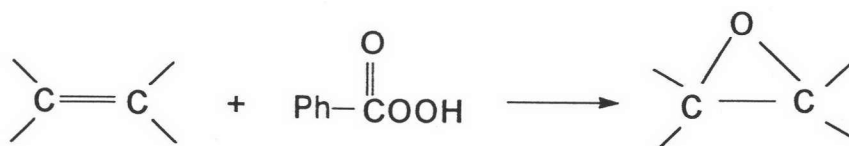


CHAPTER II

THEORY AND LITERATURE REVIEW

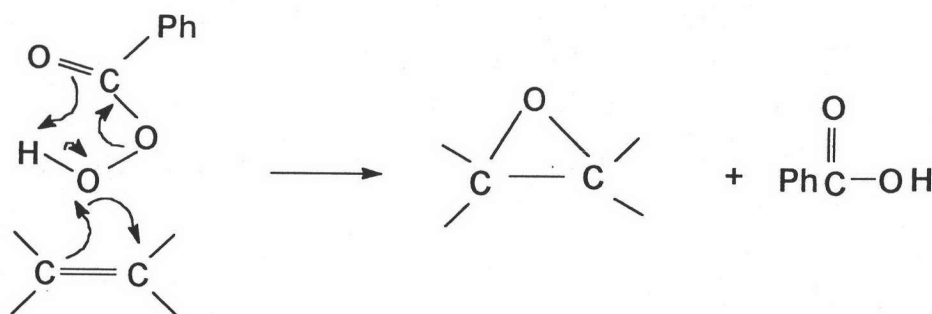
2.1 Synthesis of Epoxides

There are many approaches for the epoxide synthesis [14,15], mainly achieved by the epoxidation of alkenes with peroxides so called the "Prilezhaev reaction" (Scheme 2.1). Electron-donating groups of unsaturated increase the rate of the reaction and this reaction is particularly rapid with tetraalkyl olefins. The yields are high in a mild condition. Several peracids are particularly used such as peracetic acid, perbenzoic acid, etc.



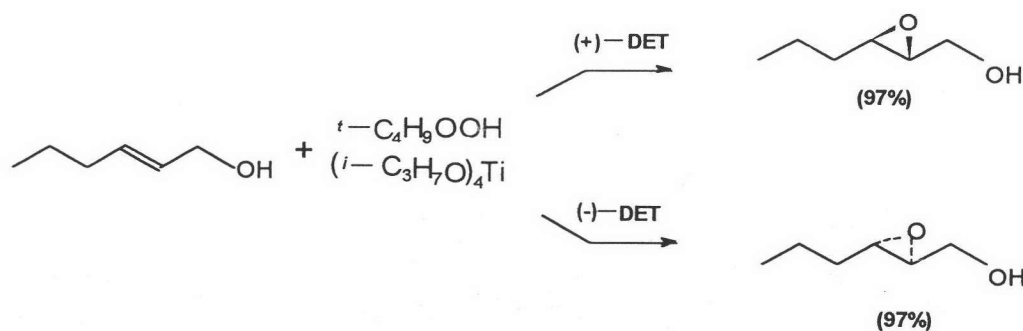
Scheme 2.1

The following one-step mechanism of the reaction shown in Scheme 2.1 was proposed by Bartlett [16] as shown in Scheme 2.2.



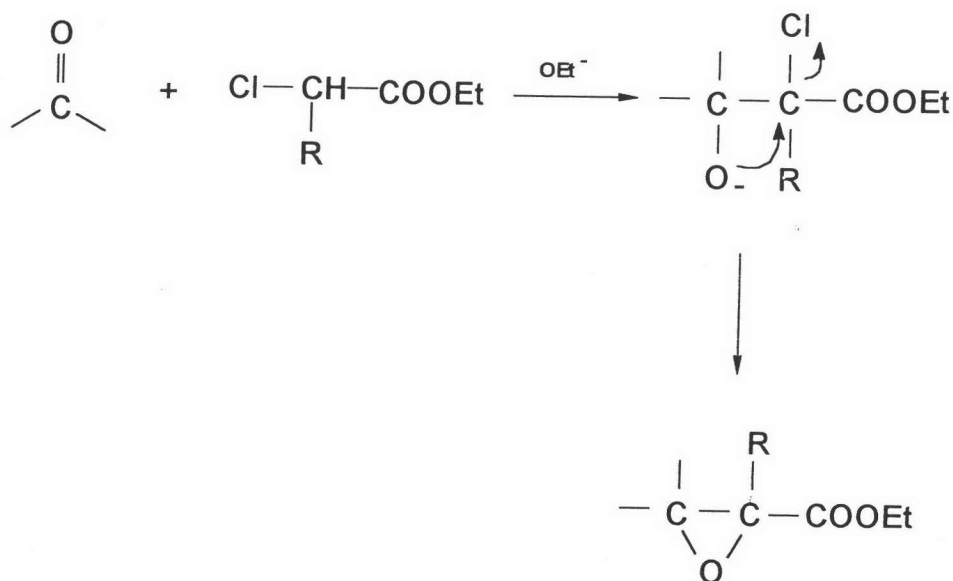
Scheme 2.2

Epoxides can also be prepared by treating olefins with oxygen or with an alkyl peroxide, and catalyzed by a complex of V, Mo, Ti or Co [17]. The reaction with oxygen, which can be also carried out without a catalyst, is probably a free-radical process. When the reaction is carried out with a mixture of tertiary butylperoxide, titanium tetrakisopropoxide, and diethyl tartrate (DET), allylic alcohols can be converted to optically active epoxides in more than 90% enantiomeric excess (Scheme 2.3) [18].



Scheme 2.3

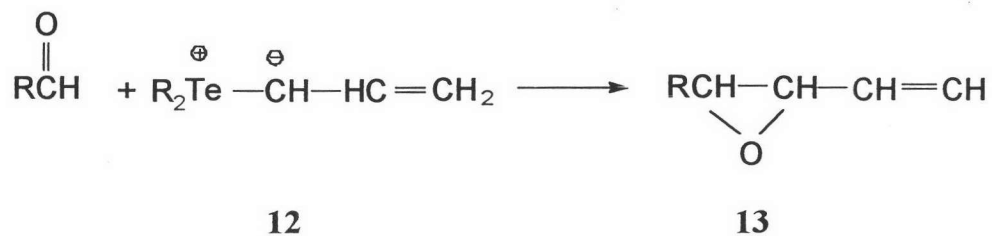
Aldehydes or ketones condense with α -halo esters in the presence of bases to give α,β -epoxy esters, or glycidic esters. This is so called "Darzen's condensation". The reaction consists of an initial Knoevenagel-type condensation following by internal $\text{S}_{\text{N}}2$ reaction (Scheme 2.4) [19].



Scheme 2.4

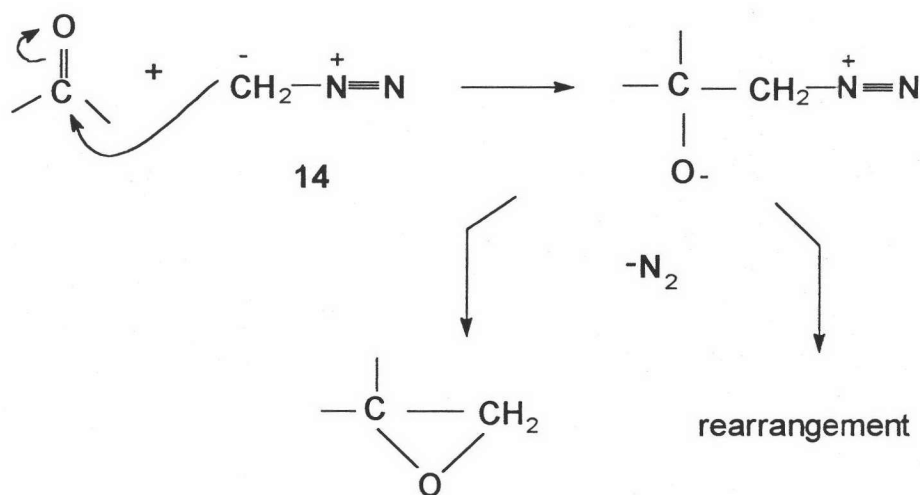
Sodium ethoxide is often used as the base, although other bases including sodium amide are sometime used. Aromatic aldehydes and ketones give good yields but aliphatic groups react poorly. However, the reaction can be made to give good yields (~80%) with simple aliphatic aldehydes as well as with aromatic aldehydes and ketones.

The Darzen's condensation has also been carried out on α -halo ketones, α -halo nitriles, α -halo sulfones, α -halo N,N-disubstituted amides and even on allylic and benzylic halides by using phase transfer catalysis [20]. For example, aldehydes react with dialkyltelluronium iodide (**12**) to give α,β -unsaturated epoxides (**13**) (scheme 2.5.)



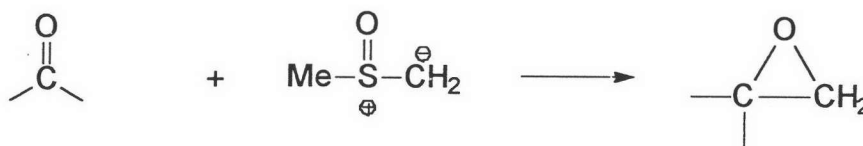
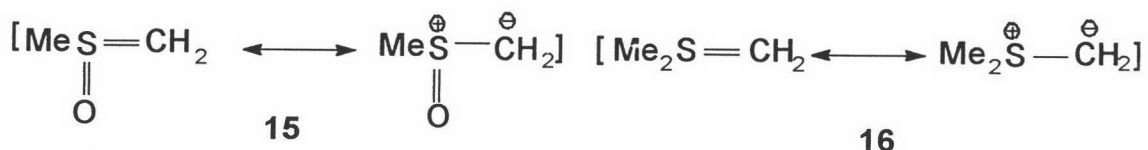
Scheme 2.5

Aldehydes, ketones, and quinones can be converted to epoxides by treating with diazoalkane (14) [21], mostly diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound. A mechanism that accounts for both products is shown in Scheme 2.6.



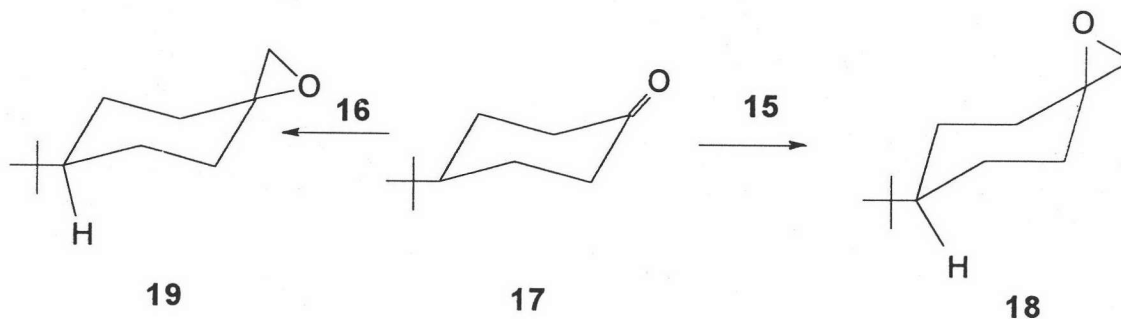
Scheme 2.6

Aldehydes and ketones can be converted to epoxides in good yields with the sulfur ylides, dimethyloxosulfonium methylide (15) and dimethylsulfonium methylide (16). The generally accepted mechanism for the reaction between sulfur ylides and aldehydes or ketone is shown in Scheme 2.7.



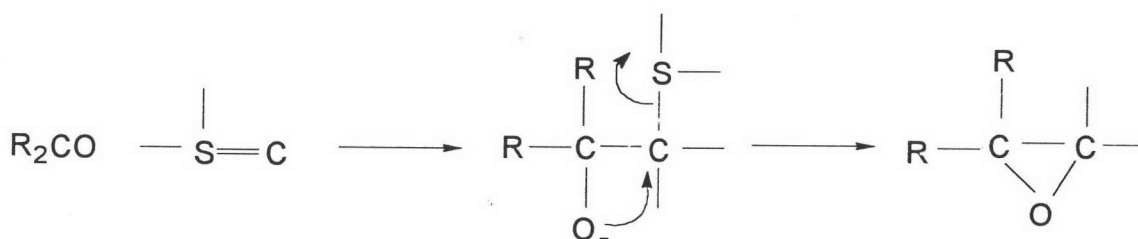
Scheme 2.7

The ylide **15** is the reagent of choice, because ylide **16** is much less stable. However, when diestermeric epoxides can be formed, the ylide **16** usually attacks from the more hindered side. Thus, reaction of 4-*t*-butylcyclohexanone (**17**) with ylide **15** and **16** gives epoxide **18** and **19**, respectively (Scheme 2.8).



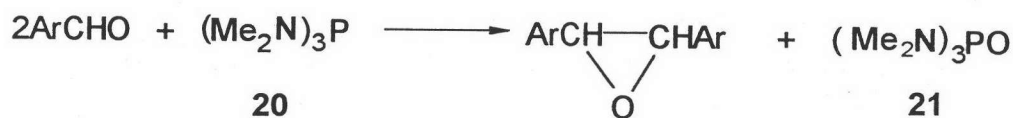
Scheme 2.8

The generally accepted mechanism for the reaction between sulfur ylides and aldehyde or ketones is shown in Scheme 2.9.



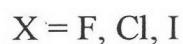
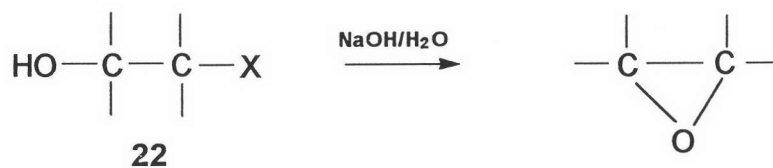
Scheme 2.9

Aromatic aldehydes can be dimerized to epoxides by treatment with hexamethylphosphorus triamide (**20**) [22]. The reaction can be used for the preparation of mixed epoxides by the use of a mixture of two aldehydes in which the less reactive aldehyde predominates (Scheme 2.10).



Scheme 2.10

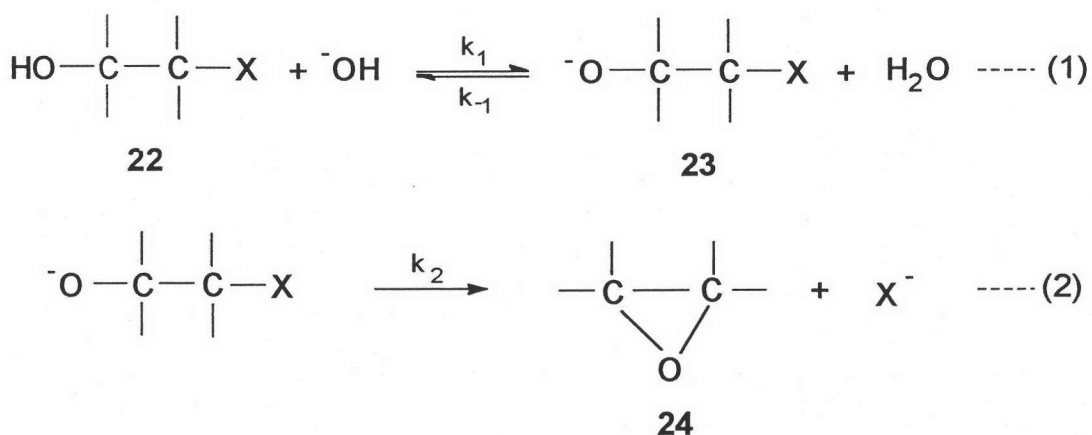
One of the most method for epoxide synthesis is the reaction of halohydrins (**22**) with bases (Scheme 2.11) [23-28]. This method offers a useful route to epoxide preparation and is often a more satisfactory method for the preparation of low molecular weight epoxide than the direct reaction of the olefins with a peracid.



Scheme 2.11

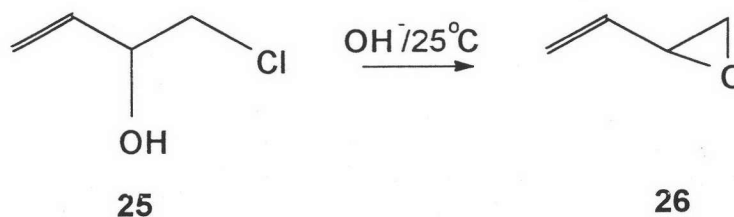
Lucas [23] proposed that the closing of an epoxide ring brought about by the action of alkali, involves an intramolecular variety of the usual bimolecular exchange reaction in which the attacking group is the adjacent negatively charged oxygen atom (Scheme 2.12).

The halohydrin compound **22** is converted to the epoxide **24** by the reaction of alkali to form an alcoholate ion **23** and the negatively charged oxygen atom of **23** attacks the adjacent carbon atom on the face opposite to the halogen atom, thus leading to a Walden inversion of the usual bimolecular exchange type.



Scheme 2.12

Kadesch [24] reported that the hydrolysis of propylene chlorohydrin by water is stated to be bimolecular reaction. The hydrolysis of allyl type chlorides in basic media has been shown to involve simultaneous unimolecular (S_N1) and bimolecular (S_N2) mechanisms. The relative amounts of which depend on the structure and the reaction conditions. The rate expression derived from this mechanism indicates that the overall rate depends both on the acidity of the chlorohydrin (k_1/k_{-1}) or the equilibrium constant and on k_2 . One example of this reaction is the treatment of 2.5% aqueous 3-hydroxy-4-chloro-1-butene (**25**) with sodium hydroxide at room temperature to form 3,4-epoxy-1-butene (**26**).



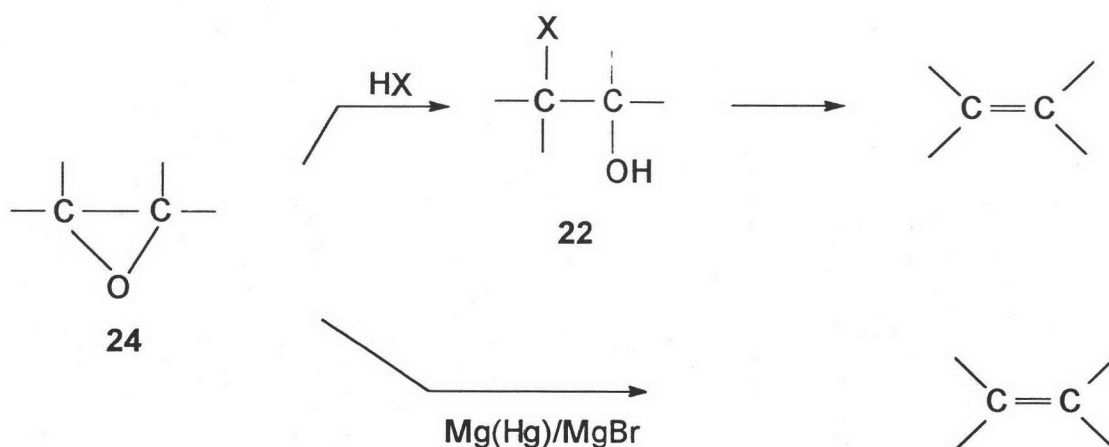
Scheme 2.13

Warner *et.al.* [25] studied the kinetic of the reaction between ethylene chlorohydrin and hydroxide ions such as in mixed solvents. They summerized that the increase in rate with the decrease in dielectric constances was the principal factor influencing the rate of reaction. Therefore, in the mixture of methanol and water, the reaction rate decreases continuously with increasing in methanol concentration. This may be explained by the possible influence of the acid-base level in this solvents upon the initial equilibrium step.

2.2 Reaction of Epoxides

2.2.1 Deoxygenation and Reduction [29]

Reaction for conversion of an epoxide into the halohydrin (22) and for the reductive elimination reaction of the 22 to give an alkene have been combined in a procedure for the direct conversion of an epoxide into the alkene by treatment with magnesium amalgam and magnesium bromide (Scheme 2.14).

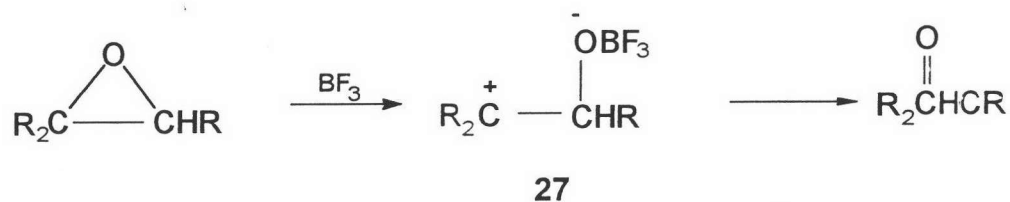


Scheme 2.14

2.2.2 Rearrangement [29]

The rearrangement of epoxides to carbonyl compounds may be effected by numerous catalysts and has been widely studied. Several aspects of the boron trifluoride-catalyzed reaction have been recently investigated. Earlier studies indicated that a discrete carbonium ion species

(27) was formed in the rate determining step of some rearrangements (Scheme 2.15).

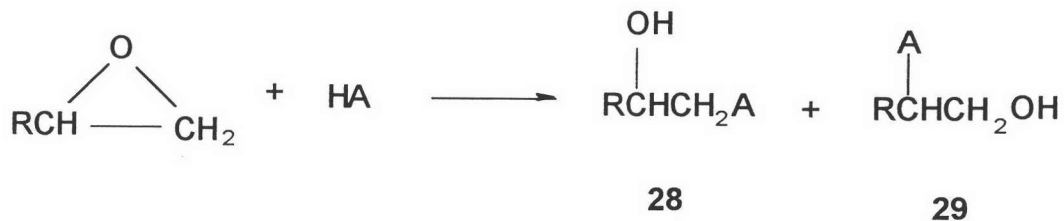


Scheme 2.15

2.2.3 Nucleophilic Substitution

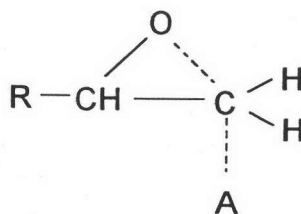
Epoxides undergo ring-opening reaction by variety of nucleophiles. These include oxygen compounds (water, alcohols, phenols), nitrogen compounds (amines and derivatives), sulfur compounds, acids, and various carbon nucleophiles [30]. Ring opening can occur in either neutral, basic or acidic condition. It is generally agreed that the reaction follows $\text{S}_{\text{N}}2$ mechanism in neutral and basic solution. In acid solution, the reaction has been most often termed borderline $\text{S}_{\text{N}}2$ (or modified A_2).

The reaction of an unsymmetrically substituted epoxide generally gives two products at the less or more substituted end of the epoxide to form normal (28) and abnormal products (29), respectively [31]. (Scheme 2.16)



Scheme 2.16

Under the basic or neutral conditions, most reactions yield the normal isomer is almost the major product. This provides a strong evidence for an $\text{S}_{\text{N}}2$ attack of a reagent or ion on the epoxide carbon atom which is involving a transition state shown below.

Figure 2.1 Transition state of the $\text{S}_{\text{N}}2$ reaction of epoxide

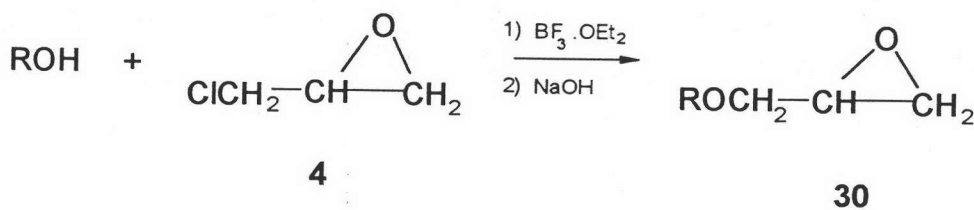
Such a reaction is wellknown about the sensitivity of the steric hindrance, If the R-group of the epoxide has no appreciable polar or conjugative effect, the normal isomer will be formed for steric reasons.

A marked tendency toward the formation of abnormal products can be found, however, in the case of reaction under acidic conditions. Many epoxides that give entirely normal products under basic

conditions to produce a mixture of normal and abnormal products under acidic conditions. The polar, hyperconjugative, and steric effects can give rise to electron release, these effects can stabilize a positive charge on the adjacent carbon atom, so that both unimolecular (S_N1) and bimolecular reactions (S_N2) are considered to be involved in the production of such a charge [32].

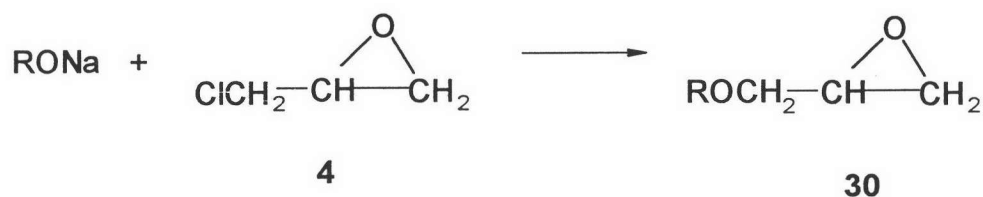
2.2.3.1 Reaction with Hydroxy Nucleophiles

Two methods have been described for making the glycidyl ethers (30). The first, opening the ring of an epichlorohydrin (4) in acidic medium, such as sulfuric acid, perchloric acid, or a Lewis acid. The most widely use of which is boron trifluoride etherate. The intermediate chlorohydrin ether was prepared in an anhydrous solvent and cyclized with the glycidyl ether in the presence of sodium hydroxide (Scheme 2.17).



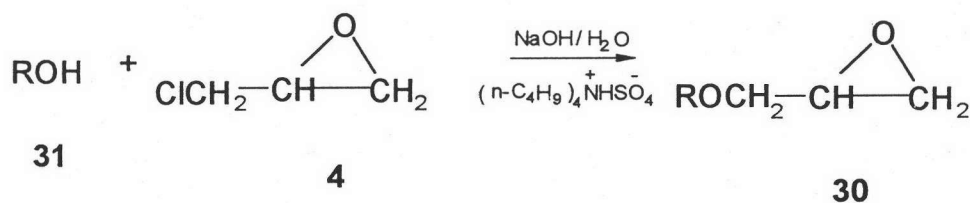
Scheme 2.17

The second is the etherification of an epichlorohydrin in anhydrous, basic medium by condensation with sodium alkoxide. The preparation in basic medium was carried out in a single step but as the previous case, anhydrous solvents must be used (Scheme 2.18).



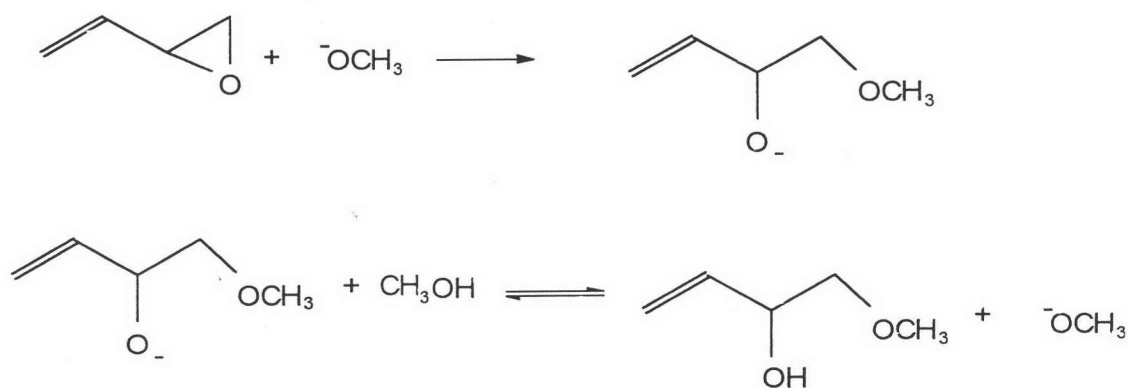
Scheme 2.18

Mouzin *et.al.* [33] have developed a new single step method for etherification of epichlorohydrin using a phase transfer catalyst technique. Alcohols (31) are etherificated with epichlorohydrin (4) in aqueous sodium hydroxide solution, using a quaternary ammonium type of catalyst, tetrabutylammonium hydrogensulfate (Scheme 2.19) to give the glycidyl ethers 30 in high yields.



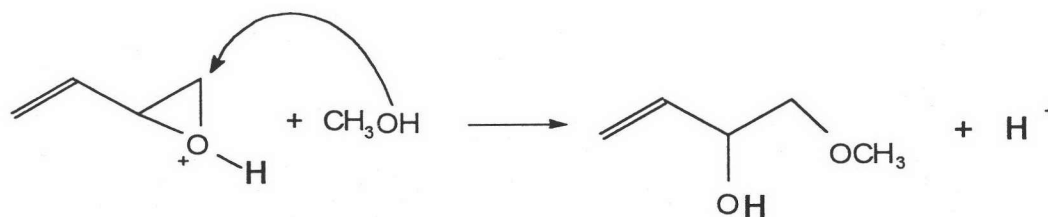
Scheme 2.19

Kadesch [34] suggested the mechanism of the reaction of 3,4-epoxy-1-butene (32) with methanol. The normal reaction which occurs with methanol in the presence of a little sodium is due to bimolecular nucleophilic displacement by a generated methoxide ion (Scheme 2.20)



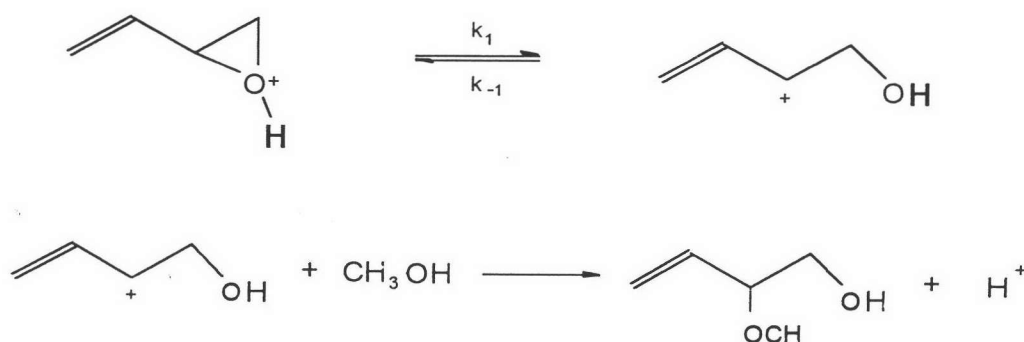
Scheme 2.20

This type of $\text{S}_{\text{N}}2$ mechanism might also be expected to lead to the normal product in the acid catalyzed reaction (Scheme 2.21).



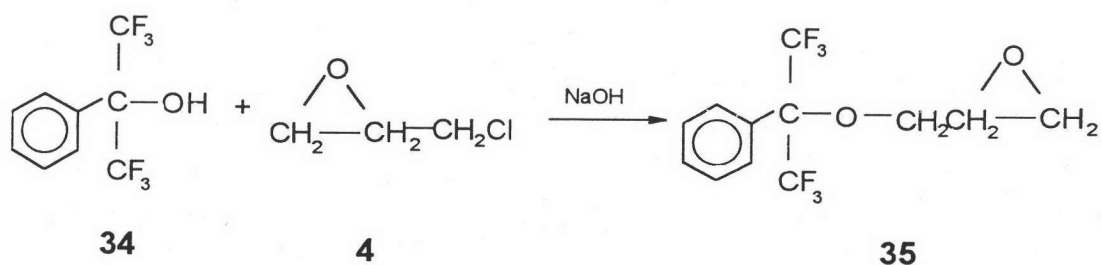
Scheme 2.21

If a unimolecular ring opening occurs in the acid-catalyzed reaction, the formation of the abnormal products may be observed. The proposed mechanism is shown in Scheme 2.22. The unimolecular ring opening is assisted by the resonance stabilization of intermediate carbonium ion. It was found that the rate of reaction depends upon the methanol concentration.



Scheme 2.22

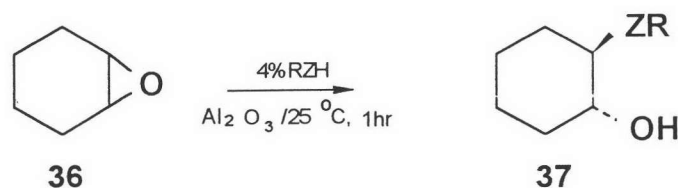
Reines *et.al.* [35] have found that arylbis(trifluoromethyl) carbinol (**34**) react with excess epichlorohydrin in much the same manner as do phenols (Scheme 2.23). This reaction is a convenient new means for obtaining 2,3-epoxy-1-propoxy compounds (**35**), or glycidyl ethers, which contain fluorocarbon.



Scheme 2.23

Posner *et.al.* [36-40] studied some organic reactions on the alumina surface. They have discovered that commercially available chromatographic alumina promotes highly efficient heterogeneous opening of a wide range of epoxides by the variety of nucleophilics, e.g. alcohols, acetic acid, amines, mercaptans, and selenols under the extraordinarily mild (25 °C)

and neutral conditions (Scheme 2.24 and Table 2.1) [38]. This procedure is the method for clean-nucleophilic opening of medium ring epoxides.



Scheme 2.24

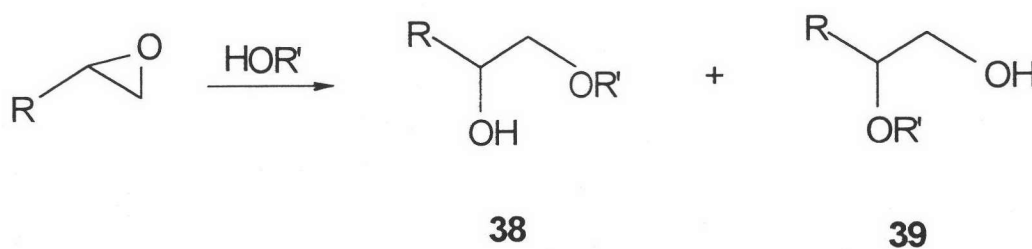
Table 2.1 The reaction of cyclohexene oxide with various nucleophiles

ZR	% yield of 37
OMe	66
OCH ₂ Ph	47
SEt	78
SPh	70
SePh	95
NH(Bu) ₂	73

They reasoned that organic compounds containing one or more heteroatoms are usually adsorbed by alumina. When the heteroatom carries a hydrogen atom (RZ-H), the adsorption on the alumina surface sometimes involves the heterolytic cleavage of the heteroatom-hydrogen bond (RZ + H). The adsorption of organic electrophiles (e.g. sulfonate esters, epoxides) and RZH-doped alumina might bring electrophile and nucleophile into proximity; the juxtaposition of electrophile and nucleophile and the enhanced nucleophilicity (and basicity) of the nucleophile might work

synergistically to produce a chemical reaction under unusually mild conditions.






Otera *et al.* [41] investigated the highly regioselective ring opening of epoxides with alcohols catalyzed by organotin phosphate condensates. This catalyst was prepared by treating organotin oxides or chlorides with trialkyl phosphates at 200-250 °C. They reported the successful addition of alcohols to epoxides to afford highly regioselective β -alkoxy alcohols. (Scheme 2.25 and Table 2.2).



Scheme 2.25

As shown in Table 2.2, the catalyst is effective for both acyclic and cyclic epoxides even in the presence of various functional groups. Of special interest in the present method is high regioselectivity for asymmetrical epoxides. The alkoxy group is incorporated preferentially at the less hindered epoxide carbon atom and regiochemical outcome is dependent upon epoxides.

Table 2.2 Synthesis of β -alkoxy alcohols

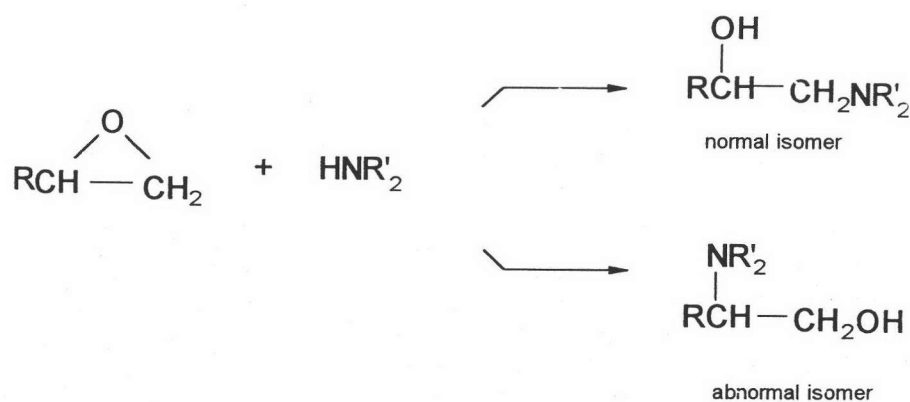
epoxide	ROH	% yield of 38	ratio 38/39
	PhCH ₂ OH	83	100/0
	PhCH ₂ OH	86	100/0
	CH ₂ =CHCH ₂ OH	74	98/2
	MeOH	71	95/5
	CH ₂ =CHCH ₂ OH	60	98/2
	MeOH	65	100/0
	PhCH ₂ OH	57	100/0
	CH ₂ =CHCH ₂ OH	62	100/0
	MeOH	86	-
	MeOH	86	77/23

2.2.3.2 Reaction with Amine Nucleophiles

The Nitrogen compounds has also been used for the ring opening nucleophile to form amino alcohols. Horne and Shriner [42] found that pure dry diethylamine did not react with ethylene oxide, the reaction would take place in the presence of water or alcohol. Methyl alcohol was easier to separate by fractional distillation and hence is the best solvent. There was no evidence that the ethylene oxide reacted with the solvent under the conditions used. The other method, suggested by Headlee *et al.* [43], used the

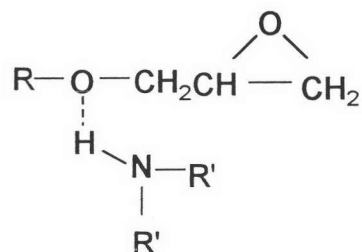
copper autoclave as the reactor for the preparation of diethylamino ethanol giving higher yield.

The reaction between a secondary amine and an unsymmetrical epoxide compound may proceed via two different pathways, as shown in Scheme 2.26.



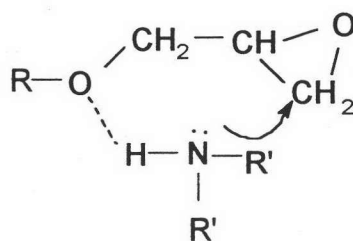
Scheme 2.26

Reines [35] investigated the reaction of glycidyl ethers with dibuthylamine. They suggested that at the least part of the activation caused by the glycidyl ether oxygen may be due to its ability to hydrogen bond with the attacking amine as in 40.



40

Association of this type between the amino hydrogen and ether oxygen that would enhance the approach of the amine and place it in a favorable position to attack the epoxide ring. In the six membered ring intermediate (41) which results from terminal attack, the ether oxygen might also stabilize the transition state by delocalizing the positive charge on nitrogen during formation of the C-N bond. This mechanism is consistent with the absence of abnormal isomer, which would require a five- rather than six-membered ring intermediate for its formation.

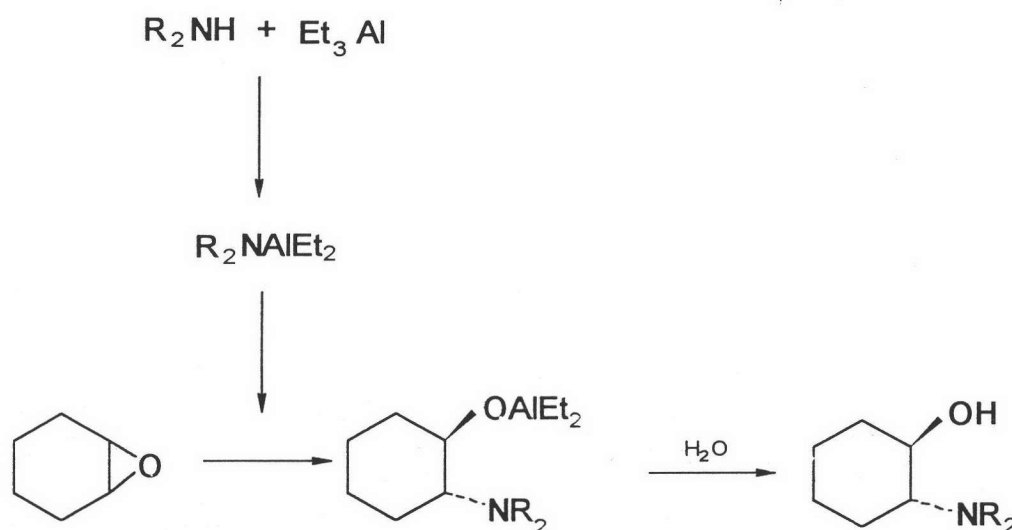


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They also reported the possibility of alcoholysis of the epoxide ring by solvent molecules. Ethanol does not attack phenyl glycidyl

ethers in neutral solution, and even refluxing in the presence of phenoxide anion led to only 2% reaction between ethanol and phenyl glycidyl ether.

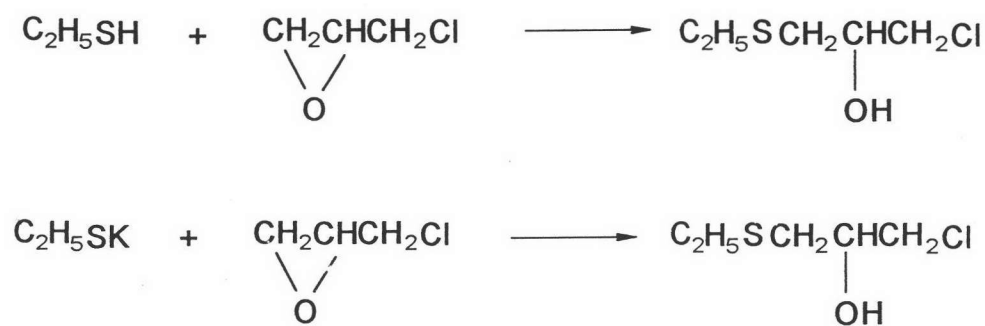
Overman and Flippin [44] reported that a variety of diethylaluminum amines react stoichiometrically with epoxides at room temperature to give, after hydrolysis, β -amino alcohols in good yields (Scheme 2.27).



Scheme 2.27

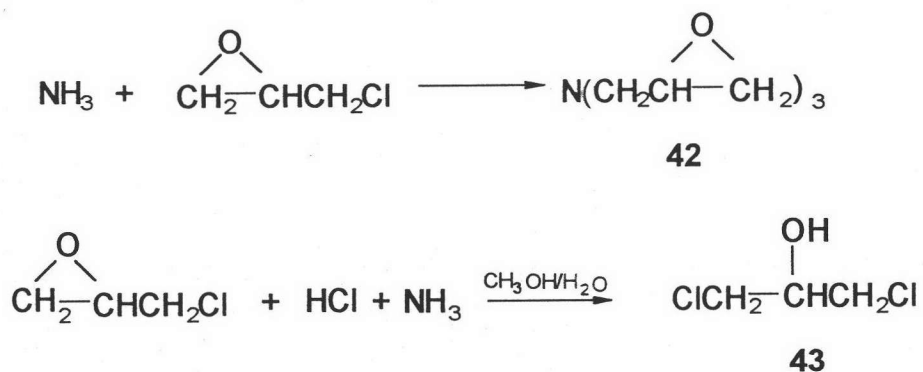
Petrov and Al'bitskaya [45] reported the reaction of butadiene monoxide to excess aqueous solution of various amines gave amino alcohols in the good yields.

Nenitzescu and Scarlatescu [46] have reported the addition of various alkyl mercaptans to epichlorohydrin. (Scheme 2.28)



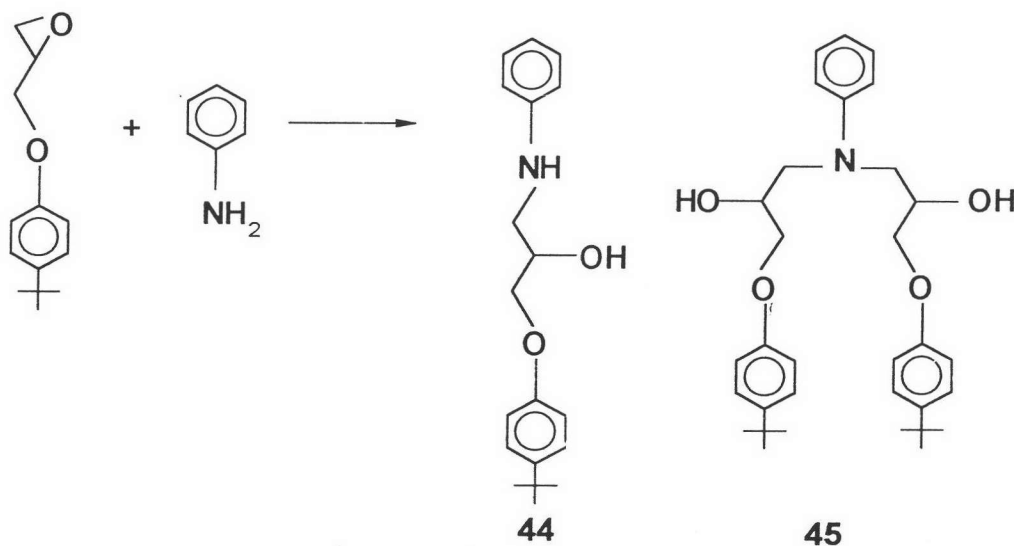
Scheme 2.28

The reaction of epichlorohydrin with variety of amines were studied [47-49]. The preparation of N,N,N-tris(3-chloro-2-hydroxypropyl) amine by saturating epichlorohydrin with ammonia gas at room temperature in a five-day reaction is mentioned by Fauconnier [48]. McKelvey *et al.* [49] studied the reaction of epichlorohydrin in amines with various reaction media. It was observed that in the petroleum ether solution, ammonia can react with epichlorohydrin to form N,N,N-tris(2,3-epoxypropyl)amine (**42**). However in aqueous solution, dioxane, and mixed water-methanol the 1,3-dichloro-2-propanol (**43**) was observed in high yield (Scheme 2.29).



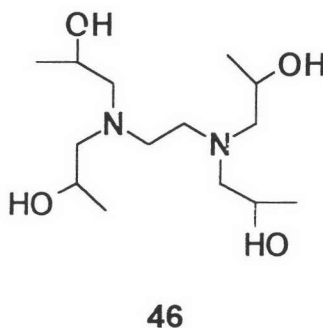
Scheme 2.29

Kaplan [50] reacted glycidyl ethers with aromatic amines and found that a mixture of monoadduct (**44**) and diadduct (**45**) was obtained.



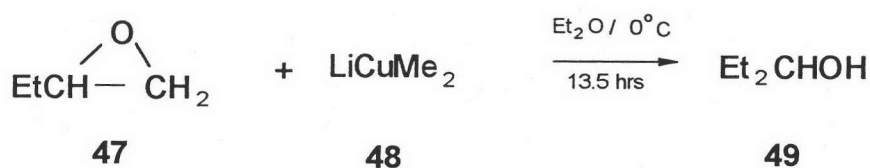
Scheme 2.30

Quadrol, N,N,N',N'-tetrakis(2-hydroxypropyl)ethylene diamine (**46**), is a viscous colorless liquid. It was synthesized by addition of propylene oxide to a solution of ethylenediamine in ethanol [50-53]. **46** has been used as a metal complexing agent, a polar base in buffers for automatic protein sequencing and used as a crosslinking agent and catalyst in the synthesis of urethane foams. Because of its polyfunctional hydroxy groups, it can react with isocyanate end cap results in structure rich in urethane group.



2.2.4 Reactions with Organometallic Compounds

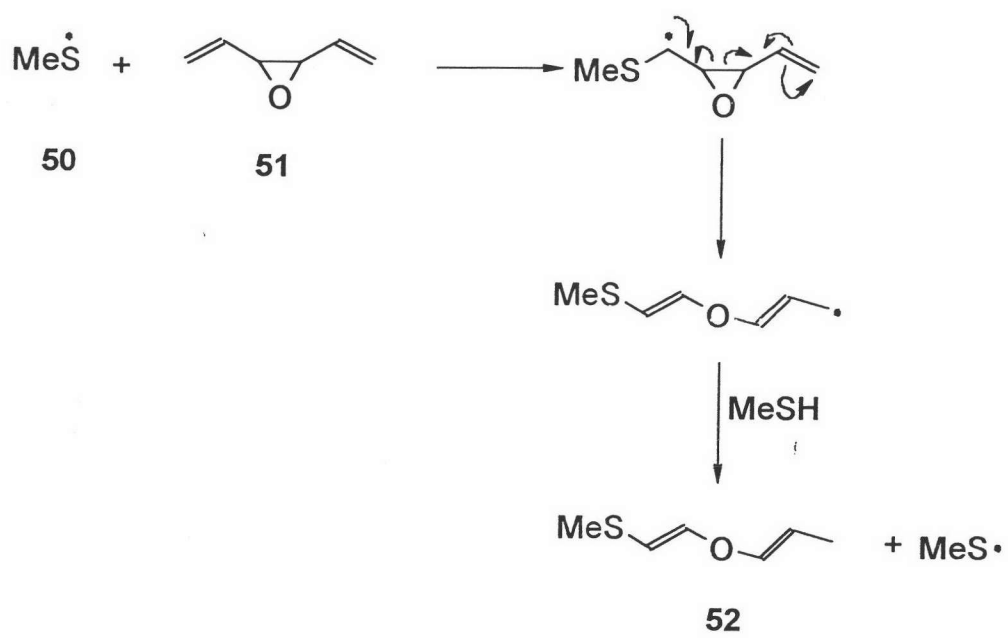
Organocopper reagents, such as lithium dimethylcuprate and lithium diphenylcuprate, show considerable promise for the preparation of alcohols by nucleophilic ring-opening of epoxides. Pentan-3-ol (**49**) was obtained in 88% yield under mild conditions from 1,2-epoxybutane (**47**) and lithium dimethylcuprate (**48**) (scheme 2.31), with little formation of by-products.



Scheme 2.31

2.2.5 Miscellaneous Reactions

The homolytic addition of methanethiol (**50**) to vinyloxi-
ranes such as **51** has provided rare examples of reactions in which fission of
the oxirane C-C bond occurs (Scheme 2.32) [29].



Scheme 2.32