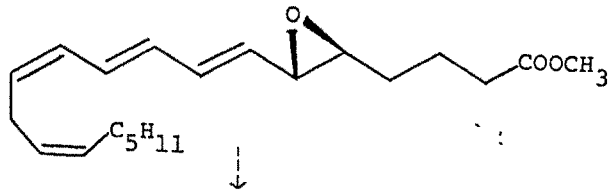
CHAPTER I

ASYMMETRIC SYNTHESIS OF OXIRANES - A REVIEW

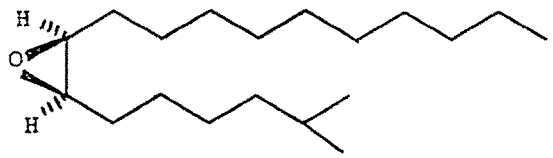
A. INTRODUCTION

Oxiranes are the simplest known oxygen containing heterocycles. It was the French chemist, Wurtz[1], who isolated in 1859 a new substance isomeric with acetaldehyde, which he called ethylene oxide. Since then, oxirane and its various derivatives have become one of the most widely utilized classes of research and industrial chemicals. The preparation and properties of oxiranes have been extensively reviewed[2] by several authors from time to time.

Non-racemic oxiranes are important chiral synthons. They easily undergo stereospecific ring opening to form bifunctional compounds. For example, they have been used as key intermediates in the synthesis of biologically active compounds such as leukotriene C-1[3a],1, erythromycin[3b] and disparlure, 2[3c].



Leukotriene C-1 1



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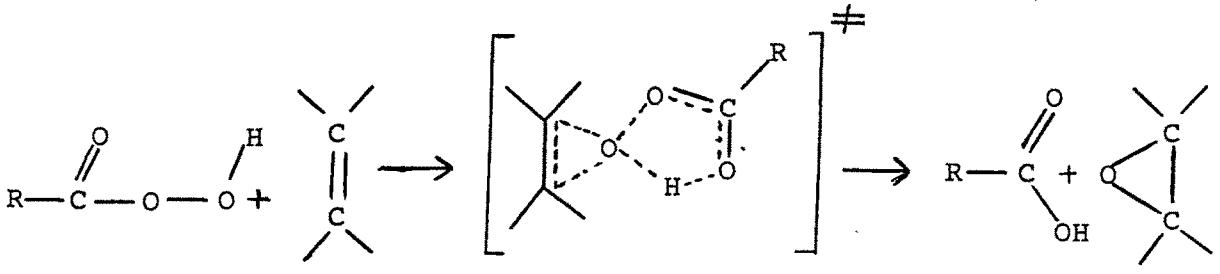
This explains the great interest in the development of methods for the synthesis of optically pure oxiranes. The present review highlights certain important chemical methods available for the asymmetric synthesis of oxiranes.

B. ASYMMETRIC SYNTHESIS OF OXIRANES

I. EPOXIDATION OF OLEFINS WITH PERACIDS

The synthesis of oxiranes by the reaction of alkenes with peroxy acids (The Prilezhaev reaction)[4] has long been known. The mechanism of the reaction involves[5] the electrophilic attack of peracid on the olefin as shown in Scheme 1.



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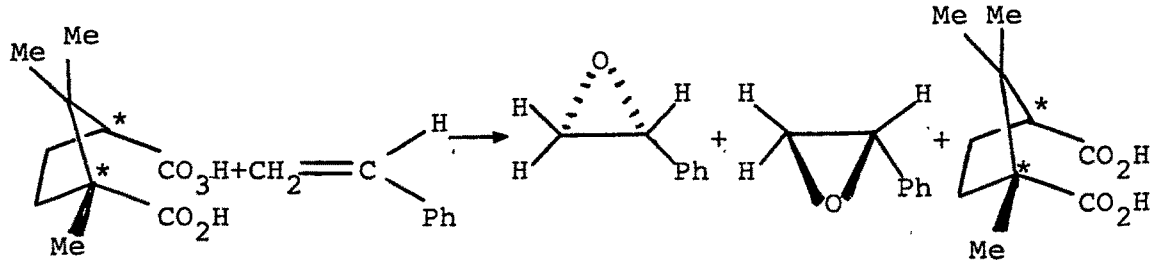
Scheme 1

Daniel Swern[6], in 1948 was the first to show that epoxidation with peracids is stereospecific, i.e., a trans olefin gives a trans oxirane and a cis olefin gives a cis oxirane. The first asymmetric synthesis of oxiranes using (+)-monoperoxy

camphoric acid and several terminal olefins was presented by Henbest[7] (Scheme 2).



(R)-(-) (S)-(+)

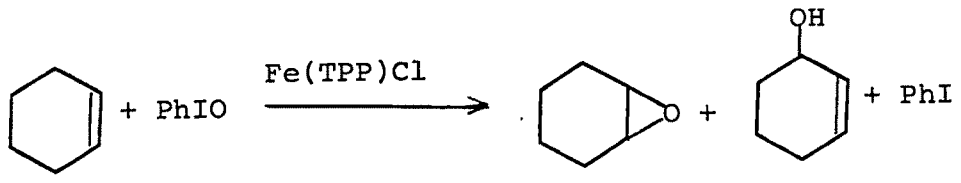
48% 52%

Scheme 2

The asymmetric induction was very poor (less than 5% ee). The epoxidation of styrene using highly purified (+)-monoperoxy camphoric acid gave styrene oxide with 9.2 % ee[8]. This low ee can be attributed presumably because the controlling stereocentres are too remote from the actual reaction site[9]. Use of a complex optically active hydroperoxide[10] gave excellent chemical yields ($\succ$ 85%) of oxirane but again ee achieved was less than 35 % .

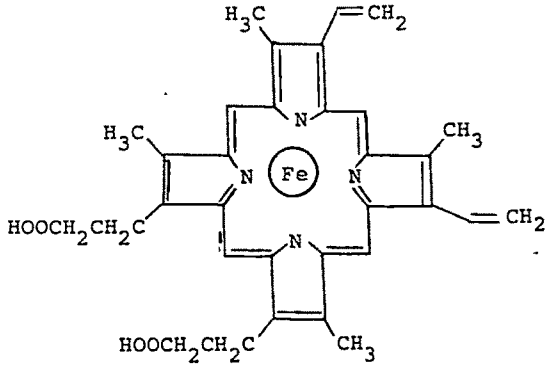
II. ASYMMETRIC EPOXIDATIONS CATALYSED BY METALLOPORPHYRINS

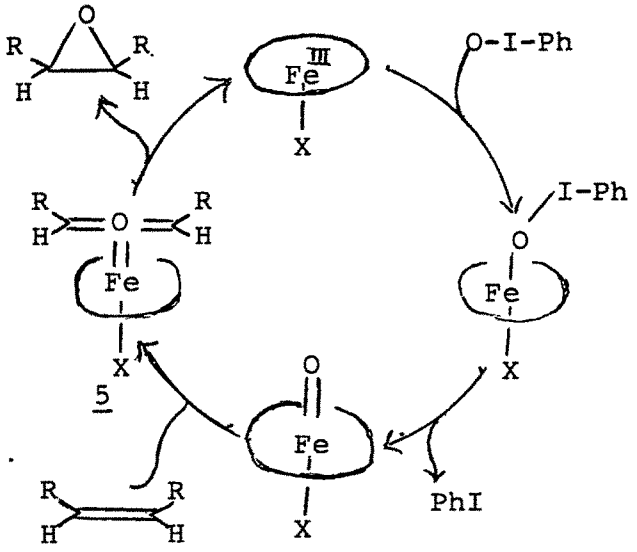
In 1979, Groves et al[11] published the first paper describing the use of Iron (III) porphyrin as catalyst for the epoxidation of alkenes (Scheme 3) using iodosyl benzene. Ever since then, the number of publications on metalloporphyrins as epoxidation catalyst has been continuously increasing[12].



Scheme 3

Chiral metalloporphyrins have been shown to mediate catalytic oxygen transfer to afford optically active oxiranes from prochiral olefins. Synthetic chiral metalloporphyrins are analogous to the prosthetic group of heme-containing enzymes (cytochromes P-450, peroxidases etc.) which selectively catalyse oxidation reactions with the same transition metal (Iron) and the same macrocyclic ligand (protoporphyrin IX), 4. Metalloporphyrins can reproduce and mimic all reactions catalysed by heme-enzymes (cytochrome P-450). The mechanism of oxygen transfer from a porphyrin/PhIO system to an olefinic substrate involves a reactive iron-oxo intermediate[13], 5 as shown in Scheme 4.





Scheme 4

The first asymmetric synthesis of oxiranes using chiral metalloporphyrins/PhIO system was presented by Groves[13] et al. The asymmetric epoxidation of styrene and 1-octene with PhIO in presence of Fe(TPP)Cl gave 31% and 9% enantiomeric excess respectively. To increase the steric bulk in the amide portion of the above porphyrin, a new catalyst [(binaphthyl carboxyamido) phenyl] porphyrin was developed which gave R-(+)-styrene oxide in 48% ee[13]. After this discovery a large number of differently modified chiral metalloporphyrin catalysts have been developed to achieve better enantioselection in epoxidations. The asymmetric induction achieved in epoxidation with some important porphyrin catalysts is given in Table 1.

Table 1 : Asymmetric Epoxidation of Olefins using Differently Modified Chiral Metalloporphyrins

Sr. No.	Olefin	Chiral Porphyrin	Yield (%)	ee (%)	Config.	Ref
1.	Styrene	Vaulted binaphthyl Fe (III)	23	30	R-(+)	14
2.	cis-β-Methyl styrene	- Do -	9	72	(1S,2R)-(+)	14
3.	Styrene	Twin coronet Fe (III);R-(3S)	84	54	(S)	15
4.	2-Nitro-styrene	- Do -	46	89	(S)	15
5.	Styrene	Iron, Binap, Capped	62	48	(S)-(-)	16
6.	2-Vinyl naphthalein	- Do -	26	63	(-)	16
7.	Styrene	Strapped, Mn, (-)	45	48	(S)-(-)	17
8.	Indene	- Do - (+)	58	58	(1R,2S)-(-)	17
9.	Styrene	D_4, Symmetric	90	52	(S)-(-)	18
10.	cis-β-Methyl styrene	- Do -	91	76	(1R,2S)-(-)	18
11.	trans-β-Methyl styrene	- Do -	40	4	(1R,2R)-(+)	18
12.	Styrene	Threital-strapped,Mn	86	69	R-(+)	19
13.	1,2-Dihydro-naphthalein	- Do -	26	88	(1R,2S)-(+)	19

It is apparent from the table that ee reported are moderate only. The problem is that the chiral group surrounding the macrocycle must be far enough from the central metal to permit easy entry of the substrate but must be close enough to generate high

enantioselectivity. While the epoxidation of cis-disubstituted olefins with these porphyrin catalysts exhibits good level of enantioselectivity, the epoxidation of trans olefins shows poor selectivity.

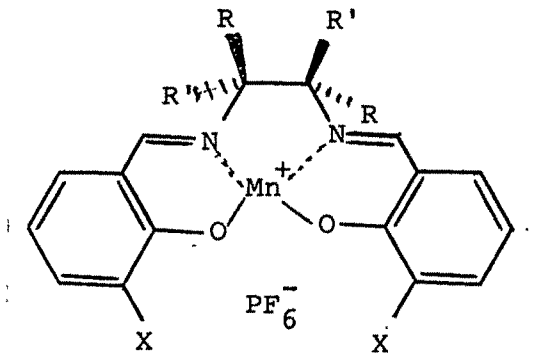
The advantages of using metalloporphyrins as epoxidation catalysts are : (i) A large variety of oxidants like iodosylbenzene, hypochlorites, molecular oxygen and an electron source can be used, (ii) A wide range of reaction conditions can be employed (mono and biphasic system, soluble or supported catalysts etc.), (iii) The design of porphyrin ligands allows shape selective epoxidation as well as epoxidation of simple olefins.

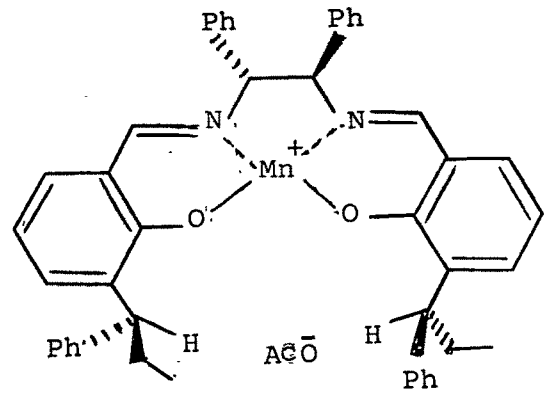
The main disadvantages are : (i) Multistep synthesis of chiral ligands accompanied by rather poor yields in some steps and use of costly chemicals, (ii) Their propensity towards oxidative degradation results in high consumption of catalyst, (iii) Almost all the research has been of a mechanistic nature and these systems have rarely been used in synthesis.

III. EPOXIDATION USING SALEN-Mn COMPLEXES

Although Kochi et al[20] reported the use of a new cationic (salen) manganese (III) complex for the epoxidation of olefins in 1986, the first asymmetric synthesis of oxiranes using such salen Mn complexes of chiral Schiff's bases, 6 and 7 was reported by

Jacobsen et al[21] in 1990. They obtained an ee of 20% (for trans β-methyl styrene) to 93% (for epoxy ketals)using these catalysts. At the same time, Katsuki et al[22] developed another optically active salen-Mn complex 8, which gave 20-49% ee in oxirane synthesis. Addition of donor ligands[23] such as 2-methyl imidazole or pyridine-N-oxide was found to be effective for altering the enantioselectivity and chemical yields.





(S,S)-6 ; R=Ph ; R'=H ; X=H

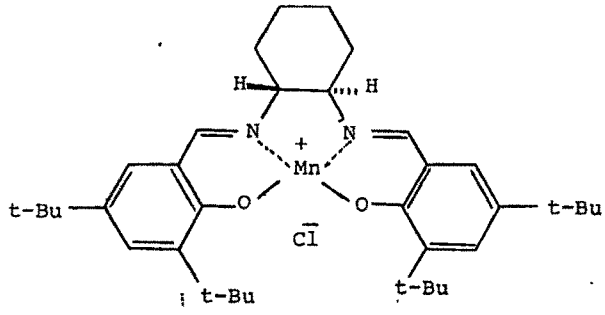
(R,R)-6 ; R=H ; R'=Ph ; X=H

8

7 ; R=H ; R'=Ph ; X=t-Bu

Contrary to the porphyrin systems, salen complexes bear tetravalent and thus potentially stereogenic carbon centres in the vicinity of the metal binding site. The proximity of the reaction site to the ligand dissymmetry improved the enantioselectivity of the reaction. Variations of the steric and electronic nature of the different substituents led to the discovery of a salen Mn complex[24] 9, which is particularly

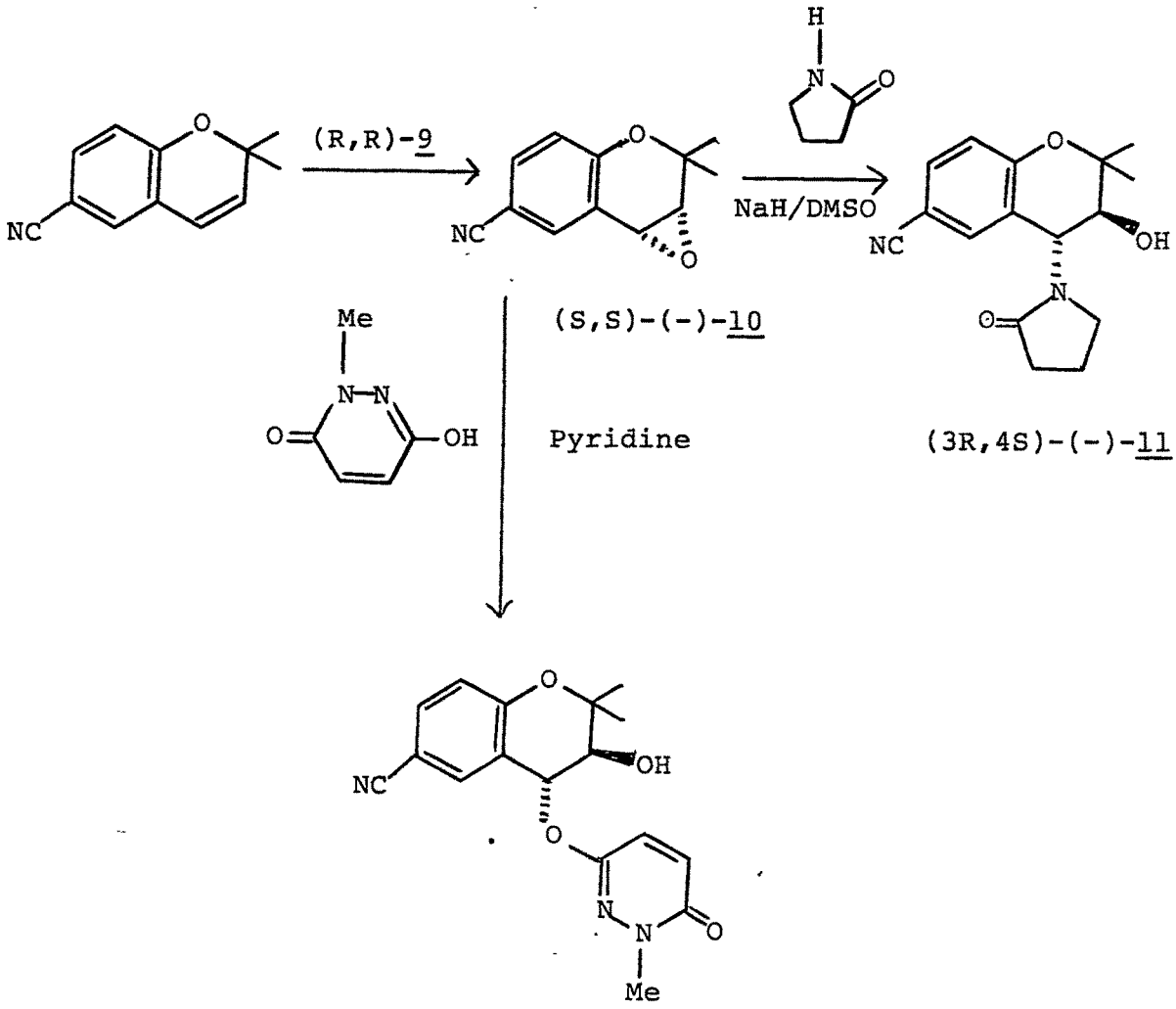
effective for the asymmetric epoxidation of a variety of olefins. Epoxidation of cis-disubstituted olefins using 9 as a catalysts and oxygen sources such as hypochlorite, iodosylbenzene etc. gave excellent chemical (65-94%) and optical (89-98%) yields. The high enantioselectivity of 9 results not only from highly dissymmetric ligands but also from limitation of competing substrate approaches such that substrate interaction with the asymmetric environment is maximised[25]. Trans olefins did not show as good enantioselectivity as cis olefins and chemical yields also were comparatively low. The Jacobsen's catalyst[25] 9 is easy to prepare and gives the best selectivity reported so far. It is being produced in multi hundred kilogram scale[26] and is available commercially.



(R,R) - 9

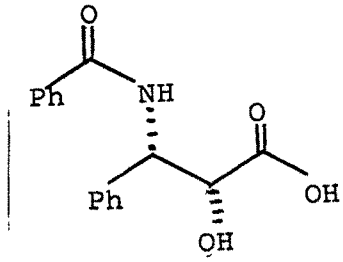
The high enantioselective properties of salen Mn complexes in the epoxidation reaction was used in the preparation of 3,4-epoxy-2,2-dimethyl chroman derivatives 10 (94-98% ee) which are biologically active compounds in both plants and animals[27]. Nucleophilic ring opening of 10 is generally regiospecific and

both steric and electronic factors favours attack at 4-position. The applicability of this technology is illustrated in the synthesis of cromakalin[27], (-)-11 and (-)-12, the active enantiomers of recently developed potassium channel activators with promising antihypertensive activity[27] (Scheme 5).



Scheme 5

A new, highly efficient and simplified synthesis[28a] of C-13 taxol side chain 13 makes use of highly enantioselective epoxidation catalysed by salen Mn catalyst (R,R)-9. The importance of taxol side chain in its antileukamic and tumour inhibiting activity has been noted in the earliest biological studies[28b].



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The scope of catalyst 9 is further increased in the epoxidation of trisubstituted alkenes[29] like 1-phenyl cyclohexene etc. with high ee (86-92%). The use of this catalyst is recently reported for the enantioselective epoxidation of cinnamate esters[30].

The advantages of salen Mn complexes catalysed epoxidation lies in, (i) Different oxygen sources like hypochlorite, iodosyl benzene, peroxides etc. can be used, (ii) The choice of variations in ligands give different selectivity for olefin epoxidation.

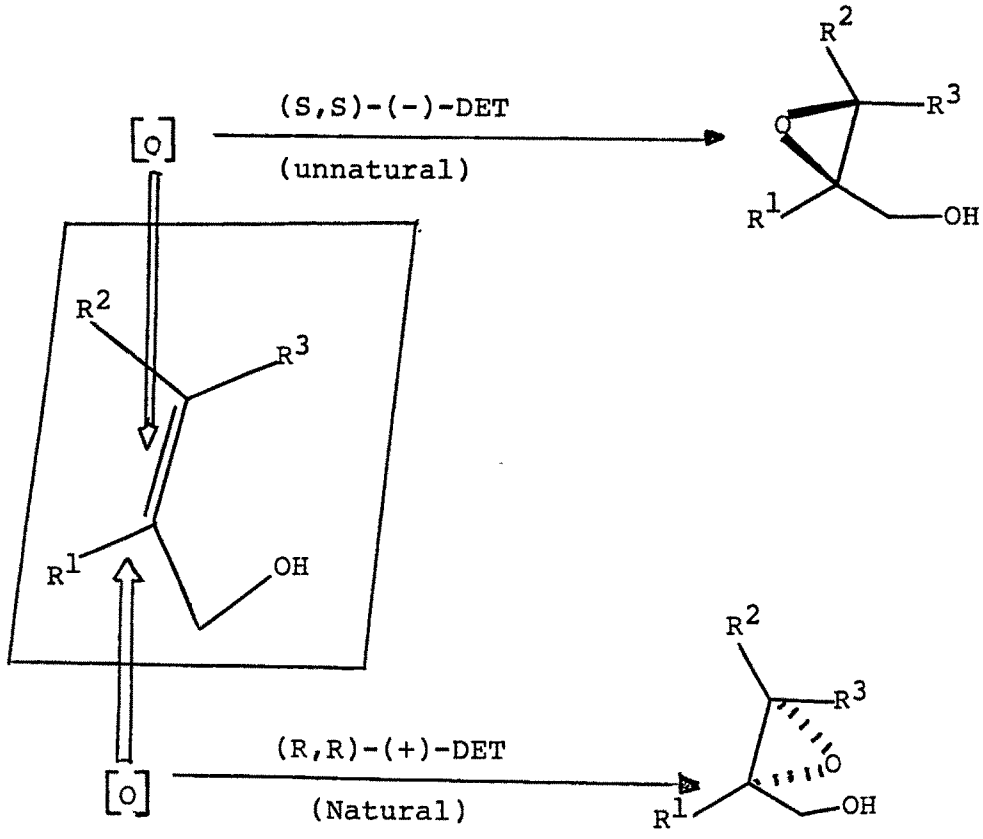
The shortcomings are : (i) Practically all the studies so

far made are on phenyl conjugated olefins (styrenic compounds), (ii) Comparatively poorer yields and lower enantioselectivity with trans olefins.

IV. KATSUKI-SHARPLESS EPOXIDATION

Regarded by many as one of the most important advances of the 1980's, the Katsuki-Sharpless[31] asymmetric epoxidation is a powerful fourth generation method for synthesizing epoxy alcohols with predictable absolute configuration and very high enantiomeric excess. Sharpless described his goal as creating "man made catalysts that are atleast as good as or probably even better than enzymes, very specific catalysts[32]".

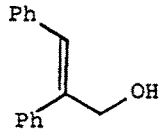
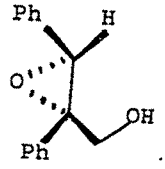
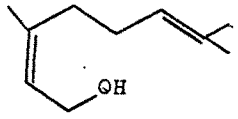
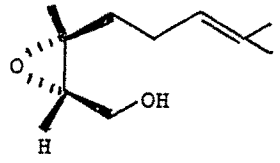
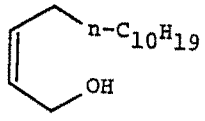
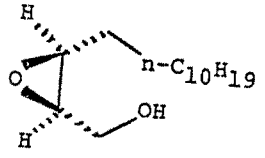
Asymmetric epoxidation of allylic alcohols using Sharpless method involves optically pure, (+) or (-)-diethyl tartrate, titanium tetraisopropoxide and anhydrous t-butyl hydroperoxide in a non-polar organic solvent (usually methylene chloride). All these reagents are commercially available at low to moderate cost. The direction of the attack depends on the optical property of the diethyl tartrate used in the reaction. Therefore, the stereochemistry of the epoxidation can be correctly predicted as shown in Scheme 6.



Scheme 6

When the olefinic unit is in the plane of drawing with the hydroxymethyl group at the lower right, the use of (+)-diethyl tartrate (DET) leads to addition of the epoxide oxygen from the bottom, whereas use of (-)-DET leads to epoxidation oxygen delivery from the top. Table 2 gives results of epoxidation of certain allylic alcohols by this method.

Table 2 : Asymmetric Induction by Sharpless Method

Sr. No.	Substrate (Allylic alcohol)	Epoxy alcohol	Yield (%)	ee (%)	Config.
1.			87	95	(2S,3S)[a]
2.			79	94	(2S,3R)[a]
3.			80	90	(2R,3S)[b]

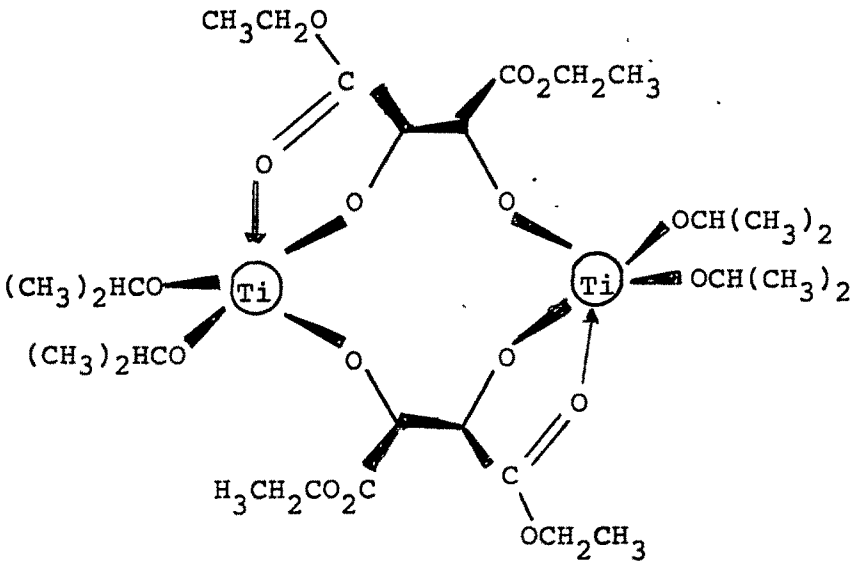
'a' denotes (+)-DET was used

'b' denotes (-)-DET was used

These results showed that whatever be the substitution pattern around the allylic alcohol, excellent chemical (> 79%) and optical (> 90%) yields are obtained.

An equimolar mixture of titanium tetraalkoxide and chiral dialkyl tartrate leads to the formation of a dimer, 14 which is identified as the active catalyst[33] responsible for high

enantioselectivity. The solution phase structure of the species is consistent with the results of an X-ray structure determination of titanium tetramide complex[34].



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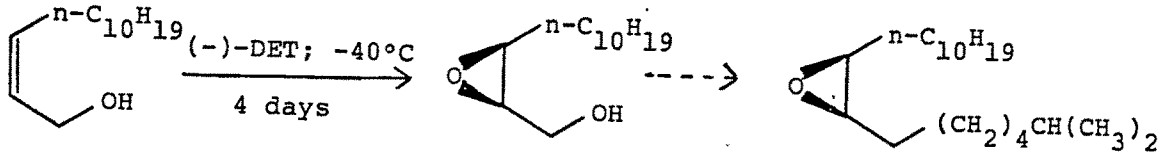
The asymmetric Sharpless epoxidation has been used as a key step in the synthesis of a diverse group of chiral compounds[35]. Some important examples are discussed below :

(1) (+)-Disparlure : This is a sex attractant of gypsy moth. The insect is a serious pest in hard wood forests and orchades. The larva, which hatch during the spring, are particularly voracious and able to denude a tree in a few weeks. The pheromone was isolated from the abdomens of female insects and active isomer was identified as (7R,8S)-(+)-7,8-epoxy-1-methyl octadecane

(disparlure). The synthesis[3c] of this compound using Sharpless epoxidation is a very important example (Scheme 7).



ee = 91%

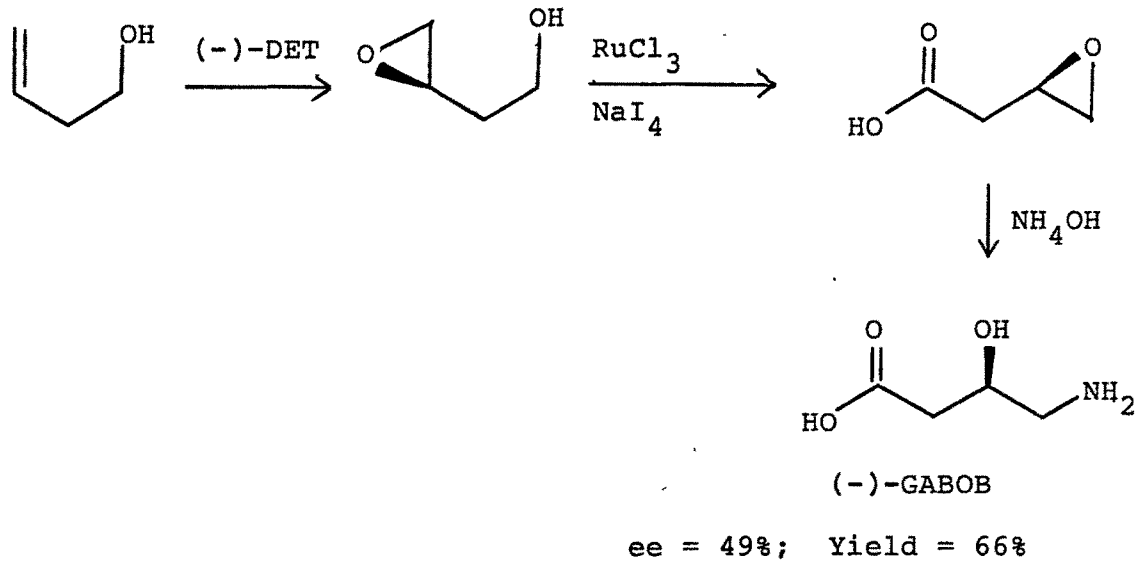
Yield = 80%

2

Scheme 7

(2) (-)-γ-Amino-β-(R)-hydroxy butyric acid (GABOB):Rossitter and Sharpless[36], in synthesising (-)-(GABOB), an antiepileptic and hypotensive drug have highlighted the particularities of reaction with homoallylic alcohols in which the selectivity rules are inversed with those known for allylic alcohols (Scheme 8). The present synthesis is an improvement over the previous synthesis[37] from ascorbic acid (10% yield, 20% ee).

The discovery of Sharpless epoxidation represent a major advance in the field of asymmetric synthesis. The reaction has, however one serious limitation in that it can be applied to allylic alcohols only.

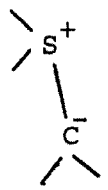


Scheme 8

V. ASYMMETRIC METHYLENE TRANSFER REACTION

(1) Sulfur Ylides

Sulfur ylides[38] are a class of compounds in which a carbanion is stablized by an adjacent positively charged sulfur atom e.g. 15 and 16.



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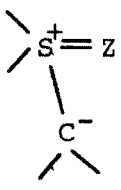

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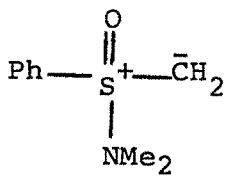

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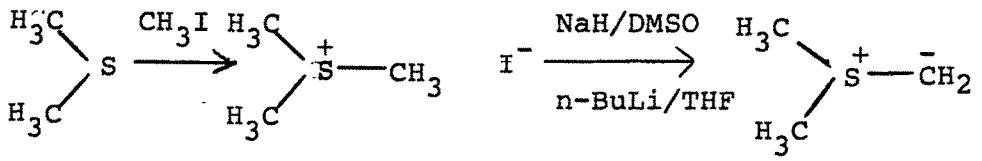
Sulfur ylides are generated from the corresponding sulfonium salt by deprotonation using a strong base (e.g. RO^-/ROH, NaH/DMSO, RLi or $LiNR_2$ in THF or ether etc.). Ylides (e.g.17) derived from simple alkyl sulfonium salts are usually generated and utilised at low temperatures. Oxosulfonium ylides (e.g. 18 and 19) are more stable and are usually generated and utilized near room temperature.



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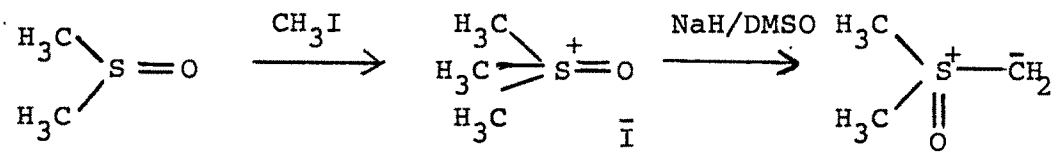

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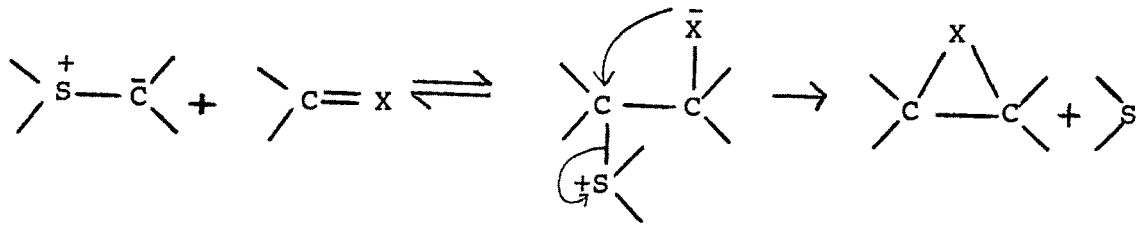
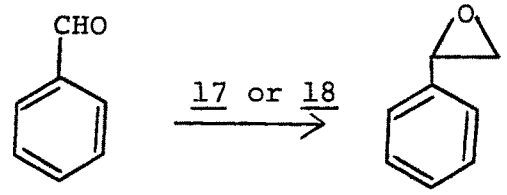
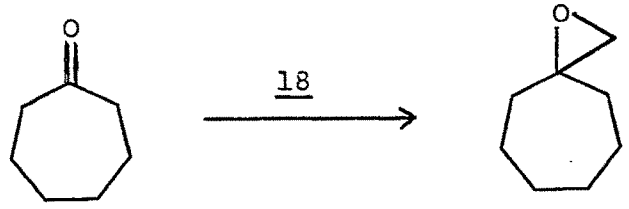
Sulfur ylides are nucleophilic reagents and their most characteristic reaction is transfer of alkylidene group to an electrophilic double bonds like C=O or electron deficient C=C with the resluting formation of a three membered ring. A general mechanism is shown in Scheme 9.



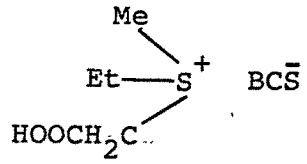
Scheme 9

The condensation of aldehydes and ketones with sulfur ylides has become an important tool in organic synthesis. Both, sulfonium and sulfoxonium ylides upon reaction with simple aldehydes and ketones give oxiranes[39].



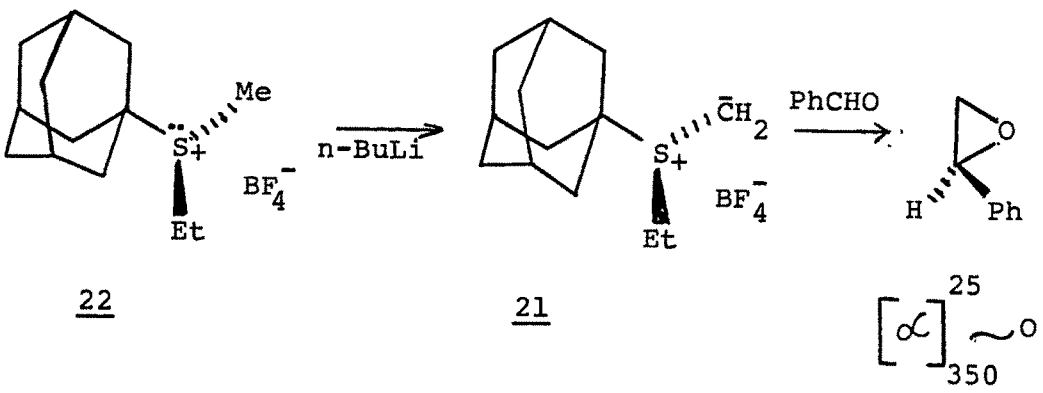


Structure and stereochemistry of sulfonium salts and sulfur ylides have been reviewed at several places[40]. Stereochemistry of sulfonium salts was pioneered by Pop and Peachey[41] who resolved the sulfonium salt 20 into enantiomeric forms as (+)-bromocamphor sulfonate.



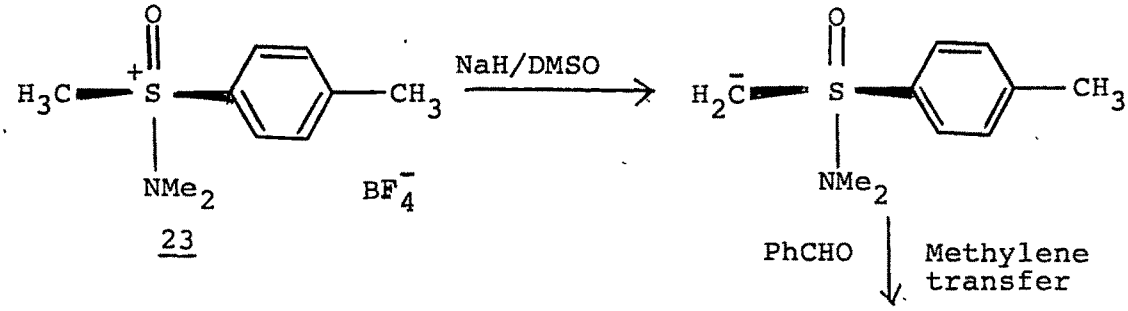
20

Most useful application of sulfonium salts in asymmetric synthesis involves the formation and reaction of chiral sulfonium ylides. Unfortunately, sulfur ylides are more likely to racemize than their sulfonium salts precursors. Despite these limitations, several examples of optical induction via optically active sulfonium ylides have been reported. The X-ray structures of several stablized sulfur ylides have been reported.[38b] The non-planarity at sulfur has been demonstrated by the reversible generation of ylides 21 from an optically pure sulfonium salt 22[38b]. The optically active ylide 21 on condensation with benzaldehyde gave styrene oxide with no ee[42].

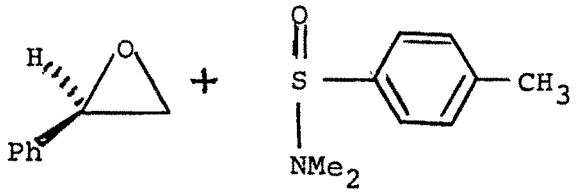


22 21 $[\alpha]_{350}^{25}$ ~O

There were several efforts in transfering chirality at sulfur in sulfur ylides to the ring carbon atom of an oxirane molecule. The first optically pure tetracoordinated oxosulfonium tetrafluoroborate 23 was prepared by Johnson et al[43] in 1967 by



23

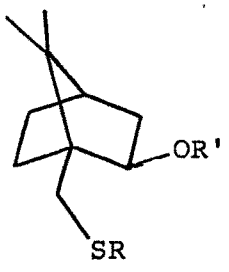


ee = 20%

Yield = 60%

the exhaustive methylation of (R)-S-methyl-S-p-tolyl sulfoximine with trimethyl oxonium tetraflouroborate. The oxosulfonium salt 23 on treatment with a base gave the ylide which on treatment with benzaldehyde give styrene oxide with 20% ee[44].

The first successful attempt in synthesizing non-racemic oxiranes using chiral sulfur ylide was reported by Furukawa[45]. The synthesis was carried out using an equimolar amount of aryl aldehydes, benzyl bromide in presence of half molar equivalent of the optically active camphoryl sulfides 24 or 25 in THF or acetonitrile under liquid-solid two phase condition to give 1,2-diaryl oxiranes in 7-47% ee with good chemical yield.



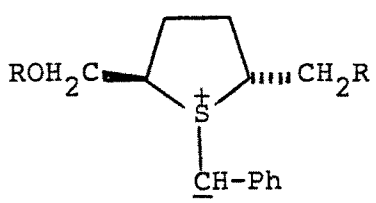
24

25

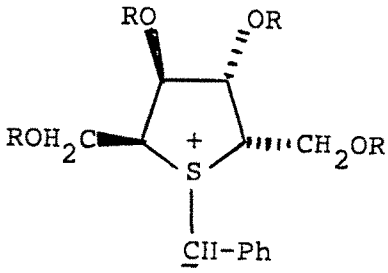
In this reaction the chiral sulfide moiety is acting as a mediator and the sulfonium ylide is being formed in situ and reacted with carbonyl compound to give oxiranes in one step.

Durst et al[46] reacted chiral S-benzyl ylides 26, 27 and 28 derived from optically active C_2 symmetric thiolanes with benzaldehydes and substituted benzaldehydes to give trans stilbene

oxides in 7-83% ee.



26



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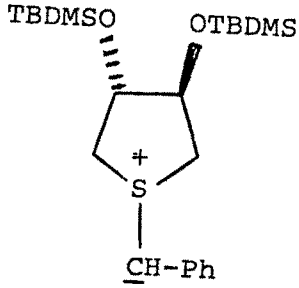
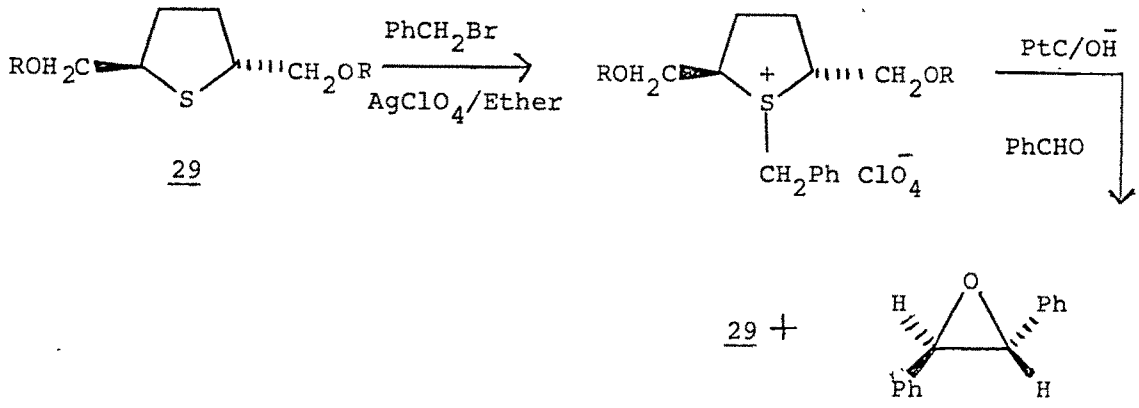
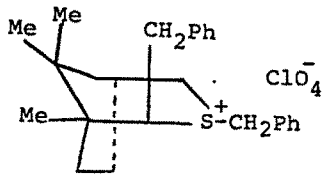


28

The reaction of ylide 26 with benzaldehyde to give (R,R)-trans stilbene oxide is shown below :

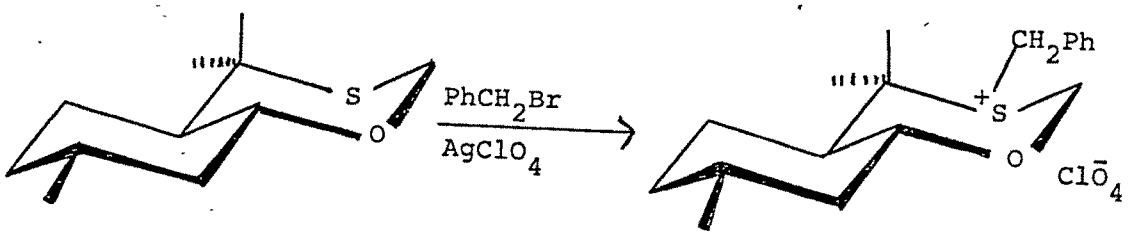


The sulfonium ylide derived from (1R,2R,3S,5S)-dibenzyl trimethyl thianium bicyclo octane 30 reacts with benzaldehyde to afford 38% (S,S)-trans stilbene oxide in 96% ee[47].



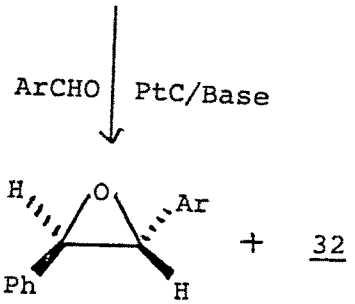
30

The chiral sulfur ylide obtained from the sulfonium salt of S-benzyl-Eliel's oxathiane reagent 31 reacts with aryl aldehydes under phase transfer condition to give trans 1,2- diaryl oxiranes with 0-100% ee[48].



(+)-(1R, 2S, 5R)-32

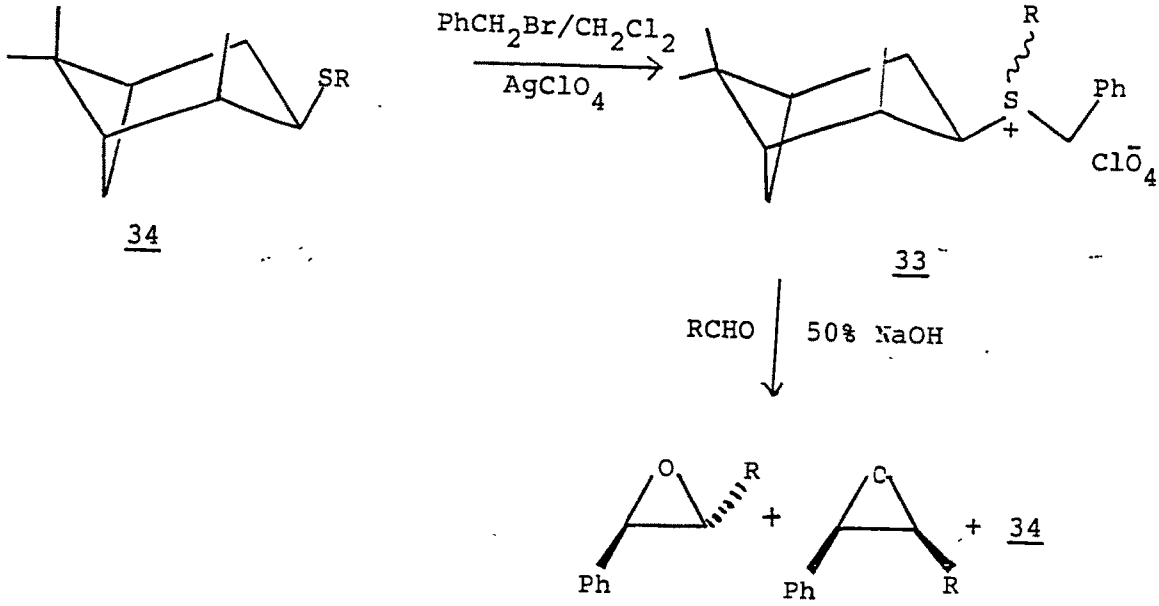
31



\+ 32

(R,R)-(+)

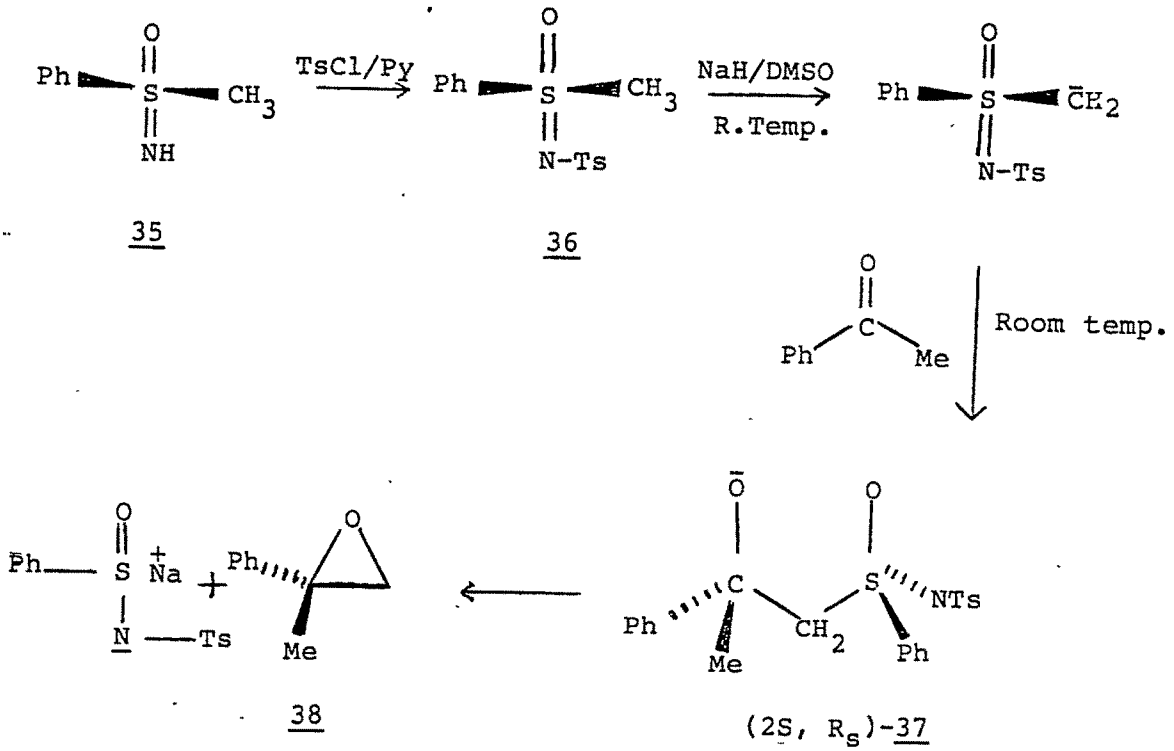
A diastereomeric mixture of sulfonium salt 33 derived from S-benzylation of (1S,2S,3R)-3-pinanyl alkyl sulfide, 34 under same PTC conditions reacts with aryl aldehydes to give 1,2-diaryl oxiranes with O (cis epoxides) to 43% ee[49].



(2) Chiral sulfoximines

Sulfoximines are an important class of compounds which can be considered as aza analogous of sulfones. It was Bentley and Whitehead[50], who in 1950 discovered that sulfoximine of methionine is the toxic factor of the wheat flour treated with nitrogen trichloride. Since then several reviews[51] have been published describing the chemistry of sulfoximines.

Sulfoximines are another class of alkylidene transfer (e.g. methylene transfer) reagents used for the synthesis of oxiranes from carbonyl compounds. Attempts at the asymmetric synthesis of oxiranes using sulfoximines having stereogenic sulfur have not been very successful[44,52] (ee, < 40%). Thus, (R)-(-)-S-methyl-S-phenyl sulfoximine 35 on treatment with tosyl chloride and pyridine gave optically pure (R)-(-)-S-methyl-S-phenyl-N-tosyl sulfoximine, 36. The latter on treatment with NaH/DMSO gave the sodium salt of carbanion of (R)-(-)-36, which on condensation with acetophenone produced (S)-(-)-2-methyl-2-phenyl oxirane, 38[52] (Scheme 10).



35 36 38 (2S, R_S)-37

Scheme 10

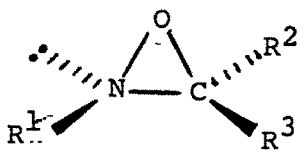
As the (S)-oxirane product must arise from the collapse of the (2S,Rs)- -oxysulfoximine intermediate 37 under kinetically controlled conditions, one would expect that the (2R,Rs)-oxysulfoximine intermediate would predominate. It has been demonstrated that under these reaction condition the 1,2 addition of 36 to ketone is reversible[53]. It is evident that under such circumstances the rate of formation of (S)-oxirane from 37 is faster than that of (R)-oxirane from the (2R,Rs) intermediate.

The other alkylidene groups which have been transfered using reagents in this series include methylidene, ethylidene, isopropylidene, benzylidene, cyclopentylidene and cyclohexylidene etc.

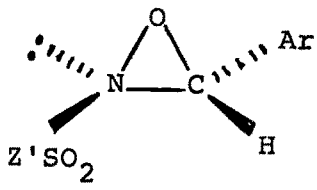
VI. OTHER METHODS

1. Chiral oxaziridines

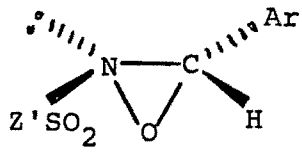
Oxaziridines[54] 39 are three membered heterocyclic ring systems, the optical activity of which is solely due to nitrogen. The asymmetric epoxidation of unfunctionalized alkene using chiral camphor-2-sulfonyloxaziridines gave oxiranes with 12-35 % ee[55]. The best ee(13-65 %) are obtained using 3-pentaflorophenyl-2-sulfamyloxaziridines 40[56] (Scheme 11) or with 3-substituted 1,2-benzisothiazole-1,1'-dioxide-N-sulfoxaziridines (ee=17.61%)[57].



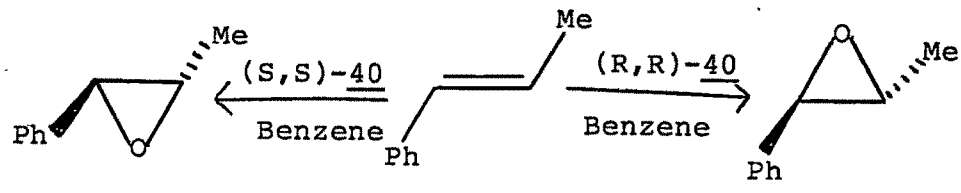
39



(R,R)-(+)-40



(S,S)-(-)-40



(1S,2S)

ee = 64.7%

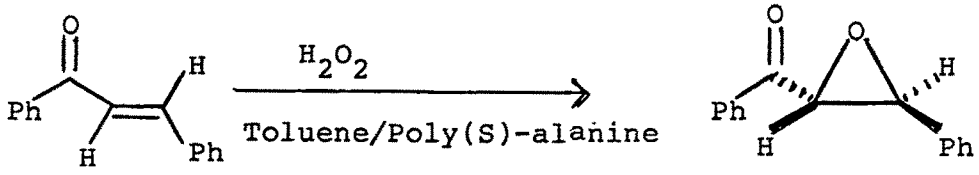
(1R,2R)

ee = 52%

Scheme 11

(2) Phase transfer catalysis

Epoxidation of electron deficient alkenes like chalcones and quinones was carried out in presence of chiral phase transfer catalysts derived from certain alkaloids like quinine etc. Chemical yields are good but enantioselectivities are low[58]. Julia et al used chiral peptides in a triphase catalysis[59] and could get upto 93% ee.

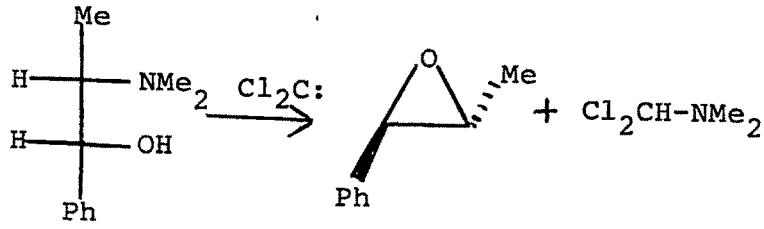


Yield = 85%

ee = 93%

(3) From chiral precursors

Optically pure compounds isolated from natural sources or obtained from synthesis can be utilized in the synthesis of non-racemic oxiranes. The reaction of dichloro carbene with optically active tertiary -ethanolamines gives high yield of oxirane with complete stereospecificity (ee, $\geq$ 95%)[60].



ee = 95%

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