THE DEVELOPMENT OF NEW CALIXSALEN EPOXIDATION CATALYSTS

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The Development of New Calixsalen Epoxidation Catalysts

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ABSTRACT

Catalytic asymmetric synthesis is a very efficient and challenging chirotechnology. During the last decade Mn^{III}-(salen) complexes [salen = *N'N*-bis-(salicylidene)-ethylenediamino)] have emerged as practical catalysts for the asymmetric epoxidation of various unfunctionalized alkenes. This research focuses on the development of new macrocyclic Mn^{III}-(calixsalen) catalysts for asymmetric epoxidation of unfunctionalized alkenes.

Direct Schiff-base condensation of diamine with dialdehyde under high dilution and with a metal ion template produces different macrocyclic calix[n]salens consisting of methylene linked salen units. Subsequent coordination of macrocyclic calix[n]salens with manganese(III) afforded two different binuclear catalysts, $[Mn_2(calix[2]salen)]Cl_2$, one of which was identified previously, and a tri-nuclear catalyst, $[Mn_3(calix[3]salen)]Cl_3$.

The catalytic asymmetric epoxidation of several olefins by all three of these complexes has been investigated. Each of the Mn^{III}-(calixsalen) catalysts has shown promising results with good turnovers and enantiomeric excesses greater than 90% for conjugated olefins. For styrene, epoxidation at -78 ^{o}C with *m*-CPBA as terminal oxidant in the presence of the *N*-methylmorpholine *N*-oxide achieved a high turnover and enantioselectivity as compared to the biphasic epoxidation with bleach at room temperature. It was noteworthy that, for the epoxidation of styrene, *the sense of chiral*

induction was opposite for bleach versus m-CPBA oxidants. The reversal of sense was observed for both the Mn_n^{III}(calix[n]salen)Cl_n (n=2,3) and Jacobsen's Mn^{III}(salen)Cl catalysts. Although the sense of chiral induction for indene oxide is the same for NaOCl and *m*-CPBA, the epoxidation with *m*-CPBA as oxidant at low temperature gave a very low enantioselectivity (30% ee) compared with the epoxidation with biphasic bleach system. Given the anomalous results with the indene and *m*-CPBA system, it is not possible to conclude whether *m*-CPBA gives the opposite sense of indene epoxide as compared with bleach.

Based on these results, it is proposed that the coordination of the intact oxidants plays a much more significant role in the epoxidation step than previously realized. Also, it is suggested that the mechanism should be extended to accommodate a divergent pathway.

Acknowledgements

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List of Abbreviations

C_6F_5IO	1,2,3,4,5-pentafluoro-6-iodosyl-benzene
CHP	cumyl hydroperoxide
DHDAB	dihexadecyl-dimethylammonium bromide
DMPC	dimyristoylphosphocholine
DPPC	dipalmitoylphosphatidylcholine
ee	enantiomeric excess
ES-MS	Electrospray Mass Spectrometry
equiv	equivalent
EtOH	ethanol
FAD	flavoprotein pyruvate oxidase
GC	gas chromatography
h	hour
HPLC	high pressure liquid chromatography
i-Pr	*iso*-propyl
LG	leaving group
m	meta
M	molar
MALDI-TOF/MS	Matrix Assisted Laser Desorption Ionization Time-of-flight Mass Spectrometry
m-CPBA	*meta*-chloroperbenzoic acid
MPPH	2-methyl-1-phenyl-2-propyl hydroperoxide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
4-PPNO	4-phenylpyridine *N*-oxide
salen	*N'N*-bis(salicylidene)ethylenediamino

δ	chemical shift in parts per million
PhIO	iodosylbenzene
TLC	thin layer chromatography
t-BuOOH	*tert*-butyl hydroperoxide
t-Bu	*tert*-butyl
Porph	porphyrin
λ	wavelength

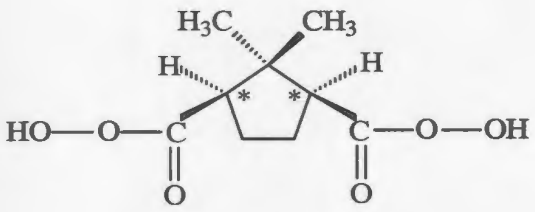
Chapter 1. Review of the Progress on the Asymmetric Epoxidation

1.1 Background

Epoxides are highly strained molecules. Their inherent polarity and angle strain make them readily undergo stereoselective ring-opening reactions with nucleophiles to provide functionalized products. Therefore, epoxides, especially optically active ones, serve as versatile intermediates for the preparation of biologically and pharmacologically active compounds.

The first effort to achieve asymmetric induction in the epoxidation of olefins commenced in 1965 with a report by Henbest that a low level of enantioselectivity (8%) was achieved in epoxidation by using percamphoric acid (**Figure 1-1**).[1] Asymmetric induction remained an elusive goal for 15 years until Sharpless and Katsuki reported the first asymmetric epoxidation of an allylic alcohol with practical enantioselectivity using a titanium-tartrate complex and *tert*-butyl hydroperoxide as the oxidant (**Figure 1-2**).[2] This reaction represented a significant breakthrough in asymmetric synthetic methodology. However, a limitation to this reaction exists because pre-coordination of the substrate to the catalyst is required, thus limiting the substrate to allylic alcohol. In order to overcome the limitations inherent to the "Sharpless" reaction and to expand the substrate domain, several groups have pursued catalytic asymmetric epoxidation of

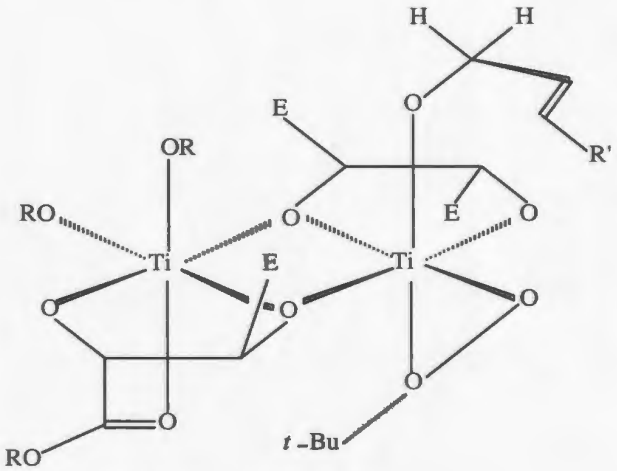
unfunctionalized alkenes that lack a site for pre-coordination to the catalyst. The epoxidation of unfunctionalized alkenes requires that catalysts can distinguish the prochiral alkene faces through non-covalent interactions, such as electrostatic, hydrogen bonding and hydrophobic interactions. [3]



Percamphoric acid

Figure 1-1

The first asymmetric epoxidation



E=CO_2R OR= O^iPr

Figure 1-2

Sharpless and Katsuki's catalyst

1.2 Metalloporphyrin-Catalyzed Epoxidation

Non-covalent interactions constitute the basis for information transfer between the unfunctionalized prochiral substrate and the chiral source. How structures best fit together, namely, molecular recognition, is one of the paradigms that have captured the attention of chemists for over two decades. The oxidizing enzyme cytochrome P-450, which contains an Fe(III)-porphyrin complex has been shown to catalyze various O-atom transfer reactions such as epoxidation, hydroxylation of C–H bonds and oxidation of

sulfides.[4] The catalytic cycle of cytochrome P-450 is believed to involve reductive dioxygen activation at the heme centre and subsequent peroxy bond cleavage to give a ferryl ion species as the active oxygen transfer agent.[5] In 1979, Groves reported the first asymmetric epoxidation of unfunctionalized olefins with porphyrin-based complexes employing iodosylbenzene as terminal oxidant.[6] However, the porphyrin's planarity in the vicinity of the metal coordination site makes it difficult to create an effective asymmetric environment near the reaction site and thereby limits the enantioselectivity of metalloporphyrin-catalyzed epoxidation. These findings prompted the development of chiral metalloporphyrin-catalyzed epoxidation of simple olefins. In 1983, Groves synthesized the first chiral iron(III)-porphyrin complex (5α, 10β, 15α, 20β-tetrakis-(*o*[(*S*)-2`-carboxymethyl-1,1`-binaphthyl-2-carboxamido]phenyl)porphyrin), which has

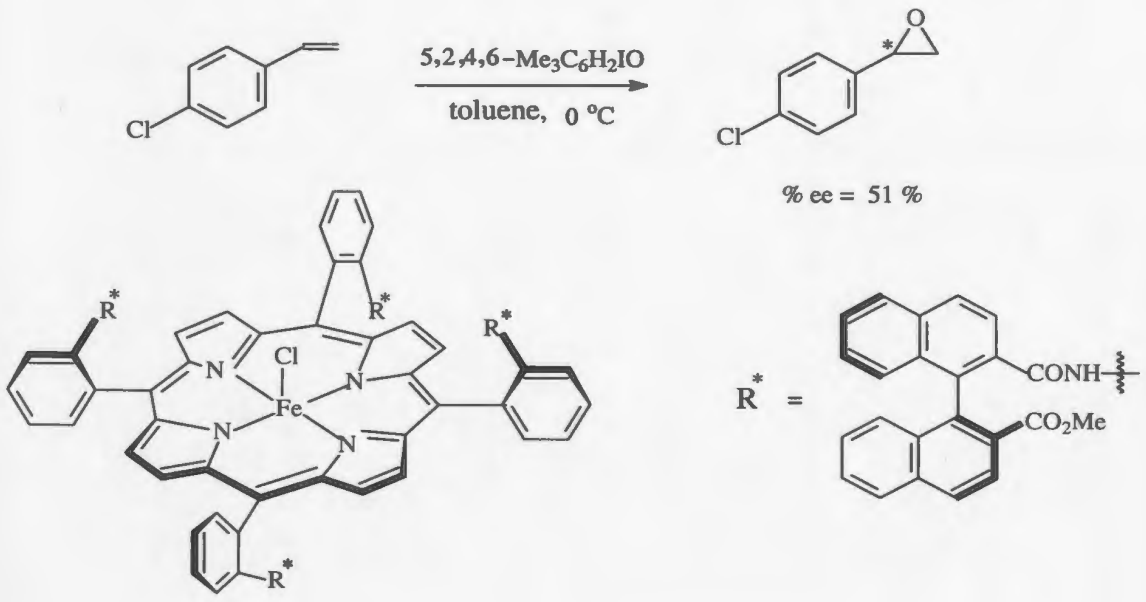


Figure 1-3 Grove's chiral Fe(III)-porphyrin catalyst

optically active functionalities at the *meso* positions and achieved moderate enantioselectivity of 51% ee in the epoxidation of *p*-chlorostyrene (**Figure 1-3**).[7]

In the wake of this report, many chiral Fe(III)-porphyrin and Mn(III)-porphyrin complexes have been synthesized and applied to the epoxidation of styrene derivatives.[8] As Groves has reported elsewhere,[9] the mechanism of the porphyrin-catalyzed oxygen transfer reaction involves an active oxo-iron intermediate (**Figure 1-4**), the oxygen of which is exchangeable with added $H_2{}^{18}O$ since ^{18}O is incorporated into the product epoxide.[6] This result of incorporation of ^{18}O into the product epoxide is inconsistent with either free or metal-coordinated peroxyacid as the oxygen transfer agent but would be expected for an oxo-iron intermediate. *Cis* olefins are more reactive than *trans* olefins toward porphyrin-catalyzed epoxidation by iodosylbenzene.[7] The degree of this selectivity has been shown to be sensitive to relatively small changes in the steric environment of the porphyrin. The opposite corner arrangement of α, β, α, β, -atropisomer chiral appendages apparently does not allow approach of the olefin to the oxo-iron intermediate without chiral interactions at the periphery. The least hindered approach to α, α, β, β, catalyst would be expected to be from the side opposite the chiral groups (**Figure 1-5**). Since negligible interactions between the approaching olefin and the chiral centre are expected for such a geometry, the racemic product obtained is understandable.[10]

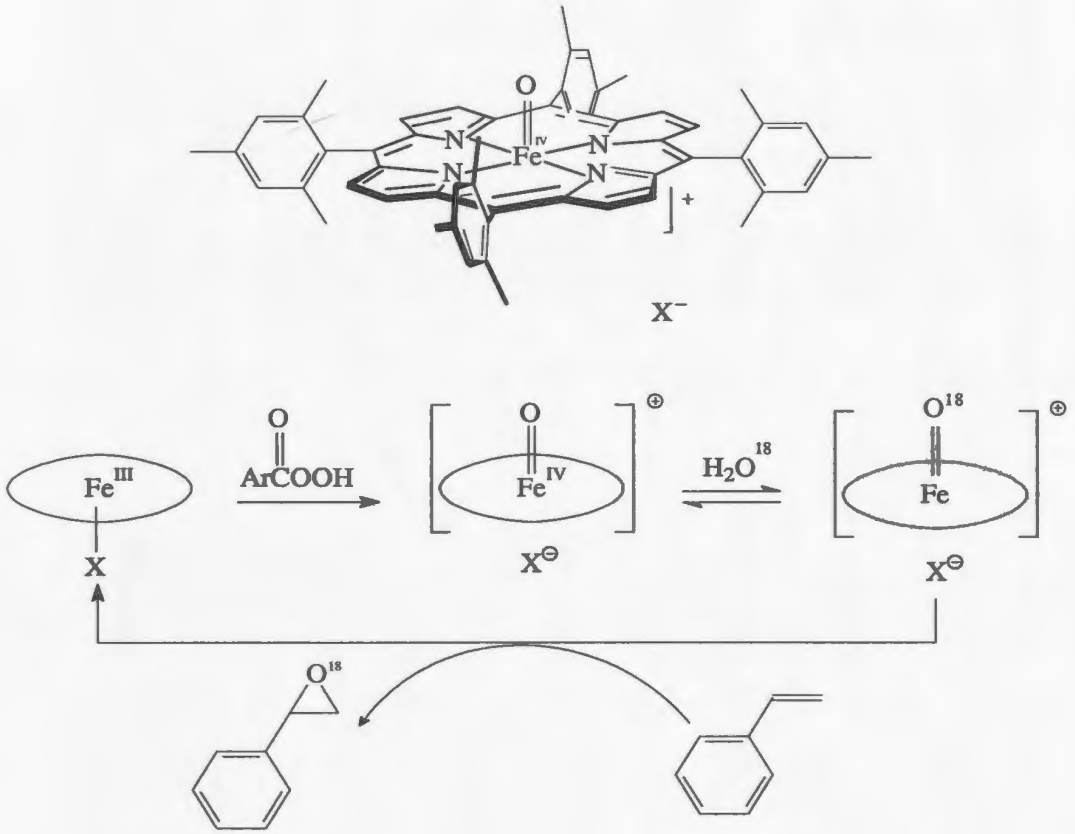
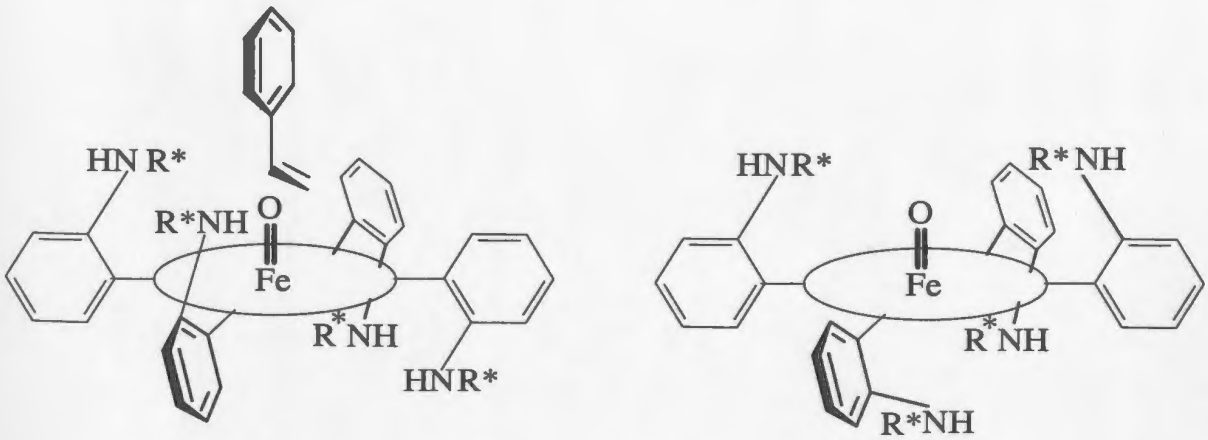


Figure 1-4 Mechanism of porphyrin-catalyzed oxygen transfer reaction[6]



α, α, β, β-catalyst

α, β, α, β-catalyst

Figure 1-5 Porphyrin-based catalysts with chiral appendages

It has been noted that the epoxidation of prochiral olefins mediated by cytochrome P-450 takes place enantioselectively under appropriate conditions where the active centre of cytochrome P-450 is bound to a cysteine thiolate group of the chiral protein molecule. Therefore, the active centre has a diastereoisomeric structure upon coordination to the chiral cysteine thiolate group. The coordinated protoheme has been suggested to exist as either of two possible optically active diastereoisomers. Thus the oxygen transfer in metabolic processes is considered to occur predominantly on either of two chemically inequivalent diastereotopic faces of the active centre (**Figure 1-6**).[11,12]

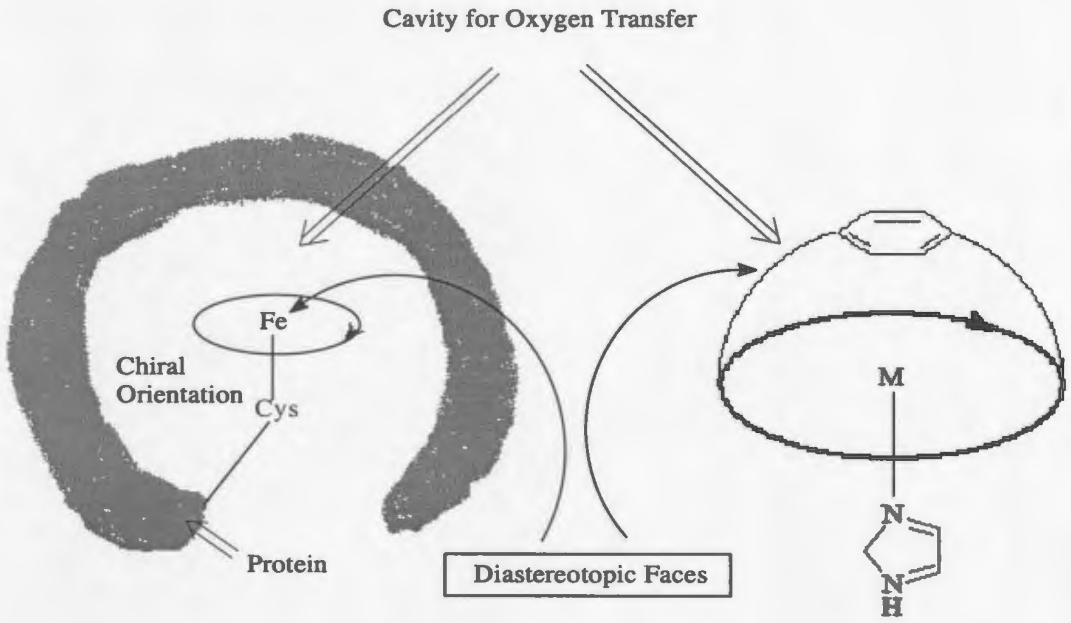


Figure 1-6 Cytochrome P-450 and chiral strapped porphyrin

In 1992, Inoue[12] proposed a fundamentally new strategy for structurally modelling the active centre of cytochrome P-450 in asymmetric epoxidation of olefins by

introducing the chiral-strapped metalloporphyrins with diastereotopic faces (**Figure 1-6**). Also, the enantioselectivity is remarkably enhanced when the reaction is carried out in the presence of imidazole. The improved selectivity can be explained by assuming that, by analogy with cytochrome P-450, the unstrapped face of the active site is considered to be blocked by coordination with imidazole, so that the access of olefins and/or iodosylbenzene is prohibited. Therefore, the epoxidation on this face is efficiently suppressed and the enantioselectivity of the product increases. Subsequently, Collman et al.[13] reported that threitol-strapped Mn(III)-porphyrin complexes show high enantioselectivity in the epoxidation of a wide range of olefins when the reaction is carried out in the presence of 1,5-dicyclohexylimidazole. The substituted imidazole in this reaction appears to play the same role as imidazole in Inoue's reaction (**Figure 1-7**).

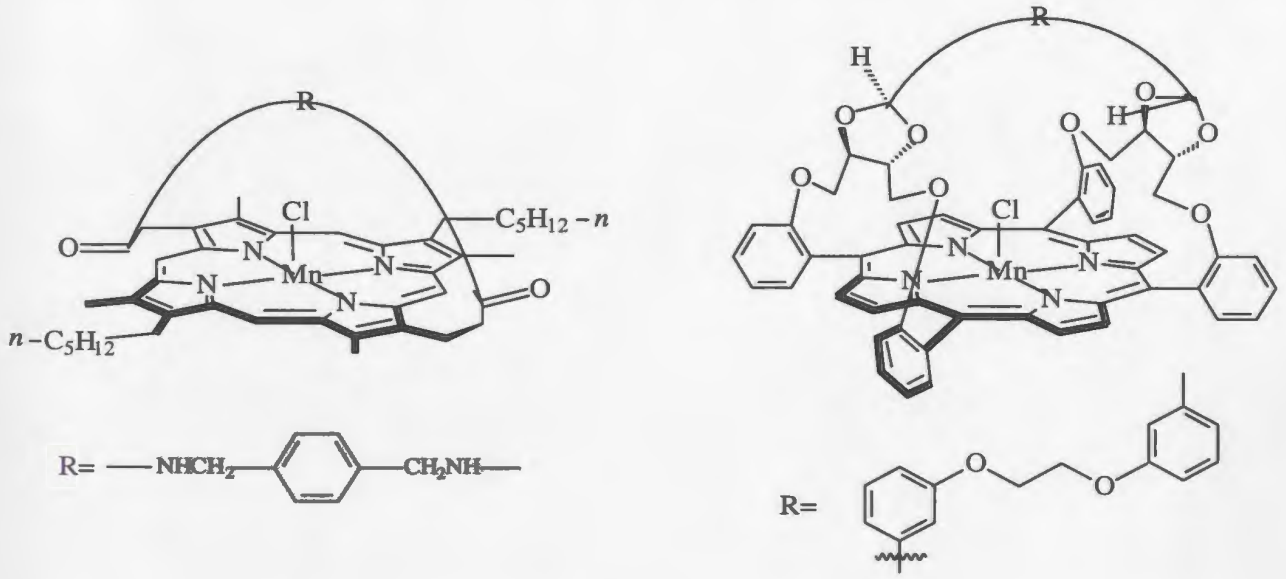


Figure 1-7 Inoue's metalloporphyrin and Collman's metalloporphyrin

More recently, researchers have tried to combine the knowledge obtained from the developing field of supramolecular chemistry and that obtained from biochemistry to construct self-assembling systems that contain all the components of the natural system and even utilize molecular oxygen as the oxidant. An intriguing aspect of cytochrome P-450 is that it is a membrane-bound enzyme in which phospholipids stimulate the transfer of electrons to the isolated enzyme and enhance its affinity for the substrate.[14] This feature has stimulated a number of groups to develop cytochrome P-450 mimics in which a hydrophobic porphyrin is incorporated in the bilayer of a vesicle membrane. In the early 1980's, Sorokin constructed the first self-assembling system by incorporating the hydrophobic Mn(III)-tetrahexadecylphenylporphyrin chloride within a dimyristoylphosphocholine (DMPC) vesicle.[15] Subsequently, Groves and co-workers incorporated a membrane-spanning Fe^{III}TPP chloride derivative containing four steroid groups, *viz.* tetrakis(*o*-cholenylamidophenyl)porphyrin (ChPP) in DMPC or dipalmitoylphosphatidylcholine (DPPC) bilayers.[16] Groves' group has developed a more complex self-assembling system in which the reductive activation of molecular oxygen by Mn^{III}ChPP in DMPC bilayers is realized with the help of the membrane-associated enzyme, flavoprotein pyruvate oxidase (FAD) (**Figure 1-8**). Nolte constructed an alternative system by incorporating the manganese porphyrin in the bilayers derived from vesicles of a polymerizable isocyanide analogue of dihexadecyl-dimethylammonium bromide (DHDAB). [17]

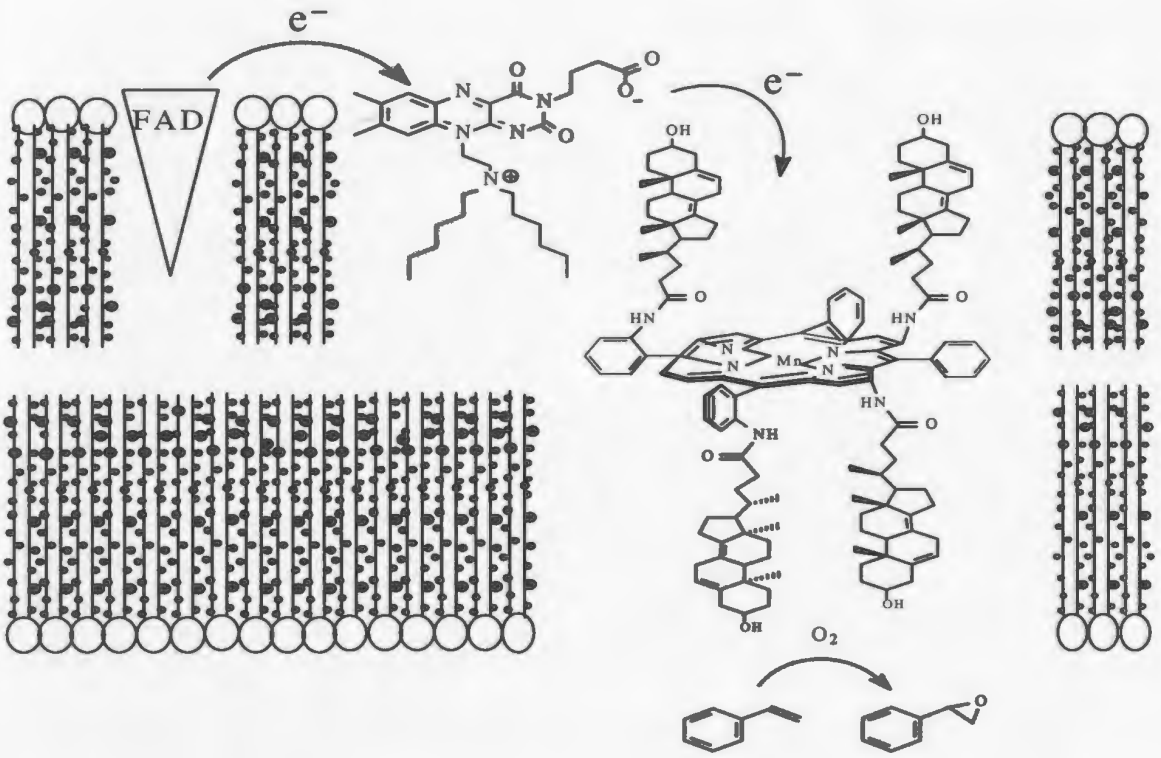


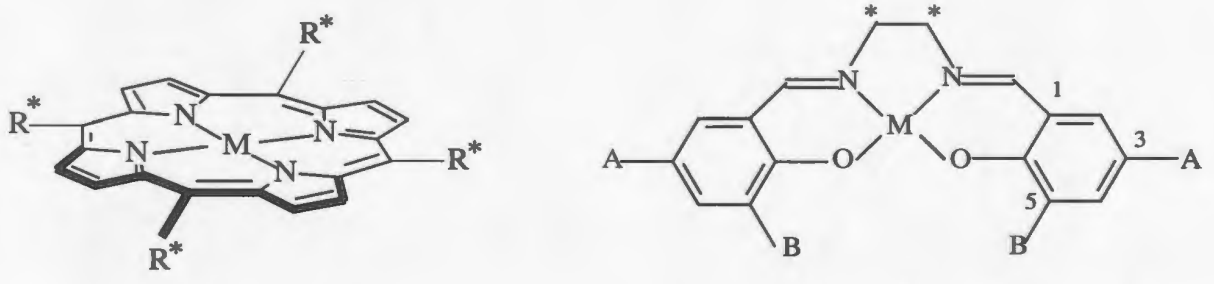
Figure 1-8 Self-assembled system with hydrophobic Mn(III)-porphyrin

During the past several years dendrimers have been used to construct cytochrome P-450 mimics with hydrophobic environments.[18] Although the electrochemical properties of this assembly mimic more closely those of the natural system than that of a free porphyrin, to date no catalytic studies have been reported. Almost all systems described still lack the substrate selectivity and product stereoselectivity of some cytochrome P-450 enzymes found in nature. Although the metalloporphyrin system was an important first step in the development of asymmetric catalytic epoxidation for unfunctionalized olefins, no truly synthetically useful epoxidation system based on chiral metalloporphyrins has yet been developed.

1.3 Metallosalen-Catalyzed Epoxidation

1.3.1 Background: Mn^{III}-(salen) Complexes as Epoxidation Catalysts

Parallel to these porphyrin bound catalysts, optically active metallosalen complexes have lately attracted considerable attention due to the ease of preparation and construction of a highly asymmetric coordination sphere as well as their versatile catalytic performance.[19] Unlike metalloporphyrins **1**, salen complexes **2** have two potentially stereogenic sp^3-hybridized carbon atoms proximal to the metal centre (**Figure 1-9**).

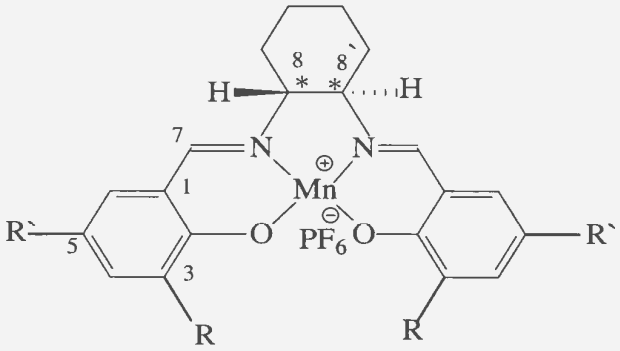


1 **2**

Figure 1-9 General structures for chiral porphyrins (1) and chiral salen complexes (2)

This closer proximity of the stereogenic centres to the metal binding site, compared to the chiral porphyrin ligands, should in principle allow better stereochemical control in the epoxidation step. The analogy between metalloporphyrin- and metallosalen-epoxidation was revealed by the careful structural and kinetic studies by Kochi et al.[20] Initial results showed that the catalytic epoxidation of various olefins with iodosylbenzene was efficiently carried out by a series of Cr^{III}-$(salen)^+$ cations.[20c]

The active species in the reaction was identified as an oxo-Cr^{V}-(salen) complex and the structure of one such complex was determined by X-ray crystallography.[19a] Also, the epoxidation was promoted by pyridine *N*-oxide (PyO) and related oxygen donors as cocatalysts.[20] Subsequently, Kochi et al. reported that Mn^{III}-(salen) complexes were effective catalysts for the epoxidation of various olefins with iodosylbenzene as the terminal oxidant.[21] Although metallosalens were introduced by Kochi and co-workers in 1983 and his efforts provided fundamentally important mechanistic studies, only achiral catalysts were utilized. A significant breakthrough was achieved by Jacobsen and Katsuki[22] in 1990, who independently reported the use of the optically active Mn^{III}-(salen) complexes **3** and **4** as epoxidation catalysts (**Figure 1-10**).



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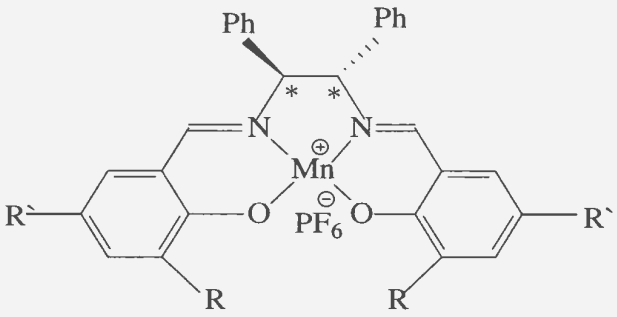

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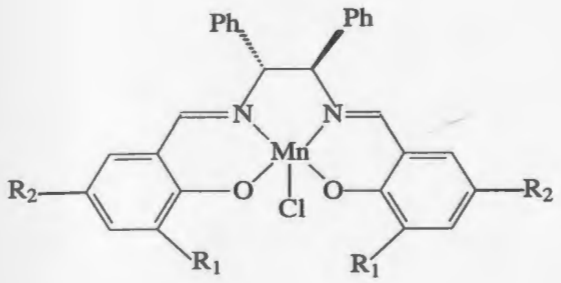
Figure 1-10 Optically active Mn^{III}-(salen) complexes

These first-generation Mn^{III}-(salen) complexes possess two sp^3 stereogenic carbons and can be modified by the introduction of asymmetric carbons at C-8 and C-8` or C-3 and C-3`. In contrast to oxo porphyrin complexes, where the active species in

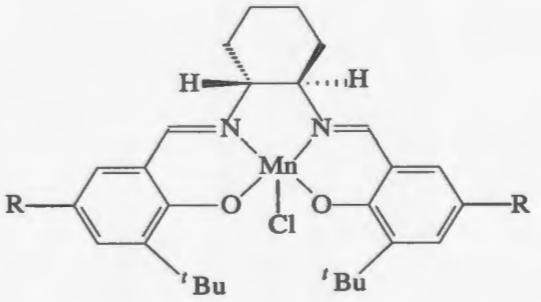
porphyrin-catalyzed epoxidation has only been identified spectroscopically, the isolation and characterization of an oxo-Cr^{V}-(salen) complex strongly suggests that other salen-catalyzed epoxidations also proceed through the corresponding oxo species. No oxo species other than oxo-Cr^{V}-(salen) complex have been isolated to date.

1.3.2 Chiral Mn^{III}-(salen) Complexes: Steric Effect on Enantioselectivity

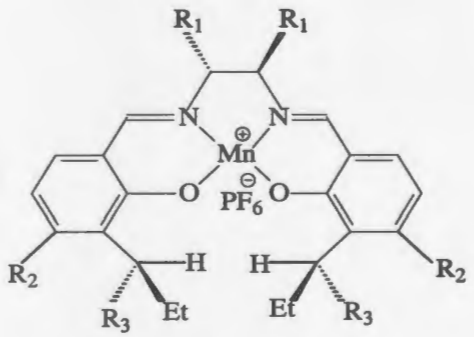
The pathway and orientation of approaching olefins to the active oxidant are crucial factors in asymmetric epoxidation of unfunctionalized olefins. Therefore, in addition to the presence of a dissymmetric diimine moiety, the achievement of high enantioselectivity relies on the steric and electronic properties of the substituents in salen complexes.[23] To achieve high enantioselectivity, the approach trajectory of the olefin to the active site and its orientation must be strictly regulated. The first generation catalysts were designed based on the following premises: 1) the salen ligand has a planar structure; 2) the olefin approaches the oxo-metal bond side-on, parallel to the salen ligand plane; 3) the olefin approaches along the sterically less-congested pathway. According to these assumptions, Jacobsen and Katsuki further modified the first generation catalysts and designed more effective optically active Mn^{III}-(salen) catalysts. Representative examples of Jacobsen-type and Katsuki-type catalysts are presented in **Figure 1-11**.



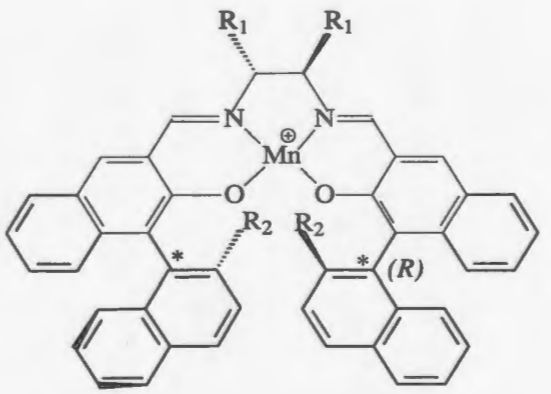
5 : R_1= H R_2 = H
6 : R_1= *t*-Bu R_2 = H
7 : R_1= *t*-Bu R_2 = Me
8 : R_1= 9-methyl-9-fluorenyl R_2 = Me
9 : R_1= *t*-Bu R_2 = OMe
10 : R_1= *t*-Bu R_2 = OSi(*i*-Pr)$_3$
11 : R_1= *t*-Bu R_2 = Br



12 : R= H
13 : R= OMe
14 : R= Me
15 : R= *t*-Bu
16 : R= OSi(*i*-Pr)$_3$



17 : R_1= Ph R_2= H R_3= Ph
18 : R_1= Ph R_2= Me R_3= Ph
19 : R_1= Ph R_2= Me R_3= 4-*t*-BuPh
20 : R_1, R_1= $(CH_2)_4$ R_2= Me R_3= 4-*t*-BuPh
21 : R_1= H R_2= Me R_3= 4-*t*-BuPh



X= $AcO^{\ominus}$, $PF_6^{\ominus}$

22 : R_1= Ph R_2= Me
23 : R_1= 3,5-Me_2Ph R_2= Ph
24 : R_1, R_1= $(CH_2)_4$ R_2= Ph

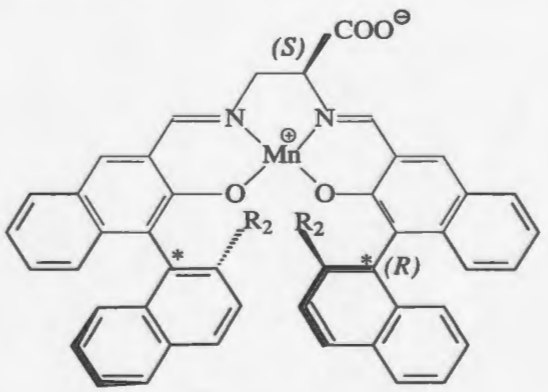


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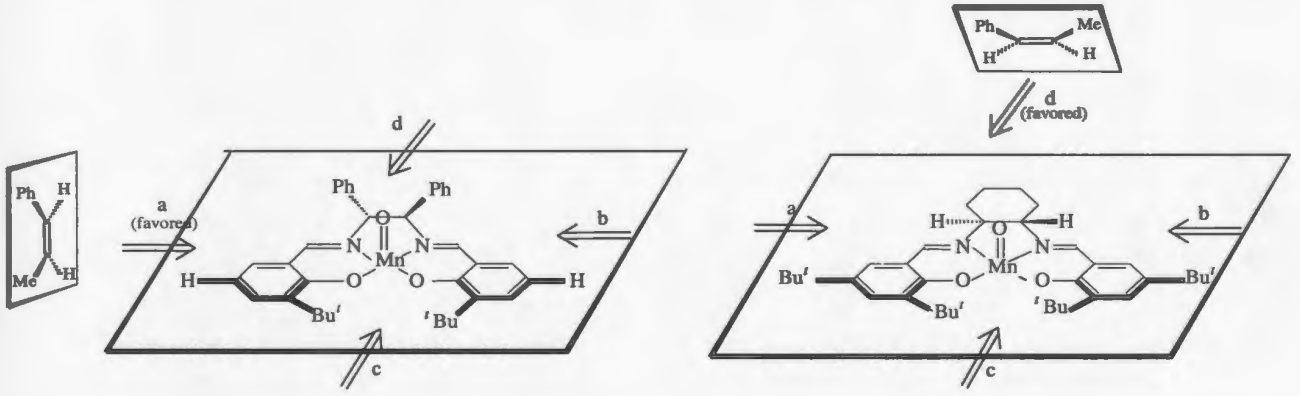
Figure 1-11 First generation salen epoxidation catalysts

Table 1-1 Asymmetric Epoxidation of Various Olefins Using Mn(III)-salen Complexes as Catalysts

Entry	Substrate	Catalyst	Oxidant	Temperature	Yield (%)	ee (%)	Configuration	Ref.
1	*trans*-stilbene	5	Me_3PhIO	25°C	63	33	1*S*, 2*S*	22
2	styrene	6	Me_3PhIO	25°C	75	57	*R*-(+)	22
3	*cis*-β-methylstyrene	7	NaOCl	RT	88	84	1*S*, 2*R*	24
4	*cis*-β-methylstyrene	8	NaOCl	25°C	35	76	---	44
5	2,2dimethyl-chromene	9	---	---	---	96	---	44
6	cyclopenta-1,3-diene	10	NaOCl	4 °C	45	64	1*S*, 2*R*	43
7	*cis*-β-methylstyrene	11	PhIO	---	76	72	---	31
8	cyclohexa-1,3-diene	12	NaOCl	25°C	30	65	---	23
9	*cis*-β-methylstyrene	13	NaOCl		83	51	---	31
10	*cis*-β-methylstyrene	14	NaOCl	RT	87	80	1*S*, 2*R*	24
11	*cis*-β-methylstyrene	15	NaOCl	0 °C	86	81	1*S*, 2*R*	43
12	*cis*-β-methylstyrene	16	NaOCl	---	86	81	---	43
13	*cis*-β-methylstyrene	17	PhIO	RT	49	65	1*R*, 2*S*	46
14	*cis*-β-methylstyrene	18	PhIO	RT	24	68	1*S*, 2*R*	46
15	*trans*-stilbene	19	PhIO	RT	70	56	1*R*, 2*R*	44
16	dihydronaphthalene	20	PhIO	RT	38	91	1*S*, 2*R*	30
17	*trans*-stilbene	21	PhIO	RT	64	61	1*R*, 2*R*	30
18	*cis*-β-methylstyrene	22	PhIO	RT	48	88	---	23
19	cyclopenta-1,3-diene	23	PhIO	-18 °C	54	94	---	30
20	*cis*-β-methylstyrene	24	PhIO	-30 °C	91	77	---	44
21	2,2-dimethylchromene	25	PhIO	RT	99	92	---	36

The steric and electronic effects on enantioselectivity for Mn^{III}-(salen) catalysts were recognized early.[24] Based on the side-on approach model proposed for the epoxidation catalyzed by metalloporphyrins, Jacobsen rationalized the possible approaches of *cis*-alkene to an oxo-Mn^{V}-(salen) species as shown in **Figure 1-12**.[25]



6 **15**

Figure 1-12 Possible approaches to an oxo-Mn^{V}-(salen) species

In Jacobsen's model of catalyst **6**, olefins are expected to approach the oxo-metal bond along the approach **a**, directing their bulky substituents away from the substituents at C-3 and C-3` in the epoxidation. The dissymmetry of the diimine bridge disfavours attack from the side *syn* to the phenyl group (approach **b**), but leaves an accessible approach *anti* to the phenyl group (approach **a**). Approach **d** is presumably disfavoured due to the steric bulk of the diimine bridge.[26] When a second set of *tert*-butyl groups were introduced *para* to the salen oxygens as in C-5 and C-5`, approach **a** was blocked. Approach **d** was proposed to account for the enantioselectivity achieved with complex **15** as catalyst and resulted in a further improvement in catalyst selectivity, presumably by

strongly disfavouring all side-on olefin approaches with the exception of approach **d**.[27]

Jacobsen observed that the introduction of *tert*-butyl groups at C-3 and C-3` of the salicylidene ligand was crucial to attain high enantioselectivity.[28] The effect of substituents at C-3 and C-3` positions is illustrated by comparing catalysts **5** and **6** (**Figure 1-11**). The salen complex bearing no substituents at C-3 and C-3` exhibits a very low enantioselectivity (~33%). On the contrary, the introduction of bulky substituents at C-3 and C-3` enhances the enantioselectivity (~78%) presumably because the substituents block the approach of olefins from the pathway which is far away from stereogenic centres. Increasing the size of the R group in **27** leads to a minor improvement in selectivity, but more hindered system such as **28** tend to be less selective (**Figure 1-13**).[29]

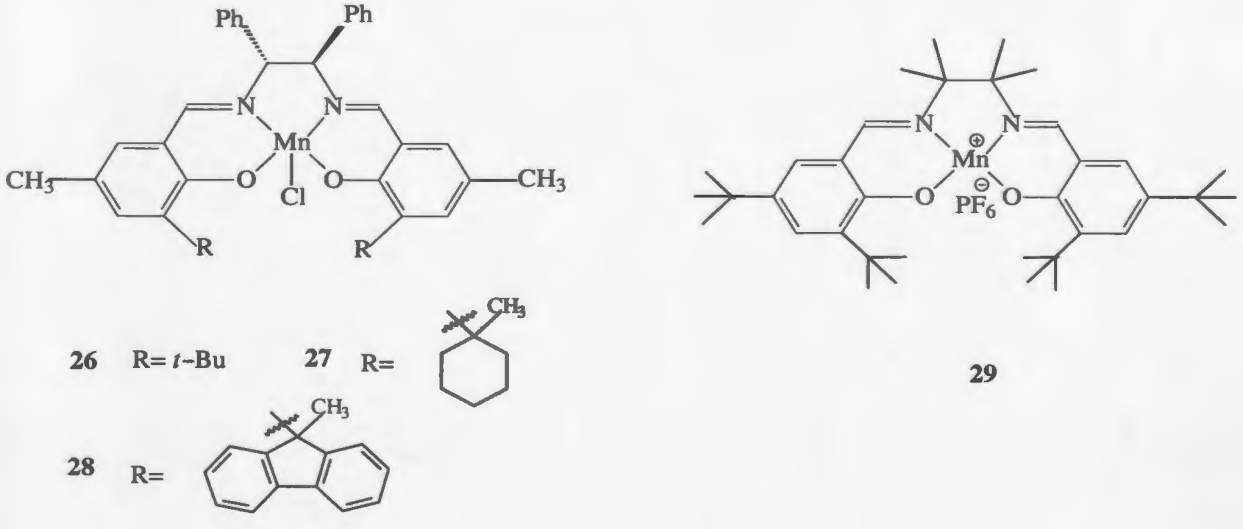


Figure 1-13 Structures of substituted Mn^{III}-(salen) complexes

To explore the effect of C-8 and C-8` stereogenic centres on the asymmetric

induction, Katsuki and co-workers further synthesized Mn^{III}-(salen) complexes **18** and **19** (**Figure 1-11**). Results obtained with these complexes showed that the conformation of C-3 and C-3` chiral substituents has considerable influence on the asymmetric induction. Replacement of C-8 and C-8` phenyl groups with more bulky 4-*t*-butylphenyl group produces more effective catalysts.[30] Mn^{III}-(salen) complexes with C-4 and C-4` methyl groups which confine the conformation of the C-3 and C-3` substituents with hydrogen atoms in the aromatic plane are generally better catalysts than the complexes without C-4 and C-4` methyl groups.

Discussions to this point are based on the hypothesis that the ligands of the putative oxo-Mn(V) intermediates have planar structures by analogy to metalloporphyrin complexes and Mn^{III}-(salen) complexes **15** and **17**, the structures of which were determined by X-ray crystallographic analysis.[31] However, the assumption that the ligand of the oxo-Mn^{V}-(salen) complex is planar failed to explain that the epoxidation of *cis*-*β*-methylstyrene with smaller catalyst **5** shows the lowest selectivity, but the epoxidation with catalysts **6** and **7** exhibits a similar level of moderate selectivity. In addition, Jacobsen et al. reported that the epoxidation of *cis*-enynes with **15** proceeded with high enantioselectivity since the acetylenic substituent behaved as a larger group than the other alkyl groups. Jacobsen maintained that the location of the radical stabilizing group is responsible for the determination of the sense of the enantiofacial selectivity of enynes (**Figure 1-14**).[32]

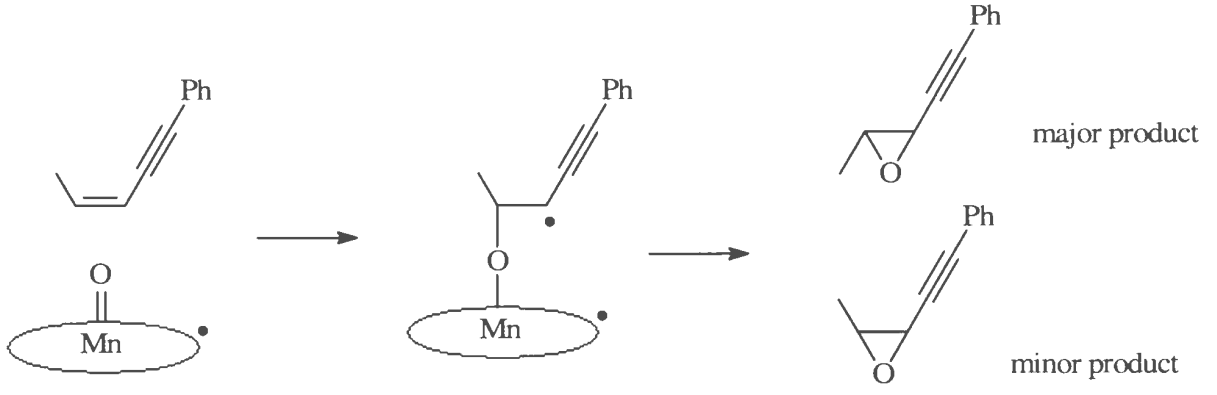


Figure 1-14 Enantiofacial selectivity of enynes stabilized by radical group

These results suggest that the *tert*-butyl groups at C-5 and C-5` also have a significant, although generally less important effect, on the epoxidation selectivity and that further increase in the size of the C-5 and C-5`substituents has only a small effect on selectivity.[33] These results are inconsistent with the assumption that the ligand of oxo-metal species is planar. However, as the structures of oxo-Cr^{V}-(salen)[19a] indicate, the corresponding oxo-Mn^{V}-(salen) intermediates may adopt a non-planar structure. Indeed, the non-planarity of oxo-Mn^{V}-(salen) intermediates has been proven by Katsuki's experiments.[34] Katsuki also considered the approaching pathway of olefins to oxo-Mn^{V}-(salen) species, and proposed a non-planar stepped conformation for the oxo-Mn^{V}-(salen) intermediate as well as another approaching pathway **c** to rationalize the stereoselectivity observed in Mn^{III}-(salen) catalyzed epoxidation (**Figure 1-15**).

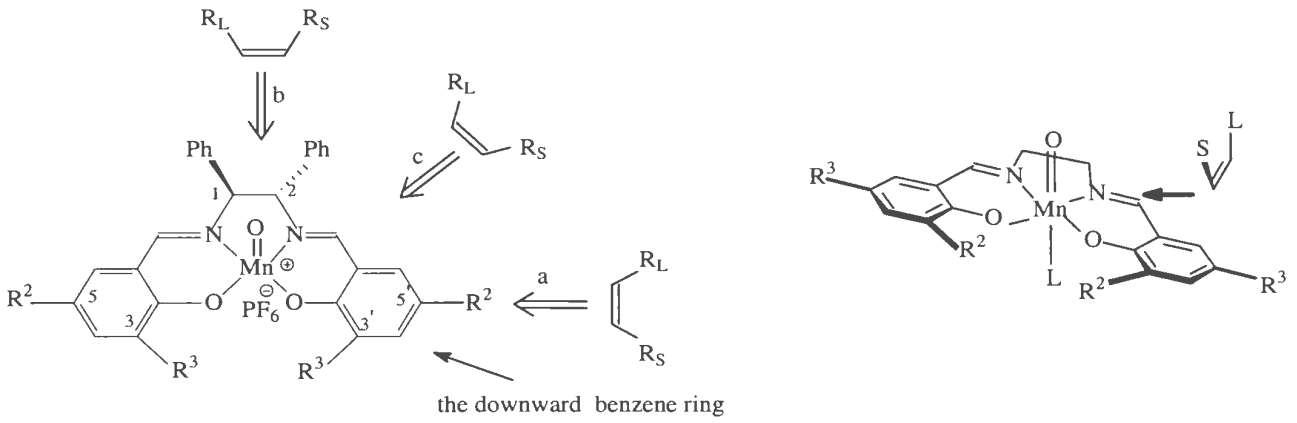
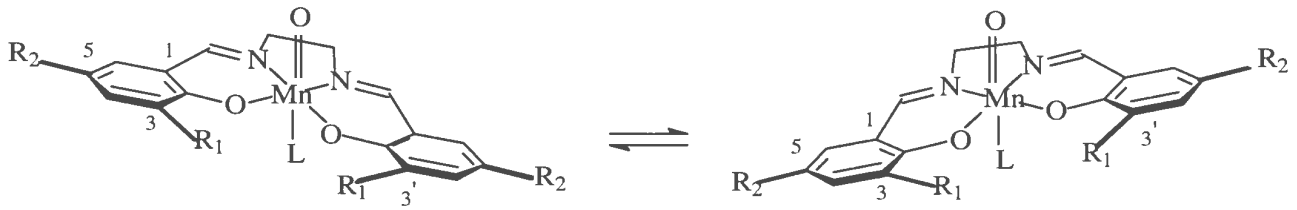


Figure 1-15 Proposed approaching pathways for non-planar stepped oxo-Mn^{V}-(salen) intermediate

If the salen ligand adopts a non-planar conformation, then an oxo-Mn^{V}-(salen) complex bearing an achiral ligand must exist in a 1:1 equilibrium mixture of enantiomeric conformers A and *ent*-A (**Figure 1-16**). Epoxidation with an achiral Mn^{III}-(salen) as



A ***ent*-A**

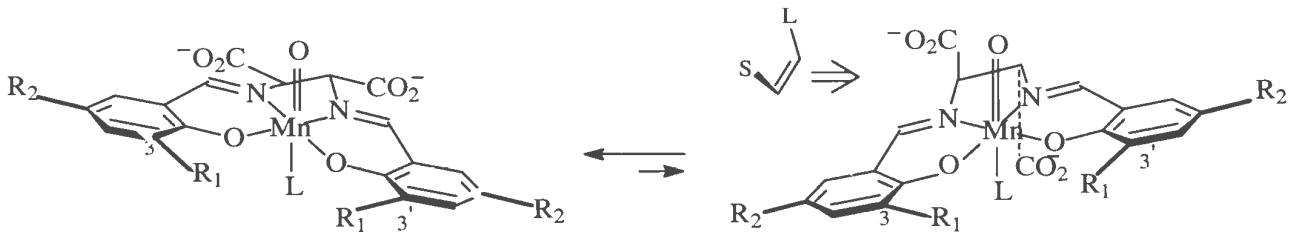
Figure 1-16 Equilibrium between enantiomeric conformers **A** and ***ent*-A**

catalyst gives a racemic epoxide because these conformers are mirror images. However, epoxidation will be stereoselective if the equilibrium is shifted toward one conformer by some means. For example, if the cationic oxo-Mn^{V}-(salen) is coordinated by an apical chiral ligand L, the enantiomeric conformers become diastereomeric to each other and the

equilibrium will favour one conformer, thus cationic achiral oxo-Mn^{V}-(salen) complexes can be used as chiral catalysts.[35] As an example of this approach, the epoxidation of **2**, 2-dimethylchromene derivatives with achiral complex **23** (**Figure 1-11**) as catalyst showed high enantioselectivity (92% ee) in the presence of the optically active donor ligand, (+)-bipyridine *N, N`*-dioxide.[35c] In the epoxidation catalyzed by this non-planar oxo-$Mn^{V}$-(salen) complex, the olefin approaches the prevailing conformer over the downward-bent benzene ring, directing the bulkier substituents ($R_L$) away from the bulky C-3 or C-3` substituent (R_1), to give the major epoxide enantiomer. The presence of bulky C-3 or C-3` substituents is indispensable for regulating the orientation of the incoming olefin. Furthermore, the ligand conformation suggests that the presence of a bulky substituent at C-5 effectively blocks the undesired substrate approach over the upward benzene ring, leading to the wrong enantiomer. The postulation that the salen also assumes a stepped non-planar structure in the oxo-Mn^{V}-(salen) complex has led to a new asymmetric epoxidation system using the non-symmetric Mn^{III}-(salen) complex **25** as the catalyst (**Figure 1-11**).[31]

It is reasonable to assume that the oxo-Mn^{V}-(salen) intermediate derived from C_2-symmetric Mn-(salen) complexes preferably exists as the conformers eq-B in which both substituents at the ethylenediamine moiety occupy pseudo-equatorial position because the diaxial conformer, ax-B, suffers from steric repulsion with both the oxo atom and the apical ligand (**Figure 1-17**).[36] Thus, olefins approach the conformer eq-B from

the downward benzene ring side to give the observed major epoxide enantiomer. X-ray structural data for **30a** and **30b** confirm that the ligand of **30** is structurally pliable and takes a stepped conformation.[37]



30a **30b**

eq-B ***ax*-B**

Figure 1-17 Equilibrium between conformers **eq-B** and **ax-B**

1.3.3 Chiral Mn^{III}-(salen) Complexes: Electronic Effect on Enantioselectivity

The electronic effects of salicylidene ligand substituents on the reactivity of Mn^{III}-(salen) complexes were studied by Kochi et al. Their work showed that the presence of electron-withdrawing groups, such as –Cl or $–NO_2$ at C-5 and C-5` enhanced catalytic activity.[38] Subsequently, Jacobsen et al. investigated the electronic effects of the substituents at C-5 and C-5` position. Their studies have unequivocally showed that complexes bearing electron-donating groups afford higher enantioselectivity than complexes with electron-withdrawing groups and a strong correlation between $\Delta\Delta H^{\neq}$ and the electronic character of the catalyst was observed.[39]

It was suggested that these effects might be interpreted based on the Hammond Postulate, wherein ligand substituents influence enantioselectivity by modulating the

reactivity of the high-valent oxo-Mn-(salen) intermediate. Thus, electron-withdrawing substituents were proposed to lead to a more reactive oxo-Mn-(salen) intermediate, which adds to olefin in a comparatively early transition state and affords the lower level of enantioselectivity. Conversely, electron-donating groups attenuate the reactivity of the oxo species, leading to a comparatively late transition state and concomitantly higher enantioselectivity.[39b]

However, Katsuki et al. reported somewhat different results with their catalysts. The introduction of an OMe substituent on the salicylidene moiety was found to result in slightly diminished enantioselectivity.[40] This was explained by assuming that a metallaoxetane intermediate was involved in Mn^{III}-(salen) catalyzed epoxidation. The electronic nature of the substituents affects the reactivity of oxo species and, therefore, influences enantioselectivity in metallaoxetane formation. However, the cleavage of metallaoxetane ring is controlled by other factors such as steric effect and the ability of radical stabilization of olefinic substituent. Thus, the electronic effect of substituents does not necessarily correspond to the σ-values if the metallaoxetane intermediate is involved in Mn^{III}-(salen) catalyzed epoxidation.

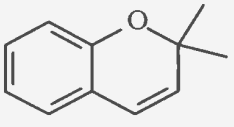
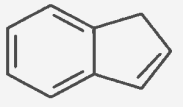
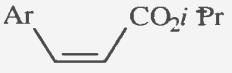
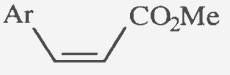
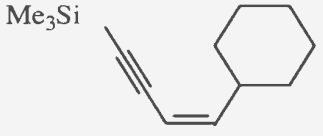
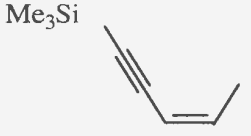
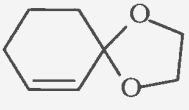
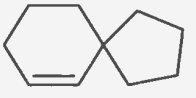
1.3.4 Asymmetric Epoxidation: Substrate Effect

Asymmetric induction by chiral Mn^{III}-(salen) complexes also depends on the olefin. Olefinic substrates that favour high enantioselectivity with Jacobsen-type catalysts generally have: 1) a conjugated double bond, 2) a *cis* geometry, 3) a bulky

substituent. Some typical examples of asymmetric epoxidation of unfunctionalized alkenes with Mn^{III}-(salen) complexes are shown in **Table 1-2**.

Cyclic and acyclic *cis*-disubstituted alkenes conjugated with an unsaturated double bond are generally very good substrates for Mn^{III}-(salen) catalyzed epoxidation. High enantioselectivities have been achieved in the epoxidation of 2,2-dialkylchromene

Table 1-2 Substrates Favouring High ee% in the Epoxidation with Jacobsen-type Catalyst

Alkene	ee%	Alkene	ee%
	97		88
	96		72 – 85
	93		78
	94		25

derivatives with all terminal oxidants.[41] Non-conjugated alkyl-substituted alkenes are generally observed to react slower than conjugated alkenes and give low yield and poor enantioselectivities. Jacobsen has explained the difference in reactivity and selectivity between conjugated alkenes and non-conjugated alkenes by assuming that different epoxidation mechanisms are involved.[42] Katsuki explained these results by considering both steric and electronic effects.[34]

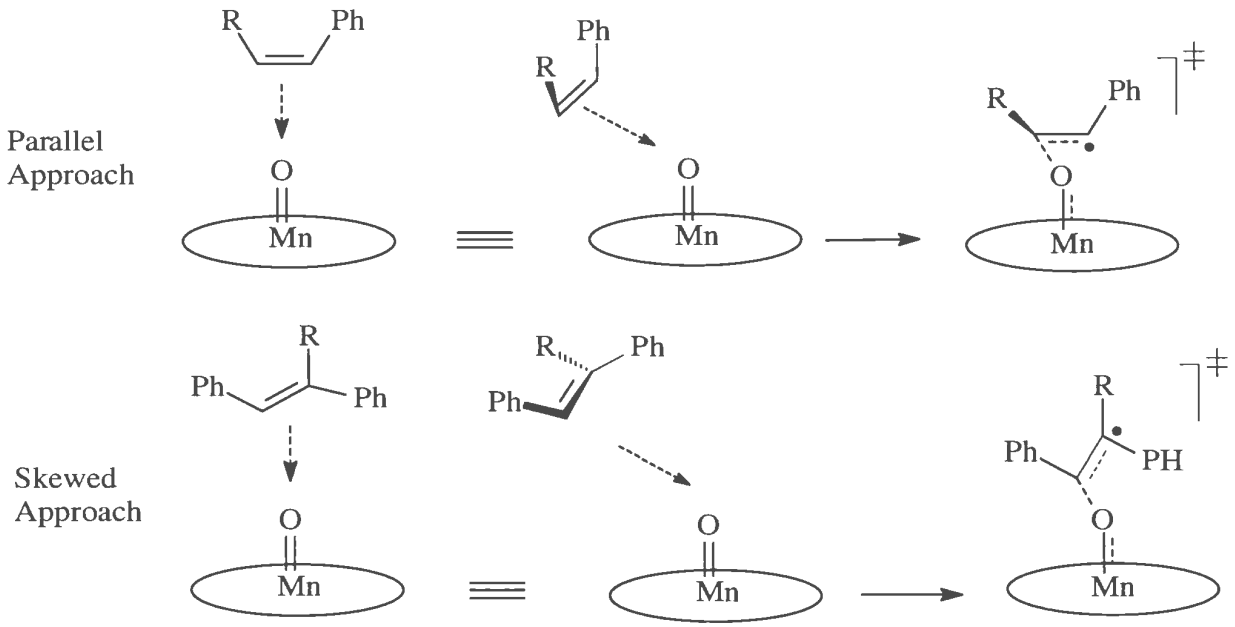
Non-conjugated alkenes are epoxidized with high stereoselectivity, while the epoxidation of conjugated alkenes affords a mixture of *cis*- and *trans*-epoxides.[42] Aryl-substituted alkenes give *cis*-epoxides as major products, while conjugated dienes and enynes afford *trans*-epoxides. These result have been explained by assuming that the reaction proceeds via a radical intermediate.[41] Moreover, Jacobsen et al. found that the epoxidation of *cis*-alkenes in the presence of a chiral quaternary salt provides *trans*-epoxides preferentially, but the mechanism for this effect is not clear.[43]

As expected on the basis of the side-on approach mechanism for chiral induction, the epoxidation of *trans*-disubstituted alkenes gives low to moderate enantioselectivity depending on the Mn^{III}-(salen) catalyst and reaction conditions.[41, 44]

The epoxidation of terminal alkenes, such as styrene, gives low enantioselectivity under the usual reaction conditions. This also was explained by a stepwise mechanism involving a radical intermediate. Jacobsen et al. solved this problem by using *m*-CPBA as oxidant in the presence of NMO as additive at low temperature (-78°C).[45]

Chiral Mn^{III}-(salen) complexes have been demonstrated to be highly enantioselective catalysts for the epoxidation of tri-substituted and tetra-substituted alkenes.[46] This is surprising because the tri-substituted and tetra-substituted alkenes should be poor substrates for epoxidation by oxo transfer catalysts based on the transition-state geometries involving side-on approach of olefin in either a parallel or a

skewed orientation relative to the ligand plane. Jacobsen et al. explained the high enantioselectivity for tri-substituted and tetra-substituted alkenes using a transition-state model for epoxidation which involved a skewed, side-on approach of olefins to an oxo-Mn^{V}-(salen) intermediate (**Scheme 1-18**).[47]



Scheme 1-18 Parallel and Skewed, Side-on Approach of Olefins to an oxo-Mn^{V}-(salen) Intermediate

1.3.5 Axial Ligand Effects

The importance of donor ligands was initially discovered by Kochi et al. in their mechanistic studies of the chromium-catalyzed epoxidation of olefins. The addition of donor ligands such as pyridine *N*-oxide led to a dramatic enhancement in the rate of epoxidation as well as an increased yield of epoxides, presumably by stabilizing oxo-metal intermediates *via* axial coordination. The X-ray diffraction study of a donor

adduct showed that the salen ligand was significantly "pulled back" by coordination with the axial ligand (**Scheme 1-19**).[20c] Katsuki et al. were the first to report the donor ligand effects in asymmetric epoxidation conducted with iodosylbenzene. They found that donor ligands such as 2-methylimidazole, pyridine *N*-oxide or lutidine *N*-oxide enhanced the enantioselectivity for the epoxidation of (*E*)-1-phenylpropene catalyzed by Mn^{III}-(salen) complexes. Katsuki et al. assumed that the effect of donor ligands arose from the conformational change of optically active oxo-M^{V}-(salen) complexes owing to the coordination of axial ligands.[33c,46]

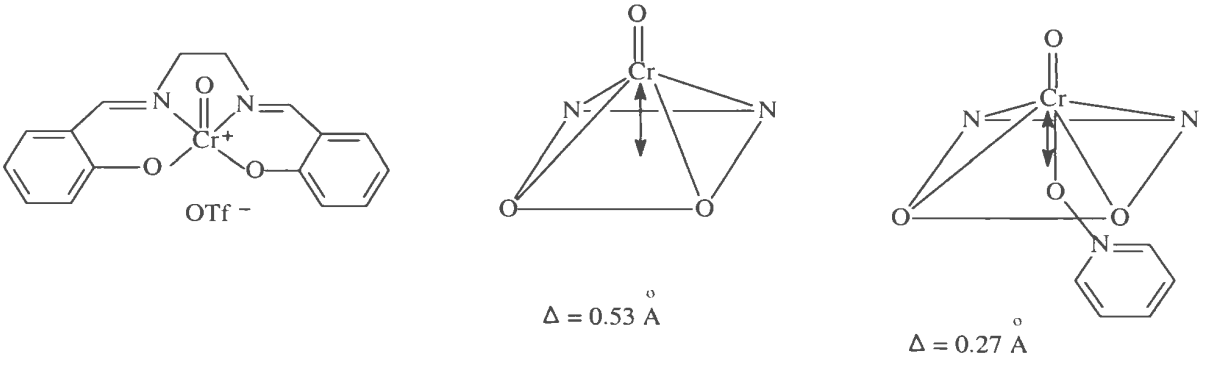


Figure 1-19 Effect of axial ligand on the structure of oxo-Cr^{V}-(salen) complexes

On the other hand, a reversed donor ligand effect was observed for the epoxidation of *trans*-stilbene,[33,46] namely, enantioselectivety is diminished when pyridine *N*-oxide is added to the reaction medium. The reason for this unexpected negative effect is unclear to date.

Jacobsen et al. reported that the addition of a catalytic amount of 4-phenylpyridine *N*-oxide had a slight, yet consistently beneficial effect on

enantioselectivity, reaction rate and product yield of the epoxidation with Mn(III)-based systems.[45,47] They proposed that *N*-oxide additives affect equilibrium in which the active oxo-Mn^{V}-(salen) couples with a Mn^{III}-(salen) complex to generate an inactive μ-oxo dimer. *N*-oxide additives were proposed to assist dissociation of unreactive μ-oxo dimer to form reactive oxo-Mn^{V}-(salen) complexes.[47] Evidence that *N*-oxide additives function as axial ligands has been provided by isolation and characterization of Mn^{III}-(salen) complex with a tethered *N*-oxide unit.[48] Hughes et al. showed in a comprehensive study that *N*-oxides also participate in transportation of the oxidant HOCl into the organic layer in biphasic bleach oxidants.[49]

There are also other possible modes of action for *N*-oxide additives. For example, *N*-oxide additives may increase the epoxide yield by lowering the Lewis acidity of Mn^{III}-(salen) complexes and by suppressing some unexpected reaction pathways or by decreasing the contribution of uncatalyzed epoxidation pathways.[45b, 50]

1.3.6 Mechanistic Implications

The high efficiency of Mn^{III}-(salen) catalyzed asymmetric epoxidation is widely acknowledged but the detailed mechanism of the epoxidation of olefins remains controversial.[48,49,50a,51] The mechanistic scheme adopted for oxygen transfer to alkenes by salen complexes is based on the isolation and characterization of the oxo-Cr^{V}-(salen) complex by Kochi et al. The isolated oxo-Cr^{V}-(salen) complex was shown to be capable of oxidizing alkenes under both stoichiometric and catalytic conditions.[19] This result is

in accordance with the properties and reactivity of an analogous oxo-Cr^{V}-porphyrin complex studied earlier by Groves and Kruper.[52] That metal-oxo species in the Mn^{III}-(salen) catalyzed epoxidation are active intermediates acting as a "staging post" for oxygen transfer is generally accepted.[53]

The existence of key intermediates in Mn^{III}-(salen) catalyzed epoxidation has recently been confirmed by MS/MS studies.[53] The most controversial mechanistic issue concerns the oxygen transfer from the putative oxo-Mn^{V}-(salen) to the olefin double bond. Three different mechanisms for oxygen transfer have been proposed (**Figure 1-20**): 1) concerted pathway A, 2) pathway B involving a radical intermediate, 3) pathway C involving manganaoxetane.

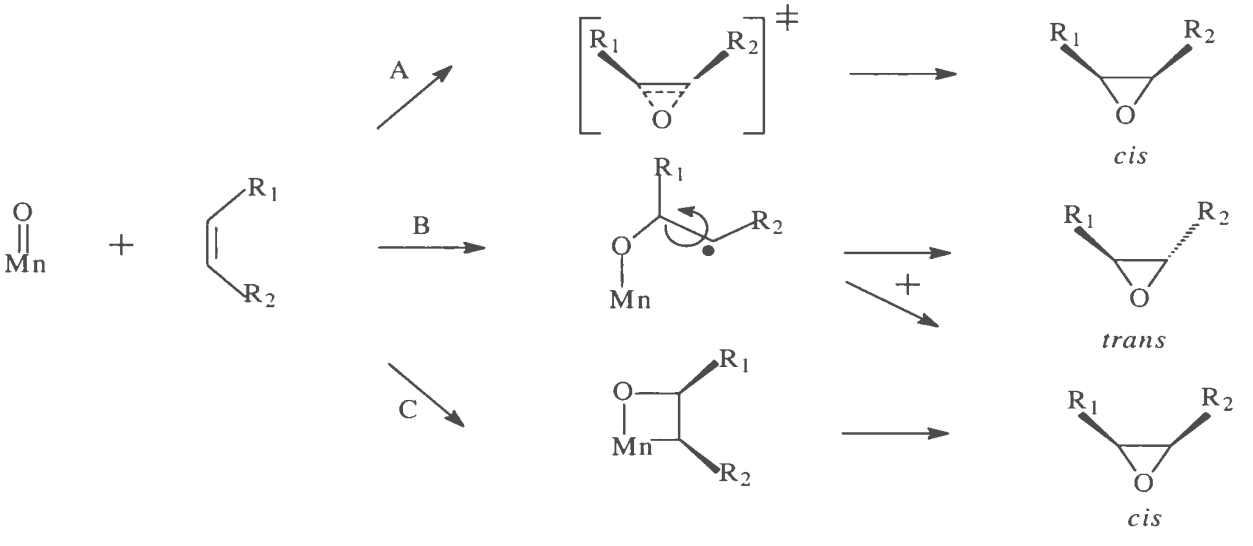


Figure 1-20 Different mechanisms for oxygen transfer

Alkyl-substituted *cis*-alkenes react stereospecifically to produce exclusively *cis*-epoxides. Therefore, epoxidation has been proposed to proceed by way of the concerted pathway A.[42,54] However, the epoxidation of conjugated *cis*-alkenes

produces a mixture of *cis*-epoxide and *trans*-epoxide with the extent of *trans*-epoxide depending on the nature of substrates. This lack of stereospecificity was interpreted by Jacobsen et al. by assuming pathway B involving a radical intermediate which allows the C-C bond rotation to give both *cis*- and *trans*-epoxides.[42,54] Katsuki et al.[50] independently proposed a manganaoxetane intermediate (pathway C) to rationalize the observed nonlinear Erying plots for relative rates of formation of the enantiomeric epoxides.[50a] However, if one compares experiments with results obtained for *cis*-β-methylstyrene under various reaction conditions, it becomes clear that stereoselectivity is strongly dependent on the oxidant, the catalyst and the additive. What is especially surprising is the high *trans* selectivity obtained when quaternary ammonium salts are added; a result difficult to bring into accordance with a radical intermediate.[55]

Mechanistic discussion relevant to Jacobsen-Katsuki epoxidation was reviewed by Norrby [51] based on calculations using MacroModel/MM3. Norrby's modelling work shows that the energy difference of diastereomeric manganaoxetanes predicts enantioselectivity. Results from experiments of Katsuki et al. supported the formation of manganaoxetanes, since a nonlinear relationship between enantioselectivity and temperature was found to be consistent with the presence of a reversible step in the reaction.[50a] However, Jacobsen observed a linear correlation between enantioselectivity and temperature over a wide temperature range and contested the existence of

manganaoxetanes as possible intermediates due to severe steric problems when *N*-oxide as axial ligand is coordinated to manganese.[48] Recently, Jacobsen and Cavallo examined the mechanism of Jacobsen-Katsuki epoxidation in a quantum chemical study based on density functional theory.[52e] The calculations were consistent with an epoxidation that occurs by direct attack of the olefin at the oxo-Mn^{V}-(salen) complex and that is likely to involve radical intermediates. The relative stability of the radical intermediates and the relative height of the activation barriers for collapse and rotation determine the amount of *cis-trans* isomerization in the final epoxidation product. Oxametallacycle formation via pathway C was excluded for energy reasons and the formation of a manganaoxetane was disfavoured compared to the radical route, even if a free coordination site is available.[56]

Among the factors that influence the diastereoselectivity in the epoxidation of *cis*-stilbene, it was recently shown that ligation of the counterion in Mn(salen)X plays an important role.[57] That the oxygen source may affect the selectivity of metal-catalyzed oxidation has been demonstrated by Nam and co-workers.[58] If the oxo-Mn^{V}-(salen) complex were the only oxidant in this epoxidation, the *cis/trans* selectivity should be the same, irrespective of which oxygen source is used to produce the reagent. Yet this is not the case. Aside from some qualitative similarity, each oxygen donor displays a distinct *cis/trans*-epoxide ratio.[59] Roschmann et al. proposed that the Jacobsen-Katsuki epoxidation cycle must be extended to accommodate a divergent mechanism A and B

(**Figure 1-21**). After ligation between Mn^{III}-(salen) catalyst and oxygen donor to give the Mn^{III}(OLG) adduct, the oxo-Mn(V) oxidant is released by splitting off the leaving group LG. Subsequent unselective epoxidation of olefins affords a mixture of *cis* and *trans*-epoxides. Alternatively, the ligand adduct Mn^{III}(OLG) functions directly as Lewis-acid-activated epoxidant by concerted oxygen transfer to give the *cis*-epoxide.[60] The latter alternative has been suggested for Mn(salen)- and Fe(porph)-catalyzed epoxidation with *m*-CPBA as oxygen donor. [61]

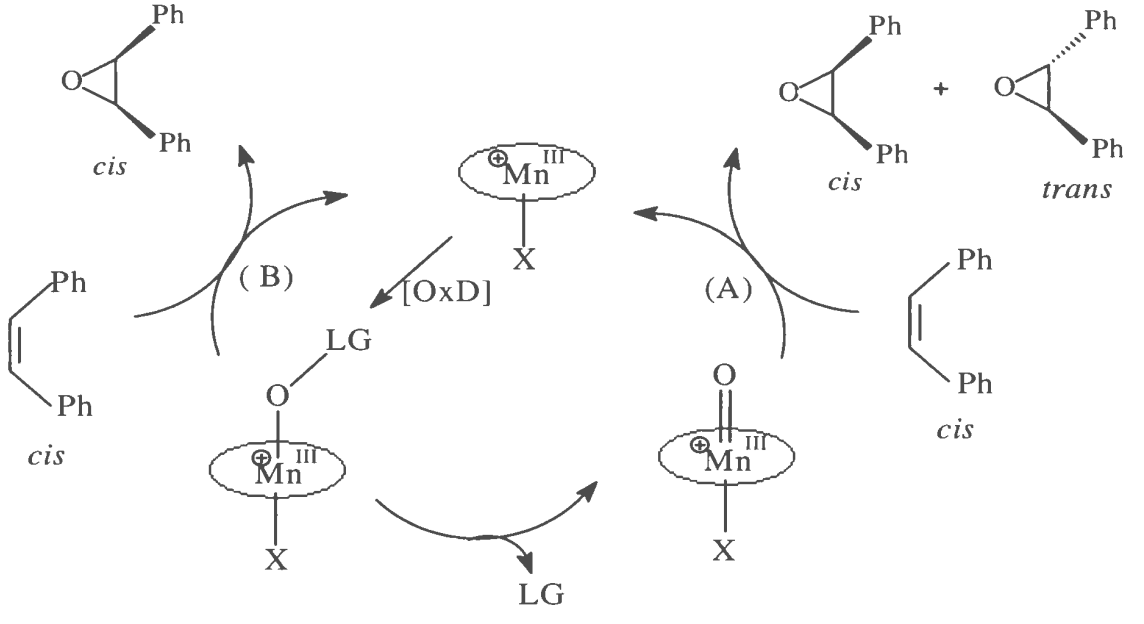


Figure 1-21 Roschmann proposed mechanism A and B for oxygen transfer

In summary, mechanistic discussion remains open and there is need for further studies to discern a clear understanding of the mechanism of asymmetric epoxidation. For instance, the formation of isomerized stilbene oxide with different *cis/trans* ratios by using different oxidants provided evidence that the presence of reactive species other than

oxo-Mn(V) species cannot be ruled out. Relatively, Groves and Stern have shown that an oxo-Mn(IV) species can be formed along with the normal oxo-Mn(V) species in the epoxidation of olefins catalyzed by Mn(III)-porphyrin complex.[62] The existence and the role of oxo-Mn(IV) species have been reported recently.[63]

1.3.7 The Development of Chiral Mn^{III}-(salen) Catalyst: "Calixsalen" Epoxidation Catalyst

Enzymes represent the highest expression of chemical catalysis, typically displaying excellent stability, high selectivity with respect to both the substrates used and the products produced. This is accomplished by deploying intermolecular forces to direct the captured substrates very precisely along a reaction pathway towards the transition state and beyond. Therefore, they are a key source of inspiration for designing catalysts. Most enzymes are comprised of a highly potent catalytic centre and a surrounding protein superstructure, which usually presents a "pocket", such as concavity, groove, or depression. In contrast to many or most man-made catalysts, naturally occurring enzymes tend to rely upon the superstructure, rather than the catalytic site itself, to achieve substrate selectivity. The superstructure serves to isolate the catalytic centre from other reactive centres, thereby enhancing the catalytic centres stability and extending its functional lifetime. The great majority of biomimetic synthetic receptors have used macrocyclic rings to enforce the formation of a concave surface. Based on the activity and selectivity of Mn^{III}-(salen) complexes, the work in this lab has developed

new macrocyclic "calixsalen" ligands in an attempted to incorporate Mn^{III}-(salen) units into a host structure with a deep chiral pocket that will bind small organic molecules (**Figure 1-22**). The rigid chiral pocket is maintained by conformational constraints intrinsic to the architecture of these synthetic receptors, thereby precisely directing the incoming substrates to enhance selectivity.

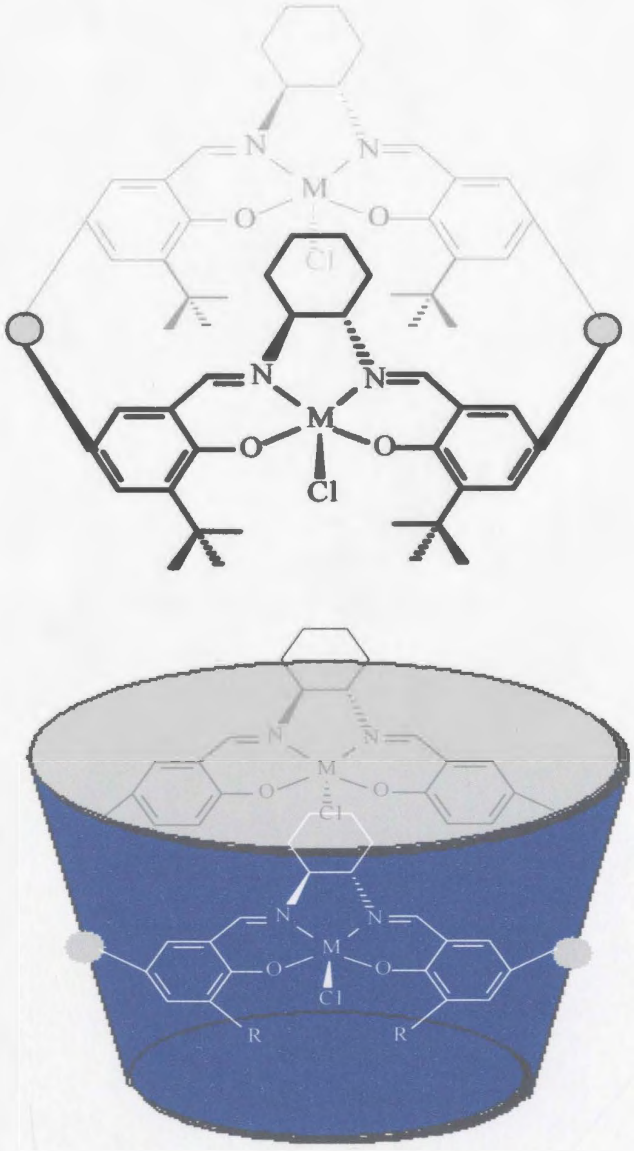


Figure 1-22 Macrocyclic Mn^{III}-(calixsalen) catalyst with chiral cavity

References:

1. (a) Henbest, H. B. *Chem. Soc. Spec. Publ.* **1965**, *19*, 83. (b) Ewins, R. C.; Henbest, H. B.; Mckervey, M. A. *J. Chem. Soc. Chem.Commun.* **1967**, 1085.
2. Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974.
3. Schneider H. J. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1417.
4. (a) Sato, R.; Omura, T. *Cytochrome P-450*, Kodansha Ltd., Tokyo, **1978**. (b) Dawson, D. H.; Sono, M.; *Chem. Rev.* **1987**, *87*, 1255. (c) Gunter, M. J.; Turner, P. *Coord. Chem. Rev.* **1991**, *108*, 115. (d) *Cytochrome P-450, Structure, Mechanism and Biochemistry,* ed. P. R. Ortiz de Montellano, Plenum Press, New York, **1995**.
5. (a) Coon, M. J.; Vermilion, J. L.; Vatsis, K. P.; French, J. S.; Dean, W. L.; Haugen, A. *ACS Symp. Ser.* **1977**, *44,* 46. (b) Peterson, J. A.; Ishimura, Y.; Baron, J.; Estabrook, R. W. *"Oxidases and Related Redox Systems"* University Park Press, Baltimore, **1973**, 565. (c) Pryor, W. A. "*Free Radicals in Biology*" , W A. Pryor, Ed., Academic Press, New York, **1976**, 1. (d) Groves, J. T.; McClusky, G. A.; White, R. E.; Coon, M. J. *Biochem. Biophys. Res. Commun.* **1978**, *81*, 154.
6. Groves, J. T.; Haushaalter, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1981**, 103, 2884.
7. (a) Mansuy, D.; Battioni, P.; Renaud, J. P.; Guerin, P. *J. Chem. Soc. Chem. Commun.* **1985**, 155. (b) Groves, J. T.; Viski, P. *J. Org. Chem.* **1990**, *55*, 3628. (c) Halterman, R. L.; Jan, S. T. *J. Org. Chem.* **1991**, *56*, 5253. (d) Naruta, Y,; Tani, F.; Maruyama, K.

Chem. Lett. **1989**, 1269. (e) Naruta, Y,; Tani, F.; Ishihara, N.; Maruyama, K. *J. Am. Chem. Soc.* **1991**, *113*, 6865. (f) Berkessel, A.; Frauenkron, M, *J. Chem. Soc. Perkin Trans.* **1997**, *1*, 2265. (g) Groves, J. T.; Haushaller, R. C.; Nakamura, M.; Nemo, T. E.; Evans, B. J. *J. Am. Chem. Soc.* **1988**, *103*, 2884.

8. (a) Groves, J. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 5786. (b) Groves, J. T.; Myers, R. S. *J. Am. Chem. Soc.* **1983**, *105*, 5791.
9. Groves, J. T.; Kruper, W. J. *J. Am. Chem. Soc.* **1979**, 101, 7613.
10. (a) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (b) Groves, J. T.; Kruper, W. J.; Nemo, T. E.; Myers, R. S. *J. Mol. Catal.* **1980**, *7*, 169.
11. (a) Ortize de Montellano, P. R.; Kunze, K. L.; Belian, H. S. *J. Biol. Chem.* **1983**, *258*, 45. (b) Kunze, K. L.; Mangold, B. L. K.; Wheeler, C.; Belian, H. S. *J. Biol. Chem.* **1983**, *258*, 4202.
12. Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1992**, *114*, 1313.
13. Collman, J. P.; Kellen-Yuen, C. J.; Zhang, X.; Ibers, J. A.; Brauman, J. I. *J. Am. Chem. Soc.* **1995**, *117*, 692.
14. Feiters, M. C.; Rowan, A. E.; Nolte R. J. *Chem. Soc. Rev.* **2000**, *29*, 375.
15. Sorokin, A. B.; Khenkin, A. M.; Marakushev, S. A.; Shilov, A. E.; Shteinman, A. A. *Dokl. Phys. Chem. (Engl. Trans.)* **1984**, *29*, 1102.
16. Groves, J. T.; Neuman, R. *J. Am. Chem. Soc.* **1987**, *109*, 5045; Groves, J. T.; Neuman,

R. *J. Am. Chem. Soc.* **1989**, *111*, 2900.

17. Esch, J. V.; Roks, M. F. M.; Nolte, R. J. M. *J. Am. Chem. Soc.* **1986**, *108*, 6093.

18. (a) Jiang, D. L.; Aida, T. *Chem. Commun.* **1996**, 1523. (b) Aida, T.; *J. Am. Chem. Soc.* **1998**, *120*, 10895. (c) Collman, J. P.; Fu, L.; Zingg, A.; Diederich, F. *Chem. Commun.* **1997**, 193.

19. (a) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606. (b) Nakajima, K.; Kojima, M.; Fujita, J. *Chem. Lett.* **1986**, 1483. (c) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

20. (a) Sidall, T. L.; Miyaura, N.; Huffman, J. C.; Kochi, J. K. *J.Chem. Soc.Chem. Commun.* **1983**, 1185. (b) Srinivasan, K.; Kochi, J. K. *Inorg. Chem.* **1985**, *24*, 4671. (c) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606. (d) Srinivasan, K.; Michaud. P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

21. Srinivasan, K.; Michaud. P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

22. (a) Zhang, W.; Loebach, J, L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Irie, R.; Noda, K.; Ito, Y,; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.

23. (a) Katsuki, T. Coord. *Chem. Rev.* **1995,** *114*, 189. (b) Katsuki, T. *J. Mol. Catal. A: Chem.* **1996**, *113*, 87. (c) Ito, Y. N.; , K. *Bull. Chem. Int. Ed. Engl.* **1997**, *36*, 2060.

24. (a) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2291. (b) Jacobsen, E. N.; Zhang, w.; Muci, A. R.; Ecker, J. R.; Deng. L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.

25. Jacobsen, E. N. *In Comprehensive Organomettalic Chemistry II,* Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; Eds.; New York, 1995, Vol. 12, Chapter 11.1.

26. Jacobsen, E. N.; Zhang, W.; Muci, L. C.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113,* 7063.

27. Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113,* 2296.

28. (a) Zhang, W.; Loebach, J, L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.

29. Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.

30. (a) Hosoya, N.; Irie, R.; Katsuki, T. *Synlett.* **1993**, 261. (b) Hosoya, N.; Hatakeyama, A.; Yanai, K.; Fujii, H.; Irie, R.; Katsuki, T. *Synlett.* **1993**, 641.

31. (a) Zhang, W.; Loebach, J, L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Pospisil. P. J.; Carsten, D. H.; Jacobsen E. N.; *Chem. Eur. J.* **1996**, *2*, 974. (c) Finney, N. S.; Pospisil. P. J.; Chan, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen E. N.; *Angew. Chem. Int. Ed.* **1997**, *36*, 1720.

32. Lee, N. H.; Jacobsen E. N. *Tetrahedron Lett.* **1991**, *32*, 6533.

33. O' Connor, K. J.; Wey, S. J.; Burrows, C. J.; *Tetrahedron Lett.* **1992**, *33*, 1001. (b) Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* **1991**, *32*, 1055. (c) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Asymmetry* **1991**, *2*, 481.

34. Hamada, T.; Irie, R.; Katsuki, T. *Synlett.* **1994**, 479.

35. (a) Hashihayata, T.; Irie, R.; Katsuki, T. *Synlett.* **1996**, 1079. (b) Hashihayata, T.; Irie, R.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541. (c) Miura, K.; Katsuki, T. *Synlett.* **1999**, 783.

36. Katsuki, T. *Adv. Synth. Catal.* **2002**, *344*, 131.

37. (a) Irie, Y. N.; Hashihayama, T.; Katsuki, T.; Akita, M.; Moro-oka, Y. Chem Lett. 1998, 1041. (b) Punnuyamurhty, T.; Irie, Y. N.; Katsuki, T.; Akita, M.; Moro-oka, Y. *Synlett.* **1999**, 1049.

38. (a) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606. (b) Srinivasan, K.; Michaud. P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

39. (a) Jacobsen, E. N.; Zhang, W.; Güler, M. L, *J. Am. Chem. Soc.* **1991**, *113*, 6703. (b) Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güller, M. L.; Ishida, T.; Jacobsen, E. N.; *J. Am. Chem. Soc.* **1998**, *120*, 948.

40. Hamada, T.; Fukuda, T.; Imanishi, H.; , K. *Tetrahedron Lett.* **1996**, *52*, 515.

41. Lee, N. H.; Muci, A. R.; Jacobsen, E. N. *Tetrahedron Lett.* **1991**, *32*, 5055.

42. (a) Jacobsen, E. N. *Catalytic Asymmetric synthesis*, Ojima, I., Ed.; VCH: New York, **1993**, Chapter 4.2. (b) Jacobsen, E. N. *Comprehensive Organometallic Chemistry II,* Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; Eds. Pergamon: New York, **1995**, Vol. 12, Chapter 11.1.

43. (a) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937. (b) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669.

44. Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189.

45. (a) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457. (b) Palucki, M.; Palucki, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.

46. Irie, R.; Yoshio, R.; Katsuki, T. *Synlett.* **1991**, 265.

47. Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323.

48. Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Ind. Ed. Engl.* **1997**, *36*, 1720.

49. Hughes, D. L.; Smith, G. B.; Liu, J.; Dexeny, G. C.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2222.

50. (a) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515. (b) Janssen, K. B. M.; Parton, R. F.; Jacob, P. A. *Tetrahedron Asymmetry* **1997**, *8*, 3039.

51. (a) Linker, T. *Angew. Chem. Ind. Ed. Engl.* **1997**, *36*, 2060. (b) Norrby, P.-O.; Linde, C.; Åkermark, B. *J. Am. Chem. Soc.* **1995**, *117*, 11035. (c) Linde, C.; Arnold, M.; Norrby, P.-O.; Åkermark, B. *Angew. Chem. Ind. Ed. Engl.* **1997**, *36*, 1723. (d) Jacobsen, H.; Cavallo, L. *Chem. Eur. J.* **2001**, *7*, 800. (e) Jacobsen, H.; Cavallo, L. *Eur. J.* Inorg. *Chem.***2003**, 892. (f) Linde, C.; Nordine, K.; Norrby, P.-O.; Norrby, P.-O.; *Chem. Eur. J.* **2002**, *8*, 2568. (g) Cavallo, L. ; Jacobsen, H. *Angew. Chem. Ind. Ed. Engl.* **2000**, *39*, 589. (h) Feichtinger, J. D.; Plattner, D. A. *Chem. Eur. J.* **2001**, *3*, 591.

52. Groves, J. T.; Kruper, W. J. *J. Am. Chem. Soc.* **1979**, *101*, 7613.

53. (a) Feichtinger, J. D.; Plattner, D. A. *Angew. Chem. Ind. Ed. Engl.* **1997**, *36*, 1718. (b) Feichtinger, J. D.; Plattner, D. A. *J. Chem. Soc. Perkin Trans.* **2000**, *2*, 1023.

54. Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 6497,

55. Linker, T. *Angew. Chem. Ind. Ed. Engl.* **1997**, *36*, 2060.

56. (a) Cavallo, L.; Jacobsen, H. *Angew. Chem. Ind. Ed. Engl.* **2000**, *39*, 589. (b) Linde, C.; Åkermark, B.; Norrby, P.-O.; Svensson, M. *J. Am. Chem. Soc.* **1999**, *121,* 5083.

57. Adam, W.; Roschmann, K. J.; Saha-Moller, C. R. *Eur. J. Org. Chem.* **2000**, 3519.

58. (a) Nam, W.; Lim, M. H.; Lee; J. H.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122,* 6641. (b) Nam, W.; Han, H. J.; Oh, S.-Y.; Lee, Y. J.; Choi, M.-H.; Han, S. Y.; Kim, C.; Woo, S. K.; Shin, W. *J. Am. Chem. Soc.* **2000**, *122,* 8677. (c) Nam, W.; Lim, M. H.; Moon, S. K.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122,* 10805. (d) Nam, W.; Lim, M. H.; Oh, S.-Y.; Lee; J. H.; Woo, S. K.; Kim, C., Shin, W. *Angew. Chem. Ind. Ed. Engl.* **2000**, *39*, 3646.

59. Ferrer, M.; Gibert, M.; Sánchez-Baeza, F.; Messaguer, A. *Tetrahedron Lett.* **1996**, *37*, 3585.

60. Adam, M.; Roschmann, K. J.; Saha-Möller, C. R.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068.

61. (a) Bryliakov, K. P.; Babushkin, D. E.; Talsi, E. P. *J. Mol. Catal. A* **2000**, *158*, 19. (b) Toy, P. H.; Newcomb, M.; Coon, M. J. Vaz, A. D. N. *J. Am. Chem. Soc.* **1998**, *120,*

9718.

62. Groves, J. T.; Stern, M. K.; *J. Am. Chem. Soc.* **1987**, *109*, 3812.

63. (a) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937. (b) Adam, W.; Mock-Knoblauch, C.; Saha-Möller, C.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122*, 9685.

Chapter 2. Synthesis and Characterization of Calixsalen Epoxidation Catalysts

2.1 Introduction and Research Objective

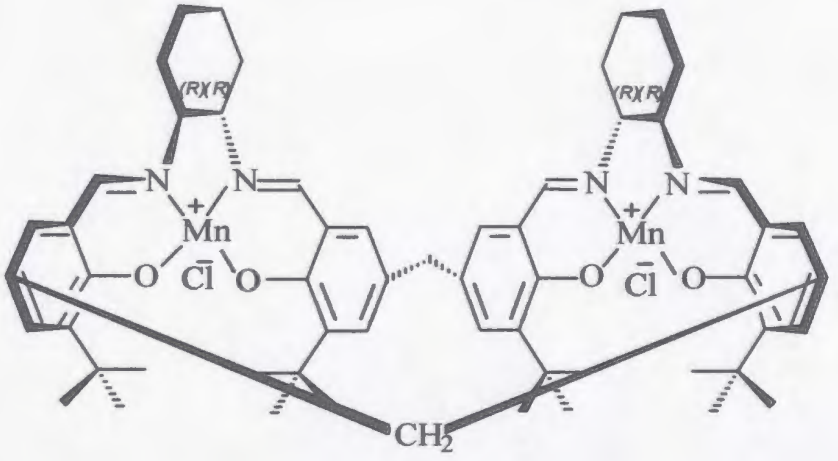
As demonstrated by enzymes and other asymmetric catalytic systems, selectivities and efficiencies are critically dependent on the 3-dimensional structure of catalysts. Especially for unfunctionalized olefins, effective chiral communication and hence the extent of stereochemical control depends exclusively on a balance of a large number of relatively weak intermolecular forces to direct the captured substrates very precisely along a reaction pathway towards the transition state and to products.[1] Therefore, the crux of the design and synthesis of asymmetric metal-based coordination complexes as catalysts is focused on the ligand. As described in Chapter 1, the greatest difficulty in the selective epoxidation of unfunctionalized alkenes is the control of the olefin approach to active oxidant.

The most successful approach to achieve high stereoselectivity in asymmetric epoxidation of unfunctionalized alkenes has involved a biomimetic strategy, utilizing chiral porphyrin- and salen-based transition metal complexes as catalysts.[2] Metalloporphyrin epoxidation catalysts were initially developed as part of efforts to mimic the reactivity of biologically interesting metalloporphyrin-contained enzymes such as cytochrome P-450.[3] Both classes of complexes are kinetically inert and sterically well defined with square-planar metal coordination, and therefore provide a feasible strategy for ligand design. In 1993, Jacobsen and Katsuki independently developed effective Mn^{III}-(salen) based catalysts for the asymmetric epoxidation of unfunctionalized

alkenes.[4] Since then, Mn^{III}-(salen) catalyzed asymmetric epoxidation has been thoroughly reviewed.[5] Most reviews have widely described the essentials of Mn^{III}-(salen) catalysts, such as the design of the salen ligand and the steric as well as electronic effect of catalysts.[6] Some literature has reported on suitable stoichiometric oxidants and additives for asymmetric epoxidation.[7] However, regarding the more sophisticated substrate/catalyst recognition mechanism, it is necessary that appropriate functional groups are present in a special 3-dimentional arrangement that is complementary to binding sites in guest molecules (i.e. shape-based recognition).

Supramolecular chemistry offers the prospect that bimolecular reactions of guests can be efficiently accelerated or catalyzed within the well-defined host cavity of macrocycles such as cyclodextrins, crown ethers and calixarenes.[8] Macrocyclic hosts can induce conformational constraints in the guest and thus possibly reduce the number of diastereoisomeric transition states during the reaction course.[9] For example, the Mn^{III}-(calixsalen) complexes[11] of this study are basket-shaped macrocyclic hosts which have a cavity to accommodate an incoming guest. Calixsalen complexes represent an interesting subcategory of macrocycles since they possess unbridged binuclear coordinated sites in which two metal sites can cooperatively direct a substrate within the cavity and then induce a reaction on a functional group of the guest.[10] Chiral macrocycles with a cavity proximal to chiral centres are of particular interest because they are excellent metalloprotein mimics. By analogy to the protein superstructure employed by iron heme in active cytochrome, the research in this lab encapsulates active centres in a supramolecular cavity to impart both conformational stability and reaction selectivity. The objective of this research is to design and test new chiral macrocyclic

catalysts for enantioselective epoxidation with the general structure as shown in **Figure 2-1**.



Mn^{III}-(calix[2]salen) Catalysts

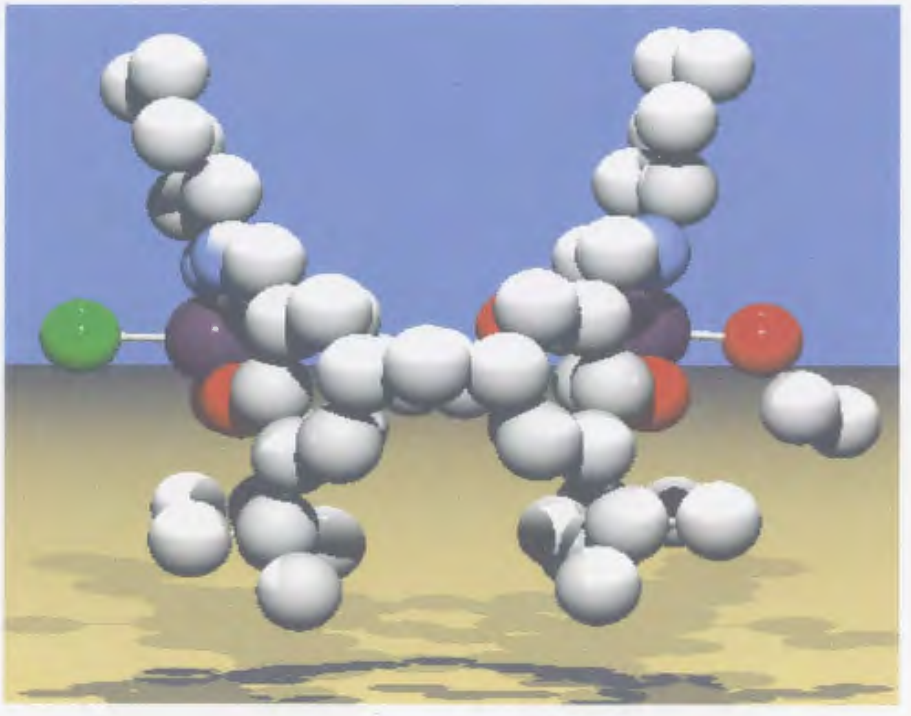
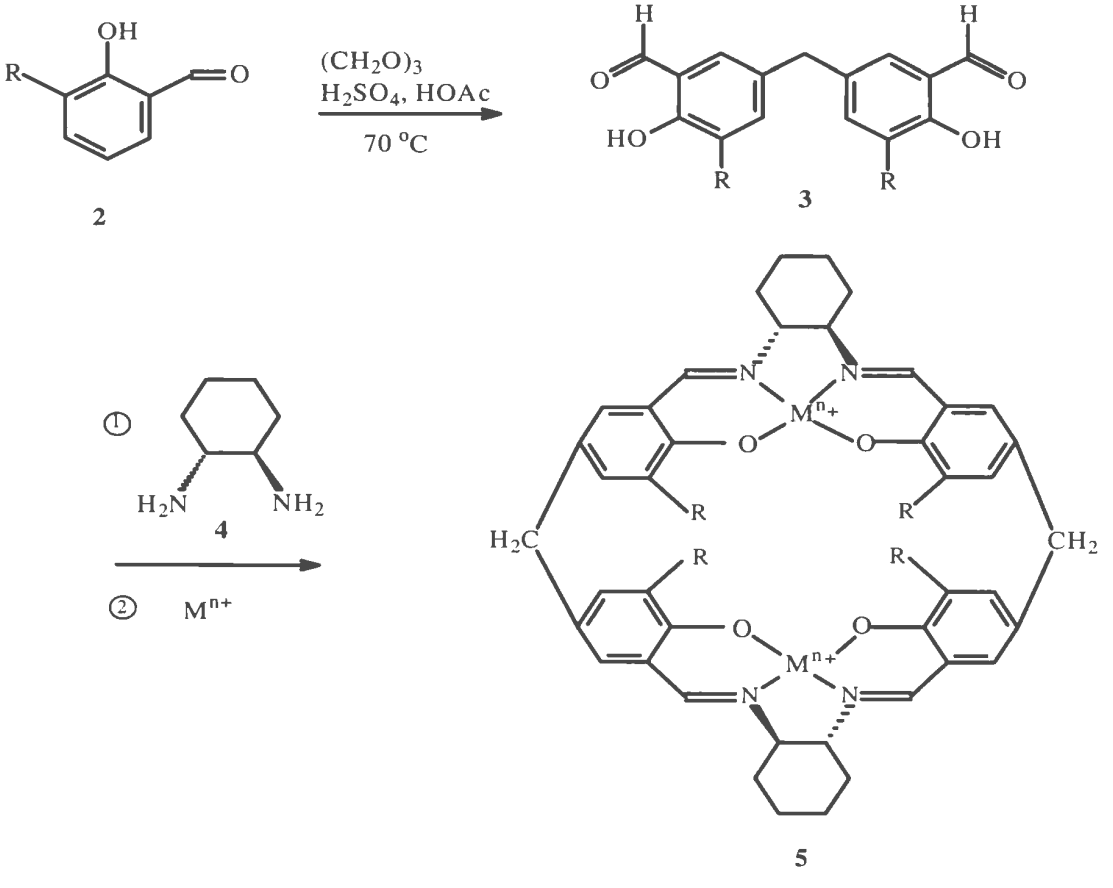


Figure 2-1 3D structure for Mn^{III}-(calix[2]salen) catalysts

The first novel "calix[2]salen" macrocyclic Schiff-base ligand was synthesized in this laboratory in the late 1990's.[11] Since then, a number of M-(calix[2]salen) complexes have been isolated and characterized. Initial catalysis trials indicated that the manganese complexes are promising enantioselective alkene epoxidation catalysts.[11] The research described in this thesis aims to: i) **improve** the reproducibility, scale-up and overall yield of calixsalen ligands; ii) **study** the conformation of these calix[2]salen ligands; iii) **identify** Mn^{III}-(calix[3]salen) and Mn^{III}-(calix[4]salen) complexes; and iv) **optimize** conditions for maximum enantioselectivity in the epoxidation of prochiral, unfunctionalized alkenes. The ligand syntheses as shown in **Scheme 2-1** follow the initial approach developed in this laboratory.[11]



Scheme 2-1 General procedure for synthesis of Mn^{III}-(calixsalen) catalysts

2.2 Improvement on Calix[2]salen, Synthesis and Characterization of Calix[n]salens (n=3,4,5)

The synthesis of calix[2]salen by template-induced cyclization has been reported,[11] but the chemical yield is rather low (11%). The research in this thesis modified the procedure to maximize the chemical yield, and identified two different calix[2]salen conformations as well as their interconversion. Also, a high dilution procedure was employed to increase the ratio of calix[n]salens (n=3,4) to calix[2]salen and characterize the calix[n]salens (n=3,4).

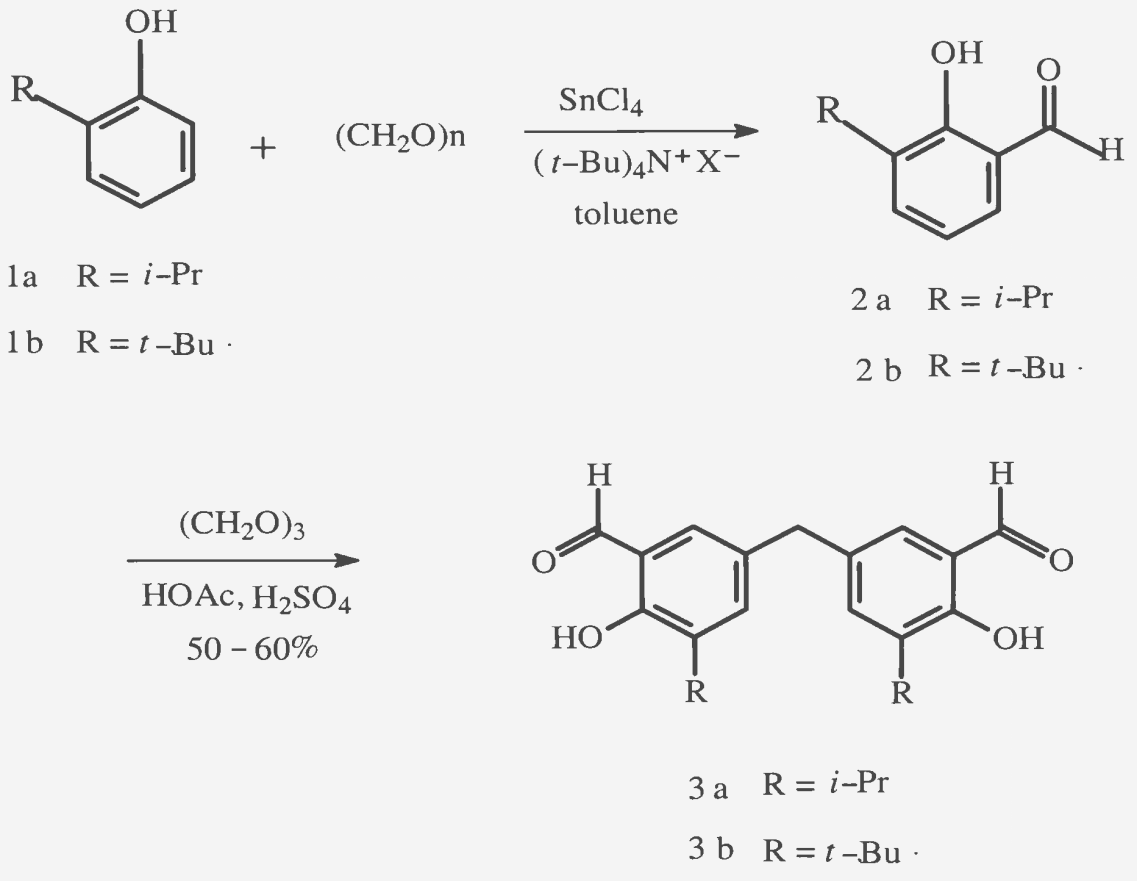
2.2.1 Preparation of *trans*-1, 2-Diaminocyclohexane

Trans-1,2-diaminocyclohexane was prepared from a commercial diastereomerically pure tartrate salt according to the modified procedure developed by Whitney.[12] Aqueous potassium hydroxide was added to *trans-(1R,2R) or (1S,2S)*-diaminocyclohexane tartrate, received as a gift from SepraChem Inc. but available from Aldrich, to release *trans*-1,2-diaminocyclohexane. Diaminocyclohexane was extracted with ether, dried with metallic sodium sulfate, and then sodium metal. The dried ether extract was filtered under N_2 (g) and dried under oil vacuum pump, leaving a white solid crystalline product in 75% yield. The ^{1}H-NMR spectrum was consistent with that of an authentic sample. The enantiomeric purity was 99.9% determined by analysis of chiral HPLC with an (*S, S*)-Whelk-O 1 column (25cm × 0.46 cm).

2.2.2 Synthesis of 5, 5`-Methylene-bis-salicylaldehyde

The synthesis of 5,5`-methylene-bis-salicylaldehyde has been previously

reported[11] (**Scheme 2-2**).



Scheme 2-2 Synthesis of 5, 5`-methylene-bis-salicylaldehyde

2.2.3 Synthesis of Macrocyclic Calixsalens

2.2.3.1 Template-directed Schiff-base Macrocyclization

The templated Schiff-base condensation of *(R, R)*- or *(S, S)*-cyclohexane-1,2-diamine and an appropriate dialdehyde in the presence of Ba^{II} has been reported [11, 13] as shown in **Scheme 2-3**. The research in this thesis improved the yield of calix[2]salen from 11% to about 30% - 40%, identified two different calix[2]salen conformations and their interconversion, and proved that calix[3]salen, calix[4]salen and calix[5]salen were

formed but could not be separated. The ^{1}H-NMR spectrum of the crude product mixture from the condensation of **3** and **4** showed that more than three major cyclic Schiff-base products with Schiff-base peaks at 8.09 ppm, 8.21 ppm and 8.39 ppm formed with no acyclic product or leftover reactants. Separation of the crude reaction mixture by column chromatography (silica or basic alumina) afforded several products that showed similar ^{1}H-NMR spectra (**Figure 2-2**) and ^{13}C-NMR spectra (**Figure 2-3**). MALDI-TOF mass spectra of these cyclic products are shown in **Figure 2-4** and **2-5**. The most mobile product on the silica column, **5b**, gave a Schiff-base peak at 8.08 ppm in the ^{1}H-NMR spectrum. The MALDI-TOF/MS of **5b** showed a peak at *m/z* 893.57, which was consistent with the calculated mass for a **2+2** dimer. Crystals of dimer **5b** with suitable quality for X-ray analysis have not been obtained to confirm the ligand conformation. Based on the structure of a single crystal complex made from dimer **5b**, it is suggested that dimer **5b** has a "*syn*" structure as shown in **Figure 2-9**.

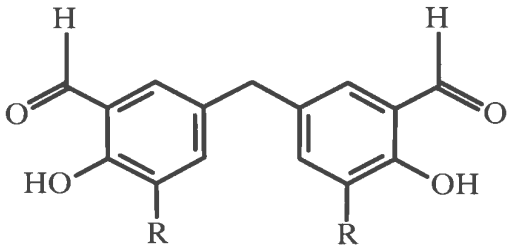
The product mixture obtained from the second eluted fraction gave one unique Schiff-base peak at 8.21 ppm in the ^{1}H-NMR spectrum. The MALDI-TOF/MS had five successive evenly-spaced peaks at *m/z* 893.57, 1339.65, 1786.65, 2233.69 consistent with the calculated masses for the cyclized dimer **6**, trimer **7**, tetramer **8**, pentamer **9** (up to nonamer). The dimer was the major product and the amounts decreased with increasing ring size such that the pentamer and higher mass products were of insignificant yield (<5%). Subsequent complexation of this n-mer product mixture with Mn(III) acetate gave relatively stable complexes which could be separated by column chromatography over silica with 15% ethanol in dichloromethane elution. To this date, crystals of dimer **6** with suitable quality for X-ray analysis have not been obtained to confirm the ligand

conformation.

It was found that the chloroform soluble dimer **6** (which gave a different ^{1}H-NMR spectrum from dimer **5b**) could be extracted from the product mixture. The MALDI-TOF/MS of **6** shows a mass peak at *m/z* 893.57 as shown in **Figure 2-6** and was presumed to be isomeric with **5b**. Spectroscopic study shows that **6** is not stable and converts into dimer **5b** in solution over a period of several days. This was established conclusively by the observation that a $CDCl_3$ solution of pure **6** (with Schiff-base peak at 8.21 ppm) converted after 2 weeks in solution at room temperature to a mixture of the two different calix[2]salen isomers **5b** and **6** (with both Schiff-base peaks at 8.08 ppm and 8.21 ppm) in a ratio of **5b/6** = 1.72/1.00 as shown in **Figure 2-7**. Dimer **6** is suggested to have the *"anti"* structure as shown in **Figure 2-9**.

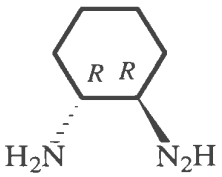
It was found that the cyclic ligands other than dimer cannot be easily separated by chromatography because they have the same R_f value on TLC and undergo facile Schiff-base hydrolysis as shown by the appearance of dialdehyde peak at 7.37 ppm in the ^{1}H-NMR spectrum of the eluent during chromatography.

It is noteworthy that one major product with Schiff-base chemical shift 8.39 ppm in ^{1}H-NMR spectrum was unstable both in solution and in the solid state. Over a period of days, it converted to both dimer products **5b** and **6** at room temperature as shown in **Figure 2-8**. This product was too unstable to isolate such that it was not characterized.



3a R = *i* – Pr
3b R = *t* – Bu

+



4

$Ba(ClO_4)_2$ or $Ba(SCN)_2$
THF/MeOH

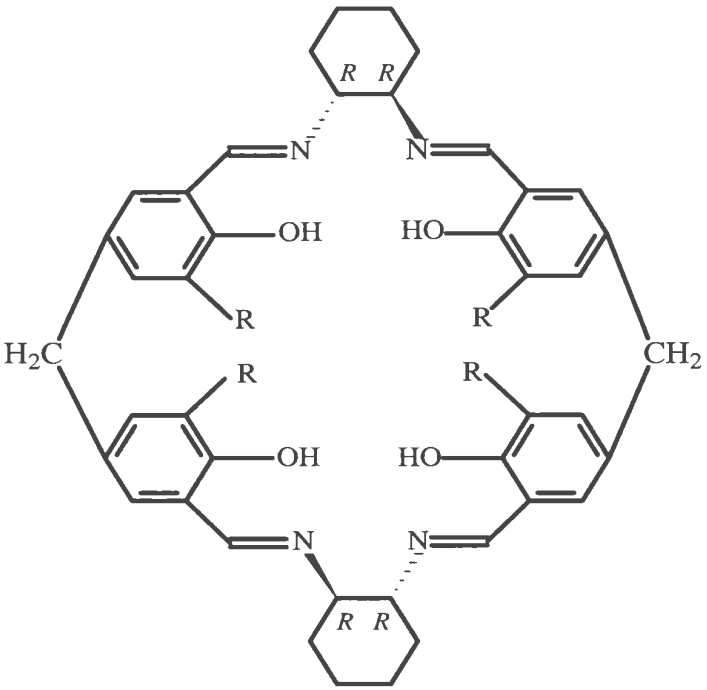
syn – dimer : 30–40 %

anti – dimer, trimer etc. } 30–40 %

high dilution
THF/MeOH

syn – dimer : 25–30 %

anti – dimer, trimer etc. } 40–45%



5a R = *i* – Pr
syn –**5b** R = *t* – Bu

anti – dimer + trimer + tetramer + pentamer

6 **7** **8** **9**

Scheme 2-3 Synthesis of chiral macrocyclic calixsalens

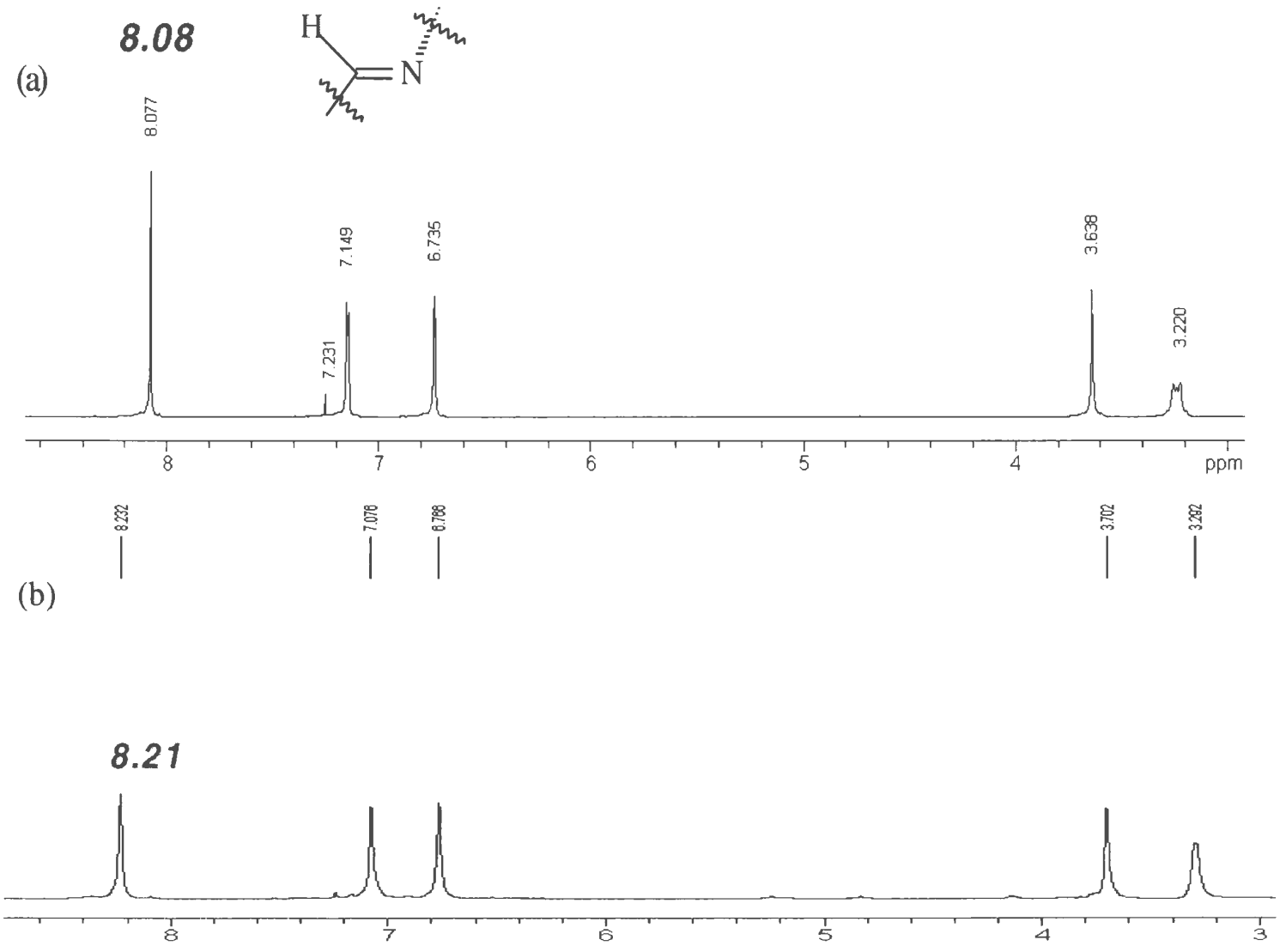


Figure 2-2 ^{1}**H-NMR** for **(a)** single conformer of 2+2 dimer **5b** in $CDCl_3$

(b) mixture of 2+2 dimer **6**, 3+3 trimer **7**, 4+4 tetramer **8**, 5+5 pentamer **9** in $CDCl_3$

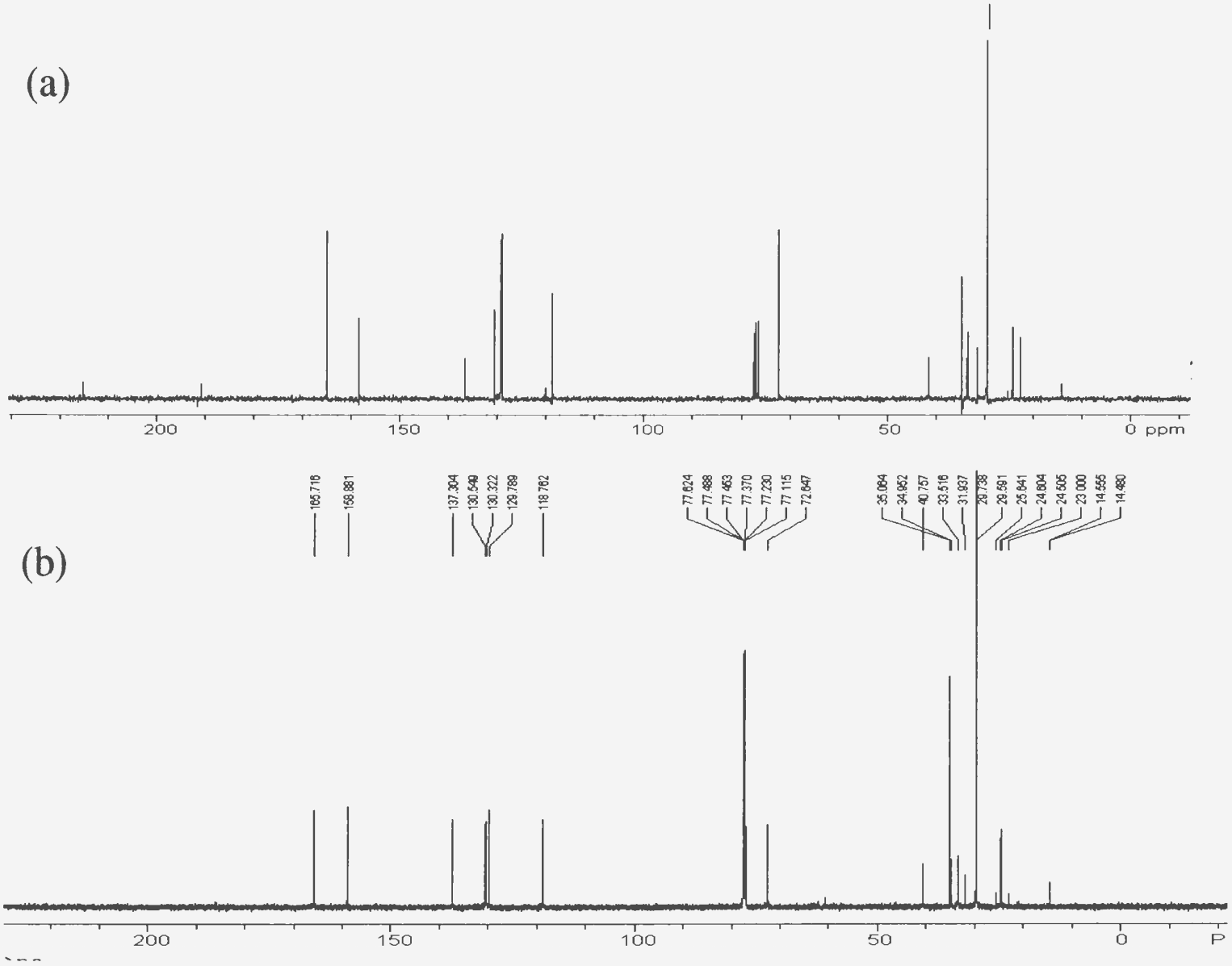


Figure 2-3 ^{13} **C-NMR** for **(a)** single conformer of 2+2 dimer **5b** in $CDCl_3$

(b) mixture of 2+2 dimer **6**, 3+3 trimer **7**, 4+4 tetramer **8**, 5+5 pentamer in $CDCl_3$

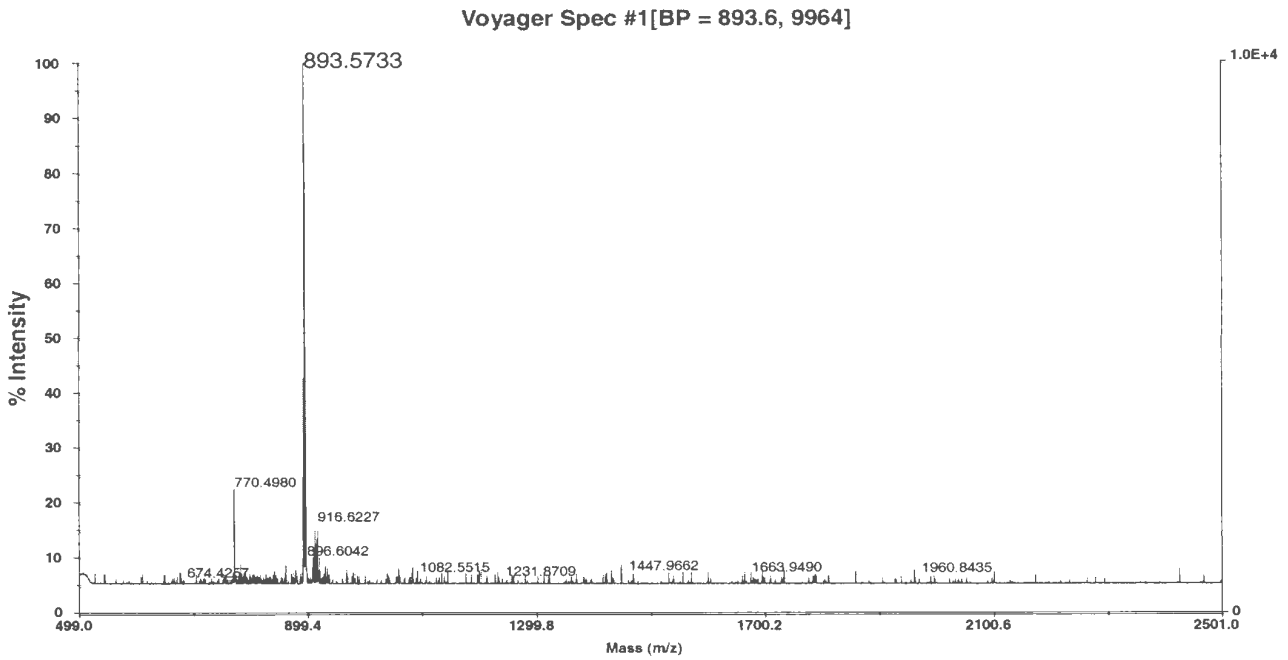


Figure 2-4 MALDI-TOF/MS of 2+2 dimer **5b**

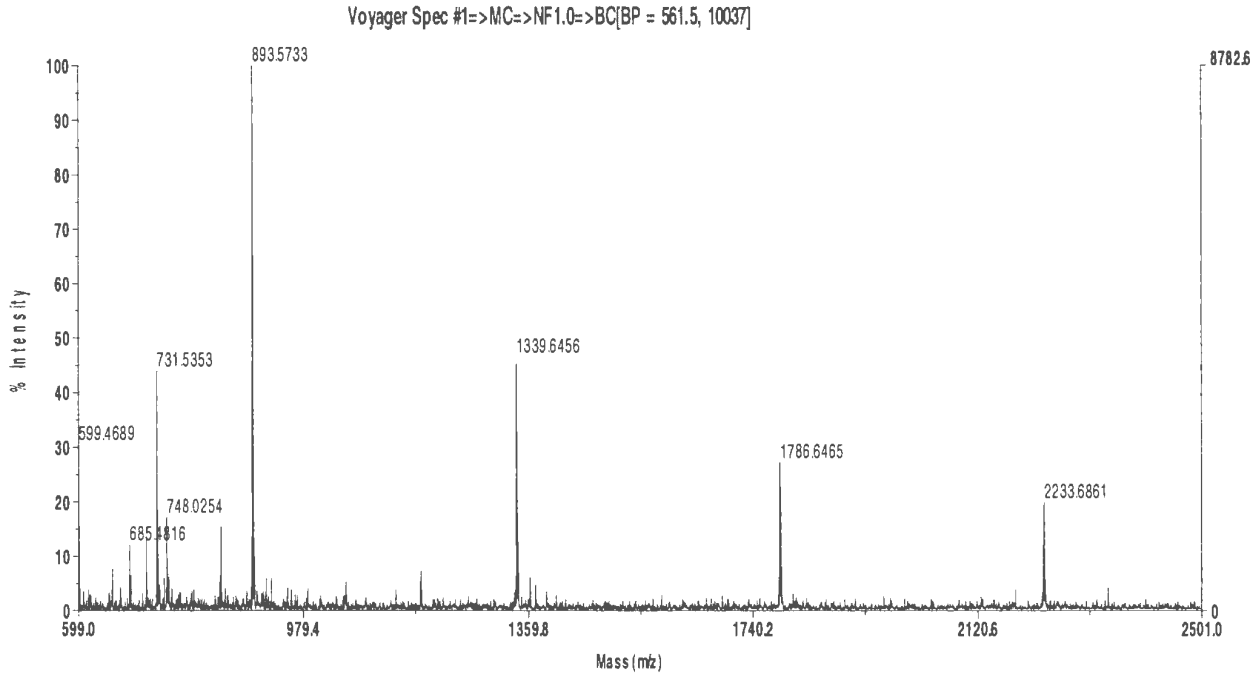


Figure 2-5 MALDI-TOF/MS of 2+2 dimer **6**, 3+3 trimer **7**,

4+4 tetramer **8**, 5+5 pentamer mixture **9**

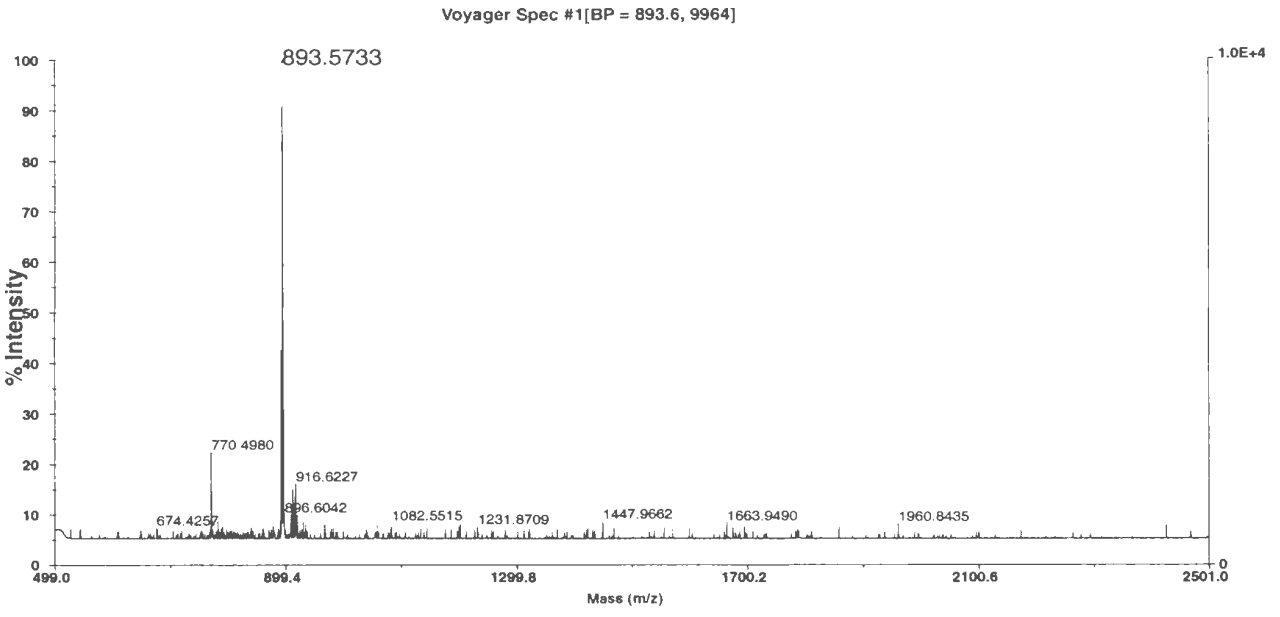


Figure 2-6 MALDI-TOF/MS of calix[2]salen isomer **6**

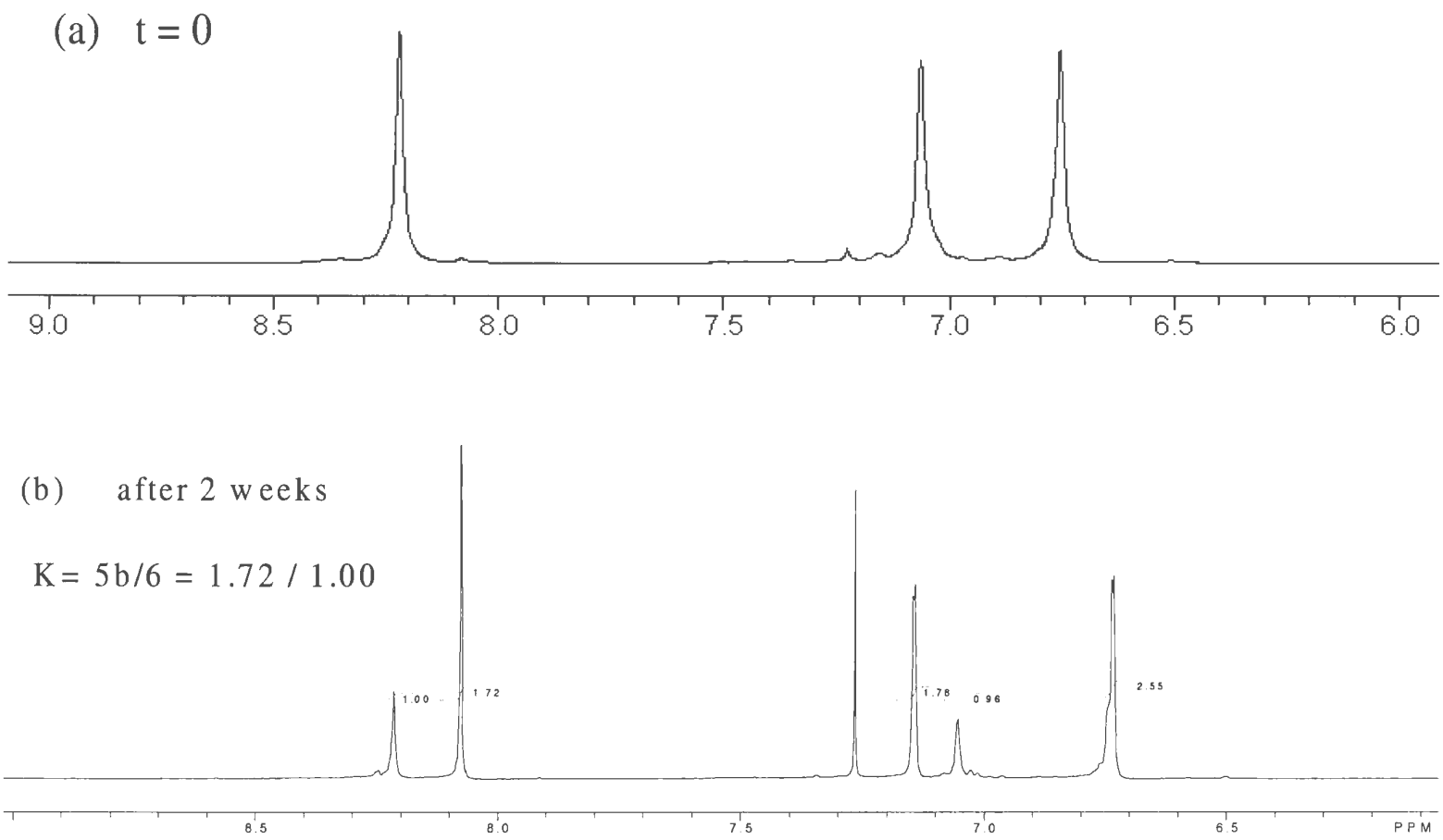


Figure 2-7 ^{1}H-NMR for **(a)** pure dimer with Schiff-base peak at 8.21 ppm

(b) pure dimer **6** with Schiff-base peak at 8.21 ppm over a period of 2 weeks in $CDCl_3$ solution

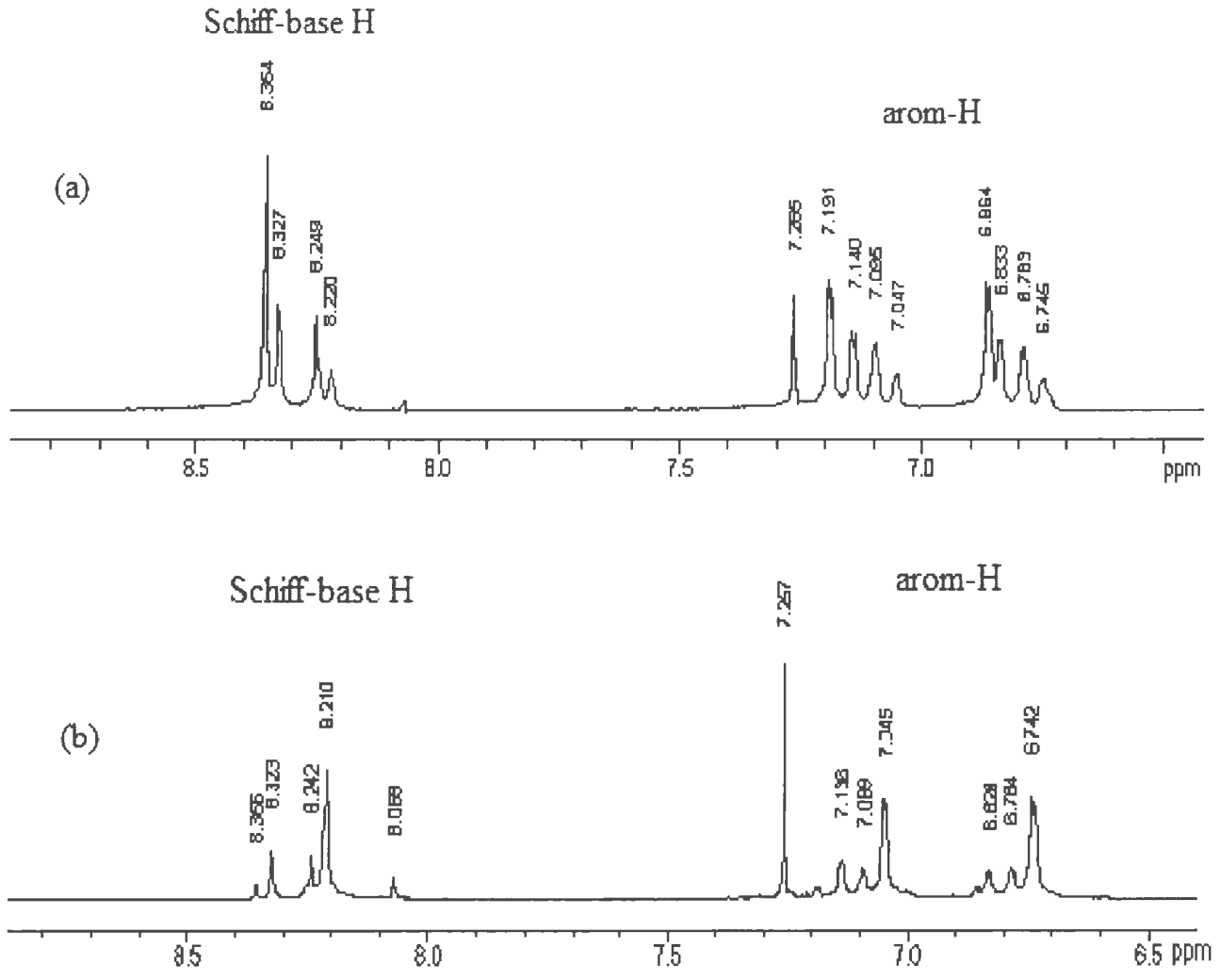
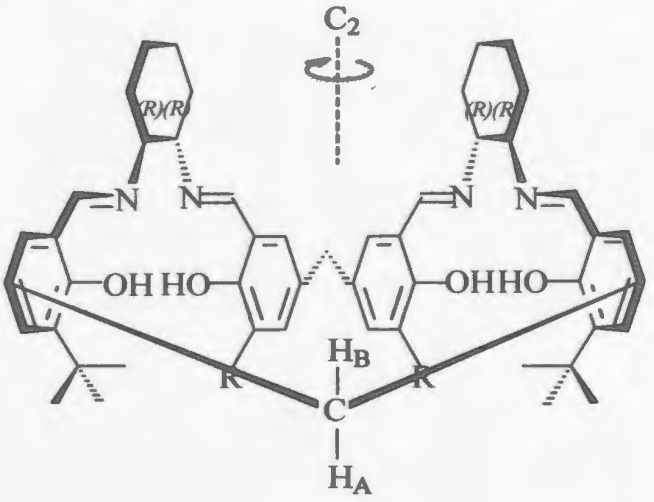
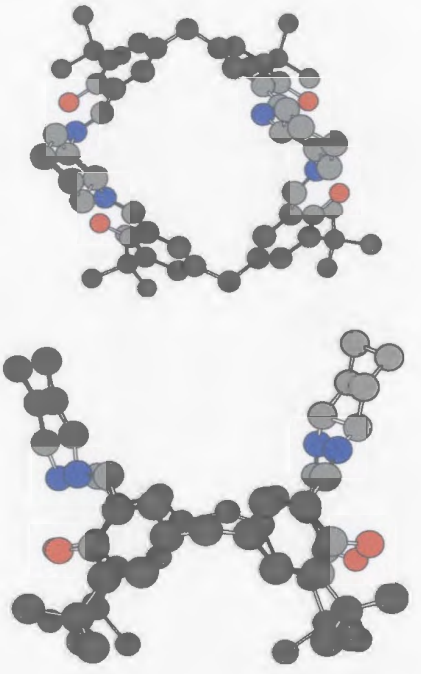


Figure 2-8 ^{1}H-NMR for **(a)** products with Schiff-base peak at 8.33 ppm

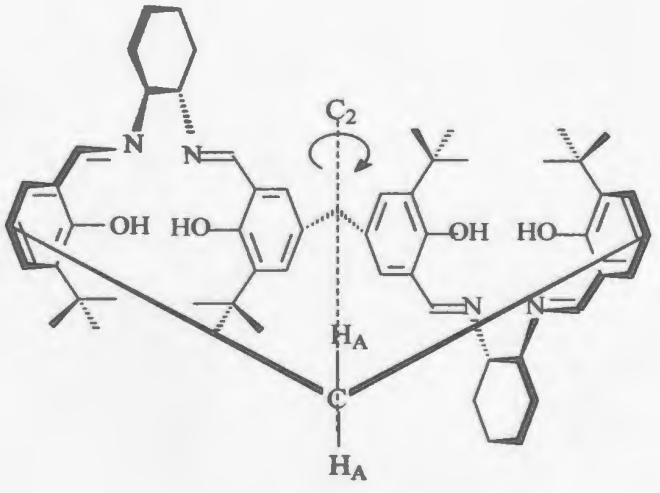
(b) products with Schiff-base peak at 8.33 ppm over a period of 4 weeks



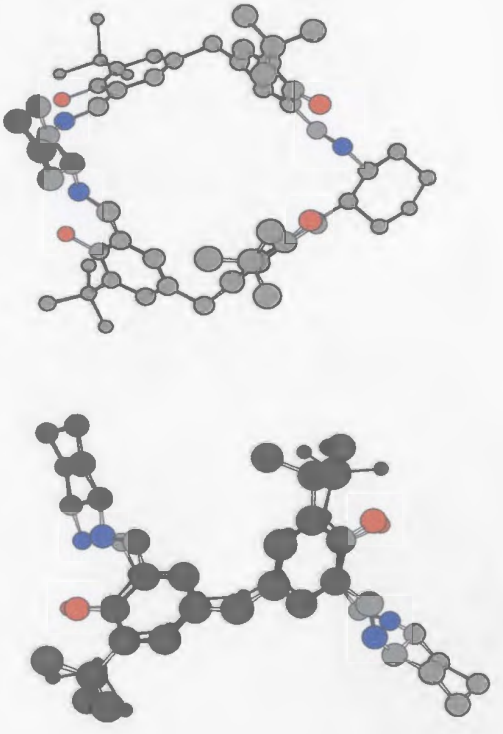
Calix[2]salen *syn*-dimer **5b**



Top and Side views for **5b**



Calix[2]salen *anti*-dimer **6**



Top and Side views for **6**

Figure 2-9 Suggested structures for calix[2]salens

2.2.3.2 Direct Synthesis of Macrocyclic calixsalens

In direct synthesis, cyclization does not depend on the directing influence of a metal ion. Two reagents incorporating the required fragments for the target macrocycle were combined in equimolar amounts under high dilution conditions by slow addition of a solution of dialdehyde in THF and a solution of (*1R,2R*)- or (*1S,2S*)-diaminocyclohexane in MeOH to a vigorously stirred 1:1 MeOH and THF solvent mix at room temperature (**Scheme 2-2**). As a consequence of high dilution, the condensation reaction tends to favour cyclization by enhancing the prospect of the "half-condensed" moiety reacting with itself "head to tail" rather than undergoing intermolecular condensation.[14] This procedure produced the same cyclic products as those in the template-directed procedure in a total yield of 60-70%, but the ratio of these products is different from that in the template-directed procedure as shown in **Table 2-1**. In template-directed synthesis, cyclization produced more dimer isomer with Schiff-base peak at 8.08 ppm.

Table 2-1 Product Distribution for Direct Synthesis and Template Synthesis

Products / Procedure	*Syn*-dimer	*Anti*-dimer, trimer and tetramer etc.
Direct Synthesis	25-30%	35-40%
Template Synthesis	30-40%	30-40%

2.3 Synthesis and Characterization of Chiral Mn^{III}-(calixsalen) Complexes

2.3.1 Synthesis of Mn^{III}-(calixsalen) Complexes

Transition metals can catalyze oxo-transfer reactions such as the alkene epoxidations studied in this work. The coordination geometry and electronic properties of the coordinating ligands have a significant effect on the effectiveness of the metal catalysts.[15] Successful catalysts have been developed using porphyrin or salen ligands, which coordinate with the transition metal in square planar N_4 and N_2O_2 geometries respectively. Chiral porphyrins or salen ligands provide a chiral coordination environment for the transition metal, in which the transition metal can undergo an oxygen transfer reaction and serve as a relay for oxygen atom transfer from the terminal oxidant to the alkene via an oxo-transition-metal reactive intermediate. Therefore, changes in oxidation state and chiral environment of the transition metal centre affect enantioselective catalyses.

The interest in manganese complexes as catalysts for alkene epoxidations derives mainly from the relationship of these catalytic systems to the biologically relevant metalloporphyrins. In the past two decades, the use of chiral metallosalen complexes as oxidation catalysts[16] has resulted in the development of new models of synthesis. The majority of biomimetic synthetic receptors have used macrocyclic rings to form a concave surface, the essential characteristic of a natural receptor.[17] The bisalen complexes reported in this work have a folded structure as shown in **Figure 2-10**, wherein two

methylene carbons form a hinge-like bridge between two almost parallel salen planes, resulting in an unbridged, molecule sized cavity with an intermetallic distance of about 7.7 Å.

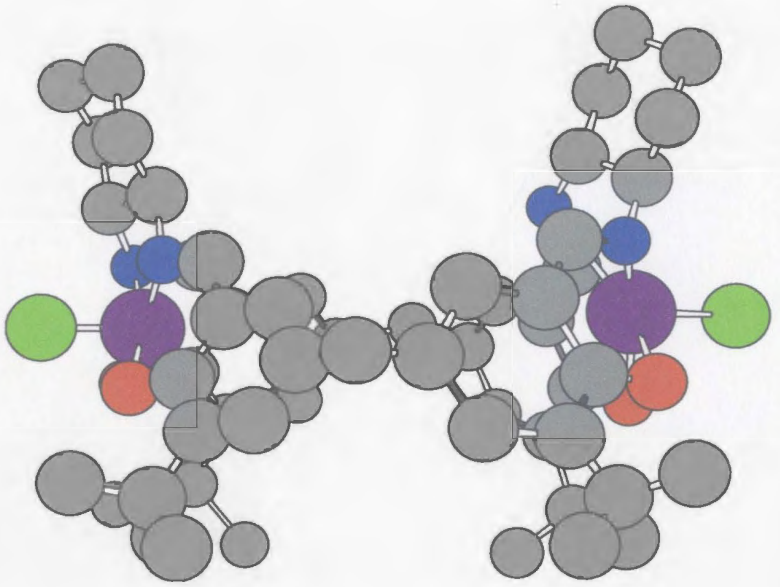


Figure 2-10 Mn^{III}-(calix[2]salen) complex

As described in the preceding section, it was not possible to separate the different macrocyclic salens from the crude cyclization product mixture by chromatography (other than *syn*-conformer of the calix[2]salen dimer) because these products have similar R_f values. Separation was also complicated by Schiff-base hydrolysis. However, coordination of the ligand mixture with Mn(III) gave a more stable complex mixture amenable to separation by chromatography on silica. It was found that the acetate complexes did not move on silica, presumably because the acetate is a weak donor that cannot bind strongly enough to the $[Mn_n(calix[n]salen)]^{n+}$ cations. Based on the literature that chloride is a stronger donor ligand which more tightly binds with $[Mn^{III}\text{-}(salen)]^+$ to afford neutral $[Mn^{III}\text{-}(salen)]Cl$ complex,[18] treatment of the acetate

derivative with LiCl afforded neutral $[Mn_n(calix[n]salen)]Cl_n$ complexes which moved well on silica. It should be noted that the chloro complexes were prepared by adding LiCl in EtOH:CH_2Cl_2 (1:1) and that MeOH was avoided.

Calix[2]salen **5b**, which could be separated from the other macrocyclic salens by column chromatography over silica, coordinated with Mn(III) to afford the complex $Mn_2(calix[2]salen)Cl_2$ **10b**. Because the paramagnetic Mn(III) prevents simple NMR spectral analysis, identification of this complex was carried out by MALDI-TOF/MS. The MS spectrum is shown in **Figure 2-11**. Complex **10b** (**Figure 2-13**) showed peaks at *m/z* 893.57, 945.60, 998.33, and 1033.28, which can be assigned as the $[calix[2]salen+H]^+$, $[Mn(III)(calix[2]salen-2H)]^+$, $[Mn(III)_2(calix[2]salen-4H)]^+$, and $[Mn(III)_2(calix[2]salen-4H)Cl]^+$ fragments respectively. The MS spectrum indicated that the complex **10b** is binuclear and presumably loses one chloride to form the +1 cation as the major mode of ionization.

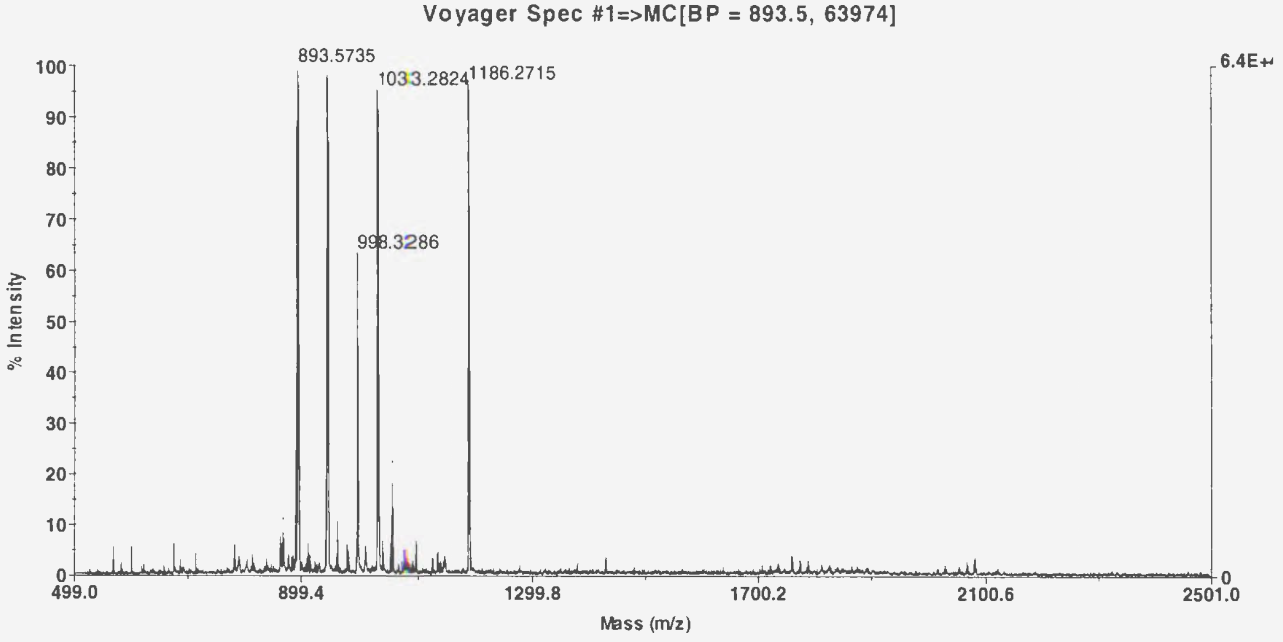


Figure 2-11 MALDI-TOF/MS for Mn^{III}-(calix[2]salen) complex **10b**

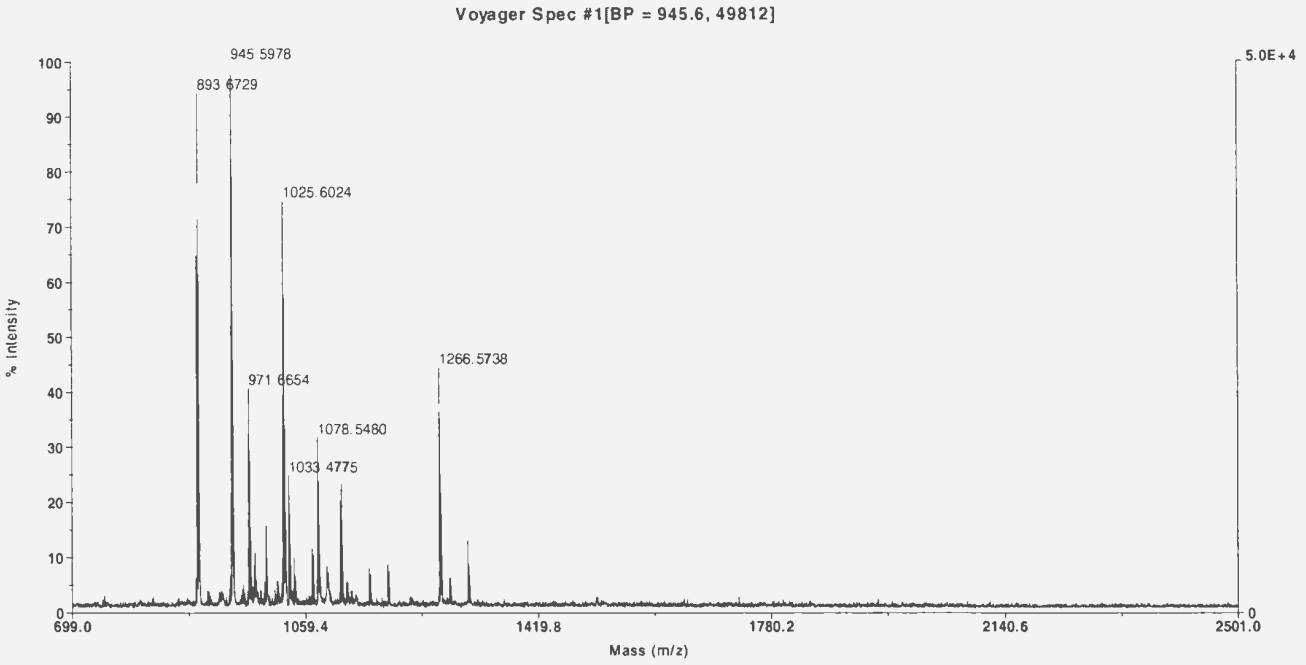
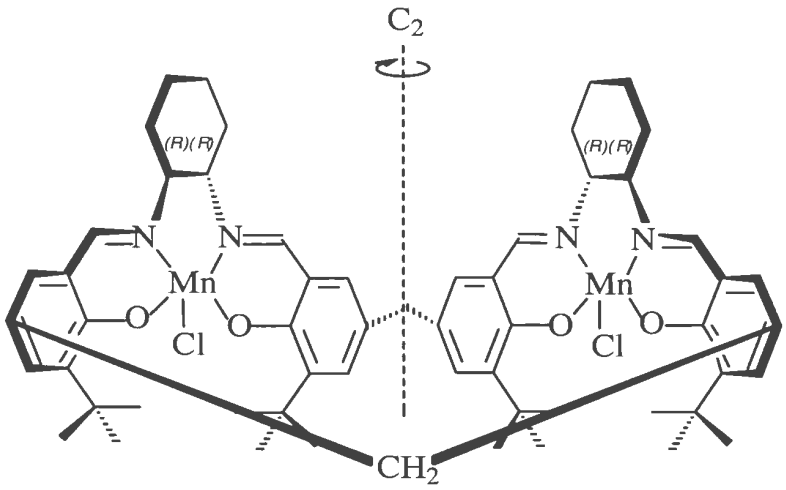


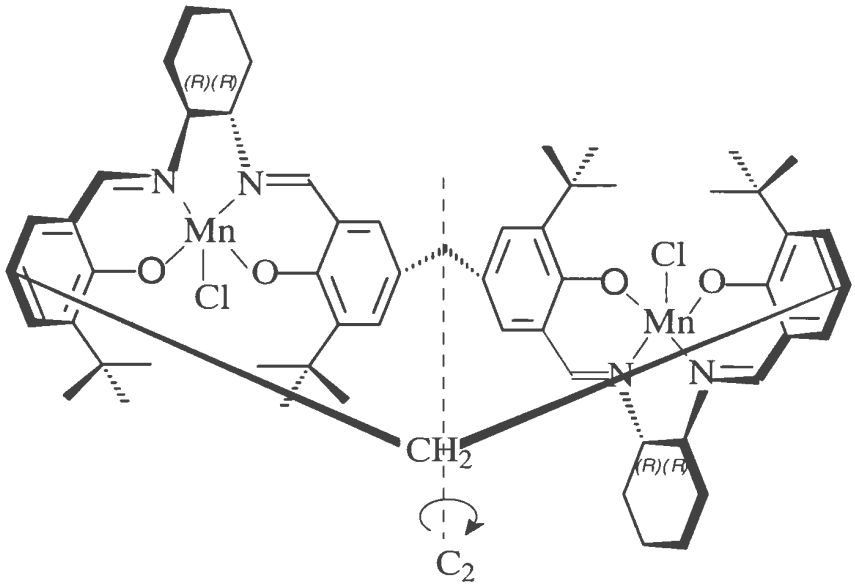
Figure 2-12 MALDI-TOF/MS for Mn^{III}-(calix[2]salen) complex **11**

The Mn(III) chloro complexes of the free ligand mixture containing the calix[2]salen conformer **6**, the trimer, and the tetramer macrocyclic calixsalen ligands were easily separated by column chromatography on silica. The first eluted complex **11** in EtOH/CH_2Cl_2 gave the MS spectrum shown in **Figure 2-12**. The MS spectrum contains four significant peaks at *m/z* 893.67, 945.60, 1033.48 and 1078.55 which are in agreement with the $[calix[2]salen+H]^+$, $[Mn(III)(calix[2]salen-2H)]^+$, $[Mn(III)_2(calix[2]-salen-4H)Cl]^+$, and $[Mn(III)_2(calix[2]salen-4H)Cl(EtOH)]^+$ fragments respectively. The peak at *m/z* 1078.55 is consistent with $[Mn(III)_2(calix[2]salen-4H)Cl(EtOH)]^+$, indicating that the complex is binuclear and bound with one Cl^- and one EtOH. Complex **11** has the same significant mass peaks, but the free ligand presumably has a different conformation from the ligand of complex **10b**. X-ray crystallography[19] indicated that complex **10b** adopts face-to-face *syn*-comformation, so the complex **11** was assumed to

have an *anti*-comformation as shown in **Figure 2-13**.



Complex 10 b



Complex 11

Figure 2-13 Structure for complexes **10b** and **11**

The MS spectrum of the second eluted Mn(III) complex **12** (**Figure 2-16**) has peaks at *m/z* 1339.88, 1392.78, 1445.69, and 1498.57, as shown in **Figure 2-14**, which are in agreement with $[calix[3]salen+H]^+$, $[Mn(III)(calix[3]salen-2H)]^+$, $[Mn(III)_2(calix[3]salen-4H)]^+$, $[Mn(III)_2(calix[3]salen-4H)Cl]^+$, and $[Mn(III)_3(calix[3]salen-6H)]^+$. The MS spectrum confirms that the complex is trinuclear and bound with at least one Cl^-. Presumably, the isolated complex is a neutral trichloride since it is mobile on silica.

The tetramer Mn(III)-calix[4]salen **13** (**Figure 2-16**) was also separated by silica column chromatography. The MS spectrum, shown in **Figure 2-15**, contains characteristic peaks at m/z 1788.50, 1840.38, 1893.31, 1945.23, and 1998.16, which are in agreement with the $[calix[4]salen+H]^+$, $[Mn(III)(calix[4]salen-2H)]^+$, $[Mn(III)_2(calix[4]-salen-4H)]^+$, $[Mn(III)_3(calix[4]salen-6H)]^+$, and $[Mn(III)_4(calix[4]salen-8H)]^+$ cations respectively. The MS spectrum indicated that the complex is tetra-nuclear. Presumably, the complex is neutral chloride since it is mobile on silica.

Although no pure Mn^{III}-(calix[5]salen) complex **14** was isolated, the MS spectrum contains characteristic peaks at m/z 2231.91, 2286.77, 2339.69, 2402.11, 2393.71 and 2449.27, which are consistent with the $[calix[5]salen+H]^+$, $[Mn(III)(calix[5]salen-2H)]^+$, $[Mn(III)_2(calix[5]salen-4H)]^+$, $[Mn(III)_2(calix[5]salen-6H)Cl]^+$, $[Mn(III)_3(calix[5]salen-6H)]^+$, and $[Mn(III)_4(calix[5]salen-8H)]^+$ cations respectively.

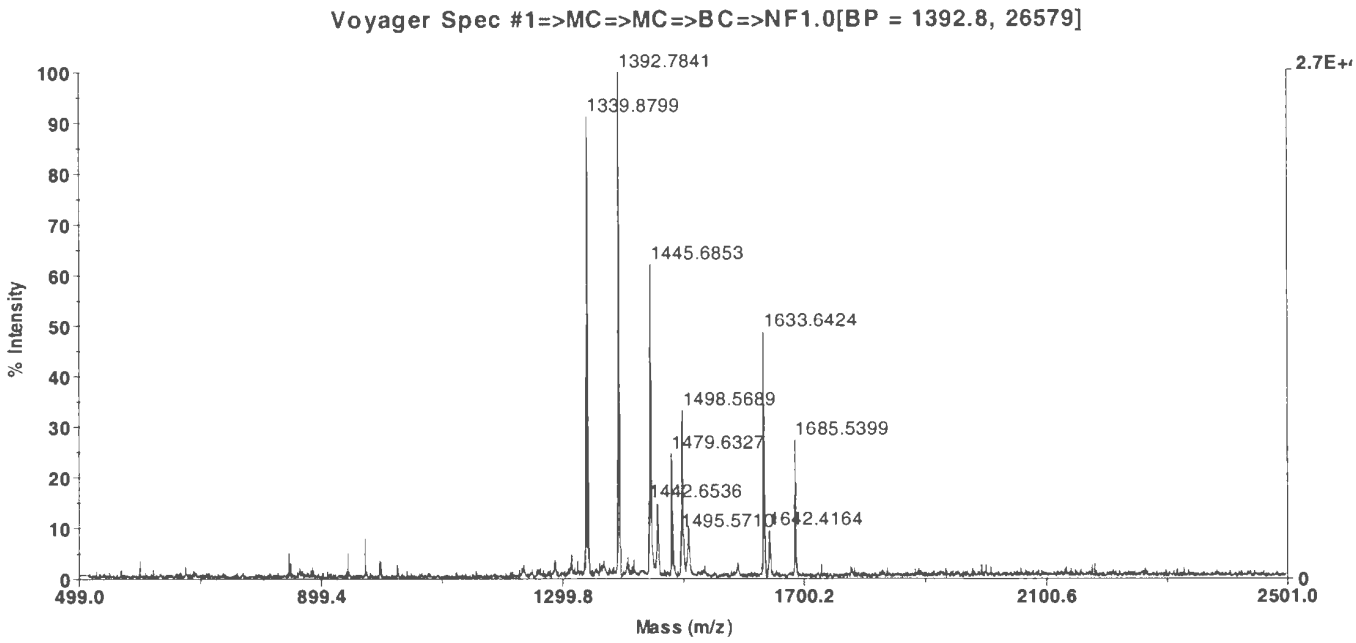


Figure 2-14 MALDI-TOF/MS for Mn^{III}-(calix[3]salen) complex **12**

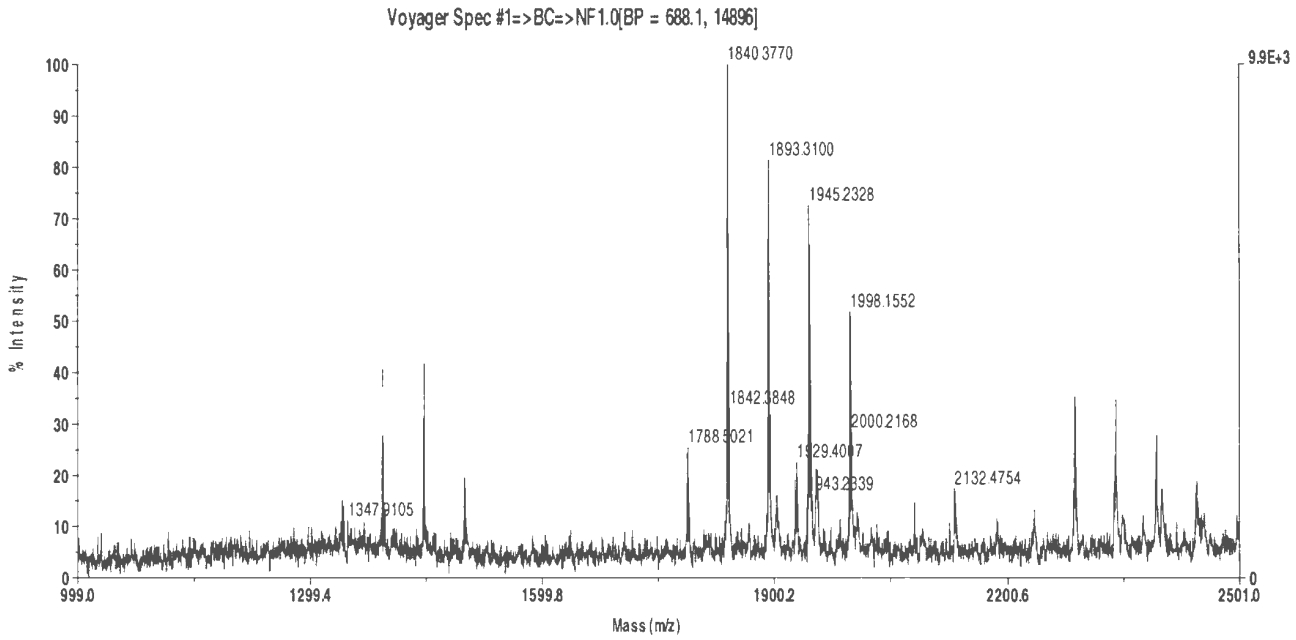
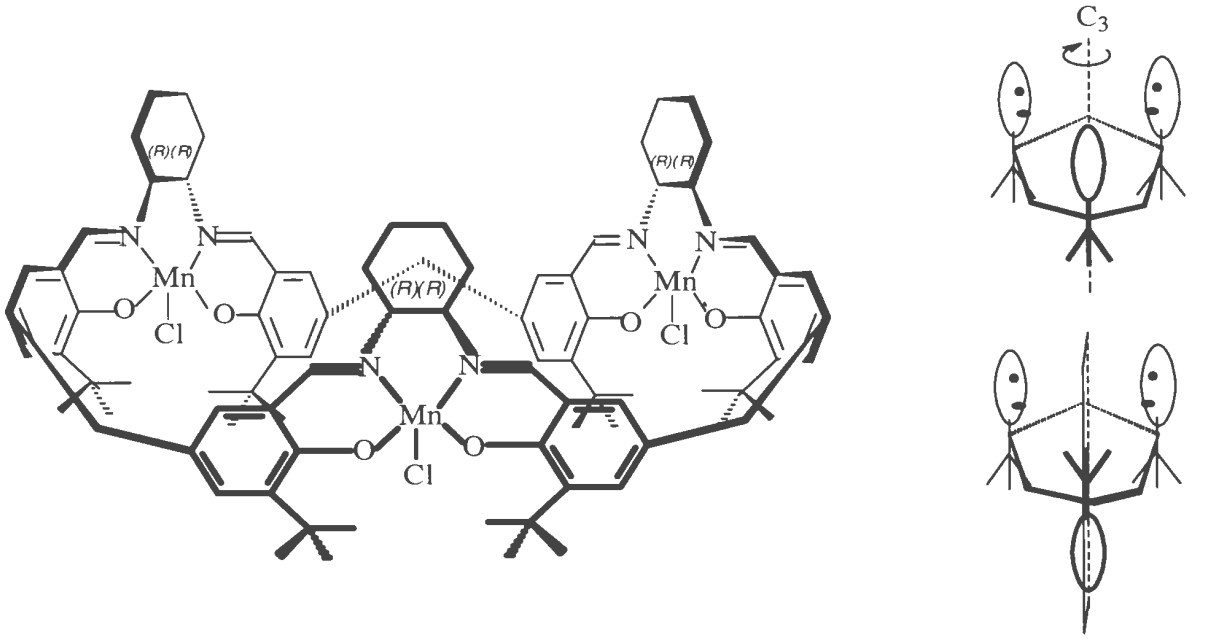
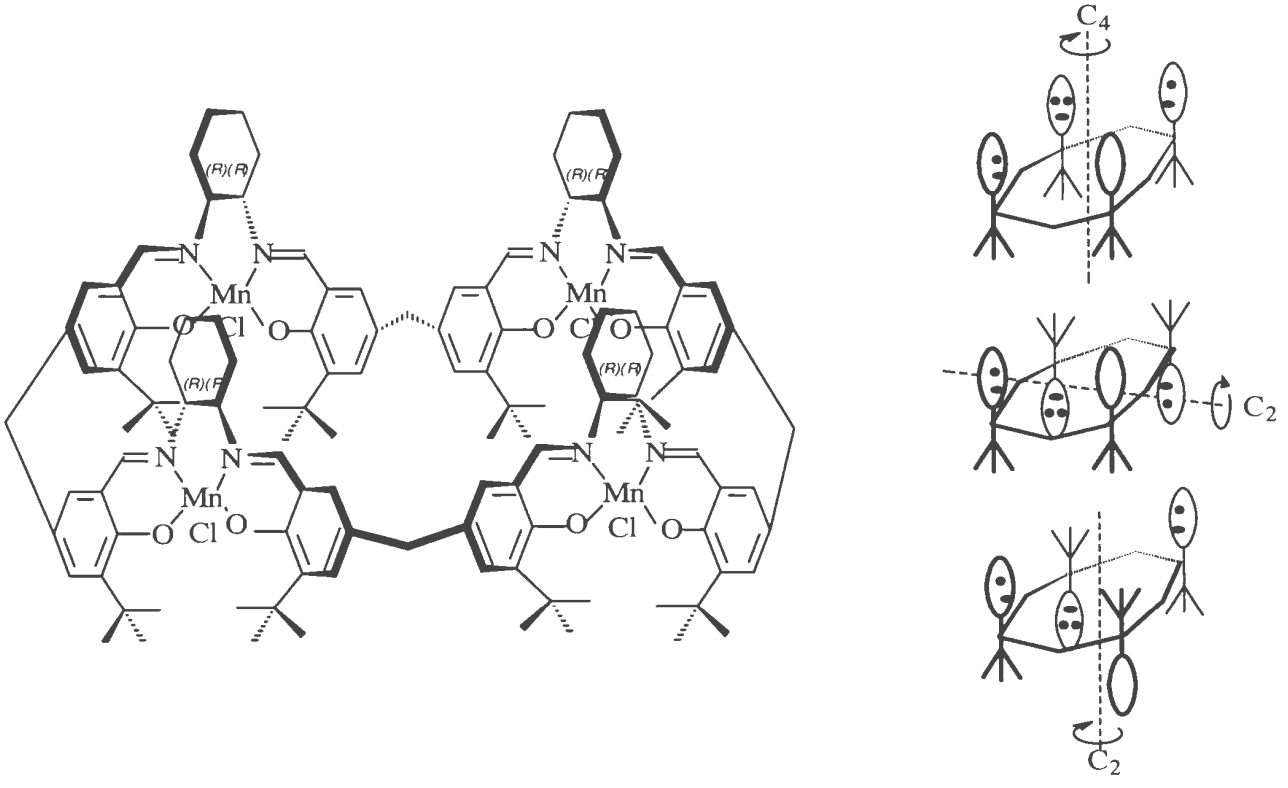


Figure 2-15 MALDI-TOF/MS for Mn^{III}-(calix[4]salen) complex **13**



C_3 symmetric Mn^{III}-(calix[3]salen) **12** and the other possible conformations



C_4 symmetric Mn^{III}-(calix[4]salen) **13** and other possible conformations

Figure 2-16

2.3.2 Characterization of Mn^{III}-(calix[2]salen) Complex

The structure of a single crystal of $[Mn_2(calix[2]salen)Cl(EtOH)]^+$ (obtained by slow evaporation of a CH_2Cl_2 and EtOH solution of $Mn_2(calix[2]salen)Cl_2$, **10b**) was previously determined by X-ray crystallography.[19] The top and side views of the structure are shown in **Figures 2-17** and **2-18**.

The structure of the complex indicates that the Mn^{III}-(calix[2]salen) complex is isostructrural with binuclear Cu^{II}- and Ni^{II}-(calix[2]salen) complexes, and the two salen units adopt a face-to-face conformation with a metal-metal separation of about 7.7 Å. The complex has a *syn*-conformation, with C_2 symmetry and a pseudo-C_2 axis passing through the cavity centre. These two salen units form a basket-shaped cavity of approximately 7 Å x 11 Å. The two cyclohexyl rings located on the open side of the cavity form a chiral "gate", and the four *tert*-butyl groups on the "closed" side have only a small (~3 Å) opening. Therefore, it is expected that a guest molecule would prefer to enter the cavity through the cyclohexyl side. This gate, which is close to the chiral centres, should result in a more effective chiral communication, thereby enhancing the enantioselectivity of the catalysis. **Figure 2-17** indicates that the molecule of EtOH resides in the cavity with the ethyl group between the two Mn(III) atoms and the hydroxyl group directed towards one of the Mn(III) centres.

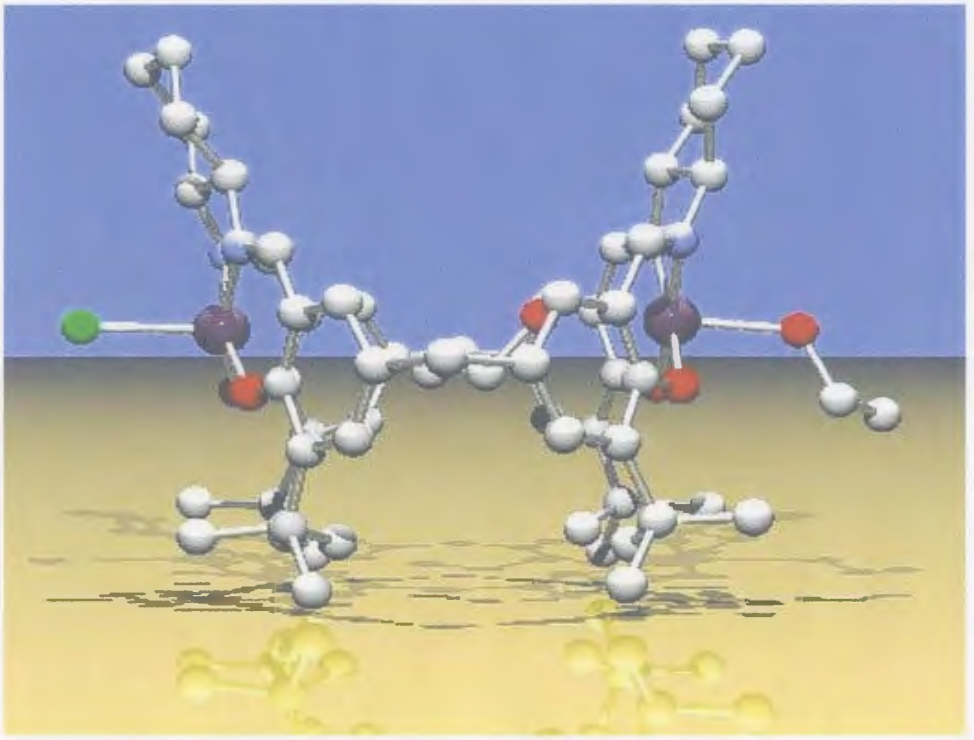


Figure 2-17 Side-view of *syn*-[Mn_2(calix[2]salen – 4H)Cl]·2EtOH

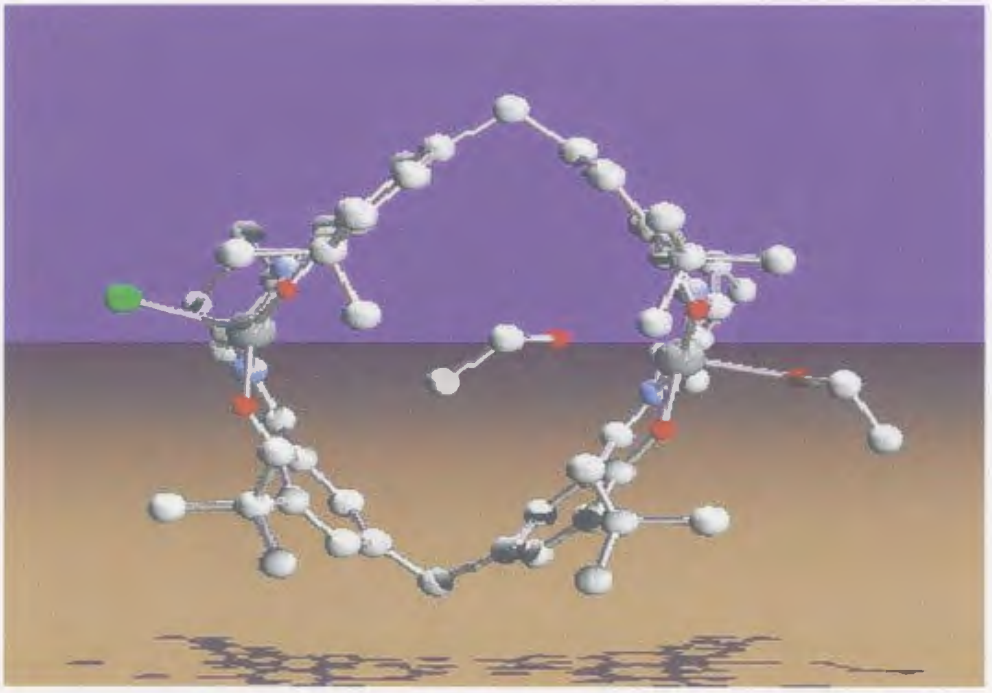


Figure 2-18 Top view of *syn*-[Mn_2(calix[2]salen – 4H)Cl]·2EtOH

2.4 Summary

This research clarified the synthetic products of Schiff-base cyclization. The NMR spectra of the macrocyclic salen products are consistent with two conformations of the calix[2]salen free ligands. X-ray crystallography[19] of the complex Mn_2(calix[2]salen)-Cl(EtOH) **10b** established that the first eluted calix[2]salen **5b** has the *syn*-conformation. However, for the calix[2]salen **6**, crystals of suitable quality for X-ray analysis have not been obtained to confirm the ligand conformation.

Many previous attempts showed that it is difficult to separate the free ligands other than *syn*-calix[2]salen **5b** by chromatography. This research successfully isolated the calix[2]salen **6** from the trimer and tetramer products by extraction with $CDCl_3$. The calix[2]salen **6** was observed to convert into calix[2]salen **5b** in $CDCl_3$ solution if left for a period of weeks.

Calix[3]salen and calix[4]salen were also formed, but it was not possible to separate them from the crude cyclization product mixture by chromatography. Separation was also complicated by Schiff-base hydrolysis on silica. Coordination of the ligand mixture with Mn(III) gave a more stable complex mixture amenable to separation by chromatography on silica. Identification of these complexes by MALDI-MS confirms that the complex is tri-nuclear or tetra-nuclear bound with at least one Cl^-. Presumably, the isolated complex is a neutral tri-chloride or tetra-chloride since it is mobile on silica.

2.5 Experimental Section

Materials

Chemical reagents and solvents were purchased from Aldrich and used as received. THF used for synthesizing calixsalens was further purified by fractional distillation. *(1R,2R)-* or *(1S,2S)*-diaminocyclohexane-L-tartrate salts were obtained as a gift from SepraChem Inc. Extreme care should be taken when handling with $Ba(ClO_4)_2$ which is shock sensitive.

Methods

All reactions for the syntheses of calix[n]salen proceeded under a nitrogen atmosphere. Nitrogen gas was purified by passing through a series of columns containing DEOX (Alpha) catalyst heated to 120 °C, granular P_4O_{10}, and activated 3Å molecular sieves. Flash column chromatography was performed with silica gel (230-400 mesh). Analytical thin layer chromatography was performed on Fertigfolien Pre-coated plastic sheets with fluorescent indicator UV_{254} (Macherey-Nagel GmbH & Co. KG, Germany). The ratio of silica gel to compound being purified was approximately 50-150. The eluting solvent for each purification was determined by TLC analysis.

Instruments

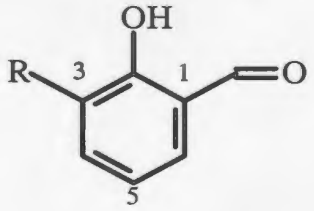
^{1}H-NMR and ^{13}C-NMR were recorded in $CDCl_3$ on GE-300 MHz spectrometer or on Bruker AM-500 Fourier Transform spectrometer with Me_4Si as an internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd =

doublet of doublets, t = triplet, b = broad, m = multiplet), coupling constant (*J*, Hz), integration and assignment (mH-x, m for the H numbers in the position x of a molecule). ^{1}H-NMR and ^{13}C-NMR spectra were processed using Nuts software. Chemical shifts for ^{13}C-NMR spectra are relative to the solvent 77.23 ppm for $CDCl_3$.

MS spectra were recorded on Applied Biosystems DE-RP equipped with a reflectron, delayed ion extraction and high performance nitrogen laser (337 nm). Samples were prepared at a concentration of 1 mg/mL in 50% CH_2Cl_2 in EtOH. The sample was mixed with a matrix compound of α-cyano-4-hydroxycinnamic acid at a concentration of 10 mg/mL in 50% CH_2Cl_2 in EtOH to promote desorption and ionization.

Syntheses:

3-alkyl-2-hydroxy-benzaldehydes (2a, 2b)[11, 20]



2 a : R = *i*–Pr, 2 b : R = *t*–Bu

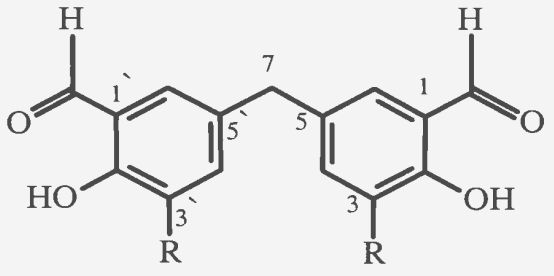
To a three-necked round-bottomed flask (500 mL) equipped with a reflux condenser, a stirring bar, and nitrogen source, the appropriate phenol (0.50 mol), tin(IV) chloride (6.0 mL, 0.05 mol), anhydrous toluene (100 mL), and tri-*n*-butyl amine (34.7 mL, 0.20 mol) were added. The mixture was stirred for 20 min. at room temperature, then paraformaldehyde (3.3 g, 1.1 mol) was added. The resulting yellow solution was heated at 100 °C overnight. After cooling, the resultant black mixture was poured into water (2

L), acidified to pH=2 with 6 mol/L hydrochloric acid, and extracted with Et_2O (3 x 100 mL). The combined ether extracts were evaporated and purified on silica gel (hexane/CH_2Cl_2). **2a** was obtained as pale yellow liquid in 70-80% yield.

2a: Yield: 63 g (78%). ^{1}H-NMR: δ 11.37 (s, 1H, OH), δ 9.88 (s, 1H, CHO), 7.47 (dd, 1H, J_{6-5}=7.2, J_{6-4}=1.5, H-6), 7.40 (dd, 1H, J_{4-5}=7.8, J_{4-6}= 1.5, 1H, H-4), 6.98 (t, 1H, J=8.7, H-5), 3.37 (m, 1H, J=6.0, *i*-Pr), 1.23 (d, 6H, J=6.9, *i*-Pr).

2b: Yield: 69 g, (77%). ^{1}H-NMR: δ 11.81 (s, 1H, OH), δ 9.83 (s, 1H, CHO), 7.51 (dd, 1H, J_{6-5}=7.8, J_{6-4}=1.2, H-6), 7.36 (dd, 1H, J_{4-5}=7.2, J_{4-6}= 1.2, 1H, H-4), 6.92 (t, 1H, J=7.4 H-5), 1.41(d, 9H, *t*-B u).

5, 5`-Methylene-bis-salicyaldehyde [21]



3a R = *i* – Pr, **3b** R = *t* – Bu

To a solution of 2-hydroxy-3-alkyl-benzaldehyde (**2a** or **2b**) (0.06 mol) in 20 mL of acetic acid, trioxane (0.9 g, 0.02 mol) was added at room temperature. A mixture of 0.25 mL H_2SO_4 in 10mL acetic acid was dropped into the stirred solution at 70 °C over a one hour period. The resultant solution was stirred for 12 hours at 70 °C and then poured onto ice water. The reaction mixture was allowed to stand overnight, and then hexane or chloroform (2 x 100 mL) was added to extract the product. The concentrated

extract was purified on silica gel (hexane/ethyl acetate) and a pale yellow crystalline product was obtained in 60-70% yield.

3a: Yield: 6.3 g, (65%). GC-MS (*m/z*): Calculated for $C_{21}H_{24}O_4$: 325; found: 325. ^{1}H-NMR: δ 11.28 (s, 2H, OH), δ 9.83 (s, 2H, CHO), δ 7.29 (d, 2H, J=2.1, H-6, H-6`), δ 7.13 (d, 2H, J=2.1, H-4, H-4`), δ 3.95 (s, 2H, H-7), δ 3.36 (m, 1H, *i*-Pr), δ 1.23 (d, 6H, J=6.9, *i*-Pr). ^{13}C NMR: δ 196.94 (CHO), 158.05 (C-2, C-2`), 137.60 (C-1, C-1`), 134.53 (C-6, C-6`), 131.85 (C-5, C-5`), 130.88 (C-4, C-4`), 120.20 (C-3, C-3 `), 40.03 (C-7, C-7`), 26.51 (*i*-Pr), 22.40 (*i*-Pr).

3b: Yield: 7.2 g (68%). GC-MS: (*m/z*): Calculated for $C_{23}H_{28}O_4$: 353, found: 353. ^{1}H-NMR: δ 11.71 (s, 2H, OH), δ 9.83 (s, 2H, CHO), δ 7.38 (d, 2H, J=2.1, H-6, H-6`), δ 7.15 (d, 2H, J=2.1, H-4, H-4`), δ 3.95 (s, 2H, H-7), 1.42(d, 18H, *t*-Bu). ^{13}C NMR: δ 197.19 (CHO), 159.96 (C-2, C-2`), 138.68(C-1, C-1`), 135.10 (C-5, C-5`), 131.42 (C-6, C-6`), 131.34 (C-4, C-4`), 120.64 (C-3, C-3`), 40.22 (C-7, C-7`), 35.02 (*t*-Bu), 29.37 (*t*-Bu).

***(R, R)* or *(S, S)*-cyclohexane-1, 2-diamine**

An aqueous solution of KOH (8.0 g in 10 mL H_2O) was added to solid *(R, R)*-diaminocyclohexane- (L)-tartrate (~ 2 g), and the mixture was stirred. The amine layer was separated and the solution was extracted with 3 x 50 mL ether. The ether layers were combined, dried over sodium sulfate, and then dried with sodium (~ 500 mg) overnight. Evaporation of the ether under oil pump afforded a clear colourless crystalline product in 75% yield. ^{1}H-NMR spectra were consistent with the standard

diamines purchased from Aldrich. The optical purity determined by chiral HPLC analysis is 99.9%. Diamines are hydroscopic and should be handled properly.

Synthesis of Ligands 5, 6 and 7: High Dilution

Two solutions, *(R, R)*-cyclohexane-1, 2-diamine (0.12 g, 1.0 mmol) in 15 mL methanol and the appropriate dialdehyde (1.0 mmol) in 15 mL THF, were added simultaneously by syringe pump to 40 mL of 1:1 MeOH :THF at room temperature over a 8-10 hr. period. When the two reactants were mixed, a bright yellow solution quickly formed. After the reaction was completed, the solvent was removed at aspirator vacuum. The ^{1}H-NMR spectrum of the crude product mixture showed at least three major cyclic Schiff-base products with Schiff-base peaks at 8.08 ppm, 8.21 ppm, 8.39 ppm, and no acyclic or leftover reactants.

The calix[2]salen dimer, **5b**, was isolated by first stirring the reaction mixture in 5% ethyl acetate in hexane, which dissolved all of **5b**, and some of the trimer and tetramer side products. Column chromatography of this filtrate solution over silica with 5% ethyl acetate in hexane afforded the pure free ligand **5b**. ^{1}H-NMR spectroscopy showed one Schiff base peak at 8.08 ppm and one peak at 3.69 ppm for the methylene bridge.

The remaining (undissolved in 5% ethyl acetate in hexane) side product mixture was soluble in 40% ethyl acetate in hexane. The ^{1}H-NMR spectrum of this insoluble side product mixture in 5% ethyl acetate/hexane showed only one Schiff base peak at 8.21 ppm. MALDI-TOF/MS of this mixture showed the cyclized dimer, trimer, tetramer, pentamer (up to nonamer) free ligand products. However, it was found that this mixture

could not be separated and extensive Schiff-base hydrolysis occurred during chromatography over silica or basic alumina. Subsequent complexation of this side product mixture with Mn(III) acetate gave relatively stable complexes which could be purified by chromatography over silica with 15% ethanol/dichloromethane and then increasing ratio of ethanol/dichloromethane.

Calix[2]salen 5

5a: Yield: 0.16 g (20%). MALDI/TOF MS: calculated: $C_{54}H_{68}N_4O_4$, 836.52; Found: for $(M+H)^+$, 837.53. ^{1}H-NMR: δ 13.50 (s, 4H, OH), 8.07 (s, 4H, H-7, H-21, H-28, H-42), 7.09 (s, 4H, H-9, H-16, H-34, H-41), 6.75 (s, 4H, H-11, H-20, H-32, H-37), 3.65 (s, 4H, H-14, H-35), 1.86, (m, 16H, cyclohexyl ring), 1.340, [s, 24H, H-43 (CH$\underline{Me}_2$), H-44 (CH$\underline{Me}_2$), H-45 (CH$\underline{Me}_2$), H-46 (CH$\underline{Me}_2$)]. ^{13}C NMR: δ 164.83, (C-7, C-21, C-28, C-42), 156.94 (C-13, C-18, C-34, C-39), 135.97 (C-8, C-19, C-29, C-40), 131.80 (C-12, C-17, C-33, C-38), 128.83 (C-9, C-20, C-30, C-41), 128.71 (C-11, C-16, C-32, C-37), 118.57 (C-10, C-15, C-31, C-36), 73.02 (C-1, C-6, C-22, C-27), 41.73 (C-14, C-35), 33.72 (C-2, C-5, C-23, C-26), 26.59 [C-43 ($\underline{C}$HMe$_2$), C-44 ($\underline{C}$HMe$_2$), C-45 ($\underline{C}$HMe$_2$), C-46 ($\underline{C}$HMe$_2$)], 24.43 (C-3, C-4, C-24, C-25), 22.69 [C-43 (CH$\underline{Me}_2$), C-44 (CH$\underline{Me}_2$), C-45 (CH$\underline{Me}_2$), C-46 (CH$\underline{Me}_2$)], 22.48 [C-43 (CH$\underline{Me}_2$), C-44 (CH$\underline{Me}_2$), C-45 (CH$\underline{Me}_2$), C-46 (CH$\underline{Me}_2$)].

5b: 0.17 g (30%). MALDI/TOF MS: calculated: $C_{58}H_{76}N_4O_4$, 892.586; Found: for $(M+H)^+$, 893.57. ^{1}H-NMR: δ 13.780 (s, 4H, OH), 8.077 (s, 4H, H-7, H-21, H-28, H-42), 7.140 (s, 4H, H-9, H-20, H-30, H-41), 6.738 (s, 4H, H-11, H-16, H-32, H-37), 3.638 (s, 4H, H-14, H-35), 3.265 (m, 8H, H-1, H-6, H-22, H-27,) 1.859, (m, 16H,

cyclohexyl ring), 1.340, [s, 36H, H-43 ($C\underline{Me}_3$), H-44 ($C\underline{Me}_3$), H-45 ($C\underline{Me}_3$), H-46 ($C\underline{Me}_3$]. ^{13}C NMR: δ 165.226, (C-7, C-21, C-28, C-42), 158.579 (C-13, C-18, C-34, C-39), 137.201 (C-8, C-19, C-29, C-40), 136.913 (C-12, C-17, C-33, C-38), 130.273 (C-9, C-20, C-30, C-41), 129.346 (C-11, C-16, C-32, C-37), 118.310 (C-10, C-15, C-31, C-36), 77.421 (C-1, C-6, C-22, C-27), 40.344 (C-14, C-35), 34.689 (C-2, C-5, C-23, C-26), 24.847 [C-43 ($\underline{C}Me_3$), C-44 ($\underline{C}Me_3$), C-45 ($\underline{C}Me_3$), C-46 ($\underline{C}Me_3$)], 24.164 (C-3, C-4, C-24, C-25), 33.234 [C-43 ($C\underline{Me}_3$), C-44 ($C\underline{Me}_3$), C-45 ($C\underline{Me}_3$), C-46 ($C\underline{Me}_3$)].

Calix[2]salen 6

Yield: about 20%. MALDI/TOF MS: calculated: $C_{58}H_{76}N_4O_4$, 893. 59 m/z; Found: 893.57. ^1H-NMR: δ 13.695(s, 4H, OH), 8.213 (s, 4H, H-7, H-21, H-28, H-42), 7.072 (s, 4H, H-9, H-20, H-30, H-41), 6.762 (s, 4H, H-11, H-16, H-32, H-37), 3.700 (s, 4H, H-14, H-35), 3.291 (m, 8H, H-1, H-6, H-22, H-27,) 1.577, (m, 16H, cyclohexyl ring), 1.340, [s, 36H, H-43 ($C\underline{Me}_3$), H-44 ($C\underline{Me}_3$), H-45 ($C\underline{Me}_3$), H-46 ($C\underline{Me}_3$].

Calix[3]salen 7

Yield: about 15%. MALDI/TOF MS: calculated: $C_{87}H_{114}N_6O_6$, 1339.88 m/z, found: 1340.88 m/z. ^1H-NMR: δ 13.695(s, 6H, OH), 8.213 (s, 6H, $C\underline{H}$=N), 7.072 (s, 6H, aromatic H), 6.762 (s, 6H, aromatic H), 3.700 (s, 6H, $C\underline{H}_2$), 3.291 (m, 12H, N-$C\underline{H}$) 1.577, (m, 24H, cyclohexyl ring), 1.340, (s, 54H, $C\underline{Me}_3$).

Calixsalen complexes

To a yellow solution of ligand **5a** or **5b** (0.060 mmol) in 4 mL of 1:1

CH_2Cl_2/EtOH was added a solution of $Mn(OAc)_3 \cdot 2H_2O$ (2.5 equiv., 0.040 g, 0.15 mmol) in 2 mL of 1:1 CH_2Cl_2/EtOH. The mixture was stirred for 2.5 h at room temperature and monitored by TLC (15% EtOH in CH_2Cl_2 as mobile phase). The solvent was removed at aspirator vacuum and the resulting brown residue was dissolved in 4 mL of CH_2Cl_2 and filtered through a 1 mL celite plug. The filtered solution was evaporated to dryness yielding a glassy black solid. To a solution of the acetate solid in 4 mL of 1:1 CH_2Cl_2/EtOH was added an excess of LiCl (10 equiv., 0.028 g, 0.65 mmol) as a solid. The solution was stirred at room temperature for 3 h, then chromatographed over silica with 15% EtOH in CH_2Cl_2. Slow evaporation of the brown band eluted gave clear brown triclinic crystals suitable for X-ray analysis.

An analogous procedure was performed for the *anti*-dimer, trimer, and tetramer complexes etc. The reaction mixture of complexes was separated by column chromatography to give pure *anti* calix[2]salen complex **11** and calix[3]salen complex **12**.

Calix[2]salen complex 10 a

Yield: about 78 %. MALDI-TOF/MS: calculated: $Mn_2C_{56}H_{68}N_4O_4Cl_2$, 1017.30 m/z; Found: 1017.80 m/z (EtOH displace Cl^-).

Calix[2]salen complex 10 b

Yield: about 80%. MALDI-TOF/MS: calculated: $Mn_2C_{58}H_{76}N_4O_4Cl_2$, 1068.37 m/z; Found: significant peaks, free ligand: 893.57, $MnC_{58}H_{74}N_4O_4$: 947.42, $Mn_2C_{58}H_{72}N_4O_4$: 998.31, $Mn_2C_{58}H_{72}N_4O_4Cl$: 1035.24, $Mn_2C_{58}H_{72}N_4O_4Cl$(EtOH): 1078.55 m/z.

Anti-calix[2]salen complex 11

Yield: ~ 50%. MALDI-TOF/MS: calculated: $Mn_2C_{58}H_{72}N_4O_4Cl_2$, 1068.37 m/z; Found: significant peaks, free ligand: 893.67, $MnC_{58}H_{74}N_4O_4$: 945.60, $Mn_2C_{58}H_{72}N_4O_4$: 998.31, $Mn_2C_{58}H_{72}N_4O_4Cl$: 1033.48, $Mn_2C_{58}H_{72}N_4O_4Cl(EtOH)$: 1078.55 m/z.

Calix[3]salen complex 12

Yield: ~ 25%. MALDI-TOF/MS: calculated for $[Mn_3C_{87}H_{108}N_6O_6Cl_3]$: 1062.55 m/z. Found: significant peaks, free ligand: 1339.88, $MnC_{87}H_{102}N_6O_6$: 1392.78, $Mn_2C_{87}H_{110}N_6O_6$: 1445.69, $Mn_3C_{87}H_{108}N_6O_6$: 1498.59.

Calix[4]salen complex 13

Yield: ~ 10%. MALDI-TOF/MS: calculated for $[Mn_4C_{116}H_{144}N_8O_8Cl_4]$: 1996.86 m/z. Found: significant peaks, free ligand: 1788.50, $MnC_{116}H_{150}N_8O_8$: 1840.38, $Mn_2C_{116}H_{148}N_8O_8$: 1893.31, $Mn_3C_{116}H_{146}N_8O_8$: 1945.23, $Mn_4C_{116}H_{144}N_8O_8$: 1998.1552.

Calix[5]salen complex 14

Yield: ~ 10%. MALDI-TOF/MS: calculated for $[Mn_5C_{145}H_{182}N_{10}O_{10}Cl_5]$: 2673.92 m/z. Found: significant peaks, free ligand: 2231.91, $MnC_{145}H_{188}N_{10}O_{10}$: 2286.77, $Mn_2C_{145}H_{186}N_{10}O_{10}$: 2339.69, $Mn_3C_{145}H_{184}N_{10}O_{10}$: 2402.11, $Mn_4C_{145}H_{182}N_{10}O_{10}$: 2444.32.

References:

1. Sanders, J. K. M. *Chem. Eur. J.* **1998**, *4*, 1379.
2. (a) Campbell, L. A.; Kodadek, T. *J. Mol. Catal.* **1996**, *113*, 293. (b) Gonsalves, A. M. D. R.; Pereira, M. M.*J. Mol. Catal.* **1996**, *113*, 209. (c) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107,* 7606. (d) Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am.* Chem. *Soc.* **1986**, *108,* 2309.
3. (a) Dawson, D. H.; Sono, M.; *Chem. Rev.* **1987**, *87*, 1255. (b) Gunter, M. J.; Turner, P. *Coord. Chem. Rev.* **1991**, *108*,115. (c) *Cytochrome P-450, Structure, Mechanism and Biochemistry,* ed. P. R. Ortiz de Montellano, Plenum Press, New York, **1995**.
4. (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J . Am.* Chem. *Soc.* **1990**, *112,* 2801. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Kastuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345.
5. (a) Kastuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189. (b) David, L. H.; Smith, G. B.; Liu, J.; Dezeny, G. C.; Senanayake, C. H.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2222. (c) Adam, W.; Mock-Knoblauch, C.; Saha-Möller, C. R.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122,* 9685.
6. (a) Jacobsen, E. N. *Catalytic Asymmetric synthesis,* Ojima, I., Ed.; VCH: New York, **1993**. (b) Jacobsen, E. N. *Comprehensive Organomettalic Chemisty II,* Abel, E. W.; Stone, F. G. A.; Wilkinson, G., Eds.; Pergamon: New York, **1995**. (c) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189. (d) Katsuki, T. *J. Mol. Catal. A: Chem.* **1996**, *113*, 87. (e) Linker, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2060.
7. (a) Pietikäinen, P. *J. Mol. Catal. A: Chem.* **2001**, *165*, 73. (b) Senanayake, C. H.; Smith, G. B.; Ryan, K. M.; et al *Tetrahedron Letters*, **1996**, *37*, 3271. (c) Pietikäinen, P.

Tetrahedron Letters, **1995**, *36*, 319.

8. Moran, J. R.; Karbach, S.; Cram, D. J. *J . Am. Chem. Soc.* **1982**, 104, 5826.
9. Kyba, E. P.; Helgeson, R. C.; Madan, K.; Gokel, G. W.; Tarnowski,T. L.; Moore, S. S.; Moran, J. R. *J . Am. Chem. Soc.* **1977**, *99.* 2564.
10. (a) Wilcox, C. S.; Greer, L. M.; Lynch, V. *J. Am. Chem. Soc.* **1987,** *109,* 1866. (b) Veggel, F. C. J.; Verboom, W.; Reinhoudt, D. N. *Chem. Rev.* **1984**, *94,* 280. (c) Lynam, C.; Jennings, K.; Nolan, K.; Kane, P.; McKervey, M. A.; Diamond, D. *Anal. Chem.* **2002**, *74*, 59.
11. (a) Jablonski, C.; Li, Z. *Chem. Comm.* **1999**, 1531. (b) Jablonski, C.; Li, Z. *Inorg. Chem.* **2000**, *39*, 2456.
12. Whitney, T. A. *J. Org. Chem.* **1980**, *45*, 4214.
13. Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: New York, **1989**.
14. Jørgensen, K. A. *Chem. Rev.* **1989**, *89*, 431.
15. (a) Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107,* 7606. (b) Jacobsen, E. N.; Zhang, W.; Giiler, M. L, *J. Am. Chem. Soc.* **1991**, *113*, 6703. (c) Palucki, M.; Finey, N. S.; Pospisil, P. J.; Guller, M. L.; Ishida, T.; Jacobsen, E. N.; *J. Am. Chem. Soc.* **1998**, *120,* 948.
16. (a) Yoon, H.; Burrows, C. J. *J. Am. Chem. Soc.* **1988**, *110,* 4087. (b) Yoon, H.; Wagler, T. R.; O'Connor, K. J.; Burrows, C. J. *J. Am. Chem. Soc.* **1990**, *112,* 4568. (c) Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.
17. (a) Wilcox, C. S.; Greer, L. M.; Lynch, V. *J . Am. Chem. Soc.* **1987**, *109,* 1865. (b) Tabushi, I.; Sasaki, H.; Kuroda, Y. *J. Am. Chem. Soc.* **1976**, *98*, 5727. (c) Rebek, J.,

Jr.; Askew, B.; Islam, N.; Killoran, M.:Nemeth, D.: Wolak, R. *J. Am. Chem. Soc.* **1985**, *107*, 6736. (d) McKenna, J.; McKenna, J. M.; Thornwaite, D. W. *J .Chem. Soc., Chem. Commun.* **1977**, 809.

18. (a) Larrow, J. F.; Jacobsen. E. N. *J. Org. Chem.* **1994**, *59*. 1939. (b) Zhang, W.; Loebach, J. L.; Wilon, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. (c) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897.
19. K. Coulter unpublished results from this laboratory.
20. Veggel, F. C. J. M.; Bos, M.; Harkema, S.; Bovenkamp, H.; Verboom, W.; Reedijk, J.; Reinhoud, D. N. *J. Org. Chem.* **1991**, *56*, 225.

Chapter 3. Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by Mn^{III}-(calixsalen) Catalysts

3.1 Maximization of Enantioselectivity for Conjugated Olefins

As characterized in Chapter 2, Mn^{III}-(calixsalen) complexes structurally resemble natural receptors with rigid cavities that support internal host-guest substrate interactions. Therefore, these complexes are anticipated to achieve high selectivities and catalytic efficiencies by controlling the steric environment around the active centres to orient the captured substrates and maximize chiral communication. In addition, the rigid macrocyclic frameworks might have an advantage in their robustness against various terminal oxidants. In metallosalen catalyzed epoxidation, in addition to steric and electronic effects of the catalysts, other important features include the nature of the axial ligand and the choice of oxidants which also affect the enantioselectivity. As for the general reaction conditions, asymmetric epoxidation is usually carried out in the presence of a catalytic amount of the Mn^{III}-(salen) complex with 1-2 equivalents of a stoichiometric oxidant and axial ligand at temperatures varying from room temperature to -20 °C. In some cases even lower temperatures have been used.[1] Generally, enantioselectivity is enhanced as the reaction temperature is lowered. The most common solvents are dichloromethane and acetonitrile, but many other non-polar solvents are also applicable.[2] A variety of stoichiometric oxidants such as PhIO, NaOCl, peroxyacids, H_2O_2, $KHSO_5$, and

dimethyldioxirane are effective for Mn^{III}-(salen) catalyzed epoxidations. The beneficial effect of axial ligands capable of coordinating and stabilizing the metal centre in porphyrins has also been observed in metallosalen catalyzed epoxidation. This chapter reports the optimization of the asymmetric epoxidation system catalyzed by Mn^{III}-(calixsalen) complexes based on literature reports using Jacobsen and Katsuki catalysts.

3.1.1 Effects of Oxidants

In principle, a variety of stoichiometric oxidants can be used in catalytic oxidation reactions. However, many factors influence the choice of oxidants, for instance, price, availability, nature of the waste product, active oxygen content and ease of recycling. Based on these factors, oxidants such as O_2/reductant and hydrogen peroxide should be ideal since they have high oxygen content and produce only water as a by-product. In fact, molecular oxygen and hydrogen peroxide have rarely been used in asymmetric epoxidation probably because of the presence of competing reactions.[3]

3.1.1.1 Asymmetric Epoxidation with NaOCl

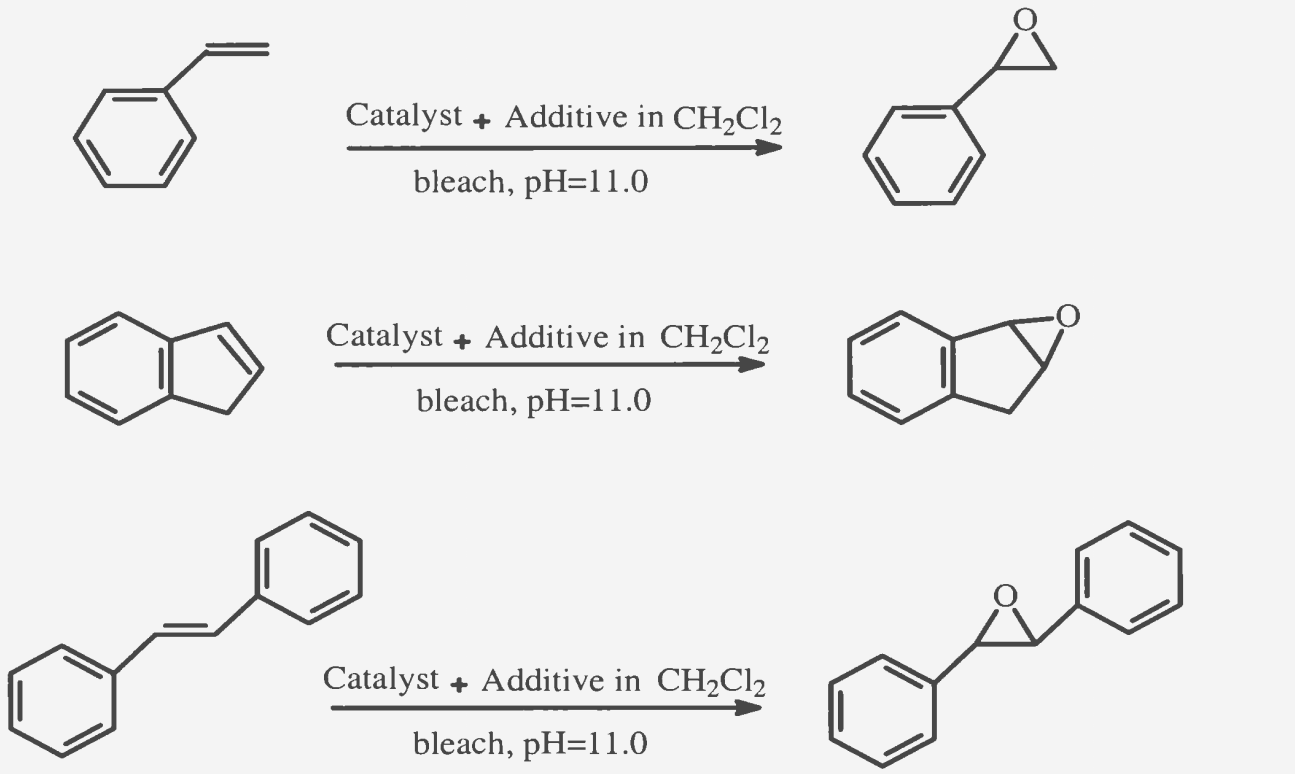
Aqueous sodium hypochlorite, NaOCl(aq.), is an inexpensive and readily available oxidant with many applications in organic chemistry. For more than two decades, oxidations of manganese porphyrin complexes by sodium hypochlorite were carried out to understand the mechanism of water oxidation in photosynthesis.[4] At the same time, it was also used as an oxidant in the search for macrocyclic complexes that would catalyze

the olefin epoxidation reaction. The association of NaOCl(aq.) with metallosalen complexes was first reported by Burrows et al. as one of the most efficient systems for the asymmetric epoxidation of nonactivated olefins.[5] In 1991, Jacobsen et al. developed an efficient asymmetric epoxidation procedure consisting of a biphasic system with an aqueous phase containing commercial bleach and an organic phase composed of a solution of substrate and catalyst in a suitable solvent.[6] Usually pyridine *N*-oxide is added to the reaction system to improve both catalyst turnover and enantioselectivity.[7]

In this work, the biphasic system with commercial bleach as oxygen source (eq. 1)

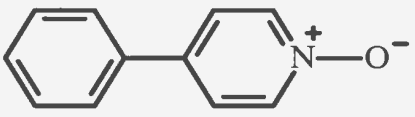
$$ClO^- + H_2O + 2e \longrightarrow Cl^- + 2OH^- \qquad E^o = +0.890\ v \qquad \text{eq.1}$$

was first used to evaluate the turnover and enantioselectivity of Mn^{III}-(calixsalen) asymmetric catalysts. Reactions were typically conducted at room temperature and 0^oC because the temperature window available for reactions with such aqueous oxidant systems is limited by the high freezing temperature of water. The epoxidation of conjugated *cis*-disubstituted and trisubstituted olefins has been achieved with high ee (greater than 90%), but terminal olefins such as styrene undergo epoxidation with relatively low ee.[8] Therefore, the epoxidation of styrene provided a useful model for evaluating enantioselectivity, and this substrate was used to screen various oxidants. In addition, the *cis*-substituted olefin, indene, and the *trans*-substituted olefin, *trans*-stilbene, were used to investigate the substrate scope as well as the level to which the enantioselectivity may be raised by modification of the asymmetric oxidation system as shown in **Figure 3-1**.



Additives:

4- phenylpyridine N-oxide (4- PPNO)



N- methylmorpholine *N*-oxide (NMO)

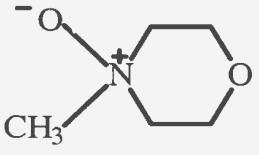


Figure 3-1 Asymmetric epoxidation of unfunctionalized olefins

According to the published results that 4-PPNO was the most effective additive for reactions involving aqueous oxidants such as NaOCl(aq.),[9] the epoxidation of the conjugated olefins, styrene, indene and *trans*-stilbene was conducted using the combination of NaOCl(aq.) and 4-PPNO with the biphasic system protocol. The data in **Table 3-1** indicate that each of Mn^{III}-(calixsalen) catalysts investigated shows promising results with

good turnovers and high enantiomeric excesses (ee) of 78% compared with the previous best one of 57%.[7a] For indene, high enantioselectivity greater than 90% has been achieved. However, styrene undergoes epoxidation with only 56-78% ee. This apparent difference may be attributed to a special type of mechanism for asymmetric epoxidation of terminal olefins. Epoxidation via oxo-Mn(V) species has been demonstrated to proceed via both *cis* and *trans* pathways.[10] As illustrated in **Figure 3-2**, the *trans* pathway results in a decrease in enantioselectivity with terminal olefins because with these substrates the *cis* and *trans* products are enantiomeric.[8]

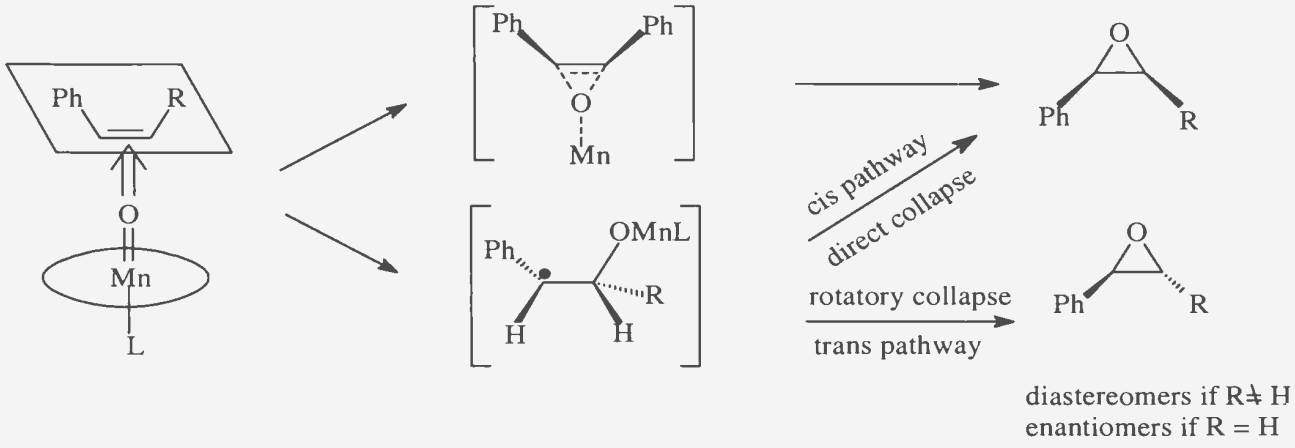


Figure 3-2 Mechanism for asymmetric epoxidation of terminal olefins

The epoxidation of *trans*-stilbene proceeded rather slowly at room temperature. It is possible that steric interactions between the substituents of these olefins and the ligand plane prevent the approach of olefins to the oxo-Mn(V) centre. Consequently, the *trans* olefins should be poor substrates for epoxidation catalyzed by macrocyclic Mn^{III}-(calixsalen) catalysts.

Table 3-1 Asymmetric Epoxidation of Conjugated Olefins with NaOCl

Catalyst	Alkene	S/C	Additive	T/°C	Turnover	ee%±3%	Config.
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	styrene	100/1	4-PPNO	R. T.	25.3	73.0%	*R*
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	styrene	100/1	4-PPNO	R. T.	24.7	66.0%	*R*
(*R*, *R*)-Mn_3(calixsalen)Cl_3(trimer)	styrene	100/1	4-PPNO	R. T.	64.1	56.0%	*R*
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	styrene	100/1	4-PPNO	0	67.5	46.0%	*R*
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	styrene	100/1	4-PPNO	0	12.8	78.3%	*R*
(*R*, *R*)-Mn_3(calixsalen)Cl_3(trimer)	styrene	100/1	4-PPNO	0	41.8	56.7%	*R*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	indene	100/1	4-PPNO	R. T.	49.3	93.8%	*R, S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	indene	100/1	4-PPNO	R. T.	31.7	91.8%	*R, S*
(*R*,*R*)-Mn_3(calixsalen)Cl_3(trimer)	indene	100/1	4-PPNO	R. T.	31.2	98.5%	*R, S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	indene	100/1	4-PPNO	0	34.2	96.3%	*R, S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	indene	100/1	4-PPNO	0	33.2	93.0%	*R, S*
(*R*,*R*)-Mn_3(calixsalen)Cl_3(trimer)	indene	100/1	4-PPNO	0	29.1	97.5%	*R, S*

3.1.1.2 Asymmetric Epoxidation with *m*-CPBA

As discussed in the previous section, the epoxidation of terminal olefins proceeds via direct substrate attack at the oxo-Mn(V) complexes in a concerted or sequential fashion involving radical intermediates.[11] More recent experimental results seem to provide evidence for substrate attack at the oxo-Mn(V) complex only,[12] as well as for the existence of manganaoxetanes.[13] The *trans* pathway resulted in a decrease in enantioselectivity with terminal olefins. When comparing the rotatory collapse with direct collapse (**Scheme 3-2**), the latter represents the path of lower activation barrier, even for the sterically unencumbered model olefins.[10] This is in agreement with the experimentally observed limited conversion of *cis* olefins such as *cis*-β-methylstyrene into the thermodynamically more stable *trans* epoxide.[12] It is therefore reasonable that lowering the epoxidation reaction temperature might provide a straightforward approach toward both minimizing the *trans* pathway and improving the enantiofacial selectivity in the first step. However, the high freezing temperature of the aqueous NaOCl oxidant system limited the temperature range under which the reaction could be studied. Jacobsen's evaluation of non-aqueous terminal oxidant systems indicated that *m*-chloroperbenzoic acid can induce the epoxidation of styrene in organic solvent such as CH_2Cl_2 at -78 °C in the presence of Mn^{III}-(salen) catalysts, and the epoxidation was "remarkably rapid",[14] hence this oxidant system was used to assess the Mn^{III}-(calixsalen) epoxidation catalysts at low temperature.

Axial ligation of the metallosalen catalyst is known to have a favourable influence

on asymmetric induction. This has been explained by a shortening of the Mn-O bond length and a decrease in the reactivity of the oxo species upon axial coordination.[1] Recently, an electrospray tandem mass spectrometric study of highly reactive intermediates provided experimental evidence that the axial coordination of an *N*-oxide ligand by oxo-Mn(V) complexes raises the oxygen transfer reactivity of the catalyst dramatically.[15] Since it is also known from the literature that *N*-methylmorpholine-*N*-oxide (NMO) is an effective additive for anhydrous oxidant systems,[16] the combination of *m*-CPBA and NMO was used as an anhydrous oxidant system to investigate the low temperature protocol leading to improved ee's with a range of unfunctionalized olefins.

The data in **Table 3-2** show that the epoxidation of styrene at -78 °C with *m*-CPBA as the oxidant in the presence of the *N*-methylmorpholine *N*-oxide achieves a good turnover and high ee (97%) compared with the previous best one (86%).[9] For indene, good turnovers (45) and high ee's (93%) were obtained at room temperature or 0 °C with the combination of NaOCl and 4-PPNO as biphasic oxidation system. However, the evaluation of non-aqueous terminal oxidant system at low temperature reveals that epoxidation with *m*-CPBA proceeded with good turnovers but low ee's (30%). The low ee% may be in part due to participation of an isomerization pathway leading to by-products. In 1995, Katsuki et al.[17] found that some acid-sensitive epoxides slowly rearranged to ketones under the epoxidation condition. Since the Mn^{III}-(salen) complex itself did not catalyze the rearrangement, the oxo-Mn^{V}-(salen) complex was considered to be

Table 3-2 Asymmetric Epoxidation of Conjugated Olefins with *m*-CPBA

Catalyst	Alkene	S/C	Additive	T/°C	Turnover	ee%±3%	Config.
(*R, R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	styrene	100/1	NMO	-78	48.7	96.7%	*S*
(*R, R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	styrene	100/1	NMO	-78	30.3	64.7%	*S*
(*R, R*)-Mn_3(calixsalen)Cl_3(trimer)	styrene	100/1	NMO	-78	18.1	72.3%	*S*
(*R,R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	indene	100/1	NMO	-78	68.5	71.4%	*R, S*
(*R,R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	indene	100/1	NMO	-78	53.8	35.7%	*R, S*
(*R, R*)-Mn_3(calixsalen)Cl_3(trimer)	indene	100/1	NMO	-78	56.8	42.1%	*R, S*

responsible for the rearrangement. This suggested that oxo-Mn^{V}-(salen) complexes would serve as Lewis acid catalysts and induce epoxides to rearrange to ketones. Although the oxo-Mn^{V}-(salen) complex is a strong oxo transfer reagent and this makes its use as Lewis acid catalyst difficult, it was found that the reduced temperature suppressed the function of the oxo-Mn^{V}-(salen) complex as an oxidizing agent without impairing its Lewis acidity.[18] The result of the epoxidation of indene provided further strong evidence that oxo-Mn^{V}-(salen) complexes promoted the rearrangement of epoxides under the epoxidation conditions at low temperature. In this work, the rearranged product has been detected by HPLC with the same molecular weight and a different retention time from indene epoxides.

It is rather surprising that the sense of chiral induction for styrene epoxide is opposite for bleach versus *m*-CPBA. Based on the mechanistic model for oxygen-atom transfer [19] that the key oxo-Mn(V) species (detected by electrospray mass spectrometry) is acting as the staging post for oxygen transfer, the sense of chiral induction depends only on this active intermediate. Thus, different terminal oxygen atom sources should lead to epoxidation activity with the same chiral induction. However, recent reports[20] show this may not be the case and that the catalytic cycle must be extended to accommodate some divergent mechanisms. The fact that the type of oxygen donor affects the chiral induction of the epoxidation of styrene requires that, besides oxo-Mn(V) species, at least one other oxidant must be involved in this catalytic process. If the same active species acted as staging post for oxygen transfer in both aqueous system with buffered bleach and

non-aqueous system with *m*-CPBA, the epoxidation should proceed with the same chiral induction. The results for asymmetric epoxidation of styrene emphasize the need for the continued efforts to elucidate the detailed mechanism of oxygen-atom transfer and the basis for selectivity in this and related systems.

The epoxidation of *trans*-stilbene with the anhydrous *m*-CPBA and NMO oxidant system proceeded rather slowly, consistent with the *trans* olefins being poorer substrates for epoxidations catalyzed by macrocyclic Mn^{III}-(calixsalen) catalysts.

In conclusion, a variety of oxidants are effective oxygen atom donors for olefin epoxidation in the presence of chiral Mn^{III}-(calixsalen) complexes. The combination of *m*-CPBA and NMO at low temperature was found to be particularly effective for the epoxidation of terminal olefins such as styrene, but it is not effective for the epoxidation of indene.

3.1.1.3 Asymmetric Epoxidation with *t*-BuOOH

Alkyl hydroperoxides are easily produced by the auto-oxidation of alkanes having one tertiary C-H bond (isobutane, cumene). These oxidants are very good oxygen atom donors in olefin epoxidation catalyzed by molybdenum, vanadium, or titanium complexes. Alkyl hydroperoxides are also the oxidants of choice for the Sharpless asymmetric epoxidation of allylic alcohols.[21] The epoxidation with *tert*-butyl hydroperoxide as oxidant catalyzed by achiral Mn^{III}-(salen) complexes was first studied by Kochi et al.[22] Although it is a very effective oxidant in the epoxidation of allylic alcohols in the presence

of Sharpless' catalyst, the evaluation of the epoxidation with anhydrous *t*-BuOOH as oxidant catalyzed by Mn^{III}-(salen) complexes showed that the rate of reaction was extremely slow and afforded epoxide only in low yields along with a mixture of by-products. In this work, the evaluation of anhydrous *t*-BuOOH as an oxidant in the epoxidation catalyzed by the Mn^{III}-(calixsalen) complexes gave the same result. It is not an effective oxidant.

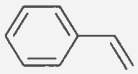
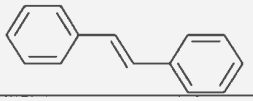
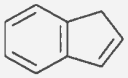
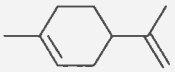
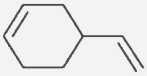
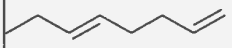
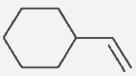
The new insights into the mechanism of O–O bond cleavage of *tert*-alkyl hydroperoxides by metalloporphyrins showed that the main problem in transition metal complexes (metalloporphyrin, salen catalysts) catalyzed epoxidation with alkyl hydroperoxide is the homolytic cleavage of the weak O–O bond to form an oxo-iron(IV) complex and a radical $RO^{\cdot}$, which is able to abstract one hydrogen atom from alkenes but is unable to produce epoxides.[23] In the presence of a nitrogen axial ligand, the activation of alkyl hydroperoxides by metalloporphyrins is greatly enhanced and produces oxo-metal(V) porphyrins, a reactive species leading to the epoxidation of alkenes, and the corresponding alcohol. However, heterolytic versus homolytic O–O bond cleavage of the hydroperoxides was found to be significantly affected both by the electronic nature of the metalloporphyrin and the substituents of *tert*-alkyl peroxides. In contrast, hydrogen peroxide or *tert*-alkyl peroxides together with transition metal complexes (metalloporphyrins, salen complexes) afforded epoxides in very low yield and induced poor enantioselectivity in the epoxidation of various alkenes.

3.1.2 Substrate Effects

Asymmetric induction by chiral Mn^{III}-(salen) catalysts is also dependent on the alkene substitution pattern. Based on the published literature [18] and the above results that the combination of *m*-CPBA and NMO is the optimum oxidation system at low temperature, a number of olefins were subjected to this low temperature procotol and biphasic oxidation system by using NaOCl. The results indicated that conjugated substrates (conjugated to aryl, alkenyl or alkynyl group) give the highest enantioselectivities in the epoxidation by Mn^{III}-(calixsalen) catalysts. As listed in **Table 3-3**, the epoxidation of limonene, vinyl-cyclohexane, or 4-vinyl-cyclohexene, each with a non-conjugated double bond gave very low turnovers, even after a long reaction time. It should be noted that these low turnover results are not conclusive because the alkenes were so volatile that their GC-MS peaks were obscured by the solvent. In future, care should be taken to repeat these results with an appropriate GC column.

A concerted mechanism has been proposed for the Mn^{III}-(salen) mediated epoxidation of unfunctionalized alkyl-substituted olefins whereas a non-concerted mechanism is proposed for the epoxidation of aryl-substituted olefins.[24] In the non-concerted mechanism with stepwise formation of the two C–O bonds in the product epoxide, the intermediate radical is stabilized by benzene. This analysis supported the fact that aryl-substituted olefins react much faster than aliphatically substituted olefins. Enantioselectivities are also very different for these two substrate classes. Possibly, the

Table 3-3 Substrate effects for Mn^{III}-(calixsalen) catalysts

Alkene	turnover	ee%	Alkene	turnover	ee%
	24.7	73		4	
	34.2	96.3		0	
	0			<10	
	0			0	
	0			0	

aryl substituted olefins have enhanced chiral interactions with the catalysts because of their planar structure.

The epoxidation of *trans*-stilbene gave only a trace amount of epoxide, even though the double bond is conjugated to an aryl group. The intermetallic distance of Mn^{III}-(calix[2]salen) complex cavity is about 7.7 Å, so the substituents connected to the double bond should not be bulky; otherwise, it is too difficult for bulky olefins such as *trans*-stilbene to fit in the cavity in order to approach the active centre. Therefore, unlike Jacobsen-type catalysts which react via side-on approach, the epoxidation of olefins catalyzed by Mn^{III}-(calixsalen) complexes proceeds via the internal host-guest pathway over the diimine bridge or along the N—Mn bond axis to fit in the cavity to approach the active centres.

It was rather surprising that there was not any epoxide detected in the epoxidation of 2, 3-dimethyl-1, 3-butadiene, a conjugated alkene without bulky substituents.

3.1.3 Axial Ligand Effects

It was first observed by Kochi et al. in their kinetic and structural studies of metallosalen catalyzed epoxidations that the addition of a donor ligand such as pyridine *N*-oxide stabilizes oxo-metal intermediates via axial coordination resulting in enhanced reaction rates and epoxidation yields.[25] There are many reports that highlight the effect of axial ligation on the selectivity of metalloporphyrins and metallosalens in epoxidation reactions.[26] It is well established that the active site of biochemically functioning proteins such as haemoglobin and cytochrome P-450 is axially coordinated by imidazole or thiolate functions of amino acids. Also, the chemical, electrochemical and spectroscopic properties of related transition metal complexes are profoundly influenced by axial coordination because of the *trans*-relationship of the axial ligand to the transferable oxygen atom.[27] Similarly, the active species of Mn^{III}-(calixsalen) complexes could be stabilized by coordination with an appropriate axial ligand. The data in the **Table 3-4**, **Figure 3-3** and **Figure 3-4** show that both 4-PPNO and NMO axial ligands significantly improved the turnover and enantioselectivity. The literature provides indirect evidence for a correlation of axial coordination of the high valent manganese intermediate in the catalytic cycle with electronic properties of the amines. However, there is no obvious dependence on the

electron donating power of substituted pyridines. Thus, the increase in enantioselectivity cannot be solely attributed to electronic effects. A plausible explanation for the general improvement by axial ligation is that the binding of the organic bases in the highly crowded environment would restrict the rotational freedom of the salen-phenol rings against the salen plane, leading to a comparatively more rigid pocket for more efficient chiral molecular recognition.

For Mn^{III}-(calixsalen) catalysts, the increase in enantioselectivity may be related to the blockage of external approach of the substrate to the active centre upon coordination of axial ligand, leading to a more enhanced chiral substrate interaction inside the calixsalen cavity. Moreover, the coordination of a bulky axial ligand outside of the cavity of Mn^{III}-(calixsalen) complexes strongly enhances the stability of the catalyst, which in this approach is protected from further oxidative decomposition. A possible complication with the involvement of *N*-oxides as axial ligand is that the amines are prone to oxidation although it is regarded as a minor problem in alkene epoxidation.[28] Another important consideration is the involvement of different reactive species generated depending on the axial ligands.[29]

Table 3-4 The effect of additives in the epoxidation of styrene

Entry	Catalyst	Axial ligand	Turnover	ee%
1	(*R*, *R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	No additive	9.1	42.5
2	(*R*, *R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	No additive	15.3	32.6
3	(*R*, *R*)-Mn_3(calixsalen)Cl_3(trimer)	No additive	4.3	27.8
4	(*R*, *R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	4-PPNO	26.7	73.0
5	(*R*, *R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	4-PPNO	25.0	66.7
6	(*R*, *R*)-Mn_3(calixsalen)Cl_3(trimer)	4-PPNO	64.1	56.0
7	(*R*, *R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	NMO	48.7	96.7
8	(*R*, *R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	NMO	30.3	64.7
9	(*R*, *R*)-Mn_3(calixsalen)Cl_3(trimer)	NMO	18.1	72.3

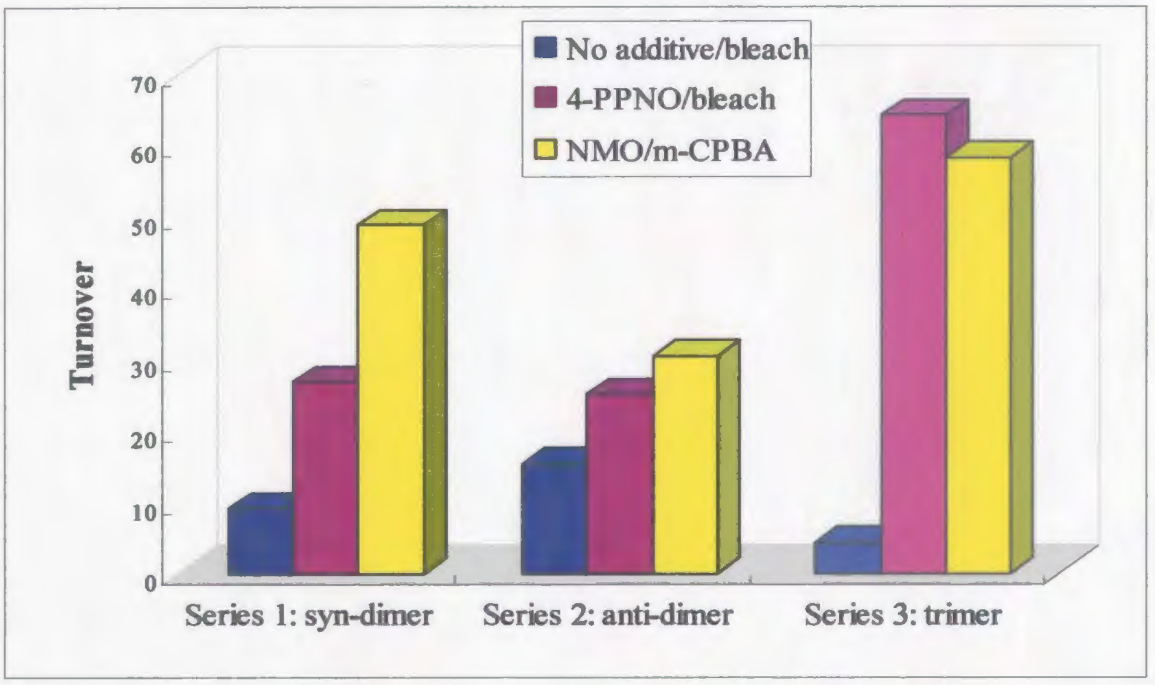


Figure 3-3 The effect of axial ligand on the turnover

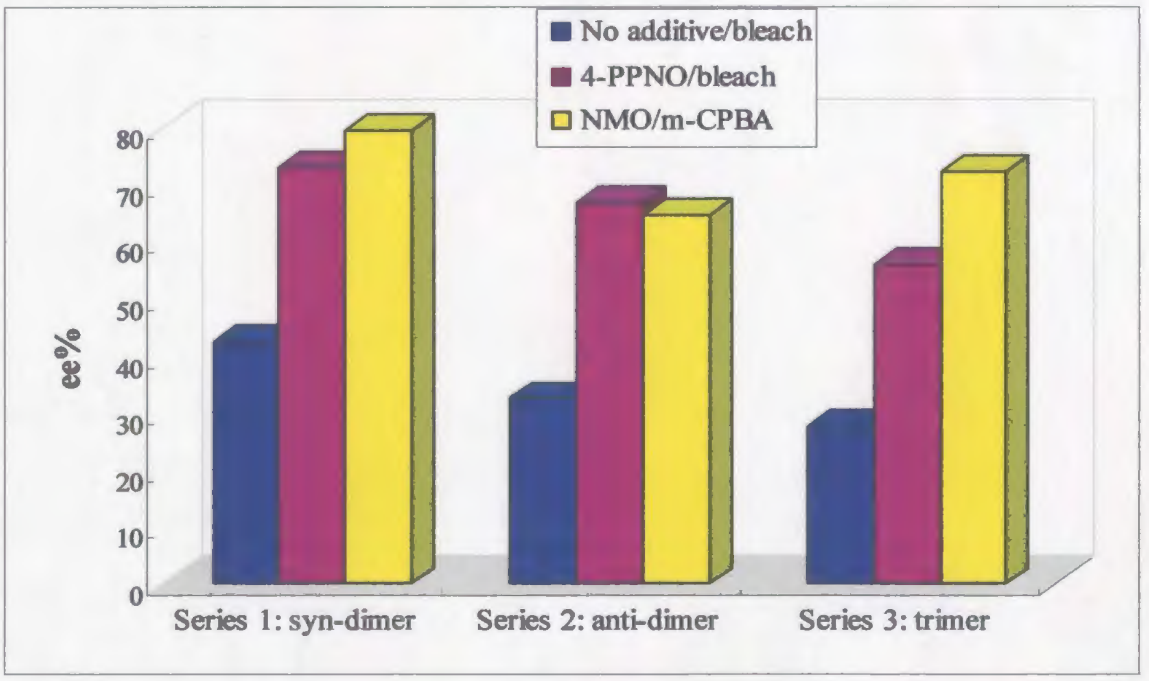


Figure 3-4 The effect of axial ligand on ee%

3.2 Results

The Mn^{III}-(calixsalen) catalyzed epoxidation of unfunctionalized olefins in biphasic media was carried out with 1 mol % of catalyst and 4 equiv. of NaOCl(aq.) at room temperature and 0 °C. The results summarized in **Table 3-1** indicate that each of Mn^{III}-(calixsalen) catalysts investigated shows good turnover and high ee of 78% compared with the previous best reported value of 57%.[7a] For indene, high enantioselectivity greater than 90% has been achieved. However, styrene undergoes epoxidation with only 50-78% ee. This apparent difference may be attributed to a special type of mechanism for asymmetric epoxidation of terminal olefins. Epoxidation via oxo-Mn(V) species has been demonstrated to undergo both *cis* and *trans* pathways.[9] The *trans* pathway results in a decrease in enantioselectivity with terminal olefins.

The combination of *m*-CPBA and NMO was used as an anhydrous oxidant system to investigate low temperature protocol. The epoxidation of styrene at -78 °C with this non-aqueous oxidant system was carried out with 1 mol % of catalyst and 2 equiv. of *m*-CPBA at -78 °C, achieving a good turnover and high ee of 97% as compared to biphasic oxidation system with bleach.

Asymmetric induction by chiral Mn^{III}-(calixsalen) catalysts is also dependent on the alkene substitution pattern. A number of olefins were subjected to both low temperature procotol with the combination of *m*-CPBA and NMO and biphasic oxidation system by using NaOCl(aq.). The results indicated that conjugated substrates (conjugated

to aryl, alkenyl or alkynyl group) give the highest enantioselectivities in Mn^{III}-(calixsalen) catalyzed epoxidation. As listed in **Table 3-3**, the epoxidation of limonene, vinyl-cyclohexane, or 4-vinyl-cyclohexene, each with a non-conjugated double bond gave very low turnovers, even after a long reaction time. It should be noted that these low turnover results are not conclusive because the alkenes were so volatile that their GC-MS peaks were obscured by the solvent.

The epoxidation of *trans*-stilbene gave only a trace amount of epoxide, even though the double bond is conjugated to an aryl group. The inter-metallic distance of Mn^{III}-(calix[2]salen) complex cavity is about 7.7 Å, so it is difficult for bulky olefins such as *trans*-stilbene to fit in the cavity in order to approach the active centre. Therefore, unlike Jacobsen-type catalysts which react via side-on approach, the epoxidation of olefins catalyzed by Mn^{III}-(calixsalen) catalysts proceeds via the internal host-guest pathway over the diimine bridge or along the N—Mn bond axis to fit in the cavity to approach the active centres.

The effect of axial ligation on the selectivity of the Mn^{III}-(calixsalen) catalyzed epoxidation was also investigated. The data in the **Table 3-4**, **Figure 3-3**, and **Figure 3-4** show that both 4-PPNO and NMO axial ligands significantly improved the turnover and enantioselectivity. Similar to metallosalens in epoxidation reactions, the active species of Mn^{III}-(calixsalen) complexes may be stabilized by coordination with an appropriate axial ligand. For Mn^{III}-(calixsalen) catalyzed epoxidation, the increase in enantioselectivity

may be related to the blockage of external approach of the substrate to the active centre upon coordination of axial ligand, leading to a more enhanced chiral substrate interaction inside the Mn^{III}-(calixsalen) cavity.

3.3 Summary

Each of Mn^{III}-(calixsalen) catalysts has shown promising results with good turnovers and high enantiomeric excesses (ee). For indene, high enantioselectivity greater than 90% has been achieved with commercial bleach as the terminal oxygen source. However, styrene undergoes epoxidation with only 50-78% ee. This apparent difference may be attributed to a special type of mechanism for asymmetric epoxidation of terminal olefins. The epoxidation of styrene with *m*-CPBA as oxidant at -78 °C achieves a good turnover and high ee of 97% as compared to biphasic oxidation system with bleach.

Asymmetric induction by chiral Mn^{III}-(calixsalen) catalysts is also dependent on the alkene substitution pattern. The results indicated that conjugated substrates (conjugated to aryl, alkenyl or alkynyl group) give the highest enantioselectivities in the epoxidation by Mn^{III}-(calixsalen) catalysts. In addition, both 4-PPNO and NMO axial ligands significantly improved the turnover and enantioselectivity.

3.4 Experimental Section

Materials

Hexane (HPLC grade), isopropanol (HPLC grade) used for high performance liquid chromatography were purchased from Aldrich. Dichloromethane, sodium hydroxide, sodium hydrogen phosphate, sodium sulfate, *m*-chloroperbenzoic acid, 4-phenylpyridine *N*-oxide, *N*-methylmorpholine-*N*-oxide, *tert*-butylhydroperoxide for the epoxidation of olefins were purchased from Aldrich and used as received. Bleach was used as undiluted commercial household bleach (5.25%).

Styrene, indene, *trans*-stilbene, 2,3-dimethyl-1,3-butadiene, vinyl-cyclohexene, 4-vinyl-cyclohexene, limonene, cyclohexene, 1,5-octadiene, 3,4-dihydropyrone for epoxidation substrates were purchased from Aldrich. Styrene, indene and limonene were further purified by fractional distillation.

Methods

Gas chromatography (GC) analyses were performed on a Hewlett-Packard 5890 Series II instrument equipped with an FID detector and a Hewlett-Packard 3396 A integrator using an HP-5 capillary column (30 m × 0.32 mm). The separation of compounds on the column containing an achiral stationary phase was performed with a He head pressure of 12 psi.

High pressure liquid chromatography (HPLC) was performed on a Spectra Physics

instrument equipped with a ALTEX model 110 pump, a model 153 UV wavelength detector at 254nm, and a JCL6000 integrator. Values for enantiomeric excess were determined by using a chiral (*S, S*)-Whelk-O 1 column (25cm × 0.46 cm), with 0.25% isopropyl alcohol in hexane as mobile phase (1.0 ml/min, λ = 254 nm).

Configurational assignments of styrene epoxides were based on comparisons with literature reports of epoxide products from the Jacobsen-type catalyst epoxidations.

General Procedure for the Epoxidation of Olefins Catalyzed by Mn^{III}-(calixsalen) Catalysts in the Buffered Bleach Biphasic System

A small sample vial equipped with a stir bar was charged with Mn^{III}-(calixsalen) catalyst (0.0010 mmol), 4-phenylpyridine *N*-oxide (0.0040 mmol) in CH_2Cl_2 (1.5 mL), and then olefin (0.10 mmol) was added. This solution was cooled to 0 °C, and 1.2 mL of buffered bleach solution (prepared by combining 0.5 ml of 0.05 M Na_2HPO_4 with 0.6 mL commercial household bleach 5.25% (No Name) and adjusted to pH 11.3 with ~ 6 drops 1.0 M NaOH), pre-cooled to 0 °C, was added to the olefin solution. The biphasic reaction mixture was vigorously stirred at 0 °C. After 1 h, the brown organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic phases were dried over Na_2SO_4 and then chromatographed over a ~ 4 cm silica column with CH_2Cl_2 to remove the residual catalyst. GC-MS analyses were performed using tri-chlorobenzene as an internal standard to determine the chemical yields and turnovers. The solution of olefin and epoxides was placed on a rotary evaporator to remove the

solvent and olefin. The epoxide residue was re-dissolved in hexane (HPLC grade). HPLC analyses (0.25% isopropyl alcohol in hexane) were used to determine the enantiomeric excess of epoxides.

General Procedure for the Epoxidation of Olefins Catalyzed by Mn^{III}-(calixsalen) Catalysts at Low Temperature with the Combination of *m*-CPBA and NMO

A small sample vial equipped with a stir bar was charged with a solution of Mn^{III}-(calixsalen) catalyst (0.0010 mmol) and *N*-methylmorpholine *N*-oxide (0.0040mmol) in CH_2Cl_2 (1.5 mL), and then the olefin (0.10 mmol) was added. The solution was cooled to -78 °C, and *m*-chloroperbenzoic acid (0.20 mmol) was added as a solid in three roughly equal portions over a 15-minute period. The reaction mixture was stirred for 1 h at -78 °C, and then allowed to warm to room temperature. The solution was chromatographed over a ~ 5 cm silica column with CH_2Cl_2 to remove the residual catalyst. GC-MS and HPLC analyses were used to determine the turnovers and ee% as described above.

Determination of the Enantiomeric Excess (% ee)

The enantiomeric excess is calculated based on following equation:

$$\% \text{ ee} = \frac{R - S}{R + S} \times 100$$

The relative amount of each enantiomer *R* or *S* was measured by HPLC, using a chiral (*S, S*)-Whelk-O 1 column (25cm × 0.46 cm), and the mobile phase isopropyl alcohol in hexane (0.25/100).

References:

1. (a) Katsuki, T. *Coord. Chem. Rev.* **1995**, *140*, 189. (b) Katsuki, T. *J. Mol. Catal. A: Chem.* **1996**, *113*, 87. (c) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis,* Ojima, I., Ed.; VCH, New York, **1993**.
2. (a) Chang, S.; Heid, R. M.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *35*, 669. (b) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1994**, *36*, 5457.
3. Barf, G. A.; Sheldon, R. A. *J. Mol. Catal. A: Chem.* **1995**, *102*, 23.
4. (a) Holm, R. H. *Chem. Rev.* **1987**, *87*, 1401. (b) Hager, L. P.; Morris, D. R.; Brown, F. S.; Eberwein, H. *J. Biol. Chem.* **1966**, *241*, 1769. (c) Blanke, S. R.; Hager, L. P. *J. Biol. Chem.* **1988**, 263, 18739. (d) Atkins, W. M.; Sligar, S. G. *J. Am. Chem. Soc.* **1989**, *111*, 2715. (e) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (f) Finn, M. G.; Sharpless, B. *J. Am. Chem. Soc.* **1991**, *113*, 113. (g) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032.
5. Yoon, H.; Burrows, C. J. *J. Am. Chem. Soc.* **1988**, *110*, 4087.
6. Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.
7. Deng, L.; Jacobsen, E. N. *J. Org. Chem.* **1992**, *57*, 4320.
8. (a) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N . *J. Am. Chem. Soc.* **1990**, *112*, 2801. (b) Jacobsen, E. N.; Zhang, W.; Muci, A. R., Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063. (c) Irie, R.; Ito, Y.; Kastuki, T. *Synlett.* **1991**, 265. (d) Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457.

9. Palucki, M.; Pospisil, P. J.; Zhang, W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 9333.

10. (a) Srinivasan, K.; Perrier, S.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309. (b) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323.

11. Linker, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2060.

12. (a) Finnley, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1723. (b) Finnley, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem.* **1997**, *109*, 2150.

13. Linde, C.; Arnold, M.; Norrby, P.-O.; Åkermark, B. *Angew. Chem.* **1997**, *109*, 1802.

14. (a) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martinez, L. E. *Tetrahedron* **1994**, *50*, 4323. (b) Jacobsen, E. N.; Zhang, W.; Güler, M. L. *J. Am. Chem. Soc.* **1991**, *113*, 6703.

15. Feichtinger, D.; Plattner, D. A. *Chem. Eur. J.* **2001**, *7*, 591.

16. Palucki, M.; McCormick, G. J.; Jacobsen, E. N. *Tetrahedron Lett.* **1995**, *36*, 5457.

17. (a) Mikame, D.; Hamada, T.; Katsuki, T. *Synlett.* **1995**, 827. (b) Hamada, T.; Irie, R.; Katsuki, T. *Synlett.* **1994**, 479.

18. Yamashita, Y.; Katsuki, T. *Synlett.* **1995**, 829.

19. Feichtinger, D.; Plattner, D. A. *J. Chem. Soc. Perkin Trans.* **2000**, *2*, 1023.

20. Adam, W.; Roschmann, K. J.; Saha-Möller, C.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068.

21. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (c) Finn, M. G.; Sharpless, B. *J.* Am. *Chem. Soc.* **1991**, *113,* 113. (d) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.

22. Srinivasan, K.; Perrier, S.; Kochi, J. K. *J. Mol. Catal.* **1986**, *36*, 297.

23. (a) Nam, W.; Han, H. J.; Oh, S.-Y.; Lee, Y. J.; Choi, M.-H.; Han, S.-Y.; Kim, C.; Woo, S. K.; Shin, W. *J.* Am. *Chem. Soc.* **2000**, *122,* 8677. (b) Traylor, T. G.; Tsuchiya, S.; Byun, Y.-S.; Kim, C. *J. Am. Chem. Soc.* **1993**, *115,* 2775.

24. Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497.

25. (a) Samsel, E. G.; Srinivasan, K.; Kochi, K. J. *J. Am. Chem. Soc.* **1985**, *107*, 7606. (b) Srinivasan, K.; Michaud, P.; Kochi, K. J. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

26. (a) Liu, S. Q.; Pécaut, J.; Marchon, J. C. *Eur. J. Inorg. Chem.* **2002**, 1823. (b) Lai, T. S.; Liu, H. Y.; Yeung, L. L.; Chang, C. K. *Synlett.* **2002**, *9*, 1475. (c) Kerrigan, N. J.; Langan, I. J.; Dalton, C. T.; Daly, A. M.; Bousquet, C.; Gilheany, D. G. *Tetrahedron Lett.* **2002**, *43*, 2107. (d) Daly, A. M.; Renehan, M. F.; Gilheany, D. G. *Org. Lett.* **2001**, *3*, 663. (e) Miura, K.; Katsuki, T. *Synlett.* **1999**, 783. (f) Hashihayata, T., Ito, Y.; Katsuki, T. *Tetrahedron* **1997**, *53*, 9541. (g) Elemans, J. A. A. W.; Bijsterveld, E. J. A.; Rowan, A. E.; Nolte, R. J. M. *Chem. Commun.* **2000**, 2443.

27. (a) Nam, W.; Jin, S. W.; Lim, M. H.; Ryu, J. Y.; Kim, C. *Inorg. Chem.* **2002**, *41*, 3647.

(b) Nam, W.; Lim, M. H.; Oh, S. Y.; Lee, J. H.; Woo, S. K.; Kim, C.; Shin, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3646. (c) Suzuki, N.; Higuchi, T.; Urano, Y.; Kikuchi, K.; Uekusa, H.; Ohashi, Y.; Uchida, T.; Kitagawa, T.; Nagano, T. *J. Am. Chem. Soc.* **1999**, *121*, 11571.

28. Collman, J. P.; Chien, A. S.; Eberspacher, T. A.; Zhong, M.; Brauman, J. I. *Inorg. Chem.* **2000**, *39*, 4625.

29. (a) Nam, W.; Lim, M. H.; Moon, S. K.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122*, 10805. (b) Adam, W.; Roschmann, K. J.; Saha-Möller, C. R.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068.

Chapter 4. Oxo-transfer Mechanism

Although the high efficiency of the Mn^{III}-(salen) based asymmetric epoxidation method is widely acknowledged, the exact mechanism of the reaction remains controversial.[1] The first metallosalen epoxidations were reported by Kochi et al. using Cr^{III}-(salen) complexes as the catalyst.[2] In that work, a (salen)-Cr^{V}=O complex was isolated and characterized. This is consistent with Jacobsen's early observation[3] that the ee % did not depend on the identity of the oxidant (bleach vs. PhIO), which was taken as evidence for a "common oxo intermediate as the active oxidant". The common factor in these metallosalen catalyzed epoxidations is the formation of a high valent oxo-metallo intermediate via the reaction of an oxygen donor with the metal salen complex. This oxo species is undetectable under the conditions usually employed for oxidations, and is considered only to be a short-lived intermediate.[4] Independent on the nature of the investigated oxidants, there is considerable debate concerning the structure of the high-valent oxo-metallo species generated by the reaction of the oxidant donor with metallosalen and the mechanism of oxygen transfer from this oxo-metallo species to the substrate. It is now generally accepted that, in the case of Mn^{III}-(salen) catalysts, the intermediate [(salen)-Mn^{V}(O)]L acts as a "staging post" for oxygen transfer.[5] A variety of mechanisms have been proposed for oxygen transfer from the active species to the olefin, in which a concerted reaction or intermediates such as a metallaoxetane, π-radical cation, carbocation or radical have been suggested.[6]

Despite a large amount of work on the mechanism of formation of oxo species and on their reactivity, little attention has been given to the first step of the reaction where oxygen transfer to the transition metal from dioxygen or an oxygen donor can yield several different species with quite diverse reactivities or to the transient nature of the catalytically active species. Recently, electrospray ionization tandem mass spectrometry was employed by Plattner[5,7] to study the formation of oxo-Mn^{V}-(salen) complexes upon oxidation of [(salen)-Mn^{III}]$^{+}$ salts with iodosylbenzene. Two species were characterized as the principal oxidation products: the oxo-Mn(V) complex [(salen)-Mn=O]$^{+}$, the presumed oxygen-transfer agent in epoxidation reactions, and the dimeric, μ-oxo bridged [PhIO(salen)Mn-O-Mn(salen)OIPh]$^{2+}$ with two terminal iodosylbenzene ligands, which acts as a reservoir species for parking the catalytically active complex in a more stable form. Based on this mechanism, which was termed "oxygen-rebound", the chiral induction for olefin epoxides is dependent only on this active [(salen)-Mn=O]$^{+}$ species.[5] However, in this work, it was found that for the epoxidation of styrene, *the sense of chiral induction was opposite for bleach versus m-CPBA oxidants.* This reversal of sense was observed for both Mn^{III}(calixsalen)Cl and Mn^{III}(salen)Cl, Jacobsen catalysts.

4.1 Experimental Observation That the Sense of Chiral Induction Depends on the Oxidant

The Mn^{III}(calixsalen)-catalyzed epoxidations of styrene and indene were carried out with 1.0 mol% of catalyst and 2.0 equiv. of oxygen donor for single-phase system

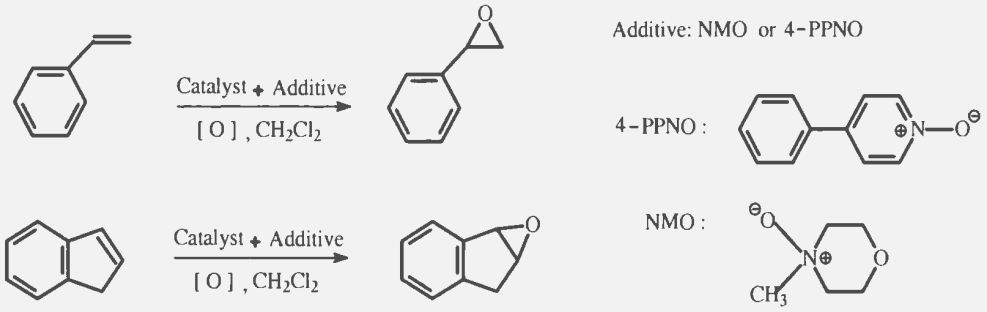
with *m*-CPBA, or 4.0 equiv. of oxygen donor for biphasic system of bleach. The results are summarized in **Table 4-1**. The sense of chiral induction for styrene epoxide is opposite for NaOCl versus *m*-CPBA. Although the sense of chiral induction for indene oxide is the same for NaOCl and *m*-CPBA, the epoxidation with *m*-CPBA as oxidant donor at low temperature gave a very low enantioselectivity (30% ee) compared with the epoxidation with biphasic bleach system. Given the anomalous results with the indene and *m*-CPBA system (discussed in Chapter 3), it is not possible to conclude whether *m*-CPBA gives the opposite sense of indene epoxide as compared to bleach.

This reversal of sense must be taken with caution since Zheng et al.[8] reported that their polymeric (*R,R*)-Jacobsen catalyst gives the same (*R*)-styrene oxide for both NaOCl and *m*-CPBA epoxidations. To be sure of the results reported in this thesis, the epoxide products were eluted separately from the HPLC column and analyzed by GC-MS to verify that they were indeed the un-decomposed epoxide products. Furthermore, both (*R,R*)- and (*S,S*)- Jacobsen's catalyst enantiomers were tested to be sure that the sense of chiral induction was reversed, verifying the validity of the chiral HPLC results.

4.2 Mechanistic Implications of the Reversal of Chiral Induction

That the oxygen source may affect the selectivity of metal-catalyzed oxidations has recently been demonstrated by Nam and co-workers, who have investigated the mechanisms of the epoxidation by iron complexes.[9] When peroxidic oxygen donors such as hydrogen peroxide, *tert*-butyl hydroperoxide, and *m*-CPBA, were employed with

Table 4-1 Oxygen Donor Effects on the Enantioselectivity of the Epoxides in Mn^{III}(calixsalen)-catalyzed Epoxidations



Catalyst	Alkene	Oxidant	T/°C	Turnover	ee% ±3%	Config.
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	styrene	bleach	0	67.5	46.0%	*R*
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	styrene	bleach	0	12.8	78.3%	*R*
(*R*, *R*)-Mn_3(calixsalen)Cl_3(trimer)	styrene	bleach	0	41.8	56.7%	*R*
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	styrene	*m*-CPBA	-78	48.7	96.7%	*S*
(*R*, *R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	styrene	*m*-CPBA	-78	30.3	64.7%	*S*
(*R*, *R*)-Mn_3(calixsalen)Cl_3(trimer)	styrene	*m*-CPBA	-78	18.1	72.3%	*S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	indene	bleach	0	34.2	96.3%	*R, S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	indene	bleach	0	33.2	93.0%	*R, S*
(*R*,*R*)-Mn_3(calixsalen)Cl_3(trimer)	indene	bleach	0	29.1	97.5%	*R, S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	indene	*m*-CPBA	-78	68.5	71.4%	*R, S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*anti*-dimer)	indene	*m*-CPBA	-78	53.8	35.7%	*R, S*
(*R*,*R*)-Mn_2(calixsalen)Cl_2(*syn*-dimer)	indene	*m*-CPBA	-78	56.8	42.1%	*R, S*

Fe(Porph) complexes, it was generally believed that high-valent oxo-iron(IV) porphyrin cation radical intermediate **3** is the only reactive species responsible for the oxygenation of hydrocarbons, as shown in **Figure 4-1**. In addition to the intermediacy of **3**, recent studies provide strong evidence that the oxidant-iron(III) porphyrin intermediate **1**, an FeOOR(Porph) adduct, initially forms. Intermediate **1** is capable of transferring oxygen to hydrocarbons prior to the formation of **3**, especially in the epoxidation of olefins by peracids at low temperature.[10] The ligated Fe^{III}(O-LG) adduct functions directly as a Lewis-acid-activated epoxidant by concerted oxygen transfer to give *cis*-epoxides (pathway A). This pathway has already been suggested for Mn(salen)-catalyzed[11] and Fe(Porph)-catalyzed[12] epoxidation with *m*-CPBA as oxygen donor as well as for the Mn-catalyzed sulfimidation.[13] Notably, Vaz et al. also reported elegant results that iron(III)-hydroperoxide (Fe^{III}-OOH) and iron(III)-hydrogen peroxide (Fe^{III}-H_2O_2) intermediates function as electrophilic oxidants in olefin epoxidation and alkane hydroxylation reactions by cytochrome P-450 enzymes and their mutants.[14]

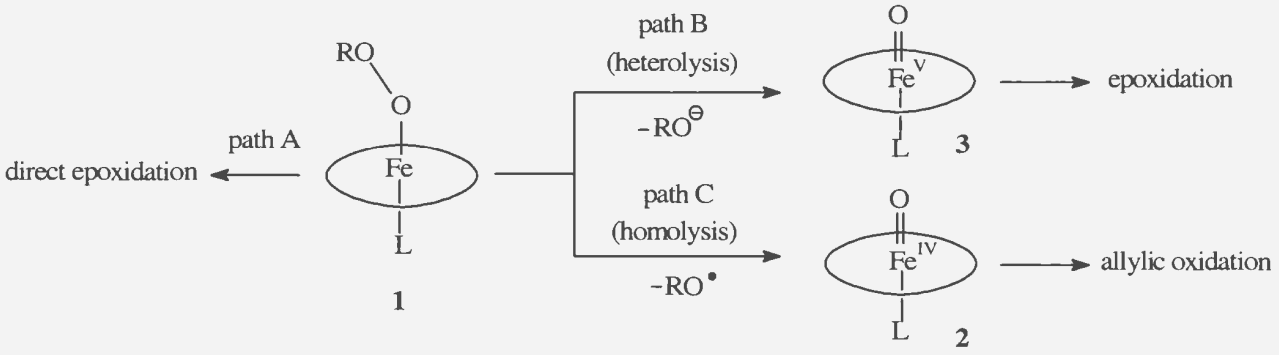


Figure 4-1 Three pathways (A-C) for the reaction of the FeOOR(Porph) adduct in the Fe(Porph)-catalyzed epoxidation

Clearly, the Fe(Porph)-catalyzed epoxidations proceed via a much different mechanism from the Cr-(salen) complexes, yet the Mn-(salen) chemistry was originally considered to be analogous to the Cr-(salen) (and not the Fe(Porph)) chemistry without much justification. In fact, recent reports[15] have shown that the putative Mn(V)=O intermediate cannot be the only active oxo-transfer species in Mn-(salen) epoxidations. In particular, Roschmann et al.[16] reported that several different oxidants, including NaOCl and PhIO, had a significantly different characteristic *cis/trans* ratio of the resulting *cis*-stilbene epoxide. That the *cis/trans* selectivity should depend so greatly on the nature of the oxidant implied the participation of more than one type of Mn-oxo intermediate. These results led Roschmann to propose that OCl^- axially coordinates to the metal centre. Also, a kinetic study[17] of indene epoxidation with bleach found that the rate of epoxidation is directly proportional to the [HOCl], implying that HOCl is involved in the rate-determining step. In view of these experimental results, the mechanism of the Fe(Porph)-catalyzed epoxidations or at least in a fast pre-equilibrium can be considered relevant to the Mn(salen)-catalyzed epoxidations.

Based on the study that the oxygen source plays a crucial role for the selectivity in olefin epoxidation reactions, oxygen donors fall into two classes: PhIO, C_6F_5IO, $TBA^+IO_4^-$, and O_3 afford the Mn^V(oxo) species as the dominant oxidant through the stepwise radical process; while for $TBA^+HSO_5^-$, NaOCl, *m*-CPBA, and DMD, the concerted process via Lewis-acid catalysis (pathway A in **Figure 4-1**) is also

operative.[10-14] Epoxidation with NaOCl and *m*-CPBA should proceed via a similar mechanism and achieve similar enantioselectivity. However, this is definitely not the case because these two oxygen donors display opposite selectivity.

The results of epoxidation of styrene and indene suggest that, under the catalytic epoxidation conditions, the participation of the ligated Mn^{III}(O-LG) adduct and Mn^{V}(oxo) oxidants is controlled by the electronic structure of oxygen donors. While the epoxidation with the biphasic bleach system was carried out at room temperature and 0°C, and the epoxidation with *m*-CPBA was carried out at -78°C, the involvement of the ligated Mn^{III}(O-LG) adduct in the epoxidation at high temperature is dependent on the relative rates of k_1 and k_2 as shown in **Figure 4-2**. Although the catalytic cycle of Mn(salen)-catalyzed epoxidation was extended[18] to accommodate this divergence mechanistically, it is still difficult to explain the reversal of sense with the biphasic bleach system versus *m*-CPBA observed in this work.

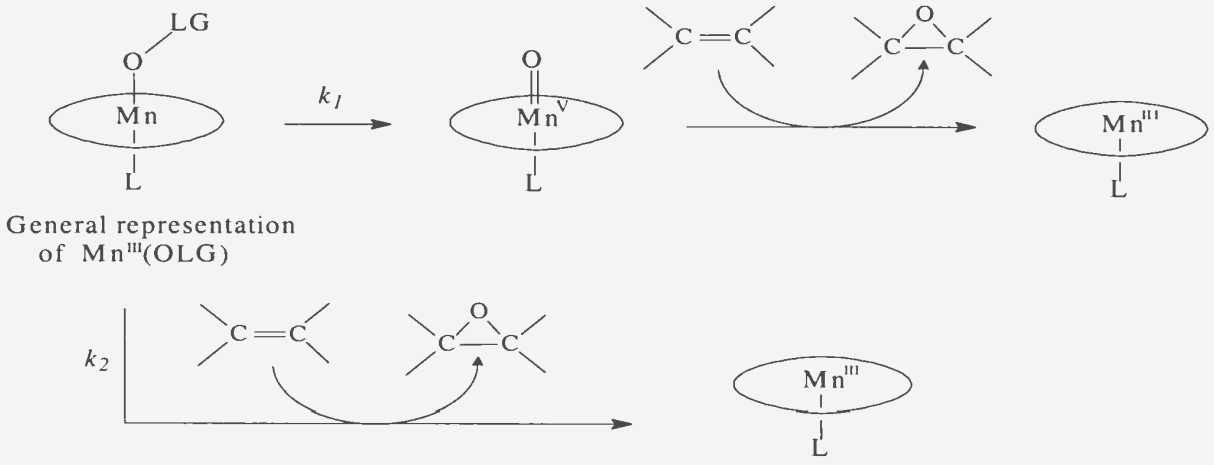


Figure 4-2 Catalytic cycle of Mn(salen)-catalyzed epoxidation involving ligated Mn^{III}(O-LG) adduct

4.3 Implication of the "Green Intermediate" in Peroxide Epoxidations

In addition to the above mentioned reversal of chiral induction for bleach versus *m*-CPBA, there is also a different reaction colour for each of these oxidants. Regardless of the Mn-(salen) catalyst used, epoxidations with bleach remain the dark brown Mn(III) colour, whereas epoxidations with *m*-CPBA form a distinguishable green colour immediately upon the addition of *m*-CPBA. The green colour fades over a period of 5-15 minutes depending on the conditions.

Although Chipperfield et al.[19] have observed a green intermediate, they did not report the UV-visible data. Therefore, in this work, the green intermediate was generated by the reaction of Jacobsen's catalyst with excess *m*-CPBA, and then the UV-visible spectrum was recorded within five minutes (**Figure 4-3**).

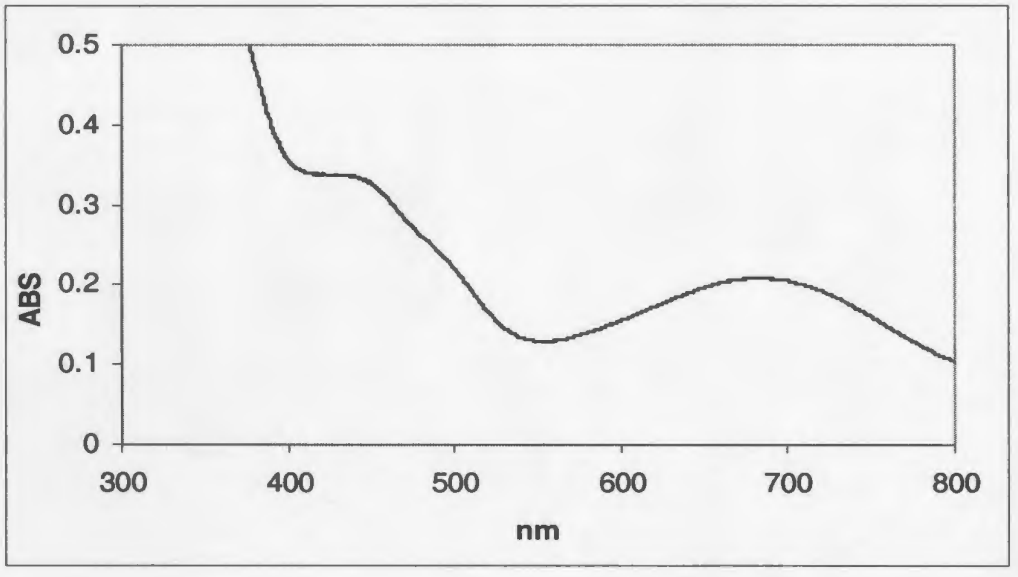


Figure 4-3 UV-Visible spectrum of Green intermediate from Jacobsen's catalyst with *m*-CPBA (λ_{max} = 680nm)

The UV-visible spectrum immediately after mixing Jacobsen's catalyst [(*R,R*)-Mn(salen)Cl, R = *t*-Bu)] with *m*-CPBA gave a peak at 680 nm (**Figure 4-3**). It is possible that this green band is due to the charge transfer from ligand to metal because there is a precedent in di-μ-oxo bridged manganese complexes from low-lying oxo to Mn CT bands.[20] The colour of green intermediate fades quickly so that an accurate measurement of intensity was not possible. On the basis of *in situ* ES-MS, Chipperfield et al. concluded that the green intermediate is a μ-oxo bridged Mn(III)-Mn(IV) dimer, often considered to be the "staging post" or "resting state" form of the catalyst.[21] Further evidence of a μ-oxo bridged Mn(III)-Mn(IV) dimer was provided by Britt et al.'s dual-mode EPR study of the *in situ* epoxidation.[22] It is noteworthy that the observation[19] in the Chipperfield study that both the absorbance change and the rate of formation of the green intermediate depended on the concentration of cumyl hydroperoxide ([CHP]). This observation led Chipperfield to propose that the peroxide axially coordinates to Mn, either before or after the formation of the dimer. However, there is an apparent contradiction in these results that should be resolved: if the green intermediate is a μ-oxo dimer, and the dual-mode EPR shows a μ-oxo dimer for the NaOCl epoxidations, then why do the NaOCl epoxidations not have the green colour?

4.4 Proposed Mechanism for the Reversal of Chiral Induction

Based on these mechanistic studies, there are two possible explanations for the reversal of chiral induction with different oxidants. First, it could be that the

coordination of the intact oxidants plays a much more significant role in the epoxidation step than previously realized. Axial coordination of a bulky alkyl peroxide could significantly alter the approach and orientation of incoming alkene substrate compared to the coordination of the non-bulky OCl^-. Second, the evidence that alkyl peroxides produce a μ-oxo bridged Mn(III)-Mn(IV) dimer is so strong that it may be that the dimer is the active oxo transfer species in the peroxide epoxidations. The most favourable approach of the incoming alkene to the μ-oxo dimer could have the opposite chiral induction compared to a monomeric (possibly OCl^- ligated) Mn-(salen) complex in the NaOCl epoxidations. Although it is highly speculative, it may be that the polymer-bound Jacobsen's catalyst[23] gives the same sense of chiral induction for NaOCl vs. *m*-CPBA because it cannot form a μ-oxo dimer and therefore has a similar intermediate for both oxidants.

4.5 Mechanisms for Heterolytic versus Homolytic Cleavage of the Ligated Mn^{III}(O-LG) Adduct

The presence of "catalyst-oxidant" molecular adducts has been demonstrated by kinetic studies. Molecular adducts between PorphM and NaOCl, iodosylbenzene or peracids have also been suggested.[24] However, the incidence of oxygen transfer from these reactive intermediates to the substrates becomes noticeable only when reaction conditions do not allow their conversion to the corresponding high-valent oxo-metallo species. Kinetic studies on the competitive oxidation of *cis*-stilbene and naphthalene

catalyzed by Mn^{III} *meso*-tetra(2,6-dichloro-4-R-phenyl)porphyrins (RTDCPPMnCl) in the presence of peracids suggested that *cis*-stilbene and naphthalene were oxidized by distinct high-valent oxo-Mn species which are formed from the same "catalyst-oxidant" intermediates, and are in equilibrium.[25]

If that is so, how do these "catalyst-oxidant" molecular adducts transform into an equilibrium mixture of two high-valent oxo-Mn species? The mechanisms of heterolytic versus homolytic cleavage of O—O bond of putative Mn(III) hydroperoxide porphyrin intermediates, forming high-valent oxo-Mn(IV) porphyrin cation radical intermediates and oxo-Mn(IV) porphyrin intermediates, have been investigated in depth by Groves,[26] Morishima,[27] Traylor[28] and Nam[29] who independently recognized some general factors influencing the reactions. These factors can be summarized as follows: (*i*) the hydroperoxide O—O bond is cleaved both heterolytically and homolytically and partitioning between heterolysis and homolysis was significantly affected by the electronic nature of the Mn-porphyrin complexes (i.e., electronic properties of porphyrin and axial ligands); (*ii*) the heterolytic versus homolytic O—O bond cleavage of the hydroperoxides was also found to be significantly affected by the hydroperoxide substituent;[30] (*iii*) from the intermediate **1**, homolysis produces an oxo-Mn(IV)

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[30] The tendency of O—O bond heterolysis of the hydroperoxides follows the order *m*-CPBA > H_2O_2 > *t*-BuOOH > MPPH. The O—O bond of hydroperoxides containing electron-donating *tert*-alkyl groups such as *t*-BuOOH and MPPH tends to be homolytically cleaved, whereas an electron-withdrawing substituent such as an acyl group in *m*-CPBA facilitates O—O bond heterolysis.

complex **2**, while via heterolysis an oxo-Mn(V) complex **3** becomes the actual oxidizing species as shown in **Figure 4-4**.

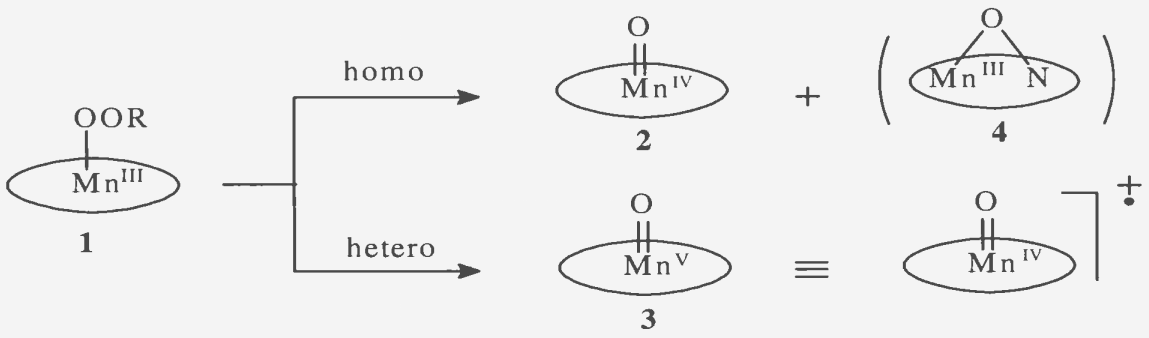

Figure 4-4 Heterolysis versus homolysis of an oxo-Mn(V) complex

Furthermore, some peculiar aspects of the formation and reactivity of high valent oxometallo porphyrins were found by different authors. An important outcome indicated by Groves concerns the reactivity of the Mn^{V}=O species **3** which was able to transfer a single oxygen atom to olefins with very high reaction rates and selectivites.[31] The Mn^{IV}=O species **2** slowly oxidizes olefins through a one-electron oxidation mechanism and epoxidizes *cis*-alkenes to give both isomers in low yield, indicating that the epoxidation of olefins by species **2** is non-stereospecific.[32]

Effects of electronic nature of porphyrin complexes and the substituent of hydroperoxides on the O—O bond cleavage have been investigated by Groves[33] and Nam.[29] The very small activation enthalpy observed for heterolytic cleavage of the O—O bond suggests a substantial interaction of the cleavable bond with iron in the transition state. The phases of pertinent orbitals as shown in **Figure 4-5** indicate that the

iron d_{xz} and d_{yz} orbitals are favourably disposed to interact with the σ^* orbital of the bound peroxide. The maximum assistance for heterolytic O—O bond cleavage should derive from a doubly occupied d_{xz} and d_{yz} orbital. It is well-known that the types and rates of O—O bond cleavage are significantly affected by the electronic properties of axial ligands.[34] Also, the electron density in the σ^* orbital of the hydroperoxide O—O bond should be influenced by the substituent of hydroperoxides. Therefore, the electron density in the σ^* orbital of the hydroperoxide O—O bond is expected to be controlled by both the electronic nature of iron porphyrin complexes (i.e., the electronic properties of porphyrin and axial ligands) and the substituent of hydroperoxides.

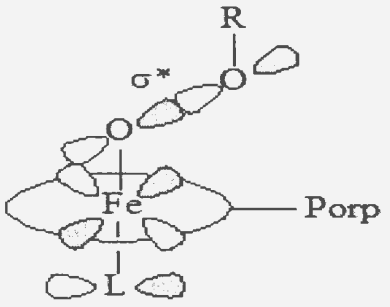

Figure 4-5 The phases of pertinent orbitals of porphyrin complexes

By analogy with the behavior of PorFeOOCOR, the formation of oxo-Mn^V-(salen) from Mn^{III}(O-LG) during Mn^{III}-(salen) catalyzed epoxidations with perbenzoic acids and NaOCl (aq.) has been investigated.[35] Both perbenzoic acids and NaOCl (aq.) are strong oxidants able to generate Mn^V(oxo) and Mn^{IV}(oxo) complexes by heterolytic O—O bond cleavage. However, the stronger electron-donating group, Cl^-, has a different effect on the O—O bond cleavage of Mn^{III}(O-LG) adducts from the

electron-withdrawing acyl group in *m*-CPBA, thus influencing the partition between heterolyis and homolysis. It was also reported that nitrogen ligands lengthen and weaken the M—O bond in the oxidized form of the catalyst by donating electron density into the M—O *anti*-bonding orbital, which can account for the improved reactivity.[36] Although the mechanism of metallosalen catalyzed epoxidation was reconsidered and extended to accommodate some divergence, the reversal of chiral induction for styrene epoxidation with different oxidants in this work cannot be completely interpreted. More detailed studies are in progress to gain a better understanding of the different chiral inductions for indene and styrene.

4.6 Summary

The sense of chiral induction for styrene epoxide is opposite for bleach versus *m*-CPBA. Based on the mechanistic model for oxygen-atom transfer[19] that the key oxo-Mn(V) species are acting as the staging post for oxygen transfer, the sense of chiral induction depends only on this active intermediate, different terminal oxygen atom sources should lead to epoxidation activity with the same chiral induction. In addition, there is also a different reaction colour between these oxidants. The fact that the type of oxygen donor affects the chiral induction of the epoxidation of styrene requires that, besides oxo-Mn(V) species, at least one other oxidant must be involved in this catalytic process, and the epoxidation cycle must be extended to accommodate a divergent mechanism.

4.7 Future Work

Although the epoxidation of unfunctionalized alkenes catalyzed by Mn^{III}-(calixsalen) was achieved with good turnover and high ee% as compared with the previous best result, controversy still remains regarding the exact mechanism of Mn^{III}-(calixsalen) catalyzed epoxidation and the pathway (inside or outside) via which the alkenes approach the active centers. Further experiments are needed that the epoxidation of the bulky alkene, *cis*-stilbene, and non-bulky alkene, *cis*-β-methylstyrene, catalyzed by $[Mn_2^{III}(calixsalen)](SCN)_2$, in which the SCN^- binds strongly enough to the $[Mn_2(calix[2]salen)]^{2+}$ cation to block the external pathway, would provide some evidence that the epoxidation catalyzed by Mn^{III}-(calixsalen) catalysts proceeds via the internal host-guest pathway or external pathway to approach the active centers.

Also, it remains to be seen whether the sense of chiral induction depends on the nature of oxidants. The epoxidation of indene with *m*-CPBA as oxidant was complicated by formation of side products; therefore, further experiments on the epoxidation of terminal alkenes with different oxidants are needed to clarify this important result.

References:

1. (a) Linker, T. *Angew. Chem. Int. Ed. Engl.* **1997**, *36,* 2060. (b) Finney, N. S.; Pospisil, P. J.; Chang, S.; Palucki, M.; Konsler, R. G.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem. Int. Ed. Engl.* **1997**, *36,* 1720. (c) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515. (d) Sabater, M. J.; Álvaro, M.; García, H.; Palomares, E.; Scaiano, J. C. *J. Am. Chem. Soc.* **2001**, *123*, 7074. (e) Norrby, P.-O.; Linde, C.; Åkermark, B.; *J. Am. Chem. Soc.* **1995**, *117*, 11035. (f) Linde, C.; Arnold, M. Norrby, P.-O.; Åkermark, B. *Angew. Chem. Int. Ed. Engl.* **1997**, *36,* 1723.
2. Samsel, E. G.; Srinivasan, K.; Kochi, J. K. *J. Am. Chem. Soc.* **1985**, *107*, 7606.
3. Zhang, W.; Jacobsen, E. N. *J. Org. Chem.* **1991**, *56*, 2296.
4. Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1987**, *109*, 3812.
5. Feichtinger, D., Plattner, D. A. *J. Chem. Soc. Perkin Trans.* **2000**, *2*, 1023.
6. (a) Fu, H.; Look, G. C.; Zhang, W.; Jacobsen, E. N.; Wong, C.-H. *J. Org. Chem.* **1991**, *56*, 6497. (b) Hamada, T.; Fukuda, T.; Imanishi, H.; Katsuki, T. *Tetrahedron* **1996**, *52*, 515. (c) Linde, C.; Åkermark, B.; Norrby, P.-O.; Svensson, M. *J. Am. Chem. Soc.* **1999**, *121,* 5083.
7. Katsuki, T. *Adv. Synth. Catal.* **2002**, *344*, 131.
8. Song, Y.; Yao, X.; Chen, H.; Pan, G.; Hu, X.; Zheng, Z. *J. Chem. Soc., Perkin Trans. I*, **2002**, 870.
9. (a) Nam, W.; Lim, M. H.; Lee, H. J.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122,* 6641. (b)

Nam, W.; Han, H. J.; Oh, S.-Y.; Lee, H. J.; Choi, M.-H.; Han, S.-Y.; Kim, C.; Woo, S. K.; Shin, W. *J. Am. Chem. Soc.* **2000**, *122,* 8677. (c) Nam, W.; Lim, M. H.; Moon, S. K.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122,* 10805. (d) Nam, W.; Lim, M. H.; Oh, S.-Y.; Lee, H. J.; Woo, S. K.; Kim, C.; Shin, W. *Angew. Chem. Ind. Ed.* **2000**, *39*, 3646.

10. (a) Machii, K.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1995**, *117*, 6691. (b) Nam, W.; Lim, M. H.; Lee, H. J.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122,* 6641.
11. Bryliakov, K. P.; Babushkin, D. E.; Talsi, E. P. *J. Mol. Catal. A* **2000**, *158*, 19.
12. (a) Nam, W.; Lim, M. H.; Lee, H. J.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122*, 6641. (b) Nam, W.; Lim, M. H.; Oh, S.-Y.; Lee, J. H.; Lee, H. J.; Woo, S. K.; Kim, C.; Shin, W. *Angew. Chem. Int. Ed.* **2000**, *39*, 3646.
13. Ohta, C.; Katsuki, T. *Tetrahedron Lett.* **2000**, *42*, 3885.
14. (a) Newcomb, M.; Shen, R.; Choi, S.-Y.; Toy, P. H.; Hollenberg, P. F.; Vaz, A. D. N.; Coon, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 2677. (b) Toy, P. H.; Newcomb, M.; Coon, M. J.; Vaz, A. D. N. *J. Am. Chem. Soc.* **1998**, *120*, 9718.
15. (a) Chipperfield, J. R.; Clayton, J.; Khan, S. A.; Woodward, S. *J. Chem. Soc., Dalton Trans.*, **2000**, 1087. (b) Campbell, K.; Lashley, M. R.; Wyatt, j. K.; Michael, H. N.; Britt, R. D. *J. Am. Chem. Soc.* **2001**, *123*, 5710. (c) Adam, W.; Roschmann, K. J.; Saha-Möller, C.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068. (d) Adam, W.; Mock-Knoblaunch, C.; Saha-Möller, C.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122*, 9685.

16. Adam, W.; Roschmann, K. J.; Saha-Möller, C.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068.

17. Hughes, D. L.; Smith, G. B.; Liu, J.; Dezeny, G. C.; Senanayake, C. H.; Larson, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, 62, 2222.

18. Adam, W.; Roschmann, K. J.; Saha-Möller, C.; Seebach, D. *J. Am. Chem. Soc.* **2002**, *124*, 5068.

19. Chipperfield, J. R.; Clayton, J.; Khan, S. A.; Woodward, S. *J. Chem. Soc. Dalton Trans.* **2000**, 1087.

20. (a) Cooper, S. R.; Calvin, M. *J. Am. Chem. Soc.* **1977**, *99*, 6623. (b) Dingle, R. *Acta. Chem. Scand.* **1966**, *20*, 33.

21. Srinivasan, K.; Michaud, P.; Kochi, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 2309.

22. Campbell, K.; Lashley, M. R.; Wyatt, j. K.; Michael, H. N.; Britt, R. D. *J. Am. Chem. Soc.* **2001**, *123*, 5710.

23. Song, Y.; Yao, X.; Chen, H.; Pan, G.; Hu, X.; Zheng, Z. *J. Chem. Soc., Perkin Trans. I*, **2002**, 870.

24. (a) Balasubramanian, P. N.; Schmidt, E. S.; Bruice, T. C. *J. Am. Chem. Soc.* **1987**, *109*, 7685. (b) Gopinath, E.; Bruice, T. C. *J. Am. Chem. Soc.* **1991**, *113*, 6090. (c) Almarsson, O.; Bruice, T. C. *J. Am. Chem. Soc.* **1995**, *117*, 4533.

25. Banfi, S.; Cavazzini, M.; Pozzi, G.; Barkanova, S. V.; Kaliya, O. L. *J. Chem. Soc. Perkin Trans.* **2000**, *2*, 871.

26. (a) Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1987**, *109*, 3812. (b) Groves, J. T.; Watanabe, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8443.

27. (a) Tsurumaki, H.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1993**,*115,* 11784. (b) Machii, K.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1995**, *117,* 6691.

28. (a) Traylor, T. G.; Tsuchiya, S.; Byun, Y.-S.; Kim, C. *J. Am. Chem. Soc.* **1993**, *115,* 2775. (b) Traylor, T. G.; Ciccone, J. P. *J. Am. Chem. Soc.* **1989**, *111,* 8413.

29. (a) Nam, W.; Lim, M. H.; Oh, S.-Y. *Inorg. Chem.* **2000**, *39,* 5572. (b) Nam, W.; Goh, Y. M. *Inorg. Chem.* **1999**, *38,* 914. (c) Nam, W.; Jin, S. W.; Lim, M. H.; Ryu, J. Y.; Kim, C. *Inorg. Chem.* **2002**, *41,* 3647. (d) Nam, W.; Lim, M. H.; Lee, H. J.; Kim, C. *J. Am. Chem. Soc.* **2000**, *122,* 6641.

30. Groves, J. T.; Lee, H. J.; Marla, S. S. *J. Am. Chem. Soc.* **1997**, *119,* 6269.

31. (a) Groves, J. T.; Stern, M. K. *J. Am. Chem. Soc.* **1987**, *109*, 3812. (b) Arassasingham, R. D.; He, G.-X.; Bruice, T. C. *J. Am. Chem. Soc.* **1993**, *115,* 7985.

32. Groves, J. T.; Watanabet, Y. *J. Am. Chem. Soc.* **1988**, *110,* 8443.

33. (a) Yamaguchi, K.; Watanabe, Y.; Morishima, I. *J. Am. Chem. Soc.* **1993**, *115*, 4058. (b) Suzuki, N.; Higuchi, T.; Urano, Y.; Kikuchi, K.; Uekusa, H.; Ohashi, Y.; Uchida, T.; Kitagawa, T.; Nagano, T. *J. Am. Chem. Soc.* **1999**, *121*, 11571.

34. (a) Adam, W.; Mock-Knoblauch, C.; Saha-Mo1ller, C. R.; Herderich, M. *J. Am. Chem. Soc.* **2000**, *122,* 9685. (b) Campbell, K. A.; Lashley, M. R.; Wyatt, J. K.; Nantz, M. H.; Britt, R. D. *J. Am. Chem. Soc.* **2001**, *123,* 5710.

35. (a) Banfi, S.; Cavazzini, M.; Coppa, F.; Barkanova, S. V.; Kaliya, O. L. *J. Chem. Soc. Perkin Trans.* **1997**, *2*, 1577. (b) Grove, J. T.; Lee, Jinbo, Marla, S. S. *J. Am. Chem. Soc.* **1997**, *119*, 6269.

36. (a) Gold, A.; Jayaraj, K.; Doppelt, P.; Weiss, R.; Chottard, G.; Bill, E.; Ding, X.; Trautwein, A. X. *J. Am. Chem. Soc.* **1988**, *110*, 5756. (b) Razenberg, J.; Nolte, R. J. M.; Drenth, W. *Tetrahedron Lett.* **1984**, *25*, 789.