The Chemistry of Heterocycles

Structure, Reactions, Syntheses, and Applications

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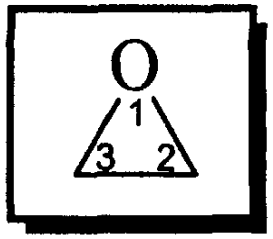
3. Three-Membered Heterocycles

The properties of three-membered heterocycles are mostly a result of the great bond angle strain (BAEYER strain).

The resultant ring strain imparts on the compounds high chemical reactivity. Ring opening leading to acyclic products is typical.

As set out above, the heterocycles will be treated in decreasing priority, starting with those with one heteroatom. The parent system of the three-membered heterocycles with one oxygen atom is called oxirene.

Oxirenes are thermally very labile. They were postulated as intermediates in some reactions. However, oxirane, the saturated three-membered heterocycle with one oxygen, is of great importance.



3.1 Oxirane

[A] Oxiranes are also known as epoxides. Microwave spectra as well as electron diffraction studies show that the oxirane ring is close to being an equilateral triangle.

The strain enthalpy was found to be 114 kJ mol^{-1}. The ionization potential is 10.5 eV; the electron which is removed derives from a nonbonding electron pair of the O-atom. The dipole moment is 1.88 D. The UV spectrum of gaseous oxirane has λ= 171 nm.

The chemical shift in the NMR spectrum are δ_H= 2.54, δ_C= 39.7. With a rise in the s-orbital component of the relevant C-H bonds, the ^{13}C-H coupling constant increases. The value of 176 Hz for oxirane is much greater than for aliphatic CH_2 groups. To explain this fact, one can imagine that the bonding MO of the C-O bonds are formed by interaction of the HOMO of an ethene molecule with an unoccupied AO of an O-atom, and also through interaction of the LUMO of the ethene molecule with an occupied AO of the O-atom. As a result, the C-H bonds have more s-character than normal sp^3-hybridized C-atoms.

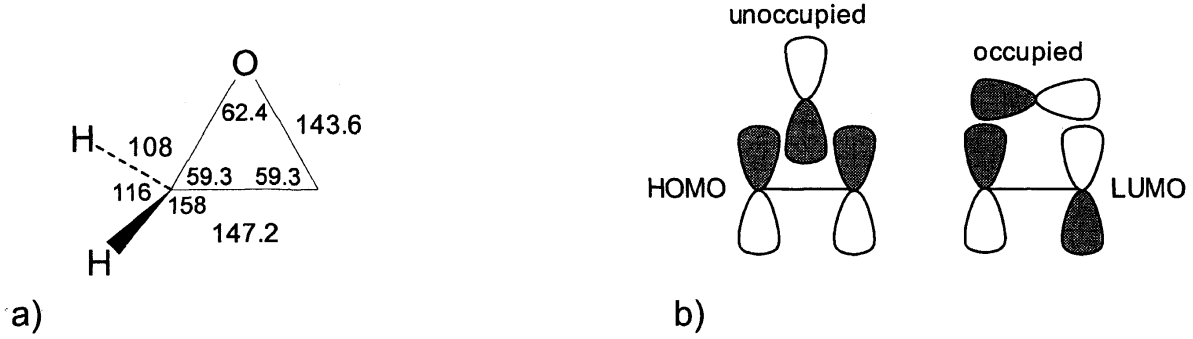


Fig. 3.1 Structure of oxirane
(a) Bond lengths in pm, bond angles in degrees
(b) Model for the bonding MO

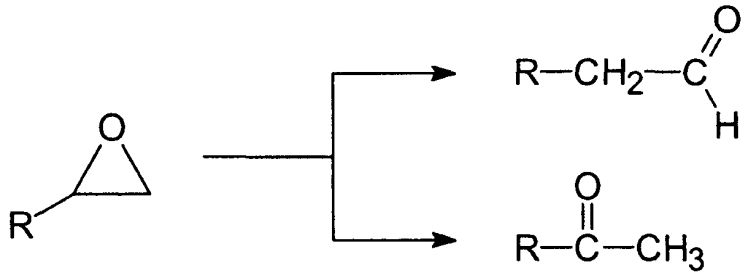
[B] Apart from the ring strain, a significant property of oxiranes is their BRÖNSTED and LEWIS basicity, because of the non-bonding electron pairs on the O-atom. Consequently, they react with acids. When handling oxiranes, it should also be borne in mind that many of them are carcinogenic.

The most important reactions of oxiranes are described below.

Isomerization to carbonyl compounds

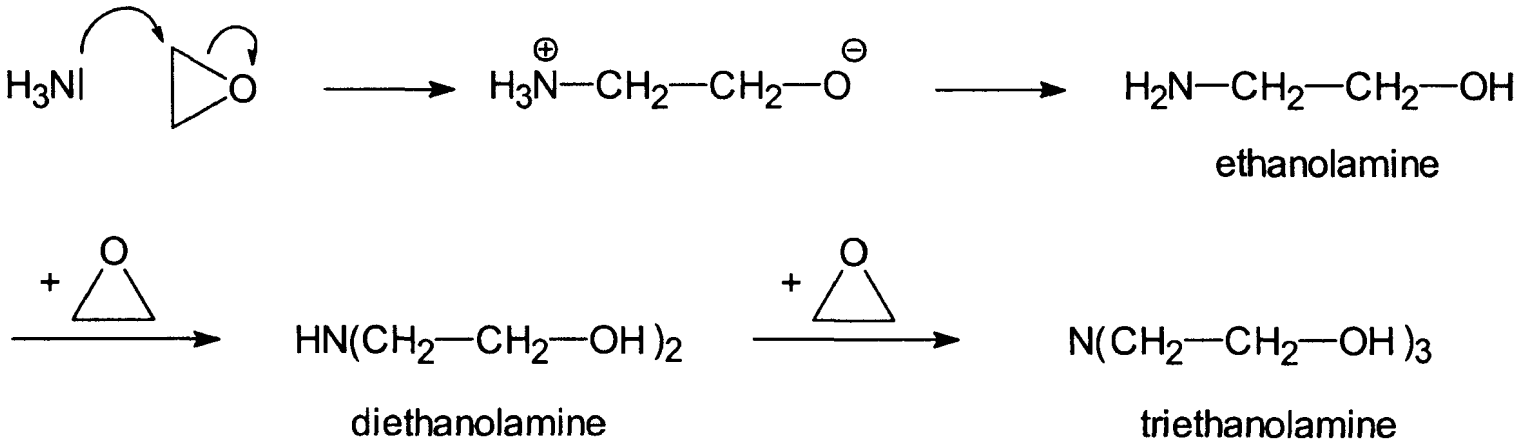
In the presence of catalytic amounts of LEWIS acids, e.g. boron trifluoride, magnesium iodide, or nickel complexes, oxiranes isomerize to give carbonyl compounds. Oxirane itself gives acetaldehyde:

Substituted oxiranes yield mixtures. The nickel(II) complex $NiBr_2(PPh_3)_2$ yields aldehydes regioselectively.



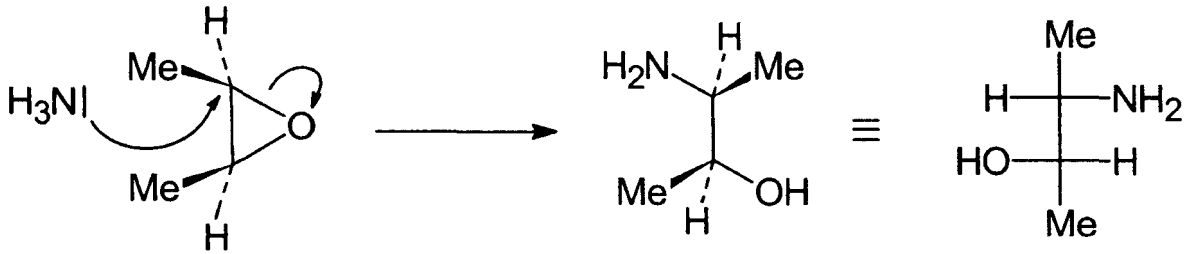
Ring-opening by nucleophiles

Nucleophiles, e.g. ammonia or amines, cause oxiranes to ring-open to give amino alcohols:

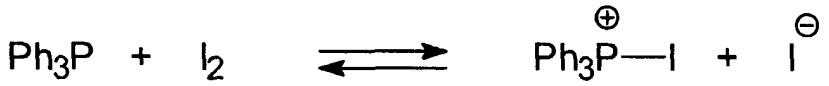


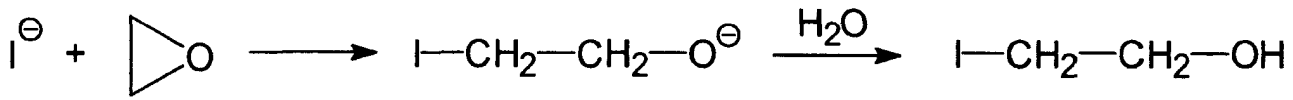
The concerted reaction corresponds to an S_N2 mechanism of a nucleophilic substitution on a saturated C-atom and is stereospecific.

For example, from *cis*-2,3-dimethyloxirane, (±)-*threo*-3-aminobutan-2-ol is formed. From *trans*-2,3-dimethyloxirane, the (±)-*erythro*-diastereomer is formed in an analogous manner.



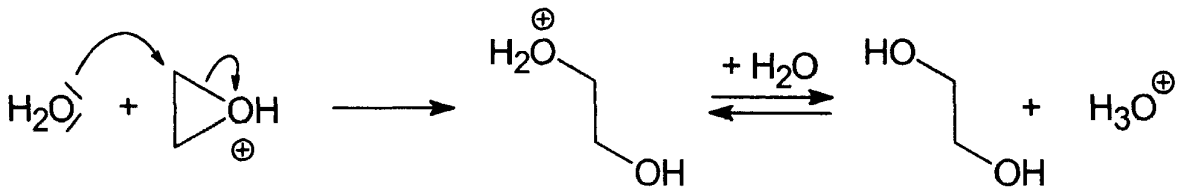
Halogens react with oxiranes in the presence of triphenylphosphane or with lithium halides in the presence of acetic acid to give β-halo alcohols (halohydrins).





Acid-catalyzed hydrolysis to 1,2-diols (glycols)

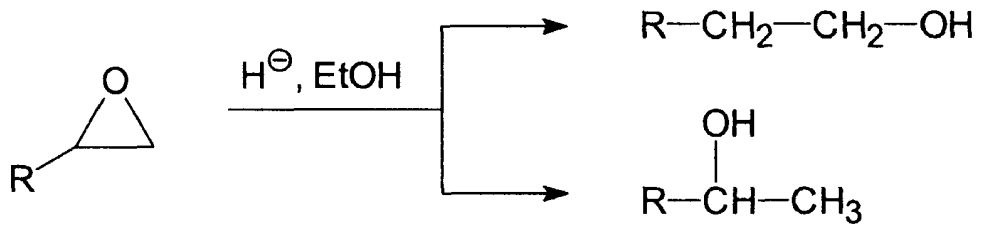
An acid-base equilibrium precedes the nucleophilic ring-opening of the oxirane ring.



Such an A2 mechanism (A stands for acid, 2 indicates a bimolecular rate-determining step) results in a stereospecific reaction. Thus (±)-butane-2,3-diol is formed from *cis*-2,3-dimethyloxirane and *meso*-butane-2,3-diol from *trans*-2,3-dimethyloxirane. The oxirane obtained by epoxidation of cyclohexene is *trans*-cyclohexane-1,2-diol.

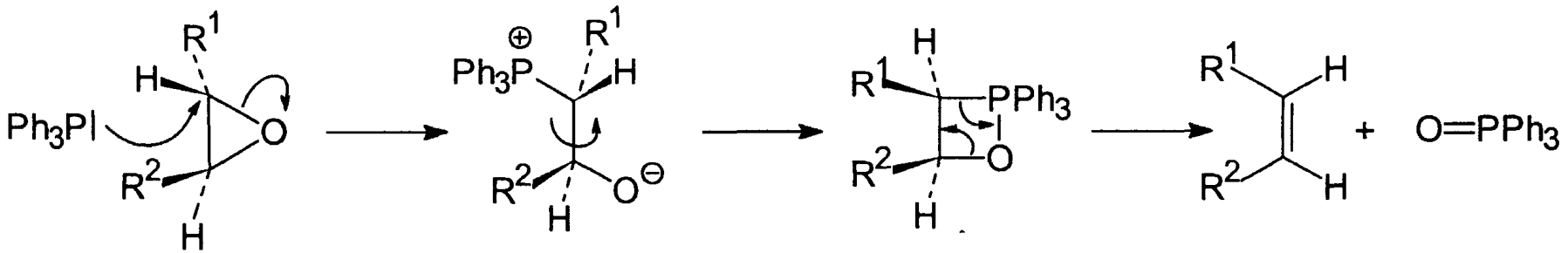
Reduction to alcohols

Oxiranes are reduced by sodium borohydride to give alcohols. This reaction can be viewed as a ring-opening by the nucleophilic hydride ion:



Deoxygenation to olefins

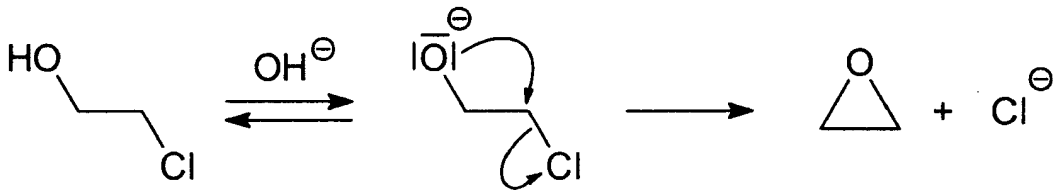
A number of reagents deoxygenate oxiranes to give olefins. For instance, a *trans*-oxirane yields a (*Z*)-olefin on treatment with triphenylphosphane at 200 °C. An (*E*)-olefin can therefore be converted into a (*Z*)-olefin via a *trans*-oxirane.



[C] For the synthesis of oxiranes, four reactions have proved useful. The oxirane syntheses described under (1), (3) and (4) are based on the same principle: an anionic oxygen atom substitutes intramolecularly a leaving group situated on a β-C-atom.

(1) Cyclodehydrohalogenation of β-halo alcohols

Bases deprotonate β-halo alcohols to give the corresponding conjugate bases. This is followed by an intramolecular displacement of the halogen atom as the rate-determining step.



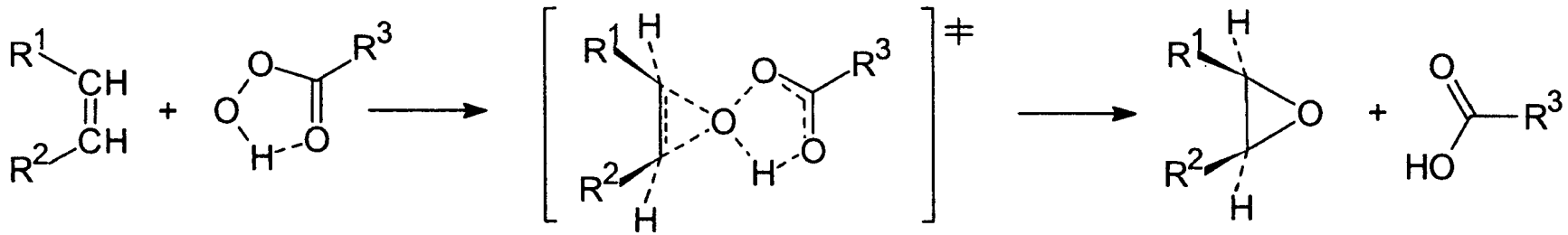
In spite of the ring strain in the product and the considerable activation enthalpy, the reaction occurs rapidly at room temperature owing to favorable entropy. The activation entropy is affected only by the loss of the degree of freedom of the internal rotation in the 2-chloroalkoxide ion because of the mono-molecular rate-determining step.

Oxirane was first prepared by WURTZ (1859) by the action of sodium hydroxide on 2-chloroethanol.

(2) *Epoxidation of alkenes*

Peroxy acids react with alkenes to give oxiranes. In the PRILESCHAJEW reaction, peroxybenzoic acid, *m*-chloroperoxybenzoic acid or monoperoxyphthalic acid is used.

In weakly polar solvents, the reaction occurs in a concerted manner:

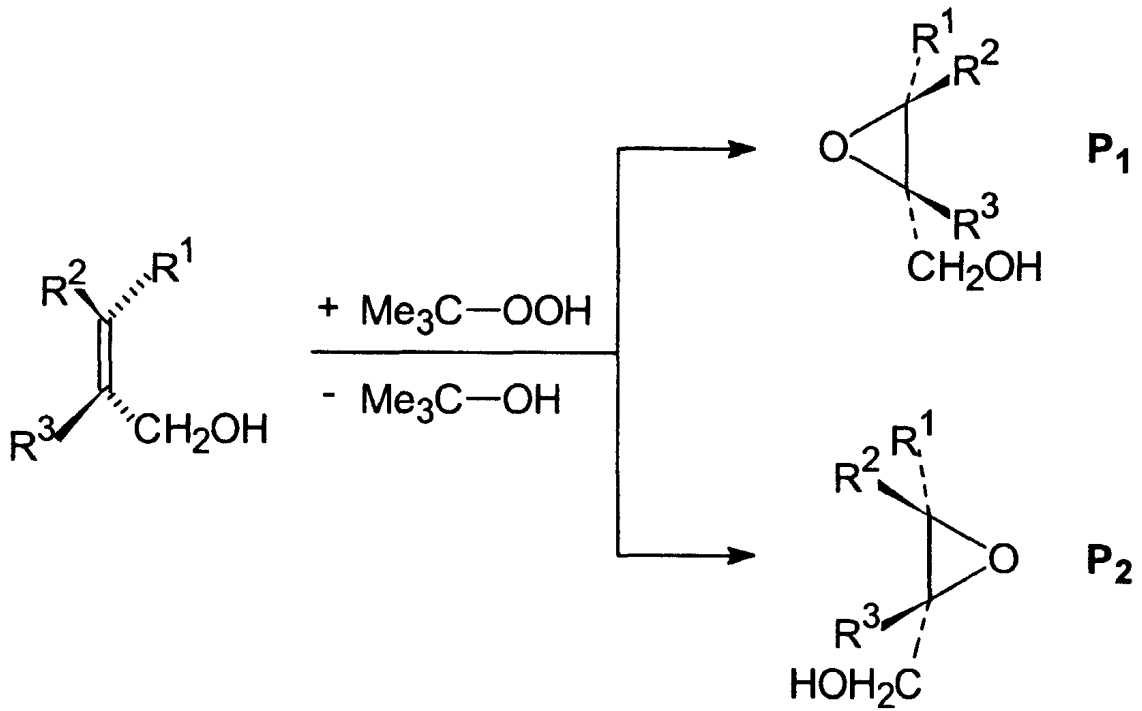


Peroxy acids possess strong intramolecular hydrogen bonds. The concerted progress results in a stereospecific reaction. (*Z*)-alkenes yield *cis*-oxiranes, (*E*)-alkenes yield *trans-oxiranes.*

tert-Butyl hydroperoxide is used for the SHARPLESS epoxidation. The epoxidation of allyl alcohol and substituted allyl alcohols with this reagent in the presence of titanium tetraisopropoxide $Ti(OCHMe_2)_4$ and (*R,R*)-(+)- or (*S,S*)-(-)-diethyl tartrate (DET) occurs enantioselectively (KATSUKI and SHARPLESS 1980):

In the presence of (*R,R*)-(+)-DET, the enantiomer P_1 is formed with ee 90%, while in the presence of (S,S)-(-)-DET, the enantiomer P_2 is obtained, also with ee > 90%.

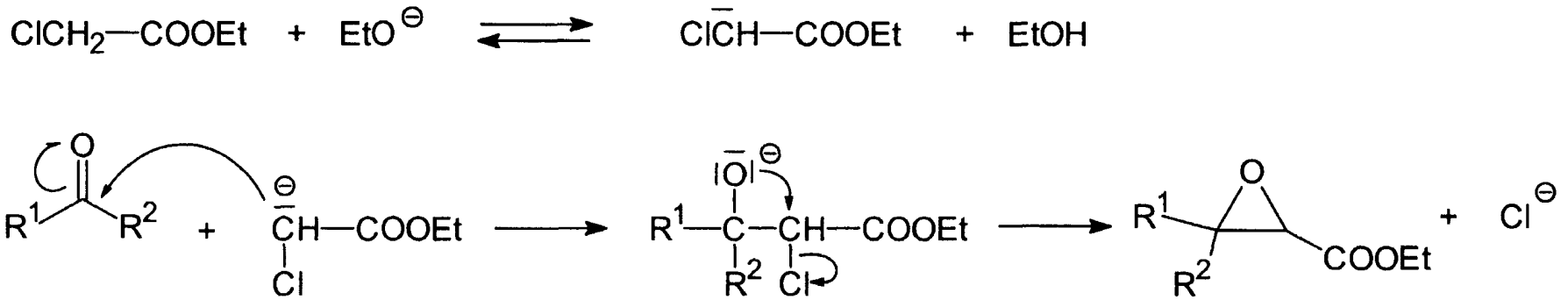
The SHARPLESS epoxidation is, therefore, an important method for asymmetric synthesis.



(3) *Darzens reaction (glycidic ester synthesis)*

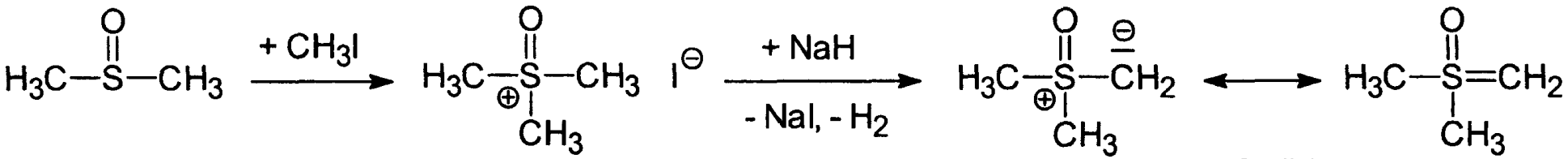
The reaction of α-halo esters with carbonyl compounds in the presence of sodium ethoxide leads to 2-(ethoxycarbonyl)oxiranes (DARZENS 1904). They are known as glycidic esters.

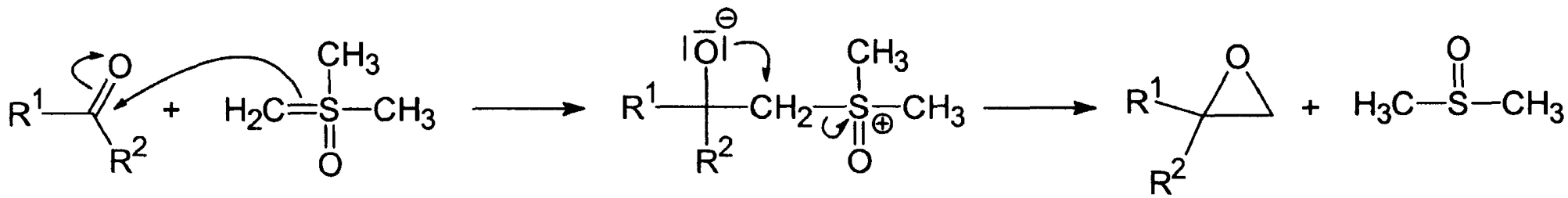
In the first step, the α-halo ester is deprotonated by the base to the corresponding carbanion. This nucleophile adds to the carbonyl compound in a rate-determining step. Finally, the halogen atom is intramolecularly substituted.



(4) *Corey synthesis*

In this synthesis, S-ylide nucleophiles derived from trialkylsulfonium or trialkylsulfoxonium halides are made to react with carbonyl compounds (COREY 1962).



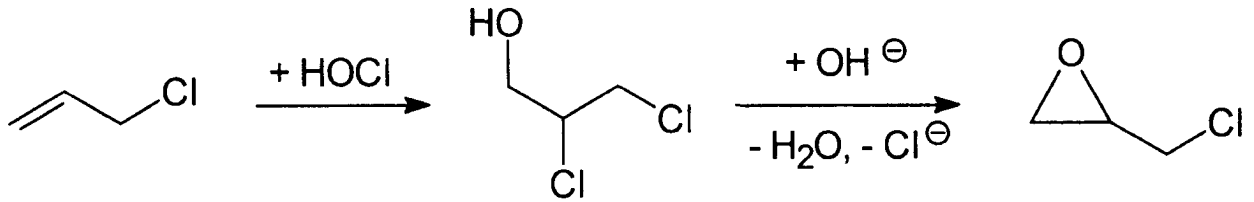


[D] Oxirane (ethylene oxide), a colorless, water-soluble, extremely poisonous gas of bp 10.5 °C, is made on an industrial scale by direct air oxidation of ethene in the presence of a silver catalyst.

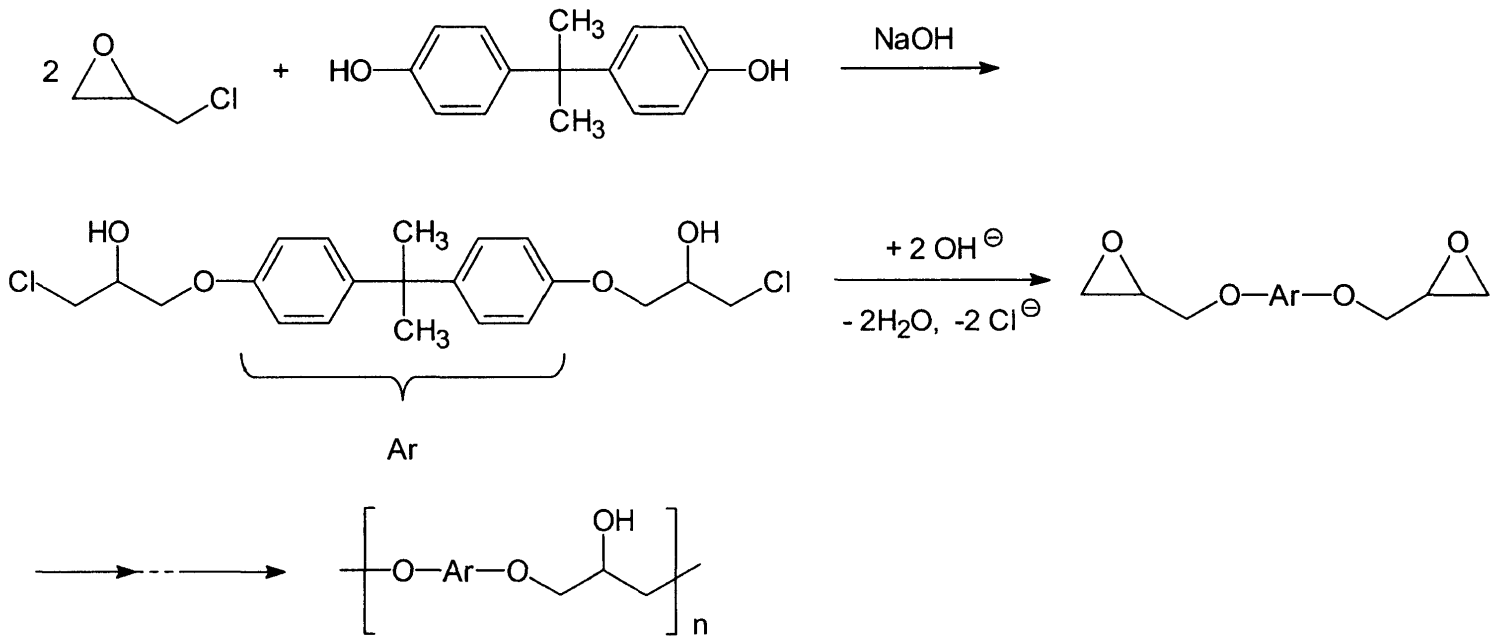
Oxirane is important as an intermediate in the petrochemical industry. The annual production world-wide is estimated to be 7 million tons.

Methyloxirane (propylene oxide) is a colorless, water-miscible liquid, bp 35 °C. It is produced commercially from propene and *tert*-butyl hydroperoxide in the presence of molybdenum acetylacetonate.

(Chloromethyl)oxirane (epichlorohydrin) is prepared from allyl chloride as follows:



Epichlorohydrin is the starting material for epoxy resins. When used in excess, e.g. with bis-2,2-(4-hydroxyphenyl)propane, the so-called bisphenol A, in the presence of sodium hydroxide, it reacts to give linear polymers with oxirane end-groups.

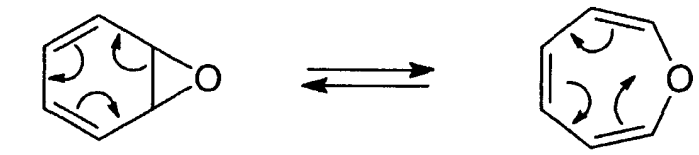


Thus propagation proceeds in two steps which are continuously repeated: opening of the oxirane ring by phenol interaction and closing of the oxirane ring by dehydrogenation.

When mixed with diacid anhydrides, diamines or diols, an interaction with the oxirane end-groups of the macromolecules ensues, resulting in cross-linking (hardening). Epoxy resins find use as surface coatings, laminated materials and adhesives.

(Hydroxymethyl)oxirane (glycidol) is produced industrially by the oxidation of allyl alcohol with hydrogen peroxide in the presence of sodium hydrogen tungstate. It serves as a useful starting material in various syntheses.

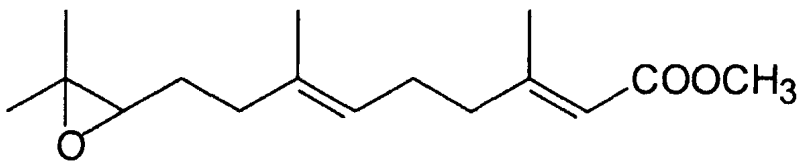
Benzene oxide (7-oxabicyclo[4.1.0]hepta-2,4-diene) was obtained in an equilibrium mixture with the valence isomer oxepine (VOGEL 1967):



benzene oxide oxepine

Benzene dioxide and benzene trioxide are also known. Arene oxides are crucial intermediates in the carcinogenic action of benzo[a]pyrene and other polycondensed arenes.

Oxiranes are found relatively rarely in nature. An example of an oxirane in a natural product is, however, the juvenile hormone of the sphinx moth.

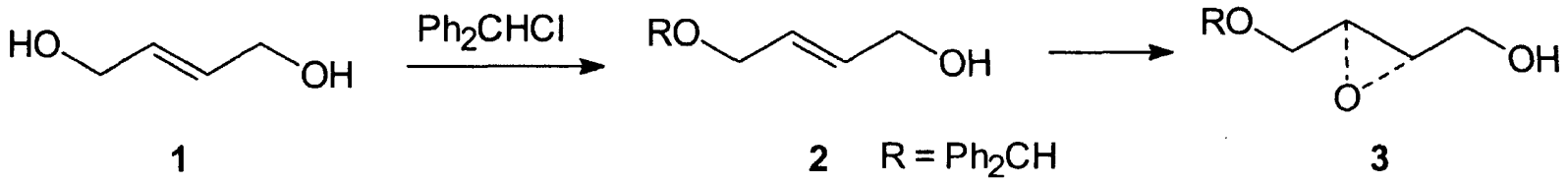


Furthermore, attention must be drawn to the part played by squalene epoxide as an initiator of steroid biosynthesis in eukaryotes. Antibiotics with oxirane rings, e.g. oleandomycine, have also been isolated.

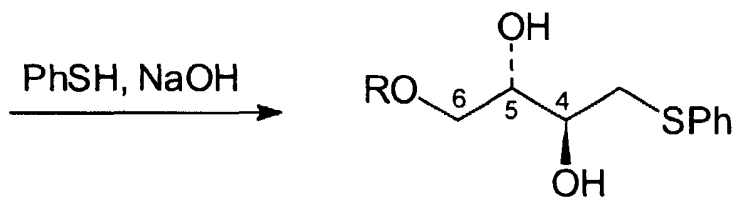
[E] Oxiranes are of considerable importance as intermediates for multistep stereospecific syntheses of complex target molecules, because closing and opening reactions of the oxirane ring often occur without side reactions. Moreover, they proceed stereospecifically.

The first steps in the total syntheses of all 16 stereoisomeric hexoses may serve as an example. These syntheses start from (*E*)-but-2-ene-1,4-diol, **1**, which is obtainable from acetylene and formaldehyde via butyne-1,4-diol.

First a hydroxy group is protected by reaction with benzhydryl chloride (**2**). This is followed by a SHARPLESS epoxidation in the presence of *(R,R)-(+)-DET* to give **3**. This reacts with thiophenol and sodium hydroxide to give **4**, in which the C-atoms 4, 5 and 6 of the L-hexoses are already in place.

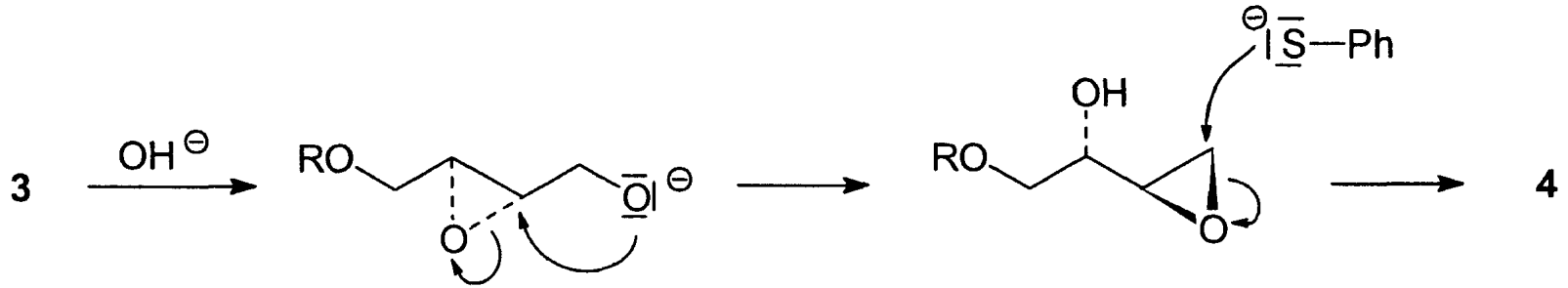


1 **2** R = Ph_2CH **3**



4

The SHARPLESS epoxidation leads into the D-series with (*S,S*)-(-)-DET. In the course of steps **3** → **4**, two openings and one closure of the oxirane rings are observed:



The presence of the thioether group CH_2SPh in **4** is essential for linking the remaining two C-atoms by a PUMMERER rearrangement and a WITTIG reaction.