Tetrahedron Vol. 36, pp. 557 to 604
Pergamon Press Ltd., 1980. Printed in Great Britain

TETRAHEDRON REPORT NUMBER 77

OLEFIN INVERSION

PHILIP E. SONNET
Insect Attractants Laboratory, USDA, P.O. Box 14565, Gainesville, FL 32604, U.S.A.

(*Received in U.S.A. 9 August 1979*)

CONTENTS

INTRODUCTION

THE carbon–carbon double bond is a basic structural unit in organic chemistry, and research programs often deal with the syntheses, purifications, analyses, and chemical reactivities of alkenes, dienes, polyenes, etc. as the focal point of the research. Excellent reviews of olefin chemistry are available.[1] The development of new reaction methods, as well as the modification of known reactions to stereospecifically create double bonds or multiply unsaturated systems deservedly continues to receive much attention.[2] Moreover, reviews have been published of the methods for stereospecific olefin synthesis.[3] The interconversion of olefinic geometrical isomers, however, has received less attention. In principal, unique molecular features such as strain or proximite functional groups may prevent direct access to a double bond of desired geometry by common methods, and inversion of the isomeric compound may be the route of choice. Thus an all-*trans* carotenoid structure could potentially be obtained by reduction of an all-*trans* polyeneyne.[4] Known methods for reducing acetylenes to *trans*-alkenes are often not applicable to conjugated systems,[5] and investigators have catalytically hydrogenated the alkyne linkage following which they have inverted the newly formed *cis*-double bond to *trans*.[4] Additionally, the only preparations described for the highly strained *trans*-cyclooctene and its derivatives have begun with the *cis*-isomer (see below). Naturally, ready availability of one isomer to an investigator, perhaps due to the unique circumstances of the research program, may also prompt consideration of inversion to the desired isomer.

This review will deal with the subject of olefin inversion, that is the interconversion of *Z* and *E* isomers, with special emphasis on methods which produce product compositions other than that of a

thermal or photo equilibration. Methods for double bond migration[6] and olefin metathesis[7] will not be included. Following the conventions to which an earlier review adhered,[3b] reactions which were not stereospecific (productive of only one geometrical isomer) will be referred to as having a degree of stereoselectivity.[8] Since we will be concerned with both the processes by which olefins were inverted as well as the geometrical constitution of the product olefins, some confusion may arise through the use of the terms *cis* and *trans* to describe both the process and the product. The terms *syn* and *anti* shall be used to qualify reaction mechanism, while *cis* (or *Z*) and *trans* (or *E*) shall serve to define olefin (or other molecular) geometry[9] using established priority rules.[10]

(a) *Analyses of alkene composition*

A brief summary of the methods of analyzing and characterizing alkenes follows. Prior to the advent of gas chromatography, physical measurements including melting (freezing) point, index of refraction, density, boiling point, and dielectric constant were employed to assess the purity of simple alkenes.[11] Conclusions based on these data were often the result of considerable energy and devotion to chemistry. Because the diastereomeric bromine adducts of *Z*- and *E*- olefins were reduced by potassium iodide/methanol or acetone at different rates, these reduction rates could be useful for identification also.[12] Thus, the dibromide from *trans*-stilbene (*erythro*) was reduced in acetone over 100 times faster than was the *threo* isomer. Various chromatographic methods are now, of course, commonly employed in the analysis of product composition. However, simple alkenes, conjugated dienes, and fatty acid/alcohol derivatives have posed problems which taxed the limits of even glc resolution in recent years. Reviews are available for chromatographic determination of *Z*–*E* unsaturation in fats and oils,[13] argentation thin layer chromatography,[14] and liquid crystals in chromatography.[15] The use of silver nitrate on polar liquid phases for glc has been found useful, but is limited to very volatile compounds since the temperature limit for the phase is *ca.* 65°.[16] Electrophilic addition to, or epoxidation of, geometrically isomeric alkenes produces glc-separable diastereomers, and this topic has also received review.[13] Glass capillary columns have been advocated for the separation of unsaturated fatty acids,[17] and high performance liquid chromatography using silver nitrate–silica gel[18] has been successfully employed for both analytical and preparative purposes including the resolution of the four geometrical isomers of 3,13-octadecadien-1-yl acetate, components of the sex pheromone of certain lepidopterous peach pests.[19] The use of smectic liquid crystals as phases for gas chromatographic separation of long chain alkenes[20] and of cholesteric phases in capillary columns for the resolution of conjugated dienes[21] further extends the use of chromatographic techniques for the analysis of difficult isomer mixtures.

(b) *Purification*

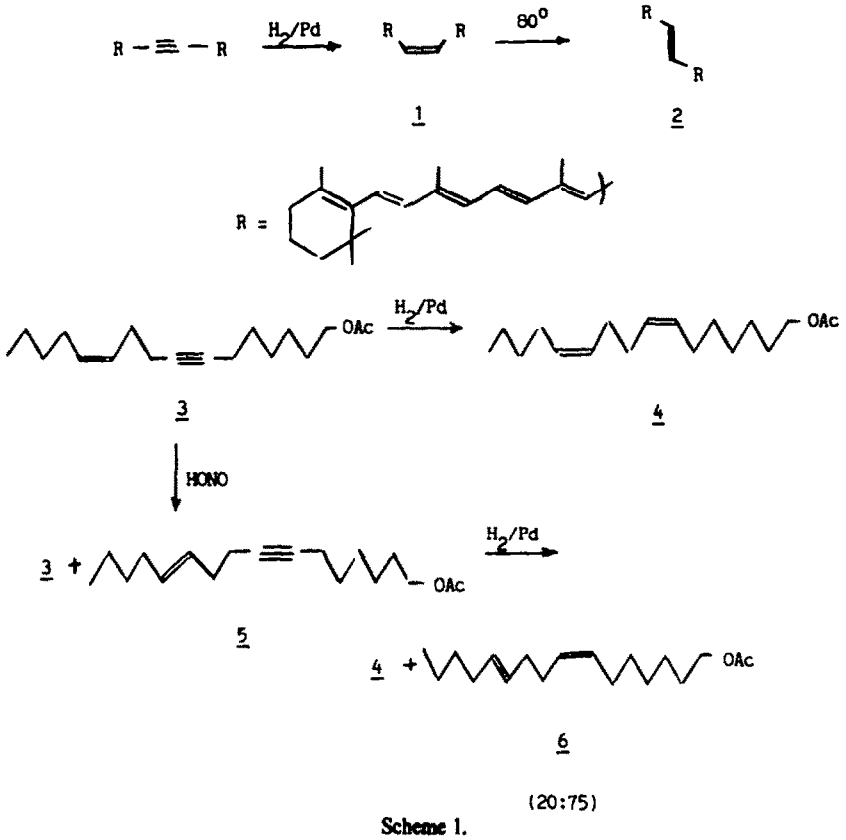
Rigorous purification of an alkene (diene, etc.) to remove traces of isomeric impurities has often been a difficult problem. Solutions have included $AgNO_3$- preparative thin layer chromatography,[22a] $AgNO_3$ column chromatography,[22b] and AgNO–HPLC.[18] The formation of a solid dibromide from a liquid alkene followed by recrystallization to obtain a pure diastereomer has been used to purify the alkene.[23] The olefin was then recovered by zinc debromination of the adduct (*anti*, but see below). Conjugated dienes could sometimes be purified through the formation of Diels–Alder addition products with SO_2[24] or with tetracyanoethylene.[25] Since the *E,E*-dienes react most readily, such a procedure was useful if the *E,E*-isomer was specifically sought, or if it was the contaminant to be removed. Urea inclusion complexes have also found great utility for otherwise difficult olefin purifications.[26] Several recent patents also describe the separation of isomers by means of zeolites.[27]

I. DIRECT ISOMERIZATION

(a) *Thermal–chemical isomerization*

Gilman[28] provided a brief summary of the most frequently employed techniques for affecting *cis-trans* isomerism. Such isomerizations could be complete only if the energy difference between a pair of isomers was substantial. Otherwise, mixtures resulted and the chemist was left the task of separating the required isomer from the equilibrated mixture. Maleic and angelic acids were, in fact, effectively converted by heating to fumaric and tiglic acids, respectively. Conjugation generally has the additional effect of lowering energy barriers to interconversion and this fact can be exploited for synthesis. A classic illustration was provided by the preparation of (all *trans*)-β-carotene, 2 (Scheme 1).[4] An alkyne precursor was hydrogenated (Pd catalyst) yielding 15,15′-*cis*-β-carotene, 1. The more stable all *trans* isomer 2 was then readily obtained by heating 1 in petroleum ether at 80°.

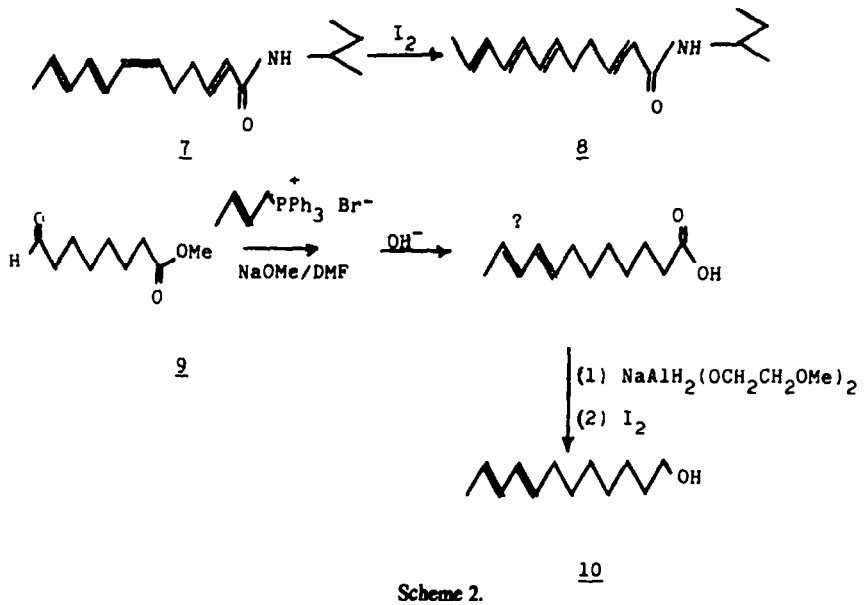
Additionally, a wide variety of chemical reagents can be made to add reversibly to olefins and thereby generate equilibrated mixtures.[28] Halogen, halogen acids, nitric and nitrous acids, and PCl_5 were reportedly effective. Nitrous acid treatment of oleic acid to give mixtures containing the isomer, elaidic acid, led to the term "elaidinization" to describe the process whereby olefin geometry became equilibrated in order to obtain the geometrical isomer.[28a] A more definitive study indicated that NO_2 radical was probably adding reversibly, and in common with other reversible radical additions, (1) the intermediate carbon radical species had an opportunity to invert configuration and (2) the double bond did not readily shift position.[28b] An example of this reagent's utility involves the synthesis of the two components of the sex pheromone of the pink bollworm, *Pectinophora gossypiella*; namely (*Z,Z*)- and (*Z,E*)-7,11-hexadecadien-1-ol acetates, **4** and **5**, respectively (Scheme 1).[30] The (*Z,Z*)-isomer **4** was



Scheme 1.

obtained by hydrogenation of the acetylenic linkage of the common intermediate, (*Z*)-11-hexadecen-7-yn-1-ol acetate, **3**. Treatment of **3** with aqueous HONO produced a mixture rich in the (*E*)-enyne, **5**, hydrogenation of which gave a diene mixture in which the (*Z,E*)-isomer, **6**, predominated. Suitable blending of the two preparations afforded the 1:1 ratio of isomers required for optimum attraction of the male moth.

The most useful reagents to promote geometrical isomerism have been iodine (→I·) and diphenyl thioglycolic acid (→RS·). Isomerization of olefins with iodine are brought about in a nonpolar solvent sometimes with additional light (sunlamp). Extensive positional isomerism occurs, however, with nonconjugated olefins before equilibration of geometrical isomers can be achieved.[31] For conjugated olefins it is often possible to cause rapid equilibration and, by lowering the temperature, cause the all-*trans*-isomer to precipitate from solution. Numerous examples are available in chemical literature and only two examples will be given as demonstration. An insecticidal amide derived from several trees of the families Rutaceae and Compositae, α-sanshool, **7** (Scheme 2), was isomerized to the all-*trans*, β, isomer, **8**, which precipitated from solution.[32] Roelofs *et al.*[33] identified and synthesized the sex pheromone of the codling moth, *Laspeyresia pomonella*, which is (*E,E*)-8,10-dodecadien-1-ol, **10** (Scheme 2). The diene structure was generated by the condensation of an allylic phosphorane with the aldehyde, **9**. The geometrical constitution of the condensation product was not homogeneous. Reduction



Scheme 2.

gave the crude dienol which was treated with I_2 and sunlight to obtain a mixture in which the *E,E*-isomer, **10**, predominated (50% of the total dienols).

Nonconjugated olefins when heated with selenium or sources of sulfur radicals underwent both geometrical and positional isomerism. However, sulfur radicals generated from diphenyl sulfide and diphenyl disulfide by long wave length light (> 300 nm) produced mixtures of geometrical isomers whose composition represented thermodynamic equilibrium with only 2–3% migration of the alkene linkage. Table 1 provides a comparison of equilibrium ratios obtained with several olefins by using UV-induced

Table 1. *Z,E*-Interconversion by direct isomerization[a]

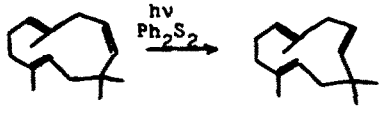
Alkene	Method	%E	%Z	Positional isomerism
(Z)-2-Butene	Acetophenone (>320nm)	75	25	none
(Z)-2-Butene	Diphenyl sulfide (>300nm)	72	28	none
(E)-2-Butene	Diphenyl sulfide (>300nm)	72	28	none
(Z)-2-Butene	Na/Al_2O_3	73	27	equilibrated
2-pentene[b]	Acetophenone (>320nm)	85	15	none
	Diphenyl sulfide (>300nm)	81	19	none
	Na/Al_2O_3	82	18	equilibrated
(Z)-5-decene	Acetophenone (>320nm)	89	11	none
(E)-5-decene	Acetophenone (>300nm)	89	11	none
(Z)-5-decene	Diphenyl sulfide (>300nm)	84	16	none
(E)-5-decene	Diphenyl sulfide (>300nm)	85	15	none
(E)-Stilbene	- (>280nm)	29	71	-
(E)-Stilbene[c]	Diphenyl disulfide (>320nm)	40	60	-
(E)-Stilbene[c]	Diphenyl disulfide (>360nm)	93	7	-
(E)-Stilbene	Na/Al_2O_3	100	0	-

[a] Ref. 31a

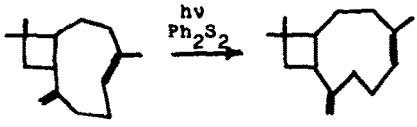
[b] 56% Z : 44% E.

[c] 70% Z : 30% E.

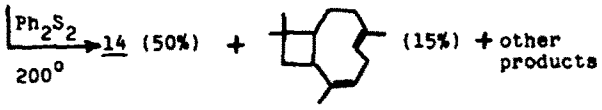
reversible radical addition, Na/Al_2O_3, and acetophenone photosensitized equilibration.[31] The studies reported in Table 1 were also extended to a number of nonconjugated cyclic dienes.[34] Evidently, however, thermally generated sulfur radicals sometimes can be successfully employed to affect geometrical isomerization. Thus, for example, (*Z,E,E*)-1,5,9-cyclododecatriene and the (*E,E,E*)-isomer were interconverted by heating in benzene under reflux with a catalytic quantity of thiolglycolic acid.[35,36] The synthesis of humulene 12 (Scheme 3) provides an example of olefin inversion promoted by



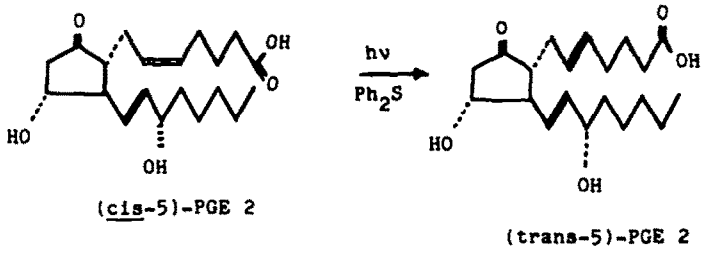
11 12



13 14 (95%)



15

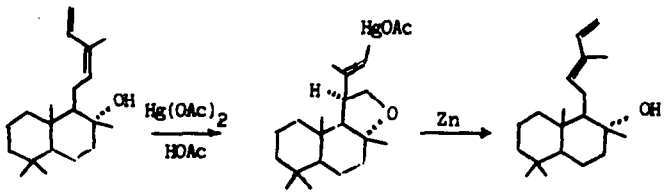


(cis-5)-PGE 2 (trans-5)-PGE 2

Scheme 3.

photoinduced sulfur radicals.[37] Exposure of the triene 11 to diphenyl disulfide and light of >350 nm generated a mixture of products from which both the starting material and humulene were extracted with 50% aqueous $AgNO_3$.[38] Preparative glc afforded pure humulene. In similar fashion (−)-caryophyllene, 13, was converted in 95% yield to (−)-iso-caryophyllene, 14 (Scheme 3).[39] Attempted thermal isomerization of 13 gave only a 50% yield of the isomer 14 accompanied by polymers and two other compounds, one of which was identified as the positional isomer, 15. Using light of >350 nm and diphenyl sulfide in benzene-MeOH, Bundy *et al.*[40] isomerized the prostaglandin, (*cis*-5)-PGE 2. The (*trans*-5) isomer was obtained in 22% yield after careful chromatography on acid washed silica gel. Finally, it should be noted that simple alkenes have also been equilibrated employing photoinduced radicals from tetrabutyltin[41a] and tributylgallium,[41b] although these procedures seem to offer no significant advantage.

Ordinarily, electrophilic addition to olefins is not useful for *Z–E* interconversion because the addition may be highly stereoselective and/or lacks reversibility. Some exceptions, however, exist. Thus, a strained cyclic olefin such as (*E*)-cyclononene could be isomerized to the *Z*-isomer with β-naphthalenesulfonic acid at 150°.[42] Presumably this inversion would not be successful for unsymmetrically substituted strained cyclic alkenes. An interesting inversion was provided by Mills[43] who found that the $Hg(OAc)_2$ adduct of the oleoresin, *Z*-abienol, 16, (Scheme 4) was reduced by zinc to give the *E*-isomer. The fortuitously placed OH group guided the formation of the adduct 17. It was also possible to catalytically convert the *cis* to *trans* using $Hg(OAc)_2$; the ratio of isomers at equilibrium was 4:1 (*E*:*Z*). A study of Pd-catalyzed reactions of olefins permitted equilibration of (*E*)-1,2-dideuterioethylene in the presence of palladium chloride complexed with benzonitrile.[44] This reaction occurred without isotope



16 17

Scheme 4.

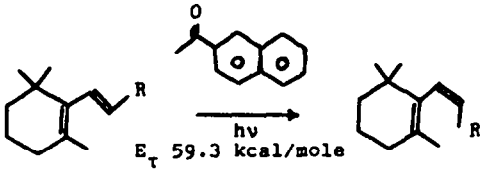
redistribution; i.e. mono- and tri-deuterioethylenes were not obtained as was the case for other Pd complexes examined. $PdCl_2$ likewise affected isomerization of *E*-1,2-diphenylpropene.[45] Preferential precipitation of the Pd complex containing the potential *Z*-isomer aided in purifying that compound.

Sulfur dioxide adsorbed on a variety of metal oxides and zeolites has the capacity for interconverting *cis* and *trans* isomers.[46] These isomerizations also occurred without positional isomerism.

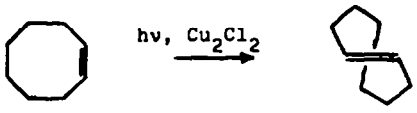
(b) *Photoisomerization*

Excellent and detailed discussions of olefin photoisomerization have been published.[47,48] Calculations of Mulliken *et al.* predicted that both the lowest energy excited singlet and triplet states would have energy minima at that configuration in which the planes of the methylene groups were mutually perpendicular. This twisted geometry was expected to minimize electron–electron repulsion. The derived potential energy diagram for the electronic states of ethylene indicated that the twisted singlet could produce either the *cis* or *trans* olefin by internal conversion and that intersystem crossing from the twisted triplet could likewise produce either olefin. Practically speaking, however, direct irradiation of alkenes will likely produce $\{\Pi^2s + \Pi^2s\}$ cycloaddition in competition with the desired isomerization.

The pioneering efforts of Hammond *et al.*[49] demonstrated that the compositions of the mixtures of a photostationary state obtained by photosensitization was a function of the nature of that photosensitizer. Hence, the investigator could in principal determine in advance a photosensitizer so as to favorably affect the composition of his isomerized mixture. Sensitizers having low excitation energies functioned as true photocatalysts, which is to say the photostationary state of the reaction mixture approached that at thermal equilibrium. Actually, the sensitized photoisomerization of alkenes is rather complex and several sensitizer–olefin interactions may be operative.[50] Nevertheless, the selective transfer of energy to a geometric isomer of lower triplet energy in order to enrich the material in the other isomer remains a valuable synthetic tool for the chemist.[49] An illustrative example was provided by Ramamurthy *et al.*[51] who inverted several trans-β-ionyl derivatives in high yield to the crowded *cis* isomers (Scheme 5). The critical E_T was 65 kcal/mole. At higher photosensitizer triplet energies, the products contained *trans* isomer indicating excitation of the *cis* compound. The E_T of the *cis* compounds was estimated as 75 kcal/mole, expectedly higher (noncoplanarity of the *cis*-diene) than that normally observed for conjugated dienes (55–60 kcal/mole). Although E_T's of a given pair of geometrical isomers may preclude complete alkene inversion, it is clear that mixtures enriched in the isomer of greater E_T can be easily generated.



R = Me, Et, Ch_2OH, CN, $COCH_3$, CO_2H, Ph, $CH(CH_3)OH$



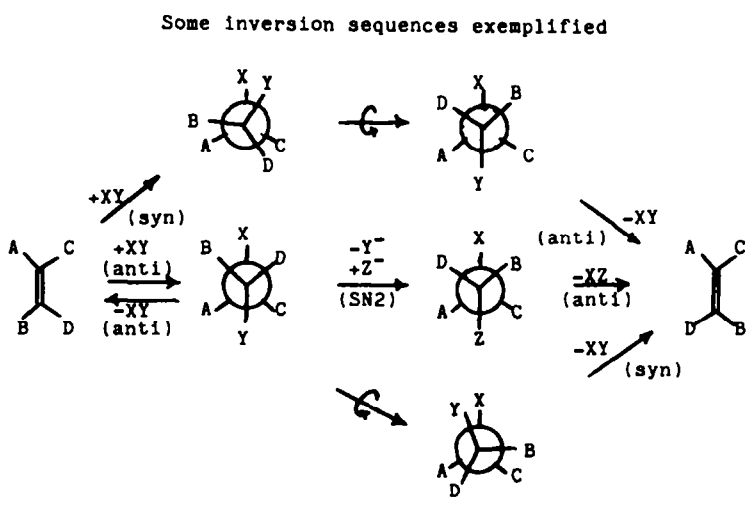
Scheme 5.

Excitation of olefin complexes to achieve isomerization appears to have been less well studied. Ferrocene and 2,4-pentadiene formed a complex which, when irradiated, dissociated to a triplet state of ferrocene and a triplet state of the olefin.[52] The latter either relaxed to *cis* or *trans*-2,4-pentadiene, or reacted (by addition) to a ground state olefin molecule. Of greater utility, Deyrup and Betkowski[53] irradiated cyclooctene at 2537 nm for 24 hours with Cu_2Cl_2 (Scheme 5). *Trans*-cyclooctene was recovered in 19% yield and 99% purity by virtue of its greater solubility in aqueous $AgNO_3$. Moreover, the recovered *cis*-cyclooctene could be recycled. The considerable stability of a *trans*-cyclooctene-Cu^I complex was responsible for the shift in photoequilibrium toward *trans* product.[54] Similarly (*Z,E*)-1,5-cyclooctadiene was obtained from the (*Z,Z*)-isomer (30–40% yield). *Cis-trans* isomerism has also been reportedly induced by polyenes.[55] Low lying triplet levels in the polyenes and sufficient S–T splitting in the olefin polyene complex were deemed responsible for the isomerization.

Cycloadditions and cycloreversions of, for example, conjugated dienes are controlled by orbital symmetry considerations,[56] and proceed therefore with opposite stereochemical consequences when induced thermally or photochemically. Thus, (*E,E*)-2,4-hexadiene was transformed photochemically to *cis*-1,2-dimethyl-3-cyclobutene (disrotatory closure) which, upon heating, reverted to (*E,Z*)-2,4-hexadiene (conrotatory opening).[57] In general, both conrotation and disrotation can occur in two ways; i.e., each cyclobutene isomer would lead to two of the four diene isomers. Hence, preparation of a (*E,E*)-diene could in principle be accompanied by the (*Z,Z*)-isomer in a ratio determined by the steric bulk of the rotating groups. In the case of *E*-1,2-dimethyl-3-cyclobutene, only (*E,E*)-2,4-hexadiene was obtained.[57] Clearly, also, two (*E,Z*)-isomers would be isolated in the case of the synthesis of an unsymmetrical conjugated diene. Thus, while many examples exist to show how faultlessly the symmetry considerations predict the geometry of an alkene product, the process of interconversion by photoclosure/photoaddition or thermal reversion has not been generally useful for interconverting conjugated dienes.[58]

2. OXIDATIVE ADDITIONS TO ALKENES FOLLOWED BY REDUCTIVE ELIMINATION

The sequence of oxidative addition to an alkene involving one or more S_N2 displacements on carbon, and reductive elimination will return an olefin of inverted geometry (providing each step is stereospecific) if the total number of invertive steps is odd (Scheme 6). Since *anti* addition of XY (invertive) followed by *anti* elimination of XY (invertive) constitutes an even number of invertive steps, retention of geometry is observed (e.g. alkene + Br_2, then Zn debromination). However, an intervening S_N2 displacement, for example of Y by Z, followed by *anti* elimination of XZ should invert olefin geometry. A *syn* addition (noninvertive) followed by *anti* elimination likewise constitutes an odd number of inversions and should produce an olefin of opposite geometry. In addition to the several sequences enumerated in Scheme 6 (in principle, one can imagine an infinite number of sequences if no restrictions are placed on the number of steps and neither the chemist nor his molecules wear out), the large numbers of reagents which could be employed for addition and reduction provide a very large potential

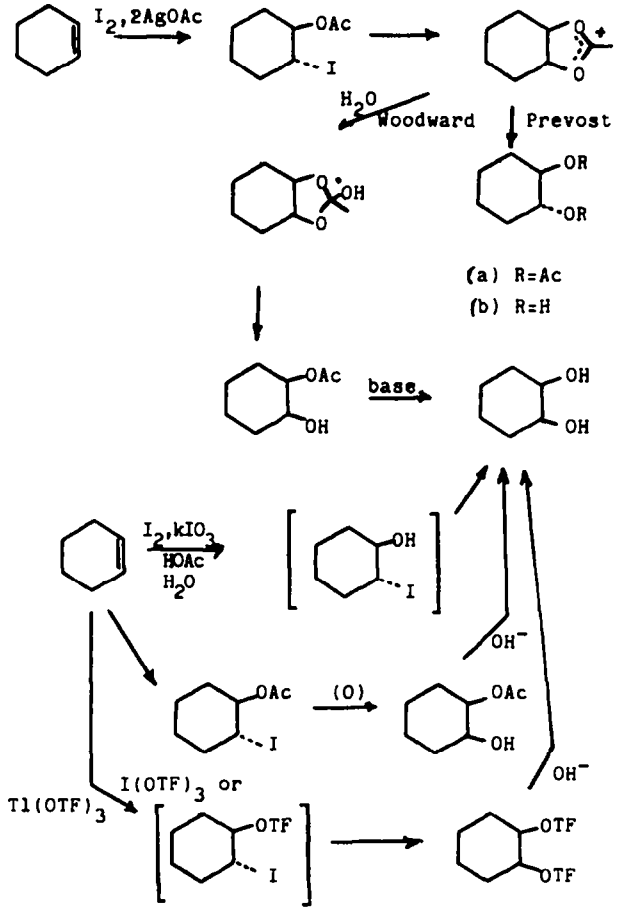


Scheme 6.

for olefin inversion. Relatively few studies, however, have been directed toward this goal. Therefore, the reagents and processes of addition, and of elimination, have been separately summarized. The data includes particularly those reagents for addition which are deemed appropriate for this subject, i.e. the added groups must be reasonably easily displaced from carbon. It will be evident that many sequences can still be examined for inverting olefin geometry, which, because of the availability of reagents, ease of handling, and mildness of reaction conditions, may be superior to the sequences which have been thus far described.

(a) Anti *additions summarized*

This is not intended to be an exhaustive compilation of *anti* additions to olefins; excellent discussion of mechanism and compilation of electrophilic reagents are available.[59-62] The addition of electrophilic reagents to olefins is generally *anti*.[59,60] Thus, it is possible to produce stereospecifically *erythro* difunctionalized compounds from *trans* alkenes and *threo* from *cis* alkenes with a wide variety of reagents. If the substituents themselves do not qualify as "good leaving" groups, then they can often be transformed to such. Bromine and modified brominating agents, such as pyridinium bromide perbromide,[59] bromine chloride,[63] and chlorine[61] have been most commonly employed for controlled *anti* addition of halogen. *Trans*-halohydrins and ethers of halohydrins can be obtained most directly using N-haloimides in moist solvents[62,64] or in alcohols,[59] respectively. Also, iodohydrins can be obtained by direct iodination using I_2 and iodous acid,[65] or aqueous I_2 in tetramethylene sulfone-$CHCl_3$.[66] N-halosuccinimide in carboxylic acids offers access to *trans* halohydrin esters,[59,67] and the reaction of *vic*-diols with α-acetoxyisobutryl halides also results in the formation of *vic*-haloesters which are the result of a single inversion of carbon.[68] *Anti* dihydroxylation can be achieved by the Prevost reaction,[59,69] which entails treating an alkene with an equivalent of I_2 and two equivalents of the silver salt of a carboxylic acid (forming the Simonini complex). The *trans* haloester which is initially formed (Scheme 7) becomes transformed to a *trans* diester (backside involvement by the ester carbonyl as the halide ion



Scheme 7.

departs), which, upon saponification, produces a *trans* 1,2-diol. A recent report suggested thallous acetate instead of the silver acetate.[70] Treatment of alkenes with hydrogen peroxide-formic acid[71a] (or persuccinic,[71b] or pertrifluoroacetic acids[71c]) followed by saponification also affords *trans* diols. Additionally, these may be obtained by acid-catalyzed hydration of epoxides[72] or directly from the alkene with *ortho*-percarboxybenzenesulfonic acid.[73] Complications during the addition of electrophilic reagents to alkenes do arise, however, when the alkene has the potential for molecular rearrangement or can afford stabilization for an incipient carbonium ion. The situation is further complicated if the initial Π-complex or onium ion formed by reaction of electrophile with double bond is weak. Thus, for example, trisubstituted alkenes do not add chlorine cleanly,[61] and the crowded 1,2-disubstituted olefin, (*E*)-di-t-butylethylene, reacts with chlorine producing 2,4-dichloro-2,3,5,5-tetramethylhexane which arises from the migration of a methyl group.[74] Clearly, however, *anti*-addition can provide a spectrum of stereospecifically derivatized olefins with which to proceed.

(b) Syn *additions summarized*

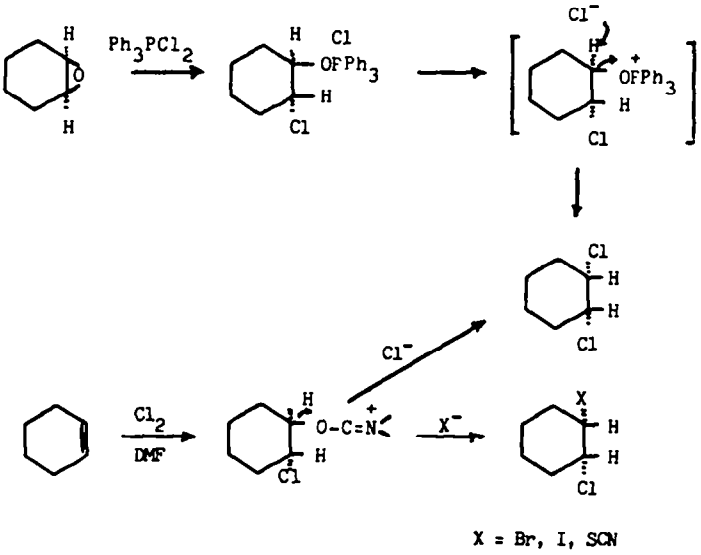
A stereospecific *syn* addition to an olefinic double bond has always been of considerable interest because it constitutes an exception to the general observation of *anti* addition. In 1963, Dewar and Fahey reported *syn* addition of DBr to acenaphthene, indene and 1-phenylpropane.[75] Cristol *et al.* had found that chlorine also added *syn* to acenaphthene.[76] *Syn* addition of HX has been reviewed,[77] and mechanistic interpretations for these additions have been advanced.[78,79] Many of the reactions which produce *syn* additions to alkenes, however, occur by initial *trans* addition to the alkene. The initial adduct may undergo an inversion of carbon configuration *in situ*, or as the result of a discrete subsequent laboratory operation, producing a *cis* adduct. Such a transformation will be referred to as a (net) *syn* addition.

The "wet Prevost" reaction, or Woodward hydroxylation procedure,[80] for example, provided a method for net *cis*-hydroxylation (Scheme 7). The intermediate *trans*-haloester solvolyzed with acetate participation. Interception by water of the onium ion produced a *cis*-diol monoacetate.

An effort has been made to modify, or improve upon, the Woodward hydroxylation procedure; in particular to circumvent the use of silver salts (Scheme 7). *Vic*-iodoacetates, which are available as *trans* addition products (olefin, I_2, KIO_3, acetic acid)[81] were converted via corresponding iodohydrins to *cis*-diols in refluxing aqueous acetic acid (76%).[82] Alternatively, the sequence of alkene → *cis*-diol could be carried out using the same reagents without isolation of intermediates in 70% yield after saponification (Scheme 7).[82] *Trans* iodoacetates and iodotrifluoroacetates reacted with *meta*-chloroperbenzoic acid to substitute OH for I.[83] This replacement occurred with inversion of configuration, hence the products were glycol monoesters of (net) *syn* addition. Parenthetically, the reaction was found useful for converting primary (but not secondary) alkyl iodides to alcohols. *Vic*-diol derivatives which were products of (net) *syn* addition were also available through reaction of alkenes with iodine *tris*-trifluoroacetate[84] (I_2, fuming nitric acid and trifluoroacetic anhydride)[85] or with thallic trifluoroacetate.[86] Additional experiments indicated that the *bis*-trifluoroacetates from the iodine *tris*-trifluoroacetate reactions were formed from intermediate *trans*-iodoesters by further reaction with iodine trifluoroacetate. Positive iodine in the solution was responsible for electrophilic pull on bound iodine with solvent displacement occurring from the rear. *Trans-2-iodocyclohexanol trifluoroacetate exposed to iodine tris*-trifluoroacetate in pentane formed the *bis*-trifluoroacetate (95% *cis*). These reactions are summarized in Scheme 7. In analogous fashion the reaction of 5α-cholest-2-ene with thallic trifluoroacetate in acetic acid produced mostly the 2β,3β-diol (9:1) after saponification.[86] The authors noted that a 5-hydroxyl group facilitated the reaction and produced a cleaner *syn* addition.

These (net) *syn* additions to form *vic* diols, or their esters, share in common the generation of *vic*-functionalization of the more hindered side of, for example, cyclic olefins offering steric differentiation of direction of initial electrophilic attack. Thus thallic acetate converted 5-α-cholest-2-ene to the *cis*-β-diol. By contrast, osmium tetroxide and potassium permanganate oxidations produced the *cis*-α-diol.[87] Modifications to the OsO_4 dihydroxylation include the use of OsO_4 catalytically with amine oxides as the oxidizing agents[88] and the reactions of alkenes with potassium osmate-sodium chlorate.[89] A phase transfer catalysis method for *vic*-dihydroxylation was introduced by Weber and Shepard[90] which employs $KMnO_4$. The yields were comparable or better than those reported by the use of $KMnO_4$ or OsO_4 in prior methodology.[87] An interesting photochemical reaction of cyclohexane with nitrobenzene produced an unstable 1,3,2-dioxazolidine which upon hydrogenation over platinum yielded 51% *cis*-1,2-dihydroxycyclohexane (and aniline).[91]

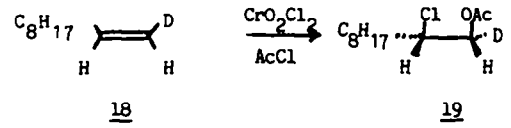
Several procedures are available for the conversion of alkenes to *cis*-1,2-dihalogen adducts. Uemura and co-workers reported that antimony pentachloride in CCl_4 reacted with cyclohexene producing *cis*- and *trans*-1,2-dichlorocyclohexanes (4.36:1).[92] Additions to the isomeric 2-butenes likewise yielded a predominance of *syn* addition. The reactions of the isomeric 2-octenes, however, were much less selective. Triphenylphosphine dibromide reacted with cyclohexene oxide producing mixtures of the diastereomeric 1,2-dibromides.[93] The *cis*-1,2-dichloride, however, was obtained from the epoxide in 80% yield and 95% geometrical purity with triphenylphosphine in CCl_4,[94] and in 72% yield free of *trans*-isomer by reaction of the epoxide with triphenylphosphine dichloride.[95] The initial product of epoxide cleavage, probably a *trans*-chlorooxyphosphorane,[96] suffered a second nucleophilic displacement by chloride, producing triphenylphosphine oxide as the byproduct (Scheme 8). Yields of dibromides from both *cis*- and *trans*-1,2-dialkylepoxides reacted stereospecifically with triphenylphosphine dichloride to efficiently provide *erythro* and *threo* dichlorides, respectively. Chlorine in DMF reacted with cyclopentene and cyclohexene forming *trans*-1,2-haloiminium salts (Scheme 8).[98] Displacement of the iminium



Scheme 8.

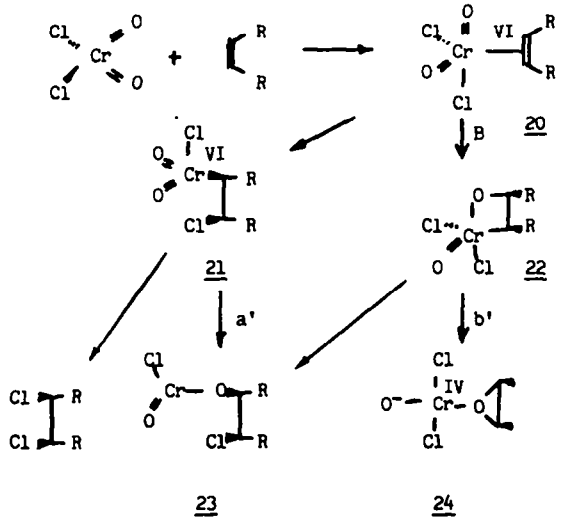
substituent was achieved with chloride, bromide, iodide, and thiocyanate ions giving the corresponding *cis* adducts in 40–60% yields. The successful backside displacement of a substituent adjacent to a Cl-bearing carbon can be attributed to the relatively high energy of a chloronium ion[99] which, apparently, did not intercede in any of the reactions described above whether the carbon framework was cyclic (which should tend to favor such interaction from an initial *trans* adduct) or not.

An intriguing reaction was that of chromyl chloride with olefins. Chloroketones were found to be the principal products when reactions were conducted in acetone,[100] but at low temperatures in CH_2Cl_2, *vic*-chlorohydrine and epoxides were the major products formed.[101] In fact, if the reaction was conducted with acetyl chloride as a cosolvent, chloroacetates were formed in 50–90% yields.[102] *Cis*-5-decene yielded a chloroacetate in which the *threo*:*erythro* ratio was 2:1; the *trans*-olefin produced a *threo*:*erythro* ratio of 45:1. *Trans*-cyclododecene produced the *threo*-isomer (19:1), and cyclohexene gave a chloroacetate in which *threo* predominated (25:1). The reaction of (*Z*)-1-deuterio-1-decene, **18** (Scheme 9) produced *erythro*- and *threo*-2-chloro-1-acetoxy-1-deuteriodecane, **19** (Scheme 9) in a ratio of 4:1. A mechanistic picture was derived by Sharpless to account for the (previously)[101] observed formation of *cis*-1,2-dichlorides and epoxides, as well as the tendency to produce *cis*-chloroacetates by depicting an initial Cr^{VI}-olefin II-complex, **20**, which either was transformed into the frontside addition product, **21**, or into the cyclic structure, **22**. Both of these possible intermediates involved formal C–Cr σ-bonds. The chlorometallated structure could undergo a reductive elimination to form the *cis*-dichloride or could rearrange to the chlorochromate, **23**; both processes would have to proceed with retention of configuration on carbon. The cyclic intermediate, **22**, similarly rearranged to the chlorochromate or underwent a 1,2-shift leading to epoxide via **24**.[103] Chloroacetate production, therefore, was viewed as a competition between interception of the chlorochromate yielding a *cis*-addition product, and reaction of the acetyl chloride with the epoxide producing the *anti* diastereomer.



18 19

(4:1, erythro:threo)



23 24

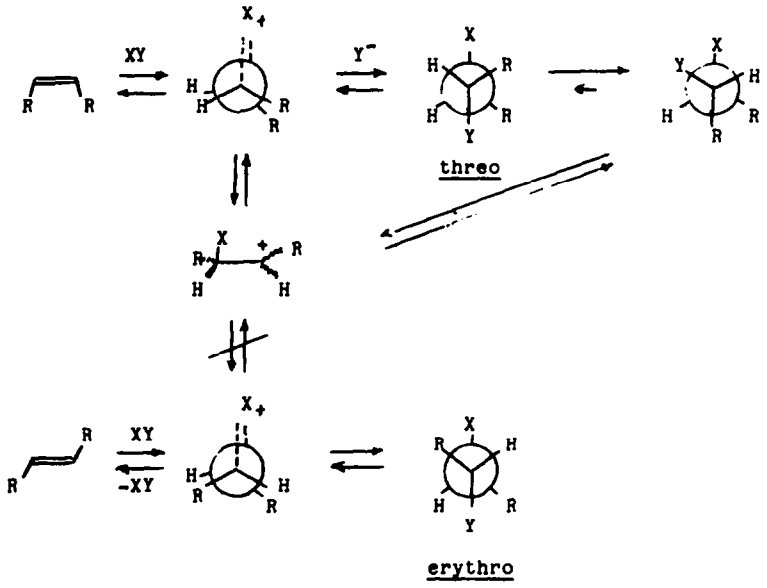
Scheme 9.

(c) Anti *eliminations summarized*

In order to complete an olefin inversion following *syn* or (net) *syn* addition, an *anti* reductive elimination must be accomplished. The most commonly observed stereochemical consequence for reduction of *vic*-disubstituted compounds has been *anti*. Hence, olefins may be protected as *anti* adducts from which they are subsequently recovered by reductive elimination.[104] Miller *et al.*, exhaustively studied reducing agents for *meso*- and *d,l*-stilbene dibromides. The *meso*-dibromide gave *trans*-stilbene with all reducing agents examined. Reductions of the *d,l*-isomer gave variable stereochemical results. Anionic species (iodide, benzenesulfinate, phenylthiolate and hydride) as well as Pt^{2+} gave 75–90% *dis*-stilbene (the product of *anti* reduction), while one-electron agents (β-naphthol, cuprous, ferrous, chromous, titanous) produced stilbene that was 96–100% *trans*. Metals (Zn, Cd, Sn) gave variable results.

For aliphatic systems, reductive elimination by iodide likewise generally proceeded with *anti* stereochemistry.[105] Since the *anti* reductions were first order in iodide as well as dibromide,[106] the mechanism had for some time been viewed as a concerted loss of both groups which were being eliminated. Very careful kinetic studies by Miller's group[107,108] led to the proposal of a stepwise ionic path for debromination and a reiteration of the suggestion that considerable mechanistic simplification was achieved if one viewed such eliminations as ionic retroadditions or solvolytic eliminations (Scheme 10).[109] When conformational alignment of the departing groups may be easily attained (such is the case for an *erythro* compound), the elimination is stereospecifically *anti* and evidence for a short-lived "onium" ion intermediate has not been obtained. The iodide ion could be involved in aiding the formation of the onium ion or reacting with a small equilibrium concentration of such an ion to drive the reaction toward olefin (and trihalide ion). Reduction of *d,l*-stilbene dibromide, however, was best explained by intervention of aryl-stabilized carbonium ions. The phenyl substituents of the stilbenes aggravated the steric stress for proper conformational alignment during the reduction of the *d,l*-dibromide, and they stabilized the incipient carbonium ions. By comparison, reduction of aliphatic 1,2-dibromides was more nearly stereospecifically *anti* from both diastereomers (however, see the section dealing with (net) *syn* eliminations).

Recently described modifications and additions to the methodology for elimination by iodide include the use of hexadecyltributylphosphonium bromide as a phase transfer catalyst in a toluene-H_2O system.[110] Sodium iodide was used catalytically and sodium thiosulfate was employed to regenerate iodide ion. The reduction of *meso*-stilbene dibromide was cleanly *anti*, and the *d,l*-dibromide provided



R = alkyl: less crossover from threo diastereomer.

R = phenyl: considerable crossover.

Scheme 10.

much purer *cis*-stilbene (89%) than had been heretofore obtained. Sodium iodide reductions of methoxy-mercuration adducts (*anti* elimination) have been described,[111] and sodium iodide was also effective for the reduction of epoxides in acetic acid (probably proceeding via iodoesters or iodohydrins).[112] In the latter reaction zinc has been used as a coreagent.[113] Zinc and sodium iodide likewise have been combined for reducing ditosylates, although the stereochemical outcome was not evaluated.[114]

Sodium sulfide was employed to reduce *vic*-dinitro compounds.[115] This particular reduction was light-catalyzed and probably proceeded via radical anions. Therefore the reaction would be expected to lack stereospecificity. Sodium selenide reduced 1,2-dibromides to terminal alkenes producing Se as the byproduct,[116] and sodium dithionite in refluxing DMF converted *meso*-stilbene dibromide quantitatively to *trans*-stilbene.[117] This apparent *syn*-elimination was probably due to *cis-trans* isomerization of the product, however, because each of the 2,3-dibromobutanes produced 1:1 mixtures of 2-butenes under these conditions. Another reduction involving sodium dithionite employed DMSO as the solvent[118] under which conditions *erythro*-1,2-dibromo-1-phenyl alkanes were reduced to (*E*)-1-phenylalkenes by *anti* elimination. This reagent, as well as thiourea,[119] has doubtful utility for the debromination of phenyl substituted systems (yields were low and pure *cis* not obtained), but may be worth examining with aliphatic dibromides. Reduction of *vic*-dihalides by mercaptides was thwarted by S_N2 displacement even in simple aliphatic systems.[120] Additionally, it should be noted that potassium selenocyanate in DMF reduced *vic*-ditosylates but the stereochemistry of the reaction has apparently not been examined.[121]

Lithium aluminum hydride reduced *vic*-dibromides and bromotosylates to olefins.[122] Favorable geometry encouraged *anti*-elimination, but substitution of hydride and *syn*-elimination occurred also. Sodium hydride-sodium *tert*-amyloxide in THF reduced dibromides to olefins, but dehydrohalogenation was also observed.[123] The reactions of this reagent and related "activated" hydrides with *vic*-disubstituted aliphatics have not been reported as yet. Reductions with tributyltin hydride were nonstereospecific.[124]

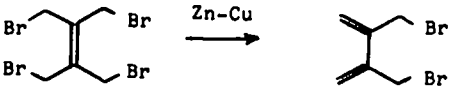
Lithium dialkyl cuprates reduced (rather than alkylated) *vic*-dibromides.[125] Reduction of *d,l*-stilbene dibromide at −78° gave a 9:1 (*E*:*Z*) product. Did *cis*-stilbene isomerize to *trans* (at −78°) or was a *syn* mechanism operative? Tests of the reaction stereochemistry in aliphatic substrates would be interesting. Electrochemical reductions also tend to produce *anti*-elimination.[126]

Other reagents which bear negative charge and which have been shown to effect dehalogenation of *vic*-dibromides include potassium diphenylphosphide,[127] phenyllithium[128] and trialkyl phosphites.[129] The phenyllithium-induced elimination of the diastereomeric 2,3-dibromobutanes was almost completely stereospecific (*meso* gave 99.5% *E*-2-butene; *d,l* gave 97.8% *Z*-2-butene).[128] Elimination with phosphite

esters succeeded only if the halogens were activated (by an adjacent electron withdrawing group) toward displacement; otherwise the normally observed Michaelis–Arbuzov reaction prevailed.[130]

Corey and Grieco reported the reductive elimination of a *trans*-iodohydrin with methanesulfonyl-chloride in pyridine.[131] Prompted by this observation, the iodohydrin was treated with $POCl_3$-pyridine omitting the usual reducing agents (Sn^{2+}, Zn).[113] The authors suggested that the intermediate iodomesylate (iodophosphate) may have reversibly eliminated, perhaps assisted by pyridine. The reducing agent then acted simply to drive the reaction to completion. A subsequent investigation showed that iodohydrins derived from the 4-octenes were reduced completely *anti* by $POCl_3$-pyridine although the yields were only 35–50%.[132] Certain iodoacetates and trifluoroacetates likewise have been observed to eliminate in refluxing acetic acid[133] without an added reducing agent. Coumarin and isocoumarin dibromides were debrominated in refluxing DME with 1,8-*bis*-dimethylaminonaphthalene,[134] a reagent which does not quaternize with trimethyloxonium tetrafluoroborate. Perhaps again the added reagent merely acted to scavenge bromine from the onium ion which might have been in equilibrium with the dibromide.

Reductive eliminations catalyzed by any of several metals have often lacked stereospecificity.[108] Zinc[135] had been shown to reduce *vic*-dibromides by *anti*-elimination[136] although a more searching subsequent study indicated deviation from complete stereospecificity (*d*,1-3,4-dibromohexane gave 6.4% *trans*-3-hexene; *d*,1-4,5-dibromooctane gave 19.5% *trans*-4-octene: Zn in hot aqueous ethanol).[137,138] Epoxides,[139] halohydrins,[140] diol monoacetates,[141] and *vic*-halotrifluoroacetates[142] have been reduced with Zn in acetic acid but the reactions have only tended toward *anti*-elimination. Magnesium amalgam reportedly reduced epoxides to olefins in fair yield in the presence of magnesium bromide,[143a] (stereochemistry not reported) and calcium amalgam reduced *vic*-dinitro compounds.[143b] However, magnesium (THF) reduced both *meso* and *d*,1-dibromobutanes stereospecifically *anti*.[137] Parenthetically, sodium reduced both dibromides to the same mixture of 2-butenes,[137] although sodium was found useful for obtaining cyclic alkenes.[143c] An intriguing Sn–Cu reduction of the tetrabromide **25** (Scheme 11) to a



25

Scheme 11.

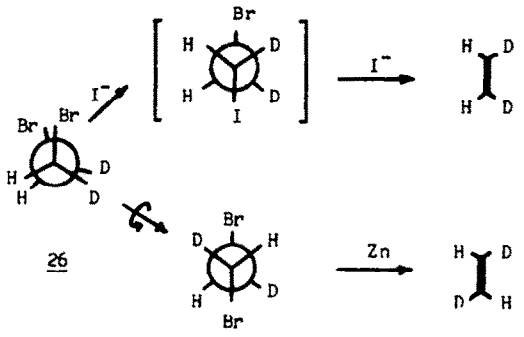
conjugated diene (53% yield) has been described.[144] The eliminated halogens, however, required activation and the reduction proceeded sluggishly, if at all, with ethylene dibromide.

Chromous salts[145] have been employed for the reduction of *vic*-difunctionalized aliphatics[146] and, because one-electron, or radical-promoted, reductions by metal salts produce carbon radical intermediates, these reductions only have utility for molecules with structural bias; e.g. alicyclics. McMurry has prepared Ti^{2+} from $TiCl_3$ with LAH.[147] Reduction of halohydrins was, as expected, not stereospecific. Titanocene ($\{C_{10}H_{10}Ti\}_2$) reduced *vic*-dibromides and dichlorides to olefins, but the stereochemical consequences of this reduction have not been assessed.[148] Cu(I) has also been used to reduce *vic*-dibromides[149] (stereospecificity not expected). Anion radicals, namely those formed from sodium and α-dimethylaminonaphthalene,[150] anthracene,[151] and naphthalene,[151] reduced *vic*-dimesylates to alkenes. Interestingly, zinc did not reduce dimesylates even in refluxing acetic acid.[151] It should also be mentioned that hydrazine has been employed to reduce dimesylates[152] and azidotosylates.[153]

Elimination of other *vic*-disubstituted compounds such as β-hydroxysilanes, phosphorus betaines, etc. will be deferred to the section dealing with epoxides. Such compounds are more generally obtained from epoxides than from alkenes, and elimination does not require the mediation of a reducing agent.

(d) Syn *eliminations summarized*

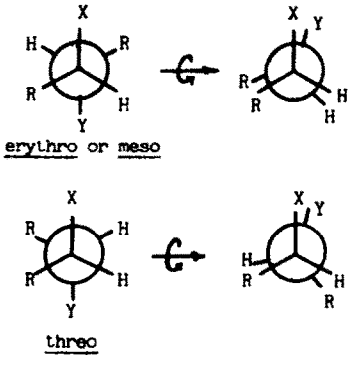
The elimination of bromine from *d*,1- and *meso*-dibromobutanes with sodium iodide was completely *anti* (as judged by physical measurements conventionally employed at the time).[154] In contrast, Schubert *et al.* showed that *meso*-1,2-dideuterio-1,2-dibromoethane, **26**, with potassium iodide produced pure (*Z*)-1,2-dideuterioethylene in 93–94% yield,[155] although reduction with zinc produced the expected (*E*)-isomer (Scheme 12). The apparent anomaly was explained by an initial displacement of bromide by iodide ion from carbon if a primary carbon was involved, whereas direct elimination occurred when both carbons were secondary.



Scheme 12.

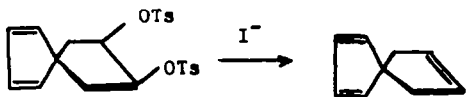
It is interesting to speculate on the possibility of a true *syn*-elimination of such *vic*-disubstituted compounds. A theoretical explanation for the E2 mechanism of HX elimination which explained the preference for *anti* stereochemistry has been advanced.[156] A dihedral angle of 180° between leaving groups (referring to HX elimination) maximized orbital overlap and, hence, minimized transition state energy. However, calculations indicated that a 0° dihedral angle, or *syn*-periplanar conformation for elimination was at a potential energy minimum,[157] and *syn* HX elimination has been observed.[158] Since the rotational energy for a given acyclic molecule would generally be higher for the *syn* (eclipsed) conformation than for the *anti*, *syn*-eliminations are not commonly observed unless, perhaps, the two leaving groups are first bonded together.

Twenty-one years after the experiments of Schubert *et al.*[155] it was observed that *vic*-dichlorides and bromochlorides derived from internal alkenes likewise underwent (net) *syn*-elimination with iodide ion[159] with 93–100% stereospecificity. Here, too, it was concluded that displacement of chloride (bromide) preceded elimination of iodine halide. In order for these reactions to succeed stereospecifically it was necessary for the elimination of the presumed intermediate iodochloride to proceed much faster than displacement of iodide by iodide from carbon. In the dibromide series, *erythro* compounds reduced faster with iodide than did the *threo*-isomers, presumably because it was easier to attain the preferred *trans*-antiplanar alignment of bromines. If the reaction had been a true *syn*-elimination one would expect the *threo*-isomer to react faster; i.e. *threo* should more easily attain the conformation with the halogens in close proximity (Scheme 13). *Erythro* isomers reduced more readily; thus no evidence was found to favor a strictly *syn*-elimination.



Scheme 13.

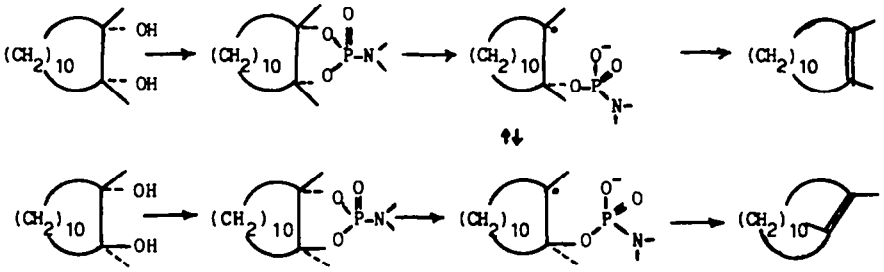
Net *syn* eliminations have also been observed when *vic*-chloro- and bromotrifluoroacetates were treated with sodium iodide.[160] Reduction of mesylates and tosylates with sodium iodide proceeded readily for terminal olefins;[161] the more sluggish reaction of secondary sulfonates can proceed via (net) *syn* elimination. For example, the ditosylate of *meso*-3,4-dihydroxyhexa-1,5-diyne produced (*Z*)-hexa-1,5-diyne-3-ene.[162] The reduction was performed in refluxing 2-ethoxyethoxyethanol under vacuum removing the enediyne as it formed. Another example of reductive elimination of ditosylates was reported by Semmelhack[163] who reduced the *cis*-ditosylate **27** (Scheme 14) with sodium iodide to obtain the spiro {4.4}-nonatriene. These reductions seem to have been exploited primarily in sugar chemistry,[160] and their utility for olefin inversion has apparently not been assessed.



27

Scheme 14.

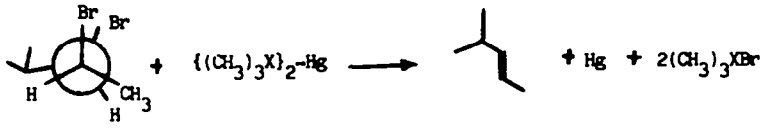
Several very intriguing stereoselective or stereospecific *syn* eliminations of *vic*-diols have been reported. Treatment of *cis*-1,2-dihydroxycyclododecane as its dialkoxide with dipotassium hexachlorotungstate[165] in THF under reflux produce *cis*-cyclododecene (93% purity)[166] whereas the *trans*-diol produced 79% *trans*-olefin. This *syn* elimination was particularly noteworthy as it constituted the first instance of a formal reversal of osmium tetraoxide dihydroxylation. Comparable stereochemical results were obtained when the diols were converted first to cyclic amidophosphates (Scheme 15), and then



Scheme 15.

reduced with either lithium/NH_3 or titanium/THF.[167] The reduction was viewed as proceeding through a radical anion. Either the radical anion, or a subsequently derived dianion, could undergo some inversion prior to elimination. Titanium (obtained by the reduction of titanium trichloride with lithium aluminum hydride)[168] reduced *vic*-diols with some *syn*-selectivity also. *Meso*-5,6-decanediol was reduced to a 6:4 (*E*:*Z*) ratio of 5-decenes, while the *d*,l-diol yielded a 9:1 mixture of *E*:*Z*.

A unique reduction of *vic*-dibromides with *bis*-trimethylsilyl (or germyl) mercury has been reported.[169] The *threo* diastereomer of 2,3-dibromo-4-methylpentane 54 produced *E*-4-methyl-2-pentene quantitatively (Scheme 16). The *erythro*-isomer yielded the *Z*-alkene. The reactions were 96–98% stereoselective. Reductions of dibromoethane to ethylene by these and closely similar reagents had been reported previously.[170] Further work to delineate the scope and mechanism of this interesting transformation needs to be accomplished.



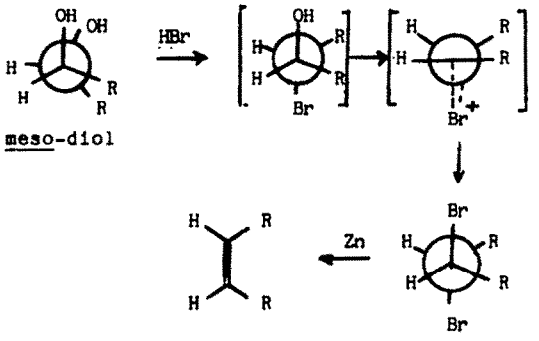
X = Si, Ge

Similarly, erythro produced the Z-alkene

Scheme 16.

(e) *Inversions exemplified*

In 1937, Young *et al.*[11a] found that treatment of *meso*-4,5-dihydroxyoctane with zinc bromide in HBr at 20° afforded a *vic*-dibromide which upon treatment with a copper-activated zinc in ethanol produced (*Z*)-4-octene (Scheme 17). The glycol had undergone an odd number of inversions of configuration. Judging from later studies of the stereochemistry of reactions of 3-bromo-2-butanols,[171] the intermediate 5-bromo-4-octanol reacted with retention of configuration. Similarly, the *d*,l-glycol ultimately was converted to (*E*)-4-octene via the intermediate *meso*-dibromide. The *meso*-glycol also produced 4,4-dibromooctane during the bromination step, an indication that stereospecificity and high yields by solvolytic pathways for olefin inversion would not always be the case. This same sequence of reactions was subsequently employed to prepare elaidic acid from palmitoleic acid after an initial two carbon



meso-diol had been obtained from (E)-4-octene.

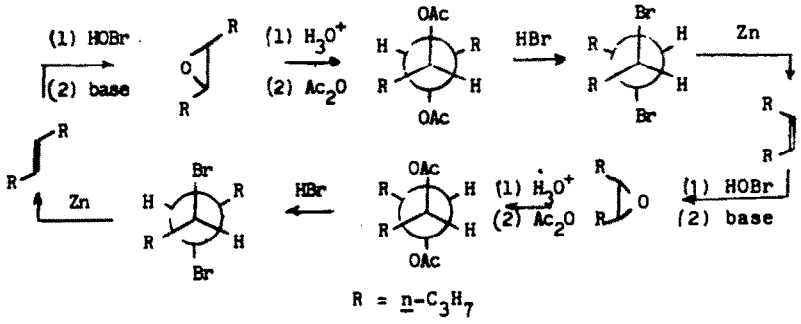
d,l-diol, obtained from (Z)-4-octene ultimately gave (E)-4-octene.

R = n-C_3H_7

Scheme 17.

chain extension;[172] the *anti* addition of two hydroxyl groups being accomplished with performic acid followed by base.

Another rather laborious, but exactingly performed, inversion sequence was described by Lucas *et al.* in 1941 (Scheme 18).[11b] Alkenes were converted to epoxides by addition of hypobromous acid and

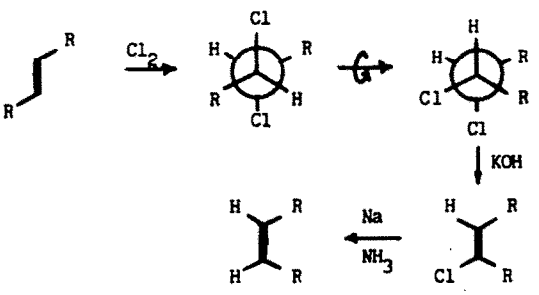


R = n-C_3H_7

Scheme 18.

cyclization (net retention of geometry). Ring cleavage provided the corresponding diols (one inversion) which were then acetylated. Treatment of the diacetates with HBr provided dibromides which were the result of one inversion. Zinc debromination (*anti* elimination) completed the sequence. The inversions of Young[11a] and Lucas[11b] have in common the replacement of vicinal oxygen functions with bromine (OH in the former; OAc in the latter). In both cases the first C–Br bond was formed by S_N2 displacement; the initially installed bromine then assisted in the second C–O cleavage thus inducing retention for the second replacement.

An interesting sequence was devised involving initial chlorine addition (*anti*), KOH-promoted elimination of HCl, and finally sodium/liquid ammonia reduction (Scheme 19).[173] Cristol[174] had

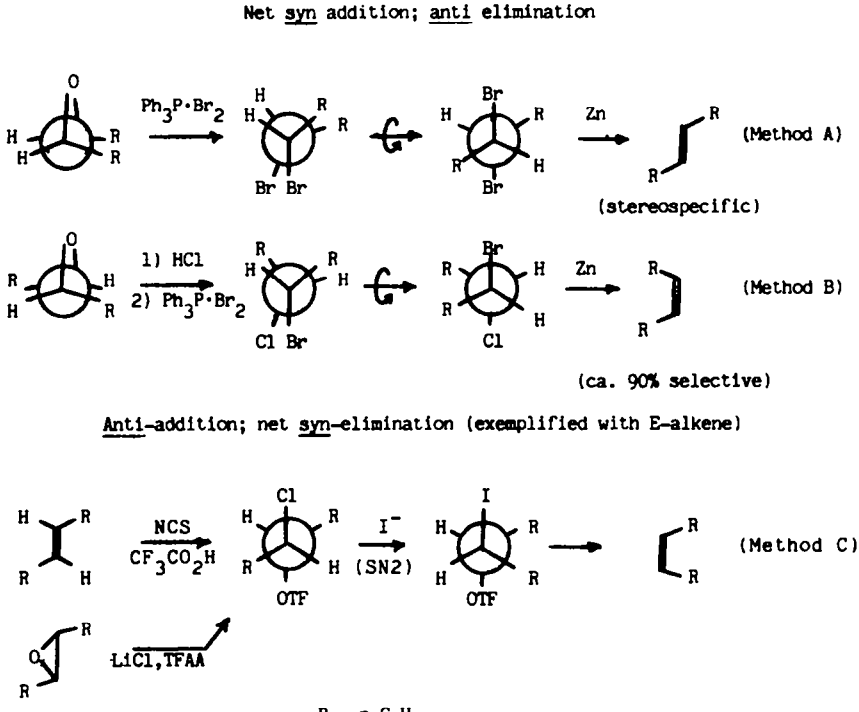


R = various alkyl groups.

Scheme 19.

established that the dehydrochlorination step was *anti*, and the isolation of olefins geometrically isomeric to the starting materials established that the alkali metal reduction had proceeded with retention of configuration (an early indication that the configuration of vinyl anions might be preserved). Overall yields averaged 81% and stereospecificity was 94–97% for several simple *cis* and *trans* alkenes.

The conversion of epoxides to *vic*-dihalides by double inversion formally constitutes a (net) *syn* addition to a double bond,[93–95] and was exploited as the basis for olefin inversion.[97] *Erythro*-dibromides were cleanly prepared from *Z*-epoxides with triphenylphosphine dibromide in benzene (Scheme 20)



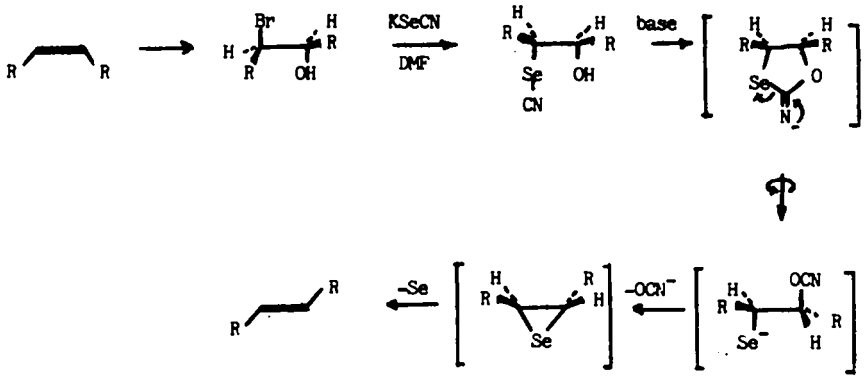
Scheme 20.

while both diastereomeric dichlorides were prepared stereospecifically from *Z*- and *E*-epoxides. Although reductions of the *erythro* dibromides with zinc were stereospecific, reductions of the dichlorides with several reagents usually employed for *anti* elimination gave variable results. *Threo*-bromochlorides could be obtained from *E*-epoxides by the sequence of HCl addition (one inversion) and triphenylphosphine dibromide to replace the hydroxyl group (one inversion) (Scheme 20). Zinc reduction could be made *ca* 90% selective if carried out as 0–5° in DMF.

Net *syn* eliminations of *meso*-1,2-dideuterio-1,2-dibromoethane,[155] *vic*-dichlorides and bromochlorides,[159] and *vic*-chloro (and bromo) trifluoroacetates[160] have already been mentioned. These reactions have been used to invert olefin geometry, the vicinally substituted compounds having been first obtained by *anti* addition. The *vic*-halotrifluoroacetates had been obtained either directly from the alkenes with N-chloro(bromo) succinimide in trifluoroacetic acid, or from the epoxides with trifluoroacetyl chloride or bromide (Scheme 20).

Another example of olefin inversion, involving a Walden inversion sandwiched between two *anti* processes, uses the nucleophilicity of selenocyanate (Scheme 21).[175] Bromohydrins were converted to *vic*-hydroxyselenides with KSeCN in DMF.[176] *Anti* elimination was promoted with potassium carbonate to produce an olefin of inverted geometry. The overall yields were modest and the reactions were only stereoselective.

In summary, many readily available reagents can be used to achieve olefin inversion by a series of displacements incorporated within an addition-elimination scheme. The several transformations which occur, however, may lose stereospecificity if the olefinic substrate is prone to rearrangement or has the



R = various alkyl groups

Similarly for conversion of E to Z-isomers

Scheme 21.

potential for forming relatively stable carbonium ions. Moreover, this approach does not have the power to invert conjugated dienes nor does it appear capable of generating highly strained double bonds. Significantly, no reports were found of the inversion of α,β-unsaturated carbonyl structures by this general method. The results of the inversion sequences described have been summarized in Table 2.

Table 2. Olefin inversions by addition—elimination sequences

Reference	Scheme	Starting Material	Product	Yield, %[a]	Stereoselectivity, %[b]
11a	17	meso-4,5-octanediol	(E)-4-octene	49	c
11a	17	d,l-4,5-octanediol	(Z)-4-octene	41	c
11b	18	(Z)-2-pentene	(E)-2-pentene	~22	~90–91
11b	18	(E)-2-pentene	(Z)-2-pentene	~22	~90–91
173	19	(E)-2-pentene	(Z)-2-pentene	~66	94
173	19	(E)-2-hexene	(Z)-2-hexene	~66	97
173	19	(E)-3-hexene	(Z)-3-hexene	~66	96
173	19	(E)-2-octene	(Z)-2-octene	~66	96
173	19	(E)-4-octene	(Z)-4-octene	~66	96–97
173	19	(Z)-3-hexene	(E)-3-hexene	~66	97
97	20A	(Z)-9-pentacosene oxide	(E)-9-pentacosene	75	99
97	20A	(Z)-7-octadecene oxide	(E)-7-octadecene	70–80	104
97	20A	(Z)-2-methyl-7-octadecene oxide	(E)-methyl-7-octadecene	70–80	109[d]
97	20A	(Z)-11-tetradecen-1-ol acetate	(E)-11-acetate	70–80	102
e	20A	(Z,Z)-1,7,13-pentacosatriene	(E,E)-triene	44	>98
97	20B	(E)-11-tetradecen-1-ol acetate	(Z)-11-acetate	70–80	97
155	11	meso-1,2-dibromo-1,2-dideuterioethylene[f]	(Z)-1,2-dideuterioethylene	~60	93–94
159	g	(Z)-2-methyl-7-octadecene	(E)-2-methyl-7-octadecene	-	100(I)[g]
159	g	(E)-2-methyl-7-octadecene	(Z)-2-methyl-7-octadecene	88(I), 95(II)	96(I), 100(II)[g]
159	g	(Z)-7-octadecene	(E)-7-octadecene	67(I), 79(II)	100(I), 97(II)[g]
159	g	(E)-8-dodecen-1-ol acetate	(Z)-8-acetate	95(I), -(II)	93(I), 93(II)[g]
160	20C	(Z)-3-octene oxide	(E)-3-octene	>85[h]	100(I), 100(II)[h]
160	20C	(E)-3-octene oxide	(Z)-3-octene	>85[h]	100(I), 94(II)[h]
160	20C	(Z)-5-decene oxide	(E)-5-decene	>85[h]	99(I)[h]
160	20C	(E)-5-decene oxide	(Z)-5-decene	>85[h]	>95(I)[h]
160	20C	(Z)-2-methyl-7-octadecene oxide	(E)-2-methyl-7-octadecene	>85[h]	100(I), 94(II)[h]
160	20C	(E)-2-methyl-7-octadecene oxide	(Z)-2-methyl-7-octadecene	>85[h]	>97(I), 98.5(II)[h]
e	20C	(Z,E)-1,7,13-pentacosatriene	(E,Z)-triene	80	>98(I)[h]
169	16	erythro-2,3-dibromo-4-methylpentane	(Z)-4-methyl-2-pentene	~100	96–98
169	16	threo-2,3-dibromo-4-methylpentane	(E)-4-methyl-2-pentene	~100	96–98
176	21	(E)-2-octene	(Z)-2-octene	45(I), 38(II)	75(I), 92(II)[i]

Table 2. (*Contd*).

Reference	Scheme	Starting Material	Product	Yield, %[a]	Stereoselectivity, %[b]
176	21	(Z)-2-octene	(E)-2-octene	39(I), 35(II)	88(I), 98(II)[i]
176	21	(E)-4-octene	(Z)-4-octene	- , 26(II)	70(I), 90(II)[i]
176	21	(Z)-1-methoxy-9-octadecene	(E)-1-methoxy-9-octadecene	21(I), 42(II)	85(I), 88(II)[i]
176	21	(E)-2-decene	(Z)-2-decene	54(I), 56(II)	72(I), 92(II)[i]
176	21	(Z)-2-decene	(E)-2-decene	58(I), 35(II)	70(I), 91(II)[i]

[a] Isolated.

[b] Calculation was based on initial geometrical composition.

[c] Quantitative data not available. Yields were probably >95%.

[d] Initial composition was 85% Z, and the product alkene was 93% E. The E-to-Z conversion was not stereospecific.

[e] P.E.Sonnet, J.Chem.Ecol. (in press).

[f] Obtained by adding bromine to the E-alkene.

[g] Data labeled (I) refer to bromine chloride adducts; (II) refers to chlorine adducts.

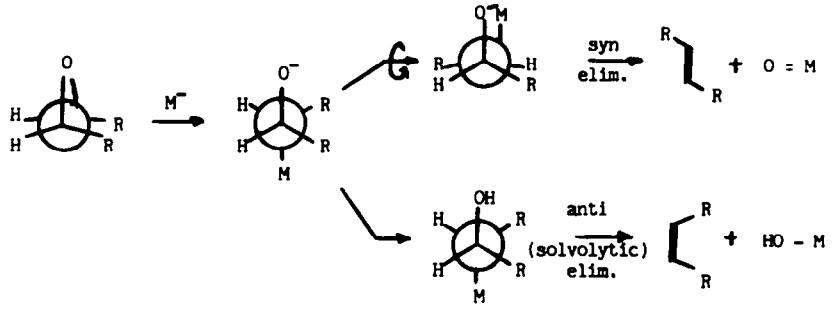
[h] Yields were determined by glc and were >85%. Data labeled (I) refer to reactions involving vic-chlorotrifluoroacetates; (II) refers to reactions involving vic-bromotrifluoroacetates.

[i] Data labeled (I) refer to reactions involving potassium thiocyanate; (II) refers to reactions involving potassium selenocyanate.

3. CLEAVAGE OF EPOXIDES FOLLOWED BY *ANTI* OR *SYN* ELIMINATION

(a) *Synthesis of epoxides summarized*

Recent intense interest in the stereospecific deoxygenation of epoxides prompts a separate discussion of olefin inversion processes (potential as well as realized) that could be brought about by the reduction of an epoxide. Cleavage of epoxides to form *trans*-diols, *vic*-dihalides, and haloesters followed by a separate reduction of these adducts has already been discussed. The emphasis in this section will be on reagents that reduce epoxides to olefins by means of a nucleophilic cleavage followed (usually directly) by elimination (Scheme 22).

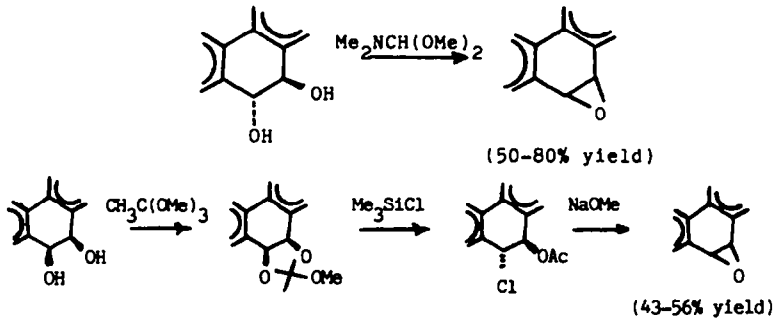


Sequence demonstrated with a Z-epoxide and a charged nucleophile

Scheme 22.

Various syntheses of epoxides from olefins have been compiled.[177] Generally, the most common preparations (peracid oxidation and *anti* HOX-addition followed by base-promoted cyclization) provided epoxides of the same geometry as that of the starting olefin. Recent methods for epoxidizing olefins with retention of geometry are: $Mo(CO)_6$ and hydroperoxides[178a] or peracids,[178b] peroxyacetyl nitrate,[179] N-bromoacetamide followed by KOH,[180] bromine-DMF (yielding *vic*-bromoformates) followed by hydroxide,[181] phenyl isocyanate-H_2O_2,[182a] ferric acetylacetonate-H_2O_2,[182b] and *bis*-1,2,4-triazolyl ketone-H_2O_2.[183] Iodine-Ag_2O has been employed to prepare epoxides from olefins[184a] as has iodine-sodium ethoxide.[184b] A polymer-bound peracid has been described for this purpose,[185a] and a two phase system (*m*-chloroperbenzoic acid in methylene chloride is the oxidizing phase), in which aqueous $NaHCO_3$ neutralizes *m*-chlorobenzoic and thereby acts to protect acid-sensitive functionality, has also been reported.[185b] Additional methods include the use of acetaldehyde/oxygen[186a] and benzeneseleninic acid-H_2O_2.[186b] In order to complete an olefin inversion following such epoxidations, the epoxide must be reduced to an olefin with inversion of configuration.

The preparation of vicinal *cis*-diol monoesters (previous section), for example, offers potential for olefin inversion via the inverted epoxide. However, this seems not to have been systematically studied. Since *vic*-diols can be obtained by *syn*- as well as *anti*-addition (as already discussed), the potential for inversion of olefin geometry is implicit in any sequence that transforms a diol stereospecifically into an epoxide. Two examples of such transformation have arisen from the interest in arene oxides.[187] Goh and Harvey described the reaction of *trans*-diols with dimethylformamide dimethylacetal.[188] Epoxides were formed in 50–80% yields with one inversion of configuration of carbon (Scheme 23). In another



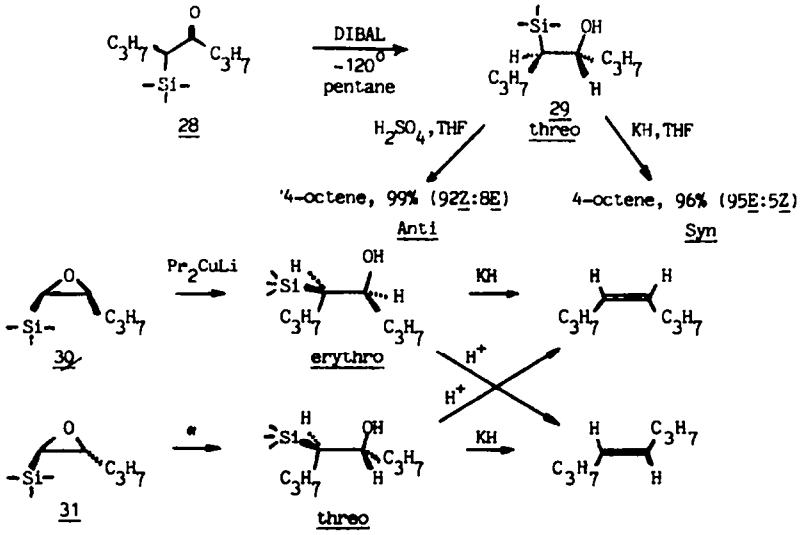
Scheme 23.

sequence, Dansette and Jerina converted *cis*-diols to epoxides with two inversions of carbon (Scheme 23).[189] Dioxolanes, **99**, prepared from the diols with trimethyl orthoacetate were reacted with trimethylchlorosilane. The resulting *trans*-chloroacetates, **100**, were then cyclized in methanol containing sodium methoxide. Overall yields were 43–56%. Although more work on the preparation of epoxides from olefins with structural inversion would be desirable, it seems fair to surmise that olefin-to-olefin inversions are possible, culminated via either *syn*- or *anti*-reduction of epoxides.

(b) *Reductions of (and olefin inversions from) epoxides summarized*

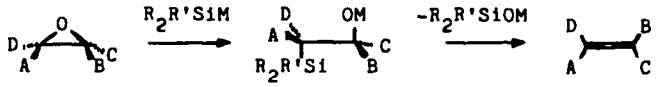
A wide variety of heterocyclic nucleophiles react with epoxides to generate β-hydroxy (or oxido) intermediates. Some of these are isolable (see below and Scheme 24), and a controlled elimination can be performed in a discrete second step. In other instances the product of ring cleavage suffers elimination directly. These same intermediates can often be prepared as well by the reaction of aldehydes or ketones with α-heteroatom-stabilized anions. In fact, one major element of current research in organometallic chemistry is the generation of such β-hydroxy (or oxido) derivatives diastereomerically pure[190,191] since their decomposition to alkenes can often be directed with *syn* or *anti* specificity.

Olefination of carbonyl compounds with α-silyl carbanions has been described.[192] In a related study that led to the knowledge of elimination stereochemistry, the α-ketosilane **28** was stereospecifically reduced to the *threo* β-hydroxysilane **29** with diisobutylaluminum hydride (Scheme 24).[193] Acid treat-



Scheme 24.

ment provided the usual *anti* elimination observed with, e.g. β-halosilanes,[194] while *syn* elimination predominated when the β-hydroxysilane was converted to an oxy anion with potassium hydride. That the stereochemistry of the acid-catalyzed elimination reaction was *anti*, while that of the base-promoted elimination was *syn*, was determined by examining the constitution of olefins obtained by reactions of epoxysilanes with organocuprates (Scheme 24).[195] The *cis* epoxysilane **30** reacted with lithium dipropylcuprate to give presumably the *erythro* isomer which was reduced to (*Z*)- and (*E*)-4-octenes with base and acid, respectively. An analogous set of transformations was performed on the *trans*-epoxysilane **31**. While research is continuing to explore the several possible approaches to generating diastereomerically pure β-hydroxysilanes[194] for the purpose of creating di- and trisubstituted olefins stereospecifically, advantage has been taken of the knowledge that silylmetallic reagents react stereospecifically with epoxides,[196] in order to obtain diastereomerically pure β-hydroxysilanes. Epoxides and dimethylphenylsilyllithium reacted presumably to form the β-lithium oxidosilyl derivative which eliminated directly (Scheme 25).[197] *Cis*- and *trans*-stilbene oxides were reduced with inversion (97–99%). Yields were high



a) $R=CH_3$, $R'=C_6H_5$, M=Li

b) $R=R'=CH_3$, M=K

A,B,C,D = alkyl and C_6H_5

Scheme 25.

for reduction of terminal epoxides; no information was available for epoxides of other internal olefins. In another study trimethylsilylpotassium (from hexamethyldisilane and KOMe) also reduced epoxides to inverted olefins directly (Scheme 25).[198] The inversion was virtually stereospecific (98–99%) for both di- and trisubstituted epoxides. Reductions of epoxides are summarized in Tables 3 (reduction with retention of geometry) and 4 (reduction with inversion).

Table 3. Reductions of epoxides with retention of geometry[a]

Reference	Scheme	Product	Yield, %[b]	Stereospecificity, %
195	24	(E)-4-nonene[c]	93,A	100
195	24	(Z)-4-nonene[c]	98,A	98
199	d	(Z)-2-butene	-	100
199	d	(E)-2-butene	-	100
206	-	(E)-stilbene	83,A	100
224a	e	(E)-4-octene	e	>95
224a	e	(Z)-2-octene	e	>95
224b	e	1-dodecene	70	e
224b	e	(E)-7-tetradecene	88	e
224b	e	2-methyl-2-tridecene	80,90	e
224b	e	2-methyl-2-nonene	80	e
224b	e	2,3-dimethyl-2-dodecene	83	e
224b	e	2,3-dimethyl-4-phenyl-2-butene	85	e
225	32	1-octene	71,B	-
225	32	(E)-2-octene	68,B	~100
225	32	(Z)-2-octene	73,B	~100
225	32	(Z)-stilbene	~71,B	97.5
225	32	cyclohexene	53,B	-
230	34	cyclohexene	100,B	-
230	34	styrene	90,B	-
230	34	vinyl chloride	100,D	-
230	34	(E)-stilbene	97,A	f
230	34	(Z)-stilbene	95,A	f
232a	35	(Z)-2-butene	64,A[g]	>98
232a	35	(E)-2-butene	50,A[g]	>98

Table 3. (*Contd*).

Reference	Scheme	Product	Yield, %[b]	Stereospecificity, %
232a	35	(Z)-stilbene	82,A[g]	>98
232a	35	(E)-stilbene	83,A[g]	>98
232a	35	(E)-ethyl crotonate	96,A[g]	>98
233	h	(Z)-stilbene	22,A	i
233	h	(E)-stilbene	22,A	i
234	j	(E)-cyclododecene,I,IV,VI,VIII	98,B	95
234	j	(Z)-cyclododecene,I	89,B	95
234	j	(E)-4-octene,II + 2LiI	97,B	>98
234	j	(Z)-4-octene,V	81,B	93
234	j	(E)-stilbene,I	86,B	100
234	j	(Z)-stilbene,I	89,B	8
234	j	1-dodecene,I	80,B	-
234	j	4-ethylcyclohexene,I	75,B	-
234	j	geraniol methyl ether,I	37,B	72
234	j	citronellol methyl ether,I	83,B	-
234	j	stigmasterol acetate,[k] II	83,B	-
240	37	cyclohexene	77,B	-
240	37	1-decene	91,A	-
240	37	(Z)-5-decene	95,A	~100
240	37	(E)-5-decene	95,A	~100
240	37	(Z)-2-methyl-7-octadecene	90,B	~100
240	37	(E)-2-methyl-7-octadecene	90,B	>99.5
241	37	1-dodecene	60,B	-
241	37	5α-androst-2-en-17-one	99,A	-
241	37	methyl elaidate	99,A	i
241	37	methyl oleate	95,A	i
241	37	methyl (Z)-13-docosenoate	86,A	i
241	37	citronellol methyl ether	74,A	-
241	37	cholest-5-ene	91,A	-
241	37	cholest-4-en-3-one	99,A	-

[a] Starting material was the corresponding epoxide unless otherwise indicated. Reductions of geometrically symmetrical epoxides employing the reagents which were the subject of this tabulation were included for comprehensiveness.

[b] Account was taken of initial geometrical composition.

[c] The actual starting material was derived from the reaction of a geometrically pure epoxysilane and lithium dibutylcuprate (Scheme 24) followed by *syn*-elimination.

[d] Elimination of β-hydroxystannanes.

[e] Yields were good to excellent with either methyl- or phenylselenol, and refer to the *anti*-elimination of the β-hydroxyselenides. Reactions were stereospecific as judged by nmr spectra of derived thionocarbonates.

[f] Reaction was reportedly stereospecific.

[g] Yields given are for the olefin complexes.

[h] Reaction of the epoxides with iron pentacarbonyl.

[i] Reaction was reportedly stereospecific.

[j] Numerals refer to several preparations of low valent tungsten and are explained below.

[k] Starting material was the diepoxide.

Numerals for (j) above:

$$WCl_6 + 2RLi \xrightarrow{THF} I$$

$$WCl_6 + 3RLi \xrightarrow{THF} II$$

$$WCl_6 + 4RLi \xrightarrow{THF} III$$

$$WCl_6 + 2Li \xrightarrow{THF} IV$$

$$WCl_6 + 3LiI \xrightarrow{130^\circ} V$$

$$WCl_6 + 2LiI \xrightarrow{130^\circ,\ vac.} VI$$

$$WCl_6 + 2KI \xrightarrow{130^\circ,\ vac.} VII$$

$$VII + 2LiCl \xrightarrow{THF} VIII$$

Table 4. Reductions of epoxides with inversion of geometry[a]

Reference	Scheme	Product	Yield,%[b]	Stereospecificity,%[b]
195	24	(E)-4-nonene[c]	96-102,A	98-99
195	24	(Z)-4-nonene[c]	94-98,A	99.5
195	24	2-methyl-2-heptene[c]	79,A	-
195	24	1-hexene	88,A	-
197	25	(Z)-stilbene	75,A	>97
197	25	(E)-stilbene	83,A	>99
197	25	1-pentene	60,B	-
197	25	1-octene	64,B	-
198	25	(E)-3-hexene	99,B	>99
198	25	(Z)-3-hexene	86,B	>99
198	25	(E)-4-octene	96,B	>99
198	25	(Z)-4-octene	93,B	>99
198	25	(E)-2,5-dimethyl-3-hexene	93,B	>98
198	25	(Z)-2,5-dimethyl-3-hexene	75,B	>92
198	25	(E)-3-methyl-2-pentene	91,B	>99
198	25	(Z)-3,methyl-2-pentene	99,B	>99
208a	26	(E)-stilbene	95,A	>99
208a	26	(Z)-stilbene	95,A	>98
208a	26	(E)-2-octene	77,A	>99.5
208a	26	(Z)-2-octene	75,A	>99.5
208a	26	(E)-cyclooctene	70,A	>99.5
208a	26	(Z,E)-1,5-cyclooctadiene	60,A	>99.5[d]
208a	26	(Z,E)-1,4-cyclooctadiene	40,A	>99.5[d]
208b		(E)-10-nonadecen-2-one	85,A	-
208c		(E)-1-methylcyclooctene	70,A	99
209	e	(E,E)-7,11-hexadecadien-1-ol acetate	35,A[e]	>99
209	e	(E,Z)-7,11-hexadecadien-1-ol acetate	35,A[e]	>99
210	28	(E)-cyclooctene	46,A	99.9
210	28	(E)-1-methylcyclooctene	38,A	99.9
210	28	(Z,E)-1,5-cyclooctadiene	51,A[d]	99
210	28	Tetramethylethylene	32,A	-
232b	35	(E)-stilbene, Method 1[f]	96,A	>99
232b	35	(Z)-stilbene, Method 2[f]	92,A	94
232b	35	(E)-2-butene, Method 2[f]	86,A	>99
232b	35	(Z)-2-butene, Method 2[f]	69,A	99
232b	35	(E)-2-pentene, Method 2[f]	61,A	>99
232b	35	(Z)-2-pentene, Method 2[f]	63,A	>99
232b	35	(Z,E)-2,4-hexadiene, Method 2[f]	62,A	94(Z,E),6(E,E)[g]
232b	35	2,4-hexadiene, Method 2[f]	51,A	45(Z,Z),48(Z,E),7(E,E)[h]
232b	35	(Z)-3-penten-2-one, Method 2[f]	54,A	85Z:15E
232b	35	(Z)-ethyl crotonate, Method 1[f]	-	52Z:48E
232b	35	(Z)-ethyl crotonate, Method 2[f]	93,81A	53Z:47E
232b	35	(Z)-ethyl crotonate, Method 3[f]	76,A	57Z:43E
232b	35	ethyl cinnamate, Method 2[f]	61,A	21Z:79E[i]
232b	35	ethyl cinnamate, Method 3[f]	53,A	37Z:63E[i]
235	36	dimethyl mesaconate	-	95
235	36	Dimethyl citraconate	-	99

a Starting material was the corresponding epoxide unless otherwise indicated.

b Account was taken of initial geometrical composition. A—isolated; B—glc; C—nmr; D—dibromide derivative.

c Starting material was formally the epoxide of opposite geometry. The actual starting material was derived from the reaction of a geometrically pure epoxysilane and lithium dibutylcuprate (Scheme 24) followed by anti-elimination.

d Monoepoxide of the (Z,Z)-isomer was the starting material.

e Lower yield due in part to extra steps required for protecting the alcohol (acetate) function. Method of Vedejs and Fuchs (refer to Scheme 26).

f Method 1 - a standard reaction procedure; Method 2 - continual removal of alkene as it formed in vacuo; Method 3 - a flow method.

g Starting material was the monoepoxide of (E,E)-2,4-hexadiene.

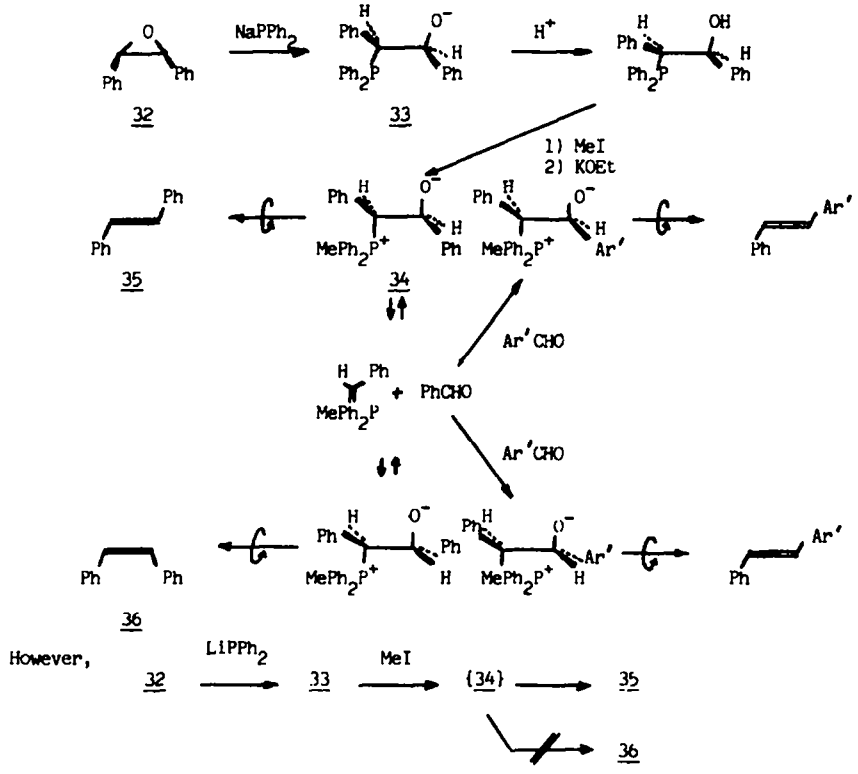
h Starting material was the diepoxide of (E,E)-2,4-hexadiene.

i Starting material was the (E)-isomer.

Triphenylstannylsodium reacted with epoxides to produce stable β-hydroxystannanes which were diastereomerically pure.[199] These intermediates decomposed stereospecifically under acidic conditions; *cis*-butene oxide yielded *cis*-2-butene and the *trans*-oxide gave *trans*-olefin. As ring cleavage was expected to involve a carbon inversion, the elimination would have been *anti*. Interestingly, *syn*-elimination of the intermediate β-hydroxystannanes has not been observed.[200]

The Wittig reaction and its many phosphorus analogs[201] proceeds via β-oxidophosphorus derivatives which undergo *syn* elimination. Epoxides reacted with triphenylphosphine at elevated temperatures to give olefins;[202] presumably the intermediates were oxidophosphonium salts. The transformation would be expected to invert olefin geometry, but both the substrate choices and the vigorous conditions necessary for reaction precluded an assessment of reaction stereochemistry. The reduction of 2-butene oxides with tributylphosphine required 150° and the product butenes were of mixed geometry.[203] Reactions of epoxides with triethyl phosphite have also been reported.[204] Epoxyacids were reportedly converted stereospecifically by PH_4I into alkenoic acids,[205] and diphosphorus tetraiodide (phosphorus trichloride plus sodium iodide) reduced epoxides to olefins with retention of configuration.[206] Since 1,2-dialkylepoxides reacted less rapidly than epoxides of terminal olefins, this reagent could find use for selective reductions.

Sodium diphenylphosphide reacted with, for example, *cis*-stilbene oxides to give a β-hydroxydiphenylphosphine (Scheme 26).[207] On treatment with methyl iodide and then ethoxide, elimination

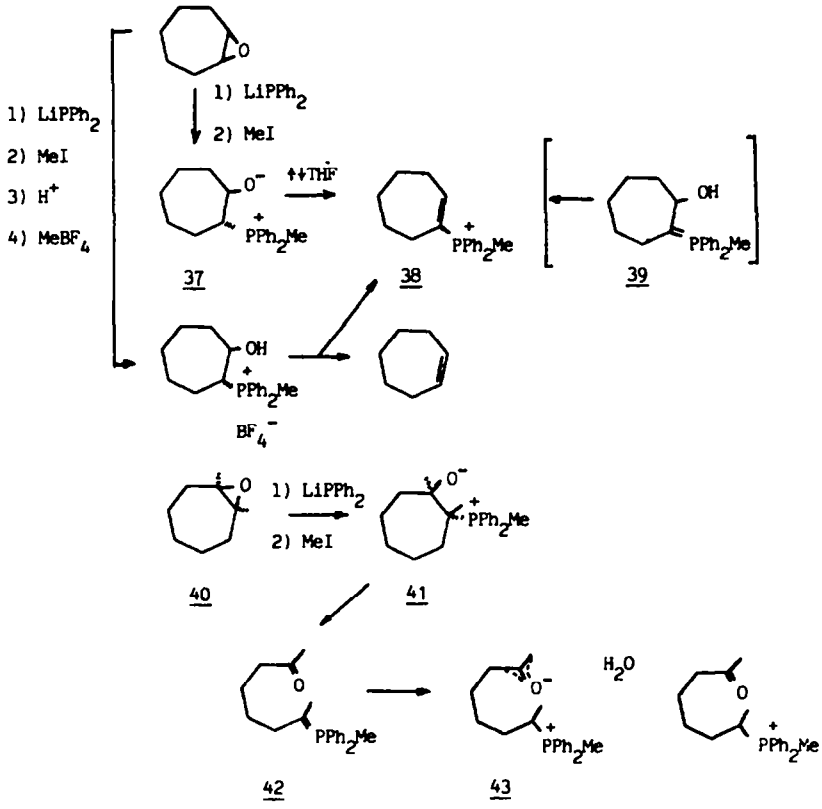


Scheme 26.

occurred. The stilbenes were obtained with about 60–70% inversion. The thrust of this research, however, was to ascertain whether the betaines dissociated to any extent to benzaldehyde and benzylidenemethyldiphenylphosphorane. Indeed, if *m*-chlorobenzaldehyde was present, *m*-chlorostilbene was formed. The reversibility of betaine formation, therefore, precluded the inversion, at least of stilbenes, in this manner.

Vedejs *et al.*, however, discovered that if the intermediate oxidophosphines 33 (Scheme 26) were treated with methyl iodide directly, the stilbene oxides were inverted and deoxygenated stereospecifically in good yields.[208] A trisubstituted allylic alcohol in which the alcohol was protected as a tetrahydropyranyl ether was successfully inverted,[208b] and a pair of isomeric 1,5-dienes ({*Z,Z*}- and {*Z,E*}-7,11-hexadecadien-1-yl acetate, which is the sex pheromone of the pink bollworm moth) were inverted by this sequence to the *E,E*- and *E,Z*-isomers, respectively.[209] The Vedejs method of olefin

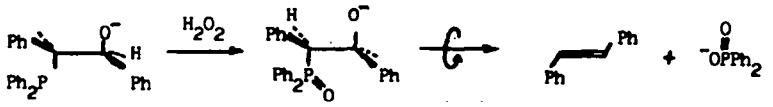
inversion from epoxides is one of the most generally applicable because both epoxide cleavage and the elimination of phosphine oxides are stereospecific. Both di- and trisubstituted olefins can be inverted, and the procedure worked well for both the synthesis of *trans*-cyclooctene (95% yield, 99.5% *trans*) and (*Z,E*)-1,5-cyclooctadiene (60% yield, 99.5% geometrical purity).[208c] The principal limitation of the method was the basic phosphide which was shown to be incompatible with carbonyls.[208b] Although *trans*-cycloheptene could not be synthesized in this way, valuable information was obtained concerning the fate of a betaine which could not undergo *syn*-elimination.[208c] The vinylphosphonium salt **38** (Scheme 27) was the principal product when the betaine **37** was heated under reflux in THF. Although



Scheme 27.

isolation of the hydroxyphosphines was complicated by the readily oxidized phosphorus, they could be isolated as crystalline salts of $MeBF_4$. The salts reacted in THF with added diazabicycloundecene (DBU) producing a mixture of the vinylphosphonium salt **38** and *cis*-cycloheptene. It was suggested that the cycloheptene was derived by an epimerization via the ylid **39**. Furthermore, if suitable substitution prevented the elimination of hydroxyl to give a vinylphosphonium salt as in epoxide **40** (Scheme 27), retro reaction of the betaine **41** occurred to the "unstabilized" ylid **42**. Further reaction of the keto group was blocked by transprotonation forming the enolates **43**. Although specific experiments to effect *anti* elimination of β-hydroxyphosphorus derivatives have not been performed, it is apparent that solvolytic elimination to olefin does not occur and vinyl phosphonium salts would be isolated.[201] A modification of Vedejs' method involved H_2O_2 oxidation of the intermediate oxidophosphine **33** (Scheme 28); the elimination byproduct, a diphenylphosphinate salt, was water soluble which facilitated product isolation.[210] This sequence proceeded with stereochemical consequences equivalent to that of Vedejs.

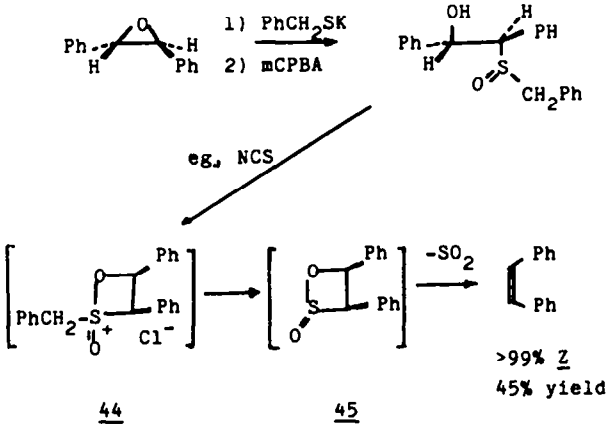
Corey and Cane determined that β-hydroxyphosphinamides were formed stereospecifically from epoxides and lithium bisdimethylaminophosphide.[211] The alcohols, which were also obtained by pro-



Scheme 28.

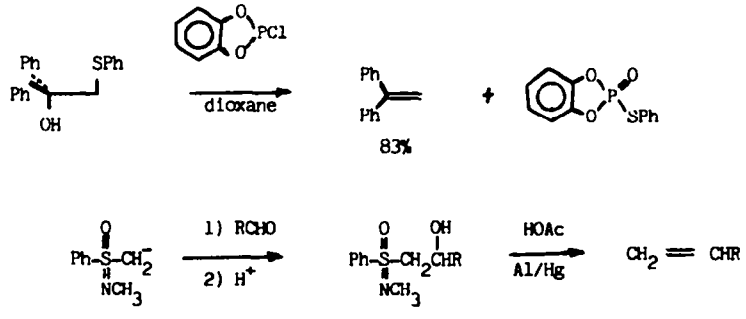
tonating the condensation products of carbonyl compounds and α-metallated *bis*-dimethylaminophosphinyl derivatives,[212] were crystalline solids and could be potentially purified were they synthesized as mixtures of diastereomers. Elimination was effected by heating the alcohols in toluene at 80°. Although yields were disappointing (20%), elimination was very stereoselectively *syn* (96–99%) for the 2-butenes.

Elimination of β-hydroxysulfides, sulfones, etc. have received less attention. Reactions of aldehydes with α-lithiosulfinamides have been described.[213] The β-hydroxysulfinamides undergo *syn* elimination at 80–110° producing sulfur dioxide and the amine as byproducts. A sequence for olefin inversion was developed involving cleavage of epoxides with potassium benzyl sulfide and oxidation of the product to β-hydroxysulfinyl derivatives (Scheme 29).[214] These compounds apparently did not eliminate directly,



Scheme 29.

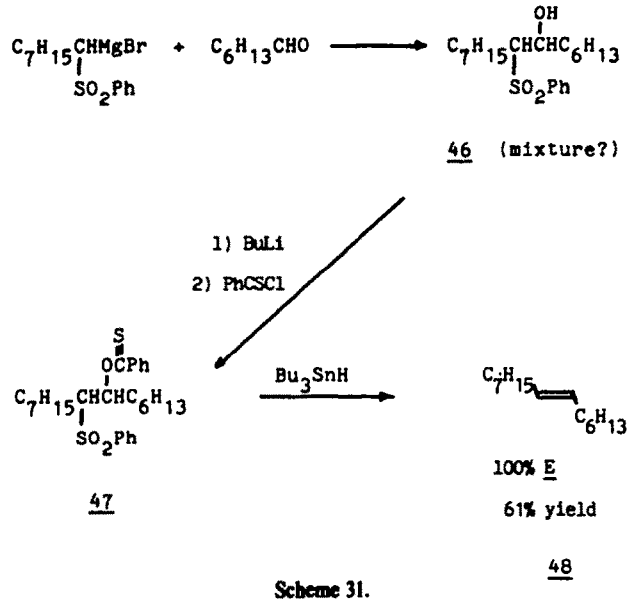
but further oxidation with, for example, NBS, NCS or SO_2Cl_2, produced olefin, SO_2 and benzyl halide. The reaction, which was depicted as proceeding through a β-sultine **45**, succeeded best with more highly substituted epoxides. The yields were only fair, but *cis*-stilbene was obtained in >99% purity.[214] Eliminations from β-hydroxysulfides[215] and β-hydroxysulfoximides[216] have been reported (Scheme 30)



Scheme 30.

but little is known of the scope of the reactions. Also, olefins were obtained by reducing β-hydroxysulfones with Bu_3SnH.[217] In one intriguing experiment, reduction of the thiobenzoate ester of a β-hydroxysulfone **47** (a mixture of diastereomers?) gave exclusively a *trans*-alkene **48** (Scheme 31).[217]

Organoselenium chemistry has been reviewed recently.[175,218] Sodium phenylselenide cleaved epoxides with *anti* stereochemistry.[215b,219] This reagent, which was prepared from diphenyldiselenide with $NaBH_4$ in dry ethanol,[220] usually gave β-hydroxyselenides in good yield although longer reaction times were required for hindered epoxides. Both phenyl- and n-propylselenol added to epoxides if catalytic amounts of phenyl selenolate were present.[221] Reduction of the β-hydroxyselenides occurred when they were exposed to methanesulfonyl chloride and triethylamine.[22] The intermediate mesylates (unlike the mesylates of β-hydroxysulfides)[223] were unstable and *anti* elimination seemed likely based on previous research regarding the reduction of β-hydroxyselenides under acidic conditions.[224a] A variation of this theme employed thionyl chloride and triethylamine in CH_2Cl_2 at room temperature.[224b] The β-hydroxy-



46 (mixture?)

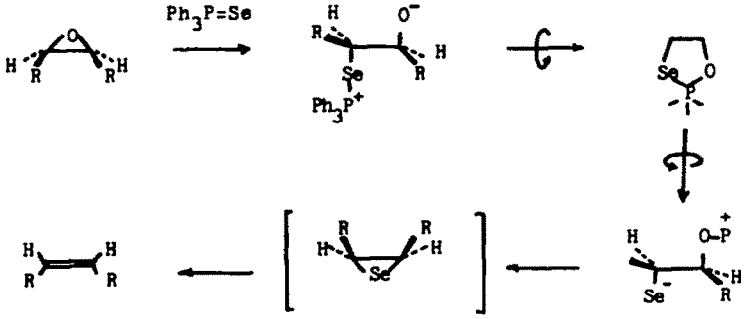
47

48

Scheme 31.

selenides had been obtained from epoxides through addition of phenyl selenol. Di-, tri- and tetra-substituted alkenes were obtained stereospecifically from their epoxides by overall *syn* elimination.

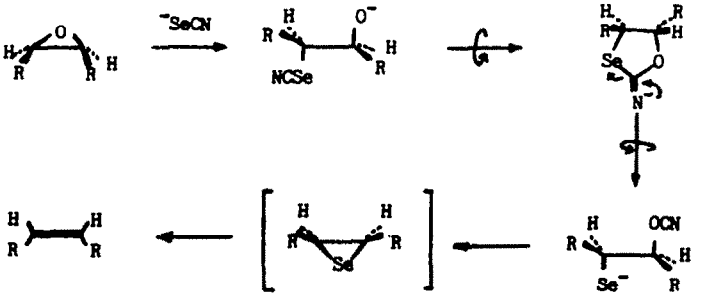
Clive and Denyer reported the stereospecific deoxygenation of epoxides with triphenylphosphine selenide and trifluoroacetic acid.[225] The reaction proceeded at room temperature in CH_2Cl_2 and deposited metallic Se. In order to explain the retention of geometry the sequence in Scheme 32 was proposed



48

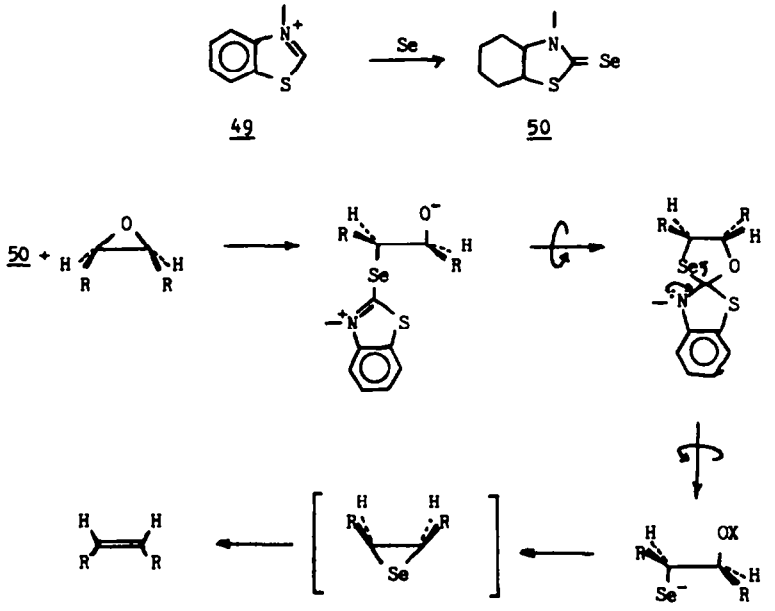
Scheme 32.

wherein a selenirane **48** spontaneously decomposed to give alkene. Episelenides, or seleniranes, have not been isolated although their formation and decomposition have been followed spectroscopically,[226] and the nmr spectrum of a seleniranium salt has been reported.[224b] Epoxides were also deoxygenated with KSeCN in methanol (Scheme 33).[227] The transformation involved (net) *syn* elimination (>90%



Scheme 33.

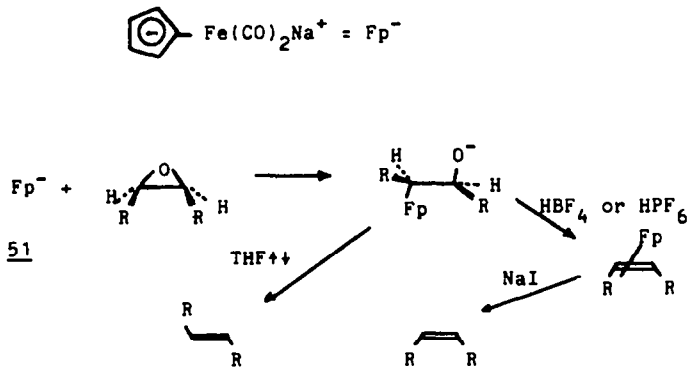
stereospecificity) and a mechanism was proposed in analogy to the reduction of bromohydrins with KSeCN described earlier.[176] The reaction was quite solvent-dependent[228] (did not succeed in DMF or DMSO), was most successful for terminal alkenes,[229] and failed with the epoxides of cyclopentene, cyclooctene and cyclododecene.[228] An interesting reagent for similarly deoxygenating epoxides is 3-methyl-2-selenoxobenzothiazole **50** (Scheme 34).[230] The reagent can be prepared from 3-methylben-



Scheme 34.

zothiazolium iodide **49** with selenium in pyridine. Although stilbene oxides were btained in good yield stereospecifically, information concerning the reactions of other epoxides would be useful. Epoxides were also converted to olefins with the sodium salt of 0,0-diethylphosphorotelluroate.[231] Terminal alkenes are readily prepared from their epoxides with this reagent.

Sodium (cyclopentadienyl) dicarbonyl ferrate, **51**, cleaved epoxides in THF at, or below, room temperature (Scheme 35).[232] A *syn*-elimination was brought about by heating the oxidoferrate inter-

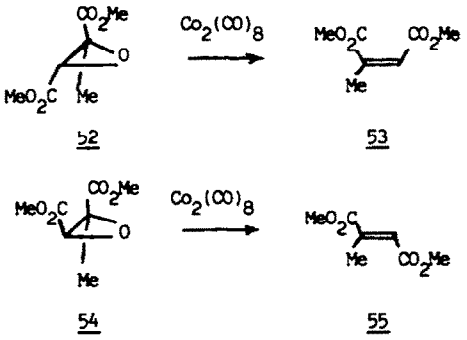


Scheme 35.

mediate by any of several methods. The protonated oxide ferrate, however, underwent *anti*-elimination. Stilbenes and 2-butenes were produced stereospecifically and in good yield. The reaction did not appear useful for α,β-unsaturated systems. Iron pentacarbonyl in tetramethylurea has been described for deoxygenating epoxides.[233] The reactions described showed a tendency toward *syn*-elimination, and reductions to conjugated systems gave good yields, although the stereochemistry for such systems was not reported.[223]

Other *syn* deoxygenations of epoxides include the use of low valent tungsten. A solution obtained from tungsten hexachloride and two equivalents of butyllithium in THF deoxygenated epoxides stereospecifically.[234] Other low valent tungsten preparations, and low valent molybenum may have synthetic utility too.[234]

Dicobalt octacarbonyl reduced epoxides with inversion of stereochemistry (Scheme 36).[235] The scope of the reaction is apparently limited; no data was provided for substrates not containing α-ester groups.

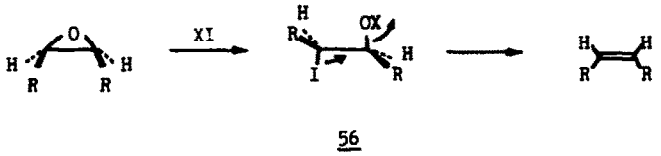


Scheme 36.

However, *cis*-dimethyl epoxymethylsuccinate, **52**, gave a product containing 95% of mesaconate ester, **53**; 3% citraconate, **55**; and 2% of residual epoxide. The isomeric epoxide gave 99% citraconate product. However, if only one ester group was present (methyl epoxycrotonate) the product was a 1:1 mixture of isomeric alkenoates.

Reduction of epoxides by low valent iron (ferric chloridebutyllithium) was reported,[236] and magnesium amalgam in the presence of magnesium bromide has also been employed for this purpose.[143a] Reductions to olefins have also been accomplished using chromous salts,[237] Zn–Cu,[238] and low valent titanium;[239] but these reactions were shown to be nonstereospecific.

Solutions of trifluoroacetyl iodide containing excess iodide ion reduced epoxides to olefins with retention of geometry also.[240] Iodotrifluoroacetates, **56a**, which were the products of bimolecular epoxide cleavage (Scheme 37) underwent *anti*-elimination at room temperature in THF–CH_3–CN. An analogous



56

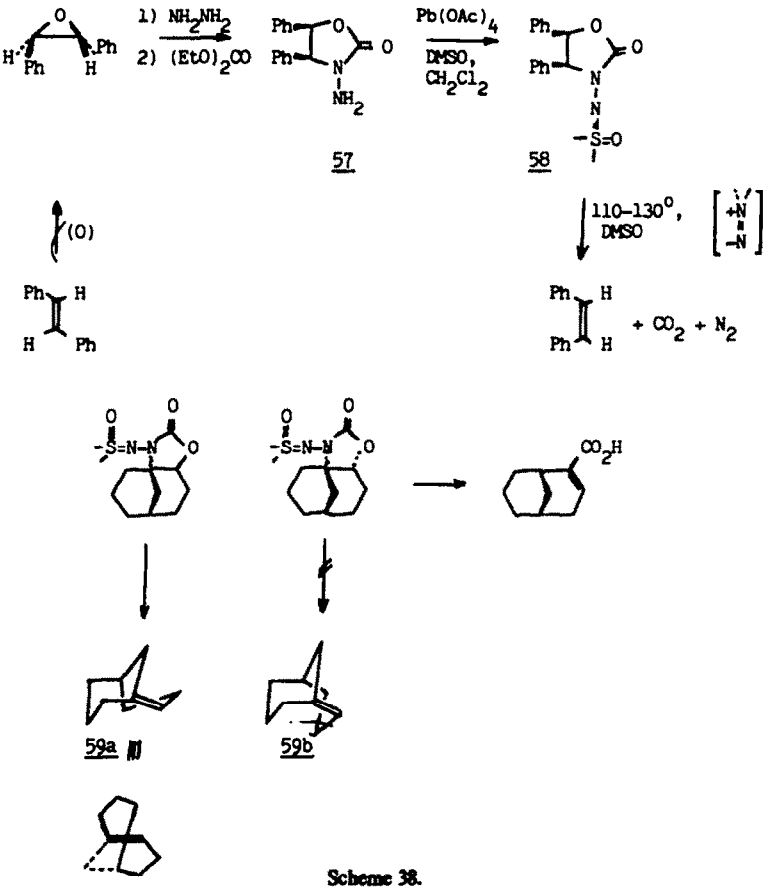
a) X = $CF_3\overset{O}{\overset{\|}{C}}-$

b) X = $(MeO)_3\overset{O}{\overset{\|}{P}}Me$

Scheme 37.

stereospecific reduction occurred with methyl trimethoxyphosphonium iodide and boron trifluoride etherate.[241] An iodohydrin was suggested as an intermediate, the phosphorylated derivative of which, **56b**, underwent *anti*-elimination. Perhaps a bromo- or chlorohydrin intermediate could be obtained analogously that would produce olefins of opposite geometry on further treatment with excess iodide. This particular reduction succeeds for trisubstituted olefins[241] whereas epoxides of trisubstituted alkenes did not react cleanly with trifluoroacetyl iodide.

White and Kim[242] reported a route for olefin inversion exemplified by stilbenes (Scheme 38). The epoxides reacted with hydrazine (one inversion); the resulting β-hydroxyalkylhydrazines were cyclized to 3-amino-1,3-oxazolidin-2-ones, **57**, with diethyl carbonate. Oxidation to a sulfoximine, **58**, was accomplished with lead tetraacetate in methylene chloride and dimethyl sulfoxide. The crystalline sulfoximines decomposed smoothly at 110–130° in dimethyl sulfoxide (via diazenes) producing the stilbenes by a stereospecific *syn*-elimination in high yield. That this intriguing chelotropic reaction could generate highly strained double bonds was demonstrated by the synthesis of bicyclo[3.3.1]non-1-ene, **59a**



Scheme 38.

(Scheme 38) in 53% yield.[242b] The isomeric alkene, **59b**, which contains a *trans*-cyclohexene ring, however, was not obtained by analogous treatment of the appropriate N-aminooxazolidinone.

4. FRAGMENTATIONS OF THIIRANES

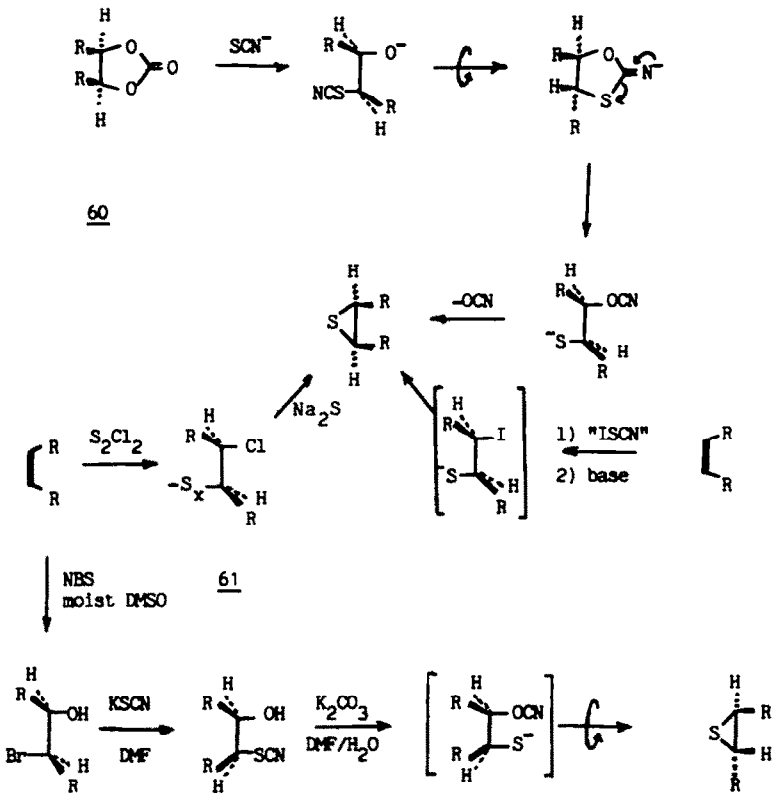
(a) *Syntheses of thiiranes from alkenes summarized*

Few descriptions of olefin inversion via thiiranes or related sulfur heterocycles exist. Because many thiirane preparations from olefins are stereospecific, and several stereospecific fragmentation reactions of these rings are known, it seems useful to enumerate these studies and briefly describe the relevant chemistry.

Thiiranes can be synthesized from olefins via epoxides through reaction with either thiourea or thiocyanate ion.[243] Both procedures entail two inversions of configuration of carbon, hence the transformation of olefin to thiirane is stereoretentive. Cyclic carbonates of 1,2-diols, e.g. **60**, react with thiocyanate to produce thiiranes with two inversions (Scheme 39).[243b] However, since 1,2-diols are readily available by either *syn*- or *anti*-addition to double bonds (see above), a route from olefin to thiirane by inversion of olefin geometry is feasible, albeit somewhat lengthy.

Reaction of alkenes with sulfur dichloride was employed to make thiiranes more directly.[244] The reaction products were mixtures of chloroalkylmono-, di- and trisulfides, **61**, treatment of which by sodium sulfide produced thiiranes stereospecifically with retention of geometry. The addition of iodine thiocyanate ($I_2+\{SCN\}_2$) to olefins proceeded *anti*;[245] the products reacted with base to produce thiiranes in 26–57% yield and the overall effect was again that of *syn*-addition of sulfur across the double bond (Scheme 39). This particular synthesis, Hinshaw noted, was not extended successfully to acyclic alkenes and would fare poorly for olefins containing oxidizable groups in the starting olefin. Thiiranes may also be prepared from epoxides with 3-methylbenzothiazole-2-thione.[246]

Thiocyanate reached with bromohydrins, which are obtainable by the usual *anti*-addition process, to displace the halogen and thereby invert that carbon (Scheme 39).[176] Subsequent base treatment expelled cyanate ion; hence, this process produced thiiranes with stereoinversion from the olefin. The geometrical



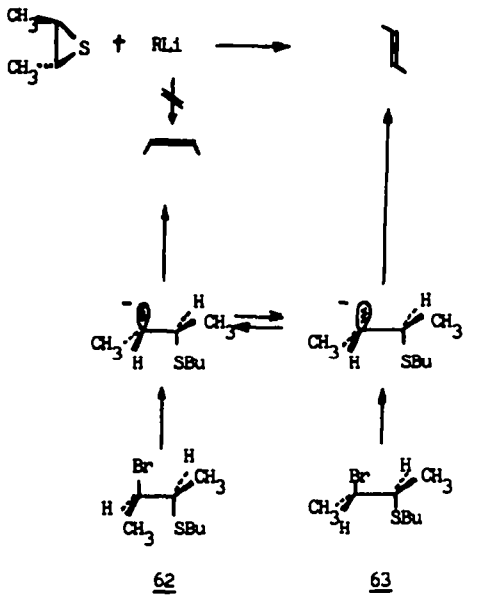
Scheme 39.

purities of the diastereomeric β-hydroxythiocyanates were 70–88%. Evidently the displacement of bromine from secondary carbon by thiocyanate was not strictly S_N2.

(b) *Fragmentations of thiiranes*

Although epoxides reacted with phosphines only at elevated temperatures, thiiranes were converted to olefins[247] smoothly at room temperature with triphenylphosphine and triethyl phosphite. The reaction was, in contrast to that of epoxides and phosphines,[202–204] stereospecifically *syn*.[204] Moreover, *syn*-eliminations could be promoted also by alkyl lithium reagents,[248,249] by lithium aluminum hydride,[249b] and by excess methyl iodide.[248] The methyl iodide reductions of thiiranes were studied in detail and found to proceed via a β-iododimethylsulfonium iodide.[248c] The apparent stereospecificity of the alkyllithium reductions was surprising in view of predictions based on orbital symmetry considerations for cheletropic reactions[56a,250] which suggested that 3-membered ring cleavage would not proceed by a concerted pathway. Hence these reactions might have been expected to proceed by ionic or radical intermediates through which the stereointegrity could be lost.

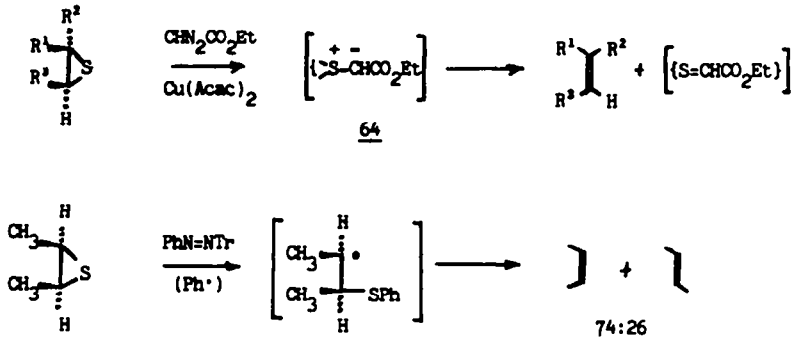
A pertinent study by Trost and Ziman[251] established that anions were not involved. *Threo*- and *erythro*-2-bromo-3-ethylthiobutanes, **62**, **63**, were synthesized (Scheme 40) and each diastereomer was converted by halogen-metal exchange to the anion suspected as an intermediate in the thiirane decomposition. The stereochemical consequences (mixtures of 2-butenes from each anion) left no doubt that bond rotation–anion inversion competed with elimination. Consequently, the thiirane reduction, by which the isomeric 2-butene sulfides were converted to butenes stereospecifically, did not proceed via these anions. The specificity of this reaction need not require that the reaction be concerted and other possible pathways exist.[251] In addition, the symmetry considerations for three-membered rings were reexamined,[56b] and a concerted pathway was deemed possible which would occur by disrotation. Thus the stereospecific fragmentation of thiiranes (and other 3-membered rings subsequently discussed) can occur either by a "nonlinear" cheletropic reaction or by discrete intermediates which have virtually no detectable opportunity to lose configuration. The nature of such intermediates appears not to have been clearly defined yet for this thiirane decomposition.



62 63

Scheme 40.

Thiiranes decomposed stereospecifically to olefins when exposed to carbenes (Scheme 41).[252] For example, ethyl diazoacetate was decomposed with cupric salts in the presence of several thiiranes. The olefins were believed to arise from the stereospecific decomposition of an intermediate sulfonium ylid, **64**. Also, cyclohexane episulfide was transformed to cyclohexene in 67% yield by nickel dicyclooctadiene complex (Ni{COD}$_2$).[253] In contrast to the specificity of anion and ylid reductions of thiiranes, elimination induced by radicals[254] was less specific. Reduction of *cis*-2-butene sulfide yielded 74% *cis*-2-butene, and the *trans* sulfide gave 82% *trans* olefin. The tendency was for *syn*-reduction indicating that the elimination occurred before complete equilibration of the intermediate carbon radicals. Finally, thiiranes may also be reduced to alkenes with 3-methyl-2-selenoxobenzothiazole.[230] The reaction was completely analogous to epoxide reduction described earlier and gave a *syn*-elimination.



64

74:26

a) R^1=CH_3, R^2=H, R^3=i-C_3H_7 >99.5 Z

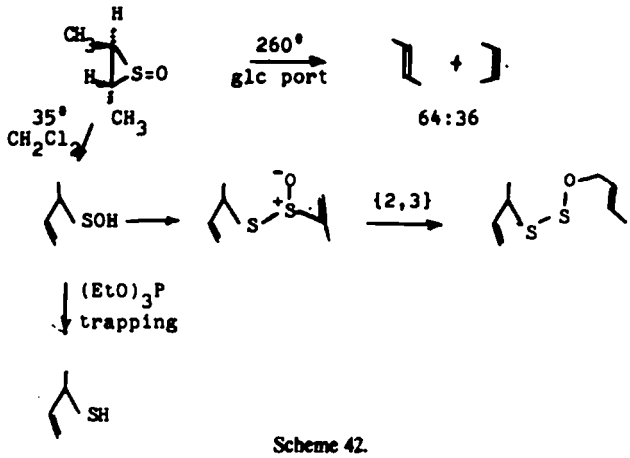
b) R^1=H, R^2=CH_3, R^3=i-C_3H_7 100 E

c) R^1=R^3=C_6H_5, R^2=H 94 Z

Tr = trityl

Scheme 41.

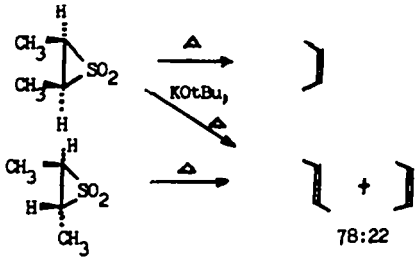
Episulfoxides (thiirane 1-oxides) are generally obtained from thiiranes by oxidation with sodium *meta*-periodate[255] or peracid.[256] Dialkyl episulfoxides (Scheme 42) lost sulfur monoxide when heated to 100° in a glc port.[255] The reduction lacked stereospecificity and, in fact, these compounds underwent a more elaborate series of rearrangements at an intermediate temperature in methylene chloride.[257] The stilbene analogs were pyrolyzed in toluene at several temperatures.[258] Although *trans*-2,3-diphenylthi-



Scheme 42.

irane-1-oxide gave exclusively *trans*-stilbene, the *cis* episulfoxide gave mixtures whose composition was temperature dependent. Experimental evidence, namely trapping with a radical scavenger, argued for diradical species as reaction intermediates.

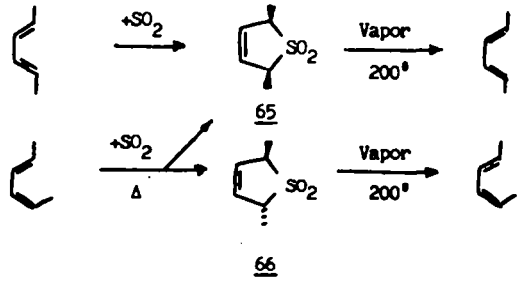
Episulfones readily expelled sulfur dioxide to form olefins.[259,260] Although the episulfone of *cis*-2-butene (Scheme 43) decomposed exclusively to *cis*-2-butene, the *trans* analog yielded a 78:22



Scheme 43.

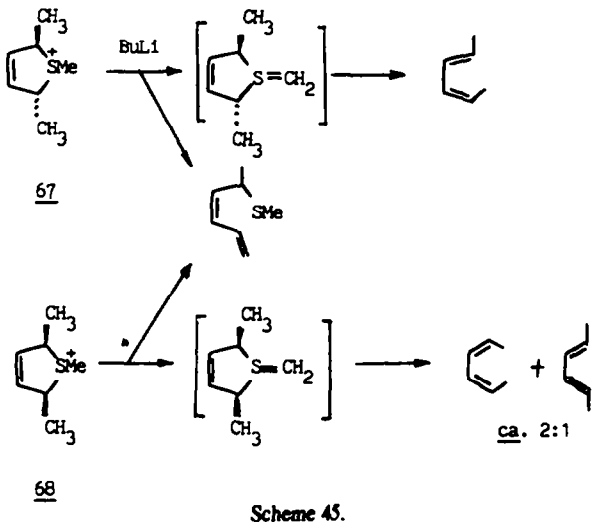
(*trans*:*cis*) mixture of butenes.[261] The diphenyl episulfones eliminated stereospecifically *syn*,[262] but a more intensive study revealed that these reactions were not concerted.[263] The potential for an inversion of geometry exists, since the *cis*-2,3-dialkyl and diphenyl episulfones isomerized in base faster than they decomposed. Thus the *cis*-2,3-dimethyl compound produced the same ratio of *trans* to *cis* in the 2-butene product upon treatment with potassium t-butoxide as had the *trans*-episulfone upon thermal decomposition without base (Scheme 43).[261b] Both diphenyl episulfones gave *trans*-stilbene with sodium hydroxide,[263] an observation which could prove useful for *cis*-to-*trans* inversions.

Cycloadditions of conjugated dienes with sulfur dioxide proceed in disrotatory fashion if thermal and in a conrotatory sense if photochemical.[56] In addition, the adducts may be capable of chemical manipulation, such as epimerization, so that the overall process from cycloaddition through cycloreversion might, in principle, offer useful techniques for selectively altering the geometrical composition of conjugated dienes. The thermal reaction of 2,4-hexadienes with sulfur dioxide (Scheme 44) was stereospecific only with the *E,E*-isomer.[264] Geometrical isomerism of the *E,Z*-isomer occurred at the



Scheme 44.

elevated temperatures required to bring about its reaction. The thermal reversion was disrotatory but the fragmentation had to be performed in the vapor to avoid isomerizing the diene product. Dihydrothiophenium salts, formed from conjugated dienes and sulfur dichloride followed by methylation, fragmented to form mixtures of thioethers and conjugated dienes (Scheme 45).[265] The dienes were



Scheme 45.

formed, however, stereospecifically. Interestingly, the *Z,Z*-isomer (not observed from the thermal decomposition of either (*E*)-1,2-dimethyl-3-cyclobutene[57] or (Z)-2,5-dimethyl-2,5-dihydrothiophene-1,1-dioxide) **65**[264] was the major isomer of the diene product from the salt, **68**. The transition state for the disrotatory mode leading to *E,E*-diene had been adversely affected by steric interaction of the ring methyls with the sulfur alkyl group.

In summary, some opportunity exists for the interconversion of olefin geometrical isomers via thiiranes and episulfones, but the use of sulfur heterocycles for selectively altering the geometry of conjugated dienes seems quite limited.

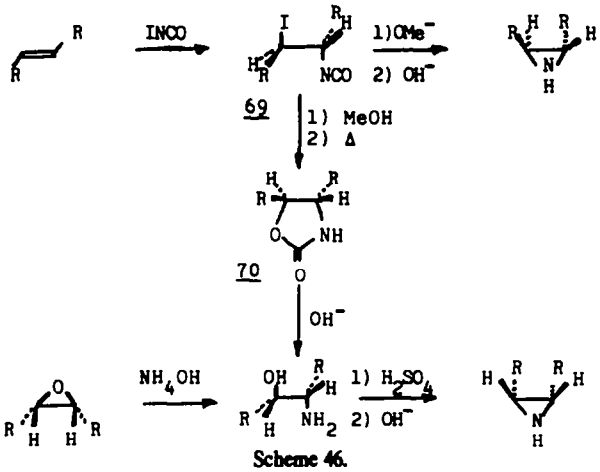
5. FRAGMENTATION OF AZIRIDINES AND RELATED HETEROCYCLICS

(a) *Syntheses of aziridines from alkenes summarized*

Developments in aziridine chemistry were reviewed.[266] Syntheses of aziridines from olefins which have broad scope include sequences initiated by addition of iodine isocyanate[267] and iodine azide.[268] These reactions generally proceeded by *anti*-addition, and the aziridine ring is subsequently formed by intramolecular displacement. These syntheses share with other procedures the retention of olefin geometry in the aziridine product. The following constitutes an update on aziridine syntheses from alkenes.

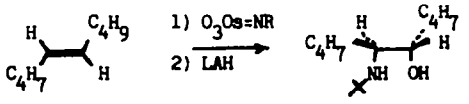
A modification to the iodine azide method allowed preparation of N-substituted aziridines.[269] Aryl- and alkyldichloroboranes reacted with *vic*-iodoazides to produce N-aryl- and N-alkylaminoiodides which in base cyclized to the aziridines. *Vic*-bromoazides, which are conveniently prepared from olefins in aqueous dimethoxyethane from N-bromosuccinimide and sodium azide,[270] were reduced with lithium aluminum hydride to give aziridines with overall retention of geometry. Bromoamination was also achieved using N,N-dibromodiethylphosphoramidate followed by HCl treatment of the resulting *trans*-adduct,[271] and *syn*-addition of primary amines to olefins by aminopalladation has been described.[272] Aziridines have also been prepared from β-hydroxyamines with triphenylphosphine-carbon tetrachloride and triethylamine.[273] It is not clear what the scope or stereochemistry of this transformation is. Also, epoxides reacted with iminotriphenylphosphoranes to give aziridines, and the scope of this reaction is not known yet either.[274]

When a *vic*-iodoisocyanate adduct of an olefin, **69** (Scheme 46) was treated with methanol and the resulting iodocarbamate was heated to 180°,[275] an oxazolidinone, **70**, was formed by inversion at the iodine-bearing carbon. The β-hydroxyamine, which was obtained therefrom by basic hydrolysis, was treated sequentially with acid and base to form the aziridine. The latter transformation of an aminoalcohol to an aziridine is the well known Wenker synthesis of aziridines[276] and involves another inversion of carbon configuration. The modification of Carlson and Lee[275] appears to be the only case of aziridine



Scheme 46.

synthesis with inversion from alkene. Although the route was lengthy, overall yields were good (*E*-2-octene was stereospecifically obtained in 41% yield from the *Z*-isomer). Recently, Sharpless *et al.*[277] employed an aza analog of osmium tetraoxide to oxidize cyclohexene to a *cis*-β-hydroxyamine (Scheme 47). That the reaction was very stereoselectively *syn* was determined by similarly treating *trans*-1D-1-decene (<5% *anti* adduct). Application of Wenker's aziridine synthesis from this point forward would provide aziridines of geometry opposite to that of the olefins.

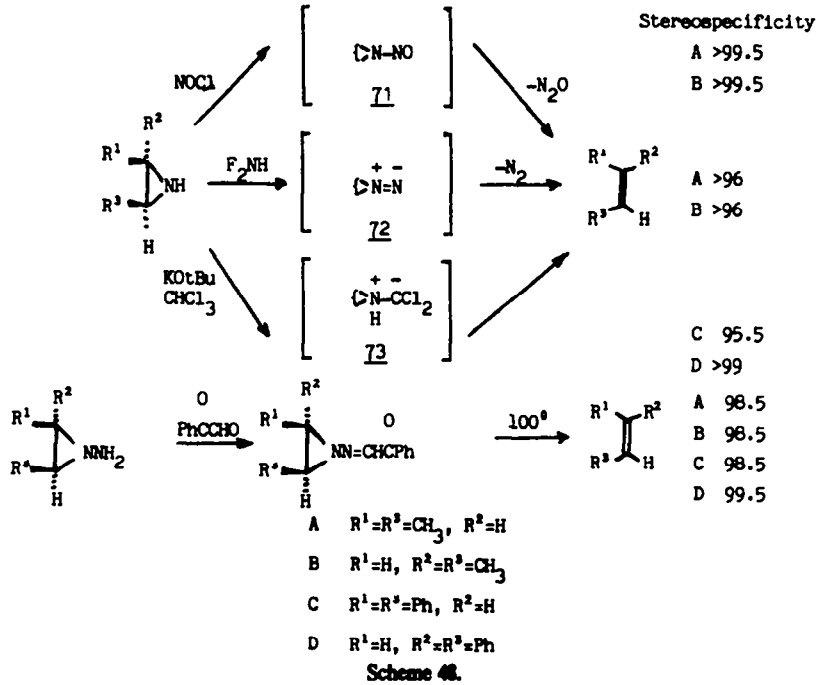


R = t-butyl, adamantyl

Scheme 47.

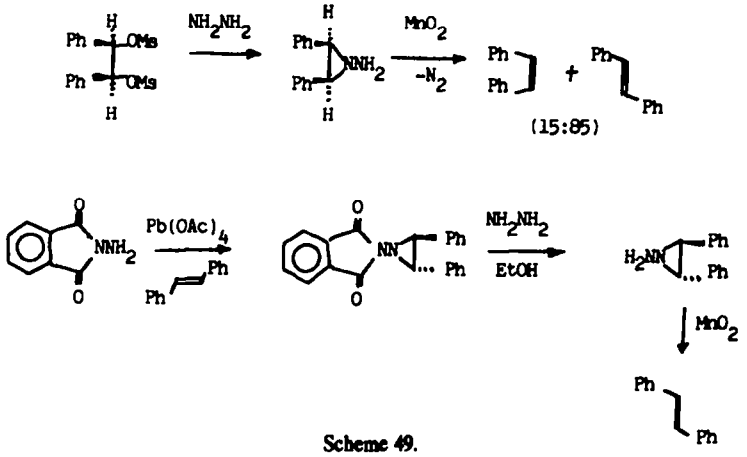
(b) *Fragmentations of aziridines*

Nitrosation of aziridines with nitrosyl chloride, nitromethane, or 3-nitro-N-nitrosocarbazole produced nitrous oxide and alkenes with 99% *cis* deamination (Scheme 48).[278] Intermediate N-nitrosoaziridines, **71**, were inferred spectrally. This deamination has been employed to complete an olefin inversion sequence.[275] Aziridines reacted with carbenes stereospecifically via presumed aziridinium ylids, **72**, to yield imines and olefins of the same stereochemistry as the aziridine (Scheme 48).[279] The reactions of



Scheme 48.

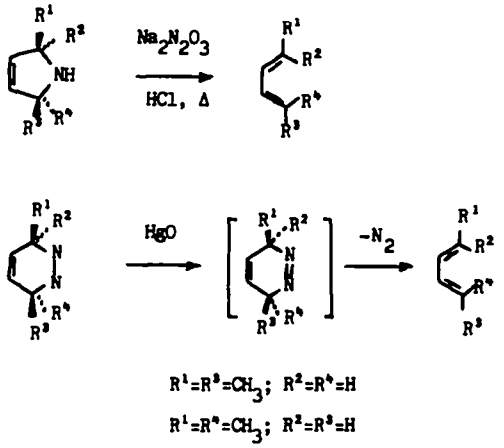
cis- and *trans*-2,3-diphenylaziridine with chloroform and t-butoxide produced *cis*-stilbene (95.5%) and *trans*-stilbene (>99%) respectively, although in only 30% yield. Difluoramine reacted with aziridines producing diazenes, 73, as intermediates[280] which expelled nitrogen and again produced olefins with high *syn* specificity. However, Carpino found that the diphenylaziridines did not decompose specifically from the corresponding diazenes.[281] The syntheses of the required diphenylaziridines was interesting, and one notes that a 1,2-diol was converted via its dimesylate with hydrazine to the N-aminoaziridine which was then oxidized with manganese dioxide to obtain the alkene (Scheme 49). Since diols can be obtained by



Scheme 49.

anti-addition to alkenes, a potentially viable route for inverting olefin geometry is possible by similar conversion to an aminoaziridine followed by a chelotropic fragmentation. N-aminoaziridines could also be reduced stereospecifically *syn* via hydrazones, which when heated (100°) expelled diazoketones (Scheme 48).[282]

Related nitrogen heterocycles, which fragment to produce olefins are 2,5-dihydropyrroles (by oxidation to diazenes)[283] and 1,2,5,6-tetrahydropyrazines (by mercuric oxide oxidation to the 2,4-dihydro analogs).[284] Decompositions were stereospecific and disrotatory, although the utility of such reactions for selective alteration of olefin geometry appears limited (Scheme 50).

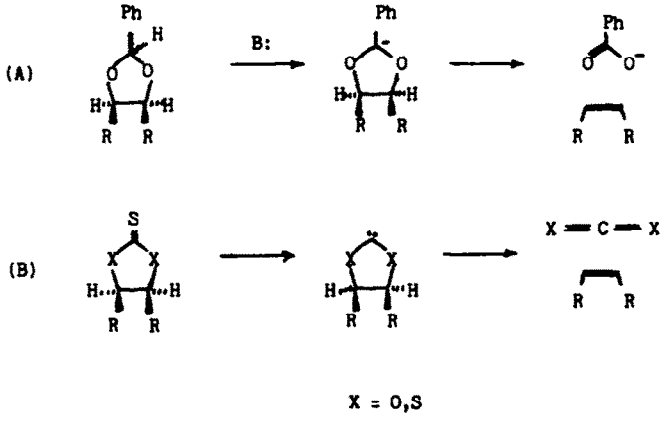


Scheme 50.

Chlorosulfonyl isocyanate added to alkenes stereospecifically *syn* to produce β-lactams.[285] Orbital symmetry-controlled {$\pi^2s + \pi^2a$} cycloadditions are energetically so demanding[56] that this addition was described in terms of dipolar intermediates.[285] Fragmentation of these β-lactams was accomplished only at elevated temperatures (600°, 2 seconds contact time).[286] The olefins were formed stereospecifically *syn* and the fragmentation was viewed, in fact, as a rarely observed {$\pi^2s + \pi^2a$} cycloreversion. The overall sequence of cycloaddition-cycloreversion reproduces the original olefin geometry and, as matters stand, these transformations have no demonstrated utility for interconverting alkene geometrical isomers.

6. FRAGMENTATIONS OF HETEROCYCLES BASED ON *VIC*-DIOLS, DITHIOLS

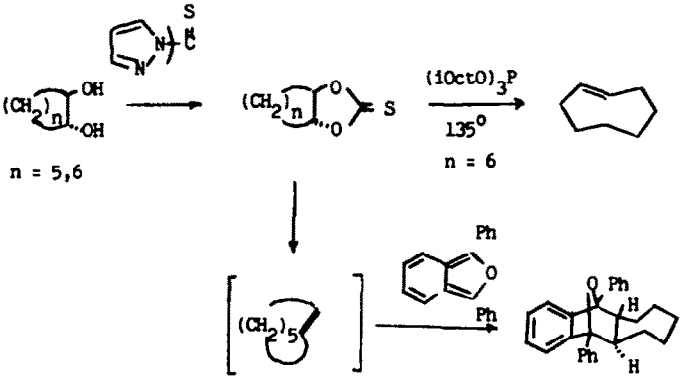
The reactions described in this section are concerted *syn* eliminations in which orbital symmetry is conserved by disrotatory cleavage ({$\pi^2s + \pi^4s$} cycloreversion) from anions or carbenes to form the alkene (Scheme 51). The heterocycles are often obtained from *vic*-diols or dithiols which are readily available as *trans*-adducts of alkenes. *Syn* fragmentation of the heterocycle to an olefin therefore provides a good route for inverting olefin geometry.



Scheme 51.

(a) *Thiono- and trithiocarbonates*

Reaction of *vic*-diols with thiocarbonyldiimidazole,[287] or somewhat less satisfactorily sequential reaction of the diol with base, carbon disulfide and methyl iodide, provided the thionocarbonates. Hindered diols such as pinacol did not react with thiocarbonyldiimidazole and the alternative procedure had to be used. High yields of olefin resulted when the thionocarbonates were heated under reflux in trimethyl or triethyl phosphite. Moreover, the elimination was stereospecific and the sequence was successfully applied to the synthesis of *trans*-cyclooctene (Scheme 52). This strained alkene was swept



Scheme 52.

from the reaction mixture (triisooctyl phosphite, 135°) with argon as it formed (75% yield, >99% *trans*). Although *trans*-cycloheptene could not be isolated from an analogous reaction, its formation was verified by isolation of its 2,5-diphenylisobenzofuran adduct.

Because elevated temperatures and lengthy reaction times seemed to be the rule for thionocarbonate decomposition, other reagents were sought that might achieve the same result more effectively. Both iron pentacarbonyl {$Fe(CO)_5$}[288] and $Ni(COD)_2$,[289] did produce olefins from thionocarbonates. Reaction with $Fe(CO)_5$ occurred at 100°, but was not specific for thionocarbonates yielding stilbenes. The reaction of $Ni(COD)_2$ for which a nickel–carbene complex was tentatively proposed, stereospecifically produced the isomeric 4-methyl-2-pentenes from the diastereomeric thionocarbonates.[289] Reaction of the thionocarbonate of *trans*-1,2-cyclooctanediol, however, produced only *cis*-cyclooctene and it was surmised that nickel catalyzed isomerization of the *E*-isomer.

Table 5. Selected *syn*-fragmentation of diol/dithiol derivatives to alkenes[a]

Reference	Scheme	Starting Material	Product(s)	Yield, %[b]	Stereospec.,%
287a	51B	meso-hydrobenzoin thionocarbonate	(Z)-stilbene	92	c
287a	51B	d,l-hydrobenzoin thionocarbonate	(E)-stilbene	87	c
287a	51B	(Z)-1,2-cyclodecanediol	(Z)-cyclodecene	84	c
287a	51B	(E)-1,2-cyclodecanediol	(E)-cyclodecene	81	c
287a	51B	pinacol	2,3-dimethyl-2-butene	-	-
287b	51B	meso-2,3-diphenylbutane-2,3-diol	(Z)-1,4-diphenyl-2-butene	96	100
287b	51B	d,l-2,3-diphenylbutane-2,3-diol	(E)-1,4-diphenyl-2-butene	99	100
287b	51B	cyclohexanolpinacol	dicyclohexylidene	95	-
287b	51B	(E)-1,2-cyclooctanediol thionocarbonate	(E)-cyclooctene	75	>99
287b	51B	meso-hycrobenzoin thrithiocarbonate	(Z)-stilbene	94	c
287b	51B	d,l-hydrobenzoin trithiocarbonate	(E)-stilbene	100	c
287b	51B	meso-2,3-butanediol trithiocarbonate	(Z)-2-butene	-	c
287b	51B	d,l-2,3-butanediol trithiocarbonate	(E)-2-butene	-	c
307	59	(+)-(E)-1,2-cyclooctanediol thionocarbonate	(-)-(E)-cyclooctene	84	>99[d]
307	59	(-)-(E)-1,2-cyclooctanediol trithiocarbonate	(+)-(E)-cyclooctene	68	99[e]
296	56	(Z)-4,5-diphenyl-1,3-dithiolan-2-thione	(Z)-stilbene	90	90[f]
296	56	(E)-4,5-diphenyl-1,3-dithiolan-2-thione	(E)-stilbene	62	100
299	51A	(E)-1,2-cyclooctanediol benzylidene acetal	(E)-cyclooctene	75	100
299	51A	d,l-hydrobenzoin benzylidene acetal	(E)-stilbene	9[g]	100
308	51A	I(R=H)[h]	II(R=H)	30	100[d]
308	51A	I($R=CH_3$)[g]	II($R=CH_3$)	60	100[d]
308	51A	III[g]	IV	67	100[c]

[a] Preparations of olefins which do not exist as geometrical isomers have been included for the sake of greater comprehensiveness.

[b] Isolated yields.

[c] Reaction was reportedly stereospecific.

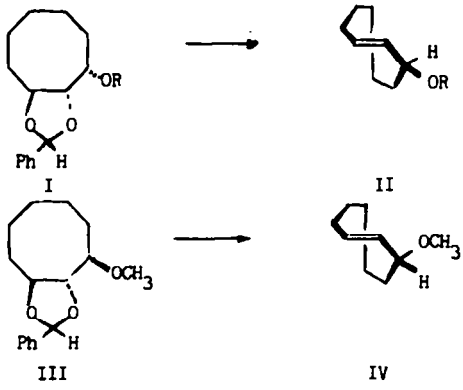
[d] Optical purity ~100%.

[e] Optical purity 96%.

[f] Isomerization of the product alkene occurred.

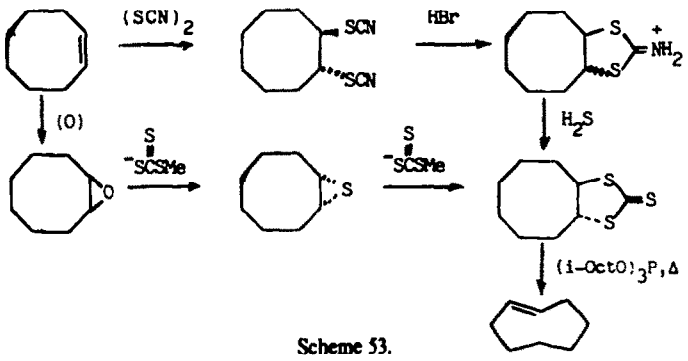
[g] Also isolated: desoxybenzoin (66%) and 1-phenylpentan-1-ol (64%). No (Z)-stilbene was obtained from the meso-isomer.

[h] Structures for I - IV given below.



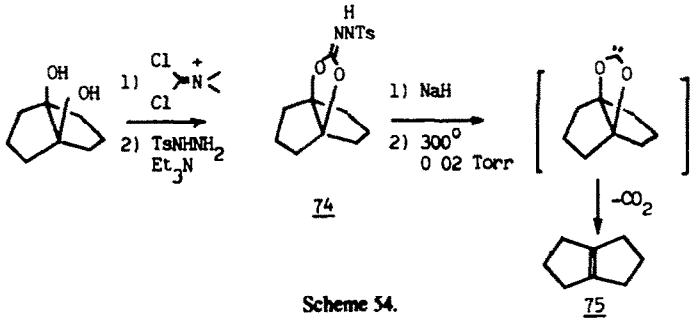
Decomposition of thionocarbonates in sterically crowded molecular environments sometimes failed. Alkylation of the thione sulfur with methyl- or isopropyl iodide produce a *vic*-iodo thiocarbonate by S_N2 displacement by the iodide ion. Reduction with either Zn or Mg amalgam, however, was not stereospecific. The systems examined were dire tests of specificity (attempts to prepare *trans*-cyclooctene and the stilbenes) for which the metal reducing agents might be expected to fail.[107]

The related trithiocarbonates were also examined.[287b] Preparation of the *trans*-1,2-trithiocarbonate of cyclooctane was accomplished by *anti*-addition of dithiocyanogen to *cis*-cyclooctene (Scheme 53),



Scheme 53.

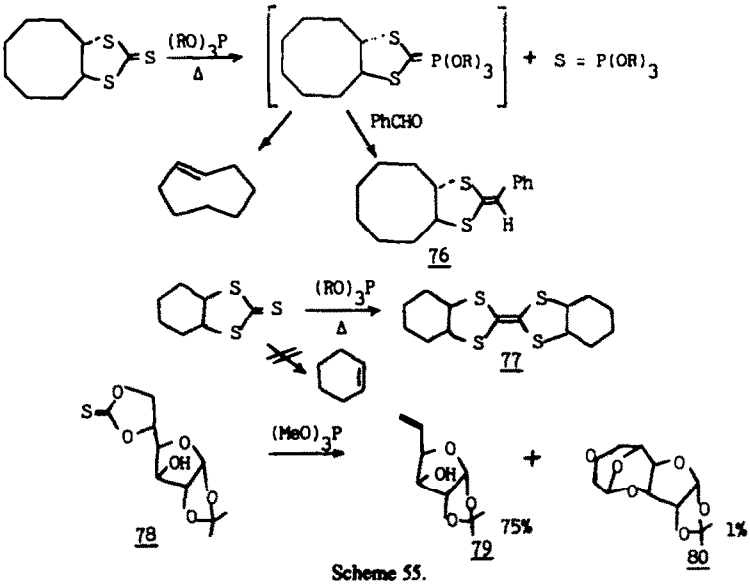
cyclization with HBr, and treatment of the resulting iminodithiocarbonate with hydrogen sulfide. Alternatively, trithiocarbonates can be prepared from epoxides with potassium methyl trithiocarbonate,[291] a procedure which had been demonstrated to occur with an odd number of Walden inversions.[292] Elimination from trithiocarbonates was again stereospecific and the yields (2-butenes, stilbenes) were high, but extended reflux in trimethyl phosphite was required. An interesting variation of this reaction involved the carbonate tosylhydrazone, 74 (Scheme 54).[293] The tosylhydrazone was



Scheme 54.

prepared from the diol with phosgene immonium chloride followed by tosylhydrazine. The bicyclic olefin, 75, was obtained from the sodium salt of the hydrazone at 300°. Pyrolysis of the thionocarbonate of pinacol gave only tetramethylethylene, whereas both 2,3-dimethylbutadiene and 2,3-dimethylbuten-3-ol in addition to the alkene were produced from the hydrazone decomposition. The suggestion was made, therefore, that the reactions may not be mechanistically equivalent.

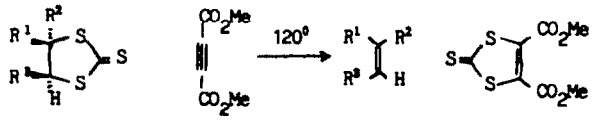
That the mechanism of the trithiocarbonate fragmentation involved the initial generation of an ylid (Scheme 55),[294] was demonstrated by intercepting that ylid with added aldehyde forming 76. Once such an ylid is formed it may decompose competitively to alkene, react with accessible electrophiles such as aldehydes, or react with trithiocarbonate to form a dimer; e.g. 77. Ylids were also formed when the reaction was extended to the homologous trithiocarbonate of 1,3-propanedithiol. These ylids did not



Scheme 55.

fragment to cyclopropanes and were found useful for condensations with aldehydes as a chain-extension reaction. The pyrolysis of the thionocarbonate, **78** (Scheme 55)[295] produced the insertion product, **80**, in addition to the expected olefin, **79**, which was advanced as evidence that a carbene intermediate was involved in thionocarbonate fragmentation.

When *cis*- and *trans*-4,5-diphenyl-1,3-dithiolan-2-thiones reacted with dimethyl acetylenedicarboxylate, an addition–elimination sequence occurred (Scheme 56).[296] Stilbenes were formed rapidly at 120°, conditions which are less vigorous than for trithiocarbonate and thionocarbonate decompositions. The *trans*-isomer was formed stereospecifically, while the *cis*-stilbene isomerized partially as it formed. These observations are provocative; they may point the way to greater utilization of carbonate fragmentation reactions by substantially reducing reaction times and temperatures.



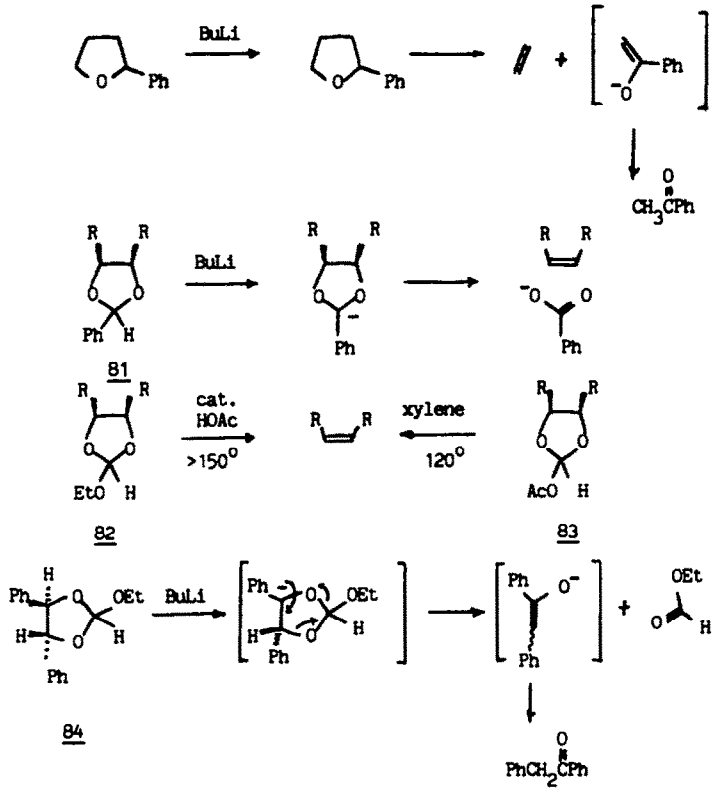
a) $R^1=R^3=Ph$, $R^2=H$ >90% stereospec.

b) $R^1=H$, $R^2=R^3=Ph$ 100% stereospec.

Scheme 56.

(b) *Dioxolanes*

The initial observation of the cleavage of a cyclic ether via an α-carbanion to form an olefin appears to have been made by Letzinger and Pollart (Scheme 57).[297] Treatment of 2-phenyltetrahydrofuran with alkyllithium gave ethylene and acetophenone. Wharton *et al.* observed the decomposition of the benzaldehyde acetal of ethylene glycol, **81**, with phenyllithium in ether at room temperature to ethylene (80–94%).[298] Although benzoic acid was not recovered from the reaction mixture, the isolation of both benzophenone and triphenylmethanol was consistant with an initial fragmentation to benzoate ion



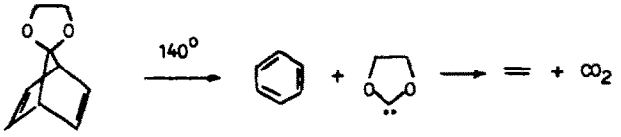
Scheme 57.

(Scheme 57). The scope of this reaction was examined subsequently by Hines *et al.*[299] who determined the *syn*-stereospecificity of the decomposition enabling a facile, ambient temperature preparation of *trans*-cyclooctene (75% yield, 100% *trans*).

Orthoformate esters of 1,2-diols (82 and 83) could be cleaved to olefins stereospecifically by heating to > 150° with acetic acid catalyst (Scheme 57).[300] This reaction appeared to be particularly useful for the preparation of α,β-unsaturated systems. In contrast, deprotonation of the orthoester, 84 (Scheme 57) with butyllithium gave phenylacetophenone and ethyl formate.[301] No stilbene was observed.

2-Acetoxy-1,3-dioxolanes, which may be intermediates in the acetic acid-catalyzed decomposition of 2-ethoxy-1,3-dioxolanes, were converted to alkenes (CO_2, acetic acid) when heated neat to 120°.[302] The reaction was not clean and produced the mixed (formate–acetate) diester of the *vic*-diol in varying amounts. Reportedly, decomposition of the acetoxydioxolanes produced only olefins in xylene under reflux. Aminodioxolanes have been prepared from *vic*-diols (dimethylformamide dimethyl acetal).[303] These were pyrolyzed in refluxing acetic anhydride to produce dimethyl acetamide, CO_2, acetic acid, and olefin. The reactions were not generally stereospecific, however, and some carbonium ion character was evident. In one case, for example, 1,1-diphenylethylene and *trans*-stilbene accompanied the major product, *cis*-stilbene.

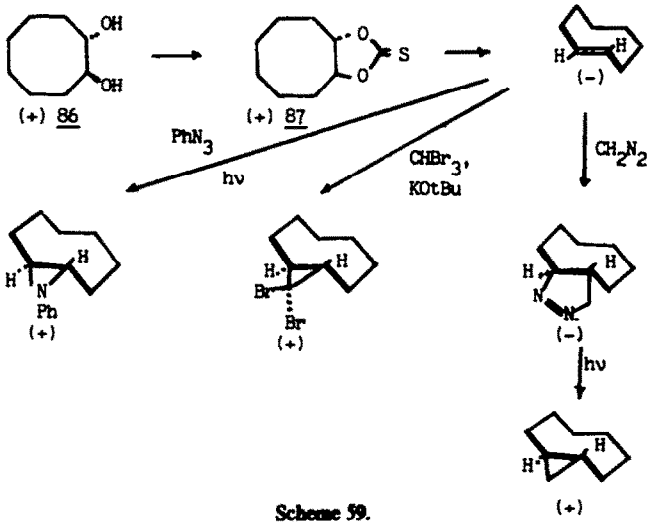
The ethylene ketal of norbornadienone, 85, fragmented to give ethylene (Scheme 58).[304] Although this reaction appears to have little utility for olefin synthesis, it was pursued as a possible source of dialkoxycarbenes (dimethyl rather than ethylene ketal).



85

Scheme 58.

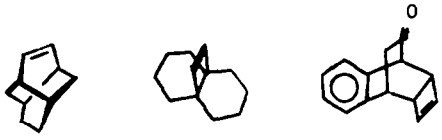
Syn-fragmentations of thionocarbonates, 1,3-dioxolanes, and related heterocyclics discussed above have considerable utility for olefin synthesis. The following discussion permits an assessment of the degree to which such reactions may be employed as a key step for olefin inversion. Shortly after Cope *et al.* proved that molecular disymmetry would be a property of *trans*-cyclooctene by resolving the *trans*-olefin with platinum complexes of α-methyl benzylamine,[305] they established the absolute configurations of both the cyclooctane-1,2-diols and the *trans*-olefin.[306] The (+)-*trans*-1,2-diol, 86 (Scheme 59) was obtained then by fractional crystallization of the strychnine salt of the monophthalate



Scheme 59.

half-ester.[307] Fragmentation of the derived thionocarbonate, 87, produced optically pure (−)-*trans*-cyclooctene in 84% yield. A route was also established via the trithiocarbonate; resolution was performed on the iminodithiocarbonate intermediate (refer to Scheme 53) with the salt of (−)-1-

phenylethanesulfonic acid. Again, high optical purity was achieved. A series of optically pure 3-substituted *trans*-cyclooctenes were prepared and absolute configurations were established.[308] In each instance the *trans*-double bond was obtained by treatment of the benzylidene derivative with butyllithium. Although the yields were not high, the stereospecificity of the reaction assured optical purity of product. Optically active *trans*-cyclooctene prepared by these routes has also been used to synthesize *trans*-fused and optically pure cyclopropanes[307,309] and aziridines[309] (Scheme 59). The thionocarbonate decomposition (Corey–Winter reaction) has been applied successfully to sugars[310] and other highly oxygenated substrates.[311] This reaction served also in the final step of the synthesis of optically active twistene, **88**, and thereby aided in the determination of the absolute configuration of both the alkene and the parent hydrocarbon (Scheme 60).[312] Fused cyclobutene systems related to propellanes, **89**,[313] and the hindered cyclobutene, **90** (Scheme 60)[314] were obtained either by direct desulfurization of a thionocarbonate or by the modification which produced an iodoester for zinc reduction.[290] Attempts to prepare benzyne from catechol via either the thionocarbonate[287b] or the benzylidene derivative[315] failed. A trimeric compound was obtained from the carbene of the thionocarbonate,[316,317] while the benzylidene derivative produced catechol and 2-phenyl-2-(2-hydroxyphenoxy)pentane.[315]



(+)-88 89 90

Scheme 60.

7. INTERCONVERSION OF OTHER ALKENE GEOMETRICAL ISOMERS

Double bonds which are conjugated with various common carbon functional groups have been, in part, discussed in the earlier sections wherein the methodology employed for inversion served as the basis for discussion. It was noted that conjugation lowered the energy barrier to thermally induced inversion of geometry, and altered the energy difference between isomers so as to favor *trans*.

Substitution of a basic nitrogen on the β-carbon of an α,β-unsaturated system to create a "push–pull" ethylene dramatically lowered the barrier to inversion.[318] Enaminoaldehydes and enaminoketones, for example, underwent *cis-trans* isomerization in solution. The equilibrium position was dependent upon both the structure of the compound and the solvent. Similarly, the equilibration of geometrical isomers of nitroenamines has been studied by NMR techniques.[319]

Heteroatoms which are not as basic as nitrogen afford more readily isolated geometrical isomers. Thus vinyl boranes may be converted to vinyl halides by either retention or inversion or geometry.[320] In this case, geometrical inversion was accompanied by a switch from one heteroatom (B) to another (Br), and the inversion was from a *trans*-vinyl borane to a *cis*-vinyl halide. A similar sequence involving vinyl silanes has permitted the preparation of vinyl chlorides,[321] bromides,[321,322] iodides,[323] acetates,[322] ethers,[322] and enamides[322] with either retention or inversion; the replacement consisting of X for Si. These reactions have in common *anti*-addition of XY followed by *anti*-elimination of XSi (or XB).

The currency of these efforts makes a thorough review of the inversion of heteroatom substituted alkenes quite premature. Clearly, however, a new area for research is developing concurrently with the developing interest in vinyl organometallics; namely that of inversion of alkene geometry with concommitant replacement of one heteroatom by another. The utility of such transformations for organic synthesis, and the thermal and photochemical[324] properties of geometrically pure heteroatom substituted alkenes, seem to offer considerable latitude for further research.[325]

Acknowledgements—The author is deeply grateful to Dr. James E. Oliver for many helpful suggestions during the preparation of this manuscript. The author also expresses appreciation to his wife, Marilyn Sonnet, for assistance in editing.

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