common intermediate for isomerization to (**115a**) and (**115b**).

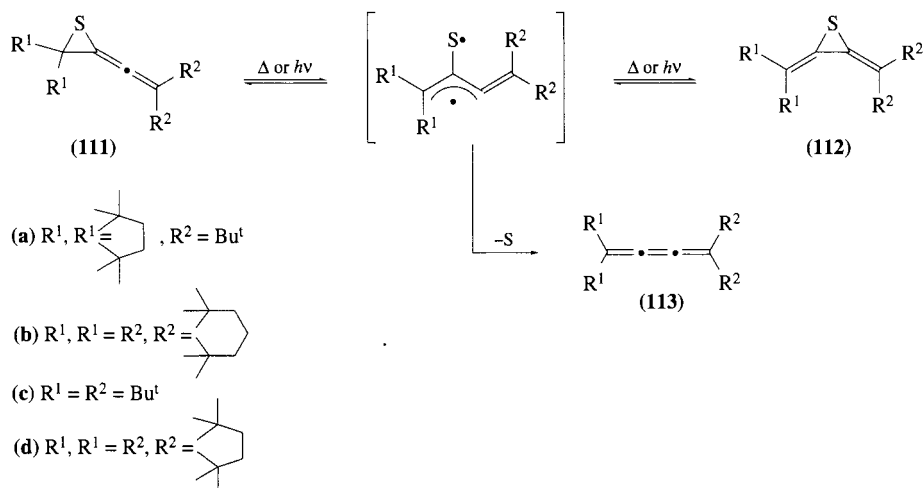


(109a, c) : R = Bu^t $E_a = 24.3 \text{ kcal mol}^{-1}$ (101.7 kJ mol⁻¹), $\Delta H^\ddagger = 23.5 \text{ kcal mol}^{-1}$ (98.4 kJ mol⁻¹), $\Delta S^\ddagger = -14.8 \text{ e.u.}$
 (109b, d) : R = TMS $E_a = 19.2 \text{ kcal mol}^{-1}$ (80.4 kJ mol⁻¹), $\Delta H^\ddagger = 18.4 \text{ kcal mol}^{-1}$ (77.0 kJ mol⁻¹), $\Delta S^\ddagger = -29.0 \text{ e.u.}$

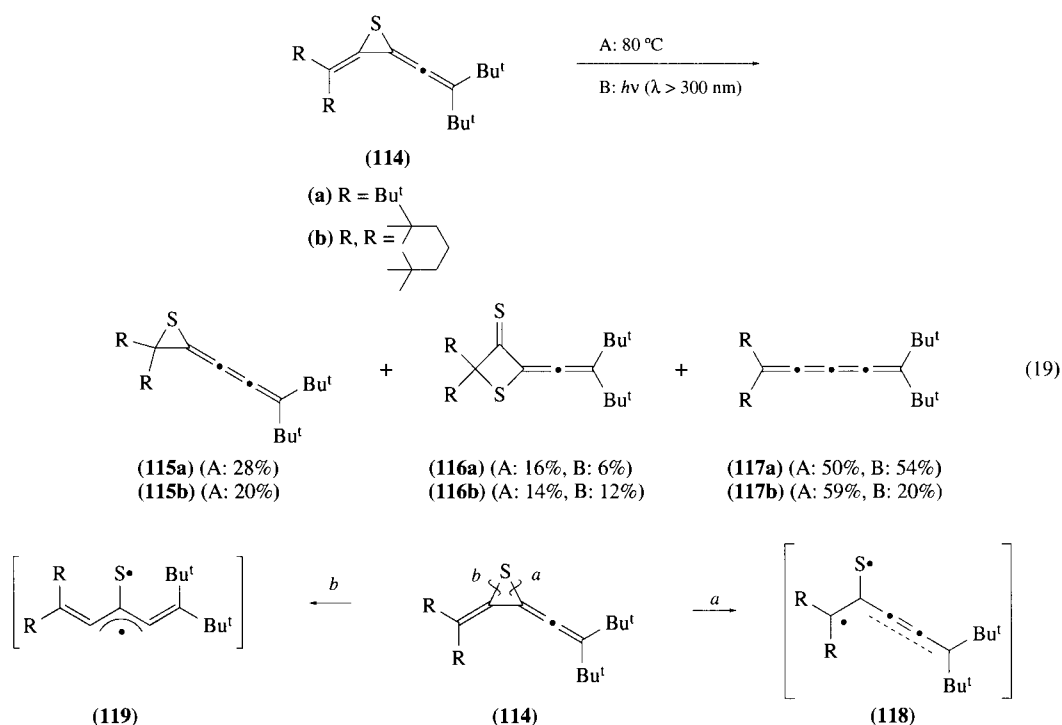
Scheme 44



Scheme 45



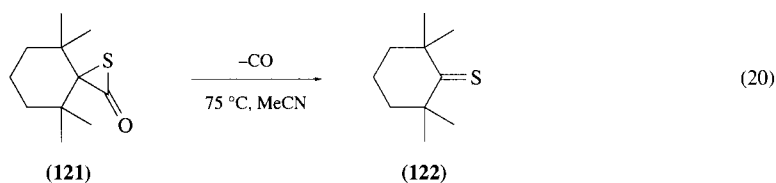
Scheme 46



Scheme 47

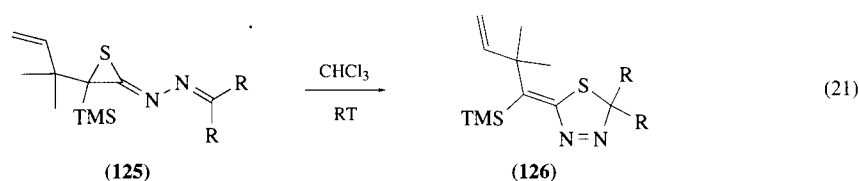
1.05.7.2.2 Thiiranone

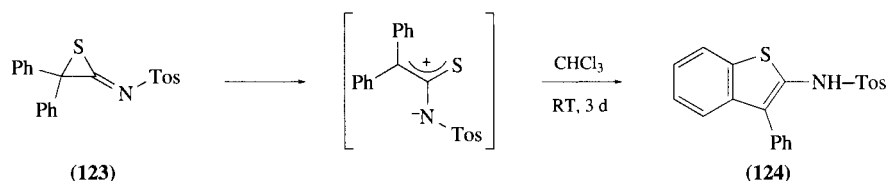
By thermolysis, thiiranone (**121**) undergoes quantitative decarbonylation without desulfurization to thioketone (**122**) (Equation (20)) <77AG(E)722>.



1.05.7.2.3 Thiiranimine

Thiiranimine (**123**) is unusually cleaved at the long S—C bond. Thus, when a chloroform solution of (**123**) is allowed to stand at room temperature for 3 days, the benzo[*b*]thiophene (**124**) is obtained in quantitative yield (Scheme 48) <78AG(E)195>. A similar reaction occurs in imine-conjugated thiiranimine (**125**) <77AG(E)722>. Thiiranimine (**125**) isomerizes to 2-alkylidene-1,3,4-thiadiazoline (**126**) in chloroform quantitatively (Equation (21)) <90TL3571, 93T1189>.

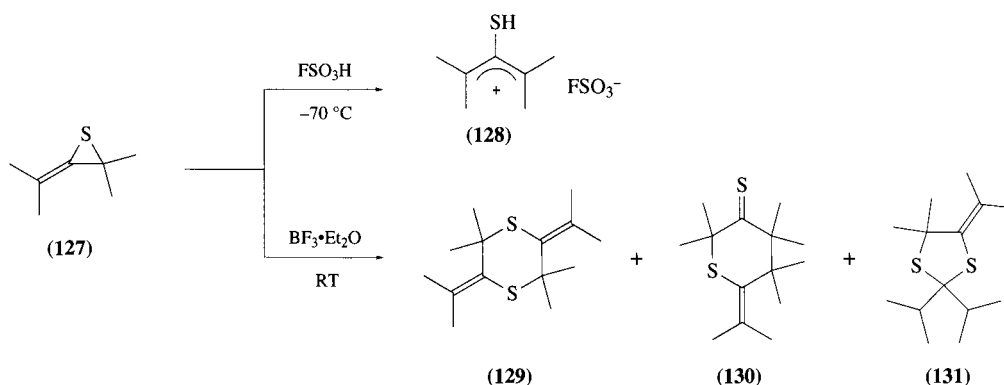




Scheme 48

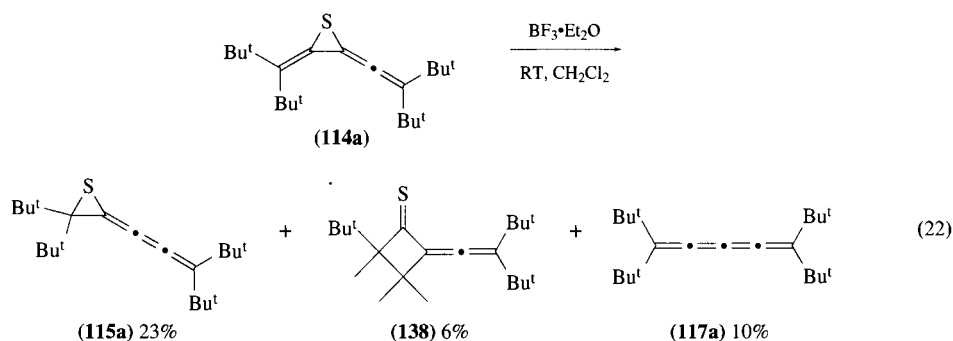
1.05.7.3 Electrophilic Attack on Sulfur

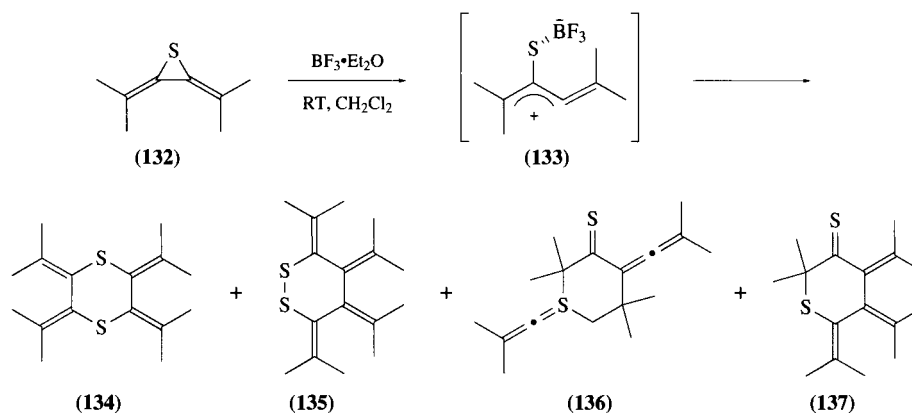
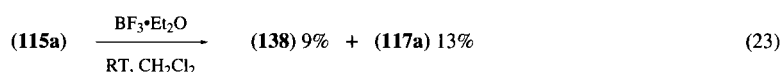
The acid ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) catalyzed reaction of allene episulfide (127) has been reported to yield dimerization products, 1,4-dithiane (129), thioketone (130), and 1,3-dithiolane (131) (Scheme 49) [83JA6151]. The formation of these products might be interpreted in terms of intermediacy of the thioallyl ion (128), which undergoes cycloadditions with either (127) or (128) to give (129) and (130). In the case of (131), thioallyl (128) undergoes a 1,4-hydrogen shift prior to cycloaddition with (127) or (128) (Scheme 49).



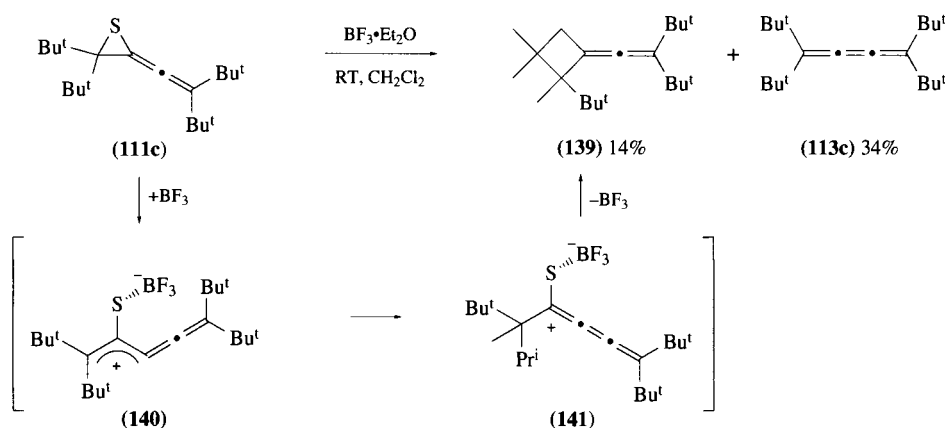
Scheme 49

The evidence for such an intermediate was observed by spectroscopic studies in super acid (FSO_3H , -70°C). Similar dimerization of 1,2,3-butatriene 2-episulfide (132) does take place readily with acid catalyst via thioallyl ion intermediate (133) to give four types of dimer: (134), (135), (136) and (137) (Scheme 50). On the other hand, treatment of pentatetraene 2-episulfide (114a) with an equimolar amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ resulted in the formation of 2-alkylidene cyclobutanethione (138) together with the isomerized 1-episulfide (115a) and desulfurized tetraene (117a) (Equation (22)) [89TL4271]. Similarly, 1-episulfide (115a) was converted into (138) and (117a) by the action of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (Equation (23)). The formation of (138) is consistently interpreted in terms of initial generation of the thioallyl cation intermediate (140) followed by the well-known methyl group rearrangement in the reaction of di-*t*-butyl-substituted allyl cation systems (141) [74JOC1723]. This methyl rearrangement also proceeded in the conversion of 1,2,3-butatriene 1-episulfide (111c) to (139) (Scheme 51).





Scheme 50



Scheme 51

1.05.7.4 Nucleophilic Attack on Carbon

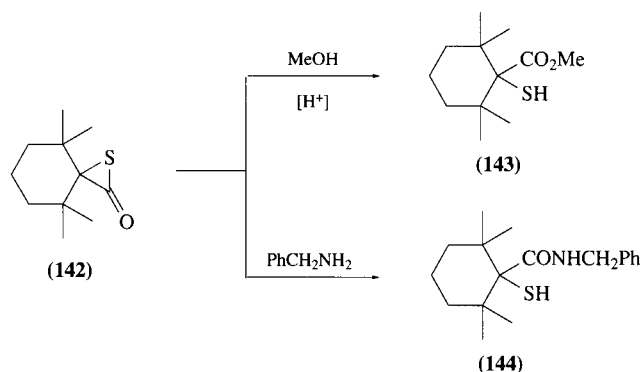
Thiiranone (142) reacts with methanol and benzylamine to yield α -thiol carboxylic acid derivatives (143) and (144) (Scheme 52) <77AG(E)722>.

Methanolysis of (108a) furnishes the thioxosulfonamide (145) as yellow crystals in quantitative yield (Scheme 53) <78AG(E)195>. *n*-Butyllithium and phenyllithium are commonly used as nucleophiles and attack the sulfur atom, but the lithium salts of isocyanides attack mainly the carbon atoms of the ring. Attack on the sulfur atom of the thiiranimine (108c) is observed in the reactions with the anion of diethyl malonate, a phosphorus ylide, *N*-methylindole and enamines or ynamines (Scheme 54) <80JOC4366>.

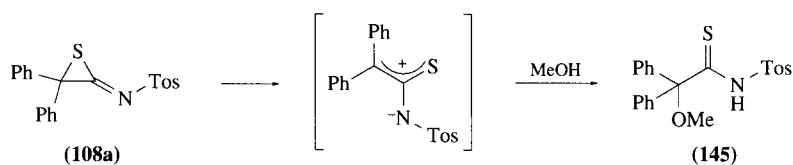
1.05.7.5 Reaction Involving Cyclic Transition States

1.05.7.5.1 Allene episulfide

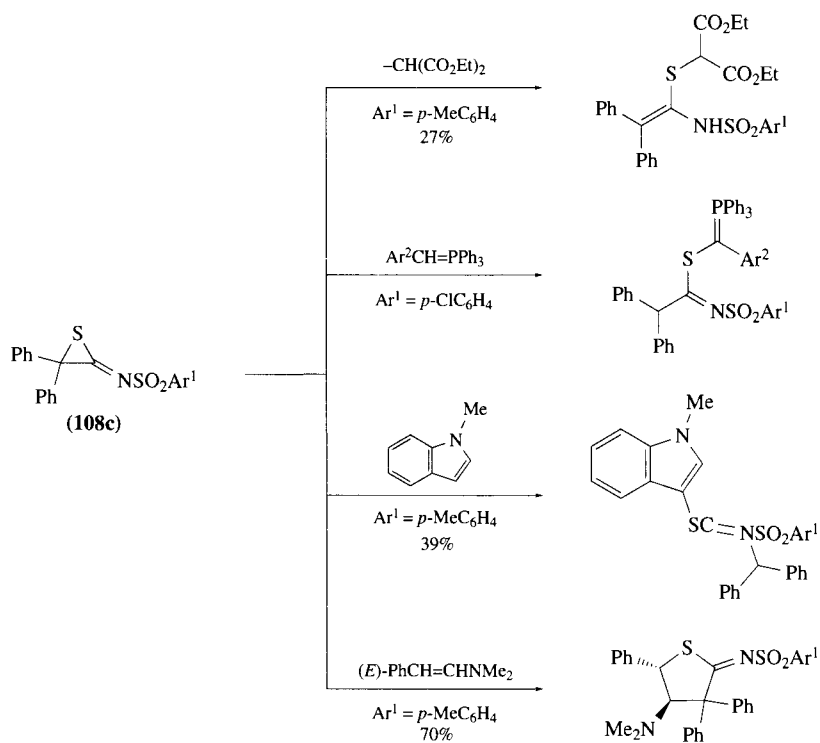
In the case of the 1,2,3-butatriene 2-episulfide bearing less-hindered substituents such as (132) and its *S*-oxide (146), intermolecular reaction with a variety of dienophiles was realized. In terms of strained alkenes, [2 + 4] addition of (132) and (146) would emerge as a powerful method for introducing a double bond into a three-membered ring fused to a six-membered ring. The compound



Scheme 52

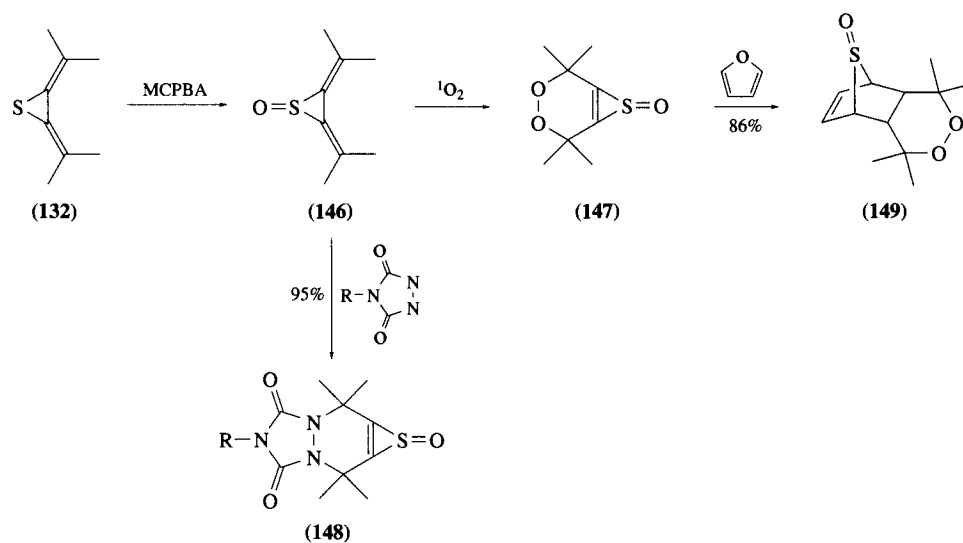


Scheme 53



Scheme 54

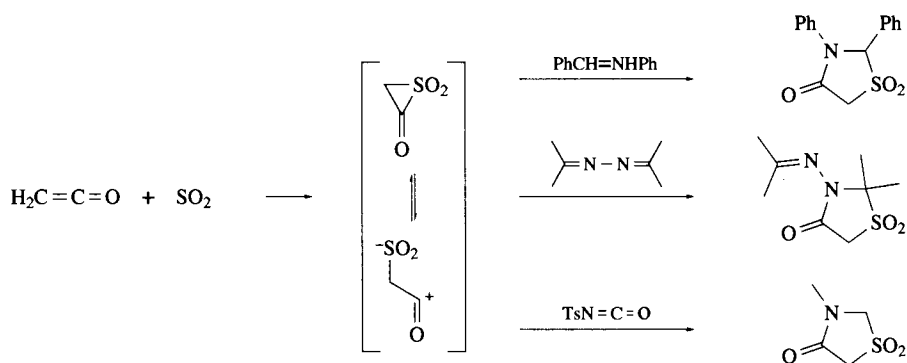
(132) reacted with singlet oxygen ($^1O_2$) to afford a novel fused thiirene sulfoxide (147), while 4-substituted 1,2,4-triazoline-3,5-dione (TAD) as a dienophile also yielded fused thiirene sulfoxide (148) quantitatively (Scheme 55). Fused thiirene sulfoxides (147) and (148) were shown to be quite reactive. The further reaction of (147) with furan gave (149), which is the first example of not only an alkyl-substituted thiirene 1-oxide but also a propellane containing the thiirene 1-oxide moiety <84TL1483>.



Scheme 55

1.05.7.5.2 Thiiranone

Thiiranimine 1,1-dioxide has not been isolated; however, it is formed *in situ* when ketene is dissolved in liquid SO_2 at -78°C . It can react with imines, azines, and tosyl isocyanate (Scheme 56) [76JOC3925].



Scheme 56

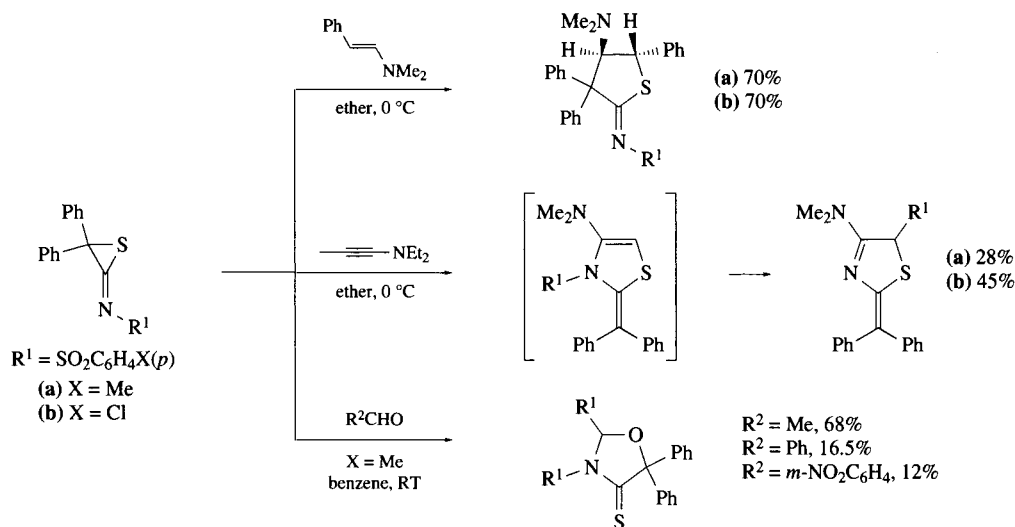
1.05.7.5.3 Thiiranimine

Thiiranimines have been found to undergo cycloaddition reactions by three pathways depending on the nature of the coreagent. Examples of these reactions, with enamines, ynamines, and aldehydes are shown in Scheme 57 [79TL1819, 79TL3213]. In the case of ynamines, exemplified with *N*-diethylaminopropyne, the primary cycloadduct (addition along the N, S part of the molecule) undergoes a sulfonyl migration from nitrogen to carbon during the reaction.

1.05.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS—THIIRANIUM IONS, THIIRENIUM IONS, AND EPISULFURANES

1.05.8.1 Introduction

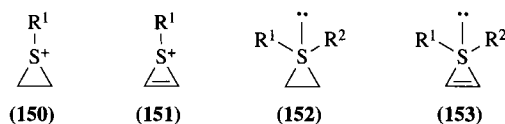
The terms thiiranium and thiirenium ions ((150) and (151)) have been used to designate the positively charged three-membered sulfur-containing ring irrespective of the location of the coun-



Scheme 57

terion. This is analogous to the original practice of Winstein who referred to the carbocation portion of all ion pairs as varieties of carbonium ions $\langle 61\text{JA}885 \rangle$. Thiiranium ions play an important role in the chemistry of bivalent sulfur compounds. They are involved as intermediates in (i) the solvolysis of β -chloroalkyl aryl sulfides; (ii) the alkylation of thiiranes and (iii) the addition of arenesulfenyl and alkanesulfenyl halides to alkenes. The naming of sulfuranes (tetracoordinate, tetravalent sulfur species) follows that suggested by Musher $\langle 69\text{AG}(\text{E})54 \rangle$. The name episulfuranes ((**152**) and (**153**)) is used to designate sulfurane structures where the sulfur atom belongs to a three-membered ring. Unlike episelenuranes, which have been reported as stable species $\langle 74\text{CJC}3599 \rangle$, episulfuranes have been proposed only as intermediates in the reactions of halogens with episulfides $\langle 73\text{USP}3725337 \rangle$, halide anions with episulfonium salts $\langle 69\text{JA}5239, 74\text{JA}3146 \rangle$, and sulfenyl halides with alkenes $\langle 69\text{JA}5239, \text{B-}81\text{MI } 105\text{-}03 \rangle$.

According to MO calculations for the gas phase, haloepisulfurane structure is more stable than the corresponding sulfonium salts $\langle 77\text{JCS}(\text{P}2)1019 \rangle$.



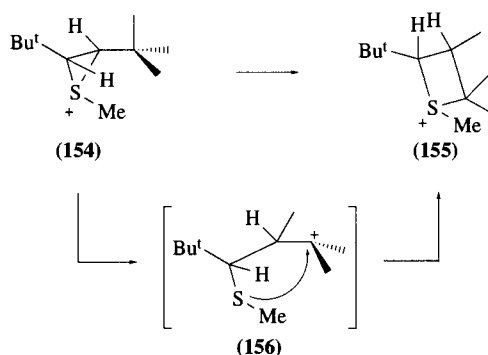
1.05.8.2 Thermal and Photochemical Reactions

c-2- R^1 -*t*-3- R^2 -*r*-1-Methylthiiranium hexachloroantimonate (**154**) ($R^1 = R^2 = t$ -butyl) is selectively converted in CD_2Cl_2 with first-order kinetics ($k = 7.93 \times 10^{-6} \text{ s}^{-1}$ at 25°C) to 1,2,2,3-tetramethyl-4-*R*-thietanium hexachloroantimonate (**155**) ($R = t$ -butyl), with 4-*t*-butyl and 3-methyl respectively *trans* and *cis* oriented to 1-methyl. The stereospecificity of the rearrangement points to concerted C—S bond breaking and methyl migration, with direct generation of the tertiary carbenium ion (**156**) (Scheme 58) $\langle 91\text{JA}6600 \rangle$.

1.05.8.3 Electrophilic Attack on Sulfur or Carbon

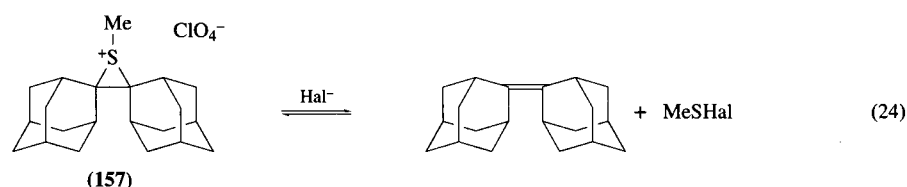
1.05.8.3.1 Episulfonium ions

S-Alkylthiiranium salts, e.g., (**157**), can be desulfurized by fluoride, chloride, bromide, or iodide ions (Equation (24)) $\langle 78\text{CC}630 \rangle$. The iodide ion has been used most generally. With chloride or bromide ions, considerable dealkylation of (**157**) occurs. In salts less hindered than (**157**),



Scheme 58

nucleophilic attack on a ring carbon atom is common. When (157) is treated with the bromide ion, only 18% yield of alkene is obtained (compared with 100% with the iodide ion), but the yield is quantitative if the methanesulfonyl bromide is removed by reaction with cyclohexene. Sulfuranes may be intermediates, although in only one case was NMR evidence observed. Theoretical calculations favor a sulfurane structure (e.g., (152)) in the gas phase, but polar solvents are likely to favor the thiiranium salt structure.



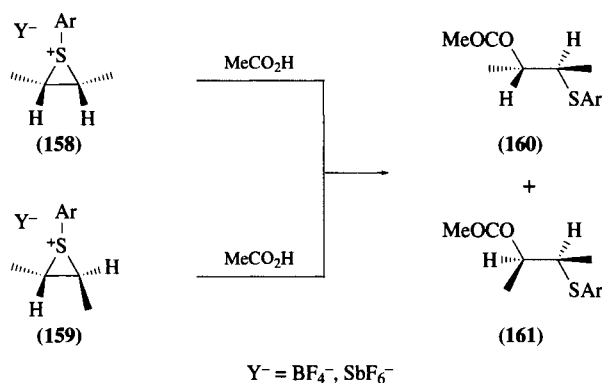
Treatment of *S*-alkylthiiranium salts with chloride ion gives products of carbon attack, but the possibility of sulfur attack followed by addition of the sulfonyl chloride produced to the alkyne has not been excluded [79MI 105-01]. In fact, the methanesulfonyl chloride formed from 1-methyl-2,3-di-*t*-butylthiiranium tetrafluoroborate has been trapped by the reaction with 2-butyne. A sulfurane intermediate is indicated by ¹H NMR experiments in liquid sulfur dioxide [79MI 105-01].

To form a stable thiiranium ion, the counterion must be a very poor nucleophile to ensure that it will not react with the thiiranium ion. Despite claims to the contrary, the products of the reaction of these stable thiiranium ions with nucleophiles are similar to those formed in the addition reactions of alkene- and arenesulfonyl chlorides to alkenes in many respects.

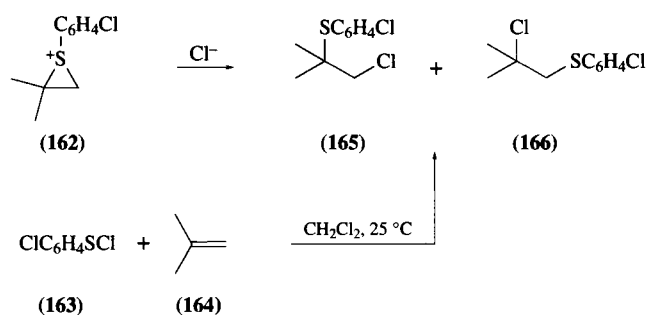
The nonstereospecific products are formed in both the reaction of stable thiiranium ions with nucleophiles and the addition of arenesulfonyl chlorides to alkenes. The reaction of the isomeric stable ions (158) and (159) with acetic acid at room temperature gives the same mixture of *erythro*-(160) and *threo*-(161) products (Scheme 59) [75TL2451, 76IZV1318]. Nonstereospecific products are also formed by the addition of 2,4-dinitrobenzenesulfonyl chloride to (*E*)- and (*Z*)-anisole [72JOC3086] and 4-methoxy- β -deuteroostyrene [84TL4983].

The stable thiiranium ion (162) forms the same proportion of regioisomers (165) and (166) as formed by the addition of 4-chlorobenzenesulfonyl chloride (163) to methylpropene (164), when the two reactions are carried out in the same solvent and at the same temperature [87JOC2403] (Scheme 60). Either stable or intermediary thiiranium ions show high reactivity towards the chloride ion rather than the solvent. Lithium chloride reacts with the stable thiiranium ion (167) in acetonitrile/dichloromethane to form products of attack by both chloride ion (80%) and acetonitrile (5%) [74JA4958].

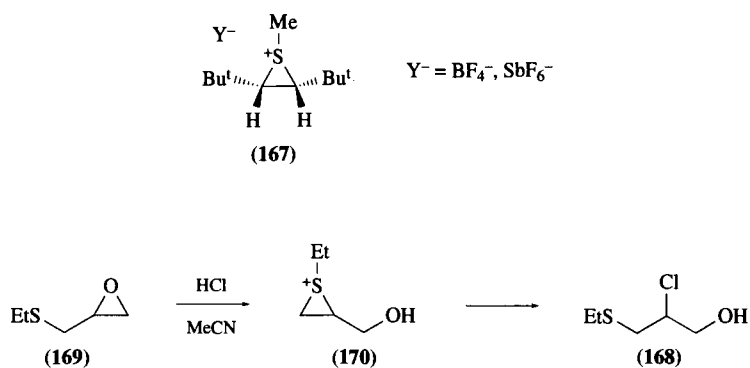
Only product (168) of the reaction with chloride ion is reported for the reaction of the stable ion (170) formed by the reaction of the epoxysulfide (169) with HCl in acetonitrile (Scheme 61) [84IZV2652]. Thus, stable ions, like their counterparts in the addition reaction, react preferentially with the stronger nucleophile. But the reactions of stable ions are not necessarily good models for the intermediates in the addition of arenesulfonyl chlorides to alkenes, because in the addition of arenesulfonyl chlorides the ratio of products depends on the reaction conditions. Thus the reaction of thiiranium ion intermediate competes with that of an open β -substituted alkyl carbocation [87CJC1945].



Scheme 59

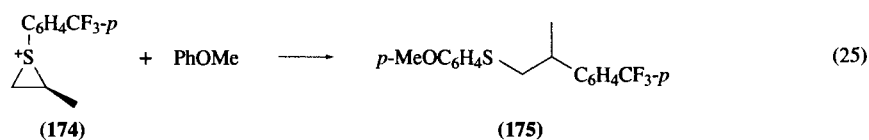


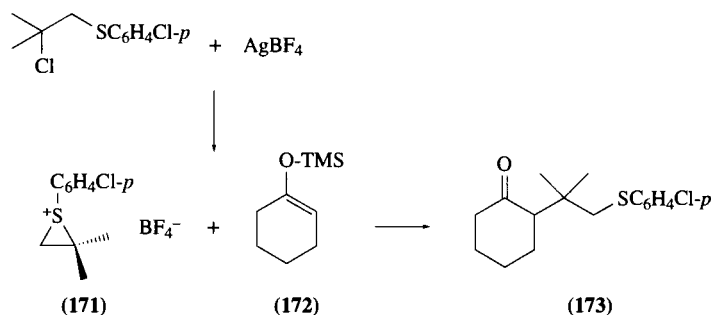
Scheme 60



Scheme 61

The reaction of episulfonium salts with silyl enol ether is a convenient method for introducing the β -arythioalkyl group into carbonyl compounds. The cleavage of the episulfonium ring in these reactions proceeds regio- and stereospecifically. The reaction of (171) with (172) gives (173) (Scheme 62) <83IZV1839>. Episulfonium salts (174) are cleaved with nucleophiles (PhOMe, mesitylene, etc.) to give 12–94% $\text{ArCR}^1\text{R}^2\text{CHR}^3\text{SAr}^1$ (175) (e.g., $\text{R}^1, \text{R}^2, \text{R}^3, \text{Ar}, \text{Ar}^1 = \text{Me}, \text{H}, \text{H}, 4\text{-CF}_3\text{C}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4; \text{Me}, \text{Me}, \text{H}, 4\text{-O}_2\text{NC}_6\text{H}_4, 2,4,6\text{-Me}_3\text{C}_6\text{H}_2$) (Equation (25)) <83IZV161, 83IZV1204>.

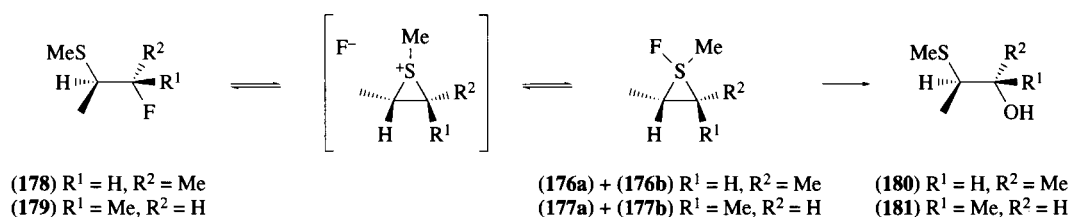




Scheme 62

1.05.8.3.2 Episulfuranes

The formation of episulfuranes from β -halothioethers may be understood in terms of the slow equilibrium of β -halothioethers with the episulfonium salt (Scheme 63). The β -halothioether ((178) or (179)) is regenerated by attack of the halide ion on carbon (kinetic control), whereas the attack on sulfur yields the episulfurane. The episulfurane ((176) or (177)) becomes the thermodynamic product ((180) or (181)) in the case of fluorothioethers, presumably because of the stability of the F—S bond <87TL4593>. The stabilizing effect of the ring systems has also been invoked to explain the stability of sulfuranes.



Scheme 63

1.05.9 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

1.05.9.1 From Nonheterocyclic Sulfur Compounds

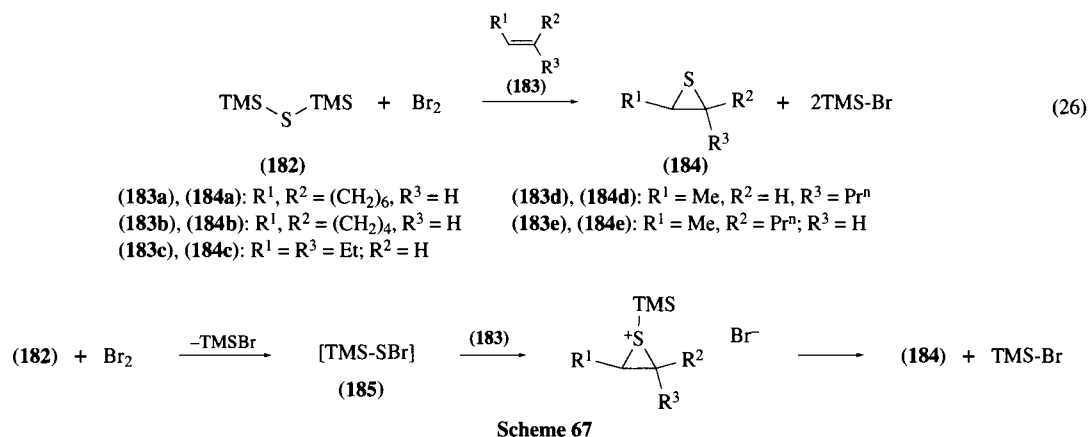
1.05.9.1.1 General survey of synthesis

There are three main approaches for the synthesis of thiiranes: the first is C—S bond formation (Scheme 64), the second is C—C bond formation (Scheme 65), and the third is based on the formation of two bonds (Scheme 66), which includes the reaction of elemental sulfur with alkenes and the reaction of thiocarbonyl compounds or elemental sulfur with carbenes derived from diazo compounds. These methods are described in detail in CHEC-I, and references until 1983 are cited therein <84CHEC-I(7)171>. A survey of reports, published mainly after 1983, of the formation of thiiranes, thiirane *S*-oxide, and thiirane *S,S*-dioxides is given in the following sections.

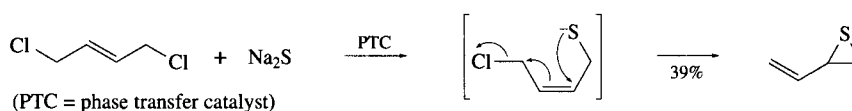
1.05.9.1.2 By formation of a C—S bond

Treatment of bis(trimethylsilyl)sulfide (182) with bromine in anhydrous dichloromethane at -78°C followed by addition of 1,2-disubstituted alkenes (183) to the reaction mixture at the same temperature gave the thiiranes (184) in about 30% yields (Equation (26)) <88TL4177>. Mono-substituted, 1,1-disubstituted, tri- and tetrasubstituted alkenes failed to give the corresponding thiiranes. The synthesis reported above shows the following features: (i) it is highly selective, since only 1,2-disubstituted alkenes undergo the transformation to thiiranes; (ii) it is stereospecific since

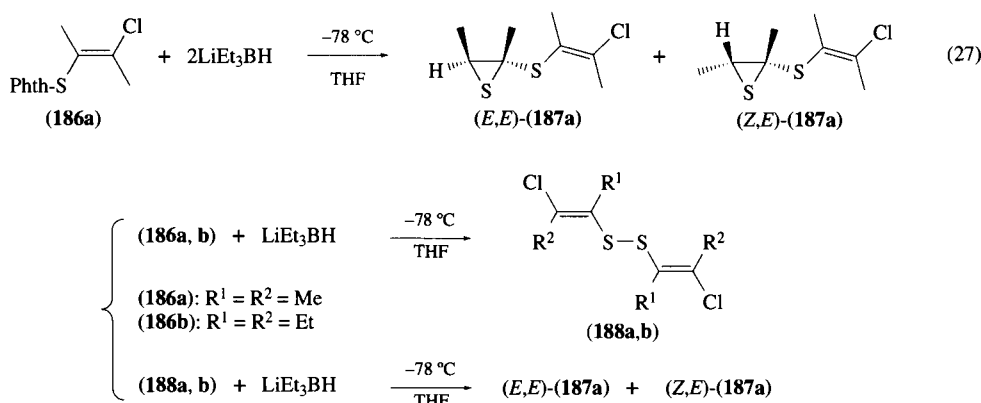
the stereochemistry of the alkene is retained in the thiirane, as indicated by the synthesis of **(184d)** and **(184e)** from **(183d)** and **(183e)**, respectively. The nature of the reagents suggests that the silyl-substituted sulfenyl bromide **(185)**, formed by attack of bromide to **(182)**, might be an intermediate in the reaction (Scheme 67) <88TL4177>.



The synthesis of 2-vinylthiirane can be achieved from *cis* and *trans* mixtures of 1,4-dichloro-2-butene and saturated aqueous solution of Na₂S using phase transfer catalyst (Scheme 68) <89JPS(C)381>.

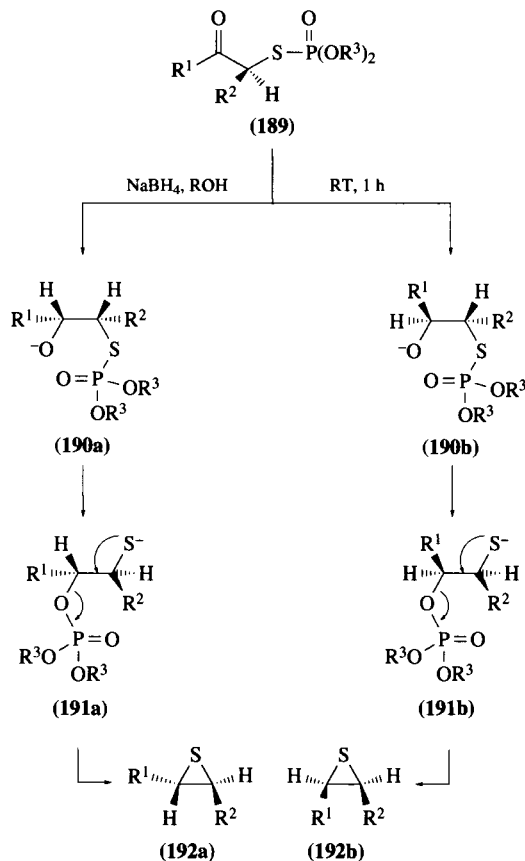


The reaction of **(186a)** (R¹ = R² = Me) with 2 equiv. of lithium triethylboron hydride in THF at -78 °C under nitrogen gave the diastereomeric thiiranes **(187a)** as a 93 : 7 mixture of the (*E,E*) and (*Z,E*) isomers in satisfactory yields (66%) (Equation (27)). The same mixture of products is obtained when **(186a)** is reacted with other hydrides such as NaBH₄ or LiAlH₄. This reaction proceeds as illustrated in Scheme 69. Substrates **(186a)** and **(186b)** react with one equivalent of LiEt₃BH to yield **(188a)** and **(188b)**. Further reaction of the disulfide **(188a)** or **(188b)** with one equivalent of LiEt₃BH gives a mixture of the thiiranes **(187a)** (or **(187b)**) identical to that obtained directly from **(188a)** or **(188b)** and 2 equiv. of LiEt₃BH <91T7185>.



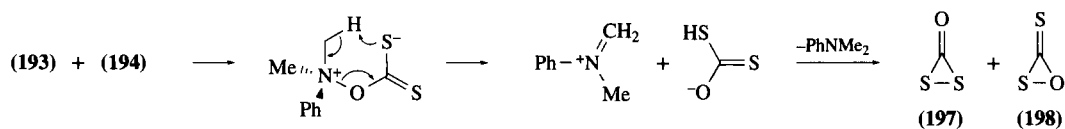
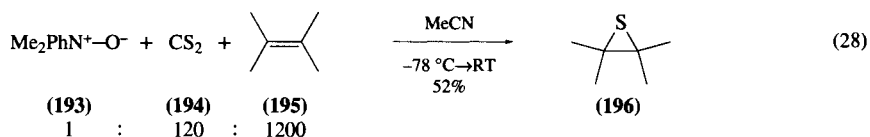
The reaction of *S*-(β-oxoalkyl)thiophosphates **(189)** with sodium borohydride results in the formation of the corresponding diastereoisomeric oxyanions **(190a)** and **(190b)**. The intermediates **(190a)** and **(190b)** undergo rearrangement involving migration of a phosphoryl group from sulfur

to oxygen to afford the thiolate anions **(191a)** and **(191b)** (Scheme 70) <68CC1399, 70JCS(B)1123, 86T629>. Subsequent cyclization of **(191a)** and **(191b)** with elimination of phosphate anion provides episulfides **(192a)** and **(192b)**. It is obvious that such a cyclization proceeds with inversion of configuration at the carbon adjacent to the phosphate moiety <91TL4385>.



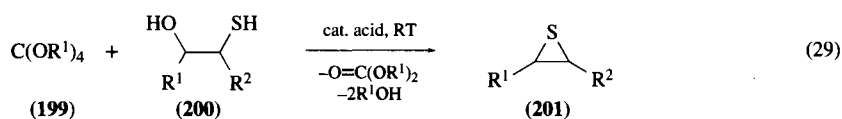
Scheme 70

In the presence of 2,3-dimethyl-2-butene **(195)**, the reaction of **(193)** with CS₂ **(194)** provides tetramethylethylene sulfide **(196)** as a product (Equation (28)) <85JOC3228>. This reaction needs a large excess of alkene, because thionation reagents **(197)** or **(198)** rapidly decompose with a low energy of activation (Scheme 71).

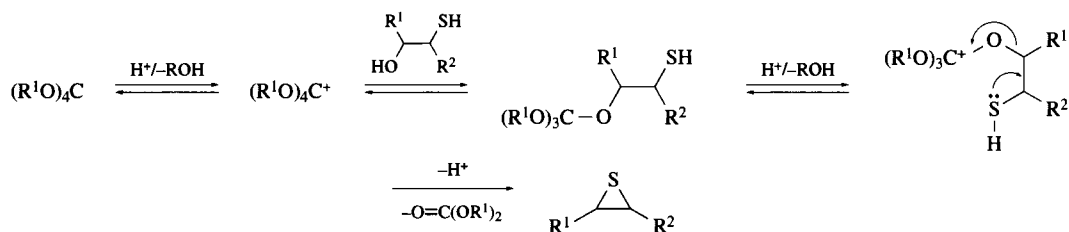


Scheme 71

Tetraalkyl orthocarbonates **(199)** have been shown to serve as effective dehydrating agents for 2-mercaptoalkanols **(200)** to give the corresponding thiiranes **(201)** in good yields in acid-catalyzed reactions in aprotic solvents. When **(199)** is mixed with an equimolar amount of **(200a)** in the presence of an acid catalyst such as *p*-toluenesulfonic acid, thiirane **(201)** is formed in more than 95% yield (by NMR) along with a dialkyl carbonate and an alkanol (Equation (29)) <88BCJ1818>. Without such an acid, no reaction takes place. A conceivable mechanism is shown in Scheme 72.



	yield of thiirane
(a) $\text{R}^1 = \text{R}^2 = \text{H}$	95%
(b) $\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}$	77%
(c) $\text{R}^1 = \text{Ph}, \text{R}^2 = \text{H}$	80%
(d) $\text{R}^1 = \text{H}, \text{R}^2 = \text{Ph}$	63%



Scheme 72

1.05.9.1.3 Synthesis by formation of a C—C bond

Primary sulfonyl chlorides $\text{RCH}_2\text{SO}_2\text{Cl}$ (R = alkyl or aryl) (202) react with triethylamine in acetonitrile at -40°C to give mixtures of *cis*- and *trans*-2,3-disubstituted thiirane 1,1-dioxides (203) (Equation (30) and Table 36) [89TL3131, 90CB1989]. The reaction mechanism is shown in Scheme 73. The stereochemistry is influenced by the amine base (B) in the ring closure reaction and partially by epimerization of the episulfones (203).

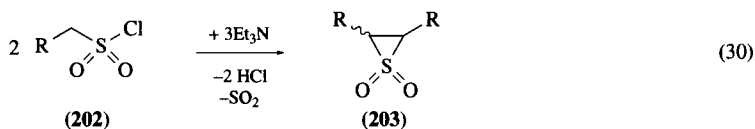


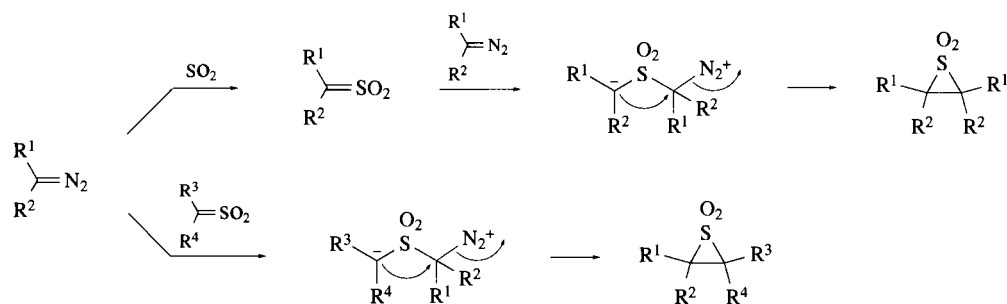
Table 36 Yields of thiirane 1,1-dioxides.

(202) R	(203) Yield (%)	
		trans : cis
(a) H	43 ^a , 64 ^b	100 : 0
(b) CH ₃	95	52 : 48
(c) CH ₃ (CH ₂) ₆	88	69 : 31
(d) C ₆ H ₅ CH ₂	90	76 : 24
(e) Cyclohexyl	91	95 : 5
(f) C ₆ H ₅ C(CH ₃) ₂	58	100 : 0
(g) C ₆ H ₅	c	55 : 45
(h) 4-NO ₂ -C ₆ H ₄	c	100 : 0
(i) 2-NO ₂ -C ₆ H ₄	c	100 : 0

^a Pr₃N⁺Et instead of Et₃N. ^b In Et₂O instead of MeCN at 0°C .

^c Not isolated.

When an intimate mixture of phenyliodonium bis(arylsulfonyl)methylides (204) and excess *p,p'*-dimethylthiobenzophenone (205) containing a catalytic amount of $\text{Cu}(\text{acac})_2$ is briefly heated without any solvent until it melts, 2,2-di-*p*-tolyl-3,3-bis(phenylsulfonyl)thiirane (206) is obtained in 27% yield (Equation (31)) [89JCS(P1)379]. With *p,p'*-dimethoxythiobenzophenone (207) no thiirane is formed but instead 3-*p*-methoxyphenyl-6-methoxy-2-phenylsulfonylbenzo[*b*]thiophene (208) is obtained in 39% yield (Equation (32)).



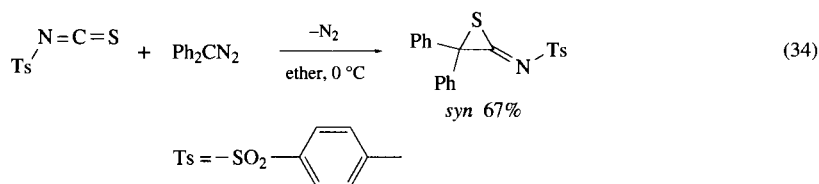
Scheme 76

<75RCR138>. This synthetic strategy is widely applied to thiirane derivatives (e.g., allene episulfides and allene episulfides *S*-oxide) <87TL1787>.

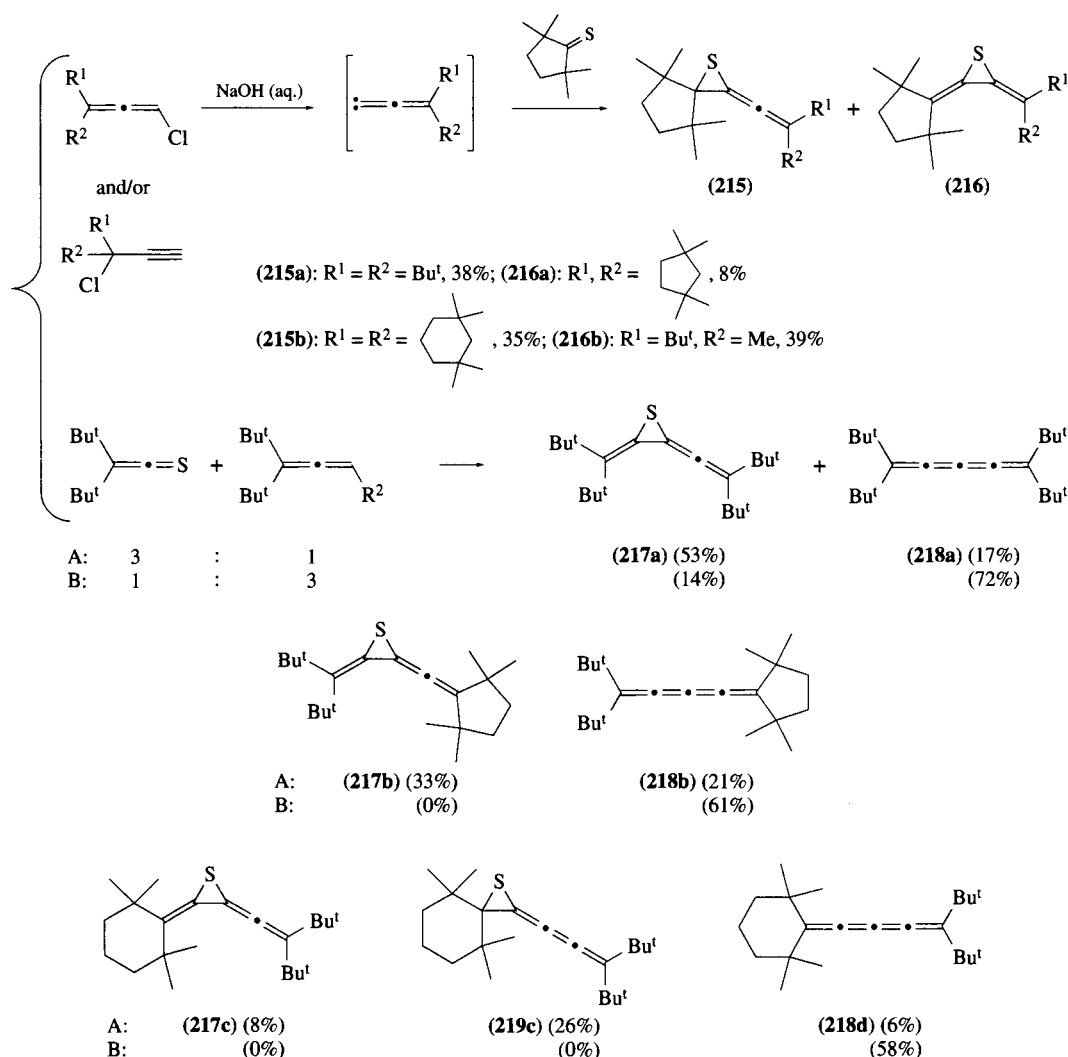
Thioketenes react with diazo compounds in the presence of metal catalyst ([Rh(OAc)₂], CuCl, or CuSO₄) to yield the corresponding allene episulfides <81T219>. Allene episulfide *S*-oxide can be formed from thioketene *S*-oxide and diazo compounds <88T1827>.

In a similar way to the carbene addition reaction to stable thioketene, 1,2,3-butatriene 1- and 2-episulfides, (**215a**, **b**) and (**216a**, **b**), are synthesized by the addition of alkenylidene carbene to thioketones using several kinds of chloroallenes and/or chloroalkynes as the carbene source under phase transfer catalytic reaction conditions <88TL5161> (Scheme 77). A new and convenient method for the synthesis of novel pentatetraene episulfide ((**217a–c**) and (**219c**)) has been reported: by the addition of alkenylidene carbene to thioketene, which can be useful in turn as a route to 1,2,3,4-pentatetraene (**218a–c**) <89TL4271>. When thioketenes are treated with several kinds of haloalkenes under phase transfer reaction conditions, the corresponding 1,2,3,4-pentatetraene 2-episulfides (**217a–c**) are obtained in moderate yields based on the carbene sources, along with a small amount of desulfurized 1,2,3,4-pentatetraene (**218a–c**) (Method A). Using an excess amount of carbene sources (3 equivalent to thioketene) resulted in an almost exclusive formation of (**218a–c**) in good yields (Method B). In the last case, isomerized 1-episulfide (**219c**) was formed together with (**217c**) and (**218c**). Method B is of particular note as a useful synthetic method for a variety of substituted 1,2,3,4-pentatetraenes, which are difficult to construct by the common carbene coupling reactions.

Thiiranimine is prepared by the reaction of isothiocyanate with diphenyl-diazomethane at 0 °C in 67% yield (Equation (34)) <78AG(E)195>.

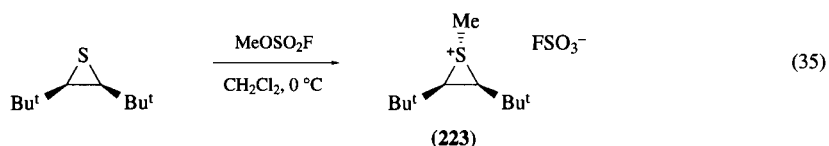


Thiiranium ions are postulated as intermediates in (i) solvolysis of β -chloroalkyl aryl sulfides, (ii) alkylation of thiiranes, and (iii) addition of alkane- or arenesulfonyl derivatives to alkenes <B-77MI 105-01, B-77MI 105-02>. They can be prepared and isolated by a variety of reactions in which thiiranium ions are proposed as intermediates <68JA1635, 75TL1975, 78IZV2156>. Stable thiiranium ions have been prepared under very different experimental conditions <79ACR282, B-81MI 105-03>. Two different methods of synthesizing stable thiiranium ions are shown as (1) and (2) in Scheme 78. Reaction (1) is the addition of methanesulfonyl chloride (**220a**) or 4-chlorobenzenesulfonyl chloride (**220b**) to methylpropene leading to the formation of a thiiranium ion intermediate (**221**) <79ACR282, B-81MI 105-03>. Reaction (2) is the preparation of a thiiranium ion (**221**) by the addition of acid to methyl-3-(methylthio)propene (**222a**) or methyl-3-(4-chlorophenylthio)propene (**222b**) <87JOC2403>. To form a stable thiiranium ion, the counterion must be a very poor nucleophile which will not react with the thiiranium ion. Thus, alkylation agents which involve nonnucleophilic anions—e.g., Et₃O⁺BF₄[−], MeOSO₂F, Me₃O⁺2,4,6-(NO₂)₃C₆H₂SO₃[−]—are required for isolation of *S*-alkylthiiranium salts (**223**) (Equation (35)). Stable thiiranium ions (**224**) <75TL2984>, (**225**) <75TL2451, 76IZV1318>, (**226**), (**227**) <87CJC1945> and (**228**) <84TL157> are obtained as follows. Thiiranium ion *S*-(4-chlorophenyl)-2,2-dimethylthiiranium trifluoromethanesulfonate (**227**) is prepared by dissolving methyl-3-(4-chlorophenylthio)propene, prepared by the reaction of 4-chlorothiophenoxide with



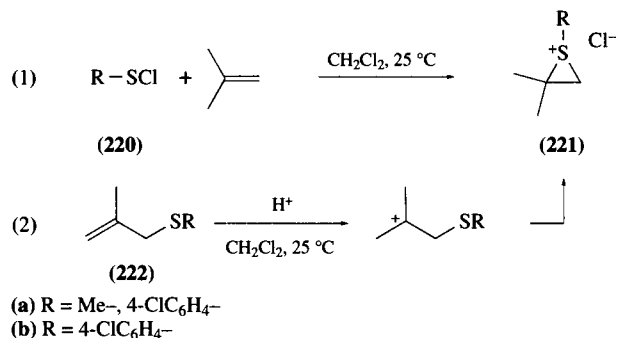
Scheme 77

methallyl chloride in methanol, in hexane and adding the resultant solution slowly to trifluoromethanesulfonic acid <87JOC2403>. Methyl episulfonium perchlorate (**229**) is prepared from Ac-Cys-OH in 4 steps. A key step is the treatment of $\text{CF}_3\text{CO}_2\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}(\text{NHAc})\text{CO}_2\text{Me}$ with HClO_4 which gives (**229**) $\cdot\text{HClO}_4$. Episulfonium perchlorate (**229**) served as a model for the putative carcinogenic intermediate resulting from hydrolytic activation of *S*-(2-haloethyl)-*N*-acetylcystein. The compound is stable both in the solid state and in aqueous solution. Such stabilization could be present in the putative carcinogenic intermediates derived from glutathione <88JMC1279>.

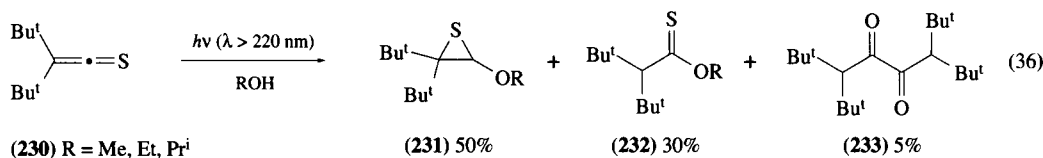
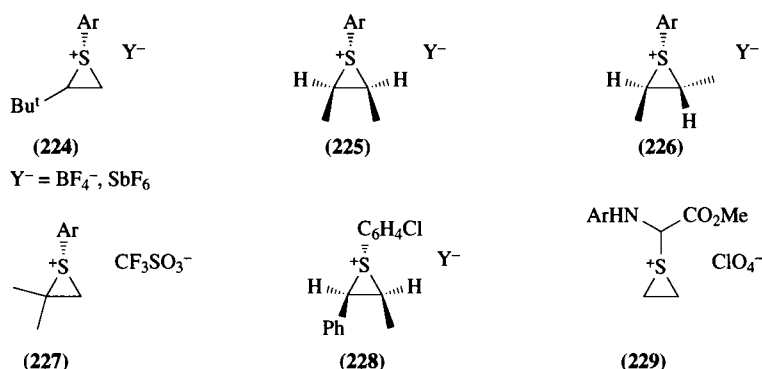


1.05.9.3 Miscellaneous Method

Irradiation of thioketene (**230**) in alcoholic solvents is known to be a clean and useful method to give 2-alkoxy-3,3-di-*t*-butylthiirane (**231**) as the major product ($\approx 50\%$) along with thiopivalic acid ester (**232**) and diketone (**233**) (Equation (36)) <84JOC393>.



Scheme 78

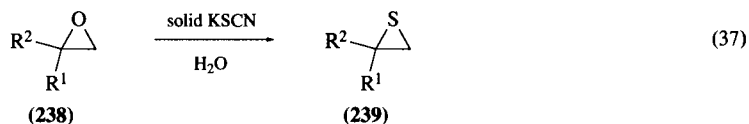


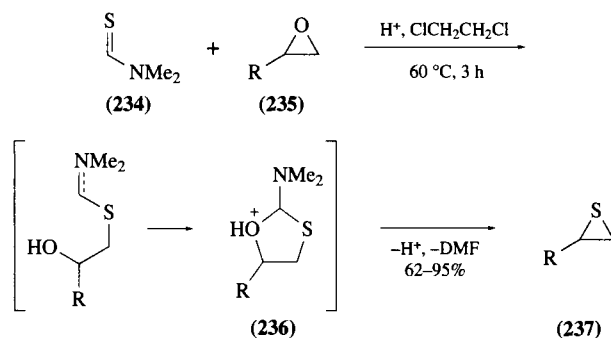
1.05.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

1.05.10.1 Formation from Oxirane

Dimethylthioformamide (DMTF) (234) reacts with oxiranes (235) in the presence of a catalytic amount of trifluoroacetic acid under mild conditions to form the corresponding thiiranes in good yield as shown in Scheme 79 and Table 37 (86S779). A possible reaction mechanism is postulated based on the mechanism observed in the preparation of oxiranes with thiocyanate or thiourea (66CRV297). Intermediate (236) is generated by the nucleophilic attack of the sulfur atom of (234) on the carbon atom of (235) followed by ring closure reaction of the hydroxy oxygen atom with the iminium carbon atom. Subsequent elimination of dimethylformamide affords thiirane (237).

Transformation of epoxides (238) into thiiranes (239) are first carried out in the presence of potassium thiocyanate in the absence of both solvent and phase-transfer catalysts (Equation (37) and Tables 38 and 39).





Scheme 79

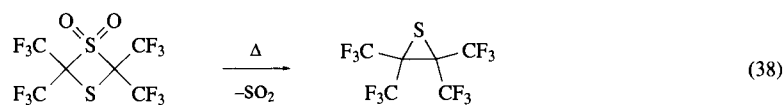
Table 37 Yields of thiiranes (237) (see Scheme 79).

R	Yield of (237) (%)	R	Yield of (237) (%)
	92	$n\text{-C}_4\text{H}_9\text{—OCH}_2\text{—}$	64
$n\text{-C}_6\text{H}_{13}\text{—}$	83		66
	82	$\text{H}_2\text{C=CH—CH}_2\text{—OCH}_2\text{—}$	94
	72		

1.05.10.2 Formation from Four-membered Heterocycles

A few syntheses of thiiranes from four-membered sulfur-containing heterocycles are reported. 2,2,3,3-Tetrakis(trifluoromethyl)thiirane is yielded by thermolysis of 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithietane 1,1-dioxide with loss of sulfur dioxide (Equation (38)) <61USP3136781>.

Allene episulfide and butatriene 2-episulfide are formed by thermolysis of the lithium tosyl-hydrazone of thietan-3-ones (Scheme 80) <76JA7081, 81TL4815>.



1.05.10.3 Formation from Five-membered Heterocycles

The reactions of thiocarbonyl compounds with diazoalkanes may proceed via 2,5-dihydro-1,3,4-thiadiazoles or possibly 4,5-dihydro-1,2,3-thiadiazoles, since these thiadiazoles are known to decompose with loss of nitrogen to give thiiranes (Schemes 81 and 82) <75RCR138>. Thioketenes react with diazo compounds to give 2-alkylidene-1,3,4-thiadiazolines, which give allene episulfides on thermolysis (Schemes 83 and 84) <69JOC3201, 92OM607>. Photolysis of 2-alkylidene-1,3,4-thiadiazolines gives thiiranimine derivatives (Equation (39)) <90TL3571, 93TI1189>.

Table 38 Thiirane synthesis without solvent (see Equation (37)).

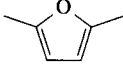
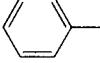
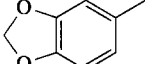
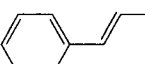
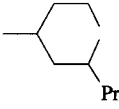
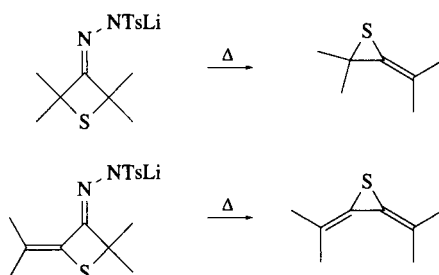
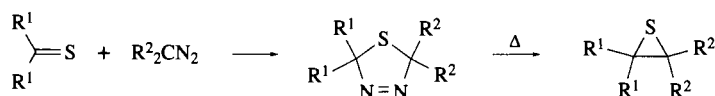
R^1	R^2	Thiirane yield (%)
	H	98
	H	98
	CH ₃	80
	H	98
	H	30
	H	50
	H	50

Table 39 Thiirane synthesis with solvent (ethanol) (see Equation (37)).

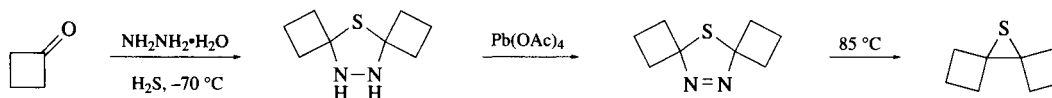
R^1	R^2	Thiirane yield (%)
	H	0
	-CH(CH ₃) ₂	50
	-(CH ₂) ₆ -CH ₃	0
CH ₃ CH ₂ -	H	90
CH ₃ (CH ₂) ₆ -	H	95
		98
		50
		60



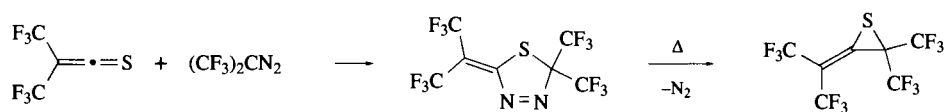
Scheme 80



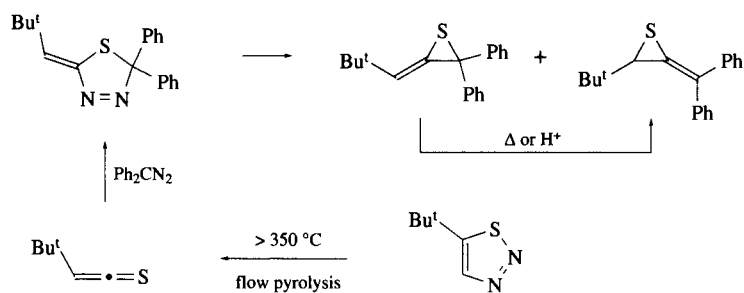
Scheme 81



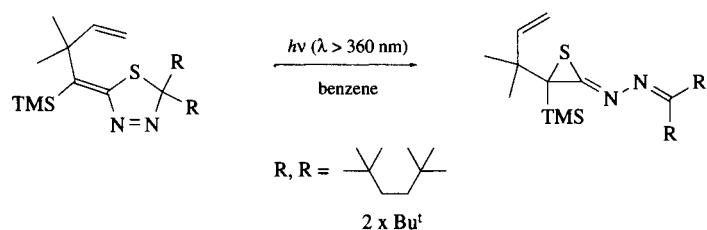
Scheme 82



Scheme 83



Scheme 84



(39)

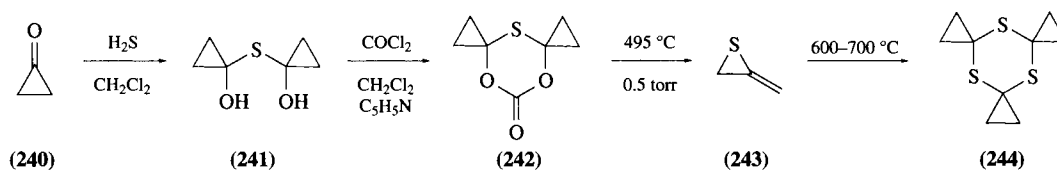
Thiirenes have been isolated in argon matrices at 8 K by photolysis of 1,2,3-thiadiazoles or vinyl trithiocarbonates (Scheme 85) <80PAC1623, 81JA486>. They are highly reactive and decompose to thioketenes and alkynes. Electron-withdrawing substituents stabilize thiiranes somewhat, but no thiirenes stable at room temperature are known, unlike the relatively stable thiirene 1-oxides and thiirene 1,1-dioxides.



Scheme 85

1.05.10.4 Formation from Six-membered Heterocycles

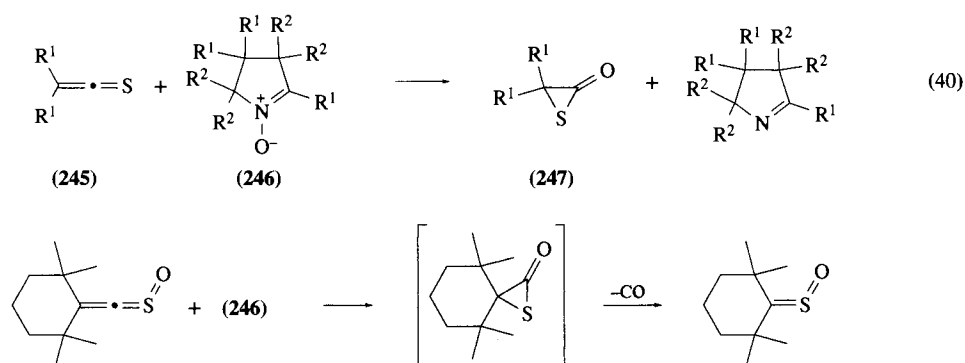
Thermolysis of trithiane (**244**) or carbonate (**242**) under reduced pressure gives allene episulfide (**243**) which is stable in cold, dilute solution (Scheme 86) <78JA7436, 78RTC214>. Reaction of cyclopropanone (**240**) with 1/2 equivalent of hydrogen sulfide gives the bisadduct (**241**) (90% yield), which yields the cyclic carbonate (**242**) on reaction with phosgene (48%) in the presence of pyridine. Thermolysis under low pressure (500 °C, 0.5 torr) of the carbonate (**242**) followed by condensation of the volatile degradation products at liquid nitrogen temperatures indeed gives methylenethiirane (**243**) in 90% yield <78RTC214>.



Scheme 86

1.05.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

The oxidation of thioketene (**245**) by nitrones (**246**) of the 1-pyrroline 1-oxide type furnishes α -thiolactones (thiiranones) (**247**) (Equation (40)) <77AG(E)722>. But the oxidation of thioketene *S*-oxide gives thioketone *S*-oxide via thiiranone *S*-oxide (Scheme 87).



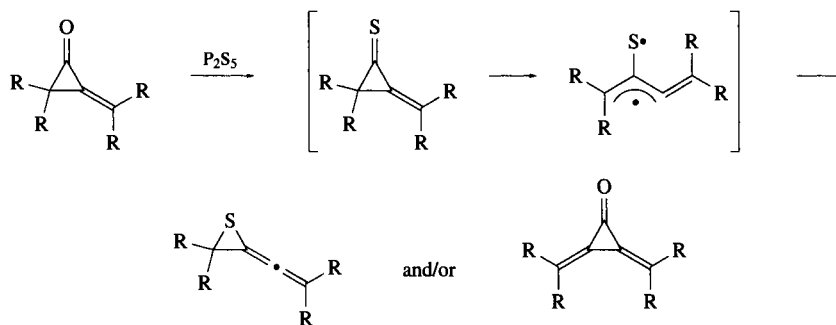
Scheme 87

Sulfurization of alkylidene cyclopropanones by P_2S_5 gives triene episulfides via cyclopropanethione intermediates (Scheme 88) <87TL1803>.

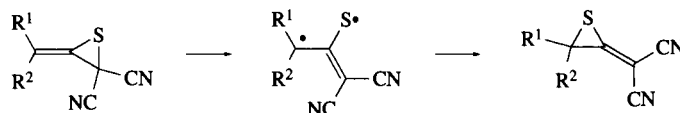
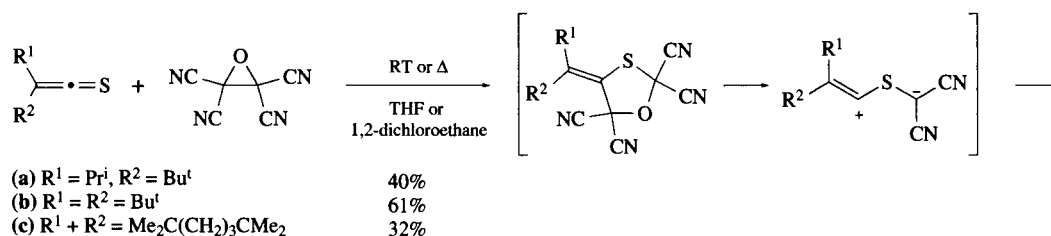
Treatment of dialkylthioketenes with tetracyanoethylene oxide yields dicyanomethylenethiiranes

via sequential reactions involving [3 + 2] cycloaddition, cycloreversion and rearrangement (Scheme 89) <93JCS(P1)2385>.

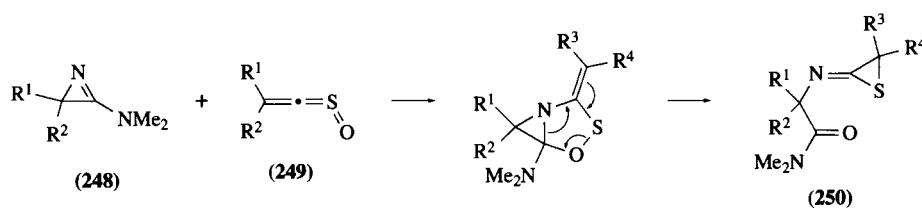
Reactions of 3-dimethylamino-2H-azirines (**248**) with thioketene S-oxides (**249**) provide the thiiranimine derivatives (**250**) (Scheme 90 and Table 40) <82AG(E)694>.



Scheme 88



Scheme 89



Scheme 90

Table 40 Thiiranimines (**250**) from (**248**) and (**249**) (see Scheme 90).

(250)	R^1	R^2	R^3	R^4	Yield (%)
(a)	CH_3	CH_3	$\text{CH}(\text{CH}_3)_2$	CH_3	96
(b)	CH_3	$\text{CH}_3-\text{C}(\text{CH}_3)_2-(\text{CH}_2)_3-$ $\text{C}(\text{CH}_3)_2-$	93		
(c)	CH_3	CH_3	$\text{C}(\text{CH}_3)_3$	$\text{C}(\text{CH}_3)_3$	91
(d)	$\text{CON}(\text{CH}_3)_2$	H	$-\text{C}(\text{CH}_3)_2-(\text{CH}_2)_3-\text{C}(\text{CH}_3)_2-$		80
(e)	$\text{CON}(\text{CH}_3)_2$	H	$\text{C}(\text{CH}_3)_3$	$\text{C}(\text{CH}_3)_3$	71
(f)	CH_3	C_6H_5	$-\text{C}(\text{CH}_3)_2-(\text{CH}_2)_3-\text{C}(\text{CH}_3)_2-$		11

1.05.12 IMPORTANT COMPOUNDS AND APPLICATIONS

1.05.12.1 Naturally Occurring Thiiranes

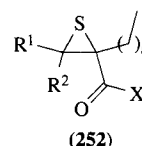
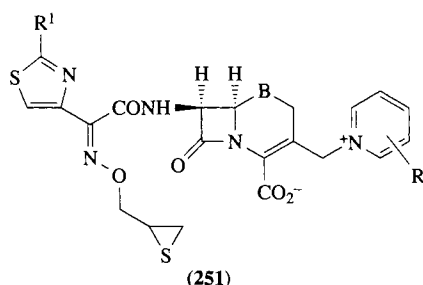
Thiiranes occur naturally in cruciferous vegetables. Thiirane and 2-methylthiirane have been detected by GC-MS in the aroma of canned beef. Beer with an onion-like off-flavor was found to contain (1-methylethyl)thiirane and 2-mercapto-3-methyl-1-butanol <88MI 105-01>. Thiirane is in the aroma of cooking mutton and is formed in the brewing of foods. 1-Cyano-4,5-epithiopentane was the major component of rape seeds at ≥ 3 days of germination <85ABC217>.

1.05.12.2 Polymers

Polymers and copolymers of thiiranes have been widely investigated. The polymers and copolymers are obtained by anionic homopolymerization <88MIP142485>, anionic ring-opening polymerization <89MM2020>, ring-opening group-transfer polymerization <88PP120>, radical polymerization <88EUP295675>, and electrochemical "ring-opening" polymerization <89MI 105-02>. The thiol-terminated polymers are useful for the preparation of block copolymers by radical polymerization as elastomers for the preparation of (alkyl)styrene polymers <88EUP295675>. The living polymerization of thiirane followed by an epoxide gives a block copolymer consisting of polythioether and polyether blocks of uniform block lengths <90MM2612, 90MM3887>. Thiirane derivatives are useful for rubber plasticizers, curing agents, and coating agents for textiles. Copolymer rubbers prepared from alkylidene sulfides 15–70 mol%, epihalohydrin 30–85 mol%, and unsaturated epoxides 0–15 mol% are useful for automobile fuel hoses <88JAP(K)6381143, 88JAP(K)6381144>.

1.05.12.3 Drugs

Cephalosporins (**251**) are prepared as antibiotics <86BRP2168971>. The thiiranes (**252**) are claimed to be hypoglycemic agents <80USP4196300>. Thiirane is more bactericidal than oxirane, and derivatives of 2-mercaptomethylthiirane inhibit tuberculosis.



$R^1 = R^2 = \text{H, alkyl}$
 $X = \text{OH, OR}^1, \text{NH}_2, \text{NHR}^1, \text{NR}^1_2, \text{NHCH}_2\text{OH}$
 $n = 10\text{--}15$

1.05.12.4 Toxicity

When toxic but sublethal oral doses of 125 mg kg^{-1} (1.1 mmol kg^{-1}) of 1-cyano-3,4-epithiobutane (CEB) were given by gavage to male CDF rats once daily for 1, 2, or 3 days, CEB-induced changes included degeneration and necrosis of the *pars recta* of the renal proximal tubules, ulceration and necrosis in the forestomach, a mild increase (4.5-fold) in daily urinary thiocyanate (SCN^-) excretion (only in rats treated for 3 days) and 1.5- to 2.4-fold increases in hepatic and pancreatic nonprotein thiol (RSH) concentrations (in all CEB-treated groups) <88MI 105-02>. The metabolite and distribution of $[2\text{-}^{14}\text{C}]$ - and ^{35}S -labeled 3,4-epithiobutanenitrile (4ETN) was studied in rat. A dose of $11 \text{ mg 4ETN/kg body wt.}$ was rapidly transformed into water-solution compounds and was mainly excreted in the urine, irrespective of the route of administration (oral or IP). The main metabolite in the urine was identified by GC-MS as a mercapturic acid derivative. Thiirane may function as a weak biological alkylation agent <84MI 105-01>. The LD_{50} values for a 30 minute survival time were

4000 ppm for thiirane, 5000 ppm for 2-methylthiirane and 750 ppm for 2-chloromethylthiirane <64MI 105-01>. 2-Chloromethylthiirane is about twice as toxic as thiirane and 2-methylthiirane <71MI 105-01, 71MI 105-03>.

1.05.12.5 Insecticides and Herbicides

Several thiirane 1-oxides are reported to be insecticides, molluscicides, or herbicides <68USP3413306>. Thiophosphates of 2-thiomethylthiirane are strong contact insecticides.

1.06

Thiiranes and Thiirenes: Fused-ring Derivatives

SCOTT R. HARRING and TOM LIVINGHOUSE
Montana State University, Bozeman, MT, USA

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1.06.1 INTRODUCTION

1.06.1.1 Historical Perspective

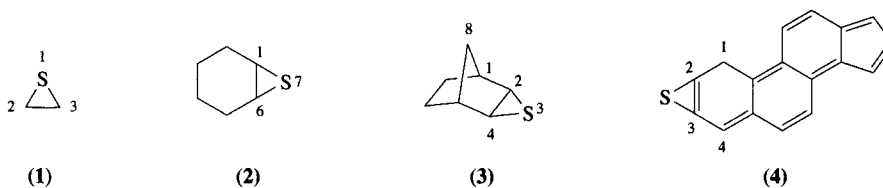
Fused-ring thiiranes and thiirenes have received considerably less study than their monocyclic counterparts. The only general review devoted solely to this class of compounds was that which appeared in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(7)185>.

In contrast, three extensive reviews of monocyclic thiiranes and thiirenes have been published <83HC(42/1)333, 84CHEC-I(7)131, B-84MI 106-01>.

Most of the published literature concerning the preparation and chemistry of thiiranes and thiirenes involves monocyclic derivatives, with an occasional fused-ring example being included for the sake of completeness. This chapter focuses mainly on fused-ring thiiranes and thiirenes, with an emphasis on highlighting the significant advances that have been made from the early 1980s to the mid-1990s.

1.06.1.2 Nomenclature

In contrast to simple compounds which are named as derivatives of the parent thiirane (1), fused-ring thiiranes are named as derivatives of the parent hydrocarbon with a prefix containing a number and "thia" to denote the location of the sulfur atom. Accordingly, compounds (2) and (3) are appropriately named 7-thiabicyclo[4.1.0]heptane and 3-thiatricyclo[2.2.1.0]octane, respectively. Other, less systematic systems of nomenclature that are frequently used for fused-ring thiiranes include: (name of alkene) + "sulfide"; "episulfide"; or "thioepoxide". Until the early 1990s, virtually all known fused-ring thiirenes were those in which the sulfur-bearing ring is fused to an aromatic hydrocarbon. In these cases, numbers (to denote location) + "epithio" + name of parent hydrocarbon have been universally used to designate nomenclatural assignment (e.g., (4) is named 2,3-epithio-1H-cyclopenta[a]-phenanthrene). This manner of nomenclature has also been used for more complex fused-ring thiiranes such as steroid and sugar compounds. Sulfoxide and sulfone analogues of fused-ring thiiranes and thiirenes are correctly named by appending the number denoting the location of the sulfur atom + "oxide" or "dioxide", respectively, to the thiirane name. In some instances the terms episulfoxides and episulfones are encountered.



1.06.2 THERMODYNAMIC ASPECTS

1.06.2.1 Physical Properties and Physical Constants

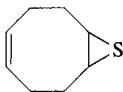
Simple fused-ring thiiranes are colorless, distillable liquids or oils. As expected, the boiling points of these compounds increase with the size of the parent hydrocarbon ring <69JOC3991>. Unsaturation also tends to slightly elevate boiling point relative to fully saturated derivatives (Table 1). Cyclo-octene episulfide is a low-melting solid (m.p. = 25–26°C) <64JOC2702>. More complex fused-ring thiiranes, their oxides and dioxides are also solids with varying melting points. All of the fused-ring thiirenes discussed in this chapter are relatively high-melting solids (m.p. > 100°C). The refractive index (RI) values of several thiiranes and fused-ring thiiranes have been reported <69JOC3991>. Fused-ring thiiranes have significantly higher RIs ($n_D = 1.52$ – 1.57) than most monocyclic thiiranes ($n_D = 1.48$ – 1.49). The RIs of fused-ring thiiranes tend to get larger as the size of the hydrocarbon ring increases.

Dipole moments of fused-ring thiiranes and thiirenes have not been reported. In contrast, dipole moments have been measured at 1.66 D, 3.72 D, and 4.41 D for thiirane, thiirane-1-oxide, and thiirane-1,1-dioxide, respectively <84CHEC-I(7)131>.

1.06.2.2 Thermodynamic Stability and Ring Strain

Three-membered rings are well known for being highly strained and much of their chemistry is dictated by this feature. The strain energy of simple thiiranes and thiirenes has previously been

Table 1 Boiling points of selected fused-ring thiiranes.

Thiirane	b.p. (mm Hg)
	30°C (1.0)
	69°C (10)
	70°C (1.0)
	44°C (0.3)

reported in detail <83HC(42/1)333, 84CHEC-I(7)131>. Fusion of thiiranes and thiirenes to cyclic compounds would be expected to increase the strain energy, but the measured or calculated values from this additional contribution have yet to be reported.

Fused-ring thiiranes are thermally quite stable, although they have been reported to exude sulfur at greatly elevated temperatures. Most thiirane oxides and dioxides are also reasonably stable at room temperature. The latter compounds, however, decompose slowly at temperatures slightly above ambient and rapidly at temperatures of about 100°C. Generally, the loss of SO₂ from episulfones is more facile than loss of SO from episulfoxides. In contrast to fused-ring thiiranes, monocyclic and fused-ring thiirenes are very unstable species which have very short half lives even when prepared in frozen matrices <78JOC2490, 81JA486>. These species, however, have been postulated as intermediates in several reactions <78JOC2487, 79LA1734, 83CJC2268, 92ACS482>. In addition to their highly strained nature, the instability of thiirenes can be attributed to the fact that they are Hückel [4*n*] antiaromatic compounds (*n* = 1). Conversely, thiirene oxides and dioxides obey the Hückel [4*n* + 2] rule for aromaticity (*n* = 0) and enjoy substantial electronic stabilization. As a result, these species are even more thermally stable than their saturated counterparts. This reactivity profile parallels that of cyclopropane, cyclopropene, and cyclopropenone.

1.06.2.3 Conformational Analysis

As has been pointed out by Hart <84CHEC-I(7)185>, thiiranes fused to cyclopentanes adopt a boat conformation with C(3) and the sulfur atom on the same side of the C(1)C(2)C(4)C(5) plane. The angle of deviation from this plane is about 30° for C(3) and 60–70° for the S atom. Cyclohexane rings having fused thiiranes prefer a twisted half-chair conformation. Thiiranes fused to larger cycloalkanes can adopt a wide variety of conformations.

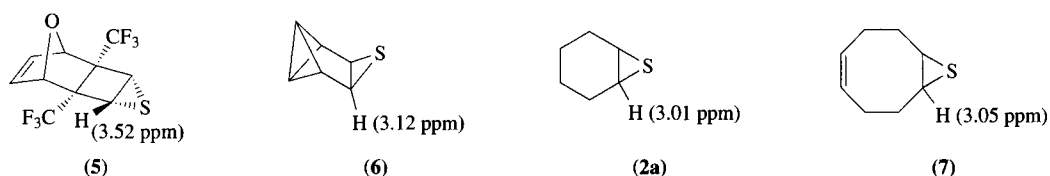
1.06.3 EXPERIMENTAL STRUCTURAL METHODS

1.06.3.1 NMR Spectroscopy

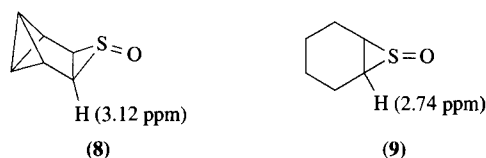
Several structural factors which affect the chemical shift and coupling constants in the ¹H NMR of monocyclic thiiranes have been examined. In many of these cases the details of the spectra have been compared to those of oxiranes, aziridines, and cyclopropanes <83HC(42/1)333, 84CHEC-I(7)131>. To date, however, a general account of the spectroscopic characteristics of fused-ring thiiranes has not appeared in the literature. The following discussion summarizes the general features of the ¹H and ¹³C NMR spectra of fused-ring thiiranes.

The chemical shift values (δ) of the methine ring junction protons are noticeably more downfield (from TMS) than the methylene protons of thiirane (δ = 2.27 ppm) or the methine protons in

2-methylthiirane ($\delta = 2.84$ ppm). This feature is exemplified by the δ values for compounds (**2a**) <79JCS(P1)765>, (**5**) <84TL1917>, (**6**) <82CB3213>, and (**7**) <77CC661>. It can readily be seen that the chemical shift associated with these compounds remains fairly constant as the size of the fused ring changes. As would be expected for *cis*-fused three-membered rings, the ring junction protons are eclipsed, and consequently little proton–proton coupling is observed. The coupling constant, J , in (**6**) is 0.8 Hz, whereas the ring junction protons in (**5**) and (**2a**) are reported as multiplets (m) with no defined J values given. The latter situation is also commonly observed in the ^1H NMR spectrum of fused-ring thiiranes.

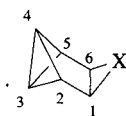


Stable thiirane sulfoxides have an *anti* relationship of the sulfinyl oxygen with respect to the alkyl groups. Consequently, the protons *syn* to the oxygen atom are deshielded and shifted downfield relative to the same protons in the thiirane. As expected, the opposite is true for protons *syn* to the lone pair of electrons on sulfur. Although this effect is much more pronounced for the protons on the alkyl group (and has been used as a tool for assigning relative stereochemistry), protons bonded directly to the thiirane ring also follow this trend. However, the same is not necessarily true for fused-ring thiiranes. The chemical shifts of the ring junction protons of the S-oxides of (**8**) <82CB3213> and (**9**) <83HC(42/1)333> are 3.12 ppm and 2.74 ppm, respectively. This data suggests that fused-ring thiirane oxides favor a conformation that has the sulfinyl oxygen *syn* to the alkyl ring, which causes the observed upfield shift of the ring junction protons. Alternatively, these compounds might adopt a conformation that imparts no observable shielding. The reported ^1H NMR signals of episulfones are multiplets (with no reported J values) with δ values typically around 3.60 ppm <93JCS(P1)2317>.



The ring junction carbons appear at about 40 ppm and 155 ppm in the ^{13}C NMR spectrum of fused-ring thiiranes and thiirenes, respectively. Conjugation of π -systems to the site of ring fusion causes a downfield shift of approximately 10 ppm. The chemical shift of these carbons in fused-ring thiirane oxides and dioxides is generally in the 50–55 ppm range.

Generally, the presence of a fused three-membered ring has little effect on the chemical shifts of other carbons in the molecule. A notable exception is tetracyclo[4.1.0.0^{2,4}.0^{3,5}]heptane (**6d**). Christl *et al.* made an extensive ^{13}C NMR study of this rigid system (**6d**) and its 7-hetero derivatives (**6a–c**) <82JOC661>. The presence of the three-membered ring imparts a substantial shielding (“*syn*”) effect upon C(4) causing an upfield shift of -6.3 to -14.2 ppm of this carbon relative to its position in the non-annulated hydrocarbon. An even greater deshielding (“*anti*”) effect upon C(3) was observed which resulted in a downfield shift of 19.7–29.0 ppm. Interestingly, the observed *syn* effect on C(4) increases in the order $\text{X} = \text{S} < \text{O} < \text{CH}_2 < \text{NH}$, whereas the *anti* effect on C(3) increases in the order $\text{X} = \text{CH}_2 < \text{O} < \text{NH} < \text{S}$.



- (**6a**) $\text{X} = \text{S}$
 (**6b**) $\text{X} = \text{O}$
 (**6c**) $\text{X} = \text{NH}$
 (**6d**) $\text{X} = \text{CH}_2$

1.06.3.2 Infrared, Raman, Ultraviolet, and Microwave Spectroscopy

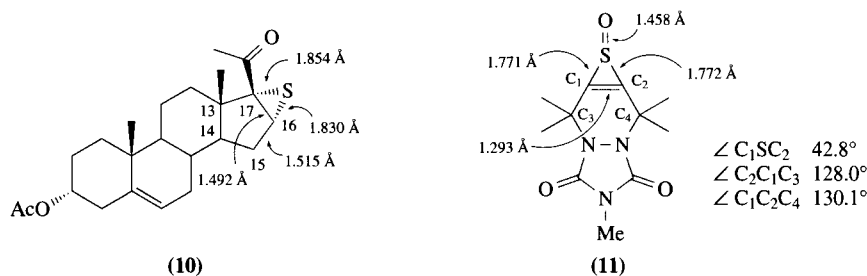
A detailed examination of the IR and Raman spectra of thiiranes and thiirenes has appeared in previous reviews $\langle 83\text{HC}(42/1)333, 84\text{CHEC-I}(7)131 \rangle$. The absorption frequencies observed for thiiranes and thiirenes tend to be characteristic for the three-membered ring and are not significantly shifted upon its fusion to carbocycles. However, the S—O bond stretch occurs at 1115 cm^{-1} for fused ring thiirene oxides but is observed at 1060 cm^{-1} in 2,3-diphenylthiirene-1-oxide.

The solution phase UV spectrum of 7-thiabicyclo[4.2.0]heptane has a maximum absorbance of 262.5 nm and a minimum of 237.0 nm, which are nearly identical to those of thiirane and 2-methylthiirane $\langle 58\text{JOC}216 \rangle$.

The microwave spectrum of 7-thiabicyclo[4.2.0]heptane has been reported $\langle 73\text{CJC}529 \rangle$ and the results are consistent with the twisted half-chair conformation described in Section 1.06.2.3.

1.06.3.3 X-ray Crystallography

Some bond lengths (in Å) and bond angles of the 16,17-epithio-steroid (**10**) $\langle 82\text{T}165 \rangle$ and thiirene oxide (**11**) $\langle 82\text{JA}4981 \rangle$ are shown. The D-ring of (**10**) assumes a boat conformation with C(14) lying 38° below the plane of C(13) C(15) C(16) C(17) and the sulfur atom situated 68° below the same plane. These results are in accordance with the expected conformation of a three-membered ring fused to a cyclopentane (Section 1.06.2.3). The S—O bond length of (**11**) is much shorter than that in 2,3-diphenylthiirene 1-oxide (1.467 Å). This feature results in shorter C—S and C=C bonds in (**11**) compared with those of the diphenyl compound (1.784 Å and 1.305 Å, respectively). In addition, the oxygen atom of (**11**) has a deviation angle of 63.9° relative to the thiirene ring.



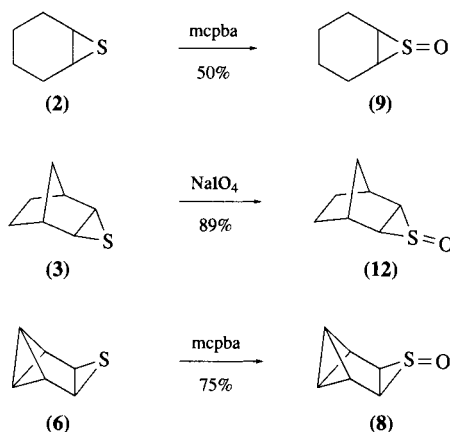
1.06.4 REACTIVITY OF THE THREE-MEMBERED RING

1.06.4.1 Oxidation of Sulfur

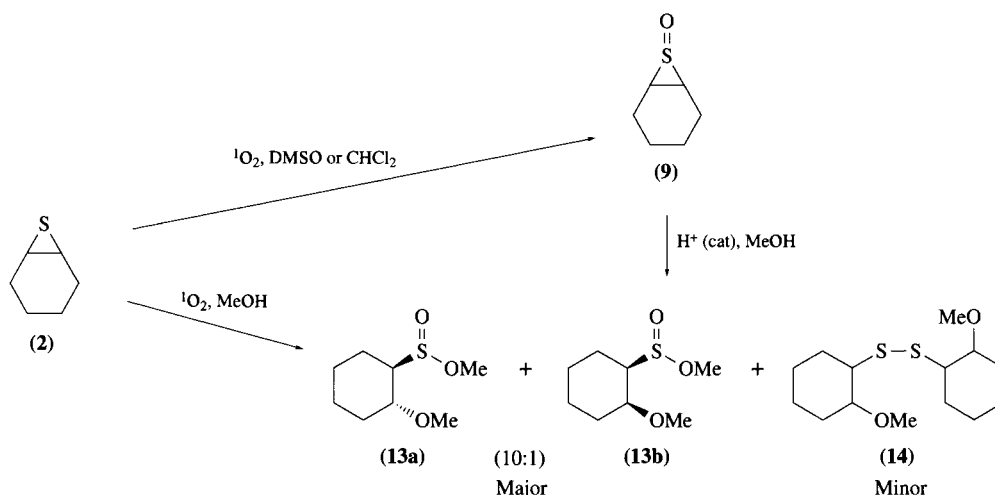
The isolation of thiirane oxides prepared by oxidation of the corresponding thiiranes has been somewhat problematic, and the isolation of thiirane dioxides from the direct oxidation of thiiranes or thiirane oxides has yet to be reported. Traditional methods of sulfide oxidation typically give low yields of impure materials when applied to thiiranes. Opening of the strained three-membered ring is the primary cause of these difficulties.

Despite the general shortcomings associated with the oxidation of monocyclic thiiranes, highly strained fused-ring thiiranes can be successfully oxidized to thiirane oxides under carefully controlled reaction conditions. Oxidation of thiiranes (**2**) $\langle 69\text{TL}2461 \rangle$, (**3**) $\langle 74\text{JAP}(K)7435375 \rangle$, and (**6**) $\langle 82\text{CB}3213 \rangle$ with MCPBA or NaIO_4 afforded good yields of thiirane oxides (**9**), (**12**), and (**8**), respectively, as shown in Scheme 1. Photosensitized oxygenation of (**2**) in non-nucleophilic solvents such as DMSO or CH_2Cl_2 also afforded (**9**) as the major or exclusive product $\langle 87\text{JA}1478 \rangle$. Photooxygenation of (**2**) in MeOH, however, gave a (1 : 10) *cis* : *trans* mixture of the ring-opened β -methoxy sulfinate esters (**13a**) and (**13b**) as the major products. Ando has reported formation of disulfide (**14**) in addition to (**13a**) and (**13b**) under similar conditions $\langle 88\text{JA}494 \rangle$. Sulfinate esters (**13a**) and (**13b**) were also

obtained by acid-catalyzed methanolysis of thiirane oxide (9). These results are illustrated in Scheme 2. In light of the results shown in Scheme 2, it is interesting to note that reaction of (3) with $^1\text{O}_2$ in MeOH reportedly furnished thiirane oxide (12) quantitatively.



Scheme 1



Scheme 2

1.06.4.2 Reduction of Sulfur

In contrast to oxidation of the sulfur atom, reduction of sulfur (also called extrusion or elimination) from thiiranes and thiirenes is a relatively facile process. Virtually all thiiranes and thiirenes, as well as their oxides and dioxides, undergo thermal extrusion of the sulfur moiety with increasing facility according to the trend $\text{S} \ll \text{SO} < \text{SO}_2$.

In addition to thermal extrusion, a variety of reagents have been shown to facilitate the loss of sulfur from thiiranes and thiirenes (83HC(42/1)333). The most frequently encountered reagents for this purpose are trivalent phosphines (both trialkyl and triaryl) which give alkenes stereoselectivity.

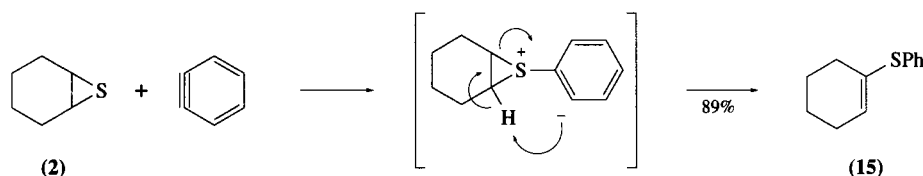
Two new methods for thiirane reduction have been described. The first entails reduction with lithium(0) in refluxing DME (84JJC(B)879). Both cyclohexene episulfide and cyclohexene oxide are cleanly converted to cyclohexene under these conditions, and both *cis*- and *trans*-2,3-diphenylthiirane (or a mixture of isomers) gave only *trans*-stilbene. An explanation for the latter result was not stated. Cyclohexene was also formed quantitatively by treatment of cyclohexene sulfide with

tetramesityldisilene, whereas formation of a silyl enol ether was the predominant reaction pathway with cyclohexene oxide <93CC1348>. Neither of these methods seems to offer a distinct advantage over existing methods of thiirane desulfurization.

1.06.4.3 Reactions of the Three-membered Ring with Electrophiles

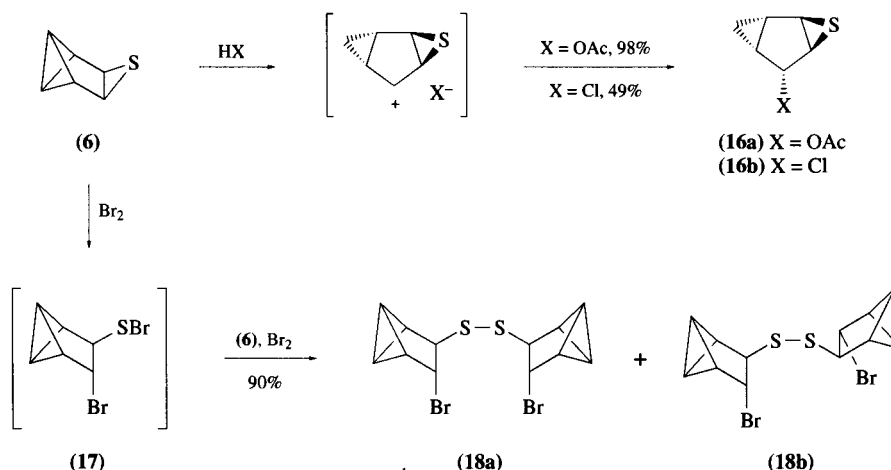
The reactions of thiiranes with electrophiles has been extensively studied and well reviewed <83HC(42/1)333, 84CHEC-I(7)131>. Generally, electrophilic additions to thiiranes may be stereoselective and result in both Markovnikov and anti-Markovnikov ring-opened products from unsymmetrical thiiranes. The nature of the products in terms of stereochemistry and mode of addition are reflective of cyclic (thiiranium or episulfonium ion) and open-chain (carbocation) intermediates. The generation and chemistry of episulfonium ions has been reviewed in detail and is not elaborated further here <B-92MI 106-01>. The following is an overview of the chemistry of thiiranes with electrophiles.

Benzyne was shown to react with a variety of monocyclic and fused-ring thiiranes to produce vinyl thiophenyl ethers <84TL2679>. Initial reaction gives an intermediate betaine, which abstracts the most acidic (kinetic) ring proton, with concomitant C=C bond formation and C—S bond scission, to give excellent yields of products (illustrated for (2) in Scheme 3). The stereochemistry of the starting thiiranes is preserved in the product vinyl sulfides.



Scheme 3

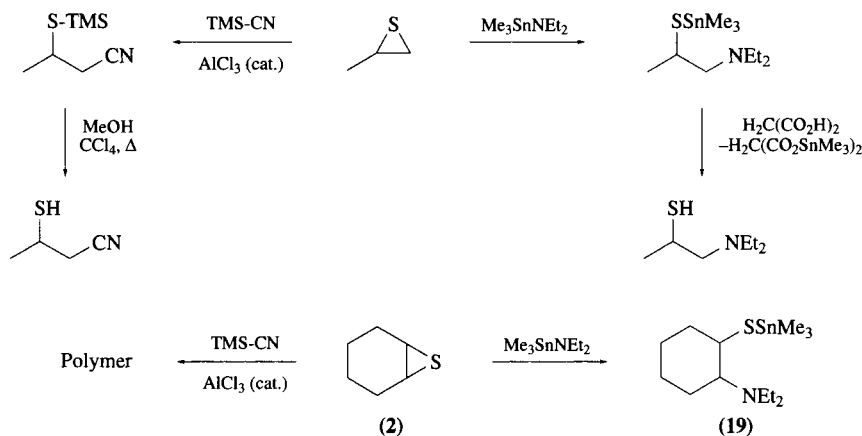
In addition to oxidation, the chemistry of 7-thiatetracyclo[4.1.0.0.^{2,4}.0^{3,5}]heptane (6) with acids and halogens was investigated and gave contrasting results (Scheme 4) <82CB3213>. Treatment of (6) with acetic or hydrochloric acid leads exclusively to protonation and ring opening of the cyclopropane. Subsequent capture of the resultant carbonium ion gave fused cyclopentane derivatives (16a; X = OAc) and (16b; X = Cl) in 98% and 49% yields, respectively. On the other hand, bromination of (6) gave sulfenyl bromide (17) which underwent further reaction with (6) and bromine to afford a (1 : 1) mixture of meso- and d,l-disulfides (18a) and (18b), respectively, in 90% overall yield.



Scheme 4

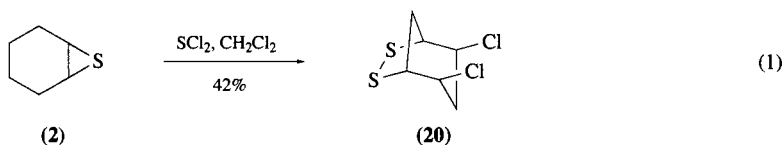
Methylthiirane undergoes regioselective nucleophilic ring opening with TMS-CN in the presence of AlCl_3 to give 3-thiolbutyronitrile following cleavage of the S—TMS group with MeOH in

refluxing CCl_4 . Reaction of 7-thiabicyclo[4.1.0]heptane (**2**) under these conditions leads only to polymerization catalyzed by the Lewis acid. In similar fashion to methylthiirane, (**2**) reacted with $\text{Me}_3\text{SnNEt}_2$ without added catalyst to afford bisfunctionalized cyclohexane (**19**) (stereochemistry undefined). Cleavage of the S—Sn bond in the methylthiirane adduct was achieved by heating with one equivalent of malonic acid under vacuum. The reactions of thiiranes with group 14 organo-metallic reagents are summarized in Scheme 5 <83TL2311>.



Scheme 5

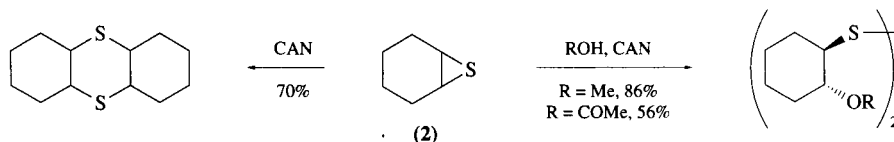
Cyclohexene sulfide (**2**) gave disulfide (**20**) in 42% yield when exposed to SCl_2 in CH_2Cl_2 (Equation (1)) <83TL319>. A mechanism to account for this novel transformation was not suggested.



1.06.4.4 Reactions of the Three-membered Ring with Nucleophiles

Nucleophilic ring opening has probably been the most intensively studied and well documented of the reactions of thiiranes <83HC(42/1)333, 84CHEC-I(7)131>. As would be expected, this mode of ring opening occurs predominantly at the least hindered carbon, and *trans*-addition of the nucleophile to fused-ring thiirane is observed almost exclusively. As with the chemistry of electrophiles, relatively little effort has been directed toward further development of the reactions of thiiranes with nucleophiles in the past decade. The following is a brief account of some advances in this area, with an emphasis placed on fused-ring thiiranes.

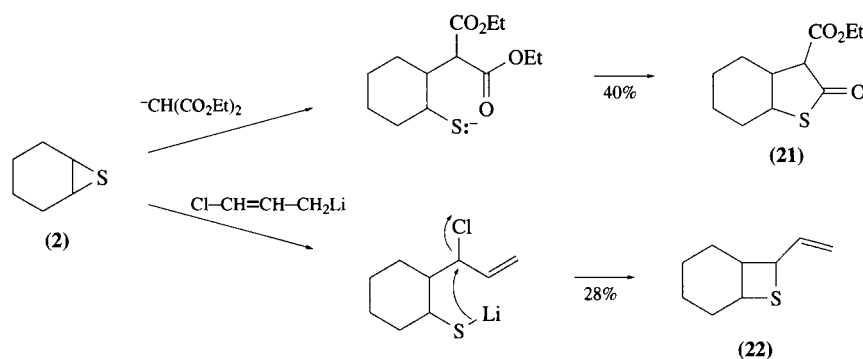
Cerium(IV) salts have been shown to promote the ring opening of thiiranes <91T149>. Accordingly, reaction of thiiranes with several alcohols or acetic acid in the presence of ceric ammonium nitrate (CAN) gave good to excellent yields of *trans*-bisalkoxy (or bisacetoxo) disulfides. Furthermore, by refluxing a CCl_4 solution of thiiranes and CAN in the absence of external nucleophiles, dimeric products were obtained. The observations are summarized for (**2**) in Scheme 6.



Scheme 6

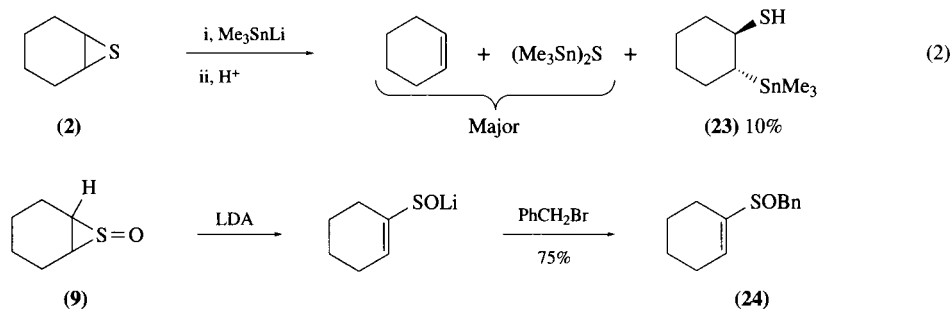
The reaction of active methylene compounds in the presence of base with thiiranes is well known; however, yields tend to be diminished by intervening polymerization under the conditions that have

been employed. Taguchi and Suhara reported that reasonable yields of dihydro-2(3*H*)-thiophenone derivatives could be obtained from the reactions of thiiranes and active methylene compounds under appropriately chosen reaction conditions <86BCJ2321>. Only a 40% yield of the heterocyclic product (**21**) was realized from cyclohexane episulfide (**2**) and diethyl malonate, but yields as high as 70% were reported for the corresponding reactions of 2,2-dimethylthiirane. The reagent 3-chloroallyllithium reacts via the α -chloro carbon atom to ring open thiiranes at -90°C <85S1069>. The intermediate thiolate subsequently displaces chloride to furnish 2-vinylthietanes which are difficult to prepare by other routes. Under these reaction conditions, ring opening of sterically hindered thiiranes (e.g., (**2**)) is apparently slow and gives only 20–30% conversion to vinyl thietane (**22**). Scheme 7 summarizes the chemistry of (**2**) with carbon-based nucleophiles.



Scheme 7

Trimethylstannyl lithium ring opens oxiranes and simple thiiranes at the least-hindered carbon, affording β -stannyl alcohols and thiols following hydrolytic workup <86G239>. Reaction of (**2**) with this reagent, however, gave predominantly cyclohexene and bis(trimethylstannyl)sulfide accompanied by about 10% of the difunctionalized cyclohexene (**23**) (Equation (2)). The latter result is not particularly surprising as alkylolithiums and Grignard reagents are well known for desulfurization of thiiranes by initial attack on the sulfur and subsequent decomposition. Much effort has been devoted to elucidating the chemistry of bases toward thiiranes and thiirenes (i.e., S-attack, C-attack, and H^+ abstraction). Schwan *et al.* have shown that thiirane oxides are selectively deprotonated by hindered amide bases to generate *trans*-substituted ethenesulfenate anions which can be alkylated *in situ* to provide the corresponding sulfenate esters <93CC1312>. Sulfenate ester (**24**) was also formed in good (75%) yield from thiirane oxide (**9**) (Scheme 8).



Scheme 8

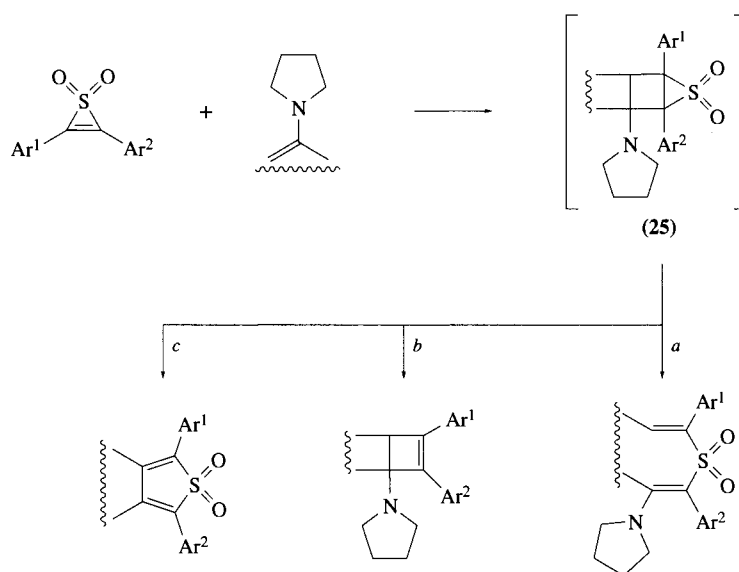
1.06.5 CYCLOADDITIONS INVOLVING THIIRANES AND THIIRENES

A unique approach to the synthesis of fused-ring thiiranes and thiirenes involves the utilization of cycloaddition methodology. The use of diphenylthiirene oxide and the corresponding dioxide as dieneophiles in $[2 + 2]$, $[4 + 2]$, and 1,3-dipolar cycloadditions is well established. Often the initial

cycloadducts are unstable and eliminate SO or SO₂, giving alkenes as the isolated products. Cycloadducts which still bear the sulfur moiety readily undergo a subsequent cycloaddition or other chemistry.

1.06.5.1 [2 + 2] and [4 + 2] Cycloadditions

The first, and up to 1995 only, examples of monocyclic thiirenes being utilized as components in [2 + 2] cycloaddition chemistry involve the reaction of 2,3-diaryl thiirene dioxides with enamines, as reported by Rosen and Bonet <74JOC3805>. They postulated that the thiirene dioxide and enamine underwent an initial thermal, *non-concerted*, [2 + 2] cycloaddition to give an intermediate fused-ring thiirane dioxide (25) which underwent fragmentation via one of three pathways. These are: (a) cycloreversion with opening of the cyclobutane ring; (b) SO₂ extrusion; and (c) elimination of HNR₂; as shown in Scheme 9. The observed products and yields were highly dependent on the exact nature of the substrate and reaction conditions.

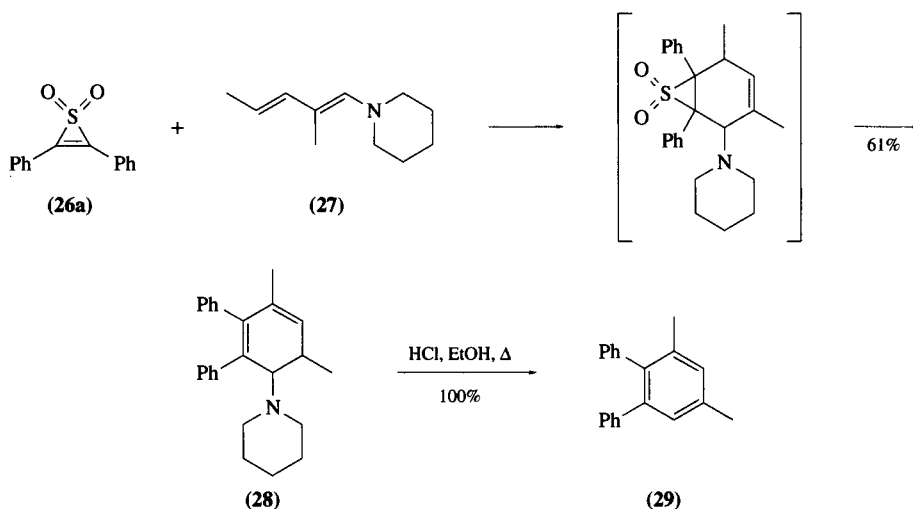


Scheme 9

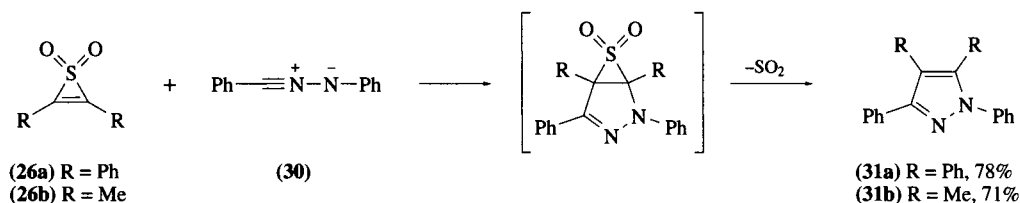
Diphenylthiirene dioxide (26a) was found to react with 1-piperidino-2-methyl-1,3-pentadiene (27) to afford dihydrobenzene (28) in 61% yield following loss of SO₂. Deamination with refluxing HCl in ethanol gave the highly substituted benzene (29) quantitatively (Scheme 10) <84JOC1300>. Diels–Alder reaction between dimethylthiirene dioxide (26b) and (27) provided 1,2,3,5-tetramethylbenzene directly but in only 12% overall yield.

1.06.5.2 1,3-Dipolar Cycloadditions

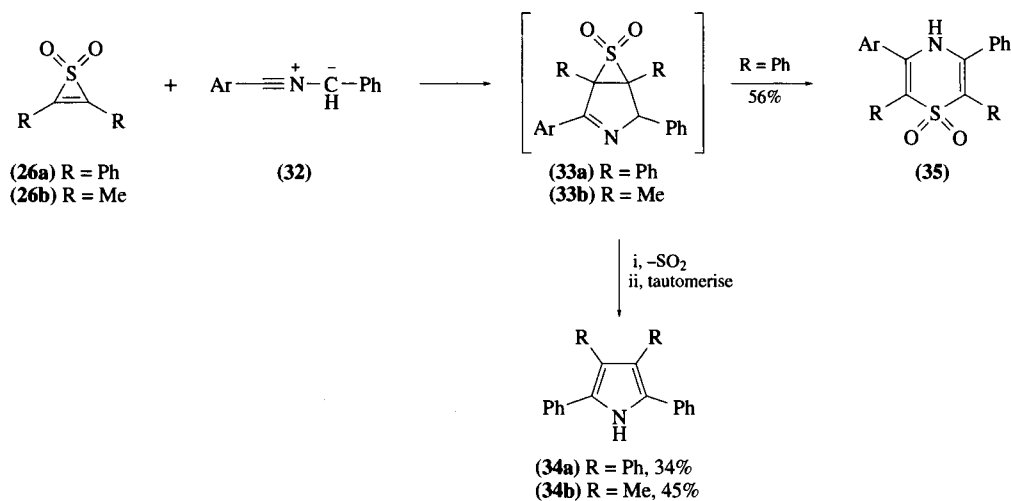
Diphenyl and dimethyl thiirene dioxides (26a) and (26b) were also shown to be excellent dipolarophiles, as evidenced by their smooth cycloadditions with various 1,3-dipoles <84JOC1300>. The highly substituted pyrazoles (31a) and (31b) were obtained in 78% and 71% yield, respectively, upon cycloaddition with benzonitrilium *N*-phenyl-imide (30) followed by SO₂ extrusion (Scheme 11). An analogous dipolar cycloaddition with benzonitrilium dipole (32) afforded (33a) and (33b) as the initial cycloadducts. Cycloadduct (33b) underwent *in situ* sulfur dioxide elimination and subsequent tautomerization to afford pyrrole (34b) in 45% yield as the sole product. In addition to providing pyrrole (34a) (34%), cycloadduct (33a) also afforded thiazine (35) in 56% yield via ring enlargement (Scheme 12). A similar thiazine dioxide was observed from the reaction of (26a) with azide ion <78TL3781>. It is noteworthy that thiirene dioxides (26a, b) failed to react with benzonitrile oxide, however.



Scheme 10



Scheme 11

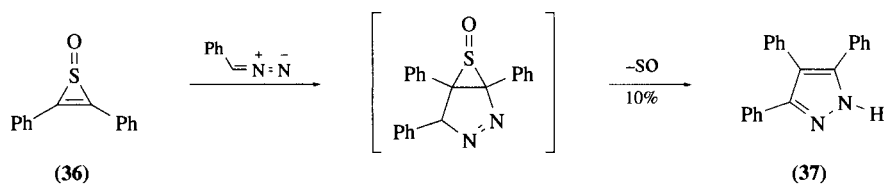


Scheme 12

Carpino found that diphenylthiirene oxide **(36)** reacted with phenyl diazomethane to afford a low yield of 3,4,5-triphenylpyrazole **(37)** presumably by cycloaddition/SO-extrusion (Scheme 13) <79JA390>.

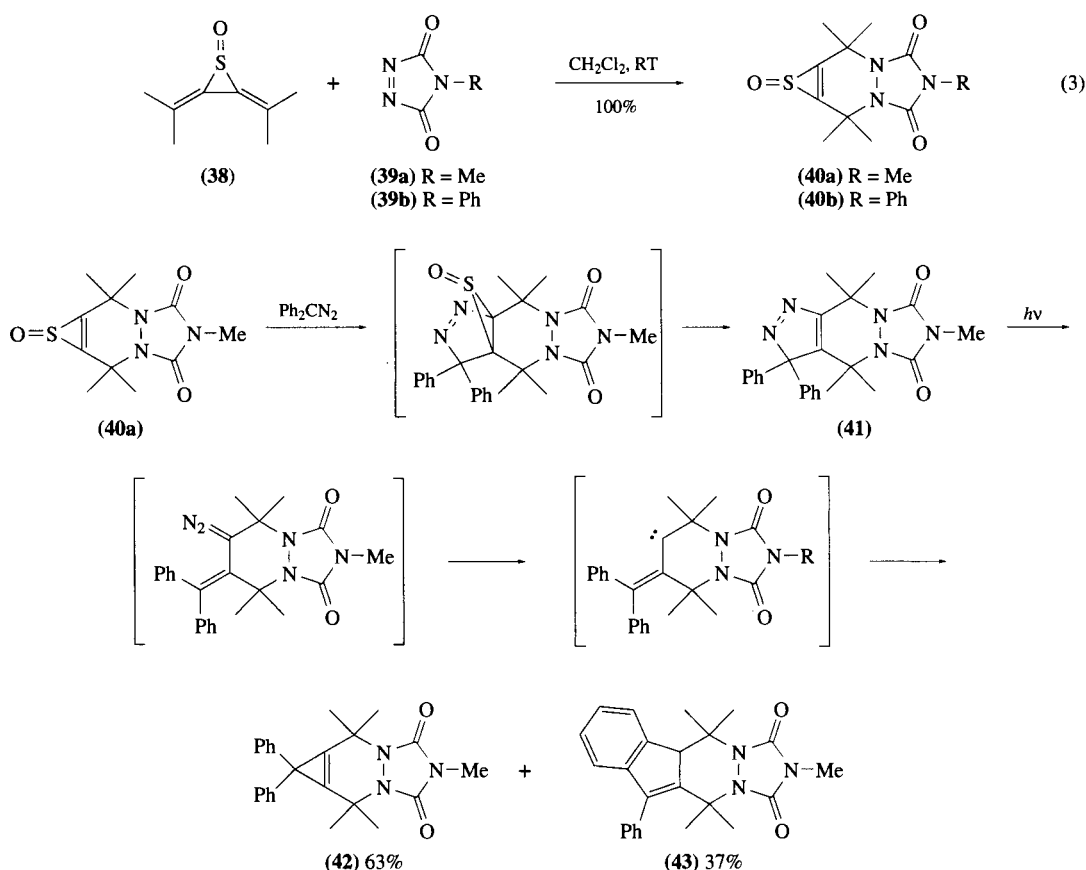
1.06.5.3 Synthesis of Fused-ring Thiirenes via Cycloadditions

Perhaps the most significant advancement in the chemistry of thiiranes and thiirenes in the 10–15 years to the mid-1990s has been the synthesis of stable non-aromatic fused-ring thiirenes. Ando *et al.* have pioneered the use of the thiiranoradialene sulfoxide **(38)** as the diene component in



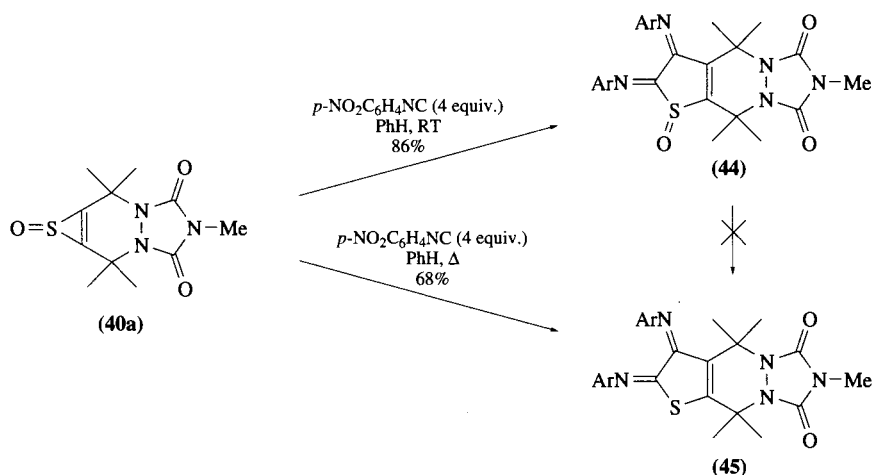
Scheme 13

several cycloadditions which result in the preparation of fused-ring thiirenes ^[81TL4815]. Accordingly, reaction of (38) with 4-substituted 1,2,4-triazoline-3,5-diones (39a) and (39b), in CH₂Cl₂ at room temperature, gave quantitative conversion to the cycloadducts (40a) and (40b) (Equation (3)) ^[82JA4981]. It is noteworthy that attempted cycloaddition of the deoxygenated analogue of (38) resulted in complex reaction mixtures, presumably due to competing [2 + 2] cycloadditions, ene reactions, etc. Fused-ring thiirene (40a) was shown to undergo a subsequent dipolar cycloaddition with excess diphenyldiazomethane, giving 54% chromatographed yield of 3-H pyrazole (41) following loss of SO. Irradiation of (41) gave the fused cyclopropene (42) and phenyl C—H insertion product (43) in 63% and 37% yield, respectively, as outlined in Scheme 14 ^[84JA2216]. Reaction of (40a) with four equivalents of 4-nitrophenyl isocyanide in benzene at room temperature gave the bis-iminosulfoxide (44) in 86% yield, whereas refluxing the same components in benzene gave a 66% yield of the deoxygenated product (45). It was further shown that (45) does not arise from (44), but was probably deoxygenated following the addition/ring-expansion involving one equivalent of the isocyanide (Scheme 15) ^[86JOC2122].



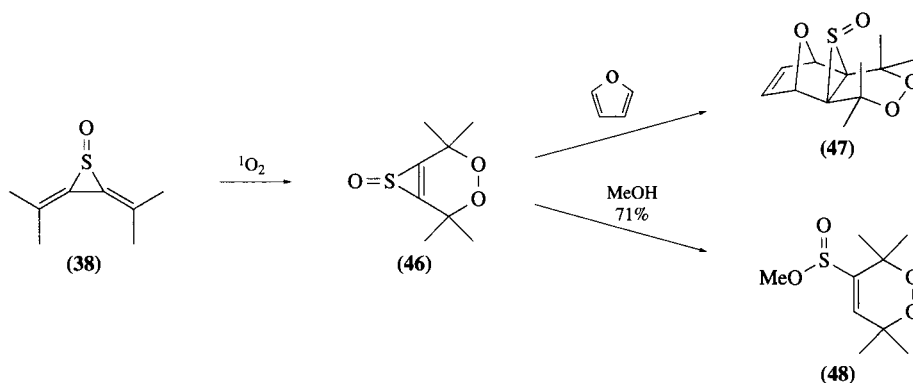
Scheme 14

Thiiranoradialene sulfoxide (38) was also found to participate in [4 + 2] cycloaddition with singlet O₂ to afford endoperoxide (46), which underwent a second Diels–Alder reaction in furan to give the



Scheme 15

novel cycloadduct (**47**). Alternatively, exposure of (**46**) to methanol resulted in nucleophilic attack at sulfur with concomitant ring opening to give the vinyl sulfinate ester (**48**) in 71% yield (Scheme 16) <84TL1483>. In contrast, exposure of 2,3-diphenylthiirene oxide to methanol gave quantitative recovery of starting material, thus highlighting the reactive nature of thiirene oxides in fused-ring systems.



Scheme 16

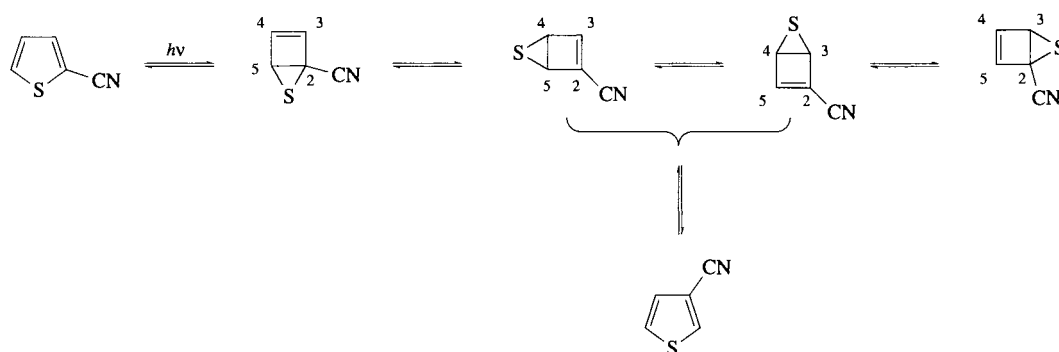
1.06.6 PHOTOCHEMICAL PROCESSES INVOLVING THIIRANES

1.06.6.1 Photolysis of Thiophenes

Photolysis of thiophenes is known to result in formation of Dewar thiophenes. The transposition of functional groups upon irradiation of thiophenes has been explained by the familiar "sulfur-walk" mechanism via the initial formation of a Dewar thiophene as illustrated for 2-cyanothiophene in Scheme 17 <79CC881>. The presence of trifluoromethyl groups imparts special stability on the Dewar thiophene, and this feature has been used to advantage by several organic chemists.

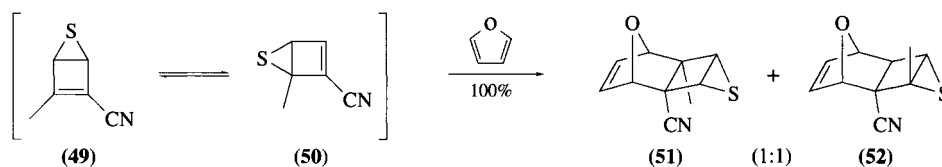
1.06.6.2 Cycloadditions of Dewar Thiophenes

Dewar thiophenes are sufficiently long lived (and in some cases isolable) to be trapped by dienes and 1,3-dipoles. Thiabicyclo[2.1.0]pentene, (**49**), is an example of an isolable Dewar thiophene which, when warmed in CDCl_3 containing 5% furan, afforded a 1 : 1 mixture of cycloadducts (**51**)

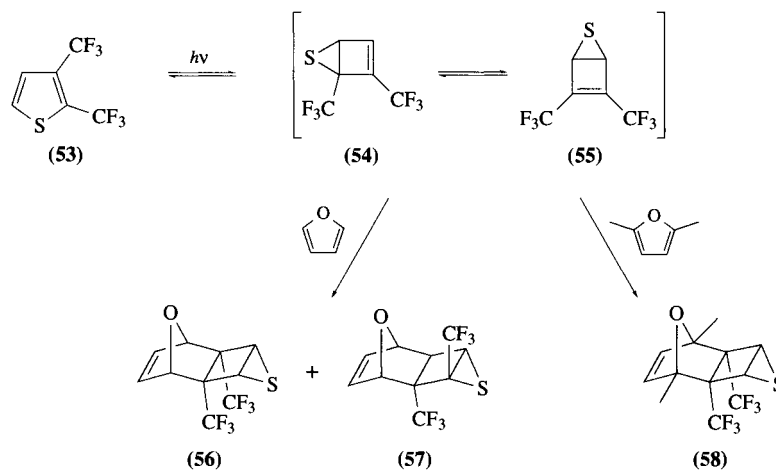


Scheme 17

and (52) quantitatively (Scheme 18) <79CC966>. At low temperatures it was shown by NMR that (50) is rapidly ($t_{1/2} = 2$ min at -35°C) isomerized to (49). It was further suggested that at 35°C interconversion between (49) and its tautomer (50) occurs at a rate comparable to the rate of reaction with furan to allow formation of both (51) and (52). Photolysis of 2,3-bis(trifluoromethyl)thiophene (53) gave a similar equilibrium mixture of Dewar thiophenes (54) and (55) which reacted with furan to afford cycloadducts (56) and (57). Interestingly, a single cycloadduct (58) was obtained by irradiation of (53) in the presence of 2,5-dimethyl furan. The preceding results are summarized in Scheme 19 <84TL1917>.



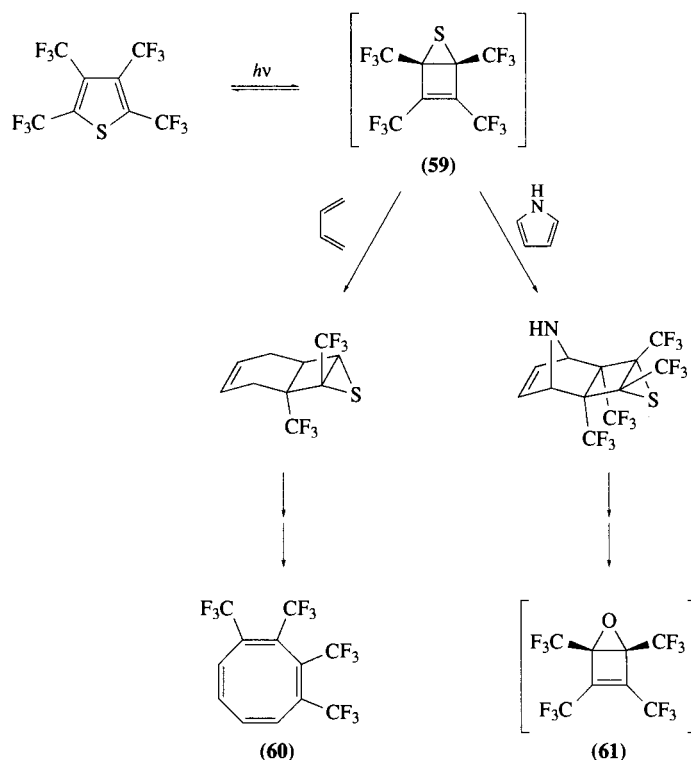
Scheme 18



Scheme 19

Dewar tetrakis(trifluoromethyl)thiophene, (59), has served as a dieneophile (dipolarophile) in several cycloadditions. Diels–Alder reaction of (59) with butadiene <81CC1289> and pyrrole <82JA847> has served as the starting point for the synthesis of 1,2,3,8-tetrakis(trifluoromethyl)cyclooctatetraene (60) and tetrakis(trifluoromethyl)Dewar furan (61), respectively, as illustrated in Scheme 20. It is noteworthy that (61) was unattainable by direct photolysis of the substituted furan. Moreover, (59) served as a common precursor for the preparation of tetrakis- <80JA6633> and penta- <83JA3563> (trifluoromethyl)cyclopentadienides (64) and (65), respectively (Scheme 21). Accordingly, photolysis

of per(trifluoromethyl)thiophene gave (59), which reacted with diazomethane or 2,2,2-trifluoromethyldiazoethane to give dipolar cycloadducts (62) and (63), respectively. Desulfurization of (62) with 1,3-dimethylimidazole-2-thione is noteworthy in the sense that it did not promote protiotopic tautomerism of the azole as was observed with (63) in the presence of PPh_3 . Treatment of (63) with several weak acids or bases, however, promoted this tautomerism without desulfurization. Anion (64) was eventually converted to the diazocyclopentadiene derivative (66).



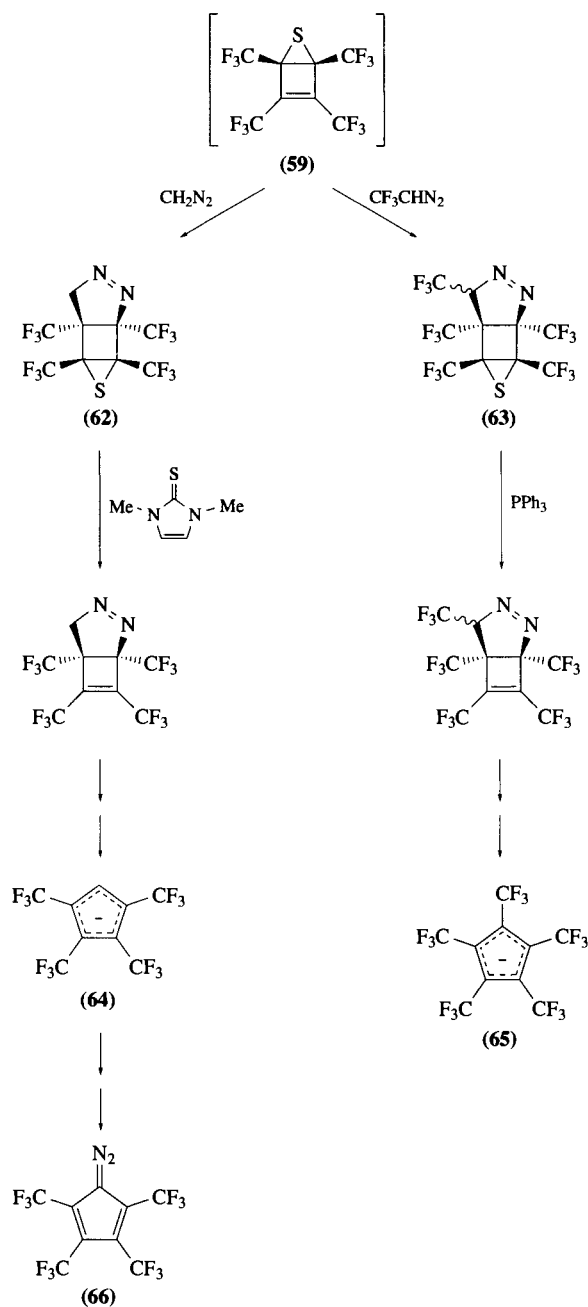
Scheme 20

Dewar thiophene itself was formed during solution phase photolysis of thiophene, as evidenced by the isolation of its furan cycloadduct. The same product was obtained by the photolysis of thiophene as a rigid glass phase at -170°C followed by reaction with furan in the dark. Irradiation of thiophene in an argon matrix at 10 K gave, in addition to Dewar thiophene, cyclopropenyl thioaldehyde, 2,3-butadienethial, carbon disulfide, propyne, and vinyl ethyne, depending on the wavelength of light that was used for irradiation (86JA1691).

1.06.6.3 Miscellaneous Photolytic Reactions Involving Thiiranes

Heterononins are 10 π -electron, nine-membered heterocycles, which are of interest due to their potential aromaticity. Photolysis of heterobicyclo[4.2.0]nona-2,3,6-trienes has been successfully employed to synthesize the oxygen and nitrogen members of this class of compounds, but has failed with the sulfur analogue. Oxidation of the bicyclic sulfide, (67a) to sulfoxide (67b) with NaIO_4 at -15°C , however, afforded the all *cis*-dihydrobenzothiophene oxide (69) (85TL6293). It was suggested that (67b) was unstable under the reaction conditions and subsequently ring expanded to the thiononin oxide (68) (of unknown alkene geometry), which itself underwent a facile intramolecular electrocyclic rearrangement to give (69) (Scheme 22). The *cis* ring junction stereochemistry of (69) contrasted with that found for the analogous phenyl phosphoindole oxide (71) which was formed upon preparation/rearrangement of the analogous bicyclo phosphorus oxide compound (67c). In the latter case, the intermediate phosphonin oxide (70) was sufficiently stable to allow its characterization by spectroscopic techniques, which proved it to possess *cis, cis, cis, trans*-alkene geometry.

Photolysis of thiadiazoles give rise to biradicals which collapse to give thiirenes. Irradiation of thiadiazole (72) in furan or 2,5-dimethylfuran gave low yields of cycloadducts (73) and (74) and

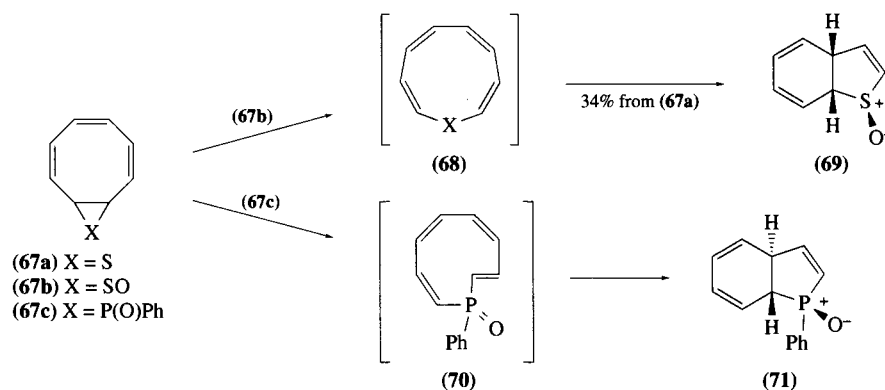


Scheme 21

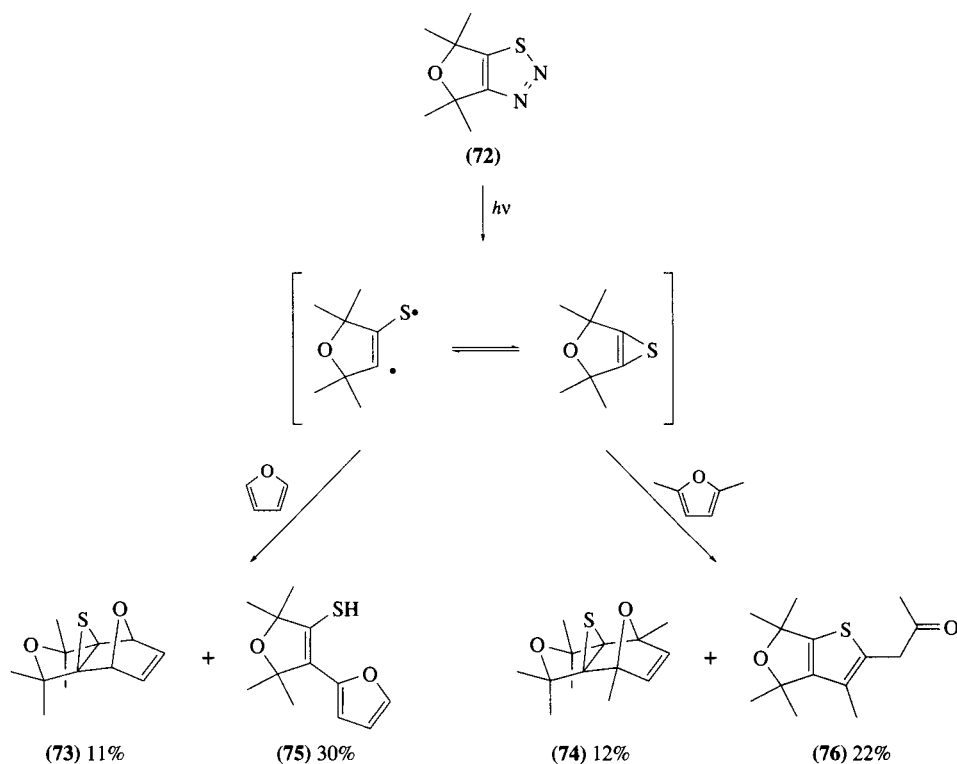
substantial amounts of products (75) and (76) resulting from trapping of the biradical intermediate (Scheme 23) <87TL2867>. This methodology also served to produce the first stable selenirane via cycloaddition of an intermediate selenirene.

1.06.7 SYNTHESIS OF FUSED-RING THIIRANES AND THIIRENES

Several comprehensive accounts on the synthesis of thiiranes on the basis of bond formed <84CHEC-I(7)131>, starting material (i.e., "from") <83HC(42/1)333>, and reagent used <B-84MI 106-01> have appeared in the literature. Mechanistically, all preparatively useful methods for the synthesis of thiiranes rely, at some point, on displacement of a leaving group β to a thiolate anion which is



Scheme 22

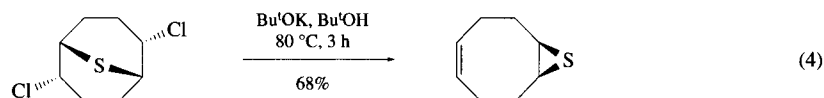


Scheme 23

usually introduced in some protected form and then unmasked by subsequent treatment with an appropriate reagent.

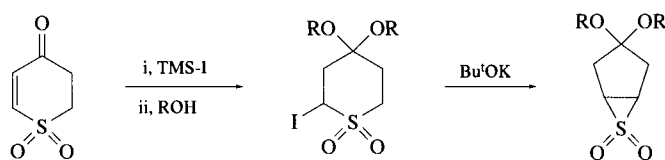
The most general method for preparing fused-ring thiiranes involves treatment of a cycloalkene epoxide with ^-SCN [\(59JA4924\)](#). Alternatively, thiocyanic acid [\(90JMC229\)](#), thioamides [\(86S779\)](#), and phosphine sulfides [\(72JA2880\)](#) have been used in place of thiocyanate to synthesize various fused-ring thiiranes from the corresponding epoxides. These compounds have also been prepared from 2-thiolcycloalkanols by cyclodehydration with either 2,2,2-triphenyl-4,5-(2,2-biphenylene)-1,2,3-dioxaphospholane [\(86JOC4473\)](#), or tetraalkyl orthocarbonates [\(88BCJ1818\)](#). Superhydride reduction of *trans*-2-iodocyclohexylisothiocyanate gave 7-thiabicyclo[4.1.0]heptane (**2**) in excellent 93% yield [\(82H\(19\)1501\)](#). Modest yields of thiiranes (including (**2**)) have been obtained directly from alkenes by reaction with triorganosilylsulfonyl halides [\(83JOM\(258\)1, 88TL4177\)](#). A novel approach to the formation of thiiranes that are fused to larger rings involves the base-induced dehydrohalogenation of

thiabicyclic dihalides as shown in Equation (4) <77CC661>. This method provides an entry to monothioepoxides of biscycloalkenes which might be difficult to synthesize by other means.



The only isolated and characterized fused-ring thiirenes are those resulting from [4 + 2] cycloaddition chemistry as discussed in Section 1.06.6.3. Both photolysis (or thermolysis) of benzo-1,2,3-thiadiazolines and internal halide displacement from 2-halothiophenoxides have previously been reported <83HC(42/1)333, 84CHEC-I(7)131> to give dimeric bis-sulfides via initial formation of a fused-ring thiirene.

The oxidation of fused-ring thiiranes has been the only reported method for preparing fused-ring thiirane oxides (Section 1.06.5.1). A modified version of the Ramberg–Backlund reaction has been shown to afford fused-ring thiirane dioxides in high yield from cyclic sulfones, as shown in Scheme 24 <93JCS(PI)2317>. Analogous methodology has been repeatedly utilized to synthesize several monocyclic thiirene oxides and dioxides.



Scheme 24

1.06.8 USES OF FUSED-RING THIIRANES AND THIIRENES

The major industrial use of thiiranes, thiirenes, and their fused-ring derivatives is as monomers for polymerization. Over half of the listings in *Chemical Abstracts* under the general subject “thiirane”, as well as those under specific compound names, are devoted to polymers or polymerization, many of which are references to patents.

Cyclic thiocarbonyl ylides, in the absence of a trapping agent, collapse to form fused-ring thiiranes which eliminate sulfur to afford cyclic alkenes <91SL287>. The *in situ* formation and rearrangement of thiocarbonyl ylides has been exploited by Danishefsky and co-workers in syntheses of ISO-A58365A <89TL3625>, Chilenine alkaloids <89TL2747, 90JOC831>, and Indolizomycin <90JA2003, 93JA30>. Fused-ring thiiranes have also found use as potential thromboxane receptor antagonists <90JMC229>, and have been postulated as intermediates in the synthesis of the 9,11-dithia analogue of the biosynthetic prostaglandin intermediate 13,14-dehydro-PGH₂ <87JOC862>.

1.07

Three-membered Rings with One Selenium or Tellurium Atom

NORIHIRO TOKITOH
University of Tokyo, Japan

and

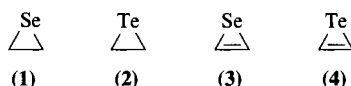
WATARU ANDO and NAMI CHOI
University of Tsukuba, Japan

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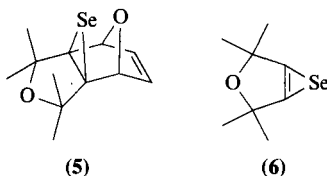
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1.07.1 INTRODUCTION

This chapter is devoted to the chemistry of three-membered carbacyclic compounds containing one selenium or tellurium atom in the ring systems, which are commonly known as seleniranes (**1**) or telluriranes (**2**) for saturated systems. Other systems of nomenclature, for example (i) name of alkene plus chalcogenide, or (ii) name of alkene plus epichalcogenide, have been frequently used in the literature as in the case of thiiranes. Three-membered rings with one selenium or tellurium atom and one C=C double bond may be named as selenirenes (**3**) or tellurirenes (**4**), as well as their oxygen and sulfur analogues.



Differences between thiiranes and their heavier chalcogen analogues, for example seleniranes (**1**) and telluriranes (**2**), are related to the greater size of selenium and tellurium atoms, their greater polarizability, their lower electronegativity, and their lower bond energies with other elements. Due to these differences, seleniranes and telluriranes have lower stability than thiiranes and they have been postulated only as reactive intermediates which undergo ready extrusion of chalcogen atoms to give the corresponding alkenes <B-86MI 107-01>. As a stable example of this class of compounds, only one isolable selenirane (**5**) has been synthesized as a [2 + 4]-cycloadduct of the corresponding selenirene (**6**) with furan, which has considerably bulky substituents <87TL2867, 88JPO317>.



Since most of the literature up to the mid-1990s on the three-membered carbacyclic compounds with one selenium or tellurium, is restricted to those dealing with their intermediacy in a variety of reactions, the present chapter comprises sections on theoretical and experimental structural methods followed by sections on the ring synthesis and reactivity mainly based on these intermediary, unstable examples.

1.07.2 THEORETICAL METHODS

1.07.2.1 Introduction

Although there had previously been no calculated structures for seleniranes at any level of theory, geometries for molecules in the (CH₂)₂X and (CH₃)₂X series (X = O, S, Se) were obtained in 1992 <92JPC7301> by *ab initio* calculations at the MP2 level of theory with the 6-31G* basis set <72JCP(56)2257, 73TCA213, 75JCP(62)2921, 82JCP(77)3654> for H, C, O, and S and the HUZ-SV* basis set for Se. The latter was derived from the minimal (4333/433/4) basis of Huzinaga *et al.* <84MI 107-07>; the value s and p functions were split to give (43321/4321/4), and the basis set was augmented by a single D-type polarization function with $\alpha_d(\text{Se}) = 0.338$, as recommended. It is therefore related to,

but more flexible than, the 3-21G* basis set of Dobbs and Hehre <86MI 107-02> and it is identical with that used by Duke <90JST(208)197> in work on gallium compounds.

1.07.2.2 Geometries

The emerged geometrical parameters for $(\text{CH}_2)_2\text{X}$ and $(\text{CH}_3)_2\text{X}$ series ($\text{X} = \text{O}, \text{S}, \text{Se}$) are listed in Tables 1 and 2 respectively, together with the relevant data from the experimental substitution structures. It is obvious that the calculated bond lengths and angles for oxirane and thiirane correspond almost exactly to the experimental data, while the calculated structure shown here for selenirane is apparently the first for this molecule at any level of theory.

Table 1 Calculated and experimental structures of $(\text{CH}_2)_2\text{X}$ ($\text{X} = \text{O}, \text{S}, \text{Se}$)^a.

Property	$(\text{CH}_2)_2\text{O}$		$(\text{CH}_2)_2\text{S}$		$(\text{CH}_2)_2\text{Se}$
	Calculated	Experiment ^b	Calculated	Experiment ^c	Calculated
C—X	1.436	1.431 ± 0.002	1.811	1.815 ± 0.003	1.981
C—C	1.462	1.466 ± 0.002	1.479	1.484 ± 0.003	1.470
C—H	1.082	1.085 ± 0.003	1.080	1.083 ± 0.002	1.080
$\angle \text{CXC}$	61.2°	61.6°	48.2°	48.3° ± 0.3°	43.5°
$\angle \text{HCH}$	115.6°	115.6° ± 0.3°	114.9°	115.8° ± 0.2°	115.6°
θ^d	22.2°	22.0° ± 0.3°	27.7°	28.2° ± 0.2°	27.3°

^a Bond lengths in angstroms, angles in degrees. ^b<74BCJ1311>. ^c<74CPL(24)111>. ^dAngle between bisector of HCH angle and line defined by C—C bond.

Table 2 Calculated and experimental structures of $(\text{CH}_3)_2\text{X}$ ($\text{X} = \text{O}, \text{S}, \text{Se}$)^a.

Property	$(\text{CH}_3)_2\text{O}$		$(\text{CH}_3)_2\text{S}$		$(\text{CH}_3)_2\text{Se}$	
	Calculated	Experiment ^b	Calculated	Experiment ^c	Calculated	Experiment ^d
C—X	1.412	1.410 ± 0.003	1.803	1.802 ± 0.002	1.951	1.945 ± 0.001
C—H _a	1.094	1.110 ± 0.005	1.087	1.091 ± 0.002	1.085	1.096 ± 0.004
C—H _s	1.085	1.091 ± 0.007	1.086	1.091 ± 0.002	1.085	1.086 ± 0.013
$\angle \text{CXC}$	111.0°	111.7° ± 0.4°	98.4°	98.9° ± 0.2°	95.8°	96.3° ± 0.2°
$\angle \text{XCH}_a$	111.5°	110.8° ± 0.4°	111.3°	110.8°	110.1°	110.3° ± 0.3°
$\angle \text{XCH}_s$	107.1°	107.2° ± 0.6°	107.6°	106.6°	107.1°	105.0° ± 0.7°
$\angle \text{H}_a\text{CH}_a$	108.3°	108.7° ± 0.5°	109.4°	109.5° ± 0.3°	110.5°	109.9° ± 0.5°
$\angle \text{H}_a\text{CH}_s$	109.2°	109.6° ± 0.6°	108.6°	109.6° ± 0.3°	109.4°	110.6° ± 0.5°

^aBond lengths in angstroms, angles in degrees; the H atoms of both CH_3 groups have a staggered conformation with respect to rotation about C—X bonds; H_a = the out-of-plane hydrogen atom with regard to the CXC plane, while H_s = the in-plane hydrogen. ^b<63JCP(38)2753>. ^c<61JCP(35)479>. ^d<77ZN(A)482>.

No experimental data for the geometries of seleniranes has been reported so far. However from the results in Table 1, selenirane would be expected to be highly strained but nevertheless very similar to its oxygen and sulfur analogues. As shown in Tables 1 and 2, the C—Se bond is longer in selenirane than in dimethyl selenide, and similar lengthenings are predicted and have been observed for C—S and C—O bonds in the relevant species.

1.07.2.3 Dipole Moments

In relation to the dipole moments of $(\text{CH}_2)_2\text{X}$ and $(\text{CH}_3)_2\text{X}$, the overall outcome apparent from the data in Table 3 is that, with the diffusely polarized 6-31G(+sd+sp) basis set, the experimental results come much closer to the MP2 values than the SCF values, as expected. The weak trends that

are evident on replacement of oxygen by sulfur and, in turn, selenium are qualitatively explicable in terms of two main factors; the decrease in electronegativity ($O > S \approx Se$), which tends to decrease the dipole moment, and the decrease in the CXC angle (see Tables 1 and 2).

Table 3 Calculated and experimental dipole moments of $(CH_2)_2X$ and $(CH_3)_2X$ ($X = O, S, Se$)^a.

Calculated		$(CH_2)_2O$ Experimental	Calculated		$(CH_2)_2S$ Experimental	Calculated		$(CH_2)_2Se$ Experimental
SCF	MP2		SCF	MP2		SCF	MP2	
8.27	6.91	6.27 ± 0.03^b	7.91	6.37	6.14 ± 0.07^b	8.27	6.19	
5.64	4.91	4.37 ± 0.03^c	6.42	5.64	5.00 ± 0.03^d	6.19	5.28	4.70 ± 0.07^e

^aDipole moments expressed here as $10^{30} \mu_e/\text{C m}$. ^b<51JCP676>. ^c<63JCP(38)2753>. ^d<61JCP(35)479>. ^e<66JSP(21)414>.

1.07.3 EXPERIMENTAL STRUCTURAL METHODS

1.07.3.1 Far Ultraviolet Spectra of Seleniranes

Photolysis of CSe_2 in the intense bands produces $CSe(X^1\Sigma^+)$ and atomic selenium in the 4^3P state. Since at ambient temperatures, the CSe persists for ~ 1 s even in an excess of oxygen, flash photolysis of CSe_2 provides a clean source of atoms. The atomic selenium may be observed directly by the allowed transition at $1960 \text{ \AA}$, and its reaction with alkenes is especially interesting because the products also give intense bands in the far ultraviolet, and therefore the reactant and product can be simultaneously observed by kinetic spectroscopy <65TFS2395, 66TSF371, 66TFS2760>.

Atomic selenium was monitored in flashed CSe_2 by kinetic absorption spectroscopy, and its rate of reaction with ethylene was measured in the temperature range $302\text{--}412 \text{ K}$. The rate of appearance of a new spectrum in the far ultraviolet (intense bands at 2259 and $2208 \text{ \AA}$) was symmetrical with atomic decay, and was assigned to ethylene selenide, i.e. selenirane (**1**) (Equations (1a) and (1b)). Absorption spectra of flashed CSe_2 and alkene mixtures show band systems in the $2000\text{--}2300 \text{ \AA}$ region which do not occur in flashed saturated-hydrocarbon and CSe_2 mixtures. The band centers obtained from their spectra are listed in Table 4.

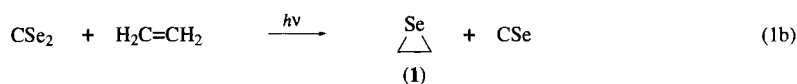
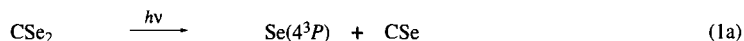


Table 4 Far ultraviolet spectra of the reaction products of atomic selenium with alkenes.

Alkene	Band centers
Ethylene	2258, 2208, 2160, 2020
Propylene	2265, 2244, 2213, 2196, 2065
1-Butene	2258, 2244, 2160
<i>trans</i> -2-Butene	2250, 2230, 2196, 2160
<i>cis</i> -2-Butene	2160
Isobutene	2293, 2270, 2160
1-Pentene	2250
1,3-Butadiene	
2,3-Dimethyl-2-butene	

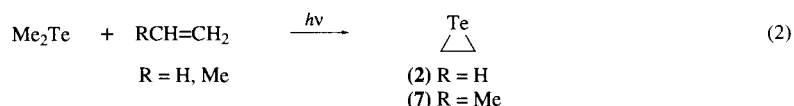
The spectra of alkene selenides persists for several minutes after flashing. A spectrum observed in flashed $COSe$ and ethylene mixture is identical to that produced in flashed CSe_2 and ethylene mixture. In Ar or N_2 , flash photolysis of $COSe$ produces Se_2 but no CSe . An added alkene inhibits Se_2 formation in experiments either with $COSe$ or CSe_2 . In flashed CSe_2 , the rate of decay of $Se(4^3P)$ is identical to the rate of appearance of the far ultraviolet bands, within an experimental scatter of $\sim \pm 20\%$ in the pseudo first-order rate constant. Therefore the absorption in the far

ultraviolet must result from products of the reaction of Se (4^3P) with the added alkenes, i.e. seleniranes. Furthermore, these spectra can be assigned to cyclic selenides because the spectrum which resulted from flashing CSe₂ with *trans*-2-butene was not obtained from the *cis*-isomer <64PCS296>.

1.07.3.2 Far Ultraviolet Spectra of Telluriranes

Besides the atomic reactions of the group 16 elements such as oxygen, sulfur, and the previously mentioned selenium, the reactions of tellurium atoms with alkenes have also been reported. In the case of tellurium, the ultraviolet photolysis of dimethyl telluride (DMT) is a usable source of $^3P_{2,1,0}$ tellurium atoms <69PCS304>. In flashed mixtures of DMT vapor ($10^{-3} \sim 10^{-1}$ torr with CO₂ diluent) using kinetic absorption spectroscopy, intense absorptions at 2143–2259 Å, which correspond to known transitions of Te($^3P_2$), and at 2386 and 2383 Å corresponding to Te($^3P_1$) and ($^3P_0$), respectively, were observed <69JA5695>.

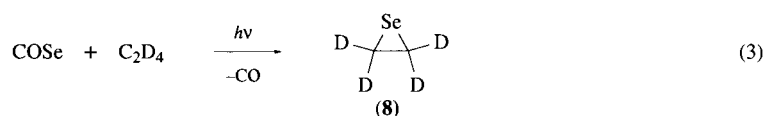
In the presence of added ethylene two further band systems have been observed. The system between 2400 and 2500 Å (band heads at 2472, 2410, and possibly at 2356 Å) has a lifetime of several milliseconds and has been assigned to the unstable ethylene epitelluride molecule (Equation (2)). The other system around 2300 Å decayed faster ($\sim 250 \mu\text{s}$) in an apparent first-order process. Analogous spectra (at 2480 and 2458 Å), which can be assigned to the absorptions of 2-methyl-tellurirane (7), have also been obtained with added propylene.



1.07.3.3 Mass Spectra of Seleniranes

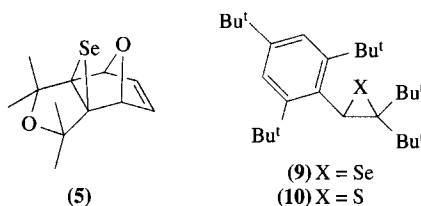
Mass spectra of short-lived, unstable episelenides were obtained by taking advantage of a mass spectrometric technique developed for the time-resolved detection of transient intermediates in flash-photolyzed systems <66JA4277>. Detection does not depend on the electronic absorption characteristics of the transient, and, in combination with kinetic absorption spectroscopy, the technique assumes great flexibility. The apparatus consists, essentially, of a photolysis cell attached to a small leak into the ion source of an Atlas CH₄ mass spectrometer. Selected mass peaks can be studied with a response time of a few milliseconds, and thereafter at times limited by bleeding of the photolyzed mixture into the ion chamber. Typical photolytic flash energies were ~ 480 calories, passed into a reaction volume of ~ 5 ml.

The mass spectra obtained for a flashed mixture of C₂D₄ and COSe showed a decay of an adduct at m/e 112, which is likely to be the selenirane (8) (Equation (3)). The seleniranes from a series of substituted alkenes (C₂F₄, CH₂=CHSiH₃, CH₂=C(CF₃)CH₃, CH(Cl)=CH(Cl), etc.) have also been detected. All are inherently unstable at room temperature and decay with half-lives between 30 ms and a few seconds.



As for the more stable seleniranes such as (5) <87TL2867, 88JPO317> and (9) <94CL1289>, their mass spectra can be obtained using a normal mass spectrometric technique (electron impact method). Both seleniranes (5) and (9) showed their characteristic cluster pattern of molecular ion peak, and in the case of (5) the molecular composition was satisfactorily confirmed by high-resolution mass spectroscopy. The base peaks in both cases are based on the corresponding alkenes resulting from

the extrusion of selenium atom. No intensive studies on their fragmentation in the mass spectra have been reported.



1.07.3.4 Mass Spectra of Telluriranes

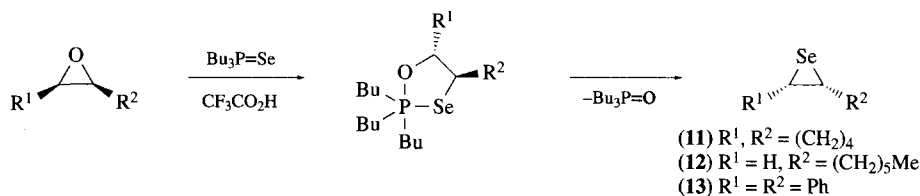
The formation of transient tellurirane molecules has also been confirmed by kinetic mass spectroscopy [69JA5695]. Flashing 0.2 torr of DMT in the presence of 10 torr of propylene, the parent adduct C_3H_6Te (m/e 172) has been detected. In 50 ms, little decay had taken place.

1.07.3.5 NMR Spectra

Very little is known about the NMR spectra of seleniranes, since there is only one example of isolable selenirane (5) [87TL2867, 88JPO317]. In 1994, another selenirane (9) which is stable in solution at low temperature was reported [94CL1289]. Since (5) has tetrasubstituted selenirane structure, no information is available for the ^1H NMR spectroscopic data of the selenirane ring system. Meanwhile, the ^1H NMR spectrum of the trisubstituted selenirane (9) showed a characteristic sp^3 methine proton on the selenirane ring at δ 5.3, much deshielded compared to that in the corresponding sulfur analogue (10) (δ 4.5), although these protons are in benzyl positions.

As for ^{13}C NMR spectra, selenirane (5) showed a signal at δ 71.8 assignable to that of ring carbons, while selenirane (9) showed a signal at δ 57.9 which can be attributable to the signal of benzylic ring carbon. Since only the distortionless enhancement by polarization transfer (DEPT) spectrum of (9) was measured for its ^{13}C NMR, the chemical shift for the other quaternary carbon of the selenirane ring of (9) is not available.

In the reaction of cyclohexene oxide with tri-*n*-butylphosphine selenide in benzene at room temperature in the presence of an equimolar amount of trifluoroacetic acid, the NMR spectrum of the reaction mixture showed a new multiplet at 3.6 ppm, which was reasonably assigned as the methine protons of the expected cyclohexene episelenide (11) (Scheme 1) [74TL2091]. In a similar manner, 1-octene and *trans*-stilbene were converted to the corresponding episelenides (12) and (13), respectively, the latter of which showed a new NMR signal at 5.1 ppm in $CDCl_3$ assignable to the methine protons of stilbene selenide (13).

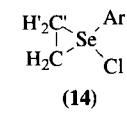
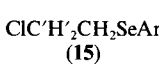


Scheme 1

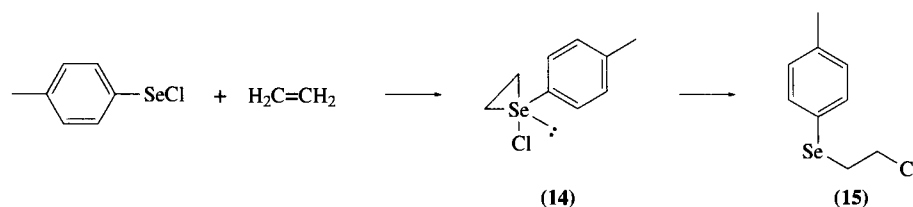
On the other hand, the structure of episelenurane (14), the first product from the addition of 4-tolueneselenenyl chloride to 1–90% [^{13}C] ethylene, has been assigned as 1-chloro-1-(4'-tolyl)-selenocyclopropane on the basis of its ^1H and ^{13}C NMR spectral data, which is listed in Table 5 (Scheme 2) [74CJC1027]. In the ^1H NMR spectra, the methylene protons of (14) appear as a tightly coupled AA'BB' pattern. In general, the chemical shifts of the protons in (14) are deshielded relative to those of the ring opened isomer (15) which was obtained upon standing (14) for a few days at 25°C. These downfield shifts are consistent with oxidation of Se(II) to Se(IV) [69JA1649, 73JA964]. A similar result is found by comparing the ^{13}C NMR spectra of (14) and (15). Further structural information is available from the ^{13}C – ^{77}Se spin–spin coupling constants obtained from the spectrum of a sample of (14) prepared from 1–90% [^{13}C] ethylene. Both methylene carbons of (14) show ^{13}C –

^{77}Se spin-spin coupling while (15) shows ^{13}C – ^{77}Se spin-spin coupling only for the carbon attached to selenium. No ^{13}C – ^{77}Se spin-spin coupling is observed. This result strongly supports the cyclic structure of (14). The ^{13}C –H spin-spin coupling constants are in accord with the proposed structures of (14). The magnitude of $J_{\text{C-H}}$ for the carbon attached to Se in (14) is quite similar to those of reported acyclic selenides <67MP243, 68MP295, B-72MI 107-01>. For example, $(\text{CH}_3)_2\text{Se}$, 140.3 Hz; CH_3SeH , 142.7 Hz; and $(\text{CH}_3)_3\text{Se}^+$, 145.8 Hz. Similarly, the value of J_{CH} for the carbon bonded to chlorine is of normal magnitude. The similarity of the values of J_{CH} for both carbons in (14) rules out an acyclic structure. The increase in the value of J_{CH} for carbons bonded to selenium in (14) relative to the one of (15) is consistent with the change of oxidation state of selenium in (14) as can be seen from the relative magnitudes of J_{CH} in the sulfur or phosphorus analogues. For example $(\text{CH}_3)_2\text{S}$, 138 Hz; $(\text{CH}_3)_3\text{S}^+$, 146 Hz; and $\text{P}(\text{CH}_3)_3$, 127; $\text{P}^+(\text{CH}_3)_4$, 134 Hz.

Table 5 Calculated NMR chemical shifts and coupling constants for episelenurane (14) and its ring-opened isomer (15)^a.

Compound (Ar = 4'-phenyl)	Chemical shifts					
	δ_{H}	$\delta_{\text{H'}}$	$\delta_{\text{H(Ar)}}$	$\delta_{\text{H(CH}_3\text{)}}$	δ_{C}	$\delta_{\text{C'}}$
 (14)	4.37	4.53	7.89 7.38	2.40, s	65.20, t(t)	38.06, t(t)
 (15)	AA'BB' 3.10	A2B2 3.63	7.46 6.97	2.28, s	29.28, t(dd)	43.29, t(dd)
Spin-spin coupling constants (Hz)						
(14)	$J_{\text{SeC}}, \pm 59.25; J_{\text{SeC'}}, \pm 18.54; J_{\text{CC'}}, 37.25; J_{\text{CSeC}}, 13.84; J_{\text{H(Ar)}}, 9.0$					
(15)	$J_{\text{SeC}}, \pm 66.32; J_{\text{SeCC'}}, <8; J_{\text{CC'}}, 28.8; J_{\text{H(Ar)}}, 7.8; J_{\text{CH}}, 145.55; J_{\text{CH'}}, 155.60; J_{\text{CC'H}}, 4.22, 6.84; J_{\text{C'CH}}, 4.80, 7.80$					

^aChemical shifts δ ppm relative to TMS; s = singlet, t = triplet, dd = doublet of doublets; t(t) = $J_{\text{CH, triplet}}, J_{\text{CCH, triplet}}$.

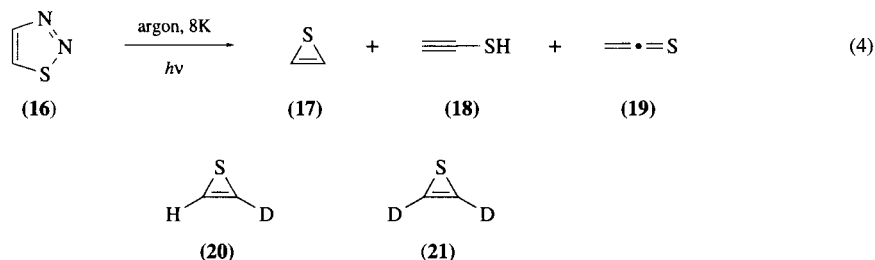


Scheme 2

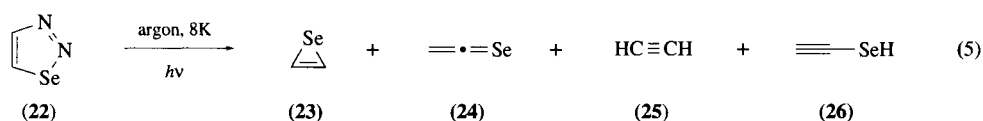
On the basis of the known stereochemistry about selenium in selenium(IV) compounds, the structure of (14) may be assigned as a trigonal bipyramid. If the assumption is made that those factors which govern the stability of isomeric trigonal bipyramidal phosphoranes <70JA634, 70JA644> are also applicable for selenuranes, the three-membered ring will prefer to span an apical equatorial position and the electronegative chlorine atom may occupy the remaining apical position.

1.07.3.6 Infrared Spectra

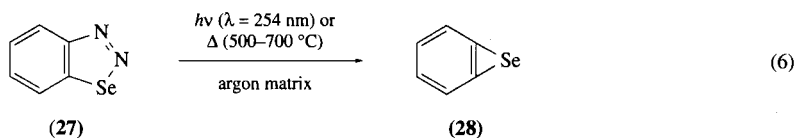
Infrared spectroscopy is one of the useful techniques for the characterization of matrix-isolated thiirene and selenirene <77JA4842>. Irradiation of argon matrix-isolated 1,2,3-thiadiazole (16) with light of $\lambda = 2350\text{--}2800\text{ \AA}$ produces ethynyl thiol (18) and thioketene (19) along with thiirene (17) which possesses bands at 3207, 3169, 3166, 1663, 912, and 563 cm^{-1} (Equation (4), structures (20) and (21)). The positions of these bands are reminiscent of bands in the spectrum of cyclopropene <61JA1226, 66TFS371, 67JCP(47)946>. Deuterium substitution of (17) to (20) and (21) resulted in remarkable shifts to low frequency of the absorption at 1663 cm^{-1} (for (17)) to 1611 and 1567 cm^{-1} (for (20) and (21), respectively). Very marked low frequency shifts ($\sim 50\text{ cm}^{-1}$) of the “double-bond stretch” have been observed for cyclopropene upon deuterium substitution <66MI 107-01, 66TFS371>.



Similarly, irradiation ($\lambda = 2350\text{--}2800 \text{ \AA}$) of 1,2,3-selenadiazole (**22**) produces selenoketene (**24**) alkyne (**25**) and ethynyl selenol (**26**), as well as a species (**23**) absorbing at 3197, 3161, 3155, 1681, 1637, and 868 cm^{-1} (Equation (5)). The positions and shapes of these bands are strikingly similar to those of thiirene (**17**) and are reasonable for the analogous selenirene (**23**), though the assignment of these bands to selenirene is entirely tentative.

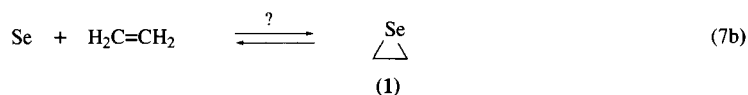
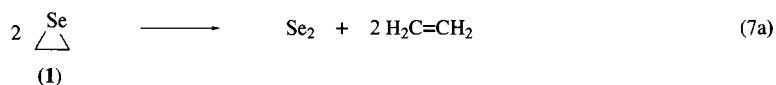


In 1984, the IR spectroscopic detection of benzoselenirane (**28**) was reported in the photochemical and thermal reactions of 1,2,3-benzoselenadiazole (**27**) (Equation (6)) $\langle 84\text{TL}2337 \rangle$. Benzoselenirene (**28**) showed characteristic absorption at 1672, 1433, 1145, 1156, 1052, 973, 940, 926, and 655 cm^{-1} .



1.07.4 THERMODYNAMIC ASPECTS

Although there have been no systematic arguments on the thermodynamic aspects of three-membered rings containing selenium and tellurium, they are known to be very labile ring systems which readily undergo decomposition to release the chalcogen atom giving the corresponding alkenes or alkynes. In the case of the decomposition of selenirane (**1**), if it occurs in the gas phase, a bimolecular reaction mechanism giving Se_2 and two alkene molecules has been postulated (Equations (7a) and (7b)) $\langle 66\text{JA}4277 \rangle$. Homogeneous, unimolecular decomposition of selenium would lead to the equilibrium shown in Equations (7a) and (7b), which would be contradictory to the excellent data reported in the pioneering works of Callear and Tyerman $\langle 66\text{TFS}371 \rangle$. The rate of addition of $\text{Te}(^3P_2)$ atoms to several alkenes was determined using the flash photolysis of dimethyl telluride as the source of tellurium atoms $\langle 71\text{JA}560 \rangle$. The rate constants and activation energies for ethylene, propylene, and tetramethylethylene (TME) are given in Table 6. The rate constants for the addition of the $\text{Te}(^3P_2)$ atom to TME correspond to an activation energy of $(-1.6 \pm 1.4) \text{ kcal mol}^{-1}$, which is the first reported case of a negative temperature coefficient for an addition reaction in its second-order region. The activation energy of the reaction of $\text{O}(^3P)$ with TME is $2.6 \text{ kcal mol}^{-1}$ lower than that of $\text{O} + \text{C}_2\text{H}_4$ and is estimated to be about $-1.1 \text{ kcal mol}^{-1}$ $\langle 60\text{CJC}1657, 63\text{JCP}(38)989, 69\text{JPC}1181 \rangle$. As for selenium, extrapolation of Callear and Tyerman's idea $\langle 66\text{TFS}2760 \rangle$ correlating the activation energies of the atomic selenium reactions with the ionization potential of the alkene involved indicates that the E_a of $\text{Se} + \text{TME}$ is also negative.



It would therefore appear that the activation energies of the reactions of all the group 16 atoms with alkenes become negative when the ionization potential of the alkene is sufficiently low. To account for this phenomenon, it was suggested that the atom and alkene initially approach a potential surface with a shallow minimum. The repulsive part of this surface intersects an attractive potential surface and the crossing between the two surfaces is the rate-determining step of the reaction. A positive activation energy clearly corresponds to the crossing point lying at higher energies than the separated reactants. However, if the intersection lies below the separated reactants, an increase in temperature decreases the probability of crossing between surfaces due to the higher average velocity of the collision complex at the crossing point. This is responsible for the negative temperature coefficient found in the reactions with TME.

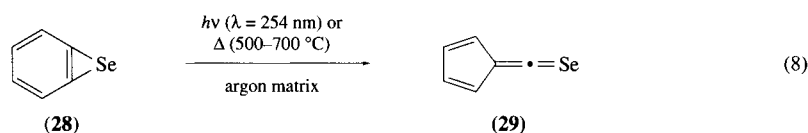
1.07.5 REACTIVITY OF FULLY CONJUGATED RINGS

1.07.5.1 Introduction

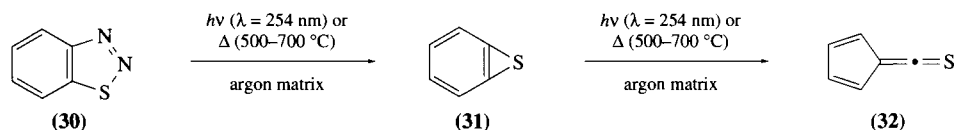
Due to their strain and putative electronic destabilization, such three-membered heterocycles possessing a cyclic array of 4π -electrons offer a considerable challenge to synthesis. Such molecules are expected to be both unimolecularly and bimolecularly reactive, if they exist at all as energy minima. Since no isolable tellurirenes have been reported, only some reactions of selenirenes are described in this section. Selenirene and its kindred systems, oxirene, azirine, and thiirene, are of interest because of their theoretical significance as prototypes of antiaromatic species.

1.07.5.2 Thermal and Photochemical Reactions

As mentioned in Section 1.07.3(b), irradiation (254 nm, 4 min) of 1,2,3-selenadiazole (**27**) in argon matrix produced a reactive intermediate benzoselenirene (**28**) (see Equation (6)), the formation of which was confirmed by IR spectra. The matrix-isolated benzoselenirene (**28**) undergoes ready rearrangement to 6-fulveneselone (**29**) on further irradiation (Equation (8)). Benzoselenirene (**28**) is also formed in gas-phase pyrolysis (560°C, ca. 10^{-3} min) of 1,2,3-benzoselenadiazole (**27**) if the reaction temperature is kept a little lower than required for complete fragmentation of (**27**). Selenirene (**28**) was found to undergo thermal rearrangement to (**29**), the IR spectrum of which is identical with that obtained in the exhaustive photolysis of (**27**). With increasing temperature, the amount of the new product steadily decreased and at 700°C its IR bands were at the limit of detection.



The thermal and photochemical behavior of benzoselenirene (**28**) derived from 1,2,3-benzoselenadiazole (**27**) is very similar to that of benzothiirene (**28**) generated by the thermolysis or photolysis of the 1,2,3-benzothiadiazole (**30**) <78JOC2490, 83ZN(B)611>. Thus, benzothiirene (**31**) was also found to undergo thermal or photochemical rearrangement to the corresponding 6-fulvenethione (**32**) (Scheme 3).

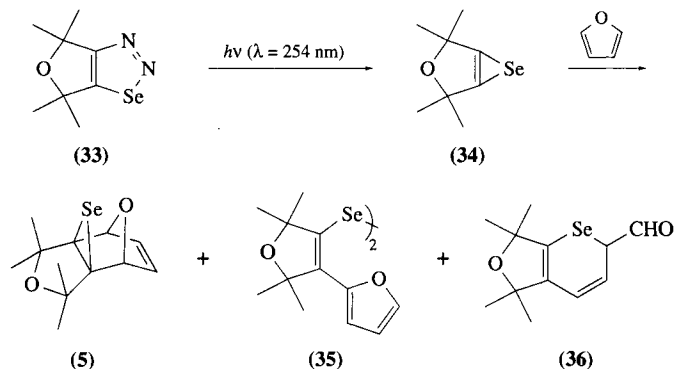


Scheme 3

1.07.5.3 Cycloaddition Reactions

Although no intermolecular cycloaddition reactions have been examined for the matrix-isolated unstable selenirenes (**23**) and (**28**), selenirene (**34**), which was generated by the photolysis of the

sterically crowded fused 1,2,3-selenadiazole (**33**), was found to undergo an interesting cycloaddition reaction with furan giving the first stable selenirane (**5**) (12%) as a [4 + 2]-cycloaddition product of selenirene (**34**) together with the diselenide (**35**) (41%) and bicyclic aldehyde (**36**) (11%) (Scheme 4) <87TL2867, 88JPO317>.



Scheme 4

1.07.6 REACTIVITY OF NONCONJUGATED RINGS

1.07.6.1 Introduction

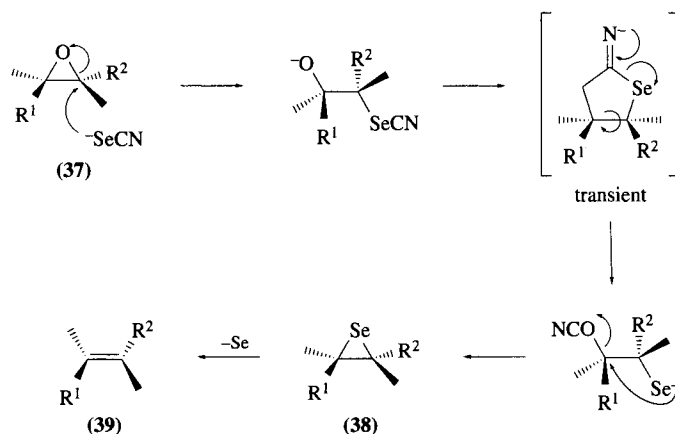
Although seleniranes and telluriranes have been known to be highly reactive and unstable chemical species and their reactivity has not been fully disclosed, examples of stable seleniranes offer an opportunity to reveal the intrinsic nature of these interesting small ring systems. This section covers the characteristic reactions of both intermediary and stable seleniranes and telluriranes.

1.07.6.2 Thermal Reactions

Cyclopropane analogues containing selenium or tellurium, that is seleniranes or telluriranes, are known to be unstable chemical species at ambient temperatures, and they readily undergo extrusion of the chalcogen atoms to give the corresponding alkenes. Alternatively, the use of selenium compounds as reagents in organic synthesis has aroused considerable interest. The conversion of epoxides into alkenes has been effected by a wide variety of methods, one of which makes use of the instability of the intermediary seleniranes. When epoxides (**37**) were treated with the readily available potassium selenocyanate in aqueous methanolic solution, selenocyanate anion generated in a slightly alkaline solution (pH 8–9) reacts with epoxides at room temperature to deposit selenium via the selenirane intermediates (**38**) and forms the corresponding alkenes (**35**). The course of the reaction can be followed by weighing the precipitated selenium, and the rate is greater at higher temperatures. The kinetic data indicates that the reaction is second order in epoxide and selenocyanate. A suggested mechanism for the reaction is shown in Scheme 5, and Table 6 shows the epoxides which have been converted into alkenes.

The treatment of bromohydrins (**41**), which can be readily prepared from alkenes (**40**), with potassium selenocyanate in DMF produces the β -hydroxyselenocyanates (**42**) in high yields. When (**42**) are subjected to a treatment with base such as potassium carbonate in DMF/H₂O, alkenes (**44**) are obtained stereoselectively (Scheme 6). The intermediacy of seleniranes (**43**) is reasonably postulated by the fact that the reactions of (**41**) with potassium thiocyanate followed by treatment with a base resulted in the isolation of the corresponding thiiranes (**44a**) which is in turn transformed to alkenes (**44**) by known procedures. In view of the high percentage of Walden inversion in the transformation and the stereospecific extrusion of selenium atoms from the intermediary seleniranes (**43**), this transformation may have a potential utility for stereoselective isomerization of di-substituted alkenes.

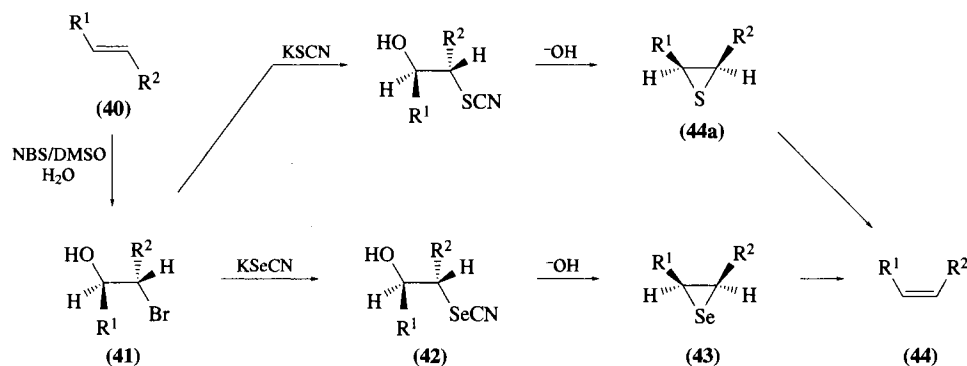
The thermal instability of the telluriranes is also utilized in the transformation of epoxides to alkenes <77CC658, 80JOC2347>. When epoxides are treated with sodium *O,O*-diethyl phos-



Scheme 5

Table 6 Reactions of $\text{Te}(\text{}^3\text{P}_2)$ atoms.

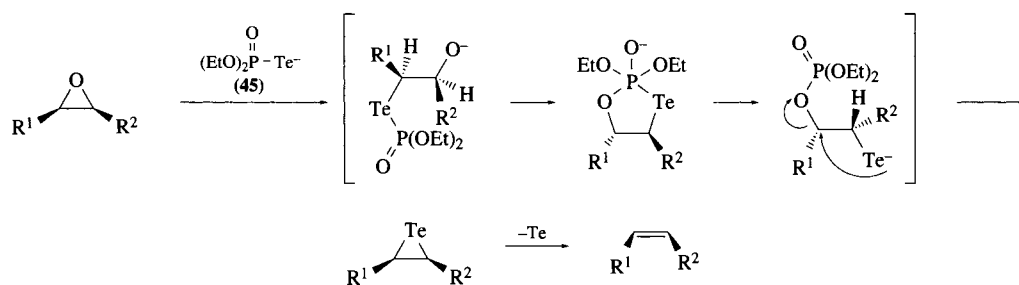
Substrate	k ($\text{l mol}^{-1} \text{s}^{-1}$) ^a		E_a (kcal mol^{-1})
	25°C	80°C	
DMT	1.65 ± 0.25	$1.5 \pm 0.2 \times 10^{11}$	
C_2H_4	1.3 ± 0.3	$2.4 \pm 0.5 \times 10^7$	2.5
C_3H_6	1.2 ± 0.3	$1.4 \pm 0.3 \times 10^8$	0.6
TME	3.9 ± 0.8	$2.6 \pm 0.9 \times 10^9$	-1.6 ± 1.4



Scheme 6

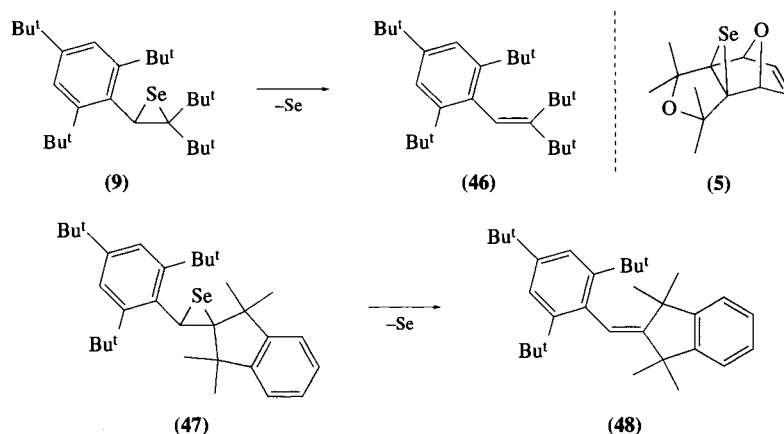
phorotelluroate (45), they are converted into the corresponding alkenes at room temperature. Terminal epoxides are deoxygenated readily and nonterminal epoxides react slowly and therefore selective deoxygenations are possible. For example, limonene diepoxide gave 1,2-epoxy-*p*-menth-8-ene in 76% yield. The double-bond mobility of this transformation was examined by the reaction of 1,2-epoxyoctane with (45), which resulted in the regiospecific formation of 1-octene. In the case of epoxides formally derived from acyclic alkenes, the *Z* compound reacts more easily than the *E* isomer and the deoxygenation is stereospecific. 1,2-Epoxycyclohexanes react faster than 1,2-epoxycyclopentanes. As for the case of *Z*-epoxide, a reasonable mechanism of deoxygenation is shown in Scheme 7. Since under the reaction conditions (45) reacts very slowly with epoxides but readily with elemental tellurium, this deoxygenation can be carried out as a catalytic process.

As for the isolable seleniranes (5) and (9), there have been reported some difference between their thermal stability. While the tetrasubstituted selenirane (5) was isolated by purification with gel-permeation liquid chromatography and was found to be thermally stable at room temperature even in solution, the trisubstituted selenirane (9) underwent gradual decomposition in solution at room



Scheme 7

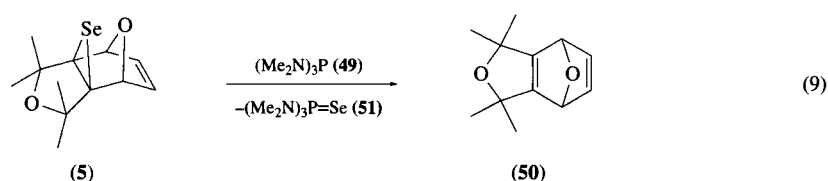
temperature giving the corresponding alkene (**46**) during one hour via the extrusion of selenium atoms, though (**9**) was found to be stable in solution at low temperature or in the solid state at room temperature (Scheme 8). The synthetic method applied to the selenirane (**9**) can also produce analogous sterically crowded trisubstituted selenirane (**47**), the thermal stability of which is approximately the same as that of (**9**); (**47**) is stable at -40°C for a long time, but is converted to (**48**) at room temperature after about 2 h (Scheme 8). The noticeable thermal stability of the selenirane (**5**) might be indebted to not only its tetrasubstituted structure but also the intramolecular coordinative interaction of the oxygen atom in the fused dihydrofuran ring.



Scheme 8

1.07.6.3 Reactions on Ring Chalcogen Atoms

Although no information has been available for intermolecular reactions of seleniranes or telluriranes so far because of their thermal instability, the reaction of isolable selenirane (**5**) with a trivalent phosphorus reagent was reported as the only example of the intermolecular reaction of selenirane on the ring chalcogen atom <87TL2867, 88JPO317>. Thus, selenirane (**5**) was treated with an equimolar amount of hexamethylphosphorus triamide (**49**) in chloroform at room temperature to give the corresponding deselenated alkene (**50**) and phosphine selenide (**51**), respectively, in quantitative yields (Equation (9)). This paper also described the instability of selenirane (**5**) toward acid which resulted in the formation of unidentifiable polymeric product <87TL2876>.



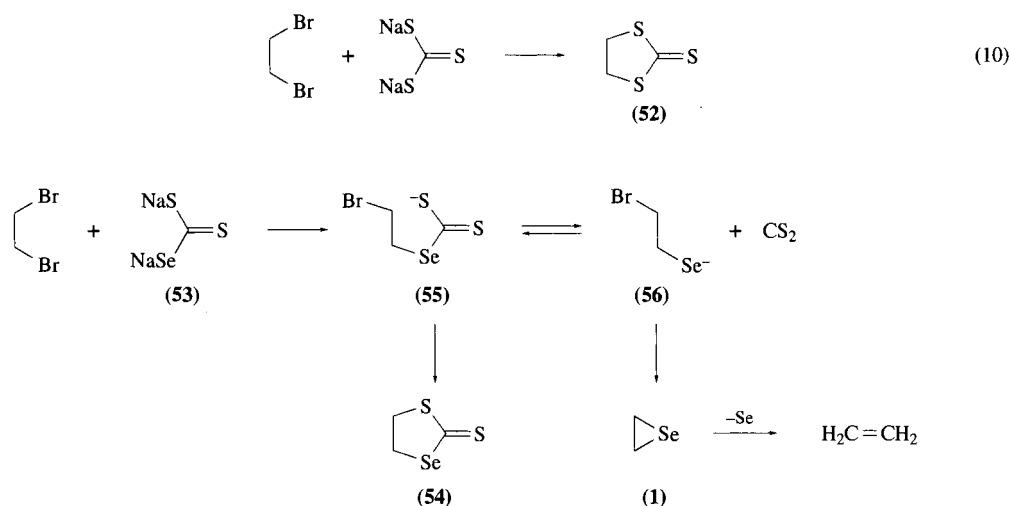
1.07.7 RING SYNTHESSES CLASSIFIED BY NUMBER OF RING ATOMS IN EACH COMPONENT

1.07.7.1 From Alkenes

As discussed in Section 1.07.3, several kinds of seleniranes and telluriranes can be synthesized by the reactions of alkenes with the atomic chalcogen generated in the flash photolysis. In the case of seleniranes, carbon diselenide or carbon oxyselelide were used as the source of the selenium atom, while dimethyltelluride was subjected to the flash photolysis to provide the reactive tellurium atoms which react with alkenes to give the expected telluriranes.

1.07.7.2 From Nonheterocyclic Chalcogen Compounds

In contrast to the facile formation of ethylene trithiocarbonate (**52**) by the reaction of ethylene dibromide with sodium trithiocarbonate as shown in Equation (10) and Scheme 9, the major course of the reaction of ethylene dibromide with the selenodithiocarbonate ion (**53**) <71ZAAC(384)235> has been reported to lead to the precipitation of red selenium (75%), accompanied by the vigorous evolution of ethylene, and the expected thiaselenorane (**54**) was obtained only in 2% yield. The reaction process can be rationalized by assuming that the initially formed monoalkylated anion (**55**) is in equilibrium with carbon disulfide and the β -bromoethylselenide ion (**56**); the latter can rapidly cyclize to the extremely thermolabile ethylene episelenide (**1**).

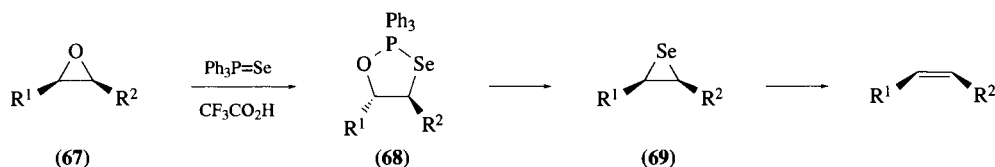


Scheme 9

As for the example of the formation of tellurirane from alkene, the reaction of alkenes with tellurium tetrachloride has been reported. While the addition of one mole of tellurium tetrachloride to two moles of an alkene is known to produce a bis(2-chloroalkyl)tellurium dichloride (**57**) <70BCJ496, 71AG(E)73>, equimolar quantities of alkene and tellurium tetrachloride similarly gave a 2-chloroalkyltellurium trichloride (**58**) <59TL11, 70BCJ496>. Furthermore, treatment of the 2-chloroalkyltellurium trichloride with aqueous Na_2S has been reported to result in the separation of tellurium and formation of the inverted alkene via a tellurirane intermediate <81TL1919>. Scheme 10 shows the schematic illustration of the reaction mechanism for the transformation of *E*-deuterio-1-decene (**59**) into *Z*-deuterio-1-decene (**60**) via the tellurirane (**61**).

Another example of the formation of tellurirane using a nonheterocyclic tellurium compound has been shown in the reaction of sodium *O,O*-diethyl phosphorotelluroate (**45**) with α -haloketones (**62**). As shown in Scheme 11, the starting α -haloketones (**62**) are converted into the corresponding dehalogenated parent ketones (**63**) via epitelluride intermediate (**64**) together with the formation of elemental tellurium.

This method is rapid at room temperature and is stereospecific, proceeding in a fashion that preserves the relative stereochemistry about the C—C bond of the epoxides. By analogy with the conversion of epoxides into alkenes through the corresponding episulfides, the formation of alkenes in this transformation has been rationalized by the extrusion of selenium from the corresponding episelenide intermediates (**69**). Furthermore, by taking advantage of the similar method, that is the combination of tri-*n*-butylphosphine selenide and trifluoroacetic acid, cyclohexene, 1-octene, and *trans*-stilbene were converted into the corresponding episelenides (**11**), (**12**), and (**13**) (see Section 1.07.3.5) <74TL2091>. These episelenides were found to be difficult to purify chromatographically; however, spectroscopic study of the reaction mixture enabled us to observe the characteristic ring protons by ¹H NMR.

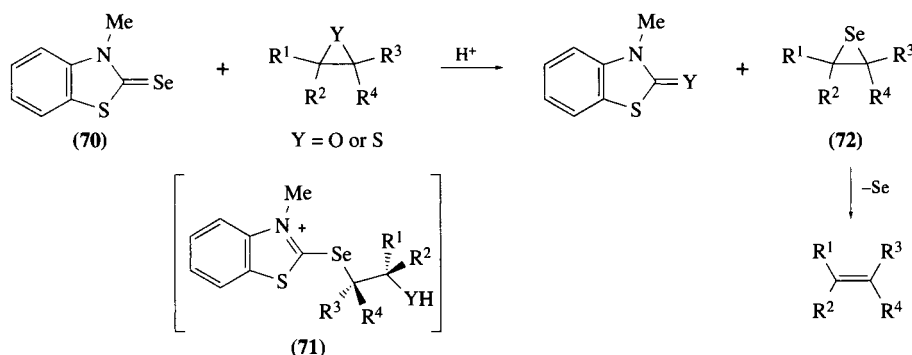


Scheme 12

Thermally labile telluriranes can also be generated from oxiranes by treatment with sodium *O,O*-diethyl phosphorotelluroate, and this reaction was especially applied to the selective deoxygenation of terminal epoxides (see Section 1.07.6.2).

1.07.8.2 From Thiiranes

As an extension of 3-methyl-2-thioxobenzothiazole which was found to be a useful reagent to convert epoxides into episulfides <75CC621>, a new reagent for selenation was developed—3-methyl-2-selenoxobenzothiazole (**70**) <76S200>. Thus, (**70**) was found to react with epoxides even at -15°C in dichloromethane in the presence of trifluoroacetic acid to give the corresponding alkenes in high yields (Scheme 13). The episulfides were also desulfurized by (**70**) though more slowly. The presence of acid is indispensable in these reactions, since a mixture of epoxides or episulfides with the reagent in dichloromethane remained unchanged. By analogy to the conversion of epoxides into episulfides with 3-methyl-2-thioxobenzothiazole, the deoxygenation or desulfurization of epichalcogenides with (**70**) occurs through the formation of β -hydroxy- or β -thiolselelenides as illustrated (**71**) which decompose to give the seleniranes (**72**). Two Walden inversions must take place during the reaction in order to obtain a selenirane with the same configuration as the starting compound. Extrusion of selenium from (**72**) without loss of the stereochemical integrity give the alkenes. This latter reaction, although unusual, resembles the stereospecific thermolysis of episulfides <68JA7164>.

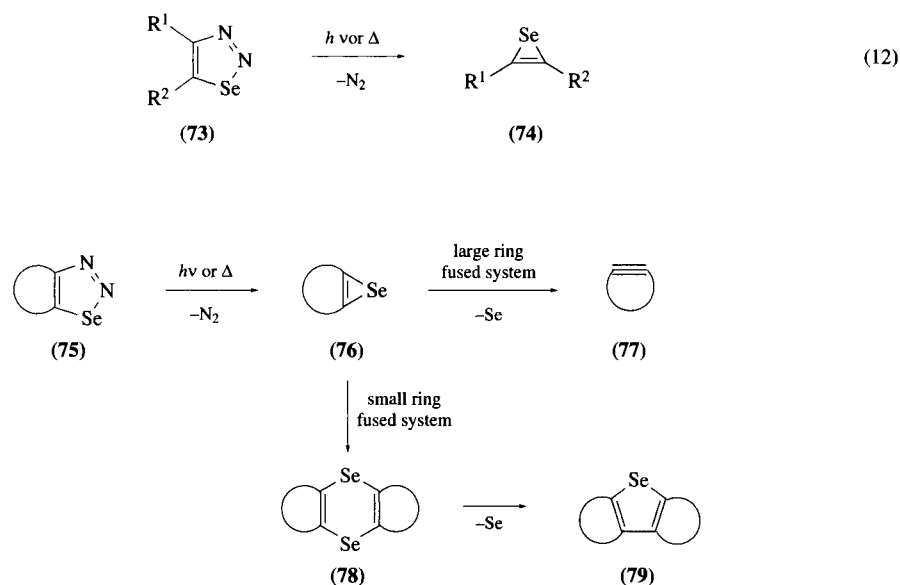


Scheme 13

1.07.8.3 From 1,2,3-Selenadiazoles

Thermolysis and photolysis of 1,2,3-selenadiazoles (**73**) are known to be useful methods for the generation of selenirenes (**74**) (Equation (12) and Scheme 14). This method has the following

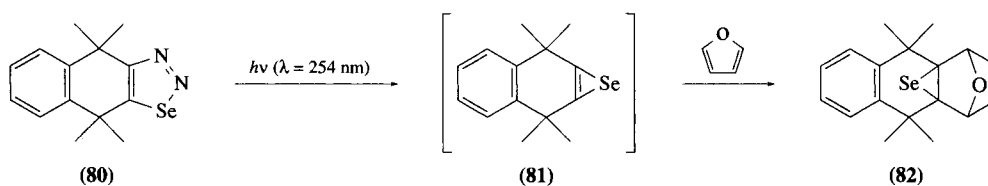
advantages: (i) the starting materials, that is, 1,2,3-selenadiazoles are easily prepared and readily available in a pure form; (ii) generally, thermolysis and photolysis of this ring system proceeds with high efficiency. Therefore, some examples of selenirenes were successfully isolated in the low-temperature matrices using this methodology as mentioned in the section on IR spectra of selenirenes (**23**) and (**28**) (Section 1.07.3.6). Furthermore, in the cases of 1,2,3-selenadiazoles (**75**) fused to appropriate carbacycles, these reactions have been applied to the synthesis of cyclic alkynes (**77**) by taking advantage of the high lability of the resulting intermediary seleniranes (**76**) to liberate the selenium atom (Equation (12) and Scheme 14) <72JHC1411, 72T187, 78S596>. On the other hand, when the selenadiazole ring is fused to a ring which is lower than eight-membered, the alkyne formation is unfavored and the denitrogenated intermediate, selenirane (**76**), can dimerize to diselenin derivatives (**78**), which can in turn lose a selenium atom to give the selenophene derivatives (**79**) <72JHC1411, 75JHC801, 76CB1650>.



Scheme 14

1.07.8.4 From Selenirenes

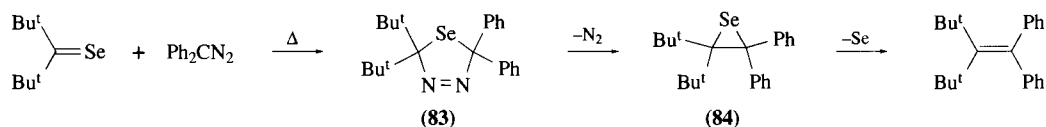
Stable selenirane (**5**) bearing a bulky substituent has been synthesized by the [4 + 2]-cycloaddition reaction of furan with the selenirene (**34**), which was generated in the photolysis of the corresponding 1,2,3-selenadiazole (**33**) fused with tetramethyl-substituted furan ring <87TL2867, 88JPO317>. Under similar reaction conditions to the case of (**33**), the 1,2,3-selenadiazole (**80**) fused with sterically crowded six-membered ring also gave the corresponding selenirane (**82**), though in a very low yield <B-89MI 107-01>. The formation of selenirane (**82**) can also be interpreted in terms of the [4 + 2]-cycloaddition of initially formed selenirene intermediate (**81**) as in the case of selenirane (**5**) (Scheme 15).



Scheme 15

1.07.8.5 Miscellaneous

Thermolabile 2,2,5,5-tetrasubstituted Δ^3 -1,3,4-selenadiazolines (**83**) are useful in the preparation of sterically very crowded alkenes (Scheme 16). Episelenides (**84**), which provide access to the alkenes by ready loss of selenium, are postulated as the intermediates in the thermal decomposition of (**83**) <76JCS(P1)2079>.



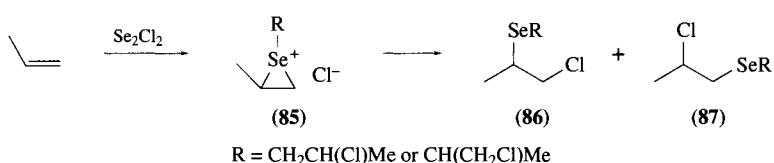
Scheme 16

1.07.9 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

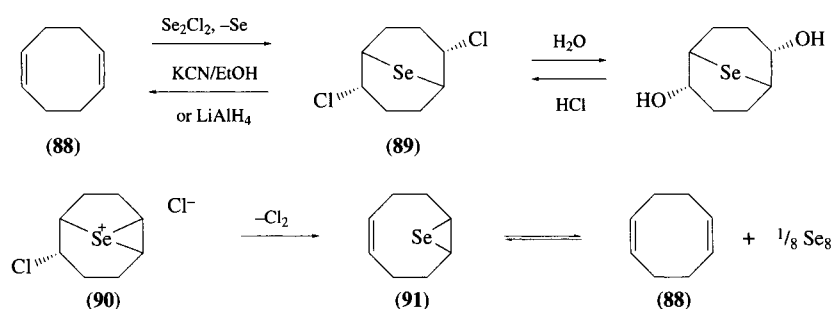
1.07.9.1 Synthesis of Three-membered Rings Containing Highly Coordinate Selenium Atom

As another example for the synthesis of selenium-containing three-membered ring systems, the addition of 4-tolueneselenenyl chloride to ethylene has been reported <74CJC1027>. In this reaction, the quantitative formation of an episelenurane derivative, e.g., 1-chloro-1-(4'-tolyl)selenirane (**14**), was observed on the basis of its NMR study and (**14**) was found to undergo the ring-opening reaction leading to the isomer 2-chloroethyl 4-tolyl selenide (**15**), upon standing for a few days at 25°C in solution (see Section 1.07.3.5).

The reaction of selenium monochloride with propylene was also shown to give the two isomeric bis(β -chloroalkyl)selenides (**86**) and (**87**) via the episelenium intermediate (**85**) (Scheme 17) <69JOC4003>. As compared to the reaction of propylene with sulfur monochloride, the isomer distribution (**86**) and (**87**) remains essentially identical to that observed in the sulfur case within experimental limits. On the other hand, the reaction of 1,5-cyclooctadiene (**88**) with selenium monochloride was reported to result in the formation of 2,6-dichloro-9-seleno-bicyclo[3.3.1]nonane (**89**), which can be transformed into the starting cyclooctadiene (**88**) by treatment with potassium cyanide or lithium aluminum hydride via the episelenium intermediate (**90**) and episelenide (**91**) as shown in Scheme 18 <69JOC4003>.

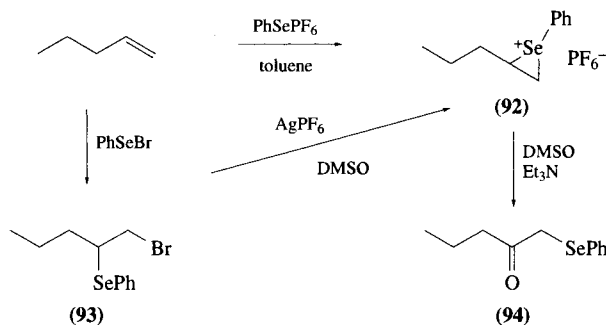


Scheme 17



Scheme 18

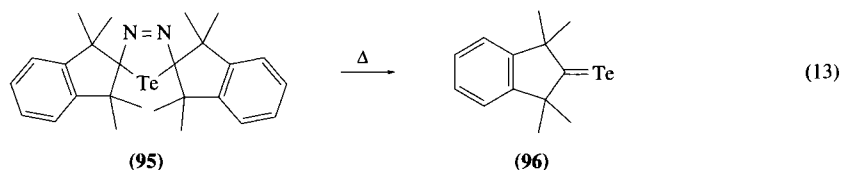
The reaction of 1-hexene with phenylselenenyl hexafluorophosphate (PhSePF_6) in toluene which resulted in the formation of the seleniranium ion (**92**) has been reported <75TL3991>. This seleniranium ion (**92**) was also shown to be an intermediate in the reaction of 2-bromohexyl phenyl selenide (**93**) with dimethylsulfoxide in the presence of silver hexafluorophosphate (AgPF_6) and triethylamine which leads to the formation of α -phenylselenoketone (**94**) (Scheme 19) <78TL2261>.



Scheme 19

1.07.9.2 Comparison of the Various Synthetic Routes Available for Three-membered Rings with One Selenium or Tellurium Atom

Only a few examples of stable three-membered ring compounds containing selenium are known and no examples of stable derivatives of tellurirane have been reported. It is meaningless to make a comparison between the synthetic methods described for these thermally labile small ring systems, however, the best method for the synthesis of selenirenes is the photolysis of the corresponding 1,2,3-selenadiazoles. As can be seen in the cases of stable selenirane derivatives, steric protection with appropriate bulky substituents might be useful to suppress their polymerization or extrusion of the selenium atom. Thermodynamic stabilization by intramolecular coordination of a chalcogenophilic atom-containing functional group to the chalcogen atom may also be useful to isolate these unstable strained ring systems. As for the synthesis and isolation of a stable tellurirane, development of a new and stable precursor such as a 1,2,3-telluradiazole or a telluroketone is required. The first example of a telluroketone kinetically stabilized derivative (**96**) has been synthesized <93JA7019> by thermolysis of the corresponding 1,3,4-telluradiazoline (**95**) <93CL1047> (Equation (13)).



1.07.10 APPLICATIONS OF SELENIRANES AND TELLURIRANES

There are only a few examples of stable three-membered ring systems containing one selenium, that is, selenirenes, seleniranes, and selenuranes, and no stable examples have been reported for their tellurium counterparts. Therefore, in contrast to the widely explored chemistry of their oxygen and sulfur analogues such as oxiranes and thiranes, their intrinsic nature has not yet been fully explored due probably to their extremely thermolabile character leading to the ready extrusion of the chalcogen atom. From another point of view, however, the thermolability of these three-membered ring systems has been utilized successfully in several synthetic reactions. For example, (i) the stereospecific transformation of epoxides to alkenes, (ii) synthesis of strained cycloalkynes, and (iii) sterically congested alkenes. Remarkable progress in the chemistry of heavier typical elements, especially in that of heavier chalcogen atoms, will provide new examples of this class of compounds and their new reactivities and applications.

1.08

Phosphiranes, Phosphirenes, and Heavier Analogues

FRANÇOIS MATHEY

Ecole Polytechnique, Palaiseau, France

and

MANFRED REGITZ

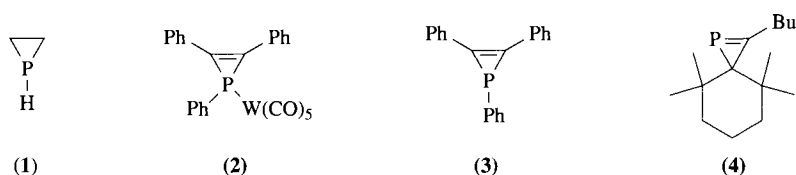
Universität Kaiserslautern, Germany

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1.08.1 INTRODUCTION

The first phosphiranes, including the parent compound (**1**), were mentioned by Wagner in two patents issued in 1963 <63USP3086053, 63USP3086056>. Although considered with some skepticism, this discovery was fully confirmed in 1967 <67JA1102>. Almost two decades later, the first stable phosphirene derivative (**2**) was unambiguously characterized by Marinetti and Mathey on the basis of a x-ray crystal structure analysis <82JA4484>. The same authors obtained the first, potentially anti-aromatic, trivalent 1*H*-phosphirene (**3**) two years later <84CC45>. The story was completed in 1987

with the discovery of the first stable 2*H*-phosphirene (**4**) by Wagner *et al.* <87AG(E)1257>. In 1995, both the parent 1*H*- and 2*H*-phosphirenes remain unknown.



It is striking to compare the relative novelty of these phosphorus-carbon three-membered rings with the well-established history of aziridines dating back to 1888. However, since 1963, progress has been extremely fast, in part due to the powerful ^{31}P NMR tool, and the overall shape of the field is now definitively established. The last comprehensive review concerning these rings was published in 1990 <90CRV997> and is often referred to in this chapter.

1.08.2 STRUCTURE OF PHOSPHIRANES AND PHOSPHIRENES

1.08.2.1 Theoretical Data

Only theoretical data from the late 1980s and early 1990s are treated here. For a presentation of older results, the reader is referred to <90CRV997>. *Ab initio* calculations with a 4-31G(*) basis set were performed by Gonbeau and Pfister-Guillouzo <87JC1799> on the parent phosphirane. The computed geometry is satisfactory: P—C 1.844 (1.867) Å, C—C 1.504 (1.502) Å, P—H 1.407 (1.428) Å, $\angle \text{C—P—C}$ 48.1° (47.4°), $\angle \text{H—C—P}$ 96.4° (95.2°). The experimental data in parentheses come from a microwave study <69JA17>. The calculations indicate that phosphorus bears a significant positive charge (+0.207), whereas the carbons of the ring are negative (−0.478). The HOMO at −9.85 eV corresponds to the lone pair, whilst the NHOMO and the LUMO, which result from the bonding and antibonding combinations of $p_{(\text{P})}$ and $\pi^*_{(\text{C}=\text{C})}$, correspond to the $\sigma_{(\text{P—C})}$ bent bonds. The P—C bonds are weak according to a Mulliken population analysis. A similar picture was obtained in 1988 by Dobbs *et al.* <88JPC4886>, whose use of a 6-31G* basis set led to a better geometry: P—C 1.853 Å, $\angle \text{C—P—C}$ 47.4°. The replacement of hydrogen by chlorine at phosphorus induces a substantial shortening of the P—C bonds (1.840 Å). This was explained by a large increase of the positive charge at phosphorus (from +0.24 for PH to +0.50 for PCl) which leads to a stronger ionic interaction between phosphorus and carbon. Some time later, a calculation of the inversion barrier at phosphorus was reported by Bachrach <89JPC7780>. The extremely high value of 68.3 kcal mol^{−1} (285.9 kJ mol^{−1}) at the MP2/6-31G*//HF/6-31G* + ZPE(3-21G*) level was seen as a consequence of the large increase of the H—P—C angle, combined with a stretch of the C—C bond by 0.088 Å during the inversion process. In parallel, Boatz and Gordon <89JPC3025> calculated some thermodynamic parameters for phosphirane at the MP2/6-31G(d) level. Their data include the heat of formation from the heteroatomic subunit (here PH) and ethylene: the computed ΔH of −72.3 kcal mol^{−1} (−302.6 kJ mol^{−1}) may be compared with −109.7 kcal mol^{−1} (−459.2 kJ mol^{−1}) for aziridine, −128.7 kcal mol^{−1} (−538.7 kJ mol^{−1}) for oxirane and −84.3 kcal mol^{−1} (−352.9 kJ mol^{−1}) for thiirane; the corresponding strain energies are ΔE = −22.0 kcal mol^{−1} (−92.1 kJ mol^{−1}) for phosphirane vs. −29.5 kcal mol^{−1} (−123.5 kJ mol^{−1}) for aziridine, −30.0 kcal mol^{−1} (−125.6 kJ mol^{−1}) for oxirane and −17.7 kcal mol^{−1} (−74.1 kJ mol^{−1}) for thiirane. A remarkable agreement for the fragmentation energy of phosphirane into phosphinidene and ethylene exists between the results of Boatz and Gordon and the more recent calculations of Nguyen *et al.* <94JCS(F)1771>: ΔE = +76.6 kcal mol^{−1} (320.7 kJ mol^{−1}) vs. +74.2 kcal mol^{−1} (310.6 kJ mol^{−1}). This latter paper deals more precisely with the various ring-chain rearrangements of phosphirane. The transformation of phosphirane into vinylphosphine is predicted to be a concerted process with an energy barrier of only 56.2 kcal mol^{−1} (235.2 kJ mol^{−1}) at the QCISD(T)/6-31G(d,p) + ZPE level (see Equation (23)). Two related works deal with the phosphiranium cation $[\text{C}_2\text{H}_4\text{PH}_2]^+$ <87JST(152)69> and the phosphiranylium cation $[\text{C}_2\text{H}_4\text{P}]^+$ <93JOC1379>. The first one predicts a substantial increase in the strain energy upon protonation: ΔE = −47.3 kcal mol^{−1} (−198.0 kJ mol^{−1}) at the 6-31G*//3-21G level. The second predicts an easy disrotatory ring opening of the phosphiranylium ion into the bis(methylene)phosphonium cation. The open cation is more stable than its cyclic isomer by 17.5 kcal mol^{−1} (73.2 kJ mol^{−1}) and the activation energy for the opening of the ring is only 15.2 kcal mol^{−1} (63.6 kJ mol^{−1}). Finally, some calculated properties of triphospha[1.1.1]propellane have

been reported <94IC1153>, including a long C—C bridge at 1.63 Å and a lower ring strain than [1.1.1]propellane.

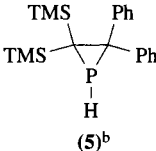
The first *ab initio* (Hondo) analysis of the electronic structure of phosphirene was made by Gonbeau and Pfister-Guillouzo <85NJC71>. The ring was treated as a combination of phosphinidene and ethyne: the HOMO at -9.13 eV is a combination of $n_{p(P)}$ and $\pi_{1(C\equiv C)}$ (perpendicular to the ring plane). The NHOMO and LUMO result from the bonding and antibonding combinations of $p^*_{(P)}$ and $\pi^*_{2(C\equiv C)}$ (in the ring plane). Subsequent studies have mainly addressed the question of the relative stability of 1*H*- and 2*H*-phosphirenes. For example, at the MP4/6-31G** level, Nguyen *et al.* <92CB923> calculated that 1*H*-phosphirene is higher in energy than 2*H*-phosphirene by 11.2 kcal mol⁻¹ (46.9 kJ mol⁻¹). Similar values have been obtained by Bachrach <91JOC2205> (12.3 kcal mol⁻¹ (51.5 kJ mol⁻¹)) and Berger *et al.* <94OM640> (10 kcal mol⁻¹ (41.9 kJ mol⁻¹)). Furthermore, all of these authors confirm the experimental observations that 1-halophosphirenes are more stable than their 2*H*-isomers. Thus, Nguyen *et al.* found that 1-fluorophosphirene is more stable by 21.3 kcal mol⁻¹ (89.2 kJ mol⁻¹) and 1-chlorophosphirene by 10.3 kcal mol⁻¹ (43.1 kJ mol⁻¹) than the corresponding phosphorus-dicoordinated species. The same authors calculated a substantial shortening of the P—C ring bonds upon halogenation, from 1.821 Å (PH) to 1.773 Å (PF) and 1.778 Å (PCl). This stabilizing effect of halogens on 1*H*-phosphirenes was ascribed to a higher contribution of the aromatic phosphirenylium cation [C₂H₂P]⁺ to the electronic structure of the ring, induced by the increasing electronegativity of the phosphorus-substituent. Similar results and interpretations were provided by Bachrach <92JST(255)207>. Another interesting point concerns the pyramidal inversion barrier of phosphorus in 1*H*-phosphirenes. According to the calculations of Bachrach at the HF/6-31G* level <91JOC2205>, this barrier is very high, at 92.6 kcal mol⁻¹ (387.6 kJ mol⁻¹). The potentially antiaromatic character of the planar 1*H*-phosphirene may explain why the inversion of phosphorus is even more difficult than for phosphirane. Finally, the first *ab initio* treatment of phosphirenylium cation was released by Maclagan in 1989 <89CPL(163)349>. Among the possible [C₂H₂P]⁺ isomers, the cyclic species was predicted to be the most stable. The optimized geometry at the MP3/6-31G* level suggested a substantial cyclic delocalization within the ring: P—C 1.729 Å, C=C 1.349 Å. The formation of this ion in interstellar clouds was indicated as a possibility when C₂H₂ is present together with PH_n⁺. These data have been corroborated by a study in 1994 at the HF/6-31 + G* level <94JA9407> indicating P—C and C=C bond lengths of 1.7032 Å and 1.3406 Å, respectively. The missing electron density at the C=C double bond is predicted to be localized in the phosphorus lone pair orbital and, consequently, the C=C bond order is reduced by comparison with 1-fluorophosphirene (b.o. = 1.776 vs. 1.943).

1.08.2.2 Structural Data

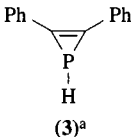
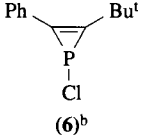
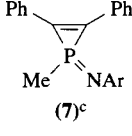
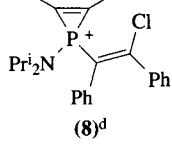
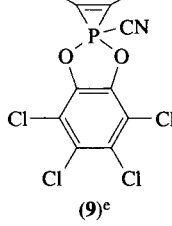
A listing of all the structural data concerning phosphiranes and phosphirenes that were available in 1989 has been published <90CRV997>. Since then, numerous phosphirane complexes have been characterized by x-ray analysis, but no new original features have been brought to light. Table 1 lists the structural parameters of two representative monocyclic phosphiranes which have been characterized in the free state. Typically, the $\angle$ C—P—C intracyclic angles of phosphirane derivatives fall in a range from 47° <89CC973> to 51° <89CB453>. In fact, the ring can “breathe” as is indicated by the length of the intracyclic C—C bond, which varies between 1.460 Å <89CC973> and 1.588 Å <89AG(E)900>. The same effect is found for the intracyclic P—C bonds, which lie in a range which extends from 1.78 Å <89POL2671> to 1.89 Å <86CB1977>. This explains the observation that the dissociation of the phosphirane ring into alkene and phosphinidene is highly dependent on the nature of the ring substituents.

Some representative x-ray crystal structure analyses of phosphirene derivatives are collected in Table 2. As in the phosphirane case, it is clear that significant variations in structural parameters take place with variation of the substitution pattern. A comparison of the structures of (3) and (6) supports the theoretical assertion that the halogen substituent stabilizes the phosphirene ring: a substantial shortening of the P—C bonds is observed in the ring of (6). In the same vein, the structure of the phosphirenium salt (8) suggests some kind of electronic delocalization within the cycle. The very short P—C ring bonds of the pentacoordinate phosphirene (9) are also noteworthy, but no obvious explanation of this phenomenon can be offered at the moment. Finally, the only known 2*H*-phosphirene (4) has been structurally characterized as its P-W(CO)₅ complex. The

Table 1 Structural parameters of monocyclic phosphiranes.

<i>1-R-phosphirane</i>	<i>Bond angles (°)</i>			<i>Bond lengths (Å)</i>		
	<i>C—P—C</i>	<i>C—P—R</i>	<i>P—C—C</i>	<i>P—C</i>	<i>C—C</i>	<i>P—R</i>
 (1)^a	47.4	95.2	66.3	1.867	1.502	1.428 (P—H)
 (5)^b	49	110.6 115.1		1.87 1.89	1.56	

^aMicrowave study <69JA17>. ^bX-ray crystal structure analysis <86CB1977>.**Table 2** Structural parameters of some monocyclic phosphirene derivatives.

<i>1-R-phosphirene</i>	<i>Bond angles (°)</i>			<i>Bond lengths (Å)</i>		
	<i>C—P—C</i>	<i>C—P—R</i>	<i>P—C—C</i>	<i>P—C</i>	<i>C=C</i>	<i>P—R</i>
 (3)^a	41.8	104.0 104.4	69.1	1.820 1.821	1.299	1.842
 (6)^b	42.9	103.7 104.2	68.4 68.7	1.781 1.784	1.303	2.166
 (7)^c	43.5		68.2	1.75	1.30	1.80 (P—Me)
 (8)^d	46.1		66.9 67.0	1.730 1.732	1.36	1.640 (P—N) 1.799 (P—C)
 (9)^e	46.8		66.3 66.9	1.709 1.715	1.360	1.784 (P—C) 1.668 (P—O) 1.700 (P—O)

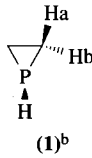
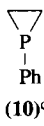
^a<84CC45>. ^b<91CB1207>. ^c<93CB649>. ^d<88CC462>. ^e<90TL3429>.

structure shows an intracyclic $\angle \text{C—P—C}$ angle of 49.2° and a $\text{P}=\text{C}$ double bond of $1.634 \text{ \AA}$ $\langle 87\text{AG(E)}1257 \rangle$.

1.08.2.3 Spectroscopic Data

Table 3 lists ^1H , ^{13}C , and ^{31}P NMR data for two representative phosphiranes. The main spectroscopic features associated with the phosphirane ring include: (a) an extreme high field shift of the ^{31}P resonance; (b) correspondingly high field shifts of the ^1H and ^{13}C resonances, as expected for any three-membered ring; (c) a large negative $^1J(\text{C—P})$ coupling within the ring; and (d) a low $^1J(\text{H—P})$ coupling, the values for acyclic secondary phosphines being in the range 169–217 Hz. The authors also note a study of the correlation between the $\delta^{31}\text{P}$ value and the nature of R for a series of 1-R-phosphiranes $\langle 89\text{CB}453 \rangle$ and the measurement of the ^{31}P magnetic shielding tensor components of phosphirane (**5**) $\langle 88\text{CPL}(149)363 \rangle$.

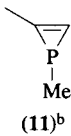
Table 3 NMR data for some representative phosphiranes.

Phosphirane	$^1\text{H}^a$			$^{13}\text{C}^a$	$^{31}\text{P}^a$
	PH	Ha	Hb	CH_2	
 (1)^b	−0.59 (158.34)	1.21 (−2.64)	0.66 (16.14)	0.7 (−33)	−341
 (10)^c		0.3–1.0		11.04 (−39.7)	−234

^a δ (ppm) from TMS or external 85% H_3PO_4 . Values in parentheses are couplings to ^{31}P in hertz. ^b $\langle 83\text{OMR}(21)494 \rangle$.
^c $\langle 69\text{T}1097, 76\text{JA}2109 \rangle$.

The NMR characteristics of phosphirenes once again include a strong upfield shift of the ^{31}P resonance and very high $^1J(\text{C—P})$ coupling constants. The parameters for a representative phosphirene are listed in Table 4. The ^{31}P magnetic shielding tensor components of phosphirene (**3**) have also been measured $\langle 87\text{CPL}(136)224 \rangle$.

Table 4 NMR data for a representative phosphirene.

Phosphirene	$^1\text{H}^a$	$^{13}\text{C}^a$			$^{31}\text{P}^a$
	$=\text{CH}$	$=\text{CH}$	$=\text{CMe}$	<i>Cipso (Mes)</i>	
 (11)^b	7.43 (22)	113.38 (45)	129.33 (47.5)	140.43 (72.5)	−192.0

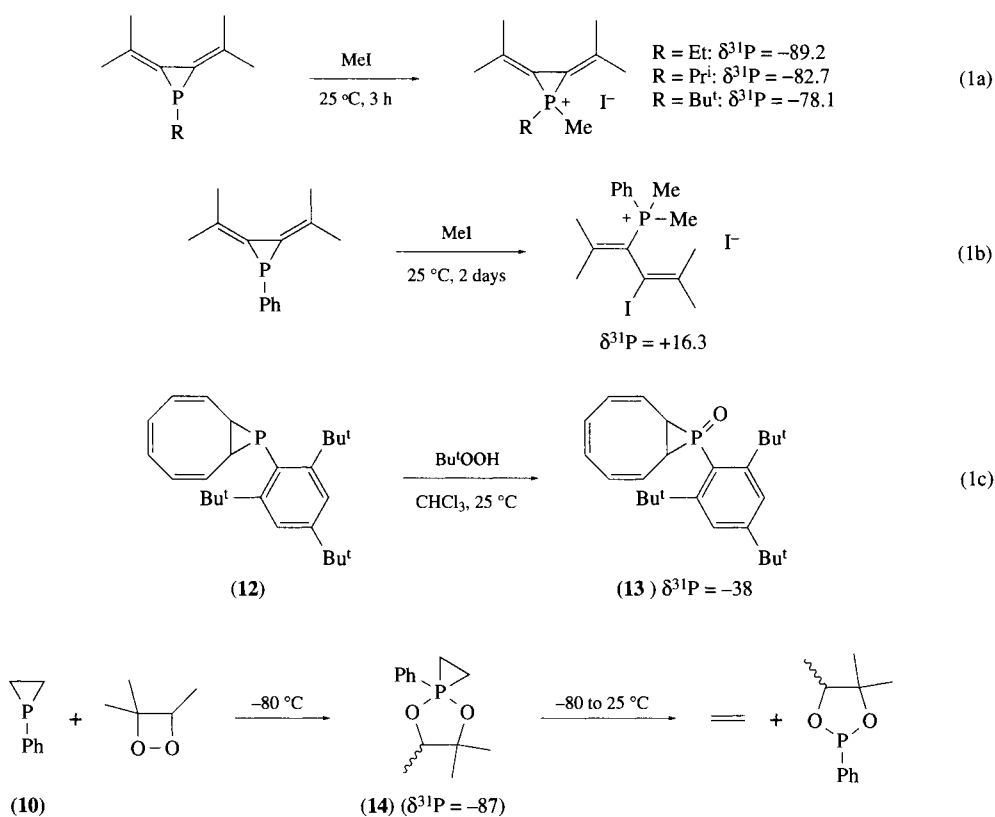
^a δ (ppm) from TMS or external 85% H_3PO_4 . Values in parentheses are couplings to ^{31}P in hertz.
^b(11) $\langle 91\text{T}6673 \rangle$.

A description of the IR and mass spectra of phosphiranes has appeared $\langle 69\text{T}1097 \rangle$. A combined IR–Raman study of deuterated phosphirane (**1**) has shown that the P—C stretching vibrations are shifted to low frequencies relative to those of Me_2PH . The relative weakness of the P—C ring bonds of (**1**) is thus established $\langle 69\text{SA(A)}819 \rangle$. For further IR data, see also $\langle 70\text{SA(A)}249 \rangle$ and $\langle 73\text{JST}(18)75 \rangle$. Other spectroscopic studies of phosphiranes include microwave $\langle 70\text{JCP}(52)2831 \rangle$ and ion cyclotron resonance spectrometry $\langle 75\text{ZN(A)}1470 \rangle$.

1.08.3 REACTIVITY OF PHOSPHIRANES AND PHOSPHIRENES

1.08.3.1 Reactions at Phosphorus with Retention of the Cyclic Structure

The nucleophilic reactivity of the lone pair of phosphiranes is very low. Thus, acids or quaternizing agents (RX) do not generally give the corresponding $[\text{PH}]^+$ or $[\text{PR}]^+$ phosphiranium salts. Phospha-[3]radialenes, for which well-characterized phosphiranium salts have been prepared (Equation (1a)) <91CB933>, are a notable exception to this rule. These salts display a characteristic upfield shift of the ^{31}P resonance and are sensitive to moisture. In some instances, a ring opening is observed during the quaternization reaction (Equation (1b)). Of course, in these cases, the substitution pattern induces a special reactivity that is not representative of phosphiranes as a class. In a further demonstration of the influence of the substitution pattern, Quin was able to perform the atypical oxidation of a sterically protected phosphirane to the corresponding oxide without collapse of the ring (Equation (1c)) <87TL1077>. Denney <78CC854> was able to monitor the related formation of an unstable phosphorane (**14**) at low temperature upon reaction of a dioxetane with phosphirane (**10**) (Scheme 1).

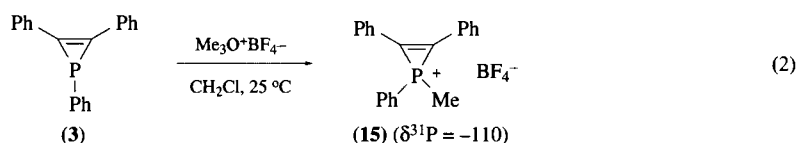


Scheme 1

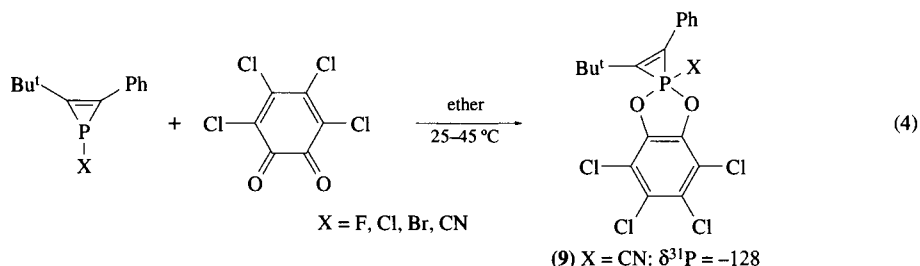
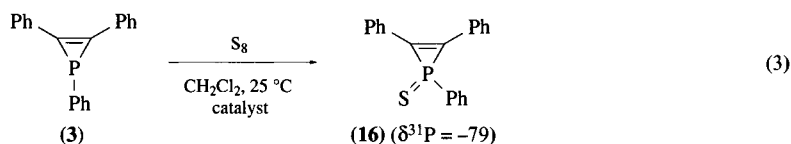
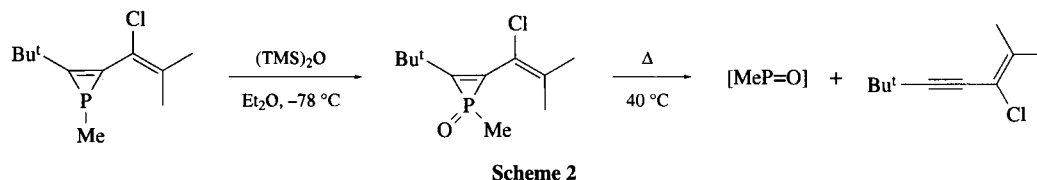
Numerous stable complexes of phosphiranes, especially with molybdenum and tungsten carbonyls, have been described in the literature. Most of them have been obtained via the building of the phosphirane ring directly within the metal coordination sphere, taking advantage of the stabilizing effect of the metal (see below). Nevertheless, some of these complexes have been prepared from preformed phosphiranes. Amongst these, the most interesting are some rhodium(I) cationic complexes of optically active 1-*l*-menthyl-2-phenylphosphirane that induce the asymmetric hydrogenation of dehydro-aminoacids with enantiomeric excesses up to 76% <93OM1207>.

As a general rule, tetra- and pentacoordinated derivatives of phosphirenes display a much higher stability than the corresponding derivatives of the phosphirane ring. Some kind of electronic stabilization is probably at work in phosphirenium salts (see the structural data of one such salt: <88CC462>), which can either be synthesized directly (see below) or from tervalent phosphirenes (Equation (2)) <85JA4700>. Methyl triflate in chloroform at -50°C has also been used successfully

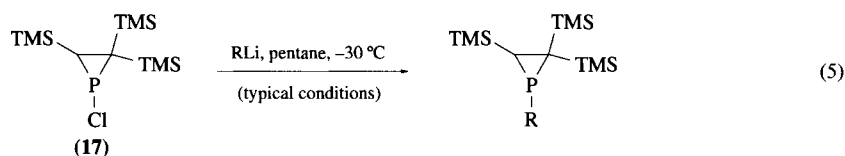
to quaternize a wide range of 1-alkyl, 1-alkoxy, and 1-aminophosphirenes <94RHA61>. In the same way, bromine and AlCl_3 react with (3) to give the corresponding bromophosphirenium salt.



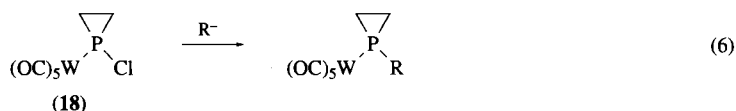
Up to 1995, a phosphirene oxide has been transiently observed during the oxidation of a tervalent phosphirene at low temperature in only one case (Scheme 2) <94RHA61>. Several sulfides and selenides have been prepared by direct reaction of sulfur or selenium with phosphirenes in the presence of a basic tertiary amine as a catalyst <85JA4700, 94RHA61>, as for example, in Equation (3). Similarly, tosyl azide readily reacts with phosphirenes at room temperature in ether to give the expected phosphirene imines <94RHA61>; these display a good thermal stability and can also be synthesized directly <93CB649>. Among the findings on the subject, one of the most surprising is undoubtedly the synthesis of very stable pentacoordinate derivatives by oxidative addition of an orthoquinone to tervalent phosphirenes (Equation (4)) <90TL3429>. Finally, as in the case of phosphiranes, numerous stable complexes of phosphirenes are known. They are discussed later in this chapter.



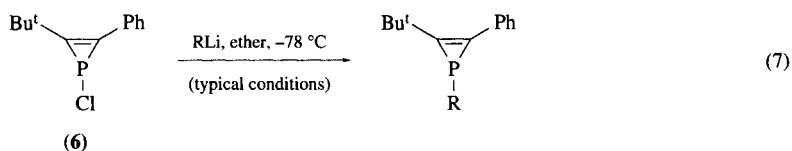
The availability of 1-chlorophosphiranes <87TL2693, 88ZN(B)1285, 89CB453, 91OM3949, 91SL743> and 1-chlorophosphirenes <89AG(E)225, 89TL3951> either in the free state or as $\text{P}-\text{W}(\text{CO})_5$ complexes <88NJC755, 89POL2671> has led to a series of studies on the reactions of nucleophiles with such species. Some significant results are quoted in Equations (5)–(7).



$\text{R} = \text{Me, Bu}^n, \text{Bu}^s, \text{Bu}^t, \text{TMS-CH}_2, (\text{TMS})_2\text{CCl, Et}_2\text{N, MeO, Bu}^t\text{S, Bu}^n_2\text{P, H, etc.}$ <89CB453>;
 $\text{R} = \text{Cp}^*, \text{CpFe}(\text{CO})_2, \text{Cp}^*\text{Mo}(\text{CO})_3$ <91OM3949>

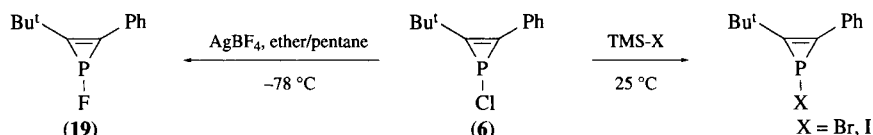


R = EtO, -O-, (EtO)₂P(O), H (89POL2671)

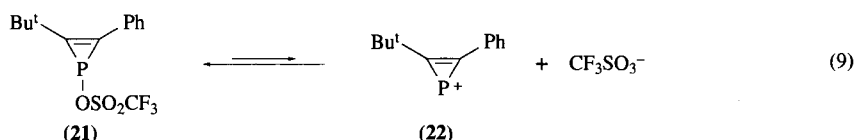
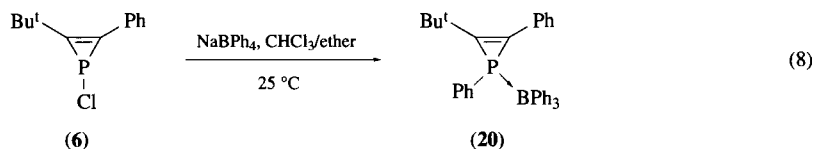


R = Prⁱ₂N, (TMS)₂P, R¹₂C=P, Bu^tC≡C, N₃, TMS(N₂), etc. (89AG(E)225, 94RHA61)

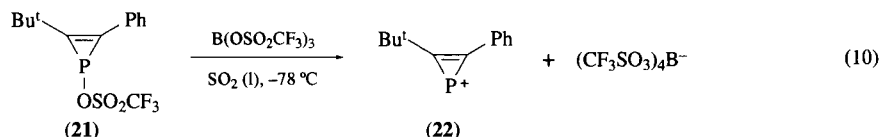
A systematic study of the exchange of chlorine for other halogen (F, Br, I) or pseudohalogen substituents, with the question of the stability of the phosphirenylium cation in mind, was carried out on (6) by the group of Regitz (91CB1207). Some representative experiments are depicted in Scheme 3. The formation of the PF compound (19) from (6) and AgBF₄ probably involves the abstraction of F⁻ from BF₄⁻ by a transient phosphirenylium cation. A similar reaction was observed between (6) and BPh₄⁻ (Equation (8)). The NMR data of the triflate derivative (21) also suggest the reversible formation of a phosphirenylium cation (Equation (9)).



Scheme 3

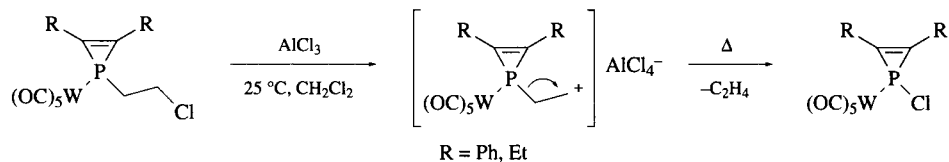


The ³¹P chemical shift of (21) is at relatively low field: δ³¹P = -9.5 vs. -73.4 for (6) in [D₈] toluene; no ¹J (¹⁷O—³¹P) is observed; both ³¹P and ¹³C ring resonances are shifted to low fields when the polarity of the solvent increases: i.e., δ³¹P = -9.5 → +10.5 when toluene is replaced by nitromethane. The highly electrophilic nature of the system (21) ⇌ (22) is shown by the easy formation of a salt with pyridine and by the ready *para*-substitution of the phenyl ring of *N,N*-dimethylaniline (94RHA61). Definitive evidence for the formation of a phosphirenylium cation has been produced (Equation (10)) (94JA9407).

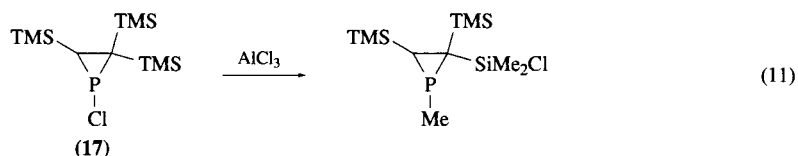


The phosphirenylium cation (22) displays a very strong and characteristic downfield shift of the ³¹P resonance: δ³¹P = +309.7. The ¹J (P—C) couplings increase from 77.0 Hz and 66.0 Hz in (21) to 94.9 Hz and 83.3 Hz in (22). The requirement of an extremely strong Lewis acid to prepare (22) and its relatively low thermal stability (it must be kept below -40°C), suggest that the phos-

phirenylium cation does not benefit from a very significant electronic stabilization. An earlier observation that bis(1-phosphirenyl)ethers are not split by AlCl_3 had led to the same conclusion (88NJC755). Nonetheless, an experiment suggesting also some aromaticity for phosphirenylium $\text{P}-\text{W}(\text{CO})_5$ complexes must be mentioned (Scheme 4) (85TL4595, 88NJC755). Here, the driving force for the elimination of C_2H_4 is thought to be the extra stability associated with a transient phosphirenylium complex. Finally, a related attempt to prepare a phosphiranylium cation led to a curious result (Equation (11)) (89CB453).

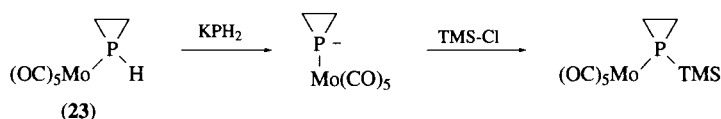


Scheme 4

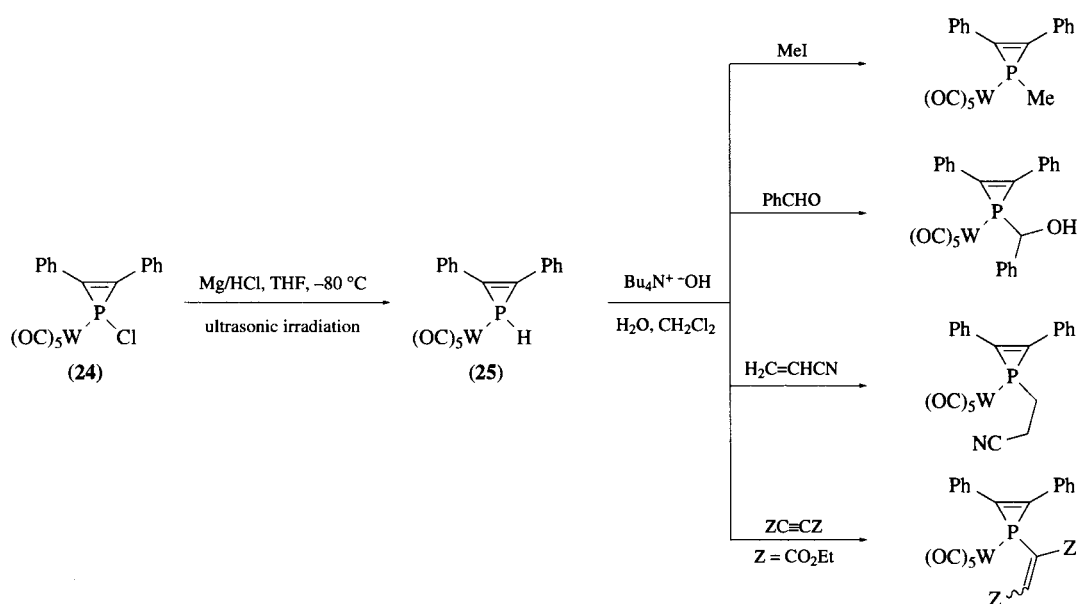


(11)

The metalation of the $\text{P}-\text{H}$ bond of phosphorus-unsubstituted phosphiranes has only been achieved in the coordination sphere of a transition metal (Scheme 5) (71AG(E)125). Analogous chemistry has been carried out on a phosphorus-unsubstituted phosphirene complex (Scheme 6) (88NJC755). Without the stabilizing effect of the transition metal coordination sphere, the free phosphirane and phosphirene anions appear to be very unstable and cannot be used for synthetic purposes. Even the anion of (25) displays some instability, perhaps due to some antiaromaticity, and must be used under phase-transfer conditions.



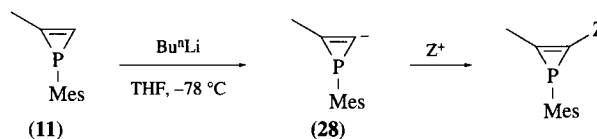
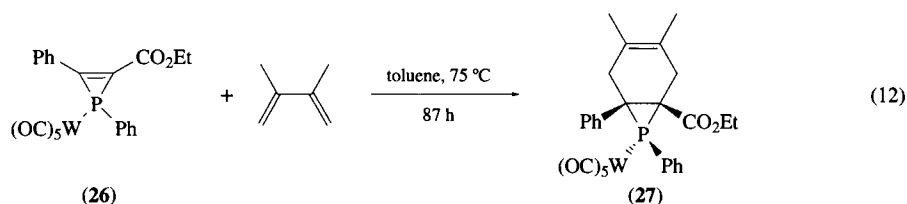
Scheme 5



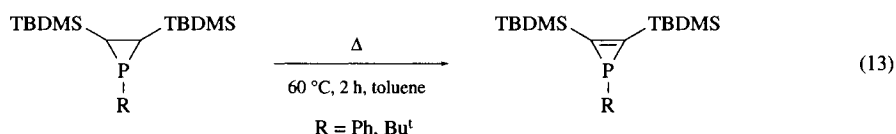
Scheme 6

1.08.3.2 Reactions at the Carbons of the Ring with Retention of the Cyclic Structure

Only a few such reactions are known for phosphirenes. In one instance, it proved possible to carry out a [4 + 2] cycloaddition involving the phosphirene double bond by employing an activated phosphirene complex (Equation (12)) <85JA4700>. The cycloaddition selectively takes place on the tungsten side of the ring. In another instance, a phosphirene carbanion has been made and trapped (Scheme 7) <91T6673>. At room temperature, carbanion (**28**) rearranges to give an open-chain alkynylphosphide (see Equation (32)). The thermal conversion of a phosphirane into a phosphirene has been reported (Equation (13)) <91TL6537>.

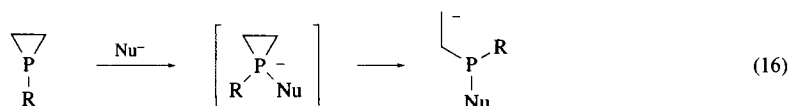
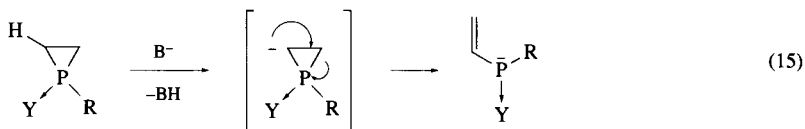
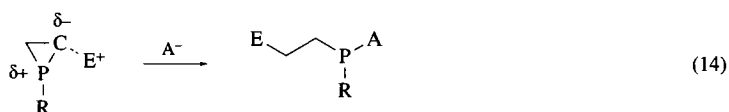


Scheme 7



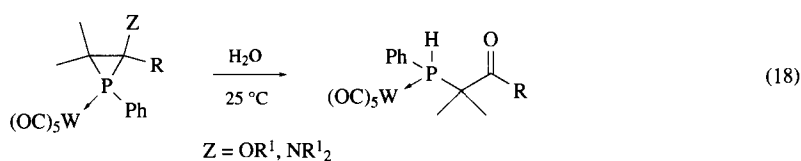
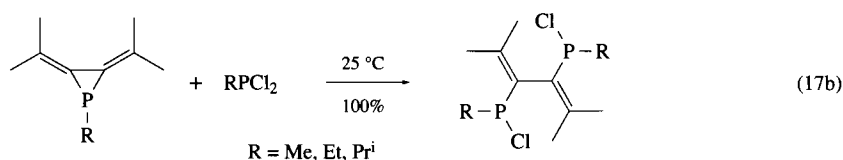
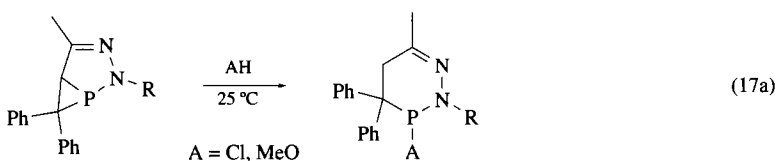
1.08.3.3 Reactions with Cleavage of One P—C Bond of the Ring

It must be recalled here that theoretical calculations have shown that the P—C bonds of the phosphirane ring are high in energy and polarized in the sense $\text{P}^{+\delta}-\text{C}^{-\delta}$. In fact, they have a behavior which strongly resembles that of classical π -bonds. Three main mechanisms leading to the cleavage of these bonds have been recognized; these involve electrophilic attack or proton abstraction at one carbon of the ring, or nucleophilic attack at phosphorus (Equations (14)–(16)).

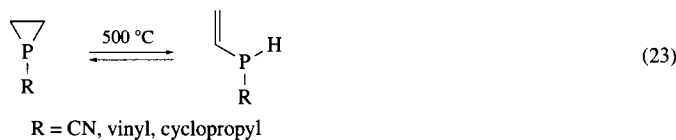
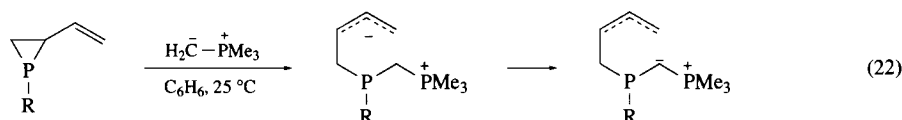
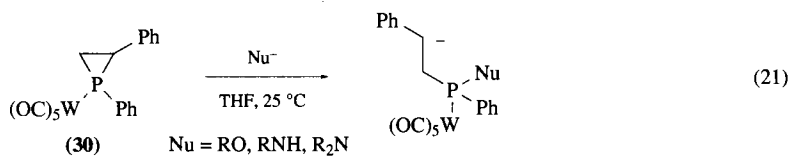
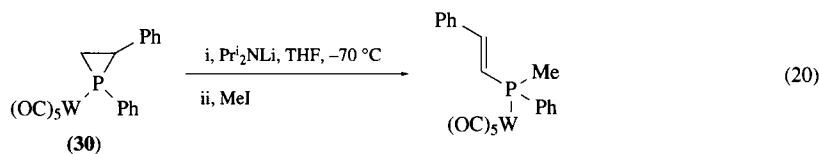
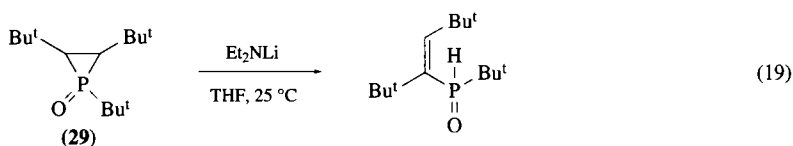


The first mechanism is probably operative in the cleavage of a bicyclic phosphirane whose polarization of the P—C bond is enhanced by a nitrogen substituent at phosphorus (Equation (17a)) <79DOK(244)117>. The cleavage of phosphaz[3]radialenes by dichlorophosphines <91CB933> probably belongs in the same category (Equation (17b)). Interestingly, when a substituent bearing a lone pair

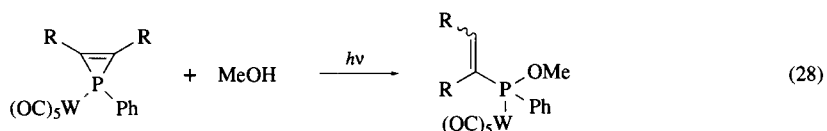
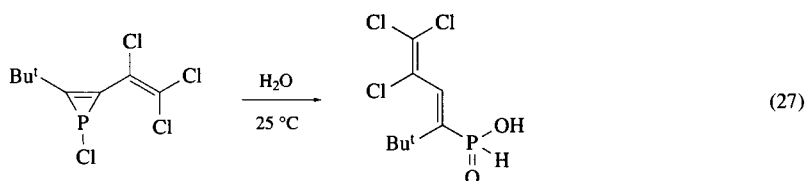
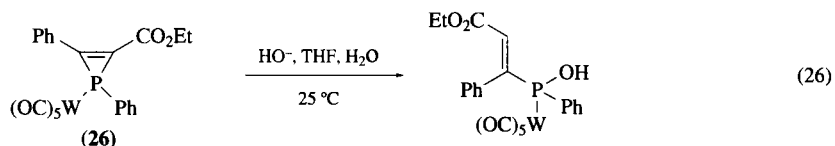
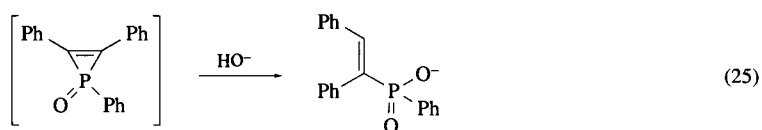
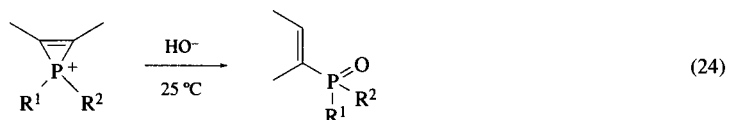
is located on the carbon of the ring, the polarity is reversed and, upon hydrolysis, the proton ends on phosphorus (Equation (18)) <84OM456, 84OM1492>.



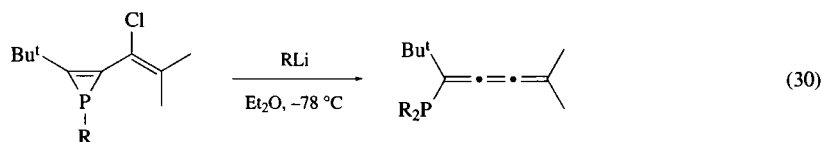
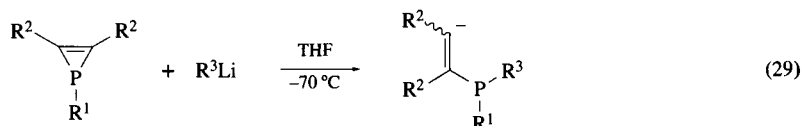
The second mechanism has been illustrated by Quast and Heuschmann <81LA977> and by Marinetti and Mathey <89T3061> (Equations (19) and (20)). The third mechanism can operate with (30) <89T3061> and with some free 2-vinylphosphiranes <84T3273> (Equations (21) and (22)). At high temperature, the behavior of phosphiranes is entirely different. Around 500 °C, an equilibrium takes place between phosphiranes and secondary vinylphosphines (Equation (23)) <92CC1799, 93PS(75)225>. This equilibrium has been investigated from a theoretical standpoint by Nguyen *et al.* <94JCS(F)1771> and found to be a concerted process with an activation energy of 56.2 kcal mol⁻¹ (235.3 kJ mol⁻¹) (R = H).

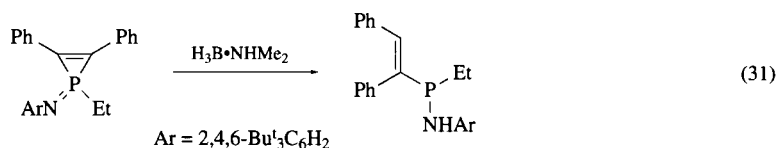


Ring opening is also frequently observed in phosphirene chemistry. For example, phosphirenium salts are readily opened upon hydrolysis (Equation (24)) <84TL1345, 85JA4700, 94RHA61>. The same type of reaction has been observed for a transient phosphirene oxide (Equation (25)) <72CC1085, 79CC390>, for an activated phosphirene complex (Equation (26)) <85JA4700> and for a 1-chloro-phosphirene (Equation (27)) <91SL433>, where, in all cases, the phosphorus atom displays an enhanced electrophilicity over more conventionally substituted phosphirenes. When the electrophilicity of phosphorus is low, it is still possible to promote the opening of the ring using UV irradiation (Equation (28)) <85JA4700>.

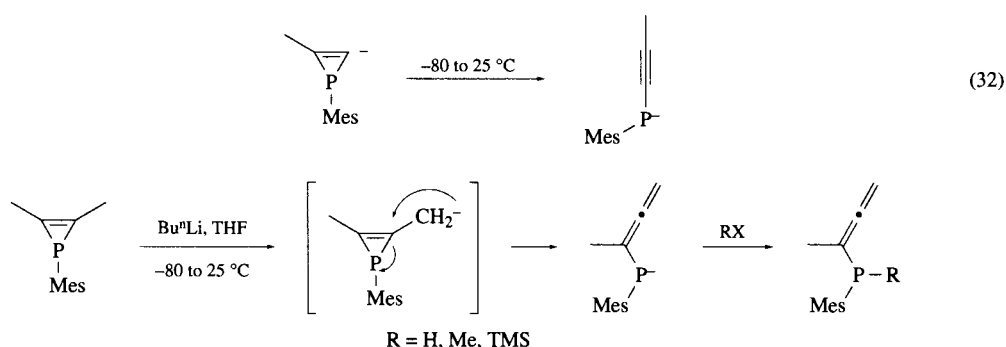


Another type of reaction relying on the same fundamental mechanism involves organolithium compounds <85JA4700>. The general scheme is depicted in Equation (29). The vinyl carbanion product isomerizes rapidly even at -70°C , hence a mixture of (*E*) and (*Z*) isomers is obtained upon reaction with electrophiles. This kind of chemistry has been used to prepare some unusual phosphino-1,2,3-butatrienes (Equation (30)) <92SL635>. Formally involving an hydride ion and related to the same scheme is the reaction of a phosphirene imine with a borane complex (Equation (31)) <94CB313>.

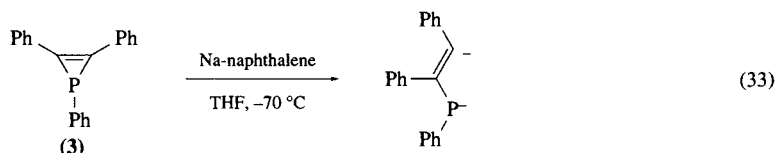




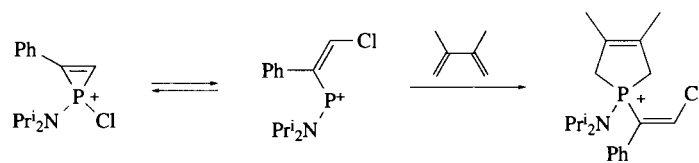
Apart from nucleophilic attack at phosphorus, other mechanisms can lead to the opening of the phosphirene ring. For instance, the phosphirene carbanion (**28**) depicted in Scheme 7 rearranges at around room temperature to give an open-chain phosphide (Equation (32)) <91T6673>. The mechanism is similar to that described in Equation (15) for the opening of the phosphirane ring. In the same work <91T6673>, it was also shown that phosphirenylmethyl carbanions rearrange to give allenylphosphides (Scheme 8). It is clear that the mesityl group serves to block the nucleophilic attack of butyllithium at phosphorus in the chemistry depicted in Scheme 7, Equation (32), and Scheme 8. Another item concerns the reductive cleavage of the phosphirene ring by alkali metals (Equation (33)) <85JA4700>.



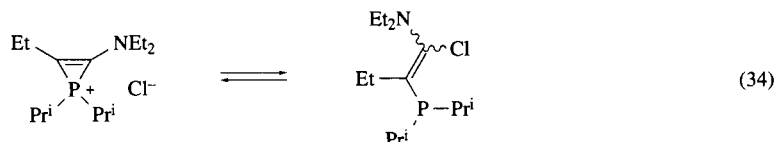
Scheme 8



Finally, mention should be made of the ring-chain tautomerism observed in some phosphirenium salts (Scheme 9 and Equation (34)) <90TL819, 93TL1331>. In the first case, the existence of the phosphenium salt was demonstrated through its trapping by a conjugated diene.



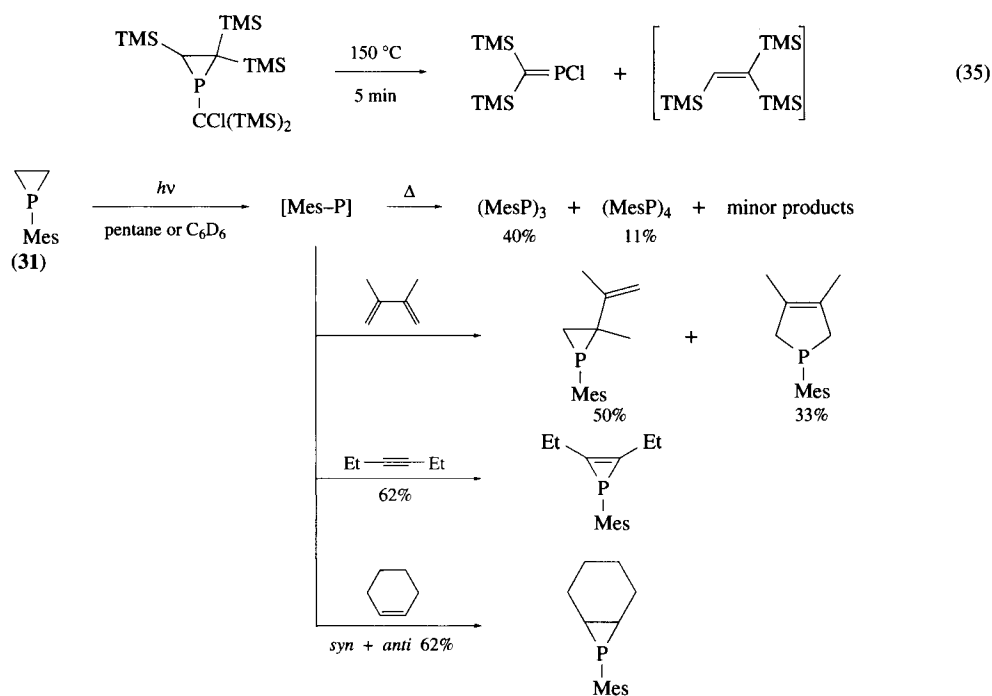
Scheme 9



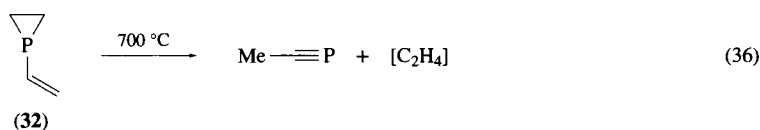
1.08.3.4 Reactions with Cleavage of Two P—C Bonds of the Ring

According to theoretical calculations, the fragmentation of phosphirane to yield ethylene plus singlet phosphinidene is a viable proposition ($\Delta H \approx 74 \text{ kcal mol}^{-1}$ (310 kJ mol^{-1}) <94JCS(F)1771>),

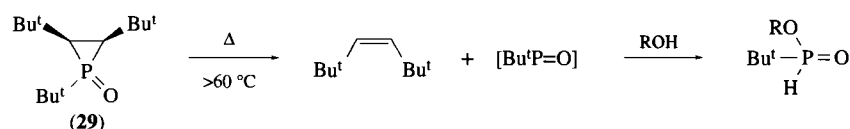
but many other competing processes, including the isomerization into vinylphosphine may occur (Equation (23)). Thus, any phosphirane derivative can be viewed as a potential phosphinidene precursor but, as experimental data clearly demonstrate, clean and easy fragmentation is profoundly dependent upon the substitution pattern of the ring, both at phosphorus and carbon. In the case of tervalent phosphiranes, the first serious evidence of such a splitting came from the work of Niecke *et al.* <89CB453> (Equation (35)). In 1992, a thorough study of the thermal and photochemical decomposition of 1-mesitylphosphirane (**31**) by Gaspar and co-workers <92JA8526> yielded convincing evidence for the formation of mesitylphosphinidene. Some of the most significant results of that study are summarized in Scheme 10. Later in 1992, the flash thermolysis of 1-vinylphosphirane (**32**) was shown to give phosphapropyne, probably via the rearrangement of vinylphosphinidene (Equation (36)) <92CC1799>. The mechanism of this reaction has been studied in some depth from a theoretical standpoint <94OM640>.



Scheme 10

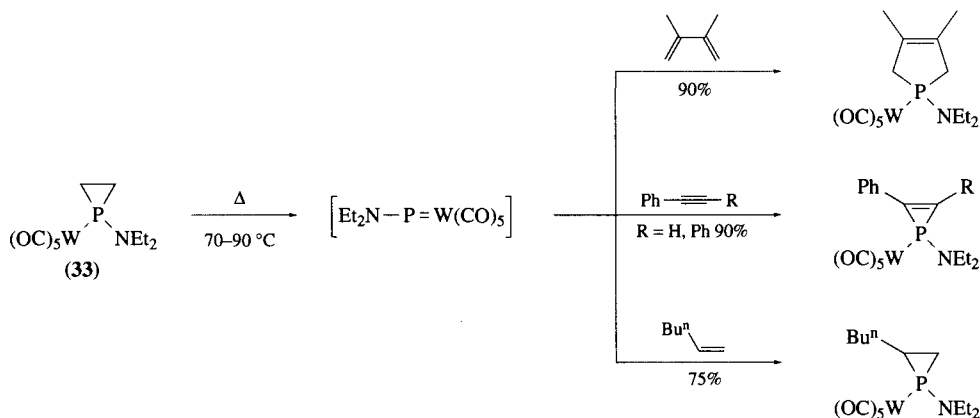


The first splitting of a phosphirane derivative into an alkene and a phosphinidene fragment was described by Quast and Heuschmann <82CB901>, and involved an oxide (**29**) (Scheme 11). The retention of the stereochemistry of the alkenic fragment suggests a concerted mechanism. A clean thermal splitting has also been observed for several phosphirane complexes (Schemes 12 and 13) <89JA9098, 92S157>.

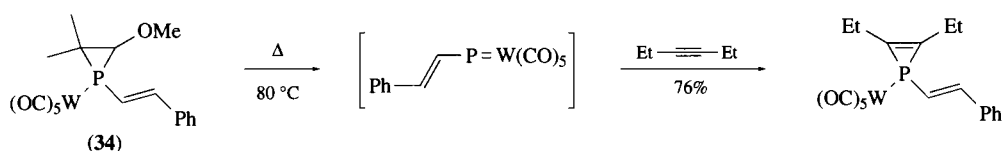


Scheme 11

Another type of splitting has been observed in the reaction of some nucleophiles with phosphirane derivatives. For example, the reaction of aryllithium compounds with a heavily substituted 1-chlorophosphirane (**35**) leads to the collapse of the ring (Equation (37)) <87TL2693>. Transiently,

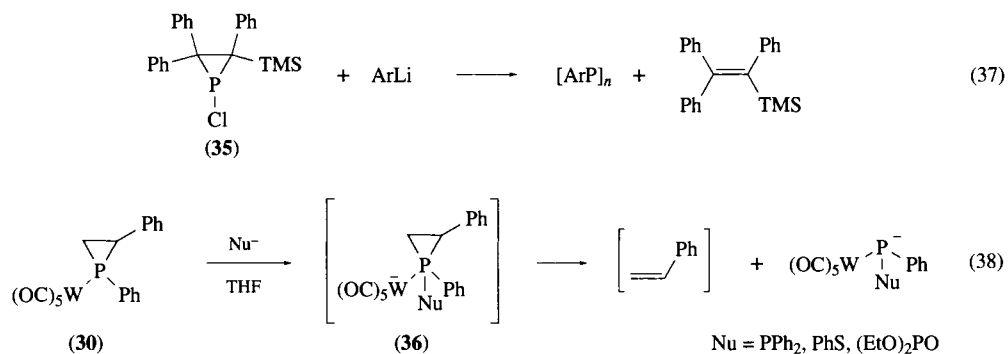


Scheme 12

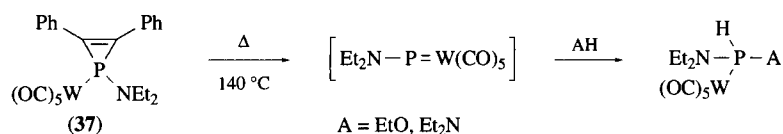


Scheme 13

a destabilized 1-arylphosphirane is probably formed. The finding that phosphirane complex (30) also splits upon reaction with soft nucleophiles is more significant (Equation (38)) $\langle 89T3061 \rangle$. It is interesting to compare this observation with the data of Equation (21), where hard nucleophiles have been used. The explanation proposed involves a common transient phosphorane (36) whose behavior depends on the nature of the nucleophile.



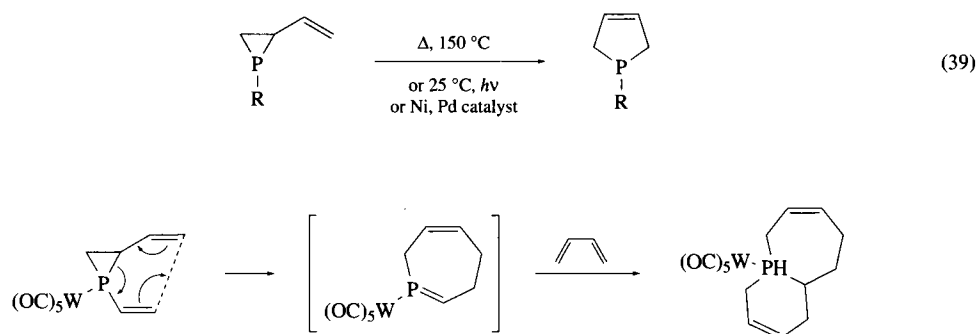
In contrast to phosphiranes, phosphirenes do not tend to dissociate into phosphorus and C_2 units. Only one well-documented case of such a splitting has been described (Scheme 14) $\langle 89JA9098 \rangle$. However, as a phosphinidene precursor, complex (37) is far less efficient than its phosphirane counterpart (33) (see Scheme 12).



Scheme 14

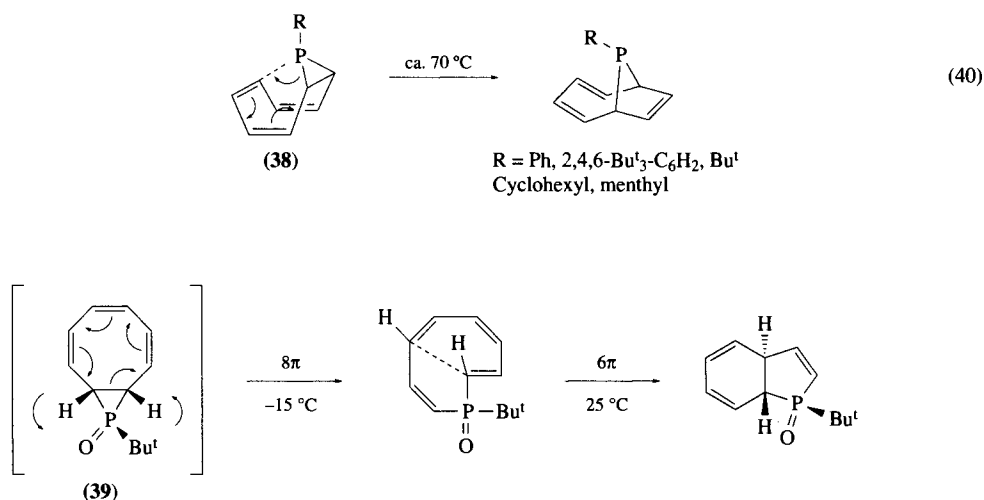
1.08.3.5 Ring Expansions

The ring expansions of phosphiranes and phosphirenes can occur either via an internal reorganization or via an insertion reaction. The former case was first illustrated for 2-vinylphosphiranes by Richter (Equation (39)) <82AG(E)292, 83CB3293>. A two-step biradical mechanism was proposed on the basis of a kinetic study <85CB1575>. A similar rearrangement has been found to occur for 2-vinylphosphirane complexes <84OM456>. However, in the latter case, a structural study of the initial three-membered and final five-membered rings has shown the reaction to proceed via a concerted [1,3] sigmatropic shift with complete inversion at phosphorus <92JOC6557>. This parallel with carbon chemistry is even more striking in the case of 1,2-divinylphosphirane complexes. They undergo a concerted phospho-Cope rearrangement leading to a seven-membered ring which has been isolated as its [4 + 2] cycloadducts with conjugated dienes (Scheme 15) <92OM1438>.

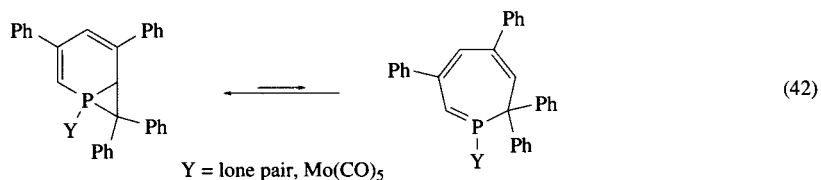
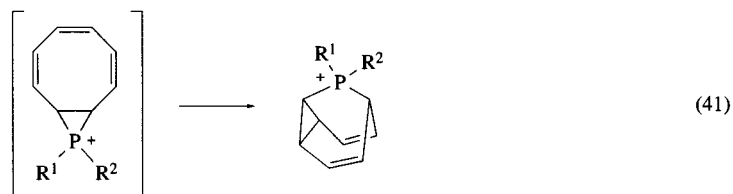


Scheme 15

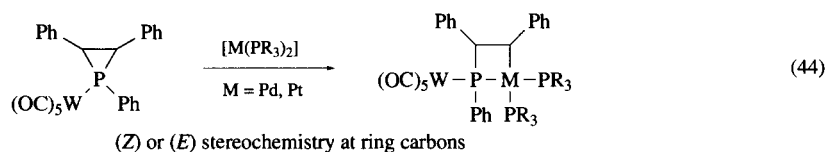
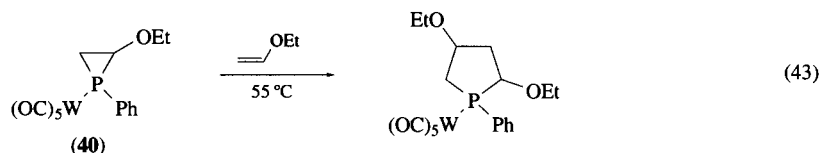
Several ring reorganizations have also been shown to occur with 9-phosphabicyclo[6.1.0]nonatrienes. The first one is a thermal [1,5] sigmatropic shift with initial retention of stereochemistry at phosphorus: discovered by Katz and co-workers <66JA3832, 73JA4292>, it has also been studied by Richter <85CB97> and Quin *et al.* <87TL1077> (Equation (40)). The second one is a 8π -conrotatory opening of the eight-membered ring, leading to a phosphonin which tends to recyclize via a 6π -disrotatory ring closure to give a dihydrophosphindole. This alternative pathway was first demonstrated by Quin and co-workers for a P-oxide such as (39) <83JA5960, 86JA4519, 86PS(27)109> (Scheme 16) and has subsequently been shown to occur with tervalent derivatives <85CB97>. Finally, the quaternary salts of (38) have been shown to rearrange into 9-phosphabarbaralanes, probably via phosphonin intermediates <83TL3981> (Equation (41)). These products behave as degenerate Cope systems. A further type of internal reorganization has been described by Märkl *et al.* who have shown that 1-phosphanorcaradienes are in equilibrium with 2*H*-phosphepines <87AG(E)1134> (Equation (42)).



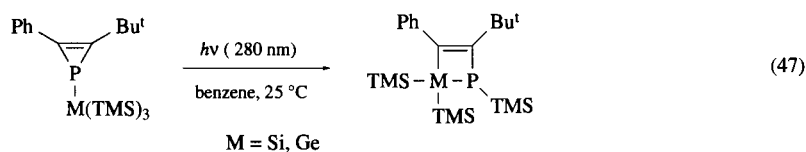
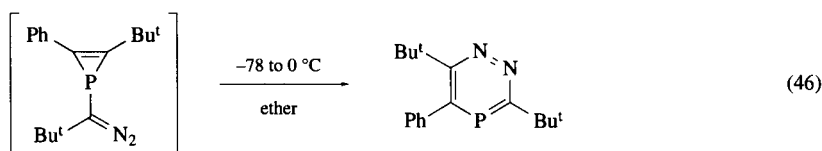
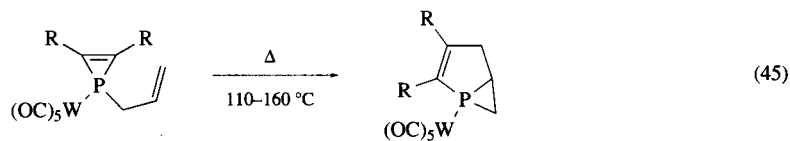
Scheme 16



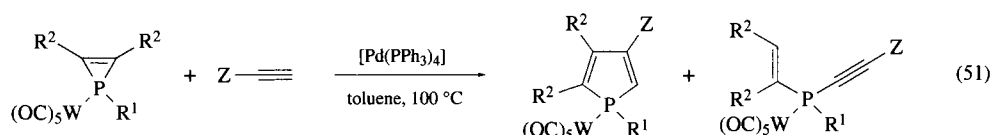
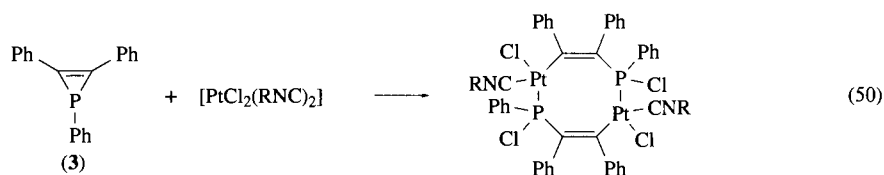
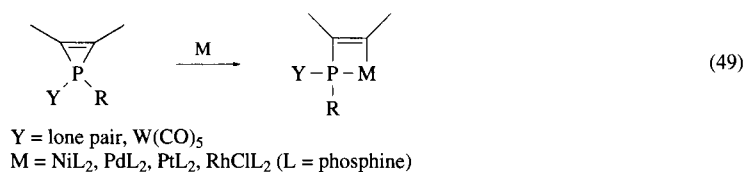
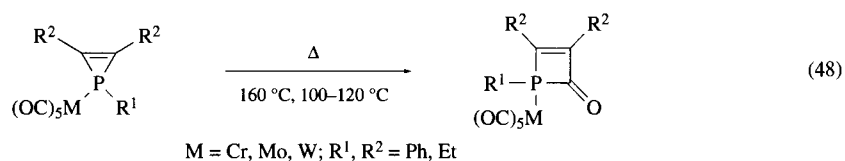
In contrast to the various rearrangements summarized above, only a few insertion reactions have been described with phosphiranes. An activated phosphirane complex (**40**) has been shown to insert a molecule of enol ether (Equation (43)) <84OM456>. Similarly, several 14-electron metallic fragments can be inserted into phosphirane complexes (Equation (44)) <89CC1389, 93JCS(D)1811>. The retention of stereochemistry at the C—C bond of the ring suggests a concerted mechanism which probably proceeds via a η^2 -complex of the initial P—C ring bond.



Three intramolecular reorganizations leading to an expansion of the phosphirene ring have been mentioned in the literature. In the first one, a 1-allylphosphirene complex is transformed into a bicyclic phosphirane (Equation (45)) <86OM1161>. In the second, an intermediate 1-diazoalkylphosphirene, generated from the corresponding 1-chloro-1*H*-phosphirene and Bu^tC(=N₂)Li, rearranges to a 1,2,4-diazaphosphinine (Equation (46)) <94RHA61>. In the third, 1-silyl and 1-germylphosphirenes give four-membered rings upon UV irradiation (Equation (47)) <90AG(E)1436>.

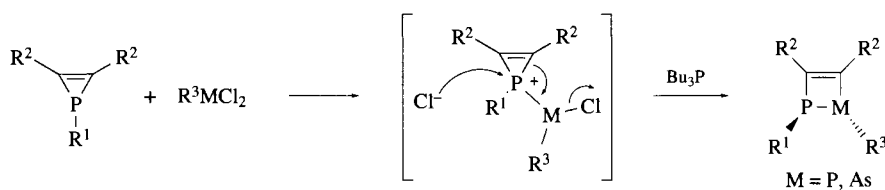


Several insertion reactions have also been described in the literature. At high temperature, phosphirene pentacarbonylmetal complexes insert CO (Equation (48)) $\langle 85JA5001 \rangle$. The carbon monoxide originates from the $M(CO)_5$ complexing group, and the mechanism probably involves an intermediate four-membered metallacycle. This hypothesis receives some support from the fact that phosphirenes and their complexes readily insert a variety of 14-electron metallic fragments (Equation (49)) $\langle 86CC762, 88CC1156, 91JCS(D)905, 92CC750 \rangle$. The nickelacycle has indeed been shown to insert CO at room temperature. It must be pointed out here that, with tervalent phosphirenes, platinum(II) species tend to give either normal η^1 -P-complexes or dimeric insertion products via halogen transfer from platinum to phosphorus (Equation (50)) $\langle 93CC142 \rangle$. Transition metals are also able to promote the insertion of monosubstituted alkynes into the phosphirene ring (Equation (51)) $\langle 87TL5021, 93BSF695 \rangle$. Once again, a transient four-membered metallacycle is very probably involved that also rationalizes the formation of the alkynylphosphine complex as a side product of the reaction.

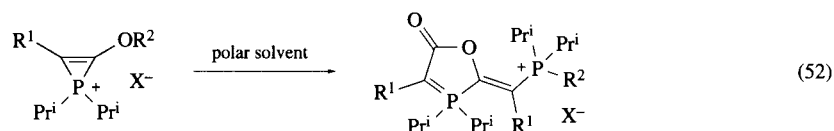


Without the help of any transition metal, it is also possible to insert a phosphinidene or an arsinidene unit into the phosphirene ring (Scheme 17) $\langle 87AG(E)548, 93BSF521 \rangle$. The yields are moderate, but the reaction is rather general and represents the best ($M = P$), or the only ($M = As$) access to the resulting four-membered heterocycles. The intermediacy of a phosphirenium salt has been demonstrated for $M = P$ using $AlCl_3$ as a trap for the chloride ion. It is interesting to compare the reactivity of phosphirenes and phosphiranes toward dichlorophosphines. In the second case, a ring opening has been observed only when the phosphirane has a special substitution pattern (see Equation (17b)). This different behavior may reflect the lower nucleophilicity of phosphorus and the lower stability of the phosphonium salts in the phosphirane series. It is also worth mentioning that Niecke and co-workers have shown $\langle 94CB313 \rangle$ that it is possible to insert the phosphorus of an iminophosphane into the three-membered ring of a phosphirene imine in certain cases. See also $\langle 93MC68 \rangle$.

Finally, a spontaneous and complex dimerization of a series of 2-alkoxyphosphirenium salts $\langle 87ZOB2482 \rangle$ has been reported to give five-membered cyclic ylides (Equation (52)).



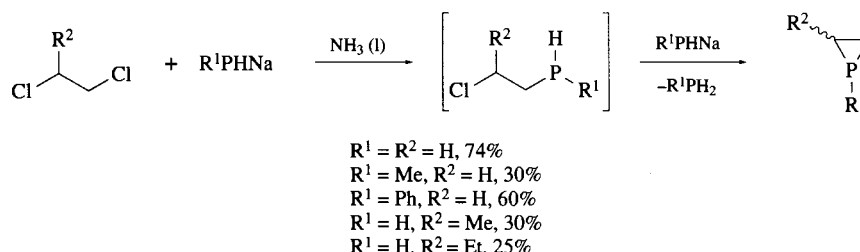
Scheme 17



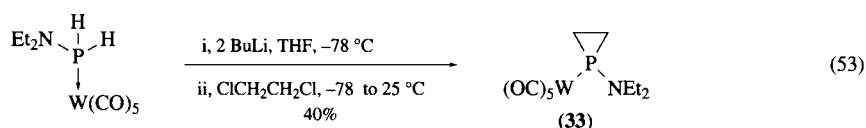
1.08.4 SYNTHESSES OF PHOSPHIRANES AND PHOSPHIRENES

1.08.4.1 Synthesis from P and C₂ Units

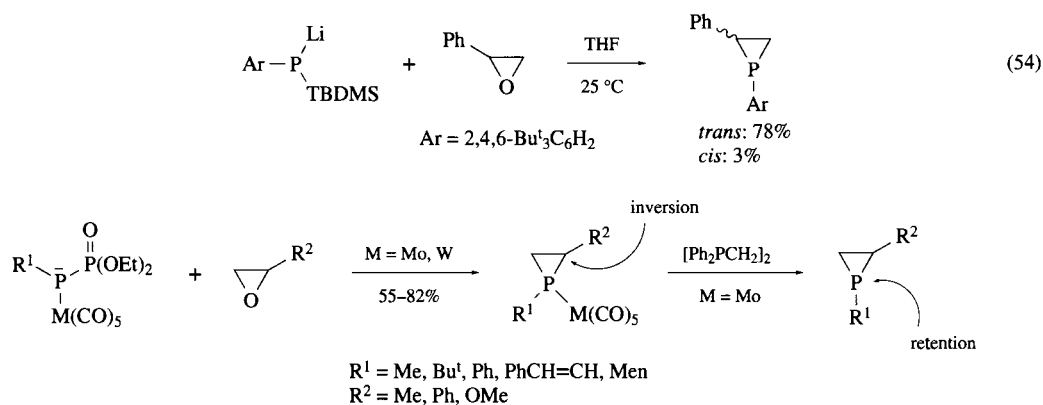
Basically, the syntheses of phosphiranes from P and C₂ units fall into three formal categories: (a) $\text{RP}^{2-} + \text{XC}-\text{CX}$; (b) $\text{RPX}_2 + ^-\text{C}-\text{C}^-$; (c) $\text{RP} + \text{C}=\text{C}$ (X = halogen or pseudohalogen). The original synthesis, due to Wagner $\langle 63\text{USP}3086053, 63\text{USP}3086056, 67\text{JA}1102, 69\text{T}1097 \rangle$, belongs to the first category (Scheme 18). Variations include the use of HMPA as the solvent to obtain the P-D and C-D derivatives $\langle 69\text{JA}17 \rangle$, the replacement of chlorine by the mesyloxy leaving group in the C₂ unit $\langle 74\text{JA}317 \rangle$ and the replacement of the sodium derivatives by dilithiophosphines $\langle 85\text{CB}4285, 94\text{CC}475 \rangle$. The same chemistry can be carried out in the coordination sphere of tungsten (Equation (53)) $\langle 89\text{JA}9098 \rangle$.



Scheme 18

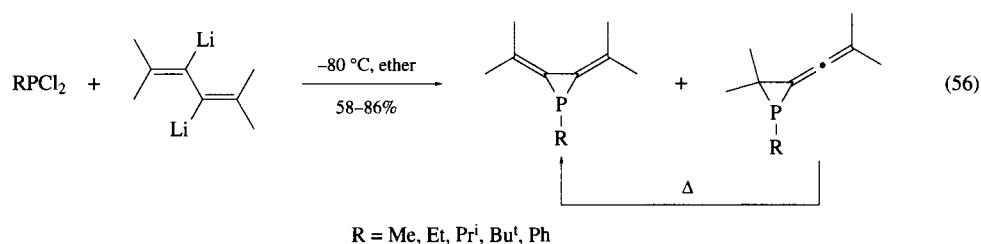
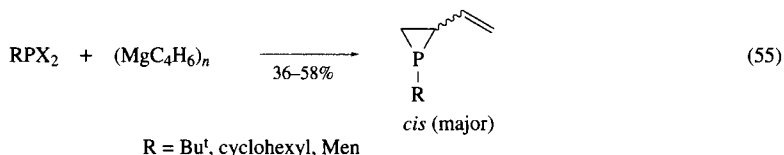


It has been shown that oxiranes can replace 1,2-dihaloalkanes in the synthesis of phosphiranes, provided that appropriate anionic RP reagents are used. The first example was described by Yoshifuji *et al.* (Equation (54)) $\langle 85\text{CL}441 \rangle$. Subsequently, it has been shown by Marinetti *et al.* that the so-called “phospha-Wittig” reagents transform oxiranes into phosphiranes with an inversion of configuration at carbon (Scheme 19) $\langle 92\text{S}157, 93\text{OM}1207 \rangle$. Decomplexation by 1,2-bis(diphenylphosphino)ethane is easily achieved in the molybdenum series. Optically active phosphiranes are readily accessible by this route.



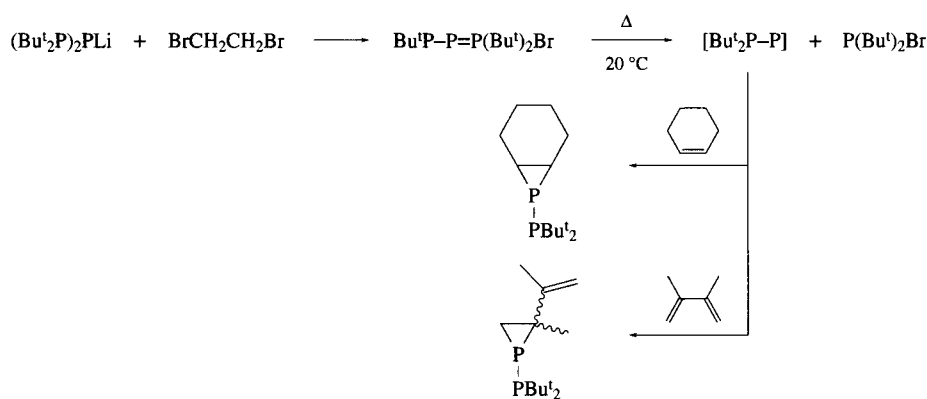
Scheme 19

The use of the second approach is restricted by the availability of 1,2-dimetallic derivatives of alkanes. The first example of a synthesis of 2-vinyl-substituted phosphiranes was described by Richter, using the magnesium-butadiene polymeric adduct (Equation (55)) <82AG(E)292, 83CB3293>. A second example concerning the synthesis of phospha[3]radialenes has also been disclosed (Equation (56)) <91CB933>. The allenyl-substituted phosphiranes isomerise into phospha[3]radialenes upon distillation at standard pressure.

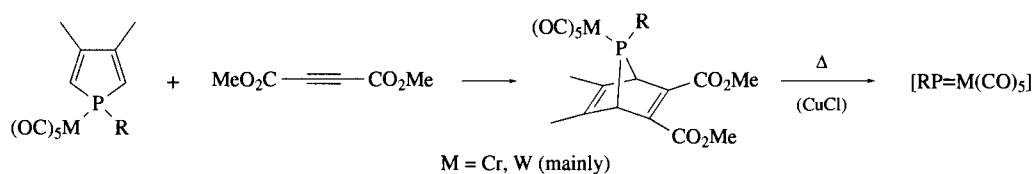


The third, neutral approach involves either free or complexed phosphinidenes. With free phosphinidenes, the problem is to find an efficient precursor. The first example was disclosed by Fritz *et al.* (Scheme 20) <89AG(E)315, 89ZAAC(570)54>. Gaspar and co-workers <92JA8526> have proposed another method based on the photolysis of 1-arylphosphiranes (Scheme 10) which has the potential to be more general. Using this technique, triplet mesitylphosphinidene is generated in a methylcyclohexane glass at 77 K and may be characterized at 4 K by ESR <94JA7899>. None of these methods, however, can compete for generality and efficiency with the condensation of electrophilic terminal phosphinidene complexes with alkenes. These transient species are usually generated by thermal decomposition of 7-phosphanorbornadiene complexes, themselves prepared from phosphole complexes by [4 + 2] cycloaddition (Scheme 21) <82CC667>.

Alternatively, some phosphirane complexes can also be used as precursors (Schemes 12 and 13).

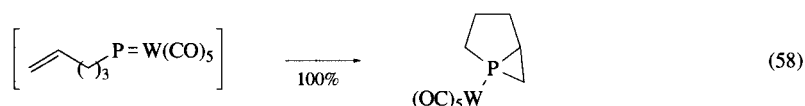
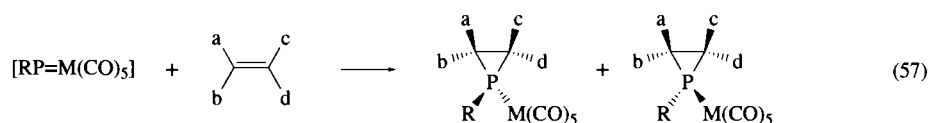


Scheme 20



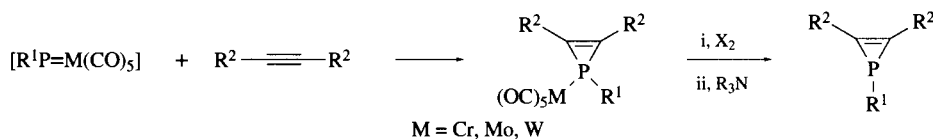
Scheme 21

The condensation of these terminal phosphinidene complexes with alkenes takes place with full retention of stereochemistry at the C₂ unit (Equation (57)) <84OM456>. A large variety of alkenes has been successfully used in this condensation, including ethylene itself, methylenecycloalkanes <93JOC6786>, conjugated dienes <84OM456, 92JOC6557>, cyclohexadienes <93JOC1800>, norbornadiene <93OM1401>, enol ethers, acrylic esters <84OM456>, and enamines <84OM1492>. The Hammett reaction constants ρ^+ , which have been measured for the styrene addition to [PhP=W(CO)₅] and [MeP=W(CO)₅] (−0.76 and −0.60, respectively), indicate a mild electrophilicity <88OM1875, 92OM4365>. The reaction with conjugated dienes gives 2-vinylphosphirane complexes which rearrange upon mild heating to the corresponding five-membered phospholene complexes via a concerted [1,3] shift <92JOC6557>. A large variety of substituents at phosphorus, including alkoxy <86NJC321> and amino groups <89JA9098>, have also been used. Double condensation with [(PCH₂CH₂P)W(CO)₄] <87OM586> and self-condensation with phosphinidenes bearing alkenic substituents have been observed (Equation (58)) <86OM1161>.

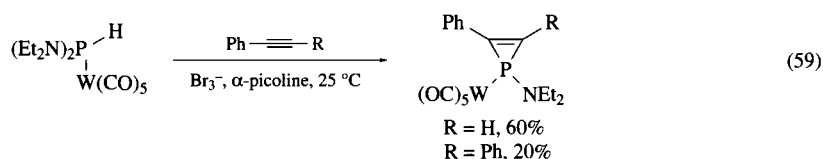


Decomplexation of phosphorus has been achieved in a limited number of cases. Initially, halogenation at low temperature with I₂ or Br₃[−] transforms the W(CO)₅ into the W(CO)₄X₂ complexing group, then displacement of the phosphorus ligand from the coordination sphere of tungsten may be performed with *N*-methylimidazole or 2,2′-bipyridyl; for example, see <84CC45>. Finally, phosphirane complexes have been obtained as major by-products in the reaction of terminal phosphinidene complexes with oxiranes <87OM2189> and ethoxyethyne <90PS(47)477>. See also <86JOM(306)29>.

The first synthesis of phosphirenes also involved electrophilic terminal phosphinidene complexes. These species react efficiently with a variety of alkynes to give the corresponding phosphirene complexes whose decomplexation is easily achieved via the halogen–tertiary amine procedure (Scheme 22) <82JA4484, 84CC45, 85JA4700>. Besides classical alkyl and aryl groups, a large variety of functional substituents at phosphorus have been used, including allyl <86OM1161>, alkoxy <86NJC321, 88OM1796>, amino <89JA9098>, cyano <88OM1796>, chloro <89JA9098>, chloroalkyl <85TL4595, 88JOM(354)83>, ethoxycarbonyl <88OM1796>, and (ethoxycarbonyl)alkyl groups <93BSF695>. The reaction works with mono- and disubstituted alkynes. Among functional alkynes, propiolates can be used, but amino and alkoxy-substituted alkynes give phosphole complexes directly, via a formal [1 + 2 + 2] cycloaddition <90PS(47)477>. A transient aminophosphinidene complex is also probably involved in the chemistry depicted in Equation (59) <86TL1323>.

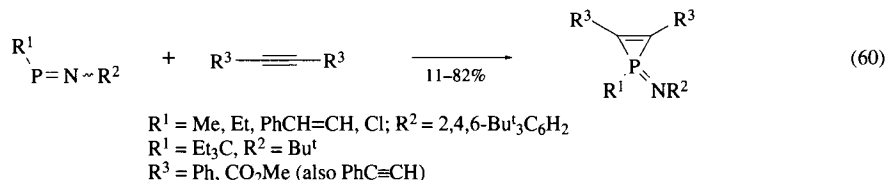


Scheme 22

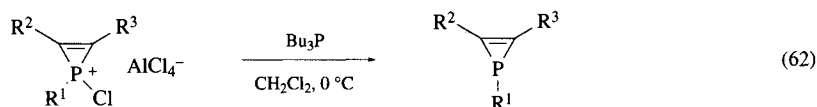
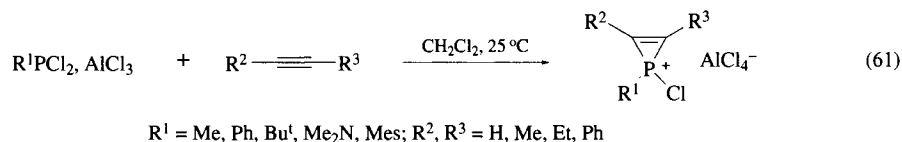


This basic scheme has been extended to free arylphosphinidenes by Gaspar and co-workers (Scheme 10) <92JA8526>. A related chemistry has also been developed by Niecke and co-workers <88TL605, 93CB649>, using the phosphinidene-like behavior of iminophosphanes (Equation (60)). The

reaction has been extended to 1,4-diphenylbutadiyne for which mono and double condensation have been observed <94CB313> and to 1-amino and 1-alkoxyalkynes <93MC68, 93TL1331>. In these two cases, both phosphirenes and 1,2-dihydro-1,2-diphosphetes are obtained.

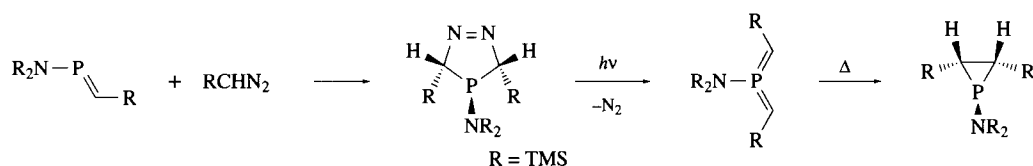


The only other $\text{P} + \text{C}_2$ approach for the synthesis of phosphirenes involves the electrophilic addition of dihalophosphine- AlCl_3 complexes to alkynes as discovered by Hogeveen and co-workers (Equation (61)) <83TL643>. The method has been extended to monohalophosphines by Breslow and Deuring <84TL1345> and to well-defined phosphonium ions by Cowley and co-workers <88CC462>. The chlorophosphirenium salts thus obtained are easily reduced by tributylphosphine to afford the corresponding trivalent phosphirenes (Equation (62)) <86TL2635, 91T6673>. In the cases where it is applicable, this method is the most convenient route to substantial quantities of phosphirenes.



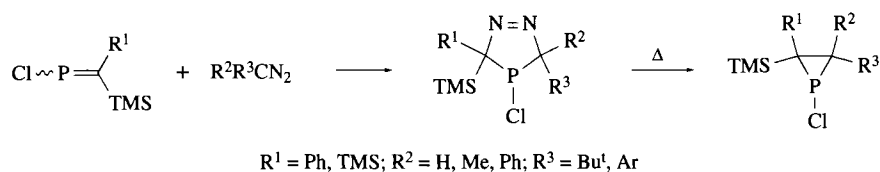
1.08.4.2 Synthesis from PC and C Units

The availability of phosphalkenes $\text{R}^1\text{P}=\text{CR}^2$ and phosphalkynes $\text{RC}\equiv\text{P}$ has led to the development of another route to phosphiranes and phosphirenes involving the formal addition of carbenes to phosphorus-carbon multiple bonds. When using diazoalkanes as the carbene source, the reaction mechanism involves the series of steps demonstrated by Niecke and co-workers in Scheme 23 <81AG(E)131, 83CC1171>; see also <75AG(E)363>.



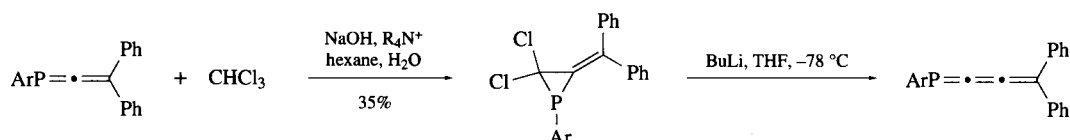
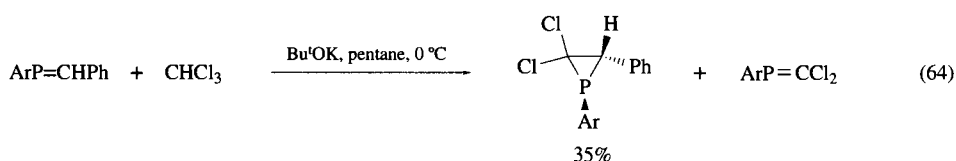
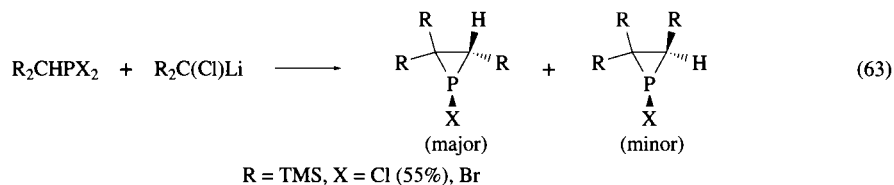
Scheme 23

The 4π -electrocyclic closure of the intermediate bis(methylene)phosphorane is conrotatory according to the Woodward-Hoffmann rules <83CC1171>. Several other authors have developed similar approaches <85CB3419, 86CB1977, 87TL2693, 88ZN(B)1285>. The first stable 1-chlorophosphiranes have also been prepared by this type of route (Scheme 24) <87TL2693, 88ZN(B)1285, 89TL3951>.

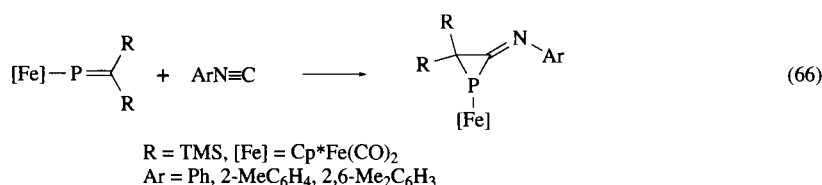
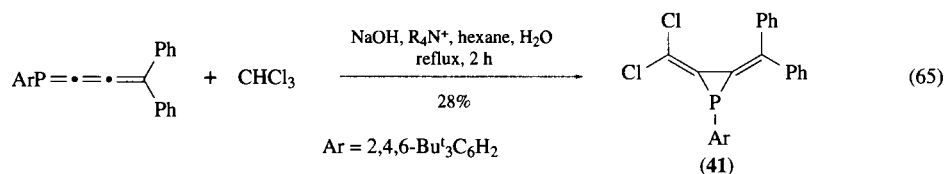


Scheme 24

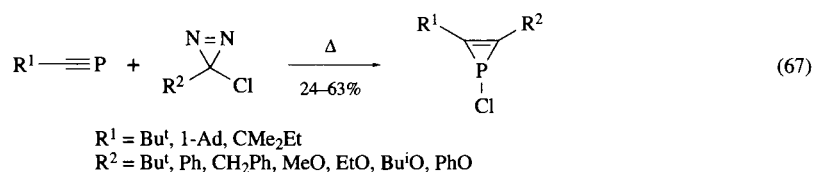
Other carbene sources which have also been used with some success include several organometallic carbenoids (Equation (63)) <89CB453>, (Equation (64)) <90CL827>, (Scheme 25) <91CC124> and (Equation (65)) <91TL6879>. The formation of phospharadialene (**41**) results from the isomerization of an intermediate 2-(ethenylidene)phosphirane. Its structure was confirmed by x-ray analysis <92POL385>. In the same vein, Weber *et al.* have shown that isonitriles readily react with transition metal-substituted phosphalkenes (Equation (66)) <93OM4653>.

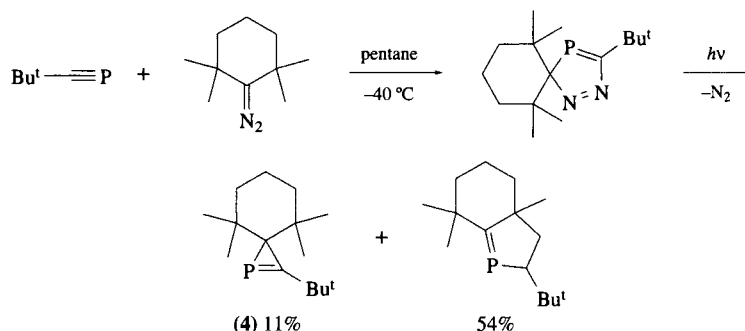


Scheme 25

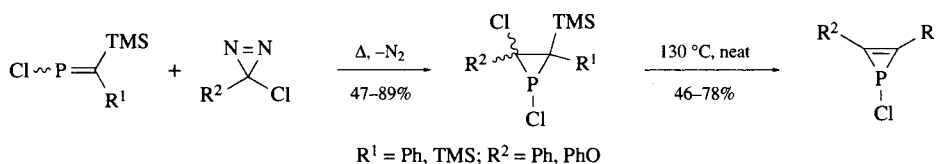
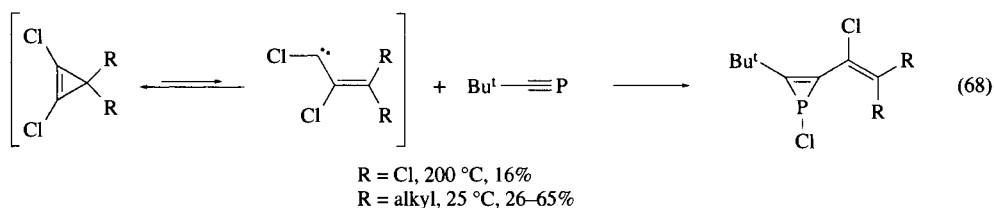


The condensation of a carbene with a $\text{P}\equiv\text{C}$ triple bond theoretically affords a 2*H*-phosphirene. This was indeed shown to be the case by Regitz and co-workers in the synthesis of the only characterized 2*H*-phosphirene (**4**) (Scheme 26) <87AG(E)1257>. Some time later, Regitz showed that the use of a chlorocarbene precursor leads to the formation of 1-chlorophosphirenes via a formal [1,3] shift of chlorine in the initial 2*H*-phosphirenes (Equation (67)) <89AG(E)225, 91CB1207>. Chlorodiazirines can be replaced by 1,2-dichlorocyclopropenes <91SL433> in this kind of chemistry (Equation (68)). Finally, phosphalkynes too can be replaced by silylated chlorophosphalkenes (Scheme 27) <89TL3951>.





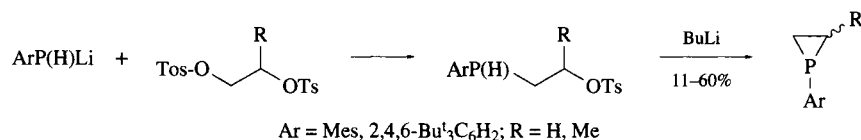
Scheme 26



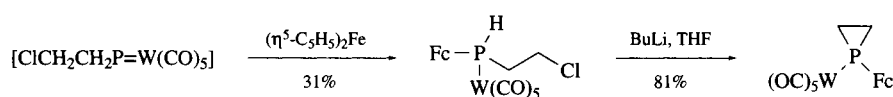
Scheme 27

1.08.4.3 Synthesis by Cyclization of a P—C—C Unit

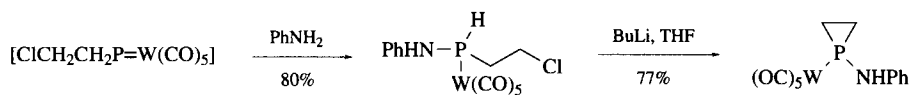
As shown in Scheme 18, the synthesis of phosphiranes by Wagner involves an intermediate secondary β -chloroalkylphosphine. A preformed XCCPH unit is thus a potential precursor of phosphiranes. This approach was first developed by Oshikawa and Yamashita (85S290); see also (Scheme 28) (92JA8526). The availability of a 7-phosphanorbornadiene precursor of the transient terminal phosphinidene complex $[\text{ClCH}_2\text{CH}_2\text{P}=\text{W}(\text{CO})_5]$ (see Scheme 21), also allowed the development of similar routes in the coordination sphere of tungsten. The first (86OM1159) involves an initial insertion of the phosphinidene into one of the C—H bonds of ferrocene (Scheme 29). The second includes an initial reaction with aniline (Scheme 30) (89POL2671). The third involves the initial formation of a “phospha-Wittig” reagent (this transforms the character of the phosphinidene from electrophilic to nucleophilic) which undergoes a self-alkylation (Scheme 31) (91SL743). At the moment, this scheme represents the only known synthesis of the parent 1-chlorophosphirane.



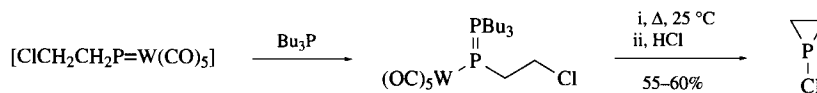
Scheme 28



Scheme 29



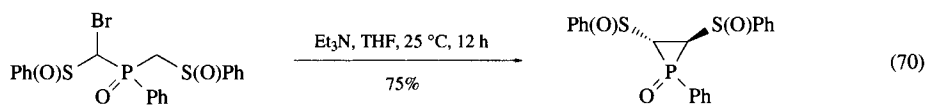
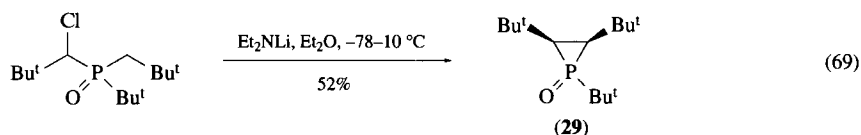
Scheme 30



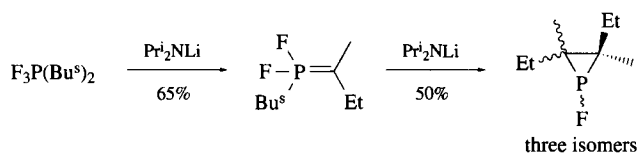
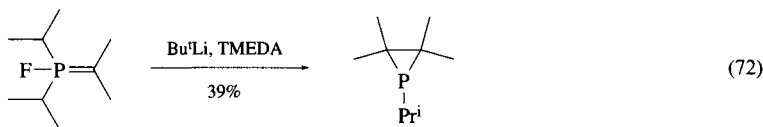
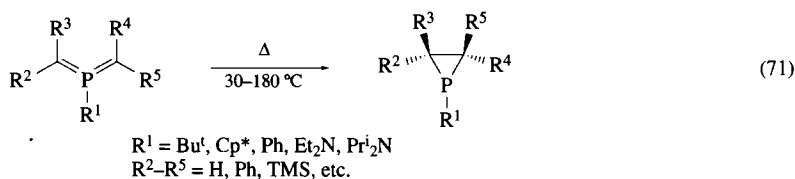
Scheme 31

1.08.4.4 Synthesis by Cyclization of a C—P—C Unit

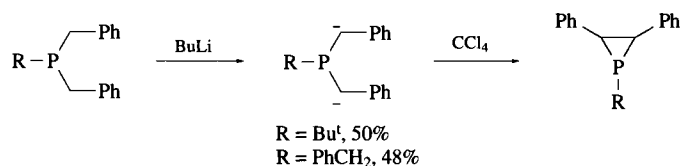
This approach was initially developed by Quast and Henschmann <78AG(E)867, 81LA977> for the synthesis of the first stable, sterically hindered, phosphirane oxide (**29**) (Equation (69)). Subsequently, Oshikawa and Yamashita <86BCJ3293> reported a similar chemistry (Equation (70)). Curiously, the stereochemistries of these two phosphirane oxides are different.



As is already obvious from Scheme 23, another potential route to phosphiranes involves the cyclization of bis-ylides. The thermal cyclization of such species has been studied in some depth by Niecke and co-workers <92CB771> (Equation (71)). The conrotatory cyclization does not work for highly hindered bis-ylides; e.g., $\text{R}^1 = \text{Et}_2\text{N}$, $\text{R}^2 = \text{R}^3 = \text{Ph}$, $\text{R}^4 = \text{R}^5 = \text{TMS}$. Some time earlier, Fluck and Braun <86CZ379, 89PS(44)291> had also described some applications of this scheme, e.g., Equation (72). Finally, a similar chemistry has been described by Kolodyazhnyi and Ustenko <92ZOB464, 92ZOB1418> (Schemes 32 and 33).



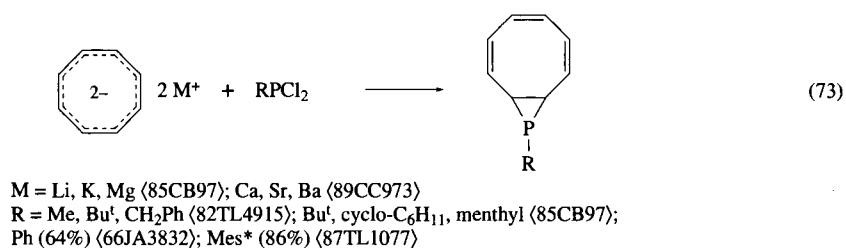
Scheme 32



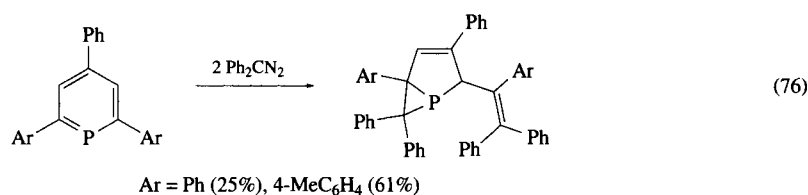
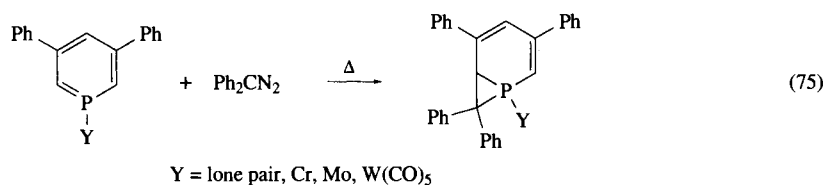
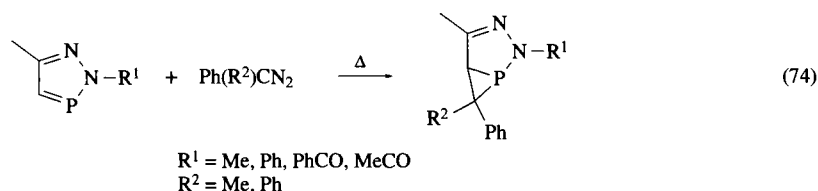
Scheme 33

1.08.4.5 Specific Syntheses of Polycyclic Phosphiranes

The first specific synthesis of a polycyclic phosphirane was depicted by Katz *et al.* in 1966 <66JA3832, 73JA4292>, soon after the discovery of phosphirane itself by Wagner. It involves the reaction of cyclooctatetraene dianion with dihalophosphines (Equation (73)) <66JA3832, 82TL4915, 85CB97, 89CC973>.

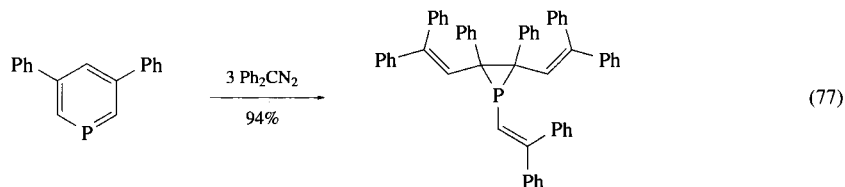


Another route to bicyclic phosphiranes takes advantage of the ready availability of aromatic phosphorus heterocycles containing formal $\text{P}=\text{C}$ double bonds. This kind of chemistry was first exemplified by Arbuzov, Dianova, and co-workers (Equation (74)) <77IZV1453, 79DOK(244)117, 82IZV2730, 83DOK(273)613, 87CB597>. The reaction proceeds via an intermediate [2 + 3] cycloadduct <81IZV1113, 83IZV2395>. A similar chemistry was performed by Märkl and co-workers with the phosphinine ring, either in the free or the complexed state (Equation (75)) <87AG(E)236, 87AG(E)1134>. The reaction does not give the 1-phosphanorcaradiene when CH_2N_2 , MeCHN_2 or Me_2CN_2 are used as the carbene precursors. An excess of Ph_2CN_2 leads to a complicated rearrangement (Equation (76)) <90TL4849>.

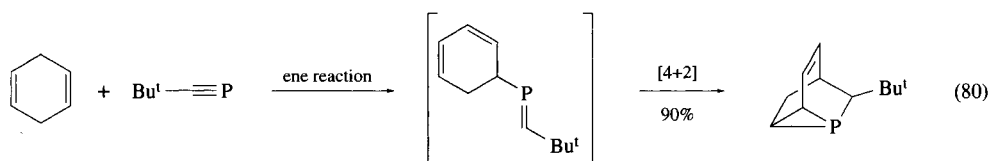
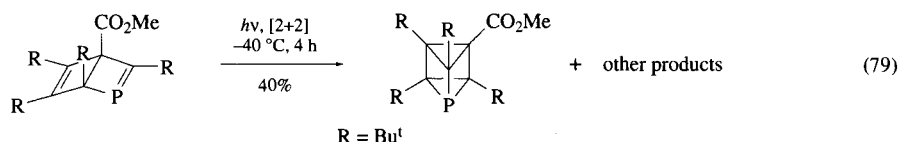
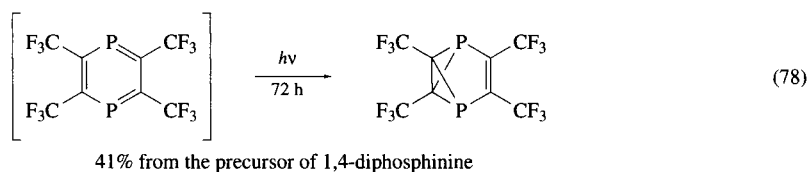


The structure of one bis-adduct has been confirmed by x-ray analysis. The proposed mechanism involves the isomerization of the initial 1-phosphanorcaradiene into a 2*H*-phosphepine (Equation

(42)), followed by a second addition of carbene onto the $P=C$ double bond of the seven-membered ring. A ring-contraction via a formal [1,3] shift then affords the observed product. With 3,5-diphenylphosphinine, the reaction goes one step further to give the tris-adduct (Equation (77)).

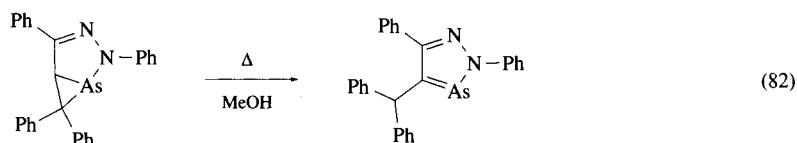
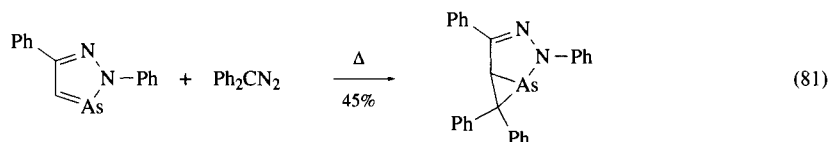


Finally, a series of rearrangements leading to polycyclic phosphiranes have also been described (Equations (78) <77JA8511, 78H(9)98, 80JOC4683>, (79) <87AG(E)85>, and (80) <87AG(E)1011>).

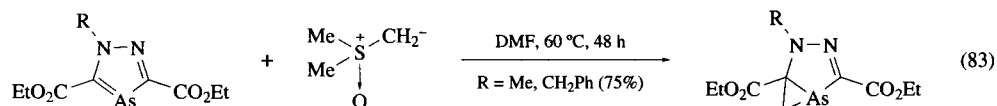


1.08.5 THE CHEMISTRY OF ARSIRANES

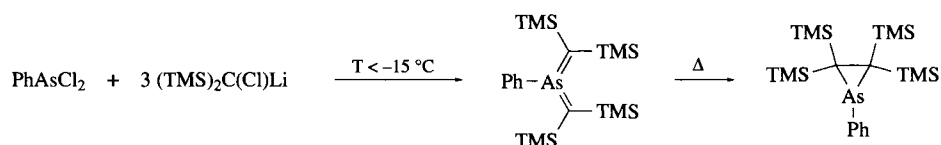
Among all the possible heavier analogues of phosphiranes, only arsiranes have been the subject of any study up to now. The first reported arsirane was prepared by Arbuzov, Dianova, and co-workers <82IZV1432, 83ZOB835>, using a transposition of the route already described in Equation (74) for the preparation of a bicyclic phosphirane (Equation (81)). The structure of this bicyclic arsirane has been fully established by x-ray analysis at -120°C <84DOK(274)828>. Upon heating in MeOH, it rearranges to give a substituted 1,2,3-diazaarsole (Equation (82)) whose structure has also been checked by x-ray analysis <83DOK(268)885>. It is interesting to recall here that MeOH preferentially cleaves the $C-P$ bond at the junction of the analogous bicyclic phosphirane (see Equation (17a)).



Hamelin and co-workers have extended this type of chemistry using 1,2,4-diazaarsoles and sulfur ylides as carbene precursors (Equation (83)) <90TL7607>.

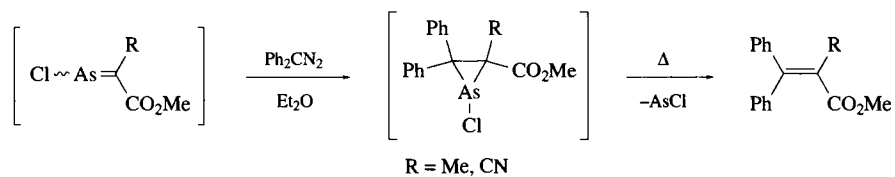


The first monocyclic arsirane was prepared by Appel *et al.* <85AG(E)419> by a transposition of the synthesis of phosphiranes from bis-ylides (Scheme 34). The structure of this arsirane has been established by x-ray analysis: As—C ring bond 2.023 Å, C—C ring bond 1.581 Å, intracyclic C—As—C angle 46.0°, exocyclic (Ph)C—As—C angle 111.8°. No chemistry has been described.



Scheme 34

Finally, it is interesting to mention that an attempted synthesis of arsiranes by reaction of diphenyldiazomethane with some chloroarsaalkenes led to the formation of alkenes via the spontaneous fragmentation of the expected heterocycles (Scheme 35) <91TL2755>. Apparently, arsiranes are situated at the limit of stability beyond which no extensive chemistry can be developed. Their thermodynamic parameters being even less favorable, the C₂Sb and C₂Bi three-membered heterocycles will probably remain elusive.



Scheme 35

1.09

Three-membered Rings with One Silicon, Germanium, Tin, or Lead Atom

ERIC ROSKAMP and CARRIE ROSKAMP
Pfizer Inc., Groton, CT, USA

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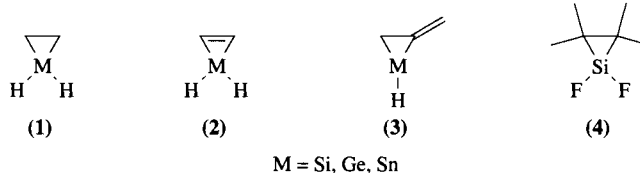
1.09.1 INTRODUCTION

1.09.1.1 Scope

The following chapter covers three-membered carbocycles containing one silicon, germanium, tin, or lead atom (<82COMC-I(2)86, 82COMC-I(2)206, 84CHEC-I(1)575>). The scope of this chapter is limited to carbocycles with tetravalent heteroatoms and focuses primarily on the synthesis and reactivity of these compounds. A very brief survey of theoretical methods that have been brought to bear on these ring systems is presented to provide lead references. The spectroscopy section provides an overview of compounds that were fully characterized in the literature. The bulk of this chapter deals with carbocyclic silanes, since only a few germanium and tin compounds have been isolated and no examples of three-membered rings containing lead were found. Throughout the entire chapter, but particularly within the more abundant silicon literature, emphasis is placed on compounds that had been isolated and/or characterized. Some uncorroborated claims of transformations proceeding through sila-, germa-, or stannacyclopropanes have been reviewed elsewhere (<82COMC-I(2)206, 84CHEC-I(1)575>).

1.09.1.2 Structural Types and Nomenclature

Saturated three-membered rings, (1), with one silicon, germanium, or tin are called siliranes, germiranes, and stanniranes, respectively. The more common names for these rings are silacyclopropane, germacyclopropane, and stannacyclopropane. Compounds of type (2) are called silirenes, germirenes, and stannirenes, or more commonly silacyclopropene, germacyclopene, and stannacyclopene, respectively. Compounds that have an exocyclic double bond, (3), are called alkylidene siliranes or alkylidene silacyclopropanes. The more common names will be used in this chapter, for example, compound (4) would be named 1,1-difluoro-2,2,3,3-tetramethylsilacyclopropane.



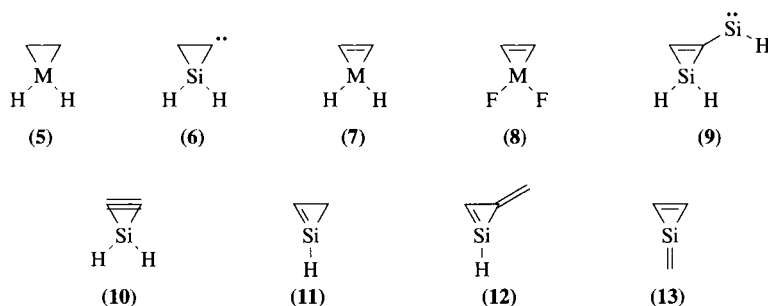
1.09.2 THEORETICAL METHODS

1.09.2.1 Ab Initio Studies

1.09.2.1.1 Bond lengths and angles for three-membered rings

Silacyclopropane (5) (<90JA3408>), was calculated to have a Si—C bond length of 1.86 Å and a C—C bond length of 1.57 Å by CEP-31G (Table 1).

Germacyclopropane (5) was calculated to have a Ge—C bond length of 1.94 Å and a C—C bond length of 1.54 Å at the double zeta plus d (DZ + d) SCF level of theory (<92JA2093>). Silacyclopropane

Table 1 Bond lengths and angles for three-membered rings.

Compound	M	M—C	C—C	C=Y	C—M—C angle	M—C—C angle
(5)	Si	1.86	1.57		47°	
(5)	Ge	1.94	1.54			
(6)	Si	1.88 (2.01)	1.54			
(7)	Si	1.87	1.32	1.32 ^a	41.5°	69.3°
(7)	Ge	1.91		1.32 ^a		
(7)	Sn	2.12		1.32 ^a		
(8)	Si	1.76		1.36 ^a		
(8)	Ge	1.86		1.35 ^a		
(8)	Sn	2.08		1.35 ^a		
(9)	Si	1.88		1.33 ^a	41.6°	69.3°
(10)	Si	1.91		1.27 ^b	38.8°	
(11)	Si	1.91	1.59	1.69 ^b	52°	71.1°
(12)	Si	1.80	1.49	1.67 ^b	69.1°	60.1°, 50.8°
(13)	Si	1.77		1.35 ^a	44.7°	67.7°

^aY = C. ^bY = Si.

(6) was calculated to have a Si—C bond length of 1.88 Å and a Si—C: bond length of 2.01 Å. The C—C bond length of (6) was determined to be 1.54 Å via a 6-31G*/3-21G *ab initio* calculation. Restricted Hartree–Fock 3-21G(d) and SCF wave functions were used to calculate the structures of sila-, germa-, and stannacycloprenes (7) <81CPL(80)114, 81JA2939, 90JPC5488>. The M—C bond lengths were 1.87 Å, 1.91 Å, and 2.12 Å, and all three compounds had a C=C bond length of 1.32 Å. In the difluoro series (8), the M—C bond lengths were 1.76 Å, 1.86 Å, and 2.08 Å, and the C=C bond lengths were 1.36 Å, 1.35 Å, and 1.35 Å respectively.

Silacyclopropene (9) <84OM583>, with a silylene substituent, had a Si—C bond length of 1.88 Å and a C=C bond length of 1.33 Å at the 6-31G*/3-21G level of theory. Silacyclopropyne (10) had a Si—C bond length of 1.91 Å and an alkyne bond length of 1.27 Å in an optimized structure at the double zeta-SCF level of theory <86JA2169>. Silacyclop-1-ene (11) had a Si—C bond length of 1.91 Å, a C—C bond length of 1.59 Å, and a Si=C bond length of 1.69 Å as determined by *ab initio* 6-31G*/3-21G calculations. Silacyclopropylidene (12) had a Si—C bond length of 1.80 Å, a C—C bond length of 1.49 Å, and a Si=C bond length of 1.67 Å <87OM1977>. Silacyclopropene (13) had a Si—C bond length of 1.77 Å and a C=C bond length of 1.35 Å at the 6-31G* level of theory. The C—Si—C internal bond angle of compounds (7), (9), (10), (11), (12), and (13), were 41.5°, 41.6°, 38.8°, 52°, 69.1°, and 44.7°, respectively. CNDO/2 minimum energy structures for a series of silacyclopropanes have also been calculated <79JOM(181)399>.

1.09.2.1.2 Relative energies

The relative energies for compound (5) were 36.7 kcal mol⁻¹ (Si) and 38.1 kcal mol⁻¹ (Ge). The relative energy for (6) was 84.3 kcal mol⁻¹, for (7) 14.79 kcal mol⁻¹, for (9) 36.2 kcal mol⁻¹, for (11) 65.22 kcal mol⁻¹, for (12) 66.9 kcal mol⁻¹, and for (13) 43.6 kcal mol⁻¹. Energies of decomposition of sila- and germacyclopropane to silylene or germylene and alkene were calculated at DZ + d SCF level of theory and found to be 33.9 kcal mol⁻¹ and 9.3 kcal mol⁻¹, respectively. Relative enthalpies of formation for sila-, germa-, and stannacycloprenes (7) were calculated at RHF/3-21G(d) level and found to be -48.3 kcal mol⁻¹, -19.9 kcal mol⁻¹, and -1.4 kcal mol⁻¹. In the difluoro

series, the relative enthalpies of formation for sila-, germa-, and stannacyclopropenes (**8**) were $-38.6 \text{ kcal mol}^{-1}$, $4.6 \text{ kcal mol}^{-1}$, and $23.6 \text{ kcal mol}^{-1}$, respectively. *Ab initio* molecular orbital calculations were used to evaluate the ring strain in cyclopropane, cyclopropene, silacyclopropane, and silacyclopropene. Ring strain was predicted to increase in the order cyclopropane, silacyclopropane, silacyclopropene, cyclopropene $\langle 80\text{JA}7419 \rangle$.

1.09.2.1.3 Dipoles, intrinsic frequencies, and coupling constants

The dipole moments for compounds (**6**), (**7**), and (**11**) were calculated to be 2.21 D, 0.11 D, and 1.41 D, respectively. Intrinsic vibrational frequencies were also calculated for sila-, germa-, and stannacyclopropenes (**7**) and (**8**). For sila-, germa-, and stannacyclopropenes (**7**), the M—C frequencies were 898, 727, and 668 cm^{-1} , whereas the C=C frequencies were 1648 cm^{-1} , 1686 cm^{-1} , and 1640 cm^{-1} , respectively. For sila-, germa-, and stannacyclopropenes (**8**), the M—C frequencies were 982 cm^{-1} , 805 cm^{-1} , and 723 cm^{-1} , and the C=C frequencies were 1557 cm^{-1} , 1598 cm^{-1} , and 1578 cm^{-1} , respectively. Nonempirical calculations using an equations of motion method were used to calculate one-bond coupling constants for silacyclopropane (**5**) and silacyclopropene (**7**). For silacyclopropane (**5**), $J(\text{C—C}) = 18.23 \text{ Hz}$, $J(\text{Si—C}) = -29.85 \text{ Hz}$, $J(\text{C—H}) = 180.56 \text{ Hz}$, and $J(\text{Si—H}) = -250.17 \text{ Hz}$; in silacyclopropene (**7**), $J(\text{C—C}) = 34.79 \text{ Hz}$, $J(\text{Si—C}) = -38.44 \text{ Hz}$, $J(\text{C—H}) = 171.26 \text{ Hz}$, and $J(\text{Si—H}) = -248.99 \text{ Hz}$ $\langle 87\text{JMR}(71)229 \rangle$.

1.09.2.2 Semiempirical Methods

1.09.2.2.1 Silacyclopropene

MINDO/3 calculations relative to cyclopropane and cyclopropene show that the two highest molecular orbitals for silacyclopropane and silacyclopropene are destabilized. As a result, silacyclopropane and silacyclopropene are predicted to be more reactive toward electrophiles than their carbon analogues $\langle 79\text{JCS}(P1)443 \rangle$.

1.09.2.2.2 Orbital symmetry

An analysis of the dimerization of silacyclopropene was carried out by Orbital Correspondence Analysis in Maximum Symmetry (OCAMS). This analysis showed that the dimerization of silacyclopropene follows an allowed pathway $\langle 82\text{JOM}(240)129 \rangle$.

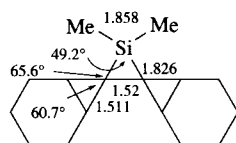
1.09.3 EXPERIMENTAL STRUCTURAL METHODS

1.09.3.1 Spectroscopic Methods

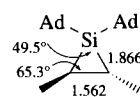
1.09.3.1.1 X-ray diffraction

X-ray diffraction studies have been carried out on several silacyclopropyl compounds, for example (**14**) $\langle 76\text{JA}1779 \rangle$, (**15**) $\langle 91\text{JA}1281 \rangle$, (**16**) $\langle 85\text{JA}7706 \rangle$, and (**17**) $\langle 82\text{CC}726 \rangle$, as well as a germacyclopropene (**18**) $\langle 85\text{JOM}(209)\text{C}27 \rangle$, and a stannacyclopropene (**19**) $\langle 88\text{JA}5208 \rangle$. X-ray diffraction remains the best method for ascertaining the structure/identity of this class of compounds. The silacyclopropanes have C—Si—C bond angles ranging from 49° to 52° , and the C—C—Si bond angles are $\sim 65^\circ$. Bond lengths for Si—C range from ~ 1.80 – $1.90 \text{ \AA}$ and the C—C bond from 1.52 – $1.64 \text{ \AA}$. Silacyclopropenes differ from silacyclopropanes in that the C—Si—C bond angle is smaller, 43.5° for (**17**).

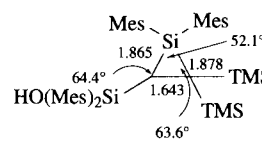
The C=C bond length in (17) is 1.349 Å, slightly longer than an average C=C bond, suggesting an interaction between the π system and silicon.



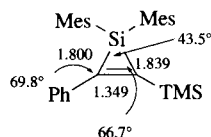
(14)



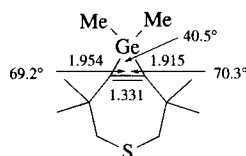
(15)



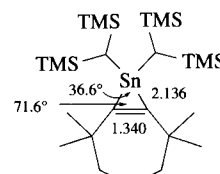
(16)



(17)



(18)



(19)

The x-ray diffraction structure for germacyclopentene (18) and stannacyclopentene (19) show increasingly smaller C—M—C bond angles, 40.5° and 36.6°, and longer M—C bond lengths ~1.95 Å, and ≈2.13 Å, respectively. Although both (18) and (19) appear to be symmetrical compounds, the three-membered ring in each is tilted to one side creating a slightly asymmetrical structure. The Ge—C bond lengths in (18), for example, are 1.954 Å and 1.915 Å.

1.09.3.1.2 NMR studies

Although x-ray diffraction remains the most reliable method for ascertaining the structures of three-membered rings with one silicon or tin, ^{13}C NMR and ^{29}Si NMR can be quite useful (Table 2). In silacyclopentanes, the chemical shifts for the ring carbons range from 10–23 ppm; for silacyclopentenes, the range is 147–195 ppm.

Table 2 Summary of ^{13}C , ^{29}Si , and ^{119}Sn NMR values.

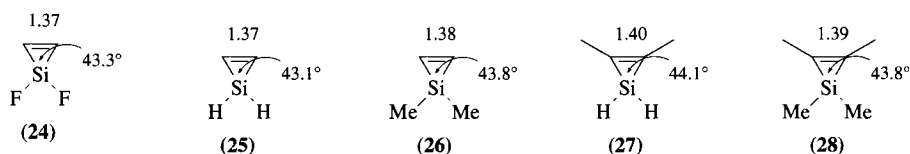
Method	 (20)	 (21)	 (22)	 (23)
^{13}C NMR ^a	10–23	147–195	–89	163.9
$^{29}\text{Si}/^{119}\text{Sn}$ NMR	–43 to –85	–86 to –116	–89	–537

^a ^{13}C NMR values are for the ring carbons in the three-membered ring.

An even more diagnostic tool is ^{29}Si NMR. The chemical shift for silicon in silacyclopentanes has been observed to be from –43 ppm to –85 ppm <76JOM(122)311, 88AG(E)1355, 88JA3310, 91JA7790>. In silacyclopentenes, the signals are further downfield at –86 to –116 ppm <76JA6382, 93TL6541>, whereas in alkylidene silacyclopentane (22), the signal was observed at –89 ppm <93OM1996>. The chemical shift of silicon varies considerably as a function of the substituents on both silicon and the ring carbons. Stannacyclopentene (23) was reported to have a ^{13}C NMR signal at 163.9 ppm for the ring C=C, and a ^{119}Sn NMR signal at –537 ppm for tin <88JA5208>.

1.09.4 AROMATICITY

The structures for silacyclopentenes (24)–(28) were calculated using CNDO/2. The small C—Si—C bond angle and the short C=C bond length suggest that the π bond interacts with acceptor orbitals on silicon. This interaction leads to a net stabilization, described as aromatic character <78JOM(154)C33>.

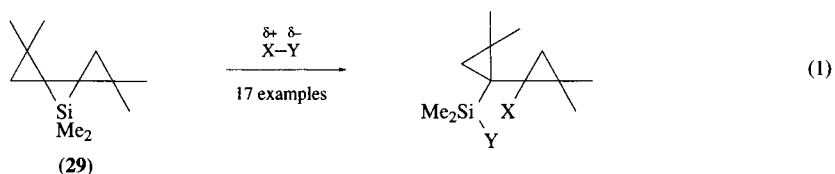


1.09.5 REACTIVITY OF NONCONJUGATED RINGS

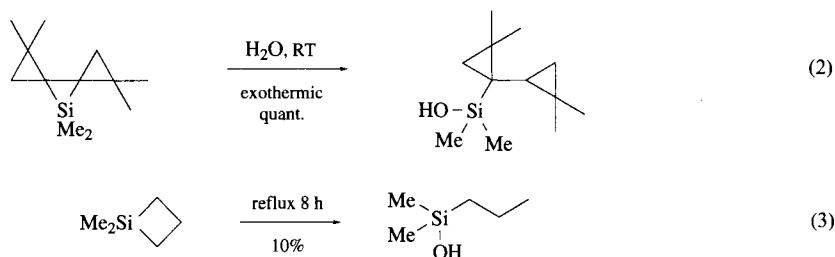
1.09.5.1 Silacyclopropanes

1.09.5.1.1 Ring-opening reactions

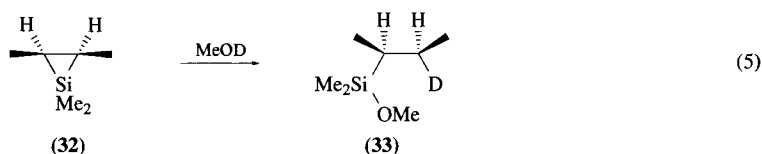
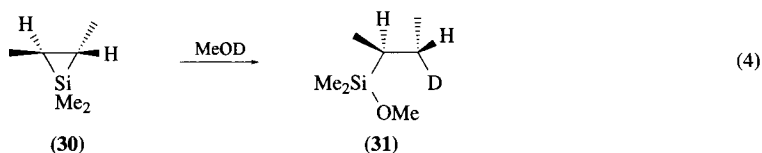
An extensive study of the ring-opening reactions of dispirosilacyclopropane (**29**) was done with 17 different nucleophilic and electrophilic reagents (Equation (1)). The direction of attack of these simple polar reagents was as predicted, with the nucleophile adding exclusively to the more electropositive silicon atom $\langle 75JOM(100)237 \rangle$.



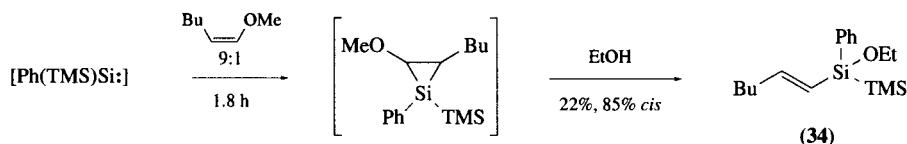
The Si—C bond in silacyclopropanes is far more reactive than the Si—C bond in silacyclobutanes. Thus, 1,1-dimethyl-*trans*-bis-2,3-[2',2'-dimethylcyclopropylidene]-1-silacyclopropane displayed higher reactivity than 1,1-dimethyl-1-silacyclobutane in reactions with water, alcohols, acids, amines, oxygen, sulfur, and alkylolithiums (Equations (2) and (3)). $\langle 73JOM(56)C7, 75JOM(100)237, 78JOM(152)131 \rangle$.



Addition of methanol to silacyclopropanes is a common method used for obtaining stable products that can be more readily isolated and characterized. This ring opening occurs stereospecifically and in a *cis* manner $\langle 83OM759 \rangle$. For example, addition of MeOD to *trans*-silacyclopropane (**30**) gave methoxysilane (**31**) (Equation (4)), whereas addition of MeOD to *cis*-silacyclopropane (**32**) gave the corresponding diastereomer (**33**) (Equation (5)).

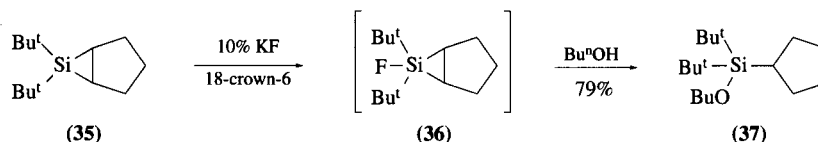


In the case of silacyclopropanes derived from vinyl ethers, addition of alcohol resulted in a stereoselective rearrangement. For example, *cis*-methoxyhexene (99 : 1) was converted to vinyl silane (**34**) in 22% yield with greater than 85% *cis* selectivity (Scheme 1) (81JA4170).



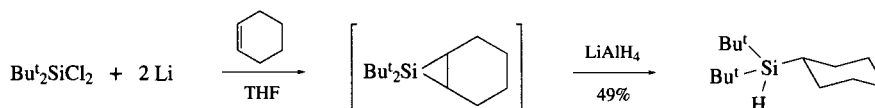
Scheme 1

In contrast to the facile ring openings with dimethylsilacyclopropanes, sterically hindered di-*t*-butylsilacyclopropanes react poorly with alcohols. For example, di-*t*-butylsilacyclopropane (**35**) was converted to silane (**37**) in only 12% yield after refluxing for 20 h in *n*-butanol. Addition of 10% potassium fluoride and 1% 18-crown-6 to silacyclopropane (**35**) and *n*-butanol produced (**37**) in 79% yield after 15 min at room temperature (Scheme 2). A pentacoordinate siliconate (**36**) was proposed to account for the rate acceleration (90TL3987).



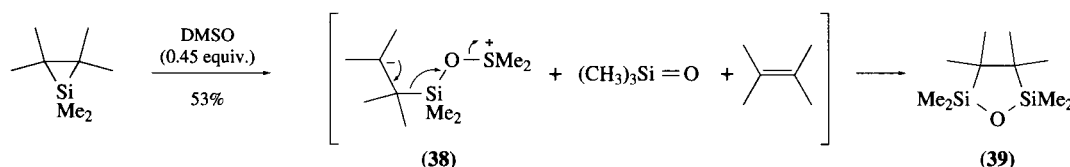
Scheme 2

Addition of lithium aluminum hydride to silacyclopropanes gives hydridosilanes. In a convenient one-pot procedure, di-*t*-butyldichlorosilane was converted to a silacyclopropane via an established procedure, then treated with lithium aluminum hydride to give the ring-opened silane (Scheme 3) (93JA4514).



Scheme 3

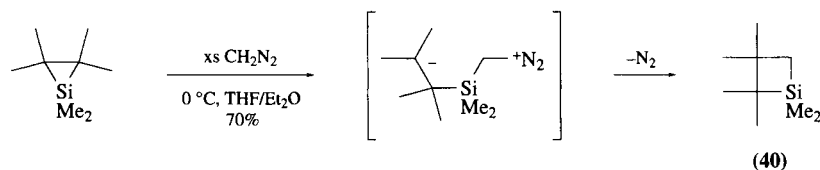
Dimethylsulfoxide and pyridine *N*-oxide behave as oxygen nucleophiles toward hexamethylsilacyclopropane (Scheme 4). For example, ring opening of hexamethylsilacyclopropane with dimethyl sulfoxide generated ylide (**38**), which fragmented to silanone, tetramethylethylene, and dimethyl sulfide. Insertion of the highly reactive silanone into another silacyclopropane gave siloxane (**39**) in 53% yield, (78JA1626).



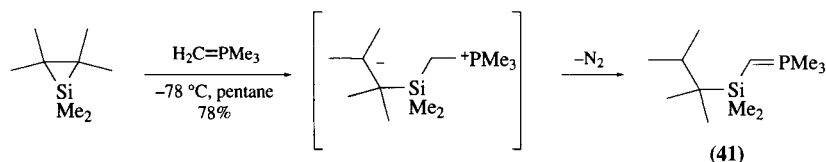
Scheme 4

Dipolar reagents diazomethane and methylenetrimesylphosphorane act as carbon nucleophiles in their reactions with silacyclopropanes. Reaction of diazomethane with hexamethylsilacyclopropane gave silacyclobutane (**40**) in 70% yield (Scheme 5), whereas reaction with methylenetrimesylphosphorane afforded phosphorus ylide (**41**) in 78% yield (Scheme 6). These

results are consistent with initial nucleophilic attack at silicon, followed by either cyclization or proton transfer <78JOM(159)137>.

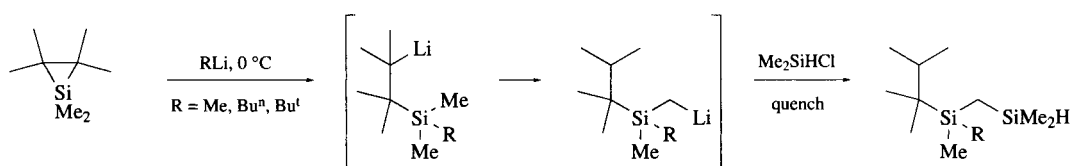


Scheme 5



Scheme 6

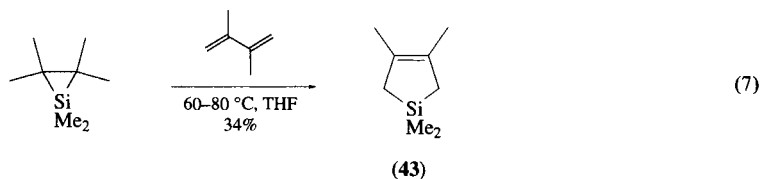
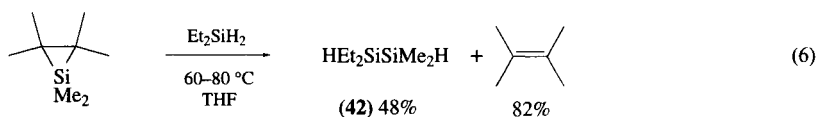
Addition of an alkyllithium reagent to hexamethylsilacyclopropane at 0 °C gave a ring-opened silane in which one of the methyl substituents on silicon had been alkylated. Apparently, the initially formed tertiary alkyllithium metallates one of the methyl substituents on silicon to give $\text{RSiMe}(\text{CH}_2\text{Li})\text{CMe}_2\text{CMe}_2\text{H}$, which is then quenched to give the final product, (Scheme 7) <84JOM(264)149>.



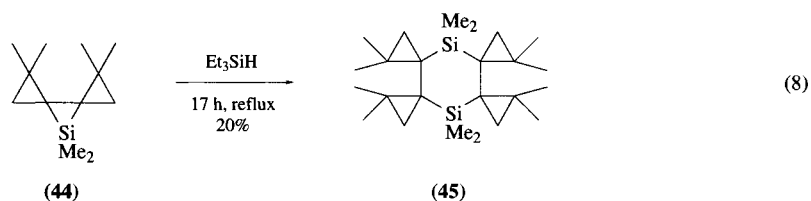
Scheme 7

1.09.5.1.2 Generation of silylenes from silacyclopropanes

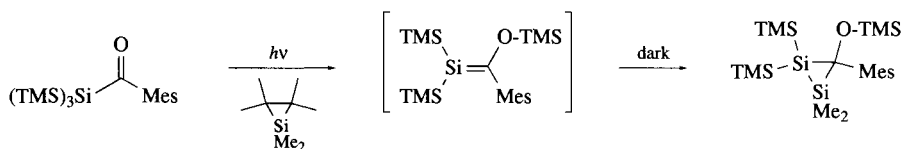
Thermolysis of hexamethylsilacyclopropane at 60–80 °C generates dimethylsilylene and tetramethylethylene. The half-life of this reaction is greater than nine days at room temperature <75JA2273>. Dimethylsilylene can be trapped by various substrates when the thermolysis is conducted in their presence. For example, interception of dimethylsilylene with diethyl silane gave disilane (42) in 48% yield, whereas trapping with 2,3-dimethyl-1,3-butadiene gave 1,1,3,4-tetramethyl-1-silacyclopent-3-ene (43) in 34% yield (Equations (6) and (7)) <75JA7162>.



Some types of silacyclopropanes are more thermally stable and do not serve as a source of silylene. For instance, thermolysis of dicyclopropylsilacyclopropane (44) in triethylsilane for 17 h gave dimer (45) in 20% yield along with oligomeric material, but yielded no disilane (Equation (8)).

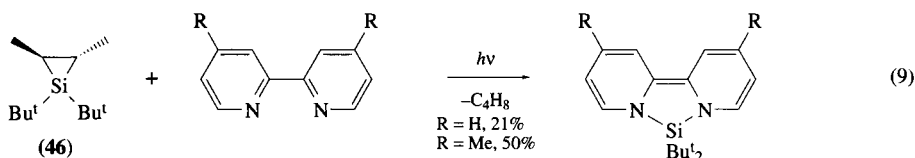


Photolysis of mesitoyltris(trimethylsilyl)silane in the presence of hexamethylsilacyclopentane gave a disilacyclopentane, presumably via addition of dimethylsilylene to the C=Si bond of the intermediate silene (Scheme 8) <85OM1487>.



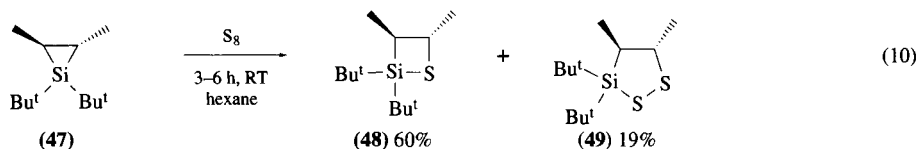
Scheme 8

Photolysis of di-*t*-butylsilacyclopentane (46) in the presence of 2,2'-bipyridyl or 4,4'-dimethyl-2,2'-bipyridyl yielded di-*t*-butyl-2,2'-bipyridyl-*N,N'*-silanes. Apparently, the intermediate di-*t*-butylsilylene undergoes [4 + 1] cycloaddition with the aromatic ring of the bipyridyl, converting it to a conjugated double-bond system (Equation (9)) <90JOM(385)C47>.



1.09.5.1.3 One- and two-atom insertions

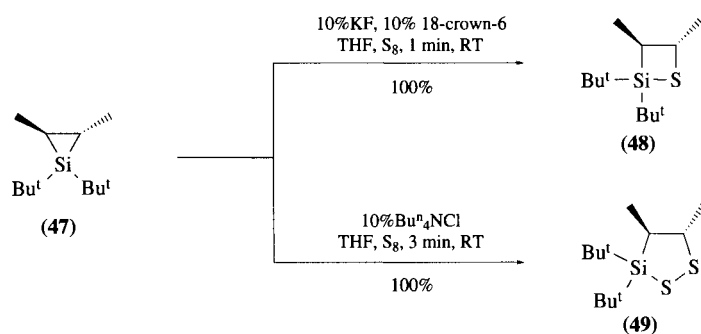
Sulfur reacts with hexamethylsilacyclopentane in tetrahydrofuran (THF) to give 2,3-dithia-1-silacyclopentane in 38% yield <79JOM(164)305>. Exposure of *trans*-1,1-di-*t*-butyl-2,3-dimethylsilacyclopentane (47) to elemental sulfur at room temperature for 3–6 h gave *trans*-1,1-di-*t*-butyl-1,2-silathietane (48) and *trans*-3,3-di-*t*-butyl-4,5-dimethyl-1,2-dithia-3-silacyclopentane (49) in 60% and 19% yield respectively (Equation (10)). Identical results were obtained with the *cis*-silacyclopentane, suggesting a stepwise radical mechanism <90OM2205>. The presence of *t*-butyl substituents on silicon was a key factor in this reaction, since sulfur insertion cannot be stopped at a single atom when there are small substituents on silicon <79JOM(164)305>.



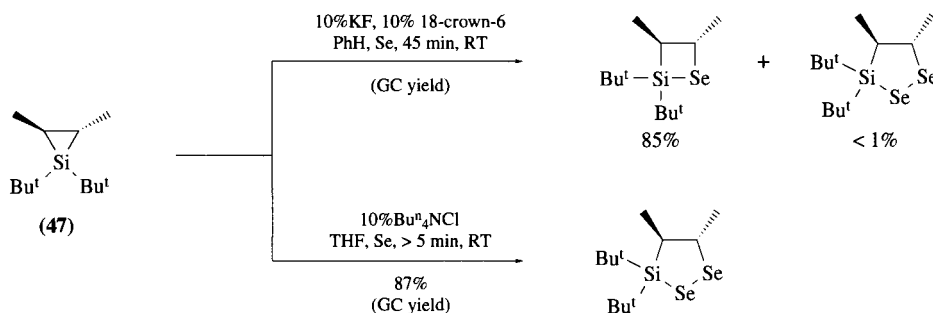
In 1994, it was found that the rate and selectivity of both one- and two-atom sulfur insertions could be dramatically affected by the addition of salts and crown ethers. Thus, reaction of *trans*-silacyclopentane (47) with sulfur in the presence of 10% potassium fluoride and 10% 18-crown-6 gave thiasiletane (48) exclusively, in quantitative yield, in under 1 min. By contrast, treatment of (47) with sulfur in the presence of 10% tetrabutylammonium chloride for 3 min yielded only silacyclopentane (49) (Scheme 9) <94OM3715>.

A similar protocol was found to be successful for the one- and two-atom insertions of selenium into silacyclopentanes (Scheme 10). In the absence of these additives, silacyclopentane (47) is practically inert toward selenium.

Hexamethylsilacyclopentane reacted with conjugated aldehydes, ketones, and imines at room temperature to give two-atom insertion products (Equation (11)). Saturated aldehydes and ketones

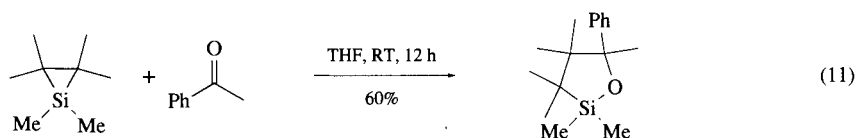


Scheme 9

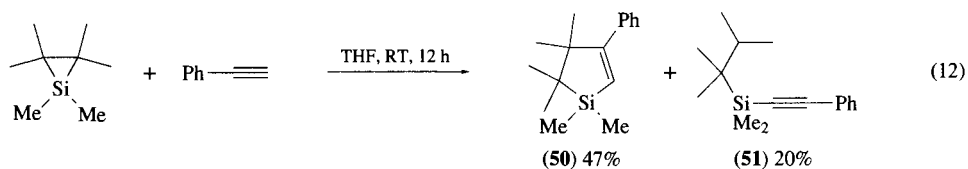


Scheme 10

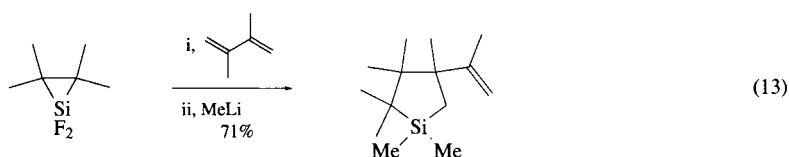
did not react with hexamethylsilacyclopentane unless irradiated with ultraviolet light <77JOM(125)C5, 77JOM(135)C37>.

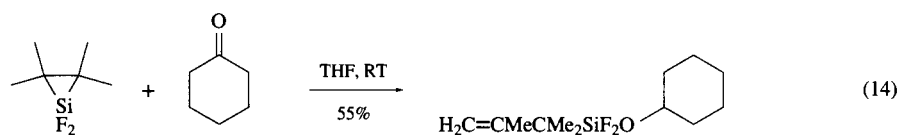


Hexamethylsilacyclopentane reacted with conjugated alkenes and terminal 1,3-dienes to give silacyclopentanes. Similarly, reaction with conjugated terminal alkynes and benzyne yielded silacyclopentenes. For example, reaction of hexamethylsilacyclopentane with phenylethyne gave silacyclopentene (**50**) in 47% yield, along with alkynylsilane (**51**) in 20% yield (Equation (12)) <84OM574, 84OM579>.



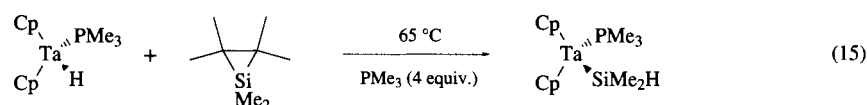
The more reactive 1,1-difluoro-2,2,3,3-tetramethylsilacyclopentane gave two-atom insertion products with styrene, phenylethyne, benzaldehyde, and acetophenone (Equation (13)). Reaction with cyclohexanone or pivaldehyde, on the other hand, yielded acyclic products (Equation (14)) <78JA7734>. These reactions were thought to proceed via a radical intermediate.



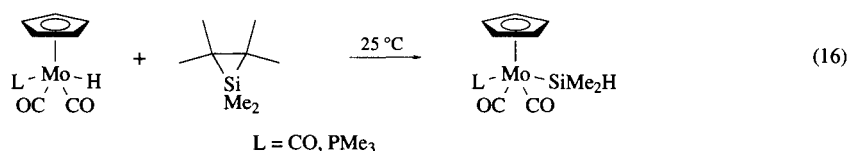


1.09.5.1.4 Organometallic reactions

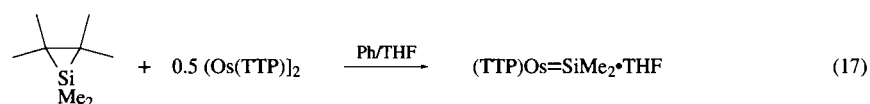
Treatment of tantalum hydride complexes with hexamethylsilacyclopentane at 65°C in the presence of a Lewis base gave the corresponding silyl–tantalum compounds in excellent yield. It appears that this reaction takes place via direct insertion of dimethylsilylene into the tantalum–hydride bond, which would make it the first example of silylene trapping by a transition-metal substrate (Equation (15)) <87JA6210>.



Reaction of molybdenum hydride complexes with hexamethylsilacyclopentane at 25°C resulted in net insertion of dimethylsilylene into the molybdenum–hydride bond (two examples, ca. 70%). A radical chain mechanism was proposed for this transformation (Equation (16)) <87JA3777>.

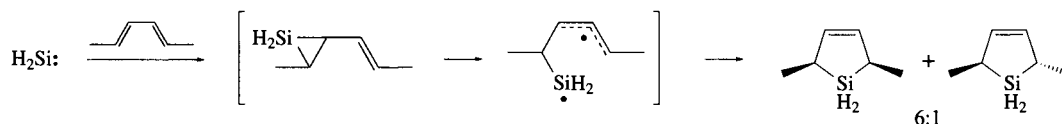


Reaction of osmium tetra-*p*-tolylporphyrin dimer [Os(TTP)]₂ with excess hexamethylsilacyclopentane at room temperature gave a metalloporphyrin dimethylsilylene complex (Equation (17)) <91OM3977>. The mechanism for this reaction was thought to involve an initial electron transfer followed by a radical chain process.

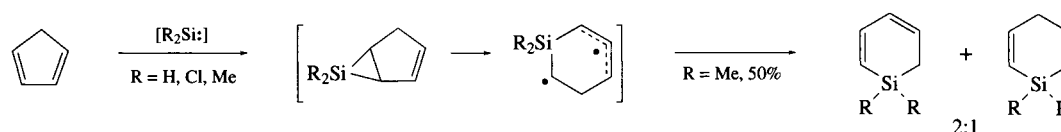


1.09.5.1.5 Vinylsilacyclopentane rearrangements

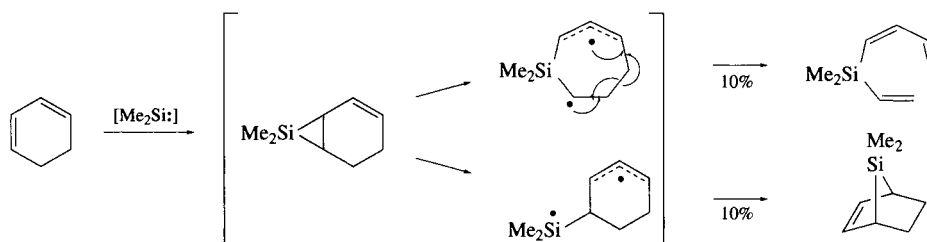
The reaction of silylenes with 1,3-dienes proceeds via 1,2 addition to the C=C bond to give vinylsilacyclopentanes, which generally undergo further rearrangements <84JOM(271)129>. Vinylsilacyclopentanes derived from acyclic dienes give silacyclopentenes <74JA6198>; those from cyclic dienes give ring expansion or fragmentation products <74TL4033, 75JOM(94)C38>. There is evidence to suggest that all these rearrangements proceed through diradicals (Schemes 11–14).



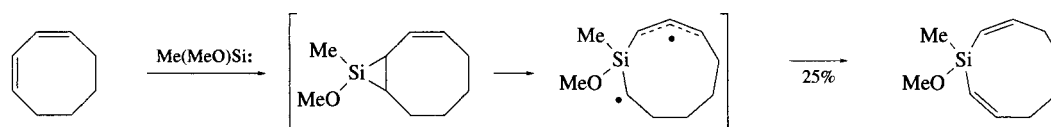
Scheme 11



Scheme 12



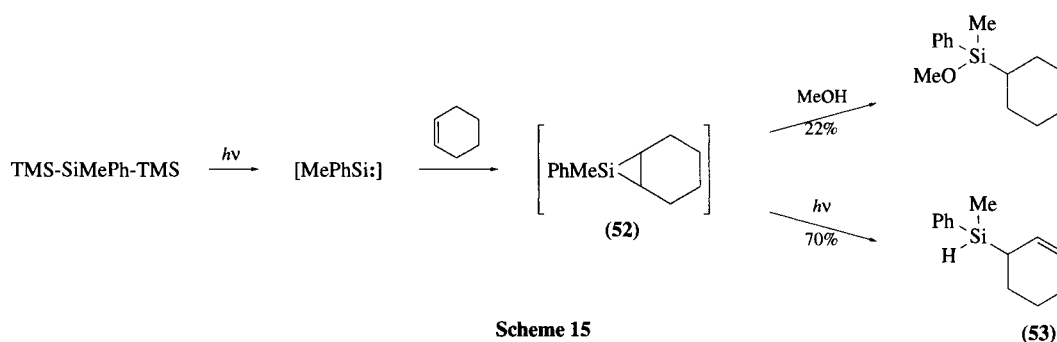
Scheme 13



Scheme 14

1.09.5.1.6 [1,2]- and [1,3]-Hydrogen shifts and [1,2]-halide shifts

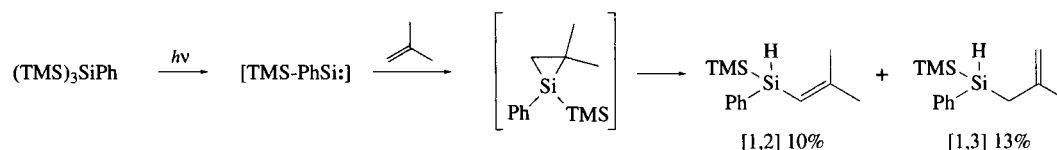
Photolysis of an organopolysilane in the presence of an alkene gives a silacyclopentane via [2 + 1] addition of the intermediate silylene to the $\text{C}=\text{C}$ bond. Continued irradiation of the silacyclopentane generally results in a [1,3]-hydrogen shift to give an allylsilane as the final product. For example, irradiation of 2-phenylheptaamethyltrisilane in the presence of cyclohexene gave silacyclopentane (**52**), which could be stored in solution or isolated as its methanolysis product. Further irradiation of (**52**) using a high-pressure mercury lamp with a quartz filter gave allylsilane (**53**) in 70% yield (Scheme 15) <74JOM(81)C3>. Photolysis of the same organopolysilane in the presence of allylsilane or isopropenyltrimethylsilane gave intermediate silacyclopentanes which also underwent [1,3]-hydrogen shifts <75TL645>.



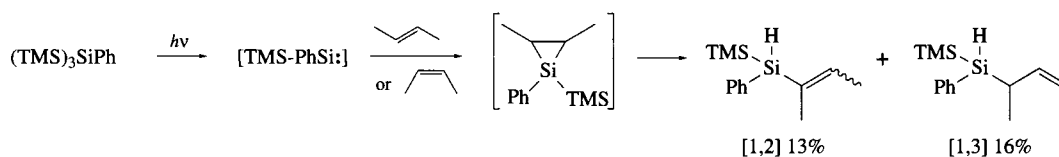
Scheme 15

Photolysis of tris(trimethylsilyl)phenylsilane generated trimethylsilylphenylsilylene, which could be trapped by alkenes to give the respective silacyclopentanes. Further photolysis using a high-pressure mercury lamp with a quartz filter gave both vinylsilanes and allylsilanes as products, via [1,2]- and [1,3]-hydrogen shifts, respectively (Schemes 16 and 17) <79JOM(178)105>.

When the photolysis of tris(trimethylsilyl)phenylsilane was done in the presence of vinyl chlorides or vinyl bromides, 1-alkenyl-1-halo-1-phenyltrimethyldisilanes were obtained in fair yield. The

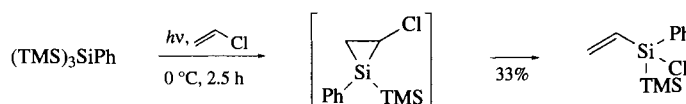


Scheme 16



Scheme 17

mechanism of this reaction was thought to involve formation of the silacyclopropane, followed by a [1,2]-halogen shift (Scheme 18) (81JA4170).



Scheme 18

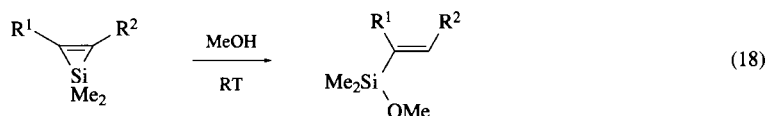
1.09.5.2 Silacyclopropenes

1.09.5.2.1 Review

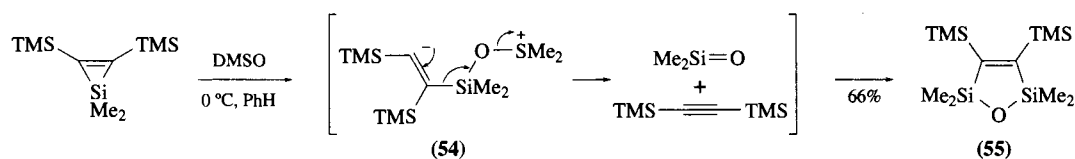
The synthesis, structural and spectroscopic properties, and some transformations of silacyclopropenes have been previously reviewed (87PAC993). Reactions include the addition of alcohols, two-atom insertions, and silylene insertions.

1.09.5.2.2 Ring-opening reactions

Alcohols add readily and stereoselectively to the C—Si bond of silacyclopropenes to give vinyl silanes (Equation (18)) (87PAC993).



Oxidation of silacyclopropene (54) with dimethyl sulfoxide gave cyclic siloxane (55) in 66% yield (Scheme 19) (78JA1626).



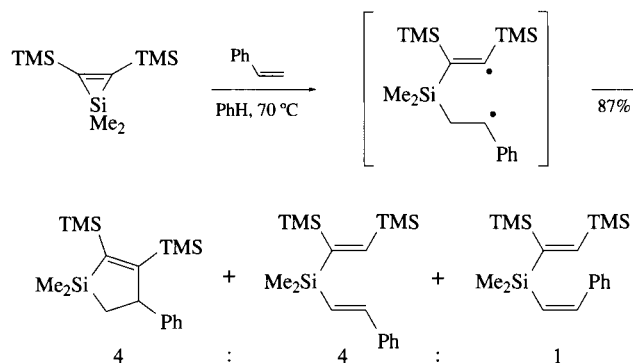
Scheme 19

1.09.5.2.3 One- and two-atom insertions

(i) Thermal

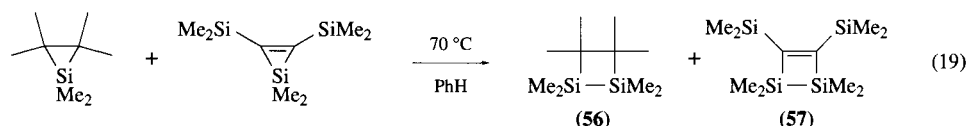
A radical mechanism was proposed for insertion reactions between silacyclopropenes and compounds containing C=O, C=N, C=C, or C≡C bonds. Two-atom insertion reactions with alde-

hydes, ketones, and unsaturated imines gave five-membered cyclic organosilicon products. Both cyclic and acyclic products were formed in C=C and C≡C insertions (Scheme 20) <84OM1897>.

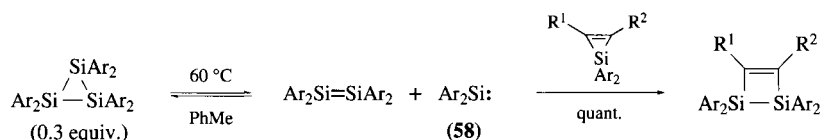


Scheme 20

Thermolysis of hexamethylsilacyclop propane in benzene at 70 °C generated an intermediate dimethylsilylene, which inserted into starting material to give a 1,2-disilacyclobutane (**56**) in 40% yield (Equation (19)). When this reaction was conducted in the presence of a silacyclop propane, both 1,2-disilacyclobutane (**56**) and 1,2-disilacyclobut-3-ene (**57**) were isolated <77JOM(125)C11>.

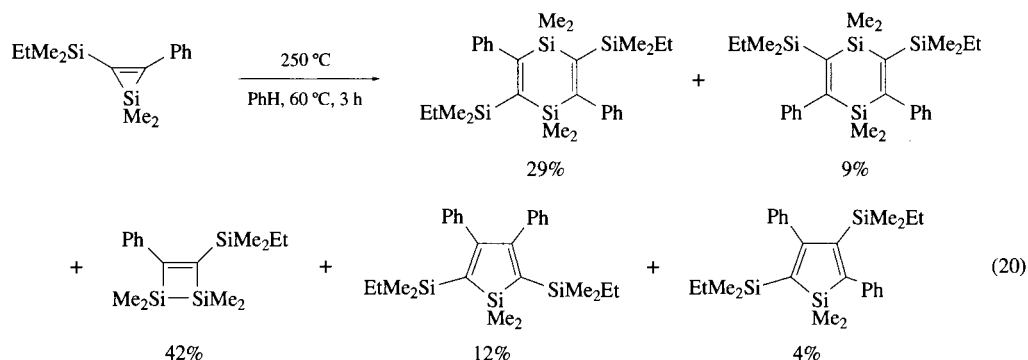


Insertion of diarylsilylene (**58**) into three different silacyclop ropenes gave the corresponding 1,2-disilacyclobutenes in quantitative yield (Scheme 21) <94CC1989>. Diarylsilylene (**58**) was generated *in situ* by thermolysis of a cyclotrisilane under mild conditions.

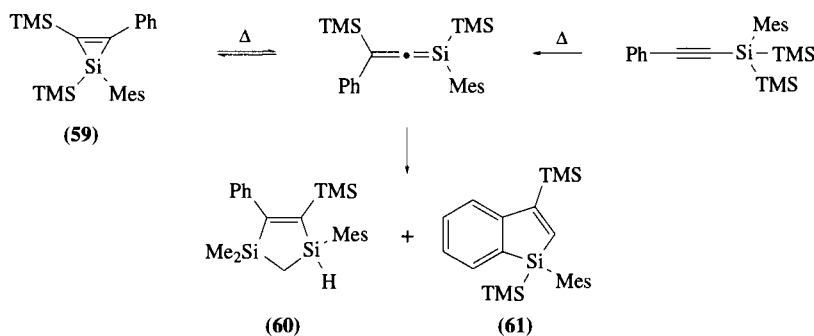


Scheme 21

Thermolysis of silacyclop ropenes in a sealed glass tube at 250 °C led to various mixtures of four-, five-, and six-membered ring products depending on the substitution pattern of the starting material. The six-membered ring products, two isomeric 1,4-disilacyclohexa-2,5-dienes, were formed via dimerization of the silacyclop ropene. The four- and five-membered ring products were derived from insertion of silylene and ethyne, respectively, into silacyclop ropene (Equation (20)) <77JOM(142)C45, 83OM974>.

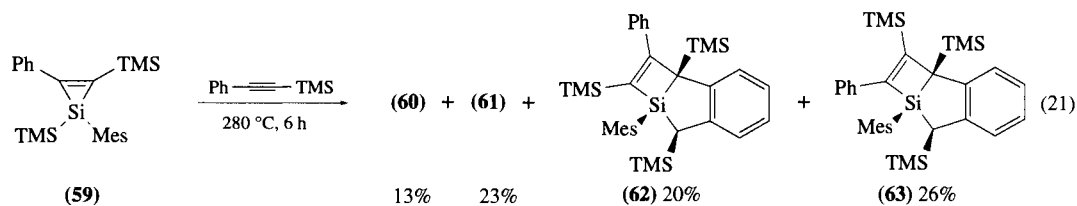


Thermolysis of 1-mesityl-3-phenyl-1,2-bis(trimethylsilyl)-1-silacyclopentene (**59**) at 280 °C yielded 1,3-disilacyclo-4-pentene (**60**) and 1-silaindene (**61**) derivatives in 49% yield and 28% yield, respectively. The same two products were obtained in 25% yield and 18% yield from thermolysis of 2-mesityl-2-(phenylethynyl)hexamethyltrisilane under similar conditions. A 1-silapropadiene intermediate was proposed to explain these results (Scheme 22) <86JOM(314)261, 91JOM(402)C20>.



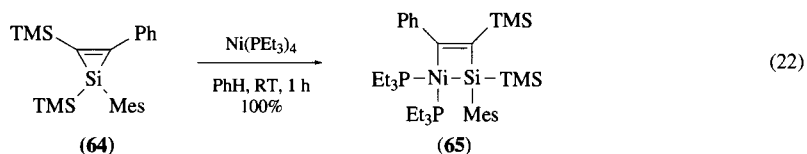
Scheme 22

When the thermolysis of silacyclopentene (**59**) was carried out in the presence of excess phenyl-trimethylsilylethyne, (**60**) and (**61**) were obtained in 13% yield and 23% yield, respectively, along with *cis*- and *trans*-7a-mesityl-1-phenyl-2,2a,7-tris(trimethylsilyl)cyclobutenosilainden (**62**) and (**63**) in 20% yield and 26% yield, respectively (Equation (21)). The structure of (**62**) was determined by x-ray diffraction <92OM597>.

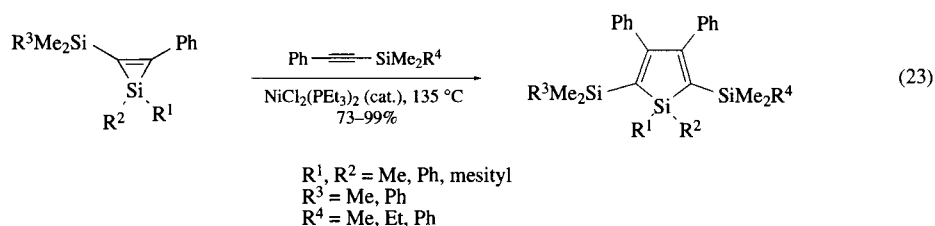


(ii) Metal catalyzed

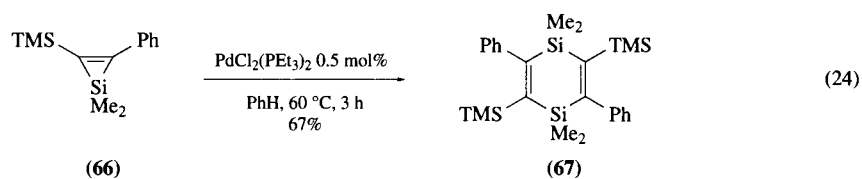
Stoichiometric reaction of tetrakis(triethylphosphine)nickel(0) with silacyclopentene (**64**) gave nickelasilacyclobutene (**65**) in quantitative yield (Equation (22)). The structure was supported by spectroscopic analysis and subsequent chemical reactivity <86JA7417, 89OM2050>.



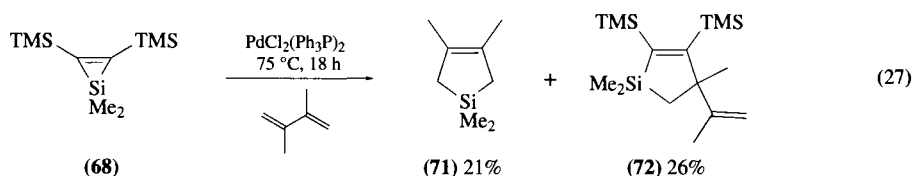
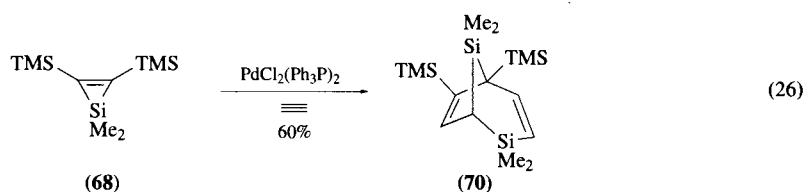
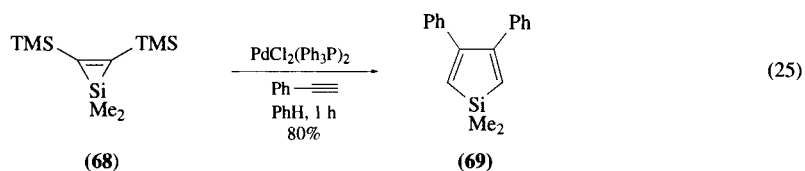
1-Silacyclopenta-2,4-dienes were synthesized on a preparative scale by reacting silacyclopentenes with alkynes in the presence of a nickel catalyst. The reaction proceeded regioselectively and in high yield when the ring silicon was substituted with alkyl or aryl groups (Equation (23)) <81JOM(217)43>.



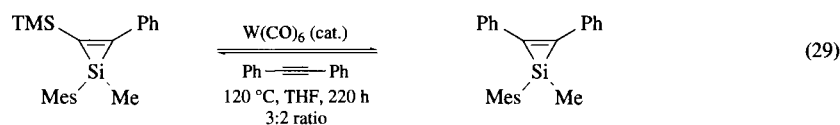
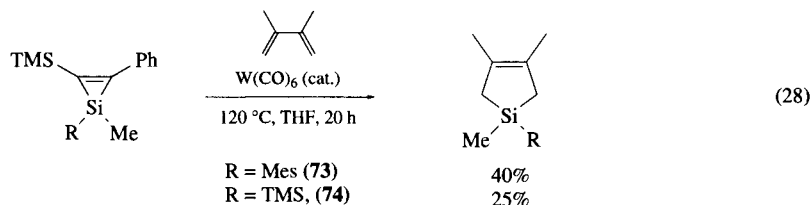
Silacyclopentene (**66**) was converted to its dimer (**67**) in 67% yield under mild thermal conditions in the presence of a catalytic amount of $[\text{PdCl}_2(\text{PEt}_3)_2]$ (Equation (24)) <77CC352, 82OM1473>. No other isomers of disilacyclohexa-2,5-diene were detected.

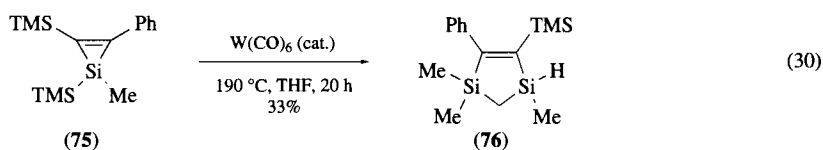


Reaction of silacyclopentene (**68**) with phenylethyne in the presence of $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ gave 3,4-diphenylsilacyclopentadiene (**69**) in 80% yield (Equation (25)). Reaction of (**68**) with ethyne in the presence of $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ gave disilabicyclo[3.2.1]norbornadiene (**70**) in 60% yield (Equation (26)). Finally, reaction of (**68**) with 2,3-dimethylbutadiene in the presence of $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ gave silacyclopentenes (**71**) and (**72**) in 21% yield and 26% yield, respectively (Equation (27)) <85OM57>.



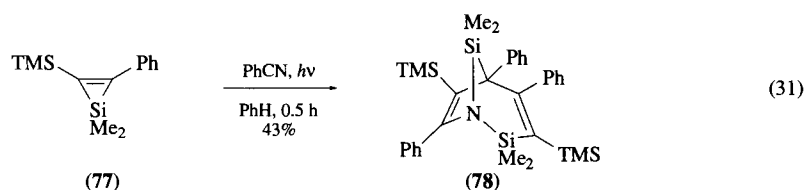
Addition of a catalytic amount of hexacarbonyltungsten(0) to silacycloprenes (**73**) or (**74**) resulted in abstraction of silylene by the transition-metal complex. The silylene could then be trapped with butadiene (Equation (28)) or an equilibrium achieved between two silacycloprenes via addition of a second alkyne (Equation (29)). In the absence of tungsten, the silacycloprenes were recovered unchanged. Thermolysis of silacyclopentene (**75**) in the presence of tungsten but no trapping agent led to disilacyclopentene (**76**) in 33% yield along with six minor products (Equation (30)) <91JOM(407)157>.





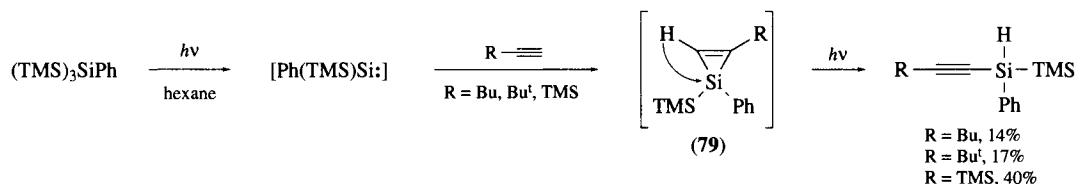
(iii) Photochemical

Irradiation of silacyclopropene (77) in the presence of excess nitrile gave aza-2,8-disilabicyclo-[3.2.1]octa-3,6-diene (78) (four examples, 15–43% yield) (Equation (31)). This reaction is thought to proceed via sequential [2 + 2] and [4 + 2] cycloadditions, consuming two equivalents of silacyclopropene and one equivalent of the nitrile <78CC80>.



1.09.5.2.4 [1,2]-Hydrogen shifts

Photolytic generation of phenyl(trimethylsilyl)silylene in the presence of terminal alkynes gave silacyclopropenes, which upon further irradiation, rearranged to disilylethyne derivatives (79) via a [1,2]-hydrogen shift (three examples, 14–40% yield), (Scheme 23) <77JOM(131)C15, 79JOM(179)377, 80JOM(190)117>.

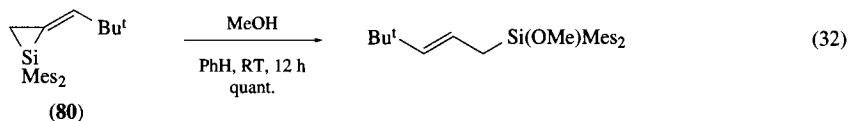


Scheme 23

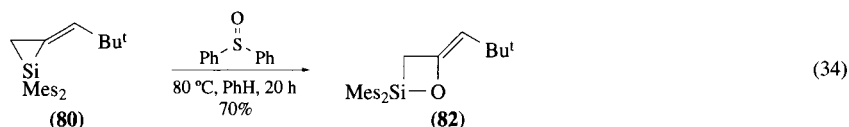
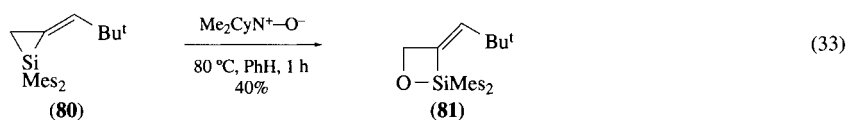
1.09.5.3 Alkylidene Silacyclopropanes

1.09.5.3.1 Reaction with nucleophiles

The chemistry of 1,1-dimesityl-2-*Z*-neopentylidenesilacyclopropane (80) was reviewed, including its ring-opening reactions with alcohols, aldehydes, nitrones, oxidants, reducing agents, acids, as well as its palladium-catalyzed couplings with alkynes and allenes. The selectivity of the Si—C bond cleavage in these reactions was found to depend on the nature of the nucleophile. For example, ring opening with methanol gave allyl silane exclusively (Equation (32)), whereas trifluoroacetic acid gave a 1 : 1 mixture of a vinyl silane and an allylsilane <89T1929>.

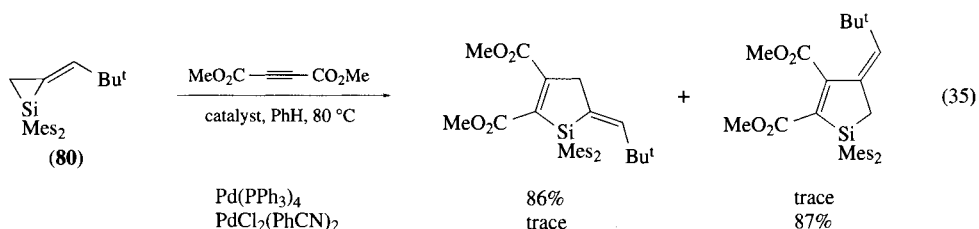


Oxidation of (80) with cyclohexyldimethylamine *N*-oxide and diphenyl sulfoxide yielded isomeric 1,2-oxasilatanes (81) and (82) regiospecifically, (Equations (33) and (34)) <88TL4747>.



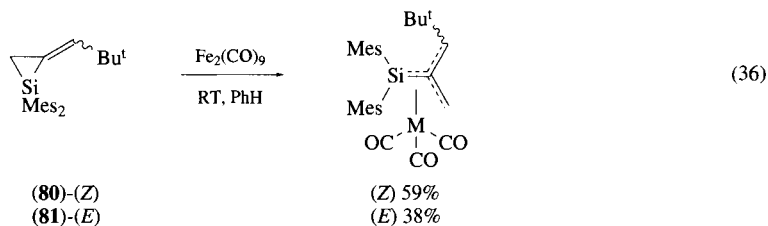
1.09.5.3.2 Two-atom insertions

The palladium-catalyzed reaction of *Z*-neopentyldenesilacyclopropane (**80**) with dimethyl ethynedicarboxylate led to a mixture of two-ring expansion products, the ratio of which varied dramatically with the nature of the catalyst. The yield of the Si—C3 insertion product was maximized using Pd(PPh₃)₄ as catalyst, while the highest yield of the Si—C2 insertion product was obtained with PdCl₂(PhCN)₂, (Equation (35)) <88CL1567>.

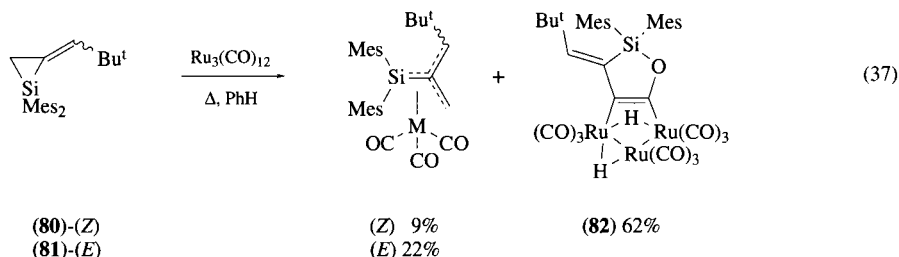


1.09.5.3.3 Organometallic reactions

Silatrimethylenemethane iron complexes were synthesized by reaction of *Z*- and *E*-alkylidene silacyclopropanes (**80**) and (**81**) with Fe₂(CO)₉ (Equation (36)). Structure assignments were based on spectroscopic data as well as an x-ray crystal structure of the *Z*-iron complex.

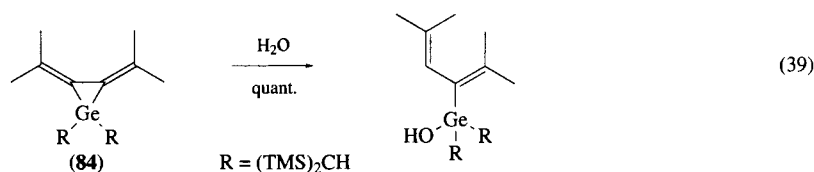
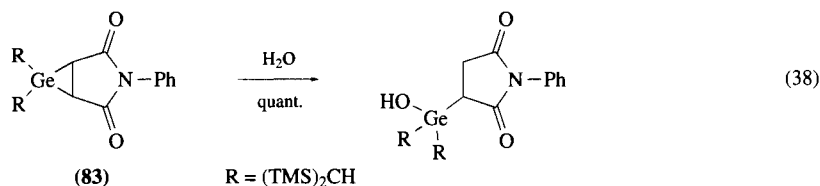


Treatment of (**80**) and (**81**) with Ru₃(CO)₁₂ gave the η⁴-silatrimethylenemethane-ruthenium complexes in 9% and 22% yield, respectively. The major product of the *Z*-alkylidenesilacyclopropane reaction was trinuclear ruthenium carbonyl cluster (**82**), whose structure was established by x-ray diffraction (Equation (37)). This appears to be the first example of a main group metal-bound carbonyl inserting into a silacyclopropane <91JA2791, 94OM4606>.

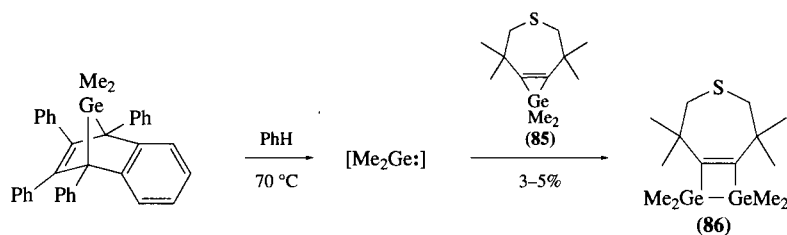


1.09.5.4 Reactions of Germacyclopropanes and Germacyclopropenes

Treatment of bicyclic germacyclopropane (**83**) and bis(alkylidene)germacyclopropane (**84**) with water gave ring-opened germanols in quantitative yield (Equations (38) and (39)) <94AG(E)659>.



Attempts to insert dimethylgermylene into the C—Ge bond of germacyclopropene (**85**) were largely unsuccessful, and gave mainly a germanium polymer. The desired 1,2-digermycyclobutene (**86**) was formed in only 3–5% yield (Scheme 24) <86JOM(301)C21>.

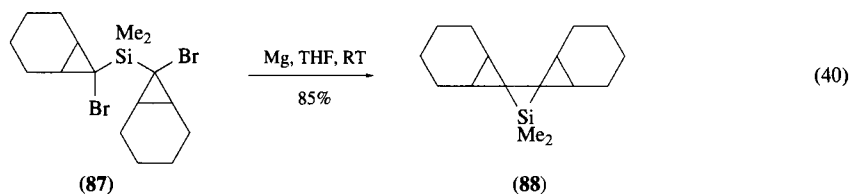


1.09.6 SYNTHESIS OF THREE-MEMBERED RINGS WITH ONE SILICON ATOM

1.09.6.1 Silacyclopropanes

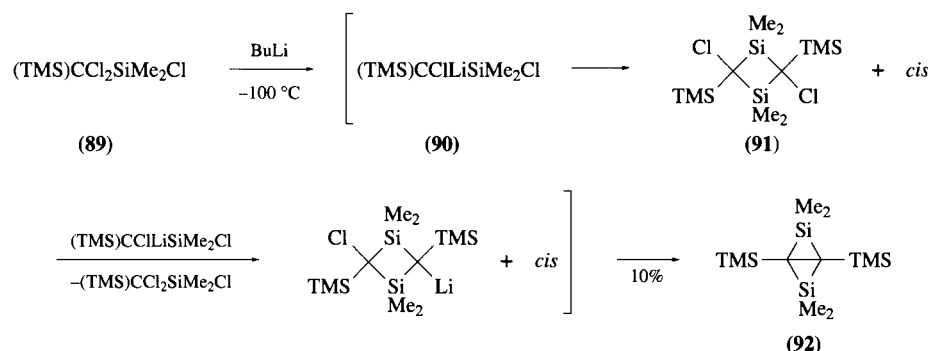
1.09.6.1.1 From acyclic compounds by formation of one C—C bond

The first silacyclopropanes <69AG(E)469, 87ACR329> to be prepared and isolated were synthesized via magnesium-induced ring closure of 1,3-dihalides (three examples). Thus, dispirobicyclo[4.1.0]heptane-7-2'-silacyclopropane-3',7''-bicyclo[4.1.0]heptane (**88**) was obtained as a mixture of diastereomers in 85% yield from dibromide (**87**) (Equation (40)) <72JA9246, 76JOM(122)311>.



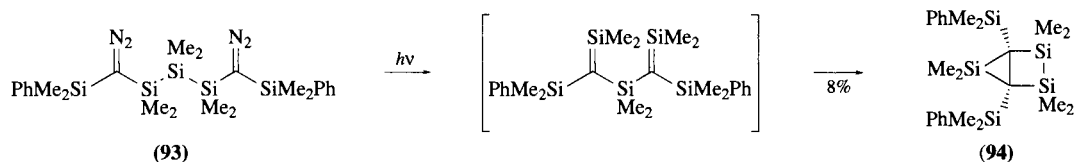
Disilabicyclo[1.1.0]butane (**92**) was synthesized in low yield by lithiation of 2,4-disilapentane (**89**) at -100°C . The following four-step mechanism was proposed for this reaction: (1) metallation of the CCl_2 group of (**89**) to give carbenoid (**90**); (2) dimerization of the carbenoid to *cis*- and *trans*-

disilacyclobutane (**91**); (3) metal–halogen exchange to give lithiated *cis*- and *trans*-carbenoids; and (4) intramolecular elimination to form bicyclo[1.1.0] butane (**92**) (Scheme 25) <84JOM(271)107>.



Scheme 25

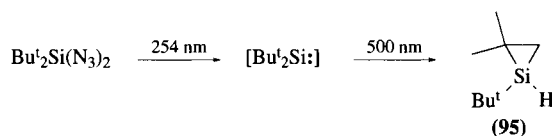
Irradiation of bis(silyldiazomethyl) compound (**93**) generated an intermediate 1,5-disila-1,4-diene, which underwent a [2 + 2] cycloaddition to give strained trisilabicyclopentane adduct (**94**) in low yield (Scheme 26) <91JA7790>.



Scheme 26

1.09.6.1.2 From acyclic compounds by formation of one Si—C bond

Photolysis of di-*t*-butyldiazidosilane at 254 nm in 3-methylpentane glass at 77 K or in an argon matrix at 10 K led to a highly reactive di-*t*-butylsilylene intermediate with λ_{max} 480 nm. Subsequent irradiation at 500 nm resulted in formation of 1-*t*-butyl-2,2-dimethyl-1-silacyclopropane (**95**), the first stable silacyclopropane with an Si—H bond (Scheme 27) <88JA6689>.



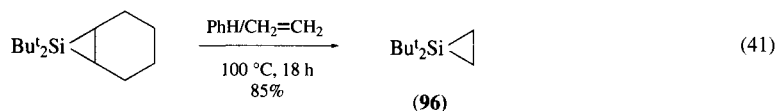
Scheme 27

1.09.6.1.3 Ring formation by [2 + 1] cycloaddition

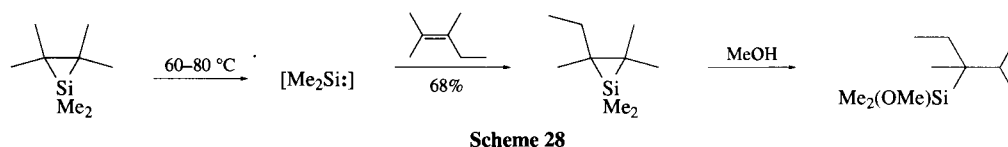
The [2 + 1] cycloaddition of silylenes and alkenes is the most common preparative route to silacyclopropanes.

(i) Silylenes by thermolysis

A silacyclopropane (**96**) with no substituents on its ring carbons was prepared in 85% yield by thermolysis of 7,7-di-*t*-butyl-7-silabicyclo[4.1.0]heptane in the presence of ethylene (Equation (41)), <91OM2095>.

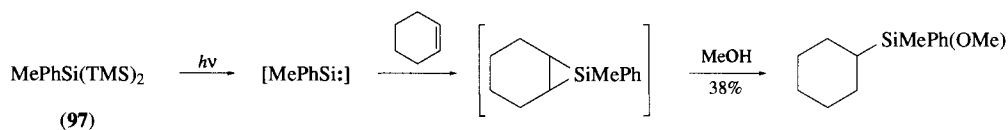


Generation of dimethylsilylene from hexamethylsilacyclop propane in the presence of *cis*- and *trans*-4-octene, cyclooctene, propenyltrimethylsilane, and trimethylethylene gave the corresponding silacyclop propane. The yields of these reactions were determined by gas-liquid chromatography (GLC) and structures indicated by their methanolysis products (Scheme 28) <76JOM(117)C51>.

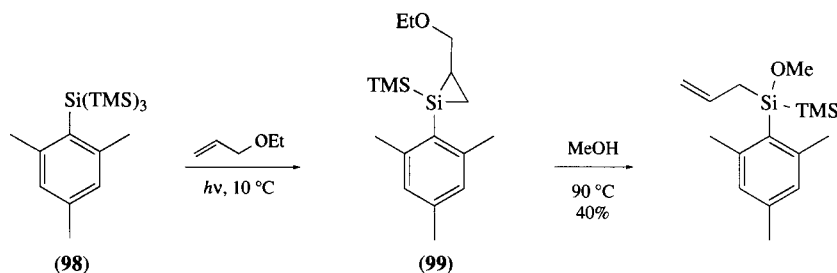


(ii) Silylenes by photolysis

Photolysis of 2-phenylheptamethyltrisilane (97) generated methylphenylsilylene, which readily added to terminal, internal, and cyclic alkenes. Under the best conditions, irradiation of this trisilane with a low-pressure mercury lamp in the presence of alkenes that lacked methyl substituents yielded silacyclop propane in 27–50% yield (Scheme 29). These silacyclop propane were detected by ¹H NMR and were characterized as their methanolysis products <78JOM(152)155>.

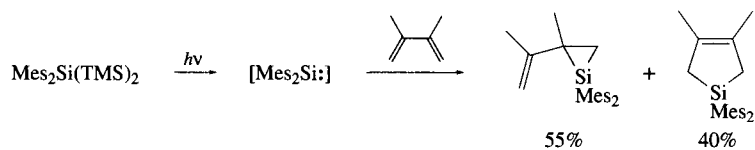


Photolysis of tris(trimethylsilyl)mesitylene (98) in the presence of allyl ethyl ether at 10 °C afforded a thermally stable silacyclop propane (99) which could not be isolated in pure form. Treatment of the photolysis mixture with methanol gave 1-allyl-1-mesityl-1-methoxytrimethyldisilane in 40% yield (Scheme 30). Similar reactions of less highly substituted silylenes gave much poorer yields of the methanolysis products <83JOM(248)251>.

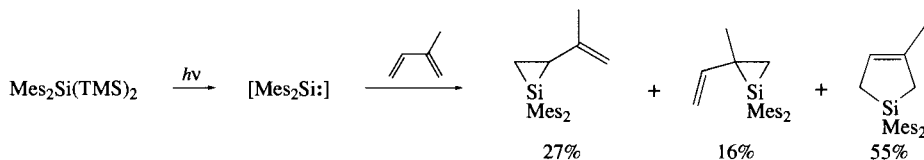


Irradiation of hexamethyl-2,2-dimesityltrisilane in the presence of 1,3-dienes gave 2-vinyl-1,1-dimesitylsilacyclop propane (seven examples) (Scheme 31). Experiments with nonsymmetrical dienes gave mixtures of silacyclop propane, the major product resulting from addition to the least substituted π bond of the diene (Scheme 32). Silacyclop pent-3-enes were significant side products in all of these reactions <91JA4272>.

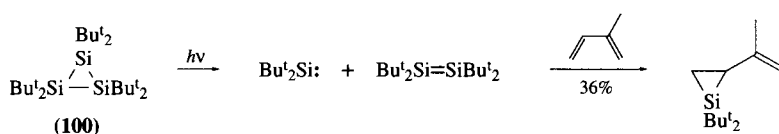
Photolysis of cyclotrisilane (100) in the presence of simple alkenes or 1,3-dienes gave silacyclop propane in modest yield (three examples). For example, reaction of cyclotrisilane with 2-methylbutadiene gave 1,1-di-*i*-butyl-2-isoprenylsilacyclop propane exclusively, via addition of the intermediate silylene to the less-hindered double bond (Scheme 33) <94CC1233>.



Scheme 31

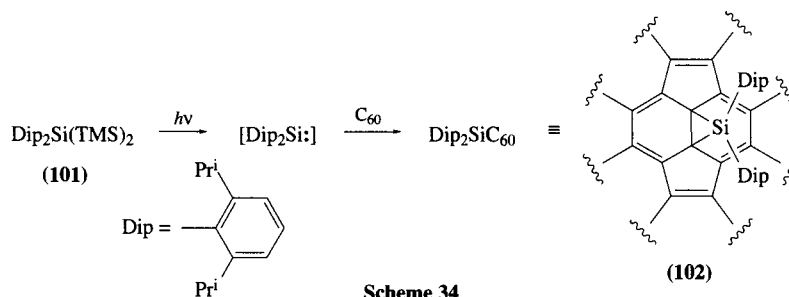


Scheme 32



Scheme 33

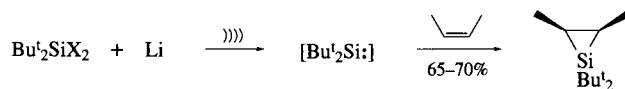
Fullerene silacyclopropane derivative (**102**) was prepared in 58% yield by photolysis of trisilane (**101**) in the presence of C_{60} . The spectral data for the product was consistent with a silacyclopropane of C_{2v} symmetry, which would arise from addition of the silylene across the six-ring–six-ring junction (Scheme 34) <93JA1605>.



Scheme 34

(iii) Silylenes by reduction of dihalosilanes

A preparative method for the generation of di-*t*-butylsilylene via metal promoted α -elimination of dihalosilanes has been developed. The silylene could be trapped with alkenes to give silacyclopropanes in 65–70% yield (Scheme 35) <64AG(E)226, 88AG(E)1355>.

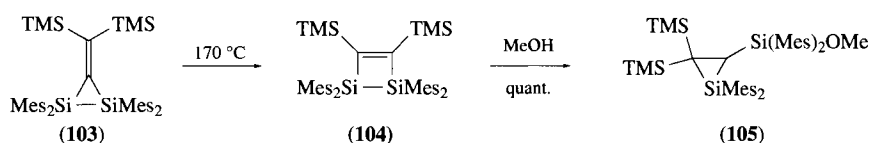


Scheme 35

1.09.6.1.4 By ring contraction

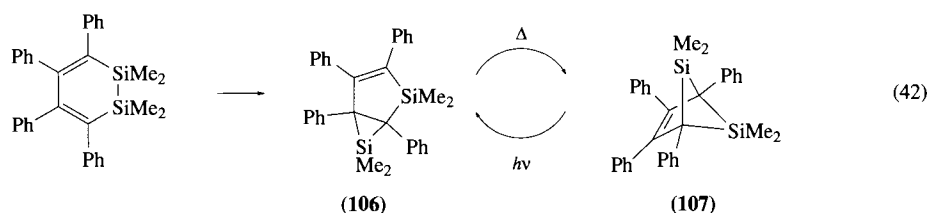
Silacyclopropanes were prepared via a two-step ring-expansion/ring-contraction sequence from 1,1,2,2-tetramesityl-1,3-bis(trimethylsilyl) methylene-1,2-disilacyclopropane (**103**). Thus, thermolysis

of disilacyclopropane (**103**) gave 1,2-disilacyclobutane (**104**), which was converted to silacyclopropane (**105**) in quantitative yield upon treatment with water or methanol (Scheme 36) <85CC588>.



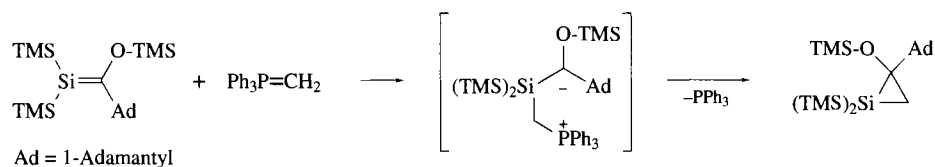
Scheme 36

Photolysis of 1,2-disila-3,5-cyclohexadienes yielded 2,6-disilabicyclo[3.1.0]hex-3-ene derivatives (**106**). The photoadducts could not be isolated in pure form because of sensitivity to air and moisture, and were isomerized thermally to the 5,6-disilabicyclo[2.1.1]hex-2-ene isomers (**107**) (Equation (42)) <74JA5621, 74JA5623>.



1.09.6.1.5 By reaction of silylene with Wittig reagents

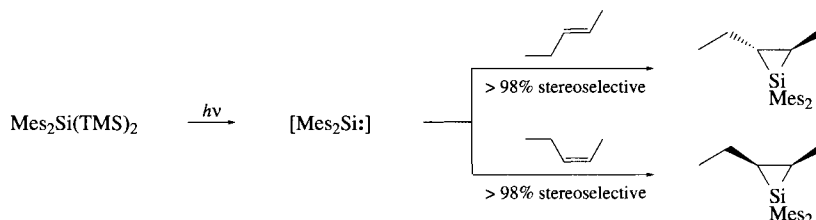
Silacyclopropanes were synthesized via the reaction of a stable silene (**108**) with both phosphorus and sulfur ylides. The products were characterized spectroscopically and then converted to their methanolysis products (Scheme 37) <88JOM(341)C9>.



Scheme 37

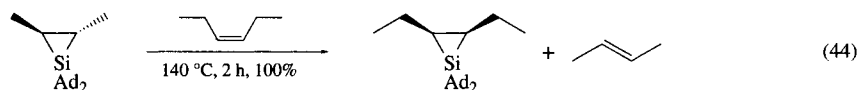
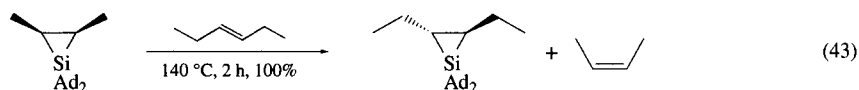
1.09.6.1.6 Stereochemistry of the [2 + 1] cycloaddition

Dimethylsilylene and diphenylsilylene added stereospecifically to both *cis*- and *trans*-2-butene to give the corresponding silacyclopropanes <80JA1425, 83OM759>. Dimethylsilylene added stereospecifically to *cis*- and *trans*-2-pentenes as well as *cis*- and *trans*-4-octenes, refuting an earlier report claiming nonstereospecific addition of this bulky silylene (Scheme 38) <88JA3310, 91JA4278>.



Scheme 38

Thermolysis of 1,1-diadamantyl-2,3-dialkylsilacyclopropanes generated diadamantylsilylene, which was then trapped with *cis*- and *trans*-2-butene and -3-hexene. The complete stereospecificity of silacyclopropane decomposition and silylene-alkene addition suggests an intermediate silylene in a singlet ground state (Equations (43) and (44)) <91JA1281>.



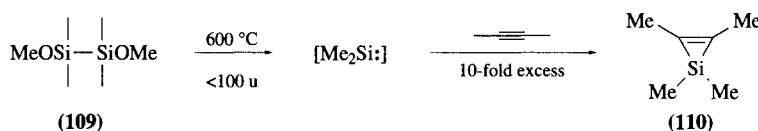
1.09.6.2 Silacyclopropenes

1.09.6.2.1 Ring formation by [2 + 1] cycloaddition

The most common way to prepare silacyclopropenes is by [2 + 1] cycloaddition of silylenes to alkynes. The silylenes can be prepared thermally, photochemically, or by metal reduction.

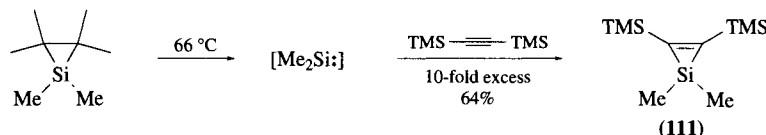
(i) Silylenes by thermolysis

Tetramethylsilacyclopropene (**110**) was prepared by flash thermolysis of disilane (**109**) in the presence of a 10-fold excess of 2-butyne. The product was detected spectroscopically and its methanolysis product isolated (Scheme 39) <76JA3715>.



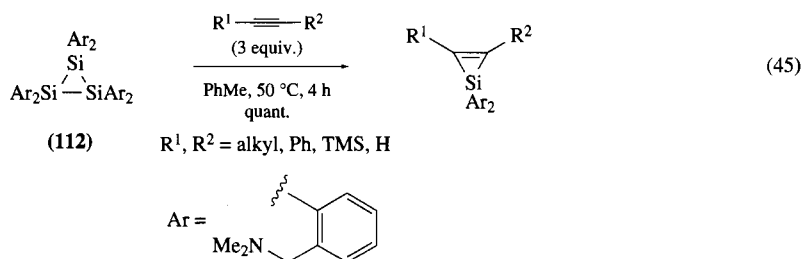
Scheme 39

The first isolated silacyclopropene (**111**) was prepared by thermolysis of hexamethylsilacyclopropane in the presence of bis(trimethylsilyl)ethyne. The product proved to be thermally stable with a half-life of ca. 60 h at 70 °C, (Scheme 40) <76JA6382, 84JOM(272)123>.



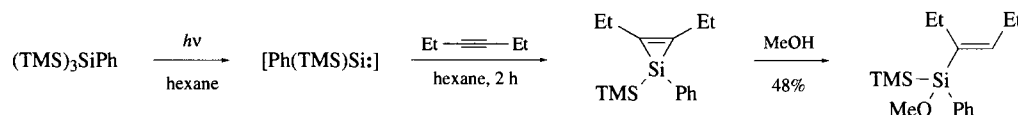
Scheme 40

Thermolysis of cyclotrisilane (**112**) generated an intermediate diarylsilylene, which added to alkynes to give silacyclopropenes in quantitative yield (five examples). This method allows for the preparation of rings with hydrogen at the vinylic carbon (Equation (45)) <93TL6541>.



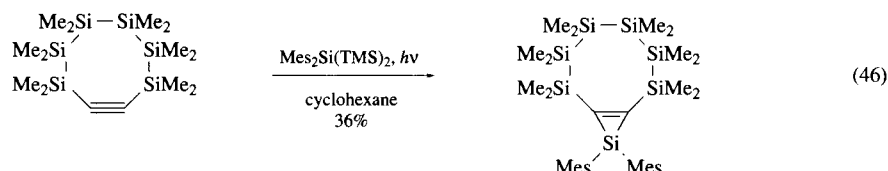
(ii) Silylenes by photolysis

Irradiation of tris(trimethylsilyl)phenylsilane in the presence of alkynes gave silacyclopropenes in moderate yield, which were characterized as their methanolysis products (four examples) (Scheme 41) <77JOM(131)C15>.

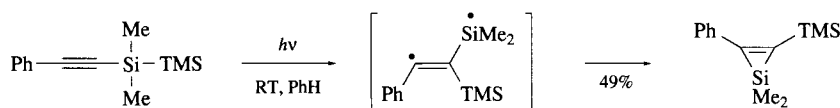


Scheme 41

Photolysis of 2,2-dimesitylhexamethyltrisilane in the presence of hexasilacyclooctyne gave heptasilabicyclo[6.1.0]non-1(8)-ene in 36% yield (Equation (46)) <93OM803>.

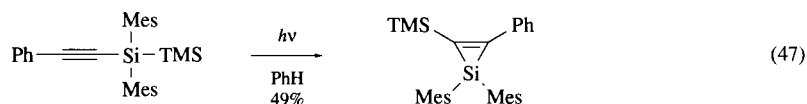


Photolysis of phenylethynylpentamethyldisilane in the absence of a quenching agent gave 1,1-dimethyl-2-phenyl-3-trimethylsilyl-1-silacyclopriene as the major product in 49% yield. Based on molecular orbital calculations and emission spectra, the mechanism of this transformation was thought to involve formation of an intermediate singlet diradical (Scheme 42) <82JA2872, 83OM174>.



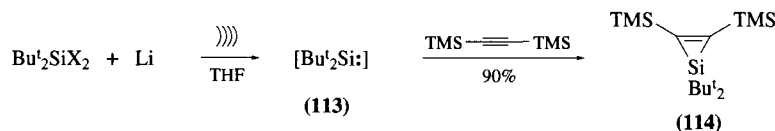
Scheme 42

1,1-Dimesitylsilacycloprienes are stable to atmospheric oxygen, moisture, or alcohol at room temperature, and can be prepared by photolysis of 1,1-dimesitylalkynyldisilanes. Previously reported silacycloprienes were extremely unstable under these conditions (Equation (47)) <80JOM(194)147>.



(iii) Silylenes by reduction of dihalosilanes

Treatment of di-*t*-butyldichlorosilane with lithium in THF generated silanediyl (**113**), which was trapped with bis(trimethylsilyl)ethyne to give silacyclopriene (**114**) in excellent yield (Scheme 43) <88AG(E)1355>.

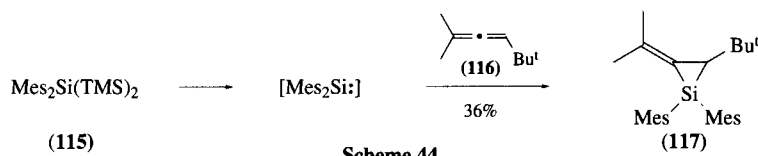


Scheme 43

1.09.6.3 Alkylidene Silacycloprienes

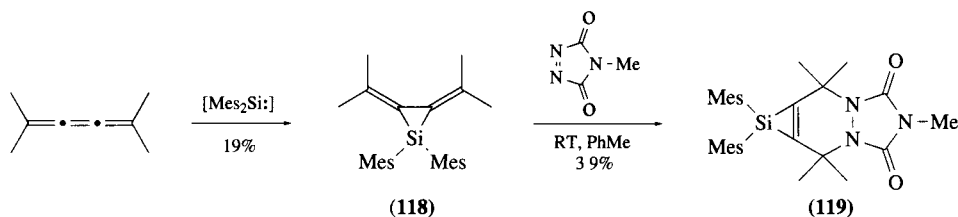
The first alkylidenesilacyclopriene (**117**) was prepared in low yield via photolysis of trisilane (**115**) in the presence of excess sterically hindered allene (**116**) (Scheme 44). This highly hindered alkylidenesilacyclopriene was thermally stable and inert to methanol <86TL5625>.

The first bis(alkylidene)silacyclopriene (**118**) was prepared in similar fashion by reaction of dimesitylsilylene with tetramethylbutatriene. X-ray analysis of the product showed that the diene moiety was almost planar and the termini close enough to engage in cycloaddition reactions. This



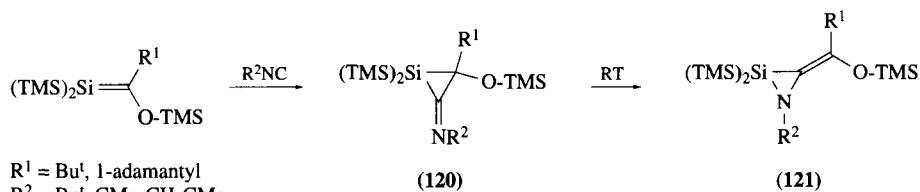
Scheme 44

was confirmed by subsequent Diels–Alder reaction with 4-methyl-1,2,4-triazoline-3,5-dione to give a ring-fused silacyclopene (119) (Scheme 45) <93OM1996>.



Scheme 45

Silaaziridenes, the first known three-membered rings containing both silicon and nitrogen, were prepared by reaction of stable silenes with isonitriles (four examples). The mechanism of this reaction is thought to involve initial formation of a silacyclopropanimine (120), followed by rapid isomerization to the isomeric silaaziridine (121) (Scheme 46) <88OM2245>.

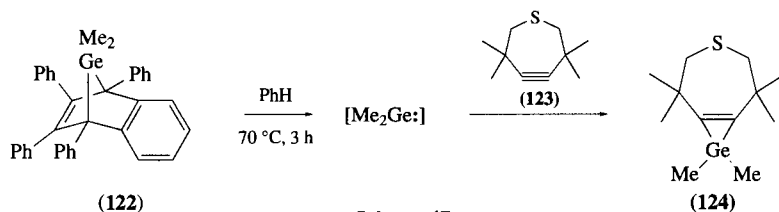


Scheme 46

1.09.7 SYNTHESIS OF THREE-MEMBERED RINGS WITH ONE GERMANIUM, TIN, OR LEAD ATOM

1.09.7.1 Ring Formation by [2 + 1] Cycloaddition

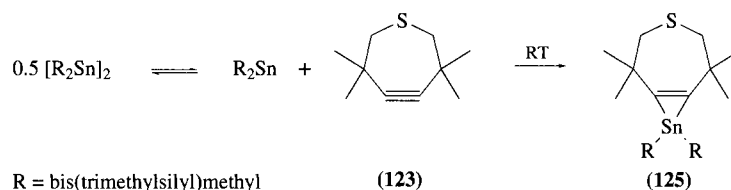
Germacyclopene (124) was prepared in quantitative yield by reaction of germanorbornadiene (122) with thioalkyne (123) in benzene at 70°C. The product was isolated in a pure crystal form by sublimation in vacuum, and its structure determined by x-ray diffraction (Scheme 47) <83TL4083, 85JOM(290)C27, 90MI 109-01>.



Scheme 47

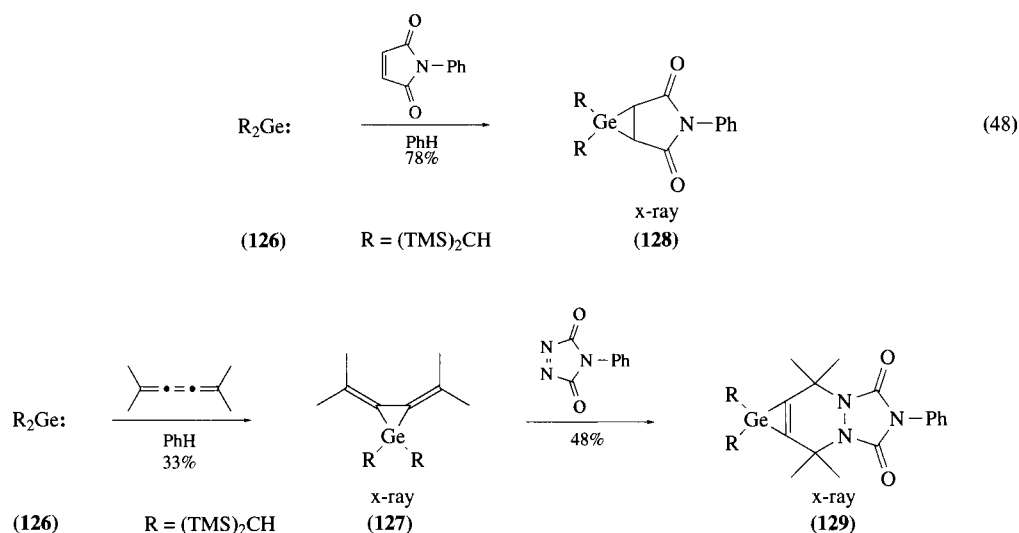
The first stannacyclopene (125) was obtained by reaction of bis[bis(trimethylsilyl)]methylstannylene with thioalkyne (123) in methylcyclohexane at room temperature (Scheme 48). The

product was purified by recrystallization from methylcyclohexane at -40°C , and its structure determined by x-ray crystallography <88JA5208>.



Scheme 48

The first two germacyclopropanes to be isolated and characterized were prepared by reaction of stable germylene (**126**) with tetramethylbutatriene and *N*-phenylmaleimide in benzene. Thus, treatment of tetramethylbutatriene with (**126**) gave bis-alkydenegermacyclopropane (**127**) in 33% yield, whereas reaction of (**126**) with *N*-phenylmaleimide gave bicyclic germacyclopropane (**128**) in 78% yield (Scheme 49 and Equation (48)). In addition, bis-alkydenegermacyclopropane (**127**) underwent [4 + 2] cycloaddition with 1,2,4-triazoline-3,5-dione to give tricyclic germacyclopropane (**129**) in 48% yield. The structures of (**127**), (**128**), and (**129**) were confirmed by x-ray crystallography <94AG(E)659>.



Scheme 49

1.10

Three-membered Rings with One Boron Atom

IRINA V. SHCHERBAKOVA

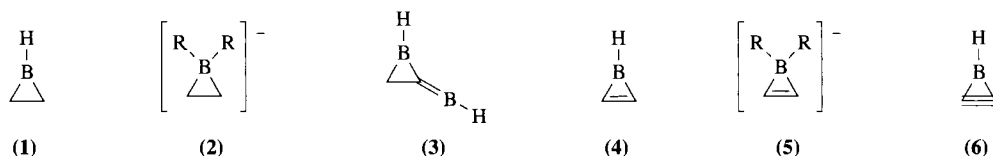
*Institute of Physical and Organic Chemistry, Rostov on Don,
Russia*

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1.10.1 INTRODUCTION

The small ring boron compounds with one boron as heteroatom represent an excellent example of the state-of-the-art chemistry where theoretical calculations preceded and guided the subsequent experimental investigations. The concept of three-membered heteroaromatic compounds was broached by Vol'pin *et al.* (60RCR129, 62T107), and the potential aromaticity of borirene was first mentioned. No three-membered boron-containing heterocycles were known at that time. The authors suggested the synthetic route to borirenes by addition of a borene, also called borylene (62T107, 79JOM(171)141) or boryne (77JA3182), a carbene analogue, to alkynes; a similar approach might be used in the synthesis of boriranes by addition of a borene to alkenes. However, all attempts to isolate three-membered boron heterocycles thus failed, and only the indirect evidence of their formation was discussed (cf. Section 1.10.9.2.2). The intensive systematic theoretical investigations to predict geometry, thermodynamic stability, and reactivity of the three-membered boron heterocycles among other small rings were started in the early 1980s by von Schleyer and co-workers; the first syntheses of borirenes and boriranes were reported a few years later. The intention of this chapter is to summarize the research on three-membered heterocycles with one boron atom reported since the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). There, only some calculations on geometry and aromaticity of borirene and a few unsuccessful attempts of the borirene synthesis were briefly mentioned (84CHEC-I(1)629).

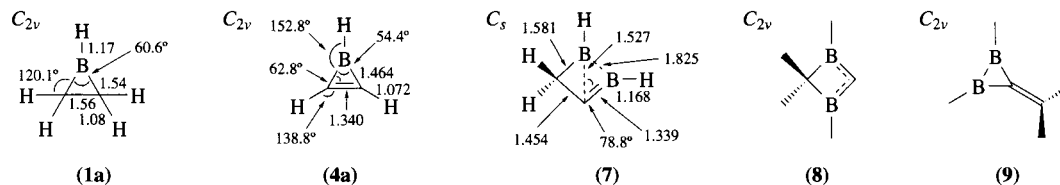
Three-membered rings with one boron atom are classified under two categories, and the use of an appropriate suffix indicates a saturation in the heterocyclic ring: (i) saturated derivatives of borirane (1), boratirane (2), and borirane-2-ylidene borane (3); and (ii) unsaturated derivatives of 1*H*-borirene (4), boratirene (5), and 1*H*-boriryne (6). The latter heterocycle was studied only theoretically and is treated in the corresponding section. The stabilities and overall profiles of chemical reactivity of these heterocycles are attributable to the combined effects of the nature of the boron atom, bond shortening, angle compression, and the substituents at the ring; the predicted heteroaromatic character of borirene (4) is evidenced experimentally.



1.10.2 THEORETICAL METHODS

The INDO calculations (74JOC373) and *ab initio* study (81JA2589) indicated that borirene (4) has a large resonance energy, 70% of that of the isoelectronic cyclopropenyl cation. The aromaticity criterion as a relation between magnetic ring current and the weakest bond was studied by SINDO-1 and confirmed a high aromaticity of borirene (4) (84JOC4475). Geometry of (4) was reported by semiempirical calculations (74JOC373) and by *ab initio* method at the Hartree-Fock levels using various basis sets, 4-31G, 3-21G, 6-31G*, and 6-31G** (85JA2773, 85OM429, 91JA3689); the levels produce minor changes in geometry, although the use of a polarization basis is essential for quantitative energy estimations (85OM429). The latest *ab initio* geometry calculations, ring bond lengths and angles, confirmed aromaticity of the strained planar (4); the boron *p*-orbital is occupied by 0.34 electron and the π bond orders are 0.59 and 0.83 for the C—B and C—C bonds, respectively (91JA3689). Geometry of borirane (1) was determined by a semiempirical INDO program and systematically refined via *ab initio* STO-3G and then 3-21G basis sets (85OM429, 86JOM(317)1). Relative and absolute energies for borirane and some of its ring-opened isomers, studied at HF/6-31G* and 6-31G** basis sets, revealed (1) as a true minimum on the C_2H_5B energy surface (86JOM(317)1, 91JA2466, 92MI 110-01). The Hessian matrix of the 3-21G optimized geometry of boriryne (6) showed one negative eigenvalue indicating that boriryne is a transition state and not a minimum at this level of theory (84CPL529). *Ab initio* study of effects of substituents was reported by von Schleyer and co-workers both for borirane (1a) and borirene (4a) systems (85JA2773, 85OM429, 91JA2466, 92MI 110-01). The first synthesis of a substituted borirane-2-ylidene borane (83AG(E)877) generated an intensive theoretical study of this system. Independently, Frenking and Schaefer (84CPL521), and von Schleyer and co-workers (84AG(E)825, 85JA2773) showed a preferable existence of (3) as a four-membered coordinated cycle (7) among other possible structures (3), (8), and (9).

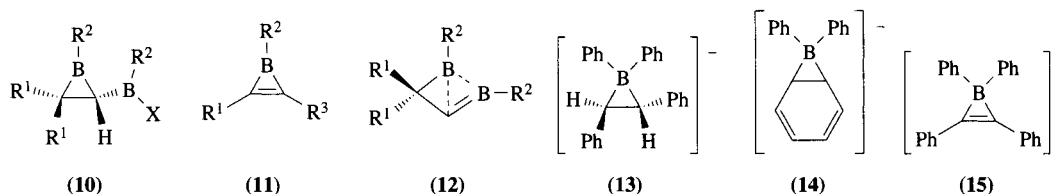
Those results were confirmed by x-ray diffraction data $\langle 84\text{AG(E)372, } 90\text{AG(E)398} \rangle$ (cf. Section 1.10.3.1). Such a strong hyperconjugation in neutral (3) is due to an interaction of a strained three-membered ring and atoms of low negativity. It was shown that a carbene structure (8) is on the pathway of topomerization of (3) $\langle 85\text{JA2773} \rangle$ (cf. Section 1.10.6.3).



1.10.3 EXPERIMENTAL STRUCTURAL METHODS

1.10.3.1 X-ray Diffraction

The representatives of all known heterocycles (1)–(5) have been investigated by a single x-ray diffraction method. Standard bond lengths were suggested from *ab initio* calculations to be: B—C (tricoordinate) 1.54 Å and B—C (tetra-coordinate) 1.57 Å $\langle 75\text{JA3402} \rangle$. The unsymmetrical borane (10) was found to have the following endocyclic bond lengths: B—C(1) 1.500 Å, B—C(2) 1.539 Å and C(1)—C(2) 1.636 Å $\langle 92\text{AG(E)1384} \rangle$. In symmetrical borirene (11; $R^1 = R^2 = R^3 = 2,3,4,5$ -tetramethylphenyl), the three-atom ring formed an equilateral triangle with all bond distances at 1.42 Å and bond angles at 60° $\langle 87\text{JA2526} \rangle$, whereas unsymmetrical (11) had separations of 1.44–1.45 Å and 1.46–1.52 Å for the C—B ring bonds, and the C—C ring bond fell in the region of 1.37–1.38 Å; the B—C—C and C—B—C ring angles had the values of 62–65° and 54–56°, respectively $\langle 90\text{JA1847} \rangle$. The data obtained strongly supports the conclusion that the two π -electrons in the borirene ring are completely delocalized (cf. Section 1.10.2). The theoretically predicted bridged structure (7) has been confirmed for (12) $\langle 90\text{AG(E)398} \rangle$, and the results were in good agreement with calculations (cf. Section 1.10.2). The data obtained for (10)–(12) illustrate the reliability of the results of high level *ab initio* calculations for such system types. Tetraphenylboratirene (13) $\langle 88\text{JA6252} \rangle$ and boratanocaradiene (14) $\langle 88\text{JA7569, } 91\text{JA2149} \rangle$ had the boron-containing ring as an equilateral triangle with the B—C and C—C ring bond distances of 1.61 and 1.49, and 1.60 and 1.58 Å, respectively. The B—C—C and C—B—C ring angles had the values of 55° and 62°, and 60° and 58°, respectively. In the ring of tetraphenylboratirene (15) $\langle 89\text{JA2316, } 91\text{JA2155} \rangle$, the C—B—C bond angle was 50.6°, and the two C—C—B bond angles had different values of 65.4° and 64.0°; the two C—B bond lengths had the values of 1.578 and 1.597 Å.



1.10.3.2 UV Spectroscopy

Ab initio calculations predicted borirenes to be optically transparent in ordinary solutions, and only a weak long wavelength band could be expected due to σ – π^* transactions $\langle 75\text{JA752} \rangle$. As expected, only aryl-substituted borirenes displayed a maximum in the UV absorption spectra at about 300 nm, whereas other substituted borirenes were transparent. Heterocycles with tetra-coordinated boron atom and phenyl substituents in the ring displayed the bands at 280 nm ($\epsilon = 18000$) for (13) $\langle 88\text{JA6252} \rangle$, 269 ($\epsilon = 21500$), 350 ($\epsilon = 4500$) and 450 nm ($\epsilon = 600$) for (15) $\langle 91\text{JA2155} \rangle$, and 294 ($\epsilon = 19000$) and 510 nm ($\epsilon = 2700$) for (14) $\langle 88\text{JA7569} \rangle$. The strong band for (14) in the visible region is due to interaction of the strained three-membered borane ring with the diene chromophore, whereas π -electron transitions are responsible for the other bands for (13)–(15).

1.10.3.3 IR Spectroscopy

Vibrational frequencies for (1) have been calculated *ab initio* <86JOM(317)1>; no experimental data have been reported up to 1995. Stretching vibrations for (12) were found at about 1675 cm^{-1} ($^{11}\text{B}=\text{C}$) and 1715 cm^{-1} ($^{10}\text{B}=\text{C}$) with the intensity ratio of 4:1 <83AG(E)877>, whereas the calculated values were about 1798 cm^{-1} <84CPL521>; the stretching vibrations for (11) fall in the region $1620\text{--}1705\text{ cm}^{-1}$ <84AG(E)313, 84CB2531>.

1.10.3.4 NMR Spectroscopy

Proton NMR spectral data for (10) <92AG(E)1384>, (11) <84AG(E)313, 84CB2531, 89AG(E)186, 90JA1847>, (12) <83AG(E)877, 90AG(E)398>, (13) <88JA6252>, (14) <88JA7569, 91JA2149>, and (15) <89JA2316, 91JA2155> have been applied to the general problems of structure elucidation, whereas ^{13}C and ^{11}B NMR spectroscopy are of the most importance for the ring description. The boron isotopes, ^{10}B and ^{11}B , are both NMR active, and the latter isotope has an abundance of 80% that makes it the most useful in the spectral measurements. The chemical shifts of ^{11}B in the ring fall in the region $\delta\ 70\text{--}73$ (10) (calculated $\delta\ 93.4$ for 1-methylborane <91JA2466>), $27\text{--}49$ (11), $34\text{--}52$ (12), -9.4 (13), -26.6 (14) and -16.1 (15). The wide range of values for (11) and (12) is caused by a variety of the substituents at the ring. The shielding of the ^{11}B signal for (11) compared to (10) confirmed the aromaticity of borirene; the deshielding of the same signal for (14) is due to interaction of the strained three-membered ring with the diene fragment. Carbon-13 NMR chemical ring shifts have been reported in the region $\delta\ 33\text{--}39$ (B_2C , $^1J(^{13}\text{C},\text{H}) = 140\text{ Hz}$; calculated 170 Hz <87JMR(71)229>) (10), $150\text{--}215$ (11), $25\text{--}31$ (C) and $115\text{--}126$ ($\text{C}=\text{B}$) (12), $37\text{--}38$ (13) and (14), and $150\text{--}161$ (15). The spectra of (13)–(15) revealed the carbon multiplets strongly coupled to the boron atom.

1.10.3.5 Mass Spectrometry

In the structural determination of compounds (10)–(12), mass spectral data have frequently been used. In all cases, the molecular peak was accompanied with the isotope peaks, and the fragmentation could be interpreted similarly to the carbon analogues.

1.10.4 THERMODYNAMIC ASPECTS

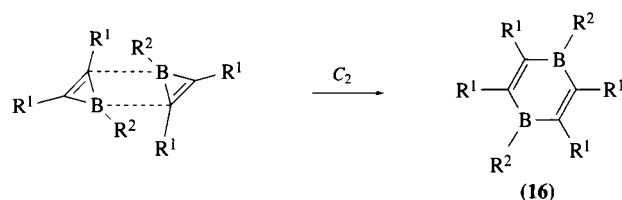
Borirane (1) was found to be a true minimum on the $\text{C}_2\text{H}_3\text{B}$ energy surface (cf. Section 1.10.2). Any distortion towards one of its probable interconversion products increases the energy of (1) by at least 8 kcal mol^{-1} <86JOM(317)1>. This is in contrast to the isoelectronic cyclopropyl cation, which opens spontaneously through the disrotatory motion of its methylene hydrogen atoms. Earlier, the borirane system was reported to have a high strain energy, ca. 16 kcal mol^{-1} higher than that of cyclopropane, and was described as a less stable system than vinylborane <85OM429>. The synthesis of boriranes showed that the system is thermodynamically stable. Borirene (4) shows a large resonance energy of about 47 kcal mol^{-1} ; this compensates for the strain of the small ring system, and substituted borirenes were expected to be chemically stable <85OM429>. This prediction was confirmed by synthesis of substituted borirenes. The nonclassical four-membered structure (7) is the local minimum for borirane-2-ylidene borane (3) and thus determines the great flexibility of the molecular skeleton <84AG(E)825, 85JA2773> (cf. Sections 1.10.2, 1.10.3.1, and 1.10.11).

1.10.5 REACTIVITY OF BORIRENES AS FULLY CONJUGATED RINGS

1.10.5.1 Dimerization

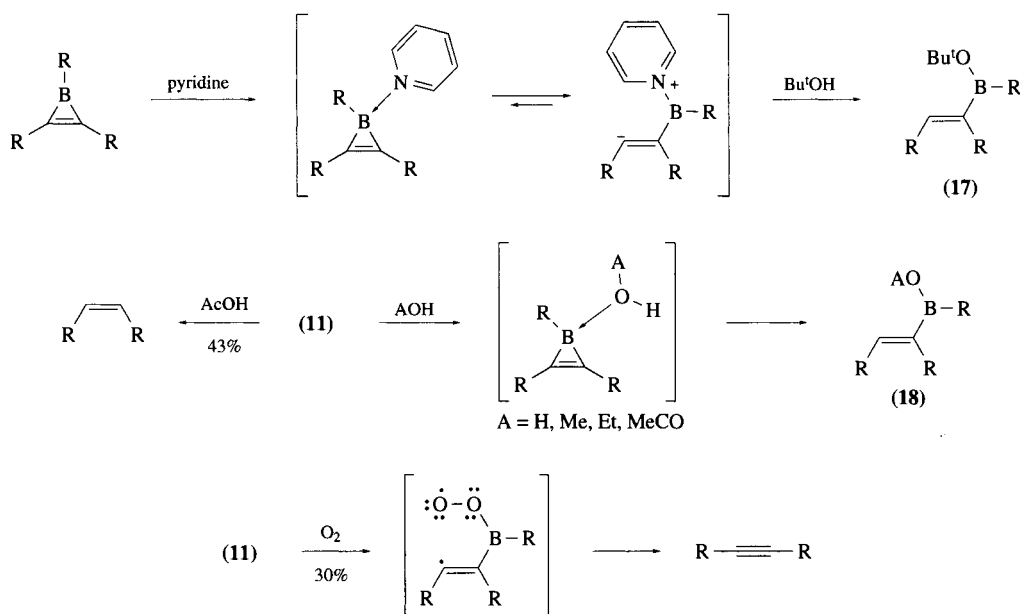
The 1*H*-borirene dimers, 1,4-diboracyclohexa-2,5-dienes (16), were first isolated on addition of a generated borene to alkynes and reported as the evidence of a borirene formation <67JA1629, 67JOM(8)53, 68JA4585>. The theoretical study of the mechanism of borirene dimerization both by semiempirical and *ab initio* methods revealed that the activation energy calculated for C_2 symmetry path to (16; $\text{R}^1 = \text{R}^2 = \text{H}$) is only 11 kcal mol^{-1} <86JA3960>. This indicates that borirenes would

easily dimerize unless π -donor groups at boron atom or bulky substituents are present at the ring (cf. Section 1.10.9.2.2). As was shown later, (11; $R^1 = R^2 = R^3 = 2,4,6$ -trimethylphenyl) for instance, remained unchanged on heating up to 250°C or on irradiation in a toluene solution for 48 h at 300 nm <90JA1847>.



1.10.5.2 Nucleophilic Reactions

The electron deficiency of the 1*H*-borirene ring caused by the available p -orbital on the sp^2 -hybridized boron atom results in reactions with electron excessive molecules by an attack at the boron atom. When the tricoordinate boron atom of the borirene ring became tetracoordinate by ligation with pyridine or a sterically suitable alcohol, the borirene ring was ruptured and, in the presence of a proton source, irreversibly converted at room temperature into the acyclic boronic esters (17) and (18), or on heating with acetic acid, into alkene. Prolonged treatment of a solution of (11) in toluene with dry oxygen converted about one third of borirene into alkyne by a suggested radical mechanism (Scheme 1). This transformation was accompanied by a formation of a small amount of 1,3-dioxa-2-borole indicated by mass spectrometry <90JA1847>.



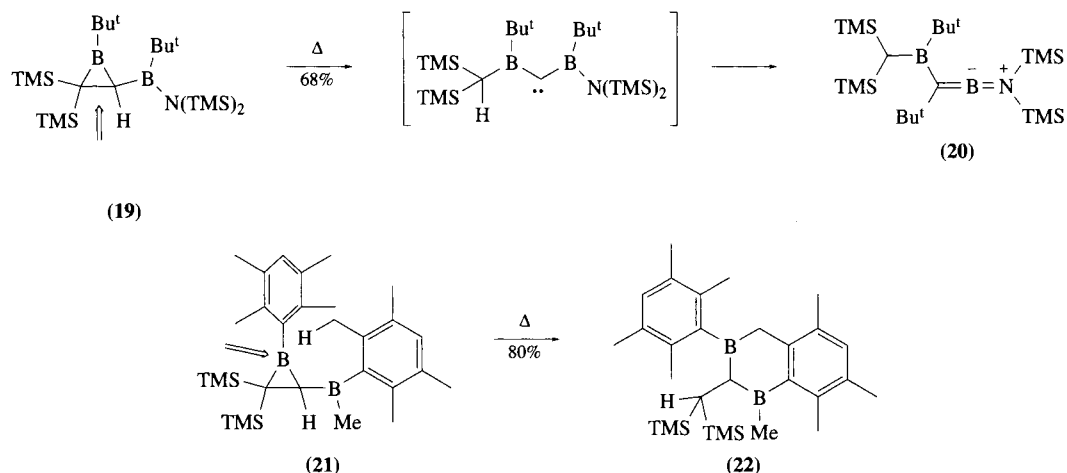
Scheme 1

1.10.6 REACTIVITY OF BORIRANES AND BORIRANE-2-YLIDENE BORANES AS NONCONJUGATED RINGS

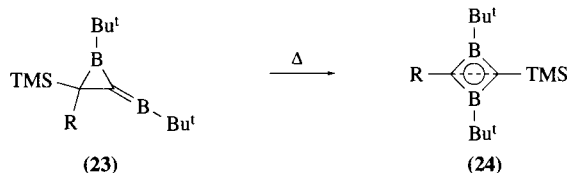
1.10.6.1 Thermal Reactions

Thermolysis of boriranes results in the cleavage of a C—B or a C—C ring bond depending upon the substituents. Thus, on heating in chloroform for 48 h, borirane (19) yields borylaminomethyl-

eneborane (**20**). The mechanism of this transformation could possibly include the formation of diborylcarbene followed by 1,2-Bu^t shift. Cleavage of the borirane C—B bond occurred on thermolysis of a sterically crowded compound (**21**) <92AG(E)1384>. Tetrahydrodiboranaphthalene (**22**) thus formed is the result of a C—H bond addition of an *ortho*-methyl of the chain aryl substituent at the endocyclic boron atom.



According to *ab initio* calculations, 1,3-dihydro-1,3-diboretes (**24**) are the derivatives of the lowest energy C₂B₂H₄ system <81JA2589>. This theoretical result was confirmed by a smooth isomerization of (**23**) into (**24**) on heating at 170°C <84AG(E)372>.



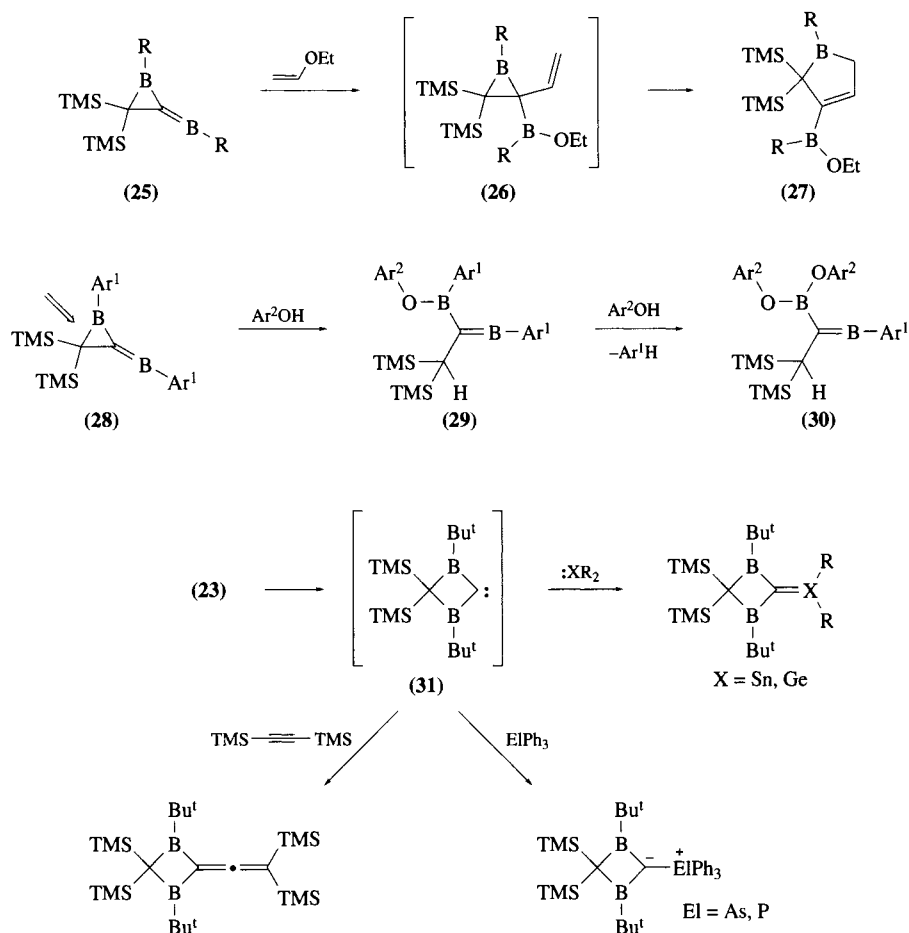
1.10.6.2 Nucleophilic Reactions

There is no data in the literature on reactions of a few known boriranes with electron excessive molecules. Cleavage of the cyclic C—B bond occurred during the reaction of (**25**) with ethyl vinyl ether even at room temperature <92AG(E)1384>. The vinylboranes (**26**) were suggested as possible intermediates followed by formation of 2,6-dihydroboroles (**27**). Borirane-2-ylidene boranes (**28**) formed the ring-opened boronic esters (**29**) similarly to 1*H*-borirenes (cf. Section 1.10.5.2), and further nucleophilic substitution at the ex-endocyclic boron atom gave rise to diesters (**30**) <92ZN(B)983>.

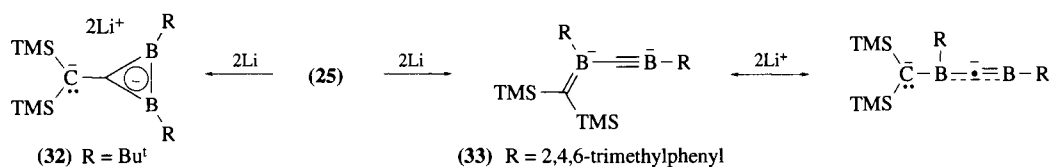
1.10.6.3 Reactions Involving Rearrangements

From the coalescence temperatures for ¹H, ¹³C, and ¹¹B NMR chemical shifts and the accompanying shift differences, topomerization of (**23**; R = TMS) was found to have an energy barrier of 11.4 kcal mol⁻¹ <83AG(E)877>, and the energy calculations showed nonclassical (**7**) and carbene (**8**) structures are on the lowest energy pathway <84AG(E)825> (cf. Section 1.10.2). Theoretically predicted intermediate carbene (**31**) <85JA2773> was confirmed experimentally in reactions of (**23**; R = TMS) with alkyne, or with carbene trapping reagents <84AG(E)826, 87AG(E)546, 87AG(E)798>.

The existence of borirane-2-ylidene boranes as a nonclassical structure (**7**) leads to the formation of two types of dianions, (**32**) and (**33**), on reduction of (**25**) with lithium <88AG(E)960, 88ZN(B)801>.



The formation of (33) could proceed via the cyclic dianion of type (32) followed by a C—B ring bond cleavage caused by the bulky substituents at the ring.



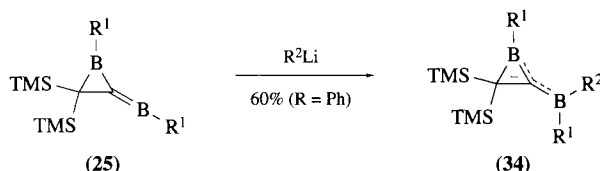
Thermal rearrangement of 2,5,7,7-tetraphenyl-7-borabicyclo[4.1.0]hepta-2,4-diene via suggested electrocyclic ring opening resulted in the inversion of the three-membered boron cycle <91JA2149>.

1.10.7 REACTIVITY OF BORATIRENES AND BORATIRANES

On reduction with diimide, 1,1,2,3-tetraphenylboratirene gave *trans*-1,1,2,3-tetraphenylboratirane (cf. Section 1.10.9.3), whereas hydrogenation with Lindlar's catalyst initiated reductive cleavage of the three-membered ring to give acyclic borohydrides <91JA2155>. Ring cleavage was also reported on reaction of the same boratirene with some electrophiles: pyridine hydrochloride, dimethyl sulfate and methyl iodide gave rise to *cis*- and/or *trans*-stilbenes as the major products; oxidation of boratirene yielded 2,4,5-triphenyl-1,3-dioxo-2-borole <89JA2316>. *trans*-1,1,2,3-Tetraphenylboratirane was oxidized by oxygen to give 2,4,5-triphenyl-1,3-dioxo-2-borolane and *trans*-stilbene in 45% and 5% yield, respectively <88JA6252>. Photolysis of 2,5,7,7-tetraphenyl-7-borabicyclo[4.1.0]hepta-2,4-diene solutions in THF or acetonitrile in the absence of oxygen led to the formation of *p*-terphenyl in 85–95% yield <90JOC4537>.

1.10.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

The addition of HX at the C=B double bond of borirane-2-ylidene boranes yielded boranes $\langle 92\text{AG(E)}1384 \rangle$ (cf. Section 1.10.9.4), and 1,2-cycloaddition of acetone or alkynes was reported to give 1,2-oxaboretane $\langle 83\text{AG(E)}877 \rangle$ or 2-boretanes, respectively $\langle 83\text{AG(E)}877, 84\text{AG(E)}369 \rangle$. The formation of 1,3-diboraallyl anions (**34**) occurred on addition of R^2Li to (**25**) $\langle 92\text{AG(E)}1238 \rangle$. Thermolysis of (**34**) led to homodiboranides, the simplest charged homoaromatic compounds.

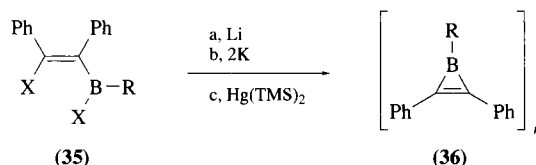


1,2-Di-*t*-butyl-3-(1-chloro-1-*t*-butylboryl)borirane and (**25**; $\text{R}^1 = \text{Bu}^t$) formed the stable Lewis adducts with pyridines at the exocyclic boron atom $\langle 84\text{AG(E)}313, 88\text{AG(E)}960 \rangle$.

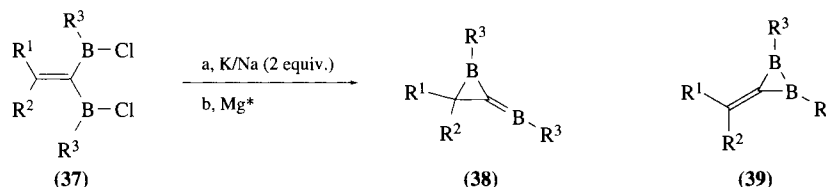
1.10.9 SYNTHESIS OF THREE-MEMBERED HETEROCYCLES WITH ONE BORON ATOM

1.10.9.1 From Acyclic Compounds by Formation of One Bond to a Boron Atom

Eisch *et al.* have attempted to synthesize borirenes on reductive ring closure of the haloboration products of diphenylacetylene (**35**) $\langle 67\text{JOM}(8)53, 79\text{JOM}(171)141 \rangle$. The authors failed to isolate borirenes, and their occurrence was inferred from the dimerization products (**36**; $n = 2$), or from the products of deuteration (cf. Section 1.10.9.2.2).



Berndt and co-workers reported the first isolated three-membered boron containing heterocycle, borirane-2-ylidene borane (**38**), obtained on reaction of 1,1-bis(chloroboryl)ethenes (**37**) with two equivalents of K/Na alloy $\langle 83\text{AG(E)}877, 84\text{AG(E)}372 \rangle$. The formation of (**38**), and not of the alternative (**39**) followed from ^1H , ^{13}C , and ^{11}B NMR spectral data (cf. Section 1.10.3.2). Bogdanovic magnesium as a reductive agent was also used in synthesis of (**38**) $\langle 90\text{AG(E)}398 \rangle$.

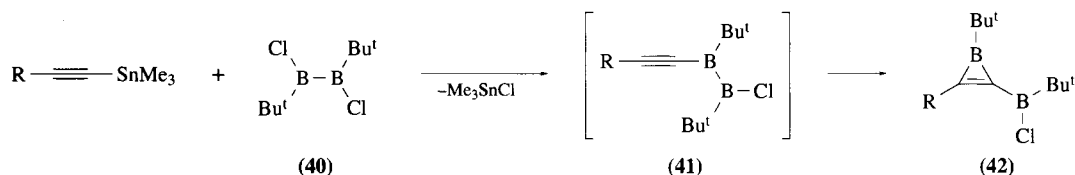


1.10.9.2 Formation of Two C—B Bonds

1.10.9.2.1 Displacement reactions

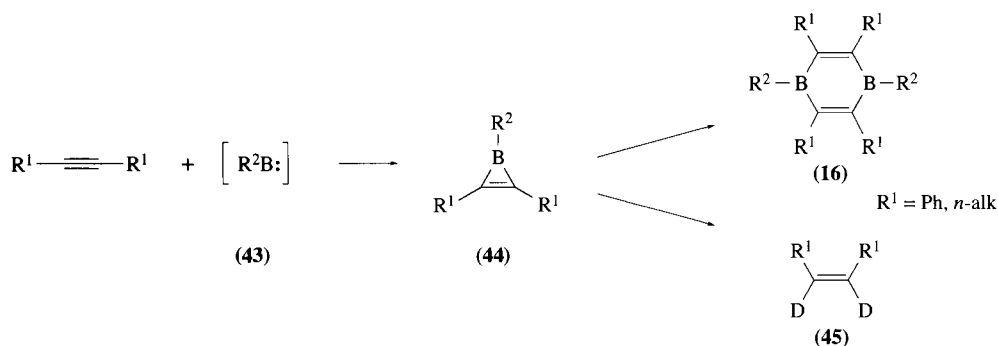
Borirenes (**42**) were obtained by Berndt and co-workers on reaction of trimethylstannylalkynes with 1,2-di-*t*-1,2-dichlorodiborane (**40**) $\langle 84\text{AG(E)}313, 89\text{AG(E)}186 \rangle$. The intermediate (**41**) is trans-

formed into borirene via a strong p_{σ} - p_{π} interaction within a $\text{C}\equiv\text{C}-\text{B}$ fragment where the boron atom is an active p_{σ} component. This reaction is an example of a step-by-step formation of two $\text{C}-\text{B}$ bonds first by displacement and then by addition reaction.



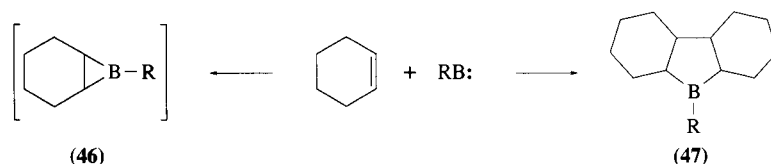
1.10.9.2.2 Addition reactions

A possible synthesis of borirenes by addition of a borene (**43**) to alkynes was first suggested by Vol'pin *et al.* in 1962 <62I107>. In the years following, a few attempts were made both to generate borenes and to obtain borirenes <67JA1629, 67JOM(8)53, 73ACR118, 79JOM(17)141, 83AG(E)48, 84AG(E)454, 84POL271, 89JOC1627>, but until 1983 only 1,4-diboro-2,5-cyclohexadienes (**16**), the formal dimers of borirene, and/or the products of deuterolysis (**45**) were isolated.

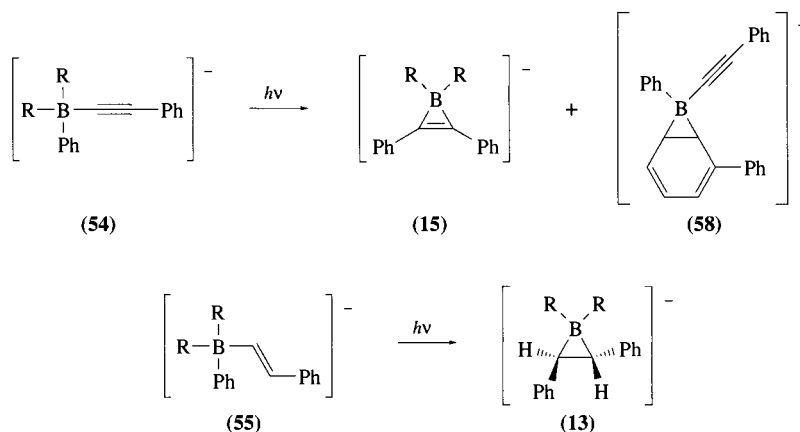


It has been suggested by von Schleyer in collaboration with van der Kerk *et al.* that dimerization of borirenes may be avoided by introduction of bulky substituents into the ring $\langle 83\text{AG(E)48} \rangle$. Another approach by the same authors to stable borirenes suggested the use of alkynes with electron-donating groups, which offer better chances of trapping a borene than diphenylethyne since borenes are expected to have an even more electrophilic character than carbenes $\langle 84\text{POL271} \rangle$. Van der Kerk *et al.* isolated borirene (**44**; $\text{R}^1 = \text{R}^2 = \text{Bu}^t$) along with 1,3-diboretene by addition reaction of borene-generating system, $2\text{C}_8\text{K/R}^2\text{BBr}_2$, to di-*t*-butylalkyne $\langle 83\text{AG(E)48, 84POL271} \rangle$, and Pachaly and West reported the photochemical generation of (**43**; $\text{R}^2 = \text{Ph}_3\text{Si}$) and its reaction with di(trimethylsilyl)ethyne yielding a stable borirene derivative $\langle 84\text{AG(E)454} \rangle$.

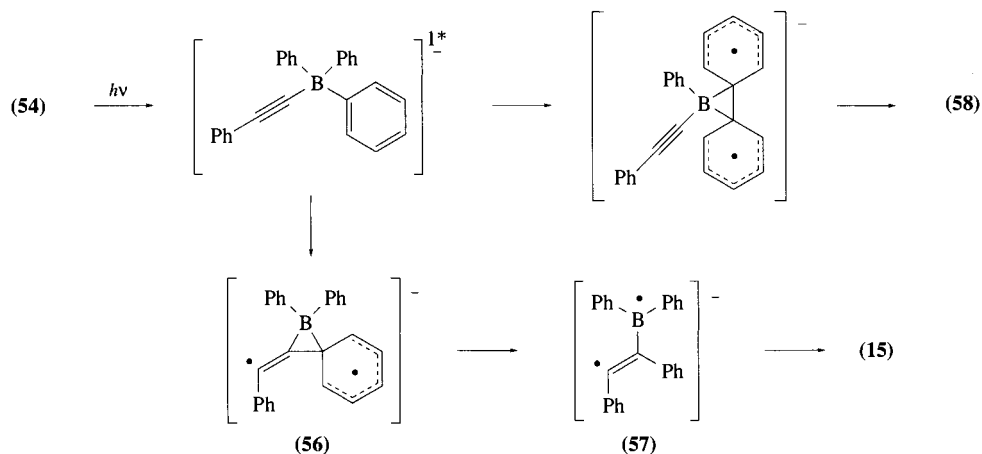
The addition of borylenes to cyclohexene was reported to give reactive boranes (**46**) [76TL4765, 77JA3182], but reinvestigation of this reaction proved the formation of boratricyclic derivative (**47**; **R** = **Me**) [83POL1337].



The study in 1993 of a pulsed laser evaporated boron reaction with ethyne in argon matrix discovered the formation of the borirene radical BC_2H_2 (**48**) among other cyclic and linear products (Equation (1)) ^[93JA2510, 93JPC5839]. The reaction was monitored by matrix IR spectra, and the radical (**49**) is photosensitive and forms spontaneously on annealing above 18 K. The excellent

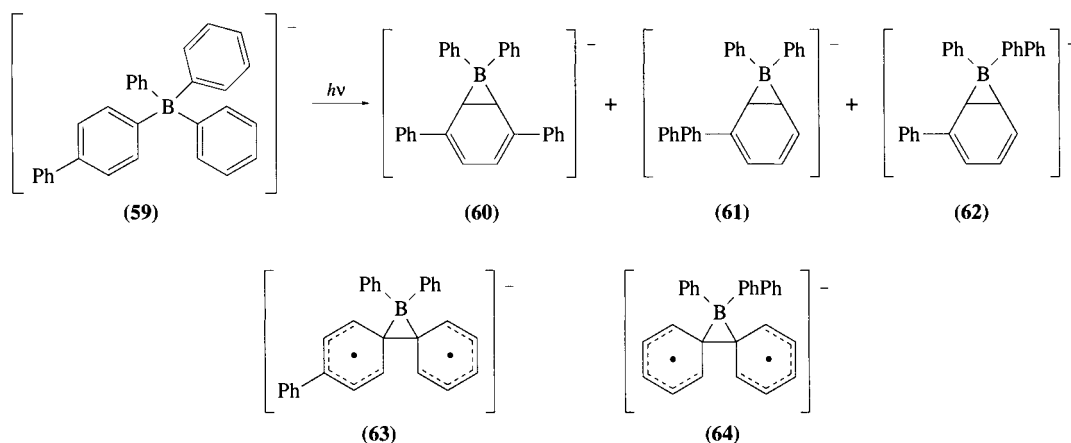


Scheme 2



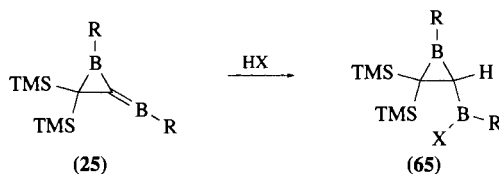
Scheme 3

free solutions ^{<87JOC2117>}. Photolysis of (*p*-biphenyl)triphenylborate (**59**) resulted in the isolated isomeric boratanocaradienes (**60**)–(**62**) ^{<88JA7569, 91JA2149>}. The formation of three isomers in this case is in agreement with the reference to the di- π -methane rearrangement: two intermediate biradicals, (**63**) and (**64**), are the subject of the C–B bond cleavage followed by the postulated [1,5] sigmatropic shifts to give (**60**) and (**61**), and (**62**), respectively. The authors noted that the mechanism outlined cannot be distinguished from one where [1,2] sigmatropic shifts from the excited state of borate (**59**) give borates (**60**)–(**62**) directly.



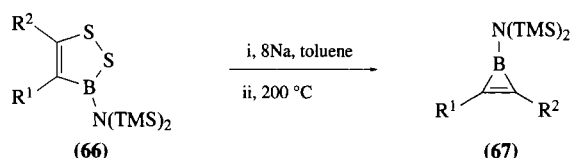
1.10.9.4 Miscellaneous

The addition of HX (X = Cl, (TMS)₂N) at the C=B double bond of borirane-2-ylidene boranes (**25**) resulted in the first synthesis of boriranes (**65**) <92AG(E)1384>.

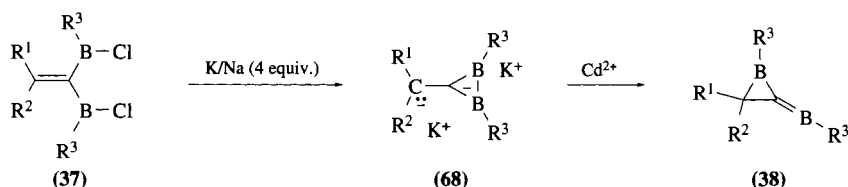


1.10.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

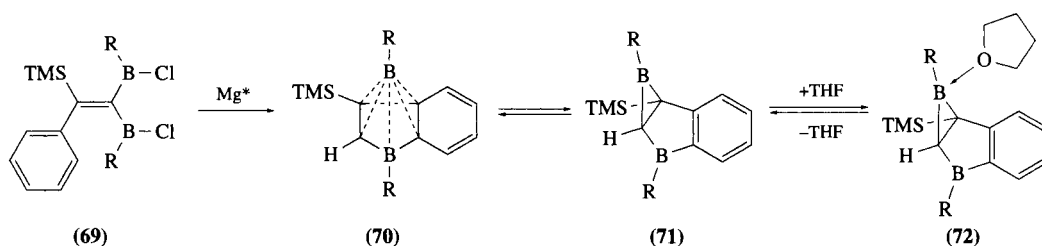
The reaction of 3-[bis(trimethylsilyl)amino]1,2,3-dithioloboroles (**66**) with sodium followed by thermolysis led to the ring contraction with formation of 1-[bis(trimethylsilyl)amino]borirenes (**67**) <84CB2531>.



The reductive ring closure of 1,1-bis(chloroboryl)ethenes (**37**) with four equivalents of K/Na alloy gave diboriranides (**68**). Oxidation of (**68**) with CdCl₂ yielded borirane-2-ylidene boranes (**38**) <85AG(E)788> (cf. Section 1.10.9.1).



The use of Bogdanovic magnesium on reductive ring closure of (**69**) gave the nonclassical aromatic compound (**70**) <92AG(E)607> which was reported considerably lower in energy than its classical isomer (**71**) <84AG(E)969, 86JA3960>. The rapidly established equilibrium between nonclassical and classical compounds resulted in the formation of an adduct of (**71**) with THF, (**72**), and both structures (**70**) and (**72**) were confirmed by an x-ray structure analysis <92AG(E)607>.



1.10.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

1.10.11.1 Synthesis of Borirane-2-Ylidene Boranes

Borirane-2-ylidene boranes (**38**; $R^1, R^2, R^3 = \text{TMS}, \text{Bu}^t, \text{Bu}^i\text{CH}_2$) <83AG(E)877> were obtained by a reductive ring closure of the corresponding 1,1-bis(chloroboryl)ethenes in 60% yield (cf. Section 1.10.9.1). Bogdanovic magnesium as a reductive agent was applied in the same reaction to give (**38**; $R^1, R^2, R^3 = 2,3,5,6\text{-tetramethylphenyl}, \text{TMS}, \text{GeMe}_3, \text{SnMe}_3$) <90AG(E)399>; no yields were reported. Oxidation of diborane (**68**) with CdCl_2 (cf. Section 1.10.10) gave rise to (**38**) with no reported yield <85AG(E)788>. Thus, by now the reductive ring closure has no competition with other methods for synthesis of borirane-2-ylidene boranes.

1.10.11.2 Synthesis of Boriranes and Boratiranes

Boriranes (**65**; $R = \text{Bu}^t, X = \text{N}(\text{TMS})_2$; $R = 2,3,5,6\text{-tetramethylphenyl}, X = \text{Cl}$) were synthesized by addition of HX to the corresponding borirane-2-ylidene boranes (**25**) in 55–65% yield (cf. Section 1.10.9.4). Interaction of the latter compound with methyl lithium gave (**65**; $R = 2,3,5,6\text{-tetramethylphenyl}, X = \text{Me}$) in 65% yield <92AG(E)1384>. The fused borirane (**72**; ($R = 2,3,5,6\text{-tetramethylphenyl}$)) was obtained on interaction of its nonclassical aromatic isomer with THF <92AG(E)607> (cf. Section 1.10.10).

The three-membered heterocycles with tetravalent boron as heteroatom, potassium salt of boratirane (**13**; $R = \text{Ph}$) <88JA6252>, and its fused derivatives, sodium 2,7,7-triphenyl-7-boratobicyclo-[4.1.0]hepta-2,4-diene <87JOC2117>, and phenyl-substituted boratanocaradienes (**60**)–(**62**) <88JA7569, 91JA2149> obtained as a mixture of tetramethylammonium salts, were synthesized on irradiation of the corresponding borates (cf. Section 1.10.9.3). Compound (**60**) was isolated in 70% yield <91JA2149> (cf. Section 1.10.3.1), and the presence of (**61**) and (**62**) in the mixture was confirmed by ^1H NMR spectral data. Boratirane (**61**) is thermally unstable and isomerizes to (**60**). Thus, the intramolecular photochemical reactions are a good route for synthesis of boratiranes, and the further progress depends upon the availability of the corresponding borates.

1.10.11.3 Synthesis of 1H-Borirenes and Boratirenes

First attempts to obtain and isolate alkyl substituted 1H-borirenes remained unsuccessful due to their easy dimerization (cf. Section 1.10.5.1). Introduction of sterically demanding substituents into the appropriate starting materials enabled synthesis of 1H-borirene derivatives by the following routes: (i) addition reactions of borenes to alkynes (cf. Section 1.10.9.2.2); (ii) interaction of alkynes with 1,2-dichlorodiboranes (cf. Section 1.10.9.2.1); (iii) photocyclization of triarylethynyl boranes (cf. Section 1.10.9.3); and (iv) ring contraction in 1,2,3-dithioloboroles (cf. Section 1.10.10). The first method allowed synthesis of a few 1H-borirenes (**11**; $R^1, R^2 = \text{TMS}, \text{Ph}_3\text{Si}, \text{Bu}^t, \text{Me}$) in a moderate yield <83AG(E)48, 84AG(E)454, 84POL271>, but the reaction is restricted by availability of borene-generating systems. The second route made available two 1H-borirenes (**25**; $R = \text{Bu}^t, \text{Me}_3\text{Sn}$) in excellent yield <84AG(E)313>, but its development was not reported later. The photocyclization of both symmetrically and unsymmetrically substituted ethynylboranes afforded 1H-borirenes (**53**; $R^1 = R^2 = 2,4,6\text{-trimethylphenyl}$; $R^1 = 2,4,6\text{-trimethylphenyl}, R^2 = 2,6\text{-dimethylphenyl}$) in a yield of 65% <87JA2526, 90JA1847> (cf. Section 1.10.9.3). The starting ethynylboranes were obtained on interaction of (*p*-tolylsulfonyl)ethyne with fluoro(diaryl)boranes, and the latter compounds are easily available from boron trifluoride etherate and the corresponding Grignard reagent, ArMgX . Dialkyl-substituted 1-[bis(trimethylsilyl)amino]borirenes (**67**; $R^1 = \text{H}, \text{Me}, \text{Et}, \text{Pr}^n$; $R^2 = \text{Et}, \text{Pr}^n, \text{Bu}^n, \text{Ph}$) were reported by ring contraction of dithioloboroles <84CB2531> (cf. Section 1.10.10), and a variety of substituents R^1 and R^2 in (**67**) is introduced by a starting alkyne which is readily transformed into dithioloborole. However, a poor yield of 1H-borirenes (**67**) (2–7%) unveils no experimental interest to this method. Irradiation of potassium triphenyl(phenylethynyl)borate afforded potassium 1,1,2,3-tetraphenylboratirene in 50% yield <89JA2316, 91JA2155> (cf. Section 1.10.9.3). The starting borate was obtained in 60% yield on interaction of phenylethyne and triphenylborane in the presence of *n*-butyllithium followed by the cation exchange, and the experimental scale of this reaction is thus determined by a variety of trisubstituted boranes available.

1.10.12 APPLICATIONS

A few applications of the three-membered boron containing heterocycles have been mentioned so far. Eisch reported borirenes among other novel organoboranes as intermediates for ceramic precursors and high energy fuels <89MI 110-01>, and some polymers containing a small ring boron compounds were used in waterless lithographic original plates <92JAP(K)04172456>.

1.11

Diaziridines and Diazirines

REMIR G. KOSTYANOVSKY

Russian Academy of Sciences, Moscow, Russia

and

RAMIAH MURUGAN

Reilly Industries, Inc., Indianapolis, IN, USA

and

MURUGAN SUTHARCHANADEVI

Indianapolis, IN, USA

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1.11.1 INTRODUCTION

Three-membered heterocycles are an extensively studied class of compounds. Those with two nitrogen atoms, diazirine (unsaturated) (1) and diaziridine (saturated) (2) systems are fairly readily available compounds.

Diaziridines and diazirines were discovered by Abendroth <59AG283, 59AG340, 60GEP1082889, 60GEP1088978, 61AG67, 62BRP890334, 62GEP1127907>, Schmitz <59AG127, 61AG115, 61CB2166>, and Paulsen <60AG781, 61CB968, 61GEP1118787, 62GEP1126395, 62GEP1123330, 62GEP1136343> independently, and almost simultaneously. Schmitz was the first to report these works in his lecture in the International Symposium in Tavrishesky Palace in Leningrad on December 15, 1961 <62MI 111-01>. Afterwards he reviewed the works in this field systematically and critically analyzed the early structural proposals <B-67MI 111-01, 79AHC(24)63, 84CHEC-I(7)195, B-87MI 111-01>. A fundamental monograph on the chemistry of diazirines contains references through 1986 <87MI 111-02>. Existing reviews on diazirines and/or diaziridines are: chemistry of aziridines <75MI 111-01, 83CHE547>, nitrogen inversion in strained heterocycles <B-92MI 111-01>, compounds with the chiral centers at nitrogen atoms <B-84MI 111-01>, and electrochemistry <87MI 111-02>. There are also reviews on specific aspects of diazirine chemistry <82CSR127, 89ACR15, 91PAC507, 92ACR31, 94ACR287>.

Diaziridines are rather stable, while the pure simple diazirines and many of the substituted diazirines are explosives. Both diazirines and diaziridines play an important role in many aspects of organic chemistry and of organometallic chemistry <87MI 111-02>. Diazirines, as the sources of carbenes, has opened up a large field for research <82CSR127, B-87MI 111-01, 89ACR15, 94ACR287>. Diazirines fulfill most of the requirements as a useful photoactivatable reagent especially the stability and inertness of the diazirine ring towards many reagents <B-83MI 111-01>. Thus diazirines caused a revolution in molecular biology and biochemistry and are widely used now for photoaffinity labeling <B-87MI 111-01>. These studies have enriched the chemistry of diazirines and diaziridines substantially, since they have demanded the synthesis of hydrazo- and azo-containing biologically active compounds. Strangely enough, neither diazirines nor diaziridines have yet been found in nature. However, there are certain grounds to believe them to be possible interstellar molecules; the microwave frequencies for their astrophysical identification in dense interstellar clouds are already predicted using *ab initio* calculations <89MI 111-01>. The above interests have driven many theoretical and experimental studies of molecular and electronic structure and the reactivity of diazirines and diaziridines <B-87MI 111-01>.

1.11.2 SCOPE

This chapter focuses on the findings since the mid-1980s and builds on earlier work <84CHEC-I(7)195>. In this chapter, the discussion of diazirine (unsaturated) (1) systems, is followed by diaziridine (saturated) (2) systems.

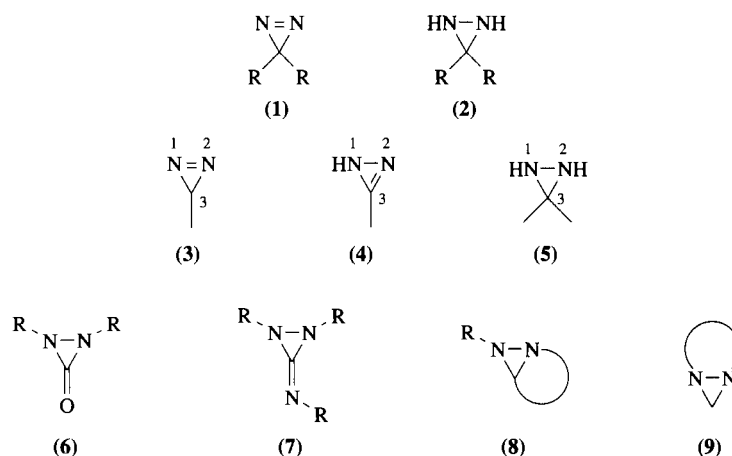
1.11.3 STRUCTURE AND NOMENCLATURE

Nomenclature of both unsaturated and saturated systems follows the Hantzsch–Widman system. The prefix “diaz” denotes the presence of two nitrogen atoms, while the stems “irine” and “iridine” indicate the unsaturated and saturated three-membered ring systems, respectively; thus the names diazirine (unsaturated) (1) and diaziridine (saturated) (2). The numbering of the atoms in the diazirine ring is illustrated by the valence isomers (3) and (4) of diazirines and are named “3*H*-” and “1*H*-diazirines,” respectively. The latter (4) are sometimes named “isodiazirines” <89CPH157>. Diaziridines are also named as “diazocyclopropanes” (Paulsen) or “cyclo diazomethanes” (Schmitz) or “isohydrazones” (Abendroth). The numbering of the atoms in the diaziridine ring is demonstrated below by the example of 3,3-dimethyldiaziridine (5). A convenient short name for the NHNH fragment of the diaziridine ring is “hydrazir” (e.g. 1-hydrazirglucoses <91PAC507>).

Thus, diaziridine (5) is also named as a 2-hydrazirpropane. A convenient short name for the N-N fragment of the diazirine cycle is “azi” (not to be confused with the similar abbreviations “azy” and “azo” for the residues of aziridine 2-carboxylic acid and azetidine 2-carboxylic acid, respectively <84YKG390>). The chemical structures of diaziridinone (6), diziridinimine (7), as well as fused diaziridine C—N bridged (8) and N—N bridged (9) (usually *cis*) systems are given.

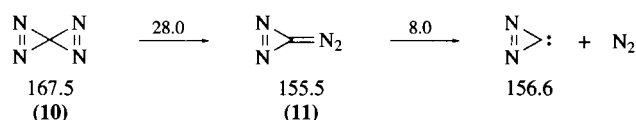
1.11.4 THEORETICAL METHODS

Theoretical studies on diazirine and diazirine systems, using methods such as *ab initio* calculations, SCF-LCAO-MO calculations with and without basis sets (STO-3G, 4-31G, and 6-31*),

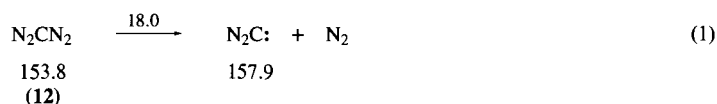


enabled the determination of bond lengths, dipole moments, valence isomerism, and absolute configuration. Results obtained from earlier theoretical studies are discussed with illustrations <84CHEC-I(7)195>.

A challenging task since the early 1990s has been the study of the possible synthesis of tetraazospiropentadiene (diazimethane) (10), azidiazomethane (11), or bisdiazomethane (tetrazomethane) (12) (Scheme 1 and Equation (1)) as theoretically interesting molecules and useful sources of atomic carbon <90JA3374, 92JA3892>. Of interest are attempts to synthesize (10), since its similarity to the carbon analogue, spirocyclopentadiene (bowtiediene) (13) prepared in 1991 <91JA5084>, allows one to expect it to be kinetically stabilized by spiroconjugation <78JA760, 78JA1036>. On the contrary, for diazocyclopropene (14), the carbon analogue of (11), significant antiaromatic destabilization is predicted by *ab initio* calculations with basis set 6-31G* <92JA5362>.

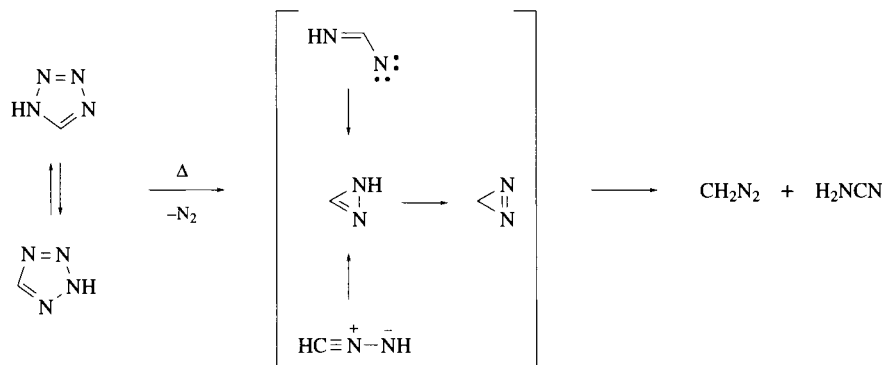


Scheme 1

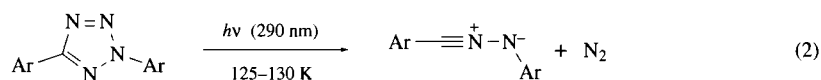


All possible valence isomers of the simple diazirine have been studied theoretically by MNDO and *ab initio* calculations <83MI 111-02>. The MNDO calculations provided the following values of heat of formation (ΔH_f°) of the species and the activation energies (kcal mol⁻¹) of their transformations <94UP 111-01>. According to theoretical predictions, it is not possible to obtain aminodiazomethane (see Figure 1, Section 1.11.6.1.1). The exchange reactions of halodiazirines with amines leads to aminodiazirines followed by nitrogen loss and the liberation of aminocarbenes <84TL1023>. The 1*H*-diazirine isomer could not be identified in flash thermolysis (1100K) of a unsubstituted 1*H*-tetrazole in low temperature matrixes <85ZC106>. In the first case, the formation of cyanamide and diazomethane has been identified by PE spectra and preferential pathways through 1*H*-diazirine (Scheme 2) have been suggested (on the basis of MNDO and *ab initio* calculations). In the second case, only the formation of diarylnitrilimines have been identified by IR (Equation (2)). 3-Alkylidenediaziridines and 3-alkylideneazirines (aziethenes) are also unknown, although the carbon analogue of the latter, methylene cyclopropene, is thoroughly studied both experimentally and theoretically <86JA7912>. Alkylidenecarbenes have been generated from other

sources, for example difluorovinylidene from difluoropropadienone $\langle 90JA4046 \rangle$. Vinylidene, which easily isomerizes to ethyne with propadienylidene and butadienylidene have been studied theoretically and experimentally $\langle 92CRV14 \rangle$.



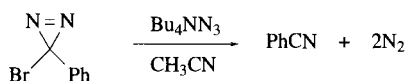
Scheme 2



1.11.5 EXPERIMENTAL STRUCTURAL METHODS

Experimental methods have been remarkably useful especially in three-membered heterocycles. At the time of discovery of these compounds, mainly chemical methods were available to prove their structures, which yielded erroneous results. Experimental methods such as x-ray analysis, ^1H NMR, ^{13}C NMR, IR/Raman, UV, PES, and MS provided data on molecular geometry, bond connectivity, absolute configuration of the molecule, and configurational stability at nitrogen. Experimental data corrected and confirmed the chemical structures of title compounds. Complete experimental data from earlier studies on some diazirines and diaziridines, are provided and discussed with illustrations $\langle 84CHEC-I(7)195 \rangle$.

In ^{15}N experiments it has been shown that in the reaction of 3-bromo-3-phenyldiazirine with azide ion, only benzonitrile (where the nitrogen atom originates not from azide ion, but from one of the ring nitrogens of halodiazirine) was observed (Scheme 3) $\langle 89TL4901 \rangle$. 3-Azido-3-aryldiazirines were obtained independently. They happened to be more stable and were characterized in solution by NMR spectra. However, the fragmentation can be described by a different mechanism: the nitrogen of benzonitrile formed originates from the nitrite ion only $\langle 92ACR31 \rangle$.



Scheme 3

The intermediate tris(methylimino)methane biradicals were trapped in a high yield as the products of the reactions with solvents $\langle 69JOC2994 \rangle$; they were also detected by ESR spectra in a low-temperature matrix $\langle 78JA1306 \rangle$.

1.11.6 THERMODYNAMIC ASPECTS

1.11.6.1 Valence Isomerism

1.11.6.1.1 Diazirines

Valence isomers of a simple diazirine system are depicted by structures (3) and (4). All possible valence isomers of the simple diazirine have been studied theoretically by MNDO and *ab initio*

calculations <83MI 111-02>. The order of thermodynamic stability depends strongly on type of substituent and charges by metal ion complexation (Li^+) and *N*-protonation <93JA11074>. The 3*H*-isomer is more thermodynamically stable than the 1*H*-isomer, which has lower 4π -antiaromatic destabilization (Figure 1). In the case of the *N*-protonated form the antiaromatic destabilization is avoided and becomes more stable compared to the 1*H*-isomer *N*-protonated 3*H*-diazirine (Figure 2).

Thus, isomerization of the latter into the former is thermodynamically preferred. A similar effect is caused by *N*-complexation with metal ion (Li^+) <93JA11074>. This effect explains the considerable higher proton affinity of 1*H*-diazirine ($201.9 \text{ kcal mol}^{-1}$) compared to 3*H*-isomers ($165.3 \text{ kcal mol}^{-1}$) <93JA11074>. However, protonated 1*H*-diazirine is less stable as compared with the most stable at CN-protonated cyanamide (the same *N*-protonated carbodimide) <93JPC4239>. Experimental proton affinity of cyanamide and anion $[\text{HNCN}]^-$ <93JPC4239> are 194.5 and $349.8 \text{ kcal mol}^{-1}$, that is in

XCHN_2	>	$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{X} \end{array}$		$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{X} \end{array}$	>	XCHN_2
0		E		0		E
X		E		X		E
BH ₂		22.2		F		12.4
AlCH ₂		22.1		HO		7.3
Li		21.6		Cl		1.9
Na		20.7		H ₂ N		1.4
SiH ₃		14.2				
CH=O		12.6				
PH ₂		10.6				
CN		9.5				
SH		7.2				
HC≡C		7.1				
H ₂ C=CH		5.6				
CF ₃		4.9				
H		4.8				
Me		1.9				
HF / 6-31 G* // 6-31 G*				HF / 6-31 G* // 6-31 G*		
		<92JA6553>				<92JA6553>

$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{N}_3 \end{array}$	>	$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{CN}_2 \end{array}$
0		2.8
HF / 6-31 G* // 6-31 G*		
		<93JOC7700>

$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{Ph} \end{array}$	>	$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{CN}_2 \end{array}$
0		1.7
HF / 6-31 G* // 4-31 G		
		<93JOC7700>

The order of thermodynamic stability of valence isomers:

$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{F} \quad \text{F} \end{array}$	>	CF_2N_2	>	$\begin{array}{c} \text{F} \\ \\ \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{F} \end{array}$	>	F_2NCN
(15)				(16)		
0		15.7		61.9		67.6
MP2 (full) / 6-31 G* // MP2 (full) / 6-31 G*						
$\begin{array}{c} \text{N}=\text{N} \\ \diagup \quad \diagdown \\ \text{F} \end{array}$		CHFN_2				
0		15.7				

Figure 1 Relative thermodynamic stability of substituted diazirines and diazomethanes (kcal mol).

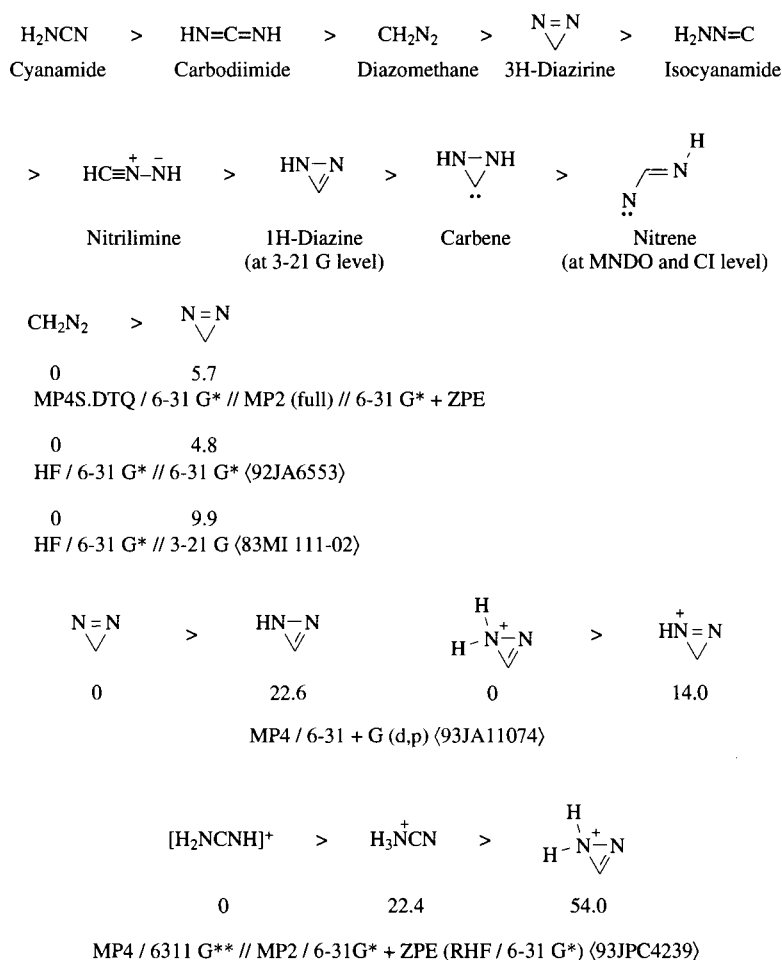


Figure 2 The order of thermodynamic stability of valence isomers of diazirine (relative stability of isomers) at the MP3/6-31*/3-21G level (89CPH157) and relative energies (kcal mol⁻¹).

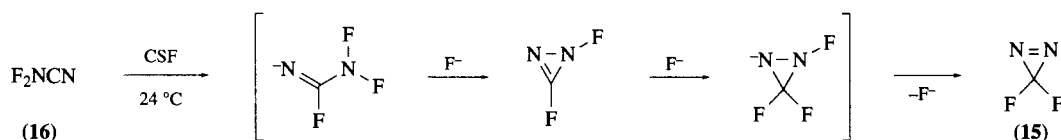
excellent agreement with the theoretical values of 191.7 and 347.8 kcal mol⁻¹, respectively (93JPC4239). Protonation of diazomethane has also been studied: C-protonation from $\text{MeN}^+=\text{N}$ is by 39.3 kcal mol⁻¹ more stable than N-protonation from $\text{CH}_2=\text{N}^+=\text{NH}$ (94JA8985).

The order of thermodynamic stability of valence isomers of diazirines strongly depends on the characters of substituents (Figure 1). The dramatic reverse stability in the order of diazirine isomers was predicted for electronegatively substituted derivatives (87MI 111-03, 92JA6553). In accordance with these calculations, fluorodiazomethanes CHFN_2 and CF_2N_2 are not expected to be visible chemical species, because they have no barriers toward exothermic dissociation into N_2 and carbenes. In contrast, fluorodiazirines have high energy barriers toward dissociation despite being high in energy.

Theoretical predictions on photochemical and thermal isomerization of diazirines may explain numerous experimental values. Due to low and reversible relative stability of diazirines and diazomethanes, which depend on substituents (Figures 1 and 2), the spontaneous (63TL1405), photochemical (64JA292), or thermal (77JCS(P2)1214) isomerization of diazirines into diazoalkane has been observed, as well as reversible isomerization of diazocarbonyl compounds and corresponding diazirines. Interconversions of diazirines and diazo compounds have been considered in detail (B-87MI 111-01).

In accordance with theoretical prediction, a fast quantitative fluoride ion-catalyzed isomerization of difluorocyanamide (16) into stable difluorodiazirine (15) (Scheme 4) has been known for a long time (66IC1455, 68JOC1847). Perfluorodiazomethanes $(\text{RF})_2\text{CN}_2$ and corresponding diazirines have also been synthesized (65IZV761, 65IZV926, 66JA3617) while difluorodiazomethane is unknown. The latter was mentioned only as a postulated intermediate in the decomposition of difluorodiazirine (15) with formation of azine $\text{CF}_2=\text{N}-\text{N}=\text{CF}_2$ (66JOC3833). However, it was noted that this azine

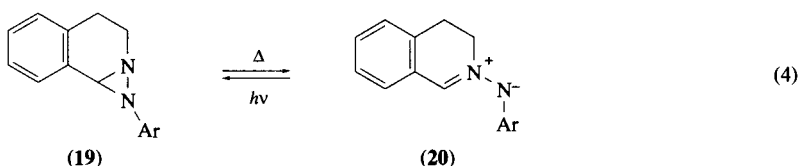
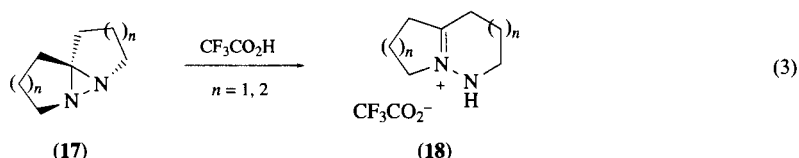
can be obtained by the direct reaction of difluorocarbene with diazine <67JPC1229>. In multiple photolyses of halo diazirines in low temperature matrices, the formation of halo diazomethanes has not been observed <65JA4270, 84JA436, 87IZV463, 93JOC979>. The traces of diazo compounds have been detected in photolysis of chloro- and bromo-substituted phenyl- and alkyldiazirines <86JA1517, 93JA8943>. During the photolyses of 3-halo-3-trifluoromethyldiazirines, where Hal = F, Cl, Br, only 3-bromo-3-trifluoromethyldiazirine gave the corresponding bromo(trifluoromethyl)diazomethane, in nitrogen cryogenic matrices trapping conditions <92JA3581>. The nitrogen-trapping carbene reactions are well known both under matrix isolation condition and in the gas phase <68TL4177, 90JA4046>.



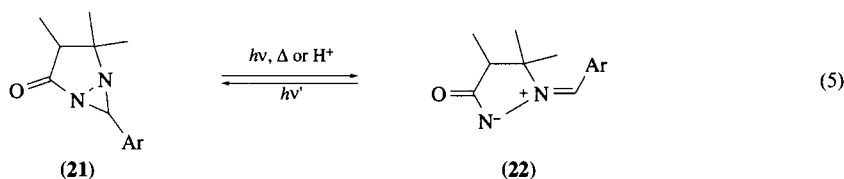
Scheme 4

1.11.6.1.2 Diaziridines

Strained tricyclic diaziridines (**17**) are stable during distillation, but they easily isomerize under the action of CF_3COOH to form protonated azomethine imines (**18**) (Equation (3)). The reverse transformation has not been studied <89AG(E)1381>. The isomerization of diaziridines into azomethine imines is facilitated by the substituents that stabilize the positive charge on the carbon atom and the negative one on the nitrogen atom. Thus, bicyclic diaziridine (**19**) is thermally isomerized quantitatively into an azomethine imine (**20**), which is transformed into the starting diaziridine under the photolytic conditions (Equation (4)) <80TL4877>.

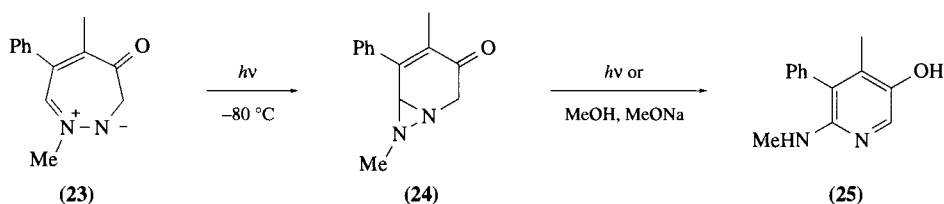


Diaziridines (**21**) and the corresponding azomethine imines (**22**) are photoreversible systems (λ_{max} 100 nm). The cleavage of the diaziridine ring in the molecule of (**21**) also occurs on heating or protonation (Equation (5)) <70JPR161, 80JPR623, 83JPR205, 83JPR995>.



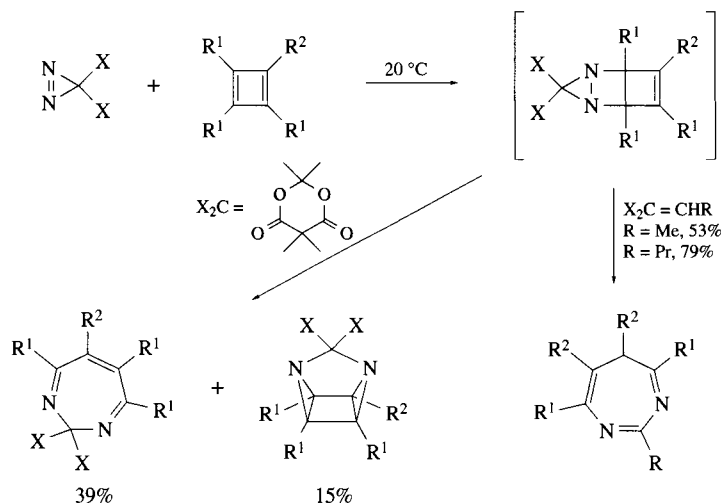
It is well known that photoisomerization of the 1,2-diazepine system (**23**) takes place to give the stable bicyclic diaziridine (**24**), which, in turn, undergoes further photoisomerization into 2-

aminopyridine (**25**). Two types of chemical isomerization of diaziridine (**24**) (Scheme 5) were also found <68JA4738>.



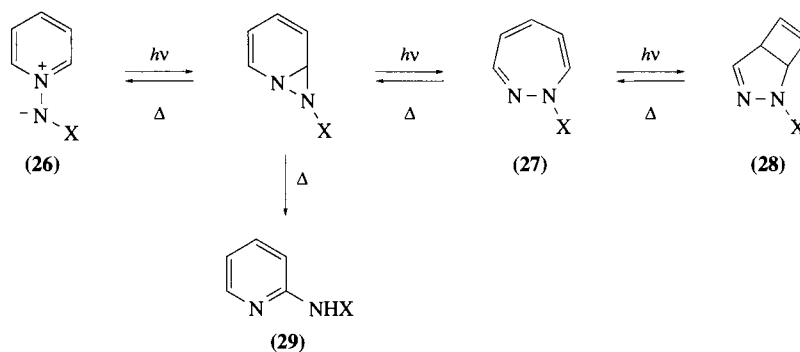
Scheme 5

Valence isomerization of the intermediate [4 + 2] cycloadducts of diazirines and kinetically stabilized cyclobutadiene was also observed. It occurs with the opening of the ring at the N—N bond to form 5*H*-1,3-diazepines, 2*H*-1,3-diazepine, and the highly stable 1,4-diazaquadricyclone (Scheme 6).



Scheme 6

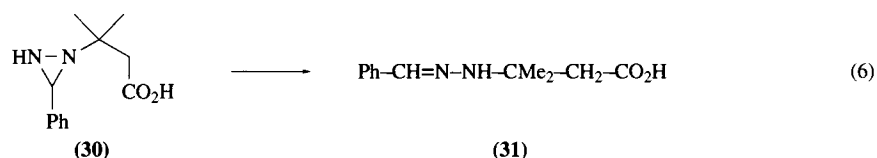
Photoisomerization of pyridine *N*-imides (**26**) into 1,2-diazepines (**27**) and further into (**28**) and 2-aminopyridines (**29**) via the transient diaziridines (Scheme 7), has been thoroughly investigated <68AG(E)129, 81ACR348, 89KGS1443>. Compound (**27**) may formally be considered as a hydrazone, and consequently, the reaction (Scheme 7) can be regarded as a reversible diaziridine-hydrazone rearrangement with ring enlargement and the shift of the double bonds. There are grounds to believe that the isomerization (**23**) → (**24**) also proceeds via transient hydrazone <68JA4738>. However, the rearrangement of a hydrazone into a diaziridine has not been effected explicitly as yet, although the



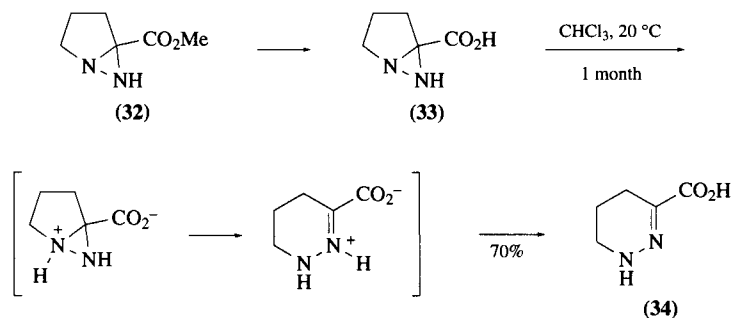
Scheme 7

reverse transformation is a typical reaction of diaziridines <61AG67, 67CB142, 76JOC3229>. An example of the rearrangement of hydrazone into diaziridine has been described, the acid-catalyzed transformation of the CH_2N_2 -tetracyanoethylene adduct into the bicyclic diaziridine was not confirmed <87CB153, 87CB159>.

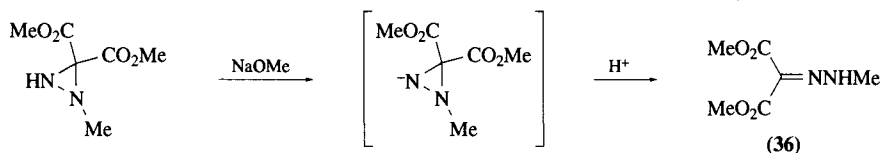
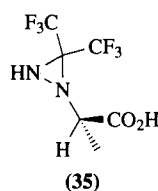
The direction of the diaziridine isomerization is determined by the character of the substituents. Thus in an acid medium, bicyclic *N*-acyldiaziridine (**21**) form (**22**) (Equation (5)), while the corresponding diaziridino acid (**30**) is isomerized quantitatively into hydrazone (**31**) (Equation (6)) <73JPR711>.



Electronegative substituents at the carbon atom of the ring hinder the acid-catalyzed diaziridine-hydrazone rearrangement, apparently because of the decrease in the basicity of diaziridines. Diaziridine (**32**) is stable in ether under reflux in the presence of CF_3COOH (35 h). The corresponding acid (**33**) (m.p. 108°C) is stable in the pure form; in solution, it isomerizes to hydrazone (**34**) very slowly (Scheme 8) <86IZV2266>. Diaziridino acid (**35**) (m.p. 86°C) does not alter under prolonged heating as a melt <82T949, 84T2151>. On the other hand, electronegative substituents at the ring carbon atom favor an unusual diaziridino-hydrazone rearrangement (**36**) under the effect of bases (Scheme 9) <77DOK(232)1081>.



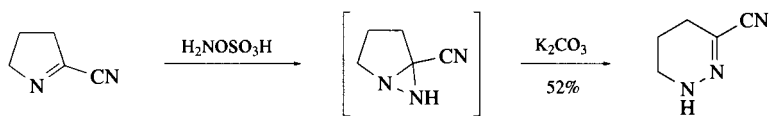
Scheme 8



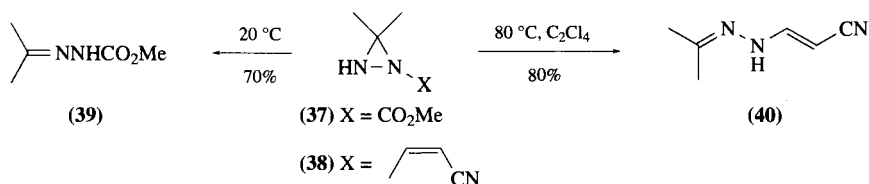
Scheme 9

Transformation of an intermediate bicyclic diaziridine under the effect of K_2CO_3 (Scheme 10) <86IZV1831> can be explained analogously. The π -electron-accepting substituent at the *N*-atom make the diaziridine-hydrazone rearrangement of (**37**), (**38**) (Scheme 11) <88IZV2581> and (**41**) (Scheme 12) <73JOC2984> easier. Vinylhydrazone (**42**) undergoes further valence isomerization to azine (**43**).

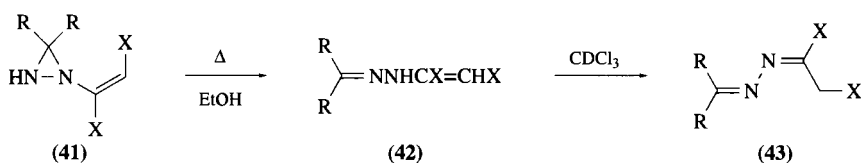
The diaziridino derivatives are difficult to isolate because of their easy isomerization to hydrazones (Scheme 13) <75IZV875>.



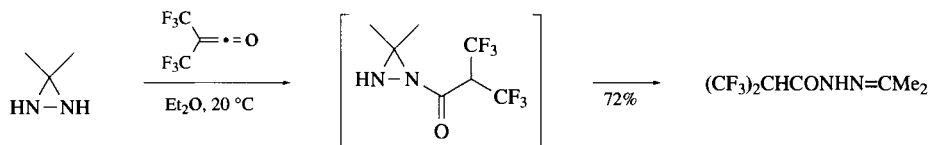
Scheme 10



Scheme 11

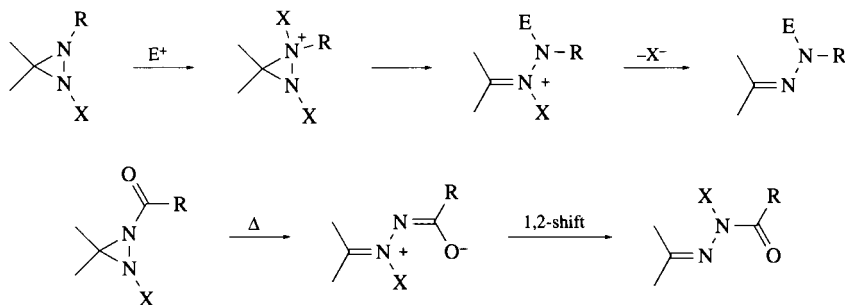


Scheme 12

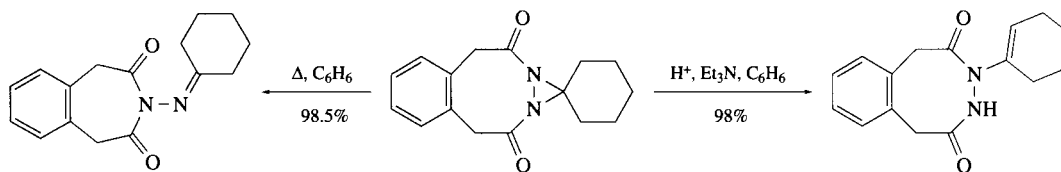


Scheme 13

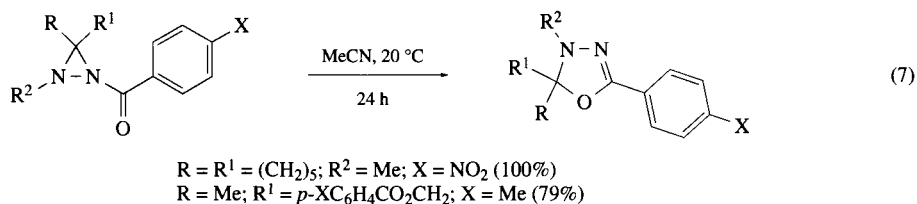
The examples considered show that the diaziridine–hydrazone rearrangement is initiated by an external (E^+) or an internal electrophile (e.g. $RCON$ group) (Scheme 14). The endocyclic $C-N$ bond with the acylated or protonated nitrogen atom becomes substantially longer (see below) and, consequently, weaker. The influence of the nature of substituents is discussed <86IZV1831>. The essential stage of the process is elimination or migration of the substituent X (Scheme 14). When X is an acyl group, it can migrate under thermal conditions to afford the diacylhydrazone. Although, when acid-catalyzed transformation takes place, the intermediate is stabilized by the elimination of a proton from the C -substituent, the isomerization following, subsequently, another direction (Scheme 15) <76JOC3229>. When the migration of the N -substituent, X , is impossible ($X = R$), thermal isomerization with ring enlargement occurs, this is also typical of N -acyldiaziridines and oxadiaziridines (Equation (7)) <76JOC3229, 87CC212>.



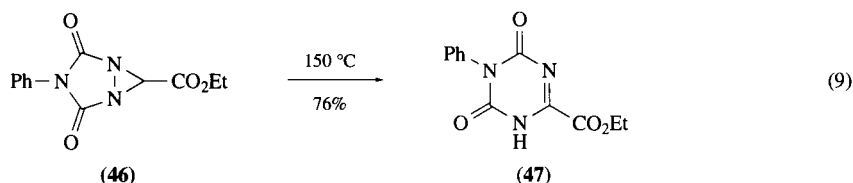
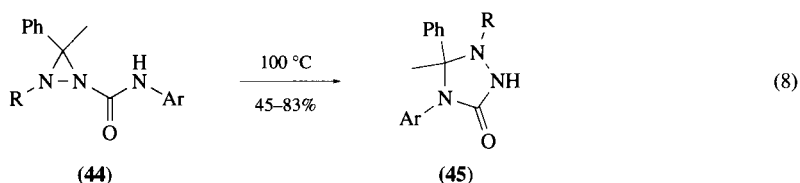
Scheme 14



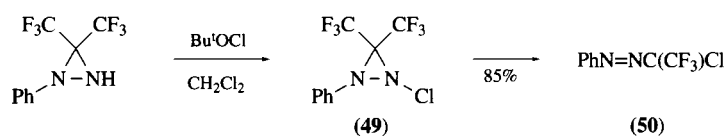
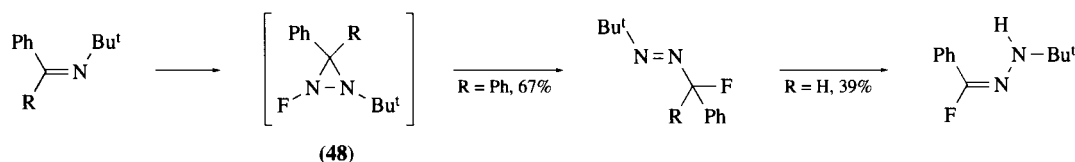
Scheme 15



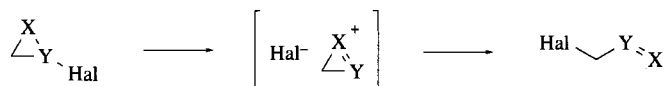
N-Carbamoyldiaziridines (**44**) undergo thermal isomerization to 1,2,4-triazolidin-3-ones (**45**) (Equation (8)) <73JOC3758, 79JOC3935>. It is worthy to note that thermal isomerization of 1,2,3-triacetyldiaziridine (**46**) to triazine (**47**) proceeds through the cleavage of the N—N bond and 1,2-H shift (Equation (9)) <75JA5611>.



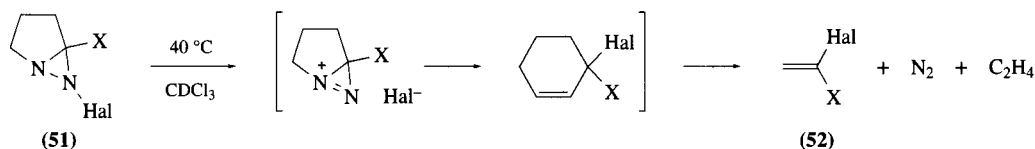
N-Halodiaziridines (**48**) and (**49**) are readily isomerized to α -haloazo compounds (Scheme 16) <66JA4677, 88IZV1599>. This is the cyclopropylallyl-type rearrangement of halogenated three-membered heterocycles. The rearrangement is accelerated substantially by the presence of a heteroatom ($X = \text{N}, \text{O}, \text{S}$) in the ring <70JCS(C)576>, the acceleration being the result of $n_X \rightarrow \sigma^*_{\text{XHal}}$ interaction (Scheme 17) <82T2319, 85T575, 89MI 111-02>. When the $n_N \rightarrow \sigma^*_{\text{NHal}}$ interaction enables the preparation of stable bicyclic *N*-halodiaziridines (**51**) <83IZV1930, 83CC1275, 85CC680, 86KGS1330, 89MI 111-02, 95JST(350)49>. The latter undergo thermal isomerization to cyclic α -haloazo compounds with further fragmentation to (**52**), nitrogen, and ethylene (Scheme 18). When $X = \text{MeO}_2\text{C}$, they are formed in 89–95% yields. With $X = \text{Cl}$ and Br , $t_{1/2}$ is 6.3 and 4.6 h, respectively.



Scheme 16

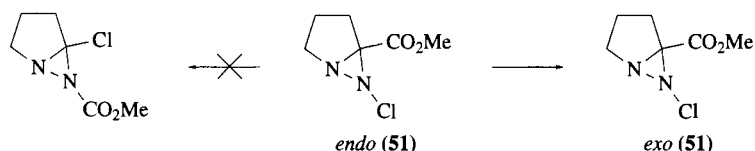


Scheme 17



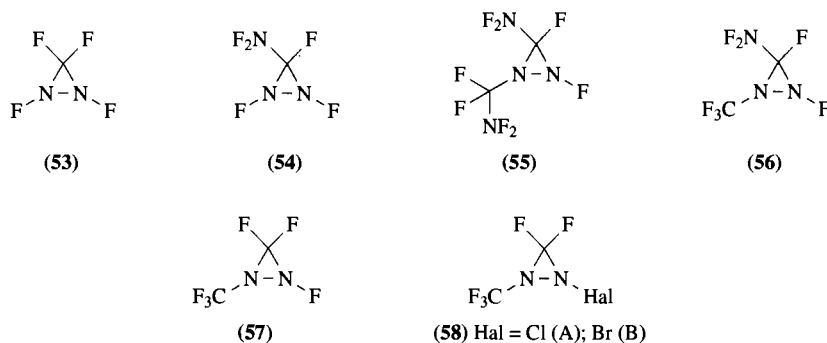
Scheme 18

The transformation of the *endo* isomer (51), which was described earlier as a 1,2-acyl migration (<83CC1275>), appears to be an *endo*–*exo* nitrogen inversion process (Scheme 19) (<85CC680, 86KGS1330>).



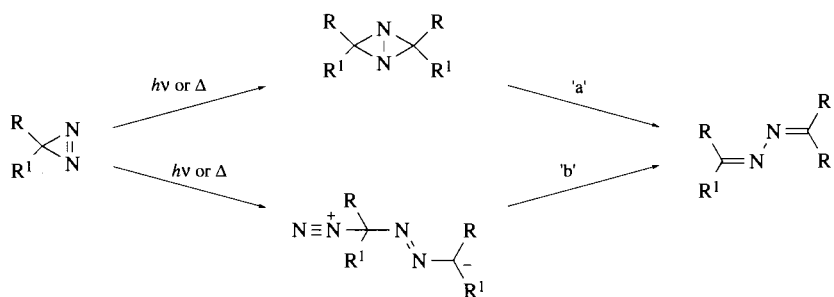
Scheme 19

Perfluoro-*n*-halodiaziridines (53)–(55) (<68JOC3489>), (56) (<68JOC1847>), (57) (<82POL129>), and (58) (<84JOC3590, 88JOC4443>) do not isomerize to azo compounds, since their N–Hal bond does not undergo ionization, thus in turn, being the result of the weakening of $n_{\text{N}} \rightarrow \sigma^*_{\text{NHal}}$ interaction by the competitive hyperconjugation of the lone pair of the donating nitrogen atom with the bonds of CF_3 group and the strong -I effect of the fluorine atom. The bond N–F undergoes ionization, though, by the specific metal catalysis with the consequent quantitative transformation of diaziridine (57) into the diazine $\text{CF}_3\text{N}=\text{NCF}_3$ (<83JOC771>).



The irreversible fluoride anion-catalyzed valence isomerization of the perfluoroformamidine CF_3NFCFNF into diaziridine (57) is known. It was assumed earlier that under photolysis or thermolysis diazirines give azynes by the route of diaziridine–azyne rearrangement via the intermediate 1,3-diazabicyclo[1.1.0]butane (Scheme 20, route a) (<66JA3617, 68JHC41, 69JOC2728>). For example, azynes are formed quantitatively under thermolysis of azirines ($\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$ or Cl) at 130°C in PhCl or PhNO . However evidence to support another mechanism of the reaction was obtained later (Scheme 20, route b) (<77TL3139>).

According to theoretical studies, the insertion of the N–N bond into the molecules of tetrahedranes or prismanes decrease their relative thermodynamic stability (3–21 G) (<89MI 111-03>); in the series of di-, tri-, and tetraazatetrahedranes the corresponding azetes are more stable; for example, tetrazete (59) is more stable than tetraazatetrahedrane (60), $\Delta E = 83 \text{ kJ mol}^{-1}$ (6–31G*/4–31G) (<87MI 111-04>).

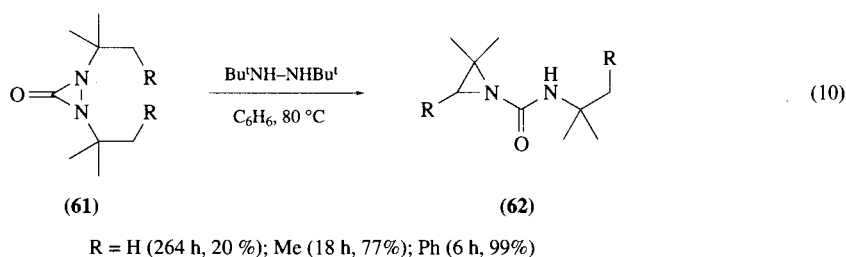


Scheme 20

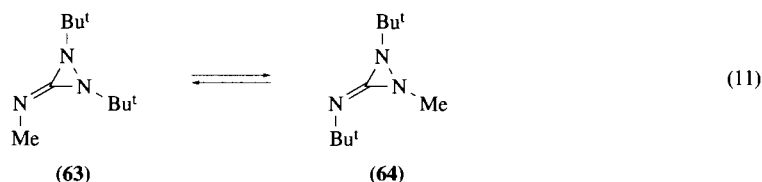


1.11.6.1.3 Diaziridinones and diaziridinimines

Highly thermally stable (up to 180°C) di-*t*-alkyldiaziridinones (**61**) are rearranged into *N*-carbamoylaziridines (**62**) under the conditions of hydrazine catalysis by a radical mechanism (Equation (10)) <69JOC2263>. The valence isomers, carbodimide *N*-oxide and oxaziridinimine, are believed to be the intermediates in Greene's synthesis of diaziridinones <69JOC2269, 70JOC2813>.

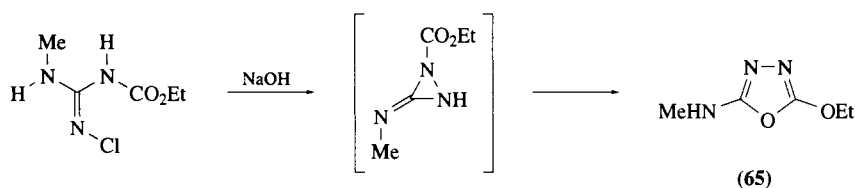


The reversible valence isomerization of diaziridinimines (**63**) → (**64**) is likely to proceed via an intermediate biradical (Equation (11)) <70CB1234>. The similar isomerization is responsible for the behavior of cyanodiaziridinimines and results in the formation of amino-substituted benzimidazoles and pyrazoles only <84CHEC-I(7)195>. As L'abbe and co-workers showed, dehydrogenation of *N*-chloroguanidine yields not diaziridinimine described earlier <73JAP85565> but its valence isomer, 1,3,4-oxadiazole (**65**) (Scheme 21) <78BSB493>. The intermediate trisubstituted *N*-acyl diaziridinimines isomerize in a similar way (Scheme 22) <81JOC4478>.

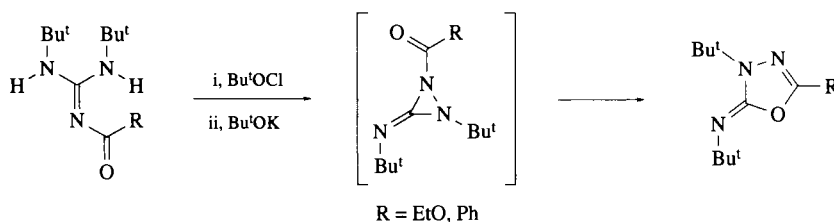


1.11.6.2 Nitrogen Inversion of Diaziridines

Diaziridines differ from simple amines and hydrazines radically in many properties. First of all, the nitrogen atoms of diaziridines feature high pyramidal stability. The inversion of nitrogen atoms in diaziridine rings has been studied actively since 1967 <67CB1778>. Optically active diaziridines with an asymmetric nitrogen atom have been studied since 1974 <74IZV1671>. In the molecules of



Scheme 21



Scheme 22

diaziridines, all kinds of conjugation with the participation of the lone electron pairs of nitrogen atoms are weakened. This is reflected in the rules that forbid the amide conjugation with the nitrogen atom of the aziridine ring (in *N*-acyldiaziridines the nitrogen atom is pyramidal) <74TL4207> and the α -*N*-diaziridinoalkylation (Mannich reaction) <88KGS390>. These features of diaziridines were not considered at all in the previous reviews, although they have made possible the synthesis of a number of diaziridine derivatives most typical of the common hydrazines.

1.11.7 REACTIONS AND REACTIVITY

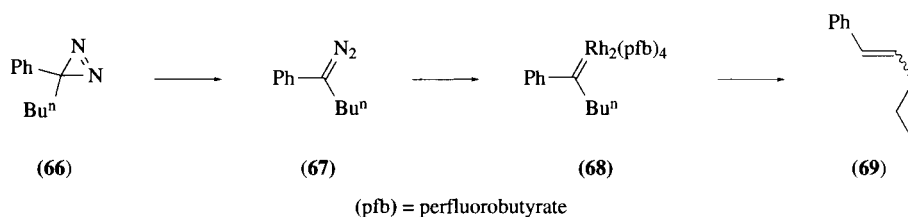
1.11.7.1 Diazirines

There has been increasing interest in the investigation of reactions of diazirines which may be attributed to their innocuous nitrogen-leaving group, remarkable stability and inertness to many reagents, and tolerance of heteroatomic substituents. The reactions of diazirines can be broadly grouped into two categories: reactions without ring cleavage and reactions with ring cleavage.

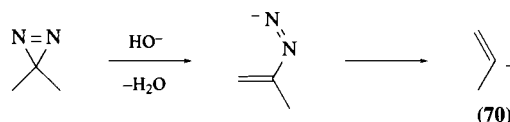
Under the first category, the inertness to electrophiles, ozone, and to the reagents such as oxidizing agents dichromate, bromine, chlorine or hypochlorite enable one to accomplish many functional group conversions without affecting the diazirine ring structure. Reduction of the N=N double bond yields diaziridine. Reagents such as Grignard, phenyllithium, or ethylzinc iodide easily add to the N=N double bond. Formation of metal complexes at one or both nitrogen atoms with metal carbonyls is common for diazirines.

Reactions resulting in ring cleavage of diazirines is achieved under either photolytic or thermolytic conditions. These reactions result in the cleavage of the C—N bond along with either conserving the nitrogen atoms in the molecule or extrusion of nitrogen atoms from the molecule. Photolysis of diazirine with extrusion of nitrogen atoms result in the generation of carbene, which is extensively exploited in organic synthesis. Electrophiles such as strong Lewis acids and concentrated sulfuric acid result in ring cleavage products. Earlier literature on reactions and reactivity of diazirines is discussed <84CHEC-I(7)195, 90PHC22>. When diazirine (66) was heated in the presence of rhodium(II) catalyst, it underwent ring cleavage, C—H insertion, and a 1,2 hydride shift to yield the alkene (69) via (67) and (68) (Scheme 23) <89TL3049, 90PHC22>. A general and convenient method for the generation of vinyl ions (70) is developed from diazirine with hydroxide in gas phase (Scheme 24) <89TL3049, 90PHC22>.

Considering the synthesis of 3-halodiazirine, Graham proposed that the valence isomerization of the intermediate *N*-substituted 3*H*, 1*H*-aziri-di-1*H*-diazirine to *C*-halosubstituted 3*H*-diazirine occurs either through a diazirinium ion (pathway a), or by a S_N2' process (pathway b). Realization of any of these pathways could explain the formation of a mixture of 3-halodiazirine <65JA4396>. Later it was shown that in this reaction isolable chlorodiazirines, initially formed under the reaction conditions, are transformed into 3-chlorodiazirines <80CB2040>. Padwa and Eastman found two



Scheme 23



Scheme 24

possible directions of reactions of 3-halo-3-phenyldiazirine with *C*-nucleophiles [69JOC2728]. The first one, confirmed later by reaction with phenylmagnesium bromide [90JA368], gives *N,N'*-diphenylbenzamidine in almost quantitative yield. The formation of this product could be explained by isomerization of 1,3-diphenyldiazirine intermediate, formed in the first step of S_N2' process, into iminonitrene [69JOC2728, 90JA368]. However, the isomerization probably leads to the more stable diphenylcarbodiimide. This problem could be easily solved experimentally by application of labeled PhLi or ArLi with following identification of an anilide, formed after amidine hydrolysis. Isomerization of this antiaromatic intermediate is probably caused by destabilization because of conjugation with the PhN-substituent and thus planar conformation of the *N*-atom, and also because of more difficult lithiation in comparison with 1-methyl-3-phenyldiazirine. The latter, when lithiated, is also stabilized by Li^+ association [93JA11074] and therefore in this case the second direction of this reaction (with retention of the three-membered ring and following S_N2' reaction) takes place. However, because of the absence of a good leaving group at the *N*-atom, this process results in formation of diazirine, which probably could be separated in NH-form by treatment of the reaction mixture under neutral conditions. Then this reaction could be considered as a new approach to a synthesis of 1,2,3-trisubstituted diaziridines using Grignard reagents. The results of the reaction with dimethylsulfonium methylide as nucleophile could be explained by easy fragmentation of the deprotonated 1-alkyldiazirine [69JOC2728].

The formation and fragmentation of azidodiazirines intermediates have been studied by many research groups. By *ab initio* calculations at the HF/3-21G* level significantly lower thermodynamic stability of 1-azidodiazirine compared to 3-azidodiazirine was predicted and the reaction intermediate for their decomposition to HCN + 2N₂ determined [89TL4901, 90JA368, 92ACR31].

1.11.7.2 Diaziridines

Diaziridines possess moderate ring stability in comparison with diazirines. Similar to diazirines, diaziridines are also stable towards strong oxidizing agents. Diaziridines are less sensitive to bases than to acids, treatment with the latter leads to hydrolysis yielding carbonyl compounds with nitrogen atoms intact in the molecule. In general, high temperature (above 100°C) causes ring opening, and rearrangement leading to open-chain isomers. The presence of two heteroatoms confer moderate stability on the ring and facilitate the easy substitution on the ring. As for diazirines the reported reactions can be broadly grouped into two categories: reactions without ring cleavage and reactions with ring cleavage (see Section 1.11.7.1).

Reactions without ring cleavage would include *N*-alkylation (most of the *N*-alkylated diaziridines are easily synthesized as and when the ring is synthesized), *N*-arylation, *N*-acylation, *N*-phosphorylation, *N*-tosylation, *N*-silylation, and smooth *N*-deacylation [84CHEC-I(7)195].

Reactions which lead to ring cleavage are either by C—N bond cleavage or by N—N bond cleavage. At high temperature (above 100°C), the ring opens by cleaving the C—N bond followed by 1,2-*N*-acyl migration leading to either open-chain compounds or ring enlarged products. Several such thermolytic rearranged products are known in the literature. Almost all diaziridines are

hydrolyzed by acids to a carbonyl compound and a hydrazine derivative. The rate of hydrolysis depends on the temperature, acidity, and the nature of the substituents. Reactions involving N—N bond cleavage is accomplished by iodide in acidic solutions, LiAlH_4 , acid hydrolysis, or thermal decomposition. As expected these reaction products are either open-chain or ring-enlargement products $\langle 84\text{CHEC-I(7)195} \rangle$.

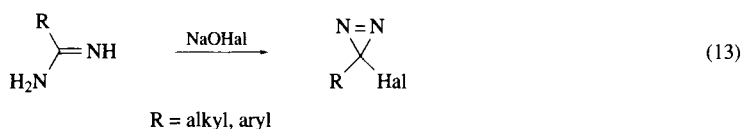
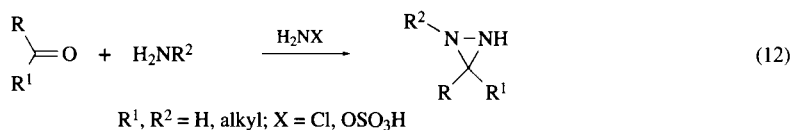
1.11.7.3 Diaziridinones and Diaziridinimines

Most of the diaziridinone systems undergo ring cleavage reactions under a variety of reaction conditions (with nucleophiles, bases, acids). In cases where the diaziridinone system is substituted with a phenyl group or fused with another ring, on heating lead to a ring enlargement reaction resulting in new heterocycles $\langle 84\text{CHEC-I(7)195} \rangle$. Diaziridinones and diaziridinimines are also well studied (see Section 1.11.6.1.3) $\langle 80\text{AG(E)276, 81JOC4478, 83CHE547, 87MI 111-02, 90TL5327, 92JOC7359, 93JOC6620} \rangle$.

1.11.8 SYNTHESIS

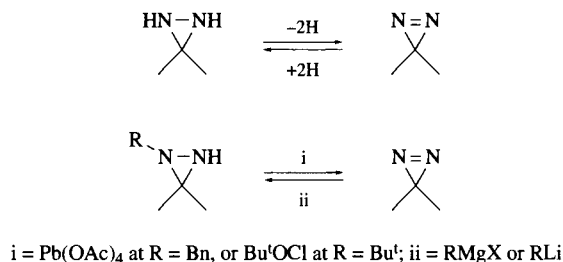
Both diazirine and diaziridine systems are widely used in organic synthesis as precursors for stereo-defined cyclic and acyclic molecules. Because the synthesis of both classes of compounds is closely interrelated, "synthesis" is discussed together in one section.

The general methods of synthesis of diaziridines and diazirines were worked out by Schmitz (Equation (12)) $\langle 84\text{CHEC-I(7)195} \rangle$ and Graham (Equation (13)) $\langle 65\text{JA4396} \rangle$ at the beginning of the study of these classes of compounds.



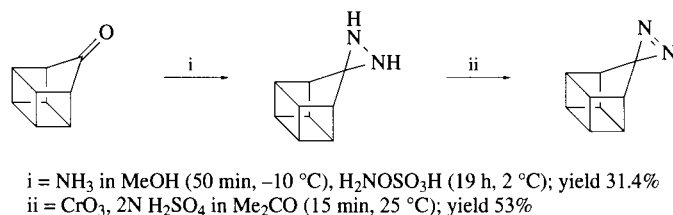
There are the approved methods for the preparation of 3,3-pentamethylenediaziridine $\langle 65\text{OS(45)83} \rangle$, 3,3-bis(trifluoromethyl)diazirine $\langle \text{B-73MI 111-01} \rangle$, and 3-chloro-3-phenyldiazirine $\langle 81\text{OS(60)53, 90OSC(7)203} \rangle$. These methods have been steadily developed ever since, and some important new approaches to the synthesis of diaziridines and diazirines have been elaborated. Diaziridines and diazirines are an easily interconvertible class of compounds (Scheme 25). The oxidative dehydrogenation of diaziridines is one of the most widespread methods for the preparation of diazirines. The reverse process is carried out via catalytic hydrogenation or through the action of sodium amalgam $\langle 84\text{CHEC-I(7)195} \rangle$. The examples of oxidative dehydroalkylation of 1-alkyldiaziridines to diazirines $\langle 75\text{ZOR2221, 80JA3888} \rangle$ are also known (Scheme 25). The reverse reaction is accomplished by the use of Grignard or similar reagents.

A number of strained spirocarbocyclic derivatives of the title classes of compounds have been



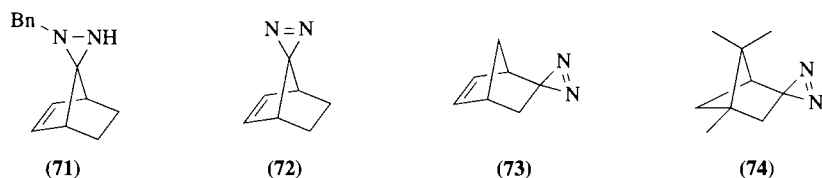
Scheme 25

studied as the precursors of carbenes. 9-Hydrazido- and the extremely explosive 9-azihomocubane were prepared from homocubane-9-one (Scheme 26) <91JA4981>.

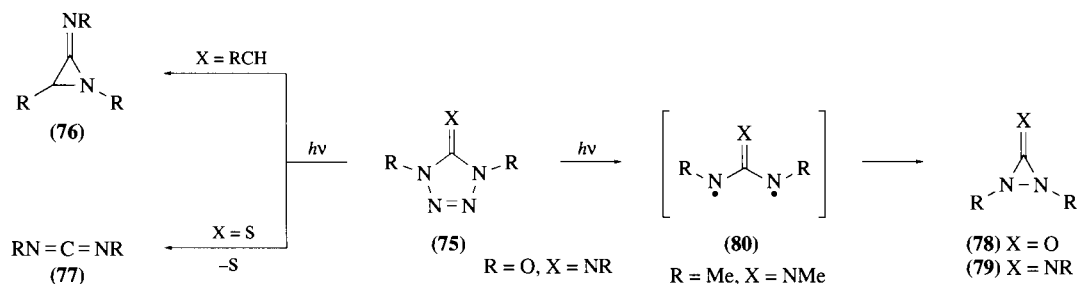


Scheme 26

It would be interesting to prepare the similar compounds on the basis of chiral D_3 -tris-homocubanonone <90JA3521>. Diaziridine (71) has been synthesized <94CC1065> by the *N*-benzylimine route <77CJC3596>, while diazirines (72) and (73) has been obtained by Schmitz's method <61CB2166>. Diaziridines of the type (74) are also known <93JA8918>. Hydrazido- and azicyclopropanes are so far unknown, whereas the carbon analogues, highly strained spiropentene derivatives, were described <94CC1263> and structurally studied <91AG(E)565, 78JA760>. The corresponding carbenes, i.e. cyclopropylidene and cyclopropenylidene, are generated from other sources, the latter is prepared, for example, by the flash pyrolysis of quadricyclene *in vacuo* <84AG(E)641>. This carbene was at first detected in space <92CRV14>.



Photolysis of tetrazoline derivatives (75) (when $\text{X} = \text{RCH}$, S) affords stable aziridinimines (76) and carbodimides (77), respectively, instead of the expected alkylidenediaziridines and diaziridinethiones. When $\text{X} = \text{O}$, RN though, diaziridinones (78) and diaziridinimines (79) are formed via the diradical (80) (Scheme 27) <75AG(E)428, 81CB3253, 89T259>. Extensive but unsuccessful efforts to prepare (12) <29M963> and diphenyl derivatives of (14) <68JA1849> are described.



Scheme 27

1.11.9 APPLICATIONS

Diazirine systems are a major source of carbenes, thus they are used as precursors for many organic and organometallic compounds. As mentioned in Section 1.11.1, diazirine systems are extensively exploited as radioactive/nonradioactive photoaffinity labels and as cross-linking reagents especially for proteins, in the field of biochemistry <B-83MI 111-01, 89MI 111-04, 94B5661, 94YZ619, 95JA3084>. In the field of molecular biology, diazirine systems are used in the novel, one-tube protocol based on specific chemical cross-linking subtraction (CCLS) method for the generation of cDNA-RNA hybrids <92MI 111-02>.

Diaziridine systems are used in adhesive primer composition for plastic films <86JAP61233541>, as

elastomers <84JAP59115307>, as propellants, in the manufacture of foam plastics as antioxidizing agents, stabilizer for fuels, and as antiknock agents <89AG(E)1381>. Diaziridines are also used in the synthesis of anticancer drugs and psychopharmaceuticals <87MI 111-05, 89AG(E)1381>, and as antibacterial agent <73JAP85565>.

Diaziridinones are used as precursors for other heterocyclic compounds important to the study of biologically active substances and material science <93JOC6620>.

1.12

Oxaziridines and Oxazirines

FRANKLIN A. DAVIS

Temple University, Philadelphia, PA, USA

and

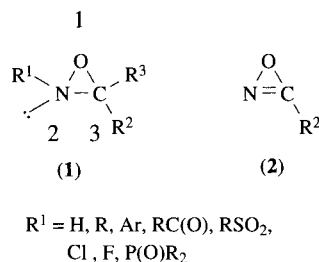
R. THIMMA REDDY

Hoffmann La Roche, Nutley, NJ, USA

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1.12.1 INTRODUCTION

Oxaziridines and oxazirines are heterocyclic compounds having oxygen, nitrogen, and carbon atoms in a three-membered ring <56JA6208>. Oxaziridines (**1**) are saturated whereas oxazirines (**2**) are unsaturated. The ring positions one, two, and three are assigned to oxygen, nitrogen, and carbon, respectively. The unusual reactivity characteristic of these classes of heterocycles is undoubtedly related to the strained three-membered ring and relatively weak N—O bond. Oxazirines (**2**) are quite unstable, only being observed as transient reaction intermediates. Very little is known of their chemistry <78JA3674>. 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 <78JA3674>.



On the other hand, the chemistry of oxaziridines (**1**) has been extensively explored and many derivatives are known bearing N—H, *N*-alkyl, *N*-acyl, *N*-aryl, *N*-chloro, *N*-fluoro, *N*-phosphinoyl, or *N*-sulfonyl substituents. Oxaziridines are among the few compounds that possess structural features necessary for a configurationally stable trivalent nitrogen atom at room temperature; ring strain and a heteroatom attached to nitrogen. Since their discovery, oxaziridines have been the subject of a number of general reviews by Emmons <56JA6208>, Horner and Jurgens <57CB2184>, Haddadin and Freeman <85MI 112-01>, and Davis and Sheppard <89T5703>. More specialized reviews deal with their ability to function as electrophilic aminating <91S327> and asymmetric hydroxylating reagents <92CRV919>. This chapter updates Schmitz's earlier treatise on oxaziridine chemistry in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) <84CHEC-I(7)195> which covered the literature up to 1982 and emphasized their synthetic utility. To provide continuity, some overlap with earlier discussions of oxaziridines is desirable.

1.12.2 STRUCTURE OF OXAZIRIDINES AND OXAZIRINES

1.12.2.1 Theoretical Methods

A detailed *ab initio* MO study has been carried out for the singlet isomers of R(CNO) including oxazirines (**2**) <78JA3674>. Two Gaussian-type basis sets were used in this study. The minimal STO-3G set was employed for the geometry optimizations and for direct calculations of transition states. Single calculations at STO-3G optimized geometries were then carried out using the split-valence 4-31G basis set. These studies revealed no theoretical evidence that any of the substituted oxazirines (**2**; R¹ = Li, Me, OH, F, Cl, CN) are kinetically-stable compounds.

The chiroptical properties of *N*-chlorooxaziridines obtained experimentally and theoretically have been reported <89JA4210>. The geometry of *N*-chlorooxaziridine (**3**) was optimized by Hartree-Fock SCF calculation at 6-31G* level using the Gaussian 82 program. The N—Cl bond (1.737 Å) is intermediate in length to that previously observed for *N*-chlorooxaziridines <88JA1719>, suggesting that the *n*_O—σNCl* interaction is weaker than the *n*_N—σNCl* interaction. The experimentally determined absolute configuration of (–)-2-chloro-1-oxa-2,2-azaspiro[2.5]octane (**4**) was confirmed by *ab initio* perturbative CI calculations on (**3**).



The importance of *N*-sulfonyloxaziridines (**1**; $R = RSO_2-$) as aprotic chiral oxidizing reagents (see Section 1.12.3.6) has prompted several theoretical studies of their oxygen-transfer reactions. Although the early part of the reaction coordinate is dominated by the four-electron repulsion of the nucleophile and the lone-pair electrons on oxygen, the “electrophilic” nature of oxaziridines is attributed to the presence of low-lying empty Walsh orbitals (LUMO) that rapidly decrease in energy during the C—O and N—O bond elongation induced by the attacking nucleophile. Calculations at the MP4SDTQ/4-31G(d)-level for the oxidation of sulfides to sulfoxides indicate that 50% of the net charge transferred to the oxaziridine resides in an oxygen σ^* orbital in the transition state <90JOC3325>.

Theoretical studies of the transfer of oxygen from an oxaziridine to an alkene, sulfide, and sulfoxide sought to identify any electronic effects pertaining to the approach of reactants that would favor a planar versus a spiro transition state (Figure 1). At the HF/6-31G* level of theory using the GAUSSIAN 86 program identical activation barriers (57.6 kcal mol⁻¹) for both first-order saddle points, planar-A and spiro-B, were obtained <90JOC3325>. The barriers for planar-C (31.1 kcal mol⁻¹) and spiro-D (31.5 kcal mol⁻¹) for the epoxidation of an alkene differed by only 0.4 kcal mol⁻¹ (MP4SDTQ/4-31G9(d) <92JOC613>). The conclusion of these studies was that the transition state orientation is steric in origin, dictated by the substituents attached to the oxaziridine oxygen and nitrogen atoms and in general agreement with experimental results (see Sections 1.12.3.6.3 and 1.12.3.6.8).

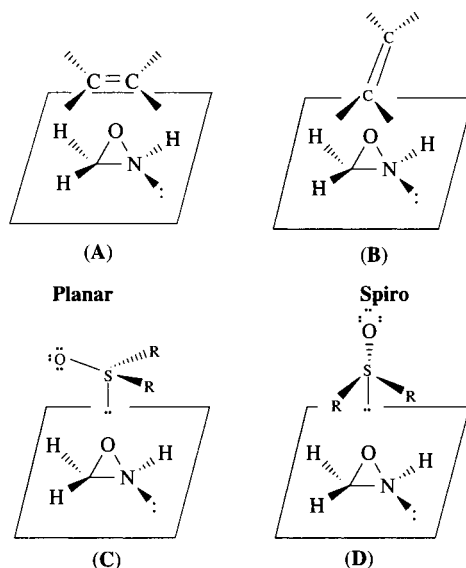


Figure 1 Transition states for oxygen transfer from an oxaziridine to an alkene and sulfoxide.

Molecular orbital calculations, by Bach *et al.*, at the HF/631 + G*/HF/4-31 + G level revealed that oxidation of the monomeric lithium enolate of an acetaldehyde proceeds by S_N2 attack of the β -carbon on the enolate along the O—N bond of the parent oxaziridine (Figure 2) <92JOC613>. In this transition state, the lithium cation is coordinated not only to the enolate oxygen atom, but to the oxaziridine oxygen and nitrogen atoms as well.

1.12.2.2 Molecular Dimensions

The x-ray structure for (2-*p*-toluenesulfonyl)-3-(*m*-nitrophenyl)oxaziridine (**5**) has been described, and as expected, the large *C*-aryl group is *trans* to the *N*-sulfonyl substituent <80JA2000>. The geometry of the oxaziridine ring agrees well with that already observed and expected in other three-membered substituted heterocycles, suggesting that the powerful electron attracting *N*-sulfonyl group has little effect on the structure of the three-membered ring. The S—N bond length of 1.734 Å is typical of a pure single bond suggesting that there is little, if any, interaction between the nitrogen lone-pair electrons and the *d*- or σ -n* orbitals on sulfur. The nitrogen atom is pyramidal with the lone-pair of electrons located *anti* to one of the sulfonyl oxygen atoms. Similar results were observed for other *N*-sulfonyloxaziridines including (–)-(2*S*,3*S*)-2-methylsulfonyl-3-

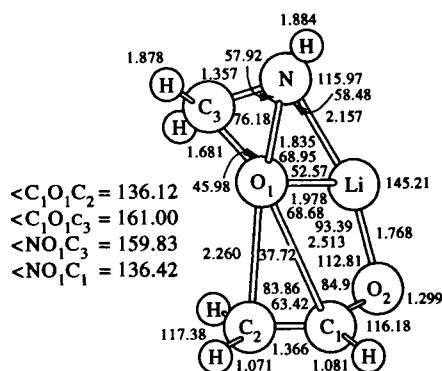
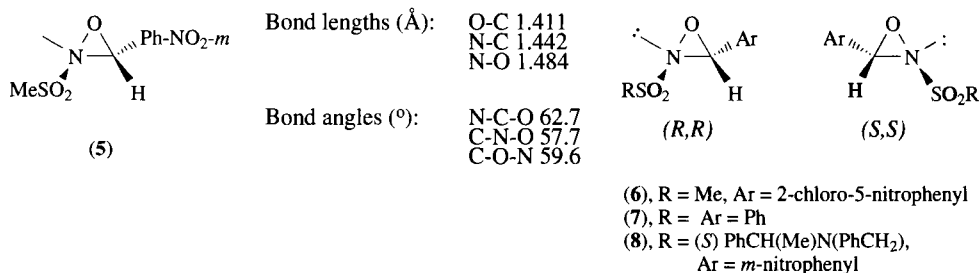
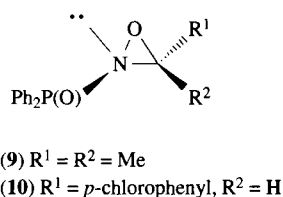


Figure 2 Geometries for the oxygen transfer of an oxaziridine to the lithium enolate of acetaldehyde.

(2-chloro-5-nitrophenyl)oxaziridine (**6**) $\langle 87\text{JCS(P2)699} \rangle$, (–)-(2*S*,3*S*)-3-phenylsulfonyloxaziridine (**7**) $\langle 88\text{JCS(P2)1595} \rangle$, and (+)-2-sulfamyloxaziridine (**8**), where x-ray structural analysis of the latter was used to establish the absolute configuration of the oxaziridine ring $\langle 87\text{JA3370} \rangle$.



In the x-ray crystal structures of 2-diphenylphosphinoyl-3,3-dimethyloxaziridine $\langle 91\text{JCS(P2)1281} \rangle$ (**9**) and 3-(4-chlorophenyl)-2-(diphenylphosphinoyl)oxaziridine $\langle 88\text{JCS(P2)1145} \rangle$ (**10**), the unusually long P—N bond length, 1.722 Å and 1.764 Å, respectively, was attributed to little if any N—P π -bonding. Bond angles and bond lengths are similar to other oxaziridines, for example (**5**)–(**8**), and the nitrogen atom is pyramidal.

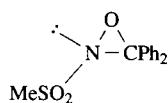


1.12.2.3 Molecular Spectra

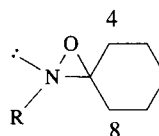
1.12.2.3.1 NMR investigations of oxaziridines; configurational stability at nitrogen

NMR investigations of *N*-alkyl oxaziridines have revealed a high degree of configurational stability of the pyramidal nitrogen atom with inversion barriers in the range 31 kcal mol^{−1} to 33 kcal mol^{−1} $\langle 84\text{CHEC-I(7)195} \rangle$. Pyramidal inversion in *N*-sulfonyloxaziridines (**5**)–(**8**) is also believed to be high because optically active examples were isolated. The inability to obtain optically active 2-methanesulfonyl-3,3-diphenyloxaziridine (**11**) by oxidation of the corresponding sulfonylimine (MeSO₂N=CPh₂) with chiral peroxy acids was attributed to stereomutation of a long-lived intermediate in the oxidation step $\langle 83\text{JCS(P2)923} \rangle$. However, studies of *N*-sulfonyloxaziridine (**12**), by Jennings *et al.*, reveal that the *N*-sulfonyl group significantly reduces the configurational stability of

nitrogen in compounds of this type <87JA8099>. This was demonstrated by inversion transfer experiments using a DANTE composite pulse to invert the lower field C-8 ^{13}C NMR resonance of (12). At 62°C the inversion barriers were determined to be 19.9–10.6 kcal mol $^{-1}$, some 12 kcal mol $^{-1}$ lower than the corresponding *N*-alkyloxaziridines. The lower barriers were attributed to a poor $n-\sigma^*$ π -interaction between the nitrogen lone-pair and sulfur in the ground state. In the transition state, where nitrogen is trigonal, overlap of its π -type lone-pair with sulfur is better. Even lower barriers were recorded for 3,3-dimethyl-2-phosphinoyloxaziridine (9), $\Delta G^\ddagger = 13.2$ kcal mol $^{-1}$. These were attributed to more efficient N—P π -bonding of the $n-\sigma^*$ type <91JCS(P2)1281>. In a related study the inversion barriers of *N*-acyloxaziridines (13) were determined to be 10.0–11.9 kcal mol $^{-1}$ at -20°C , and at -60°C rotation about the N—C(O) bond becomes slow ($\Delta G^\ddagger = 10.2$ kcal mol $^{-1}$) <92CC1078>. In solution, *N*-methoxycarbonyl-3-phenyloxaziridine exists as a 9:1 mixture of slowly interconverting *trans* and *cis*-isomers with a *cis* to *trans* inversion barrier of $\Delta G^\ddagger$ ca. 16 kcal mol $^{-1}$ <91CC435>.



(11)

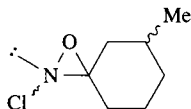


- (12a) R = MeSO $_2$
 (12b) R = *p*-tolylSO $_2$
 (12c) R = *p*-Br-PhSO $_2$
 (13a) R = MeC(O)
 (13b) R = PhCH $_2$ C(O)

1.12.2.3.2 Chiroptical properties

The circular dichroism (CD) excitation chirality method is a powerful non-empirical tool for determining the absolute configuration of chiral compounds having two or more chromophores in a dissymmetric array. Although simple oxaziridines do not absorb in the near UV they are to some degree, able to conjugate with unsaturated groups <84CHEC-I(7)195>. The CD spectra of oxaziridines (–)-(6) <87JCS(P2)699> and (–)-(7) <88JCS(P2)1595> shows that the chiroptical properties of these compounds are consistent with the (*S,S*)-configuration at the nitrogen and carbon centers, in agreement with their x-ray crystal structures. The CD spectrum is in agreement with the chiroptical behavior of a chiral benzenoid compound having an asymmetrically perturbed isolated phenyl group, which is characterized by positive and negative bands of low intensity in the 272–250 nm region, and by stronger, negative absorption at 220 nm.

Studies of the CD spectrum of optically active *N*-chlorooxaziridine diastereoisomer (14) revealed that the sign of the Cotton effect (CE) of the long-wavelength band is primarily determined by the absolute configuration at the nitrogen atom and is little affected by the configurations of the other chiral centers <89JA4210>. From these studies it was possible to assign the absolute configuration of (+)-(4) as (*R*) and, from the CE intensity at 235 nm, estimate its enantiomeric purity as 17%.



(14)

1.12.3 REACTIVITY OF OXAZIRIDINES

Almost exclusively the reactions of oxaziridines involve ring opening with all of the various combinations of C—O, C—N and N—O bond cleavage having been reported. Which bond is

cleaved is dictated by both the *N*-substituent *R* in (1) and the reaction conditions. Photolysis and thermolysis of (1) afford the isomeric amides and nitrones, while treatment with acids and bases can give hydroxyl amines and imines. Much of this chemistry has been reviewed and the reader is directed to CHEC-I for details <84CHEC-I(7)195>. Synthetically important examples of these reactions and new chemistry are illustrated below.

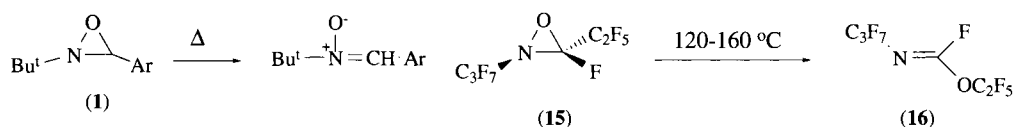
By far the preparatively most useful reactions of oxaziridines are their ability to aminate and oxidize nucleophiles. Hata and Watanabe demonstrated that oxaziridines (1) act as aminating reagents when the *N*-substituent is small, for example *R* = H, Me <79JA6671, 81JOC610>. As *R* increases in size, the site of attack shifts from nitrogen to oxygen. However, the fact that *N*-acyl and *N*-fluoro oxaziridines can act as aminating and oxidizing reagents, respectively, suggests that in addition to steric effects electronic factors are also important.

1.12.3.1 Thermal and Photochemical Rearrangements of Oxaziridines

A large number of thermal and photochemical reactions of *N*-alkyl and *N*-aryl oxaziridine have been reported <85MI 112-01, 84CHEC-I(7)195>. The possible involvement of unstable oxaziridine intermediates in the photochemical reactions of aromatic *N*-oxides has also been described <B-90MI 112-01>. The most useful of these reactions are the thermal and photochemical rearrangement of oxaziridines to nitrones and amides. Although there are some general empirical guidelines for predicating the oxaziridine substitution pattern likely to give amides or nitrones <84CHEC-I(7)195>, this aspect of oxaziridine chemistry is not well understood.

1.12.3.1.1 Rearrangement to nitrones

Thermal rearrangement of oxaziridines to nitrones, which involves cleavage of the C—O bond, appears to be limited to oxaziridines having an aryl substituent on the ring carbon <62JOC4671>. This suggests that C—O bond cleavage is heterolytic, involving a developing positive charge on the oxaziridine carbon. Indeed, this rearrangement is particularly efficient when the *C*-aryl moiety contains an electron releasing aryl substituent; Hammett $\rho^+ = -1.27$ <84TL2287>. The rearrangement is a non-stereoselective process with *cis*- or *trans*-oxaziridines affording mixtures of the *cis*- and *trans*-nitrones <71JA4075>. The thermal rearrangement of 2-(phenylsulfonyl)-3-phenyloxaziridine (7) to benzonitrile and benzenesulfonic acid is consistent with formation of an intermediate *N*-sulfonyl nitron, although one which was not detected (Scheme 1) <77CC25>. On the other hand, perfluoro-2,3-dialkyloxaziridines, such as (15), rearrange quantitatively to the isomeric alkoxy imines (16) <93JCS(P1)505>. Radical intermediates are proposed.



Scheme 1

1.12.3.1.2 Rearrangement to amides

The thermal and photochemical isomerization of oxaziridines to amides [*R*²C(O)NR¹R³] takes place with concomitant cleavage of the N—O bond and migration of one of the substituents on carbon to nitrogen <85JCS(P1)849>. In spiro oxaziridines this rearrangement has been used in the synthesis of medium to large lactams <80JHC1025>. Some representative examples are given in Table 1. The mechanism proposed for *N*-alkyl oxaziridines is thought to involve homolytic fragmentation of the N—O bond in the singlet excited state, internal conversion to the ground-state with migration

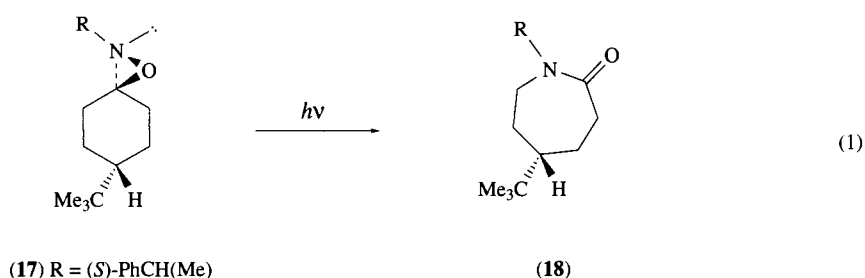
of the ring carbon <82JA3929>. A study of the sensitized photoisomerization of *N*-alkyl oxaziridines to lactams by aromatic compounds has been described <94JA6439>.

Table 1 Rearrangement of spiro oxaziridines to lactams.^a

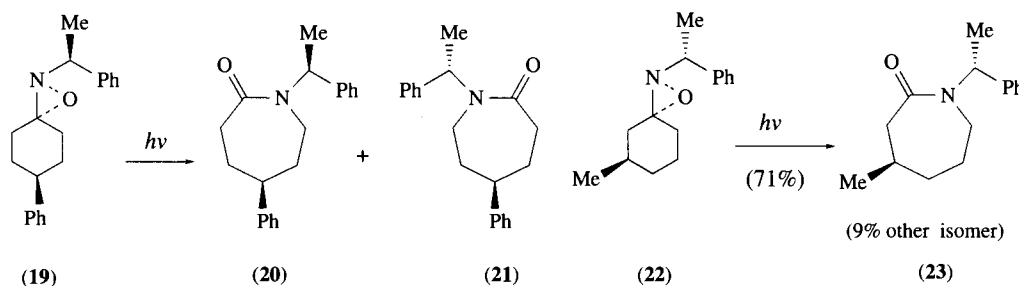
Oxaziridine	Conditions	Products	Yield (%)
	Heat <i>hν</i>		55 85
	Heat <i>hν</i>		75 28

^a<80JCS(P1)1693>.

Photolysis of (2*R*, α *S*)-6(e)-*t*-butyl-2(α -methylbenzyl)-1,2-oxazaspiro-[2.5]-octane (**17**) afforded a single lactam (**18**) in 80% yield (Equation (1)) <82JA3929>. The fact that this lactam has the (*S*)-configuration at the *t*-butyl stereogenic center demonstrates that the group that migrates is the one *anti* to the nitrogen lone-pair of electrons.



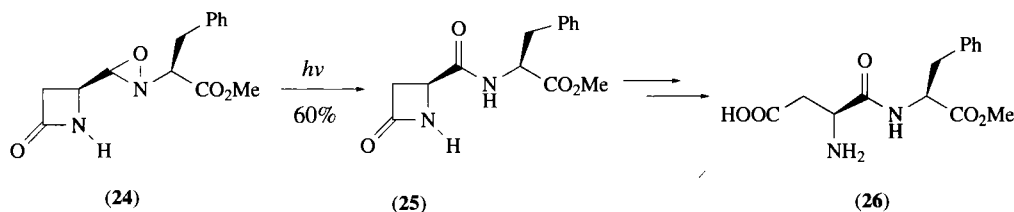
Aube *et al.* expanded these studies into general methodology for the asymmetric synthesis of nonracemic caprolactams and valerolactams <90JA4879>. For example, irradiation of oxaziridine (**19**) at 2537 Å gave a 9 : 1 mixture of (**20**) and (**21**) in 59% yield. Likewise (**22**) gave (**23**) (Scheme 2) <91JOC499>. In all cases examined the stereoselectivity depended only on the axial chirality of the substrate and not on stereochemical or conformational factors. Similarly the ring expansion of spiro oxaziridines derived from optically active β -substituted cyclohexanones is determined by the stereochemistry at nitrogen which, in turn, is controlled by the *N*- α -phenylethyl substituent <91JOC499>. However, the presence of this ring substituent results in high stereoselectivity $\geq 90\%$ in formation of the oxaziridine via MCPBA oxidation of the corresponding imine (see Section 1.12.4.1).



Scheme 2

Dissolving metal ammonia reduction (Na/NH₃) of (**20**) gives the *N*-unsubstituted lactam in 75% yield, which is a key intermediate in the synthesis of the benzomorphinan family of analgesics

<90JA4879>. A similar approach was used to prepare (–)-alloyohimbane. Photolysis of optically active (24) gave (25) which had previously been converted into the dipeptide sweetener aspartame (26) (Scheme 3) <87TL2595>.

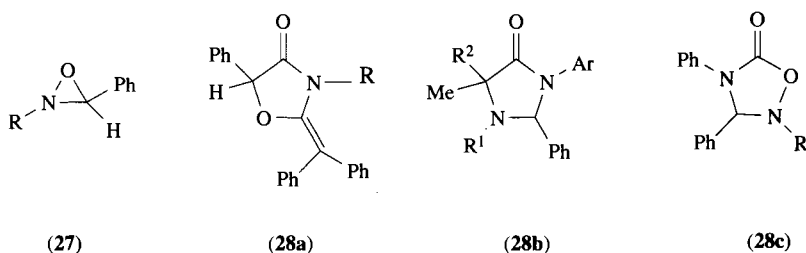


Scheme 3

N-Sulfonyl amides ($\text{ArSO}_2\text{NHC(O)Ph}$), isolated in the photolysis of *N*-sulfonyloxaziridines, are formed from the oxaziridine singlet state <77TL1721>.

1.12.3.1.3 Cycloaddition reactions

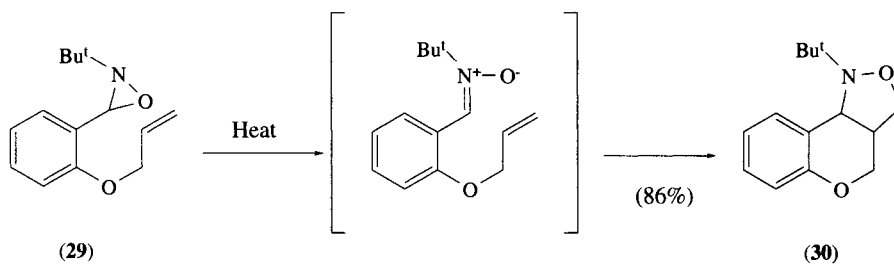
On heating with heterocumulenes oxaziridine, (27) undergoes a number of addition and cycloaddition reactions affording various types of heterocyclic compounds. These studies, primarily carried out by Agawa *et al.* <74JOC948, 74JOC957, 77JOC448, 86JOC407>, have been reviewed by Haddadin and Freeman <85MI 112-01>. Only a few of the more synthetically useful examples are presented here.



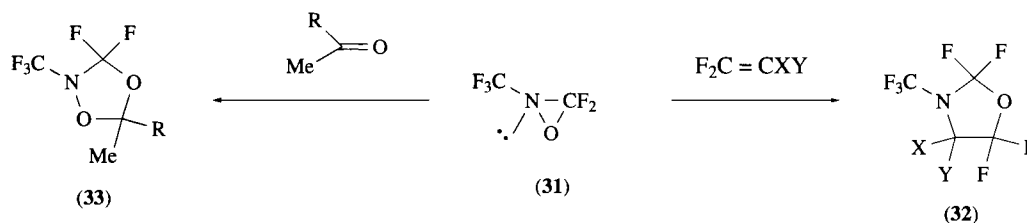
Two molecules of diphenylketene ($\text{Ph}_2\text{C}=\text{C}=\text{O}$) react with (27; R = isopropyl) on heating to give oxazolidinones (28a) in 68% yield <74JOC948>. With ketenimines ($\text{MeR}^1\text{C}=\text{C}=\text{NAr}$), (27; R = Bu^t) gave (28b) (40–60%) via a rearrangement <77JOC448> and oxadiazolidinones (28c; R = Buⁿ, Prⁱ, Bu^t) are obtained in 36–95% yield on heating (27) with phenylisocyanate <74JOC948>. Although mechanistic details of these transformations are uncertain, they have been discussed in terms of nucleophilic attack by either the oxaziridine nitrogen or oxygen atoms at the central carbon of the heterocumulene <74JOC948>.

Isoxazolidines (30) were prepared in 86% yield via the intramolecular 1,3-dipolar cycloaddition of a nitron generated on heating oxaziridine (29) (Scheme 4) <86H(24)611>.

Cycloaddition of 2-trifluoromethyl-3,3-difluorooxaziridine (31) with various 1,1-difluoroalkenes (X, Y = Br, Cl, F) gives 1,3-oxazolidines (32) in 60–85% yield, while ketones give 1,3,4-dioxazolidines (33) (Scheme 5) <86JOC4466>.



Scheme 4

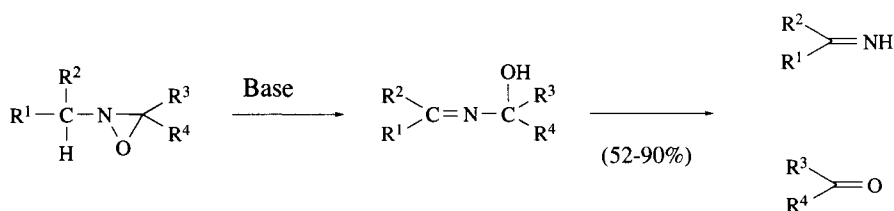


Scheme 5

1.12.3.2 Base-Catalyzed Eliminations

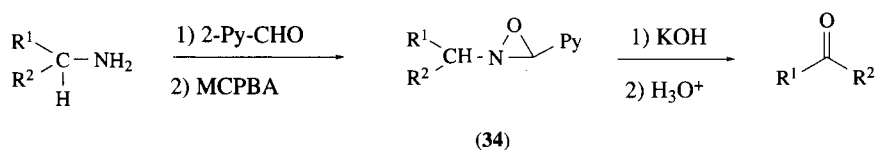
1.12.3.2.1 Synthesis of carbonyl compounds

The oxaziridine ring is generally inert toward bases such as hydroxide $\langle 57JA5739 \rangle$. However, when α -hydrogens are present in the *N*-alkyl group these heterocycles isomerize to carbinolimines in the presence of base $\langle 86JOC4232 \rangle$. Ketones or aldehydes and ammonia result on hydrolysis of the carbinolimines. Boyd *et al.* developed a synthesis of *N*-H substituted aldimines and ketimines ($R^1R^2C=NH$) by treating the fluorenone and *p*-nitrobenzaldehyde derived *N*-alkyl oxaziridines with hindered bases (DABCO, DBN and $KOBu^t$) in anhydrous solvents $\langle 82TL2907 \rangle$ (Scheme 6). A concerted E₂ elimination mechanism has been proposed for these transformations $\langle 74T2825, 82JOC419, 82TL2907, 86JCS(P1)867 \rangle$.



Scheme 6

Methodology for the oxidative deamination of amines to ketones, mediated by oxaziridines, has been described by Dinizo and Watt $\langle 75JA6900 \rangle$. The amines were transformed into their respective imines using 2-pyridinecarboxyaldehyde and oxidized to oxaziridines (34) with MCPBA (Scheme 7). With KOH in aqueous acetone containing methanol or *N,N*-dimethylformamide the oxaziridine gives corresponding ketones in good yield. In a similar way alkylated *N*-benzylidenebenzylamines are converted into ketones $\langle 79JCS(P1)2364 \rangle$.

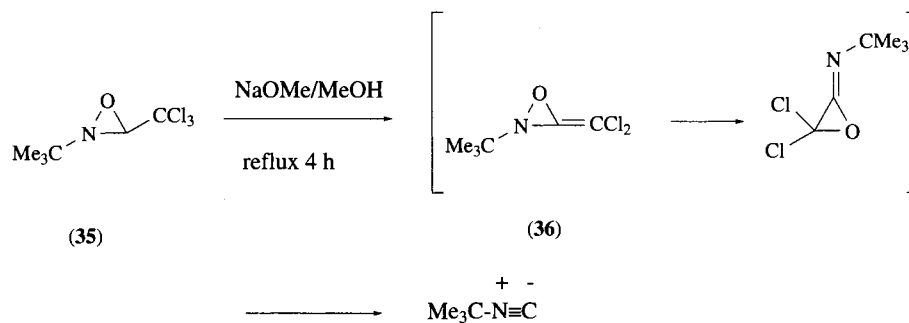


Scheme 7

2-*t*-Butyl-3-(trichloromethyl)oxaziridine (35) on treatment with base gives, among other products, *t*-butylisocyanide ($Me_3C-N=C$) in 28% yield $\langle 92T7345 \rangle$. Rearrangement via the valence isomerization of a transient methyleneoxaziridine (36) is proposed as shown in Scheme 8.

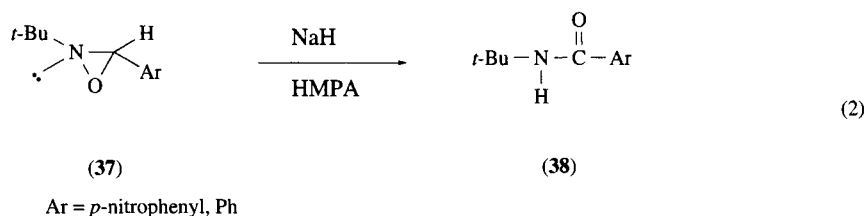
1.12.3.2.2 Synthesis of amides

Treatment of *E-t*-butyl-3-(*p*-nitrophenyl)oxaziridine (37) with NaH in HMPA gave an 83% yield of amide (38) (Equation (2)) $\langle 69TL3887 \rangle$. Amides were also observed when LDA was used to effect the ring opening $\langle 75JA6900 \rangle$. Deoxygenation to give the imine ($Me_3CN=CHPh$) is the principal



Scheme 8

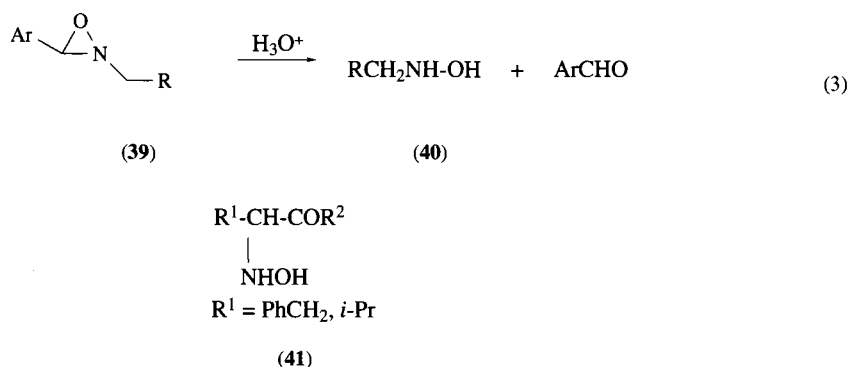
product on reaction of oxaziridine (37; Ar = Ph) with LDA <80JOC1489>. An initial electron transfer reaction from the base to oxaziridine is proposed for the deoxygenation.



1.12.3.3 Acid-Catalyzed Reaction. Synthesis of Hydroxyl Amines and Amides

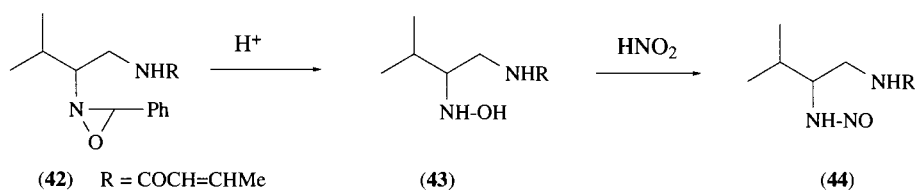
Acid-catalyzed hydrolysis of *N*-aryloxaziridines may proceed via cleavage of either the C—O or N—O bonds, depending upon the ring substitution pattern. These reactions are usually discussed in terms of initial protonation at the oxaziridine oxygen atom <77JHC1393>. Acid-catalyzed isomerization to nitrones has also been reported <64HC(19)624>.

Acid catalyzed hydrolysis of 3-aryl oxaziridine (39) takes place with nearly exclusive N—O bond cleavage to give hydroxylamines (40) in 70–85% yield (Equation (3)) <64HC(19)624>. This is particularly true when the C—Ar group is *p*-MeOPh which is able to stabilize the developing carbocation on the oxaziridine carbon atom <74TL2453, 79BAP459>. A series of biologically active *N*-hydroxyamino acid derivatives (41) was prepared in modest yield (30–40%) by transforming amino acids into oxaziridines, followed by acid catalyzed hydrolysis <73CC147, 74HCA657, 74TL2453, 79BAP459>.



Dopastin (44), a dopamine β -hydroxylase inhibitor, was prepared in eight steps from L-valinol by treating hydroxyl amine (43) with HNO₂ <73CC147>. An acidic ion-exchange resin effected hydrolysis of optically active (42) to (43) (Scheme 9).

An alternative to the base-catalyzed rearrangement of oxaziridines to ketones, discussed in Section 1.12.3.2.1, is the acid-catalyzed hydrolysis of oxaziridines derived from amines and acetone <75AJC2547>. Oxidation of *C,N*-diarylaldehydes (Ar¹CH=N-Ar²) with sodium perborate in



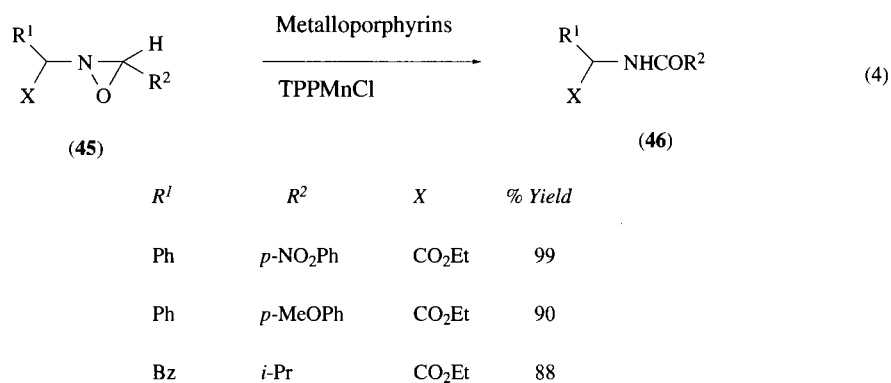
Scheme 9

trifluoroacetic acid gives *N,N*-diarylformamides ($\text{OHC}-\text{NAr}^1\text{Ar}^2$) (93TL6773). Initial oxidation of the imine to an oxaziridine, which was not detected, followed by acid-catalyzed ring opening with synchronous migration of the aryl group to an electron-deficient nitrogen was proposed.

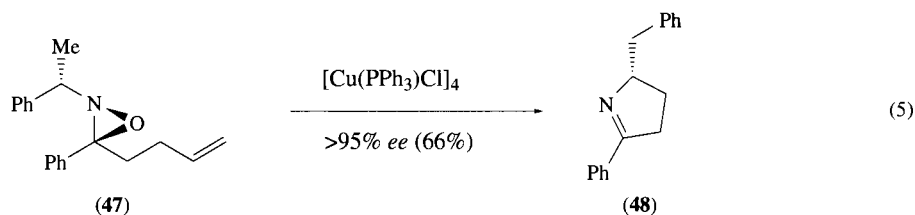
1.12.3.4 Homolytic Reactions

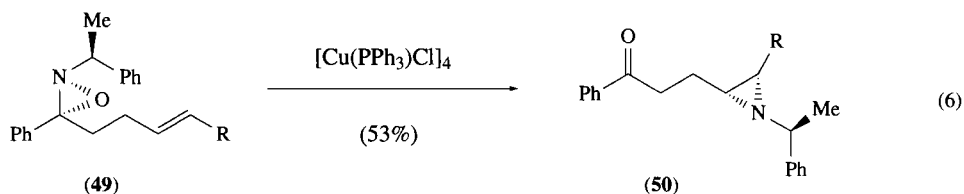
The homolytic ring opening reactions of oxaziridines catalyzed by ferrous ion were explored in detail by Emmons (64HC(19)624). In general these reactions are pictured as single-electron transfer (SET) reactions which result in N—O bond cleavage of the oxaziridine to form amino/alkoxy radicals which can undergo protonation, β -scission, or radical rearrangement depending on the substituents (84CHEC-I(7)195, 89T5703). The electrochemical behavior of 2-(methanesulfonyl)-3-phenyloxaziridine and 2-*t*-butyl-3-phenyloxaziridine have been studied polarographically at the mercury electrode in organic solvents (91MI 112-01). Following electron uptake and breaking of the N—O bond, benzaldehyde and imine are produced, respectively, by these oxaziridines.

As discussed in Section 1.12.3.1.2 rearrangement of 2-alkyl oxaziridines to the corresponding amides can be achieved by heating or irradiation with light. This transformation has been efficiently catalyzed by high-valent metalloporphyrins (90CPB839), for example oxaziridine (45), on treatment with tetraphenylporphyrin iron(III) [TPPFeCl] or chlorotetraphenylporphyrin manganese(III) [TPPMnCl], gave the corresponding amides (46) in excellent yield (Equation (4)). This novel rearrangement was also used to create a peptide bond in a precursor to the dipeptide aspartame (26) (Section 1.12.3.1.2).



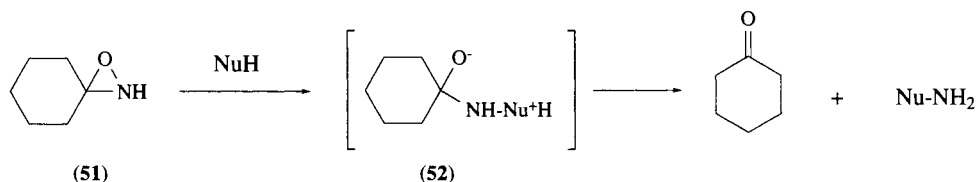
Aube *et al.* developed methodology for single-electron transfer (SET) to oxaziridines under nonaqueous, neutral conditions (92JA5566). Treatment of non-racemic 3-butenyloxaziridine (47) with the copper(I) catalysts $[\text{Cu}(\text{PPh}_3)\text{Cl}]_4$ gave pyrroline (48) in $\geq 95\%$ *ee* and 66% yield (Equation (5)). On the other hand oxaziridine (49), under similar conditions, gave the aziridine (50) (Equation (6)). The mechanism is envisioned as SET to (47/49) giving rise to radical/alkoxide pairs which rearrange to (48) or (50) depending on steric factors.





1.12.3.5 Amination Reactions of Oxaziridine

Nucleophiles react with N—H and *N*-acyl oxaziridines with transfer of NH and *N*-acyl, respectively. Because of ease of preparation (see Section 1.12.4) much of this chemistry, reviewed by Andrea and Schmitz <91S327>, has been carried out with solutions of cyclohexanespiro-3'-oxaziridine (**51**, 1-oxa-2-azaspiro[2.5]octane). Attack at the NH group of the three-membered ring by nucleophiles results in formation of intermediate (**52**) which can react either by elimination of water forming a cyclohexylidene compound, a heterocycle, or a rearrangement product (Scheme 10). Most often, cyclohexanone is formed resulting in amination of the nucleophile. Transfers of NH to *N*-, *O*-, *S*-, and *C*-nucleophiles have been reported making possible the syntheses of hydrazines, *N*-amino peptides, hydroxy amines, sulfenamides, thiooximes, sulfonamides, aziridines, and α -amino acids <91S327>.

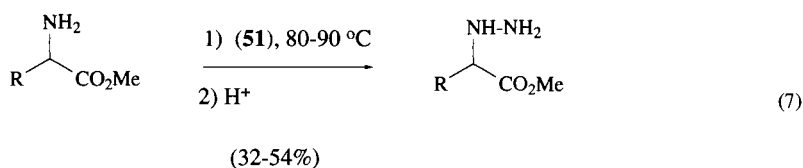


Scheme 10

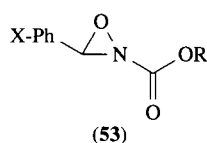
1.12.3.5.1 Amination of *N*-nucleophiles. Synthesis of hydrazines

The reactions of amines with NH oxaziridines is a useful method for the preparation of hydrazines. Many studies of amine amination using (**51**) were discussed in CHEC-I <84CHEC-I(7)195> and reviewed in 1991 <91S327>. Secondary amines react within a few minutes to give good yields of hydrazines. In some cases intermediate (**52**) can be intercepted; for example, with ephedrine to give the tetrahydrocarboline <83LA1043>. Illustrative examples are given in Table 2. Primary amines react more slowly although the amination of ammonia by an oxaziridine is used in a large-scale process for the synthesis of hydrazine <91S327>.

The reaction of α -amino acids with oxaziridine (**51**), to give the α -hydrazino acid requires higher temperatures (ca. 80–90 °C) (Equation (7)) <91S327>. More recently, in the early 1990s, electrophilic *N*-amination of optically pure α -amino acids (as their salts or esters) with the crystalline *N*-methoxycarbonyl-3-phenyloxaziridine (**53a**) has been described by Collet and co-workers <91CC435>. The oxaziridine reaction occurs at room temperature affording good yields of the carbazates (Table 3). The *N*-Boc and *N*-Cbz hydrazino acids, easily deprotected, are prepared by treating amino acids with oxaziridines (**53b**) <93JOC4791> and (**53c**) <93TL6859>, respectively. These oxaziridines also form good yields of the *N*-Boc and *N*-Cbz protected hydrazines with secondary amines <93JOC4791, 93TL6859>. α -Hydrazino acids are inhibitors of amino acid decarboxylase and are useful synthetic building blocks <87T891>.



R = Me, *i*-Pr, Ph, PhCH₂



a, R = Me, X = H
 b, R = *t*-Bu, X = *p*-CN
 c, R = Ph, X = H

Table 2 Amination of amines with oxaziridine (51).

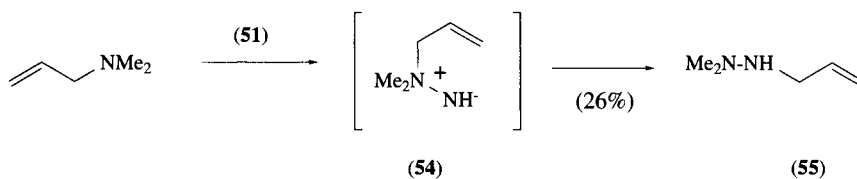
Amines	Products	Yield (%)	Ref.
		50%	63ZC190
		60	84EGP210686
^a		93	91S327
		89	77JPR195
^b			83LA1043

^aTrapped with benzaldehyde. ^bTrapped with cyclohexanone.

Table 3 Amination of α -amino acids with (53).

Oxaziridine	Amino acid	Product	Yield (%)	Ref.
(53a)			57	91CC435
(53b)			41	93JOC4791
(53b)			77	93JOC4791
(53c)			41	93TL6859

Tertiary amines are aminated to give unstable hydrazinium compounds, for example (54), is suggested by the formation of hydrazine (55) via a Sommelet–Hauser rearrangement on reaction of (51) with *N,N*-dimethylallyl amine (Scheme 11) <91S327>.



Scheme 11

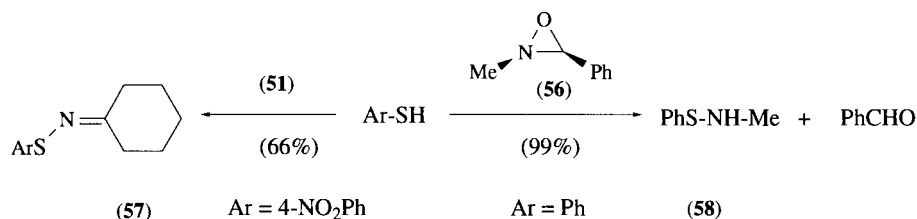
1.12.3.5.2 Amination of S-nucleophiles. Synthesis of sulfenamides and alkenes

Compounds containing bivalent sulfur react rapidly with N—H and N-methyl oxaziridines to form sulfenamides ($\text{R}^1-\text{S}-\text{NH}-\text{R}^2$), the stability of which depends on the reactivity of the substrate and the product. Ring closure and sulfinimine ($\text{R}-\text{S}-\text{N}=\text{CR}_2$) formation via intermediate (52), are frequently observed products with thioamides and thioureas. Sulfinates ($\text{ArSO}_2^-\text{Na}^+$) are aminated to sulfonamides in excellent yield. These aminations, explored in detail by Schmitz and co-workers with spirooxaziridine (51), have been reviewed (91S327) and only a few illustrative examples are given in Table 4.

Table 4 Amination of organosulfur compounds with oxaziridine (51).

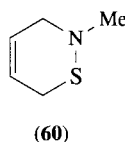
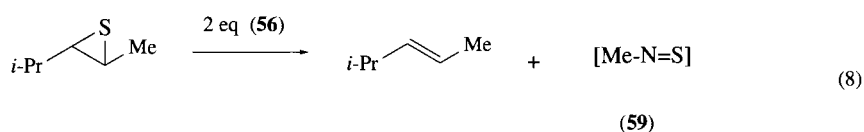
Organosulfur compound	Product	Yield (%)	Ref.
 R = H, Me, Et		80–95	91S327
 p-Tolyl	 R	56–89	93S951
 X = NH, Se, S		68–78	91S327
 p-Tol-SO2Na ⁺ NaSCN	 p-Tol-SO2NH2 NCS—NH2	77 66 91	93T3767 91S327 77JPR195

Examples of the oxaziridine mediated amination of thiols are rare (Scheme 12). 4-Nitrobenzenethiol, for example reacts with spirooxaziridine (51) to give sulfinimine (57) (79JA6671), while benzenethiol on treatment with *cis*-2-methyl-3-phenyloxaziridine (56) gives sulfenamide (58) (81JOC610).



Scheme 12

The desulfurization of episulfides by *cis*-oxaziridine (56) appears to be a general reaction affording the alkene, dimethylsulfur diimide (MeN=S=NMe), and azomethane (MeN=NMe) <80JOC1691>. These latter products are formed via the intermediate thionitrosomethane (59) (Equation (8)) which was trapped with 2,3-butadiene to give the cyclic sulfenamide (60) in 22–33% yield. The alkenes are formed in good to excellent yield (80–90%) with retention of configuration.



1.12.3.5.3 Amination of O-nucleophiles. Synthesis of oxime ethers

Formation of N—O bonds via amination with oxaziridines has been little studied. Benzaldehyde oxime *O*-ethyl ether, along with other products, are obtained on treatment of 3-phenyloxaziridine (56; Me = H) with sodium ethoxide <67LA131, 91S327>.

1.12.3.5.4 Amination of C-nucleophiles. Synthesis of amines

Amination of *C*-nucleophiles, where deprotonation was possible using weak bases such as aqueous alkali and DABCO, has been explored by Schmitz and co-workers with cyclohexanespiro-3'-oxaziridine (51) <91S327>. Some examples are given in Table 5.

N-Boc protected α -amino carbonyl compounds are prepared by treatment of the lithium enolates of ketones, esters, and amides with *N*-Boc 3-(4-cyanophenyl)oxaziridine (53b) <93JOC4791>. The modest yields (33–38%) are ascribed to aldol-type reactions of the enolate with the 4-cyano-benzaldehyde (62) by-product (Equation (9)). In one example, the lithium enolate of propiophenone gave *N*-Boc-cathione (61), the pharmacologically active constituent of the leaves of khat.

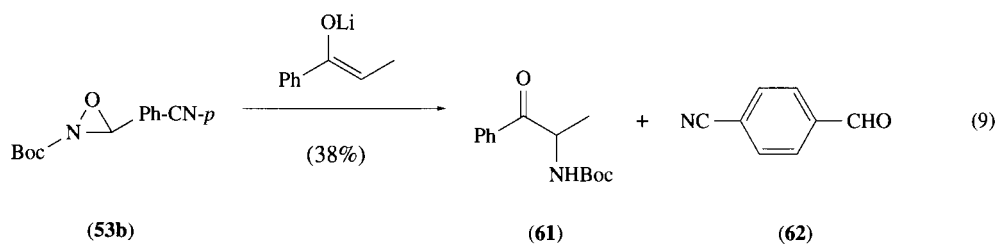
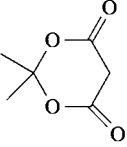
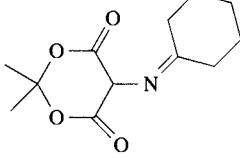
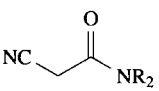
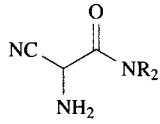
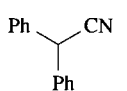
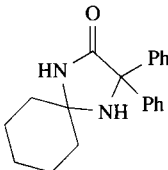
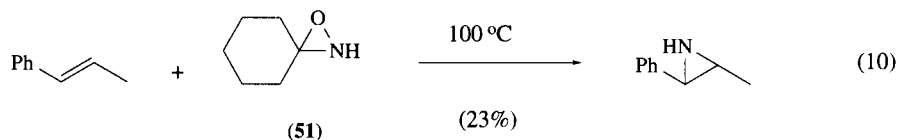


Table 5 Amination of enolates by oxaziridine (**51**).^a

Substrate	Base/conditions	Products	Yield (%)
	NaOH/H ₂ O		79
	NaOH/toluene		91–94
	DABCO, RT		75

^a <91S327>

The aziridination of alkenes by cyclohexanespiro-3'-oxaziridine (**51**) at 100 °C has been described <74KGS1629, 91S327>. The reaction is stereospecific; for example *trans*- β -methylstyrene gives exclusively the *trans*-aziridine (Equation (10)).

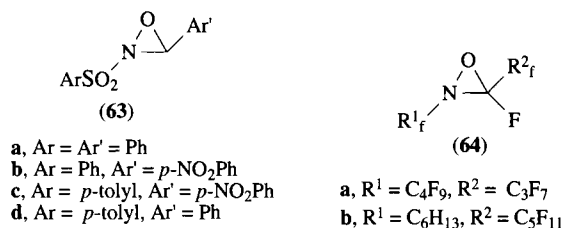


1.12.3.6 Oxygen-transfer Reactions of Oxaziridines

Oxaziridines are members of the general class of oxidizing reagents that have their active-site oxygen atoms as part of a three-membered ring <86JOC4240, B-90MI 112-01>. Included in this class of reagents are the metal (Cr Mo, W) peroxides and hydroperoxides catalyzed by high-valent *d*⁰ transition-metal complexes (Mo V, Ti), and the dioxiranes. The most well-known member of this class of compounds is the Sharpless reagent for the asymmetric epoxidation (AE) of allylic alcohols <91JA106>. The similarities in structures for the metal peroxides, dioxiranes, and oxaziridines suggest that they may share a common mechanism of oxygen-transfer. The driving force for oxygen-transfer has been related to relief of ring strain and the enthalpy associated with the formation of strong double bonds in the products <86JOC4240>.

trans-*N*-Sulfonyloxaziridines (**63**) and perfluoro-*cis*-2,3-dialkyl-oxaziridines (**64**) are the only oxaziridines able to oxidize nucleophilic substrates at rates which are comparable to peracids. The by-products of these oxidations are the corresponding imines, Ar¹SO₂N=CHAr² and R¹N=CFCR², respectively. These oxaziridines, particularly (**63**), are highly chemoselective reagents which have found many applications in synthetic organic chemistry <95MI 112-01, 95MI 112-02, 95MI 112-03>. For example, (**63**) selectively oxidizes sulfides to sulfoxides without over-oxidation to sulfones <78TL5171, 88JOC5004>. Nucleophilic substrates such as sulfides, selenides, and amines are oxidized within a few minutes at room temperature, but epoxidation of alkenes requires heating at 60 °C for several hours <81TL917>. Although alkynes and pyridine do not react with (**63**), primary, secondary, and tertiary amines are oxidized at nitrogen affording hydroxyl amines and amine oxides <83TL1213, 88JOC5856>. Since *N*-sulfonyloxaziridines are neutral, aprotic oxidants, they are among the few reagents available for the oxidation of carbanions and enolates <89T5703, 92CR919>. The fact

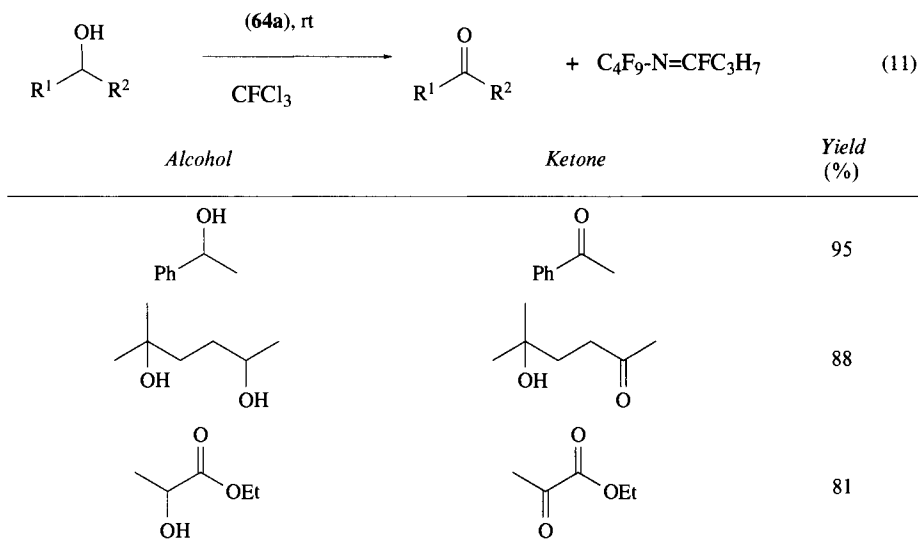
that enantiomerically pure examples of *N*-sulfonyloxaziridines are readily available means that all of these transformations can be carried out asymmetrically.



Perfluoro-*cis*-2,3-dialkyloxaziridines (**64**) are more reactive than (**63**) and are not only able to oxidize sulfides to sulfoxides, sulfoxides to sulfones <94JOC2762>, and epoxidize alkenes <86JOC4466, 91JFC(53)181, 91JFC(53)399>, but oxidize alcohols to ketones <92TL7245> and insert oxygen into the C—H bonds of hydrocarbons to give alcohols <93JA4897>. The oxidation of sulfides to sulfoxides and the epoxidation of alkenes by *N*-phosphinoyl oxaziridines (**10**) has been briefly mentioned <85CC582>.

1.12.3.6.1 Oxidation of alcohol to ketones

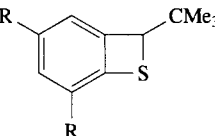
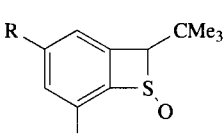
Secondary alcohols are oxidized to ketones with high regio- and stereoselectivity on treatment with perfluoro oxaziridine (**64a**) at room temperature, (Equation (11)) <92TL7245>. Yields are excellent and the reactivity of this oxaziridine is reported to be comparable to that of dioxiranes.



1.12.3.6.2 Hydroxylation of unactivated C—H bonds. Synthesis of alcohols

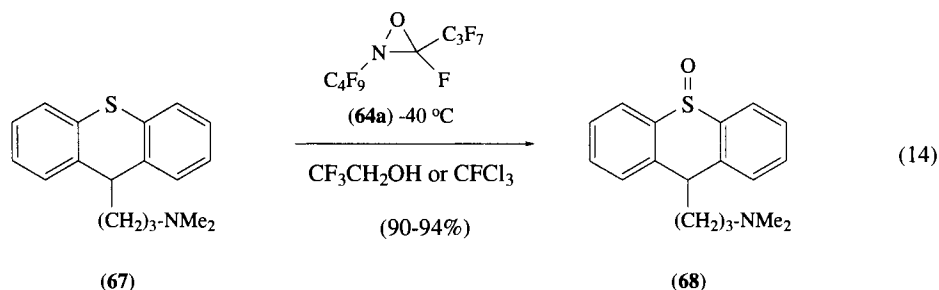
The insertion of oxygen into a C—H bond of unactivated tertiary alkanes with perfluoro oxaziridines (**64**) has been described by DesMarteau and co-workers (Equation (12)) <93JA4897>. The oxidation is carried out by treating the hydrocarbon in CFCl₃ with a slight excess of the oxaziridine at room temperature. Good-to-excellent yields are obtained from within a few minutes to several hours depending on the substrate (Table 6). Small amounts of ketones (0.6% to 6.1%) are also detected resulting from oxidation of secondary alcohols which are also formed (see Section 1.12.3.6.1). Although the mechanism of oxidation is unclear, the high selectivity suggests a concerted “oxenoid” O-atom type insertion into the C—H bond of the hydrocarbon.

Table 7 Oxidation of sulfides to sulfoxides by 2-(phenylsulfonyl)-3-aryloxaziridines (**63**) in CHCl₃ at RT.

Sulfide	Oxaziridine (equiv.)	Time (h)	Sulfoxide	Yield (%)	Ref.
PhSMe	(63a) (1)	Fast	PhS(O)Me	92	78TL5171
	(63b) (2.5)	20	PhS(O)Me	20	78TL5171
			PhSO ₂ Me	80	78TL5171
Ph ₂ S	(63a) (1)	Fast	Ph ₂ SO	80	78TL5171
(ClCH ₂ CH ₂) ₂ S	(63b)	Fast	(ClCH ₂ CH ₂) ₂ SO	>90	90JOC3664
	(63a) (1)	Fast		81	78TL5171
PhSSiMe ₃	(63a) (2)	Fast	PhS(O)OSiMe ₃	63	80JOC1650
	(63a) (1)	0.5		79	83JOC3071
R = CH ₂ CMe ₃					

While the oxidations using *N*-sulfonyloxaziridine (**63**), summarized in Table 7, are stoichiometric a catalytic variant has been developed using buffered potassium peroxymonosulfate (Oxone) to generate non-stoichiometric amounts of (**63b**) <88JOC5004>. The system is highly chemoselective affording the sulfoxides in excellent isolated yields with only trace amounts of the sulfones being detected. Sulfides producing hydrophilic sulfoxides are, however, further oxidized nucleophilically to sulfones by the peroxymonosulfate anion.

Perfluoro-*cis*-2,3-dialkylloxaziridines (**64a**) also selectively oxidizes sulfides to sulfoxides at -40°C in CFCl₃ <94JOC2762>, for example, the hydrochloride of promazine (**67**), a neuroleptic drug, is oxidized to (**68**) in 90–94% yield (Equation (14)). At higher temperatures and/or with excess oxidant the corresponding sulfones are rapidly formed even at -20 to 0°C .

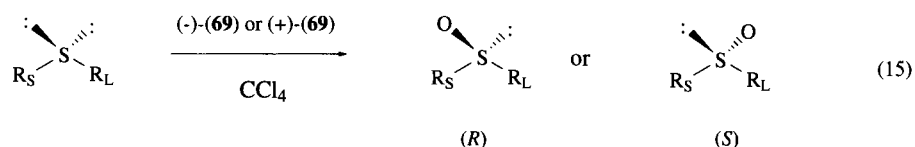
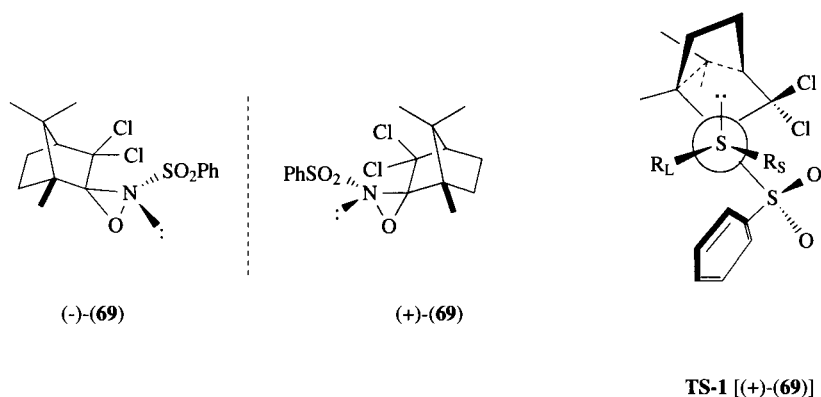


(ii) Asymmetric oxidation of sulfides to sulfoxides

Enantiomerically enriched sulfoxides, valuable chiral synthons and auxiliaries which are widely used in asymmetric synthesis <B-88MI 112-01>, are prepared by asymmetric oxidation of sulfides with enantiopure *N*-sulfonyloxaziridines <87JA3370, 88JA8477, 88JCS(P1)1753, 90ZN(B)1689, 92JA1428>. The *ees* (5% to >95%) are dependent not only on the structure of the substrate and oxaziridine, but the reaction conditions (solvent and temperature) as well. An important feature of these nonracemic *N*-sulfonyloxaziridines is that the relative and absolute configurations of the oxaziridine ring control the absolute stereochemistry of the product; the desired enantiomer can be generated simply by selection of the appropriate reagent.

The most generally effective oxaziridine for the asymmetric oxidation of sulfides to sulfoxides is *N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)-oxaziridine (**69**) as in Equation (15) <92JA1428>. Steric effects are believed primarily responsible for the molecular recognition. They are predicted using a simple active-site model, where the non-bonded interactions between large (R_L) and small (R_S)

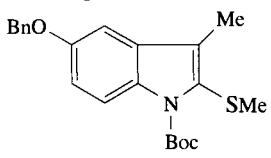
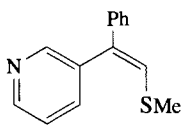
groups of the sulfide (R_L-S-R_S), and the active-site surface are minimized in a planar transition-state structure, **TS-1** [(+)-(69)] gives the (*R*)-sulfoxide <92JA1428>.



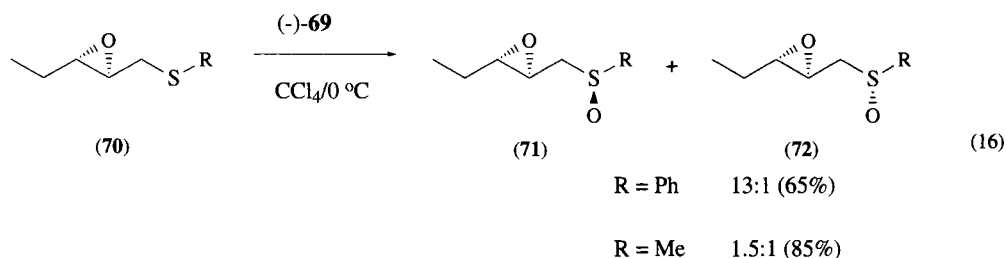
Examples of the asymmetric oxidation of prochiral sulfides to sulfoxides by (–)-(69) are given in Table 8. Oxidations are generally complete within 1–6 h, although sterically hindered sulfides or those having electron-attracting groups may require longer times. In these cases heating to ca. 65°C increases the rate of oxidation without significant loss in asymmetric induction. The highest *ees* are observed for oxidations in low dielectric solvents such as CCl_4 and for those sulfides (R_L-S-R_S) where the difference in size of the R_L and R_S groups is large <92JA1428>. With (–)-(69) (*S*)-sulfoxides are obtained, while (+)-(69) gives the (*R*)-sulfoxides.

Asymmetric oxidation of 2,3-epoxy sulfides (70) with (–)-(69), double stereodifferentiation, gave

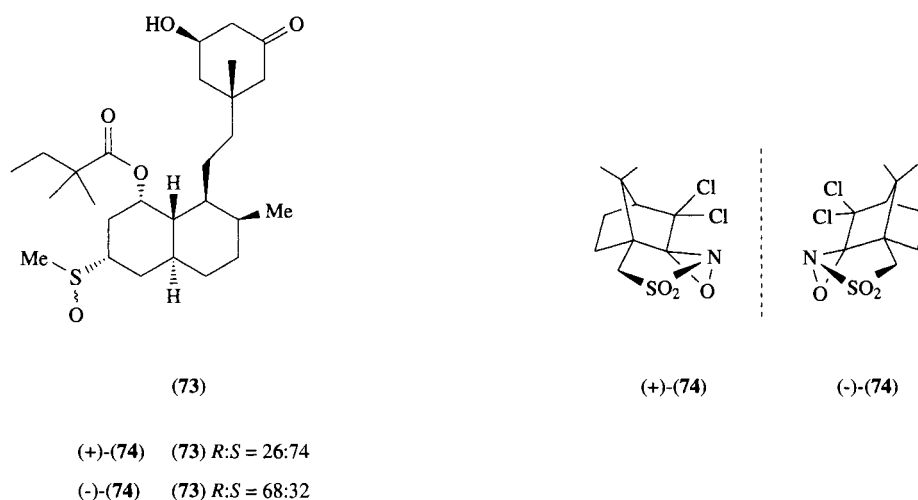
Table 8 Asymmetric oxidation of prochiral sulfides to sulfoxides using (–)-*N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (69) at RT in CCl_4 .

Sulfide	Oxaziridine	Sulfoxide			Ref.
		<i>ee</i> (config) (%)	Yield (%)	Time (h)	
<i>p</i> -Tolyl-S-Me	(–)-(69)	>95 (<i>S</i>)	95	1	92JA1428
<i>p</i> -Tolyl-S-Bu ⁿ	(–)-(69)	91 (<i>S</i>)	90	3	
<i>p</i> -Tolyl-S-Bu ⁿ	(+)-(69)	91 (<i>R</i>)	90	3	
<i>p</i> -Tolyl-S-Pr ⁱ	(–)-(69)	66 (<i>S</i>)	95	6	
Me ₃ C-S-Me	(–)-(69)	94 (<i>S</i>)	90	18	
Me ₃ C-S-CH ₂ Ph	(–)-(69)	91 (<i>S</i>)	80	48	
Me ₃ C-S-CH ₂ Ph	(–)-(69) (65°C)	85 (<i>S</i>)	80	1	
Ph-S-CH=CH ₂	(–)-(69)	85 (<i>S</i>)	60	48	
Ph-S-CH ₂ -CN	(–)-(69)	>95 (<i>S</i>)	45	48	
	(–)-(69)	86 (<i>S</i>)	84	4 d	92JA5566
	(–)-(69)	64 (<i>S</i>)	87	6	

2,3-epoxy sulfoxide diastereoisomers (71) and (72) (Equation (16)) <92TL7237>. Lower *des* were observed for the epoxy sulfide enantiomer of (70).



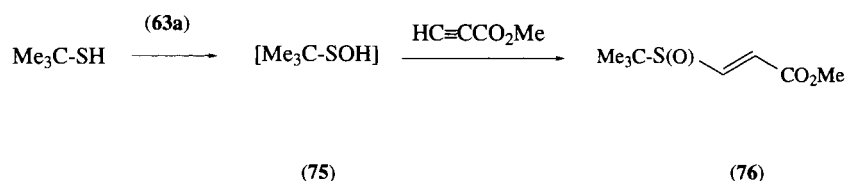
For the preparation of (*R*)-C-6 sulfoxytetrahydromevinic acid lactone (73), a precursor of a potent HMG-CoA reductase inhibitor, optimal results were obtained with (–)-[(8,8-dichloro-camphoryl)sulfonyl]oxaziridine (74) <94TL3461>.



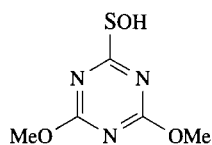
The (camphorsulfonyl)oxaziridine derivatives, for example (74), generally give lower *ees* for the asymmetric oxidation of sulfides to sulfoxides than *N*-(phenylsulfonyl)(3,3-dichloro-camphoryl)oxaziridine (69) <88JA8477, 88JCS(P1)1753, 92JOC7274>.

(iii) Oxidation of thiols to sulfenic acids

The biological activity of thiols depends, to a large extent, on the facility with which the SH group is oxidized to high sulfur oxides (RSO₂H) and disulfides (RSSR). Sulfenic acids (RSOH), transient intermediates in many organic and inorganic sulfur reactions, are generally thought to be involved in this process <86JOC1033>. Davis and Billmers, making use of the fact that *N*-sulfonyloxaziridines do not oxidize alkynes, were the first to demonstrate that sulfenic acids are intermediates in the oxidation of thiols <81JA7016>. Thus oxidation of 2-methyl-2-propanethiol (Bu^tSH) with oxaziridine (63a) in the presence of methyl propiolate gave 2-methyl-2-propanesulfenic acid (75), trapped as the vinyl sulfoxide (76), in 25–47% yield (Scheme 13). In a related study 2,6-dimethoxy-1,3,5-triazine-2-sulfenic acid (77), a stable sulfenic acid, was prepared by oxidation of the corresponding thione with 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (63b) <93ZN(B)1212>.



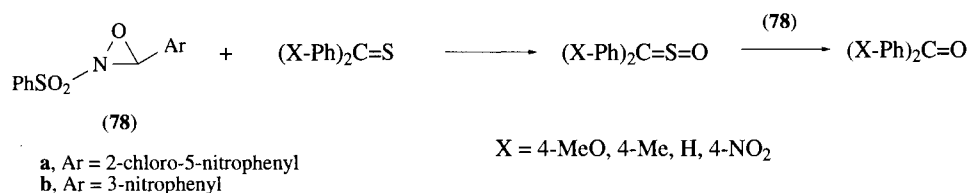
Scheme 13



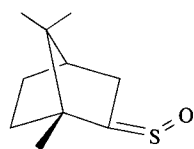
(77)

(iv) Oxidation of thiones to thiones *S*-oxides

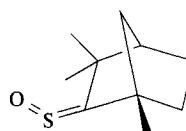
Thiones ($\text{Ar}_2\text{C}=\text{S}$) are oxidized to thiones *S*-oxides ($\text{Ar}_2\text{C}=\text{S}=\text{O}$) by *N*-sulfonyloxaziridine (**78**) (Scheme 14) <87JCS(P1)1113>. The oxidation is fast and quantitative, exhibiting second-order kinetics. Thiocamphor *S*-oxide (**79**) and thiofenchone *S*-oxide (**80**) were prepared in 91% and 76% yield, respectively by oxidation of the corresponding thiones with (**78b**). Earlier attempts to prepare these materials with other oxidants resulted in low yields and the products were difficult to purify. Phosphorothionates ($\text{R}_2\text{P}(\text{S})\text{OPh}$) are oxidized to phosphates ($\text{R}_2\text{P}(\text{O})\text{OPh}$) by *N*-sulfonyloxaziridines <88MI 112-01>.



Scheme 14



(+)-(79)

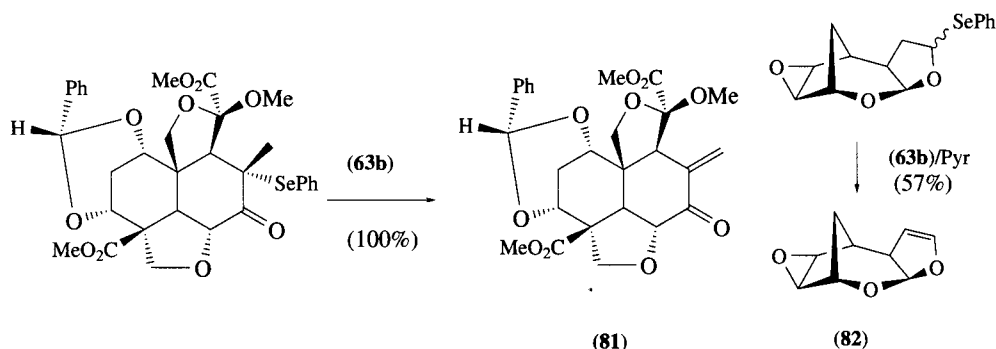


(-)-(80)

1.12.3.6.4 Oxidation of organoselenium compounds

(i) Oxidation of selenides to selenoxides

Selenides, like sulfides, are quantitatively oxidized by *N*-sulfonyloxaziridines to selenoxides without over-oxidation and can be carried out in the presence of function groups such as aldehydes, alkenes and sulfides <83TL1213, 86MI 112-01>. The resulting selenoxides may undergo [2,3]-sigmatropic rearrangements to allylic alcohols or (β)-elimination to alkenes. Selenylation-oxidative elimination, using 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (**63b**) in the presence and absence of pyridine, has been widely employed in the synthesis of enones <88TL1853, 90TA237, 91JCS(P1)667, 91TL6183> and alkenes <90TL3445, 91T6813, 92TL409, 92T9427>. Improved yields, compared to MCPBA and H_2O_2 are reported for the oxaziridine because side reactions are minimized <83TL1213, 90TA237>. Examples include *exo*-alkene (**81**), a potential intermediate in the synthesis of the insect antifeedant azadirachtin <91TL6183>, and epoxide (**82**) (Scheme 15) <91T6813>.



Scheme 15

Diphenyl diselenide (PhSeSePh) gives benzeneselenenic anhydride [(PhSeO)₂O] on oxidation with (63a) <86MI 112-01>.

(ii) *Asymmetric oxidation of selenides to selenoxides*

The difficulty in preparing optically active selenoxides is that they are configurationally unstable, forming achiral hydrates [ArSe(OH)₂R] with trace amounts of water <83TL1213, 85T4747, 92JOC2599>. Enantioselective oxidation of alkyl arylselenides with oxaziridine (69), because of its aprotic nature, affords the analogous selenoxides in 91% to >95% *ee* (Equation (17), Table 9) <92JOC2599>. In these oxidations, however, moisture and trace amounts of acids in the solvents must be rigorously excluded. The optically active alkyl 2,4,6-triisopropylphenyl selenoxides are isolated chromatographically on basic alumina, but some racemization occurs (85–87% *ee*). (–)-(69) and (+)-(69) afford the (*S*)- and (*R*)-selenoxides, respectively. This is supported by their circular dichroism (CD) spectra.

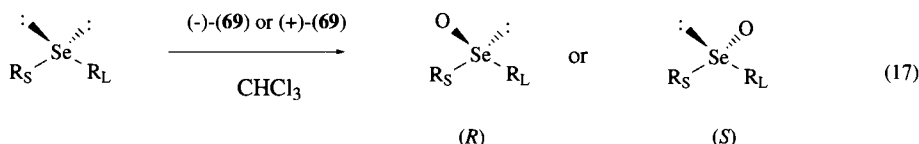


Table 9 Asymmetric oxidation of alkyl aryl selenides to selenoxides using (–)-*N*-(phenylsulfonyl) (3,3-dichlorocamphoryl)oxaziridine (69) at 0 °C in CHCl₃.^a

Selenoxide	Time (h)	ee ^b (%)	Isolate yield (%)	% ee (config.)
Ph-Se(O)-Me	< 1 min	94	74	10 (<i>S</i>)
	1.5	> 95	85	85 (<i>S</i>)
	2	91	68	86 (<i>S</i>)

^a <92JOC2599>. ^b % *ee* Determined by NMR prior to isolation.

Enantioselective oxidation of *Z*-aryl cinnamyl allylic selenide (83) with oxaziridine (–)-(69) gave 1-phenyl allyl alcohol (85) via an allyl selenoxide-selenate [2,3] sigmatropic rearrangement (Scheme

(83)

(-)-(69)

(84)

(85)

Ar = Ph

55%, 40% *ee*

Ar = 2,4,6-triisopropylphenyl

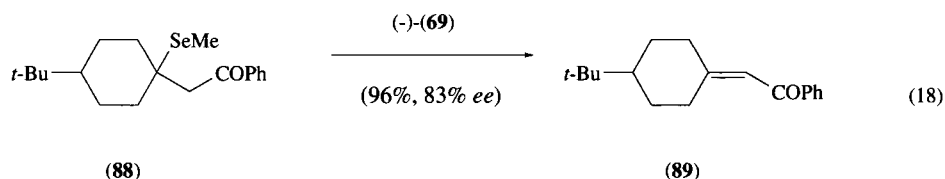
46%, 60% *ee*

Scheme 16

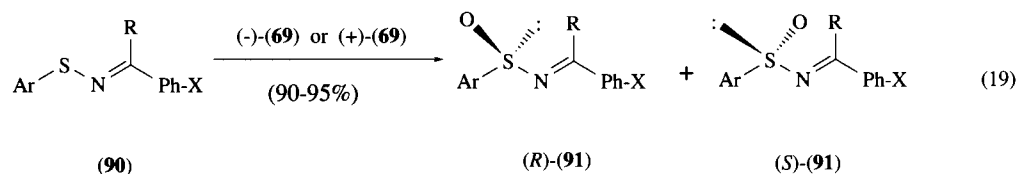
(86) $\text{R} = n\text{-C}_3\text{H}_7$, $\text{Ar} = o\text{-NO}_2\text{Ph}$

 Reaction with $(-)\text{-(69)}$ followed by $[-\text{ArSeOH}]$ yields $(R)\text{-(87)}$ in 41% yield and 28% ee.

Scheme 17



Enantiopure sulfinimines (**91**) are chiral ammonia imine synthons important in the asymmetric synthesis of amines <82JCS(P1)339, 91JOC4, 93TA2159>, β -amino acids <91JOC4, 92JOC6387, 94TL2121>, and *cis*-aziridine 2-carboxylic acids <94JOC3243>. Sulfinimines, unavailable via the Andersen synthesis (R = H) <82JCS(P1)339, 91JOC4>, are prepared by asymmetric oxidation of sulfenimines (**90**) with (+)-(**69**) or (–)-(**69**) at –20 to 20°C in CCl₄ (Equation (19)) <92JOC6387, 93PAC633>. Crystallization improves the *ees* to >95%. The sulfoxide chiral recognition model correctly predicts the configuration of the product (See Section 1.12.3.6.3).



Ar = Ph, R = X = H $\quad (-)-(\mathbf{69})$ 88% ee (R)

Ar = Ph, R = X = H $\quad (+)-(\mathbf{69})$ 88% ee (S)

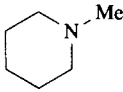
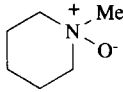
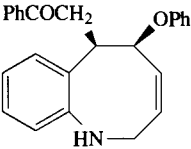
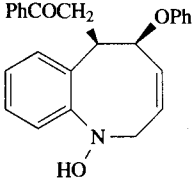
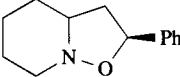
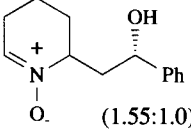
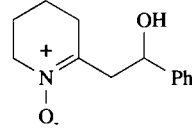
Ar = *p*-Tolyl, R = Me, X = H $\quad (-)-(\mathbf{69})$ 87% ee (R)

1.12.3.6.6 Oxidation of organonitrogen compounds

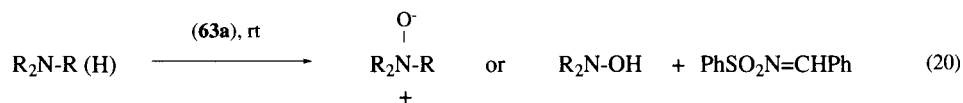
(i) Oxidation of amines

A detailed study of the oxidation of primary, secondary and tertiary amines by 2-(phenylsulfonyl)-3-phenyloxaziridine (**63**) has been reported by Zajac *et al.* <88JOC5856> (Table 10). Tertiary amines, such as triethylamine, *N*-methyl piperidine, etc., react within a few minutes to give the corresponding tertiary amine oxides ($\text{R}_3\text{N}^+-\text{O}^-$) and sulfonimine in quantitative yield (Equation (20)). A novel hydroxylamine-containing polyamine, isolated from the venom of the *Agelenopsis aperta* spider, was prepared using (**63**) <90JA6696>. With secondary amines and one equivalent of the oxaziridine both the hydroxylamine (R_2NHOH) and nitron result (Equation (20)). Nitrones are formed exclusively on treatment of the secondary amines with two equivalents of the oxaziridine. Primary amines give low yields of nitroso compounds ($\text{RN}=\text{O}$) and good yields of imines, formed by reaction of the primary amine with the sulfonimine ($\text{PhSO}_2\text{N}=\text{CHPh}$) by-product <88JOC5856>. Dibenzyl sulfide [$(\text{PhCH}_2)_2\text{S}$] is oxidized 20 times faster than dibenzylamine [$(\text{PhCH}_2)_2\text{NH}$] by (**63a**) <88JOC5856>.

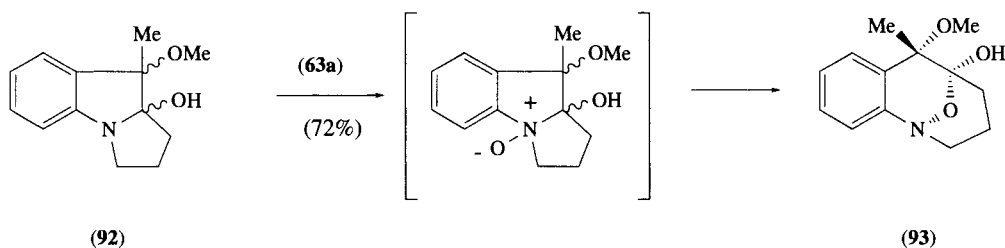
Table 10 Oxidation of amines with 2-(phenylsulfonyl)-3-phenyloxaziridine (**63**).^a

Amine	(63a) (equiv.)	Products	Yield (%)
Et_3N	1.0	$\text{Et}_3\text{N}^+\text{O}^-$	> 95
Pyridine	1.0	No reaction	
	1.0		> 95
	1.0		89 ^b
$(\text{PhCH}_2)_2\text{NH}$	1.0	$(\text{PhCH}_2)_2\text{NH}-\text{OH}$ (70) $\text{PhCH}_2\text{N}(\text{O})=\text{CHPh}$	10
	2.0	(0)	85
	1.1	 (1.55:1.0) 	88 ^c

^a<88JOC5856>. ^b<89TL6491>. ^c<91SL47>.



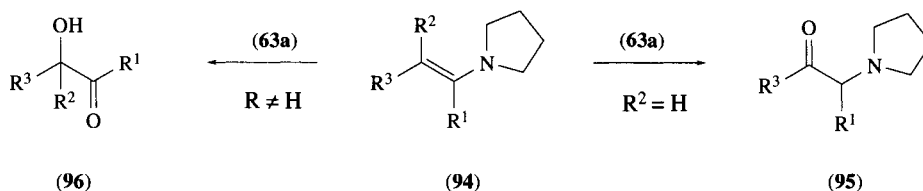
The bicyclic hydroxylamine hemiketal ring skeleton (**93**), found in the antitumor antibiotic FR900482, is produced in 72% yield by treatment of (**92**) with oxaziridine (**63a**) <92TL5705>. Rearrangement of an initially formed *N*-oxide is proposed (Scheme 18).



Scheme 18

(ii) Oxidation of imines and enamines

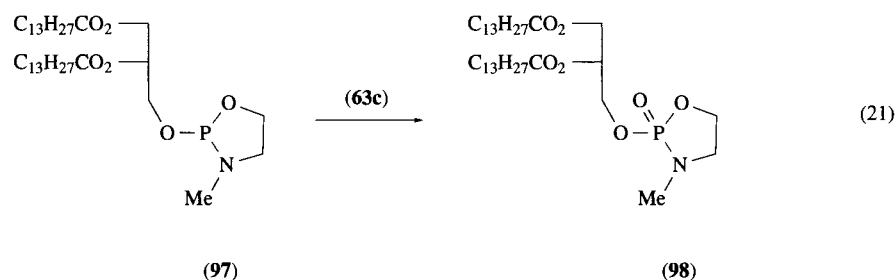
Disubstituted enamines (**94**; $R^2 = H$) give α -amino ketones (**95**) on treatment with (**63a**) while trisubstituted enamines give α -hydroxy ketones (**96**) following hydrolysis <88TL4365>. Reduction of the α -amino ketones afford β -amino alcohols <90TL5441>. A mechanism involving initial oxidation of (**94**) to an α -amino epoxide was proposed (Scheme 19). Imines ($RCH=N-R$) are oxidized to nitrones ($RCH=N(O)-R$) <85TL3791>.



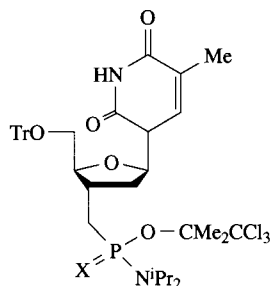
Scheme 19

1.12.3.6.7 Oxidation of organophosphorus compounds

Although the ability of *N*-alkyl and *N*-aryloxaziridine to transfer oxygen to trivalent phosphorus compounds has been known for sometime <72BCJ3179, 81JOC610> the reaction has not been investigated from a synthetic perspective until the early 1990s. Stumpf and Leeman reported a method for preparing the head group of phospholipids which involved the oxidation of glycerol-1,2,3- λ^3 -oxazaphospholane (**97**) to (**98**) with 2-*p*-tolyl-3-(*p*-nitrophenyl)oxaziridine (**63c**) (Equation (21)) <90ZN(B)1729>. In a related study the competitive oxidation of trimethylphosphite to trimethylphosphate by various *N*-sulfonyloxaziridines has been reported <92ZN(B)887>.



Studies of the asymmetric synthesis of chiral phosphorus compounds, (**100**) via the destructive-selective oxidation of (**99**) with various camphor derived oxaziridines has been described <91CB1627>. The *des* were mostly modest, for example 8–48%.

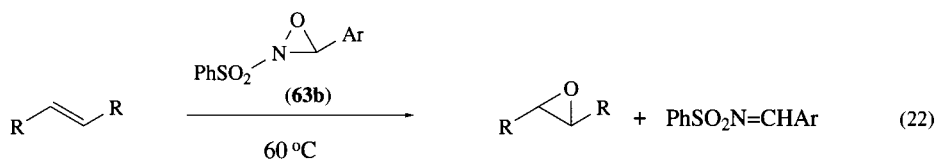


(**99**), X = electron pair
(**100**), X = O

1.12.3.6.8 Oxidation of carbon–carbon double bonds

(i) Epoxidation of alkenes

Like peracids, *N*-sulfonyloxaziridines epoxide alkenes in a *syn* stereospecific manner (Equation (22)) <81TL917, 90JOC1254, 95MI 112-03>. However, in contrast to peracids, epoxidations using these reagents are much slower requiring 3–12 h at 60 °C for satisfactory yields (Table 11). For this reason the more thermally stable 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (**63b**) is preferred. More nucleophilic substrates such as sulfides, amines, selenides, etc., can therefore be oxidized in the presence of C=C double bonds. Alkynes are not oxidized by *N*-sulfonyloxaziridines. The epoxidation of alkenes, at lower temperatures, by the perfluorooxaziridines (**64**) has also been briefly mentioned <91JFC(53)181, 91JFC(53)399>.



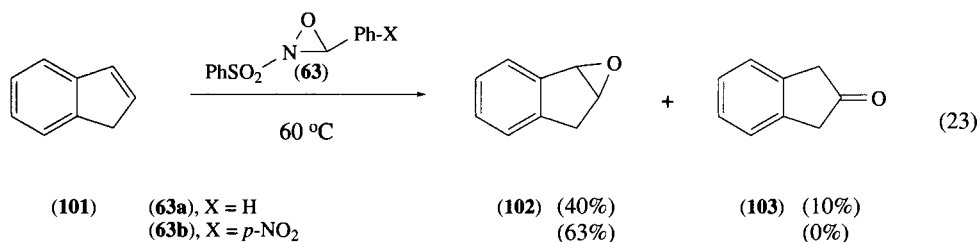
Ar = *p*-nitrophenyl

Table 11 Epoxidation of alkenes using 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)-oxaziridine (**63b**) at 60 °C in CHCl₃.^a

Epoxide	Reaction time (h)	Yield (%)
	72	42
	3	95
	12	95
	3	72

^a<81TL917>.

Acid sensitive epoxides can be prepared with *N*-sulfonyloxaziridines (**63a**) because of their neutral nature <90JOC1254>, for example, epoxidation of indene (**101**) with (**63a**) at 60°C for 3 h gave indene oxide (**102**) and 2-indanone (**103**) (Equation (23)) <81TL917>. 2-Indanone (**103**), the acid-catalyzed rearrangement product of (**102**), was not detected when the epoxidation was carried out using (**63b**), which is thermally more stable than (**63a**) (see Section 1.12.3.1.1) <77CC25>. Low yields (ca. 8%) of 2- and 4-methoxyphenols are obtained on heating anisole at 60°C for 72h with (**63b**) <83JOC5128>. A mechanism involving rearrangement of an intermediate arene oxide was proposed.



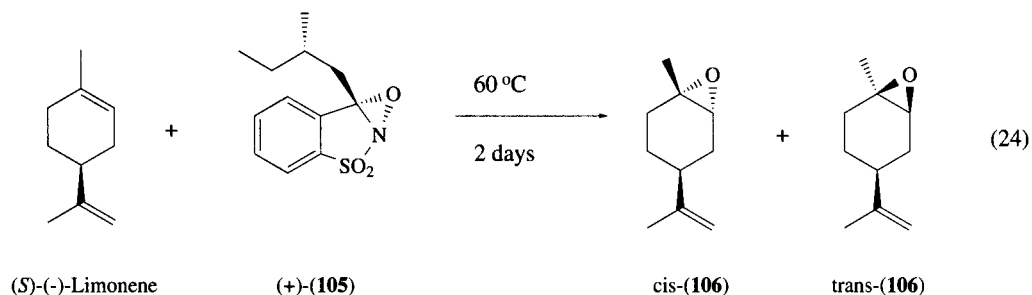
(ii) *Asymmetric epoxidation of alkenes*

Asymmetric epoxidation of nonfunctionalized alkenes using chiral nonracemic *N*-sulfonyloxaziridine gives enantiomerically enriched epoxides <83JA3123, 86TL5079, 91JOC809>. Pentafluorophenyl 2-sulfonyloxaziridine (+)-(104) and (–)-(104) gave the highest *ees* (19–65%) and the stereochemistry of the epoxide is determined by the absolute configuration of the oxaziridine three-membered ring (Table 12) <86TL5079>. Steric factors, via a planar transition state geometry, were believed largely responsible for the chiral recognition (see Section 1.12.2.1).

Table 12 Asymmetric epoxidation of alkenes.

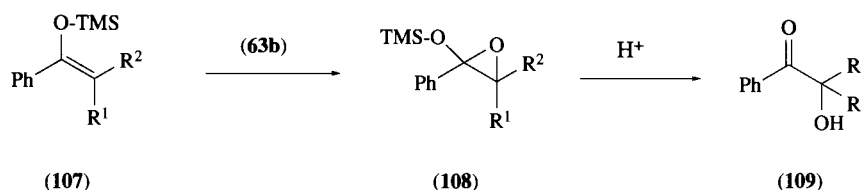
 RSO ₂	Epoxide % <i>ee</i> (config.) 25 °C			
	Oxaziridine	Solvent	<i>PhCH=CH</i> ₂	<i>E-PhCH=CHMe</i>
(+)-(R,R)-(104)	(+)-(R,R)-(104)	CHCl ₃	44.6 (R)	53.0 (R,R)
(–)-(S,S)-(104)	(+)-(R,R)-(104)	MeCN	34.2 (R)	32.3 (R,R)
R = (S) PhCH(Me)N(CH ₂ Ph)	(–)-(S,S)-(104)	CHCl ₃	61.1 (S)	61.0 (S,S)

In double stereodifferentiation, the inherent diastereofacial preferences of the chiral reactants may reinforce or oppose one another. Heating (*R*)-(+)-limonene with bicyclic oxaziridine (+)-(2*R*,3*S*)-(105) for 2 days at 60°C resulted in a 90% yield of a 55:45 *cis/trans* mixture of limonene oxides (**106**) (Equation (24)) <91JOC809>. The *cis/trans* selectivity improved to 93:7 when (*S*)-(–)-limonene was used.



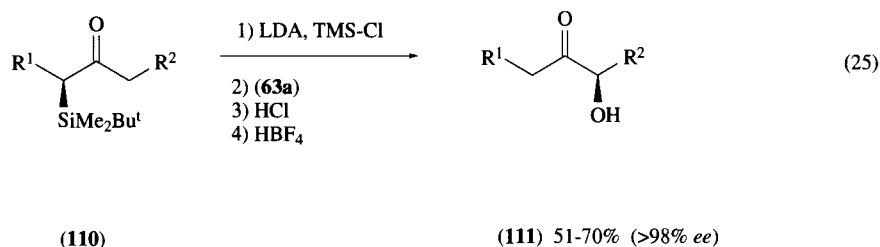
(iii) Epoxidation of silyl enol ethers

Highly acid sensitive α -siloxy epoxides (**108**; $R^1 = R^2 = \text{Me}$) are available in good to excellent yields through the epoxidation of silyl enol ethers (**107**) with *N*-sulfonyloxaziridine (**63b**) [87JOC954]. Hydrolysis of (**108**) gave the α -hydroxy carbonyl compound (**109**) in good-to-excellent yield (55–95%) and represents an alternative to peracids usually used to effect this transformation known as the Rubottom reaction. With chiral nonracemic *N*-sulfonyloxaziridines the *ees* of (**109**) were low (7–11% *ee*) because of the poor facial discrimination between the *re* and *si* faces of the silyl enol ether (Scheme 20).

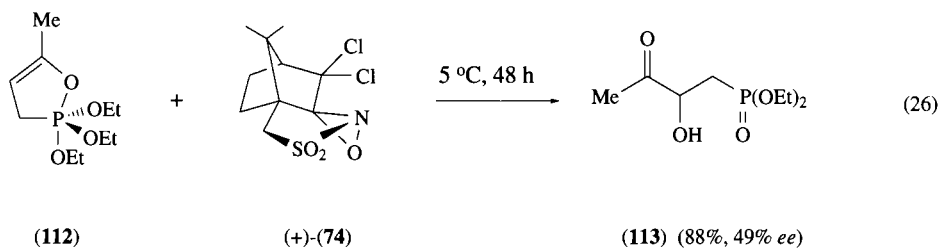


Scheme 20

α -Hydroxy ketones (**111**) of high optical purity ($\geq 98\%$ *ee*) are prepared by oxidation of the chiral silyl enol ethers derived from (**110**) with (**63a**) (Equation (25)) [89HCA980].



2,2,2-Triethoxy-1,2 λ^5 -oxaphospholene (**112**) reacts at room temperature with 2-(*p*-tolyl)-3-phenyl-oxaziridine (**63d**) to give a β -hydroxy- γ -ketophosphate (**113**) in 82% yield (Equation (26)) [91TL5313]. It seems likely that an oxirane intermediate is initially formed which rearranges on work-up to (**113**). Asymmetric oxidation with (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (**74**) gave (**113**) in 49% *ee* and 88% isolated yield. The absolute configuration of (**113**) was not established.

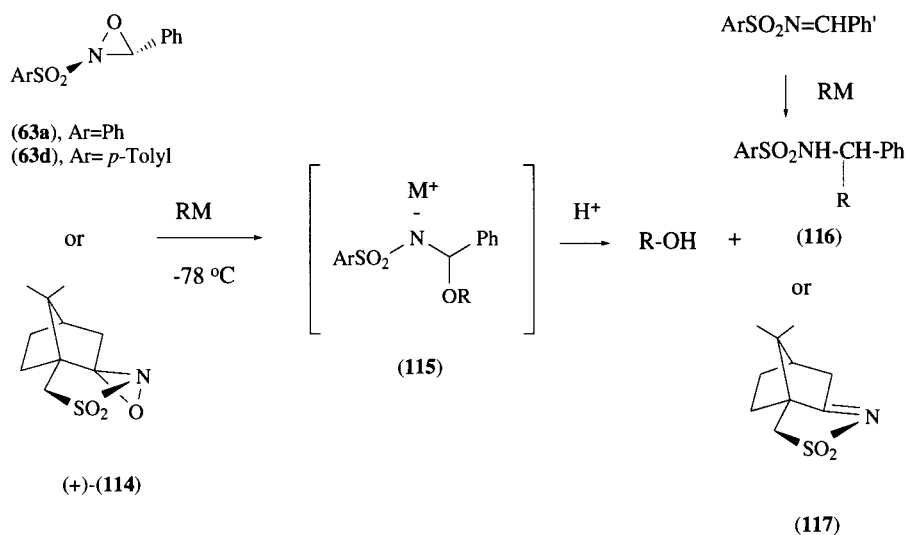


1.12.3.6.9 Oxidation of organometallic reagents

Because they are aprotic and neutral oxidants *N*-sulfonyloxaziridines are among the few reagents available for the hydroxylation of organometallic reagents. A variety of alkyl, aryl, and vinyl organometallic reagents and ylides are efficiently hydroxylated by these oxidants <89T5703, 95MI 112-02, 95MI 112-03>. Enolates give α -hydroxy carbonyl compounds, a key structural unit found in many biologically active materials <89T5703, 92CRV919>.

(i) Hydroxylation of lithium and Grignard reagents

Excess lithium and Grignard (RM) reagents react at -78°C with oxaziridines (**63a**) and (**63d**) to give alcohols and phenols (ROH) in moderate-to-good yields (Scheme 21) <79JA1044, 87TL5115>. Oxygen transfer is thought to entail attack of RM at oxaziridine oxygen atom to form a hemiaminal intermediate (**115**) which collapses to products. The modest yields result from addition of the organometallic reagent (RM) to the sulfonimine by-product giving sulfonamides (**116**). Because camphorsulfonylimine (**117**) is unreactive toward RM improved yields of alcohols and phenols were seen, at lower concentrations of RM, with (+)-(camphonylsulfonyl)oxaziridine (**114**) <87TL5115>. Examples are given in Table 13.

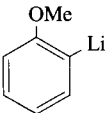
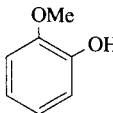
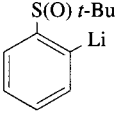
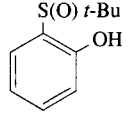
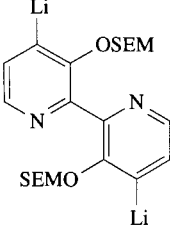
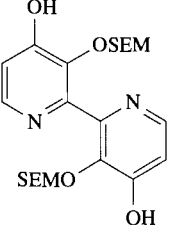
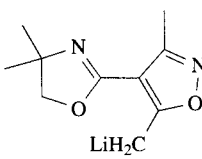
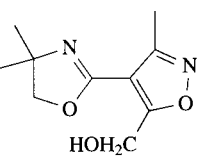


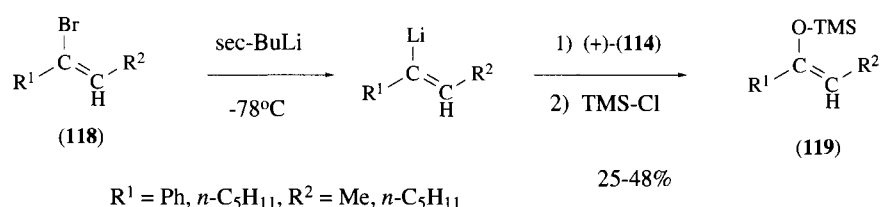
Scheme 21

E- and *Z*-Vinylolithium reagents, generated from the corresponding *E*- and *Z*-vinyl bromides (**118**) with *sec*-butyllithium, are stereoselectively oxidized with (+)-(114) to give the silyl enol ethers (**119**) in moderate yield (25–48%), following trapping of the enolate with trimethylsilyl chloride (TMS-Cl; Scheme 22) <88TL4269>. While some loss in product configuration is observed for (**114**) nearly complete retention of configuration and improved yields are obtained using bis(trimethylsilyl)peroxide ($\text{Me}_3\text{SiOOSiMe}_3$).

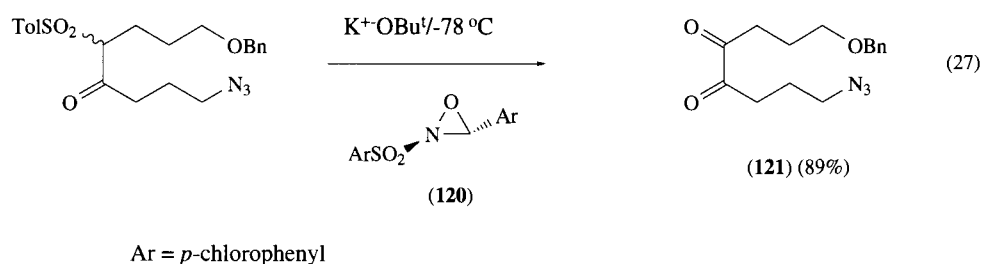
A general procedure for the synthesis of unsymmetrical α -diketones, for example (**121**), has been developed by Williams and co-workers <92JOC3740>. This methodology employs oxaziridine (**120**),

Table 13 Hydroxylation of organometallic reagents (RM) by *N*-sulfonyloxaziridines.

RM	Oxaziridine	Yield ROH (%)	Ref.
PhMgBr	(63d)	PhOH (84) ^a	87TL5115
PhMgBr	(+)-(114)	PhOH (>95)	87TL5115
PhLi	(63d)	PhOH (55) ^a	87TL5115
	(63a)	 (70) ^a	87TL5115
	(63d)	 (48)	92TL2625
	(63a)	 (22)	88HCA957
Me(CH ₂) ₆ CH ₂ MgBr	(63a)	Me(CH ₂) ₆ CH ₂ OH (77) ^a	87TL5115
	(63a)	 (57)	92JOC6271

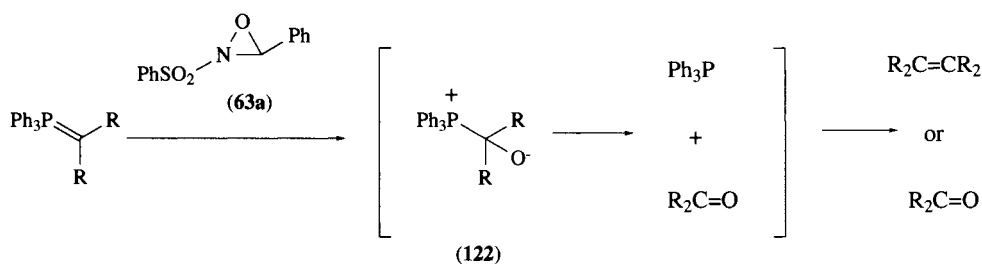
^aSulfonamide **116** isolated in 16–53% yield.**Scheme 22**

which undergoes spontaneous desulfonylation, to hydroxylate the carbanions of α -sulfonyl ketones (Equation (27)). This oxidative-desulfonylation protocol is remarkably tolerant of other functional groups including azide, alkene, and the usual ether and acetal protecting groups. Interestingly (+)-(camphonylsulfonyl)oxaziridine (**114**) is apparently not reactive enough to hydroxylate these relatively stable carbanions.



(ii) Hydroxylation of ylides

trans-Alkenes or ketones result on treatment of alkylidenephosphoranes (Wittig reagents) with *N*-sulfonyloxaziridines (Scheme 23) <90JOC360>. Bis-ylides dimerize to cycloalkadienes. Fragmentation of the oxidized ylide (122) gives triphenylphosphine and the carbonyl compound. If an aldehyde is formed and the ylide is highly reactive, the Wittig reaction occurs to give the alkene. Much better yields are seen with (63a) than triphenylphosphite ozone [(PhO)₃PO₃], previously used for this purpose <76AG(E)298>. Examples are given in Table 14.



Scheme 23

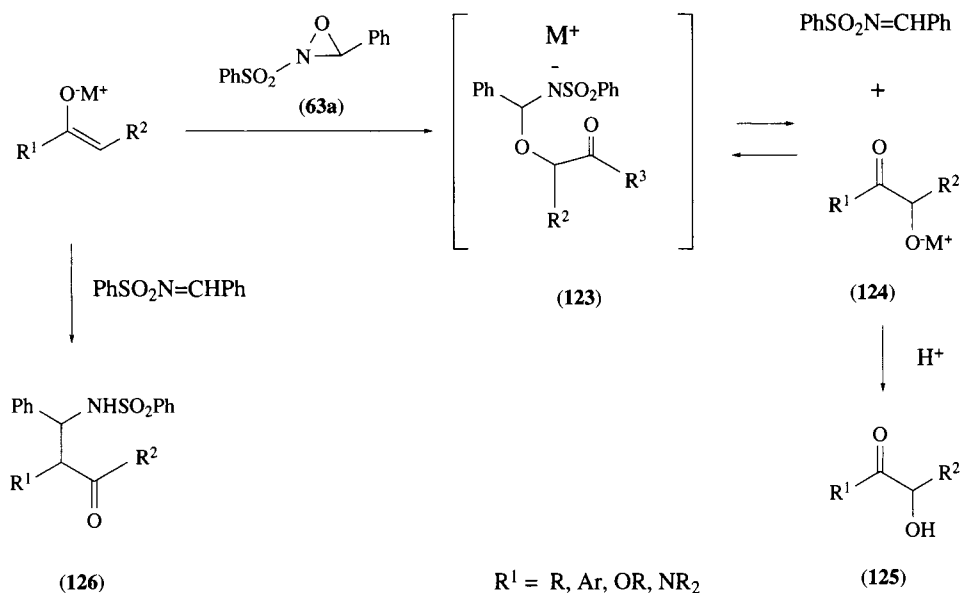
Table 14 Oxidation of alkylidenetriphenylphosphoranes with *N*-sulfonyloxaziridines.

Ylide	Oxaziridine	Yield product (%)	Ref.
Ph ₃ P = CHCO ₂ Me	(63a) (+)-(114)	MeO ₂ C-CH=CH-CO ₂ Me (99) (93)	90JOC360
Ph ₃ P = CHPh	(63a)	Ph-CH=CH-Ph (96)	
Ph ₃ P = C(=O)Ph	(63a)	Ph-C(=O)-CH=CH-C(=O)Ph (76)	
	(+)-(114)		(84)
	(63d)		(75) 93AG(E)1746
	(63d)		(92) 93AG(E)1747

1.12.3.6.10 Hydroxylation of enolates to α-hydroxy carbonyl compounds

The most widely used application of *N*-sulfonyloxaziridines is for the synthesis of α-hydroxy carbonyl compounds (125), a key structural unit found in many biologically important molecules (Scheme 24). Compounds containing this array are also useful as chiral auxiliaries and as synthetic building blocks for asymmetric synthesis. Although a number of indirect methods have been devised to prepare α-hydroxy carbonyl compounds, the enolate oxidation protocol, using *N*-sulfonyloxaziridines, is undoubtedly the most versatile because of the great diversity of metal enolate

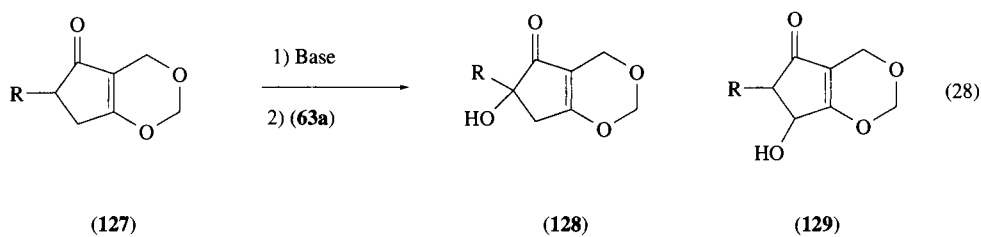
types. Furthermore, this methodology affords the target functionality directly and is effective for both acyclic and cyclic substrates. In comparison with other aprotic oxidants such as dioxxygen and MoOPH <85OS(64)127>, higher yields and fewer side reactions are seen with oxaziridines. Various aspects of the oxaziridine mediated hydroxylation of enolates have been discussed <86MI 112-02, 89T5703, B-90MI 112-01, 91MI 112-02, 92CRV919, 95MI 112-01, 95MI 112-02, 95HOU(E21e)4494>. Applications of the enolate oxidation protocol, using *N*-sulfonyloxaziridines, for the synthesis of natural products has been reviewed <92CRV919>.



Scheme 24

The hydroxylation of metal enolates by 2-(phenylsulfonyl)-3-phenyloxaziridine (63a) is fast (ca. 15 min) at -78°C ; however the lithium enolates of esters and ketones give lower yields than their sodium or potassium counterparts. Lithium enolates give, besides the α -hydroxy carbonyl compound (125), the imino-aldol product (126) resulting from addition of the enolate to the sulfonylimine by-product <85JA4346, 86JOC4083, 88JOC4314, 90JA6679> (Scheme 24). Representative examples of the hydroxylation metal enolates by *N*-sulfonyloxaziridine (63a) are found in Table 15.

Smith *et al.* described a study of the hydroxylation of enolates derived from 1,3-dioxin vinologous esters (127) with (63a) <88JOC4314>. The regioselectivity depended on both the counterion and the ester substitution pattern, for example, the lithium enolate of (127; R = H) gave primarily the α -hydroxylated product (128) while the sodium enolate afforded mixtures of both (128) and (129). Particularly noteworthy is the fact that the sodium enolate of (127; R = Me) gave (129) while the lithium enolate gave (128) (Equation (28)). Moreover, imino-aldol products (18–26%) were isolated for the lithium enolates, but not with the sodium enolates.



R	Base	% Yield	
H	LDA/DME	33	6
H	NaHMDS/THF	35	36
Me	LDA/THF	51	0
Me	NaHMDS/THF	4	76

Table 15 Hydroxylation of metal enolates to α -hydroxy carbonyl compounds with 2-(phenylsulfonyl)-3-phenyloxaziridine (**63a**) at -78°C in THF.

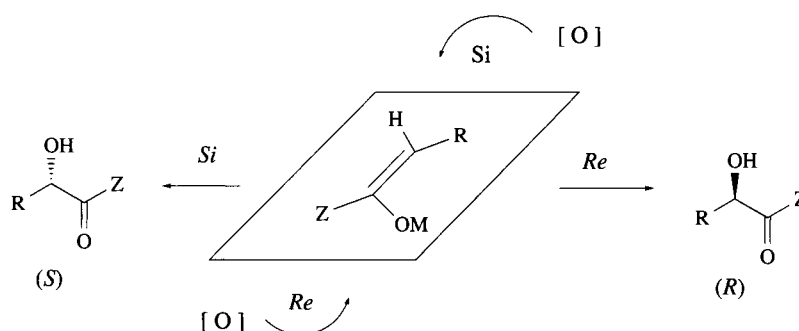
<i>Ketone/ester/amide</i>	<i>Base</i>	<i>α-Hydroxy carbonyl compound</i>	<i>Yield (%)</i>	<i>Ref.</i>
	LDA KHMDS		32 75	84JOC3241
	NaHMDS		70	84JOC3241
	NaHMDS		57	84JOC3241
	KHMDS		67	93JOC1228
	NaHMDS DMPU		77	92TL4261
	LiHMDS KHMDS		40 83	84JOC3241
	LDA KHMDS		51 68	84JOC3241
	LDA NaHMDS		74 83	84JOC3241
	KHMDS -100°C		51	92T3557

The mechanism for the oxygen transfer is envisioned as attack of a monomeric metal enolate on the oxaziridine oxygen atom to give hemiaminal intermediate (**123**) which fragments to the alkoxide (**124**) and sulfonimine (Scheme 24) <92CRV919>. The involvement of a monomeric enolate is supported by theoretical calculations of the transition state geometry <92JOC613> (see Section 1.12.2.1) and by experimental studies of solid state enolate oxidations <93TL3715>. The tendency to form imino-aldol products (**126**) is thought to be related to the equilibrium between (**123**) and (**124**) which

is counterion dependent <85JA4346, 87TL5115>. Calculations suggest, however, that the formation of (123) occurs in an equilibrium step after formation of the transition state <92JOC613>. Imino-aldol products can be avoided by employing the commercially available (camphorylsulfonyl)oxaziridines (74) and (114) because the corresponding sulfonimines, for example (117), do not add carbanions <87TL5115> (see Section 1.12.3.6.9).

(i) *Asymmetric synthesis of α -hydroxy carbonyl compounds*

Of particular concern with α -hydroxy carbonyl compounds is the stereochemistry of the hydroxy group attached to the stereogenic carbon because biological activity is often critically dependent on its orientation. *N*-Sulfonyloxaziridines have played a prominent role in the stereoselective synthesis of this key structural element (Scheme 25). Enantiomerically and diastereomerically enriched materials have been prepared by: (1) the hydroxylation of chiral nonracemic enolates with racemic *N*-sulfonyloxaziridines, for example (63a); (2) the asymmetric hydroxylation of prochiral enolates with enantiopure *N*-sulfonyloxaziridines; and (3) a combination of the first two, double stereo-differentiation.

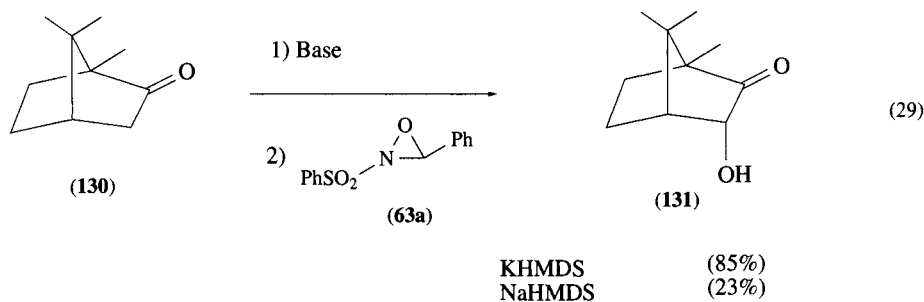


Scheme 25

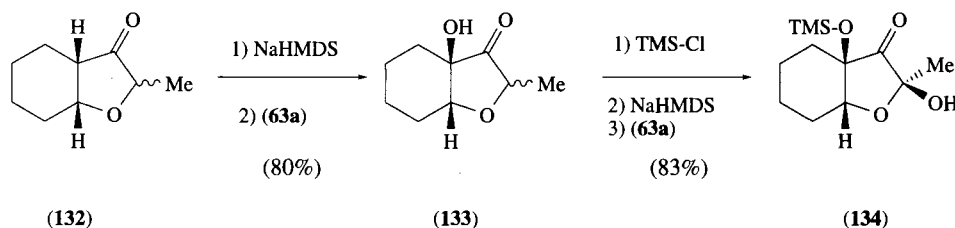
The enantioselective and diastereoselective hydroxylation of enolates with *N*-sulfonyloxaziridines has been critically reviewed in 1992 by Davis and Chen <92CRV919>. For this reason only illustrative examples and work reported since 1992 are recounted here.

(a) *Diastereoselective hydroxylations: substrate-induced hydroxylations.* For substrate-induced hydroxylations, diastereoselectivity is controlled by the presence of a covalently bound chiral subunit that is retained in the target molecule.

The potassium enolate of camphor (130) is oxidized with oxaziridine (63a) at -78°C to afford α -hydroxyketone (131) in 85% yield (Equation (29)) <84JOC3241>. As mentioned earlier lower yields were observed for the lithium enolate because of the imino-aldol side-reaction. The exclusive formation of the *endo* product is consistent with attack of the oxaziridine from the sterically least-hindered face of the enolate and is a general phenomena for these reagents.

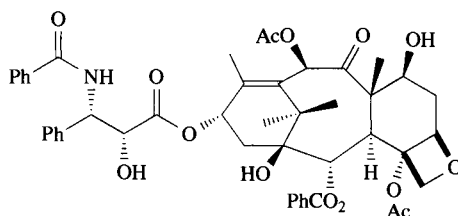
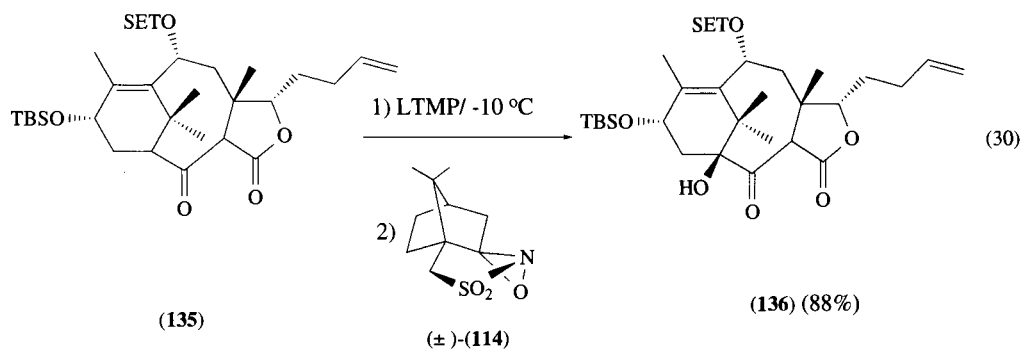


Regiospecific oxidation of the C-4 sodium enolate of furanone (132) gave the C-4 hydroxy furanone (133) as a single diastereomer in 80% yield <94TL1477>. The same sequence was used to prepare the C-2 alcohol (134) after TMS protection of the C-4 hydroxy group (Scheme 26).



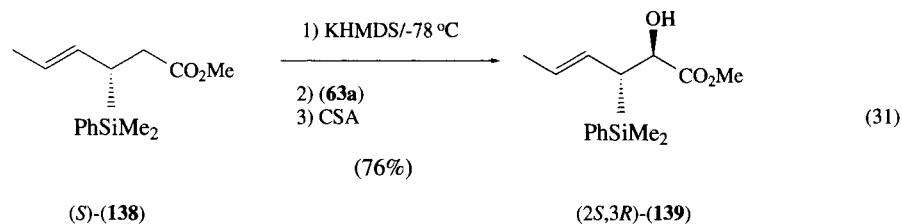
Scheme 26

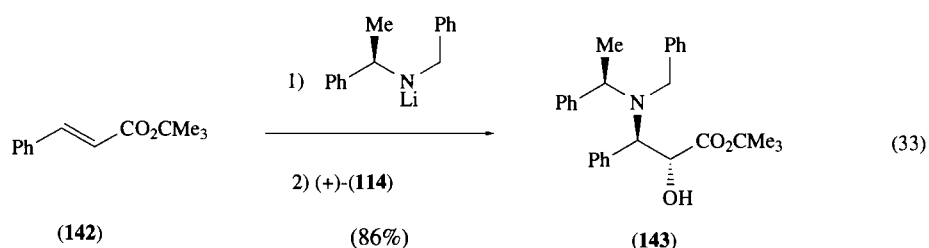
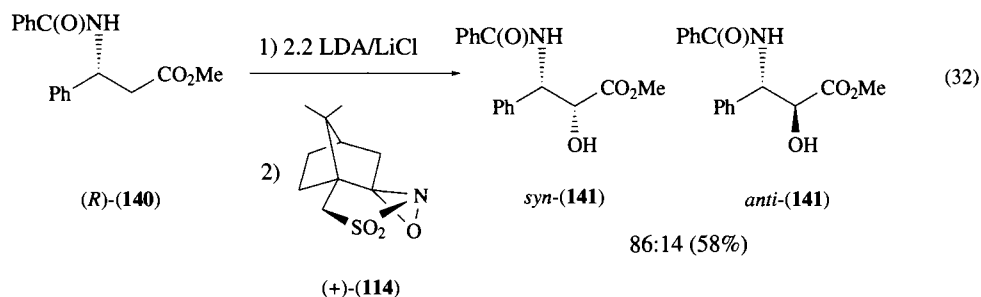
In Holton's total synthesis of the antitumor agent taxol (**137**) the C-1 hydroxy group was regiospecifically introduced using ($\pm$)-(camphorylsulfonyl)oxaziridine (**114**) <94JA1597>. Thus treatment of (**135**) with four equivalents of LTMP at -10°C followed by ($\pm$)-(114) gave an 88% yield of (**136**) (Equation (30)). Other approaches to taxol intermediates have also employed the enolate oxidation protocol and oxaziridine (**63a**) <92JOC4043, 92TL4261, 93JOC4963, 93JOC7728>.



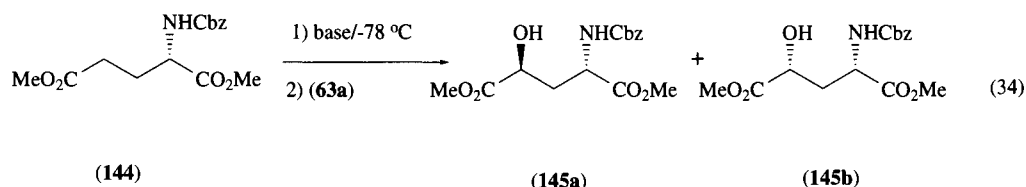
(137)

The β -silyl enolate derived from deprotonation of (*S*)-(138) with KHMDS affords α -hydroxy ester (**139**) with complete stereocontrol (Equation (31)) <93JOC1003>. On the other hand (+)-(camphorylsulfonyl)oxaziridine (**114**) mediate oxidation of the lithium enolate dianion of (**140**) resulted in a 86:14 *syn/anti* mixture of *N*-benzoyl-3-phenylisoserine (**141**), the C-13 side-chain of the antitumor agent taxol (Equation (32)) <92JOC6387>. In a related study, Davies *et al.* described a tandem lithium amide conjugate addition and hydroxylation with (+)-(114) to give (**143**) in 86% yield (Equation (33)) <93JCS(P1)1375>. The Mitsunobu reaction was used to convert this material into *syn*-(141) in 56% overall yield from (**142**). Similar approaches have been used to prepare other α -hydroxy- β -amino acids <93SL731, 94T3975, 94TA203>.





Hanessian and Vanasse explored the electrophilic hydroxylation of dimethyl *N*-benzyloxycarbonyl-L-glutamate (**144**) with various bases and oxaziridine (**63a**) in a novel synthesis of 3-hydroxy-L-aspartic acids (**145**) <93CJC1401>. The lithium enolate, generated using LiHMDS, afforded the highest selectivity (Equation (34)).



Base	% Yield	Ratio (145a):(145b)
LiHMDS	70	9:1
KHMDS	70	1:1
NaHMDS	56	2.6:1

The hydroxylation of lactones with (**63a**) or (+)-(**114**) usually affords a single diastereomeric α -hydroxy lactones resulting from approach of the oxidant from the sterically least hindered direction (Table 16). In one example, however, the diastereoselectivity proved to be strongly counterion dependent <93CJC1401>.

Yields for the hydroxylation of the lithium enolate of *N*-*t*-butoxycarbonyl-L-pyroglytamate (**146**) to (**147**) with 2-(*p*-toluenesulfonyl)-3-phenyloxaziridine (**63d**) are reported to vary from 30% <92TL1509> and 61% <88TL329>. Considerable amounts of the imino-aldol product (**148**) were also isolated (Equation (35)) <92TL1509>.

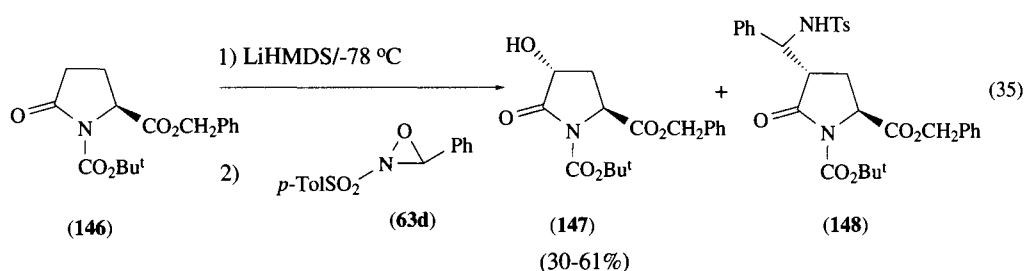
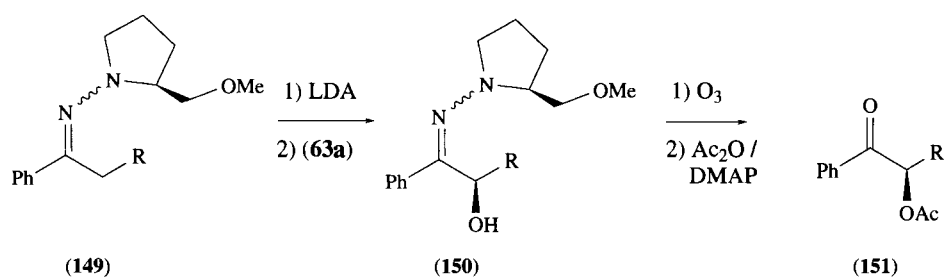


Table 16 Hydroxylation of lactones to α -hydroxy lactones at -78°C .

Lactone	Base	Oxaziridine	α -Hydroxy lactone	Yield (%)	Ref.
	LiHMDS	(63a)		48	93JOC4346
	KHMDS	(+)-(114)		74	93JA10400
	NaHMDS/ TBDMSCl	(63a)		65	92CC1775
	NaHMDS	(63a)		64%	93TL7557
	LiHMDS KHMDS NaHMDS	(63a)		4.5 : 1 50 6.5 : 1 70 14 : 1 56	93CJC1401

(b) *Diastereoselective hydroxylations: auxiliary-induced hydroxylations.* Diastereoselectivity for auxiliary-induced hydroxylations is under the control of a covalently bonded chiral auxiliary that is removed after the stereoinduction step.

Enders and Bhushan described the preparation of α -acetoxy ketones of high enantiomeric purity and good overall yield by hydroxylation of the azaenolates, derived from chiral SAMP-hydrazone (149), with (63a) as the key step ^[88TL2437]. The chiral auxiliary in (150) can be removed, without racemization, by ozonolysis of the α -hydroxy hydrazone at -78°C affording the α -hydroxy ketones which were isolated as the acetates (151) (Scheme 27). Protected α -hydroxy aldehydes, difficult to prepare in other ways, are available in high enantiomeric purity in a similar manner.



R = Me, 51% overall yield, 93% ee
R = Ph, 74% overall yield, >96% ee

Scheme 27

The Evans carboximide chiral auxiliaries and 2-(phenylsulfonyl)-3-phenyloxaziridine (**63a**) continues to be a widely used method for the synthesis of α -hydroxy acids of high enantiomeric purity <92CRV919>. Evans and co-workers, for example, reported that hydroxylation of the sodium enolate of (**152**) with a slight excess of (**63a**) gives (*S*)-(**153**) and (*R*)-(**153**) in a 95 : 5 ratio <85JA4346>. Isolation of the major (*S*)-product (**153**) was readily accomplished by flash chromatography (Equation (36)). Removal of the carboximide auxiliary was achieved without concurrent racemization by transesterification with magnesium methoxide in methanol. Other examples are given in Table 17.

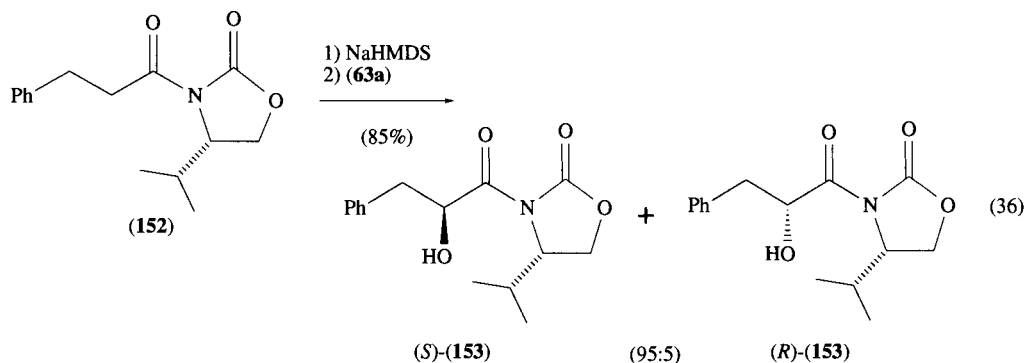
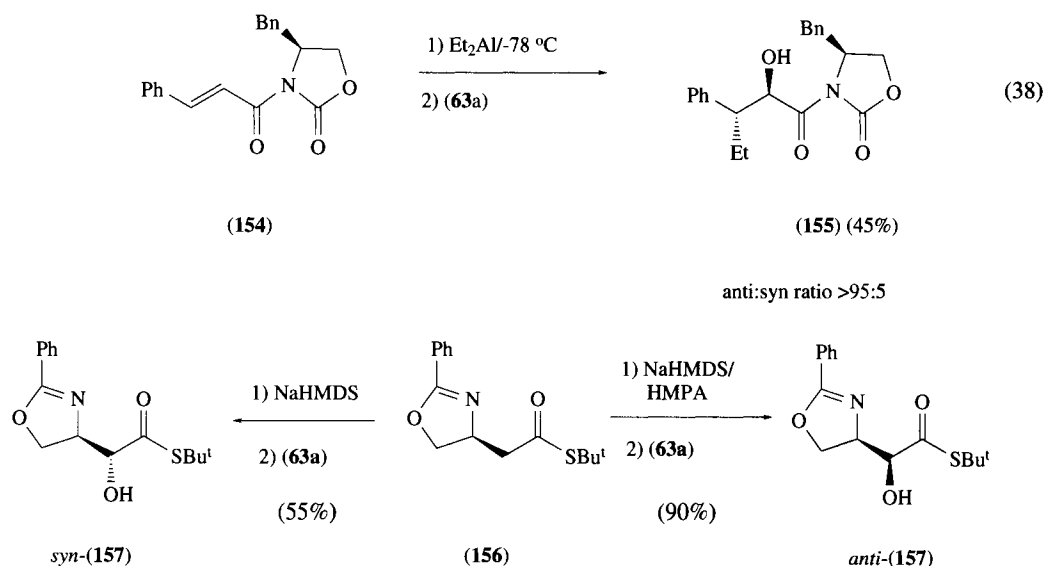


Table 17 Diastereoselective hydroxylation of carboximide enolates with oxaziridine (**63a**) at -78°C .

<i>Xc</i>	<i>R</i>	Base	% ee (config.)	Yield (%)	Ref.
	Ph	NaHMDS	80 (<i>R</i>)	55	85JA4346
	Bn	NaHMDS	88 (<i>R</i>)	86	
	Et	NaHMDS	88 (<i>R</i>)	86	
	Bu ^t	NaHMDS	98 (<i>R</i>)	94	
	Bn	NaHMDS	90 (<i>S</i>)	83	
		NaHMDS	76 (<i>S</i>)	95	87TH 112-01 92CRV889
		NaHMDS	> 99 (<i>S</i>)	88	92JOC1958

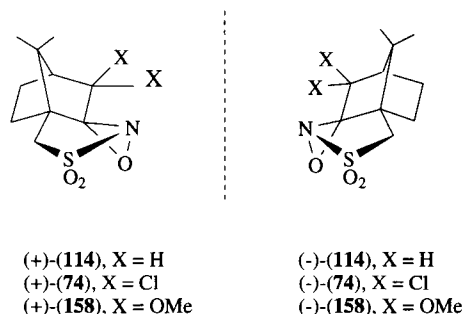
Addition of diethyl aluminum chloride at -78°C to α,β -unsaturated oxazolidinone (**154**) affords an aluminum enolate that, on hydroxylation with (**63a**), gives the β -ethyl- α -hydroxy amide (**155**) with high *anti* selectivity (Equation (38)) <91AG(E)694>. Formation of the enolate of oxazoline thiol ester (**156**) under chelation (NaHMDS) and stereoelectronic (NaHMDS/HMPA) control gives the *syn* and *anti* alcohols (**157**), respectively, on hydroxylation with (**63a**) in good to excellent yield and better than 95% diastereoselectivity (Scheme 28) <93JOC6180>. A counterion dependent reversal in stereochemistry has also been reported for the hydroxylation of chiral amide enolates where the auxiliary was 2-pyrrolidinemethanol <85TL3539>.



Scheme 28

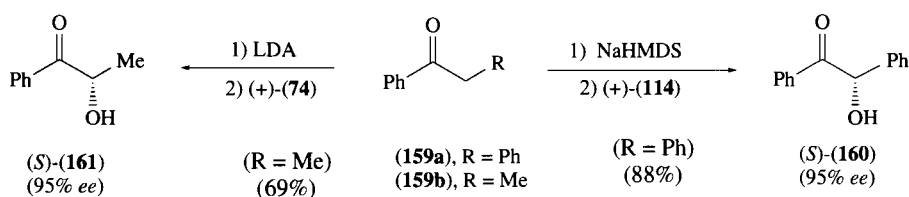
(ii) Reagent-induced hydroxylations

The product stereochemistry for reagent-induced hydroxylations are under the control of a noncovalently bound chiral reagent which avoids the introduction and eventual removal of the chiral auxiliary as discussed in the preceding section. This method requires an enantiopure *N*-sulfonyloxaziridine of which (camphorylsulfonyl)oxaziridines (**74**), (**114**), and (**158**) have proven the most useful <92CRV919>. Both epimeric α -hydroxy carbonyl compounds are readily available because the antipodal oxidant controls the absolute stereochemistry of the product (Scheme 25). Oxaziridines (**74**) and (**114**) are commercially available.



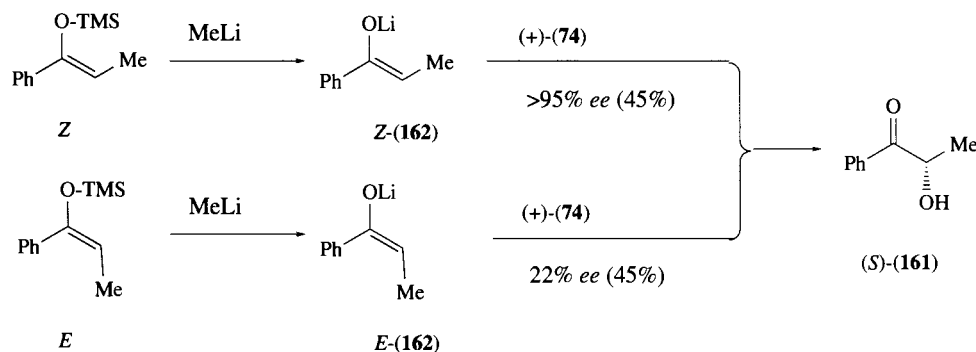
Acyclic α -hydroxy ketones of high enantiomeric purity can be prepared by choice of the appropriate conditions and (camphorylsulfonyl)oxaziridine reagent, for example, treatment of deoxybenzoin (**159a**) with NaHMDS followed by (+)-(**114**) at -78°C affords (+)-(*S*)-benzoin (**160**) in 95% *ee* and 88% isolated yield (Scheme 29) <89JOC2021, 90JA6679>. Similarly, (–)-(*S*)-2-hydroxy-1-phenyl-1-propanone (**161**) is produced in 95% *ee* by hydroxylation of the lithium enolate of

propiophenone (**159b**) with (+)-(**74**) <92JOC7274>. The product stereochemistry is predicted assuming that the oxidant approaches from the least hindered face of the enolate (Scheme 25).



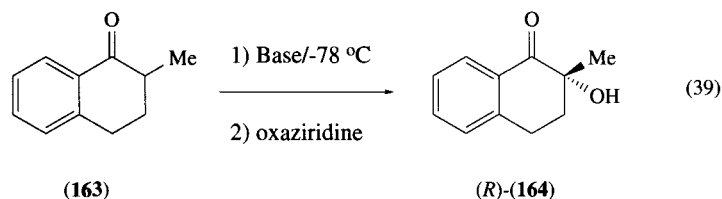
Scheme 29

The lithium *Z*-enolate (**162**) of propiophenone (**159b**), generated *in situ* from the *Z*-silyl enol ether with MeLi, produced on hydroxylation with chlorooxaziridine, (+)-(**74**), (*S*)-(**161**) in >95% *ee* (Scheme 30) <92JOC7274>. Similar treatment of the *E*-enolate (**162**) also gave (*S*)-(**161**), but in only 22% *ee*. While these results demonstrate the importance of having a single enolate regioisomer as a precondition for high *ees*, it is important to keep in mind that the molecular recognition also depends on the type of enolate, the reaction conditions and oxidant <92CRV919>. For these reasons lower *ees* are generally reported for the hydroxylation of acyclic enolates derived from esters, amides and disubstituted ketones <86JOC2402, 92CRV919>.



Scheme 30

(*R*)-(+)-2-Hydroxy-2-methyl-1-tetralone (**164**), a model system for many natural products, is prepared in >95% *ee* via treatment of the sodium enolate of 2-methyl-1-tetralone (**163**) with (+)- (8,8-dichlorocamphoryl)-sulfonyloxaziridine (**74**) at -78°C (Equation (39)) <92JOC7274>. Employment of oxaziridine (+)-(**114**) or (+)-(**158**) results in lower *ees*. Additional examples of the asymmetric hydroxylation of enolates related to this ring system are given in Table 18. In general the molecular recognition for these hydroxylations were evaluated using transition state structure **TS-2** where the enolate approaches the active site oxygen from the less-hindered direction <92CRV919, 92JOC7274>.



Base	Oxaziridine	% ee (% yield)
LDA	(+)-(114) (H)	30 (82)
NaHMDS	(+)-(114) (H)	16 (90)
LDA	(+)-(74) (Cl)	>95 (60)
NaHMDS	(+)-(74) (Cl)	>95 (66)

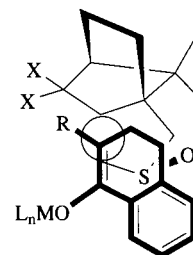
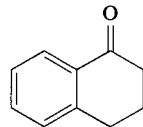
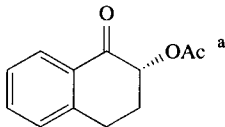
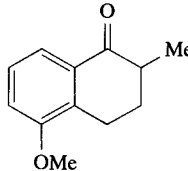
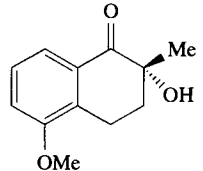
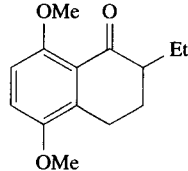
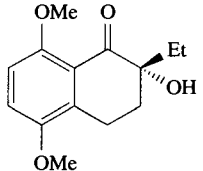
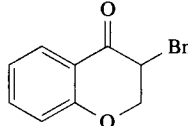
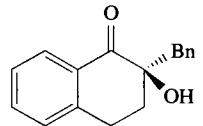
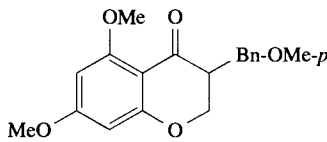
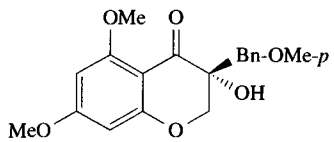
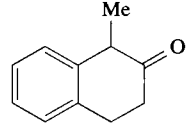
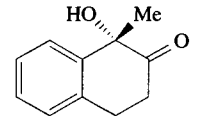


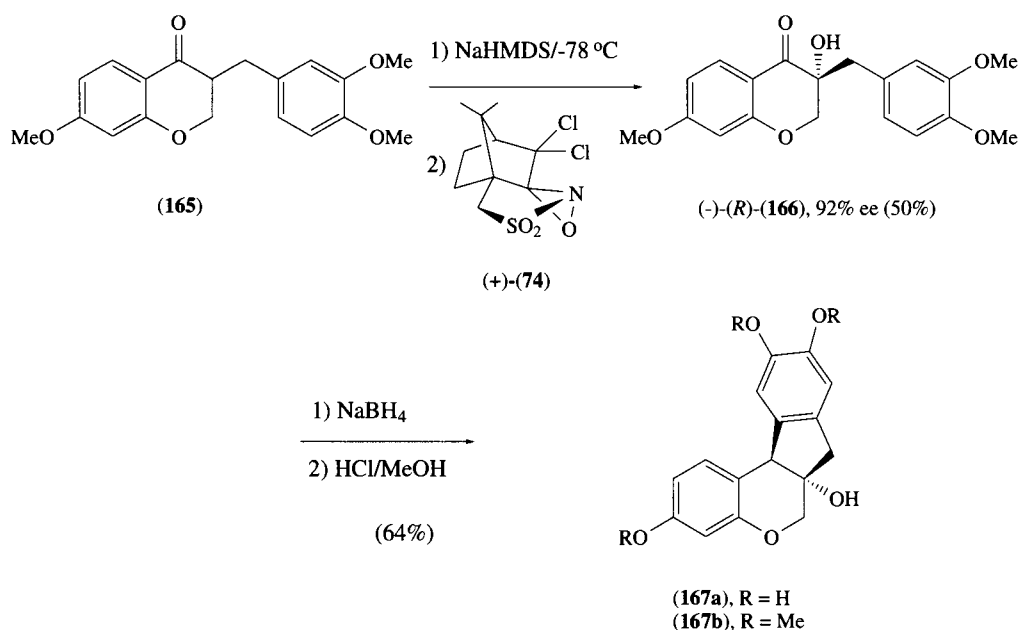
Table 18 Enantioselective hydroxylation of prochiral cyclic ketone enolates.

Ketone	Base	Oxaziridine	α -Hydroxy ketone % ee (config.)	Yield (%)	Ref.	
	NaHMDS LDA	(+)-(74)	 ^a	81 (<i>R</i>) 70 (<i>R</i>)	60 19	94JOC1184
	NaHMDS	(+)-(74)		> 95 (<i>R</i>)	62	92JOC7274
	NaHMDS LDA NaHMDS LDA	(+)-(74) (+)-(158)		68 (<i>R</i>) 73 (<i>R</i>) 60 (<i>R</i>) 95 (<i>R</i>)	70 73 56 66	91JOC1143
	NaHMDS	(-)-(74)		92 (<i>S</i>)	67	90JOC3715
	NaHMDS LDA	(+)-(158)		77 (<i>R</i>) > 96 (<i>R</i>)	73 72	90TL6823
	NaHMDS NaHMDS	(+)-(114) (+)-(74)		76 (<i>S</i>) 16 (<i>S</i>)	60 55	90JOC3715

^aTrapped as the acetate.

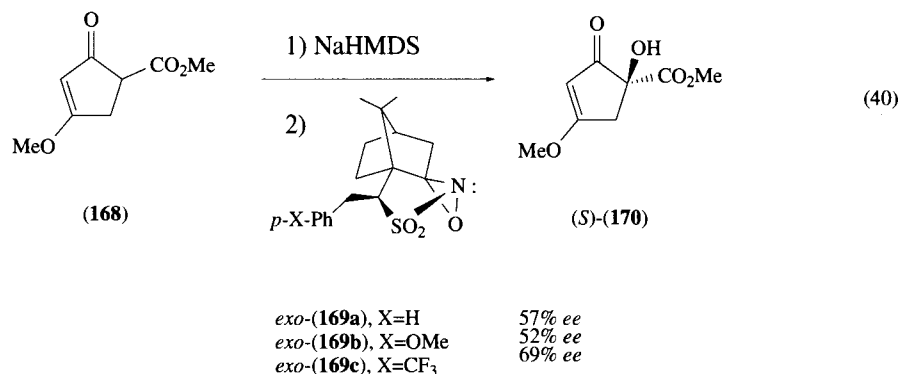
The substitution pattern, which alters the solution structure of the enolate, influences the hydroxylation stereoselectivities (Table 18). As long as the oxidant is chloro oxaziridine (**74**) high *ees* (>90%) are observed for 2-substituted-1-tetralones having a variety of groups at C-2 (Me, Et, PhCH₂). However substitution of a methoxy group into the 8-position lowers the stereoselectivity to 73% <91JOC1143>. For the 8-methoxy tetralones (+)-[(8,8-dimethoxycamphoryl)sulfonyl] oxaziridine (**158**) becomes the reagent of choice improving the *ees* to better than 94% (Table 18). Apparently the presence of an 8-methoxy group is necessary for high *ees* with (+)-(**158**), because this reagent gives significantly lower *ees* (2–36%) when this group is absent <91JOC1143>.

The key step in the asymmetric synthesis of brazilin (**167a**), a tetracyclic homoisoflavanoid which possesses antibacterial and antiinflammatory activities, was prepared by the enantioselective α -hydroxylation of the sodium enolate of chromanone (**165**) in 92% *ee* with chloro oxaziridine (+)-(**74**) <93JOC1751>. The α -hydroxy ketone (**166**) was converted into (**167b**) in 64% overall yield from (**166**), by reduction of the carbonyl and acid-catalyzed cyclization (Scheme 31).



Scheme 31

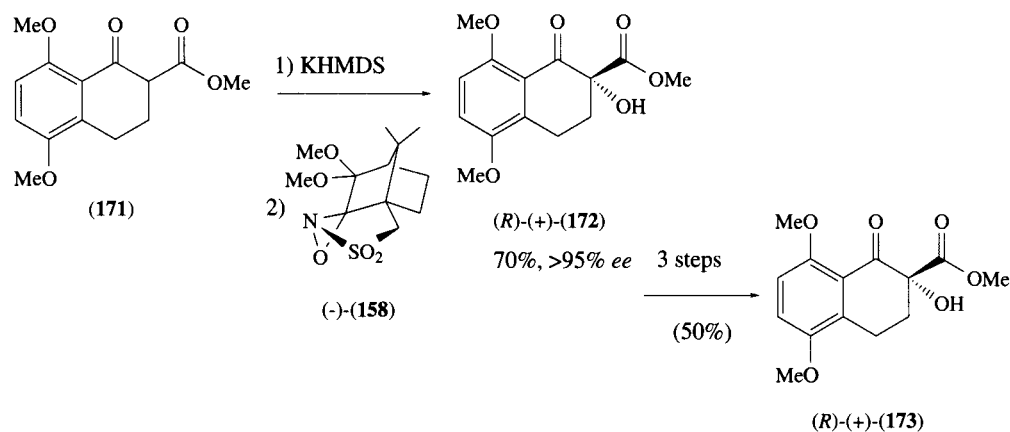
N-Sulfonyloxaziridines and dioxygen are among the few reagents that are able to hydroxylate stabilized enolates such as β -ketone esters (e.g. Vedejs MoOPH reagents fail with such compounds <85OS(64)127>). In this regard, asymmetric oxidation of the sodium enolate of β -keto ester (**168**) furnishes kjellmanianone (**170**), an antibacterial agent isolated from marine algae (Equation (40))



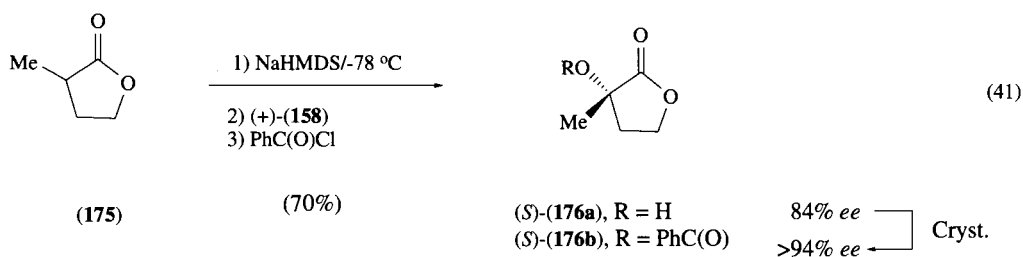
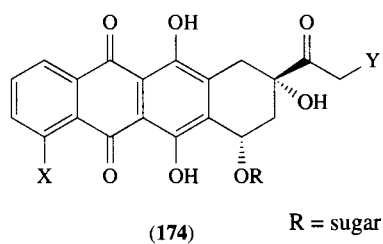
<91T173>. With oxaziridine (+)-(114) yields were better than 70%, but the *ees* were modest, ca. 40%. Remarkably, variation of the *p*-substituent in *exo*-benzyl oxaziridines (169) significantly influences the observed *ees* even though the benzene ring is separated from the active site by five bonds and is *trans*-oriented on the five-membered ring. An attractive interaction between the metal enolate and the benzene ring in (169) has been proposed to account for this. However, the absolute configuration originally proposed for (170), based on the excitation-chirality method, has been revised <94TL2787>.

(*R*)-(+)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (173) is a key intermediate in the asymmetric synthesis of anthracycline antitumor agents demethoxydaunomycin (174; X = Y = OH) and 4-demethoxydaunomycin (174; X = Y = H) <94JOC1184>. The crucial step in a highly efficient asymmetric synthesis of (173) involves the enantioselective hydroxylation (>95% *ee*) of the potassium enolate of (171) with (–)-[(8,8-dimethoxycamphoryl)sulfonyl]-oxaziridine (158) to afford (172). Conversion to (173) was accomplished in three steps in 50% overall yield from (171) without racemization (Scheme 32).

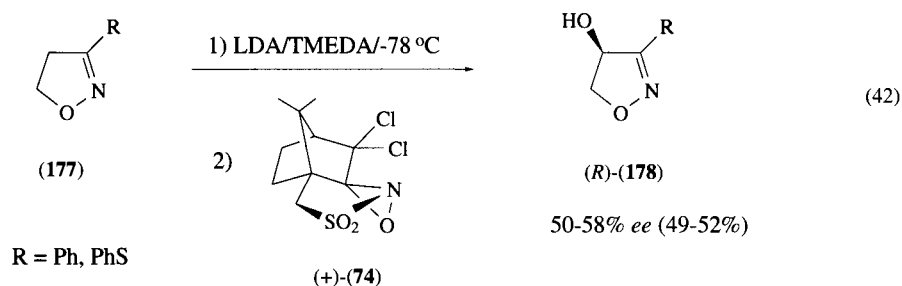
(*S*)-(–)-2-Methyl-2-hydroxy-γ-butyrolactone (176a) is a useful synthon for the asymmetric construction of acyclic tertiary α-hydroxy acids found in natural products such as the pheromone frontalin and mevalonolactone, the biosynthetic precursor of terpenoids and steroids. This compound is readily prepared from lactone (175) using the asymmetric enolate oxidation protocol and dimethoxy oxaziridine (+)-(158) <95JOC6148>. The α-hydroxy lactone (176b), isolated as the benzoate, was obtained in 84% *ee* and 70% yield. A single crystallization from ethyl acetate improved the *ee* to >94% (Equation (41)).



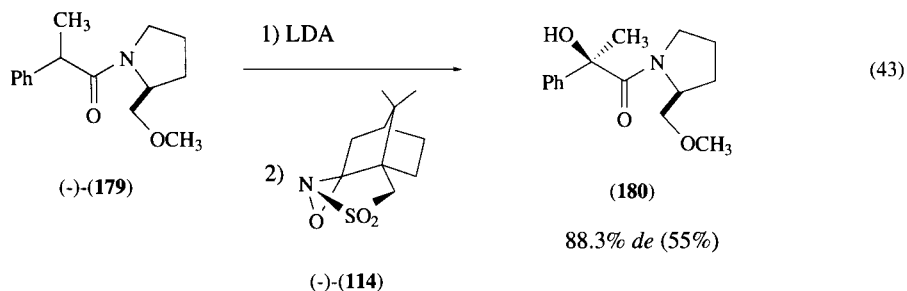
Scheme 32



Modest to low *ees* are reported for the oxaziridine mediate asymmetric hydroxylation of 4,5-dihydroisoxazoles (**177**) to 4,5-dihydro-4-isoxazolols (**178**) (Equation (42)) <93JOC7591>. Dichloro oxaziridine (+)-(**74**) and the lithium enolate, generated in the presence of TMEDA, gave the best results. Transition state **TS-2** predicts the absolute configuration of the product which was confirmed by chemical correlation.

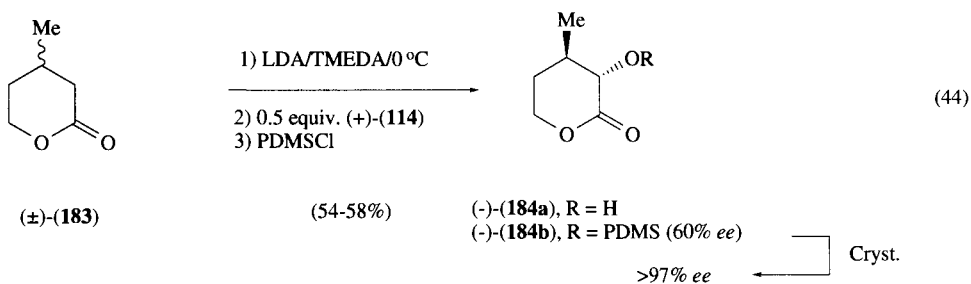


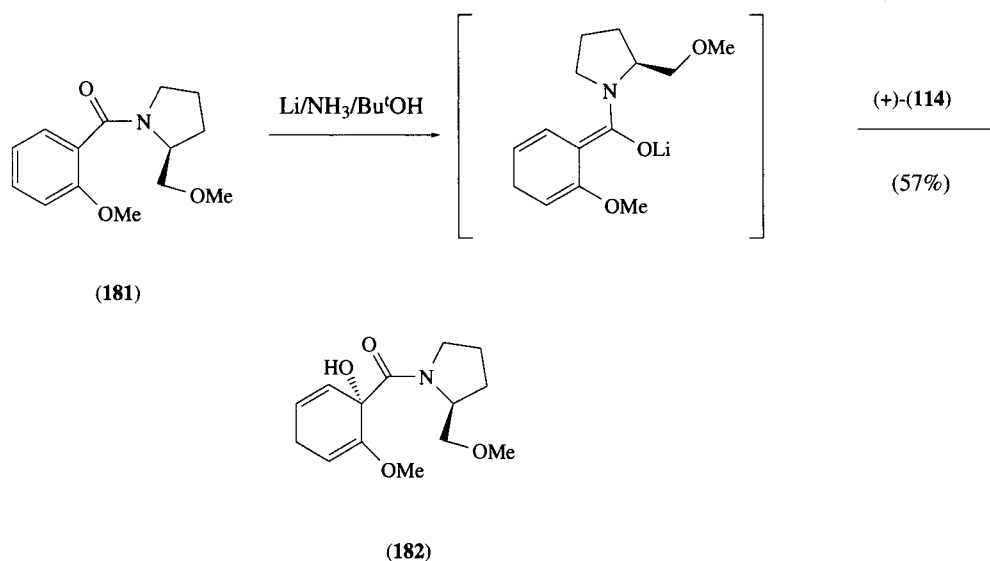
As pointed out in an earlier section, the *ees* for the asymmetric hydroxylation of acyclic enolates derived from α -branched carbonyl compounds is often low because of the difficulty in generating a specific enolate geometric isomer as well as poor enantiofacial discrimination between the *re* and *si* faces of the enolate (Scheme 25). In one example of a double stereodifferentiation process, the asymmetric oxidation of a chiral enolate, was successfully employed to circumvent these difficulties <87JOC5288>. For the matched pair, (–)-(**179**) and oxaziridine (–)-(**114**), the *de* was 88–91% (Equation (43)) whereas with the mismatched pair, (–)-(**179**) and (+)-(**114**), the *de* dropped to 48.4%. The pyrrolidine methanol chiral auxiliary in (**180**) was removed without racemization by basic hydrolysis affording nonracemic atrolactic acid in 70–89% yield.



Birch reduction of chiral benzamide (**181**) followed by oxidation of the resulting enolate with (+)-(**114**) afforded dienol (**182**) in 86% *de*, but in only 16% yield <92JOC2973>. The yield improves to 57%, (80% based on recovered starting material) if ammonia is removed prior to the oxidation (Scheme 33). Asymmetric hydroxylation of the prochiral enolate derived from the Birch reduction of methyl 2-methoxybenzoate with (+)-(**114**) gave the corresponding dienol in 50–60% yield and 30% *ee*.

A novel kinetic resolution and asymmetric hydroxylation protocol was introduced by Davis and Kumar in 1992, for the enantioselective synthesis of (2*S*, 3*R*)-(–)-verrucarinolactone (**184a**), a structural unit common to the naturally occurring macrocyclic trichothecane ester toxins <92JOC3337>. Here, the racemic enolate of (±)-(**183**) is oxidized with substoichiometric amounts of oxaziridine (+)-(**114**) to give (**184b**), trapped as the dimethylphenylsilyl ether to facilitate isolation. While the *ee* is modest, for example 60%, two crystallizations from ether affords (**184b**) in better than 97% enantiomeric purity (Equation (44)).





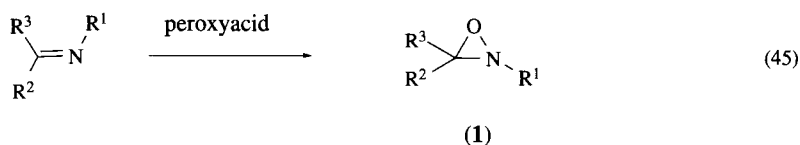
Scheme 33

1.12.4 SYNTHESIS OF OXAZIRIDINES

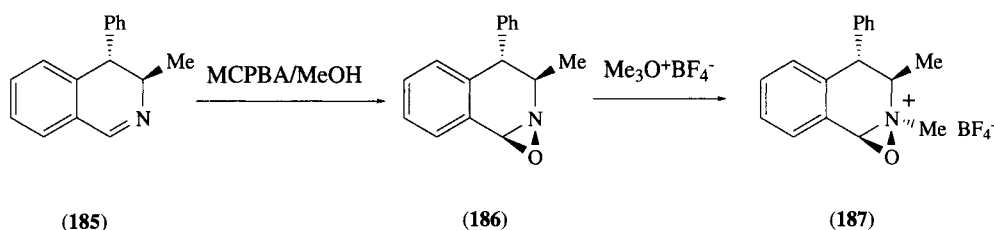
The synthesis of oxaziridines has been the subject of several comprehensive reviews and therefore is only briefly discussed here (84CHEC-I(7)195, 85MI 112-01, 89T5703, 91S327, 92CRV919).

1.12.4.1 N—F, N—Cl, N-Alkyl and N-Aryl Oxaziridines

The most generally useful method for the preparation of oxaziridines is the peracid oxidation of imines (Equation (45)) (B-85MI 112-01). The only limitation on the versatility of this procedure appears to be the availability of the imine. Earlier preparations used peracetic acid, but it was later replaced by MCPBA because of its stability, ease of handling, and commercial availability. The synthesis of a variety of *N*-alkyl-3-aryl oxaziridines, including those where R is heteroaromatic has been described (87S1084). A two-step Baeyer-Villiger type mechanism is generally accepted for these oxidations (85MI 112-01).

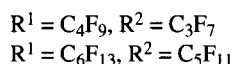
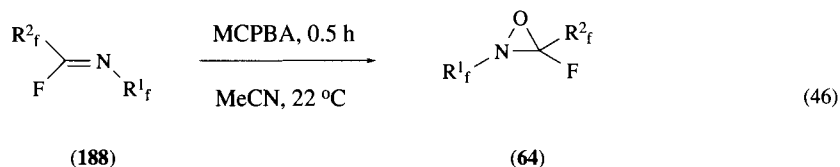


Enantiomerically pure oxaziridinium salt (187) was prepared as shown in Scheme (34) (93TL7271). Oxidation of (185) with MCPBA in MeOH gave a 9:1 mixture of oxaziridine diastereoisomers of which (186) was the major one as determined by x-ray diffraction.

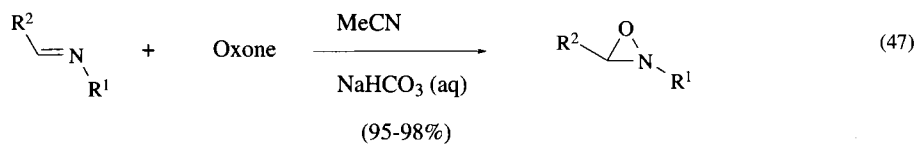


Scheme 34

Perfluoro-*cis*-2,3-dialkyloxaziridines (**64**) are prepared in good yield (68–77%) by MCPBA oxidation of the corresponding perfluoroazaalkenes (**188**) (Equation (46)) <93JOC4754>. To be successful, the peracid needs to be >80% pure, well-dried, and the solvent needs to be acetonitrile. Interestingly, oxidation does not proceed in CH₂Cl₂. A series of 3-*t*-butyl-3-(1-haloalkyl)oxaziridine were prepared by oxidation of the corresponding α -chloro, α -bromo, α,α -dichloro, and α,α -dibromo aldimines with MCPBA <92T7345>.



An efficient, high-yield synthesis of *N*-alkyl and *N*-aryl oxaziridine by oxidation of aldimines with buffered Oxone (potassium peroxymonosulfate) has been introduced by Hajipour and Pyne (Equation (47)) <92JCR(S)388>. Oxidation of the aldimine is accomplished in aqueous NaHCO₃/acetonitrile or acetone affording the oxaziridine within 15–30 minutes in excellent yield (95–98%). The active oxidizing species in acetone and acetonitrile are thought to be dimethyldioxirane and peroxyimide acid [MeC(OOH)=NH], respectively.

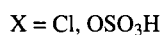
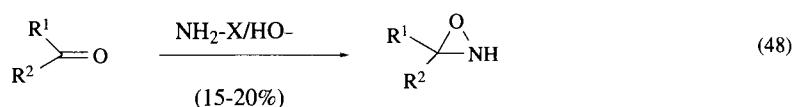


R ¹	R ²	% Yield
Me	Ph	96
<i>i</i> -Pr	Ph	96
<i>t</i> -Bu	Ph	98
Ph	Ph	98

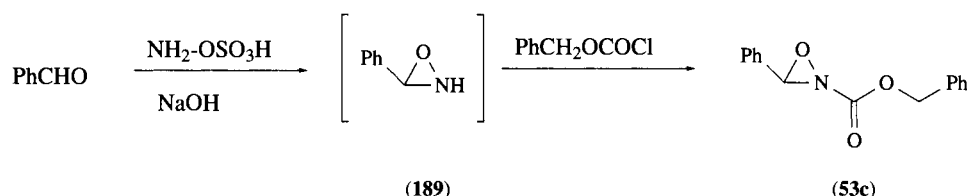
The oxidation of chiral imines with peracids and the oxidation of achiral imines with chiral peracids to give optically active *N*-alkyl oxaziridines has been reviewed <84MI 112-01>. The resolution of chiral *N*-alkyloxaziridine-3,3-dicarboxylic esters through the enzymatic hydrolysis of the racemic diesters, in moderate *ees*, has been reported <88CC1614>.

1.12.4.2 N—H and N-Acyl Oxaziridines

Oxaziridines unsubstituted at nitrogen, generally used as aminating reagents (see Section 1.12.3.5), are prepared by treatment of carbonyl compounds with chloroamine or hydroxyamine-*O*-sulfonic acid in aqueous media (Equation (48)) <91S327>. This method is, however, limited to certain carbonyl compounds with cyclohexanone (up to 85% of (**51**)), followed by butanone, benzaldehyde, and trichloroacetaldehyde giving the best results. *N*-Unsubstituted oxaziridines have also been prepared by photolysis of oximes <69TL157> and the peracid oxidation of ketimines <75CC322>.

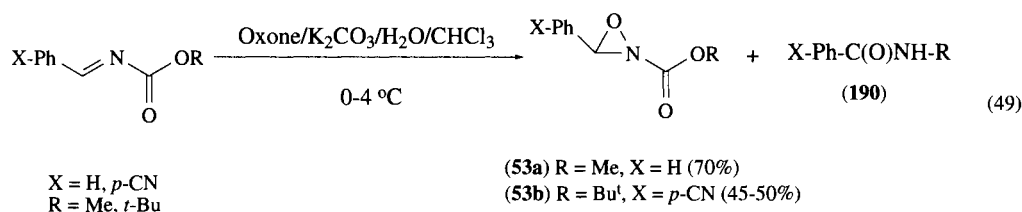


N-Acyl oxaziridines can be prepared by treatment of solutions of *N*-unsubstituted oxaziridines with acid chlorides, acetic anhydride or isocyanates <91S327>. Vederas and co-workers prepared *N*-benzyloxycarbonyl-3-phenyloxaziridine (**53c**) by the direct *in situ* acylation of 3-phenyloxaziridine (**189**) with benzyl chloroformate (Scheme 35) <93TL6859>. Although the overall yield is low, for example 12%, it is claimed that reasonable amounts of (**53c**) are easily accessible.



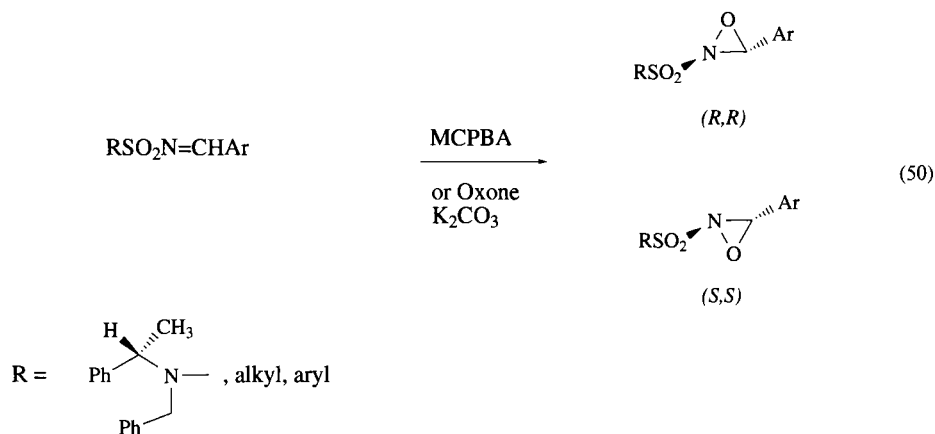
Scheme 35

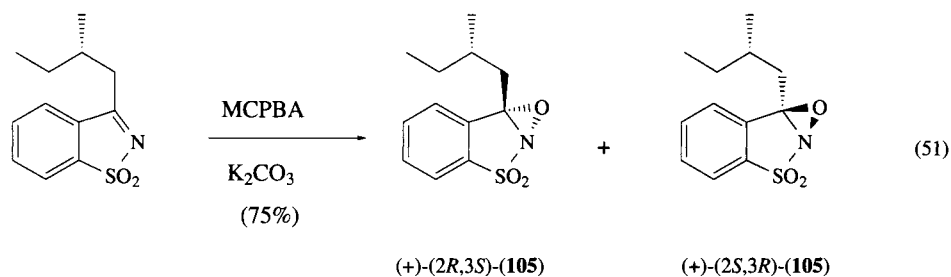
Multigram quantities of *N*-methoxycarbonyl-3-phenyloxaziridine (**53a**) and *N*-Boc-3-phenyloxaziridine (**53b**) are produced by carefully controlling the oxidation of the corresponding imines with buffered Oxone in biphasic media (Equation (49)) <91CC435, 93JOC4791>. The principle product is amide (**190**) if the oxidation is carried out at room temperature or with MCPBA.



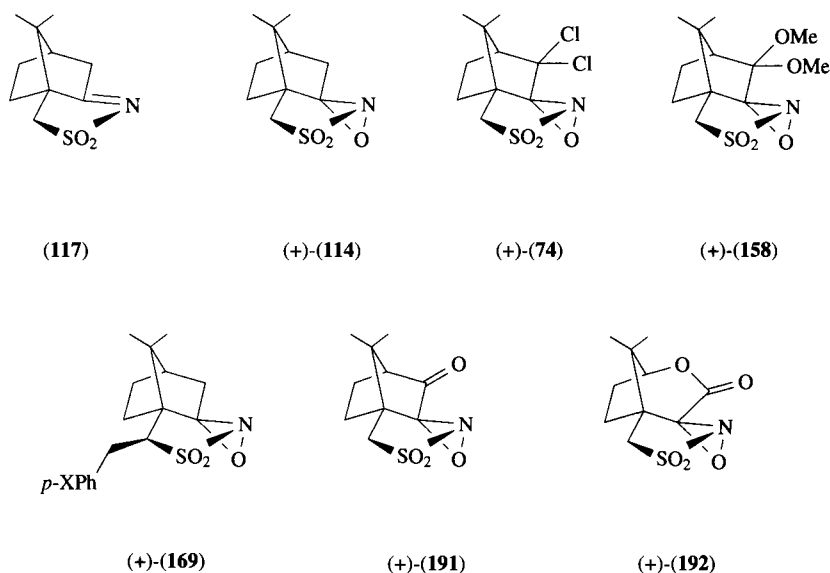
1.12.4.3 Synthesis of *N*-Sulfonyloxaziridines

Aspects of the synthesis of *N*-sulfonyloxaziridines have been reviewed elsewhere <89T5703, 92CRV919, 95MI 112-01, 95MI 112-02, 95MI 112-03>. These oxaziridines are generally prepared by the biphasic buffered oxidation of sulfonimines ($\text{RSO}_2\text{N=CHAr}$) with MCPBA <82JOC1774, 88OS(66)203> or in an improved procedure with Oxone <88JOC2087>. For acyclic sulfonimines the Baeyer-Villiger type oxidation affords only the thermodynamically more stable *trans* isomers (Equation (50)) <89T5703>. Nonracemic acyclic sulfonimines produce mixtures of oxaziridine diastereoisomers requiring separation by crystallization. Similar results are observed for the 1,2-benzisothiazole oxaziridines (**105**) (Equation (51)) <91JOC809>. Condensation of sulfonyl chlorides with *N*-unsubstituted oxaziridines such as spirooxaziridine (**51**) is a route to 3,3-dialkyl *N*-sulfonyloxaziridines <87JA8099>.



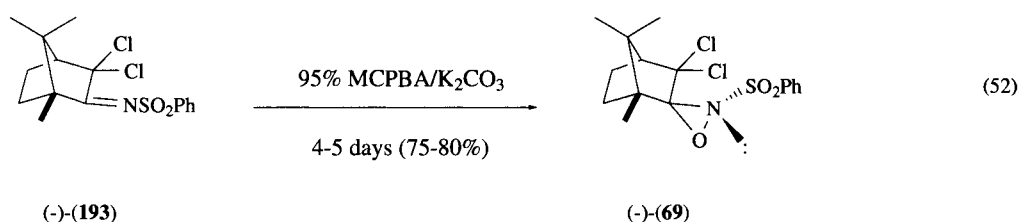


The necessity for separating oxaziridine diastereoisomers, shown by the examples given in Equations (50) and (51), limits their production on a multigram scale. In contrast, the (camphorylsulfonyl)oxaziridines of diverse structure, as shown in Scheme (36), are obtained as single isomers because the *endo* face of the C—N double bond in the corresponding camphorylsulfonimines is blocked. Multigram amounts of (camphorylsulfonyl)oxaziridine (**114**) <90OS(69)158>, [(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (**74**) <92JOC7274, 95OS(73)159> (also prepared on a multikilogram scale) <92TL161>, and [(8,8-dimethoxycamphoryl)sulfonyl]oxaziridine (**159**) <91JOC1143, 95OS(73)159> have been prepared. Oxaziridines (**114**) and (**74**) are commercially available. The common intermediate for preparing these reagents (including (+)-(**169**) <91T173>, (+)-(**191**) <88JCS(P1)1753>, and (+)-(**192**) <89ZN(B)1453>), is camphorylsulfonimine (**117**). The antipodal reagents are available starting from (1*R*)-(–)-10-camphorsulfonic acid.



Scheme 36

Biphasic oxidation of *N*-sulfonylcamphorimine (**193**) with >95% MCPBA, buffered with K_2CO_3 , for four to five days gives (–)-*N*-(phenylsulfonyl)(3,3-dichlorocamphoryl)oxaziridine (**69**) in 75% isolated yield (Equation (52)) <92JA1428>. The best results were obtained, particularly with large-scale oxidations (>40g), when (**193**) was dissolved in a minimum of CH_2Cl_2 . Imine (**193**) is prepared in two steps from camphor and benzenesulfonamide in 66% overall yield <92JA1428, 93PAC633>.



1.13

Thiaziridines and Thiazirines

URI ZOLLER

Haifa University-Oranim, Israel

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1.13.1 INTRODUCTION

1.13.1.1 Historical Perspectives

Over the years three-membered rings have received great attention in chemical research, being the basis for multitudes of publications from both experimental and theoretical perspectives. Since the late 1890s the interest in this area has shown no sign of abatement; if anything it is continuing and growing <89CRV973, 94JA9311>. Moreover, the effects of replacing one or more of the carbon atoms in these ring systems by heteroatom(s) on bonding, structure, strain energies, chemical reactivity, and reaction mechanisms are still being extensively explored in an attempt to bridge the gap between theoretical predictions and experimental tests <94JA9311, B-94MI 113-01, 94PS(95)453>.

Mono- and dihetero analogues of cyclopropane for which geometry is available have characteristically high strain energies <B-78MI 113-01, 83HC(42)333>. The perturbations of heteroatom-containing three-membered rings have been analyzed in terms of interaction of the heteroatom (or group) with ethylene <82T2843>. Regardless of whether electron donation from a suitable heteroatom orbital into the ethylene π^* -orbital, or donation from the ethylenic π -orbital into the heteroatom orbitals including d -orbitals (if available) is the operative mechanism, the ultimate result is the destabilization of the σ -framework. Furthermore, it is well established that the introduction of heteroatoms into small rings produces significant variations in the molecular geometry which reflect the changes in covalent radii, relative electronegativity, and effective hybridization. Consequently, there are changes in the bonding of these heterocyclic systems compared to that of their hydrocarbon analogues. Indeed, the carbon-heteroatom bond length shows an effective increase with increasing heteroatom electronegativity, in line with potential facile ring opening involving the carbon-

heteroatom bonds. Thus, the presence of a heteroatom, coupled with the strain in the system, makes the hetero three-membered rings become thermally unstable and highly (chemically) reactive. Both carbon–heteroatom and heteroatom–heteroatom bonds are weak compared to the corresponding bonds in unstrained systems. Consequently, electrophiles and nucleophiles, as well as thermally (no reagent) and photochemically induced reactions, are expected to initiate facile ring opening $\langle 83\text{HC}(42)333, \text{B-94MI } 113\text{-01} \rangle$. Alternatively, in the presence of either dienes under neutral condition or other appropriate multiple bond containing trapping agents $\langle 87\text{MI } 113\text{-01} \rangle$, the unsaturated members of these series are expected to undergo facile cycloadditions and thus be trapped if they prove to exist only as transient species. The latter, however, may be stabilized via complexation to appropriate metals. Indeed, small-ring heterocycles are the most chemically reactive among the class of small-ring compounds.

The theoretical determination of the structure, energy, reactivity and stability, spectra, bonding, charge distribution, and strain energy together with the relevant experimental chemistry of small-ring heterocycles have played a considerable role in the development of modern organic chemistry $\langle 89\text{CRV973}, 92\text{JA4354}, 94\text{JA9311} \rangle$. The inclusion of a heteroatom within a three-membered ring framework not only results in substantial distortion of the “natural” tetrahedral or trigonal configurations of the atoms involved (in the saturated and unsaturated systems respectively), but also in the alteration of the ring strain energy and, consequently, reactivity—making these molecules extremely intriguing for preparation and study $\langle 83\text{HC}(42)333, 92\text{JA4354}, 94\text{JA9311}, \text{B-94MI } 113\text{-01} \rangle$. In view of the crucial importance of the chemistry of three-membered ring compounds, the following question is appropriate: do three-membered ring heterocycles—including those containing sulfur—contribute uniquely, to the understanding of the characteristics and chemistry of the three-membered ring class of compounds and its role in organic chemistry? This chapter constitutes an attempt to respond to this question.

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 $\langle 16\text{CB1941} \rangle$. Following the preparation of the first pure aliphatic thiirane–ethylene sulfide by Delepine in 1920 $\langle 20\text{BSF740} \rangle$, the importance of this group of compounds as reactive substances suitable for a variety of chemical transformations was recognized. The chemistry of this class of compounds gained momentum when in 1934 Dachlauer and Jackel discovered a simple method for their synthesis from epoxides and alkali thiocyanates or thiourea $\langle 36\text{CA}(30)7122 \rangle$. Yet, excluding a few isolated cases of earlier reported preparations of thiirane oxides, thiirane dioxides, and thiiranium salts, the chemistry of these classes of compounds has been developed and established since the early 1960s $\langle 83\text{HC}(42)333 \rangle$. Thus, the first substituted unsaturated analogues, that is, thiirene dioxides $\langle 65\text{JA5804} \rangle$ and thiirene oxides $\langle 79\text{JA390} \rangle$ were synthesized and characterized by Carpino *et al.* The parent thiirene oxide and dioxide, however, are not known to date.

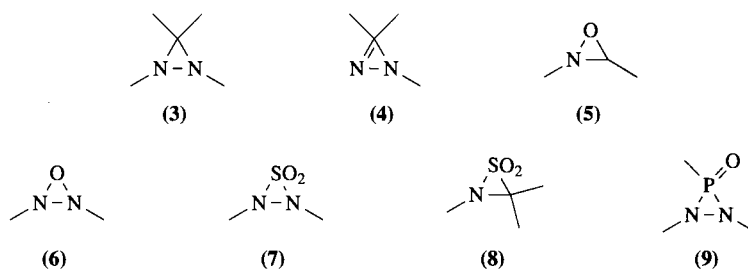
The successful synthesis of the various saturated and unsaturated three-membered rings containing one sulfur atom opened the door to extensive research involving the theoretical and experimental aspects of this class of intriguing compounds. They are reviewed partially in this work (i.e., Chapters 6.20 and 6.21) and thoroughly elsewhere $\langle 83\text{HC}(42)333, \text{B-94MI } 113\text{-01} \rangle$.

This chapter is focused on the thiaziridine and thiazirine heterocycles ((1) and (2) respectively), the three-membered ring systems containing two heteroatoms—sulfur and nitrogen—within their cyclic array.

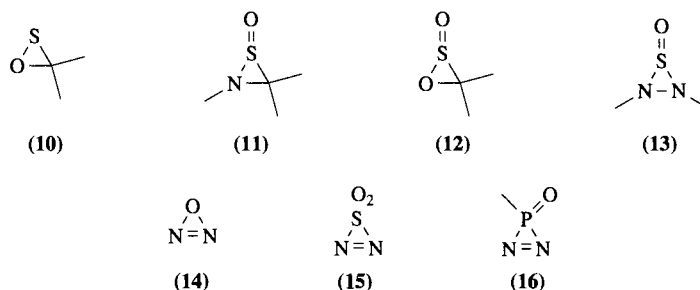


Although, no three-membered ring with two heteroatoms had been prepared before 1950, several isolable compounds incorporating at least two heteroatoms are known as of mid-1995. In this category investigation of three-membered rings containing two nitrogen atoms (i.e., diaziridines and diazirines: (3) and (4) respectively) $\langle \text{B-67MI } 113\text{-01} \rangle$ or one nitrogen and one oxygen (i.e., oxaziranes (5)) $\langle \text{B-64MI } 113\text{-01}, \text{B-67MI } 113\text{-01} \rangle$ preceded the preparation and actual isolation of three-membered rings containing sulfur as one of the heteroatoms. In fact, three-membered rings containing sulfur were first produced in the 1970s. Following the synthesis of the first three-membered ring comprised solely of heteroatoms (i.e., oxadiaziridine (6)) the synthesis of the thiadiazirine dioxide (7) was reported $\langle 73\text{JA634} \rangle$ followed by the successful isolation and characterization of the thiaziridine-S-dioxide system (8) and of the P-analogue (9) $\langle 75\text{AG487} \rangle$.

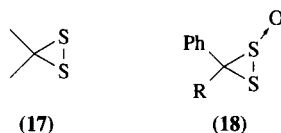
With the exception of the labile, isolable thiaziridine-S-dioxide (8) $\langle 74\text{AG(E)742} \rangle$, none of the



saturated three-membered ring systems (10)–(13) containing two or three heteroatoms within their cyclic skeleton, have been synthesized. Most of them, however, have been proposed as reaction intermediates $\langle 83\text{HC}(42)333 \rangle$. Similarly, almost nothing is known about the unsaturated three-membered ring heterocycles (14)–(16).

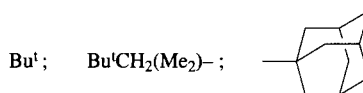


The related two-sulfur atoms containing the ring dithiirane system (17), the existence of which has been demonstrated experimentally $\langle 86\text{T}739, 90\text{SUL}83 \rangle$, was finally isolated and characterized in its S-oxide form (18) $\langle 93\text{JA}4914 \rangle$.



The high energy inherent in the sulfur-containing three-membered ring systems such as (7)–(13), turns them, by and large, into very reactive species which are sensitive chemically, particularly to nucleophiles, thermodynamically, and photochemically.

It is not surprising that in view of the well-documented stabilizing effect imparted to sensitive three-membered rings by bulky substituents $\langle 67\text{JA}362, 67\text{JA}1030, 69\text{AG}(\text{E})449, 69\text{JOC}2254, 70\text{JA}6057 \rangle$ all the successful syntheses and isolations of stable three-membered rings containing sulfur and additional heteroatoms (e.g., (7) and (8)) as well as other isolable heteroatomic three-membered rings (e.g., (9)) are those in which the ring carbon or nitrogen atom (or both) are substituted with very bulky groups, the *t*-butyl, the 1,1,3,3-tetramethylbutyl, and adamantyl respectively (Scheme 1).

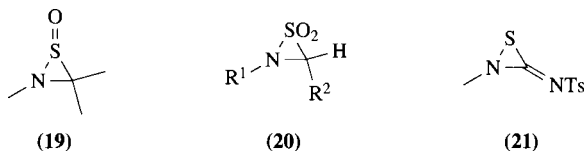


Scheme 1

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 thiazirines as well as closely related systems. The synthesis of both thiaziridines and thiazirines at as low a temperature as possible, in the absence of nucleophiles, appears to be the most promising complementing strategy for their successful isolation, characterization, and study.

1.13.1.2 Scope, Limitations, and Perspectives

Except for the bulky groups substituted thiaziridine-1,1-dioxides (**20**) (e.g., $R^1 = R^2 = \text{Bu}^t$), no other thiaziridines (i.e., (**1**), (**19**), (**21**)) have been isolated.



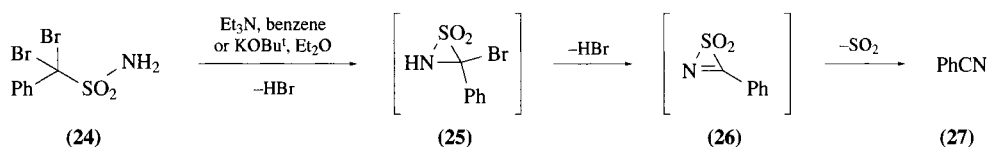
The three-membered thiaziridine rings, thiaziridinimines (**21**) in particular, have been proposed and demonstrated experimentally <75JOC1728> to be reactive intermediates along the reaction coordinate of several thermolytical or photolytical reactions. That these systems do not survive the reaction conditions on thermolysis is not surprising; they can be effectively trapped, however <76JHC883>, and thence their chemical properties can be inferred indirectly.

Neither of the unsaturated analogues of the thiaziridines (i.e., (**2**), (**22**), (**23**)) is known.



Like the saturated thiaziridines, the thiazirines (e.g., (**2**)) have been proposed as unstable intermediates generated mainly photolytically and thermodynamically in certain chemical transformations <75JA6197>.

The intermediacy of system (**23**), the aza analogue of the corresponding thiirene dioxide, has been established in the base-induced successive dehydrohalogenations of the α,α -dibromobenzylsulfonamide (**24**) to provide (**26**) which afforded benzonitrile (**27**) on losing its SO_2 moiety (Scheme 2) <74JOC1817>.

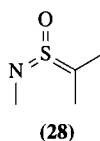


Scheme 2

The thermal instability and high chemical reactivity of these three-membered ring heterocycles make them very intriguing and challenging for preparation and study. The problem is that these predictable (and explainable) properties delimit the possibility for direct experimental testing of theoretical predictions, such as molecular geometries and bonding based on *ab initio* molecular calculations. On the other hand, gas-phase ion-molecule investigations of this class of compounds may prove to be very useful. Investigations using this technique have been demonstrated to be very useful for probing intrinsic reactivities of reactive small strained-ring intermediates (both neutral and ionic) which are difficult to examine in solution <94JA783>. The experimental results of gas-phase studies are directly comparable to *ab initio* molecular orbital calculations and, therefore, should be used in the case of the thiaziridine and thiazirine system. Experimental confirmation of theoretical predictions concerning these and closely related systems would be a very meaningful achievement.

From a theoretical point of view, three-membered ring heterocycles of type (**2**) and (**22**) are unique: they may be considered as antiaromatic as they have a cyclic array of $4n\pi$ electrons predicted by simple Hückel theory to be highly unstable <73ACR393>. Indeed, this has been proved experimentally in the case of analogous thiirenes <78JOC2490>. On the other hand, on the basis of a naive analogy with cyclopropanones, some kind of "aromaticity" can, in principle, be assigned to systems of type (**22**) and (**23**) <74JOC1817, 83HC(42)333>, assuming a possibility for *d*-orbitals to allow transmission of electronic effects via π -conjugation <78T2983, B-94MI 113-01>. Another aspect of interest associated with the thiaziridine- and thiazirine-oxides ((**19**) and (**22**) respectively) is their potential for comprising an acyclic structure (i.e., (**28**)) on their potential energy surface. Their

generation and trapping by 1,3-dipolarophiles will make it possible to determine which of the structural isomers (e.g., (19) or (22)) constitutes the deepest energy minimum.



It should be pointed out that 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 $\langle 83\text{HC}(42)333 \rangle$. In view of the remarkable stability, both thermally and toward electrophiles, of the thiirene oxides relative to their saturated analogues (i.e., thiirane oxides) in spite of their additional strain $\langle 85\text{JOC}1107 \rangle$, does it suggest that the as yet unknown thiazirine oxides (22) are more stable than their saturated analogues—the thiaziridine oxides (19)—and, therefore, should be isolable?

1.13.2 STRUCTURE OF THIAZIRIDINES AND THIAZIRINES

1.13.2.1 Theoretical Methods

The only known thiaziridines are the substituted thiaziridine-1,1-dioxides (20), R^1 and R^2 being the bulky Bu^t or Ad groups $\langle 74\text{AG}(\text{E})742, 81\text{CB}774 \rangle$. It is quite interesting that a literature survey of sulfur-containing systems, which preceded the successful synthesis, isolation, and characterization of the first thiaziridine system, convinced those who prepared the latter (i.e., (20a; $R^1 = R^2 = \text{Bu}^t$)) that of those systems which, in principle, may exist as a three-membered ring, besides the thiirane derivatives (i.e., (29)), only the 1,1-dioxides of thiaziridines (20) and thiadiaziridines (30) can be expected to be more stable than their ring-opened isomers $\langle 77\text{CB}1780 \rangle$. This conclusion is illustrated in Scheme 3.

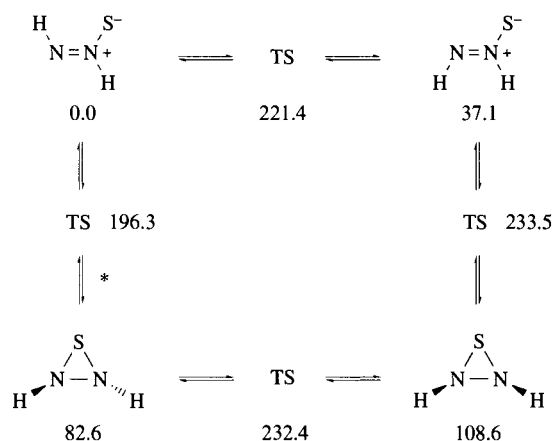


Scheme 3

In contrast to the extensive theoretical studies on three-membered heterocycles containing one sulfur atom, very few *ab initio* or other types of direct molecular calculations of thiaziridines or thiazirines are available. 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 $\langle 70\text{CC}707 \rangle$. Indeed, thiaziridines are not known thus far (except as reaction intermediates) despite some very early unfounded reports to the contrary $\langle 03\text{CB}717 \rangle$.

Relevant *ab initio* calculations with the 6-316* basis set on the thiaziridine-related *E*- and *Z*-thiadiaziridine, *E*- and *Z*-diazene *N*-sulfide and the transition structures connecting them, gave the corresponding energies (in kJ mol^{-1}) relative to the most stable structure—*Z*-diazene *N*-sulfide—as depicted in Scheme 4 $\langle 85\text{PC} 113-01 \rangle$.

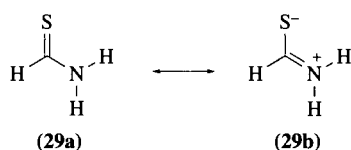
The lowest barrier, * = $113.7 \text{ kJ mol}^{-1}$, in Scheme 4 corresponds to a first-order half-life at 20°C of $\sim 350 \text{ h}$ for an Arrhenius *A*-factor of 10^{14} sec^{-1} , but half-lives will be proportionately greater for the smaller Arrhenius *A*-factors more likely to apply in practice. These results suggest that thiadiaziridine and its simple derivatives should show reasonable thermal stability. Further similar calculations for the electronegative fluorine *N*-substituted thiadiaziridines showed that such a substitution has little effect on the energy difference ($\sim 75 \text{ kJ mol}^{-1}$) between the more stable diazene *N*-sulfide (*Z*-) and the more stable thiadiaziridine (*E*-) $\langle 85\text{PC} 113-01 \rangle$. These results suggest that electronegative groups as such are not necessary for the relative thermal stability observed, for



Scheme 4

example, in the case of the bis(perfluoroethyl)thiadiaziridine <83CC658>. Whether the above theoretical predictions/conclusions are applicable to the thiaziridine system is still an open question.

In an *ab initio* MO calculations study <95JA2201>, it was found that the changes on rotating about the C—N bond of thioformamide (**29**) are closer to expectations from the simple amide resonance picture than are those for formamide.



There is a considerable transfer of π charge to the sulfur in the planar form, and the NH_2 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 thiazirine (**2**), the above results could suggest something about the chances of preparing thermally stable thiazirines.

1.13.2.2 Experimental Structural Methods

The three-membered rings (**20a–d**; (a) $\text{R}^1 = \text{R}^2 = \text{Bu}^t$; (b) $\text{R}^1 = \text{Bu}^t$, $\text{R}^2 = \text{Ad}$; (c) $\text{R}^1 = \text{Ad}$, $\text{R}^2 = \text{Bu}^t$; (d) $\text{R}^1 = \text{R}^2 = \text{Ad}$) are the only thiaziridine (dioxide) systems isolated and characterized thus far. The recorded IR and NMR spectra of these four compounds are in full accordance with their assigned structure and are summarized in Table 1 <81CB774>.

Table 1 The IR and NMR spectra of the isolable substituted thiaziridines (**20a–d**).

Compound	Substituents		IR (SO_2) (cm^{-1})		^1H NMR (ppm)		
	R^1	R^2	$\bar{\nu}_s$	$\bar{\nu}_{as}$	R^1	R^2	3- $\text{H}(s)$
(20a)	Bu^t	Bu^t	1172	1320	1.33 (Bu^t)	1.13 (Bu^t)	
(20b)	Bu^t	Ad	1173	1322–1312	1.31 (Bu^t)	1.73	2.00 (Ad)
(20c)	Ad	Bu^t	1177	1307 (m)	1.68, 1.92	1.10 (Bu^t)	
(20d)	Ad	Ad	1177	1323, 1313 1305 (m)	2.13 (Ad) 1.72, 1.92		2.13 (Ad)

The IR spectrum of (**20b**) <81CB774> given in Figure 1 illustrates its conformity with what is expected in cases of cyclic (or acyclic) sulfonamides. Further experimentally based structural

confirmation of the isolated thiaziridine-1,1-dioxides was gained via the products of their thermolysis—the extruded sulfur dioxide and the remaining imine.

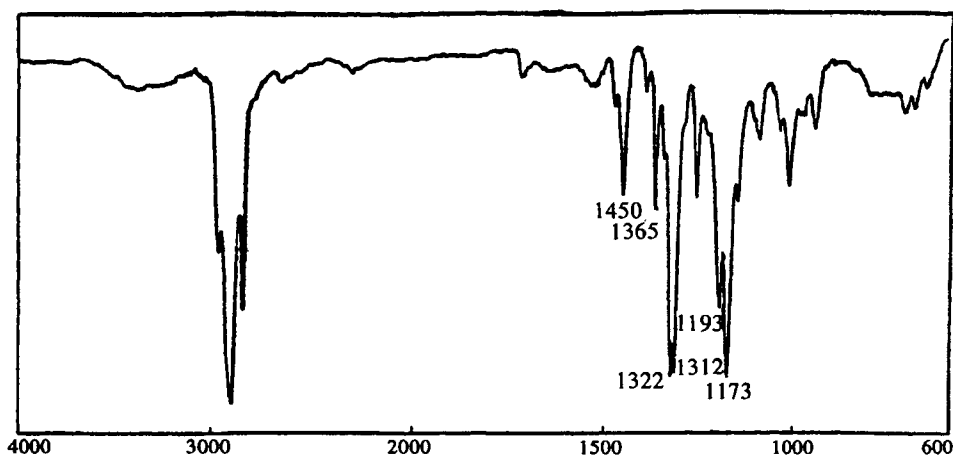
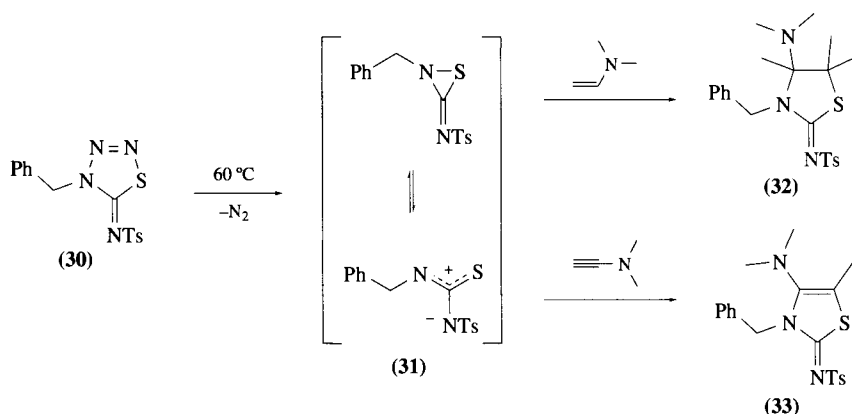


Figure 1 The IR spectrum of thiaziridene-1,1-dioxide (**20b**) <81CB774>.

UV spectroscopy and a PVC film as matrix at 10–15 K was extensively used to detect, or to infer from the absorption spectra recorded, the intermediacy of thiazirines (**2**) on thermolysis or photolysis <78JCS(P1)746>.

Given the characteristic thermal instability of strained small-ring heterocycles and, consequently, their transient existence along chemical reaction coordinates, the trapping of thiazirines appears to be a method of choice for obtaining experimental evidence (albeit indirect) concerning their structure. Such a case in point is the trapping of the thiaziridineimine (**31**) as shown in Scheme 5 <75JOC1728>.



Scheme 5

It is quite clear that distinguishing between the cyclic and the open-ring structures of the thiaziridineimine intermediate (**31**) is impossible based solely on the isolation and characterization of the final products (**32**) and (**33**). Nevertheless, their isolation in this case, or the isolation of cycloadducts containing the trapped intermediate moiety in other related cases, constitutes a strong experimental corroboration of their transitory existence.

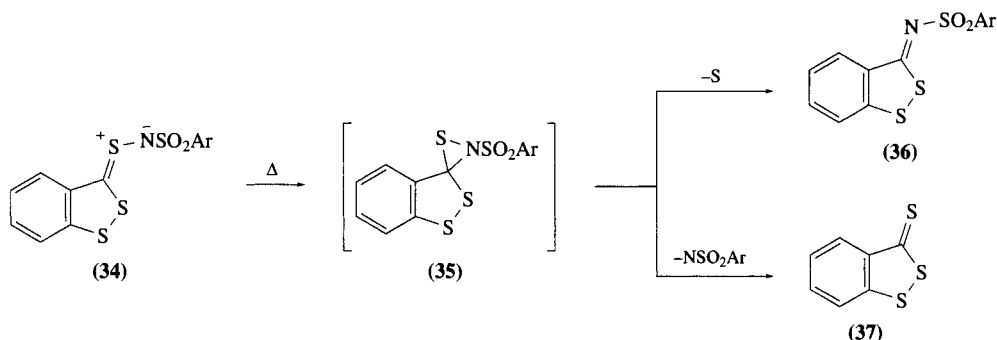
1.13.3 REACTIVITY OF THIAZIRIDINES AND THIAZIRINES

1.13.3.1 Thiaziridines as Intermediates

Up to 1995, the bulky groups substituted thiaziridine-1,1-dioxides (**20a–d**) are the only isolated compounds of this class. However, since the early 1970s, both thiaziridines (**1**) and thiaziridineimines

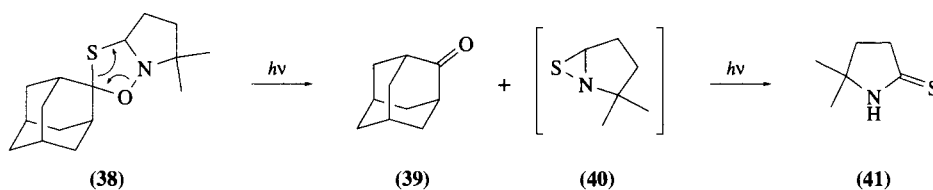
(21) have been proposed as thermally unstable reaction intermediates based on the interpretation of the experimental results.

Thus, for example, based on the increasing change in entropies of activation on going from THF to CH_3CN and the products isolated in the thermal rearrangement of iminothiocarbonyl compounds (e.g., (34)), it was concluded that the rearrangement takes place through the initial ring closure to a three-membered thiaziridine ring (35) followed by the loss of sulfur (Scheme 6) <73BCJ2608>.



Scheme 6

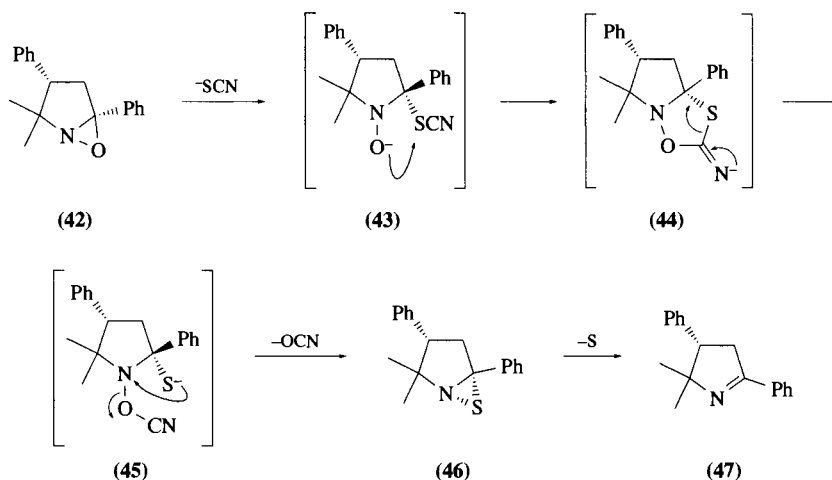
Photolysis of 1,4,2-oxathiazolidines (e.g., (38)) leading to thioamides (e.g., (41)) is proposed to involve the formation of a thiaziridine intermediate (40) by a concerted process, followed by photorearrangement of the thiaziridine to give the thiolactam (41) (Scheme 7) <73AJC2491>.



Scheme 7

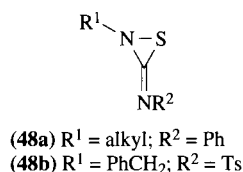
The treatment of simple and fused oxaziridines with sulfur-containing nucleophiles such as thiourea, potassium thiocyanate, potassium ethyl-xanthate, potassium selenocyanate, and triphenylphosphine sulfide resulted in the formation of the related imines, most probably—in analogy to the results of the treatment of oxiranes with the same reagents—via the corresponding thiaziridine intermediate. The proposed reaction mechanism is given in Scheme 8 <73AJC2159>.

Also, the reaction of primary alkyl azides with phenyl isothiocyanate to give 4-alkyl-3,5-bis(phenyl)-

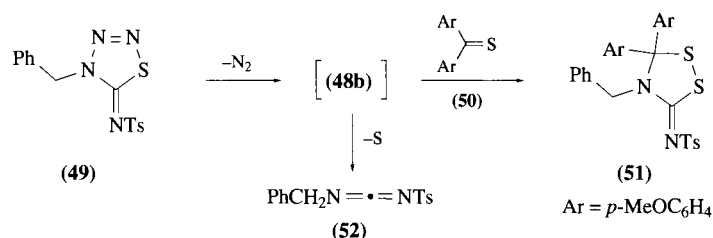


Scheme 8

imino)-1,2,4-dithiazolidines was suggested to involve the initial stepwise addition of two molecules of PhNCS via the intermediacy of the thiaziridineimine (**48a**) <75CC24>.

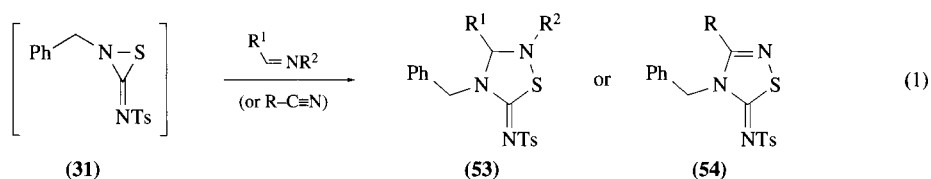


Thermolysis of 3-benzyl-5-tosylimino-1,2,3,4-thiatriazoline (**49**) in the presence of thione (**50**) furnished 1,2,4-dithiazolidine-5-imine (**51**) in moderate yield. These results have been interpreted in terms of an unstable thiaziridineimine intermediate (**48**) which is trapped by the C=S compound in a regiospecific manner as depicted in Scheme 9 <76JHC883>. Thermolysis without the presence of the thione (**50**) leads to the isolation of the sulfonyl carbodiimide (**52**).



Scheme 9

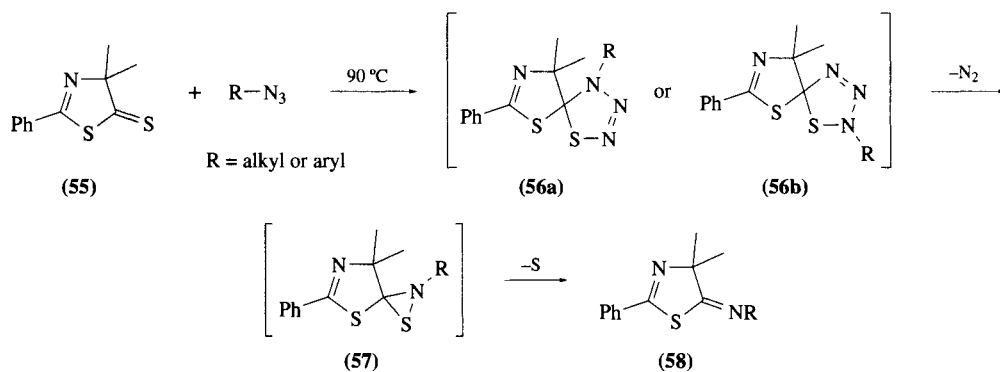
It was previously shown (see Section 1.13.3.1) that thiaziridines formed *in situ* as intermediates on thermolysis <75JOC1728> or photolysis <83HC(42)333> of “appropriately” structured five-membered ring heterocycles, can be trapped with a variety of cummulenes (e.g., ketenes, isocyanates, carbodiimides, and isothiocyanates) to give different five-membered ring heterocycles <75JOC1728>. The thiaziridines generated thermally can be easily and effectively trapped *in situ* with imines and nitriles to provide the corresponding 1,2,4-thiadiazolidines (i.e., (**53**) and (**54**)) in good yields (Equation (1)) <76JOC3403>. This “trappability” of the thiaziridines constitutes strong evidence for their existence as intermediates along the reaction coordinates of these transformations, stable enough on the reaction time-scale for being trapped.



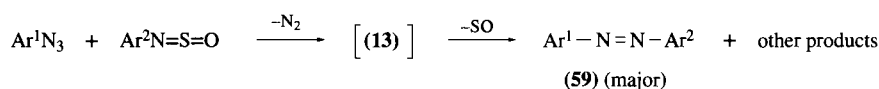
In the late 1980s, the reaction of organic azides and 1,3-thiazol-5-thiones (Scheme 10) to provide good yields of 1,3-thiazole-5-imines (i.e., (**58**)) was interpreted mechanistically in terms of successive eliminations from the initially formed adduct of N₂ and S via the thermally unstable thiaziridine (**57**) <88HCA1673>. Analogously, the photochemical reaction between aryl azides and *N*-sulfinylanilines has been shown to yield mainly azoaromatics (**59**) (Scheme 11). The experimental results (including the formation of sulfur and sulfur dioxide from the presumably extruded sulfur monoxide) were interpreted in terms of the intermediacy of thiadiaziridine-1-oxide (**13**).

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 (**20**), the only isolable compounds of the thiaziridine series. As could be predicted and in line with theoretical considerations, thermolysis of alkyl-substituted thiaziridine-1,1-dioxides (**20a,d,e**) afforded aldimines (**60a,d,e**) as a result of the cheletropic extrusion of the

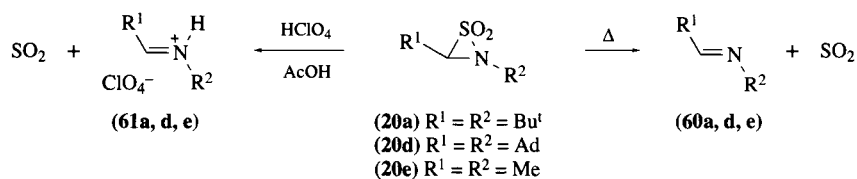


Scheme 10



Scheme 11

sulfur dioxide moiety (Scheme 12) <81CB774>. Treatment of these thiaziridine-1,1-dioxides with perchloric acid also resulted in the loss of sulfur dioxide with the concomitant formation of the corresponding ammonium perchlorate salts (61) <81CB774>.



Scheme 12

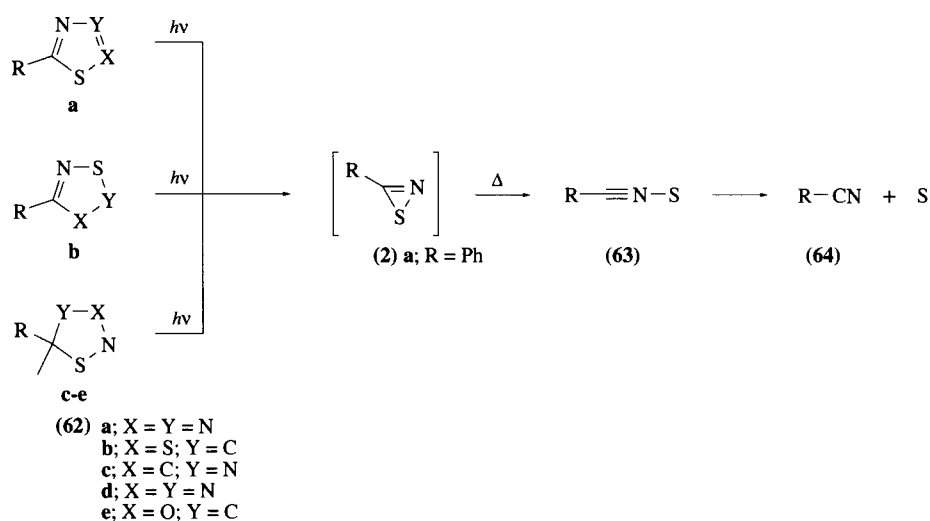
In both cases, the driving force for the reactions to take place easily is the high initial energy content of the thiaziridine three-membered strained system. Similar results (and their interpretation) were obtained with the analogous more stable thermodynamically thiadiaziridine-1,1-dioxide system <77CB1780>.

1.13.3.3 The Intermediacy of Thiazirines

Thiazirines are the aza analogues of thiirenes. As planar cyclic systems containing 4π electrons in a cyclic array, they belong to the group of antiaromatic compounds with all the thermodynamic consequences involved <73ACR393, 83HC(42)333, 85JOC1107>. Hence, 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 <77JA4842, 78JOC2490>, 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 13) <75JA6197, 78JCS(P1)746, 78JCS(P1)1445>, apparently through the intermediacy of the three-membered ring thiazirines (2) <72JCS(P1)1317>.

Interestingly, the initially formed thiazirine (claimed to be stable at the irradiation/matrix temperature <78JCS(P1)746>) rearranges above this temperature (10–15 K) to the corresponding nitrile sulfide (i.e., (2; $\text{R} = \text{Ph}$)) and only then loses sulfur to give the benzonitrile. The cheletropic extrusion of sulfur from the postulated thiazirine formed, leading directly to the nitrile, was not observed. Rather, at room temperature, the benzonitrile formed was trapped *in situ* as a cycloaddition product with dimethylenedicarboxylate <78JCS(P1)746>.

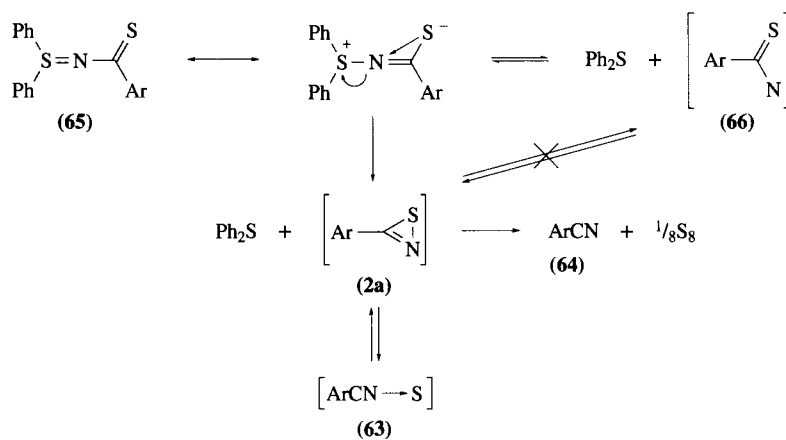
Unfortunately, although the intermediacy of thiazirine (2) does account for all the experimental results in the investigations cited, no separate spectral peak could be assigned unambiguously to



Scheme 13

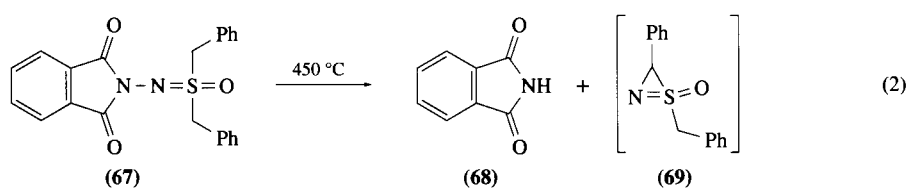
this compound because the complicated spectra was obscured by the presence of other products and starting materials <78JCS(P1)746>.

The thermal decomposition of *N*-thiocarbonyl diphenylsulfimides (65) 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 arylthiazirine (2a) and nitrile sulfide (63a) (Scheme 14). The possible intermediacy of thiocarbonyl nitrene (66) was excluded <76BCJ3124>.



Scheme 14

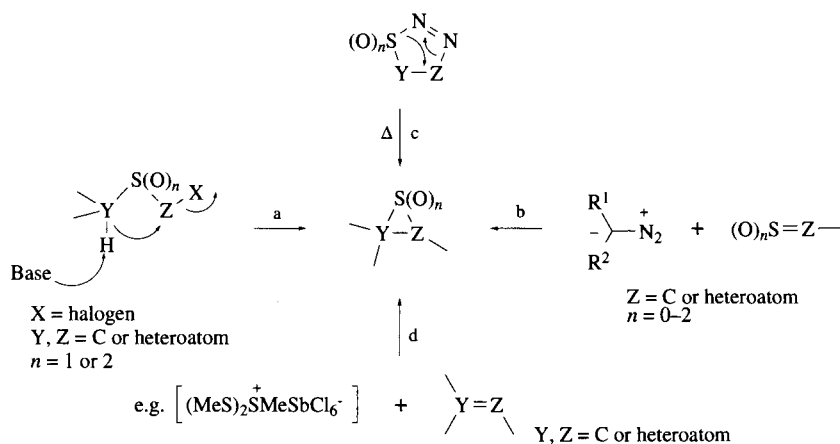
The oxidation of *N*-aminolactams with lead tetraacetate in the presence of sulfoxides gave sulfoximides. Thermolysis of the dibenzylsulfoximide (67) thus formed resulted in an N—N bond cleavage and formation of phthalimide (68) as the only product observed. It has been proposed that the sulfur-containing products generated in this hydrogen transfer process have the three-membered ring sulfoximide structure (69) (Equation (2)) <72JCS(P1)1317>. Several attempts to isolate a product other than phthalimide from the reaction were unsuccessful.



1.13.4 SYNTHESIS OF THIAZIRIDINES AND THIAZIRINES

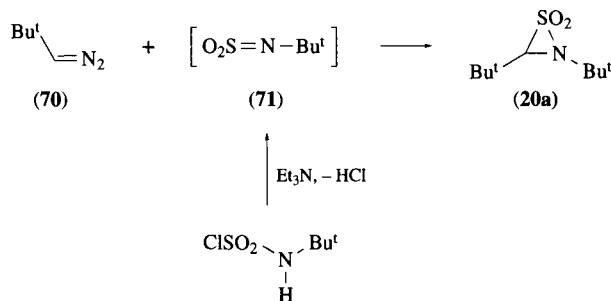
1.13.4.1 Synthesis of Thiaziridine-1,1-dioxides

In principle, just a few “general” methodologies are available for the preparation and isolation of three-membered ring heterocycles containing two heteroatoms—for the S-oxide and the S-dioxides (Scheme 15,a)—which turned out to be very productive in the preparation of aryl-substituted thiirene oxides <79JA390> and dioxides <71JA476>: the Staudinger approach <16CB1941>, in which a diazo compound reacts with a sulfur double bond (Scheme 15,b); 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 (Scheme 15,c) (the preparation of the antiaromatic thiirenes is a case in point <77JA4842, 83HC(42)333>); and the use of sulfur transfer agents which add sulfur to multiple bonds (Scheme 15,d) for which the successful synthesis of the three-membered thiirenium ions <77TL911> is a good example.



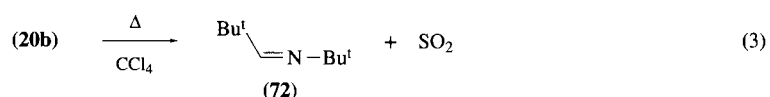
Scheme 15

Experiments towards 1,3-elimination of hydrogen halides from α -chlorosulfonamides, α -bromosulfonamides, and *N*-chlorosulfonamides (Scheme 15,a) did not yield isolable thiaziridine-1,1-dioxides <81CB774>. The only thiaziridine-1,1-dioxides (**20a–d**) known in mid-1995 were synthesized by reacting diazoalkanes (**70a,b**) with *N*-sulfonylaminates (**71a,b**) generated *in situ* by hydrogen chloride elimination from the corresponding sulfamoyl chlorides with triethylamine at 78°C. If the work-up temperature was kept below -30°C , the targeted thiaziridine dioxides (**20a–d**) were obtained in 32–47% yield <74AG(E)742, 81CB774>. The synthetic scheme for the first prepared thiaziridine dioxide (**20a**) is shown in Scheme 16 <74AG816>.



Scheme 16

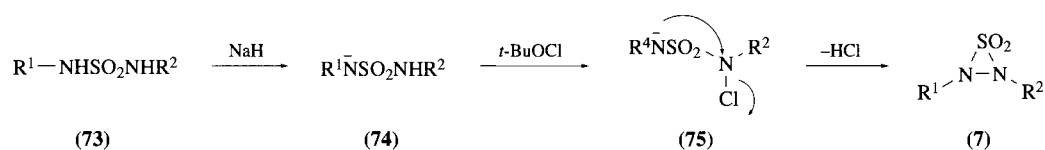
The thiaziridine dioxide (**20a**), which crystallizes as colorless needles from pentane at -78°C , is thermally unstable and easily decomposes quantitatively to sulfur dioxide and azomethine (**72**) (Equation (3)). This first-order decomposition has been shown to occur over more than three half-lives with $K(25^\circ) = (9.05 \pm 0.05) \times 10^{-5} \text{ sec}^{-1}$ <74AG816>.



The IR and NMR spectra of (20b) correspond to the assigned structures: IR (CCl₄): 1325, 1177 cm⁻¹ (SO₂); and NMR (CCl₄): λ = 1.03 (s, Bu^t), 1.33 (s, Bu^t), and 3.72 ppm, (s, CH) (see Table 1).

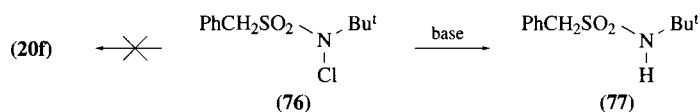
1.13.4.2 Attempted Synthesis of Thiazirine-1,1-dioxide

All known thiadiaziridine dioxides (7) have been prepared by essentially the same method: the treatment of substituted sulfamides with a non-nucleophilic base to form the monoanion of the sulfamide (i.e., (74)), which on treatment with *t*-butyl hypochlorite gives the *N*-chloroanion (75). Dehydrohalogenation in the final step affords the desired thiaziridine-1,1-dioxide system (7) (Scheme 17) <73JA634, 74AG(E)742>. This is, in fact, the general method as depicted in Scheme 15.



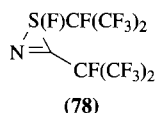
Scheme 17

All attempts to apply the same methodology for the synthesis of the thiaziridine-1,1-dioxide system (8) failed <74AG(E)742, 74JOC1817, 81CB774>. Thus, for example, the treatment of the *N*-chloro compound (76) with triethylamine in methylene chloride or with potassium *t*-butoxide in ether afforded after workup only the reduction product (77), not the expected thiaziridine-1,1-dioxide (20f; R¹ = Bu^t, R² = Ph) (Scheme 18) <74JOC1817, 83HC(42)333>.



Scheme 18

Attempted synthesis of the elusive thiazirine-1,1-dioxide system (23) using the same methodology was unsuccessful as far as the actual isolation of either the thiaziridine intermediate (25) or the targeted thiazirine (26) (see Scheme 2). However, the isolation of benzonitrile as the product of the reaction of α,α -dibromobenzylsulfonamide with triethylamine or potassium *t*-butoxide (Scheme 2) constitutes clear-cut evidence for the intermediacy of the thiazirine-1,1-dioxide (26) along the reaction coordinate <74JOC1817>. A previously assigned structure of thiazirine (78) to the product obtained in a very low yield (<4%) from the reaction of CF₃N=SF₂ and CF₃CH=CF₂ over C₃F₆ <68IC683> has no supporting experimental evidence.



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 25 years of effort by the chemical community. Therefore, although much has been accomplished thus far and the first members of these classes of compounds have been prepared, isolated, characterized, and studied, a substantial amount of work remains to be done in this area. The challenge is there, since many of these systems have been elusive and their existence has been inferred only indirectly or circumstantially.

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 many hitherto unknown three-membered rings containing sulfur and additional heteroatoms will be successfully synthesized, characterized, and thoroughly studied in the very near future.

The significance of such studies is fourfold: (i) realization of the synthesis of hitherto unknown, difficult to prepare novel heterocycles which are of particular theoretical and/or biological–medicinal importance; (ii) 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; (iii) development of novel and effective synthetic strategies and obtaining of data which will facilitate the correlation of theoretical expectations with observable properties and thus enhance the understanding of heterocyclic chemistry in general and the chemistry of small-ring heterocycles in particular; (iv) gaining insight into antiaromaticity and small-ring heterocycle carbanion chemistry via fundamental thermochemical information.

1.14

Three-membered Rings with Two Oxygen and/or Sulfur Atoms

ROBERT W. MURRAY and MEGH SINGH
University of Missouri-St. Louis, MO, USA

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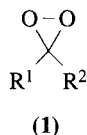
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1.14.1 INTRODUCTION

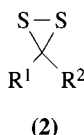
At the time of the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) (1984) little was known about compounds within the title categories. A single oxathiirane, produced by photo-rearrangement of a thioketone *S*-oxide, had been characterized by its ultraviolet (UV) spectrum in 1976 <76JCS(P1)1404>. Dimethyldioxirane was mentioned only to the extent that its existence as an intermediate had been made plausible in 1980 <80JOC4758>.

Dioxiranes have been invoked as intermediates in a variety of chemical processes. In only a few cases has evidence been obtained that dioxiranes are actually involved, however. Much of this history has been reviewed <B-88MI 114-01> and is not repeated here. Instead, attention is given to the growing literature in which dioxiranes are characterized or used in synthesis using methods where unequivocal evidence has been presented for the presence of a dioxirane.

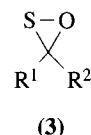
Evidence has been presented for the existence of all three systems encompassed by the title of this section, namely, the dioxiranes, (1), the dithiiranes, (2), and the oxathiiranes, (3). Contrary to the situation that existed in 1984 referred to above, there is now a large literature on the formation and reactions of dioxiranes. While dithiiranes have been suggested as unstable intermediates several times, the first isolation of a dithiirane derivative occurred in 1993 <93JA4914>. With respect to oxathiiranes, spectroscopic evidence has been presented for the existence of several additional examples of this class. Two mini reviews, which include updates on dithiiranes and the isomeric thiosulfines, have been published <86SUL213, 90SUL83>. Also a chapter in a monograph includes a review of developments in oxathiiranes and dithiiranes <83CHE333>. A section on oxathiiranes has been included in a review on the photochemistry of episulfides <72IJS(B)331>. Since the first report of their isolation in solution in 1985 <85JOC2847>, the dioxiranes have received a rapidly increasing amount of attention. Several reviews have been written describing their synthesis and chemistry <B-88MI 114-01, B-88MI 114-02, 89ACR205, 89CRV1187, B-90MI 114-01, 92MI 114-02, B-92MI 114-04, 93TCC45>. Annual updates on dioxirane chemistry also now appear <89PHC82, 90PHC22, 91PHC42, 92PHC34>.



- (a) $R^1 = R^2 = H$
- (b) $R^1 = R^2 = Me$
- (c) $R^1 = R^2 = CF_3$
- (d) $R^1 = CF_3, R^2 = CF_2Cl$
- (e) $R^1 = OMe, R^2 = Ph$
- (f) $R^1 = R^2 = Ph$
- (g) $R^1 = Ph, R^2 = CF_3$
- (h) $R^1 = Ph, R^2 = Cl$
- (i) $R^1 = Me, R^2 = H$
- (j) $R^1 = CF_3, R^2 = Me$



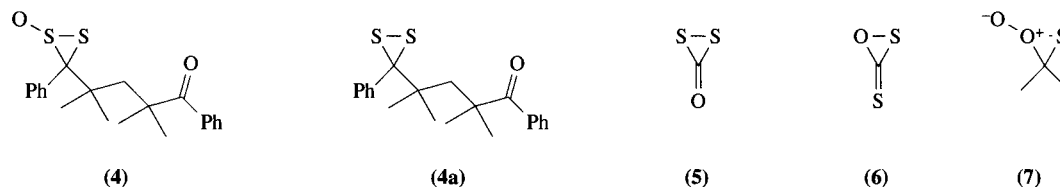
- (a) $R^1 = R^2 = H$
- (b) $R^1 = R^2 = Cl$



- (a) $R^1 = R^2 = H$
- (b) $R^1 = R^2 = Cl$
- (c) $R^1 = R^2 = Ph$

For dioxiranes, known structural types include those in which alkyl or aryl groups are attached to the ring. Some examples of spiro structures have also been synthesized. Only two dithiiranes have been synthesized, namely, oxide derivative, (4), and the parent dithiirane, (4a), containing an aryl and a complex alkyl substituent <93JA4914>. Dithiiranone, (5), has been suggested as the intermediate responsible for episulfidation of alkenes when amine oxides are treated with carbon disulfide <82BCJ3000, 85JOC3228>. This same intermediate has been suggested as a product of the reaction of oxygen atoms with carbon disulfide <76JCP(64)2528>. Other structure types claimed as intermediates are the parent dithiirane, (1a), and the dichloro derivative, (1b) <79AG(E)941>. For oxathiiranes, a number of intermediate structures have been suggested including the parent, (3a), the dichloro derivative, (3b), and the diphenyl compound, (3c) <76JCS(P1)1404>. UV-Vis spectroscopy has been

used to gain evidence for structure (3c) <76JCS(P1)1404> as an intermediate in the photolysis of thiobenzophenone *S*-oxide. Oxathiiranethione, (6), has been considered as an alternative to (5) as intermediates in the reaction between tertiary amine *N*-oxides with carbon disulfide <82BCJ3000, 85JOC3228>. Oxathiirane *O*-oxides (α -sultines) (7) have been proposed as the first product of the reaction of singlet oxygen with thiocarbonyl compounds <80JCS(P2)188>.



1.14.2 THEORETICAL METHODS

1.14.2.1 Dithiiranes

Semiempirical molecular orbital (MO) calculations have been carried out on the parent dithiirane (2a). Using CNDO/S-CI the electronic spectrum has been calculated <77JA2931>. The geometry of (2a) was optimized by the energy gradient method using the GAUSSIAN 80 programs <86JST(148)153>. The calculations predict a C_{2v} structure for (2a). The dipole moment and ground-state energy were also calculated. A theoretical analysis of dithiiranethione, (2b), with respect to its valence tautomerization concludes that the activation energy for this process (135 kJ mol^{-1}) makes it unlikely <75JCS(P2)559>.

1.14.2.2 Oxathiiranes

Using a CNDO/B framework, calculations have been made on the structures of possible intermediates in the reaction between singlet oxygen and thiocarbonyl compounds <80JCS(P2)188>. These calculations predict primary formation of an oxathiirane *O*-oxide, (7). *Ab initio* calculations using the CASSCF method have indicated that photolysis of thioformaldehyde *S*-oxide probably leads to rearrangement to the oxathiirane (3) <84JA1557>. Transformation of thioformaldehyde *S*-oxide to the oxathiirane has been predicted to be an allowed thermal process on the basis of energy-geometry optimization using an MO-SCF-CNDO procedure <74JA5005>. Use of CNDO/B semiempirical calculations predicts that the electrocyclic ring closure of sulfene (8) to oxathiirane *S*-oxide (9) (α -sultine) should be an allowed process <78JOC2216>.

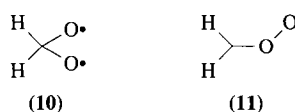


1.14.2.3 Dioxiranes

Some of the reviews of dioxirane chemistry mentioned also contain summaries of theoretical calculations on dioxiranes <B-88MI 114-02, 89CRV1187, B-90MI 114-01>. Another review on theoretical aspects of peroxides contains a section on dioxiranes <B-92MI 114-03>. While the reader is referred to the cited references for details of the theoretical calculations contained therein, some of the major conclusions, as well as some of the unreviewed data, are given here.

Bach *et al.* have calculated the energies and structures of parent dioxirane (1c) as well as the open diradical form (10) and the isomeric carbonyl oxide (11) <92JA7207>. The molecular orbital calculations were carried out using the GAUSSIAN 90 program and the second order Moller-Plesset (MP2) optimization was used to obtain the structure of (1c). The C—O and O—O bond distances were calculated to be 1.397 and 1.531 Å, respectively, which compare well to the distances

measured by microwave spectroscopy $\langle 78JA5117 \rangle$. These calculations are also similar to the majority of those reported earlier although some of the earlier reports give higher values for both C—O and O—O distances $\langle 89CRV1187 \rangle$. Calculations have also been made on the interconversion of the parent dioxirane and the isomeric carbonyl oxide. An earlier calculation on the conversion of the carbonyl oxide to (**1a**) found the barrier to be $23.9 \text{ kcal mol}^{-1}$ $\langle 81CPL(79)416 \rangle$. Bach *et al.* calculate this barrier to be $23.8 \text{ kcal mol}^{-1}$. On the other hand opening of (**1a**) to the carbonyl oxide has been found to have a barrier of $47.7 \text{ kcal mol}^{-1}$ by Bach *et al.* Experimental experience is consistent with these calculations, that is, there are several reported examples of carbonyl oxides being converted to the corresponding dioxiranes, but no reports of the reverse process. For the gas-phase transfer of an oxygen atom from (**1a**) to ethylene, Bach *et al.* calculate a potential barrier of $17.6 \text{ kcal mol}^{-1}$. This compares well with the experimental value of $14.1 \text{ kcal mol}^{-1}$ for the epoxidation of ethyl cinnamate by dimethyldioxirane (**1b**) $\langle 90JCS(P2)349 \rangle$. These workers also found that the optimized transition state for an oxygen atom transfer from (**1b**) to ethylene is the spiro structure suggested earlier by Baumstark *et al.* on the basis of rate differences in the epoxidation of stereoisomeric alkenes by (**1b**) $\langle 87TL3311 \rangle$.



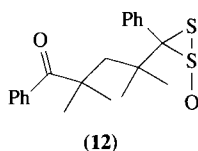
Yamaguchi *et al.* have calculated the molecular orbital energy levels for (**1a**) using the *ab initio* 4-31G MO method $\langle B-92MI 114-03 \rangle$. These calculations indicate that the LUMO of (**1a**) is a σ -type antibonding MO. Furthermore, the energy level of this LUMO is lowered when electron-withdrawing substituents are present in the dioxirane. Thus, this LUMO is an electron-accepting orbital and dioxiranes are predicted to be electrophilic, as observed experimentally. The activation energy for the transfer of an oxygen atom from difluorodioxirane (**1c**) to ethylene is calculated to be $7.2 \text{ kcal mol}^{-1}$ by Yamaguchi *et al.*, which is to be compared with the corresponding reaction using (**1a**) where the calculated barrier is $17.6 \text{ kcal mol}^{-1}$ $\langle 92JA7207 \rangle$. This comparison dramatically illustrates the effect of electron-withdrawing substituents on the reactivity of the dioxirane.

1.14.3 EXPERIMENTAL STRUCTURAL METHODS

1.14.3.1 Dithiiranes

1.14.3.1.1 X-ray diffraction

A number of structural methods have been used to characterize the only stable dithiiranes, *S*-oxides (**4**) and (**12**), and dithiirane (**4a**). X-ray single crystal structural analysis was used to unambiguously establish the structure of (**4**) $\langle 93JA4914 \rangle$. The crystals are triclinic. The C—S bond distances were found to be virtually equal. These distances are similar to those calculated for the parent dithiirane $\langle 77JA2931 \rangle$. The structure of (**12**) was determined by comparing its spectroscopic properties with those of (**4**). X-ray single crystal structural analysis has also been used to establish the structure of (**4a**) $\langle 94AG(E)777 \rangle$. The compound has no unusual bond lengths or bond angles. The S—S bond length is $2.073 \text{ \AA}$, for example.



1.14.3.1.2 Spectroscopic studies

(i) NMR spectra

NMR data have been reported for both (**4**) and (**12**) $\langle 93JA4914 \rangle$. In the ^1H spectra, the *trans* arrangement of the *S*-oxide bond (**12**) leads to a downfield shift of the methyl resonances compared to the *cis* compound (**4**). Proton and ^{13}C NMR data have been reported for the unoxidized dithiirane (**4a**) $\langle 94AG(E)777 \rangle$.

(ii) *Infrared (IR) spectra*

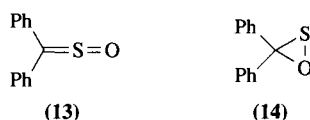
IR data for the most important bands of (4) and (12) have also been reported <93JA4914>. For dithiirane (4a) the carbonyl IR band ($\nu = 1669 \text{ cm}^{-1}$) has been reported <94AG(E)777>.

(iii) *UV-Vis spectra*

The UV-Vis spectrum of (4a) has the longest absorption maximum at 452 nm <94AG(E)777>. This absorption corresponds to the first electronic transition ($n_{\pi} \rightarrow \sigma^*$) calculated earlier to be at 422 nm <77JA2931>.

1.14.3.2 Oxathiiranes**1.14.3.2.1 Spectroscopic studies**(i) *UV-Vis spectroscopy*

With one exception there are essentially no spectroscopic data available for oxathiiranes. The one exception is the report by Carlsen *et al.* <76JCS(P1)1404> in which they conclude that an intermediate formed in the photolysis of thiobenzophenone sulfine (13) is the oxathiirane, 3,3-diphenyloxathiirane (14). The intermediate is formed when (13) is photolyzed in an EPA glass at 77 K and has a long wavelength absorption at 390 nm.

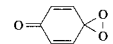
**1.14.3.3 Dioxiranes****1.14.3.3.1 Spectroscopic studies**(i) *Microwave spectroscopy*

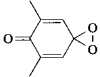
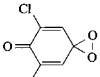
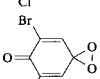
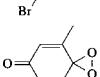
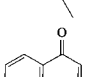
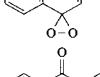
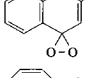
Microwave spectroscopy has been used to obtain critical evidence for the formation of the parent dioxirane (1a) in the low temperature (-130 to -75°C) reaction of ozone with ethylene <77CPL(51)453, 78JA5117>. The microwave data permitted calculation of the following molecular parameters: $r_{\text{C-H}} = 1.0903 \text{ \AA}$, $r_{\text{C-O}} = 1.3878 \text{ \AA}$, $r_{\text{O-O}} = 1.5155 \text{ \AA}$, $\angle \text{HCH} = 117.32^{\circ}$, $\angle \text{OCO} = 66.189^{\circ}$, $\mu = 2.479 \text{ D}$.

(ii) *NMR spectroscopy*

(a) *Proton NMR spectroscopy.* NMR spectroscopic data for dioxiranes are collected in Table 1. The ^1H shift values are unremarkable. The values obtained for some dioxiranes compare reasonably well with those obtained by *ab initio* calculations, provided that one allows for the facts that the calculated values do not take into account temperature effects or the effects of intermolecular interactions <87JOC2800>.

Table 1 Spectral data for dioxiranes.

<i>R</i> ¹	<i>R</i> ²	¹ H NMR	¹³ C NMR (δ ppm)		¹⁹ F NMR (δ ppm)	¹⁷ O NMR (δ ppm)	UV-vis λ _{max} (nm)	Infrared (cm ⁻¹)	Ref.
		(δ ppm)	Ring carbon	Other carbons					
Me	Me	1.65 ^a	102.0	22.68 ^a		302 ^b	335 ^a	3012s, 3005s, 2999s, 1209s, 1196w, 1094s, 1080w, 1059w, 1034w, 899s, 784s ^a	<85JOC2847, 87JOC699>
Me	Et		103.9 ^c				333 ^c		<88MI 114-02, 85JOC2847>
Me	Pr ^d		105.47	16.93, 33.99 ^d			347 ^d		<92JA1346>
Me	Bu ^d		106.41	26.50 ^e			326 ^e		<92JA1346>
F	F				-29.9 ^f			1464vs, 1259vs, 1061s, 911m, 772m, 617w, 557w, 511vw ^f	<93AG(E)905>
Me	CF ₃	1.97 ^g	97.32	14.51, 122.20	-81.5	297	347 ^g	1259, 1189, 971w, 839w, 731w, 669w ^g 3020w, 1447m, 1427m, 1402s, 1330s, 755m, 745m, 715s, 615s ^g	<88JOC3890> <91JA7654>
CF ₃	CF ₃				-76.8		306 ⁱ	1318, 1460, 1430, 1408, 1385, 1230, 660 ^h 1353s, 1276s, 1235s, 1212sh, 1111w, 1022w, 975s, 713m ⁱ	<72USP3632606>
CF ₃	CF ₂ Cl				-74.6, -65.0			1412w, 1311m, 1242s, 1215s, 1149m, 1048m, 898m, 858m, 822w, 710w ⁱ	<72USP3632606>
Ph	MeO	3.50 ^j	109.1					760m, 698m, 629w, 590w ^k	<93CJC272>
Ph	Ph							1450w, 1285w, 916vw, 759m, 693m, 628w, 588w ^k	<86AG(E)255> <89JOC333>
Ph	Cl							1330m, 1315w, 1291m, 1170s, 1057w, 1030w, 905vs, 751m, 741m, 685m, 651w ^k	<86JA1517>
Ph	CF ₃							1213s, 944s, 684m, 643m ^l	<88JOC121>
Ph	(MeO) ₂ P=O							844, 786, 691, 568, 536, 522 ^l	<92JOC6216>
—CH=CH—CH=CH—								1395w, 1382m, 1178w, 890m, 737m ^k	<86CC154>
—(CH ₂) ₅ —			104.51	24.68, 33.36 ^l			345 ^l		<92JA1346>
—CH(Me)(CH ₂) ₄ —			105.53	13.05, 33.36, 33.49, 5.62 ^m			355 ^m		<92JA1346>
—CH ₂ —CH(Me)(CH ₂) ₅ —			104.28	23.65, 31.93, 35.23, 41.98 ⁿ			337 ⁿ		<92JA1346>
—(CH ₂) ₂ CH(Me)(CH ₂) ₂ —			104.55	21.46, 30.86, 32.47, 32.83 ⁿ			350 ^o		<92JA1346>
—CH ₂ CH(Me)(CH ₂) ₂ CH(Pr ^d)—			106.45 ^p				354 ^p		<92JA1346>
								1687m, 1677m, 1644s, 1388m, 1313s, 1263s, 1070m, 889s ^a	<88JOC2091>

	1682, 1667, 1663, 1659, 1656, 1647, 1449, 1425, 1382, 1372, 1365, 1356, 1318, 1269, 1196, 1145, 1036, 1017, 932, 903, 753, 520 ^{a-d}	<92CB1851>
	1709, 1703, 1608, 1584, 1394, 1344, 1324, 1314, 1298, 1040, 1034, 900, 883, 793, 791, 766, 732 ^{a-d}	<92CB1851>
	1703, 1696, 1658, 1634, 1593, 1577, 1342, 1321, 1295, 1272, 1004, 903, 860, 759, 708 ^{a-d}	<92CB1851>
	1685, 1658, 1650, 1638, 1449, 1432, 1403, 1371, 1334, 1304, 1297, 1259, 1022, 939, 915, 903, 854 ^{a-d}	<92CB1851>
	1700, 1695, 1687, 1684, 1679, 1669, 1652, 1635, 1623, 1616, 1607, 1588, 1576, 1570, 1542, 1540, 1473, 1345, 1342, 1301, 1295, 1273, 1145, 1014, 1012, 871, 765, 667, 620, 618, 608, 530 ^{a-d}	<92CB1851>
	1681, 1659, 1608, 1599, 1465, 1445, 1432, 1389, 1371, 1360, 1347, 1334, 1330, 1316, 1301, 1297, 1287, 1265, 1246, 1214, 1163, 1157, 1081, 1015, 940, 887, 788, 776, 757, 701, 683, 580 ^{a-d}	450 ^b <92CB1851>
	1537w, 1399w, 1386w, 1343s, 1327m, 1135w, 915w, 874m, 700m ^a	<90JOC4502>

^aAll measurements in acetone solution. ^b¹⁸O-enriched acetone was used as precursor. ^cIn 2-butanone. ^dIn 3-methyl-2-butanone. ^eIn 3,3-dimethyl-2-butanone. ^fIn CFCl₃/CCl₄. ^gIn trifluoroacetone. ^hIn CCl₄. ⁱIn gas phase. ^jIn CD₂Cl₂. ^kIn Ar/O₂ matrix. ^lIn cyclohexanone. ^mIn 2-methylcyclohexanone. ⁿIn 3-methylcyclohexanone. ^oIn 4-methylcyclohexanone. ^pIn menthone. ^qPartial data in the range 1750–500 cm⁻¹.

(b) *Carbon-13 NMR spectroscopy.* Carbon-13 NMR data have been reported for a number of dioxiranes (Table 1). The most characteristic absorption is that due to the ring carbon. The value for dioxirane (**1b**) is 102 ppm which compares well with a calculated value of 99 ppm <87JOC2800>. This absorption is somewhat dependent on dioxirane substituent (Table 1).

(c) *Fluorine-19 NMR spectroscopy.* Fluorine-19 NMR data have been obtained on the few fluorine-containing dioxiranes synthesized to date (Table 1).

(d) *Oxygen-17 NMR spectroscopy.* The reporting of ^{17}O NMR data for dimethyldioxirane was instrumental in supporting the dioxirane structural assignment. These data established that the two oxygen atoms are identical thus ruling out the isomeric carbonyl oxide as a possible structure for the volatile peroxide isolated from the generation reaction <87JOC699>. Similar ^{17}O data have been reported for dioxirane (**1j**) <88JOC3890, 91JA7654>.

(ii) *UV-Vis and infrared spectroscopy*

(a) *UV-Vis spectroscopy.* Dioxiranes have a weak $n\text{-}\pi^*$ UV absorption in the 300–350 nm region (Table 1). This absorption has proved convenient for studying the kinetics of dioxirane reactions. This UV absorption tails off into the visible giving the dioxiranes a color ranging from pale yellow to golden yellow.

(b) *Infrared spectroscopy.* Infrared data have been reported for a number of dioxiranes (Table 1).

1.14.4 THERMODYNAMIC ASPECTS

1.14.4.1 Dithiiranes

The dithiirane *S*-oxide (**4**) is a rather stable crystalline compound with m.p. 124–125°C. The *trans* isomer (**12**) is less stable and could not be obtained in pure form <93JA4914>. The authors believe that isolation of these two *S*-oxides is largely due to steric inhibition to reaction by the bulky substituents. The dithiirane ring system is otherwise very reactive. The unoxidized dithiirane (**4a**), on the other hand, is a rather stable orange crystalline material which only decomposes when heated to the 68–75°C range.

1.14.4.2 Oxathiiranes

No thermodynamic data are available for oxathiiranes.

1.14.4.3 Dioxiranes

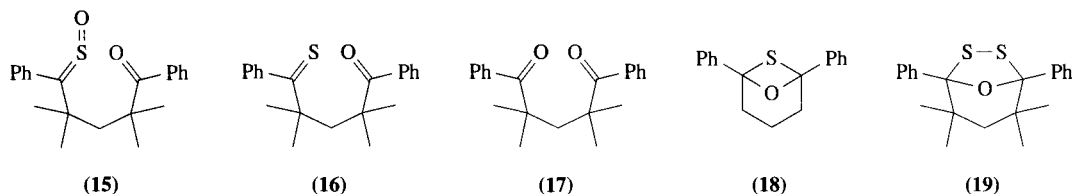
Thermochemical calculations have been made on three dioxiranes <B-88MI 114-02>. Enthalpies of formation of parent dioxirane (**1a**), methyldioxirane (**1i**), and dimethyldioxirane (**1b**) have been calculated to be 0.9, –9.5, and, –22.0 kcal mol $^{-1}$, respectively.

1.14.5 REACTIVITY OF THREE-MEMBERED RINGS WITH TWO OXYGEN AND/OR SULFUR HETEROATOMS

1.14.5.1 Dithiiranes

The stable dithiirane *S*-oxide (**4**) is converted to sulfine (**15**) and triphenylphosphine sulfide upon treatment with triphenylphosphine <93JA4914>. When heated, (**4**) decomposes to give thioketone (**16**), sulfine (**15**), and dicarbonyl compound (**17**). Compounds (**16**) and (**15**) result from loss of sulfur monoxide and sulfur, respectively, from (**4**). Thioketone (**16**) exists in equilibrium with oxathietane (**18**). The rate of thermal decomposition of (**4**) was found to be dependent on its concentration, with higher rates at higher concentrations. The authors suggest that this observation is indicative of a decomposition pathway involving the sulfur and sulfur monoxide products. Thermolysis of (**4**) also leads to isomerization of (**12**) in addition to the products described above.

The reaction is believed to involve homolysis of the S—S bond to give a biradical which is intermediate to isomerization and product formation. Thermal decomposition of (4a) gives elemental sulfur and thioketone (16) <94AG(E)777>. Treatment of (4a) with triphenylphosphine also leads to (16) plus triphenylphosphine thiooxide. Oxidation of the dithiirane with MCPBA gives the sulfine (15). Heating of a dilute solution of (4a) in 1,2-dichloroethane gives the bicyclic 1,3,4-oxadithiolane (19) along with (16) and (18).



1.14.5.2 Oxathiiranes

Since no stable oxathiiranes have been reported, no reactions have been described. Some insight into oxathiirane reactivity can be gained, however, by reading Section 1.14.6.2 concerned with the preparation of oxathiiranes where postulated reaction pathways of intermediate oxathiiranes are described.

1.14.5.3 Dioxiranes

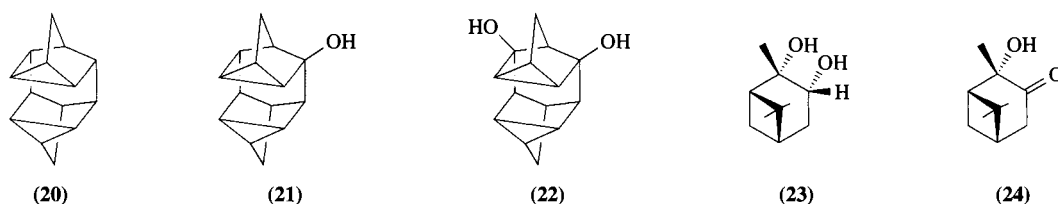
Since 1985 there has been a great increase in the number of papers describing reactions of dioxiranes. Space limitations will not permit the authors to refer to all of these papers. Instead the authors have attempted to cover all of the different reaction types. Within each type of reaction attempts have been made to indicate the various structure types encompassed by that reaction. This survey of dioxirane reactions indicates that the dioxiranes are excellent mimics of the monooxygenase enzymes <86JA2470>. In this case, mimicry is meant to refer to the range of reaction type and not the mechanistic details of the reactions. Nevertheless, studies of dioxirane reactions may provide some insights into the corresponding enzyme-catalyzed reactions.

1.14.5.3.1 The carbon–hydrogen insertion reaction

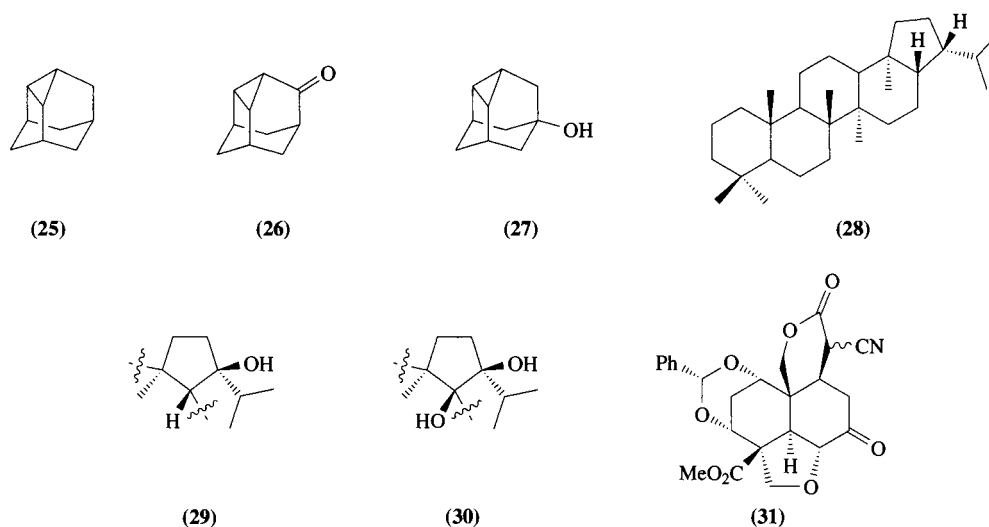
The most surprising and unusual reaction of dioxiranes is their ability to insert an oxygen atom into unactivated C—H bonds. This reaction was first reported by Murray *et al.* <86JA2470>. In that report, several examples of the reaction were described, including the very interesting observation that oxidation of *cis*- and *trans*-1,2-dimethylcyclohexanes with (1b) proceeds to give the 1,2-dimethylcyclohexan-1-ols stereospecifically with retention. Similarly, the *cis* and *trans* decalins gave the respective 9-decanols in a stereospecific manner. The reaction of (1b) with adamantane afforded 1-adamantanol in 87% yield accompanied by 2-adamantanol and 2-adamantanone in 2.6% combined yield. Oxidation of *n*-decane by (1b) gave 2-decanone and 3-decanone and several unidentified products. Further insight into the nature of the insertion reaction was obtained by comparing relative reactivities of the benzylic hydrogens in the series toluene, ethylbenzenes and cumene. The oxidation with (1b) gave relative reactivities of 1 : 24 : 91, respectively, while the comparable radical abstraction reaction (*t*-butoxy radicals at 40°C) <61JA3877> gave relative reactivities of 1 : 3.2 : 6.8, respectively. Thus the dioxirane is more selective than the radical, and the dioxirane reaction appears to have little, if any, radical character. Furthermore, when an equimolar mixture of cyclododecane and cyclododecane-*d*₂₄ is oxidized by (1b), a primary kinetic isotope effect, $k_H/k_D = 4.97$, is measured, strengthening the conclusion that the process is not radical in nature <86JA2470>. The benzylic C—H bond insertion reaction of (1b) has also been studied by Kuck and Schuster <91ZN(B)1223>. Among the observations made in that work, is that benzylic C—H bonds are slightly more reactive than tertiary bonds at remote positions in the same molecule.

These C—H insertion reactions require considerably longer times than the epoxidation or heteroatom oxidations (see Sections 1.14.5.3.2 and 1.14.5.3.5). The more reactive methyl-(trifluoromethyl)dioxirane (1j) is able to accomplish similar oxidations at a faster rate <89JA6749>.

By comparing rate constants for the reactions of (1b) and (1j) with cumene and ethylbenzene it was possible to show that (1j) is more reactive than (1b) by factors of ca. 600 and 700, respectively. Selective polyoxyfunctionalization of the bridgehead positions of adamantane by (1j) leads to formation of the 1,3-diol or a mixture of the 1,3,5-triol and 1,3,5,7-tetraol depending on the ratio of the reagents <90TL3067>. The oxidation of the head-to-head dimer of norbornadiene ("binor S", (20)) with (1b) gave first the 1-ol (21) and, by further oxidation, the 1,9-diol (22) of (20). <90JOC6105>. The stereospecificity of the dioxirane C—H insertion reaction was dramatically illustrated by Adam *et al.* when it was shown that (1j) oxidizes (*R*)-(–)-2-phenylbutane to (*S*)-(–)-2-phenyl-2-butanol in 95% yield and with complete retention of configuration <92JOC953>. Optically active *sec*, *sec*-diols are selectively oxidized by (1b) or (1j) to the corresponding α -hydroxy ketones in high optical yields <93JOC3600>. Similarly bicyclic *tert*,*sec* diols are oxidized by dioxiranes to α -hydroxyketones in high yields. In the case of (+)-pinane-1,2-diol (23) the reaction proceeds stereospecifically with retention to give ketone (24) <93TL4559>.



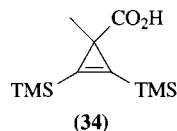
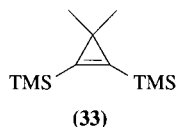
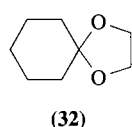
The ability of dioxiranes to undergo the C—H insertion reaction has permitted the synthesis of compounds which are either inaccessible or difficult to synthesize using more classical methods. An example of this is found in the conversion of 2,4-didehydroadamantane (25) to 8,9-didehydro-2-adamantanone (26) by reaction with (1b). The dioxirane reaction gave (26) in 29% yield accompanied by a 21% yield of 7-hydroxy-2,4-didehydroadamantane (27). Attempts to accomplish the same synthesis using ozone were unsuccessful. Use of ruthenium tetroxide gave (26) but only in 8% yield <93JOC5548>. A comparison of the results of the oxidation of (25) by (1b) with those described previously for adamantane indicates that the cyclopropyl group has a significant activating effect on the C—H bonds at C-10 in (25) <93JOC5548>. Another example of the advantage of using a dioxirane to accomplish a difficult C—H insertion reaction is found in the case of hopane (28). This compound, which is only inefficiently oxidized by *m*-chloroperbenzoic acid, is converted by (1b) to the alcohols, hopan-21 β -ol (29) and hopan-17 β -ol (30), in 50 and 30% yields, respectively. Thus the reaction is regioselective and stereospecific <93TL1131>. Dimethyldioxirane (1b) has also been used to α -hydroxylate cyanolactone (31) <92JCS(P1)2735>. The α -cyanohydrin intermediate obtained in this way was then treated with methanol and PTPS (pyridinium tosylate) to give the decalin fragment of the insect antifeedant azadirachtin.



The dioxirane C—H insertion reaction has been of great value in steroid chemistry. Marples *et al.* have described several examples of this reaction. Cholesterol or its acetate were converted to the

5,6-epoxides in high yield by dioxiranes generated from a series of ketones <91TL533>. The epoxides were obtained in an $\alpha:\beta$ ratio of approximately 1.0 which contrasts to that obtained (4:1) when peracids are used. The reactions were performed using the *in situ* conditions and a phase-transfer catalyst. When the steroid substrates are substituted at the 4-position as in 4,4-dimethyl cholesterol, then the dioxirane reaction takes a different course. Apparently because of steric interference with the required spiro transition state <88JOC3437>, no epoxidation occurs. Instead, C—H insertion reactions occur to give the 3,7-diketone (36%) and the 7-ketone (44%). Marples *et al.* have also used the *in situ* generation of (1b) to oxidize *estra-1,3,5(10)-trienes* to their 9 α -hydroxy derivatives in good yield <92JCR(S)28>. Further evidence for the selectivity of dioxirane oxidation of steroids is found in the benzylic C-9 hydroxylation of estrone <92JOC2182>, the hydroxylation of cholestane derivatives at C-25 of the side chain <92JOC5052> and the oxidation at C-5 of coprostanes <92TL7411>. Several 5 β -steroids have been converted stereospecifically to their 5 β -hydroxy derivatives by reaction with (1b) <93SC135>. Many of these steroids are cardioactive and the synthesis of their 5 β -hydroxy derivatives has been a difficult synthetic challenge <93SC135>. Pregnane and androstane steroids have shown similar selective hydroxylations by dioxiranes. Thus, 5 α -androstane-3 β -ol acetate was selectively hydroxylated to the corresponding 14 α -hydroxy derivative in 85% yield <93TL6103>. The same selectivity was observed in the related pregnane compounds which were converted stereoselectively to the 14 α -hydroxy derivatives in 90% yield.

Dioxiranes (1b) and (1j) have been used to oxyfunctionalize ethers, ketals, and acetals <92TL4225>. An example of the synthetic utility of this reaction is the oxidative cleavage of cyclohexanone ethylene ketal (32) to cyclohexanone in 95% yield. Triethyl formate was oxidized to diethyl carbonate in >95% yield. Dialkyl ethers were cleaved by the dioxiranes to alcohols, aldehydes and/or carboxylic acids. Medium ring cyclic ethers were converted to lactones or to intermediate hemiacetals <92TL4225>. These reactions are believed to involve C—H insertion by the dioxirane. This reaction appears to occur selectively at the methylene α to the ether oxygen. Benzyl ethers are selectively oxidized to their ketone derivatives by (1b). In steroids this procedure leads to the keto steroid <92SL646, 92TL4225, 92TL7399>. When tetrafluoroborate salts of amines are oxidized by (1j) no nitrogen oxidation occurs. Instead C—H insertion occurs in amine side chains <93JA7250>. A number of secondary alcohols have been oxidized by (1j) to the corresponding ketones in high yields and under mild conditions. Primary alcohols gave mixtures of aldehydes and carboxylic acids <91JA2205>. A very unusual example of the insertion reaction is the conversion of the cyclopropene (33) to carboxylic acid (34) with no reaction occurring at the double bond <91JOC5480>. The failure of the double bond to react was attributed <91JOC5480> to steric hindrance to formation of the spiro transition state required for epoxidation <88JOC3437>.



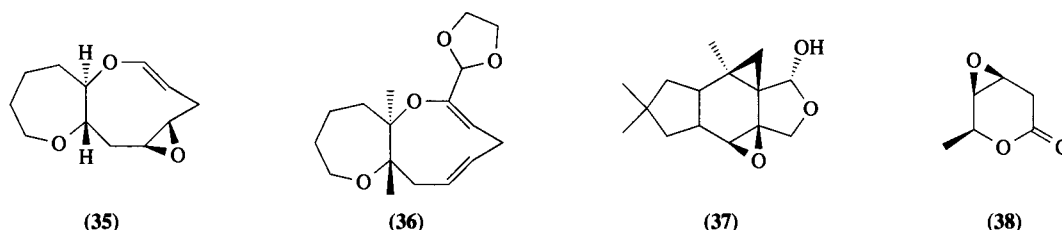
A study of the effect of solvent on the insertion reaction of (1b) with *cis*-1,2-dimethylcyclohexane shows that the reaction occurs faster in solvents with greater hydrogen bond donor capacity <94JCS(P2)451>. The rates of the insertion reaction in several binary solvents (acetone plus a second solvent) were measured and treated with a multiparameter empirical solvent equation. This correlation indicated that, of the several solvent property parameters contained in the equation, solvent donor capacity was the most influential.

1.14.5.3.2 The epoxidation reaction

The epoxidation of unsaturated materials is the most commonly used reaction of dioxiranes. The reaction, whether carried out *in situ* or using the solution method, gives high yields of epoxides, usually in rapid reactions. The isolated dioxirane method is particularly useful in cases where oxidation products are sensitive to the acidic conditions of the most commonly used epoxidation reagents or the basic conditions of the *in situ* method. Use of the isolated dioxirane permits reaction under neutral conditions so that labile epoxides are conveniently prepared. When the desired epoxide is sensitive to moisture, the dioxirane solution can be dried with molecular sieves for use in such epoxidations. The epoxidation of water-insoluble alkenes with the *in situ* method requires the use of a phase-transfer catalyst, but the reaction still proceeds in high yields. Dioxiranes, *in situ* generated

or in solution form, transfer oxygen-atom stereospecifically to alkenes; *cis*-alkenes give *cis*-epoxides and *trans*-alkenes give *trans*-epoxides <79MI114-01, 80JOC4758, 82JOC2670, 85JOC2847, 87TL3311, 88JOC3437, 92JA1346, 94TL1577>. With suitable alkene substrates the reaction is also regioselective <82JOC2670, 93T6299>. For some *cis/trans*-alkene pairs the *cis* isomers were found to be more reactive than the *trans* isomers. Baumstark *et al.* have used this observation as evidence for a spiro transition state for the epoxidation reaction <87TL3311, 88JOC3437>. Other examples of epoxidations using isolated dioxiranes include those of norbornene <85JOC2847>, norbornadiene <88JOC3007>, podocarpa-6,8,11,13,-tetraenes <91AJC1553>, bis(trimethylsilyl)alkenes <91JOC5480>, and (4-nitrophenoxy)ethylene <94JOC977>, all of which gave epoxides in excellent yields.

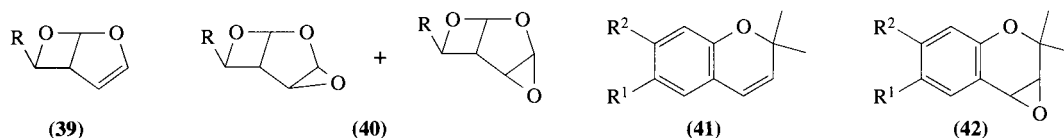
Some examples of the use of dioxirane (**1b**) in producing epoxide intermediates in natural product synthesis are the stereocontrolled synthesis of the nonacene ring system (**35**) of brevetoxin A from precursor (**36**) in which only the disubstituted double bond is epoxidized <90JA4988>, the synthesis of the marasmane sesquiterpene ($\pm$) stearylvelutinal (intermediate is (**37**)) <92JOC5979>, the synthesis of the intermediate (**38**) is used in the total synthesis of avermectin B1a <90SL331>, and the trioxadecalin ring system of mycalamides A, B, and onnamide A <93TL5421>. Dioxirane (**1b**) has been used frequently to form epoxides not accessible by the use of other epoxidation reagents. Benzvalene is converted to benzvalene oxide at -30°C <93CB1749> and methylene cyclopropanes give oxaspiropentanes <85RTC350> when treated with (**1b**).



Enantioselective epoxidation of pro-chiral alkenes with dioxiranes generated from optically active ketones affords optically active epoxides with enantiomeric excesses (*ee*) in the 9–12.5% range <84CC155>. In the late 1980s values up to 24% have been observed when employing 4,4,4-trifluoro-3-phenyl-3-methoxybutan-2-one as the ketone <89ACR205>.

The epoxidation of silyl enol ethers <89JOC4249, 89TL6497, 91CB2361, 91TL1295, 93JA354>, enol ethers <89TL257, 90EUP370946, 90GEP4023741, 93LA17>, γ -methylene- γ -butyrolactones <89TL4223>, enol esters <89TL6497, 91CB2361>, enol lactones <91CB2361>, β,γ -unsaturated lactones <92CC368>, β -oxo enol ethers <90CB2077>, phthalides <89TL6497>, enol phosphates <90TL6517, 91CB2361>, furocoumarins <92LA731>, benzo-*p*-dioxin <91TL1295>, 2,3-diphenyl-1,4-dioxene <91JA7672>, allylic alcohols <93TL8427>, and allylic hydroperoxides <91LA445> with (**1b**) or sometimes with (**1j**) gives the corresponding epoxides in good yields.

Furans react with dioxiranes to give epoxides or products arising from intermediate epoxides. A particularly noteworthy example of this reaction is the conversion of the dihydrofuran derivative, aflatoxin B₁, to its *exo*-8,9-epoxide by (**1b**). This epoxide is a powerful carcinogen and is inaccessible by use of other oxidants <88JA7929>. Reinvestigation of the reaction showed that the *endo*-epoxide is also formed, but to a smaller extent <92MI114-05>. The parent compound, 2,3-dihydrofuran, has also been epoxidized by (**1b**) <88JA7929> and (**1j**) <89TL257>. Reaction of 4,4-dimethyl-2,3-dihydro- γ -pyran with (**1b**) gives the unstable epoxide which is converted to the isomeric 2,3-diols by adventitious water <91JOC3677>. A number of furans have been oxidized by (**1b**) to products of oxidative ring opening. In some cases recyclization to new products occurs. The reactions proceed via intermediate epoxides <91CC1553>. The unsaturated aldehydes generated in some of these reactions are efficiently trapped by phosphoranes in Wittig type reactions <93CC1220>. Menthofuran is oxidized by (**1b**) to diastereomeric furan epoxides and a γ -keto enal <92JOC2744>. When the 2,7-dioxabicyclo-[3,2,0]-heptenes (**39**) are treated with (**1b**) a near quantitative yield of the *exo* and *endo* (9 : 1 mixture) epoxides (**40**) are obtained <90TL4693>. Precocenes (**41**) are converted in high yield to the epoxide derivatives (**42**). These derivatives are accessible only with great difficulty using other methods and are believed to be responsible for the cytotoxic activity of precocenes <90TL5235>. Dioxirane (**1b**) has been used to epoxidize the furan moiety of lactone and dilactone intermediates in the total synthesis of ($\pm$) bilobalide <93JA3146>. A number of benzofurans have been reacted with (**1b**). These substrates are converted to the corresponding epoxides in excellent yields at low temperatures. The epoxides are labile, but can be characterized spectroscopically. In some cases the epoxides are in equilibrium with their quinone methides through reversible valence isomerization <91AG(E)200, 91JA8005, 92CB231, 92LA1095, 93AG(E)80, 93AG(E)735, 93JA8603, 93CB2697, 94CB433, 94SI111>.



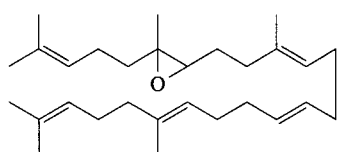
In 1989 the first direct epoxidation of glycals was achieved using dioxirane (**1b**) <89JA6661>. This report was followed by a number of others. The reaction is clean, efficient and, in many cases, epoxidation is stereoselective <90CAR(206)361, 90JOC4211, 90JOC5808, 91JOC5448, 91TL1295, 92JA3471, 92JA4518, 93JOC3761>. These epoxides are important intermediates and have been used in the synthesis of oligosaccharides <89JA6661, 92JA4518>, nucleosides <90JOC4211>, arylglycosides <90JOC5808, 92JA3471>, indole- β -N-glycosides <93JOC343>, mannose β -glycosides <94JOC1892>, α -glucosides <94JOC1895>, (–)-ovatolide <93JOC2862>, ganglioside GM₃ <93JA4933>, ganglioside GM₄ <93JOC5465>, saponin oligosaccharides <93JA8473>, glycosides of ketosugars <91TL4035>, avermectin B1a <90SL331>, the polyether antibiotic monensin <93JA7152>, valienamine <94TL2667>, and acarbose <94TL2671>. Glycals have also been epoxidized by (**1b**) to glycal epoxides during the solid-phase synthesis of oligosaccharides <93RTC609, 93SCI1307>.

While dioxirane (**1b**) is an electrophilic reagent, it can be used to epoxidize electron-poor alkenes. These reactions require longer reaction times, excess dioxirane, and elevated temperatures for complete epoxidation. The oxidation of α,β -unsaturated ketones, acids, and esters <86JOC1925, 90JCS(P2)349, 90TL331, 91CB227, 92JA1346, 93JCS(P2)2203>, chalcones <91CB227, 93JOC7615, 93TL5055>, hydroxychalcones <91CB227, 92S49>, aurones <92S436>, flavones <91JOC7292, 91TL1041>, isoflavones <92S436>, and 3-arylidene flavanones <94JOC900> with (**1b**) afforded the corresponding epoxides in good to excellent yields.

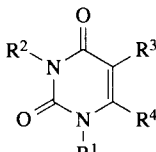
A number of *in situ* generated dioxiranes have been used to convert cholesterol and its acetate to the 5,6-epoxides <91TL533>. Earlier Curci and co-workers <82JOC2670> had used *in situ* generated (**1b**) to epoxidize cholesterol. This group subsequently described the use of solutions of (**1b**) to epoxidize 4-cholesten-3-one, progesterone, 3 β -hydroxy-5,16-pregnadien-20-one acetate, and prednisone acetate <92JOC2182>. Dioxirane (**1b**) has also been used to convert androstanone Δ^2 enol acetate to its epoxide <92JOC6379>. Several fluorinated monoterpenes and sesquiterpenes have been epoxidized with (**1b**) <93T6299>. Oxidosqualene (**43**) is converted by (**1b**) to a mixture of polyoxidosqualenes from which four dioxidosqualenes could be isolated <93JOC3991>. Dioxirane (**1b**) has also been used to epoxidize methyl farnesoate. By using excess (**1b**) diepoxides and triepoxides could also be prepared. These compounds are believed to be metabolites of an insect juvenile hormone <91TL1291>. Important *bis*- and *tris*-epoxides have been synthesized from polyeneoates using (**1b**). These materials are postulated to play a role in the biosynthesis of potent neurotoxic mycotoxins <92TL4053>. The epoxidation of *cis*-polydeltacyclene and *cis*-polynorbornene with (**1b**) also gives the corresponding polyepoxides. Such polyoxides are essential components of some adhesives, stabilizers, and plasticizers <90MM2819>. Excess (**1b**) reacts with various 6,6-disubstituted pentafulvenes to give mixtures of mono- and di-epoxides in which only the endocyclic double bonds have reacted <91TL6697>. Enamines are epoxidized by (**1b**). The epoxides are rather unstable and in most cases open to zwitterionic forms which dimerize to 1,4-dioxanes <92CB1263>. In later work it was shown that the stability of the epoxides depends on the nature of the substituents on the nitrogen atom. In particular, silylation of these groups adds sufficient stability to the epoxides that low temperature observation of their NMR spectra becomes possible <92CB2719>. When *N*-acylindoles are treated with (**1b**), epoxides are produced which slowly rearrange to a variety of other products at room temperature <93JA8867, 94JOC2733>. Oxidation of uracil derivatives (e.g. (**44**)) and pyrimidine nucleosides by (**1b**) gives the 5,6-oxiranyl-5,6-dihydro (e.g. (**45**)) and 5,6-dihydroxy-5,6-dihydro-derivatives in good yield <93TL6313>. Likewise, *N*-phthaloyl α -amino acid esters <92CB2467>, vinyl formamides <90TL2047>, and vinyl carbamates <90BBR(169)1094> are epoxidized by (**1b**). Excellent regio- and stereoselectivity was observed in the epoxidation of chiral 1,4-cyclohexadienes amides with (**1b**) <92TL6097>. An example is the conversion of amide (**46**) to epoxide (**47**) in 68% yield and with >13:1 diastereoselectivity. Fullerene (C₆₀) reacts with (**1b**) to give an epoxide and a 1,3-dioxolane derivative <92AG(E)351>.

1.14.5.3.3 Oxidation of alkynes

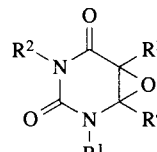
The first report of oxidation of an alkyne by a dioxirane is that of Edwards *et al.* in which they describe the conversion of phenylpropionic acid to phenylacetic acid by *in situ* generated (**1b**). The reaction is believed to proceed through an intermediate oxirene <79MI 114-01>. Curci *et al.* sub-



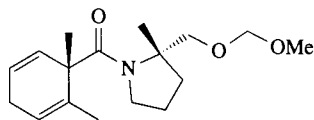
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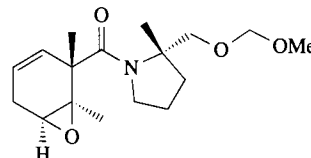
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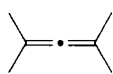


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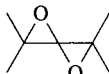
sequently described the oxidation of several alkynes with *in situ* generated and isolated (**1b**) as well as with (**1j**). These reactions are also believed to involve oxirenes which rearrange to ketenes or α,β -unsaturated compounds, or are oxidized further to α -dicarbonyl compounds <92TL7929>. They have also described the conversion of 8-hexadecyne to an unsaturated ketone by *in situ* generated (**1b**) <B-90MI 114-01>. The reaction of several alkynes with isolated (**1b**) has been described by Murray *et al.* The products isolated were conveniently rationalized by postulating the intermediacy of oxirenes and oxocarbenes. The latter serve as precursors to hydrogen atom or methyl group migration products as well as to cyclopropane insertion products in some cases <93JOC5076>.

1.14.5.3.4 Oxidation of allenes and cumulenes

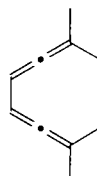
Simple as well as substituted allenes are epoxidized by (**1b**) to give the corresponding 1,4-dioxaspiro [2.2] pentanes. An example is the conversion of tetramethylallene (**48**) to dioxaspiro pentane (**49**) <88JOC1338, 88TL4791, 90JOC5929, 91JOC1153, 92T1427, 94TL1489>. Use of this procedure with allenyl alcohols <88TL4791, 92T1427>, allenyl acids <90JOC5929>, and allenic aldehydes <94TL1489> gives a route to highly functionalized tetrahydrofuran and tetrahydropyran derivatives, lactones, and cyclic acetals and hemiacetals, respectively. Oxidation of *t*-butyl-substituted [4]- and [5]-cumulenes with (**1b**) gives conjugated cyclopropanones <92JA5998>. Reaction of bisallene (**50**) with (**1b**) gives (**51**) as the sole product. When MCPBA is used in the same oxidation then a mixture of products is obtained <92JOC2976>. When allenic amine derivatives are treated with (**1b**) oxidative cyclization occurs to give highly functionalized nitrogen heterocycles <94TL2513>.



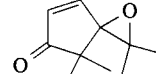
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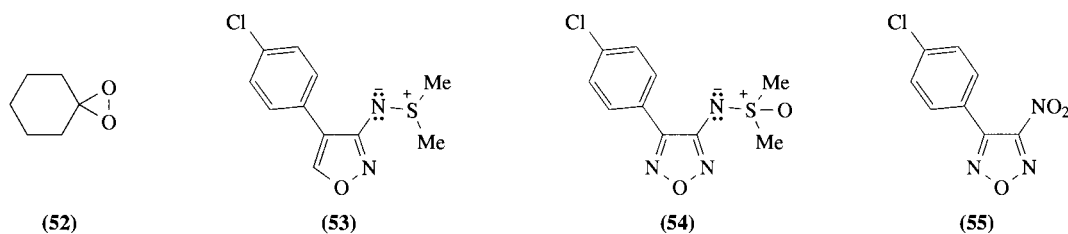
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1.14.5.3.5 Oxidation of heteroatoms

(i) Nitrogen

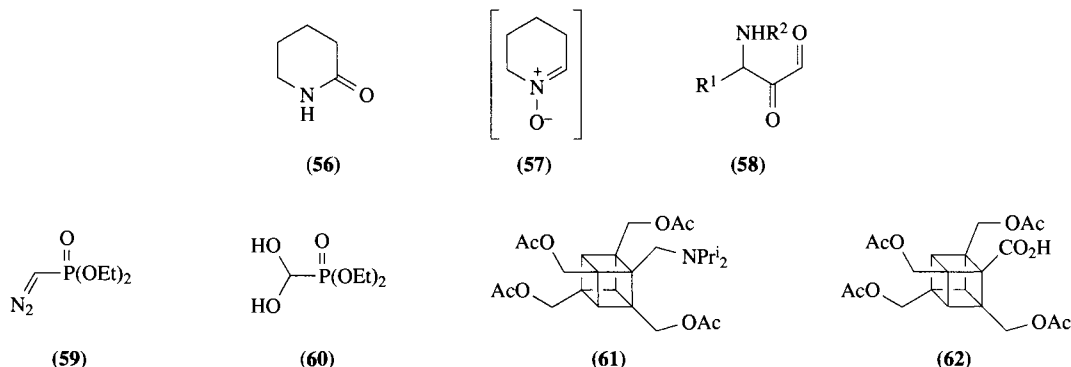
The oxidation of pyridine to pyridine *N*-oxide by *in situ* generated (**1b**) or cyclohexanone dioxirane (**52**) was the first example of *N*-oxidation by dioxiranes <81JOC1684>. Murray and co-workers have also oxidized pyridine with (**1b**) using both the *in situ* and solution methods <85JOC2847, 92JA1346>. *N*-oxidation of *cis*- and *trans*-diepoxytetrahydroquinolines with (**1b**) also afforded the corresponding *N*-oxides in quantitative yields <91JCS(P1)2189>. Solutions of (**1b**) have been used to oxidize primary amines to nitro compounds in a rapid and nearly quantitative reaction <86TL2335, 89JOC5783,

92JA1346). The process is believed to involve a succession of oxygen atom transfers. The intermediates generated in the reaction, hydroxylamines and nitroso compounds, were separately shown to be oxidized by (1b) to the nitro compound in good yield. This method has been extended to other aliphatic, cyclic, aromatic, and heterocyclic amines <88TL4501, 89JHC1883, 92JCS(P1)2503, 93JMC42>. In one of these <89JHC1883> the sulfilimino compound (53) was converted to a mixture of the sulfoximine (54) and nitro compound (55). Amine hydrochloride salts can also be oxidized directly by dioxiranes. Eaton *et al.* found that (1b) oxidizes 1,4-diaminocubane dihydrochloride to 1,4-dinitrocubane in excellent yield <88JOC5353>. Using this method avoids the need to isolate sensitive amines (as in the case cited), and also reduces the problem of starting amine and reaction intermediates reacting with each other and reducing nitro compound yield. This method has been extended to the synthesis of polynitro compounds in the adamantane series <89JOC5783>. Isocyanates have been converted to the corresponding nitro compounds in a similar fashion <88JOC5353, 93JA10195>. The oxidation of primary amines can be controlled such that the hydroxylamine is the major product. Thus, amino sugars and esters of amino acids have been converted to hydroxylamino sugars and hydroxylamines, respectively, by oxidizing with (1b) at low temperature (-45°C) <90JOC1981, 91TL1851>. Oxidation of aliphatic primary amines with (1b) using *in situ* and solution conditions sometimes leads to complex reaction mixtures containing oximes, nitroso dimers, nitroalkanes, nitrones, and oxaziridines <92JOC6759>. Products obtained in these oxidations depend very much on the precise reaction conditions.



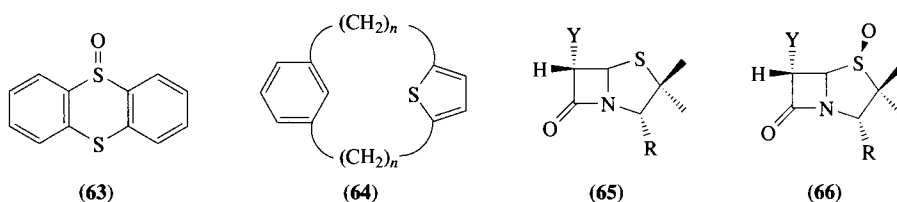
Secondary amines are converted to the corresponding hydroxylamines in quantitative yield by (1b) <89SC3509, 90JA6696, 91USP5001233, 93USP5235056>. The product of this reaction is very much dependent on the structure of the secondary amine and the reaction conditions. The hydroxylamines are obtained when exactly equimolar amounts of dioxirane and amine are used. For secondary amines having an α -hydrogen, reaction with an additional mole of (1b) gives an intermediate which loses water to give a nitron <90JOC2954, 91MRC962, 92JA1346>. When no α -hydrogen is present, reaction with the second mole of (1b) leads to the nitroxide product <88TL4677, 91JCR(S)348, 92JA1346, 92USP5087752>. The dioxirane procedure gives quantitative or near quantitative yields of nitroxides in a very rapid and convenient process that is quite superior to other methods. A number of cyclic secondary amines such as piperidine, morpholine, and their derivatives give hydroxamic acids (e.g., (56)) when oxidized at 0°C by (1b). The reaction is believed to proceed through the nitron (57), which sometimes accompanies the hydroxamic acid product <93ACS1141>. The oxidation of *N*-alkyl imines by (1b) gives the corresponding nitrones in variable yields without evidence for oxaziridine formation <90JCS(P1)301>. Tosylhydrazones <92SC1583> and ketone hydrazones <93JOC7289> were found to be readily cleaved to the corresponding ketones by reaction with (1b), generated *in situ* or used in solution form. The facile regeneration of ketones was almost quantitative. Ketoximes are also oxidized selectively and efficiently to their parent ketones by (1b) <93SL427>. Aldehyde oximes, on the other hand, are oxidized by (1b) to nitrile oxides which dimerize to furoxanes in near quantitative yields <92NKK420>. When the oxidation is carried out in the presence of alkene and alkyne dipolarophiles then isoxazolines or isoxazoles, respectively, could be isolated. Reaction of (1b) with α -diazoketones afforded α -oxo-aldehydes quantitatively <91TL6215>. A general route to *N*-protected α -amino glyoxals (58) has been developed which is based on oxidation of the precursor diazoketones with (1b) <93CC1222>. In related work oxidation of diethyl diazomethylphosphonate (59) with (1b) gave a quantitative yield of formylphosphonate hydrate (60) <94CC37>. Dimethyldioxirane has played still another role in the synthesis of substituted cubanes. Treatment of the amino compound (61) with (1b) gives the corresponding carboxylic acid derivative (62), in a reaction which is still not completely understood <93JA10195>. Tertiary amines are converted to amine oxides by (1b). Here again the reaction conditions are critical if the oxide is the desired product. Excess dioxirane leads to further reaction of the oxide apparently to give an intermediate which can lose oxygen and regenerate the amine <89CRV1187>. Dimethyldioxirane thus is one of only a few reagents that can be used to deoxygenate amine oxides. Azo compounds are converted to azoxy derivatives

by (**1b**) <86TL2335>. Uracil derivatives and pyrimidine nucleosides have been converted by (**1b**) to their 5,6-oxiranyl-5,6 dihydro- and 5,6-dihydroxy-5,6-dihydro-derivatives in good yield <93TL6313>. Oxidation of DNA with (**1b**) causes selective strand scission at the sites of guanine bases <90BBR(169)87>. This observation has led to the suggestion that this procedure could be used as an alternative to chemical sequencing procedures for locating guanine bases in DNA.

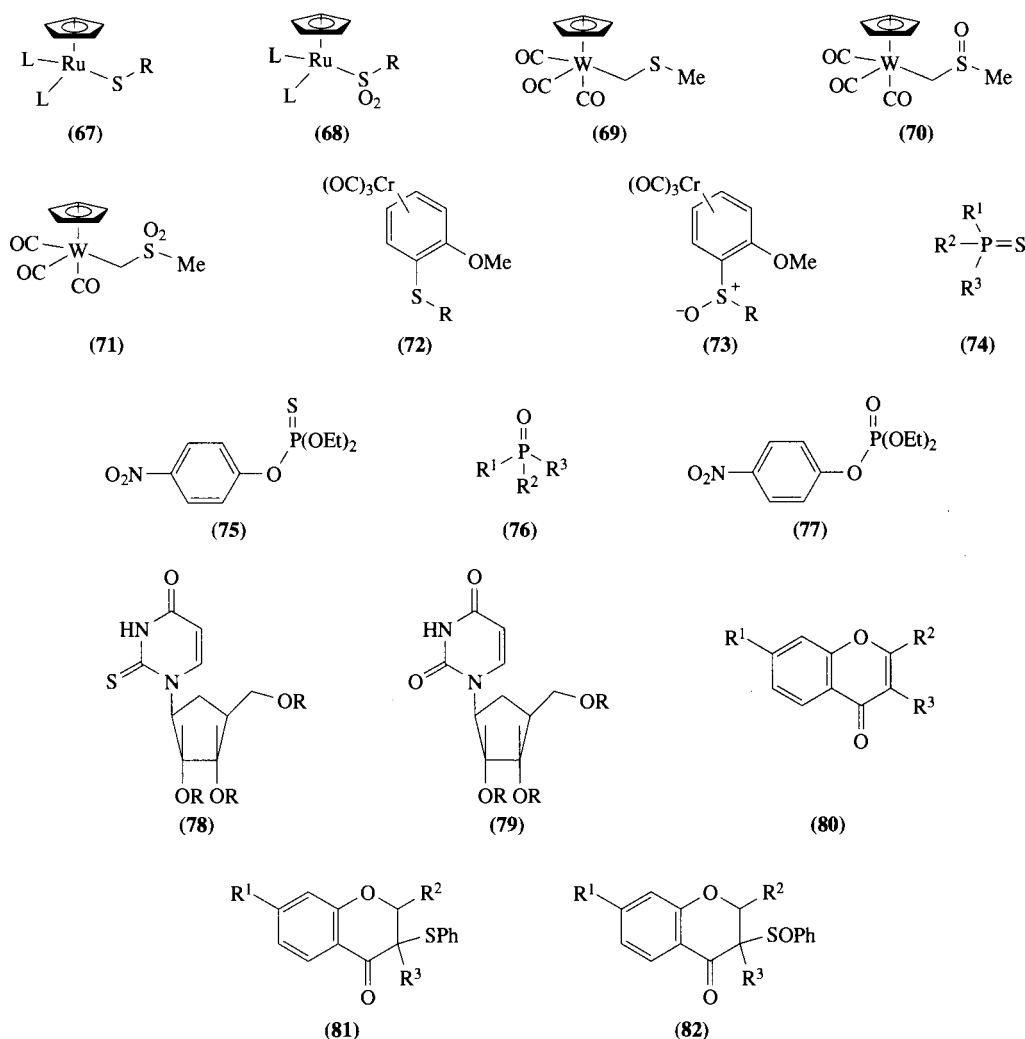


(ii) Sulfur

Solutions of dialkyldioxiranes are assayed for dioxirane content by reacting them with excess phenyl methyl sulfide. Under these conditions the sulfide is converted to the sulfoxide uncontaminated with sulfone and a convenient gas-liquid chromatography method may then be used to determine dioxirane concentration <85JOC2847>. Sulfoxides are similarly oxidized to sulfones in a rapid and high-yield process <87JOC746>. These sulfide oxidations by (**1b**) have been shown to be electrophilic by reacting a series of *p*-substituted phenyl methyl sulfides and then treating the relative rate data with the Hammett linear free-energy relationship. A similar study on the corresponding series of sulfoxides showed that this was also electrophilic with a very similar ρ value <87JOC746>. Adam and co-workers have utilized thianthrene-5-oxide (**63**), a substrate containing both sulfide and sulfoxide functional groups, to devise a scale of oxidant nucleophilicities <84JA5020, 87JOC2800, 91JA6202>. This approach indicates that (**1b**) is a nucleophilic oxidant which is in conflict with the earlier linear free-energy results <87JOC746>. Oxidation of electron-rich thiophene derivatives, including sterically hindered thiophenophanes (**64**), by (**1b**), gave the corresponding thiophene 1,1-dioxides in excellent yields <90TL5955>. Oxidation of prochiral sulfides by *in situ* generated dioxiranes, using bovine serum albumin as a chiral auxiliary (chiral phase-transfer catalyst) afforded the corresponding sulfoxides in enantiomeric excesses of up to 89%. The degree of enantioselectivity, as well as yield and reaction time, depend upon the nature of the dioxirane <89TL6233, 91T8385>. Reaction of *in situ* generated (**1b**) with a variety of thiones gave the thione *S*-oxides in good to excellent yields. This reaction contrasts with the reaction of carbonyl oxides with the same substrates in which typical cycloaddition reactions are observed <91JCS(P1)3043>. The penicillanates (**65**) are oxidized stereospecifically and quantitatively to the (1*S*)-sulfoxides (**66**) by solutions of (**1b**). The same paper describes similar oxidations for a penicillanic acid and a penam derivative <93TL7877>. Oxidation of thiol esters by (**1b**) at low temperature gave the labile α -oxo sulfones in quantitative yields. Use of other oxidants for the same oxidation leads to complex mixtures of products <92TL469>. The oxidation of alkanethiols with (**1b**) gave alkanesulfinic acids in very good yield and high purity. A stepwise process involving the intermediate sulfenic acid was suggested. The sulfenic acid is believed to be oxidized to the sulfinic acid by (**1b**) or by air oxidation. Aromatic and benzylic thiols give multiple products with sulfinic acid as the major product <93TL67>.

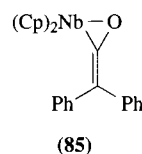
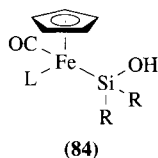
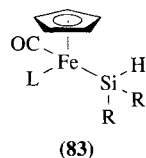


Dimethyldioxirane has also been used to oxidize organometallic thiolates. Reaction of ruthenium thiolate complexes (**67**) with (**1b**) gave sulfinato complexes (**68**) in excellent yields. Stoichiometric amounts of dioxirane failed to give the expected sulfenato intermediates. In contrast, oxidation of the α -metalated thioether complex of tungsten (**69**) with a stoichiometric amount of dioxirane gave the corresponding sulfoxide (**70**) which was further oxidized to sulfone (**71**) with an excess of dioxirane $\langle 92IC3329 \rangle$. Similarly, the oxidation of tricarbonylchromium(0) complexes of sulfenyl substituted arenes (**72**) with stoichiometric amounts of (**1b**) afforded tricarbonylchromium(0) complexes of sulfinyl substituted arenes (**73**) in good yield and with high diastereoselectivity. In contrast, oxidation of these sulfide complexes to the sulfoxide complexes with other oxidizing reagents such as mcpba, *t*-butyl hydroperoxide, or 2-hydroperoxy-2-methoxypropane gave decomposition or contaminated products $\langle 93CC1059, 94JCS(P1)629 \rangle$. While sulfides are oxidized by dioxiranes to sulfoxides or sulfones, the oxidation of phosphine sulfides (**74**) and phosphorothioates (**75**) with (**1b**) gave the corresponding oxides (**76**) and (**77**) in a rapid, clean, and quantitative reaction $\langle 90TL3359 \rangle$. A similar desulfurization of thiopyrimidine (**78**) and thiopurine nucleosides has been carried out very efficiently using (**1b**). This oxidation occurs under mild conditions and can be used to produce the oxygen derivatives (**79**) of the starting materials in the presence of water, or their alkoxy derivatives in the presence of alcohols $\langle 93TL7785 \rangle$. Several isoflavone derivatives (**80**) were prepared by oxidation of their phenylthio derivatives (**81**) by (**1b**), followed by desulfurization of intermediate sulfoxides (**82**) in refluxing toluene. Oxidation with two equivalents of (**1b**) gave the sulfones. Use of other oxidants on the sterically hindered precursors gave poor yields of the sulfoxides $\langle 93T7967 \rangle$.



1.14.5.3.6 Oxidation of organometallic compounds

Silanes react with dioxiranes to give silanols via an oxygen atom insertion into Si—H bonds. The reactions give a clean, high yield and proceed with retention of configuration $\langle 90\text{AG(E)890} \rangle$. Ferriohydridosilanes (**83**) are likewise oxidized by (**1b**) to the corresponding ferriosilanols (**84**) $\langle 92\text{CB1409} \rangle$. Wolowiec and Kochi have reported that manganese(II) tetraphenylporphyrin (tpp) and iron(II) tetramesitylporphyrin (tmp) react with (**1b**) to give the labile oxometal species $\text{O}=\text{Mn(IV)}$ (tpp) and $\text{O}=\text{Fe(IV)}$ (tmp), respectively, in quantitative yield $\langle 90\text{CC1782} \rangle$. These same authors also have shown $\langle 91\text{IC1215} \rangle$ that (**1b**) causes the oxidative decarbonylation of some metal carbonyl complexes, such as pentamethylcyclopentadienide ($=\text{Cp}^*$) Re(CO)_3 and hydridotris(1-pyrazolyl) borate ($=\text{Tp}$) MoCO^-_3 to the trioxo complexes Cp^*ReO_3 and TpMoO^-_3 , respectively. Arene chromium tricarbonyl complexes are oxidized by (**1b**) to give the arene derivatives quantitatively. This decomplexation procedure is rapid, clean, and convenient $\langle 91\text{TL5629} \rangle$. Fischer carbene complexes are similarly converted to the corresponding oxo derivatives in good yields $\langle 92\text{TL3021} \rangle$. Demetalation of aminocarbene complexes of chromium also has been reported $\langle 92\text{JA8088} \rangle$. The oxygen-atom transfer reaction of niobocene ketene complex (**85**) can be made catalytic when dioxirane (**1j**) is used as oxygen source $\langle 93\text{JA7511, 93TL7545} \rangle$.

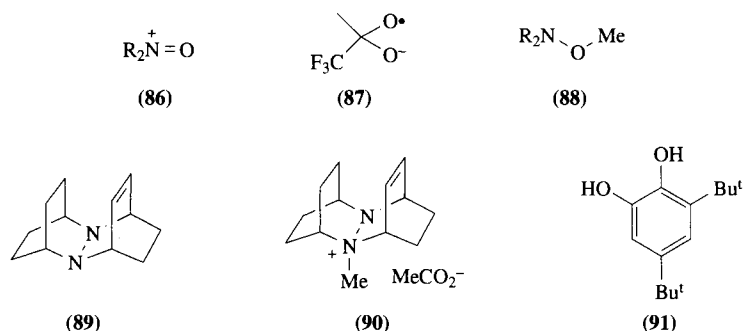


1.14.5.3.7 Electron-transfer reactions

A number of dioxirane reactions proceed in a manner which suggests the possibility of single electron-transfer pathways. It has been observed that (**1b**) can catalyze the valence isomerization of quadricyclane to norbornadiene. While the mechanism of this process is still uncertain, the possibility of electron transfer was considered. No evidence for the presence of radicals could be obtained however $\langle 88\text{JOC3007, 88TL15} \rangle$. Subsequently, the reduction potential of (**1b**) was determined to be -0.06 V (versus Hg pool) $\langle 89\text{UP 114-01} \rangle$. This value is to be compared to the -0.14 V measured versus the standard calomel electrode $\langle 93\text{JOC1657} \rangle$. Also the oxidation potential of quadricyclane was measured as 0.914 V (versus Hg pool) $\langle 89\text{UP 114-01} \rangle$ while a value of 0.91 (versus the standard calomel electrode) had been measured earlier $\langle 79\text{JA1308} \rangle$. Thus the involvement of electron transfer in the quadricyclane valence isomerization is at least a possibility. An electron-transfer mechanism has been proposed for the reaction between (**1j**) and the nitroxide, 1,1,3,3-tetramethyl-1,3-dihydroisindolin-2-yloxy. This reaction is believed to proceed through the oxammonium ion (**86**) and the dioxirane anion radical (**87**). The latter species then loses methyl radical which is trapped by the spin trap to give the adduct (**88**) a known material $\langle 91\text{CC771} \rangle$. A similar methoxyamine product has been observed when 2,2,5,5-tetramethyl-pyrroline-3-carboxamide is treated with excess (**1b**) $\langle 88\text{UP 114-01} \rangle$. Reaction of (**1b**) with the unsaturated sesquibicyclic hydrazine derivative (**89**) gave the unexpected product, *N*-methylhydrazinium acetate (**90**). This product was explained by invoking an electron-transfer mechanism leading initially to the ion pair consisting of hydrazine cation radical and the radical anion of (**1b**). As in the earlier cases, methyl transfer could then occur to give (**90**) $\langle 93\text{JOC1657} \rangle$. Electron spin resonance evidence has been obtained for an electron-transfer process in the catalytic decomposition of (**1j**) by pyrene $\langle 90\text{TL6097} \rangle$. On the other hand, a comparison of the relative rates of oxidation of some heteroarenes by (**1b**) with the rates of methylation of the same substrates by methyl iodide indicated that these reactions are proceeding by an $\text{S}_{\text{N}}2$ mechanism rather than by electron transfer. A poor correlation between the relative rates of the dioxirane reactions and the ionization potentials of the nitrogen substrates gave added support to the conclusion of no electron-transfer involvement $\langle 93\text{AG(E)737} \rangle$.

1.14.5.3.8 Oxidation of polycyclic aromatic hydrocarbons

Dioxiranes, generated *in situ* or used in solution, oxidize polycyclic aromatic hydrocarbons (PAH) to arene oxides. This reaction permits the synthesis of arene oxides which are otherwise only



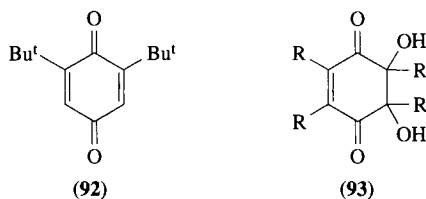
available through complex, multistep syntheses. Since the arene oxide functionality is of fundamental importance in conferring mutagenic and carcinogenic properties on some PAH, the dioxirane oxidation route is important to questions of environmentally related carcinogenesis. The *in situ* generation method of forming (**1b**) has been used to convert phenanthrenes, pyrene, and chrysene to K-region oxides in good yields. The same conditions give a low yield of the anti-dioxide from naphthalene and anthraquinone from anthracene [84JA2462, 85JOC2847]. The oxidation of several arene monoxides with a solution of (**1b**) gave arene dioxides in good to moderate yield [89TL123]. Several PAH, known to be constituents of polluted urban atmospheres, have been converted to their corresponding K-region oxides by (**1b**) [B-85MI 114-01]. The more reactive dioxirane (**1j**) has been used to convert naphthalene, phenanthrene, and anthracene into the same products as observed with (**1b**), but in higher yields [90TL6097]. A number of PAH, supported on particulate matter, have been oxidized by the products of the gas-phase reaction of ozone and an alkene in experiments designed to model atmospheric processes. Included in the product mixtures are arene oxides. It has been proposed that dioxiranes may be involved in these oxidations [90MI 114-02, B-91MI 114-01, 93JOC315, 94MI 114-01].

1.14.5.3.9 Oxidation of enolates

The direct oxidation of enolates with (**1b**) gives α -hydroxy carbonyl compounds in excellent yield [91TL715]. The reaction of (**1b**), isolated or *in situ*, with the enolates and/or enols of ketones, esters, β -diketones, β -oxo esters, and β -oxo lactones affords the α -hydroxy carbonyl compounds in good yields [91CB2369]. In 1994, Adam *et al.* have shown that the diastereoselectivity of the dioxirane-enolate reaction is dependent on the metal partner in the enolate. Specifically, use of titanium enolates give much higher diastereoselectivities than sodium enolates [94JOC2358].

1.14.5.3.10 Miscellaneous reactions

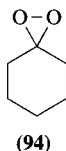
Phenols are oxidized by (**1b**) to give quinones. An example is the oxidation of 2,4-di-*t*-butylphenol to the orthoquinone. Monitoring of the reaction mixture with gas-liquid chromatography indicated that diol (**91**) is the precursor to the orthoquinone [91TL5441]. Curci *et al.* have carried out similar studies [91TL5445]. In this work dioxiranes (**1b**) and (**1j**) were used to oxidize 2,6-di-*t*-butylphenol to a variety of products including the paraquinone (**92**). The nature of the products suggested that the reaction proceeds via a radical pathway initiated by electron transfer from the phenol to the dioxirane. Catechol was oxidized by (**1j**) to (*Z*),(*Z*)-muconic acid. Hydroquinones react with (**1b**) to give the expected quinones. The reactions also give the unusual 2,3-dihydroxycyclohexene-1,4-diones (**93**). The reaction is believed to involve electron transfer from the hydroquinones to the dioxirane [92TL53].



Triphenylphosphine is oxidized by (**1b**) to triphenylphosphine oxide in a quantitative reaction. This reaction is sometimes used as an alternative method for determining dioxirane concentrations <85JOC2847>. Oxidation of chloride ion by *in situ* generated (**1b**) gives hypochlorite ion <74JA7820>. Acetaldehyde and propionaldehyde are oxidized by (**1b**) to the corresponding acids <85JOC2847>. This is one of the several reactions which can be used to distinguish dioxiranes from their isomeric carbonyl oxides. The latter oxidants react with aldehydes to give ozonides. A series of substituted benzaldehydes has been reacted with (**1b**) to give the corresponding carboxylic acids <89TL5567>.

1.14.5.3.11 Decomposition and rearrangement of dioxiranes

Photolysis of dioxiranes, formed by photolytic cyclization of carbonyl oxides in matrices at low temperature, gives esters or lactones (see Section 1.14.6.3.3). Dioxirane (**1b**) is converted to methyl acetate when treated with BF_3 etherate. Autodecomposition of (**1b**) in acetone at room temperature also gives methyl acetate, but at a very slow rate <85JOC2847, 92JOC4263>. Baumstark *et al.* find varying amounts of methyl acetate in decomposed solutions of (**1b**). However, they found that acetol is the major product of the decomposition under their conditions <89TL5567>. Methyl trifluoroacetate had been reported to be the product of thermal decomposition of (**1j**) <88JOC3890>. A subsequent study revealed, however, that the thermal or photochemical decomposition of (**1j**) is a complex free-radical process which gives methyl acetate and trifluoromethyl trifluoroacetate along with the methyl trifluoroacetate <91JA7654>. Catalytic decomposition of ketone-free (**1j**) using tetrabutylammonium iodide or lithium iodide promotes the complete conversion of the dioxirane to trifluoroacetone and dioxygen <92JA8345>. Thermolysis of dioxiranes in solutions of their parent ketone, or in mixtures of the parent ketone and a foreign ketone, leads to the formation of esters or mixtures of esters. The results are explained by invoking a free-radical decomposition of the dioxirane followed by hydrogen-atom abstraction from the ketones and reaction of the derived radicals with acyloxy radicals arising from the dioxirane decompositions <92JOC4263>. Cyclohexanone dioxirane (**94**) rearranges very slowly to ϵ -caprolactone at low temperature whereas thermal decomposition of the dioxirane gives a linear oligomer of the ϵ -caprolactone <92JA1346>. The decomposition of (**1b**) follows a complex rate law at high concentrations, but at low concentrations a first-order plot can be obtained <87JOC2800, 89TL5567, 92JOC4263>. Similar observations were made by Hull and Budhai who measured the first-order decomposition of (**1b**) ($E_a = 24.9 \text{ kcal mol}^{-1}$) under low-concentration conditions <93TL5039>.

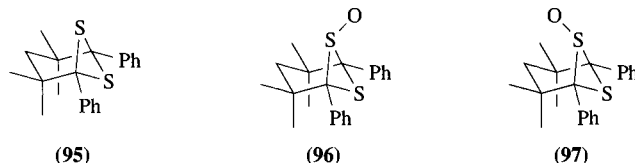


1.14.6 SYNTHESIS OF THREE-MEMBERED RINGS WITH TWO OXYGEN AND/OR SULFUR HETEROATOMS

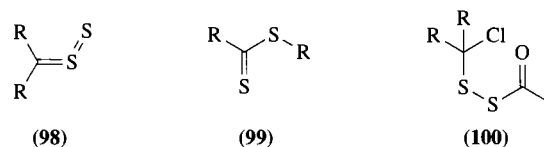
1.14.6.1 Dithiiranes

The synthesis of the first isolable dithiirane derivative was only reported in 1993 <93JA4914>. The synthesis involves oxidation of the bicyclic dithietane (**95**) with *m*-chloroperbenzoic acid to give the sulfoxides (**96**) and (**97**). The *exo* sulfoxide (**96**) was oxidized further with excess monoperoxysulfuric acid to give the *cis*-dithiirane *S*-oxide (**4**). The reaction requires use of a phase-transfer catalyst and pH control. The *endo* sulfoxide (**97**) also gave (**4**), but in lower yield. The latter oxidation also gave a low yield (2%) of the *trans*-dithiirane *S*-oxide (**12**). This same research group has also described the synthesis of the unoxidized dithiirane related to (**4**), namely (**4a**) <94AG(E)777>. In the earlier

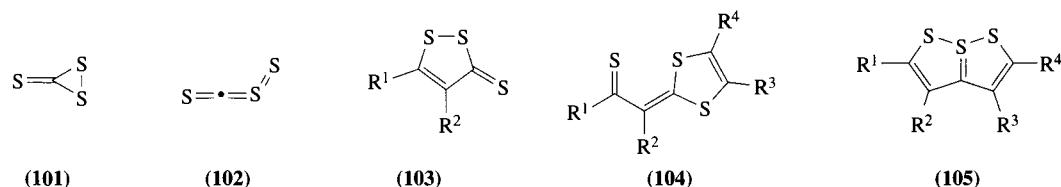
work, the sulfoxide (97) had been oxidized by oxone. In the slightly modified procedure the dithietane (95) is directly oxidized to (4a).



Up to the mid-1990s, the syntheses of (4), (4a), and (12) remain as the only examples of the synthesis of a stable dithiirane. There are a number of references in the literature, however, in which dithiiranes are invoked as unstable intermediates. In some cases, spectroscopic data has been obtained that supports these structures as intermediates. In other cases, they are suggested as intermediates because of the structure of a precursor or product compound, with little evidence for the actual existence of the dithiirane. A subgroup of these references has in common attempts to synthesize thiosulfines, or discuss reactions in which a thiosulfine or the isomeric dithiirane is believed to be an intermediate. An example of the latter is the suggestion that a dithiirane or the isomeric thiosulfine (98) is the precursor to the thioester (99) obtained when a chlorodisulfide of type (100) is treated with morpholine <79AG(E)941>.

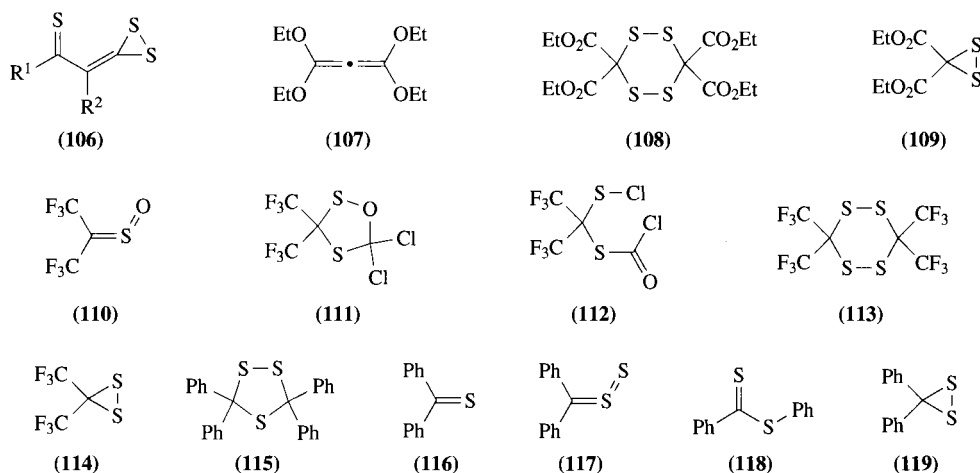


The observation that the reaction of CS₂ with triplet oxygen atoms leads to the formation of product pairs CS + SO, CO + S₂, and COS + S has led to the proposal by Senning that this reaction proceeds through several COS₂ tautomers, including dithiiranone (5) <B-81MI 114-01>. The pyrolysis of CS₂ at temperatures above 3000 K gives an intermediate, CS₃, which is considered to be (101) or (102) <B-81MI 114-01>. The same intermediates apparently are also formed when CS₂ reacts with atomic sulfur <B-81MI 114-01>. Senning has also suggested that the reaction of 3H-1,2-dithiole-3-thiones (103) with alkynedicarboxylic acid dimethylester to give a mixture of dithioles (104) and (105) may also involve formation of the dithiirane (106) or the isomeric thiosulfine <B-81MI 114-01>. In this same review <B-81MI 114-01>, Senning postulates that several other chlorodisulfides (100) may proceed via a dithiirane when they are converted to sulfenamides when treated with morpholine (see above). Senning adds, however, that, as of 1995, trapping experiments involving cycloadditions have failed to provide evidence for the dithiirane intermediates proposed in his review. In a subsequent paper, Senning discusses a number of cases in which chloro disulfides of type (100) are converted to thioamides when treated with morpholine or morpholine derivatives <86T739>. The reactions are believed to proceed through the derived dithiiranes or isomeric thiosulfines. This work is also discussed briefly in a 1982 review on compounds containing the S=S bond <82CRV333>.

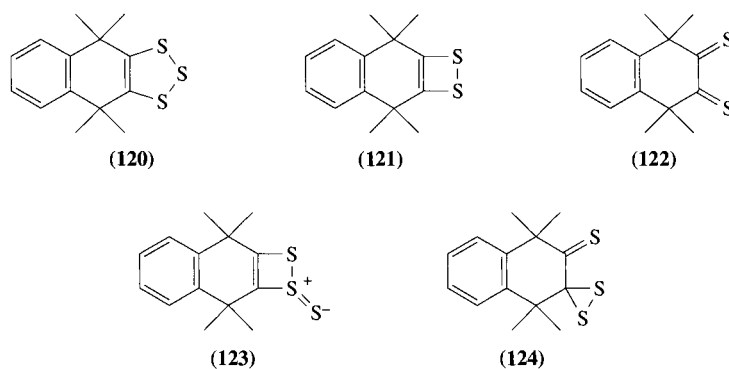


It has been reported that treatment of tetraethoxyallene (107) with disulfur dichloride, S₂Cl₂, gives an 83% yield of tetrathiane (108). The authors suggest that (108) is produced by dimerization of the dithiirane (109) or the isomeric thiosulfine <85AG(E)855>. In 1985 Elsässer and Sundermeyer reported a new synthesis of bis(trifluoromethyl)sulfine (110) as well as some of its reactions <85CB4553>. In one of these reactions (110) undergoes a 1,3-dipolar cycloaddition reaction with thiophosgene to give the dithioxolan (111) which rearranges to the sulfenyl chloride (112). This latter compound then decomposes by two different pathways. In one of these decompositions phosgene is lost and the tetrathiane (113) is formed. The authors postulate that the precursor to (113) is the dithiirane (114). In other cases there is some evidence that similar reactions probably

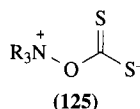
do not involve a dithiirane. Huisgen and Rapp report <87JA902> that thermolysis of trithiolane (115) gives the cycloreversion products thiobenzophenone (116) and the thiosulfine, thiobenzophenone S-sulfide (117). Evidence for formation of the products was obtained in trapping experiments. However the rearrangement of (117) to the dithioester (118) via dithiirane (119), as suggested in many of the related cases described above, could not be observed under any of a variety of thermolysis conditions <89PS(43)63>.



The synthesis of the stable 1,2,3-trithiole (120) has been reported by Tokitoh *et al.* <89TL2955>. The authors have photolyzed (120) in an argon matrix at low temperature while following changes in the electronic spectrum. This experiment revealed that two intermediates are formed, namely the 1,2-dithiete (121) and the thione (122). These intermediates are seen as forming from initial formation of thiosulfoxide (123) which is further transformed to the spirodithiirane (124) which serves as precursor to (121) and (122).



Another type of reaction has been suggested to involve the intermediacy of a dithiirane. Yoshimura *et al.* have proposed that deoxygenation of certain tertiary amine oxides with CS₂ may proceed through dithiirane (5) <82BCJ3000>. Thus nucleophilic attack of the N-oxide oxygen on the CS₂ would give intermediate (125) which then undergoes N—O bond cleavage to give the amine and either the thiirane or oxathiirane (6). Based on rate studies the authors favor intermediate (5) for the amine oxides and intermediate (6) for the nitrones included in the same study. Further evidence to support the intermediacy of intermediates (5) and/or (6) in these deoxygenation reactions was obtained by Zipplies *et al.* <85JOC3228>. The authors found that deoxygenation of *N,N*-dimethylaniline N-oxide with excess CS₂ gave *N,N*-dimethylaniline and *N*-methylaniline as the only products. Furthermore, when the reaction is carried out in the presence of tetramethylethylene, then tetramethylethylene sulfide is formed. The authors conclude that either (5) or (6) is the sulfur transfer reagent with carbon oxysulfide, COS, as the other product.



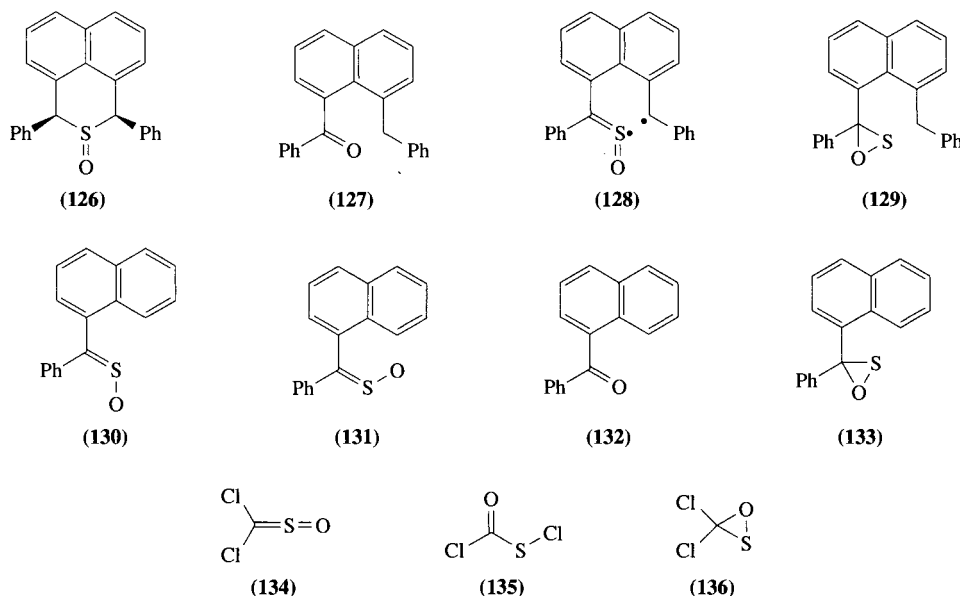
Another route to dithiiranone (**5**) has been suggested as a result of a study of the reaction of triplet oxygen atoms with CS₂. Hudgens *et al.* report <76JCP(64)2528> that this reaction gives CO with a double maxima population distribution indicating formation of an intermediate with C_{2v} symmetry. They suggest that this intermediate is dithiiranone (**5**). In a related project it has been shown that reaction of thiones with radioactive sulfur atoms gives the corresponding labeled thiones <77AG(E)725>. The labeled products are presumed to arise from formation of the thiosulfines (**98**) which rearrange to the isomeric dithiiranes (**2**).

1.14.6.2 Oxathiiranes

In contrast to the dithiiranes, no stable oxathiiranes have been synthesized. As with the dithiiranes, however, there are a number of literature reports in which this structure type has been invoked as an unstable intermediate. In some cases, structure types (**2**) and (**3**), or the derived dithiiranone (**5**) and oxathiiranthione (**6**), have been described as equally likely intermediates in some reactions. These examples will not be repeated here rather the reader is referred to Section 1.14.6.1 for this information.

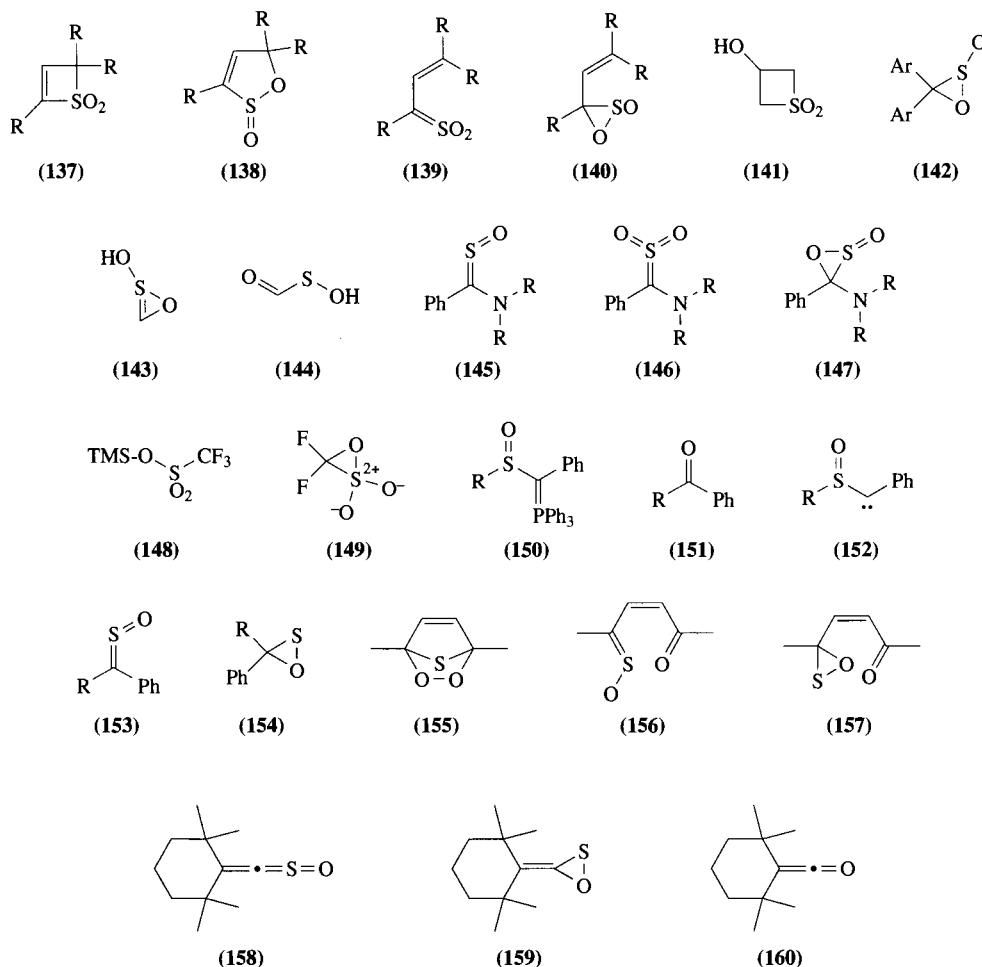
Opitz has described a synthesis of sulfines involving elimination of HCl from sulfinyl chlorides using triethylamine <67AG(E)107>. When describing the subsequent chemistry of these sulfines, the author considers the possibility that a cyclic form of the sulfine, the oxathiirane (**3**), might be involved. They also considered the corresponding *S*-oxide (**9**) as an intermediate. No evidence could be found for the intervention of either of these intermediates, however. A better case for the involvement of an oxathiirane has been made in the case of the photodesulfurization of a sulfoxide <68JA5314>. Benzophenone-sensitized photolysis of sulfoxide (**126**) gives the ketone (**127**) as the sole product. The authors believe that the reaction proceeds through diradical (**128**). After ruling out several possible fates for this diradical, the authors finally conclude that the most likely precursor to ketone (**127**) is oxathirane (**129**) which would be expected to lose sulfur in a dark reaction. This same group has also studied the photodesulfurization of sulfines <69TL4513>. They observed that photolysis of either of the isomeric sulfines (**130**) or (**131**) led to photoisomerization of the sulfines as well as to decomposition to ketone (**132**). The precise course of the reaction was determined to be concentration dependent. At high dilution quantum yield determinations suggest that a unimolecular process occurs involving sulfur loss to give the ketone. The authors suggest that this unimolecular process proceeds through oxathiirane (**133**). This same publication contains several other examples in which photolysis of sulfines is believed to involve oxathiirane formation. A synthesis of dichloromethylene sulfoxide (**134**) has been described which involves hydrolysis of trichloromethanesulfonyl chloride <69CC878>. The decomposition of (**134**) was determined to be complex, but the formation of chlorocarbonyl sulfonyl chloride (**135**) led the authors to suggest that oxathiirane (**136**) is intermediate between (**134**) and (**135**).

In an attempt to generate sulfenes, a number of thietan derivatives have been exposed to flash thermolysis <69CC32, 70CJC3704>. In one such case, thermolysis of thiete 1,1-dioxide (**137**) gave cyclic sulfinate (**138**). The latter is believed to be derived from the desired sulfene (**139**). Sulfene (**139**) is then seen as rearranging to oxathiirane *S*-oxide (**140**). Thermolysis of (**141**) is believed to follow a similar pathway leading ultimately to formaldehyde and sulfoxide, presumably via oxathiirane *S*-oxide (**9**). A mechanistic study of the reaction between perbenzoic acid and aryl sulfines has provided evidence for an oxathiirane *S*-oxide intermediate (**142**) <74JCS(P2)609>. The reaction produces a benzophenone, sulfur monoxide, and sulfur. These products are consistent with formation of (**142**) which decomposes to give the benzophenone and sulfur monoxide. The sulfur is formed in a subsequent disproportionation reaction in which sulfur monoxide is converted to sulfur and sulfur dioxide. Substituent effects on the reaction rate support a mechanism involving (**142**) as opposed to others involving attack at the carbon atom of the sulfine group. The reaction of methylene with sulfur dioxide leads to products which are easily explained by invoking an oxathiirane *S*-oxide intermediate (**9**) <74CC1014>. The reaction is believed to give energy-rich (vibrational or electronic) states of (**9**) and (**8**) which then enolize to (**143**) or (**144**). Either of these intermediates can dehydrate to give the observed carbonyl sulfide product. The oxidation of some thiobenzanilide sulfines with



a variety of oxidants, including peracids, leads, in some cases, to benzanilide formation <75LA305>. The authors suggest that the reaction proceeds through an oxathiirane which decomposes to the benzanilide and sulfur monoxide. This same research group has described <76LA1584> similar behavior when thioamide sulfoxides (145) are oxidized with hydrogen peroxide. The reaction is believed to proceed through the *S,S*-dioxide (146) which rearranges to the oxathiirane *S*-oxide (147). This intermediate then loses sulfur monoxide to give the amide product. Two mechanisms have been considered for the thermolysis of trimethylsilyl trifluoromethanesulfonate (148) <88CJC1430>. Only one of these is consistent with all products produced. This mechanism involves extrusion of trimethylsilyl fluoride with concomitant formation of the oxathiirane *S,S*-dioxide (149). Further decomposition of (149) yields the observed products SO_2 and COF_2 . In a report, it has been shown that flash vacuum pyrolysis of some alkane sulfinyl ylides (150) leads to formation of a derived ketone (151) <93CC1699>. The authors speculate that triphenylphosphine is first extruded to give a sulfinyl carbene (152) which undergoes a 1,2 shift of R to give a sulfine (153). The sulfine then cyclizes to oxathiirane (154) which loses sulfur and gives the observed ketone. Thiazonide (155) has been identified as the product of photooxidation of 2,5-dimethylthiophene. Thermal decomposition of (155) gives, among other products, sulfine (156) <86JA2775>. Among several mechanistic paths to (156), the authors consider formation of the oxathiirane (157) which would be expected to rearrange to (156).

Carlsen *et al.* have made a major effort to find evidence for oxathiiranes. In one such attempt thiobenzophenone sulphine (13) was photolyzed in glasses at low temperature <76JCS(P1)1404>. As described above for similar photolyses of sulfoxides, the product of the reaction was the ketone, benzophenone in this case. A photolysis at 77 K in an EPA (diethyl ether–isopentane–ethanol, 5 : 5 : 2) glass formed a monomeric compound with long-wavelength absorption at 390 nm. Heating of this material also led to benzophenone formation. The authors conclude that this compound is 3,3-diphenyloxathiirane (14). This oxathiirane undergoes a further photochemical transformation into a blue unstable compound with λ_{max} at 550 nm. This compound has been tentatively assigned the structure of a carbonyl sulfide, $\text{R}_2\text{C}=\text{O}=\text{S}$ <81T1257>. The photochemical and thermal conversion of sulfoxides to oxathiiranes has been predicted to be an allowed process by CNDO/B calculations <74JA5005>. The thermal reaction of (13) has also been studied by Carlsen *et al.* with the aid of differential thermal analysis (DTA) <77ACS(B)679>. When the reaction is conducted in an argon atmosphere, two competing processes occur. One of these is a dimerization reaction of (13). The other involves the predicted thermal ring closure of (13) to give oxathiirane (14). The oxathiirane then decomposes to give benzophenone and sulfur. This same research group has carried out a similar study involving thioketene *S*-oxide (158) <79C(L)851, 80JCS(P2)1206>. The thermal decomposition in this case follows three different pathways. In one of these, ring closure to oxathiirane (159) apparently occurs. This intermediate then decomposes to ketene (160) and sulfur. Using field ionization mass spectrometry, the authors have been able to estimate the half-life of (159) to be less than 10^{-4} s.



1.14.6.3 Dioxiranes

There are only four different methods of synthesis of dioxiranes, with one of these methods accounting for the majority of the dioxirane syntheses reported.

1.14.6.3.1 Synthesis from dialkoxides

A 1972 patent <72USP3632606> describes the preparation of perfluorodimethyldioxirane (**1c**) and chlorodifluoromethyltrifluoromethyldioxirane (**1d**) by the reaction of precursor dilithio alkoxides with F₂. Since this earlier report this method has apparently not been used further.

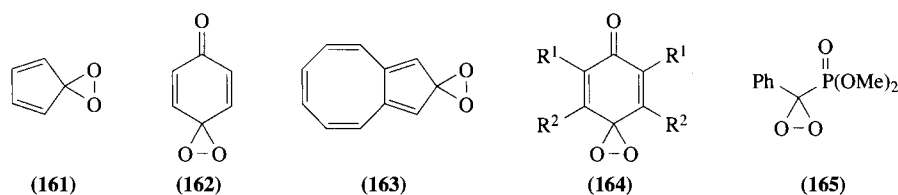
1.14.6.3.2 Synthesis by ozonolysis of alkenes

The second method of preparation involves the ozonolysis of alkenes. This method was used at low temperatures to prepare the parent dioxirane (**1a**) from ethylene <77CPL(51)453, 78JA5117>. This accomplishment permitted observation of the first microwave spectrum of a dioxirane. In some cases cyclization of energy rich carbonyl oxides to dioxiranes has been proposed to explain the formation of some products observed in gas-phase ozonolyses <82MI 114-01, 82MI 114-02>. Two other literature reports describe the formation of dioxiranes in ozonolysis reactions. In one of these Kopecky *et al.* find that ozonolysis of (*E*)- and (*Z*)-1,2-dimethoxy-1,2-diphenylethene gives a carbonyl oxide which closes to the dioxirane (**1e**) <93CJC272>. The dioxirane also reacts with the starting alkene producing the corresponding epoxide. The authors were able to obtain a ¹³C NMR spectrum of (**1e**) which showed the characteristic absorption for the ring carbon (109.1 δ). Murray *et al.* have

made a related observation in the ozonolysis of tetramethylethylene [93JOC315]. In this work it was found that ozonolysis of neat tetramethylethylene gave almost exclusively tetramethylethylene epoxide as the product. This product is believed to arise from the epoxidation of the alkene by dimethyldioxirane (**1b**) which is seen as arising from cyclization of the energy-rich carbonyl oxide, acetone oxide.

1.14.6.3.3 Synthesis by photolysis of the related carbonyl oxide

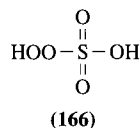
The reaction of methylenes with oxygen at low temperature in rigid glasses has long been known to provide access to the corresponding carbonyl oxide [62JA4990]. This reaction has been carried out by several groups using diazocyclopentadiene. Chapman and Hess photolyzed the diazo compound at 10 K in an argon matrix [84JA1842]. The carbene produced in the photolysis reacted with oxygen to give a new species for which both carbonyl oxide and dioxirane structures were considered. Based on the infrared spectrum of this species, the authors assigned the carbonyl oxide structure. Bell and Dunkin carried out a similar study and again, based on the presence of two nonequivalent oxygen atoms in the infrared spectrum, assigned the carbonyl oxide structure [83CC1213, 85T339]. Later Dunkin and Shields showed that photolysis of this carbonyl oxide converted it to the isomeric dioxirane (**161**) [86CC154]. The infrared spectrum of (**161**) showed that it contained two equivalent oxygen atoms consistent with the dioxirane structure. Under similar experimental conditions diphenylcarbene has been shown to react with oxygen to give a material assigned the structure of the carbonyl oxide by Scaiano and co-workers [84CJC2391]. Sander subsequently made similar observations on this system. However, Sander showed that the carbonyl oxide could be further photolyzed to give the dioxirane (**1f**) [85AG(E)988, 86AG(E)255, 87SA(A)637]. Irradiation of (**1f**) at 438 nm converted it to phenyl benzoate. In further work, Sander has shown that use of the matrix conditions permitted observation of the formation of the carbonyl oxide, trifluoroacetophenone oxide, from the reaction of 1-phenyl-2,2,2-trifluoroethylidene with oxygen [88JOC121]. This carbonyl oxide also could be further photolyzed to the dioxirane (**1g**). Irradiation of the precursor carbonyl oxides at 630 or 480 nm, respectively, gives the spiro dioxiranes (**162**) and (**163**) [88JOC2091, 90AG(E)344, 90JOC4502]. In the early 1990s, Bucher and Sander have prepared a larger group of spiro dioxiranes (**164**) containing a variety of substituents by photolyzing the precursor carbonyl oxides in argon matrices [92CB1851]. A slightly different path can be followed to the carbonyl oxide to dioxirane route. Sheridan and co-workers have photolyzed phenylchlorodiazirine in an argon matrix in the presence of oxygen [86JA1517]. Here again the carbonyl oxide was produced and subsequently photolyzed to the dioxirane (**1h**). The dioxirane was then photochemically isomerized to phenyl chloroformate. A phosphorus-containing dioxirane has been prepared by following similar chemistry [92JOC6216]. Dimethyl α -diazobenzylphosphonate was photolyzed in an argon matrix containing oxygen. The intermediate carbene was converted to the carbonyl oxide, identified by its UV-Vis and infrared spectra. Photolysis of the carbonyl oxide at wavelengths > 480 nm produced the dioxirane (**165**).



1.14.6.3.4 Synthesis by the reaction of monoperoxysulfuric acid (Caro's acid) with ketones

The genesis of this important route to dioxirane formation was an observation by Montgomery [74JA7820] that some ketones are able to enhance the rate of decomposition of monoperoxysulfuric acid (**166**). Montgomery concluded that (**166**) was adding to the ketone to give an adduct which decomposed to give the dioxirane. Using kinetic and ^{18}O -labeling experiments Edwards *et al.* obtained definitive evidence for the intervention of dioxiranes in these decompositions [79MI 114-01]. They also obtained chemical evidence for the presence of dioxiranes by showing that these oxidants could carry out stereospecific epoxidations of unsaturated substrates [80JOC4758, 81JOC1684,

82JOC2670, 84CC155, 88JOC3890). This work also established that strict pH control (pH = 7.5) is required for optimum results. The aqueous conditions used have come to be known as the *in situ* generation of the dioxirane. For water-insoluble substrates, a phase-transfer catalyst can be used to provide excellent oxygen-atom transfer reactions <80JOC4758>. Subsequently, Curci *et al.* showed that these reaction conditions could be used to convert chiral ketones to dioxiranes and that these dioxiranes would epoxidize prochiral alkenes with moderate enantiomeric excess of 9–12.5 <84CC155>.



In 1985, Murray and Jeyaraman reported that certain dialkyldioxiranes could be isolated as solutions in their precursor ketones <85JOC2847>. This is accomplished by passing a stream of an inert gas through the aqueous medium used in the *in situ* generation conditions. The yellow solution of the dioxirane is condensed at low temperatures. A slightly reduced pressure is used in the latter part of the collection period in order to maximize dioxirane yield. These conditions give solutions of the dioxirane in the 0.06–0.1 M concentration range. The dioxirane solution may be used as obtained and usually at room temperature or below. When particularly sensitive oxidation products are anticipated (e.g. some epoxides) then the solutions should be dried, first with Na₂SO₄, and then with molecular sieves. The availability of solutions of dioxiranes has brought about an explosion of interest in these interesting oxidants. In most cases the oxygen transfer reactions brought about by the dioxirane are carried out under very mild conditions. Since the reaction converts the dioxirane to a ketone, the workup is simple. This procedure, sometimes with minor modifications <87JOC699, 87JOC2800>, has now been carried out in many laboratories. Adam *et al.* have described <91CB2377> a modification to the original procedure in which no inert gas is used to carry the dioxirane from the generation medium. Instead vigorous stirring is maintained with a mechanical stirrer and the reaction temperature is cooled to 5–10°C. This procedure is described as consistently giving concentrations of dimethyldioxirane of 0.09–0.10 M.

In 1994, a new modification of the *in situ* conditions for preparing (1b) has been described <94JCR(S)114>. A solution of partially neutralized Caro's acid is prepared by combining 40.9% H₂SO₄ and 3.1% H₂O₂, with cooling, and then using sodium hydroxide to partially neutralize the solution. This solution is transferred to another vessel and acetone and NaHCO₃ added. This pH adjusted solution can be used to give solutions of the isolated dioxirane in the usual manner. This method gives a dioxirane concentration of 0.12 M. Alternatively, the solution of partially neutralized Caro's acid can be added to an aqueous solution of an alkene substrate, acetone, methylene chloride, and NaHCO₃ to give a homogeneous epoxidation mixture.

The procedure used to give solutions of (1b) also has been used to prepare solutions of methyl-(trifluoromethyl)dioxirane (1j) <88JOC3890>. In this case the dioxirane concentrations obtained are considerably higher (0.65–0.82 M) than those achieved with the simple dialkyldioxiranes. Dioxirane (1j) is also considerably more reactive than dimethyldioxirane so that relatively unreactive substrates can be oxidized <89JA6749>. In later work Adam *et al.* have described a modified preparation of (1j) that provides a solution of the dioxirane free of the ketone <91JA7654>. The solution of (1j) in trifluoroacetone is diluted with another inert solvent (CH₂Cl₂, CCl₄, CCl₂FCClF₂, etc.) and then the combined, cold solution is extracted with distilled water. This latter procedure removes the trifluoroacetone as its hydrate. These ketone-free solutions of (1j) permitted studies of the thermal and photochemical decomposition of the dioxirane. A ketone-free CH₂Cl₂ solution of (1j) was used to demonstrate that the C—H insertion reaction of the dioxirane proceeded with complete retention of configuration <92JOC953>.

A modification to the *in situ* procedure that permits isolation of additional dioxiranes has also been described <92JA1346>. In this work ketones with relatively low water solubilities are treated with the usual *in situ* conditions, but with some important modifications. The reaction medium is maintained cold with an ice-salt bath throughout the entire procedure. All handling of the dioxiranes is also done at these temperature conditions. The procedure has been used to synthesize cyclohexanone and related spiro dioxiranes. A key element of the procedure is the use of copious amounts of phosphate salts in order to salt out the dioxirane. This process leads to the separation of a second highly-colored layer containing the dioxirane in ketone (e.g. cyclohexanone) solution. These solutions contain concentrations of dioxirane (0.2–0.8 M) which are considerably higher than those obtained for the more volatile dioxiranes. The solutions may be used to obtain spectroscopic data on the dioxiranes or to carry out typical dioxirane reactions.

1.14.7 APPLICATIONS

An increasing number of references have appeared indicating that dioxiranes are being used in various industrial chemical processes. *In situ*-generated dioxiranes have been used to prepare various diepoxy derivatives used as monomers for plastics having a high transition temperature <91EUP453275>. The epoxidation of enol ethers by (**1b**) has also been patented <90EUP370946, 90GEP4023741>. The conversion of secondary amines to hydroxylamines by (**1b**) is the subject of a patent <91USP5001233>. The very convenient, high-yield dimethyldioxirane oxidation of certain secondary amines to nitroxides has also been patented <92USP5087752>.

Dimethyldioxirane *in situ* generated or in isolated form, has demonstrated excellent selectivity and reactivity in pulp bleaching. It appears to be a suitable replacement for chlorine and chlorine dioxide for bleaching both hardwood and softwood Kraft pulps <91MIP12369, 91MIP13993, 92MI 114-05, 93MI 114-01, 93MI 114-02, 94MI 114-02>. *In situ*-generated fluoroalkyl and fluoroaryl-substituted dioxiranes have also been used for delignification of wood pulps <93EUP529326>.

ACKNOWLEDGMENT

We gratefully acknowledge support of our work cited herein, as well as the writing of this manuscript, by the National Institute of Environmental Health Sciences.

1.15

Three-membered Rings with Two Heteroatoms including Selenium or Tellurium

NORIHIRO TOKITOH

University of Tokyo, Japan

and

NAMI CHOI and WATARU ANDO

University of Tsukuba, Japan

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1.15.1 INTRODUCTION

Although the chemistry of three-membered heterocycles containing one heteroatom such as nitrogen, oxygen, or sulfur has been widely explored in organic chemistry, and the literature on the theory, preparation, and applications of these common three-membered heterocycles is too vast to enable an extensive coverage of the subject, very little is known about the counterpart of this family

of heterocycles containing heavier heteroatoms such as selenium or tellurium as described in a previous chapter (see Chapter 1.07). On the other hand, three-membered heterocycles containing two heteroatoms with one carbon atom have also been scarce, probably owing to their instability, with the exception of some dioxirane derivatives, although a serendipitous synthesis of a stable dithiirane derivative has been reported $\langle 93JA4914, 94AG(E)777 \rangle$. Selenirane or tellurirane derivatives which consist of two heteroatoms and one carbon atom might be very unstable, and no systematic research on this class of heterocycles has been available, but only a few examples with peculiar structures have been reported. Therefore, in this chapter, the chemistry of not only the three-membered rings with two heteroatoms including one selenium or tellurium atom and one carbon atom but also those consisting of three heteroatoms including one selenium or tellurium atom, that is all the heteroatom analogues of seleniranes and telluriranes, will be covered in connection with the similarity in their molecular geometries and the synthetic methodology used.

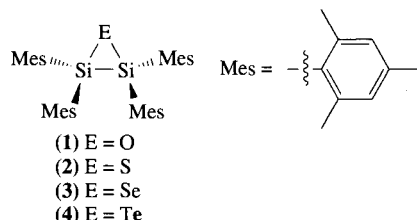
1.15.2 THEORETICAL METHODS

1.15.2.1 Introduction

There have been no calculated structures for selenirane or tellurirane derivatives including another heteroatom in the ring systems, that is $C-E-X$ ($E = Se, Te$; $X = \text{heteroatom}$) at any level of theory. Progress in the chemistry of small ring compounds of group 14 elements such as silicon, germanium, and tin has provided us with a variety of stable examples of three-membered ring compounds containing two group 14 metals and one chalcogen atom, $M-E-M$ ($E = O, S, Se, Te$; $M = Si, Ge, Sn$) and the successful structural analysis of these unprecedented three-membered ring systems prompted theoretical chemists to elucidate their intrinsic geometry and bonding character by calculation.

1.15.2.2 Metal-Alkene Bonding Models

West *et al.* have succeeded in the synthesis and isolation of a series of stable chalcogenadisiliranes (1)–(4) by taking advantage of four mesityl groups as steric protection groups and revealed their molecular structures by x-ray crystallographic analysis (Scheme 1) $\langle 85JA4942, 87JA6865, 91OM546 \rangle$.

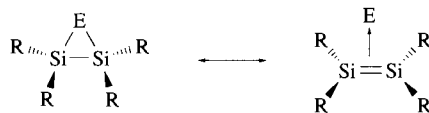


Scheme 1

An interesting structural feature of compounds (1)–(4) is that their Si—Si bond lengths, which increase gradually from (1) through (4) as electronegativity of the chalcogen atoms decrease ((1) 2.227(2) Å, (2) 2.289(2) Å, (3) 2.303(3) Å, and (4) 2.337(4) Å), are essentially shorter than a normal Si—Si single bond. The Si—Si bond length of (1) is actually closer to that of a Si=Si double bond (2.14 Å) $\langle 89HAC1 \rangle$, while that of (4) is only 0.01 Å shorter than that of a normal Si—Si single bond. The short Si—Si bond distances are not necessary features of three-membered rings, since hexakis(2,6-dimethylphenyl)cyclotrisilane has rather longer Si—Si bonds (average 2.407 Å) $\langle 82JA1150 \rangle$.

To account for the short Si—Si bond distances in (1) and (2), a bonding model was proposed in which a significant amount of double-bond character of the disilene is retained in the three-membered rings (i.e., π -complex as illustrated in Scheme 2). This model is similar to the model developed to explain the bonding of alkenes to transition metals, where the bonding is viewed in terms of donation from the π orbitals of the alkene into a vacant orbital on the metal, accompanied by back-donation from the metal d -orbital into the π^* orbital of the alkene (Scheme 2) $\langle 51BSFC71, 53JCS2939 \rangle$. In (1)–(4), such back-bonding can take place from a filled orbital on the chalcogen atom of the appropriate symmetry into the π^* orbital of the disilene. The structures arising from these

interactions lie on a continuum between a three-membered ring and a π -complex. As the chalcogen becomes more electronegative, there is less back-bonding and the compounds tend toward the π -complex structure with shortening of the Si—Si bond lengths.



Scheme 2

1.15.2.3 Structural Prediction

The unusual shortening of the Si—Si bond lengths in oxa- and thiadisiliranes in terms of partial π -complex character has been predicted by calculations $\langle 87JA6577, 88JST(169)531 \rangle$, which also revealed that the Si—Si bond lengths in the three-membered ring compounds increase with decreasing electronegativity of the substituents. On the other hand, Gordon and Boatz attributed the short Si—Si bond distances to extreme bond bending of the Si—Si bond rather than to partial Si—Si π -character $\langle 89JPC3025 \rangle$. Cremer also calculated similar bond bending of the Si—Si bonds; however, he attributed the bond bending to the π -complex character of these ring systems $\langle 88JST(169)531 \rangle$. According to Cremer, the short Si—Si bond distance may also be caused by geometrical constraints resulting from the size of the chalcogen atom (E) at the apex of the ring $\langle 88JST(169)531 \rangle$. When the Si—E bond distance is smaller than the Si—Si bond distance in a three-membered ring, there exists Bayer strain resulting from a small ($< 60^\circ$) Si—Si—E angle. To avoid this increase in Bayer ring strain for small Si—Si—E angles, Si—E distances are elongated and Si—Si bond distances reduced.

1.15.3 EXPERIMENTAL STRUCTURAL METHODS

1.15.3.1 Bond Lengths and Bond Angles

As mentioned in the previous section, a series of chalcogenadisiliranes (**1**)–(**4**) were synthesized and isolated as stable crystalline compounds by taking advantage of steric protection $\langle 85JA4942, 87JA6865, 91OM546 \rangle$. Table 1 summarizes their spectroscopic and structural data. In addition to the characteristic shortening of Si—Si bond distances compared to the normal Si—Si single bond length (see Section 1.15.2.2), one can see the increase of Si—Si—E angles (or decrease of Si—E—Si angles) on going from (**1**) to (**4**). In oxadisilirane (**1**), which has the smallest Si—Si—E angle (50.0°), the Si—Si bond length is shorter than the normal Si—Si single bond, and the Si—O bond lengths are longer (1.732(2) and 1.733(3) Å) than the normal Si—O single bond length found for other cyclic siloxanes (1.61–1.65 Å).

Table 1 Structural data^a for chalcogenadisiliranes (**1**)–(**4**)

Molecule	Pauling ^b $\chi(E)$	Si—Si bond dist.	Si—E bond dist.	Angle ^c at Si atom	Twist angle ^d	Si—E—Si angle	Si—Si—E angle
(1) (E = O)	3.44	2.227(2)	1.732(3) 1.733(3)	360.0(2)	10.0	80.0(2)	50.0(1)
(2) (E = S)	2.58	2.289(2)	2.161(2) 2.162(2)	357.3(2) 357.5(2)	12.7	64.0(1)	58.0(1)
(3) (E = Se)	2.55	2.303(3)	2.303(2) 2.309(2)	355.6(4) 356.0(3)	10.0	59.9(1)	59.9(1)
(4) (E = Te)	2.10	2.337(4)	2.523(3) 2.524(3)	355.3(6) 355.8(7)	14.5	55.2(1)	60.2(2) 62.4(1)

^aAngles are in deg and bond distances in Å. ^bPauling scale of electronegativity; values from $\langle 61JINC215 \rangle$. ^cSum of the three angles formed by the arrangement of C, C, Si atoms around each silicon atom. ^dThe twist angle is a result of the torsional distortion along the Si—Si bond.

Another interesting structural feature for compounds (**1**)–(**4**) is the planar or nearly planar arrangement of carbon and silicon atoms around each silicon atom (Table 1). This planar arrange-

ment of C, C, Si atoms can also be attributed to the π -complex character as mentioned before (see Section 1.15.2.1), and the gradual decrease in planarity on going from (1) to (4) could be due to the decreasing π -character of the Si—Si bonds. Torsional distortion along the Si—Si axis results in twist angles ranging from 10.0° in (1) to 14.5° in (4), with no apparent trend as the size of the chalcogen increases (Table 1).

On the other hand, the synthesis of the heavier congeners of chalcogenadisiliranes (2) and (3), that is thia- and selenadigermiranes (5) and (6), was recently achieved by the photochemical reactions of sterically crowded cyclotrigermane in the presence of the corresponding elemental chalcogens (Equation (1)) <88OM2015>. Although the molecular structure of selenadigermirane (6) has not been crystallographically established, x-ray structural analysis of thiadigermirane (5) showed a remarkable shortening of the Ge—Ge bond length (2.376(2) Å) as compared with the normal Ge—Ge single bond (2.44 Å) as in the cases of the chalcogenadisiliranes (1)–(4). Since the characteristic molecular feature of (5) was reasonably interpreted in terms of the π -complex bonding model as proposed in the case of chalcogenadisiliranes, one can expect a molecular geometry for a selenadigermirane ring system similar to that of (5). In the more recent report on the synthesis and structural analysis of the telluradigermiranes (7a) and (7b) (Equation (2)) <90CC1159> the Ge—Ge bond distance of tetrakis(2,6-diethylphenyl)telluradigermirane (7b) (2.435 Å) has been described as almost normal (2.44 Å); however, the bonded aryl carbon atoms and the germanium atoms are still almost coplanar as in the cases of other Ge_2X ring systems ($\text{X} = \text{S}, \text{NR}, \text{CR}_2$) <88OM2015, 89OM161>. Table 2 summarizes the spectral and structural data for chalcogenadigermiranes (5) and (7).

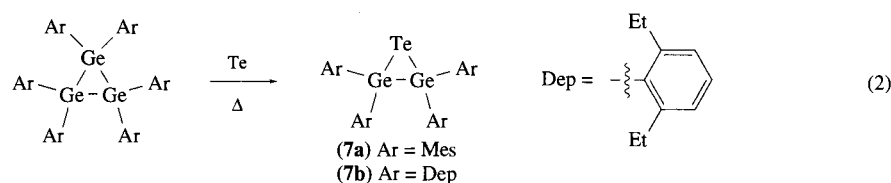
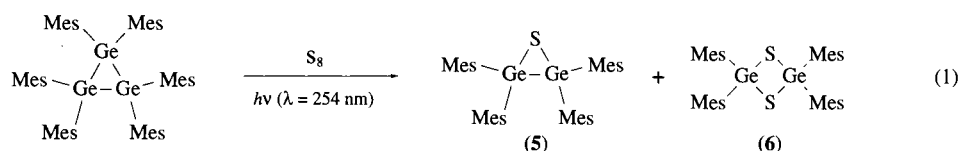


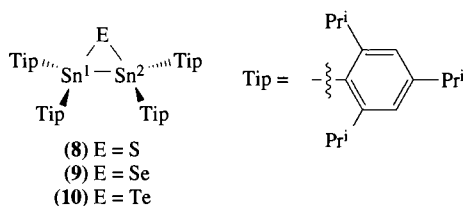
Table 2 Structural data^a for chalcogenadigermiranes (5) and (7)

Molecule	Pauling ^b $\chi(E)$	Ge—Ge bond dist.	Ge—E bond dist.	Angle ^c at Ge atom	Ge—E—Ge angle	Ge—Ge—E angle
(5) (E = S)	2.58	2.376(2)	2.277(3) 2.263(3)	357.3 356.7	63.1(1)	58.2(1) 58.7(1)
(7) (E = Te)	2.10	2.435(2)	2.597(2)	355.4 355.5	55.9(4)	62.04(4) 62.05(4)

^aAngles are in deg and bond distances in Å. ^bPauling scale of electronegativity; values from <61JINC215>. ^cSum of the three angles formed by the arrangement of C, C, Ge atoms around each germanium atom.

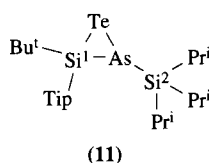
Furthermore, a series of chalcogenadistanniranes (8)–(10), that is Sn_2E ($\text{E} = \text{S}, \text{Se}, \text{and Te}$) ring systems, has been synthesized as stable crystalline compounds by taking advantage of steric protection using the 2,4,6-triisopropylphenyl group (Scheme 3) <91AG(E)834, 91AG(E)962>. Among the three chalcogenadistanniranes, the molecular structure of telluradistannirane (10) has been analyzed crystallographically to reveal the nearly equilateral triangle consisting of one tellurium and two tin atoms, where the tin—tin (2.827(1) Å) and tin—tellurium (2.800(1) and 2.779(1) Å) bonds are somewhat longer than those usually found. Especially interesting is the environment of the tin atoms; the sum of the bond angles at Sn^1 and Sn^2 atoms were 335° and 357° , respectively, indicating a nearly planar geometry. This structural feature is in good agreement with that found for telluradisilirane (4) and telluradigermirane (7), and these comparable structures indicate that the bonding is similar in all three-membered ring compounds consisting of one tellurium and two group 14 metals.

In 1995 Driess *et al.* reported the x-ray structural analysis of another member of heteroatom-



Scheme 3

containing telluriranes, i.e. tellura-arsasilirane (**11**) <95CC253>. The Si¹—Te and As—Te bond lengths in (**11**) are in good agreement with the sum of the covalent radii of these elements, and the endocyclic Si¹—As bond distance (2.354(1) Å) is significantly shorter than the exocyclic Si²—As bond (2.396(1) Å), indicating the π -complex character of the endocyclic Si¹—As bond as in the cases of chalcogenadisiliranes as mentioned above.



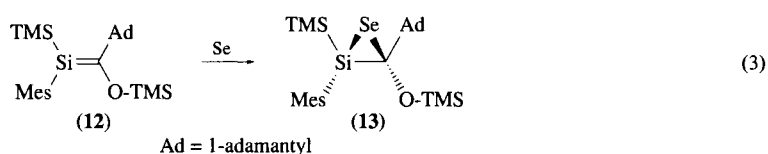
1.15.3.2 NMR Spectra

The ⁷⁷Se- and ¹²⁵Te-NMR spectral data for the disiliranes (**3**) and (**4**) <91OM827> and distanniranes (**9**) and (**10**) <91AG(E)834, 91AG(E)962> are summarized in Table 3, together with their ²⁹Si- and ¹¹⁹Sn-NMR spectral data, while those for the seleno- and telluradigermiranes (**6**) and (**7**) have not been reported in the literature. As for the ²⁹Si- and ¹¹⁹Sn-NMR, the chemical shifts for telluradi-metalliranes (**4**) and (**10**) are both shifted upfield from those for the corresponding selenadi-metalliranes (**3**) and (**9**).

Table 3 NMR spectral data for chalcogenadisiliranes (**3**) and (**4**) and chalcogenadistanniranes (**9**) and (**10**).

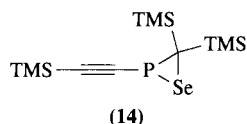
Compound	⁷⁷ Se-NMR chemical shift	¹²⁵ Te-NMR chemical shift	²⁹ Si-NMR chemical shift	¹¹⁹ Sn-NMR chemical shift
(3)	−287.1 (CDCl ₃)		−64.8 (C ₆ D ₆)	
(4)		−783.8 (CD ₂ Cl ₂)	−90.3 (CD ₂ Cl ₂)	
(9)	−378 (C ₆ D ₆)			−393 (C ₆ D ₆)
(10)		−903 (C ₆ D ₆)		−594 (C ₆ D ₆)

In the case of tellura-arsasilirane (**11**) the ¹²⁵Te- and ²⁹Si-NMR showed two sets of resonance signals at 20 °C, indicating that both diastereomeric forms are present in solution, whereas only one diastereomer (racemic mixture (*R,R*) and (*S,S*) configured) was observed in the crystal <95CC253>. The ¹²⁵Te- and ²⁹Si-NMR chemical shifts for (**11**) were reported as follows: $\delta_{\text{Te}}(\text{C}_6\text{D}_6)$ −550.0 and −547.4 and $\delta_{\text{Si}}(\text{C}_6\text{D}_6)$ −23.3 and −17.6. On the other hand, in a recent report on silaselenirane (**13**), which was successfully synthesized by the direct selenation of the corresponding stable silene (**12**) (Equation (3)), its ⁷⁷Se-NMR signal (48.84 ppm) was observed at a considerably downfield region as compared with those for (**3**) and (**9**), while ¹³C- and ²⁹Si-NMR signals for the ring carbon and silicon of (**13**) were observed at a fairly upfield shifted region ($\delta_{\text{C}} = 99.50$ and $\delta_{\text{Si}} = -48.84$) <94OM424>.



As another stable example of selenirane containing phosphorus, 1,2-selenaphosphirane (**14**) was synthesized by Appel *et al.* <85CB3419> and the $^{77}\text{Se}\{^1\text{H}\}$ -NMR signal for (**14**) in CDCl_3 was observed at -130.4 ppm (d, $J_{\text{SeP}} = 141.2$ Hz) ($^{31}\text{P}\{^1\text{H}\}$ -NMR (C_6D_6) $\delta -123.13$ (satellite, d, $J_{\text{SeP}} = 141.2$ Hz)).

Up to the present, however, no systematic studies have been reported for the NMR spectra for the heteroatom-containing seleniranes and telluriranes because of the scarcity of stable examples.



1.15.3.3 Miscellaneous Spectroscopic Properties

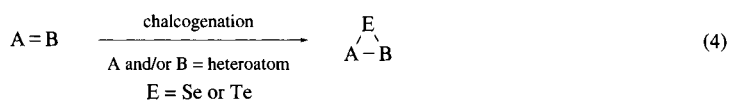
In contrast to the cases of chalcogenacyclopropanes, for example seleniranes and telluriranes, heteroatom-containing seleniranes and telluriranes generally showed molecular ion peaks in their mass spectra, suggesting the high thermal stability of this family of three-membered ring systems. Since the double-bond species containing typical heavier element(s) resulting from their dechalcogenation are much less stable than carbon-carbon double bond compounds, the fragmentation during ionization might be relatively suppressed in the cases of heteroatom-containing seleniranes and telluriranes.

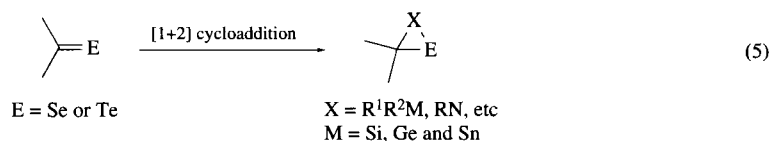
Most of the heteroatom-containing seleniranes and telluriranes described in this chapter were isolated as colorless crystals and no electronic spectral data has been mentioned for these compounds. Some of them were isolated as yellow or orange crystals. Telluradigermiranes (**7**) <90CC1159> and tellura-arsasilirane (**11**) <95CC253> were reported to be isolated as yellow and orange crystals, respectively, and telluradigermiranes (**7**) exhibit thermochromism, being colorless at -196°C , pale yellow at room temperature, and orange at about 140°C . Selenadistannirane (**9**) and telluradistannirane (**10**) were also isolated as light yellow and yellow-orange crystals, respectively ($\lambda_{\text{max}}(\epsilon)$ for (**9**) = 340 (12320) and $\lambda_{\text{max}}(\epsilon)$ for (**10**) = 378 (3060)) <91AG(E)834, 91AG(E)962>.

1.15.4 SYNTHESSES AND ISOLATION OF STABLE HETEROATOM-CONTAINING SELENIRANES AND TELLURIRANES

1.15.4.1 Introduction

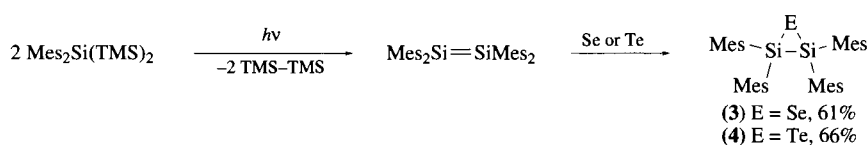
To make three-membered cyclic systems including one selenium or tellurium together with another heteroatom in the skeleton, one can hit upon several synthetic approaches similar to those applied to the cases of seleniranes and telluriranes (see Chapter 1.07). Up to the present, however, the heteroatom-containing seleniranes and telluriranes described in this chapter have been synthesized by taking advantage of only one synthetic strategy, that is the chalcogenation of highly reactive heteroatom-containing double bond compounds (Equation (5)). Although the $[1 + 2]$ cycloaddition of low-coordinate heteroatom compounds (nitrenes, silylenes, germylenes, stannylenes, and so on) to the selenocarbonyl or tellurocarbonyl compounds might be another promising synthetic approach leading to the heteroatom-containing seleniranes and telluriranes (Equation (5)), no successful examples using these approaches have been reported probably because selenocarbonyl and tellurocarbonyl compounds are known to be very unstable. Several examples of stable selenocarbonyl compounds have been synthesized by taking advantage of kinetic stabilization (steric protection); however, no reports have dealt with their $[1 + 2]$ cycloaddition reactions leading to the formation of heteroatom-containing seleniranes.





1.15.4.2 Chalcogenation of Highly Reactive Double-bond Compounds

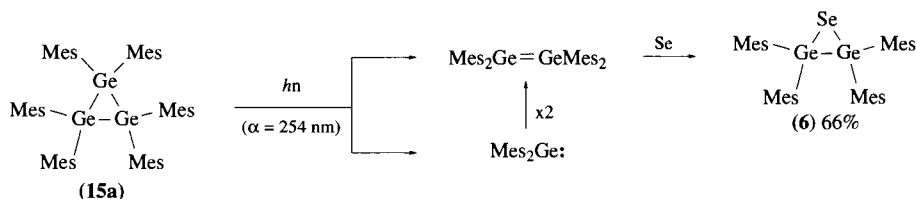
Selenadisilirane (**3**) and telluradisilirane (**4**) were synthesized by the chalcogenation of 1,1,2,2-tetramesityldisilene $\langle 81\text{SCI}343 \rangle$ in degassed benzene at room temperature as colorless solid in 61% and 66% yields, respectively (Scheme 4). In both cases, granulated elemental chalcogens were used as chalcogen sources. All reactions were carried out under an atmosphere of argon, and the solids were manipulated under nitrogen in a glovebox.



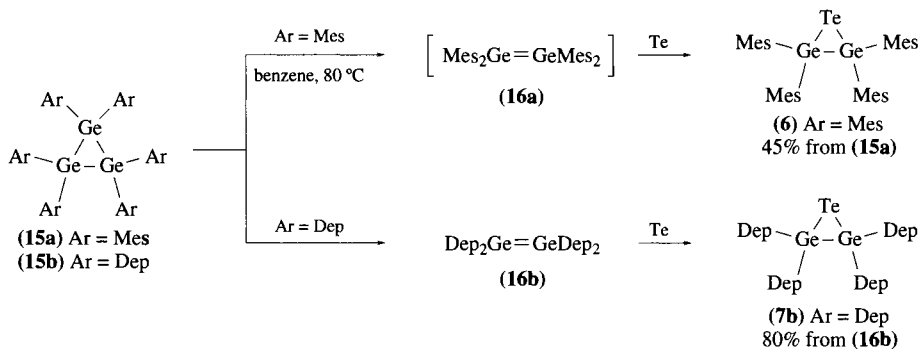
Scheme 4

Selenadigermirane (**6**) was synthesized by the photolysis ($\lambda = 254 \text{ nm}$) of hexamesitylcyclotrigermene (**15a**) $\langle 87\text{CC}1514 \rangle$ in the presence of elemental selenium in cyclohexane as in the case of thiadigermirane (**5**) (Scheme 5), while telluradigermirane (**7a**) was prepared by the thermolysis of the corresponding cyclotrigermene (**15a**) bearing bulky aromatic substituents in the presence of elemental tellurium (Scheme 6). In both cases, tetraaryldigermenes (**16**) were postulated as initial intermediates which readily underwent $[2 + 1]$ cycloaddition reactions with elemental chalcogens. Indeed, the isolable digermene, tetrakis(2,6-diethylphenyl)digermene (**16b**), reacted with tellurium in benzene at 80°C to afford the expected telluradigermirane (**7b**) in 80% yield (Scheme 6). Chalcogenadigermiranes (**5**)–(**7**) thus obtained were found to be very stable. For example, (**6**) does not decompose when heated to its melting point at $217\text{--}219^\circ\text{C}$, and (**7a,b**) are stable towards atmospheric oxygen. As previously mentioned (**7a,b**) showed thermochromism, being colorless at -196°C , pale yellow at room temperature, and orange at around 140°C .

As for the syntheses of the tin analogues of selenirane and tellurirane, tetraarylsubstituted

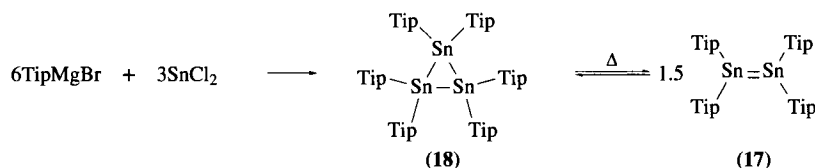


Scheme 5

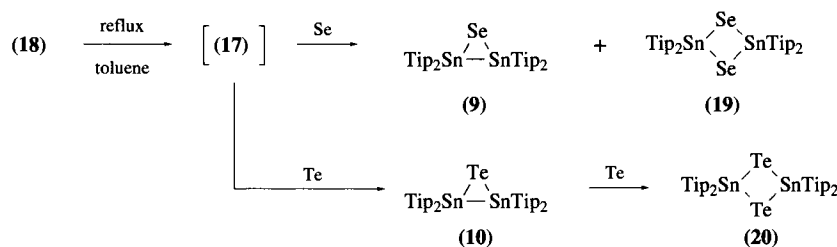


Scheme 6

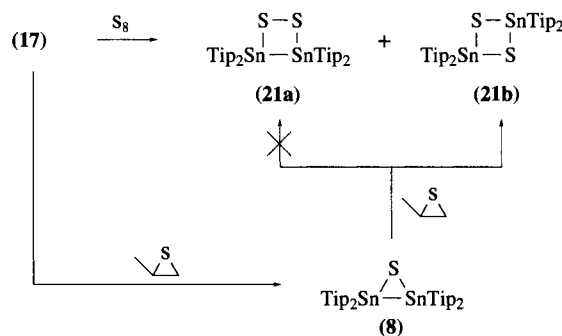
distannene (**17**), which was prepared *in situ* by the thermolysis of the hexakis(2,4,6-triisopropylphenyl)cyclotristannane (**18**) in refluxing toluene (Scheme 7), was used as a precursor to give the stable selenadistannirane (**9**) and telluradistannirane (**10**) (Scheme 8) <91AG(E)834, 91AG(E)962>. In the selenation of (**17**), only a mixture of the selenadistannirane (**9**) and 1,3-diselenadistannetane (**19**) was obtained even though a less than stoichiometric amount of selenium was used, while the reaction of (**17**) with a slight excess amount of tellurium (1.54 equivalents) resulted in the formation of only the expected telluradistannirane (**10**) (71%), suggesting the lesser reactivity of tellurium than that of selenium. The use of excess tellurium (3.09 equivalents) under similar reaction conditions gave 73% of 1,3-ditelluradistannetane (**20**). On the other hand, the thermal reaction of (**17**) with elemental sulfur in toluene at 90°C did not afford the expected thiadistannirane (**8**) but the two types of dithiadistannetanes (**21**) and (**22**), quantitatively. The synthesis and isolation of (**8**) was achieved by the reaction of (**17**) with methylthiirane as shown in Scheme 9.



Scheme 7

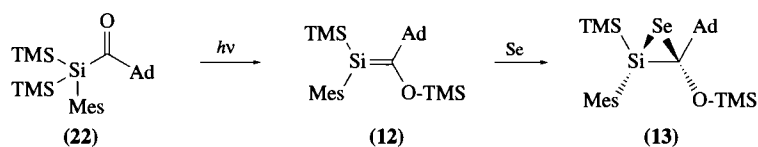


Scheme 8



Scheme 9

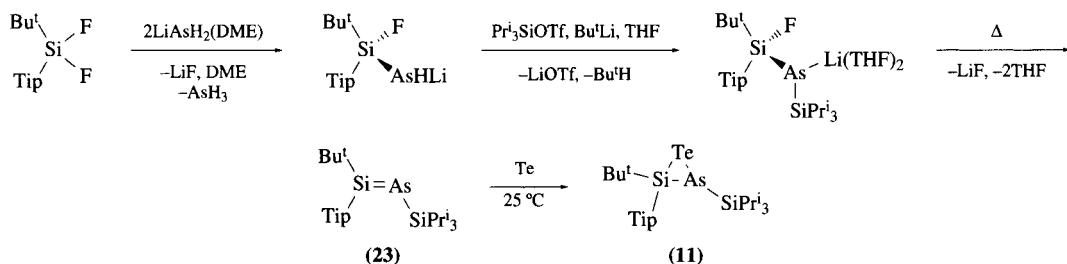
Silaselenirane (**13**), another example of group 14 metal-containing seleniranes, was prepared by the selenation of the corresponding silene (**12**), which was generated by the photolysis of acylsilane (**22**) (Scheme 10) <92OM3088>.



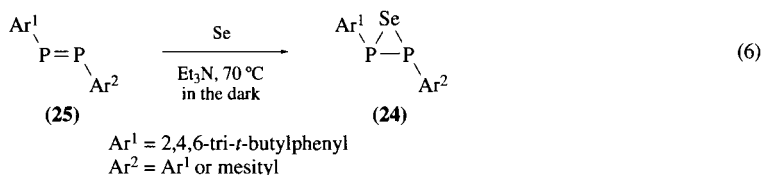
Ad = 1-adamantyl

Scheme 10

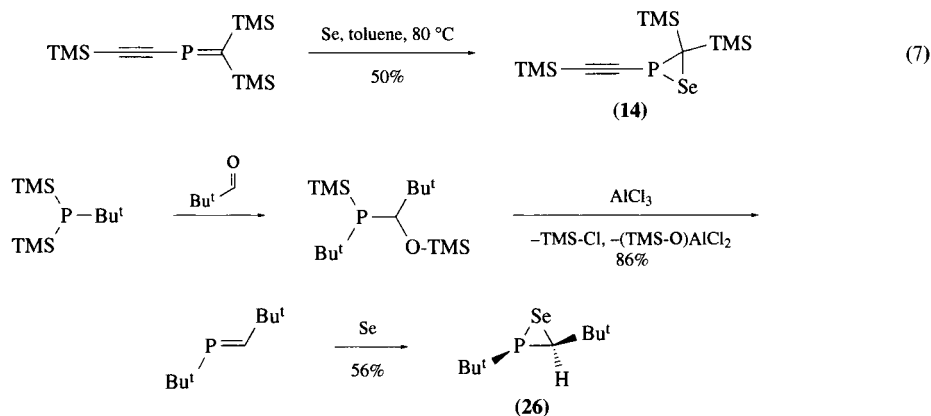
Selenirane and tellurirane derivatives containing group 15 element(s) in their ring skeleton were also synthesized by the chalcogenation of the corresponding double bond compounds containing group 15 element(s). Thus, tellura-arsasilirane (**11**) was obtained by the reaction of the novel silicon-arsenic double bond compound (**23**) with elemental tellurium at 25 °C and isolated in the form of orange crystals (Scheme 11) <95CC253>. Selenadiphosphirane (**24**) has already been synthesized by the thermal reaction of stable diphosphene (**25**) with elemental selenium in triethylamine and it was isolated as pale yellow crystals (Equation (6)) <84CL603>.



Scheme 11



As for the synthesis of chalcogenaphosphirane ring systems two different types of phosphalkenes were treated with elemental chalcogens, where selenaphosphiranes (**14**) and (**26**) were isolated as stable crystalline compounds (Equation (7) and Scheme 12) <85CB3419, 85C320>. The three-membered structure of (**26**) was confirmed by its ³¹P-NMR chemical shift at δ -62.0 and ¹J_{PSe} value (106.5 Hz), and the geometry around the core selenaphosphirane ring of (**26**) (*trans*-configuration) was proposed as illustrated in Scheme 12 by comparing its ²J_{PCH} value with those of analogously substituted phosphirane and azaphosphiridine derivatives <81AG(E)131, 81AG(E)675>.



Scheme 12

1.15.5 REACTIONS OF HETEROATOM-CONTAINING SELENIRANES AND TELLURIRANES

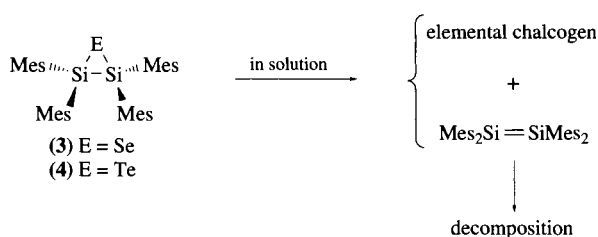
1.15.5.1 Introduction

Since most of the heteroatom-containing seleniranes and telluriranes described in this chapter have been synthesized by taking advantage of kinetic stabilization, their core three-membered rings

are sterically hindered by the bulky substituents attached to the ring elements and hence their intermolecular reactivity was considerably reduced. Therefore, the intrinsic nature of these novel three-membered ring systems have not been fully disclosed yet.

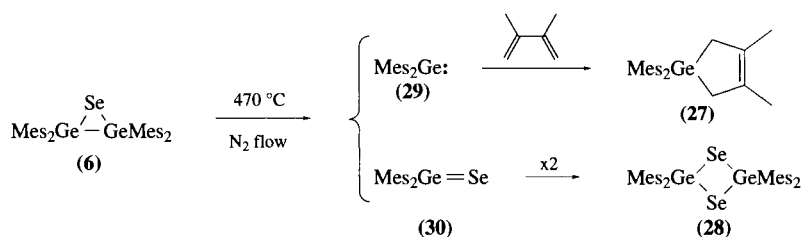
1.15.5.2 Thermal Stability and Some Reactions

Unlike seleniranes, which are known to be thermally unstable (see Chapter 1.07), selenadisilirane (**3**) did not decompose, even on heating to its melting point of 272–274°C. It decomposed slowly, however, if left dissolved in an organic solvent, liberating a reddish precipitate of elemental selenium (Scheme 13). Telluradisilirane (**4**), which is the first example of an isolated tellurirane derivative, was surprisingly stable; it was inert in air and decomposed only at its melting point of 184°C. In solution, (**4**) decomposed slowly, liberating a fine black precipitate of elemental tellurium (Scheme 13).

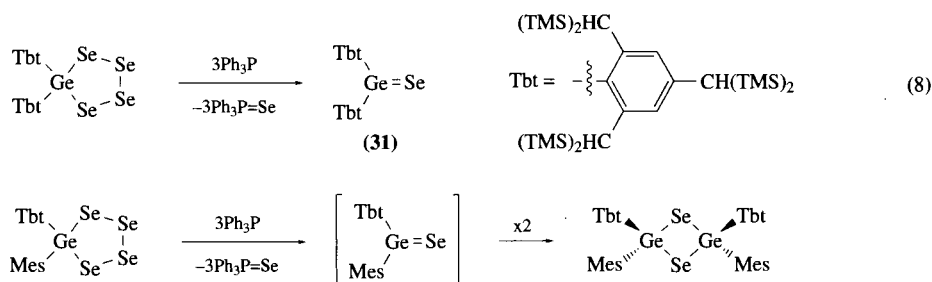


Scheme 13

Selenadigermirane (**6**) was found to be stable up to its melting point of 217–219°C, while the copyrolysis of (**6**) with 2,3-dimethyl-1,3-butadiene at 470°C under flowing nitrogen gave germacyclopentene (**27**), together with 1,3,2,4-diselenadigermetane (**28**). The formation of (**27**) and (**28**) is interpreted in terms of a thermal retrocycloaddition of (**6**) into germylene (**29**) and germaneselone (**30**) followed by the [1 + 4] cycloaddition of (**29**) with butadiene and the head-to-tail dimerization of (**30**) as shown in Scheme 14. Although stable germaneselone (**31**) was successfully isolated by taking advantage of a new steric protection group, 2,4,6-tris[bis(trimethylsilyl)methyl]phenyl <94AG(E)2316>, a sterically less hindered germaneselone, is known to be highly reactive and readily undergoes dimerization (Scheme 15 and Equation (8)) <91TL6877>.

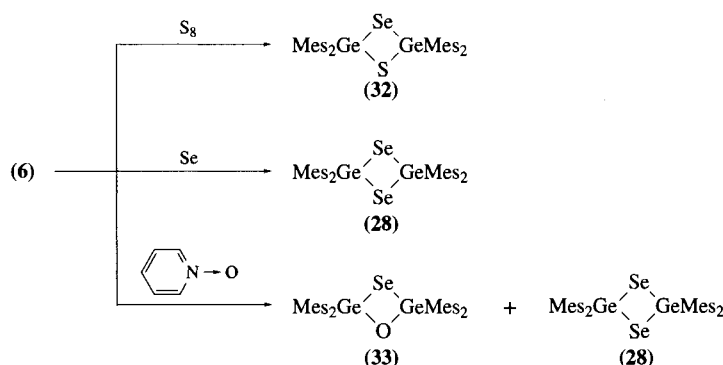


Scheme 14

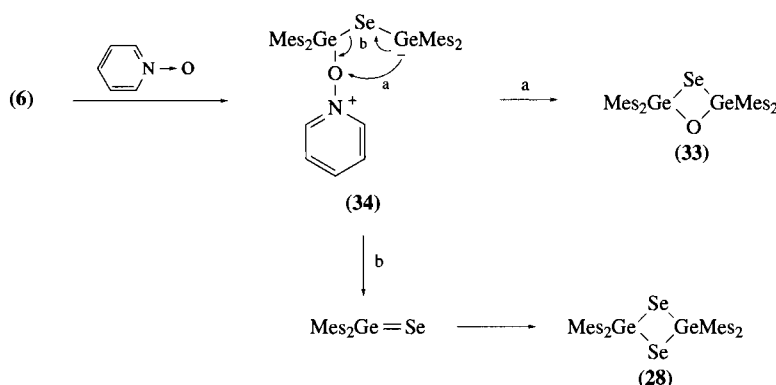


Scheme 15

Intermolecular reactions of selenadigermirane (**6**) with sulfur, selenium, and pyridine *N*-oxide were also investigated (88OM2015). Treatment of (**6**) with elemental sulfur and selenium in refluxing toluene afforded 1,3,2,4-thiaselenadigermetane (**32**) and 1,3,2,4-diselenadigermetane (**28**), the formation of which was reasonably explained by the insertion of one chalcogen atom between the strained Ge—Ge bond (Scheme 16). On the other hand, thermal reaction of (**6**) with pyridine *N*-oxide in refluxing benzene gave two dichalcogenadigermetane derivatives, that is 1,3,2,4-oxaselenadigermetane (**33**) and 1,3,2,4-diselenadigermetane (**28**), in 34% and 38% yields, respectively. The authors postulated a zwitterionic intermediate (**34**) for this reaction as shown in Scheme 17.



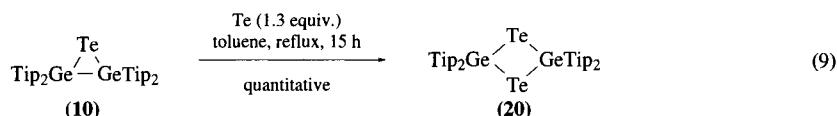
Scheme 16



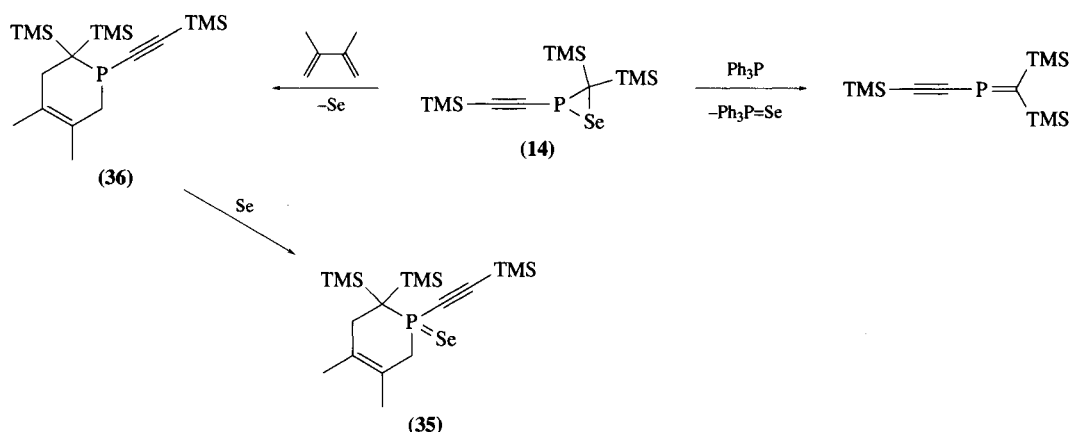
Scheme 17

As for the telluradigermetanes (**7a**) and (**7b**), no information was given for their reactivity except for their noticeable stability towards atmospheric oxygen.

Although neither unimolecular nor intermolecular reactions have been described for thia- and selenadistanniranes, the reaction of telluradistannirane (**10**) with elemental tellurium leading to the formation of 1,3,2,4-ditelluradistannetane (**20**) has been reported as the only example of intermolecular reaction of this family of chalcogenadistanniranes (Equation (9)) (91AG(E)834).



Simple dechalcogenation with triphenylphosphine has been examined for selenaphosphirane (**14**) to regenerate the corresponding phosphalkene (Scheme 18) (85CB3419). Selenaphosphirane (**14**) was also treated with 2,3-dimethyl-1,3-butadiene to give the six-membered phosphine selenide derivative (**35**), the formation of which was interpreted in terms of an initial generation of the corresponding phosphine intermediate (**36**) with an extrusion of the selenium atom followed by the reselenation of the phosphorus atom of (**36**) (Scheme 18).



Scheme 18

1.15.6 OUTLOOK OF THE CHEMISTRY OF HETEROATOM-CONTAINING SELENIRANES AND TELLURIRANES

Although the isolated examples of heteroatom-containing seleniranes and telluriranes are so scarce, and no selenirenes and tellurirenes containing a heteroatom in the three-membered ring skeleton have been synthesized as can be seen in the preceding sections in this chapter, their unique molecular structure and reactivity have attracted much attention of not only the organochalcogen chemists but also of heteroatom chemists in general. 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.

1.16

Three-membered Rings with Two Heteroatoms including Phosphorus to Bismuth

GUITA ETEMAD-MOGHADAM and MAX KOENIG
Université Paul-Sabatier, Toulouse, France

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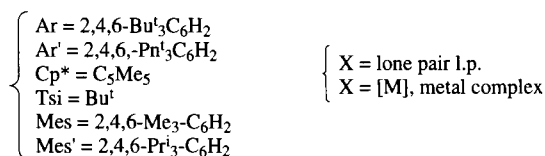
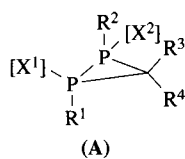
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1.16.1 INTRODUCTION

The scope of the three-membered rings with two phosphorus to bismuth heteroatoms includes essentially heterocyclopropanes with two phosphorus atoms. Few examples are described in the literature for the arsenic derivatives, and there are not yet any antimony or bismuth analogues. Despite this predominance of the phosphorus element, its chemistry is underdeveloped by comparison with its oxygen, nitrogen, and sulfur counterparts. So in the diphosphirane series, the pioneering work of Baudler resulted in the detection of the first diphosphirane in 1977 <77ZN(B)1490>, which was followed by the successful synthesis of various models. During the development of this heterocyclic chemistry, it became apparent that these rings are less stable than their carbon analogues and their thermal stability is highly dependent on the steric requirements of the substituent present. Various methods have been developed between 1984 and 1994 for the synthesis of stable diphosphiranes. Their structural, stereochemical, and thermodynamic parameters were investigated by experimental and theoretical approaches. The chemistry of these strained heterocycles has been investigated in order to make a comparison with pure carbon systems. The behavior of the diphosphiranes under various conditions opened up a versatile approach to the synthesis of tetraphosphacyclohexanes, phosphaaalkenes, 1,3-diphosphapropenes, 1,3-diphosphaallenes, and also to 1,3-diphosphaallyl anion or cation, and diphosphiranyl radical or 1,3-diphosphapropyl biradical intermediates.

The chemistry of diphosphirenes is much less developed and for stable ones, some zwitterionic character is responsible for the stability of the ring. The same strategies, which proved to be valid for the synthesis of diphosphiranes, may be also applied for their higher congeners: phosphaaarsiranes and diarsiranes.

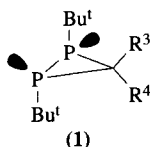
Since three-membered rings with two heteroatoms including phosphorus to bismuth were not treated in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I) we have attempted, in this review, to comprehensively cover the literature up until the middle of 1994, including several reviews already written on three-membered heterocycles <90CRV997, 92CRV1839>. Taking into account the various synthetic routes, and the different strategies for the stabilization of these strained three-membered heterocycles, we have attempted to divide them into several series.



1.16.1.1 Synopsis of Three-membered Rings with Two Heteroatoms Including Phosphorus or Arsenic

1.16.1.1.1 Series 1, Structures (1a–l)

Initiated by Baudler <80PAC755>, series 1 constitute the first diphosphirane syntheses, obtained by cyclocondensation of diphosphides with *gem*-dihalogeno derivatives. The various syntheses and structural determinations (NMR, x-ray diffraction, PES) represented a decisive step in this field.



$$\underline{R^1 = R^2 = Bu^t}$$

$$a: R^3 = R^4 = H$$

$$b: R^3 = H, R^4 = Me$$

$$c: R^3 = R^4 = Me$$

$$d: R^3 = R^4 = Cl$$

$$e: R^3, R^4 = =CH_2$$

$$f: R^3, R^4 = =C(4-Cl-C_6H_4)_2$$

$$g: R^3, R^4 = =N-2,4-Bu^t_2C_6H_3$$

$$h: R^3, R^4 = =N-2-Bu^tC_6H_4$$

$$i: R^3, R^4 = =CMe_2$$

$$j: R^3, R^4 = =P-2,4-Bu^t_2-6-Me-C_6H_2$$

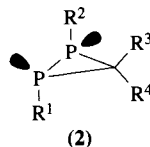
$$k: R^3, R^4 = \begin{array}{c} P-Bu^t \\ \diagdown \\ P-Bu^t \end{array}$$

$$\underline{R^1 = R^2 = P(NMe_2)_3}$$

$$l: R^3 = R^4 = H$$

1.16.1.1.2 Series 2, Structures (2a–s)

Series 2 results from cyclopropanation reactions of diphosphenes or diarsenes with various carbenoids <87T1793, 92CRV1839>. Owing to the presence of bulky substituents on the heteroatoms, these diphosphiranes are stable and their reactivity, in particular their ring opening reactions, have been investigated (*cf.* Section 1.16.4).



$$\underline{R^1 = R^2 = Ar}$$

$$a: R^3 = R^4 = H$$

$$b: R^3 = R^4 = Ph$$

$$c: R^3 = R^4 = fluorenyl$$

$$d: R^3 = R^4 = Cl$$

$$e: R^3 = R^4 = Br$$

$$f: R^3 = Ph, R^4 = Cl$$

$$g: R^3 = Me, R^4 = Cl$$

$$h: R^3 = Ph, R^4 = Br$$

$$i: R^3, R^4 = =CMe_2$$

$$j: R^3, R^4 = \triangle$$

$$k: R^3 = R^4 = =CCl_2$$

$$\underline{R^1 = Ar, R^2 = Ar'}$$

$$l: R^3 = R^4 = Cl$$

$$\underline{R^1 = Ar, R^2 = Cp^*}$$

$$m: R^3 = R^4 = H$$

$$n: R^3 = H, R^4 = TMS$$

$$\underline{R^1 = Ar, R^2 = Tsi}$$

$$o: R^3 = R^4 = Cl$$

$$p: R^3 = R^4 = Br$$

$$\underline{R^1 = R^2 = Ar'}$$

$$q: R^3 = R^4 = Cl$$

$$\underline{R^1 = R^2 = Cp^*}$$

$$r: R^3 = R^4 = H$$

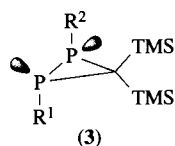
$$s: R^3 = H, R^4 = TMS$$

1.16.1.1.3 Series 3, Structures (3a–v)

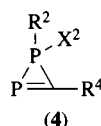
Cyclopropanation reactions with phosphalkenes and phosphinidenes are involved in this series. The stability of this class of diphosphiranes is related to the presence of intracyclic carbon substituents (trimethylsilyl), various *P*-functionalized diphosphiranes can be obtained in this way <93CB645, 93S763>.

1.16.1.1.4 Series 4, Structures (4a–e)

Series 4 consists of unsaturated three-membered rings: diphosphirenes and diphosphirenium salts. Their stability can be attributed to the participation of resonance structures <91AG(E)90, 92AG(E)1055>.



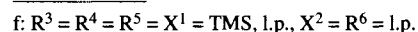
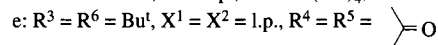
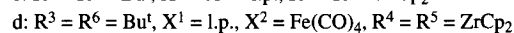
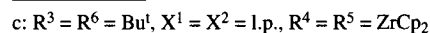
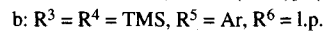
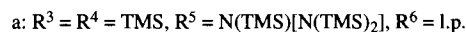
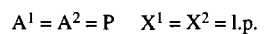
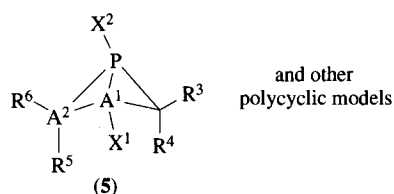
a: $R^1 = \text{Cl}, R^2 = \text{CH}(\text{TMS})_2$	m: $R^1 = \text{Cp}^*, R^2 = \text{NPr}^i_2$
b: $R^1 = \text{Cl}, R^2 = \text{N}(\text{TMS})_2$	n: $R^1 = \text{Bu}^t, R^2 = \text{NPr}^i_2$
c: $R^1 = \text{Cl}, R^2 = \text{Cp}^*$	o: $R^1 = \text{Bu}^t, R^2 = \text{Ph}$
d: $R^1 = \text{Cl}, R^2 = \text{Ph}$	p: $R^1 = R^2 = \text{Ph}$
e: $R^1 = \text{Cl}, R^2 = \text{CH}_2\text{CH}_2\text{Cl}$	q: $R^1 = -\text{C}\equiv\text{C}(\text{TMS}), R^2 = -\text{C}=\text{C}=\text{C}(\text{TMS})_2$
f: $R^1 = \text{Cl}, R^2 = \text{Bu}^t$	r: $R^1 = \text{H}, R^2 = \text{NPr}^i_2$
g: $R^1 = \text{Cl}, R^2 = \text{NPr}^i_2$	s: $R^1 = \text{Cl}, R^2 = \text{CH}(\text{TMS})_2$
h: $R^1 = \text{Br}, R^2 = \text{Bu}^t$	t: $R^1 = \text{N}(\text{TMS})_2, R^2 = \text{NPr}^i_2$
i: $R^1 = \text{Br}, R^2 = \text{NPr}^i_2$	u: $R^1 = \text{PNPr}^i_2, R^2 = \text{NPr}^i_2$
j: $R^1 = \text{I}, R^2 = \text{NPr}^i_2$	v: $R^1 = \text{AsPh}_2, R^2 = \text{NPr}^i_2$
k: $R^1 = \text{NH}(\text{TMS}), R^2 = \text{NPr}^i_2$	
l: $R^1 = \text{PPh}_2, R^2 = \text{NPr}^i_2$	



- a: $R^2 = \text{NPr}^i_2, X^2 = \text{l.p.}, R^4 = \text{N}(\text{TMS})\text{Pr}^i$
 b: $R^2 = \text{CEt}_3, X^2 = =\text{NAr}, R^4 = \text{Bu}^t$
 c: $R^2 = \text{CEt}_3, X^2 = =\text{NBu}^t, R^4 = \text{Bu}^t$
 d: $R^2 = X^2 = R^4 = \text{NPr}^i_2$
 e: $R^4 = \text{Bu}^t, R^2, X^2 =$

1.16.1.1.5 Series 5, Structures (5a–f)

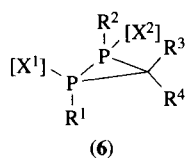
In the series 5 polycyclic models, the diphosphirane structure is inserted into a butterfly or more complex environment $\langle 87\text{AG}(\text{E})1011, 90\text{CB}67, 90\text{PS}(49)297 \rangle$.



1.16.1.1.6 Series 6, Structures (6a–q)

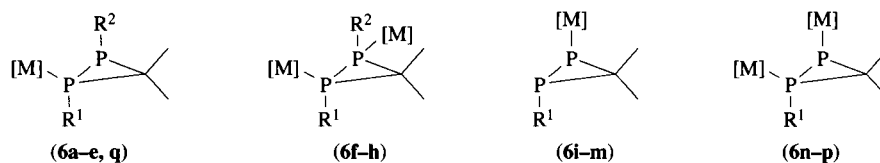
The series 6 diphosphiranes are stabilized by transition metal complexes and are prepared by $[2 + 1]$ -cycloaddition reactions of carbenoids to diphosphene complexes.

Four classes of compounds can be distinguished: those with two organic substituents on phos-



- a: $R^1 = \text{CH}(\text{TMS})_2$, $X^1 = \text{l.p.}$, $R^2 = \text{Cl}$, $X^2 = \text{Fe}(\text{CO})_4$, $R^3 = R^4 = \text{TMS}$
b: $R^1 = \text{Mes}$, $X^1 = \text{l.p.}$, $R^2 = \text{Mes}$, $X^2 = \text{Fe}(\text{CO})_4$, $R^3 = R^4 = \text{H}$
c: $R^1 = \text{Mes'}$, $X^1 = \text{l.p.}$, $R^2 = \text{Mes'}$, $X^2 = \text{Fe}(\text{CO})_4$, $R^3 = R^4 = \text{H}$
d: $R^1 = \text{Cp}^*$, $X^1 = \text{Cr}(\text{CO})_5$, $R^2 = \text{Cp}^*$, $X^2 = \text{l.p.}$, $R^3 = R^4 = \text{H}$
e: $R^1 = \text{Cl}$, $X^1 = \text{l.p.}$, $R^2 = \text{Ph}$, $X^2 = \text{W}(\text{CO})_5$, $R^3 = R^4 = \text{TMS}$
f: $R^1 = \text{Mes}$, $X^1 = \text{Fe}(\text{CO})_4$, $R^2 = \text{Mes}$, $X^2 = \text{Fe}(\text{CO})_4$, $R^3 = R^4 = \text{H}$
g: $R^1 = \text{Mes'}$, $X^1 = \text{Fe}(\text{CO})_4$, $R^2 = \text{Mes'}$, $X^2 = \text{Fe}(\text{CO})_4$, $R^3 = R^4 = \text{H}$
h: $R^1 = \text{Ph}$, $X^1 = \text{Cr}(\text{CO})_5$, $R^2 = \text{Ph}$, $X^2 = \text{Cr}(\text{CO})_5$, $R^3 = R^4 = \text{H}$
i: $R^1 = \text{Ar}$, $X^1 = \text{l.p.}$, $R^2 = \text{FeCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = R^4 = \text{H}$
j: $R^1 = \text{Ar}$, $X^1 = \text{l.p.}$, $R^2 = \text{RuCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = R^4 = \text{H}$
k: $R^1 = \text{Ar}$, $X^1 = \text{l.p.}$, $R^2 = \text{FeCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = R^4 = \triangle$
l: $R^1 = \text{Ar}$, $X^1 = \text{l.p.}$, $R^2 = \text{RuCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = R^4 = \triangle$
m: $R^1 = \text{H}$, $X^1 = \text{l.p.}$, $R^2 = \text{FeCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = R^4 = \text{TMS}$
n: $R^1 = \text{H}$, $X^1 = \text{Cr}(\text{CO})_5$, $R^2 = \text{FeCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = R^4 = \text{TMS}$
o: $R^1 = \text{H}$, $X^1 = \text{Cr}(\text{CO})_5$, $R^2 = \text{FeCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = \text{TMS}$, $R^4 = \text{Ph}$
p: $R^1 = \text{TMS}$, $X^1 = \text{Cr}(\text{CO})_5$, $R^2 = \text{FeCp}^*(\text{CO})_2$, $X^2 = \text{l.p.}$, $R^3 = \text{TMS}$, $R^4 = \text{Ph}$
q: $R^1 = \text{Ph}$, $X^1 = \text{l.p.}$, $R^2 = \text{CH}_2\text{Bu}^t$, $X^2 = \text{W}(\text{CO})_5$, $R^3 = \text{H}$, $R^4 = \text{C}(\text{Me})=\text{CH}_2$

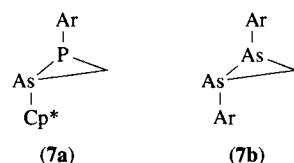
phorus atoms in which one (**6a–e, q**) or both (**6f–h**) phosphorus lone pairs are metallated, and those in which one substituent is replaced by a metal complex fragment and one (**6n–p**) or both (**6i–m**) phosphorus lone pairs are nonmetallated (Scheme 1) <85JOM(282)53, 90JOM(399)C4, 93CB1963>.



Scheme 1

1.16.1.1.7 Series 7, Structures (7a–b)

Series 7 includes the diphosphiranes where one or both phosphorus atoms are replaced by arsenic atoms leading to phosphaaarsiranes and diarsiranes <89CB1809, 92ZAAC(610)75>.



1.16.2 SYNTHESIS

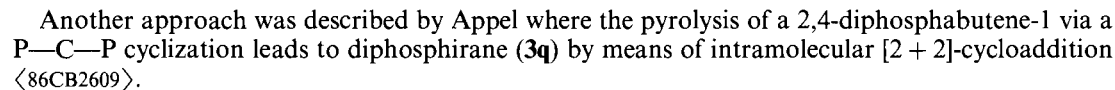
1.16.2.1 Diphosphiranes

1.16.2.1.1 [2 + 1]-Cyclocondensation from P—P and carbon units

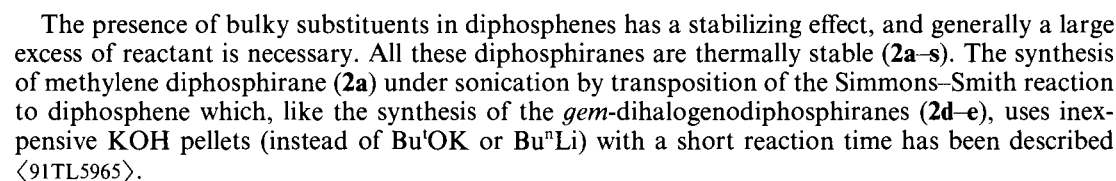
The chemistry of diphosphiranes, phosphorus analogs of cyclopropanes, was first initiated by Baudler *et al.* <77ZN(B)1490, 78ZN(B)1208, 84ZC352> through the [2 + 1]-cyclocondensation of diphosphides with *gem*-dihalogeno derivatives (alkyl- <82ZAAC(486)39>, alkene- <84CB1542>, isocyanide- <87CB421>, and methylenephosphane- <88CB281> dichlorides) in an apolar medium such as pentane

$$\begin{array}{c} \text{Bu}^t \quad \text{Bu}^t \\ | \quad | \\ \text{P} - \text{P} \\ | \quad | \\ 2 \text{ K}^+ \end{array} + \begin{array}{c} \text{Cl} \quad \text{R}^3 \\ \diagdown \quad / \\ \text{C} \\ / \quad \diagdown \\ \text{Cl} \quad \text{R}^4 \end{array} \xrightarrow[\text{low temperature}]{\text{pentane}} \begin{array}{c} \text{Bu}^t \\ | \\ \text{P} \\ / \quad \diagdown \\ \text{P} \quad \text{C} \\ | \quad / \quad \diagdown \\ \text{Bu}^t \quad \text{R}^3 \quad \text{R}^4 \end{array} \quad (1)$$

The intramolecular cyclization of the *P,P*-dihalogenodiphosphinomethane by treatment with a potassium-sodium alloy at low temperature, realized by Lutsenko and co-workers [79ZOB470, 80ZOB689, 84ZC345], constituted another approach to three-membered rings (series 1), obtained as an 80:20 mixture with its dimer (Equation (2)). Koenig and co-workers have described a similar chemistry [93TH 116-01]. The reaction has been carried out at 40°C in the presence of magnesium or at 20°C under sonication in the presence of lithium wire affording the corresponding methylene diphosphirane (Equation (2)) (series 2)

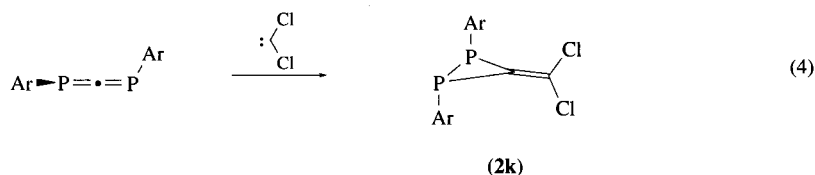


Since 1981, the availability of stable diphosphenes $\langle 81JA4587 \rangle$ has made it possible to apply the cyclopropanation reaction of alkenes to these phosphorus-phosphorus double bonds. The [2 + 1]-cycloaddition reactions of carbenoids (diazo derivatives, mono- and dihalogeno- or ethylenic carbenes, and sulfur ylide) with symmetrical and unsymmetrical *trans* diphosphenes were developed by Koenig. In all cases, the cyclopropanation reaction is stereoselective, and the corresponding *trans* diphosphiranes are obtained in good yield (Equation (3)) $\langle 86TL1145, 87PS(30)425, 87T1793, 89CC593, 89TL177 \rangle$.



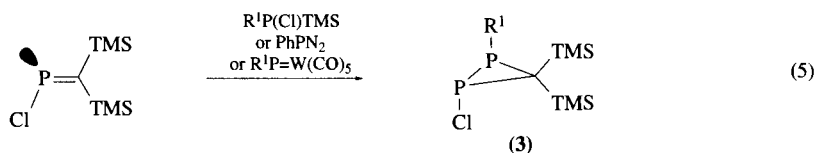
Diphosphiranes were also obtained in the reaction of dichlorocarbene with sterically protected 1,3-diphosphaallene in 34% yield (Equation (4)) ^{91CC124}. The reaction may proceed via a phos-

phinidenephosphirane as an intermediate followed by a rearrangement leading to the thermodynamically stable 3-dichloromethylene-diphosphirane (**2k**).

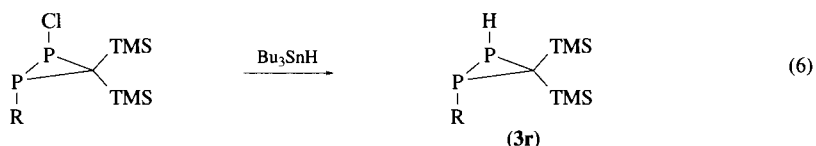


1.16.2.1.4 Cycloaddition from $\text{P}=\text{C}$ and phosphorus units

Another important approach, involving the cyclopropanation reaction of phosphinidenes with various phosphaaalkenes (Equation (5)) was first mentioned by Niece and co-workers (series 3) <83PS(18)35>.



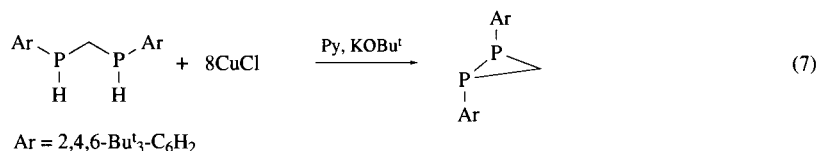
A similar scheme was proposed by Carrié leading to a *P*-chlorodiphosphirane <89NJC891>. This kind of chemistry has been extended by Niece in the reaction of chloro(trimethylsilyl)phosphanes with *P*-chlorophosphaaalkenes leading to *P*-chlorodiphosphiranes via a 1,2-diphosphapropene-2 intermediate <90CB1245>. The *P*-bromo- and *P*-iododiphosphiranes are also accessible by an exchange reaction with the corresponding halosilanes. The reaction of terminal phosphinidene complexes with phosphaaalkenes at 120°C in toluene leading to the corresponding uncomplexed diphosphiranes was described by Mathey <93S763>. The reduction of the *P*-chlorodiphosphirane by tributylstannane leads to the isolated diphosphirane (**3r**) bearing a $\text{P}-\text{H}$ bond (Equation (6)) <93CB645>.



1.16.2.1.5 Miscellaneous

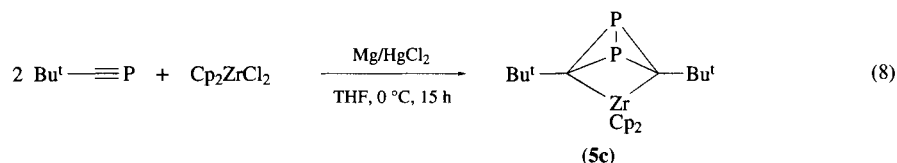
The reaction of triphosphenium salt with dichloromethane, involving the condensation of P_2 and carbon units, was described by Schmidpeter and co-workers <86AG(E)253, 86ZN(B)444>. The formation of the diphosphoniiodiphosphirane tetrachloroaluminate (**11**) suggests an initial chloromethylation followed by cleavage of the resulting intermediate and formation of the three-membered ring compound by [2 + 1] addition of a phosphoniophosphanedyl to the $\text{P}=\text{C}$ system. The unexpected synthesis of free or complexed *P*-chlorodiphosphiranes from the anionic hydrido iron complex and *P*-chlorophosphaaalkene was also reported <87CC639>.

Another synthesis of diphosphiranes was described by Stelzer via deprotonation of the bis-secondary phosphines with strong organic bases in the presence of CuCl and pyridine (Equation (7)) <90CB653>.

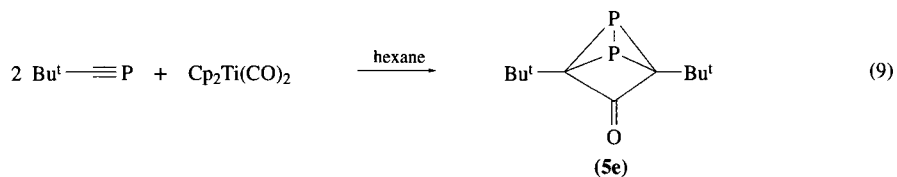


1.16.2.2 Polycyclic Diphosphiranes

Several specific syntheses of polycyclic diphosphiranes have been reported in the literature. Polycycles containing a diphosphirane ring were described by Regitz from the reaction of conjugated dienes with phosphalkynes <87AG(E)1011>. The synthesis and the x-ray structure of tetracyclic triphosphane bearing a diphosphirane system was realized by Märkl from the reaction of 1,3-azaphosphinines and Bu^t-phosphalkyne on heating for 48 h <88AG(E)389>. The decisive step in the formation of the diphosphirane unit is an ene reaction. The syntheses of triphosphabicyclobutanes involving an intramolecular P=P and P=C [2 + 2]-cycloaddition were also reported <88AG(E)957, 88CC945>. A complementary access to polycyclic diphosphiranes involves the cyclotelomerization of a phosphalkyne in the coordination sphere of a transition metal. The reactions of Bu^t-phosphalkyne with zirconocene <87AG(E)764> and with vanadium complexes <87AG(E)908> were reported (Equation (8)).



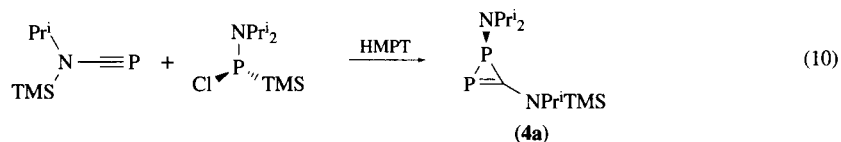
In both cases, the metal complex fragments were incorporated into the products having the diphosphirane ring and their structures were established by x-ray analysis. An analogous reaction of phosphalkyne with a titanium complex was described by Cowley (Equation (9)), but in that case, the polycyclic diphosphirane spontaneously leaves the coordination sphere of the transition metal <88AG(E)837>.



The unusual formation of the germadiphosphatricyclooctene from a phosphalkyne and an arylgermene was reported by Escudié, and its structure was established by x-ray analysis <93CC569>.

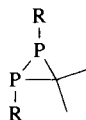
1.16.2.3 Diphosphirenes

The synthesis of 1*H*-diphosphirenes was realized by [2 + 1]-cycloaddition of iminophosphanes to Bu^t-phosphalkyne at low temperature in hexane <89TL459>. These thermally unstable air- and moisture-sensitive diphosphirenes undergo an isomerization to the thermodynamical isomers, azadiphosphetines. The synthesis and the structure of the first 1*H*-diphosphirene (**3u**) was reported by Niecke and co-workers upon reaction of the functionalized aminophosphane with the amino-substituted phosphalkyne under mild conditions (Equation (10)) <89AG(E)1673>.



The stability of the ring has been partly explained by some zwitterionic character and participation of resonance structures due to the amino-substituent. Starting from complexed phosphinidene and using the same method, Mathey and co-workers described the synthesis of the corresponding W(CO)₅—diphosphirene complex <93PS(77)229>.

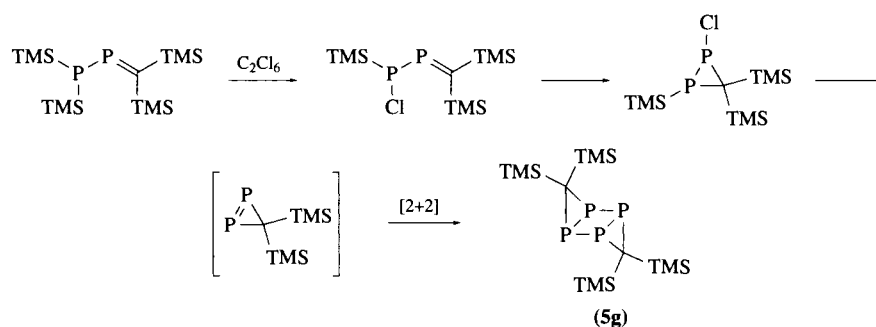
Whereas diazirines exist only in the 3*H*-form with an intracyclic N=N bond, and are widely used as precursors of electrophilic carbenes, their 3*H*-diphosphirene analogues bearing an intracyclic P=P bond are unstable and are postulated only as intermediates <94CB969>. Actually, Niecke and co-workers <91AG(E)90> described the reaction of persilylated 1,2-diphosphapropene-2 with hexachloroethane under mild conditions giving a *trans* 1,2,4,5-tetraphosphatricyclo[3.1.0.0]hexane (**5g**) (Scheme 2). Its structure was established by x-ray analysis (Table 1) and its formation can be

Table 1 Structural data of diphosphiranes and diphosphirenes^a.

Compound	No.	Bond angles, deg			Bond lengths, Å			Ref.
		P—C—P	P—P—C	C—P—R	P—P	P—C	P—R	
	(1k)	72.35	53.83		2.175		1.888	88MI 116-01
	(1f)	75.2	52.2 52.6	107.7 108.2	2.195	1.794 1.804	1.861 1.883	84CB1542
	(2k)	78.9	50.4 50.7	128.8 109.8	2.277	1.789 1.795	1.875 1.860	91CC124
	(2d)	74.3	52.7	101.8	2.245	1.863	1.858	90JOC5750
	(2o)	71.4	53.7 54.9	112.3 (Tsi) 97.8 (Ar)	2.117	1.801 1.827	1.803 (Tsi) 1.783 (Ar)	94UP 116-01
	(3u)	69.8	55.0 55.3		2.159	1.184 1.891	2.238 1.693	93CB645
	(4a)		52.3 48.9	111	2.218	1.702 1.787	1.702	89AG(E)1673
	(4d)	73.9	52.8 53.3		2.095	1.747 1.737	1.643 1.637	91JA8160
	(4e)	75.9	53.3 50.8		2.108	1.74 1.68	1.77 1.80	92AG(E)1055
	(5a)	70.0	55.1		2.158	1.880 1.883	2.215 2.226	88CC945
	(5g)	72.1	53.9	102.0	2.204	1.871 1.873	2.245	91AG(E)90

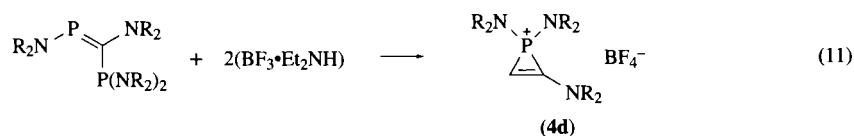
^aAll the data are from x-ray crystal.

attributed to the cyclodimerization of a 3*H*-diphosphirene intermediate. This [2 + 2]-cyclo-dimerization is typical of diphosphenes with (*Z*) configurations.

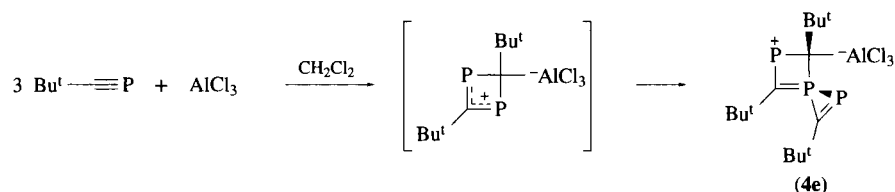


Scheme 2

On another side, the synthesis of the diphosphirenium salt (**4d**) by treatment of amino-substituted 1,3-diphosphapropene with boron trifluoride-ethylamine complex at room temperature was reported (Equation (11)) <91JA8160, 94JA6149>. Its structure has been established by x-ray diffraction study and shows a substantial participation of resonance structures and the ionic character of the salt.



Regitz and co-workers have reported a spirocyclotrimerization of a stable phosphalkyne with aluminum trichloride in a 3 : 1 molar ratio (Scheme 3) <92AG(E)1055>. The reaction gives a betaine with the incorporation of the Lewis acid and its structure, bearing a spiranic diphosphirene, was confirmed by x-ray crystal structure analysis (*cf.* (**4e**), Table 1).

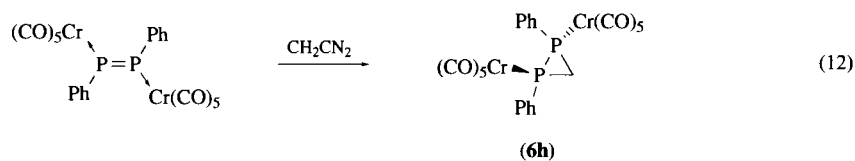


Scheme 3

The addition of the Lewis base (DMSO) to this betaine gave the tri-phospha-Dewar benzene derivatives via an unstable diphosphirene ring.

1.16.2.4 Complexes of Diphosphiranes

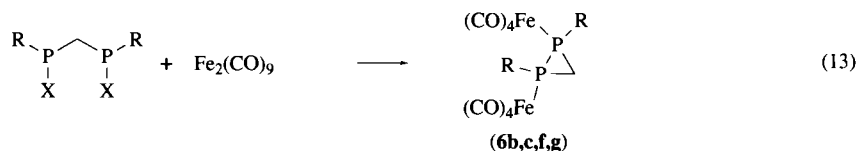
The [2 + 1]-cycloaddition of diazomethane to a diphosphene complex leading to chromium diphosphirane complex (**6h**) was first realized by Huttner (Equation (12)) <85JOM(282)53>.



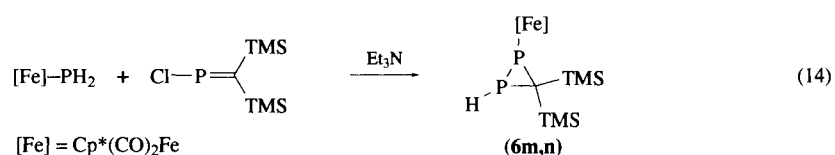
A related chemistry was reported by Weber with iron- and ruthenium-substituted diphosphenes and sulfur ylides. Thus, the presence of 1,2-diphosphaspiro[2.2]pentane system linked to the metal through an Fe—P bond was confirmed by x-ray structure <87JOM(327)C63, 88OM978>. The

iminodiphosphiranes were also obtained by a similar approach from metallodiphosphenes and trifluoromethyl isocyanide <92CRV1839>.

The bidentate halogenophosphines were dehalogenated by $\text{Fe}_2(\text{CO})_9$ to give complexes of diphosphiranes (Equation (13)) <90JOM(399)C4>.



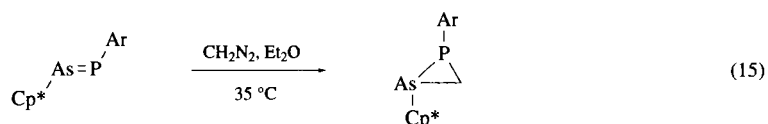
More recently, Weber realized the synthesis of an iron complex of diphosphirane by reaction of the phosphine iron complex ($[\text{Fe}]-\text{PH}_2$) with *P*-chlorophosphaalkene (Equation (14)). It was converted into the iron chromium complex, whose structure was elucidated by x-ray analysis <92CB1553>.



Another reaction for the synthesis of diphosphirane complexes by thermal rearrangement of metallo-1,2-diphosphapropenes was described by the same authors <93CB1963>. Finally, the synthesis of the $\text{W}(\text{CO})_5$ -diphosphirane complex was realized by the ene reaction of phosphalkyne with the corresponding phosphalkene complex <93T10279>.

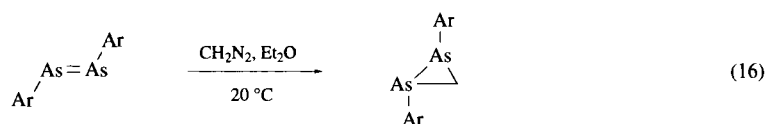
1.16.2.5 Phosphaarsiranes

The interaction of phospharsenes with diazomethane opened a synthetic route to three-membered heterocycles containing phosphorus, arsenic, and carbon atoms. Jutzi has described the creation of phosphaarsiranes as a crystalline product by treatment of the corresponding phospharsene with diazomethane at low temperature (Equation (15)) <92ZAAC(610)75>.



1.16.2.6 Diarsiranes

The synthesis of diarsirane by exposing diarsene to an ethereal solution of diazomethane at room temperature was reported by Weber (Equation (16)) <89CB1809>.

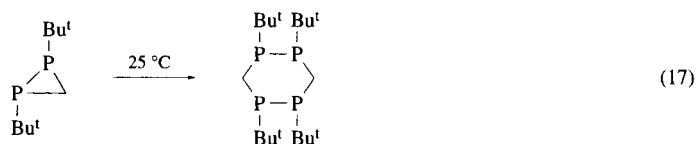


1.16.3 PHYSICOCHEMICAL DATA AND THEORETICAL CALCULATIONS

1.16.3.1 Stability

Whereas the diphosphiranes exhibit a lower stability than the cyclopropane homologues, they are the stable solids purified by crystallization or column chromatography. Their thermal stability

is highly dependent on the steric requirements of the substituents. Thus, whereas the methylene derivative (**1a**) easily dimerizes to six-membered cyclodicarbaphosphane at room temperature, its analogous (**2a**) is thermally stable, owing to the presence of sterically hindered 2,4,6-Bu^t₃-phenyl substituents on the phosphorus atoms (Equation (17)).



So, the diphosphiranes can be stabilized by the bulky substituents on the phosphorus atoms (**2a-s**) or on the intracyclic carbon atom (series 3), by aromaticity and resonance character (series 4), by the presence of a polycyclic or butterfly environment (series 5), or by complexation (series 6).

1.16.3.2 Structural and Spectroscopic Data

1.16.3.2.1 NMR studies

As do all the three-membered carbon–phosphorus rings, the ³¹P, ¹³C, and ¹H chemical shifts of diphosphiranes appear at high fields. The anisotropy induced by the ring strains is dependent on the steric hindrance and the electronegativity of the ring substituents. Thus, the ³¹P spectra of noncomplexed diphosphiranes (series 1, 2, and 3) comprise a range from 0 ppm to –200 ppm. For butterfly diphosphiranes (series 5), the supplementary ring strain involves a shielding of the ³¹P resonance ($\delta^{31}\text{P} = -347$ for (**5e**) <88AG(E)837>). The variations of the ³¹P chemical shift against the nature of *P*-substituents are reported in Figure 1 (e.g., for the unsymmetrical diphosphirane (**3e**), $\delta_{\text{P-Cl}} = -23$ and $\delta_{\text{P-CH}_2\text{CH}_2\text{Cl}} = -155$ <93S763>).

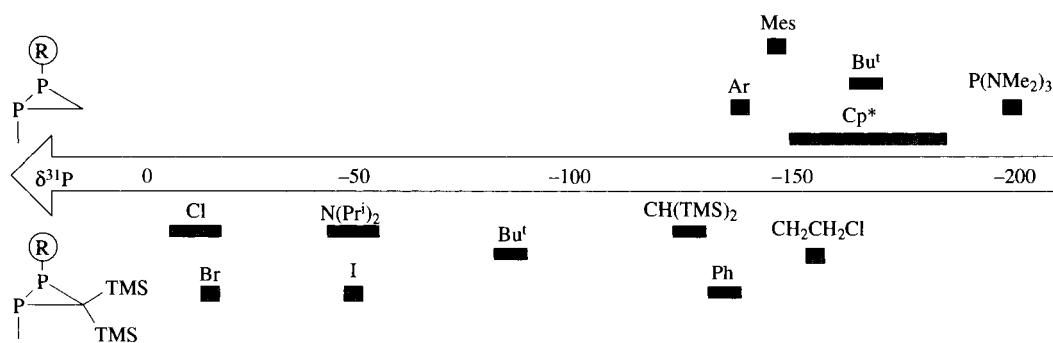


Figure 1 Influence of the *P*-substituents on the ³¹P chemical shifts of diphosphiranes.

The $\delta^{31}\text{P}$ of diphosphiranes are also dependent on the nature of the intracyclic carbon substituents (e.g., $\delta = -141$ for (**2a**) <86TL1145>, and $\delta = -70$ for (**2d**) <87T1793>) (Figure 2). The homocyclic diphosphiranes have a *trans* stereochemistry. The *cis* isomers, obtained after substitution, were detected by ³¹P NMR whereas the polycyclic homologues were isolated in *cis* form.

Although the detection of the intracyclic carbon atom in ¹³C NMR is not easily realized in each case (due to high relaxation times), the ¹³C chemical shift covers an extremely large range (e.g., $\delta^{13}\text{C} = 6$ for (**1a**) <78ZN(B)1208, 84ZC345>, 86 for (**2d**) <87T1793>, and 180 for (**1g**) <88CB281>) (Figure 3).

The ¹J_{PP} coupling constants have a negative sign and their absolute values vary widely: for example 38 Hz (**1g**) <J_{PP} < 276 Hz (**6n**) <92CB1553>. The intracyclic ¹J_{CP} coupling constants also have a negative sign and their values range from 15 Hz for (**5e**) <88AG(E)837> to 101 Hz in (**2o**) <89CC593>. The proton directly bonded to an intracyclic phosphorus atom induces a very low ¹J_{PH} coupling constant (¹J_{PH} = 153 Hz for (**3r**) <93CB645> and ¹J_{PH} = 149 Hz for (**3s**) <90CC507>). These

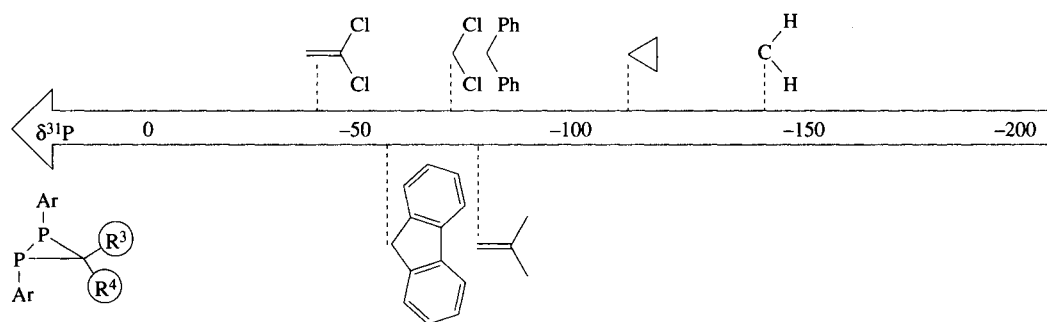


Figure 2 Influence of the C-substituents on the ^{31}P chemical shifts of diphosphiranes.

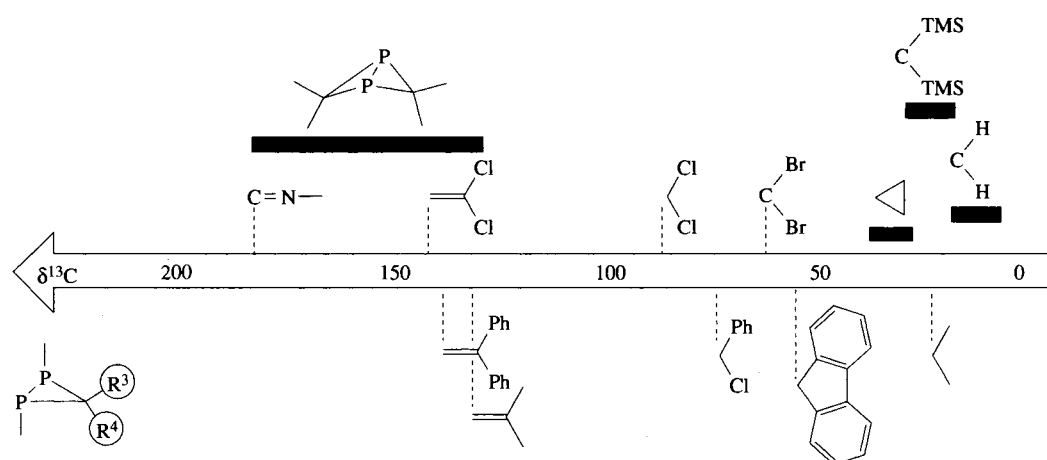


Figure 3 Influence of the C-substituents on the ^{13}C chemical shifts of diphosphiranes.

values increase when the diphosphirane is bonded to a metallic complex ($^1J_{\text{PH}} = 304 \text{ Hz}$ in (6n) <92CB1553>).

1.16.3.2.2 Structural data

About 20 structural studies of the diphosphirane and diphosphirene rings in the series 1 to 6 have been described: (1a, f, k, l), (2d, k, o), (3u), (4a, d, e), (5a, b, c, e), (6h, n, o, q). To these structures were added the polycyclic compounds reported by Regitz <87AG(E)764, 87AG(E)908>, Märkl <88AG(E)389>, and Escudié <93CC569>.

The more significant parameters concerning the nonmetallated diphosphirane and diphosphirene rings were collected in Table 1. The x-ray structure of diphosphiranes confirm the *trans* configuration of the substituents. The diphosphirane and diphosphirene rings are very flexible. The ring P—P bond lengths vary between 2.095 Å for (4d) and 2.277 Å for (2k). At the bottom of the range, the P—P bond seems to have some double bond character despite the observations of Nieceke about the instability of 3*H*-diphosphirenes in contrast to 3*H*-diazirines. At the top of the range, the P—P bond length values in diphosphiranes are very close to the P—P bond length values of diphosphanes, despite the considerable strain of these three-membered rings. This is probably due to a strong mixing of the phosphorus lone pairs and the Walsh orbitals, as assigned by theoretical calculations and photoelectron spectroscopy <81CB1004, 92IC2414>.

The intracyclic P—C bond length values cover a wide range: $1.794 \text{ Å} < d_{\text{P-C}} < 1.933 \text{ Å}$ in diphosphiranes (1), (2), (3), and ((6); $1.680 \text{ Å} < d_{\text{P-C}} < 1.737 \text{ Å}$ and $1.740 \text{ Å} < d_{\text{P-C}} < 1.787 \text{ Å}$ in diphosphirenes (4).

1.16.3.3 Theoretical Calculations

Based on PES spectra and semiempirical calculations, the HOMO of the diphosphirane was assigned to the symmetrical combination of the phosphorus lone pairs which is strongly coupled with the $\sigma_{\text{P-P}}$ orbital $\langle 81\text{CB1004}, 92\text{IC2414} \rangle$. So, the oxidation of the lone pair destabilizes the cyclic form by weakening both the P—P and P—C bonds, and promotes the cheletropic reactions (see Section 1.16.4.4).

The *cis/trans* stereochemistry of diphosphiranes is investigated by MNDO calculations of dipole moments in terms of substituent effects on intracyclic phosphorus and carbon atoms. These results compared to experimental dipole moment measurements show the presence of preferential *trans* isomers $\langle 92\text{CJC2834} \rangle$.

1.16.3.3.1 Mechanism of the addition of carbenoids to diphosphene: theoretical approach

Although carbene addition to alkenes has been studied extensively, little work has been done on the reactivity of carbenes toward heteroatomic π -bonds; in particular, the problem of the preferential site of addition (π -system or lone pair) has not been fully elucidated $\langle 72\text{TL4347}, 78\text{JOC2216} \rangle$. The theoretical approaches have been investigated using *ab initio* theory (SCF + CI level) concerning addition of singlet methylene to unsubstituted diphosphene $\langle 92\text{IC2414} \rangle$.

A priori, an addition mechanism similar to that observed for ethylene was likely for the diphosphene system; the diffuse character of the P=P π -bond and the energetic positions of $\pi_{\text{P=P}}$ and $\pi^*_{\text{P=P}}$ orbitals could lead to differences in the interactions governing the approach of the carbene. This heteroatomic system is characterized in its ground state by a quasi-degeneracy of $\pi_{\text{P=P}}$ orbital and n_{P} combination of the phosphorus lone pairs. Among the two possible mechanisms (addition to the π system and addition to the lone pair of phosphorus), the preferential process corresponds to a π addition leading to the diphosphirane ring: the approach of the carbene occurring in the σ plane of the molecule with the displacement of the methylene group toward the middle of the P—P bond, a further pivotal motion of this group leading to ring formation. The change in phosphorus lone pair hybridization only takes place at the end of the reaction at $d < 2.2 \text{ \AA}$, and the reaction occurs without any energy barrier.

Distinguishing between the electrophilic and nucleophilic phases is more difficult than in the case of addition to ethylene. The lower position of the $\pi^*_{\text{P=P}}$ orbital with respect to the $\pi^*_{\text{C=C}}$ orbital leads to a more important $\pi^*_{\text{P=P}} \leftrightarrow n_{\text{CH}_2}$ interaction throughout the reaction pathway. The calculations show that the reaction is stereospecific, giving a *trans* product, the preferential isomer of diphosphirane ($\Delta E_{\text{trans-cis}} = -102.7 \text{ kJ mol}^{-1}$) $\langle 92\text{IC2414} \rangle$.

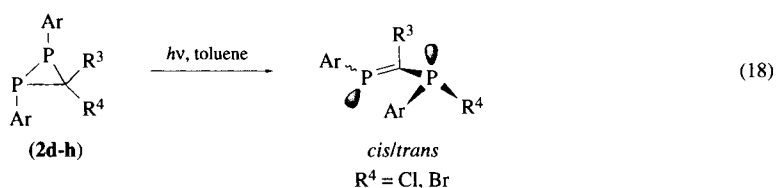
1.16.4 CHEMICAL PROPERTIES

Experimental and theoretical approaches of electrocyclic reactions constitute a well-known field in cyclopropane series. In contrast, in heterocyclic chemistry, and in particular in phosphorus chemistry, with few exceptions, electrocyclic reactions are rare. The presence of heteroatoms in the molecules makes the application of the Woodward–Hoffmann rules $\langle 69\text{AG(E)781} \rangle$ to the ring-opening process of diphosphiranes more difficult. However, the functionalized diphosphiranes constitute the appropriate models for these studies since i; owing to the presence of the skeleton disymmetry and the enthalpy difference $\Delta H_{\text{P-P}}$ and $\Delta H_{\text{P-C}}$, their ring-opening reactions with preferential P—P bond cleavage can occur under photochemical, thermal, anionic or cationic reaction conditions, and ii; due to the presence of bulky substituents on phosphorus atoms, the ring-opening products are stable and can be obtained in different conformations $\langle 91\text{JOC3438} \rangle$. Moreover, the fragmentation can occur by the cheletropic reactions in oxidative conditions giving rise to a series of phosphalkenes. Thus, the diphosphiranes can be considered as potential precursors of phosphalkenes, 1,3-diphosphapropenes, 1,3-diphosphaallenes, but also 1,3-diphosphaallyl anion or cation, and diphosphiranyl radical or 1,3-diphosphapropyl biradical intermediates. Diphosphiranes react with anionic transition metal complexes leading to σ - or π -diphosphaallyl cations.

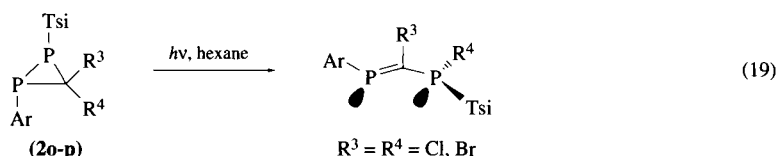
1.16.4.1 Photochemical Reactions

The irradiation of functionalized symmetrical diphosphiranes (**2d–h**) gave largely 1,3-diphosphapropenes in the *cis* and *trans* configurations in 50–80% yield $\langle 90\text{JOC5750} \rangle$. Their ^{31}P NMR

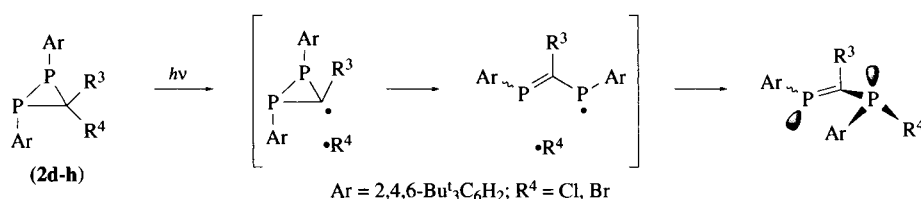
parameters are different and the ratio of *cis*:*trans* isomers is about 10:90 (Equation (18)). The structure of the *trans* isomer has been established by x-ray analysis.



Under the same conditions as above, the unsymmetrical diphosphiranes (**2o-p**) undergo a regio- and stereoselective ring-opening reaction leading quantitatively to only *trans* 1,3-diphosphapropenes (Equation (19)) <89CC593>.



The mechanism of the photochemical ring opening of functionalized diphosphiranes was studied by the spin-trapping technique using α -phenyl Bu^t-nitron (PBN) and *in situ* irradiation in the ESR cavity <90JOC5750>. The diphosphiranyl and diphosphapropenyl radical intermediates were characterized. The generation of a diphosphiranyl radical intermediate can be the consequence of the homolytic rupture of the C—R⁴ bond ($R^4 = \text{Cl}$). This unstable radical, after the preferential P—P bond cleavage, gives the 1,3-diphosphapropenyl radical which undergoes the migration of the halogen radical to one of the two phosphorus atoms, leading to *P*-chloro-1,3-diphosphapropenes (Scheme 4).



Scheme 4

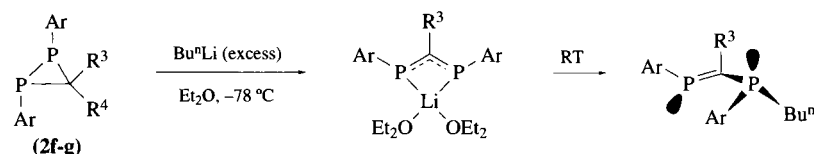
The *cis* and *trans* isomers arise neither from the previous *cis-trans* isomerization of the diphosphiranes nor from the *cis-trans* isomerization of the diphosphapropenes, but presumably they are the consequence of a disrotatory process leading to a planar diphosphaallyl intermediate with *endo-exo* substituents on phosphorus. The MNDO and *ab initio* calculations are in agreement with this mechanism <94IC596>.

1.16.4.2 Reactions with Nucleophiles (Anionic Ring Opening)

1.16.4.2.1 Organolithium reagents

The reaction, at low temperature, of a butyllithium excess on the monohalogenated diphosphiranes (**2f-g**) in diethylether, causes ring opening by cleavage of the P—P bond and leads to a quantitative formation of 1,3-diphosphapropenes (Scheme 5) <89NJC315>. The reaction is stereospecific and gives only the *trans* isomers.

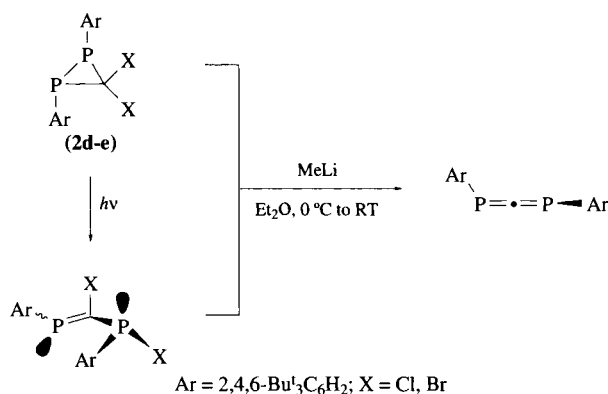
Unlike the cyanocyclopropyl anion <77JA2631>, the cyclic diphosphiranyl anion intermediate is not detectable, but the 1,3-diphosphaallyl anion is observed when the progress of the reaction is followed by ³¹P NMR at low temperature. It appears at $\delta^{31}\text{P} = 64.4$ with a $^1J_{\text{P-Li}} = 40$ Hz, characteristic of covalent phosphorus-lithium bonds <89NJC315>. The *exo-exo* configuration of this intermediate was confirmed by x-ray diffraction <93PS(77)230>. This anion, recrystallized with two molecules of diethylether, has a σ -allyl structure ($d_{\text{P-C}} = 1.71$ Å) and the lithium atom is located in



Scheme 5

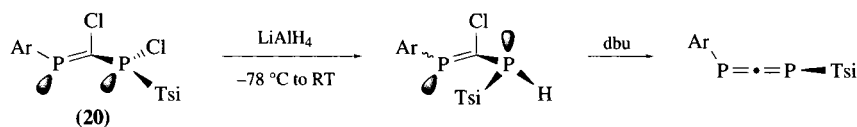
the PCP plane ($d_{\text{P-Li}} = 2.75 \text{ \AA}$). The *exo-exo* configuration of the diphosphaallyl intermediate is consistent with the conrotatory process of the ring opening of the diphosphirane, as predicted by theoretical calculations (92IC2414).

As with the analogous *gem*-dihalogenocyclopropanes (63ACS1683, 84T2805), the *gem*-dihalogenodiphosphiranes (**2d-e**) react with methyllithium at 0°C in diethylether, and lead quantitatively to the 1,3-diphosphaallene (Scheme 6) (89TL177, 89TL187). The reaction does not involve a carbenic insertion in the P—P bond (90PS(49)305) but most likely it occurs by the same anionic ring opening as above via the unstable similar diphosphaallyl anion.



Scheme 6

The *P*-chloro-1,3-diphosphapropenes, obtained by photolysis of the corresponding functionalized diphosphiranes, react with organolithium compounds under the same conditions as their precursors affording the same substituted 1,3-diphosphapropenes or 1,3-diphosphaallene in good yield (Scheme 6) (89TL177). By the same method, the unsymmetrical 1,3-diphosphaallenes were obtained (89CC1732). However, the synthesis of unsymmetrical 1,3-diphosphaallene from the corresponding *P*-chloro-1,3-diphosphapropene (**2o**) (*syn* conformation) does not occur by the organolithium pathway, and it requires a reduction of P—Cl to P—H by LiAlH_4 , followed by a dehydrohalogenation in the presence of Et_3N or DBU as base (Scheme 7) (91HAC221).

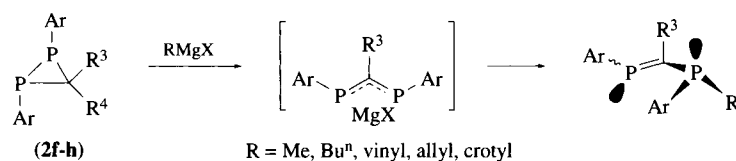


Scheme 7

1.16.4.2.2 Grignard reagents

The monohalogenated diphosphiranes (**2f-h**) as their photochemical isomers, the 1,3-diphosphapropenes, react with saturated and unsaturated organomagnesium compounds leading to a series of substituted 1,3-diphosphapropenes and 1,3-diphosphadienes. The reaction could also involve an anionic ring opening followed by substitution at phosphorus via an allylic anion inter-

mediate detected by ^{31}P NMR spectroscopy ($\delta^{31}\text{P} = 54$) (Scheme 8) <92JOM(436)169>. The reaction requires milder conditions with the opened isomers.

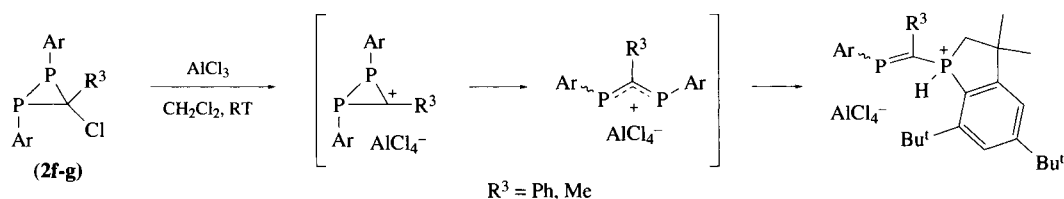


Scheme 8

With *gem*-dihalogenodiphosphiranes, the reaction gives quantitative yields of 1,3-diphosphaallene probably involving the same mechanism as Scheme 8 and an unstable allylic anion intermediate <92JOM(436)169>.

1.16.4.3 Reactions with Electrophiles (Cationic Ring Opening)

The reaction of one equivalent of aluminum trichloride to functionalized diphosphiranes (**2f–g**) in anhydrous solution of dichloromethane at 0°C affords the corresponding phosphonium phosphaaalkenes as main products, with the fragmentation derivatives as byproducts (Scheme 9) <89TL7411>. Starting from the corresponding *P*-chloro-1,3-diphosphapropenes, the formation of byproducts can be avoided <84TL3687, 86AG(E)454, 89TL7411>.

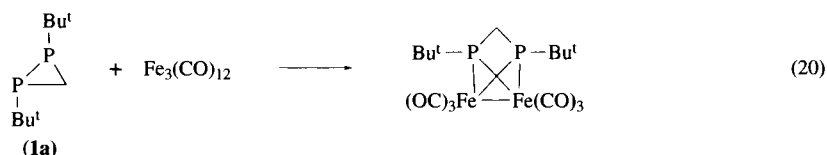


Scheme 9

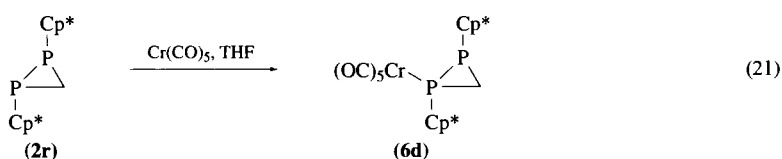
The phosphonium phosphaaalkenes are formed via the diphosphaallyl cation after the cationic rupture of an extracyclic C—Cl bond. Contrary to the photochemical or anionic ring-opening reactions, the cationic intermediates are not detected. The theoretical calculations performed on unsubstituted derivatives reveal for this reaction a P—P bond rupture by a disrotatory process leading directly to an *exo–exo* open chain structure <92IC2414>.

1.16.4.4 Reactions with Metal Carbonyls

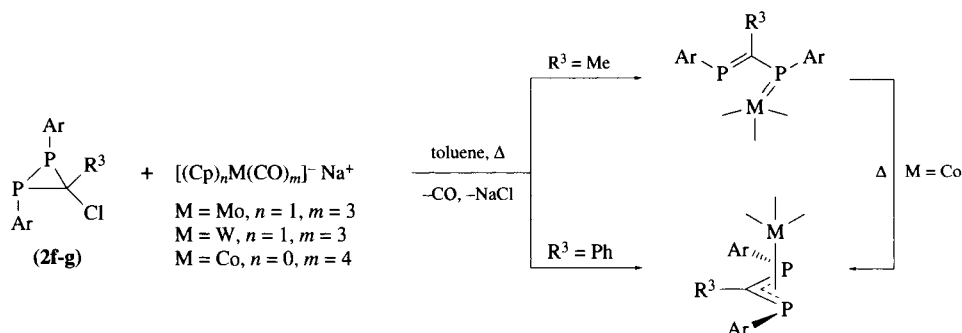
The first attempt to complex diphosphirane was by Seyferth who obtained, after the cleavage of the P—P bond, a bridged iron complex in 10% yield (Equation (20)) <87JOM(336)163>.



Subsequently Jutzi allowed a ring diphosphirane to react with $[\text{Cr}(\text{CO})_5\text{THF}]$ and obtained an η^1 -diphosphirane pentacarbonyl chromium complex (Equation (21)) <92ZAAC(610)75>.



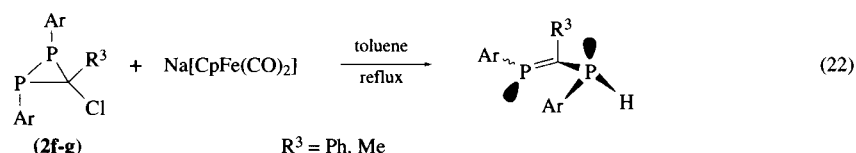
The reaction of anionic transition metal complexes ($M = \text{Mo}, \text{W}, \text{Co}$) with monohalogenated diphosphiranes (**2f-g**) occurs upon heating and leads to the σ - or π -diphosphaallyl complexes as a result of preferential P—P bond rupture, depending on the reaction conditions, the nature of the intracyclic carbon substituents, and the transition metal complexes (Scheme 10) $\langle 93\text{PS}(76)41, 93\text{JOM}(453)77 \rangle$. π -Donor substituents ($R^3 = \text{Ph}$) promote the η^3 -form, whereas σ -donor ($R^3 = \text{Me}$) afford the η^1 -complex.



Scheme 10

The complexes are thermally labile as shown by variable-temperature NMR spectroscopy. Upon heating in toluene at reflux for 3 h, the σ -diphosphaallyl cobalt complex is irreversibly transformed into the π -allylic complex. This isomerization upon heating constitutes the first example of such interconversion in the diphosphaallyl systems. The synthesis of σ - or π -diphosphaallyl complexes can also be realized from the photochemical isomers of diphosphiranes, the 1,3-diphosphapropenes. In this case, the reaction occurs more readily under milder conditions than above, and the same diphosphaallyl complexes were obtained in 70–90% yield with the same selectivity as their parent diphosphiranes $\langle 93\text{JOM}(453)77 \rangle$.

The complexation reactions do not take place with all the anionic transition metal complexes. Treatment of monohalogenated diphosphiranes (**2f-g**) with $\text{Na}[\text{CpFe}(\text{CO})_2]$ in refluxing toluene solution affords the reduced 1,3-diphosphapropenes. Similar results were observed with the *P*-chloro-1,3-diphosphapropenes (Equation (22)).

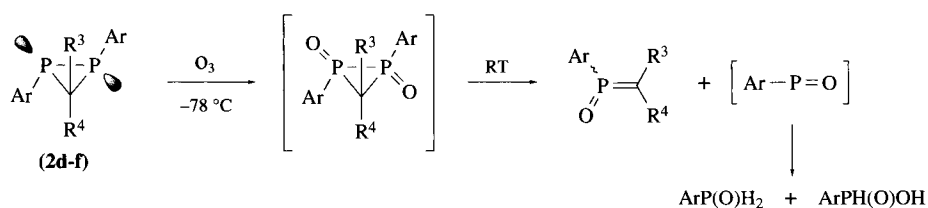


Like their behavior toward the organolithium derivatives or the Grignard reagents, the *gem*-dihalogenodiphosphiranes (**2d-e**) or their photochemically opened isomers react with the anionic metal transition complexes leading to 1,3-diphosphaallene in quantitative yield $\langle 93\text{JOM}(453)77 \rangle$.

1.16.4.5 Oxidation Reactions

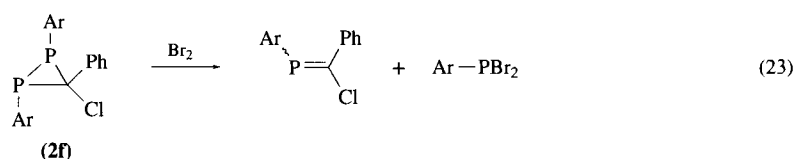
Ozonation of (**2d-f**), carried out in dichloromethane at low temperature (-78°C) (Scheme 11) (since ozone is a more suitable reagent for oxidizing the bulky phosphines) $\langle 91\text{TL}3687 \rangle$, involves the instantaneous oxidation of the phosphorus lone pairs and the formation of the oxidized diphosphirane intermediates detected by ^{31}P NMR. It decomposes at room temperature to phosphalkene oxide, phosphinic and phosphonic acids.

Consequently, the oxidation of the phosphorus lone pairs does not stabilize these strained heterocycles, but allows the production of the phosphalkene oxides not readily available by other methods $\langle 83\text{JA}4026, 84\text{AG}(E)157 \rangle$.



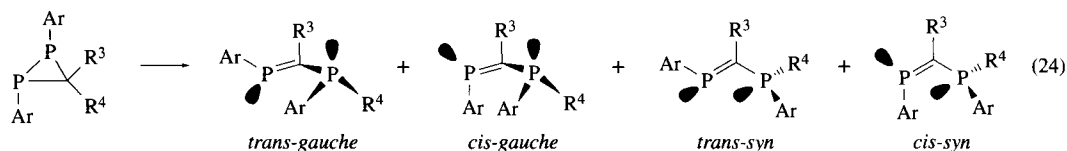
Scheme 11

The reaction of bromine (2 equiv.) with diphosphiranes in dichloromethane at room temperature also involved the fragmentation of the heterocycle leading quantitatively to phosphalkene and dibromophosphine (Equation (23)) <91TL3687>.



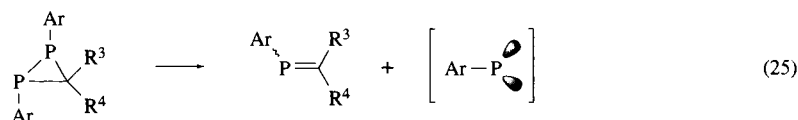
1.16.4.6 Thermal Rearrangements

The diphosphapropenes obtained after the thermal ring opening of diphosphiranes can exist as the *cis* or *trans* isomer stabilized in a *gauche* or *syn* conformation (Equation (24)) <94IC596>. In the absence of nucleophilic or electrophilic assistance, the thermal opening of mono- and dihalogenated diphosphiranes (2d–h) leads to *cis* and *trans* 1,3-diphosphapropenes in *gauche* conformation. For the unsymmetrical diphosphiranes (2o–p), the thermal ring opening is regio- and stereoselective and leads quantitatively to the *trans* diphosphapropenes in the *syn* conformation.



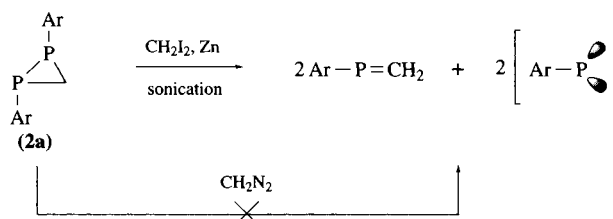
The theoretical analysis of the possible monomolecular processes for thermal opening of diphosphiranes has revealed two preferred mechanisms, by a cleavage of the P—P bond followed by a halogen migration involving biradical or radical species; either conrotatory opening via an *exo-exo* singlet biradical leading to *trans* diphosphapropenes or disrotatory process via a radical *exo-endo* species affording *cis* or *trans* diphosphapropenes <94IC596>. Only the disrotatory process is in good agreement with the presence of the *cis* isomers. For functionalized diphosphiranes, an initial homolytic cleavage of the exocyclic C—R⁴ bond (R⁴ = Cl, Br) with formation of cyclic diphosphiranyl radical, which should open relatively easily by P—P bond rupture leading to an *exo-exo* or *exo-endo* radical intermediate, allow the interpretation of all the experimental results. For diphosphiranes bearing no good leaving group substituents (e.g., diphosphaspiropentane (Section 1.16.4.7) <92AG(E)625>), the biradical mechanism appears the most appropriate <94IC596>.

In cyclopropane <71AG(E)537, 88JA982> and heterocyclopropane series, the [3 → 2 + 1] cycloelimination reactions have been studied and are conveniently used as a method of generation of silylenes <83JA776, 87AG(E)776, 88JA3310> or germylenes <88OM2015>. In the diphosphirane series where the low P—P bond enthalpy value (50 kcal mol⁻¹) compared to the P—C one (64 kcal mol⁻¹) <B-77MI 116-01> must involve ring opening by a preferential P—P bond rupture, avoiding the fragmentation reactions. (The bond enthalpy values do not take into account the strain energies of the ring. In the diphosphirane ring, the calculated strain energy is 14.7 kcal mol⁻¹ <90PS(53)7>.) However, the cheletropic reactions of diphosphiranes leading to the phosphalkene and the corresponding phosphinidene can occur under various conditions (Equation (25)).



During the synthesis of diphosphiranes from the symmetrical diphosphene by cyclopropanation, whatever the nature of the carbenoids used (diazo derivatives, carbenes or halogenocarbenes), in all cases the formation as byproducts of the phosphalkenes and the unstable phosphinidene was observed (5–20%). So, for isopropylidene carbene, the formation of the phosphacumulene, more stable than the parent diphosphirane can reach 30% (91TL3687).

The formation of the phosphalkenes can be explained either by the addition of excess carbenes on phosphorus lone pairs of diphosphirane followed by decomposition of the latter, or by the fragmentation of diphosphirane. When an excess of dichloro- or dibromocarbene is added on diphosphirane (**2f**), the formation of the corresponding phosphalkenes is not detected and the diphosphirane remains unchanged (91TL3687). In contrast, during the sonochemical Simmons–Smith cyclopropanation of diphosphene in THF at 15°C, if the sonication time is prolonged to 4 h, the methylene diphosphirane (**2a**) reacts with the excess of carbenoid, leading to methylene phosphalkene in quantitative yield (91TL5965). Thus, the addition of methylene carbene on phosphorus lone pairs destabilizes the cyclic form and promotes the cheletropic reaction. It must be noted that diphosphirane (**2a**) is stable without methylene carbene under sonication, and also in the presence of a large excess of diazomethane (Scheme 12).



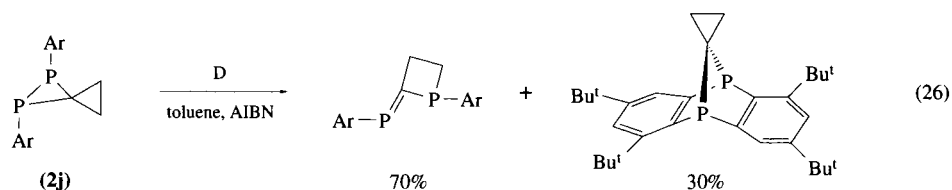
Scheme 12

The fragmentation related to cheletropic reactions of diphosphiranes can also be observed upon heating (94IC596), under photochemical irradiation at 300 nm (90JOC5750) or during reactions with Lewis acids (89TL7411) leading to a variety of substituted phosphalkenes (minor products). Under these conditions, the fragmentations occur in competition with the electrocyclic ring opening reactions involving the formation of 1,3-diphosphapropenes as main products.

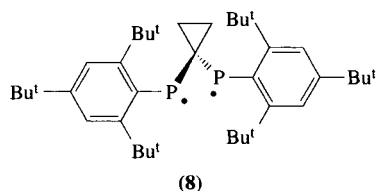
For unsymmetrical diphosphiranes, whatever the experimental conditions (during the synthesis, under irradiation or heating), the fragmentation products were never observed (91TL3687). This absence of cheletropic reactions is probably due to stronger and shorter P—C bonds for these diphosphiranes than for symmetrical ones (*cf.* Table 1) (96UP 116-01).

1.16.4.7 Ring Expansion Reactions

Studies on the synthesis and reactivity of oxa- (68JOC3291, 71CC1579) and aza- (73CC33, 73TL4795, 74JOC63) spiropentanes, the heterocyclic analogues of the well-known and highly strained spiropentane system (89JA1501), have led to an improved understanding of chemical bonding, intramolecular interactions, and reaction mechanisms (79AG(E)809, 86AG(E)312). All these spiropentanes rearrange to methylenecyclobutanes (90TL2411). In phosphorus chemistry, the first rearrangement of a diphosphaspiropentane (**2j**) has been observed upon heating at 100°C in degassed toluene leading to the expected diphosphamethylenecyclobutane (70%) but also to the unexpected 1,4-diphosphanorbornadiene (30%) (Equation (26)) (92AG(E)625). This ring expansion reaction was promoted by addition of AIBN.



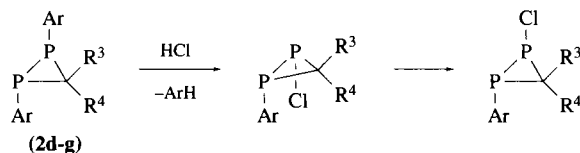
The diphosphamethylenecyclobutane and the 1,4-diphosphanorbornadiene are formed from the common biradical intermediate after the P—P bond cleavage (8).



The MNDO and *ab initio* calculations performed on unsubstituted derivatives reveal for this reaction a conrotatory process involving an *exo-exo* singlet π -biradical <94IC596>.

1.16.4.8 Substitution Reactions

Ring opening reactions of cyclopropane derivatives are commonly observed; however, there exist only a few examples of substitution reactions without ring opening which mainly involve halogen substitutions <83T913, 85JOC3255, 88MI 116-01>. In the diphosphirane series, the ring opening reactions with preferential intracyclic P—P bond rupture were observed. However, the substitution of one aryl group (2,4,6-tri-Bu^t-phenyl) by a chlorine atom leading to the *trans* *P*-chlorodiphosphirane via the *cis* isomer intermediate has recently been realized in chlorinated solvent under sonication, or in the presence of Brønsted acids or in the presence of gaseous hydrogen chloride in diethylether at room temperature (Scheme 13) <91TL5965, 94TH 116-01>. The postulated mechanism probably involved an electrophilic substitution of the aryl group by an acidic proton.



Scheme 13

Whatever the method, starting from a *trans* diphosphirane (2d-g), the *trans* *P*-chlorodiphosphirane is obtained. The substitution of the aryl group by the chlorine atom induces an increase of the ³¹P NMR chemical shift values (cf. Figure 1). The *J*_{pp} coupling constant values are slightly higher than in the starting diphosphiranes (e.g., 10–30 Hz). When the reactions were carried out under mild conditions at room temperature, it was possible to detect the formation of cyclic *cis* isomer intermediates.

For diphosphiranes belonging to series 3, the exchange reactions of *P*-chloro derivatives with halosilanes lead to the corresponding *P*-bromo- and *P*-iododiphosphiranes <90CB1245>. In the same diphosphirane series, the reduction of the *P*-chlorodiphosphirane to P—H analogous to the tributylstannane method was reported (Equation (6)) <93CB645>.

1.16.5 CONCLUSION

The different synthetic approaches have opened access to various stable or functionalized diphosphiranes and diphosphirenes. As can be seen from their behaviour under various conditions, their reactivity is essentially dominated by the ring opening reactions involving a preferential P—P bond rupture. Thus, they can be considered as potential precursors of 1,3-diphosphapropenes, 1,3-

diphosphaallenes and also 1,3-diphosphaallyl anion or cation, and diphosphiranyl radical or 1,3-diphosphapropanyl biradical intermediates, demonstrating the amazing analogy to pure carbon systems. However, their particular reactivity towards the transition metal complexes has opened original pathways to new complexes. Finally, the introduction of other heteroelements such as As, Sb, or Bi into these three-membered rings has scarcely been researched.

1.17

Three-membered Rings with Two Heteroatoms including Other Elements

FRANK L. SWITZER and CRAIG M. DAVIS
Xavier University, Cincinnati, OH, USA

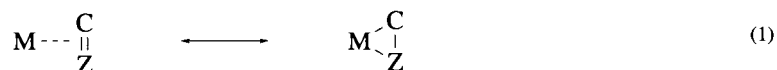
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1.17.1 INTRODUCTION

None of the ring systems described here were mentioned in the first edition of *Comprehensive Heterocyclic Chemistry* (CHEC-I). This chapter covers reports up to December 1994. The literature was searched by groups within the periodic table.

1.17.1.1 Scope

These heterocycles contain at least one transition metal as part of a strained three-membered ring. Their structures therefore are partially described as heterocycles and partially as transition metal π complexes of heteroalkenes (Equation (1)). Evidence for metallacyclic structures is therefore highlighted. A wide variety of transition metal complexes could be covered but this chapter is restricted to compounds where the ring carbon is tetravalent, bonded to hydrogen or carbon, and bonded to not more than two metal atoms. Related areas which have been reviewed include: CO bridged bimetallics $\langle 84\text{AOC}(23)219 \rangle$ and CO_2 metal complexes $\langle 83\text{AOC}(22)129 \rangle$.



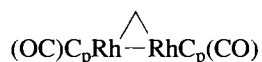
1.17.1.2 Nomenclature

IUPAC nomenclature is generally followed $\langle \text{B-79MI } 117-01 \rangle$. The cyclic structures are called heterometallacycles and dimetallacycles. When the ring is composed of a metal, a nonmetal, and a carbon, the rings are numbered in that order. When two metals are present, the higher atomic number metal takes precedence. Metallacyclic three-rings which contain a double bond may possess cyclopropenyl cation-like aromaticity and such structures have been proposed $\langle 84\text{AG}(\text{E})89 \rangle$.

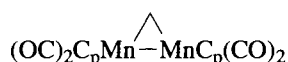
1.17.2 THEORETICAL METHODS

A few molecular orbital calculations have been reported for these metallacycles. An *ab initio* study of a postulated azoniumrhodacyclopropane produced a structure in good agreement with known azoniummetallacyclopropanes. This as yet unknown heterocycle was studied because it has been proposed as an intermediate in the stereoselective isomerization of allyl amines to enamines $\langle 92\text{OM}3167 \rangle$.

A detailed extended Hückel-type MO calculation of dirhodacyclopropane (**1**) shows considerable bonding similarity with the modern description of cyclopropane $\langle 79\text{AG}(\text{E})554, 80\text{HCA}29, 82\text{AOC}(20)159 \rangle$. A frontier MO study of dimanganacyclopropane (**2**) finds the molecule to be more stable than the analogous monometallic metal carbene complex. In this study, metal-metal bond formation was shown to enhance the stability of the metallacycle $\langle 81\text{JA}6852 \rangle$.



(1)



(2)

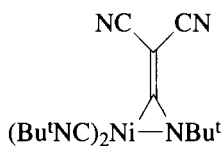
1.17.3 EXPERIMENTAL STRUCTURAL METHODS

The majority of these metallacycles have been characterized by x-ray diffraction studies which are used to determine both the stoichiometry and the structure of the complexes. NMR studies often provide more detailed bonding and dynamics information. In some complexes, NMR has been the major characterization method.

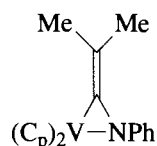
1.17.3.1 X-ray Diffraction Studies

Nitrogen-containing heterometallacyclic three-rings are of two types: complexes with trivalent nitrogens (azametallacyclopropanes) and complexes with tetravalent nitrogens (azonium-metallacyclopropanes). Diffraction studies of azametallacyclopropanes include azanickelacyclopropylidene (**3**) $\langle 73\text{JA}8590 \rangle$, azavanadacyclopropylidene (**4**) $\langle 86\text{JOM}(310)179 \rangle$, and azatungstacyclopropane (**5**) $\langle 81\text{JCS}(\text{D})2088 \rangle$. Nickel complex (**3**) has a rather short C—N ring bond (125 pm) which is consistent with a metal π complex. The longer C—N bonds of the vanadium (138 pm)

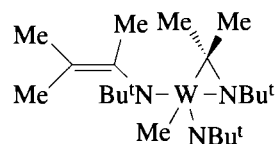
and tungsten (144 pm) complexes suggest that they are best described as azametallacyclopropanes. The nickel and vanadium compounds show symmetrical bonding to the metal but the M—N bond is 19 pm shorter than the M—C bond in the tungsten compound.



(3)

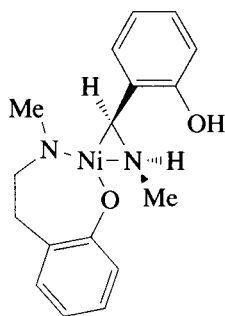


(4)

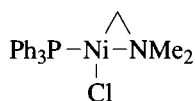


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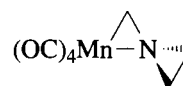
Diffraction studies of azonium metallacyclopropanes include two nickel complexes (6) <74JA6777> and (7) <76JA6178>, two manganese complexes (8) <74CC72>, and (9) <77IC3201>, zirconium complex (10) <92OM122>, and the hydrochloride salt of tungsten complex (5) <81JCS(D)2088>. All of these compounds have relatively long C—N ring bonds (139–145 pm) which suggest metallacyclic structures. Except for the spirocyclic (8) where the M—N bond is 11 pm shorter than the M—C bond, these complexes possess highly symmetrical bonding to the metal.



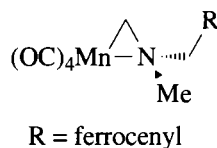
(6)



(7)

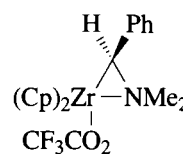


(8)



R = ferrocenyl

(9)



(10)

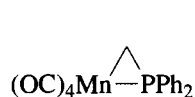
The heterometallacyclic three-rings which contain phosphorus have tetravalent phosphorus atoms. Diffraction studies on these phosphonium metallacyclopropanes include manganese complex (11) <83CB1209>, tungsten complex (12) <85JCS(D)2025>, rhenium complex (13) <82POL441>, iridium complex (14) <81JCS(D)1572>, tantalum complex (15) <83CC1101, 85JCS(D)2025>, molybdenum complex (16) <84CB127>, and platinum complex (17) <74JA5642, 79JOM(179)73>.

Most of these complexes display P—C ring bonds of 174–178 pm which is shorter than a typical P—C single bond. This suggests that their structures are intermediate between metallacycles and π complexes. Iridium complex (14) is unique with a 190 pm P—C ring bond and may be the only “true” metallacycle in the group. These complexes also possess highly symmetrical bonding to the metal despite phosphorus’ longer covalent radius.

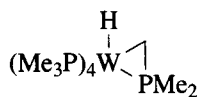
Oxametallacyclic three-rings are known both for divalent and trivalent oxygen atoms though divalent oxygen atoms are far more common. Oxoniumzirconacyclopropane (18) <86CC1403> represents the only crystallographic study where the oxygen is trivalent. The 141 pm C—O bond is consistent with a metallacyclic structure. The M—O bond is 9 pm shorter than the M—C bond in this complex.

Diffraction studies of oxametallacyclopropanes include ketene adducts (19) <81IC1173>, (20) <94JOM(476)101>, and (21) <78IC2995, 78JA1921>, benzaldehyde adduct (22) <91JA5904>, and formaldehyde adducts (23) <82JA2019>, (24) <79JA503, 82JOM(231)335>, (25) <81CB2754, 81JOM(219)353>, and (26) <83JA1056>. The vanadium ketene adducts display rather short (129 pm) C—O bonds indicative of π complexes. The longer C—O bond in the titanium ketene adduct (134 pm) probably results from its dimeric structure. Osmium complex (24) is the most metalocyclic with a 158 pm C—O bond. The C—O bonds of the other aldehyde adducts (132–137 pm) suggest intermediate structures.

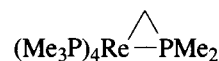
Thiametallacyclic three-rings are known both for divalent and trivalent sulfur atoms. Diffraction



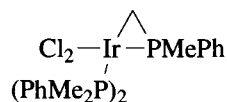
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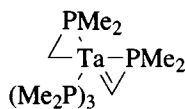
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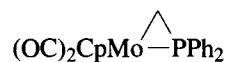
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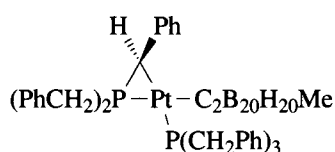
(14)



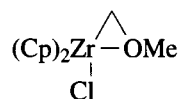
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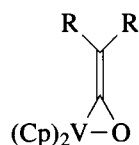
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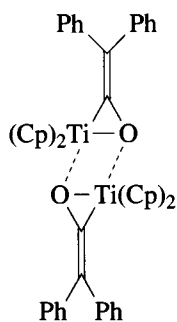
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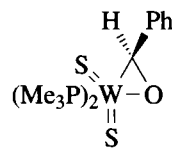
(18)



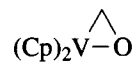
R=Ph (19)

R=CF₃ (20)

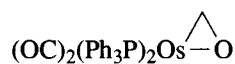
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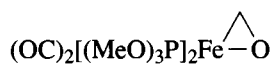
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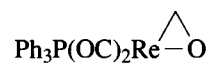
(23)



(24)

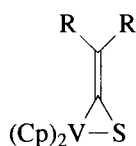


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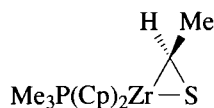


(26)

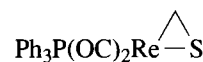
studies of thiametallacyclopropanes include a series of vanadocene thioketene adducts (27; R = tertiary alkyl) <84JOM(272)C40>, (R = Si(Me)₃, CF₃) <87JOM(320)C31>, zirconium complex (28) <87JA1590>, and cationic rhenium complex (29) <83JA1056>. The C—S bond lengths in this group (168–179 pm) indicate structures which are intermediate between π complexes and metallacycles with zirconium complex (28) having the longest bond.



(27)

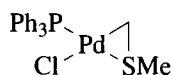


(28)

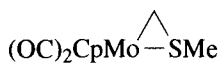


(29)

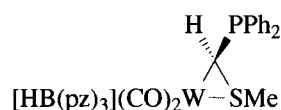
Crystallographic studies of thioniummetallacyclopropanes include three related palladium complexes such as (30) <77JOM(135)53, 81BCJ3639>, two similar molybdenum complexes such as (31) <69JA3751, 80CJC1080>, and a tungsten complex (32) <86OM2481>. The neutral complexes in this group display C—S bond distances (176–180 pm) consistent with a metallacyclic structure.



(30)



(31)

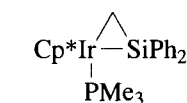


(32)

pz = pyrazole

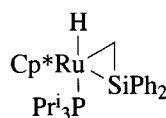
Crystallography of two cationic complexes which result from substitution of chloride in (30) with triphenylphosphine were found to have dissimilar structures. The structure of the hexafluorophosphate is similar to the neutral complexes (C—S bond = 177 pm) while the perchlorate is unusual (C—S bond = 168 pm). This shortening of the C—S bond in the perchlorate is accompanied by a lengthening of the M—C bond (15 pm) and is probably due to the influence of the perchlorate ion on crystal packing. The M—S bonds of both types of sulfur compounds are significantly longer than the M—C bonds (9–33 pm) which is consistent with sulfur's longer covalent radius.

Isolable silametallacyclopropanes have only been synthesized since the late 1980s but their structures and chemistry have been reviewed <B-91MI 117-01>. Diffraction studies of these compounds include ruthenium complex (33) <88JA7558>, iridium complex (34) <90JA4079>, and tungsten complex (35) <90JA6405>. The lengths of the C—Si bonds in these compounds (178–181 pm) suggest structures which are intermediate between π complexes and metallacycles.

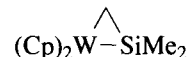


Cp* = Cp(Me)₅

(33)



(34)

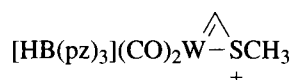


(35)

The structure and chemistry of dimetallacyclopropanes has been well reviewed through 1981 <82AOC(20)159>, so developments since then are emphasized here. Diffraction studies of the numerous dimetallacyclopropanes and dimetallacyclopentadienes show metal–metal single bonds which are somewhat shorter than the analogous bridging CO compounds. The carbon–metal bond distances are nearly identical whether or not the metal atoms are the same <82AOC(20)159, 90ICA11>.

Heterometallacyclopropenes are rare but tantalum complex (15) is an example of a metallaphosphoniumcyclopropene. The heterocycle is best described as having a Ta—C double bond but the C—P bond (172 pm) also appears to possess some double-bond character. Metallathiacyclopropenes are normally described as metal-coordinated thioketones and their structures will not be covered in this chapter. The few examples of thioniummetallacyclopropenes are, however, described as heterocycles. A diffraction study of cationic thioniumtungstacyclopropene (36) reveals a short W—C

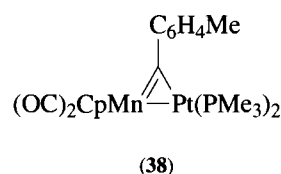
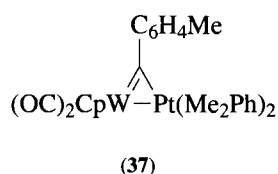
bond (198 pm) as well as partial double-bond character in the C—S bond (172 pm). Some aromatic stabilization may be present in (36) because the sulfur has a formal positive charge.



pz = pyrazole

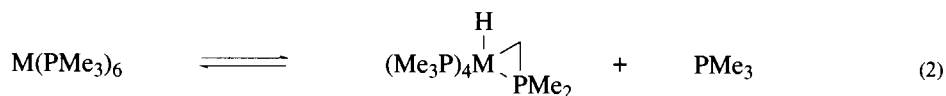
(36)

The known dimetallacycloprenes contain two different ring metal atoms. Reports of the structures of platinatungstacycloprenene (37) <79CC42> and manganaplatainacycloprenene (38) <79CC1170> describe the ring carbon as having a double bond to the early transition metal as evidenced by shorter M—C bonds (9 pm and 14 pm, respectively).



1.17.3.2 NMR Studies

Several phosphoniummetallacycloprenes are known to be fluxional. A number are also known to exist as an equilibrium mixture with complexes saturated with alkyl phosphine ligands (Equation (2)). The equilibrium concentrations of the two complexes are readily measured by ^1H NMR. The metallacycle is favored for phosphoniumtungstacycloprenene (12) <92JA4611> but disfavored for phosphoniummolybdacycloprenene (39) <85JCS(D)423>. The equilibrium constant for (12) was measured in benzene at several temperatures and thermodynamic data were obtained for the equilibrium ($\Delta H^\circ = 9.3 \text{ kcal mol}^{-1}$, $\Delta S^\circ = 37 \text{ eu}$).

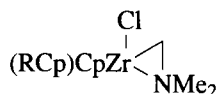


M = W (12)

M = Mo (39)

A detailed dynamic NMR study of phosphoniummolybdacycloprenene (16) reveals a low energy barrier for cyclopropane rotation ($\Delta G^\ddagger = 12.9 \text{ kcal mol}^{-1}$) with a coalescence temperature of 263 K <84CB127>. Similar studies of (12) show a coalescence at 253 K which is attributed to a phosphine pseudorotation which includes a 90° cyclopropane rotation <85JCS(D)2025>.

A dynamic study of azazirconacycloprenene (40) proposes a mechanism for exchange of the methyl groups on nitrogen ($\Delta G^\ddagger = 16.4 \text{ kcal mol}^{-1}$ in CDCl_3) which involves transient cleavage of the M—N bond followed by nitrogen inversion. Because complexes like (40) have a preferred orientation, ring rotation is unlikely <92OM534>.



R = CMe_2Ph

(40)

1.17.3.3 UV and IR Studies

Though IR studies of the CO ligands in many of these complexes are common, there have been no general IR or UV studies of the metallocyclic rings themselves. The IR stretch at 1620 cm^{-1} of the ring C—O bond in oxavanadacyclopropane (**17**) was used as a means of characterization since it occurs at much lower frequency than the ketene starting material $\langle 81\text{IC}1173 \rangle$. Oxaosmacyclopropane (**23**) displays a C—O stretch at 1017 cm^{-1} which agrees with its diffraction data.

1.17.4 THERMODYNAMIC ASPECTS

Due to the wide range of atoms which may occupy the sites in the heterocyclic ring, it is not possible to make too many generalizations about the physical and thermodynamic properties of these metallacycles. They are expected to be rather unstable due to ring strain and the existence of rather weak metal–carbon bonds. In fact, many of the reactions of these heterocycles involve cleavage of ring bonds.

1.17.4.1 Physical Properties

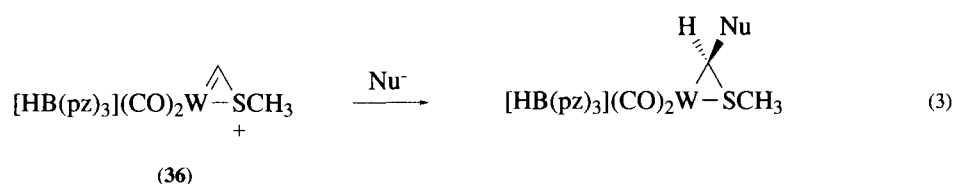
A common feature of many of these metallacycles is their sensitivity to insertion reactions and air oxidation. Therefore they are usually air-sensitive colored solids.

1.17.4.2 Conformational Studies

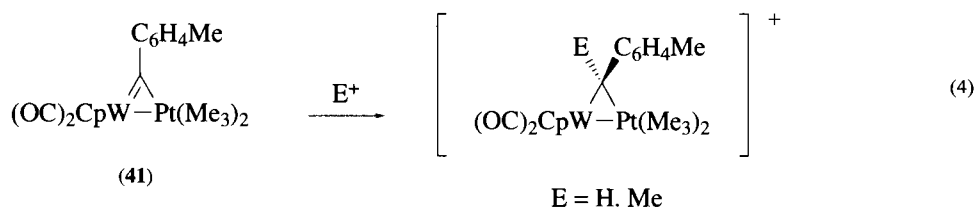
Because three-rings are rigid structures, there have been no conformational studies *per se* of these metallacycles but some complexes are known to exhibit dynamic behavior as described in Section 1.17.3.2.

1.17.5 REACTIVITY OF CONJUGATED RINGS

There have been few reactivity studies of heterometallacyclopropenes but the reactivity of cationic thioniumtungstacyclopropene (**36**) has been studied in detail. A variety of nucleophiles are known to add to the ring carbon including thiolates, phosphines, pyridines, and malonate (Equation (3)). Hydrazines and alkyl and aryl amines also appear to add but then undergo elimination to metal carbynes $\langle 86\text{OM}2489 \rangle$.



Neutral platinumungstacyclopropene (**41**), however, reacts with electrophiles and is readily protonated or methylated at the ring carbon (Equation (4)) $\langle 84\text{AG(E)}89 \rangle$.



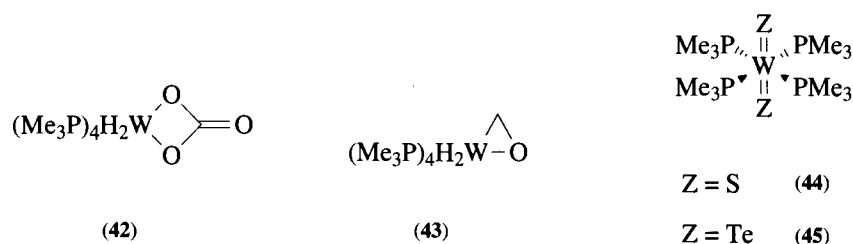
1.17.6 REACTIVITY OF SATURATED RINGS

Heterometallacyclopropanes undergo a variety of addition and insertion reactions. These reactions all involve cleavage of either the metal–carbon or metal–heteroatom ring bond. The ring

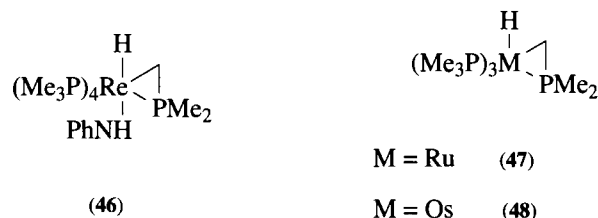
heteroatoms can also react with electrophiles when they have no formal charge. The metals can undergo ligand addition and substitution reactions. The latter reactions are only covered here when the three-ring is involved.

As previously discussed in Section 1.17.3.2, several phosphoniummetallacyclopropanes exist in equilibrium with phosphine saturated complexes. These metallacycles are typically formed by loss of a phosphine ligand followed by cyclometallation. Since the cyclometallation is reversible, it can provide additional ligand binding sites and a variety of ligands have been added to the metals of these complexes. This type of ring cleavage may be viewed as a hydride addition to the metal-carbon bond.

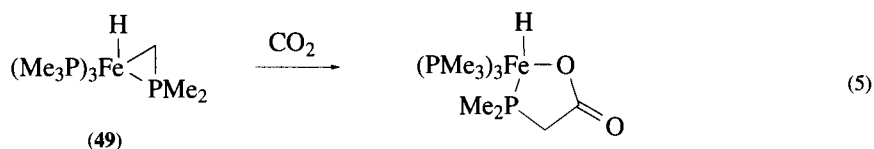
Tungsten complex (12) has been the most widely studied. The molecules which have been added to (12) include dienes, N_2 , H_2 , HF , SiH_4 [84CC1400, 86JCS(D)2227], methanol [84CC1540], H_2/CO_2 [86JOM(317)61], H_2S [91JA5904], and tellurium [91JA9421]. The addition of H_2/CO_2 results in cyclic carbonate (42), while addition of methanol affords oxatungstacyclopropane (43). The H_2S and tellurium additions provide complexes with metal heteroatom double bonds ((44) and (45), respectively), the former resulting from an unusual thermal elimination of two molecules of H_2 .



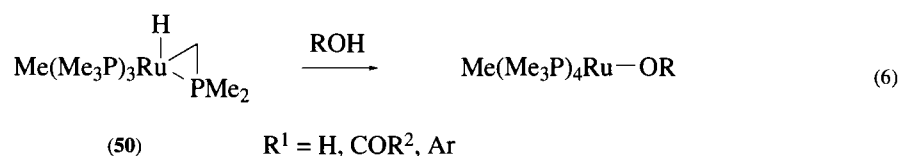
Rhenium complex (46) is also known to add H_2 and N_2 [81CC451] to the metal center. Ruthenium complex (47) and osmium complex (48) add sulfur to give complexes with unusual S_6^{-2} ligands [84AG(E)814].



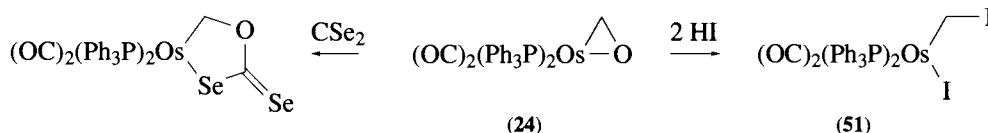
Iron complex (49) adds CO_2 by direct insertion into the $Fe-C$ bond in THF at room temperature (Equation (5)) [77CB2213]. Lower temperature and a nonpolar solvent decrease the concentration of the metallacycle and the reaction leads to other products. The iron compound also adds to 1,3-cyclohexadiene [87JCS(D)2031].



A number of protonic reagents add to phosphoniumruthenacyclopropane (50) including water [93JA5875], carboxylic acids [91JA6499], and phenols [90JOM(394)417] (Equation (6)). When phenols react with tungsten complex (12), the initial addition product undergoes *ortho* or benzylic metallation [92JA4611].



Oxaosmacyclopropane (**24**) undergoes several metal–oxygen bond additions. It reacts with carbon diselenide by insertion into the O—Os bond. Reaction with HI affords diiodide (**51**) presumably via the alcohol (Scheme 1) <83JOM(244)C53>. Reaction with other electrophiles affords ring-opened cations <82JOM(231)335>.

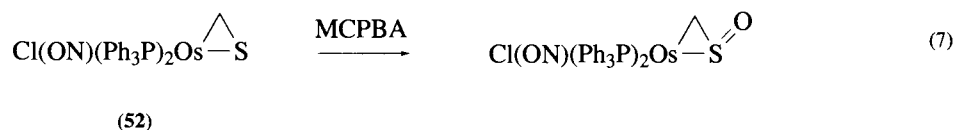


Scheme 1

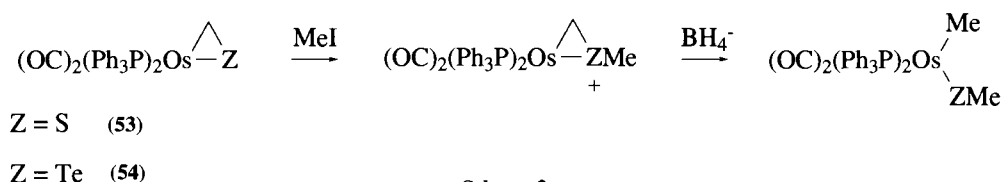
Oxatungstacyclopropane (**43**) also undergoes a number of addition reactions. Reaction with CO₂ affords cyclic carbonate (**42**). Reaction with ethene gives oxatungstacyclopentanes which result from insertion into the metal–carbon bond. Reaction with 1,3-butadiene gives a π complex where the metallacycle is retained <86CC90>.

Silatungstacyclopropane (**35**) is subject to addition reactions as well. Methanol, H₂, and H-TMS all add to the metal–carbon bond. The first two reactions lead to metal hydrides while the last reagent gives a metallasilane. Trimethylphosphine addition to (**35**) causes attack of cyclopentadienide at silicon and cleaves the silicon–metal bond <90JA6405>.

The reactivity of many of the other heterometallacycles is largely unexplored but a few reactions are known. As mentioned in Section 1.17.3.1, azanickelacyclopropane (**5**) can be protonated to the azoniumnickelacyclopropane <81JCS(D)2088>. Several thiametallacyclopropanes undergo efficient alkylation at the ring sulfur <83OM1905, 87JOM(328)287, 87JOM(328)305, 90ICA11>. Thiaosmacyclopropane (**52**) can also be oxidized to a sulfoxide (Equation (7)) <86JOM(309)C29>.



Selenaosmacyclopropane (**53**) and telluraosmacyclopropane (**54**) react with iodomethane by methylation of the ring heteroatom. Surprisingly, the product selenonium and telluronium rings react with borohydride via cleavage of the carbon–heteroatom bond (Scheme 2) <83JOM(244)C53>.



Scheme 2

The most widely studied dimetallacyclopropane is iron complex (**55**) because it is air stable and readily available <80JA1752>. Diferracyclopropane (**55**) and diosmacyclopropane (**56**) are both known to undergo reversible CO insertion into the metal–carbon bond <88JA7868>. This insertion reaction provides a basis for an efficient synthesis of acetate esters <81JOM(219)C5> from alcohols and (**55**) at 60°C. An advanced intermediate in this reaction has been isolated and characterized by x-ray diffraction <84AG(E)432>.



Iron complex (**55**) also reacts with H₂ to produce methane and ethene to afford propene <80JA1752>. Both reactions appear to involve insertion into a metal–carbon bond followed by elimination. When osmium complex (**56**) adds ethene, the diosmacyclopentane which results from ethene addition is isolated. When terminal alkynes react with (**55**), an alkene-substituted ring carbon results

<87JOM(322)103>. Other more exotic addition reactions of (55) have also appeared including reactions with allenes <90OM289> and phosphinimines <89JA7279, 92OM2613>. The former reaction is an efficient method for the preparation of iron trimethylenemethane complexes.

1.17.7 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING CARBON ATOMS

Due to the novelty and reactivity of these metallacycles, studies of this type have not appeared.

1.17.8 REACTIVITY OF SUBSTITUENTS ATTACHED TO RING HETEROATOMS

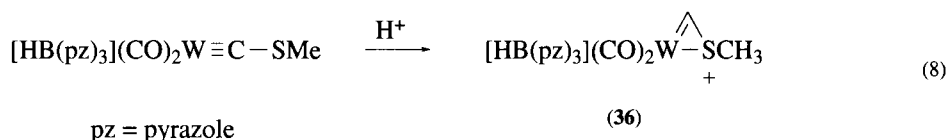
Since these molecules are coordination compounds, substituents are bound rather weakly to the metal. The metal substituents are therefore readily substituted or eliminated. Attachments to other ring atoms are considerably more stable.

1.17.9 RING SYNTHESSES

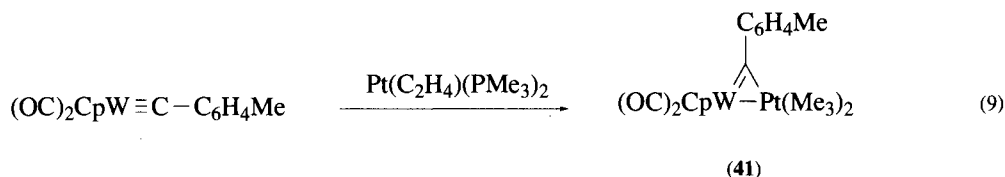
These metallacycles have been prepared by additions to multiple bonds and substitutions at carbon or metal atoms, as well as by simple acid–base reactions.

1.17.9.1 Conjugated Rings

Thioniumtungstacyclopropene (36) was prepared by protonation of a thiomethyl carbyne. The change in hybridization of carbon allows sulfur to add to the triple bond (Equation (8)).

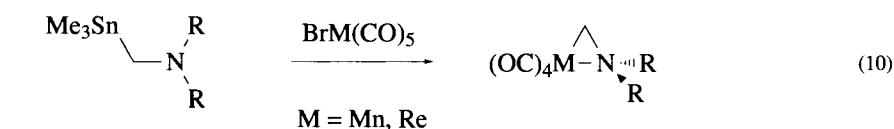


A wide variety of metal centers add to metal carbynes to afford dimetallacyclopropenes by ligand exchange <84AG(E)89, 87AOC(27)51>. The reaction shown in Equation (9) to afford (41) illustrates this approach.

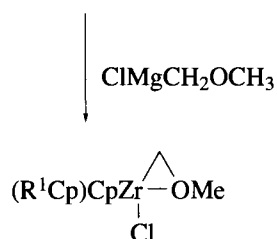
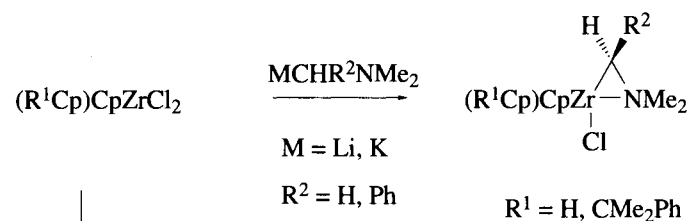


1.17.9.2 Saturated Rings

Azoniummetallacyclopropanes have been prepared via substitution of metal halides by stannyl amines (Equation (10)) <75JCS(D)1096> or organolithium and organopotassium reagents <92OM534>. Oxonium complex (18) was prepared analogously using an organomagnesium reagent (Scheme 3) <86CC1403>. In addition, transition metal alkyls react with amines to afford nitrogen three-rings (Equation (11)) <77IC3193>. These metallacycles may also be prepared for some metals from nitrogen ylides by ligand exchange. Other metals do not spontaneously adopt the cyclic structure and produce complexes where only one ylide atom is bound to the metal (Equation (12)) <75JCS(D)1100>.

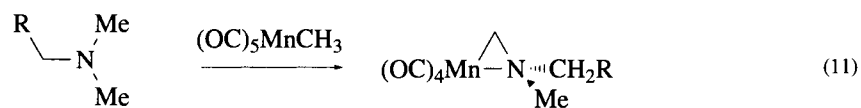


$\text{R} = \text{alkyl, cycloalkyl}$

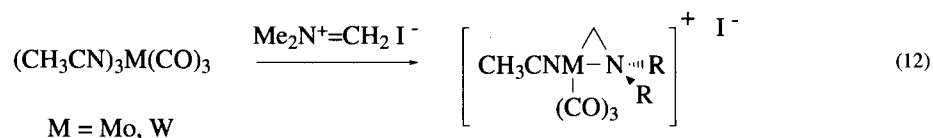


$\text{R}^1 = \text{H}$ (18)

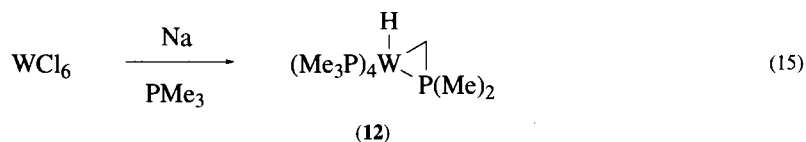
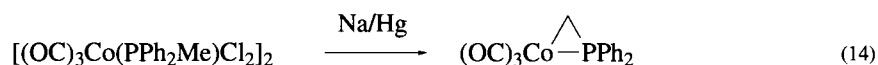
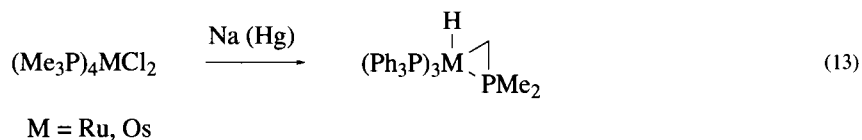
Scheme 3

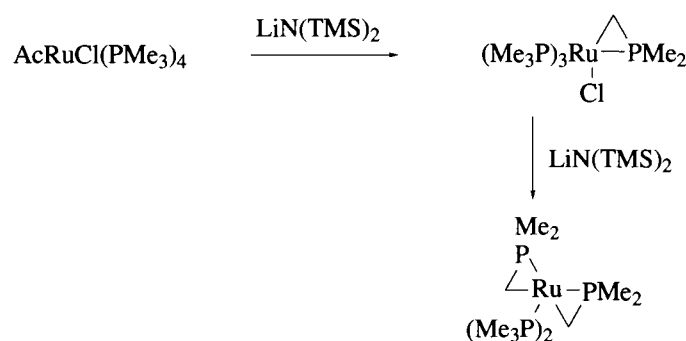
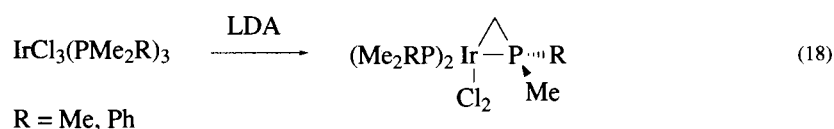
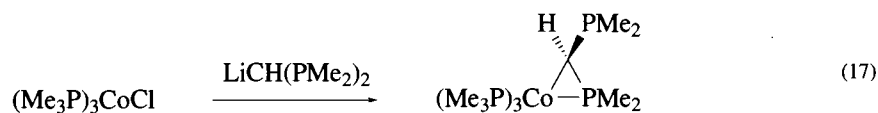
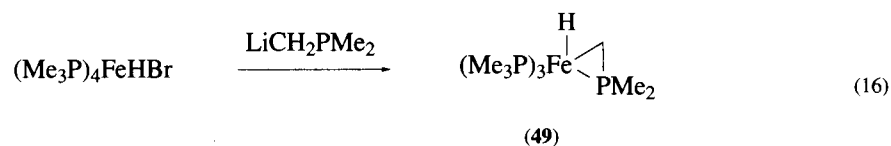


$\text{R} = \text{H, ferrocenyl}$



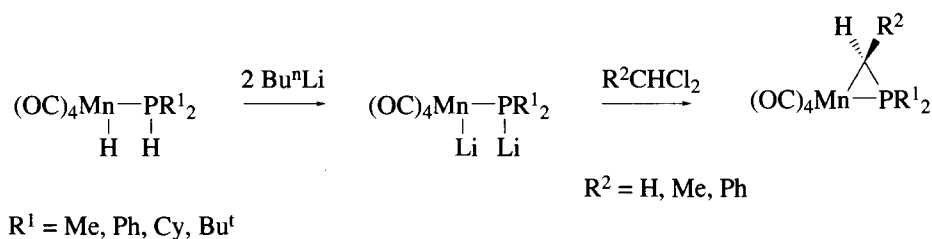
Phosphoniummetallacyclopropanes are commonly prepared by metal halide reductions in the presence of phosphines (Equation (13)) <85JOM(290)99>, (Equation (14)) <86OM2030>, (Equation (15)) <92JA4611>. They are also available by substitution of metal halides by organolithium reagents (Equation (16)) <82AG(E)311>, (Equation (17)) <82AG(E)921>. Phosphine deprotonation of metal halides also affords metallacycles (Equation (18)) <81JCS(D)1572>, (Scheme 4) <84OM675>.



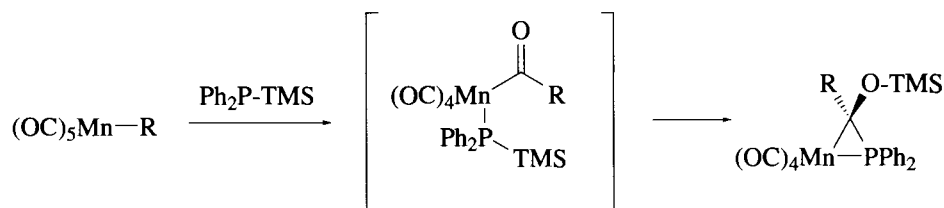


Scheme 4

A series of dianions provide phosphoniummanganacyclopropanes when treated with geminal dichlorides (Scheme 5) <87JOM(319)149, 89JOM(379)107>. Another series of manganese compounds which have an oxygen substituent on the ring have been prepared by treatment of metal alkyls with a silyl phosphine. Attack of the phosphine on the metal induces CO insertion into the metal-carbon bond. Migration of silicon to oxygen then induces ring formation (Scheme 6) <86OM936>.



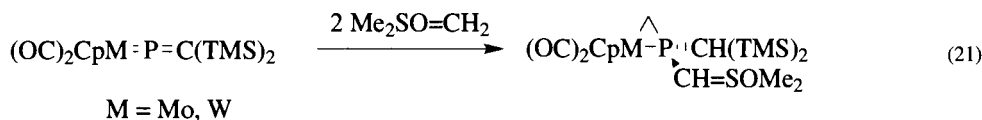
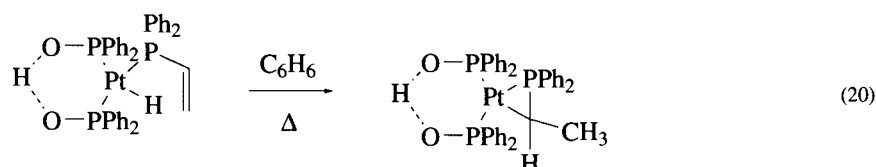
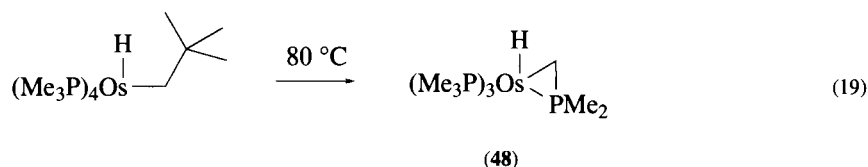
Scheme 5



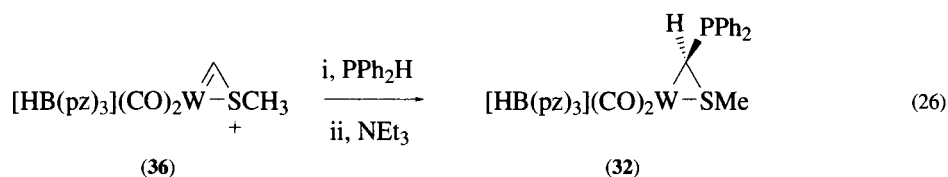
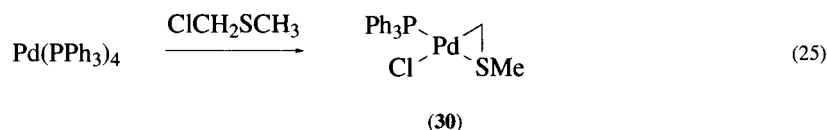
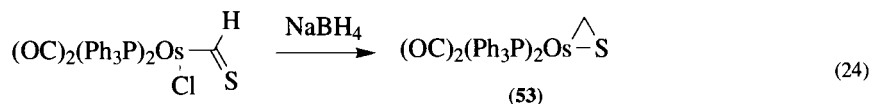
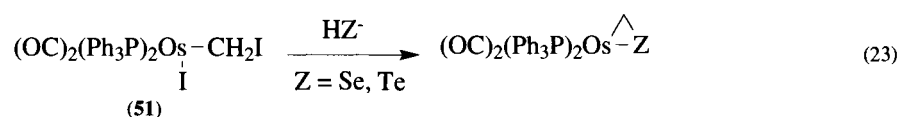
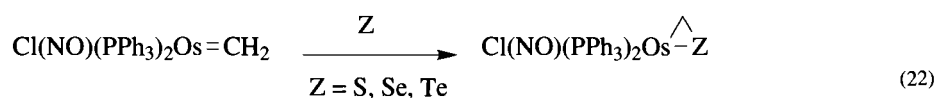
R = Me, Ph, CH₂TMS, 2-naphthyl

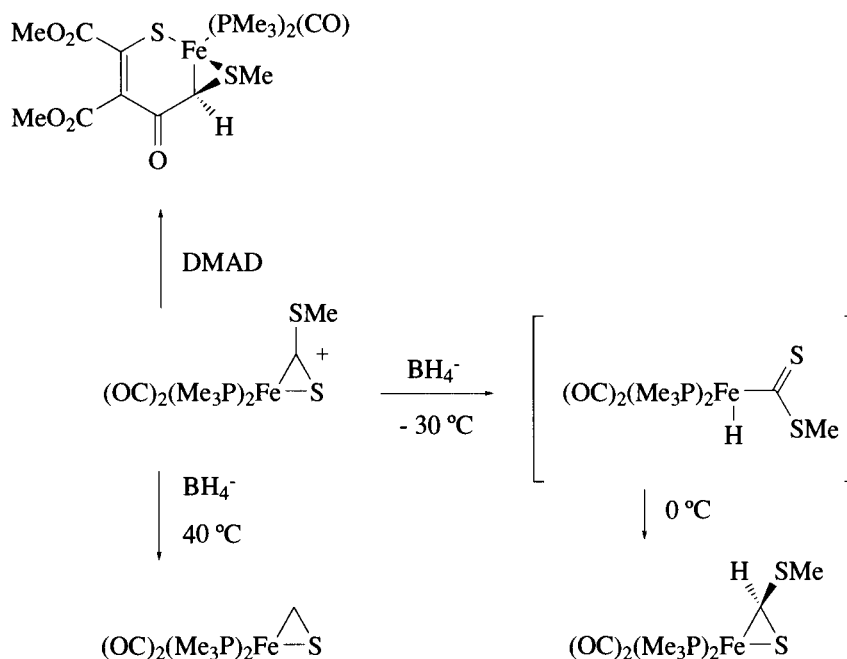
Scheme 6

Osmacycle (**48**) arises from an alkyl osmium compound by a complex thermal rearrangement which has been studied in detail (Equation (19)) <86JA1346, 90JA704>. A phosphonium-platinacyclopropane arises by intramolecular addition to an alkene (Equation (20)) <90OM1211>. Metallacycles are also available by addition of a sulfoxonium ylide to a metal-phosphorus double bond (Equation (21)) <90CB739>.



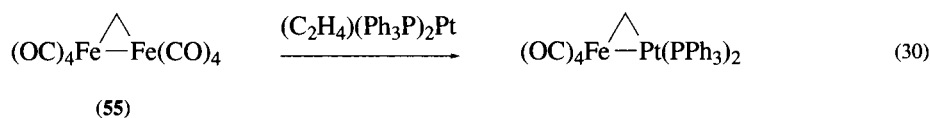
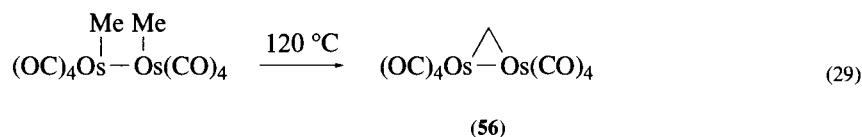
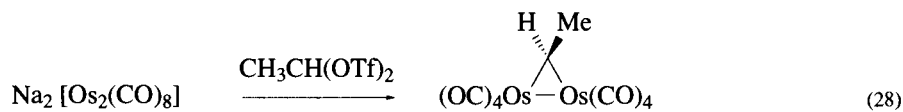
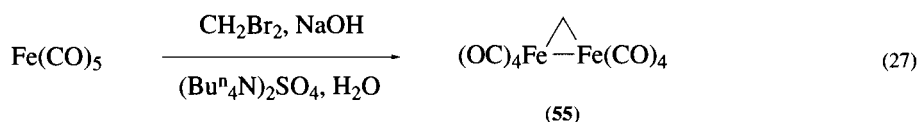
Routes to thiametallacyclopropanes and related molecules include addition to metal carbenes (Equation (22)) <83JA5939>, substitution of vicinal dihalides (Equation (23)) <83JOM(244)C53>, reductive cyclization of a halo thioaldehyde (Equation (24)) <77CC901>, and by reduction of a cationic sulfur three-ring. The same cationic complex affords an unusual fused ring product when treated with an electron-deficient alkyne (Scheme 7) <90JOM(386)95>. Syntheses of other sulfoxonium rings include metal insertion into a carbon-chlorine bond followed by ligand exchange (Equation (25)) <75JOM(92)C53, 76JOM(113)85> and by addition to a metallacyclopropene (Equation (26)) <86OM2481>. Most oxametallacyclopropanes are simply prepared by addition to a metal or by ligand exchange.





Scheme 7

Dimetallacycles are commonly synthesized by substitution of a geminal dihalide (Equation (27)) $\langle 86\text{JOM}(314)\text{C}43, 89\text{JOM}(359)205 \rangle$, (Equation (28)) $\langle 88\text{JA}7868 \rangle$. The osmium compound can also be prepared by elimination of methane from an acyclic complex (Equation (29)) $\langle 82\text{JA}7325 \rangle$. Many dimetallics have been synthesized by additions to metal carbenes $\langle 82\text{AOC}(20)159 \rangle$. Transmetalation reactions are also known (Equation (30)) $\langle 90\text{ICA}11 \rangle$.



1.17.10 RING SYNTHESIS BY TRANSFORMATION OF ANOTHER RING

These three-membered rings are normally only prepared from acyclic molecules or from other three-membered rings (see Equations (3), (4), (26), (30), and Scheme 7).

1.17.11 SYNTHESIS OF PARTICULAR CLASSES OF COMPOUNDS AND CRITICAL COMPARISON OF THE VARIOUS ROUTES AVAILABLE

Many of these three-membered rings have not been prepared by multiple synthetic routes. When a metallacycle is available by multiple routes, only the more efficient routes have been shown.

1.17.12 IMPORTANT COMPOUNDS AND APPLICATIONS

Diferracyclopropane (**55**) can be used to prepare acetates and trimethylenemethane complexes. The phosphoniummetallacyclopropanes also provide reversible protection of metal binding sites. In the mid 1990s a series of chiral azazirconacyclopropanes have been used for the asymmetric synthesis of amino acids by insertions into ring bonds <95JA986, 96JA3479>. Much of the utility of these three-membered rings remains to be discovered.