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# Recent aspects of enantioselective epoxidation reactions

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**Abstract**

The latest accepted mechanisms of Katsuki–Sharpless epoxidation, proposed by Sharpless and Corey independently, have been described. The recent developments of chiral porphyrin and salen-based metal complexes and their uses as catalysts for asymmetric epoxidation of unfunctionalized olefins (non-directed epoxidation) have been briefly reviewed.

**Key words:** Enantioselective epoxidation, mechanisms of Sharpless epoxidation, chiral metalloporphyrins, chiral (salen) Mn(III) complexes, facial selectivity, sense and degree of enantioselection.

## 1. Introduction

Enantioselective epoxidation of olefins is one of the most important aspects of asymmetric synthesis. The real breakthrough came in 1980 when Katsuki and Sharpless[1] published the first practical method for asymmetric epoxidation of primary allylic alcohol (Sharpless Epoxidation). Since then, several groups got attracted to the area and reasonable success has been achieved[2]. In this article, we review the work done in the area of enantioselective epoxidation during the last five years.

## 2. Directed epoxidation of functionalized olefins

In their original paper[1], Kasuki and Sharpless showed that reaction of primary allylic alcohols with L- or D-diethyltartrate (DET), titanium tetraisopropoxide, and *t*-butyl hydroperoxide in $CH_2Cl_2$ at −20°C gave optically active epoxides in high yield and very high enantioselectivity (90–95% ee). Later on, Sharpless and co-workers showed that the method can be used to resolve secondary allylic alcohol by taking advantage of the significant difference in the rate of epoxidation of the two enantiomers: one enantiomer is selectively epoxidized and the other remains largely untouched (kinetic resolution)[3]. General procedure of the catalytic aspects of the reaction by using molecular sieves further enhanced the scope of the reaction[4,5]. The positive aspect of

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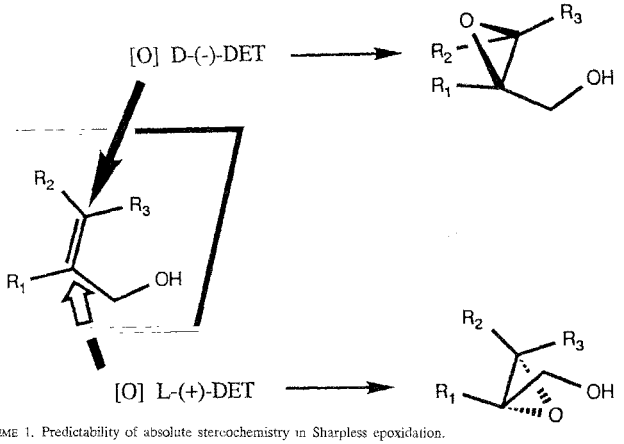
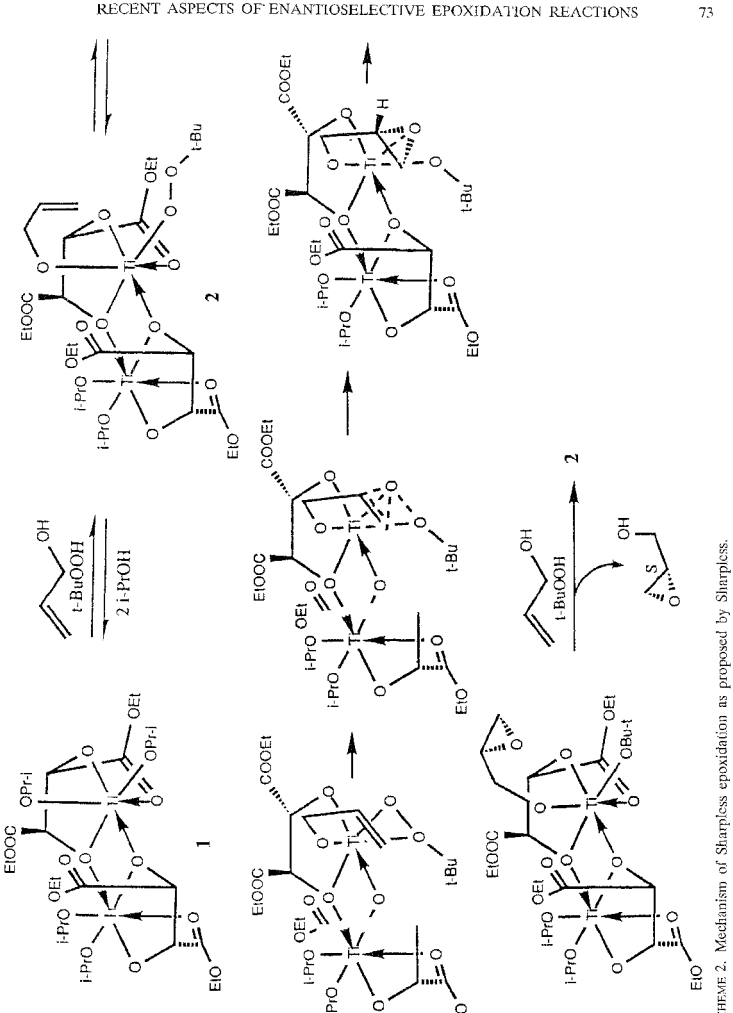
the method is that the reagents required for epoxidation are commercially available and enantioselectivity obtained is invariably very high. The ratio of titanium to ligand used in the reaction is one of the important factors for getting high selectivity. It is recommended that 1:>1.2 ratio gives the best result. This is particularly important for less-reactive substrates. The exclusion of water is very crucial as it retards the rate of the reaction and reduces enantioselectivity. The other advantage with the method is the predictability of absolute stereochemistry. If an olefin is drawn in the plane of a paper with hydroxymethyl group on the right hand side as in Scheme 1, the oxygen is delivered from top if D-(−)-diethyl tartrate (unnatural) is used, and from the bottom if L-(+)-diethyl tartrate (natural) is employed.




SCHEME 1. Predictability of absolute stereochemistry in Sharpless epoxidation.

Although synthetic aspects and applications of the method have extensively been exploited, relative importance of the factors that contribute to high enantioselection has not been established. In other words, the mechanistic aspect of the reaction is still inconclusive. What is certain in the reaction is the rapid exchange of alkoxides on $Ti(OR)_4$ with tartrate ligand. The structure of the active catalyst is assumed to be dimeric $\{[Ti(tartrate)OPr\text{-}i]_2\}$ in nature and based on analytical and spectroscopic studies its structure was postulated to be **1** which is $C_2$ symmetric, with the $C_2$ rotation axis perpendicular to the planar four-membered $Ti_2O_2$ core[2c,6]. The dimer **1** has both bridging and terminal (nonbridging) tartrate oxygen atoms and finds analogy with related complexes whose structure is known by X-ray. Recently, it was shown[6] that $^{17}O$ NMR spectra are also consistent with the tartrate-bridge dimer **1**, indicating two different tartrate alkoxide oxygens and only one type of monodentate alkoxide oxygen. The bridging tartrate oxygen structure provides a relatively rigid framework in which the bound ester carbonyl groups can dissociate and reassociate rapidly.

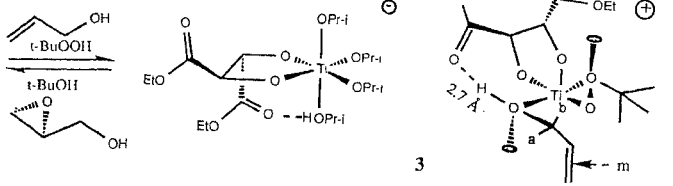


SCHEME 2. Mechanism of Sharpless epoxidation as proposed by Sharpless.

The mechanism proposed by Sharpless[2c,6] is shown in Scheme 2. It is not clear whether each metal is equally active or they act in concert or both the processes occur. It is believed that the reaction takes place on one of the two metal centers of **1** as each Ti center is equivalent by virtue of its $C_2$ Symmetry. On addition of allylic alcohol and *t*-butyl hydroperoxide, they bind to the Ti metal involving an exchange process. Since *t*-butyl hydroperoxide is thought to bind in bidentate fashion, it requires more room and exchanges with isopropoxyl group at equatorial site. Allylic alcohol is, then, left to exchange at axial side, adopting the same conformation as isopropoxyl group where Ti–O–C bond angle in ground state is 150–160°. The most favourable approach of olefin to the coordinated peroxide is along the axis of the O–O bond being broken.

Corey[7] has proposed an ion-pair mechanism for the Sharpless epoxidation reaction (Scheme 3). He has suggested the formation of ion-pair **3** from dimer **1** should be a facile process and that a hydrogen bond is a key feature of the proposal. The characteristic features of catalytic cation of the ion-pair **3** have been derived in a logical way and the following points have been expressed.

1. One molecule of the (*R,R*)-(+)-diethyl tartrate ester is chelated to the central Ti of the cationic moiety of **3**.
2. The OH group of the allylic alcohol is coordinated to that $C_2$ symmetric Ti so as to allow H-bonding to the carbonyl of the tartrate ester. The geometry of H-bond is close to linear (2.7Å).
3. The *t*-butylperoxy group is chelated to the catalytic Ti with the terminal oxygen *cis* to the coordinated allylic OH and the *t*-BuO subunit *trans* to the allylic OH.
4. Five donor atoms are coordinated to the central Ti of the cationic moiety of **3**, further coordination being strongly disfavoured by the bulk of the *t*-alkoxy subunit.
5. The specific arrangement of ligands about Ti in the cationic moiety makes Ti a chiral center with the absolute configuration having been determined by the tartrate ligand.
6. The chirality about the catalytic Ti and the fixed hydrogen bond strongly favours internal epoxidation at only one face of the double bond if stereoelectronic requirement is met, *i.e.*, the double bond approaches the O–O bond with its midpoint approximately collinear with the O–O axis.




SCHEME 3. Ion-pair mechanism for Sharpless epoxidation as proposed by Corey.

7. The *anti* arrangement of the hydroxylic oxygen ligand with respect to *t*-butyl group favours peroxidic bond cleavage (*trans*-electronic effect).

The mechanism involving hydrogen bond mandates the conclusion that homoallylic alcohols should react by coordination of homoallylic OH at the diastereotopic lone pair (relative to the allylic structure **3**) with epoxidation at the opposite face of the double bond as compared to **3**.

Based on kinetic data, Sharpless has ruled out the possibility of ion-pair mechanism. The rate of titanium–tartrate-catalyzed epoxidation is first order in substrate and oxidant. The rate is inhibited by water or any alcoholic component which is not the substrate, *e.g.*, *i*-PrOH, *t*-BuOH, etc., and the rate of the reaction is in inverse square relation with the concentration of inhibitor alcohol. According to Sharpless, the ion-pair mechanism will not be expected to show the inverse squared dependence of rate on inhibitor alcohol concentration that is observed under pseudo-first-order conditions.

Although there is no proof even for the ion-pair mechanism, it cannot be ignored just based on kinetic data when it is well known that ligand displacement with titanium alkoxides is very fast.

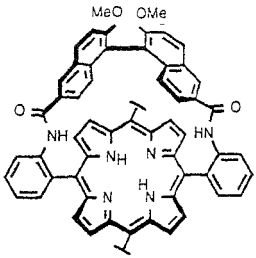
## 3. Non-directed epoxidation of unfunctionalized olefins

### *3.1. Epoxidation with porphyrin-based ligands*

The main disadvantage with Sharpless epoxidation is that it requires –OH as the directing group. The restriction of directing group makes the method limited in scope. The selectivity in enantioselective epoxidation of unfunctionalized olefins (without directing group) depends solely on non-bonded interactions, a common feature among enzymatic reactions. The chloroperoxidase[8] and cytochrome P-450[9] enzymes are known to epoxidize olefins. The former is considered better than the latter since it utilizes $H_2O_2$ whereas the latter normally needs molecular $O_2$ and a regenerable reducing reagent, usually NADH. The chloroperoxidase enzyme gives very high enantioselectivity (92–97% ee) in disubstituted *cis*-olefins. *Trans*- and terminal olefins are not very reactive as is generally the case with heme proteins. Synthetic versatility in enantioselective epoxidation reaction with these enzymes still has to be seen.

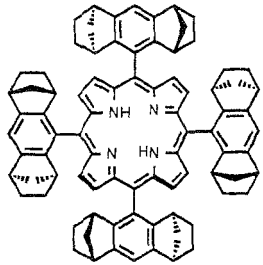
Based on the idea that active site of these enzymes is an iron porphyrin bound to the chiral protein molecule and in relation to the mechanism of asymmetric oxygen transfer, various chiral metalloporphyrins (some are shown in Scheme 4) have been exploited in the synthesis of chiral epoxides from prochiral olefins. As iron porphyrin of cytochrome P-450 is bound to cysteine thiolate group of the chiral protein molecule, each of these synthetic catalysts bears chiral groups linked to the porphyrin moiety, which models the essential role of the chiral protein molecule of cytochrome P-450 in the stereochemical course of the oxygen-transfer process.

Prompted by the observation[10] that epoxidation of olefin by iodosobenzene is catalyzed by synthetic iron porphyrins, Groves and co-workers[11] have designed a $D_2$



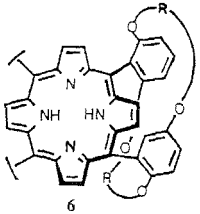

4

$D_2$ Symmetric Porphyrin
(Groves)




5

$D_4$ Symmetric Porphyrin
(Halterman)

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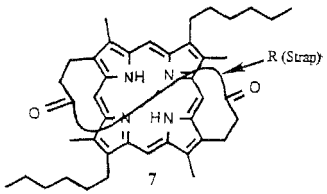
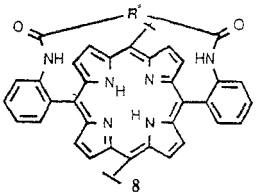
$C_2$ Symmetric Twin-Coronet Porphyrin
(Naruta)



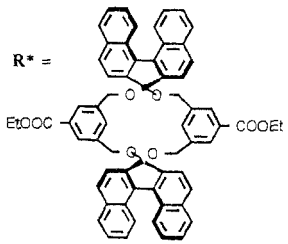

7

Chiral Strapped Porphyrin
(Inoue)




8

Binap Capped Porphyrin
(Collman)




SCHEME 4. Chiral porphyrins used in enantioselective epoxidation of alkenes.

* * *

Table I

**Enantioselective epoxidation results of some selected olefins using chiral metalloporphyrins**

| *Entry Catalysts* | *Olefins*  | | |  | | |  | | |
|---|---|---|---|---|---|---|---|---|---|
| | *Config. of epoxides* | *Yield (%)* | *% ee* | *Config. of epoxides* | *Yield (%)* | *% ee* | *Config. of epoxides* | *Yield (%)* | *% ee* |
| 1 Chloroperoxidase | — | — | — | 1*S*, 2*R* | 67 | 96 | 1*R*, 2*R* | 85 | 97 |
| 2 (*R*)-(−)-**4**-Fe-Cl | (*R*)-(+) | 23 | 30 | 1*S*, 2*R* | 9 | 72 | 1*S*, 2*R* | 61 | 42 |
| 3 (*R*)-(−)-**4**-Mn-Cl | (*R*)-(+) | 21 | 36 | 1*S*, 2*R* | 27 | 6 | — | — | — |
| 4 **5**-Mn-Cl | (*S*)-(−) | 90 | 52 | 1*R*, 2*S* | 91 | 76 | 1*R*, 2*S* | 97 | 56 |
| 5. (*S*)-**6**-FeCl R = binaphthyl derivative | (*R*)-(+) | — | 20 | — | — | — | — | — | — |
| 6. (+)-**7**-(with imidazole) R = -(NH-$CH_2$)$_2$-Ph | (*R*)-(+) | 43 | 49 | — | — | — | 1*R*,2*S* | 32 | 52 |
| 7. (+)-**7**-(No imidazole) R = -(NH-$CH_2$)$_2$-Ph | (*S*)-(−) | 72 | 18 | — | — | — | — | — | — |
| 8 **8**-FeCl | (*S*)-(−) | 62 | 48 | 1*S* , 2*R* | 59 | 29 | 1*S*, 2*R* | 45 | 21 |

symmetric binapthyl-substituted porphyrin **4** for the preparation of metalloporphyrin **4**-$Fe^{III}$Cl and **4**-$Mn^{III}$Cl complexes. Both the catalysts give poor to modest enantioselectivity in epoxidation of olefins. Although the change of metal does not affect the reaction in the case of styrene, chloroiron (III) complex is better than chloromanganese, among other olefins.

Haltermann and Tai[12] have synthesized $D_4$ symmetric tetraphenyl porphyrin **5**, whose manganese chloride complex was prepared by heating the ligand with $MnCl_2.4H_2O$ in DMF, followed by HCl treatment. The epoxidation is carried out in the presence of commercial bleach (NaOCl). The selectivity is modest for *cis*-olefins. For example, the styrene is epoxidized in 52% ee. *Trans*-olefins virtually showed no optical induction.

A $C_2$ symmetric 'Twin-Coronet' porphyrin of type **6** which has chiral biaryl auxiliary (*i.e.*, R = binaphthyl or bitetralin derivatives) linked by ethereal bond on both faces has been reported by Naruta *et al*[13]. Its iron complex has been used for epoxidation in conjunction with iodosobenzene as oxidant. Efficient chiral induction has been achieved in the epoxidation of electron-deficient styrene derivatives (for example, 89% ee in the case of 2-nitrostyrene).

Inoue and co-workers[14] have synthesized a series of chiral-strapped porphyrins of type **7**. The manganese complexes of these porphyrins are chiral due to the presence of the strap (R=*p*-xylylene derivative) on either side of the two faces. Thus, the catalyst has two chemically non-equivalent, diastereotopic faces, and models the

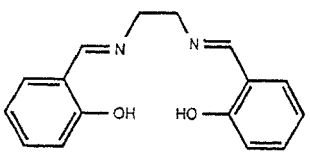
stereochemical structure of the cytochrome P-450 active site. Typically, the epoxidation is carried out with iodosobenzene as oxidant in $CH_2Cl_2$ at $-20°C$ in the presence of imidazole, and optically active epoxides have been obtained in 42–58% ee. In the absence of imidazole, the epoxides with the opposite configuration were formed in lower ee. With some modification[5a] in the strap, 'Threitol-strapped manganese porphyrins' have been synthesized which gave little improvement in the optical induction during the epoxidation reactions.

Collman and co-workers[5b] have synthesized a new kind of metalloporphyrin by treating the binap-capped porphyrin **8** with ferrous bromide, followed by dil. HCl. This catalyst is no way better than the previous ones as the enantioselectivity in the epoxidation reaction is modest (21–63% ee).

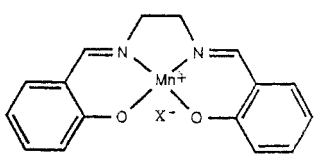
It is clear from Table I that synthetic metalloporphyrins give poor enantioselectivity in the epoxidation of olefins. The chloroperoxidase enzymes[8] should be the method of choice as it gives >90%ee in the epoxidation of a variety of olefins.

### *3.2. Epoxidation with non-porphyrin-based ligands*

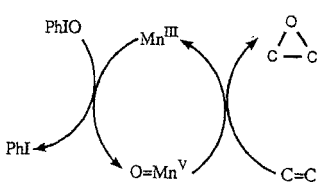
Non-porphyrin ligands, *viz.*, salen (*N, N*-bis (salicylideneamino) ethane) **9** and related ones in the form of metal complexes are used by Kochi *et al*[16] in the epoxidation of olefins using iodosobenzene as oxygen atom source. They have prepared cationic Mn(III) complexes of the type **10** which are more effective than Cr(III) complexes. A reasonable mechanism has been proposed (Scheme 5) where oxomanganese(V) species appear to be the reactive intermediate as established for the related (salen)$Cr^{III}$ complexes.



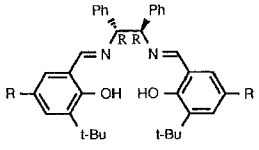

**9**




**10**

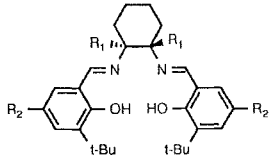



SCHEME 5. Epoxidation of olefins with (salen) Mn(III) complex.



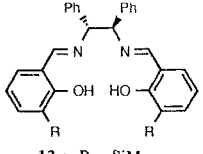
**11** **a**, R = H
**b**, R = Me

(Jacobsen)



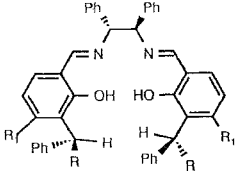
**12** **a**, $R_1 = R_2$ = Me
**b**, $R_1$ = H, $R_2$ = Me
**c**, $R_1$ = Me, $R_2$ = t-Bu
**d**, $R_1$ = H, $R_2$ = t-Bu

(Jacobsen)



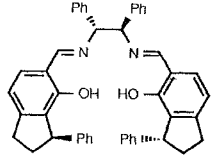
**13** **a**, R = $SiMe_3$
**b**, R = TBDMS

(Burrows)



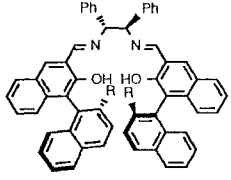
**14** **a**, $R_1$ = H, R = Et
**b**, $R_1$ = Me, R = Et
**c**, $R_1$ = Me, R = Me

(Katsuki)



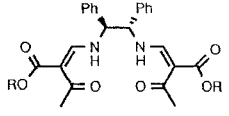
**15**

(Katsuki)



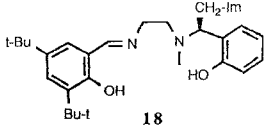
**16** **a**, R = H
**b**, R = Me

(Katsuki)



**17**

(Mukaiyama)



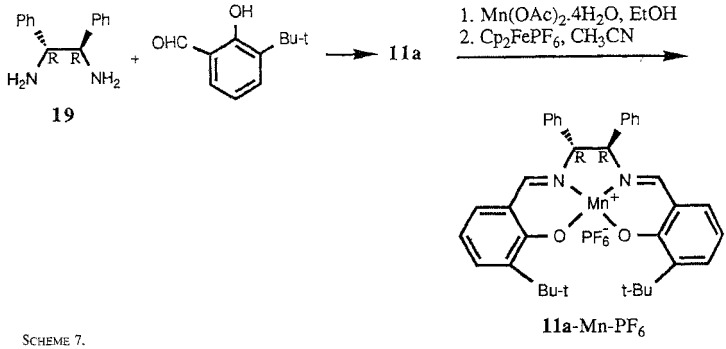
**18**

(Berkessel)

SCHEME 6. Different kinds of salen ligands used in enantioselective epoxidation reaction (only one enantiomer is shown).

In 1990, Jacobsen and co-workers[17a] showed that chiral (salen) $Mn^{III}$ complex (**11a**–Mn–$PF_6$) or its enantiomer is very effective catalyst for inducing chirality in the epoxidation of a variety of unfunctionalized *cis*-olefins using iodosylmesitylene as oxygen atom source. Since then a number of ligands (Scheme 6) have been developed for the preparation of epoxidation catalysts.

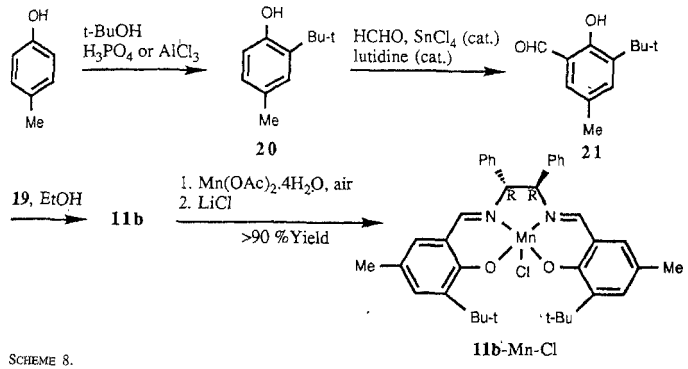
The catalyst (**11a**–Mn–$PF_6$) was prepared from $C_2$ symmetric ligand **11a**, by treating it with $Mn(OAc)_2.4H_2O$ under inert atmosphere to give Mn(II) complex which was further oxidized to Mn(III) complex by ferricenium hexafluorophosphate (Scheme 7). The ligand **11a** has been prepared from readily available chiral auxiliary (*R, R*)-1,2-diamino-1,2-diphenylethane **19** and salicyladelhyde derivative.




SCHEME 7.

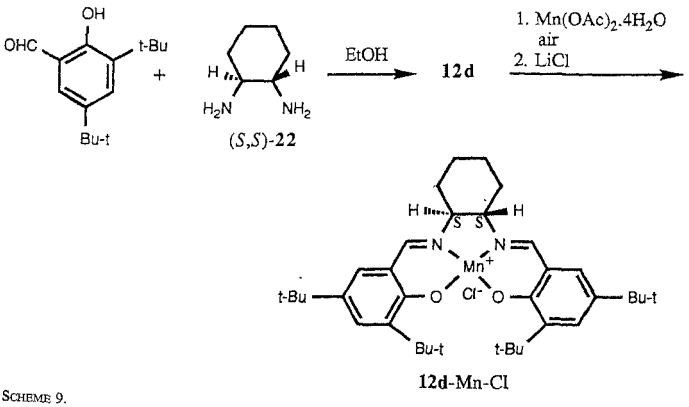
One of the problems with this method is the acquisition of the desired hindered salicylaldehyde. Moreover, the iodosylmesitylene is not a practical oxygen source. Later on these two drawbacks were rectified, and a new ligand **11b** was developed making the method more practical. This method employs commercial bleach (NaOCl) as oxygen atom source and the enantioselectivity remained the same[17b]. For example, *cis*-β-methylstyrene gives (1*S*, 2*R*)-epoxide in 84% ee with both the catalysts. The synthesis of ligand **11b** and its Mn(III) complex is shown in Scheme 8. The use of *p*-cresol in the synthesis ensures the desired selectivity in the Friedel–Crafts alkylation to produce **20** which is commercially available as well. Moreover, the salicylaldehyde **21** is solid that is easy to recrystallize.

The presence of bulky *t*-butyl group in **11** is crucial as it increases the selectivity of the reaction and stability of the catalysts. Other bulky groups work the same way as the *t*-butyl group, but the latter is preferred since it can be introduced more easily. The buffered commercial bleach with pH 11.3 have proven to give better selectivity in the epoxidation reaction.




SCHEME 8.

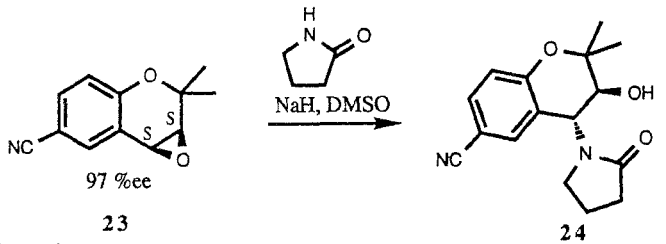
Jacobsen and co-workers[17c] have modified the chiral auxiliary and prepared the catalyst **12d**-Mn-Cl which gave the best selectivity reported so far. For example, the *cis*-β-methylstyrene now gives 92% ee in the epoxidation reaction, compared to 84% ee obtained previously. The catalyst was prepared in two steps in high yield from di-*t*-butylsalicylaldehyde and (*S,S*)-1,2-diaminocyclohexane **22** (Scheme 9). Both the antipodes of the diamine are easily available by resolution with tartaric acid. They




SCHEME 9.

are also commercially available. Combination of all these facts makes it a very superior catalyst for epoxidation of unfunctionalized olefins.

Other chiral ligands like **12a–c** proved to be inferior to **12d**. A variety of epoxychromes have been synthesized[17d] from corresponding olefins using (*R,R*)-**12d**-Mn-Cl in more than 90% ee. The application of the method has been made in the synthesis of active enantiomer of recently developed potassium channel activators with antihypertensive activity. The (*S,S*)-epoxychromene **23** was synthesized in 97% ee from the corresponding olefin using NaOCl and (*S,S*)-**12d**-Mn-Cl complex. Regioselective epoxide opening with pyrrolidone gave the target compound **24** (Scheme 10).




SCHEME 10.

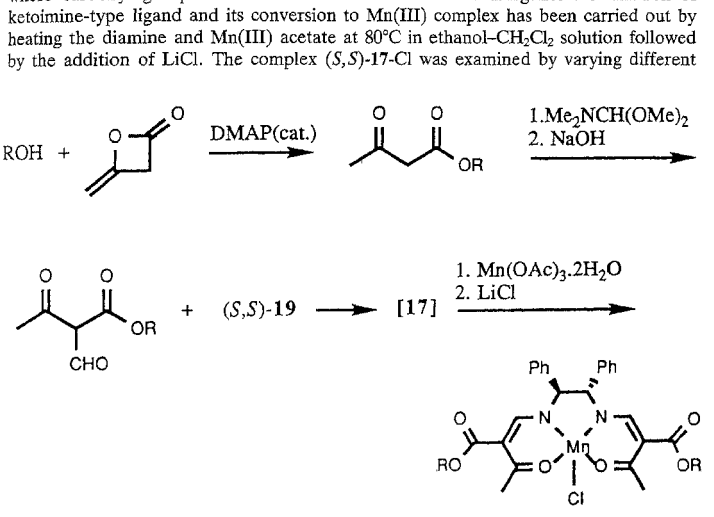
Asymmetric epoxidation of conjugated dienes and enynes has also been reported with (salen) Mn(III) complex **12d**-Mn-Cl. The epoxidation takes place with high chemoselectivity to afford monoepoxide exclusively. Reaction of *cis*-enynes proceed with high levels of asymmetric induction, with *trans*-alkyl epoxides as the major products[17e].

Burrows and co-workers[18] have synthesized new ligands **13** where *t*-butyl group is replaced by trimethylsilyl and tributyldimethylsilyl groups at position 3. Mn(III)Cl complex of this ligand showed poor selectivity in the epoxidation reaction.

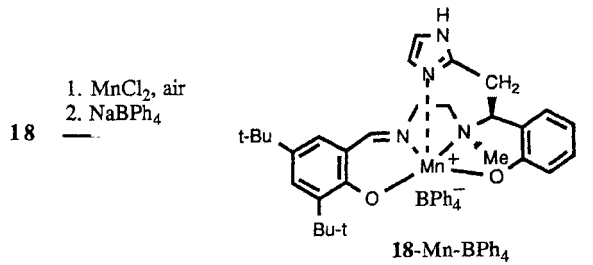
At about the same time (1990) when Jacobsen published his first report on enantioselective epoxidation with chiral salen (Mn) complexes, Katsuki *et al*[19a] published their results independently using a $C_2$ symmetric ligand **14** which differs from Jacobsen's ligand **11a** in the sense that it has stereogenic centers at substituent of position 3 on aromatic rings. The complex **14**-Mn-OAc derived from the proposed ligand gave maximum 50% ee in the epoxidation of (E)-1-phenyl-1-propene with iodosobenzene. Since then, they have synthesized a variety of ligands **14–16** but the selectivity has been moderate[19]. They have noticed that chirality of substituents at position 3 has stronger influence upon the sense of asymmetric induction than that of ethylenediamine moiety for the epoxidation of *trans*-olefins. On the other hand, in the epoxidation of *cis*-olefins the enantiofacial selection was found to be mainly controlled by the chirality of the diamine moiety. It is also reported that the addition

of donor ligands such as pyridine N-oxide or 2-methylimidazole to the epoxidation reaction system alters the enantioselectivity[19c].

Mukaiyama and co-workers[20] have synthesized a new kind of catalyst (Scheme 11) where carbonyl groups of ketoimine **17** coordinate with manganese. Formation of ketoimine-type ligand and its conversion to Mn(III) complex has been carried out by heating the diamine and Mn(III) acetate at 80°C in ethanol–$CH_2Cl_2$ solution followed by the addition of LiCl. The complex (*S,S*)-**17**-Cl was examined by varying different



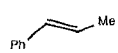

SCHEME 11.




SCHEME 12.

**Table II**

**Enantioselective epoxidation results of some selected olefins using Mn(III) complexes**

| *Entry* | Catalysts (O source) | Olefins | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | |  | | |  | | |  | | |  | | |  | | |
| | | *Config. of epoxides* | *Yield %* | *%ee* | *Config. of epoxides* | *Yield %* | *%ee* | *Config. of epoxides* | *Yield %* | *%ee* | *Config. of epoxides* | *Yield %* | *%ee* | *Config of epoxide* | *Yield %* | *%ee* |
| 1. | (*R,R*)-**11a**-Mn-$PF_6$ (Iodosylmesitylene) | R | 75 | 57 | 1*R*, 2*S* | 73 | 84 | | | | 1*R*, 2*S* | 72 | 78 | 1*R*, 2*S* | 50 | 59 |
| 2 | (*R,R*)-**11b**-Mn-Cl (NaOCl) | | | | 1*R*, 2*S* | 88 | 84 | | | | | | | | | |
| 3 | (*S,S*)-**12a**-Mn-Cl (NaOCl) | | | | 1*S*, 2*R* | 54 | 49 | | | | | | | | | |
| 4 | (*S,S*)-**12b**-Mn-Cl (NaOCl) | | | | 1*S*, 2*R* | 87 | 80 | | | | | | | | | |
| 5. | (*S,S*)-**12c**-Mn-Cl (NaOCl) | | | | 1*S*, 2*R* | 56 | 55 | | | | | | | | | |
| 6. | (*S,S*)-**12d**-Mn-Cl (NaOCl) | | | | 1*S*, 2*R* | 84 | 92 | | | | | | | | | |
| 7. | (*R,R*)-**13a**-Mn-Cl (PhIO) | R | 44 | 18 | 1*R*, 2*S* | 46 | 23 | | | | | | | | | |
| 8. | (*R,R*)-**13b**-Mn-Cl (NaOCl) | R | 86 | 33 | 1*R*, 2*S* | 60 | 53 | | | | | | | | | |
| 9 | (*R,R*)-**14a**-Mn-OAc (PhIO) | | | | 1*R*, 2*S* | 26 | 44 | 1*R*, 2*R* | 61 | 32 | 1*R*, 2*S* | 93 | 49 | | | |
| 10 | (*R,R*)-**14b**-Mn-$PF_6$ (PhIO) | | | | 1*R*, 2*S* | 12 | 68 | 1*R*, 2*S* | 25 | 17 | 1*R*, 2*S* | 24 | 60 | | | |
| 11. | (*R,R*)-**15**-Mn-OAc (PhIO) | | | | | | | | | | 1*R*, 2*S* | 50 | 45 | | | |
| 12. | (*R,R*)-**16b**-Mn-OAc* (PhIO) | | | | 1*R*, 2*S* | 48 | 89 | 1*R*, 2*R* | 68 | 28 | 1*R*, 2*S* | 77 | 86 | | | |
| 13. | (*R,R*)-**17**-Mn-Cl ($O_2$) | | | | | | | | | | 1*R*, 2*S* | 77 | 64 | | | |
| 14. | (*S*)-**18**-Mn-$BPh_4$ ($H_2O_2$) | | | | | | | | | | 1*R*, 2*S* | 72 | 64 | | | |

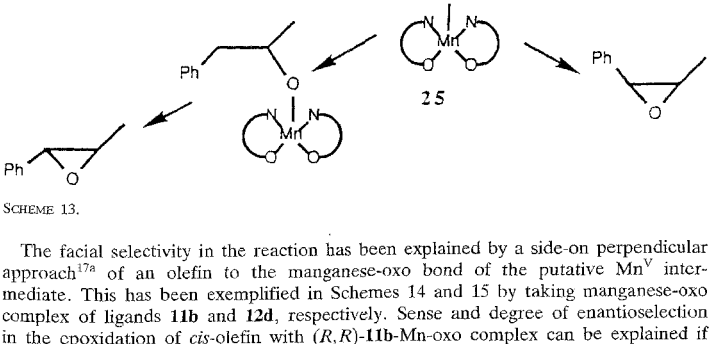
*Pyridine N-oxide is added as additive

R groups with combined use of molecular oxygen and pivaldehyde. Maximum selectivity in the epoxidation is obtained when R is very hindered.

Recently, Schwenkreis and Berkessel[21] have synthesized a chiral pentadentate dihydrosalen ligand **18**, carrying an imidazole group as the fifth donor which mimics the peroxidase enzyme. Mn(III) complex was prepared by treating **18** with manganese (II) chloride in the presence of air and sodium tetraphenylborate (Scheme 12). The epoxidation reaction was carried out by using $H_2O_2$ as oxygen atom source. Although the idea is unique, the selectivity has been poor to modest.

It is clear from Table II, which summarizes the enantioselective epoxidation results of some selected olefins using Mn(III) complex, that Jacobsen's catalyst (**12d**-Mn-Cl) is the most practical one.

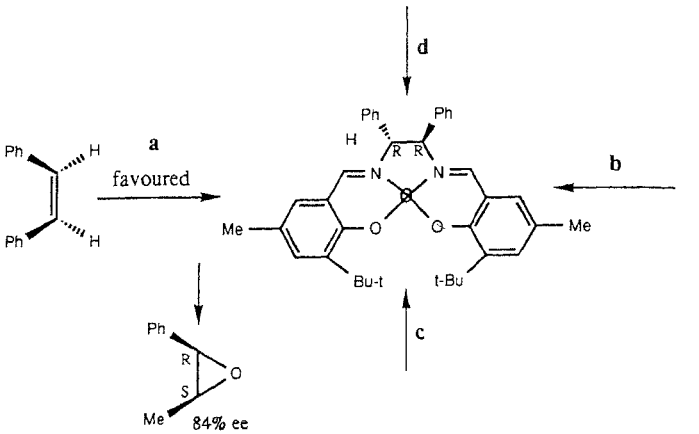
Although a lot of work has been done in the (salen) Mn(III)-catalyzed epoxidation of olefin, its precise mechanism is yet unclear. Kochi and co-workers[16] have already proposed that reaction proceeds through $Mn^V$ intermediate (*vide supra*). During the epoxidation of (Z)-1-phenylpropene, formation of some *trans*-epoxide with almost same optical yield and with same absolute stereochemistry (both *S*) at *C*-2 suggests the intervention of a radical intermediate as shown in Scheme 13.



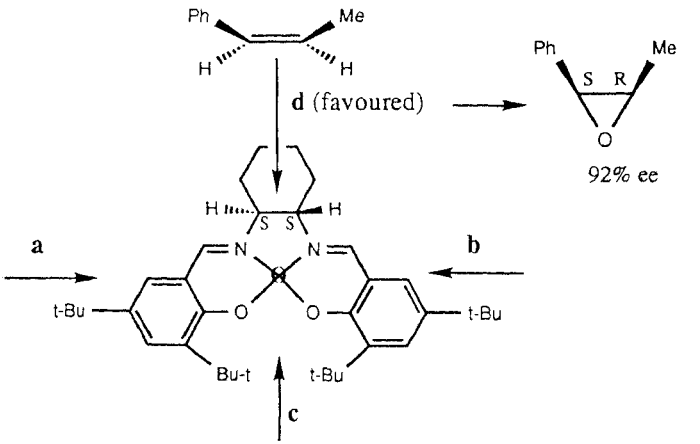

SCHEME 13.

The facial selectivity in the reaction has been explained by a side-on perpendicular approach[17a] of an olefin to the manganese-oxo bond of the putative $Mn^V$ intermediate. This has been exemplified in Schemes 14 and 15 by taking manganese-oxo complex of ligands **11b** and **12d**, respectively. Sense and degree of enantioselection in the epoxidation of *cis*-olefin with (*R,R*)-**11b**-Mn-oxo complex can be explained if the olefin approaches the Mn-oxo bond from side **a** (Scheme 14).

Approach from side **c** is prevented due to *t*-Bu groups. The dissymmetry of the diamine bridge disfavours attack from the side *syn* to the phenyl groups, *i.e.*, side **b**. Approach **d** is disfavoured due to the steric bulk of the diamine bridge. This general model explains the enantioselectivity in the epoxidation of *cis*-olefins with this type of catalyst.




SCHEME 14. Interaction of $Mn^{V}$-oxo complex of ligand **11b** with olefin.



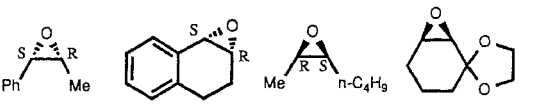

SCHEME 15. Interaction of $Mn^{V}$-oxo complex of ligand **12d** with olefin.

The enantioselectivity with the catalyst(*S,S*)-**12d**-Mn-Cl is very high and sense of asymmetric induction is opposite of that predicted from approach **a** as shown in Scheme 14. This has been explained by the approach of the olefin to the Mn-oxo bond from side **d** (Scheme 15)[17c].

These models also suggest why *trans* olefins give poor selectivity in the epoxidation reaction.

## 4. Conclusions

From the above discussions, it is clear that only two catalysts, **12d**-Mn-Cl and chloroperoxidase enzyme are practical ones for enantioselective epoxidation of unfunctionalized *cis*-olefins. The chloroperoxidase enzyme gives very high optical yield of epoxides in the epoxidation of some aliphatic olefins (Scheme 16). The main drawback with the enzymatic reaction is that it is substrate selective and is not general. Design of efficient catalysts for epoxidation of *trans*-olefins still remains a challenge to organic chemists. Further work in the area is required so that more general catalysts can be prepared.




| | | | | |
|---|---|---|---|---|
| (*S,S*)-**12d**-Mn-Cl | 92 %ee | | | 94 %ee |
| Chloroperoxidase | 96 %ee | 97 %ee | 96 %ee | |

SCHEME 16.

## Acknowledgement

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## References

1. KATSUKI, T. AND SHARPLESS, K. B. *J. Am. Chem Soc.*, 1980, **102**, 5974–5976.
2. For earher review articles on Sharpless epoxidation, see:
   a. SHARPLESS, K. B. WOODWARD, S. S. AND FINN, M.G. *Pure Appl. Chem.*, 1983, **55**, 1823–1836.
   b. ROSSITER, B. E. Synthetic aspects and application of asymmetric epoxidation. In *Asymmetric synthesis* (Morrison, J.D., ed.) Vol 5, Ch. 7, pp. 194–246, 1985, Academic Press.
   c. FINN, M. G. AND SHARPLESS, K.B. On the mechanism of asymmetric epoxidation with titanium–tartrate catalysts. In *Asymmetric synthesis* (Morrison, J. D. ed.), Vol. 5, Ch. 8, pp 246–307, 1985, Academic Press
   d. PFENNINGER, A. *Synthesis*, 1986, 89–116

| | |
|---|---|
| 3 a. MARTIN, V. S., WOODWARD, S. S., KATSUKI, T. YAMADA, Y.M, IKEDA, M. AND SHARPLESS, K. B. | *J. Am. Chem. Soc* , 1981, **103**, 6237–6240. |
| b. CARLIER, P. R., MUNGALL, W. S., SCHRÖDER, G. AND SHARPLESS, K. B. | *J. Am. Chem. Soc.*, 1988, **110**, 2978–2979. |
| 4. HANSON, R. M. AND SHARPLESS, K. B. | *J. Org. Chem.*, 1986, **51**, 1922–1925. |
| 5. GAO, Y., HANSON, R. M., KLUNDER, J. M., KO, S. Y., MASAMUNE, H. AND SHARPLESS, K.B. | *J. Am Chem. Soc.*, 1987, **109**, 5765–5780. |
| 6. a. WOODWARD, S. S., FINN, M. G. AND SHARPLESS, K.B. | *J. Am. Chem. Soc.*, 1991, **113**, 106–113. |
| b. FINN, M G. AND AND SHARPLESS, K. B. | *J. Am Chem. Soc.*, 1991, **113**, 113–126. |
| 7. COREY, E. J. | *J. Org Chem.*, 1990, **55**, 1693–1694. |
| 8. ALLAIN, E. J., HAGER, L. P., DENG, L. AND JACOBSEN, E. N. | *J. Am. Chem. Soc.*, 1993, **115**, 4415–4416 |
| 9. MIWA, G. T. AND LU, A. Y. H. | The topology of the mammalian cytochrome P-450 active site. In *Cytochrome P-450, structure, mechanism, and biochemistry* (Ortiz de Montellano, ed.), pp. 77–78, 1986, Plenum Press. |
| 10. GROVES, J. T. AND NEMO, T. E. | *J. Am. Chem. Soc* , 1983, **105**, 5786–5791. |
| 11. a. GROVES, J. T. AND MYERS, R. S. | *J. Am. Chem. Soc.*, 1983, **105**, 5791–5796. |
| b. GROVES, J. T. AND VISKI, P. | *J. Org. Chem.*, 1990, **55**, 3628–3634. |
| 12. HALTERMAN, R. L. AND JAN SHYI-TAI | *J. Org. Chem.*, 1991, **56**, 5253–5254. |
| 13. NARUTA, Y., TANI, F., ISHIHARA, N. AND MARUYAMA, K. | *J. Am. Chem. Soc.*, 1991, **113**, 6865–6872 |
| 14. KONISHI, K., ODA, K. I., NISHIDA, K., AIDA, T. AND INOUE, S. | *J. Am. Chem. Soc.*, 1992, **114**, 1313–1317. |
| 15. a. COLLMAN, J. P., ZHANG, X., LEE, V. J. AND BRAUMAN, J. I. | *Chem. Commun.*, 1992, 1647–1649. |
| b. COLLMAN, J. P., LEE, V. J., ZHANG, X., IBERS, J. A. AND BRAUMAN, J.I. | *J. Am. Chem. Soc.*, 1993, **115**, 3834–3835. |
| 16. SRINIVASAN, K., MICHAUD, P., AND KOCHI, J. K. | *J. Am. Chem. Soc.*, 1986, **108**, 2309–2320. |
| 17. a. ZHANG, W., LOEBACH, L., WILSON, S.R . AND JACOBSEN, E.N. | *J. Am. Chem. Soc.*, 1990, **112**, 2801–2803. |

b ZHANG, W. AND JACOBSEN, E. N. *J. Org. Chem.*, 1991, **56**, 2296–2298.

c. JACOBSEN, E. N., ZHANG, W., MUCI, A. R., ECKER, J. R. AND DENG, L *J. Am. Chem Soc.*, 1991, **113**, 7063–7064.

d. LEE, N. H., MUCI, A. R AND JACOBSEN, E. N. *Tetrahedron Lett.*, 1991, **32**, 5055–5058.

e. LEE, N. H. AND JACOBSEN, E N. *Tetrahedron Lett.*, 1991, **32**, 6533–6536

f. JACOBSEN, E N., ZHANG, W. AND GULER, M. L. *J Am. Chem. Soc*, 1991, **113**, 6703–6704.

18. O'CONNORS, K. J., WEY, S. J. AND BURROWS, C. J *Tetrahedron Lett.*, 1992, **33**, 1001–1004.

19. a. IRIE, R., NODA, K., ITO, Y., MATSUMOTO, N. AND KATSUKI, T. *Tetrahedron Lett.*, 1990, **31**, 7345–7348.

b. IRIE, R., NODA, K., ITO, Y. AND KATSUKI, T. *Tetrahedron Lett.*, 1991, **32**, 1055–1058.

c. IRIE, R., NODA, K., ITO, Y , MATSUMOTO, N AND KATSUKI, T. *Tetrahedron· Asymmetry*, 1991, **2**, 481–494

d. HATAYAMA, A., HOSOYA, N., IRIE, R., ITO, Y. AND KATSUKI, T. *Synlett*, 1992, 407–409.

e. SASAKI, H., IRIE, R. AND KATSUKI, T. *Synlett*, 1993, 300–302

20. MUKAIYAMA, T., YAMADA, T., NAGATA, T AND IMAGAWA, K. *Chem. Lett.*, 1993, 327–330.

21. SCHWENKREIS, T. AND BERKESSEL, A. *Tetrahedron Lett.*, 1993, **34**, 4785–4788.