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Advances in Homogeneous and Heterogeneous Catalytic Asymmetric Epoxidation

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1. Introduction

Barry Sharpless was awarded the 2001 Nobel Prize as a compliment to his great contributions in the field of asymmetric epoxidation, which has been recognized as one of the most important techniques emerging in the last 30 years. These fundamental findings have largely expanded the scope of asymmetric synthesis and allowed a more targeted preparation of pharmaceutical products, such as antibiotics, antiinflammatory drugs, and other medicines.

Chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules, in particular, of biologically active compounds.[1,2] Catalytic asymmetric epoxidation is an especially useful technique for the synthesis of chiral

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Prof. Q.-H. Xia (Qinghua Xia) was born in 1965 in Hubei, China. He graduated from Department of Chemistry of Jingzhou Normal College in 1984. From 1984 to 1987, he worked in Jingmen Petrochemical Complex of SINOPEC. In the autumn of 1987, he successfully passed the admission examination to enter Dalian Institute of Chemical Physics of Chinese Academy of Sciences as a graduate of catalysis chemistry. There he pursued research in the fields of homogeneous and heterogeneous catalysis and zeolite synthesis under the supervision of Prof. L.-B. Zheng, Prof. G.-Q. Chen, Prof. G.–W. Wang, and Prof. Q.-X. Wang and received his M.Sc. degree in 1990 and Ph.D. degree in 1993. From 1993 to 1997, as a postdoctoral fellow he worked in Fudan University under the supervision of Prof. Z. Gao and at the University of Tokyo under the supervision of Prof. T. Tatsumi. In October 1995, he was promoted to Associate Professor of Chemistry in Fudan University. In 1996, he worked for NEDO of Japan as an Advanced Technology Research Scientist. From 1997 to 2003, NUS, CPEC, and ICES of Singapore employed him as a Research Fellow. In 1999, he and his family became permanent residents of Republic of Singapore. From 2002, he started his new career as a Scholar-level professor and an institute director in Hubei University to build up a Laboratory for Advanced Materials and New Catalysis. From 2004, he was appointed as an adjunct professor by DICP and Jingmen Technological College. His research interests are mainly focused on the synthesis and application of zeolites, porous molecular sieves, nanomaterials and membranes, C_1 chemistry, homogeneous and heterogeneous catalysis, asymmetric hydrogenation and epoxidation, partial oxidation over Ti-zeolites and others, environmental catalysis, etc.

Mr. H.-Q.Ge (Hanqing Ge) was born in 1977 in Hubei, China. He received his Bachelor degree from School of Chemistry and Materials Science of Hubei University in 2002. Currently, he is in the third year of his Master studies on the asymmetric epoxidation of olefins on organic–inorganic hybrid catalyst, under the supervision of Prof. Q.-H. Xia and Prof. C.-P. Ye.

Prof. C.-P. Ye (Chuping Ye) was born in 1952 in Hubei, China. He graduated from Department of Chemistry of Hubei University in 1975. Since then, he has worked in Hubei University to teach and perform scientific research in organic chemistry. He was promoted to Associate Professor of Organic Chemistry in 1993 and to Professor of Organic Chemistry in December 2004. His research interests include applied organic chemistry, organic functional materials, adhesives, synthesis of fine chemicals, etc.

Prof. Z.-M. Liu (Zhongmin Liu) was born in 1964 in Henan, China. He graduated from Department of Chemistry of Zhengzhou University in 1983. Then he continued his postgraduate and Ph.D. programs in the field of catalysis under the supervision of Prof. L.-B. Zheng, Prof. J. Liang, Prof. G.-Q. Chen, and Prof. G.-Y. Cai in Dalian Institute of Chemical Physics of Chinese Academy of Sciences. He received his M.Sc. degree in 1986 and Ph.D. in 1990 from DICP. In 1990, he started his scientific research career in DICP, where he was promoted to Associate Professor in 1994 and to Full Professor in 1996. In 1996, he worked in CNRS of France as a postdoctoral fellow. From 2000, he was appointed as an adjunct professor by Jilin University and Zhengzhou University. Currently, he is a big group leader, an assistant director of DICP, and an editorial board member for *Chinese Journal of Catalysis* and *Journal of Natural Gas Chemistry*. He was an international scientific committee member of 13th IZC and 14th IZC. His research interests are in the areas of heterogeneous catalysis, C_1 chemistry, porous zeolites and molecular sieves, natural gas utilization and applied catalysis, etc.

compounds in both academia and industry because a chiral catalyst molecule can act as an enzyme to induce a million-level chiral product molecules.[3] The development of chiral catalysts capable of inducing asymmetric centers with high efficiency has always been an important task for asymmetric synthesis. The ability to produce desired organic compounds in enantiomerically pure forms from simple and readily available precursors by using extremely small amounts of chiral catalysts, generally with substrate/catalyst molar ratios of 100−1000 or higher, has tremendously practical implications.[4,5] A variety of carbon−carbon double bonds, for example, those of allylic alcohols, α- and β-unsaturated esters, and simple alkenes, can be catalytically epoxidized with several metal catalysts.[6−8]

In 1965, Henbest et al. oxidized olefins with an enantiomeric excess (ee) of 10% using a chiral per-

A/Prof. K.-X. Su (Kexin Su) was born in 1949 in Hubei, China. He graduated from Department of Chemistry of Huazhong Normal University in 1977. From 1977 to 1984, he worked in Jingzhou Normal College as a Lecturer of Chemistry. Then he moved to Department of Chemical Engineering of Jingmen Technological College where he presently works. He was promoted to Associate Professor of Chemistry in 1999. His research fields include organic synthesis, polymer materials, and chemical process.

oxoacid as the oxidant, which was the first research of asymmetric epoxidation.[9] In the early 1980s, Katsuki and Sharpless made a milestone discovery, by which the enantiomers of an epoxide could be produced efficiently and predictably from an allylic alcohol with a catalytic system consisting of diethyl tartrate (DET), titanium tetraisopropoxide [Ti(O-$Pr^i)_4$], and *tert*-butyl hydroperoxide (TBHP).[10] Thereafter, much important progress has been made toward the asymmetric epoxidation of other classes of alkenes.

In homogeneous catalytic systems, the reactions can be efficiently carried out with high yields and ee's, but lengthy purification procedures are inevitable and generally the expensive catalysts are quite difficult to recover and recycle. However, in heterogeneous systems, the reaction mixture can be easily separated from one another by simple filtration, and in some cases the catalysts can be reused several times, thus bestowing on heterogeneous systems more convenient potential applications in industry. Since the solid-phase synthesis of oligopeptides was first reported by Merrifield,[11] many groups have extensively developed various classes of heterogeneously asymmetric epoxidation catalysts, such as insoluble and soluble polymer-supported,[12−22] organic−inorganic hybrid-supported,[23−31] dendrimer -supported catalysts, etc.[32−34] As compared with homogeneous catalysts, heterogeneous ones also possess some disadvantages, such as low reactivity and difficult preparation, thus leading to the appearance of some new catalysts combining homogeneous and heterogeneous advantages, including “ship-in-a-bottle” trapped catalysts,[35,36] fluorous biphase catalysts,[37,38] room-temperature ionic liquids, etc.[39]

This review will systematically summarize the progress of homogeneous and heterogeneous catalytic chiral epoxidation in the past decades and grant a convenient and wide vision for the understanding of peers working in the area of asymmetric catalysis.

2. Homogeneous Systems

2.1. Sharpless Systems

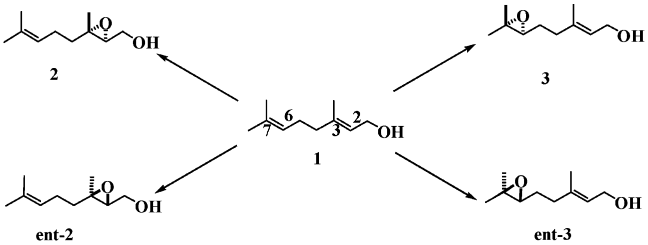
As shown in Scheme 1, four epoxides (racemic **2** and **3**) from geraniol **1** are possibly made through improving either regio- or chemoselectivity, while the formation of each of the individual enantiomers requires enantioselectivity.[40] In 1957, Henbest et al. reported that the electronic deactivation at C_1 coordinated by oxygen substituent caused the selective coordination of peroxoacids to the 6,7-position double bond, leading to racemic **3**.[41] In 1973, Michaelson et al. cracked the regioselectivity problem represented by the epoxidation of geraniol. Early epoxidation of geraniol **1** catalyzed by transition metals with alkyl hydroperoxides was highly selective for the 2,3-position compounds (racemic **2**).[42] In 1980, Katsuki et al. discovered titanium-catalyzed asymmetric epoxidation of olefins bearing allylic hydroxy groups into either **2** or ent-**2**, thereby solving one side of the problem in enantioselectivity.[10]

The resolution of the problem in regioselectivity and enantioselectivity aroused the interest of many groups in the research of asymmetric epoxidation. In 1980s, Sharpless et al. first introduced chiral ligands to transition metals Mo, Ti, and V, further developing a Sharpless asymmetric epoxidation system. They successfully converted allylic alcohols into asymmetric epoxides in high chemical yields with more than 90% ee, under the catalysis of a transition metal catalyst $Ti(OPr^i)_4$ by using TBHP as the oxidant with a chiral additive DET. However, this system holds a main disadvantage, namely, a low turnover number, which stimulates interest in searching for more efficient catalysts. For the epoxidation of allylic alcohols, many efficient systems have been reported, such as the catalytic systems consisting of vanadium catalysts and hydroxamic acids derivatives,[43−47] but the Sharpless protocol with titanium tetraisopropoxide and tartrate esters ligands is still investigated the most.[10,48]

2.1.1. Chiral Titanium Catalysts

Over the past two decades, the use of titanium alkoxide complexes as the catalysts for the asymmetric epoxidation of allylic alcohols has undergone a rapid expansion, especially since the discovery in 1980 by Sharpless et al.[10] The Sharpless epoxidation process seems to be well understood, in which the impact of a chiral ligand on enantioselectivity is

Scheme 1. Regio- and Enantioselective Monoepoxidations of Geraniol[a]

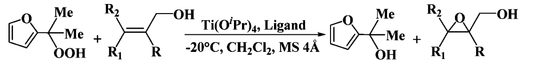


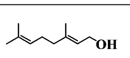
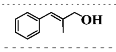
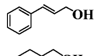
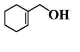
[a] Adapted from ref 40 with permission. Copyright 2002 Wiley-VCH.

critical.[49−51] Regardless of the metal-catalyzed methodology, the structure of hydroperoxides plays a significant role in the level of enantioselectivity achievable for the asymmetric epoxidation, which has resulted in the development of structurally diverse alkyl hydroperoxides.[52] In the early Sharpless epoxidation, the oxygen donor was achiral TBHP, and asymmetric induction resulted from the contribution of optically active tartrate with catalytic amounts as chiral auxiliary.[10,50] We can imagine that if optically active hydroperoxides are used, the hydroperoxides will serve not only as the oxygen donors but also as the sources of chirality without the need for tartrate as chiral auxiliary. When the optically active hydroperoxide as the oxygen donor is used to provide the chiral environment, achiral diol ligands must be chosen as additives to limit the coordination orientation between alkene molecules and the oxygen donors during the assembly of the loaded titanium complex. Generally, optically active hydroperoxides were obtained either by $^1O_2$ photooxidation of thiazolidine derivatives[53] and allylstannanes[54] or by oxidation of unsaturated glycosides.[55] Under titanium catalysis, first attempts of the epoxidation of allylic alcohols with chiral hydroperoxides only afforded ee's of less than 20%, but sugar-derived hydroperoxides showed higher enantioselectivities (up to 50% ee).[56,57]

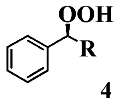
In 1997, Adam et al. reported Ti-mediated asymmetric epoxidation of a variety of prochiral allylic alcohols with optically active hydroperoxides (**4**, **5**, and **6b**) as oxygen donors and multidentate ligands as achiral additives, to achieve up to 50% ee in good yields (63−97%).[52] In the same year, Lattanzi et al. reported the application of several furylhydroperoxides **6** in the Sharpless asymmetric epoxidation of allylic alcohols.[58] The results showed that the enantioselectivity was strongly dependent on the substitution near the reactive sites, consistent with the observations made by Corey[59] and Sharpless et al.[49,50] Tertiary or alkyl hydroperoxide has been proven to ensure high ee's.[52,60,61] Anyway, an intrinsic limitation of this system is imposed by the essentiality of coordinated functional groups on the substrate to attain a high enantioselectivity. In 2002, Lattanzi et al. made a further finding that a high enantioselectivity could be obtained in the asymmetric epoxidation of allylic alcohols with tertiary furylhydroperoxide **6a** as shown in Table 1.[62] Entries 1 and 4 obtained high ee's with the addition of stoichiometric quantity of chiral catalyst, while the use of a substoichiometric amount of chiral catalyst in entries 2 and 5 resulted in a slight drop in the enantioselectivity.

Table 1. Asymmetric Epoxidation[a] of Allylic Alcohols Catalyzed by 6a



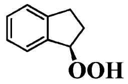
Entry	Substrate	Ligand	Time (h)	Yield (%)	ee (%)
1		L-DET	2.5^b	80	95
2		L-DET	22^c	45	85
3		L-DIPT	21^c	58	91
4		L-DET	2.5^b	90	>98
5		L-DIPT	27^c	87	97
6		L-DIPT	27^c	69	98
7		L-DIPT	21^c	64	96

[a] For experimental details, see ref 62. Adapted from ref 62 with permission. Copyright 2002 Elsevier. [b] Stoichiometric conditions. [c] Catalytic conditions.

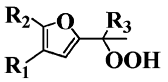


a: R=Me
b: R=Et

4

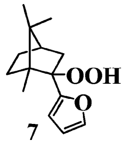


5



a: R_1=H, R_2=H, R_3=Me
b: R_1=COOEt, R_2=Me, R_3=H
c: R_1=COOEt, R_2=Me, R_3=Me

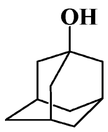
6



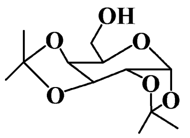
7

In 2003, Lattanzi et al. first synthesized an enantiopure tertiary hydroperoxide **7** from camphor via a stereospecific nucleophilic substitution of hydroxyl group bound to the chiral carbon center of the alcohol molecule by H_2O_2 (unlike TADOOH), in which the reactive peroxo (−OOH) group is directly bound to the stereogenic carbon center.[63] However, the so-prepared chiral tertiary hydroperoxide only offered a moderate ee up to 46% and a yield up to 59% for the asymmetric epoxidation of allylic alcohols. It is noteworthy that the chiral tertiary alcohol can be isolated at the end of epoxidation and then can be recycled for the synthesis of the hydroperoxide, thus providing a valuable chiral resource-saving protocol. However, optically active hydroperoxides as oxygen donors in the presence of multidentate diols (as achiral ligands) always afford lower enantioselectivities than the Sharpless modus operandi of employing TBHP as an achiral oxygen donor and C_2-symmetric tartrate as chiral auxiliary.

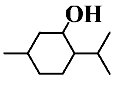
In 2003, Pérez et al. reported the synthesis of a family of titanium(IV) alkoxide compounds, i.e., $[Ti(OPr^i)_3(OR)]_2$ [OR = AdamO (**8**), DAGPO (**9**), DAGFO (**10**), or MentO (**11**)], $[Ti(OPr^i)_2(OR)_2]_2$ [OR = AdamO (**12**), DAGPO (**13**), DAGFO (**14**), or MentO (**15**)], and $Ti(OR)_4$ [OR = AdamO (**16**), DAGPO (**17**), DAGFO (**18**), or MentO(**19**)].[64] These preparations could be performed by using two different routes: (a) through the metathesis reaction of $TiCl(OPr^i)_3$ and $TiCl_2(OPr^i)_2$ with ROH in the presence of Et_3N and (b) alternatively through the alcohol exchange of $Ti(OPr^i)_4$ with a high boiling-point alcohol ROH, where RO = adamantanoxi (AdamOH), 1,2:3,4-di-*O*-isopropylidene-α-D-galacto-pyranoxi (DAGPOH), 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranoxi (DAGFOH), or (−)-(1*R*,2*S*,5*R*)-menthoxi (MentOH). Generally, the solution state of most Ti(OR)$_4$ (OR = OMe, OEt, OBu^n) appears to be an equilibrium among mono-, di-, and trinuclear species, and at room temperature trinuclear species are dominant; however, with the increase of steric bulk of an alkoxide ligand such as OR = OPr^i, OBu^t, monomeric species are predominant. Sugars are natural chiral ligands and can readily assemble transition metal complexes to form a receptor cavity with three-dimensional structural characteristics. More importantly, the entity of thus-formed molecules possesses the intrinsic properties of both sugars and metal complexes. Some of these chiral titanium(IV) Lewis acid compounds, e.g., **13** and **14** derived from diacetone galactose and diacetone glucose, have been applied in the asymmetric epoxidation of cinnamyl alcohol to receive good catalytic activity and stereoselectivity (65% yield with 22% ee for **13** and 60% yield with 17% ee for **14**). On the basis of solid-state NMR and variable temperature NMR experiments, they assumed the existence of low-level substituted dimeric titanium compounds $\mathrm{Ti(OPr^{i})_{4-n}(OR)_{n}}$ (n = 1, 2) and highly substituted mononuclear $\mathrm{Ti(OR)_4}$ in the solution and solid states due to the steric hindrance imposed by bulky alkoxide ligands with a nuclearity greater than **8**.[65]



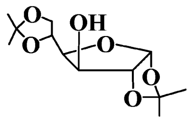
AdamOH



DAGPOH



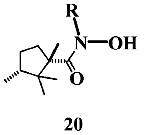
MentOH



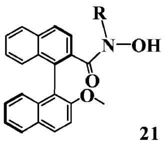
DAGFOH

2.1.2. Chiral Vanadium Catalysts

A number of asymmetric epoxidations based on chiral vanadium (V) complexes with TBHP have been reported,[4,43,45–47,66–69] in which the epoxidation of allylic alcohols is the most well-known.[42,66,67,69] Vanadium(V) alkylperoxo complexes were widely accepted as intermediates in the catalytic systems of $\mathrm{VO(acac)_2/TBHP}$[42,70–72] and $\mathrm{VO(acac)_2}$/ligand/TBHP.[46,73,74] Prior to the appearance of titanium-based catalysts, the Sharpless group had first developed asymmetric epoxidation (50% ee) catalyzed by the chiral vanadium hydroxamate complex **20**.[43] A few years later, they found again that when using proline-derived hydroxamic acid as the chiral ligand, up to 80% ee could be achieved.[72] Additionally, in 1999 Yamamoto et al. successfully applied a new chiral hydroxamic acid **21**, derived from 2,2′-binaphthol, serving as monovalent ligand coordinated with a vanadium complex in the asymmetric epoxidation of allylic alcohols to obtain an ee up to 94%.[45] To explore the potentials of these new catalysts further, they extensively tested the epoxidation of various substituted allylic alcohols. The results showed that the epoxidation of 3,3′-disubstituted allylic alcohols catalyzed by $\mathrm{VO(OPr^{i})_3}$ and **21c** proceeded smoothly to yield the corresponding epoxides in moderate to good yields (70∼87%) with mediocre ee's (41∼78% ee). However, in the case of 2,3-disubstituted allylic alcohols, high ee around 90% ee was obtained, irrespective of bearing aromatic groups. It should be noted that unlike titanium tartrate system, molecular sieves to sequester water, which has a deleterious effect on both the rate and selectivity, were not required in this case.[49,75] It seems that several characteristics of chiral vanadium complex played an important role in increasing the rate and enantioselectivity, i.e., the starting oxidation state of vanadium, the coordination ability of hydroxamic acids, and π-interaction or steric repulsion between the metal-binding site and oxidant. To improve the efficiency of vanadium-based catalysts, Yamamoto et al. in 2000 developed a family of chiral hydroxamic acid ligands with a structure similar to the complex **22**,[46] and found that the product selectivity increased gradually with an increase of the steric hindrance in the side chain of amino acid, in which the best result was achieved when using *tert*-leucine-derived hydroxamic acid as the ligand. When L-α-amino acid was partly changed into imido group, the best result (87% ee) was achieved for the epoxidation of 2,3-diphenyl-prop-2-en-1-ol with 1,8-naphthalene-dicarbonyl-protected hydroxamic acid. Whereas for the same reaction, if aryl group near the metal-coordinated site was changed, the highest ee value could reach 96% when using N-bis(1-naphthyl) methyl-substituted hydroxamic acid as the ligand.

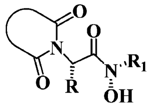


20



21

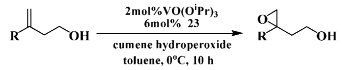
a: R=cyclohexyl
b: R=Bn
c: R=CHPh$_2$

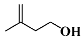
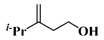
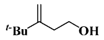
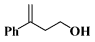
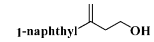


22

The asymmetric epoxidation of homoallylic alcohols was difficult to conduct with the other metal-based catalysts reported previously.[76–78] However, vanadium complexes could effectively catalyze the occurrence of this reaction to yield the corresponding epoxy alcohols with good to high stereoselectivities.[79] Yamamoto et al. prepared a chiral vanadium complex **23** from vanadium triisopropoxide and an α-amino acid-based hydroxamic acid, which was a rather efficient catalyst for the epoxidation of disubstituted allylic alcohols with up to 96% ee in high yields (almost >95%).[45,46,78] In 2003, they reported again that this chiral catalyst could also be used for the asymmetric epoxidation of 3-monosubstituted homoallylic alcohols with high enantioselectivities (84–91% ee) in moderate yields (42–89%),[80] as shown in Table 2.

Table 2. Asymmetric Epoxidation of Homoallylic Alcohols Using 23 as Ligand[a]

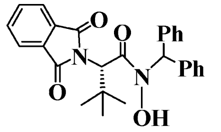


Entry	Homoallylic alcohol	Yield (%)	ee (%)
1		58	84
2		77	90
3		89	90
4		70	89
5		42	91

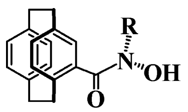
[a] Adapted from ref 80 with permission. Copyright 2003 Wiley-VCH.

Meanwhile, they observed that cumene hydroperoxide (CMHP) as the oxidant benefited a high enantioselectivity, while TBHP led to an extremely low enantioselectivity <8%.

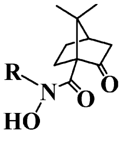
In 2000, Bolm et al. first reported the use of a vanadium-based catalyst bearing the paracyclophane planar-chiral ligand **24** in the asymmetric epoxidation of allylic alcohols.[47] Even simple TBHP could be used as a terminal oxidant to yield epoxy alcohols

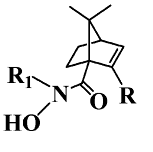

23

with 71% ee for the epoxidation of (*E*)-2-methyl-3-phenyl-2-propen-1-ol with **24c**. To identify the optimal ligand structure with respect to the substituent R at the nitrogen of **24**, they tested the epoxidation of (*E*)-2-methyl-3-phenyl-2-propen-1-ol with VO-(OPr^i)$_3$ and CMHP in toluene and found that all the ligands **24** resulted in the corresponding epoxides in high yields >86% with moderate enantioselectivities 32−52% ee. Interestingly, in contrast to Yamamoto's results with the ligand **21**, bulky aliphatic substituents rather than aromatic groups at the nitrogen of **24** remarkably increased the enantioselectivity, and the *S*-configured ligand led to an (*S*,*S*)-configured epoxide as a predominant enantiomer.


a: R=cyclohexyl
b: R=t-butyl
c: R=adamantyl
d: R=benzyl
e: R=CHPh$_2$
24

In 2002, Wu et al. reported the synthesis and application of new vanadium catalysts bearing (+)-ketopinic acid-based chiral hydroxamic acid ligands **25** and **26** for the asymmetric epoxidation of allylic alcohols.[81] Owing to poorly enantiomeric selectivity of the chiral hydroxamic acid ligand **25** derived from (+)-ketopinic acid **27** with different substituents on the nitrogen, its structure had to be modified through incorporating bulkier substituents at C$_2$ of the bornane skeleton so as to acquire a high enantioselectivity. This is a two-pronged strategy to study the effect of an *N*-substituent in a modified steric environment of the bornane moiety on the selectivity and also the impact of the size of the C$_2$ substituent of bornane on the selectivity. Chiral hydroxamic acid **26** with required structural features was prepared starting from (+)-ketopinic acid **27**. Moderate to high ee values (up to 89%) were obtained for the asymmetric epoxidation of allylic alcohols with vanadium-based catalysts coordinated by readily accessible new chiral hydroxamic acid ligands having diversely structural features, accompanied by an important characteristic that increasing the bulk of the *N*-substituent retarded the selectivity (Table 3).


a: R=H
b: R=CH$_2$Ph
c: R=Cyclohexyl
d: R=CH(Ph)$_2$
e: R=Adamantyl
25


a: R=Ph, R$_1$=H
b: R=*p*-Tolyl, R$_1$=H
c: R=*p*-^{t}Butylphenyl, R$_1$=H
d: R=1-Naphthyl, R$_1$=H
e: R=4-Biphenyl, R$_1$=H
f: R=Ph, R$_1$=CH(Ph)$_2$
26

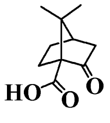
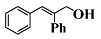
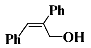
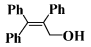
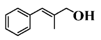
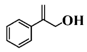
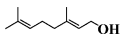
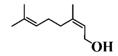
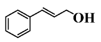
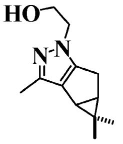

27

Table 3. Asymmetric Epoxidation of Allylic Alcohols Using 26e as Ligand[a]

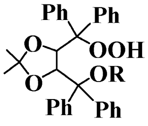
Entry	Allylic alcohol	Yield (%)	ee (%)
1		89	89
2		88	73
3		80	46
4		86	55
5		91	81
6		83	46
7		85	55
8		70	56

[a] Adapted from ref 62 with permission. Copyright 2002 Elsevier.

In 2003, Bryliakov et al. carried out the oxidation of (−)-(*R*)-linalool with TBHP to form (2*S*,3*R*)- and (2*R*,3*R*)-configured monoepoxides with moderate diastereomeric excess (de) in the presence of a vanadium(V) complex derived from the interaction of [VO(acac)$_2$] or [VO(OBu^n)$_3$] with a new chiral pyrazolylethanol ligand **28**.[9] Normally, this reaction proceeded slowly at room temperature (only conversion of 55% within 49 h); however, the coordination of chiral ligand **28** to the active center enhanced the reaction rate considerably with an improved diastereoselectivity, for which the maximal de value of about 56% was acquired at 20 °C in toluene under optimal conditions. Adam et al. also reported the vanadium(V)-catalyzed asymmetric epoxidation of primary allylic alcohols with optically active TADDOL-derived hydroperoxides **29** and **30** (as the asymmetric controller) to obtain up to 72% ee.[82] After the completion of reaction, the optically active TADDOL could be completely recovered without any loss of enantiomeric purity, which could provide the opportunity of regenerating the chiral oxygen source. This demonstrated the effect of a hydrogen-bonded template on the enantiofacial control in the vanadium-catalyzed epoxidation with a chiral hydroperoxide, in combination with an achiral hydroxamic acid ligand. This novel finding has greatly stimulated the development of more effective hydroxy-functionalized hydroperoxides for the vanadium-catalyzed asymmetric epoxidation. The initial examples of the titanium-catalyzed asymmetric epoxidation of allylic alcohols with optically active sugar-derived[52,57] or simple secondary hydroperoxides[56] achieved ee values of up to 50%. Such hydroperoxides have been recently utilized in the asymmetric Weitz-Scheffer epoxidation of α,β-enones to obtain high ee values of up to 90%.[83] However, when sterically TADDOL-derived hydroperoxide TADOOH was used, the highest enantioselectivity of 98% ee was achieved in the Weitz−Scheffer epoxidation, the Baeyer−Villiger oxidation, and sulfoxidation.[84] Also in 2003, TADOOH was successfully used as a chiral oxygen source in the catalytic asymmetric epoxidation of allylic alcohols by an oxovanadium-substituted polyoxometalate.[85]



28



29 R=H
30 R=Me

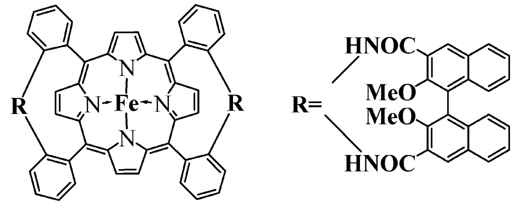
2.2. Porphyrin Systems

So far, the transition metal-catalyzed enantioselective epoxidation has been of utmost importance and widely studied over the past decades.[45−47,52,62,81,86−92] However, in practice useful catalysts should (a) be easily prepared and stored, (b) display high reactivity (turnover frequency), selectivity, and durability, and (c) contain inexpensive and environmentally benign metals in the coordination sphere by means of sterically and electronically tunable chiral ligands.[93−95] The role of porphyrins is important in a bewildering array of proteins;[96] their functions include O_2 storage (myoglobin Mb), O_2 transport (hemoglobin Hb), oxidation of inactivated carbon−hydrogen bonds (cytochrome P_{450}), and oxygen reduction (cytochrome *c* oxidase). The diversity of functions of these natural hemoproteins is dictated by many factors, such as the number and nature of axial ligands, the spin and oxidation state of the metal center, the nature of the polypeptide chain, and the geometry of the porphyrin ring.

Chiral metalloporphyrins have constituted an important class of catalysts for the asymmetric epoxidation of alkenes, which occurs basically via highly reactive oxometal (M=O) intermediates.[97] A rigid macrocyclic core and alterable periphery of porphyrins make them attractive templates for building asymmetric catalysts. Chiral groups have been attached to porphyrins in various geometries, aiming at systems that might give high enantioselectivities and turnover numbers. Most studies on metalloporphyrin catalysts are confined to the porphyrin complexes of iron,[98−102] manganese,[103] ruthenium,[104−106] and molybdenum.[103,107] Several different strategies have been adopted to append optically active groups onto the macrocyclic ring of metalloporphyrins.[108,109] Supplementary consideration lies in the nature of oxidants and metals (Fe, Ru, and Mn, etc.).[110] Of three metal complexes with the same chiral porphyrin ligand, much better results were obtained with iron and ruthenium than with manganese. It has to be pointed out that when 2,6-dichloropyridine-*N*-oxide (Cl_2PyNO) was used as the oxidant, the same chiral porphyrin ligand resulted in different ee values for stoichiometric and catalytic reactions, possibly due to the co-interaction of oxidant, axial ligand, and oxygen transfer.[111] In contrast, for the same reactions similar ee was obtained using oxygen or iodosylbenzene as the oxidant. Berkessel[105] and Che et al.[106,112,113] also described high efficiency of the catalyst systems involving different chiral porphyrin ligands for the asymmetric epoxidation of unfunctionalized olefins, reported previously by Halterman.[114] When using 2,6-dichloropyridine-*N*-oxide as terminal oxidant, the epoxide of 1,2-dihydronaphthalene was obtained with 77% ee and 90% yield.[105]

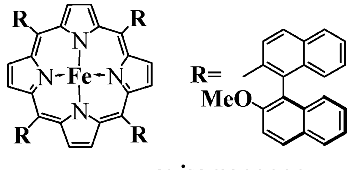
2.2.1. Iron Porphyrins

In the presence of molecular O_2, synthetic iron(II) porphyrins, which are not imposed with protection upon both faces, tend to be oxidized irreversibly to form μ-oxo Fe(III) dimers.[115] To avoid this unfavorable oxidation, several model structures with protected faces have been developed.[116−118] In 1999, Collman et al. presented a highly efficient catalyst based on a novel chiral iron porphyrin **31**.[119] This system gave very high enantioselectivities and turnover numbers for the epoxidation of styrene derivatives (83% ee for styrene, 88% ee for pentafluorostyrene, and 82% ee for *m*-chlorostyrene) and nonconjugated terminal alkenes. More significantly, this system manifested unusual chiral induction for nonconjugated terminal olefins, such as 3,3-dimethylbutene and vinyltrimethylsilane, in which the ee values for these two olefins exceeded the highest values obtained from any catalytic systems reported previously, including salen-Mn derivatives.[120−122]



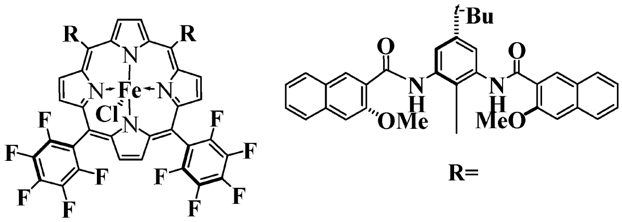
31 isomer: ααββ

In 2000, a new series of porphyrins **32** that incorporate four identical chiral binaphthyl derivatives in the meso-positions was synthesized by Reginato et al.[100] Four iron(III) chloro complexes (**Fe-32**) have been tested as catalytic precursors in the asymmetric epoxidation of styrene with iodosylbenzene as a single oxygen atom donor. The chemical yield of epoxide was about 47%; however, the ee value was strongly dependent on the structure of the catalytic precursor, ranging from 21% with the compound **32a** (αααα) to 57% with the compound **32c** (αα*ββ*), in agreement with the results reported by Collman et al.[109] In all the runs, absolute configuration of the products was (*S*), suggesting that the stereochemical outcome of this reaction was primarily decided by the absolute configuration of the binaphthyl moiety rather than by the overall molecular arrangement.

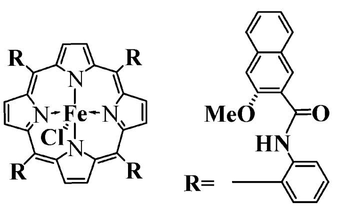


32
a: isomer αααα
b: isomer αααβ
c: isomer ααββ
d: isomer αβαβ

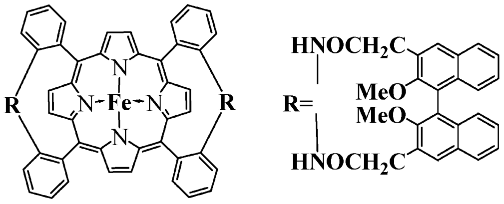
In 2000, Rose et al. developed the application of chiral iron-porphyrin **33**,[123] a "seat" porphyrin obtained by condensing a chiral binap diacid chloride with aminophenyl porphyrin; for the asymmetric epoxidation of various terminal olefins with iodosylbenzene, especially for styrene and pentafluorostyrene, 59% ee and 85% ee were, respectively, obtained.[124] In the case of bis-binaphthenylporphyrin **34**, the ee values for styrene and pentafluorostyrene were 83 and 88%, respectively,[119] while the best ee (92%) was obtained from the catalytic epoxidation of *tert*-butylethylene. Furthermore in 2004, they synthesized a new chiral binaphthyl-strapped iron-porphyrin **35**, which exhibited unprecedented catalytic activity toward the enantioselective epoxidation of terminal olefins.[125] For the epoxidation of styrene, typical ee values were measured to be 90−97%, whereas the turnover numbers (TON) averaged 16 000. The C_2-symmetric binap-strapped porphyrins have proven to be efficient for the epoxidation of terminal olefins.[119,123] The presence of two rigid binap walls efficiently directs the approach of olefin to the metal center, induces a good transfer of asymmetry, and inhibits the oxidative degradation of the catalyst as well as the formation of an unreactive μ-oxo dimer.[126] In addition, C_2-symmetric porphyrins are easily prepared from readily available $\alpha^2\beta^2$-tetrakis-(*O*-aminophenyl) porphyrin. The chemical yields based on the consumed PhIO varied from about 85% in most cases to 96% in the case of styrene. Remarkably, very good enantioselectivity was maintained when the reactions were carried out at room temperature, e.g., the epoxidation of styrene at room temperature afforded the desired epoxide in 94% ee, and the catalyst could be reused in the second run.



33



34

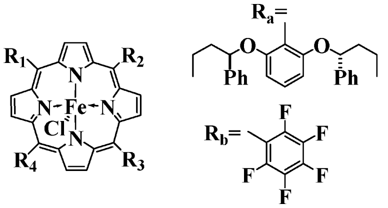


35

Groves et al. have carried out an investigation on the asymmetric epoxidation of styrene to (*R*)-(+)-styrene oxide (48% ee), catalyzed by optically active iron porphyrins such as FeT(α,β,α,β-binap)PPCl with iodosylbenzene.[127] Also, iron complexes of a binaphthyl capped porphyrin were used by Collman et al.[128] for the epoxidation of 4-chloro-styrene (50% ee) and 4-nitrostyrene (56% ee). Naruta et al. reported the catalytic performance of an iron metalloporphyrin with rigid backbones of binaphthyl groups using 1,5-diphenylimidazole as the cocatalyst and PhIO as the oxidant.[129] Thereafter, they improved the selectivity of epoxides by designing “twin coronet” porphyrin ligands,[130−133] in which each face of the macrocycle is occupied by two binaphthyl units. Because of the difference of the binding mode of chiral auxiliary, there were two topologically “eclipsed” and “staggered” isomers with D_2 symmetry. Iron(III) complex of the eclipsed isomer was observed to be an enantioselective catalyst, robust enough to exhibit higher than 500 TON with 74−96% ee for chiral epoxidation. For those olefins bearing electron-withdrawing substituents, the ee value was measured to be 74% for pentafluorostyrene, 89% for 2-nitrostyrene, and 96% for 3,5-dinitrostyrene, respectively, which was the highest stereoselectivity reported for styrene derivatives catalyzed by chiral metalloporphyrins. The ligands are usually prepared through two routes, one of which is attaching the chiral superstructure to each of the four atropisomers of the parent tetraarylporphyrin,[134] the other modifying the substituents on a single atropisomer.[135,136]

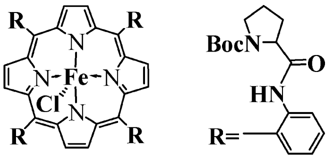
In 2003, Smith et al. observed that the ee values induced by chiral iron porphyrins **36**−**39** depended on the structure of catalysts and substrates, the temperature, and the solvent and that replacing a 2,6-di(1-phenylbutoxy)-phenyl group by a pentafluorophenyl group led to a marked improvement in the efficiency and stability of catalyst.[137] Generally, the presence of a pentafluorophenyl group on the porphyrin ring can increase the catalytic activity in three ways: (1) The electron-withdrawing fluorines activate the electrophilic high-valent oxoiron intermediate. (2) By removing electron density from the macrocyclic ring, the halogens make the porphyrin less susceptible to be attacked by the active oxidant, leading to less self-destruction of catalyst. (3) Since a pentafluorophenyl group is considerably less bulky than 2,6-di(1-phenylbutoxy)-phenyl not only does this allow easier access of the substrate to the oxoiron center during the catalytic cycle, but it also removes oxidizable 1-phenylbutoxy groups, retarding intramolecular destruction of catalyst. They likely play important roles in oxidations; however, it is difficult to determine which of three effects is the most important. Iron(III) tetra (pentafluorophenyl) porphyrin was a significantly better catalyst than the nonfluorinated analogue iron (III) tetraphenylporphyrin. Lowering the temperature from 20 to 0 °C resulted in a higher epoxidation yield and a small but significant increase in the ee values. Although the overall yields and ee values showed an obvious dependence on the solvent, the major enantiomer formed with each substrate/catalyst combination was unaffected by variations. Interestingly, no single solvent was optimal for all three systems.

In 2003, Boitrel et al. further developed the application of four atropisomers of an L-prolinoyl picket porphyrin iron complex **40** in the asymmetric epoxi-



36 R$_1$=R$_2$=R$_3$=R$_4$=R$_a$
37 R$_1$=R$_b$, R$_2$=R$_3$=R$_4$=R$_a$
38 R$_1$=R$_3$=R$_b$, R$_2$=R$_4$=R$_a$
39 R$_1$=R$_2$=R$_3$=R$_b$, R$_4$=R$_a$

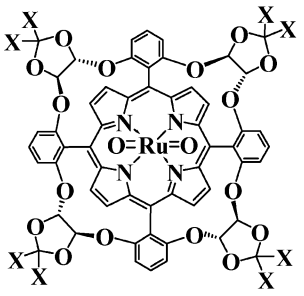
dation of *p*-chlorostyrene and 1,2-dihydronaphthalene, in which low ee values ca. 34% were obtained.[102] The results show that even in a flexible structure, too much hindrance implies a negative consequence on the selectivity of epoxidation. It is worthwhile to be mentioned that the enantioselectivity obtained with picket porphyrins was as high as that with strapped ones, and in some cases, even higher.



40

2.2.2. Ruthenium Porphyrins

Ruthenium complexes coordinated with either D$_4$-chiral porphyrins or homochiral porphyrins have been reported.[105,106,138,139] In some cases, these chiral metalloporphyrins could catalyze the oxidation of styrene derivatives with good ee values but low yields.[104,111,138] More importantly, for identical chiral porphyrin ligands the ruthenium complexes were much better at inducing the asymmetry than were the more commonly used iron, manganese, or rhodium derivatives.[104,110,140−146] In 1996, Gross et al. reported the first example of epoxidation catalyzed by a homochiral ruthenium porphyrin **41a**[104] and observed a notable effect of solvent on the enantioselectivity of chiral epoxy styrene, for which the enantioselectivity induced by benzene (44% ee) was much higher than by dichloromethane (4% ee). Recently, there was renewed interest in the oxidation reactions catalyzed by ruthenium(II) porphyrin complexes and simultaneously in the development of new chiral ruthenium porphyrins.[147,148] The catalytic reactions were mainly focused on asymmetric epoxidation of olefins,[105,139] and in some cases a gradual deactivation of catalyst was observed, possibly ascribed to the formation of inactive carbonyl complexes from *trans*-dioxo(tetramesitylporphyrinato) ruthenium (VI).[149] In 1999, new members **41a**−**c** of D$_2$-symmetric ruthenium porphyrins were reported,[111] which showed to be the most selective catalysts for the asymmetric epoxidation of terminal and trans-disubstituted olefins. The enantioselectivity obtained with **41b** was much higher than with **41a** and resulted in the exploration of ruthenium porphyrin complex **41c**, which was also based on the X-ray crystalline structures of both **41a** and its ruthenium complex[104,150] and on the molecular modeling investigation of **41b**. Indeed, **41c** was a very good catalyst, with higher chiral induction for terminal and trans-olefins but significantly poorer chiral induction for cis-olefins. The epoxidation of styrene and its *m*- and *p*-chloro-substituted derivatives proceeded with 79−83% ee.[151]

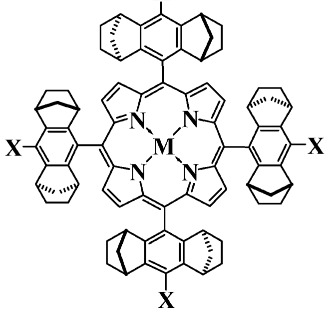


a: X= CH$_3$
b: X= Ph
c: X= 3-Cl-Ph
d: X=Et
e: X=-(CH$_2$)$_2$-

41

A strategy to catalyze highly enantioselective epoxidation of unfunctionalized trans-disubstituted alkenes would be to prepare reactive, isolable, and chiral metal−oxo complexes, which can act upon trans-alkenes to give epoxides with better enantioselectivities than cis-counterparts.[104] Once such complexes are obtained, the relationship of structure−enantioselectivity established by studying stoichiometric epoxidations of alkenes could assist future design for better metal catalysts. In 1999, Zhang et al. applied D$_2$-symmetric chiral *trans*-dioxoruthenium(VI) porphyrins **41a**, **d,** and **e**, bifacially encumbered by four chiral threitol units, to catalyze the enantioselective epoxidation of trans-β-methylstyrene (70% ee) and cinnamyl chloride (76% ee).[112]

Berkessel et al. in 1997 synthesized an enantiomerically pure ruthenium carbonyl porphyrin **42a** with very high yield by refluxing the corresponding porphyrin ligand with Ru$_3$(CO)$_{12}$ in phenol.[105] The catalytic asymmetric epoxidation of olefins over **42a** with 2,6-dichloropyridine *N*-oxide (2,6-DCPNO), which was carried out at room temperature in benzene under argon, afforded epoxides in good yields up to 88% with up to 77% ee. In 2003, they reported again the use of three enantiomerically pure and electronically tuned ruthenium carbonyl porphyrin catalysts **42b**−**d** in the asymmetric epoxidation of a variety of olefinic substrates.[152] Introduction of a CF$_3$ substituent in the remote position resulted in an improved stability, and turnover numbers up to 14 200 with an ee value of 80% were achieved for the epoxidation in benzene using 2,6-DCPNO as the oxygen donor (1.1 equiv to olefin) at room temperature.

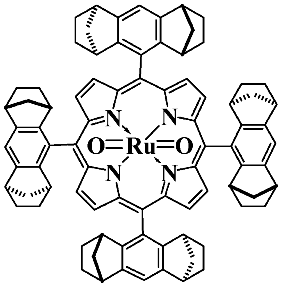


M=Ru(CO)
a: X= H
b: X= OCH$_3$
c: X= CH$_3$
d: X=CF$_3$

42

Dioxygen is the most appealing since it is economical and environmentally friendly,[153,154] but reports on the use of dioxygen in the enantioselective epoxidation of alkenes are quite sparse. Chiral Mn (β-

ketoiminato) complexes could catalyze aerobic asymmetric epoxidation of alkenes, but aldehyde was required as a sacrificial reductant.[89] In 1998, Lai et al. reported the first example of aerobic enantioselective epoxidation of alkenes catalyzed by dioxoruthenium(VI) complex **43** with a D_4-symmetric chiral porphyrin ligand, which did not rely on the use of a co-reductant.[106,155] The complex exhibited catalytic activity toward aerobic enantioselective epoxidation of prochiral alkenes with an enantioselectivity up to 73% ee under an oxygen pressure of 8 atm. However, the catalytic oxygenation of styrene using air in one atm pressure in CH_2Cl_2 gave very low turnover numbers; even less than 8 atm pressure of oxygen styrene oxide was obtained with only 10 TON and 70% ee. But when the amount of catalyst was stoichiometric, the attainable ee value was 77%. Lowering the temperature decreased the epoxide yield. For the asymmetric epoxidation of alkenes, the ee values of epoxides ranged from 40 to 77%, and the highest ee value was due to the reaction of 1,2-dihydronaphthalene with the complex in dichloromethane at −15 °C.



43

In 2003, Le Maux et al. synthesized two new C_2-symmetric chiral porphyrins bearing cyclohexyl substituents at the ortho-position of meso-phenyl groups and used their ruthenium complexes **44**−**47** to catalyze the asymmetric epoxidation of styrene derivatives with 2,6-dichloropyridine-*N*-oxide, e.g., a moderate ee value of 35% was obtained for the 1,2-dihydronaphthalene substrate.[156] The results show that the presence of various cyclohexane rings as chiral entities on metalloporphyrins appears to be an attractive mechanism for controlling both the reactivity and the enantioselectivity. However, the poor reactivity of "chiral cyclohexyl short arms" has become an indication of the level of steric incumbrance that can be tolerated in a reactive homochiral porphyrin complex. Compressing the size of the ring, e.g., choosing cyclopentane, cyclobutane, and cyclopropane rings, could be a good alternative to overcome this hurdle, as reported previously with chiral phosphines in the asymmetric hydrogenation.[157−159]

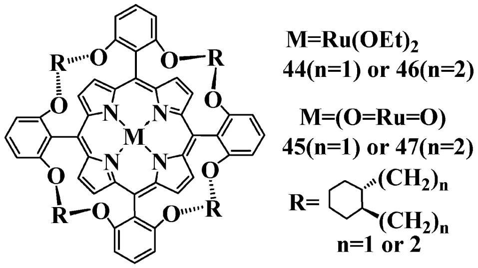
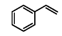
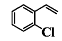


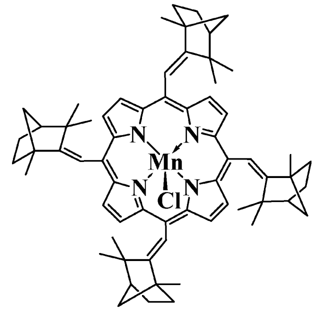
Table 4. Asymmetric Epoxidation of Olefins Catalyzed by Porphyrin Complex 48 with NaClO as the Oxidant[a]

Entry	Olefin	Time (h)	Yield (%)	ee (%)
1		40+40	78	10
2		60	50	12
3	Dodec-1-ene	48+84+48+24	64	10
4		48	6.3	16

[a] Adapted from ref 134 with permission. Copyright 1993 Elsevier.

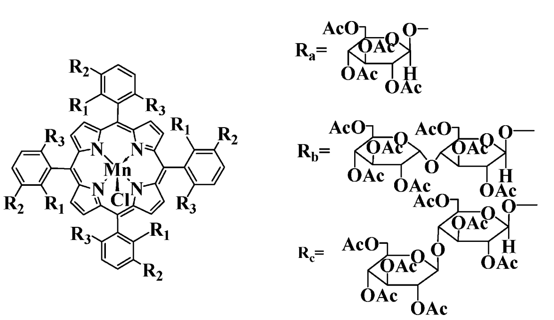
2.2.3. Manganese Porphyrins

To achieve high turnover numbers, Mn complexes of some chiral porphyrins have been synthesized and tested for asymmetric epoxidations.[97,160−162] In 1993, Proess et al. reported the application of the chiral manganese porphyrin complex **48** in the asymmetric epoxidation of olefins with sodium hypochlorite as an oxygen donor.[134] As shown in Table 4, when the reactions were carried out at the most stable pH = 13 value of porphyrin, the reaction time was usually long. When the pH value of the reaction mixture was adjusted to between 9.5 and 10.5 by the addition of solid $NaHCO_3$, all the reactions were greatly accelerated, and the catalyst decomposed rapidly. Additionally, when the catalyst was added into the reaction mixture in several batches, the first portion of catalyst decomposed faster than the latter ones.



48

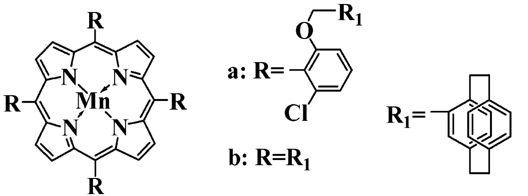
Collman et al. studied the synthesis and catalytic properties of threitol-strapped manganese porphyrins.[163] When associated with bulky cocatalysts such as 1,5-dicyclohexylimidazole, those catalysts effectively catalyzed the epoxidation of 4-chlorostyrene (70% ee) and *cis*-*β*-methylstyrene (77% ee). In 1996, Vilain-Deshayes et al. further investigated the asymmetric epoxidation of 4-chlorostyrene and 1,2-dihydronaphthalene catalyzed by a series of chiral Mn-porphyrins **49**−**54** bearing glycosyl substituents (glucose, maltose, lactose) at the ortho- or meta-position of the meso-phenyl groups with dilute H_2O_2 or iodosylbenzene as the oxidant.[162,164] The enantioselectivity was moderate ca. 29% ee and strongly dependent on the position of the glycosyl residue. The meta-glycosylated catalysts were not able to induce a significant ee level; however, when the chiral moieties were in ortho-positions, closer to the active center of the macrocycle, an environment able to induce a high enantioselectivity could be generated. The use of natural sugar derivatives as chiral motives on metalloporphyrins would be possible to catalyze the enantioselective epoxidation of poorly reactive olefins with easily accessible oxidants such as H_2O_2.



a: isomer αβαβ
b: isomer ααββ
c: isomer αααβ

49 $R_1=R_a$ $R_2=R_3=H$
50 $R_1=R_b$ $R_2=R_3=H$
51 $R_1=R_3=H$ $R_2=R_a$
52 $R_1=R_3=H$ $R_2=R_b$
53 $R_1=R_3=H$ $R_2=R_c$
54 $R_1=R_a$ $R_2=H$ $R_3=Cl$

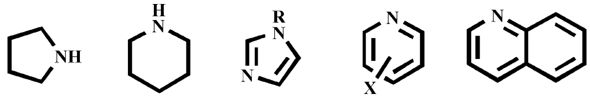
Compounds derived from 2,2-cyclophane are thought to be very stable to the action of light, oxidation, acids, and bases and relatively high temperatures.[165] In 1998, Rispens et al. reported homochiral, atropisomerically pure manganese complexes **55** containing a [2,2]-*para*-cyclophane-4-carbaldehyde building block group, which were used as the catalysts in the epoxidation of unfunctionalized olefins using aqueous NaClO, 30%-H_2O_2 and PhIO as oxygen donors.[166] Up to 780 overall turnover numbers were obtained in the presence of NaClO and PhIO, while with 30% H_2O_2 only catalase activity was observed; unfortunately, no significant enantioselectivity was achieved. However, when the Mn(III) complex of porphyrin **55b** was used in the epoxidation of unfunctionalized alkenes with aqueous NaClO, the enantioselectivities in the range of 22−31% were obtained. These encouraging results suggested that enantiopure [2,2]-*para*-cyclophane-4-carbaldehyde could be a good building block for the synthesis of new chiral porphyrins.



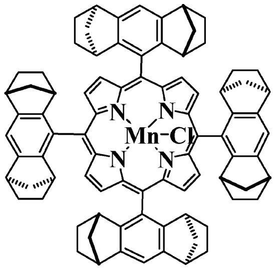
55

It has been reported that the rate of organic oxidations catalyzed by metalloporphyrins are strongly enhanced by the addition of an axial ligand, such as pyridine-type bases.[167] For the asymmetric epoxidations, the addition of axial ligand to catalytic systems is well-known to be a convenient and efficient strategy to enhance enantioselectivity. For instance, high enantioselectivity and good chemical yield were realized in the epoxidation of 2,2-dimethylchromene derivatives using achiral salen-Mn as the catalyst in the presence of chiral bipyridine *N,N′*-dioxide.[168] Also, axial ligation is important for effective asymmetry transfer during the alkene epoxidation catalyzed by single-faced chiral porphyrins because they can act as blocking agents for the unhindered face to force the incoming substrate to interact with the hindered chiral pocket.[169,170] In 2002, Lai et al. investigated the effect of multifarious organic bases (Scheme 2) in chiral Mn-porphyrin-catalyzed alkene epoxidation.[171] They observed that for substituted pyridines, the enantioselectivity of *cis*-*β*-methylstyrene epoxidation followed a linear free energy relationship (chiral catalyst **56**), which is for pyridines bearing electron-donating groups as well. Compared to the case of no amine additive, when 4-*N,N*-(dimethylamino)pyridine (DMAP) and $KHSO_5$ (Oxone) were employed as the axial ligand and the oxidant, a significant improvement in the enantioselectivity from 43 to 81% ee for the epoxidation of cis-*β*-methylstyrene with a stereospecificity of 86.5% was achieved. This was also the first successful use of Oxone in the metalloporphyrin-catalyzed asymmetric epoxidation. Very recently, Smith et al. in 2003 prepared the chiral Mn-porphyrin catalyst **57** to afford a very low ee value of 7.8% for styrene, 5.8% for *cis*-hept-2-ene, and 0.8% for 2-methylbut-2-ene, respectively.[137]

Scheme 2. Various Organic Bases Used in Chiral Mn-Porphyrin-Catalyzed Alkene Epoxidation[a]



[a] Adapted from ref 171 with permission. Copyright 2002 Georg Thieme Verlag.



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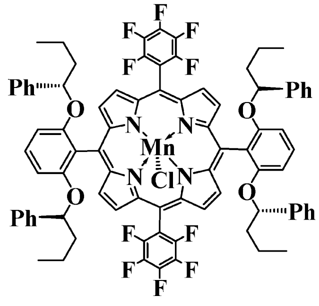


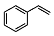
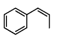
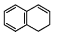
57

2.2.4. Molybdenum Porphyrins

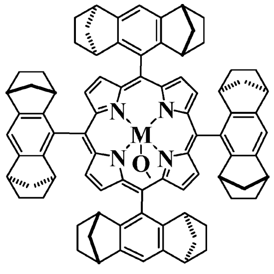
In 1970, Srivastava et al. first published the preparation of molybdenum porphyrins.[107] Numerous molybdenum complexes with porphyrin ligands have been synthesized since then; however, to our knowledge all the reported complexes bear nonchiral porphyrin macrocycles, which prevents them from functioning as catalysts in asymmetric epoxidations. In 2001, Liu et al. initiated investigations on chiral molybdenum porphyrins.[103] It had been well documented that molybdenum-catalyzed epoxidations with alkyl hydroperoxides **58** usually involved [Mo-

(η^2-O_2)] or [Mo-OOR] active intermediates;[172] therefore, the synthesis and structural characterization of [$Mo^VO(P^*)(OMe)$] bearing a chiral D_4-symmetric P* ligand (H_2P^* = 5,10,15,20-tetrakis [(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-yl] porphyrin) was performed, along with the catalytic behavior of **58** for the epoxidation of aromatic alkenes with TBHP, which represented the first molybdenum porphyrin-catalyzed asymmetric epoxidation of alkenes with an ee value up to 29% (Table 5). These findings have highlighted the potential use of chiral peroxo or alkylperoxo complexes of Mo-porphyrins for the asymmetric epoxidation of alkenes.

Table 5. Asymmetric Epoxidation of Aromatic Alkenes with TBHP Catalyzed by Complex 58[a]

Entry	Substrate	Time (h)	ee (%)
1		16	16
2		3	29
3		4	28
4		15	26
5		30	24
6		16	10

[a] Adapted from ref 103 with permission. Copyright 2001 Elsevier.



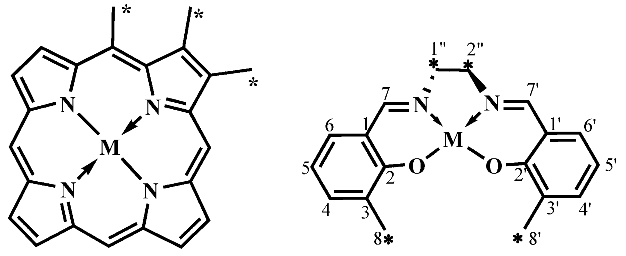
58 M=Mo=O

2.3. Salen Systems

Asymmetric epoxidation of unfunctionalized alkenes holds a considerable interest in organic synthesis because the resulting enantiomerically pure epoxides are versatile intermediates in the preparation of several classes of compounds.

Difficulty in the construction of an effective porphyrin catalyst is partially attributable to its π-conjugated planar structure, which does not allow the presence of stereogenic carbons in the porphyrin ring. In contrast to the porphyrin complex, the salen complex can contain stereogenic carbons at C_1'', C_2'', C_8, and C_8' carbons (Scheme 3).[159] Since these stereogenic centers locate close to the metal center, therefore, higher asymmetric induction can be anticipated by using optically active salen complexes as catalysts. Facile synthesis of salen ligands from a number of readily available chiral diamines has led to a successful endeavor, which in a short time span made it possible to screen a large number of ligands to optimize the catalyst structure. Very lengthy steps involved in chiral porphyrin synthesis have limited extensive applications of chiral porphyrins as catalysts. For industrial purposes, salen-Mn catalysts are preferred since manganese itself is a relatively nontoxic metal, and manganese complexes are superior to iron complexes for the selective epoxidation of olefins, chiefly because of fewer side reactions over manganese complexes.

Scheme 3. Asymmetric Carbons in Porphyrin and Salen[a]



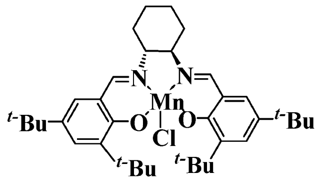
[a] Adapted from ref 173 with permission. Copyright 1993 Wiley-VCH.

2.3.1. Manganese and Chromium Salens

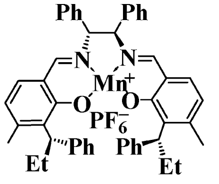
The pioneering studies performed by Katsuki and Jacobsen et al. have led to a variety of chiral salen-Mn(III) catalysts, which have made an efficient breakthrough in epoxidizing nonfunctionalized alkenes with different oxidants at high enantioselectivity.[86−88,91,120,121] A variety of alkenes have, thus, been epoxidized enantioselectively with simple oxidants such as PhIO, NaClO, H_2O_2, and Oxone, and an optimal enantioselectivity for a given substrate could be achieved by choosing the proper catalyst and reaction conditions.[121,173] Rather straightforward access to chiral salen ligands, based on the condensation of diamines with salicylaldehyde derivatives, provides a unique opportunity to finely tune the steric and electronic properties of the catalyst.[174] More importantly, chiral salen systems offer an additional advantage over the known chiral porphyrins because the asymmetric centers in salen complexes locate closer to reactive metal sites than those in porphyrin complexes.[86,87,121,175,176]

As the model to mimic the function of cytochrome P_{450}, a transition metal Schiff-base has several advantages: (a) easy availability, (b) low cost, and (c) high epoxidation activity toward a wide range of unfunctionalized olefins. This should make it to be a very attractive candidate for laboratory and industrial uses.[177] The discovery of chiral salen-Mn(III) complexes has, for the first time, allowed a convenient and inexpensive route for the efficient asymmetric epoxidation of unfunctionalized olefins.[86−88,120] The *tert*-butyl substituted catalyst **59** consisting of both commercially available enantiomers is not the most enantioselective but is much easier to prepare.[176] Note that the Jacobsen catalyst is air-stable and can be stored for a long period without appreciable decomposition.[178] Indeed, with $OSi(Pr^i)_3$ in C_5 and C_5', the ee value is higher for cis- or cyclic olefins, of which chromenes are ideal substrates, and for those substrates Katsuki catalyst **60** is also effective.[120,176]

During the past decade, a large number of chiral C_2-symmetric salen-type Schiff-base complexes have been synthesized as the catalysts for various asymmetric reactions including enantioselective epoxidation of unfunctionalized alkenes.[8,179−181] These sym-

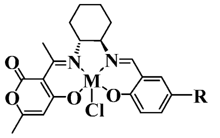


59



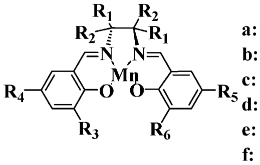
60

metrical catalysts are generally highly efficient and straightforward, while the unsymmetrical Schiff-base ligands are much less accessible, which has, accordingly, led to the scarcity of reports of chiral unsymmetrical salen ligands.[182−185] Up to now, all the methods published for chiral unsymmetrical salen ligands have involved a stepwise synthesis of non-C_2-symmetric salen ligands containing two different donor units via mono-imines. Unfortunately, those syntheses were basically unreliable, and even after purification mono-imines prepared from salicylaldehyde and 1,2-diamine were always contaminated with various amounts of C_2-symmetric bis-imine.[186] Very recently, Daly et al. succeeded in avoiding this inherent hurdle by trapping mono-aldimine as a tartrate salt;[185] however, its further reaction with different salicylaldehydes still produced an unsymmetrical bis-imine in low yield. So far, the most reliable route for the preparation of non-C_2-symmetric salen ligands has been involved in the use of a statistical method.[187] Other chiral unsymmetrical salen-like catalysts for the asymmetric epoxidation of alkenes reported recently include a biomimetic Mn-dihydrosalen complex[188,189] and Mn-picolinamide-salicylidene complexes.[190] A series of unsymmetrical chiral salen-Mn complexes **61** and **62** were also reported by Kureshy[191,192] and Kim.[193]



M=Mn(H_2O)

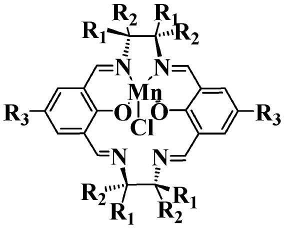
61 R=H, Cl, Me, NO_2



a: R_1=-$(CH_2)_4$-, R_2=R_3=R_4=H, R_5=R_6=^{t}Bu
b: R_1=Ph, R_2=R_3=R_4=H, R_5=R_6=^{t}Bu
c: R_1=-$(CH_2)_4$-, R_2=R_4=H, R_3=OMe, R_5=R_6=^{t}Bu
d: R_1=Ph, R_2=HR_4=H, R_3=OMe, R_5=R_6=^{t}Bu
e: R_1=-$(CH_2)_4$-, R_2=R_3=R_4= R_5=H, R_6=OMe
f: R_1=-$(CH_2)_4$-, R_2=R_3=R_4= R_5=H, R_6=OMe

62

Although the obtained ee value over the unsymmetrical Schiff-base complex is lower than that on the corresponding symmetrical one, this synthesis method could open up the possibility of designing other chiral unsymmetric Schiff-base complexes with different steric and electronic properties on different subunits. Generally, structural and electronic properties of salen ligands play important roles in controlling the activity of catalysts.[120,194] In almost all the salen complexes, two identical salicylaldehyde derivative moieties are connected to both sides of one diamine in the ligands to grant a modified structural and electronic property.[87,120,121,182,194,195] In 2000, Kim et al. synthesized fully symmetrical macrocyclic chiral salen Schiff-bases **63** through condensing two diamine molecules with two 2-diformylphenols.[196] These new macrocyclic chiral salen-Mn catalysts displayed moderate activity and enantioselectivity.

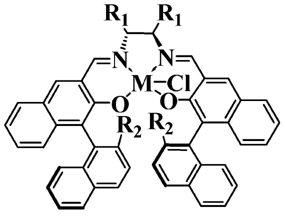


a: R_1=-$(CH_2)_4$-, R_2=H, R_3=H
b: R_1=-$(CH_2)_4$-, R_2=H, R_3=t-Bu
c: R_1=Ph, R_2=H, R_3=H
d: R_1=Ph, R_2=H, R_3=t-Bu

63

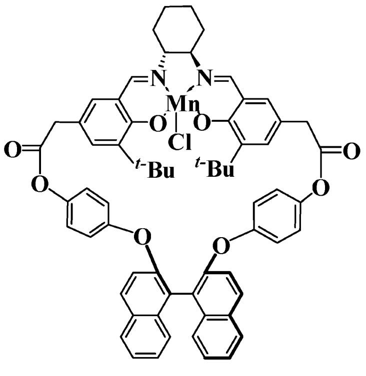
In 2001, Ahn et al. carried out the asymmetric epoxidation of olefins over the new sterically hindered salen-Mn (III) complex **64**.[197] Experimentally, the preparation of salen-Mn (III) complex **64** might be easier than Katsuki catalyst **60**. On the other hand, the presence of polar ester groups at R_2 in **64** would enhance the rate of phase transfer of oxidant molecules in an aqueous/alkene biphasic reaction system; consequently, the increase of turnover frequency in the epoxidation reactions should be anticipated.[197] Furthermore, they also found that the chirality in diamine moiety was a requirement for a high enantioselectivity and that the absolute configuration of styrene oxide was controlled by the chirality in the diamine bridge rather than by the absolute configuration of C_3 and C_3' in BINOL unit and that the enantioselectivity was as high as 96−99% ee for *cis*-methylstyrene and 2,2-dimethylchromene.[197] It is noteworthy that the epoxidation of *cis*-β-methylstyrene over the catalyst (*R*, *S*)-**64** achieved 96% ee, relatively higher than those obtained in any other NaClO-promoted reactions at 0 °C, which further proves the crucial factor governing the absolute configuration and ee values of epoxides to be the chirality of diamine groups at C_3 and C_3' in salen ligand. Very recently, Murahashi et al. in 2004 reported the novel salen-Mn complex **65** bearing a chiral binaphthyl strapping unit as an effective catalyst for the epoxidation of alkenes with iodosylbenzene (up to 93% ee).[198]

Under these considerations, dimeric homochiral salen-Mn(III) complexes **66** were synthesized and used as catalysts by Janssen,[182] Kureshy,[199−201]and Liu et al.[202] in the enantioselective epoxidation of unfunctionalized olefins with various oxidants, in which excellent conversion was obtained with the highest ee value up to 99%. Monomeric Jacobsen complex with a catalyst loading of 2 mol % gave a conversion of 96% with 97% ee within 9 h for the oxidation of cyano chromene in the presence of 4-phenyl pyridine *N*-oxide; however, the dimeric complex **66a** required only 2.5 h for 100% conversion with >99% ee under identical reaction conditions, even using simple pyridine *N*-oxide as the additive. A low catalyst loading down to 0.6 mol % was still sufficient for achieving satisfactory conversion and selectivity within 6 h. Further decreasing the catalyst loading to 0.2 mol % caused a reduction in the reaction rate and ee value (in 24 h), while the catalyst loading of below 0.2 mol % deteriorated the reaction rate and selectivity rapidly. The enhanced activity



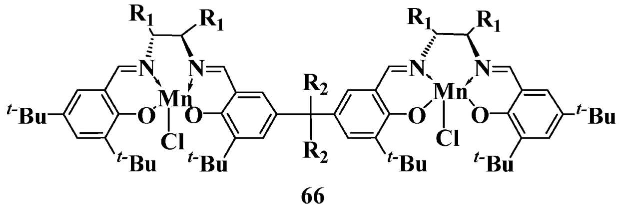
64

a R_1=H R_2=-OOC-^{t}Bu
(R,S)-b R_1=Ph R_2=-OOC-^{t}Bu
(R,R)-c R_1=Ph R_2=-OOC-^{t}Bu
(R,R)-d R_1=Ph R_2=-OOCCH$_3$
(R,R)-e R_1=Ph R_2=-OSiPh$_2$(^{t}Bu)
(R,R)-f R_1=-(CH$_2$)$_4$- R_2=-OOC-^{t}Bu
(R,S)-g R_1=-(CH$_2$)$_4$- R_2=-OOC-^{t}Bu



65

of dimeric catalyst **66a** shows that two units do not affect the isolation but have a synergic interaction. Axial bases have a pronounced effect on the reactivity and selectivity of enantioselective epoxidation and in a biphasic reaction system possess a dual role in stabilizing the oxo intermediate and transporting oxidant into the organic phase.[203] It has been reported that a monomeric catalyst with appropriate *N*-oxide derivative additives could activate and stabilize the catalyst.[203] Comparatively, the epoxidation of styrene over the dimeric catalyst **66a** proceeded faster in the presence of either 4-phenyl pyridine *N*-oxide (4-PPNO) or 4-(3-phenyl propyl) pyridine *N*-oxide (4-PPPNO) than adding pyridine *N*-oxide (PyNO), without any visible improvement in the chiral induction. In addition, the recovered catalyst by precipitation using hexane without undergoing further purification showed a visible decrease in the reactivity, without any loss of enantioselectivity.

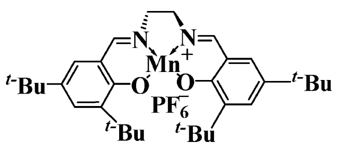


66

a: R_1= -(CH$_2$)$_4$-, R_2=H
b: R_1= Ph, R_2=CH$_3$
c: R_1= -(CH$_2$)$_4$-, R_2=CH$_3$

Complexes **66b** and **66c** were also used in the epoxidation of unfunctionalized alkenes.[200] All the reactions were completed in less than 15 min; however, the reactions using Jacobsen's monomeric catalyst were complete after 25 min. As expected, dimeric complexes showed an enhanced activity. The enantioselectivity of reactions was always high, irrespective of the loading level of catalyst, even for catalyst loading of only 0.5 mol %. A dimeric catalyst also showed better repeatability and stability than did a monomeric one. Complex **66a** could be efficiently used as many as five cycles in a biphasic reaction system, and the activity of the recovered catalyst showed a gradual decrease with recycling numbers, possibly due to either minor degradation or soluble loss of the catalyst during the reaction.

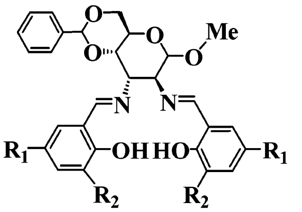
It is well-known that the chiral center on salen-Mn complexes induces the enantioselectivity in the asymmetric epoxidation of olefins. However, Hashihayata et al. in 1997 first developed a new asymmetric epoxidation system consisting of an achiral salen-Mn complex and a chiral amine, in which commerically available (−)-sparteine displayed the highest asymmetric induction.[204] It should be mentioned that the addition of water into the reaction medium improved the enantioselectivity (up to 73% ee) for the epoxidation of chromene derivative. In 1999, the same group reported again high enantioselectivity and good chemical yield in the epoxidation of 2,2-dimethylchromene derivatives using achiral salen-Mn(III) complex **67** as the catalyst in the presence of axially chiral bipyridine *N,N'*-dioxide.[168] Their research has suggested a new concept of chiral actualizer, which could have the potential to open a new avenue for asymmetrically catalytic reactions.



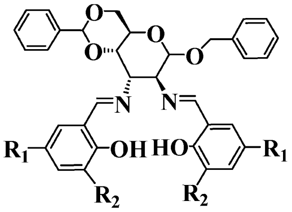
67

The chiral catalysts with salen ligands derived from appropriately modified common carbohydrates have been found to be as active as those based on 1,2-cyclohexanediamine. There was a report made by Borriello et al. in 2004 regarding the synthesis of new chiral salen-type ligands **68** and **69** derived from D-glucose and D-mannose.[205] These two compounds were obtained by introducing appropriate functions at the C_2 and C_3 positions of the sugar ring. The efficiency of the corresponding Mn complexes in the epoxidation of styrenes was shown, e.g., for functionalized *cis*-β-methylstyrene an ee value of 86% was achieved. These promising results deserve further investigation aiming at the exploration of other functional groups present naturally on the skeleton of carbohydrates. For instance, −OH groups not involved in metal coordination may be used for other purposes, such as anchoring onto a polymeric matrix or improving the solubility in alternative solvents.

Chromium-salen complexes have been extensively applied in stereoselective alkene epoxidations,[181,206−208] kinetic resolution of epoxides,[209−211] alcohol oxidations,[212] asymmetric addition of organometallic reagents to aldehydes,[213−215] and asymmetric hetero-



68 **a:** $R_1=R_2={}^t$-Bu
b: $R_1=H$, $R_2={}^t$-Bu



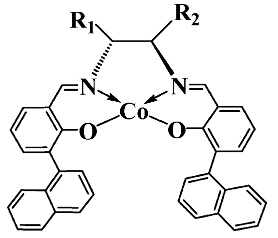
69 **a:** $R_1=R_2={}^t$-Bu
b: $R_1=H$, $R_2={}^t$-Bu

Diels−Alder reactions.[216] Distinctly different from salen-Mn-catalyzed alkene epoxidations (for recent findings on mechanisms see refs 217−221), chromium-salens give good enantioselectivities for (*E*)-alkenes, and the established oxygen-transfer Cr^V=O species is relatively stable and EPR active. For more detailed understanding of the mechanism of either Mn- or Cr-salens mediated chiral epoxidation, please refer to a recent review by Gilheany et al.[181]

Recently, Gilheany et al. investigated the substituent effect on the salen ring, which focused mainly on combinations with respect to all-important 8 positions and on a comprehensive study of effect of one substituent at all the positions.[222] The results showed that the enantioselectivity was increased at 3,3- and 6,6-positions and decreased at 4,4- and 5,5-positions by halo-substitution on the salen ring. Addition of triphenylphosphine oxide significantly increased the selectivity of the complexes coming from 3,3- or 5,5-substitution rather than 4,4- or 6,6-substitution, and the use of a nitrate counterion was beneficial in most cases. Additionally, the enantioselectivity could be elevated by the addition of many different types of phosphoryl compounds, among which tri-arylphosphine oxides were the most effective, e.g., tris(3,5-dimethylphenyl) phosphine oxide led to the highest ee value of 93%.[222b] A ceiling effect of additive has been observed, in which bulky additives were ineffective, accompanied by a saturation effect with respect to the increase of concentration; however, there was no electronic effect of substituents inside the additive. It was found that the presence of compounds containing extended π-electron systems strongly affected the ee (20% ee).[208b] In certain cases, such additives appeared to stabilize active oxidant and to slow the reaction. Unsubstituted and methyl-substituted imidazoles were found to be beneficial additives, while imidazoles with aromatic substituents were very detrimental. These results have provided actual support for Katsuki's views on the importance of π-interactions in the epoxidations catalyzed by analogous salen-Mn complexes. Compounds containing S=O and C=O bonds also showed an impact on the enantioselectivity to a lesser extent; however, whether phosphine sulfides on borane could survive contact with the oxidant would depend on the salen substitution pattern. A phosphorus ylide was found to stabilize a Cr(V) oxo species, approximately to double its lifetime.

2.3.2. Cobalt Salens

Much attention has been paid to the development of direct and selective epoxidation of olefins by the use of molecular oxygen and a suitable reductant, such as a primary alcohol,[223] aldehyde,[224] and cyclic ketone[225] that can accept one oxygen atom from molecular oxygen to enable the reaction. In 1997, Kureshy et al. first reported the asymmetric epoxidation of nonfunctionalized prochiral olefins by combined use of an atmospheric pressure of molecular oxygen and a reductant of isobutylaldehyde catalyzed by chiral salen-Co (II) complexes **70** with or without PyNO co-oxidant.[226] An up to 55% ee and a yield of 90% were achieved for the catalytic epoxidation of *trans*-3-nonene. Anyway, it should be pointed out that the presence of a catalytic amount of pyridine *N*-oxide notably improved the enantioselectivity without any change in the configuration.



a: $R_1=R_2=$-$(CH_2)_4$-
b: $R_1=H$, $R_2=Me$
c: $R_1=R_2=Ph$

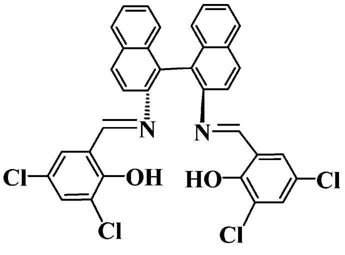
70

2.3.3. Palladium Salens

C_2-symmetric 1,1-binaphthyl unit and tetradentate Schiff bases (salen) constitute two of the most important types of chiral auxiliaries in metal-mediated asymmetric catalysis. There are a variety of Pd (II) Schiff base complexes that have been reported in the literature, of which only those bearing bidentate Schiff base ligands are well documented.[227] Although the salen-Pd (II) complex was first isolated in 1963, tetradentate Schiff base complexes of this metal ion have still been sparse, and their reactivity toward the alkene epoxidation remains unexplored.[227,228] In 2000, Zhou et al. provided the first example regarding the asymmetric epoxidation of alkenes catalyzed by a palladium complex Pd^{II}-**71**.[229] With a molar ratio of catalyst/styrene/TBHP = 1:5:20, the reaction over the complex Pd^{II}-**71** gave rise to a 16% conversion of styrene after 6 h, affording styrene epoxide in the selectivity of 37% with 17% ee and benzaldehyde in the selectivity of 50% (based on the consumed styrene). Under identical conditions, 27% of *p*-fluorostyrene was converted to *p*-fluorostyrene epoxide in the selectivity of 51% with 71% ee and to *p*-fluorobenzaldehyde in the selectivity of 32%.

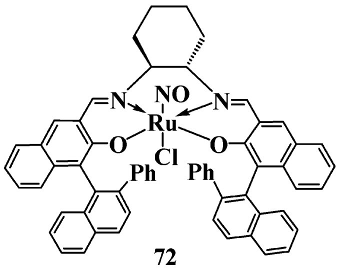
2.3.4. Ruthenium Salens

In 1999, Takeda et al. published the synthesis and catalytic application of (ON$^+$)(salen) ruthenium (II) complex [(ON)Ru-salen complex] **72** in the asym-



71

metric epoxidation of 6-acetamido-2,2-dimethyl-7-nitrochromene in the presence of various oxidants, for which 2,6-dichloropyridine *N*-oxide as terminal oxidant was preferred.[230] All the tested conjugated olefins showed high enantioselectivities greater than 80% ee, irrespective of their substitution patterns; however, the enantioselectivity decreased with elongated reaction time. This suggested the gradual decomposition of the (ON)Ru-salen complex **72** during the reaction to generate fragmental Ru-species with a lower asymmetric induction. Furthermore, the reaction was accelerated by exposure to sunlight. The sense of asymmetric induction by the (ON)Ru-salen complex **72** was similar to that of the Mn-salen complex bearing the same salen ligand.



72

In summary, metallosalens are considerably effective catalysts for the asymmetric epoxidation of conjugated cis-di-, tri-, and some tetra-substituted olefins.[231] Metallosalens can be easily synthesized from corresponding salicylaldehyde derivatives, diamines, and metal ions. The main advantages include (1) the commercial availability of a wide variety of chiral and/or achiral salicylaldehydes, chiral diamines, and metal ions, and (2) the easy preparation and use of metallosalen complex catalysts. This results in the convenient application of such catalysts in the industry. And, when these salen-complexes are employed to catalyze the epoxidation of functionalized substituted olefins, the satisfied results can still be achieved.

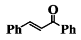
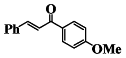
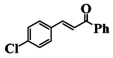
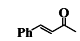
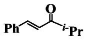
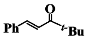
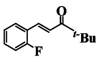
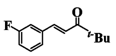
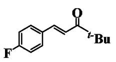
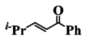
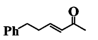
2.4. BINOL Systems

2.4.1. Lanthanum BINOLs

The catalytic asymmetric epoxidation of α,β-unsaturated carbonyl compounds is an important transformation in organic synthesis because it constructs two adjacent chiral carbon centers simultaneously, and the corresponding enantiomerically enriched epoxy compounds can be easily converted to many types of useful chiral compounds.[232−239] Although many research groups have developed efficient catalytic asymmetric epoxidations of α,β-unsaturated ketones,[232,233,236,238−242] there are only limited examples with respect to the epoxidation of α,β-unsaturated esters as substrates catalyzed by either a salen-Mn complex[243] or a chiral ketone.[244−248] In both cases, the substrate was only β-aryl-substituted α,β-unsaturated ester. Shi et al. reported excellent results for a few β-alkyl-substituted substrates but without trans-β-alkyl-substituted α,β-unsaturated esters due to the poor chemoselectivity.[248] Recently, the use of lanthanoid-BINOL complexes to catalyze the enantioselective epoxidation of enones with hydroperoxides was studied in great detail.[240−242,249−251] This catalytic system was applicable for both alkyl and aryl substituted enones, giving the product in high yields with good enantioselectivity.

Shibasaki catalyst, which resulted from an equimolar mixture of (*R*)-(+)- 1,1′-bi-2-naphthol (BINOL) and La(OPr^i)$_3$, could catalyze the asymmetric epoxidation of a wide range of (*E*)-enones in the presence of 4 Å molecular sieves.[240] When chalcone was epoxidized by cumene hydroperoxide oxidant, 93% of chemical yield and 83% ee value were obtained. Ytterbium catalysts showed a good chiral induction for the epoxidation of alkyl α,β-enones, in which 96% ee was obtained with external addition of triphenylphosphine oxide (15 mol %),[242] and the positive effect of addition of water on the enantioselectivity was observed.[249] In 1998, Daikai et al. found that the coordination of an external ligand to chiral ytterbium complex [Yb-(*R*)-(BNP)$_3$] not only increased the solubility of catalyst but also largely enhanced the enantioselectivity of hetero-Diels−Alder reaction,[242,252] indicative of the importance of saturated coordination to lanthanoid with an appropriate number of ligands for the deoligomerization of lanthanoid complexes. In addition, they further investigated the effect of additives on lanthanoid complex-catalyzed asymmetric epoxidation of enone that was developed by Shibasaki et al.[232,233,253−255] Among the additives tested, triphenylphosphine oxide showed the best result (96% ee) and a notable ligand acceleration of the reaction rate. One plausible explanation could be responsible for such a remarkable ligand effect, i.e., the interaction of ligand with Ph$_3$P=O would produce a nonpolymerically uni-structured catalyst, further leading to the occurrence of epoxidation on the coordination sphere of lanthanum, where the reaction sites might be quite close to the chiral binaphthyl ring due to the steric hindrance of bulky phosphine oxide ligand. It was also found that when CMHP was used in place of TBHP, the enantioselectivity was further raised to over 99% ee, and the amount of catalyst could be reduced to 0.5 mol % without any serious loss in the enantioselectivity. More importantly, all of the reagents required for this asymmetric epoxidation are commercially available, and low reaction temperatures usually required to attain a high enantioselectivity are not necessary, thus making it a highly practical protocol. To understand the mechanism of highly enantioselective epoxidation, the relation of enantiomeric purity of chiral ligand to that of the product was investigated. The results have shown that the ligand with only 40% ee could induce the product with more than 99% ee. This phenomenon strongly suggests that the active catalyst may not be monomeric, instead it has a particular structure that hardly changes during the reaction because of its thermodynamic stability.

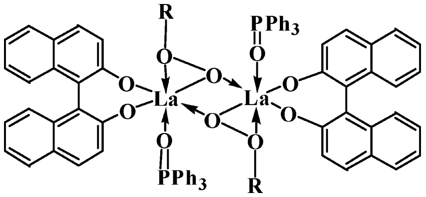
Table 6. Asymmetric Epoxidation of Various Enones with La−BINOL Complexes and TBHP[a,b]

Entry	Substrate	Additive	Time (h)	Yield (%)	ee (%)
1		none	3	86	73
2		Lutidine-N-Oxide	3	96	74
3		DMEU	3	97	68
4		$(^{n}Bu)_3P{=}O$	3	88	73
5		(*o*-Tolyl)$_3$P=O	1.5	96	73
6		(*p*-Tolyl)$_3$P=O	1	95	94
7		$(Me_2N)_3P{=}O$	1.5	99	86
8		(piperidino)$_3$P=O	1.5	97	85
9		(cyclohexyl)$_3$P=O	1.5	97	83
10		$Ph_3P{=}O$	0.5	99	96
11		$Ph_3P{=}O$	0.2	99	>99
12		$Ph_3P{=}O$	1.5	77	98
13		$Ph_3P{=}O$	1	99	>99
14		$Ph_3P{=}O$	2	93	>99
15		$Ph_3P{=}O$	3	90	>99
16		$Ph_3P{=}O$	4	72	>99
17		$Ph_3P{=}O$	3	93	>99
18		$Ph_3P{=}O$	20	53	>99
19		$Ph_3P{=}O$	12	52	>99
20		$Ph_3P{=}O$	12	45	>99
21		$Ph_3P{=}O$	0.5	88	98
22		$Ph_3P{=}O$	1	60	86
23		$Ph_3P{=}O$	1	92	87

[a] Adapted from ref 251 with permission. Copyright 2003 Wiley USA. [b] CMHP was used as the oxidant in entry 11−22.

In 2003, a highly practical way was again reported for obtaining α,β-epoxy ketones with a high optical purity (Table 6).[251] The chiral lanthanum complex self-assembled in-situ from lanthanum triisopropoxide, (*R*)-BINOL, triarylphosphine oxide, and alkyl hydroperoxide (1:1:1:1) efficiently catalyzed the epoxidation of α,β-unsaturated ketones with TBHP or CMHP at room temperature into the corresponding epoxy ketones with an enantioselectivity of >99% ee. Actually, this catalyst system has been successfully scaled up to the level of 30−80 kg, in which the product yield could reach 90% with a high ee value of >98%.[256] Also, this homochiral dimeric binuclear μ-complex, La/(*R*)-BINOL/Ph_3PO/ROOH (1:1:1:1), was proposed as an active catalyst for the reaction in Scheme 4, accompanied with a possible catalytic cycle as shown in Scheme 5.[251] One of two lanthanum ions would function as a Lewis acid to activate the substrate, and the peroxide attached to the other might be delivered as the active oxidant, thus, to control the stereochemistry of epoxidation. For the epoxidation of chalcone with CMHP, the catalyst La-$(OPr^i)_3$/(*R*)-BINOL/Ph_3PO/CMHP (1:1:1:1) afforded unusual yield (98%) and ee value (>99%). The addition of triphenylphosphine oxide seems to stabilize those intermediates, while excessive CMHP could jeopardize their structures because of the formation of an oligomeric structure.

Scheme 4. Proposed Structure of the Active Catalyst[a]



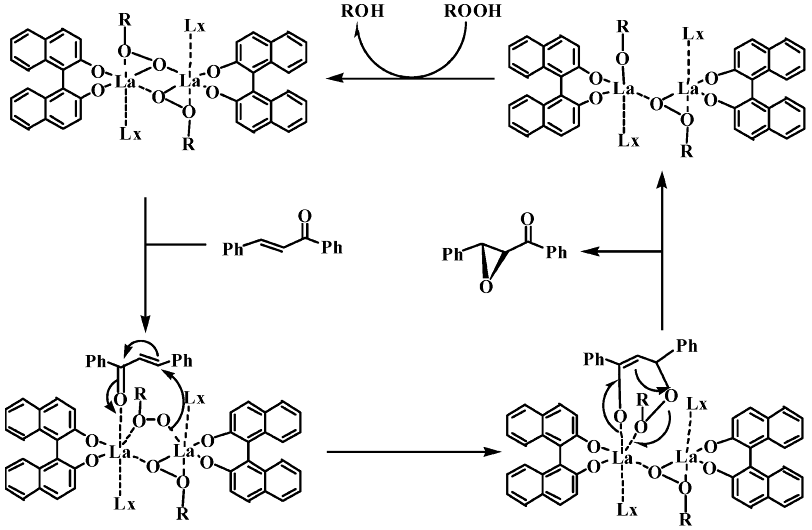
[a] Adapted from ref 251 with permission. Copyright 2003 Wiley USA.

In 2001, Nemoto et al. reported the application of the asymmetric catalyst, La−BINOL−$Ph_3As{=}O$ (1−5 mol %), for the epoxidation of a variety of enones, including dienone and *cis*-enone.[241] The reaction was completed in a reasonable time to attain the corresponding epoxy ketones in 99% yield and >99% ee. And recently, Ohshima et al. in 2003 claimed the first example of a general asymmetric epoxidation of α,β-unsaturated carboxylic acid derivatives, catalyzed by La−BINOL−$Ph_3As{=}O$ complex with TBHP.[257] This new catalytic system has been extended to the epoxidations of α,β-unsaturated carboxylic acid 4-phenylimidazolides. All the epoxidations of β-aryl-type substrates could end in a reasonable reaction time (3.5−6 h); however, only β-aryl-type substrates with either an electron-withdrawing group or an electron-donating group on the aromatic ring were smoothly epoxidized to obtain a good ee (89−93% ee). This catalyst system was also effective for highly reactive β-alkyl substituted substrates. Both primary and secondary alkyl substituted substrates gave rise to the products in high yield (72−93%) with slightly low ee (79−88% ee). In particular, this reaction was applicable to substrates that are functionalized with a C−C double bond or a ketone without overoxidation.

2.4.2. Ytterbium BINOLs

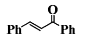
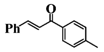
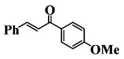
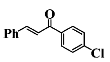
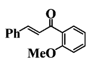
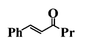
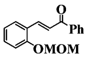
La-catalysts and Yb-catalysts can be used in a complementary manner for the asymmetric epoxidation of aromatic and aliphatic substituted enones (94% ee) at room temperature. In 1998, Watanabe et al. discovered that the addition of 4 Å molecular sieves to the catalyst was considerably effective for acquiring the product in high yield and that even the presence of a small amount of water obviously improved the ee value.[249] For example, 83% yield and 85% ee were achieved for the asymmetric epoxidation of 4-methyl-1-phenyl-pent-1-en-3-one with the addition of H_2O, while the absence of H_2O led to only 81% yield and 70% ee. However, the absence or presence of H_2O did not show any visible impact on La-catalyst. The role of water can be rationalized with the coordination of water molecules to Yb atom, thereby controlling the orientation of hydroperoxides to form an appropriate asymmetric environment. Recently, Chen et al. successfully developed a series of 6,6′-disubstituted BINOL ligands (*S*)-**73** and the corresponding ytterbium complex catalysts.[258] Especially, the ytterbium complex resulting from Yb-

Scheme 5. Speculated Catalytic Cycle[a]



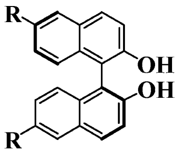
[a] Adapted from ref 251 with permission. Copyright 2003 Wiley USA.

Table 7. Asymmetric Epoxidation of Enones Catalyzed by Yb−BINOL Complexes 73 with CMHP at Room Temperature[a]

Entry	Substrate	Ligand	Yield (%)	ee (%)
1		**(*S*)-73a**	95	44
2		**(*S*)-73b**	76	62
3		**(*S*)-73c**	91	95
4		**(*S*)-73c**(1st reused)	90	95
5		**(*R*)-73c**	90	95
6		**(*S*)-73c**(0 °C)	91	97
7		**(*S*)-73d**	78	70
8		**(*S*)-73e**	86	83
9		**(*S*)-73f**	88	89
10		**(*S*)-73g**	84	63
11		**(*S*)-73c**	83	54
12		**(*S*)-73c**	85	54
13		**(*S*)-73c**	85	53
14		**(*S*)-73c**	81	66
15		**(*S*)-73c**	85	38
16		**(*S*)-73c**	88	47

[a] Adapted from ref 258 with permission. Copyright 2001 Elsevier.

$(OPr^i)_3$ and (*S*)-6,6′-diphenyl-BINOL in THF was found to be an efficient catalyst for the asymmetric epoxidation of α,β-unsaturated enones with CMHP, in which the best results were 97% ee and 91% yield for the product (*E*)-1,3-diphenylprop- 2,3-epoxy-1-one (Table 7).

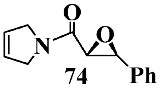


a: R=H, b: R=Br
c: R=Ph, d: R=*p*-MeC$_6$H$_4$
e: R =*p*-MeOC$_6$H$_4$
f: R=*p*-CF$_3$C$_6$H$_4$
g: R=1-Naphthyl

73

2.4.3. Gadolinium and Samarium BINOLs

The introduction of substituents into 6,6′-positions of BINOL might exert a profound impact on the activity and enantioselectivity of the catalyst due to the modified electronic and steric properties.[259−262] In 2001, Chen et al. achieved epoxy chalcone with 95% ee over 5 mol % of Gd$(OPr^i)_3$-(*S*)-6,6′-diphenyl-BINOL catalyst at room temperature.[263] In this system, CMHP was obviously advantageous over TBHP, e.g., the ee value decreased from 95% with CMHP to 86% with TBHP for the production of epoxy chalcone. The chiral ligand could be quantitatively recovered and reused with a negligible loss of chemical yield and ee. In 2003, Kinoshita et al. developed the asymmetric epoxidation of α,β-unsaturated *N*-acyl pyrroles, which are highly reactive and versatile substrates as ester surrogates.[264] Although the functional group tolerance of the Wittig reaction is good under mild conditions, this olefination is generally considered to be somewhat inefficient as a result of the production of Ph_3PO as a byproduct. They hypothesized that the reuse of waste Ph_3PO in the epoxidation reaction as a modulator for Sm−H_8−BINOL complex would partially compensate the disadvantage of the Wittig reaction. Thus, a sequential reaction from Wittig olefination to catalytic asymmetric epoxidation took place, in which Ph_3PO yielded in the first (Wittig) reaction was reused as an additive in the second reaction epoxidation. This process provided an efficient access to prepare optically active pyrrolyl epoxides from a variety of aldehydes in high yields with excellent enantioselectivities. Under optimal conditions (THF/toluene and Ph_3PO), the reaction proceeded smoothly with a low catalyst loading of 1 mol % to afford the epoxide **74** in 94% yield and 99% ee in 18 min. The reaction reached the completion over 5 mol % of the catalyst in the presence of CMHP (less explosive and reactive than TBHP) within 12 min with 91% yield and >99.5% ee.

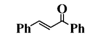
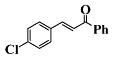
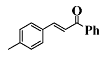
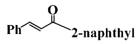
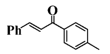
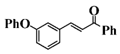
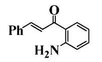
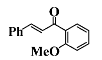
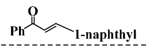
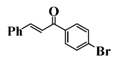


74

2.4.4. Calcium BINOLs

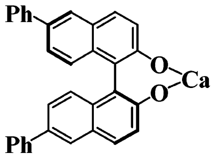
As described above, the asymmetric epoxidation of α,β-unsaturated enones is also a powerful strategy

Table 8. Asymmetric Epoxidation of α,β-Unsaturated Enones with TBHP over the Catalyst 75 in the Solvent of Cyclohexane/Toluene (9:1) in the Presence of 4 Å Molecular Sieves[a]

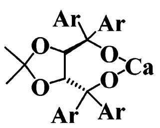
Entry	Substrate	Tempt. (°C)	Yield (%)	ee (%)
1		−10	85	70
2		−15	91	74
3		−10	78	80
4		0	72	73
5		5	68	62
6		0	82	74
7			60	26
8			70	22
9			76	25
10		−15	82	32

[a] Adapted from ref 266 with permission. Copyright 2003 Elsevier.

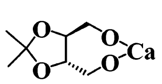
for the synthesis of enantiomerically enriched organic compounds.[265] In 2003, Kumaraswamy et al. first developed a novel and efficient chirally modified calcium complex **75** derived from commerically available low-cost $CaCl_2$ and potassium salt of (*S*)-6,6′-diphenyl BINOL, for the asymmetric epoxidation of α,β-unsaturated enones (Table 8).[266] Introduction of substituents to the 3-position and 6,6′-positions of BINOL exhibited profound effects not only on the activity but also on the enantioselectivity of epoxy chalcone.[258,263] In an effort to increase the enantioselectivity of chalcone, a wide range of substituted-BINOL and C_2-symmetric ligands were prepared. The results showed that complex **75** offered a higher ee value than did the 2′-substituted BINOL calcium complex **76** and the C_2-symmetric complex **77**. The increase in the enantioselectivity was not only due to the electronic effect of 6,6′-aryl substitution as predicted by Vries et al.[258,263] but also due to the increase in bond angle between two naphthyl rings, which may provide a favorable coordination environment at the metal−ligand site.



75



76



77

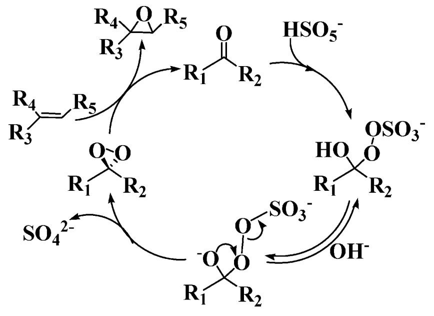
2.5. Chiral Carbonyl Compound Systems

The intermediary of dioxiranes formed in oxidation reactions was first suggested by Baeyer and Villiger in 1899 in the monoperoxysulfate oxidation of menthone into the corresponding lactone.[267] Experimental confirmation of this unusual structure was not available until 1977 when the parent dioxirane was detected during gas-phase ozonolysis of ethylene, and its existence was thus rigorously established.[268−270] In the realm of solution-phase oxidation, however, the seminal breakthrough came in 1974, when Montgomery observed that ketones could effectively catalyze the decomposition of Oxone[271] and the oxidation of halides and dyes.[272] Montgomery's speculation did not establish that dioxiranes were the active intermediates, which was experimentally evidenced by ^{18}O labeling studies of Curci.[273] These investigators demonstrated conclusively that dioxiranes were indeed produced in situ from the interaction between Oxone and ketones and that these intermediates were responsible for the accelerated decomposition of Oxone.[273] Since the isolation of dioxiranes is often difficult, therefore, the in-situ generation of dioxiranes is generally required, for which excess Oxone, a ketone and an appropriate buffer are employed. Recently, much attention has been focused on the epoxidation of alkenes with Oxone by either chiral ketones[244,274−280] (via a dioxirane[273,281−283]) or chiral-iminium salts[284,285] (via an oxaziridinium species), which is a possible alternative to solve the problem.

2.5.1. Simple Chiral Ketones

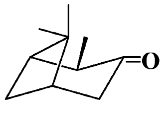
Dioxiranes, either isolated or generated in situ from $KHSO_5$ (Oxone) and ketones (Scheme 6), have shown to be efficient oxidants for the asymmetric epoxidation of unfunctionalized olefins. Owing to the rapidness, mildness, and safety of the reaction, this system has been extensively investigated.[108,273,281−283,286−295] The first chiral ketone-catalyzed asymmetric epoxidation was reported in 1984 by Curci,[274] who carried out the epoxidation (12.5% ee) of (*E*)-β-methylstyrene or 1-methylcyclohexene over the catalyst (+)-isopinocamphone **78** or (*S*)-(+)-3-phenyl-butan-2-one **79** in a biphasic mixture of CH_2Cl_2/H_2O buffered to a pH of 7−8, using Bu_4NHSO_4 as a phase transfer catalyst. Since electron-deficient ketones were generally more reactive for the epoxidation, a trifluoromethyl group was accordingly incorporated into the structure of ketones to prepare highly active ketones **80** and **81** with high yields.[276]

Scheme 6. Catalytic Cycle Involving Dioxiranes[a]

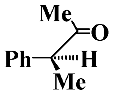


[a] Adapted from ref 291 with permission. Copyright 1998 The American Chemical Society.

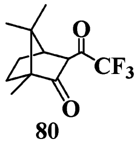
Yang et al. synthesized C_2-symmetric cyclic chiral ketones **82**−**84**, derived from 1,1′-binaphthyl-2,2′-dicarboxylic acid.[244,277,296] The design was based on the following considerations:[239] (a) C_2-symmetry was introduced to limit competing reaction modes of the



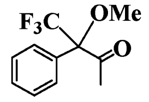
78



79

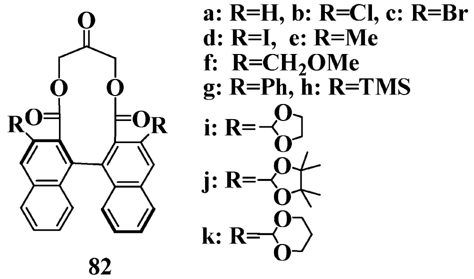


80

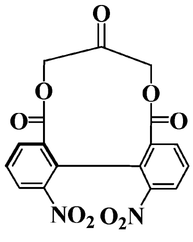


81

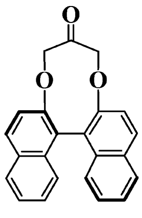
attack on dioxirane, which has two faces for the oxygen transfer. (b) Che chiral element was placed away from the catalytic center (the carbonyl group) while avoiding the occurrence of any substitution at α-carbon since α-carbons are prone to the racemization, and the steric hindrance at α-carbon decreases the catalyst activity. (c) Two electron-withdrawing ester groups were introduced to activate the carbonyl group. The resulting ketone was stable and recoverable in high yield with up to 95% ee.



82

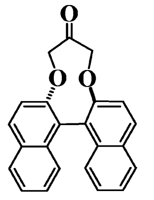


83

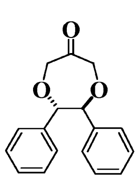


84

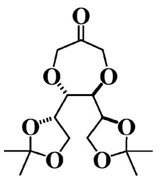
Ketone (*R*)-**83** was easily prepared in one step from (*R*)-6,6-dinitro-2,2-diphenic acid and 1,3-dihydroxyacetone using the Mukaiyama reagent. (*R*)-**82a** and (*R*)-**83** showed similar enantioselectivities for the epoxidation. Ketone (*R*)-**84** (10 mol %) was applied in the asymmetric epoxidation of *trans*-stilbene under the same reaction conditions with (*R*)-**82a**. It was found that the epoxidation reaction proceeded with 10% of conversion (determined by ^{1}H NMR) after 6 h, and the ee value of *trans*-stilbene epoxide was about 12%. The poor activity of the ketone could be associated with the fact that an ether group is a weaker electron-withdrawing group than an ester group. The ester groups giving rise to a rigid and C_2-symmetric structure of cyclic ketones seemed to be essential for effective asymmetric epoxidation. As compared to ketone **82**, ketones **85** and **86** made by Song et al. in 1997 showed a low enantioselectivity of ≤59% ee, possibly because a replacement of the ester group with the ether one that is a weaker electron-withdrawing group could bring the carbonyl group closer to the chiral center.[280] But Adam's ketones **87** and **88** exhibited a catalytic activity similar to **85** and **86**.[297] Also, Yang et al. have demonstrated the potential of C_2-symmetric chiral ketones for the catalytic asymmetric epoxidation of *trans*-olefins and trisubstituted olefins.[296] Epoxidation reactions could be performed with only 10 mol % of ketone catalysts, which could be recovered and reused without any loss of activity and chiral induction. Convincing evidence for a spiro transition state of dioxirane epoxidation has been proposed through the ^{18}O-labeling experiment, in which chiral dioxiranes were found to be the intermediates in epoxidation reactions catalyzed by chiral ketones.



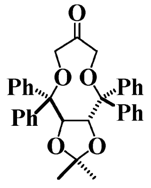
85



86

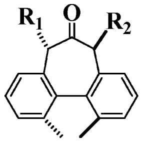


87



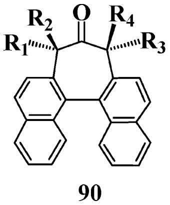
88

In 1999, Denmark et al. reported a highly active and enantioselective seven-membered carbocyclic chiral ketone **89** with a chiral center closer to the carbonyl group, in which the fluorine substitution at the α-carbon caused a dramatic impact on the epoxidation rate, leading to an ee up to 94%.[298] In 2002, Stearman et al. synthesized a series of chiral binaphthyl ketone catalysts **90** with variable distributions of fluorine atoms close to the carbonyl group.[299] The asymmetric epoxidation of *trans*-*β*-methylstyrene over catalysts **90** were all run under the same conditions with 10 mol % catalyst at pH = 9.3 and −15 °C. Parent ketone **90a** catalyzed the epoxidation of *trans*-*β*-methylstyrene to gain 35% conversion with 46% ee, while Song's ketone **85** merely offered 29% ee. This was encouraging since the nonfluorinated version of Denmark's catalyst **89a** only achieved about 5% conversion under similar conditions. Monofluorinated ketone **90b** led to 57% conversion and increased the ee to 80%, while the α,α′-difluorinated catalyst **90c** catalyzed the complete conversion of substrate to epoxide with 86% ee. However, the trifluoroketone catalyst **90d** did not show any improvement in the ee with a complete conversion. Denmark previously described a dramatic stereoelectronic effect of fluorinated cyclohexanone derivatives that are constrained conformationally, with axial fluorination resulting in little activation of the ketone moiety.[298] This is consistent with the action of the third fluorine atom in the catalyst **90d**, which presumably occupies a pseudoaxial position, thus offering no advantage as compared to the difluorinated catalyst **90c**. Tetrafluorinated ketone **90e**, which exists almost exclusively as the hydrate, gave rise to the results similar to the parent ketone **90a**. The strong preference for the formation of hydrate has made the catalyst **90e** less available for the dioxirane formation, hence decreasing the conversion and ee. Comparatively, the best catalyst is the α,α′-difluoroketone **90c**, which has catalyzed the epoxidation of *trans*-*β*-methylstyrene with 100% of conversion and 86% ee at a catalyst loading of 10 mol %.



a: R_1=R_2=H
b: R_1=H, R_2=F
c: R_1=R_2=F

89

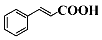
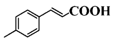
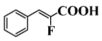
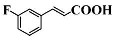
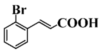
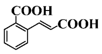
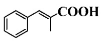


a: R_1=R_2=R_3=R_4=H
b: R_1=R_3=R_4=H, R_2=F
c: R_1=R_3=H, R_2=R_4=F
d: R_1=R_2=R_3=F, R_4=H
e: R_1=R_2=R_3= R_4=F

90

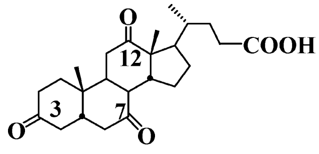
In the particular case of electron-deficient olefins, significant results have been obtained over derivatives of (−)-quinic acid and tropinone as well. Bortolini et al. in 2001 designed the ketone **91** (bile acid) with a chiral and steroid skeleton that can confer conformational rigidity, preventing any distortion and forcing three keto functional groups into different directions.[300] In addition, the carboxylic functional group on a lateral chain makes the ketone **91** soluble in a slightly basic aqueous solution and anchorable onto a suitable support. As shown in Table 9, the asymmetric epoxidation of different cinnamic acid derivatives in water−$NaHCO_3$ has been performed in the system consisting of dehydrocholic acid (an optically active ketone) and Oxone to attain a product with an ee value of 75%. The temperature was found to be an important factor for the oxidations with dioxiranes generated in situ.[301,302]

Table 9. Asymmetric Epoxidation of Prochiral Cinnamic Acid Derivatives with Ketone 91[a]

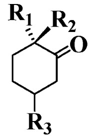
Entry	Substrate	Substrate: Oxone®:**91**	Conv. (%)	ee (%)
1		1:3:1	97	40
2		1:3:1	60	75
3		1:5:1	>99	30
4		1:3:1	90	46
5		1:3:1	98	55
6		1:3:1	98	30
7		1:3:1	98	12

[a] Adapted from ref 300 with permission. Copyright 2001 Elsevier.

In 2000, Solladié-Cavallo et al. published their results with respect to the epoxidation of methyl *p*-methoxycinnamate, *tert*-butyl *p*-methoxycinnamate, and *trans*-stilbene over α-halogenated ketones **92**.[246] When the epoxidation was catalyzed by using α-chloro ketones **92c** and **92d** having a methyl group in the α-position instead of an isopropyl group, the chlorine in the axial or equatorial position significantly enhanced the efficiency of ketone. For example, when the chlorine occupies the axial position, 73% of conversion could be realized, notably higher than 20% of conversion with α-chlorine in the equatorial position. The same behavior was also observed over α-fluoro ketones **92e** and **92f**, where α-fluorine in the axial position of **92f** largely promoted almost the complete conversion of substrate, while that in the equatorial position of **92e** led to only 43% of conversion. It, thus, appears that the ketones with an axial halogen (Cl or F) are more efficient than those with an equatorial one. Also, it was shown that the promotion effect of axial fluorine was stronger than axial chlorine.



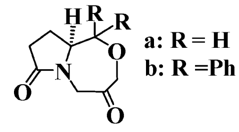
91



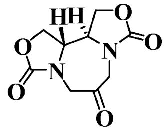
a: R_1=Cl, R_2=^{i}Pr, R_3=Me
b: R_1=^{i}Pr, R_2=Cl, R_3=Me
c: R_1=Cl, R_2=Me, R_3=^{i}Pr
d: R_1=Me, R_2=Cl, R_3=^{i}Pr
e: R_1=F, R_2=Me, R_3=^{i}Pr
f: R_1=Me, R_2=F, R_3=^{i}Pr

92

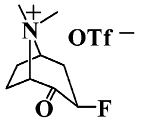
In 2002, chiral ketones **93a** and **93b** bearing a 1-aza-7-oxabicyclo[3,5,0]decane skeleton and their C_2-symmetric analogue **94** were prepared as chiral dioxirane precursors for the asymmetric epoxidation of olefins with Oxone.[303] Ketone **93b**, bearing a diphenyl steric wall, was not effective for the chiral induction with a quite poor selectivity. For example, the epoxidation of *trans*-stilbene with Oxone catalyzed by a stoichiometric amount of **93a** in acetonitrile−dimethoxymethane (DMM)−water (2:1:2) afforded (*S*,*S*)-stilbene oxide with 60% ee, while the reaction over **93b** produced (*R*,*R*)-stilbene oxide with only 6% ee. However, for the same reaction ketone **94** showed a good enantioselectivity up to 83% ee. These results have suggested that the Coulomb repulsion between carbonyl and ether oxygen atoms is operative as an electronic wall rather than as a steric wall. It, thus, seems that the maximal efficiency of chiral ketone catalysts could be reached by both choosing efficient substituents and adjusting the reaction conditions, based on the substrates and the ketone catalysts. The activating effects of fluorine substitution adjacent to the ketone carbonyl moiety are apparent for methyl (trifluoromethyl) dioxirane[304] and dioxiranes derived from 2-fluoro-cyclohexanones,[298] 2-fluoro-1-tetralones, and 2-fluoroindan-1-ones.[275] These results were influential in the design and subsequent use of oxidizing agents resulting from ketones **95**,[239,286−295] **92e**,[245,246] and more recently **90c**.[299]



93

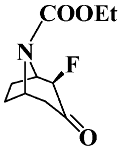


94

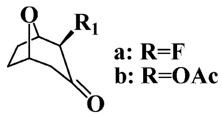


95

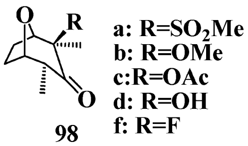
Armstrong et al. have made important contributions to the progress of this field, particularly, they rightly extolled the virtues of α-fluoro-*N*-ethoxycarbonyltropinone **96** as an efficient and readily recycled catalyst for the epoxidation of alkenes with Oxone (83% ee).[245] To improve the enantioselectivity further and to clarify the factors responsible for the asymmetric induction, many attempts to prepare bicyclo[3,2,1]octanone derivatives **95** and **97** with alternative α-substitution have been carried out.[239,286−295] Moreover, α-fluoroketone **98** displayed a much better ability to catalyze the asymmetric epoxidation of *trans*-stilbene with Oxone, for which enantiomerically enriched ketone **98** with 80% ee gave rise to stilbene epoxide with 74% ee.[305,306]



96



97



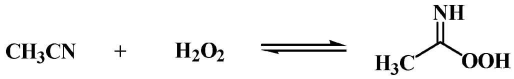
98

2.5.2. Polyhydric Compounds Derived Ketones

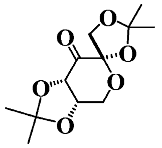
In 1996, Shi et al. first reported the asymmetric epoxidation of trans- and trisubstituted olefins with Oxone over a fructose-derived ketone **99**, which was highly efficient and mild, accompanied by high ee values.[278] Ketone **99** is an efficient epoxidation catalyst with high ee values for a variety of trans- and trisubstituted olefins; however, it is not effective toward α,*β*-unsaturated esters due to its decomposition under reaction conditions, presumably via a Baeyer−Villiger oxidation. The ketone was designed based on the following ideas: (a) stereogenic centers close to the active sites can result in an efficient stereochemical communication between the substrate and the catalyst; (b) the presence of a fused ring and a quaternary α-carbon attached to the carbonyl group minimizes the epimerization of stereogenic centers; (c) one face of the catalyst is sterically blocked to limit possible competing approaches. Carbohydrate-derived chiral ketones as the epoxidation catalysts can be rationalized by the following reasoning: (a) carbohydrates are chiral and readily available; (b) carbohydrates are highly substituted by oxygen groups with an inductive effect to activate the ketone catalysts, which would possess a good reactivity; (c) carbohydrate-derived ketones could have rigid conformations because of an anomeric effect, which would be desirable for a high enantioselectivity.

Subsequently, during the period from 1999 to 2001, Shi et al. extensively revealed high enantioselectivities (89−99% ee) of D-fructose-derived chiral ketone **99** for the asymmetric epoxidation of olefins with hydrogen peroxide or Oxone as primary oxidant under mild conditions.[307−316] The results showed that hydrogen peroxide other than Oxone could be used to generate dioxiranes and that the volume of solvent required was significantly reduced as compared to the case of potassium monoperoxysulfate (Oxone) as primary oxidant. When the reactions were carried out in the solvents, such as DMF, THF, CH_2Cl_2, EtOH, or dioxane instead of CH_3CN, GC detected only trace amounts of epoxides (<1%), suggesting that the coexistence of hydrogen peroxide and CH_3CN promoted the formation of catalytic dioxirane. Most likely, in the presence of CH_3CN the actual oxidant responsible for the formation of dioxirane was a peroxyimidic acid intermediate as depicted in Scheme 7. A control experiment showed that in the absence of any ketone, the addition of 1.0 M K_2CO_3 gained only 1% of conversion the reaction was stirred for 5 h at 0 °C, while under identical conditions the introduction of simple acetone led to a conversion of 61%, implying that dioxiranes could also be generated from other ketones rather than merely limited in ketone **99**.

Scheme 7. Formation of Peroxyimidic Acid Intermediate (dioxirane)[a]



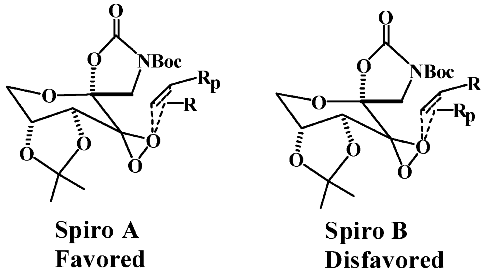
[a] Adapted from ref 307 with permission. Copyright 1999 Elsevier.



99

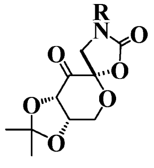
However, for the epoxidation of cis-olefins ketone **99** showed a rather poor enantioselectivity; for example, only 39% ee was obtained for *cis*-*β*-methylstyrene with a major (1*R*,2*S*)-enantiomer. Scheme 8 shows that there are likely two major competing spiro transition states **A** and **B** formed in this catalytic system. A low ee value for cis-olefins suggests that the ketone catalyst cannot provide an essentially structural environment in these two transition states to differentiate sufficiently between phenyl and methyl groups on the olefin. To solve this problem, they further prepared a new chiral ketone **100**,[311] a

Scheme 8. Structure of Competing Spiro Transition States A and B[a]



[a] Adapted from ref 315 with permission. Copyright 2001 The American Chemical Society.

nitrogen analogue of **99**, which achieved generally high ee values for a class of acyclic and cyclic cis-olefins.

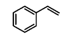
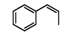
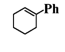
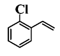
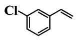
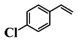
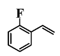
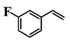
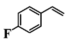
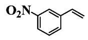
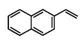
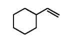


a: R=Boc, b: R=H
c: R=Me, d: R=*p*-OMePh
e: R=*p*-MePh, f: R=*p*-MeSO$_2$Ph
g: R=*p*-NO$_2$Ph h: R=*o*-NO$_2$

100

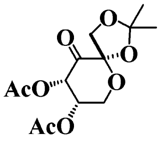
Owing to the extreme usefulness of epoxides derived from terminal olefins, asymmetric epoxidation of unfunctionalized terminal olefins has received intensive interest.[317−319] Metal−complex catalysts such as chiral porphyrin and salen complexes have been extensively studied for the epoxidation of terminal olefins, and in a number of cases the enantioselectivity reaches about 80%, even a high up to >90% ee in certain cases. In 2001, Shi et al. discovered that chiral ketones **100a**−**c** were effective catalysts for the epoxidation of terminal olefins.[313] The substitution on the nitrogen of ketone **100a** obviously enhanced the enantioselectivity, with up to 85% ee obtained for substituted styrene substrates (Table 10). As illustrated in Scheme 8, spiro **A** and spiro **B** are the most plausible transition states, and seemingly spiro **A** is advantageous over **B** for those substrates containing a π-bond system, where groups with a π-bond system prefer proximal to the spiro oxazolidinone. To probe the interaction further, ketones **100d**−**h** with substituents on the phenyl group were prepared and tested as catalysts for the epoxidation of *cis*-β-methylstyrene, styrene, and 1-phenylcyclohexene.[320] In the case of *cis*-β-methylstyrene, the ee value increased from 83% for the electron-donating MeO group to 90% for the electron-withdrawing sulfone and nitro groups. The interaction between the phenyl group of olefin and the oxazolidinone moiety of catalyst in the transition state spiro **A** could be influenced by the electronic nature of substituents on *N*-phenyl groups and favored by electron-withdrawing groups. A lower ee value obtained with **100h** is probably because the *N*-phenyl group in **100h** is no longer coplanar with oxazolidinone due to the presence of an ortho-nitro group in the phenyl group. The substituent effect on the enantioselectivity was even more explicitly displayed in the epoxidation of 1-phenylcyclohexene, for which the (*R*,*R*)-isomer was obtained with *p*-MeO and *p*-Me groups, and the (*S*,*S*)-isomer with *p*-MeSO$_2$ and *p*-NO$_2$ groups. Clearly, electron-withdrawing groups on the *N*-phenyl group in the catalyst further enhance the attractive interaction between phenyl groups of olefins and oxazolidinones in the transition state of catalyst.

Table 10. Asymmetric Epoxidation of Terminal Olefins with Ketone 100[a]

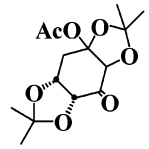
Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**100a**	100	81
2		**100b**	100	68
3		**100c**	100	78
4		**100d**	56	80
5		**100e**	60	80
6		**100f**	61	80
7		**100g**	30	79
8		**100h**	55	62
9		**100d**	71	83
10		**100e**	60	84
11		**100f**	72	90
12		**100g**	55	90
13		**100h**	59	78
14		**100d**	53	26
15		**100e**	61	25
16		**100f**	58	22
17		**100g**	44	27
18		**100h**	48	59
19		**100a**	61	81
20		**100a**	74	83
21		**100a**	90	85
22		**100a**	87	82
23		**100a**	93	81
24		**100a**	94	81
25		**100a**	88	74
26		**100a**	86	84
27		**100a**	93	71

[a] Adapted from refs 313 and 320 with permission. Copyright 2001 and 2003 The American Chemical Society.

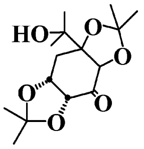
In 2002, Shi et al. further developed a chiral ketone **101**, a readily available acetate analogue of **99**, which was active and highly enantioselective for the epoxidation of α,β-unsaturated esters in the presence of Oxone.[248] They replaced the fused ketal of **99** with more electron-withdrawing groups so as to reduce the Baeyer−Villiger decomposition and to enhance the stability and reactivity of ketone. The results in Table 11 showed that an ee ranging 90−97% could be obtained for those substrates containing an electron-withdrawing group, particularly for trisubstituted α,β-unsaturated esters and conjugated enynes. The interaction of Oxone with ketones **102** and **103**, derived from 2-quinic acid, could also generate chiral dioxiranes, which then epoxidized enones (Table 12).[321,322]



101



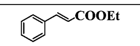
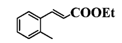
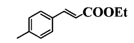
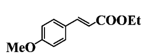
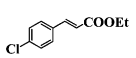
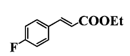
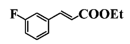
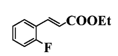
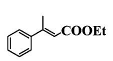
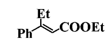
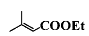
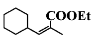
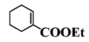
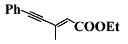
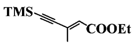
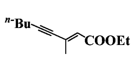
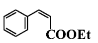
102



103

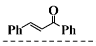
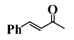
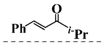
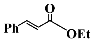
In 2002, Shing et al. investigated the asymmetric epoxidation of various alkenes catalyzed by three D-glucose-derived ulose catalysts **104a**−**c** with *n*-Bu$_4$NHSO$_4$ as the oxidant,[323] where ketone **104a** displayed a better enantioselectivity than did **104b** and **104c**, e.g., the best ee values obtained for *trans*-stilbene oxide were 71% ee for the ketone **104a**, 11% ee for **104b**, and 26% ee for **104c**, respectively. In 2003, they reported again the catalytic applications of L-erythro-2-uloses **105**, L-threo-3-uloses **106**, and **107** prepared from L-arabinose, for the asymmetric epoxidation.[324] The anomeric aglycone steric sensors with suitable size (e.g., uloses **105a** and **105d**) exhibited good stereochemical communication toward the oxidation of *trans*-stilbene (up to 90% ee). Chemical yields of epoxides with uloses **105** were poor (only

Table 11. Asymmetric Epoxidation of α,β-Unsaturated Esters with Ketone 101[a]

Entry	Substrate	Yield (%)	ee (%)
1		73	96
2		67	93
3		91	97
4		57	90
5		64	97
6		77	96
7		41	97
8		40	95
9		93	96
10		91	93
11		64	82
12		77	89
13		77	93
14		96	94
15		94	94
16		74	98
17		84	44

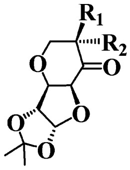
[a] Adapted from refs 248 with permission. Copyright 2002 The American Chemical Society.

Table 12. Asymmetric Epoxidation of α,β-Unsaturated Olefins with Oxoneover Ketones 102 and 103[a]

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**102**	80	94
2		**103**	85	96
3		**103**	75	82
4		**103**	70	84
5		**102**	34	86
6		**103**	35	89

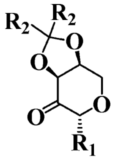
[a] Adapted from refs 321 and 322 with permission. Copyright 1997 and 1999 The American Chemical Society.

13% yield) because of the decomposition of ulose catalysts during the reaction. However, L-threo-3-uloses **106** and **107** could overcome the decomposition, ascribable to the electron-withdrawing effect of the ester group(s) at the α-position. In the same year, readily available arabinose-derived 4-uloses **108**, containing a tunable butane-2,3-diacetal as the steric sensor, was further synthesized, which showed an increased enantioselectivity up to 93% ee along with increasing the size of the acetal alkyl group in the catalytic asymmetric epoxidation of trans-disubstituted and trisubstituted alkenes.[325] Ulose **108c** was the best catalyst and chiral inducer for the epoxidation of a simple trans-disubstituted alkene (93% ee).



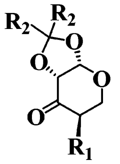
a: R_1=H, R_2=CH_2OTBS
b: R_1=Me, R_2=CH_2OTBS
c: R_2=H, R_1=CH_2OTBS

104



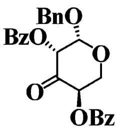
a: R_1=OBn, R_2=Me
b: R_1=OBn, R_2=Ph
c: R_1=OMe, R_2=Me
d: R_1=OCH_2-(4-Me-)Ph, R_2=Me

105

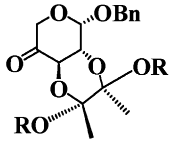


a: R_1=OBz, R_2=Me
b: R_1=OPiv, R_2=Me

106



107



a: R=Me
b: R=Et
c: R=^{t}-Bu

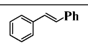
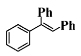
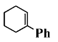
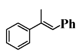
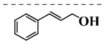
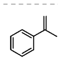
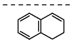
108

2.5.3. Chiral Aldehydes

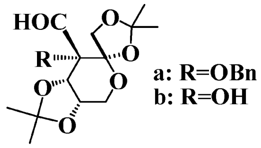
Although ketone dioxiranes have been well-known as excellent oxidants for decades,[281−283,288] only in recent years were chiral ketone dioxiranes detected to be prominent oxidants for asymmetric epoxidations.[239,247,270,299,303,320,323,326−329] In contrast, aldehyde dioxiranes ($RHCO_2$) still remain elusive, even though they have been involved in biological processes and substantiated in theoretical studies.[330,331] For example, C_{4a}-flavin hydroperoxide has been used in the bioluminescent process of bacterial luciferase to react with an aldehyde generating the corresponding dioxirane as a high-energy intermediate, which has, however, been neither isolated nor characterized.[331] So far, the only known aldehyde dioxirane is dihydrodioxirane (H_2CO_2), but it is obtained from the ozonolysis of ethane at low temperature,[270] rather than from formaldehyde directly. In 2003, Bez et al. first reported the chiral epoxidation with Oxone over optically active aldehydes **109** synthesized from fructose, which is the first direct evidence for the involvement of aldehyde dioxiranes.[332] Although ketone dioxirane may be readily prepared from the oxidation of ketone by Oxone, the preparation of aldehyde dioxirane by this way is tabooed. This is because aldehyde is reportedly prone to become the corresponding acid undergoing an Oxone oxidation.[333,334] It is clearly observed from Table 13 that aldehyde **109b** yields consistently better enantioselectivity than aldehyde **109a** for those substrates, except for terminal and cyclic alkenes.

In summary, chiral carbonyl compounds can be easily synthesized from some cheap natural compounds and have shown especially high enantioselectivities for the asymmetric epoxidation of trans-olefins, which is relatively valuable for industrial applications. Additionally, these catalysts display

Table 13. Enantioselective Epoxidation with Chiral Aldehydes 109[a]

Entry	Olefin	Catalyst	Yield (%)	ee (%)
1		**109a**	16	63.5
2		**109b**	54	93.5
3		**109a**	8	81
4		**109b**	8	92
5		**109a**	28	48
6		**109b**	12	67
7		**109a**	8	53
8		**109b**	8	82
9		**109a**	14	70
10		**109b**	50	18
11		**109b**	36	18
12		**109a**	>95	27
13		**109b**	>95	24

[a] Adapted from refs 332 with permission. Copyright 2003 Elsevier.



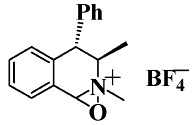
109

extensive applicability for almost all the substrates, such as functionalized and unfunctionalized substituted olefins (please refer to Table 45 in the appendix).

2.6. Chiral Iminium Salts

Oxaziridinium salts as an electrophilic oxygen source was first reported in 1976 by Milliet,[335,336]which showed extreme reactivity for the oxygen transfer to nucleophilic substrates, such as sulfides and alkenes.[337,338] Oxaziridinium salts, either used in isolated form or generated in situ from iminium salts and Oxone, are powerful electrophilic oxidants.[338,339] These organic salts were prepared either by the quaternization of the corresponding oxaziridines or by the peracid oxidation of iminium salts. Chiral iminium salts have been employed to catalyze the asymmetric epoxidation of olefins with Oxone as the primary oxidant, in which a good chemical yield but a moderate enantioselectivity was obtained, possibly due to a poor chiral recognition by the flat aryl ring attached to the central carbon of iminium salts.[284,285,319,340–344] Aryl-substituted iminium salts are more stable and easily isolated than alkyl-substituted ones; however, the intrinsic requirement for an aryl ring severely limits the design and catalytic use of chiral iminium salts. Alternatively, iminium salts can be generated in situ from the condensation of either a ketone or an aldehyde with a secondary amine, which proceeds under slightly acidic conditions that benefit the dehydration of aminol. In the reaction, iminium salts first react with Oxone to form oxaziridinium salts, which then transfer oxygen to epoxidize olefins, accompanied with a regeneration of iminium salts; subsequently, the restored iminium salts react again with an additional 1 equiv of Oxone to generate oxaziridinium salts and to complete a catalytic cycle.

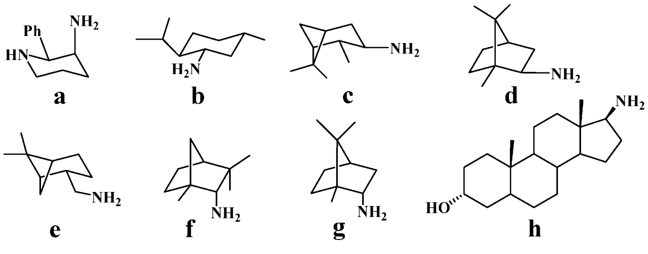
Oxaziridines, nitrogen analogues of dioxiranes, have constituted an important class of organic oxidants under nonaqueous conditions. More recently, Aggarwal et al. have described the catalytic asymmetric epoxidation of simple alkenes mediated by a binaphthalene-derived iminium salt,[284] which catalyzed the synthesis of both 1-phenylcyclohex-1-ene oxide with 71% ee and *trans*-stilbene oxide with 31% ee. Also, Armstrong et al. showed that even acyclic iminium salts could be efficient catalysts for the asymmetric epoxidations by Oxone.[285,342,345] The first enantiopure oxaziridinium salt **110** was synthesized by the quaternization of an oxaziridine derived from a chiral imine that was prepared from norephedrine in four steps.[319,340] This salt and the corresponding iminium salt could catalyze the asymmetric epoxidation of alkenes using Oxone as the stoichiometric oxidant to obtain an ee value of ca. 40%, but no cis-epoxide products were detected, suggesting a single-step oxygen transfer process. And the enantioselectivity was higher for disubstituted olefins than for mono- or trisubstituted ones. The presence of two aromatic rings on the opposite ends of disubstituted double-bond seems to favor the "transfer of chirality" from oxaziridinium salt to the epoxide via the oxygen transfer.



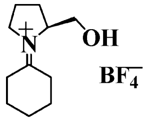
110

Minakata et al. in 2000 applied a chiral ketiminium salt **111** in the asymmetric epoxidation of 3-phenyl-prop-2-en-1-ol, but the enantioselectivity was not high (39% ee).[344] Page et al. in 2000 investigated one group of dihydroisoquinolinium salt catalysts, active at a loading as low as 0.5 mol % but low enantioselective with only ca. 40% ee in the epoxidation of alkenes.[343] Chiral primary amines (Scheme 9) could rapidly react with 2-(2-bromoethyl)benzaldehyde to produce oil compounds of dihydroisoquinolinium bromide salts, which were purified with difficulty by conventional methods. This problem was eventually solved by the counteranion exchange, which took place simply by adding an appropriate inorganic salt into the reaction mixture before the workup. As inorganic additives, fluoroborate, hexafluorophosphate, perchlorate, and periodate salts or their derivatives were not ideal, but tetraphenylborate salts **112** derived from sodium tetraphenylborate were preferred.

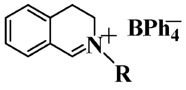
Scheme 9. Structure of Chiral Primary Amines[a]



[a] Adapted from ref 343 with permission. Copyright 2000 The Royal Society of Chemistry.

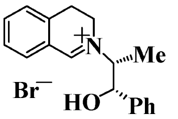


111

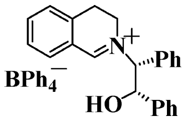


112

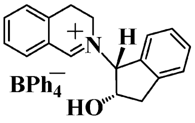
Page et al. in 2001 further examined the catalytic application of dihydroisoquinolinium salts containing alcohol, ether, and acetal functional groups in the nitrogen substituent in the asymmetric epoxidation of olefins (ca. 60% ee).[346] In addition, (1*S*,2*R*)-norephedrine derivative **113** catalyzed the epoxidation of 1-phenylcyclohexene with 30% ee, the corresponding catalyst derived from (1*S*,2*R*)-2-amino-1,2-diphenylethanol **114** led to 1-phenylcyclohexene oxide in 24% ee, while (1*R*,2*S*)-aminoindanol derivative **115** showed a lower asymmetric induction (<14% ee). The results suggested that the size of an ether substituent in such catalysts is not particularly important for the asymmetric induction during the oxygen transfer to alkene. The selectivity may be partially assigned to internal stabilization of the positive charge by adjacent oxygen atom, which increases the conformational and rotational rigidity of the molecule. Iminium salt **116** induced chiral α-methyl stilbene oxide with 52% ee at 0 °C, notably higher than 15% ee of isopinocamphenylamine-derived catalyst **117**.



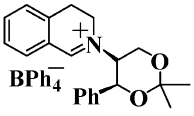
113



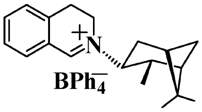
114



115

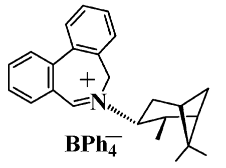


116

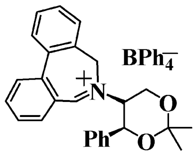


117

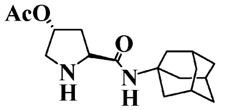
In 2002, Page et al. synthesized two new chiral iminium salts **118** and **119**, of which dibenzazepinium salt **119** induced an ee value of ca. 60%.[347] The results showed that these two new seven-membered ring catalysts were more reactive than the six-membered ring catalyst **116** in the epoxidation reaction. In all cases, the catalyst **118** gave a poorer ee value than did the catalyst **116**, while the catalyst **119** induced a somewhat different ee value from the catalyst **116**. For example, the catalyst **119** achieved an improved ee value of 60% for the substrate of phenylcyclohexene but a similar ee value of 59% to the catalyst **116** for triphenylethylene and even a lower ee value of 15% for *trans*-stilbene, while the catalyst **116** showed an extremely low enantioselectivty. In 2001, Wong et al. developed a new approach to catalyze the asymmetric epoxidation of olefins, which utilized chiral iminium salts **120** and **121**, generated in situ from chiral amines and aldehydes, as the catalysts.[348] Epoxidation reactions were conducted with 20 mol % of amines and aldehydes to obtain epoxides with 65% ee. In 2002, Lacour et al. observed that the combined use of TRISPHAT counterions **122** with catalytic amounts of **18**-Crown-**6** allowed an improvement of enantioselectivty in the case of iminium precatalyst **123** under biphasic CH_2Cl_2/water conditions, in which the ratio of enantiomers increased from 2.4:1 to 7.2:1 for the epoxidation of 1-phenyl-dihydronaphthalene.[349]



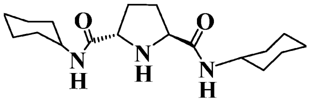
118



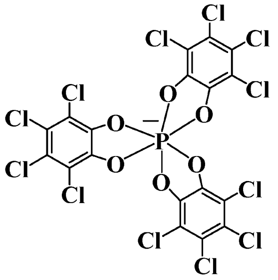
119



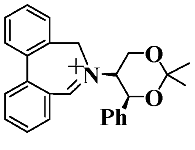
120



121



122



123

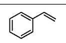
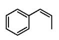
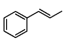
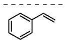
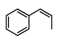
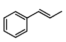
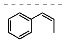
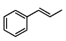
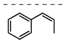
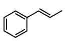
2.7. Other Homogeneous Systems

Alkene epoxidations catalyzed by transition-metal peroxo species have been studied for quite a long time. There have been several example reactions, such as the epoxidation of olefins over polyoxo tungstate ($PW_{12}O_{24}^{3-}$) in the presence of quarternary ammonium salts,[307−316] over active molybdenum peroxo complexes (to yield the corresponding epoxides in 50% yield and 40% ee),[350] and over methyltrioxorhenium (MTO) with H_2O_2.[93]

2.7.1. Mo-peroxo Complexes

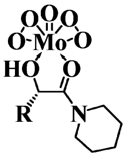
In 2000, Park et al. published their studies on the enantioselective epoxidation of styrene derivatives over transition metal (Mo)-peroxo complexes **124**.[351] As shown in Table 14, Mo-peroxo complexes achieved yields of 40−50% with 30−80% ee, and a significant solvent effect on the epoxidations was observed; for instance, the addition of solvents CH_2Cl_2 and isooctane inhibited alkenes from being epoxidized by TBHP. In 2003, Zhao et al. synthesized several molybdenum(VI)−*cis*-dioxo complexes bearing sugar-derived chiral Schiff-base ligands in a general formula of MoO_2(L)(Solv) **125**,[352] where L = *N*-salicylidene-D-glucosamine, *N*-salicylidene- 1,3,4,6-tetraacetyl-α-D-glucosamine, *N*-5-chlorosalicylaldehyde-1,3,4,6-tetraacetyl-α-D-glucosamine, *N*-salicylaldehyde-1,3,4,6-tetraacetyl-*β*-D-glucosamine, *N*-5-chloro-

Table 14. Asymmetric Epoxidation of Alkenes Catalyzed by Mo-peroxo Complexes 124a,b with TBHP[a]

Entry	Substrate	Catalyst	Tempt. (°C)	Time (h)	Yield (%)	ee (%)
1		**124a**	60	5	28	7
2			r.t.	15	45	30
3			r.t.	72	42	40
4		**124b**	60	5	29	4
5			r.t.	15	45	83
6			r.t.	72	41	63
7		**124a**	r.t.	24	42	26
8			r.t.	24	40	40
9		**124b**	r.t.	72	41	40
10			r.t.	24	49	81

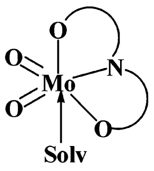
[a] Adapted from ref 351 with permission. Copyright 2000 The Korean Chemical Society.

salicylaldehyde-1,3,4,6-tetraacetyl-β-D-glucosamine, *N*-salicylidene-4,6- *O*-ethylidene-β-D-glucopyranosylamine, and Solv = methanol or ethanol. These complexes have been employed in the asymmetric epoxidation of olefins, to obtain a moderate enantiomeric induction of about 30% ee for cis-β-methyl styrene. As expected, for the epoxidation of *cis*- and *trans*-β-methylstyrene, the common observation is that the catalytic activity and asymmetric induction for cis-substrates is much better than that for trans-analogues.



a: R=Ph
b: R=CH$_2$Ph

124

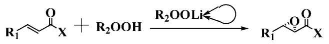


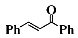
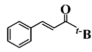
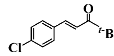
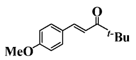
125

2.7.2. Lithium Complexes

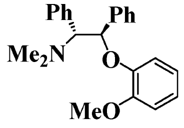
In 2003, Tanaka et al. developed the asymmetric epoxidation of α,β-unsaturated carbonyl compounds with alkylperoxides in good ee, catalyzed by external chiral tridentate aminodiether-lithium peroxides **126**–**138** (Table 15).[353] This work has revealed two novel findings: (a) a slow addition of alkylperoxide benefits the catalytic asymmetric reaction; (b) the lone-pair electron differentiating the coordination of carbonyl oxygen to lithium is a critical factor for a high enantioselectivity. A reasonable explanation could be responsible for the latter, i.e., a bulky substituent on the carbonyl group of ketone prevented the lone-pair electron from coordination at one side of the C=C double bond, hence directing a predominant coordination to lithium at the other side opposite to the bulky substituent. On the basis of these experimental facts, the researchers have come to the conclusions that (a) a chiral ligand not only activates the lithium peroxide but also controls the absolute stereochemistry of nucleophilic epoxidation reaction, (b) a tridentate aminodiether ligand with a hemilabile methoxyphenyl side chain benefits a high enantioselectivity, (c) the lone-pair electron differentiating the coordination of carbonyl oxygen to lithium is actually operative, and (d) a slow addition procedure of alkylperoxide is preferred. This has, to date, become a certain basis of developing more sophisticated conjugate addition-type, ligand-controlled catalytic asymmetric epoxidation of α,β-unsaturated carbonyl compounds.

Table 15. Asymmetric Epoxidation of α,β-Unsaturated Olefins Catalyzed by an External Chiral Tridentate Aminodiether-Lithium Peroxide[a]

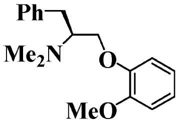


Entry	Substrate	Ligand	Yield (%)	ee (%)
1		**126**	99	40
2		**127**	74	15
3		**128**	69	0
4		**129**	72	−18
5		**130**	97	−7
6		**131**	69	−7
7		**132**	88	− 22
8		**133**	85	− 42
9		**134**	97	−9
10		**(*R*)-135**	88	16
11		**(*S*)-135**	56	− 44
12		**136**	86	−15
13		**137**	95	−23
14		**138**	70	2
15		**126**	76	71
16		**126**	81	66
17		**126**	68	64

[a] Adapted from refs 353 with permission. Copyright 2003 Elsevier.



126



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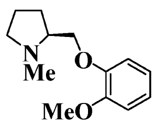
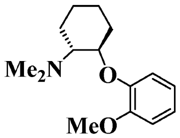


128



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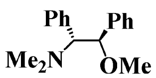
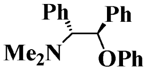


130

2.7.3. Magnesium Complexes

Jackson et al. reported earlier that chalcone could be converted into the corresponding epoxide with good to excellent ee values by an inexpensive catalyst, prepared from DET and dibutylmagnesium.[233] However, this system was not especially effective for the epoxidation of aliphatic enones, only resulting in poor conversions. In 2001, they modified the original procedure so that it was effective for the asymmetric epoxidation of simple aliphatic enones with a high ee value.[354] They found that the addition of a 4 Å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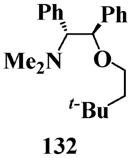
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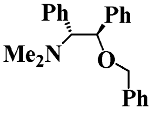
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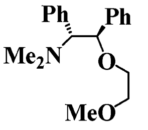
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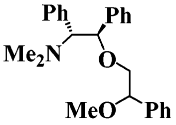
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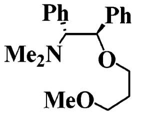
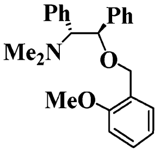
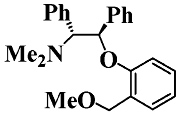
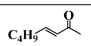
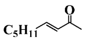
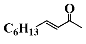
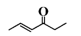
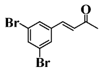

136


137

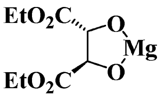

138

molecular sieve allowed a reasonable conversion of the substrate into the corresponding epoxide and that it was possible to prepare the presumed catalyst precursor **139** simply by the addition of L-(+)-DET to dibutylmagnesium soluble in heptane and followed by removing the solvent and drying. As described above, the complex **139** was rather effective for the asymmetric epoxidation of aliphatic enones with TBHP in the presence of a 4 Å molecular sieve; however, there was one drawback, i.e., the conversion to the epoxide was initially fast and subsequently sluggish, which could be improved by a portionwise addition of the solid catalyst **139** (Table 16).

Table 16. Asymmetric Epoxidation of Aliphatic Enones Catalyzed by Complex 139 with TBHP[a,b]

Entry	Substrate	Conv. (%)	ee (%)
1		89	75
2[a]		92	91
3		81	79
4[a]		96	93
5		86	71
6[a]		92	92
7		94	67
8[a]		95	71
9		88	65
10[a]		n.d.	81

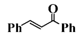
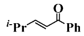
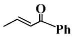
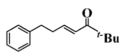
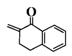
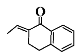
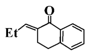
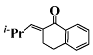
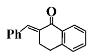
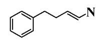
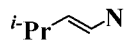
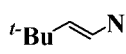
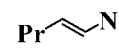
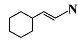
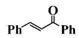
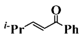
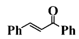
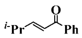
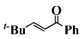
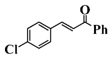
[a] Di-*tert*-butyl tartrate as the ligand; n.d.; not determined. [b] Adapted from ref 354 with permission. Copyright 2001 The Royal Society of Chemistry.


139

2.7.4. Zinc Complexes

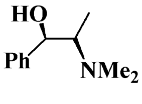
In 1996, Enders et al. discovered that (E)-α,β-unsaturated ketones could be asymmetrically epoxidized to yield trans-epoxides using a stoichiometric quantity of diethylzinc and a chiral alcohol, under oxygen atmosphere.[232] Recently, Yu et al. achieved up to 99% ee for these α,β-unsaturated ketones in the presence of chiral ligand (1*R*,2*R*)-*N*-methylpseudoephedrine **140** and chiral polybinaphthyl alcohols **141** or **142**, with almost a quantitative yield of recovery of the catalyst from the reaction mixture (Table 17).[355]

Table 17. Asymmetric Epoxidation of Various Olefins with Diethylzinc and Oxygen in the Presence of Chiral Alcohols 140–142[a]

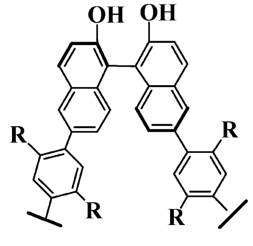
Entry	Substrate	Ligand	Yield (%)	ee (%)
1		**140**	94	61
2		**140**	97	92
3		**140**	96	85
4		**140**	99	90
5		**140**	40	3
6		**140**	85	80
7		**140**	65	90
8		**140**	98	>99
9		**140**	62	64
10		**140**	64	37
11		**140**	53	42
12		**140**	57	82
13		**140**	53	43
14		**140**	47	36
15		**141**	41	71
16		**141**	18	25
17		**142**	95	74
18		**142**	94	81
19		**142**	67	64
20		**142**	81	79

[a] Adapted from refs 355 with permission. Copyright 1999 The American Chemical Society.

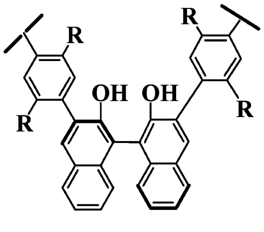
On the basis of the Weitz-Scheffer mechanism, Enders and Pu proposed a similar reaction pathway for their asymmetric epoxidations, namely, diethylzinc reacts with chiral ligand (A) to give a zinc alkoxide (B) with the release of ethane, and then the reaction of B with oxygen gives rise to a chiral metal peroxide (C), as depicted in Scheme 10.[238] Advantages of this route are that the cheapest oxidant such as oxygen or even air can be used and that the chiral ligand can be recycled by the extraction into acid (HClaq) subsequently followed by both the basification with NaOHaq and the re-extraction into ether. Enders' reagent has been extensively applied in the asymmetric epoxidation of chalcone and derivatives, alkyl-substituted enones, β-alkylidene-α-tetralones, and some (E)-nitroalkenes.[356] This has provided an access to 3-substituted *trans*-2-nitro oxiranes with



140

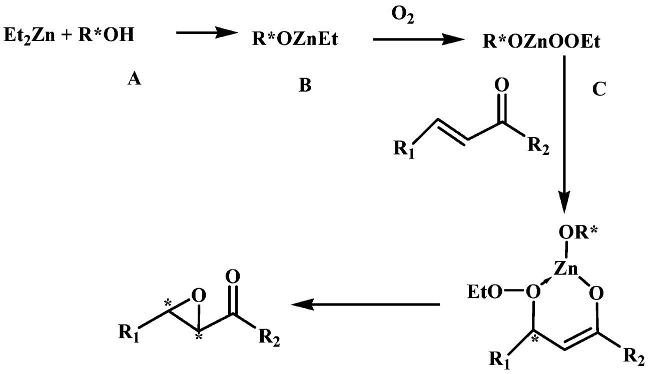


141 R=OC$_6$H$_{13}$



142 R=OC$_6$H$_{13}$

Scheme 10. Reaction Pathway Involving Zinc Complexes[a]

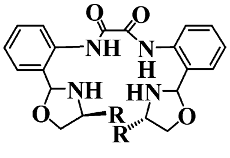


[a] Adapted from ref 238 with permission. Copyright 2000 The Royal Society of Chemistry.

excellent de values of ≥98% and good ee values of 36−82%.

2.7.5. Ruthenium Complexes

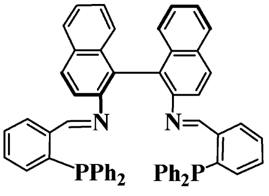
C_2-symmetric chiral oxalamides have shown to be attractive ligands for the enantiocontrol of metal-catalyzed reactions, in particular for the oxidations. Because of the π-acceptor property of α-dicarbonyl unit and oxazoline rings, these ligands are supposed to be quite resistant to the oxidation and hence suitable for the preparation of stable high-valent metal complexes. The first example was given by Yang et al., who employed a chiral *N*-donor bidentate ligand and $RuCl_3$ catalyst to obtain only a 21% ee value.[357] In 1998, End et al. developed the catalytic asymmetric epoxidation of olefins over Ru complexes with chiral oxalamides **143** using $NaIO_4$ oxidant.[358,359] Among the oxalamides tested, isopropyloxazoline derivative **143b** was found to be the most active ligand. The results showed that in the asymmetric epoxidation of (*E*)-stilbene, byproduct benzaldehyde was rapidly formed in the beginning of the reaction and that the ee value of the epoxide was very low in the beginning but increased significantly along with prolonging the reaction time. However, if the catalyst first underwent a pretreatment by the oxidant for a moment before contacting the substrate, the catalytic performance, as expected, was significantly improved with 74% yield and 69% ee.



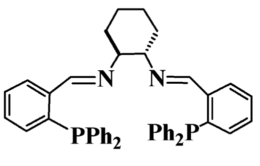
a: R=Me
b: R=^{i}-Pr
c: R=^{t}-Bu
d: R=Bn
e: R=Ph

143

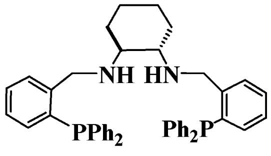
Ruthenium complexes with chiral *N,O*- and *N,N*-donor ligands have been tested as the asymmetric epoxidation catalysts.[105,110,360] In 1998, Stoop et al. prepared five-coordinated ruthenium complexes containing tetradentate chiral ligands **144**−**146** with a P_2N_2 donor, effective for the asymmetric epoxidation of alkenes with hydrogen peroxide.[361,362] An ee value of 42% was obtained for the asymmetric epoxidation of styrene catalyzed by Ru-**145**, which was the first example of the asymmetric epoxidation over ruthenium complexes using hydrogen peroxide as primary oxidant.



144

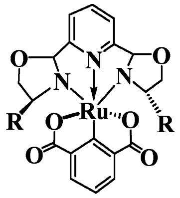


145



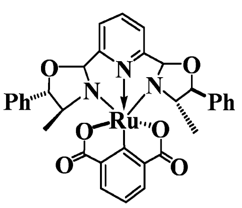
146

Tse et al. investigated the asymmetric epoxidation of *trans*-stilbene over Nishiyama's Ru-(pyridine bisoxazoline) (pyridinedicarboxylic acids) **147a** and **147b**, where pyridinebisoxazoline (pybox) ligands were easily prepared from natural amino acids.[363,364] Unfortunately, the previous work of this system revealed several drawbacks, such as a low reactivity (96 h needed for a complete conversion) and the limited catalyst. However, successful epoxidations have been made using *trans*-stilbene as the substrate, for which increasing the concentration of oxidizing agent (PhI-$(OAc)_2$) resulted in an elevated yield but a reduced enantioselectivity, and water played a crucial role in the reaction, possibly due to the enabling of the oxidation of 18-electron Ru(***S***,***S***-^{i}Pr$_2$-pybox)(pydic) **147a** via a ligand dissociation. The addition of stoichiometric amount of water increased the ee value to 71% in the case of a low concentration of $PhI(OAc)_2$ as the stoichiometric oxidant, which, however, was remained as a major disadvantage. Hence, in 2004, Bhor et al. developed a brand new system using TBHP as the oxidant instead of $PhI(OAc)_2$, for which Ru(pybox)(pydic) complexes **147**−**149** were used as the catalysts for the epoxidation of olefins with TBHP to achieve an excellent yield up to 97% with a feasible ee value of 65% at room temperature.[365]

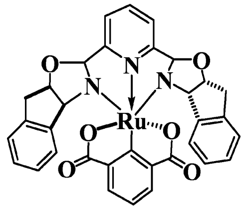


a: R=$^{i\text{-}}$Pr
b: R=Ph
c: R=Me

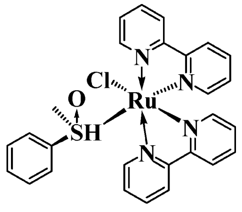
147



148



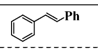
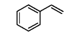
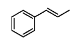
149



150

Ruthenium complexes with nitrogen ligands have been recognized by a number of researchers as powerful oxidizing catalysts, extensively applied in the oxidative transformations.[97] Since the pioneering work of Balavoine et al. in the epoxidation of olefins catalyzed by a $RuCl_3$−2,2′-bipyridine−$NaIO_4$ system,[366,367] many approaches have been proposed to render the efficiency of this system.[368−370] In 2002, Pezet et al. investigated the synthesis and catalytic application of chiral ruthenium sulfoxide **150** for the asymmetric epoxidation of olefins.[371] As presented in Table 18, most of the reactions have achieved high yields and moderate ee values at room temperature; however, in the case of *trans*-β-methyl styrene an especially high ee value of 94% is obtained, which is the best result, so far, in the ruthenium-catalyzed epoxidation of alkenes. As the stoichiometric and catalytic oxidants, oxo complexes of ruthenium with polypyridine ligands (*cis*-$[Ru\text{-}(bpy)_2(py)O]^{2+}$) have been employed in a variety of organic and inorganic reactions.[372−375] Optically pure *cis*-Δ-$[Ru\text{-}(bpy)_2(py)O]$ has also been used in the stoichiometric oxidation of methyl *p*-tolyl sulfide.[376] On the basis of these experiments, it is assumed that in the reaction, the oxygen atom transfer occurs via the in-situ formation of the oxo-ruthenium complex (Ru═O) intermediate, further confirmed by the displacement of chlorine ligand with two chiral centers (sulfoxide and metal center) to form a catalyst.

Table 18. Asymmetric Epoxidation of Olefins Catalyzed by Ru-Complex 150 with THBP at 25 °C[a]

Entry	Olefin	Oxidant	Yield (%)	ee (%)
1		$PhI(OAc)_2$	97	33
2		TBHP	82	27
3		$PhI(OAc)_2$	85	66
4		$PhI(OAc)_2$	92	94

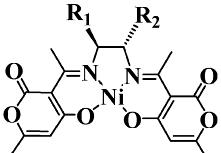
[a] Adapted with permission from ref 371. Copyright 2002 The Royal Society of Chemistry.

2.7.6. Methyltrioxorhenium (MTO)

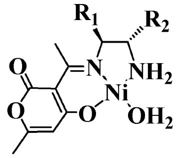
Recently, an impressive amount of work has been carried out on the catalytic property of methyltrioxorhenium (VII) (MTO) and more specifically on the possibility as a selective epoxidation catalyst using H_2O_2 as the oxidant.[377−381] The transformation of epoxide into 1,2-diols can be suppressed by replacing hydrogen peroxide with urea/hydrogen peroxide adduct (UHP) as the primary oxidant, which enables the epoxidations in nonaqueous media, whereby the epoxide ring-opening is largely avoided.[381,382] A second alternative is based on the tendency of organorhenium(VII) oxides to increase the coordination numbers to form Lewis acid−base adducts.[383,384] In this way, the complexes formed with certain nitrogen-containing bases have shown to be excellent catalysts for the epoxidations in the presence of excess amine.[93,385,386] In an attempt to achieve chirality, several chiral rhenium(VII) adducts were synthesized by adding (*S*)-(+)-2-aminomethylpyrrolidine, (*R*)-(+)-phenyl ethylamine or L-prolinamide into different solutions of MTO. Outstandingly, the addition of these chiral auxiliaries induced the enantioselective and diastereoselective oxidations of several prochiral olefins with low-to-moderate level of stereoinductivity.

2.7.7. Nickel Complexes

The first example of the epoxidations of olefins over nickel(II) complexes with iodosylbenzene was made by Kochi.[387] Later, Burrows et al. reported the synthesis, crystalline structure, and catalytic application of nickel(II) complexes for the epoxidation of a wide variety of olefins in the presence of iodosylbenzene or hypochlorite.[388−390] Dinuclear nickel(II) complexes were also synthesized and used as the epoxidation catalysts by Gelling.[391] Kureshy et al. successfully applied the symmetrical and nonsymmetrical Ni(II) square planar complexes **151** and **152** in the enantioselective epoxidation of unfunctionalized olefins, such as 1-hexene, 1-octene, *trans*-4-octene, styrene, 4-chlorostyrene, 4-nitrostyrene, and 1,2-dihydronaphthalene using NaClO or O_2 as the oxidant, in which 58% ee was achievable.[392,393]



151



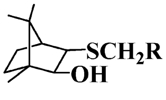
152

2.7.8. Sulfonium Ylides

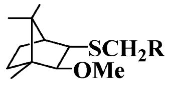
The recorded ways for preparing chiral epoxides are chiefly as follows: (a) enantiofacially differential oxidation of a prochiral C═C bond[98,120,394,395] and (b) enantioselective alkylidenation of a C═O bond, via a ylide route or a Darzens reaction. Although the former has afforded much success, the structural requirement of substrates is a limited prerequisite.

The latter provides an alternative approach in solving this problem. Enantioselective epoxidation via a ylide route is an approach, easily performed but relatively undeveloped to date.[396,397] Chiral sulfides, via the corresponding sulfonium ylides, are increasingly becoming important sources of chirality for asymmetric transformation, enantioselective epoxidation, and cyclopropanation.[398,399] As an efficient method to synthesize chiral epoxides, the base-promoted asymmetric epoxidation of aldehydes over chiral sulfides has been developed.[400−405]

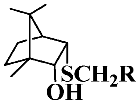
In 1996, Li et al. reported that D-(+)-camphor-derived sulfides **153**−**156** were rather efficient catalysts for the preparation of *trans*-2,3-diaryloxirane (up to 98% yield and 77% ee).[406] When benzylated sulfides **153a**−**156a** were employed in the ylide reaction, a stoichiometric enantioselective epoxidation was realized. The opposite asymmetric induction, which led to the synthesis of both (+)- and (−)-*trans*-diaryloxiranes, was achieved only when *exo*-alkylthio-substituted sulfide **153** or **154a** and *endo*-alkylthio-substituted sulfide **155** or **156** were used, respectively. This represents an efficient preparation of enantiomerically enriched (+)- and (−)-*trans*-diaryloxiranes from ylides with both high yields and reasonable ee values, although both (+)- and (−)-enantiomers have also been obtained in low yields from other routes.[407,408] The effect of asymmetric induction of **153a** (*exo*-benzylthio) was generally better than that of **155a** or **156a** (*endo*-benzylthio). It is noteworthy that the conversion of a free OH group at the C$_2$-position to a methoxy group dramatically decreased both the yield and the ee value of products. The investigation showed that increasing the amount of sulfides did not influence the ee values but shortened the reaction time and improved the yields. As expected, the opposite asymmetric induction was again observed from **153b**, which contains an *exo*-methylthio group, and from **155b** or **156b**, which contains an *endo*-methylthio group. A nonbonded interaction between the free OH in the ylides resulting from sulfides (**153**, **155**, and **156**) and the carbonyl group of aldehydes controls the access of substrates to ylidic carbon preferentially at one specified face, thus leading to a more efficient asymmetric induction than in the case of ylide coming from methyl-protected hydroxylated sulfides **154**, which cannot cause such an interaction.



153 a: R=Ph b: R=H



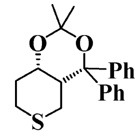
154 a: R=Ph b: R=H



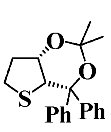
155 a: R=Ph b: R=H

156 a: R=Ph b: R=H

In 1999, Hayakawa et al. succeeded in highly enantioselective synthesis of epoxides from aldehydes catalyzed by the sulfur ylide derived from chiral β-hydroxy esters.[402] However, the sulfur ylide derived from chiral sulfide **157** resulted in (*R*,*R*)-stilbene oxide in 64% yield with only 7% ee, possibly due to the large distance from the chiral center to the reaction site. Accordingly, tetrahydrothiophene derivative **158** was prepared as the catalyst instead of the tetrahydrothiopyrane derivative, which notably increased the ee value of the product to 78%; in particular, the highest enantioselectivity reached 92% ee in the reaction of tolaldehyde.



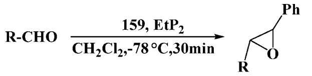
157

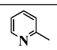
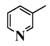
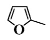
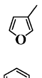
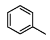


158

Chiral pyridyl alcohols, prepared by reducing the corresponding pyridyl ketones enantioselectively, have found numerous applications, e.g., as ligands in the metal-mediated asymmetric catalysis,[409,410] as resolving agents,[411] and as starting materials for preparing more advanced chiral ligands.[412,413] Similarly, chiral furyl hydroperoxides have also been used in the asymmetric epoxidation of allylic alcohols[52] and sulfides.[58,414] In 2000, Solladié-Cavallo et al. carried out the asymmetric synthesis of epoxides from pure (*R*,*R*,*R*,*S*$_S$)-(−)-sulfonium salt **159**, commercially available aldehydes and a phosphazene base [EtP$_2$=Et−N=P(NMe$_2$)$_2$(N=P(NMe$_2$)$_3$)].[403] They found that EtP$_2$ provided an exceptionally high enantioselectivity generally over 97% ee (Table 19) and that EtP$_2$H$^+$/TfO$^-$ could be recovered by simply varying the solvent polarity to regenerate the expensive base EtP$_2$ as shown in structure **159**.

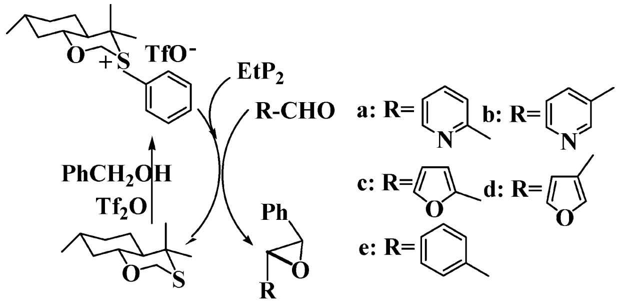
Table 19. Asymmetric Synthesis of Epoxides from Sulfonium Salt Using EtP$_2$ Base[a]



Entry	R	Tempt. (°C)	Yield (%)	ee (%)
1		−78	94	99.2
2		−78	81	96.8
3		−78	11	99.2
4		−78	82	99.8
5		− 40	69	97

[a] Adapted from ref 403 with permission. Copyright 2000 Wiley-VCH.

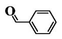
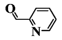
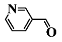
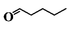
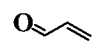
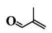
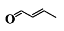
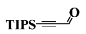
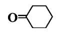
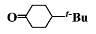
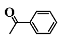
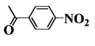
In 2001, Aggarwal et al. reported a unique process for the direct coupling of two different aldehydes to form epoxides with the control of the relative and absolute stereochemistry.[415] High enantioselectivities (up to 94% ee) were achieved for the asymmetric epoxidation of a wide range of aromatic, heteroaromatic, unsaturated, and aliphatic aldehydes catalyzed by chiral sulfide **160** with tosylhydeazone salts (tosyl = toluene-4-sulfonyl) in the presence of Rh$_2$(OAc)$_4$. It was found that the sulfide loading could be reduced from 20 to only 5 mol % without affecting



159 (R,R,R,Ss)

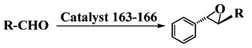
the yield and the ee value significantly. In 2002, Aggarwal et al. found again that bis(oxazolines) **161** could be used in the asymmetric epoxidation of benzaldehyde in the presence of Et_2Zn to achieve 54% ee with moderate yield, which was the highest ee value for the preparation of terminal epoxides by a sulfonium ylide mediated process.[416] In 2003, they further reported subsequent treatment of chiral sulfonium salts **162** by a carbonyl compound with either a phosphazene base at low temperature or with KOH at room temperature to offer the corresponding epoxides with high yields and enantioselectivities, as shown in Table 20.[417]

Table 20. Asymmetric Epoxidation of Various Electrophiles Catalyzed by Sulfonium Salts 162[a]

Entry	Electrophile	Salt	Yield (%)	ee (%)
1		**162a**	75	98
2		**162b**	33	84
3		**162c**	37	97
4		**162d**	96	90
5		**162e**	69	90
6		**162a**	91	95
7		**162a**	74	98
8		**162a**	58	91
9		**162a**	30	97
10		**162a**	51	96
11		**162a**	72	90
12		**162a**	50	95
13		**162a**	85	92
14		**162a**	93	>99
15		**162a**	77	93
16		**162a**	73	71

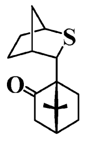
[a] Adapted from refs 415 and 417 with permission. Copyright 2001 and 2003 Wiley-VCH.

Table 21. Asymmetric Epoxidation of Various Aldehydes by Catalysts 163−166[a]

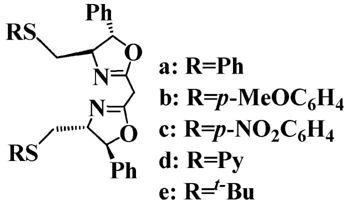


Entry	R	Catalyst	Yield (%)	ee (%)
1	Ph	**163a**	64	21
2		**163b**	32	−1
3		**163c**	47	−1
4		**163d**	17	−7
5		**164a**	42	46
6		**164b**	60	1
7		**164c**	50	6
8		**164d**	24	2
9		**165a**	22	68
10		**165b**	63	8
11		**165c**	44	37
12		**165d**	14	35
13		**165e**	9	65
14		**165f**	19	64
15		**165g**	29	61
16		**165h**	59	69
17		**165i**	14	64
18		**165j**	9	54
19		**166a**	34	48
20		**166b**	28	50
21		**166c**	27	53
22	4-MeOC$_6$H$_4$	**165a**	60	69
23		**165g**	62	61
24		**165h**	59	75
25	4-CF$_3$C$_6$H$_4$	**165a**	63	55
26		**165g**	64	47
27		**165h**	52	59
28	4-ClC$_6$H$_4$	**165h**	55	67
29	4-MeC$_6$H$_4$	**165h**	68	72
30	2-Naphthyl	**165h**	56	70
31	(*E*)-C$_6$H$_4$Ch=CH	**165h**	72	72

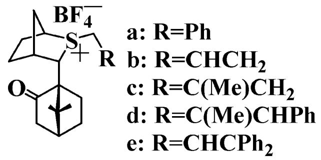
[a] Adapted from ref 418. Copyright 2003 Wiley USA.



160

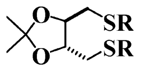


161

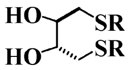


162

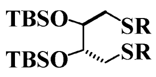
In 2003, Ishizaki et al. reported the synthesis and application of novel chiral sulfides **163**−**166** with a *C*$_2$-symmetry in the asymmetric epoxidation of aldehydes, in which the asymmetric induction of the catalyst with the electron-withdrawing group on the aromatic ring was higher than that with the electron-donating group (Table 21).[418] Additionally, *tert*-butyl phenyl salicylate ether (TBS) (**165h**) was also found to be an efficient catalyst for the asymmetric epoxidation of various aldehydes (up to 75% ee).



163a-h

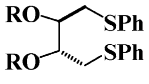


164a-h

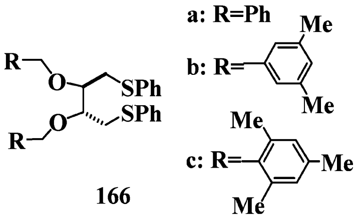


165a-h

a: R=Ph e: R= α -Nap
b: R=Bu f: R= β -Nap
c: R=c-Hex g: R=4-MeO-C$_6$H$_4$
d: R=t-Bu h: R=4-Cl-C$_6$H$_4$



165i: R=TES
165j: R=TIPS



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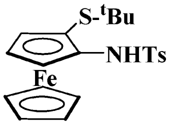
In 2003, Minire et al. performed an asymmetric epoxidation from stilbene to stilbene oxide with 0.2 equiv of sulfide **167** in reasonable yield with an unexpected diastereomeric ratio of trans/cis = 56:44, in which the trans-isomer with 67% ee was the (*S*,*S*)-enantiomer.[419] This was the first asymmetric conversion of an aldehyde into oxirane mediated by ferrocenyl sulfur ylides with planar chirality. It involved the formation of ferrocenyl sulfonium salts, observed for the first time and monitored by ^{1}H NMR. The stereochemical course kinetically favors the trans-isomer more than the usual one with other sulfides, probably related to an earlier transition state. And the steric hindrance of sulfide provides an enhanced percentage of trans-isomer, with some reversibility of the cis-conformational precursor.



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3. Heterogeneous Systems

One of the major problems in the application of homogeneous transition-metal complexes for the asymmetric epoxidations has been assigned to the decomposition or the degradation of these complexes. Deactivation pathways involve autoxidation, dimerization through μ-oxo bridges[420] and oxidative degradation via multinuclear μ-oxo complexes.[421] The degradable dimerization of catalytic centers could be decreased by the following routes, such as intercalating or encapsulating the metal complex into the layered compounds or within the cavities of a porous solid (e.g., zeolites),[422] binding the metal complex to a polystyrene matrix,[423] and employing the steric hindrance.[424,425]

Heterogeneous systems have tremendous advantages over homogeneous ones, and through heterogenizing the catalysts or the reagents certain practical limitations of homogeneous systems can be eliminated. One of the most attractive advantages of heterogeneous systems is the easy separation and facile recovery of the solid catalyst from the products for recycling without tedious experimental workup. The preparation of polymer-supported catalysts containing main-chain or pendant chirality represents one of the most interesting applications of polymers in the organic chemistry.[426−428] Accordingly, much effort has been directed toward the development of immobilized chiral auxiliaries for asymmetric processes.[429,430] The design and development of solid catalysts that can lead to a visible enantioselectivity for the epoxidation of unfunctionalized terminal olefins and other C=C double bonds constitutes a major challenge in the asymmetric catalysis.[431,432]

In summary, the immobilization of homogeneous complexes on solids has, to date, been rather successful; however, as compared with their homogeneous counterparts the supported solid catalysts do not achieve ideal stability and recyclable numbers yet. In some cases, only limited recycle numbers and low ee values are obtained, which is insufficient for large-scale industrial applications. Furthermore, some synthetic approaches are very complicated, which will limit the evolvement of heterogenization techniques. Consequently, the easy synthesis and recycling of heterogenized catalysts with ideal recyclable numbers and excellent ee values will be a long-term endeavor target.

3.1. Supported Sharpless Systems

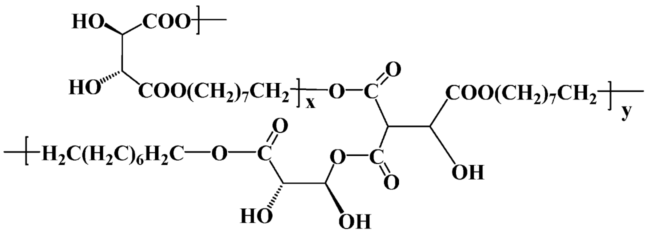
The discovery of a procedure by Katsuki and Sharpless for the asymmetric epoxidation of allylic alcohols with DET, titanium tetraisopropoxide, and TBHP was an important milestone in the asymmetric synthesis.[6] Because the methodology in the literature[49,75] involved a rather elaborate workup procedure,[6] the development of a solid-phase analogue would be a valuable improvement. To date, many approaches have been developed to prepare heterogeneous Sharpless-type catalysts for the asymmetric epoxidation of allylic alcohols.[15,77,433−439] Presently, the advantages of polymer-supported reactive species are widely recognized by organic chemists, and increasing the exploitation of these systems is occurring in both academia and industry.[440] The effective immobilization of asymmetric catalysts, reagents, and auxiliaries is a particularly important methodological target, especially for the metal−complex-based catalysts.

There has been relatively little effort to produce polymer-supported analogues of Sharpless system, possibly because the cost of tartaric acid diesters is relatively low such that their loss during the reaction can be tolerable. In addition, it has turned out that in some instances with water-soluble substrates the standard workup procedure for the soluble catalyst presents major problems to preclude convenient and cost-effective use of the methodology. Under these circumstances, a polymer-supported system would be invaluable and indeed might then be exploited more widely as a more practical methodology.

3.1.1. Insoluble Polymer-Supported Titanium Complexes

The application of polymer-supported catalysts in organic transformations has received extraordinary attention in recent years.[441,442] The immobilization of homogeneous catalysts onto polymeric carriers offers several practical benefits for the heterogeneous catalysis on the condition that the advantages of homogeneous process are retained.[443,444] Some of attractive features of polymer-supported catalysis include (a) the easy separation of catalysts from reaction products, (b) the simplification of methods to recycle expensive catalysts, (c) the nonvolatile and nontoxic characteristics imparted to the metal complexes upon anchoring to high molecular-weight polymer backbones, (d) the minimization of certain catalyst deactivation by the site isolation, and (e) no exposure to water and/or to air.[445] These attractive features could create the possibility of developing high-throughput discoverable applications and continuous catalytic processes for industrial-scale syntheses.

In 1983, Farrall et al. immobilized a single tartrate residue on a 1% cross-linked polystyrene resin and performed the Sharpless epoxidation of geraniol under the conditions employed in the literature.[446] Typically, the yield of the desired products was 60−70% with ee values ranging 50−60%, which, in retrospect, was a very good result, and surprisingly, did not follow up the earlier data.[447] In 1998, Karjalainen et al. reported the synthesis and application of novel cross-linked poly(tartrate ester)s **168** in the preparation of heterogeneous catalysts.[15,436] These heterogeneous polymer-based catalysts showed a higher level of enantioselectivity (up to 98% ee) in the epoxidation of *trans*-allylic alcohols than did the soluble linear analogues used earlier.[448] In addition, since the catalysts were heterogeneous, the workup of the reaction was considerably simplified. A recent report of this work has played down the significance of these results since authors would have been unaware of the data from the branched polytartrates.[449] However, these gel-type polymeric ligands swelled during the catalytic reaction, which is a major drawback.



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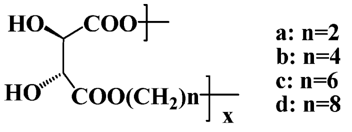
In 2000, Suresh et al. prepared a new class of cross-linked polystyrene resin tartrates to replace conventional DET used in the methodology of Sharpless epoxidation.[450] Chloromethyl groups attached to styrene could be functionalized through a nucleophilic substitution that involves reactive anions. Ester functions have been created through the reaction between triethylamine and chloromethylated groups,[451,452] in which the use of triethylamine for the esterification is well-known.[453] These chiral resins have been used as the Sharpless catalysts for the asymmetric epoxidation of allylic alcohols. The results showed that the longer chain and the greater branching in the domain of molecules possibly made access to the polymer-bound reaction sites more difficult. The highest ee value of 91% was observed in the epoxidation of cinnamyl alcohol with tartrate-functionalized polystyrene resin containing 1 mol % of tetraethyleneglycol diacrylate (TTEGDA), which was much lower than that achieved by the traditional Sharpless method but higher than those reported with earlier polymer-supported catalytic systems.[151]

Although insoluble polymer-supported reactive complexes possess many notable advantages, there are still limitations associated with these species. Soluble polymer-bound ligands, reagents, or catalysts as the alternatives to insoluble polymer-bound ones have made considerable progress in recent years.[13,19] An early attempt to develop a soluble polymer-supported system employed a single tartrate ester unit bound to a polystyrene resin;[151] however, in this case the chiral induction was ca. 50−60% ee. The linear poly(tartrate ester) system developed by Canali et al. in 1997 was successful with an enantioselectivity up to 79% ee for the epoxidation of *trans*-hex-2-en-1-ol catalyzed by Ti(OPr^i)$_4$ and TBHP using polyesters **169** and **170** as the ligands.[437] However, as compared with 98% ee obtained from a solution-phase reaction with L-(+)-dimethyl tartrate, the present enantioselectivity is still low and requires improving.



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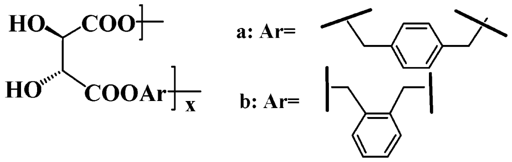

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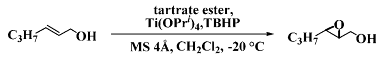
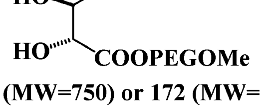
In 2002, Guo et al. reported the synthesis and catalytic use of one group of tartrate esters (**171**−**173**), together with titanium tetraisopropoxide [Ti(OPr^i)$_4$] and TBHP, in the epoxidation of *trans*-hex-2-en-1-ol, which attained a high chemical yield and a good ee value, showing that the enantioselectivity could vary significantly with the molar ratio of ligand to Ti (Table 22).[22] Experimentally, the ligand **172** was recycled four times, the ee values from first to fourth cycle were 49, 44, 32, and 30%, respectively. Although the recycled catalysts did not show satisfactory ee, the recovery of ligand by simple precipitation and filtration aided in the isolation of products. Anyway, the complicated workup required in the traditional Sharpless procedure has been considerably simplified without the occurrence of emulsification.

Table 22. Asymmetric Epoxidation of *trans*-Hex-2-en-1-ol with TBHP by L-(+)-Tartrate Ester and [Ti(OPr^i)$_4$][a]

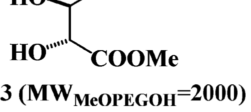


Ligand	Molar ratio (*trans*-hex-2-en-1-ol:Ti:tartrate)	Yield (%)	ee (%)
171	100:5:6	68	5
	100:20:24	81	70
	100:20:48	90	93
172	100:5:6	72	64
	100:5:10	85	93
	100:10:12	75	24
	100:20:24	80	3
173	100:5:6	79	90

[a] Adapted with permission from ref 22. Copyright 2002 Royal Society of Chemistry.



171 (MW=750) or 172 (MW=2000)



173 ($MW_{MeOPEGOH}$=2000)

3.1.2. Organic–Inorganic Hybrid-Supported Titanium Complexes

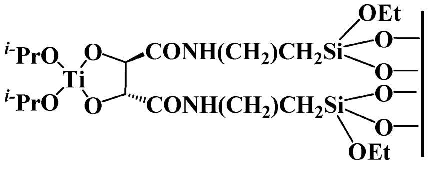
The synthesis of hexagonal mesoporous silicas MCM-41,[454] HMS,[455] and MSU[456] through a hydrothermal assembly of silica and surfactants has encouraged a great deal of research interest recently. These mesoporous materials hold noticeably structural features, such as high stability, big pore sizes (1.5−10 nm), large surface areas (~1000 m^2/g),[454,455] and numerous surface OH groups,[457,458] which offers tremendous potential as the catalysts for the conversion of large molecules and as the hosts for the assembly of a wide variety of transition-metal complexes. Zeolites and mesoporous molecular sieves containing isolated framework titanium atoms have shown potential capabilities as the epoxidation catalysts using aqueous H_2O_2 and organic peroxides as the oxidants.[459−462] In 1990, Choudary et al. carried out the immobilization of a heterogeneous chiral titanium catalyst on an inorganic support.[433] A combination of dialkyl tartrate and Ti-pillared montmorillonite resulted in excellent ee values ranging 90−98%. In fact, this heterogeneous system could be efficiently operated in the absence of molecular sieves, while no recycling experiment was reported. However, vanadium-pillared montmorillonite catalyst afforded an ee value of only 20% for the epoxidation of (*E*)-hex-2-enol.[434]

Owing to the increasing ecological and economic regulations for chemical processes, the preparation of organic−inorganic hybrid materials has been of growing interest.[23,25,27,463−468] In contrast to organic polymers, organic−inorganic hybrid materials, which do not swell nor dissolve in organic solvents, have many advantages over most organic polymers because of their superior mechanical and thermal stabilities. And any leaching can be avoided due to the covalent attachment of organic moieties to inorganic supports. As a consequence, the design and synthesis of chiral catalytic materials with a high enantioselectivity based on the hybrid materials are especially attractive. In 2002, Xiang et al. obtained success in the synthesis of organic−inorganic hybrid chiral materials by grafting a chiral tartaric acid derivative onto the surface of silica (**174**) or/and onto the mesopores of MCM-41 (**175**) material, which provided the first example of this kind of material in the heterogeneous asymmetric epoxidation of allylic alcohols.[449] The resulting heterogeneous catalysts induced appreciable ee values up to 80%, as good as the homogeneous Sharpless system (Table 23). For chiral solid hybrids, the environment surrounding the immobilized species is analogous to that of homogeneous chiral complexes with a comparable catalytic activity. This method could be a general approach to synthesize heterogeneous chiral catalysts, and one more advantage of this system is that the products can be easily separated from the catalyst by simple filtration. The key solution to obtain a high stereoselectivity is to ensure an anhydrous reaction system. For example, in the absence of water 99% ee was obtained for the epoxidation of (*E*)-α-phenylcinnamol, while the addition of one equivalent of water reduced the ee value to 48% abruptly. In these cases, substrates must contain specifically functional groups to achieve the precoordination required for the high enantioselectivity.

Table 23. Asymmetric Epoxidation of Allylic Alcohol on Organic−Inorganic Hybrid Chiral Catalysts Grafted onto the Surface of Silica (174) and in the Mesopores of MCM-41(175)[a]

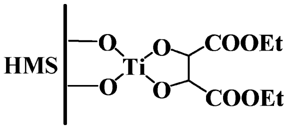
entry	catalyst	ti/substrate (%)	conversion (%)	ee (%)
1	**174**	2	29	86
2	**175**	2	22	84
3	**174**	4	49	78
4	**175**	4	43	80

[a] Adapted from ref 449. Copyright 2002 Wiley USA.

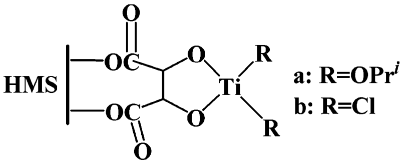


SiO$_2$ (174) or MCM-41(175)

In 2004, Fu et al. first reported the grafting of chiral Ti-tartrate complexes **176** and **177** derived from either Ti(OPr^i)$_4$ or TiCl$_4$ and D-tartaric acid (TA) onto HMS mesoporous material by an exchange reaction of Ti-compounds with surface OH groups.[469] They found that the exchange of titanium tetraisopropoxide (Ti(OPr^i)$_4$), especially titanium tetrachloride (TiCl$_4$) with the surface hydroxyls of HMS easily occurred. These assembled HMS catalysts were very stable in the catalytic epoxidation of styrene and cyclohexene with TBHP and recyclable many times without significant loss of activity. The coordination of D-(+)-diethyl to Ti-sites anchored on the support led to a decrease in the catalytic activity and an increase in the epoxidation selectivity.



HMS+Ti+DET
176

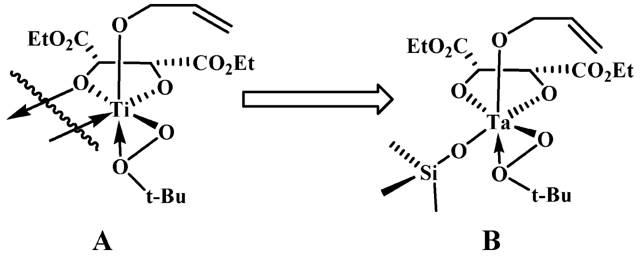


HMS+TA+Ti
177

3.1.3. Silica-Supported Tantalum Complexes

Although inorganic oxide-supported titanium compounds were prepared for the catalytic epoxidation of allylic alcohols, the enantioselectivity was not reported.[433,470−472] The leachability of metals from the support as well as the difficult preparation of the solids seem to have resulted in poor reproduction. The grafting of titanium into a Sharpless-type catalyst is, perhaps, not the right one, since the accepted mechanism usually requires a coordination sphere, where four d-electrons of Ti are involved in the formation of σ bonds with a tartrate group chelating the metal through two σ-bonded oxygen atoms, an allylic alkoxy group, and a σ/π-coordinated *tert*-butyl peroxo group (Scheme 11).[50]

Scheme 11. Formation of σ Bonds[a]



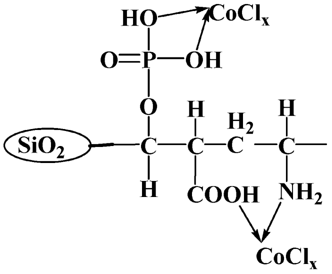
[a] Adapted from ref 50 with permission. Copyright 1991 The American Chemical Society.

Tantalum compound, which exhibits a low activity in the homogeneous catalysis, has been chosen as a candidate to prepare heterogeneous catalysts. In 1999, Meunier et al. synthesized silica-supported tantalum catalysts for the asymmetric epoxidation of 2-propen-1-ol, associated with (+)-di-isopropyl tartrate [(+)-DIPT] and TBHP.[438] Good activity and enantioselectivity (84−85% ee) were obtained in the presence or absence of molecular sieves, with a major enantiomer of (S)-glycidol. As anticipated, when (−)-DIPT was used, the major product was (*R*)-glycidol. The activity of silica-supported tantalum catalysts was assigned to the contribution of surface sites rather than to that of dissolved species because (a) the $Ta(OEt)_5$ molecule was almost inactive species, (b) the chemical analysis before and after the reaction did not indicate any metal leaching, and (c) when the solid catalyst was isolated by filtration before the addition of last reactant, TBHP or 2-propen-1-ol as recommended by Sheldon,[473] the solution was catalytically inactive. Silica-supported tantalum catalysts showed good activity and enantioselectivity for the epoxidation of *trans*-(2*S*,3*S*)-2-hydroxymethyl-3-propyl-oxirane with molecular sieves (93% ee) or without molecular sieves (89% ee). In this work, Ta-containing solid catalyst displayed a characteristic of easy separation by filtration and recycling, comparable to the high efficiency of homogeneous Sharpless reaction with molecular $Ti(OPr^i)_4$ (96% ee). Note that the preparation of organometallic tantalum compound used in the synthesis is quite difficult.[474]

The higher activity of supported Ta-complex than homogeneous one may result from the contribution of well-dispersed monomeric active Ta species on the surface of silica. On the other hand, molecular Ta alkoxides that are dimers in weakly polar solvents would lead to dimers in the presence of tartrate and reactants. These molecular Ta dimers would be poorly active as compared to silica-supported monomeric Ta species. In 2003, a new report was made on the preparation of silica-supported chiral tantalum alkoxides through grafting a metal onto silica through a ≡Si−O-metal bond and modifying its coordination sphere by an adequate chiral ligand.[475] Factors influencing the catalytic activity were carefully investigated, and it was found that the maximal ee (85−87% ee of (*S*)-glycidol) was obtained after a long-term impregnation of solid with the chiral inducer (+)-DIPT. The above-mentioned catalytic reaction was carried out in a chlorinated solvent, but good results also could be gained in pentane and toluene. The use of CMHP instead of TBHP as the epoxidizing oxidant did not improve the result of propenol epoxidation; however, with hydrogen peroxide a rather low ee (40%) was obtained at −20 °C. Temperature and alcohol concentration took a serious impact on the selectivity and enantioselectivity. Indeed, when the epoxidation of propenol was conducted at 10 °C instead of 0 °C, a kinetic resolution occurred, leading to a higher ee value and lower selectivity.

3.1.4. Silica-Supported Casein–Cobalt Complexes

Casein, a product from milk, is a cheap and abundant material. It is a copolymer of various amino acids and a small amount of phosphoric acid. The optical rotation is −100°, so it can be used as a chiral polymer ligand. It is not difficult to imagine that such a natural biopolymer complex catalyst can be used in various asymmetric reactions. In 2002, Zhang et al. found that silica-supported casein-Co complex (Si-CA-Co) **178** prepared from silica, casein, and cobalt chlorite was an effective chiral catalyst for the asymmetric epoxidation of cinnamyl alcohol to the corresponding epoxide at 70 °C under one atmospheric oxygen pressure, with 2,4-dihydroxybenzaldehyde as the reductant.[476] The results showed that the yield and ee value were greatly affected by the cobalt content in the complex; for example, an up to 92% ee was achieved with a proper content of cobalt (0.2 mmol/g) in a Si-CA-Co complex under suitable reaction conditions. The catalyst could be reused several times without any appreciable loss in the catalytic activity and enantioselectivity.



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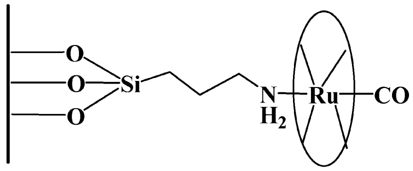
3.2. Supported Porphyrins Systems

Although some progress has been made in heterogeneous organic oxidations catalyzed by soluble and insoluble polymer-supported ruthenium porphyrins,[375,478,479] a similar strategy is not suitable for the development of polymer-supported chiral metalloporphyrins because of the difficulty involved in attaching a chiral porphyrin ligand, particularly D_4-symmetric $H_2(D_4\text{-Por*})$, onto the polymer chain. An alternative method is to attach a ruthenium porphyrin to mesoporous silica material by coordinative grafting; this would circumvent the problem encountered in the structural modification of the porphyrin ligand.

In 2002, Zhang et al. succeeded in encapsulating chiral Ru-porphyrin into uniform mesopores of ordered mesoporous molecular sieves (MCM-41 and MCM-48).[480] When these catalysts were used in the asymmetric epoxidation of olefins, ee values ranging

43−77% could be achieved. It was found that chiral Ru-porphyrin immobilized on MCM-48 (**179**) displayed higher asymmetric induction than that on MCM-41 (**180**), possibly because MCM-48 with a three-dimensional network provides a larger surface area than does MCM-41 with a one-dimensional straight pore channel for the high accessibility of reactant molecules to active sites. Notably, chiral Ru-porphyrin immobilized on MCM-48 showed a better reactivity for cis-alkenes than for trans-counterparts, closely similar to the case of free chiral Ru-porphyrin complex. This seems that chiral Ru-porphyrin complex immobilized inside the mesopores of MCM-48 behaves as a homogeneous catalyst, and the co-interaction between the coordination environment of the chiral Ru-porphyrin complex and the channels of MCM-48 helps to maintain asymmetric induction in the asymmetric epoxidation of alkenes, further enhancing the reactivity and stability of the solid catalyst.



MCM-48 (179) or MCM-41(180)

3.3. Supported Salen(Metal) Systems

The favored soluble Jacobsen complex, which is relatively costly and quite unstable in contact with the oxidant, must be used in a specific experimental protocol and cannot be recycled. When this catalyst catalyzes adequate enantioselective epoxidation under homogeneous biphasic conditions, the separation and recycling of the catalyst is really a problem, thus limiting its application only for a batch process. Consequently, there is a growing interest in heterogenizing this expensive catalyst to overcome the problem in the separation/recovery operations and to enhance the stability, activity, and selectivity.[14,174,481−485] To reach the anticipated target, various approaches have been tested, including anchoring the catalyst on a solid support or on a polymer chain, encapsulating the active centers in the pores of zeolites, wrapping the active centers by van der Waals force in the elastomeric network of a poly-dimethylsiloxane membrane, developing a biphase reaction system, and running the reaction in ionic liquids. The heterogenization of homogeneous catalysts endows attractive features to traditional homogeneous systems, such as easy product separation and catalyst recovery.[12,486−489] Numerous attempts have been aimed at the immobilization of homogeneous chiral catalysts.[490−493] These approaches include (a) the copolymerization of a functionalized salen monomer into an organic polymer, (b) the attachment or the buildup of a salen structure to a preformed polymer matrix, (c) noncovalent immobilization on zeolites, clays, or siloxane membranes,[494] and (d) covalent grafting onto inorganic supports such as silica or MCM-41.[18,25,24,26,29,31]

The most useful metal complexes for the alkene epoxidation are those containing Ti(IV), V(V), Mo(VI), and W(VI), although recently methyltrioxorhenium (MTO) has attracted significant attention.[495] Recently, salen-Mn(III) complexes also have assumed considerable importance as asymmetric epoxidation catalysts.[208] For polymer-supported systems, the most widely investigated ones are V(V)/ROOH, Mo(VI)/ROOH, W(VI)/H_2O_2, Ti(IV)/ROOH, and Mn(III)/RCO_3H. Potential technological advantages in converting a process by a homogeneous metal complex into one involving a heterogeneous polymer-supported analogue have been well rehearsed.[442,496] Suffice it to say that in a laboratory scale, supported metal complex catalysts considerably facilitate the workup and isolation of the products, while on a large scale such heterogeneous catalysts must allow processes to be run continuously in packed or fluidized-bed columns with considerable financial merits both in terms of capital expenditure in the plant and with regard to recurrent cost. Generally speaking, the problems arising with polymer-supported catalysts have been clearly highlighted and require always a continuous improvement.[497]

The asymmetric epoxidation of unfunctionalized olefins catalyzed by salen-Mn(III) complex has been proven to be the most useful reaction in the past decade;[173] in particular, the Jacobsen's catalyst **59**, one of salen-Mn(III) complexes, exhibits excellent activity and enantioselectivity. However, since salen-Mn(III) complexes undergo decomposition under reaction conditions to result in difficult recovery and reuse, much research therefore has been performed to modify the characteristics of typical salen-Mn(III) complex systems.[17,174,483] Above-mentioned disadvantages of classic salen-Mn(III) catalysts have greatly encouraged the interest of some researchers in developing supported salen-Mn(III) catalysts, such as polymer-bound catalysts[14,174,483] and inorganic solid-supported catalysts,[12,17,36,182] so as to minimize the degradation of catalysts and to allow the easy recovery and reuse of catalysts for a large number of cycles.

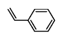
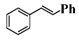
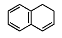
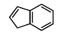
3.3.1. Polymer-Supported Salen Complexes

Optically active functional polymers have attracted increasing attention in organic chemistry as chiral reagents and catalysts for asymmetric organic transformations and as chiral stationary phases for the resolution of racemates.[498−500] More expeditious synthesis of salen-Mn(III) complexes than porphyrin systems has made the former more appealing as a class of superior asymmetric catalysts. To enhance the usefulness of this class of chiral catalysts by making them recyclable (while retaining the catalytic activity), it is desirable to prepare polymeric analogues of this interesting catalyst system. Cross-linked polymers bearing chiral auxiliaries/catalysts offer several advantages over soluble homogeneous reagents.[501−503] Other than the retention of activity of homogeneous catalysts; a polymeric approach enables the workup of the reaction and recovery of expensive chiral catalysts for easy reuse. This has been, recently, demonstrated by anchoring chiral catalysts onto poly(ethylene glycol) (soluble phase separating polymer) and by entrapping them inside a polymer membrane.[12,504] Additionally, polymer matrixes may offer unique micro-environments for the reactions that might lead to an enhanced selectivity. In the catalytic asymmetric epoxidation, the structure of Schiff-base moiety of chiral salen-Mn(III) complex usually plays a key role in bringing about an impressive enantioselectivity. Since the enantioselectivity of epoxides of unfunctionalized olefins solely relies on nonbonded interactions, the design of the catalyst structure has been aimed at incorporating chiral centers of ligands in the vicinity of metal binding sites. On the other hand, the incorporation of sterically demanding substituents around the metal coordination center would restrict the access of olefins to the limited number of sites, thereby enhancing the stereochemical communication during the epoxidation.[86,504]

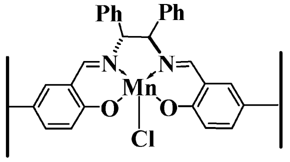
As far as state-of-the-art methods, insoluble polymer-bound catalysts have solved the separation problem but usually suffer from a notable reduction in the catalytic activity and/or stereoselectivity. Two general routes exist to synthesize polymer-anchored catalysts.[108,505,506] Because of the relative simplicity, the attachment of catalytic species onto preformed polymers through chemical modifications has been extensively used.[507,508] The other approach to obtain polymer-bound chiral catalysts involves the synthesis of appropriate functional monomers bearing chiral catalytic moieties and the copolymerization with suitable cross-linked monomers into insoluble polymer matrixes. The latter offers several distinct advantages: (a) the purity of the catalytically active species can be assured, (b) the concentration of the catalytic species in the polymer matrixes can be regulated by varying the ratio of monomer in the polymerization recipe, and (c) the physicomechanical properties of the polymer matrixes can be systematically engineered by a proper adjustment of polymerization parameters.

In 1997, De et al. reported their efforts to synthesize two polymerizable chiral salen-Mn(III) complexes **181** and **182**.[14] The structural variant of two monomers lies in the emergence of bulky substituents at close proximity to the salen moiety in one monomer, which could elucidate the role of rigidity of the polymer matrix alone (in the case of nonsubstituted salen) on the enantioselectivity. This has been long thought of and observed in certain cases in the polymeric catalysis, where the inflexibility of highly cross-linked polymer matrixes provide favorably structural rigidity required for certain stereoselective chemical transformations.[509] Two polymers **181** and **182** were evaluated as the catalysts for the chemo- and enantioselective epoxidation of unfunctionalized olefins, to obtain poor enantioselectivity <30% ee (Table 24). Although the chemoselectivity of these polymeric catalysts is comparable to their soluble counterparts, their effectiveness on inducing the enantioselectivity is inferior, which cannot be improved by the addition of an external nitrogen ligand. This is because in the asymmetric epoxidations catalyzed by Mn(III) complexes with porphyrin or salen derivatives as the ligands the use of an external nitrogenous ligand, such as imidazole or pyridine-*N*-oxide, would lead to higher enantioselectivity.[175,510] The results have shown that the rigidity of the polymer matrix alone could not sufficiently meet the steric needs required at a molecule level.

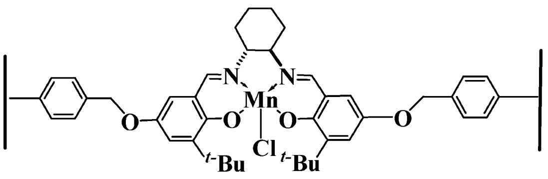
Table 24. Asymmetric Epoxidation of Unfunctionalized Olefins Catalyzed by 181 and 182 with PhIO as the Oxidant[a]

Entry	Substrate	Catalyst	Yield (%)	ee (%)
1		**181**	76	<1
2		**182**	72	<2
3		**181**	60	<2
4		**182**	55	9
5		**181**	72	8
6		**182**	70	28
7		**181**	65	9
8		**182**	60	25

[a] Adapted from ref 14 with permission. Copyright 1997 Wiley-VCH.



181



182

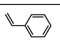
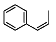
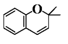
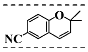
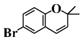
Some of the possible shortcomings of these asymmetric polymer catalysts may be ascribed to the high cross-linking density of polymer matrixes that might have resulted in nonspecific catalytic sites. As we know, the bifunctional nature of metal complexing monomers can bring about 100% cross-linking of polymers. The introduction of longer spacer arms and/or the lowering of cross-linking density by the dilution with a vinyl monomer during polymerization may help to elucidate the factors governing the enantioselectivity of these polymer-bound asymmetric catalysts. A major limitation of homogeneous metallosalen-based epoxidation catalysts is their propensity to generate catalytically inactive species after a few cycles.[163] The role of salen-Mn(III) complex during the epoxidation is to pick up an oxygen atom from the monooxygen source (PhIO) in converting Mn(III) to a high valent oxomanganese species (O=Mn(V)). This oxomanganese species is proven to be catalytically active in transferring oxygen into olefinic double bond.[482,511a] This process is reversible shuttling between Mn(III) and O=Mn(V) state; however, in addition to this redox pathway, the dimerization of O=Mn(V) with Mn(III) was also considered to take place to produce a catalytically inactive μ-oxomanganese(IV) species, which led to the depletion of active species after a few turnovers. However, recent investigation suggested that oxidants (such as μ-oxomanganese(IV)) other than O=Mn(V) are at work as well (at least sometimes).[181,511b] On the other hand, in the polymeric systems, anchoring the salen-Mn(III) moieties onto a solid polymeric carrier results in a low local concentration of the metal complex.

Once linked onto a rigid polymer framework, the mobility of metal complexes is severely restricted (site isolation), consequently minimizing the possibility of formation of undesired dimeric μ-oxomanganese(IV). Robustness of these polymeric chiral catalysts is evident from the fact that the catalyst **182** could be recycled up to five times without any visible loss of catalytic activity in terms of chemo- and enantioselectivity.

To make recyclable and economical chiral salen-Mn(III) catalyst systems with high efficiency, some groups have profoundly investigated the synthesis of polymer-bound Mn(III) complexes.[14,174,483] Of a large number of catalysts developed for this purpose, chiral metalloporphyrins[98,169] and chiral salen-Mn(III) complexes are the most effective. Several researchers have immobilized the analogues of Jacobsen's homogeneous catalysts onto the solid supports for use as recyclable catalysts in the asymmetric epoxidation of alkenes.[447,512] However, since the immobilization of those catalysts often causes a significant drop in the enantioselectivity and stability, therefore, there is still a major need to attain a stable and recyclable catalyst.

In 2000, Yao et al. claimed the synthesis and catalytic application of two novel chiral poly-salen-Mn (III) complexes **183** and **184**, derived from (*R*,*R*)-1,2-diaminocyclohexane in the enantioselective epoxidation of olefins.[513] In the case of substituted styrenes and substituted 2,2-dimethylchromenes as the substrates, 30−92% ee values and 75−97% yields were achieved in the oxidant system consisting of NaClO/4-PPNO and *m*-CPBA/NMO (Table 25). Interestingly, these two poly-salen-Mn complexes were completely soluble in dichloromethane but almost insoluble in hexane, cyclohexane, and diethyl ether. Poly-salen-Mn (III) complexes could be, thus, recovered easily and recycled efficiently several times by a simple catalysis/separation method without any loss of activity. After five cycles, an epoxide with 82% ee and 78% yield was still obtained using 2,2-dimethylchromene as the substrate (Table 26).

Table 25. Enantioselective Epoxidations Catalyzed by Chiral Poly-Salen-Mn Complexes 183 and 184 with NaClO/4-PPNO and m-CPBA/NMO as Oxidants[a,b]

Entry	Substrate	Catalyst	Oxidant	Yield (%)	ee (%)
1		**183**	NaClO	25	61
2		**184**	NaClO	28	64
3		**183**	NaClO/4-PPNO	31	84
4		**184**	NaClO/4-PPNO	36	75
5		**183**	m-CPBA/NMO	43	96
6		**184**	m-CPBA/NMO	41	91
7		**183**	NaClO/4-PPNO	56	74
8		**184**	NaClO/4-PPNO	58	69
9		**183**	m-CPBA/NMO	70	85
10		**184**	m-CPBA/NMO	68	86
11		**183**	NaClO/4-PPNO	91	82
12		**184**	NaClO/4-PPNO	92	81
13		**183**	m-CPBA/NMO	91	87
14		**184**	m-CPBA/NMO	91	85
15		**183**	NaClO/4-PPNO	86	95
16		**184**	NaClO/4-PPNO	89	96
17		**183**	NaClO/4-PPNO	88	95
18		**184**	NaClO/4-PPNO	91	94

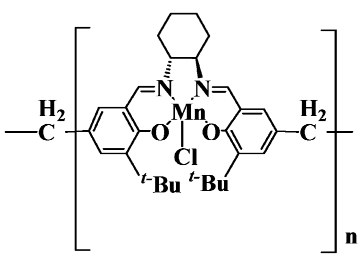
[a] Adapted from refs 513 with permission. Copyright 2000 Elsevier. [b] Entries 1 and 2: at room temperature; other entries: at 0 °C.

In 1999, Canali et al. reported the immobilization of chiral salen ligands on gel-type poly(styrene-divinylbenzene) resins.[514] Supported salen-Mn(III) complexes **185** have been used as the catalysts in the asymmetric epoxidation of dihydronaphthalene and indene using *m*-chlorobenzoic acid as the oxidant and 4-methylmorpholine *N*-oxide as the activator. The gel-type resin catalyst proved to be quite inactive, probably as a result of the formation of oxo-bridged dimer known to be problematical in this catalysis. In contrast, a macroporous resin catalyst displayed a high chemical activity, with only a low enantioselectivity (~20% ee).

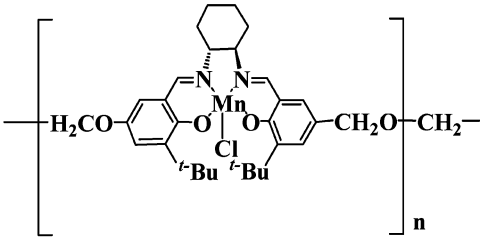
Table 26. Recycling for the Enantioselective Epoxidation of 2,2′-Dimethyl-Chromene Using NaClO/4-PPNO as Oxidant by Complex 183[a]

entry	cycle	time (h)	yield (%)	ee (%)
1	fresh	3	82	91
2	1	4	80	87
3	2	4.5	80	85
4	3	4.5	79	84
5	4	4.5	78	83

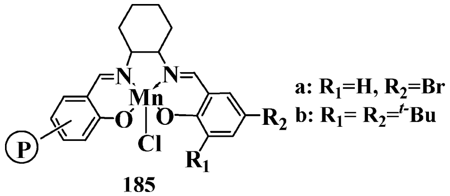
[a] Adapted from refs 513 with permission. Copyright 2000 The American Chemical Society.



183



184



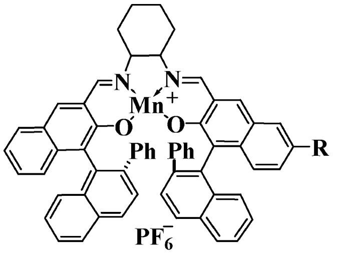
185

In 2002, Smith et al. claimed the immobilization of Katsuki-type salen-Mn on the modified Merrifield's resin through a single bonding.[515] In this synthesis, the complex **186**, an analogue of Katsuki complex **60**, was chosen as the target complex for the attachment onto a polymer. This choice was mainly based on the following reasons: (a) no supported Katsuki-type complexes were prepared previously to reveal their properties, (b) Katsuki-type complexes showed a higher enantioselectivity for the epoxidation of certain alkenes than Jacobsen-type ones,[121] (c) Katsuki-type complexes are bulky molecules and less prone to the oxidative dimerization,[516] (d) steric restriction may also render the ligand more stable against the decomposition, (e) owing to only a single site for the attachment of complex onto the support, all the catalytic sites could behave in a similar manner, (f) the hydroxyalkyl group would allow the occurrence of the attachment onto different supports, and (g) there would be a need of developing new procedures to overcome the challenges involved in the successful synthesis of **186**. Unfortunately, attempts to form a simple ether link between a model compound and benzyl chloride, with an appropriate use of complex, produced a mixture containing dibenzyl ether, which could have achieved an additional cross-linking in the polymeric version, thus resulting in a design instead to form an ester link between a model compound and polystyrene carboxyl chloride coming from the conversion of Merrifield's resin.[517] The resulting catalyst could be reused six times with a sustainable ee value up to 94% (Table 27).

Table 27. Asymmetric Epoxidation of 1,2-Dihydronaphthalene Catalyzed by Katsuki-type Salen-Mn Immobilized on Modified Merrifield's Resin[a]

entry	reused times	Mn (mmol %)	alkene (mmol %)	yield (%)	ee (%)
1	first	1.8	18	37	ca. 94
2	second	1.7	17	30	ca. 94
3	third	1.0	10	70	ca. 94
4	fourth	0.9	69	38	ca. 93
5	fifth	0.6	6	70	ca. 90
6	sixth	0.5	5	50	ca. 90

[a] Adapted from ref 515 with permission. Copyright 2002 The Royal Society of Chemistry.

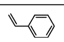
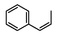
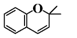
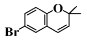
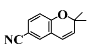
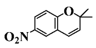


R=$CH_2CH_2CH_2OCOC_6H_4$—Ⓟ

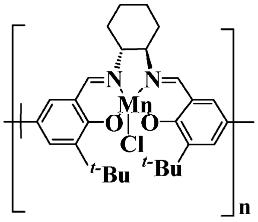
186

In 2002, Song et al. synthesized a new recyclable poly-salen-Mn (III) complex **187** through introducing two geminal methyl groups on the linking carbon atoms at 5,5′-positions, which was considered very important in inducing highly enantioselective epoxidation, with a high ee value up to 97% obtained for the asymmetric epoxidation of unfunctionalized olefins (Table 28).[518] Furthermore, poly-salen-Mn(III) catalyst **187**, very soluble in dichloromethane, slightly soluble in ether, and insoluble in hexane, was prepared according to the same procedure as that reported previously,[513] thus, granting a reasonable explanation for its easy recovery and reuse several times without any loss of enantioselectivity.

Table 28. Asymmetric Epoxidation of Olefins over Poly-Salen-Mn(III) 187[a]

Entry	Substrate	Oxidant	Yield (%)	ee (%)
1		NaClO-4-PPNO	86	37
2		MCPBA-NMO	83	51
3		NaClO-4-PPNO	87	88
4		MCPBA-NMO	87	89
5		NaClO-4-PPNO(1st)	81	96
6		NaClO-4-PPNO(2nd)	77	95
7		NaClO-4-PPNO(3rd)	75	94
8		NaClO-4-PPNO(4th)	70	96
9		NaClO-4-PPNO(5th)	63	95
10		MCPBA-NMO	73	97
11		NaClO-4-PPNO	90	95
12		MCPBA-NMO	92	97
13		NaClO-4-PPNO	96	96
14		MCPBA-NMO	89	96
15		NaClO-4-PPNO	86	94
16		MCPBA-NMO	83	95

[a] Adapted from ref 518 with permission. Copyright 2002 The Royal Society of Chemistry.

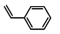
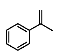
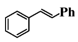
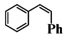


187

3.3.2. Silica-Supported Salen Complexes

Silica supports have high thermal and mechanical stability compared to polymers, and covalent attachment of chiral catalyst on silica has proven to be one of the best methods for immobilization. In 2001, Choudary et al. successfully anchored chiral salen-Mn (III) complexes on silica gel (**188**−**194**) through a covalent attachment of salen ligand using a chloropropyl spacer and subsequent complexation with manganese.[30] Good yields albeit low ee values were achieved for the asymmetric epoxidation of olefins in the presence of terminal oxidant, such as iodosylbenzene and *m*-CPBA, and a cooxidant NMO (Table 29).

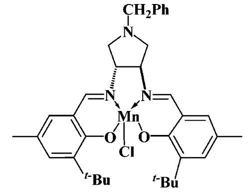
Table 29. Asymmetric Epoxidation of Olefins Catalyzed by 188−194[a,b]

Entry	Substrate	Catalyst	Oxidant	Yield (%)	ee (%)
1		**188**	*m*-CPBA	98	16
2		**189**		92	15
3		**190**		80	7
4		**191**		85	n.d.
5		**192**		82	n.d.
6		**193**		64	n.d.
7		**204**		22	n.d.
8		**189**	PhIO	80	9
9		**189**	*m*-CPBA	93	20
10		**189**		62	14
11		**189**		78	36

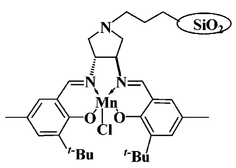
[a] Adapted from ref 30 with permission. Copyright 2001 Springer. [b] n.d.: not determined.

3.3.3. MCM-41-Supported Salen Complexes

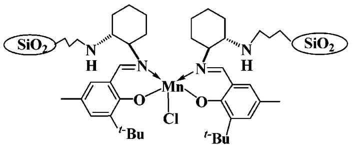
Organosilane-modified mesoporous materials have been prepared by a solvent evaporation method using C_{16}TMABr surfactant as the template under mild and acidic conditions. Mesoporous materials synthesized by using the solvent evaporation method show a fully



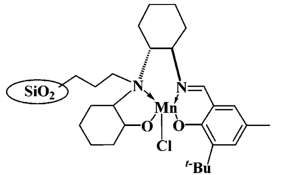
188



189



190



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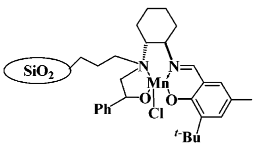

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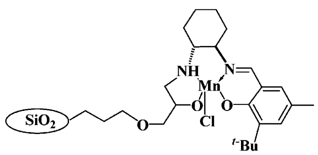
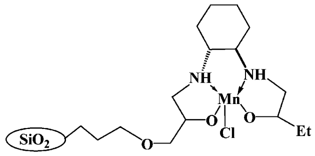
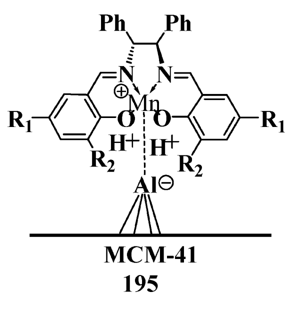


193



194

disordered pore system, but those obtained under hydrothermal conditions have highly ordered pores. Since MCM-41 possesses a large surface area (~1000 $m^2\ g^{-1}$) and uniform mesopores with a controllable diameter of 2−10 nm, it is expected as a desirable material for catalytic applications. However, in most cases, siliceous mesoporous materials do not have sufficient intrinsic activity as catalysts, and thus many studies have concentrated on introducing catalytically active sites, such as metals, metal ions, and metal complexes, into mesoporous silica.[459,519] The most popular method for the introduction of active sites is the direct hydrothermal (DHT) method; however, this method cannot ensure the incorporation of active species into the mesopore of MCM-41, usually accompanied by some contractions of channels during wet impregnation.[520] Accordingly, several groups have developed other efficient methods, such as grafting,[24,521,522] and template ion exchange (TIE).[523] In 1999, Kim et al. carried out the immobilization of new tetradentate chelates of bis-Schiff bases **195** onto mesoporous MCM-41 by a TIE method.[493]

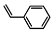
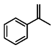


a: R_1=H, R_2=OCH_3
b: R_1=CH_3, R_2=CPh_3

195

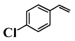
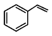
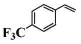
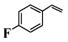
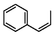
Although the salen ligand with an appropriate size (10−11 Å) trapped in the supercage (13 Å) of zeolite Y cannot escape through the pore opening (7 Å), this encapsulation method could be unsuitable for the MCM-41 system because of its one-dimensional large pore (~30 Å). Optically active salen-Mn (III) complexes in the cationic form have been found to be efficient catalysts for the asymmetric epoxidation of simple alkenes;[524] however, these bulky chiral salen ligands are too large to form in the supercage of zeolite Y. Instead, the ion-exchange ability of MCM-41 mesoporous material makes it capable of anchoring the chiral salen ligands in the cationic form as the heterogeneous catalyst, without any steric hindrance effect. Thus-prepared catalysts have been used for the asymmetric epoxidation of styrene and α-methylstyrene to obtain a high level of enantioselectivity as shown in Table 30. Although such an immobilization can sometimes enhance the activity of homogeneous catalysts, a common problem encountered in the asymmetric catalysis is the decrease of enantioselectivity upon undergoing heterogenization. Indeed, all the heterogenized catalysts developed very recently for the epoxidation of unfunctionalized alkenes exhibited considerably lower[14,36,483] or no higher[12,35] enantioseletivity than their homogeneous counterparts. However, Zhou et al. in 1999 claimed that the heterogenization of a homogeneous catalyst could largely improve the enantioselectivity of epoxidation of unfunctionalized alkenes (Table 31), in which the alkene epoxidation with PhIO was catalyzed by a chromium binaphthyl Schiff base complex **196** immobilized on MCM-41(m) that is a modified MCM-41 with a pore size of 36 Å.[525] Impor-

Table 30. Asymmetric Epoxidation of Styrene and α-Methylstyrene Catalyzed by Chiral Salen-Mn 195[a]

Entry	Substrate	Catalyst	Tempt.(°C)	Yield (%)	ee (%)
1		**195a**	0	82	27
2		**195b**	0(1st)	76	66
3		**195b**	0(2nd)	78	64
4		**195b**	0(3rd)	75	64
5		**195b**	−80	66	84
6		**195b**	0	56	38
7		**195b**	−80	47	54

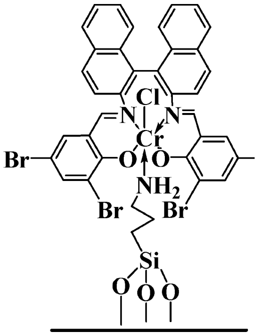
[a] Adapted from ref 493 with permission. Copyright 1999 Springer.

Table 31. Asymmetric Epoxidation of Alkenes with PhIO over 196-MCM-41 at 20 °C[a]

Entry	Substrate	Content of **196** (wt%)	Yield (%)	ee (%)
1		0.5	42	60
2		1.8(1st)	59	65
3		1.8(2nd)	62	66
4		1.8(3rd)	62	68
5		1.8(4th)	23	49
6		1.8(5th)	21	20
7		1.8(0 °C)	61	67
8		3.6(1st)	55	58
9		3.6(5th)	30	48
10		3.6(free complex, 0 °C)	48	63
11		1.8	38	55
12		1.8	31	63
13		1.8	32	56
14		1.8	32	73
15		1.8(5th)	43	54
16		1.8(5th, 0 °C)	52	62

[a] Adapted from ref 525 with permission. Copyright 1999 The Royal Society of Chemistry.

tantly, this catalyst could be reused several times without a decrease of enantioselectivity; however, a recently reported salen-Mn(III)-MCM-41 catalyst suffered from an abrupt loss of 40% ee merely for the first reuse. As anticipated, attempts to immobilize **196** onto the unmodified MCM-41, which lacks $-NH_2$ groups, have failed. Additionally, to make clear whether the environment, inside or outside the channels, is responsible for the enhancement of chiral induction, the complex **196** was anchored inside the channels of another modified MCM-41, designated MCM-41 (m-in), whose external surface was passivated with Ph_2SiCl_2, through the same surface-bound tether of terminal $-NH_2$ groups as used in MCM-41 (m).[526] Under identical conditions, with *p*-chlorostyrene as the substrate, both **196**−MCM-41 (m-in) and **196**−MCM-41 (m) catalysts afforded the corresponding epoxide in almost the same yield and ee value, showing that the environment inside the channels of the support led to the enhancement of chiral induction.



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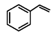
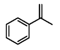
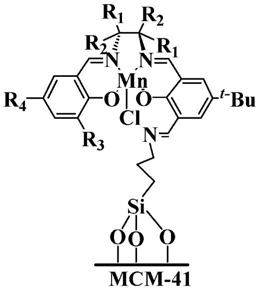
As revealed above, most of the research deals with the immobilization of chiral salen ligands either by condensing unsaturated olefin groups in the salen structure with styrene and divinylbenzene or by impregnating. But a few reports involve the subsequent anchoring by reacting a functionalized ligand with reactive groups of organic and inorganic compounds (MCM-41), step by step.[18,527] It is possible to synthesize various unsymmetrical chiral salens and to immobilize them onto inorganic supports, such as MCM-41 and silica, by a new multistep grafting method using diformylphenol as a building block of salen structure. In 1999, Kim et al. carried out the immobilization of salen-Mn (III) complexes **197** on MCM-41 by a multistep grafting method.[18] The resulting catalysts afforded a high level of enantioselectivity for the epoxidation of unsubstituted olefins, such as styrene and α-methylstyrene, as shown in Table 32.

Table 32. Asymmetric Epoxidation of Styrene and α−Methylstyrene with *m*-CPBA/NMO Using Homogeneous and Heterogenized Salen-Mn(III) Complexes 197 as Catalysts[a]

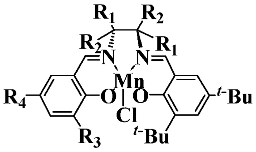
Entry	Substrate	Catalyst	Tempt.(°C)	Conv. (%)	ee (%)
1		**197a**	0	75	65
2		**197a-MCM-41**	0	75	70
3		**197a-MCM-41**	−78	77	86
4		**197b**	−78	84	59
5		**197b-MCM-41**	0	71	53
6		**197b-MCM-41**	−78	73	65
7		**197c**	−78	97	84
8		**197c-MCM-41**	−78	92	89
9		**197c-MCM-41**	0	64	87
10		**197d**	−78	98	43
11		**197d-MCM-41**	−78	90	51
12		**197d-MCM-41**	0	51	47
13		**197e**	−78	88	54
14		**197e-MCM-41**	−78	80	61
15		**197a**	−78	81	43
16		**197a-MCM-41**	−78	74	56
17		**197b**	0	98	51
18		**197b-MCM-41**	0	67	59
19		**197b-MCM-41**	−78	70	72
20		**197c**	−78	90	43
21		**197d**	−78	97	66
22		**197e**	−78	92	69

[a] Adapted from ref 18 with permission. Copyright 1999 Elsevier.



197-MCM-41

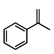
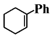
a: R_1=Ph, R_2=H, R_3=^{t}Bu, R_4=^{t}Bu
b: R_1=-$(CH_2)_4$-, R_2=H, R_3=^{t}Bu, R_4=^{t}Bu
c: R_1=Ph, R_2=H, R_3=H, R_4=H
d: R_1=-(CH_2)4-, R_2=H, R_3=H, R_4=H
e: R_1=-$(CH_2)_4$-, R_2=H, R_3=OMe, R_4=H



197

In 2002, Park et al. grafted chiral salen-Mn (III) catalysts **198** onto the surface of organosilane-functionalized MCM-41 to catalyze the epoxidation of styrene and *cis*-stilbene.[527] The results showed that low-temperature enhanced the enantioselectivity (43−51% ee) of anchored chiral salen-Mn (III) catalyst significantly, slightly higher than 35−46% ee of the homogeneous counterpart. In addition, it was observed that the conversion of olefin and the ee value of epoxide increased with the decrease of substrate/catalyst molar ratios. In all cases, homogeneous and heterogenized chiral salen-Mn (III) complexes achieved almost the same selectivity. This grafting method has opened up one route to synthesize various solid-supported salen catalysts. In 2002, Xiang et al. reported a new immobilization of chiral salen-Mn complex **199** through the complexation of Mn with oxygen atoms of phenoxyl groups grafted on the surface of MCM-41.[528] Salen-Mn complex was active and enantioselective for the epoxidation of α-methylstyrene with NaClO as the oxidant in CH_2Cl_2.[528] Once the sample was anchored onto MCM-41, the activity of the resulting heterogeneous catalyst showed an obvious decrease for the same substrate, but the heterogeneous enantioselectivity was markedly higher than that obtained for the free complex (Table 33), comparable to the results reported by Kim.[193] In the same year, Bigi et al. reported the synthesis of heterogenized salen-Mn (III) complexes **200** and **201**, which have an unsymmetric salen ligand bonded covalently onto either amorphous silica or MCM-41 through a new triazine-based single linker, to maximize the conformational mobility of the complex necessary for a high level of asymmetric induction.[31] They hypothesized that this spacer, longer than those usual ones and partially rigid to prevent possible chain folding, would allow facile access of olefinic substrate to the metal center located sufficiently away from the solid surface. A high enantioselectivity

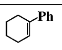
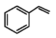
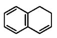
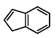
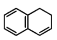
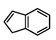
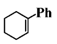
Table 33. Asymmetric Epoxidation of Nonfunctional Olefins Catalyzed by Homogeneous Salen-Mn Complex 199 and by Heterogeneous Salen-Mn Complex 199-MCM-41[a]

Entry	Substrate	Catalyst	Solvent	Conv. (%)	ee (%)
1		**199**	CH_2Cl_2	96	56
2		**199-MCM-41**	CH_2Cl_2	60	72
3		**199-MCM-41**	Acetone	99	67
4		**199-MCM-41** (1st)	EtOH	99	70
5		**199-MCM-41** (2nd)	EtOH	99	70
6		**199-MCM-41** (3rd)	EtOH	98	73
7		**199**	CH_2Cl_2	93	78
8		**199-MCM-41**	EtOH	0	0

[a] Adapted from ref 528 with permission. Copyright 2002 The Royal Society of Chemistry.

of up to 84% ee was obtained for the asymmetric epoxidation on these heterogenized catalysts on amorphous silica and MCM-41, and the catalysts could be effectively recycled. As revealed by the results in Table 34, the structure of the solid support did not exert an impact on the activity of the catalyst with low Mn-loading, and after three cycles the recovered MCM-41-supported catalyst just showed a progressive reduction of yield and ee value as often observed for other supported catalysts.[16,20,428,529] Similar results were also obtained with the supported catalyst **201** on silica gel, in which the second cycle led to a modest reduction of yield with a small drop of ee value from 82 to 78% already. This synthesis strategy may provide a general route to anchor salen-Mn (III) complexes onto the surface of mesoporous solid materials.

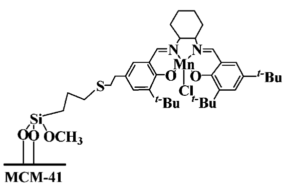
Table 34. Asymmetric Epoxidation of Olefins Catalyzed by 200 and 201[a,b]

Entry	Substrate	Catalyst	Mn loading (mmol.g^{-1})	Yield (%)	ee (%)
1		**200**	n.d.	71	89
2		**200-MCM-41**	0.3	40	26
3			0.1	31	34
4		**201-KG60**	0.06	42	82
5		**201-MCM-41**	0.1	49	82
6			0.08	38	84
7			0.06	36	84
8		**201-MCM-41**	0.06	70	30
9			0.06	48	45
10			0.06	68	70
11		**201-KG60**	0.1	55	43
12			0.1	73	65
13			0.1	43	81

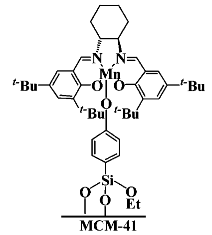
[a] Adapted from ref 31 with permission. Copyright 2002 The Royal Society of Chemistry. [b] n.d.: not determined; KG-60: one kind of commercial amorphous silica.

3.3.4. Helical Polymer-Supported Salen Complexes

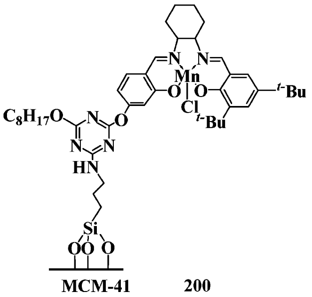
Helices are essential and fundamental motifs widely present in nature; thus, artificial helical polymers have attracted much attention in the area of asymmetric catalysis.[530,531] However, helical structures of these polymers are quite difficult established even by exhaustive spectroscopy, which is primarily ascribed to the uncertainty of directionality of the junction between the monomer units. In 2002, Meade et al. synthesized poly(binaphthyl salen-Mn) complexes **202** from a 3,3′-diformyl-binaphthol derivative, α,ω-diamine and $Mn(OAc)_2$.[532] Although for the asymmetric epoxidation of olefins these polymer complexes showed the enantioselectivity as low as about 17% ee, the chiral space provided by helical **202** was observed to be more effective than that of polymer unit models.



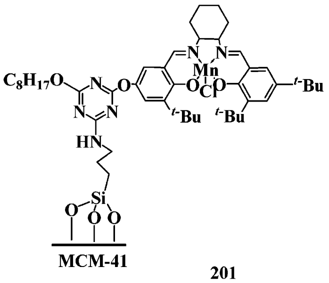
198



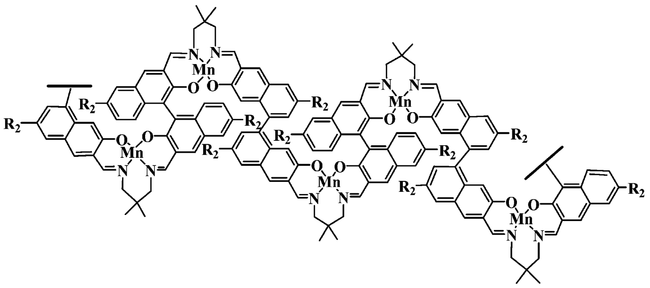
199



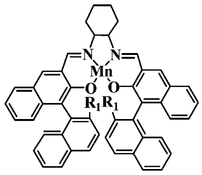
200



201



202



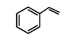
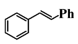
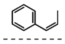
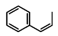
R_1=n-C_4H_9, R_2= n-C_8H_{17}

3.3.5. "Ship-in-a-bottle" Trapped Salen Complexes

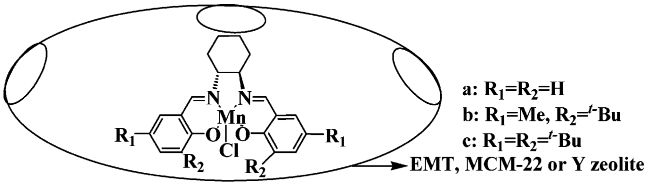
"Ship-in-a-bottle" trapped catalysts, in which the metal complex is attached to a solid surface by a covalent or ionic bond, possess many advantages over homogeneous or conventional heterogeneous catalytic systems. The main feature of this type of catalyst is the host−guest interaction that is neither covalent nor ionic. In fact, all the enantioselective enzymatic systems in nature contain in common the incorporation of the active sites into a confined space defined by the tertiary protein structure. Zeolite cage structures are attractive hosts for the design of this kind of hybrid system.[533,534] The guest is trapped in the zeolite cage by restricted pore openings, which will, in principle, retain all the properties of the homogeneous complexes. The superiority of these catalysts to homogeneous ones is attributed to enhanced thermal stability, easy separation from the reaction mixture, reliability, and environmental compatibility.[535] As compared with conventional heterogeneous catalysts, the main advantage of "ship-in-a-bottle" trapped catalysts is the enhanced accessibility of catalytically active metal complexes, due to the ability to move freely within zeolite's cavities. In addition, the "ship-in-a-bottle" trapped catalysts are unlikely to leach because of the nature of their immobilization, i.e., the physical entrapment in zeolite pores. However, it is likely that the crystalline host bestows the catalyst with both size and shape selectivity and the stabilizing effect on the organometallic complexes; therefore, multimolecular deactivation pathways, such as the formation of μ-oxo or peroxo-bridged species, will be rendered impossible.[536,537] The practical application of "ship-in-a-bottle" entrapped complexes is most likely to be in the fine chemical processes, where catalyst performance may outweigh the cost. However, this immobilization technology is beset with two problems, i.e., one challenge is to find a zeolite with a large enough pore size and the other is the method of encapsulation, which involves the assembly of complexes within the pores.

In 1997, Ogunwumi et al. reported the assembly and entrapment of asymmetric salen-Mn catalysts, i.e., both chloro[*N*,*N*′-bis(3-*tert*-butyl-5-methylsalicylidene) cyclohexanediamine] Mn(III) **203a**, and chloro[*N*,*N*′-bis(salicylidene) cyclohexane diamine] Mn(III) **203b**, in the cages of crystalline EMT zeolite, which has a hexagonal faujasite structure.[35,538,539] Hypercages of EMT are accessible through three 12-membered ring windows with free dimensions of 6.9 × 7.4 Å and two 7.4 Å circular apertures, while hypocages contain only three windows. Dimensions of chiral salen-Mn complexes are ca. 15 Å for **203a** and 13 Å for **203b**, preventing the escape of the assembled complexes from the cages within zeolite. Novel heterogeneous catalyst **203a**-EMT has been used in the asymmetric epoxidation of aromatic alkenes with NaClO to obtain high ee values up to 88% (Table 35).

Table 35. Asymmetric Epoxidation of Olefins Catalyzed by 203a-EMT[a]

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**203a**-EMT	15	34
2			29	20
3			47	88
4		**203a**	95	35
5			97	80

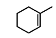
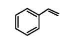
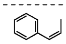
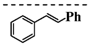
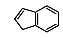
[a] Adapted from ref 35 with permission. Copyright 1997 The Royal Society of Chemistry.



203

The pore structure of Y zeolite consists of almost spherical 13 Å cavities interconnected tetrahedrally through small apertures of main pore channels of 7.4 Å. Molecular modeling predicts that both salen ligand *trans*-(*R*,*R*)-1,2-bis (salicylideneamino)-cyclohexane and the corresponding salen-Mn(III) complex can easily accommodate inside the supercages of Y zeolite. Analogously, it is also predicted that Jacobsen's catalyst having four *tert*-butyl groups on phenyl rings does not fit into the supercages of Y zeolite. In 1997, Sabater et al. obtained success in trapping a chiral salen-Mn(III) complex **203a** inside the supercages of zeolite Y.[36] When the thus-prepared catalyst was applied in the asymmetric epoxidation of olefins, moderate enantioselectivities were obtained (Table 36). Lower reaction rates obtained with heterogeneous salen-Mn/Y catalysts compared to their homogeneous counterparts could have been anticipated in view of restrictions imposed on the diffusion of substrates and products by micropores of Y zeolite, especially when the reaction was run at low temperatures. Both 1-methylcyclohexene and styrene achieved a poor ee, in agreement with previous data obtained on the Jacobsen's catalyst.[86,87] This poor enantioselectivity can be interpreted as a result of the cointeraction of two unfavorable factors, including the occurrence of a noncatalyzed unselective epoxidation in the liquid phase and the existence of an residual amount of uncomplexed Mn^{2+} acting as the catalytic sites.

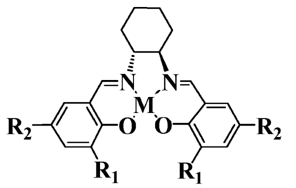
Table 36. Asymmetric Epoxidation of Alkenes with NaClO Catalyzed by 203a−Y

Entry	Substrate	Catalyst	Conv. (%)	ee (%)
1		**203a**	37	8
2		**203a-Y**	11	5
3		**203a**	47	27
4		**203a-Y**	40	20
5		**203a**	28	74
6		**203a-Y**	5	58
7		**203a**	23	41
8		**203a-Y**	11	24
9		**203a**	30	60
10		**203a-Y**	20	50

[a] Adapted from ref 36 with permission. Copyright 1997 The Royal Society of Chemistry.

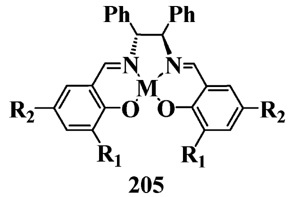
In 2001, Gbery et al. developed a novel method for trapping homogeneous catalysts within the supercages (7.1 × 18.2 Å) of zeolite MCM-22, which was used as the heterogeneous catalyst for the enantioselective epoxidation of α-methylstyrene with NaClO.[540] The synthesis of zeolite MCM-22 proceeded a layered precursor, which facilitated the intercalation of Jacobsen's catalyst between layers. Upon drying and heating of the sample to 280 °C, the layers condensed to form a crystalline MCM-22 structure. Thus, the metal complex was encapsulated during the condensation of layers with no possibility of escape through the openings of 4.0 × 5.4 Å. The reaction results showed that not only was the trapped catalyst more active than the homogeneous one, but the selectivity for epoxide was also improved. The most remarkable performance of this "ship-in-a-bottle" trapped catalyst is to improve the enantioselectivity from 51% ee for the homogeneous one to 91.3% ee. The successful immobilization of Jacobsen's catalyst in MCM-22 (**203c-MCM-22**) has dramatically provided a good example of heterogeneous chiral catalysts with an enhanced activity and enantioselectivity. This encapsulation route has displayed a certain advantage over other heterogeneous immobilizations but is not suitable for the case of using MCM-41 as the host support because the one-dimensional large pore system of MCM-41 cannot effectively confine the guest ligands in the mesopores.

In 2001, Schuster et al. reported the encapsulation of various transition-metals (V, Cr, Mn, Fe, Co, Rh, Ir) complexes of salen ligands **204** and **205** into specially modified zeolitic host materials.[541] And the thus-immobilized complexes had been tested in the diastereoselective epoxidation of (−)-α-pinene in the liquid phase in an autoclave at room temperature under elevated pressures using O_2 as the oxidant. In most cases, a conversion of 100% could be realized, and the best results were 100% conversion and 96% chemoselectivity for the epoxide with 91% diastereomeric excess achieved in the presence of the entrapped [(*R*,*R*)-(*N*,*N*′)-bis (3,5-di-*tert*-butyl-salicylidene)-1,2-diphenylethylene-diamino] cobalt(II). Computer simulations have proposed that the reaction took place inside the pore system, i.e., (−)-α-pinene was able to diffuse through microporous entrances of the carrier material. A comparative investigation between new heterogeneous catalysts and homogeneous counterparts proved that the entrapment of organometallic complexes did not result in a considerable loss of activity and selectivity. The use of molecular oxygen instead of NaClO as the oxidant was preferred, as the corresponding catalytic system is more environmentally benign than the Jacobsen's system.[120]



204

a: R_1=H, R_2=H
b: R_1=^{t}Bu, R_2=^{t}Bu
c: R_1=^{t}Bu, R_2=Me
d: R_1=^{t}Bu, R_2=H

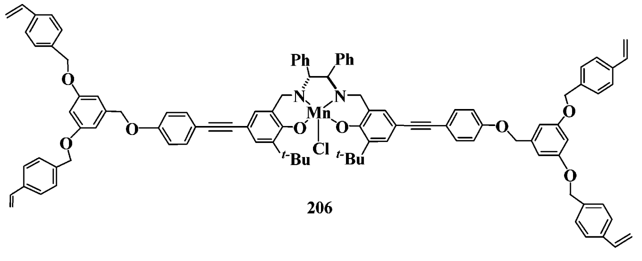


205

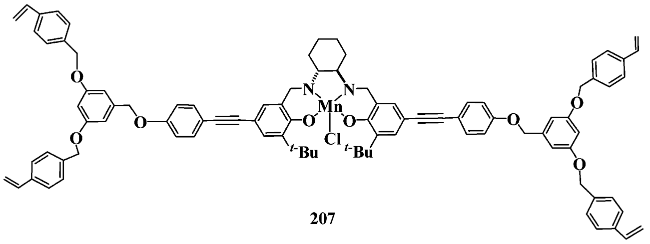
a: R_1=^{t}Bu, R_2=^{t}Bu
b: R_1=^{t}Bu, R_2=Me
c: R_1=^{t}Bu, R_2=H

3.3.6. Dendrimer-Supported Salen Complexes

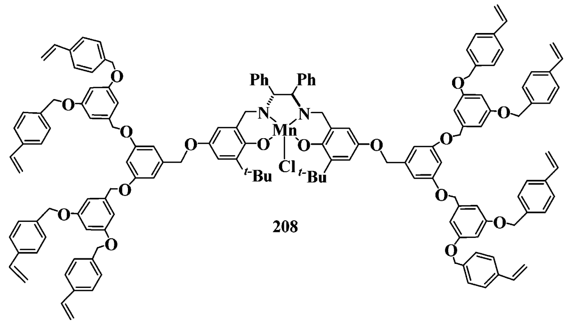
Heterogeneous catalysts prepared in the preceding ways are often less active than their homogeneous counterparts due to the hindered diffusion of substrates and products into or out of catalytic centers on the support.[12] Dendrimers, highly branched macromolecules, are of great interest to be used as the carriers of functional groups.[32,33] In analogy with the immobilization of styryl-derivatives of TADDOL and BINOL ligands by a suspension copolymerization with styrene, Sellner et al. in 2001 used dendritically modified salen cross-linkers to prepare recyclable catalysts **206**−**211** for enantioselective epoxidations.[33] However, those catalysts displayed an appreciable loss in the activity and stereoselectivity during the reactions, even after reloading fresh polystyrene-bound manganese chloride, which could be attributed to the oxidation of salen moieties (the salen cores) into the hydroquinone structure during the reactions.



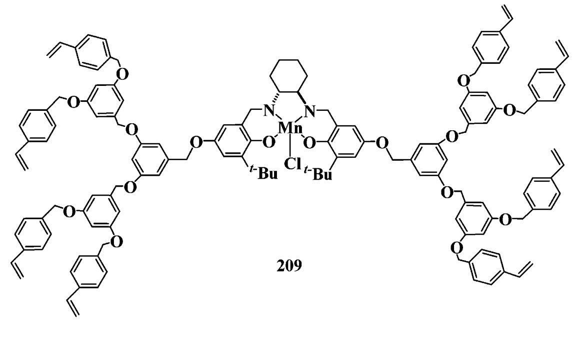
206



207



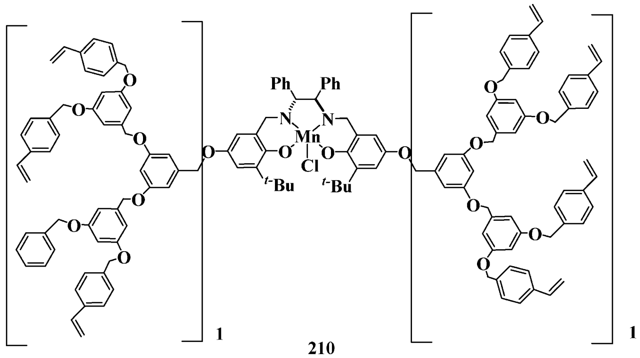
208



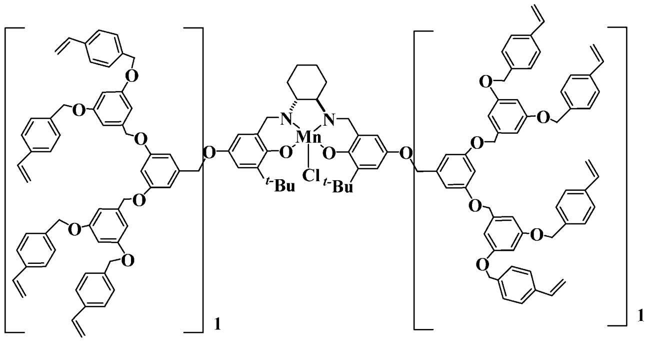
209

3.4. Phase Transfer Catalysis Systems

Phase transfer catalysis (PTC), developed initially in the mid-1960s, uses a typical organic salt, such as a quaternary ammonium salt, to transport inorganic ions into an organic phase. Highly efficient transformation in PTC processes,[542,543] i.e., the transport from an aqueous phase to an organic phase or from an organic phase to an aqueous phase, may be because PTC systems such as those containing quaternary ammonium salts, can be easily converted to the corresponding active species (ammonium hydrogen peroxides) in the presence of a mild and inexpensive oxidant such as H_2O_2. As illustrated in Scheme 12, the epoxidation of electron-deficient

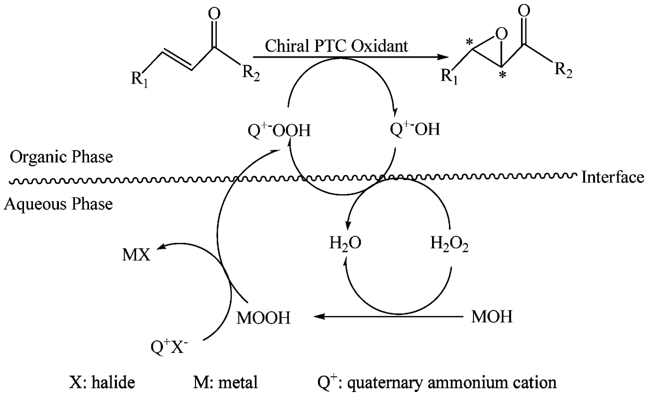


210



211

Scheme 12. Mechanism of Catalytic Epoxidation of Enones[a]



[a] Adapted from ref 565 with permission. Copyright 2002 Elsevier.

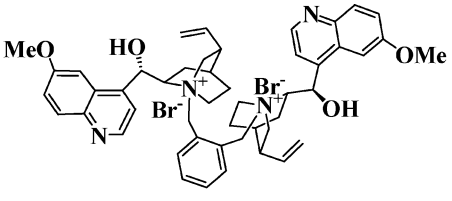
olefins (enones) could be smoothly accomplished in aqueous media to produce the desired products via a 1,4-addition and the subsequent cyclization in the presence of catalytic amount of chiral quaternary salts, with water as only a side product.[234,544−567]

Environmental protection and safety concerns are spurring the search for alternatives to the most common organic solvents. Accordingly, the use of novel reaction media, such as supercritical fluids,[547] ionic liquids,[548]and liquid biphase systems (aqueous/organic)[549] as well as purely organic phases[550] in synthetic organic chemistry, is presently investigated thoroughly.[551] In addition to offering the possibility of green technology for chemical industries, these reaction media sometimes promote reactions, accompanied by the increase of selectivity related to the unique solvation environment, which is not attainable in common organic solvents.[552,553] Perfluorocarbons are, in particular, promising in this regard because of their distinctive chemical and physical properties, such as low dielectric constant, chemical inertness, nontoxicity, and low miscibility with common organic solvents and water.[554,555] As a follow up to the pioneering work of Horváth et al.,[556] a number of reagents and catalysts bearing appropriate perfluoroalkyl substituents (fluorous compounds) have been prepared and used in “fluorous biphase chemistry”. In particular, fluorous biphasic catalytic systems have exhibited several advantages over classical homogeneous ones, such as easy product separation and catalyst recycling. The fluorous biphasic approach can now stand the comparison with extensive applications of immobilized chiral catalysts, at least in the case of asymmetric epoxidation of unfunctionalized alkenes. Electron-deficient olefins such as α,β-unsaturated ketones, which are less reactive with usual oxidants, require the enabling of highly enantioselective epoxidations. Thus, another methodology, i.e., PTC, is required to suit these types of substrates.

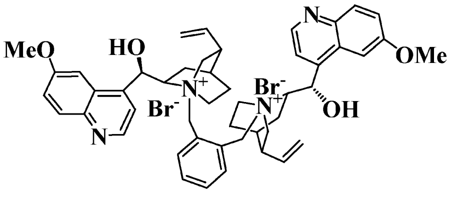
3.4.1. Conventional Phase Transfer Catalysis (PTC)

PTC systems are one of the most useful methodologies for practical syntheses because of mild reaction conditions, which enable the use of water as a cosolvent, safety, and operational simplicity.[557,558] The most common phase-transfer reagents used for the asymmetric epoxidation of enones are alkylated cinchona alkaloids. A handful of papers have reported the applications of other chiral phase-transfer salts for the asymmetric epoxidations, which, however, exhibited low ee ($\leq$37%).[559,560] Wynberg et al. first investigated the catalytic use of a chiral phase-transfer salt in a biphasic Weitz-Scheffer epoxidation in the mid-1970s.[561] Later a series of analogous research studies were published. Kawaguchi et al. carried out the phase-transfer epoxidation of cyclohexenone to obtain 63% ee over three C_2-symmetric catalysts, **212**, **213**, and *N*-(9-fluorenyl)quininium bromide (**214**) with alkaloids cinchonidine and cinchonine, respectively.[238] Phase-transfer catalysts **215a** and **215b**, derived from *N*-benzylation of quinine and quinidine respectively,[238] afforded moderate enantioselectivity (0−54% ee) for the catalytic asymmetric epoxidation of a wide range of enones with aqueous H_2O_2, TBHP, or sodium hypochlorite. In an isolated example, an ee value of 78% was achieved by Harigaya, who used the catalyst **215a** in the epoxidation of 2-aryl naphthoquinone.[238] Additionally, Taylor et al. reported their work in this field, in which *N*-benzyl-cinchonidinium chloride (**215c**) showed the best effects for the epoxidation of enone (**216**) in 32% yield and 89% ee.[562,563]

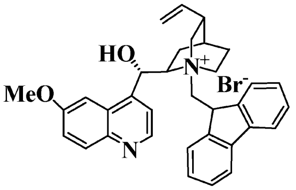
Recently, Arai et al. reported the catalytic asymmetric epoxidation of chalcone and its derivatives promoted by a new class of quaternary ammonium salts **(215c−m**) derived from cinchonine, which reacted as the phase-transfer catalyst in the presence of a safe oxidant, H_2O_2, in a two-phase system under mild reaction conditions.[564] Distinctly, *N*-(4-iodobenzyl) cinchoninium bromide (**215d**) allowed the highly stereoselective oxidation of chalcone derivatives, although the ee values were lower than those of alkyl-substituted enones. Intriguingly, the optical rotation of epoxides obtained over the cinchonine-derived



212



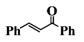
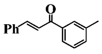
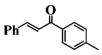
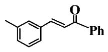
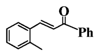
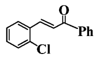
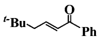
213



214

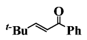
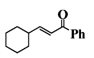
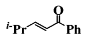
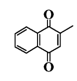
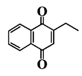
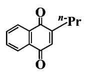
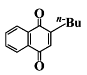
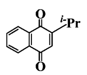
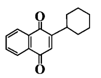
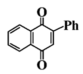
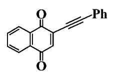
catalyst was opposite to that from Lygo's cinchonine-derived catalyst **216**. In 2002, Arai et al. reported again the asymmetric epoxidation of trans- and cis-enones, promoted by a chiral PTC reagent derived from cinchonine or quinidine under mild aqueous media.[565] As shown in Tables 37 and 38, the epoxidation enantioselectivity for chalcone was strongly dependent on the structures of substituents and PTC reagents. For example, the PTC catalysts, which contain the electron-withdrawing groups such as $-NO_2$ on the C_4-position, afforded the corresponding epoxide with good ee, while the electron-donating groups such as the MeO− group or the nonsubstituted one led to a significantly low ee value. The most important functional groups to induce a high ee value include both the benzyl group and the chiral secondary alcohol moiety. Chiral quaternary salts, derived from cinchonine and quinidine, have been proven to be considerably efficient PTC catalysts for the asymmetric epoxidation of enones. The potential advantage of this methodology is that aqueous hydrogen peroxide can be used as a mild, cheap, and environmentally benign oxidant.

Table 37. Asymmetric Epoxidation of Various Enones under PTC Using H_2O_2 as the Oxidant and n-Bu_2O as the Solvent[a]

Entry	Substrate	Catalyst	Time (h)	Yield (%)	ee (%)
1		**215e**	26	72	73
2		**215e**	74	72	1
3		**215f**	37	61	72
4		**215g**	60	70	4
5		**215k**	40	61	0
6		**215h**	88	24	3
7		**215i**	41	68	65
8		**215j**	36	56	77
9		**215d**	37	97	84
10		**215d**	36	99	87
11		**215d**	36	95	89
12		**215d**	64	100	92
13		**215d**	64	96	67
14		**215d**	47	88	65
15		**215d**	68	41	57

[a] Adapted from ref 565 with permission. Copyright 2002 Elsevier.

Table 38. Asymmetric Epoxidation of Various Enones under PTC Using H_2O_2 as the Oxidant and $CHCl_3$ as the Solvent[a]

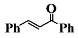
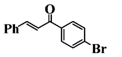
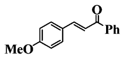
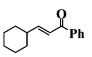
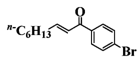
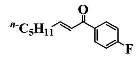
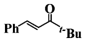
Entry	Substrate	Catalyst	Time (h)	Yield (%)	ee (%)
1		**215d**	43	41	55
2		**215d**	37	70	53
3		**215d**	43	82	42
4		**215d**	1	94	10
5		**215e**	4	76	11
6		**215l**	1	93	26
7		**215m**	1	82	31
8		**215m**	16	99	41
9		**215m**	7	93	43
10		**215m**	21	87	44
11		**215m**	5	93	70
12		**215m**	23	60	64
13		**215m**	23	47	76
14		**215m**	21	84	40

[a] Adapted from ref 565 with permission. Copyright 2002 Elsevier.

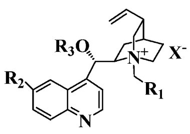
In 1998, Lygo et al. reported the preparation of catalysts **217** and **218** from cinchonidine and cinchonine, notably different from that of Wynberg-type catalysts **215a** and **215b**.[566,567] In the structure of catalysts **217** and **218**, a 9-anthracenylmethyl group was incorporated in place of the benzyl group on the nitrogen of quinuclidine, while a benzyl group on the secondary alcohol was still retained. In the presence of sodium hypochlorite as the stoichiometric oxidant, these catalysts mediated the epoxidation of a wide range of substituted chalcones and alkyl-substituted enones with 100% of diastereoselectivity and 82−88% ee (see Table 39). More recently, Corey et al. have shown that the catalyst **217** could, in high efficiency, catalyze the epoxidation of a range of enones with over 90% ee at −40 °C, using potassium hypochlorite as the stoichiometric oxidant.[235]

Trichloroisocyanuric acid (TCCA, **219**) is a safe, inexpensive, and efficient oxidant for the oxidation

Table 39. Asymmetric Epoxidation of Various Enones under PTC[a]

Entry	Substrate	Catalyst	Tempt. (°C)	Yield (%)	ee (%)
1		**217**	25	90	86
2		**217**	−40	96	93
3		**217**	25	99	88
4		**217**	−40	92	93
5		**217**	25	87	82
6		**217**	−40	70	95
7		**217**	−40	85	94
8		**217**	25	89	84
9		**217**	−40	90	91
10		**217**	25	40	85

[a] Adapted from refs 566 and 567 with permission. Copyright 1998 and 1999 Elsevier.



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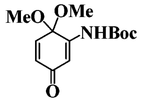
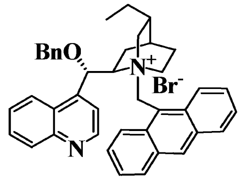
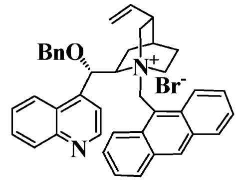
a: R_1=Ph, R_2=OMe, R_3=H, X=Cl
b: R_1=Ph, R_2=NO_2, R_3=H, X=Cl
c: R_1=Ph, R_2=R_3=H, X=Cl
d: R_1=4-I-Ph, R_2=R_3=H, X=Br
e: R_1=4-CF_3-Ph, R_2=R_3=H, X=Br
f: R_1=4-NO_2-Ph, R_2=R_3=H, X=Br
g: R_1=4-OMe-Ph, R_2=R_3=H, X=Cl
h: R_1=4-F-Ph, R_2=R_3=H, X=Br
i: R_1=4-Cl-Ph, R_2=R_3=H, X=Br
j: R_1=4-Br-Ph, R_2=R_3=H, X=Br
k: R_1=4-CF_3-Ph, R_2=H, R_3=Allyl, X=Br
l: R_1=2,4-Me_2-Ph, R_2=OMe, R_3=H, X=Br
m: R_1=α-Naphtnyl, R_2=OMe, R_3=H, X=Cl



216



217



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of ethers, thioethers, aldehydes, acetals, and alcohols.[568] Ye et al. reported first the asymmetric epoxidation of olefins in the presence of chiral quaternary ammonium salt **220** as the phase-transfer catalyst using TCCA as the oxidant in good yields with excellent enantioselectivity of up to 96% ee (see Table 40).[569,570] The reaction proceeded to afford the desired products only in nonpolar solvents such as dichloromethane and toluene and at a low temperature in favor of high enantioselectivity.

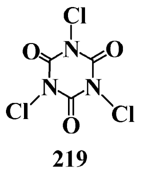

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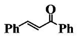
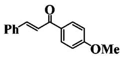
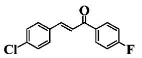
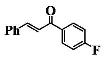
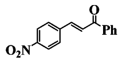
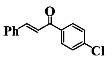
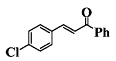
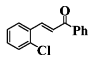
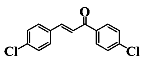
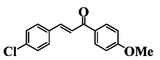
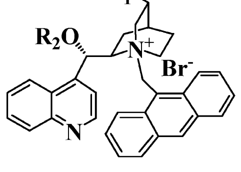
Table 40. Asymmetric Epoxidation of Enones Employing 220b as PTC and TCCA Used as the Oxidant[a]

Entry	Substrate	Yield (%)	ee (%)
1		90	96
2		82	90
3		92	96
4		79	99
5		83	99
6		85	93
7		97	99
8		89	64
9		93	79
10		74	98

[a] Adapted from ref 569 (Copyright 2003 The Royal Society of Chemistry) and ref 570 (Copyright 2004 Wiley-VCH) with permission.

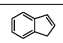
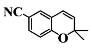
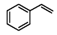
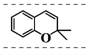
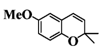
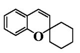


a: R_1=Vinyl, R_2=Ph
b: R_1=Et, R_2=Ph
c: R_1=Et, R_2=Allyl

220

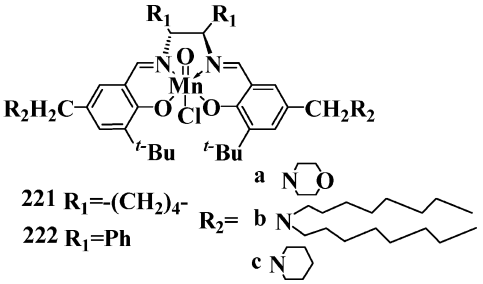
Among several catalyst systems described already, chiral salen-Mn (III) complexes have been identified to be highly enantioselective in the epoxidation of nonfunctionalized cis- or cyclic alkenes, with NaClO as the oxidant and pyridine *N*-oxide derivatives as the additives, under biphasic reaction conditions.[86−88] Furthermore, it has been reported that the use of *N*-oxides, especially 4-phenyl pyridine *N*-oxide (4-PPNO)[571,572] and 4-phenylpropyl pyridine *N*-oxide (PPPNO) as the proximal additive, not only stabilizes the catalytically active intermediate species Mn(V)-oxo but also acts as the phase-transfer reagent in transporting NaClO from the aqueous phase to the organic phase. Comparatively, 4-PPNO and PPPNO have imparted the best results, but their high cost and easy degradation under reaction conditions severely limit their extensive use. In 2002, Kureshy et al. developed new analogues of the Jacobsen's catalysts, **221** and **222**, which have inbuilt the phase transfer capability due to methylene aminoalkyl groups at 5,5′-positions of the substituted salicylaldehyde moiety, so that simple *N*-oxides could be used effectively.[573,574] These catalysts showed a high reactivity with a NaClO oxidant, even when 4-phenylpyridine *N*-oxide (PyNO) and 1,4-dioxane (1,4-D) were added as the axial bases, thus avoiding the requirement of expensively substituted pyridine *N*-oxide under biphasic conditions. Chromene and derivatives were chosen as the model substrates, as their epoxides are rather useful in the synthesis of

Table 41. Asymmetric Epoxidation of Unfunctionalized Alkenes with NaClO Catalyzed by 221 and 222 with Various Additives[a,b]

Entry	Alkene	Catalyst	Additive	Time (h)	Yield (%)	ee (%)
1		**221a**	PyNO	6	99	69
2		**222a**		5	99	68
3		**221b**		5	97	71
4		**222b**		4.5	98	84
5		**221c**		6.5	>99	53
6		**222c**		7	99	68
7		**221a**	PyNO	6	>99	>99
8		**222a**		7	99	97
9		**221b**		6	>99	99
10		**222b**		6.5	99	98
11		**221c**		6.5	>99	99
12		**222c**		7	99	97
13		**221a**	PyNO	5	>99	39
14		**222a**		5.5	99	50
15		**221a**	4-PPNO	30	42	40
16		**222a**		24	60	51
17		**221a**	PPPNO	24	60	48
18		**222a**		24	50	55
19		**221a**	MorNO	6.5	>99	36
20		**222a**		7	99	50
21		**221a**	1,4-D	6.5	98	38
22		**222a**		7	99	50
23		**221a**	DMSO	5.5	98	38
24		**222a**		5.5	99	49
25		**221b**	PyNO	4.5	99	36
26		**222b**		1.5	99	51
27		**221c**		5.5	99	39
28		**222c**		6	99	54
29		**221b**	PyNO	9	>99	81
30		**222b**		9.5	>99	75
31		**221b**	PyNO	3.5	>99	87
32		**222b**		5	>99	65
33		**221b**	PyNO	6	>99	87
34		**222b**		7	>99	78

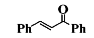
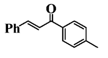
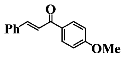
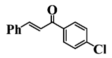
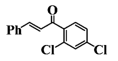
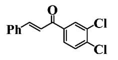
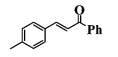
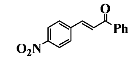
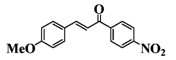
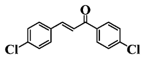
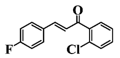
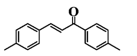
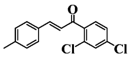
[a] Adapted from refs 573 and 574 with permission. Copyright 2002 Elsevier. [b] 1,4-D=1,4-dioxane, MorNO=morpholine *N*-oxide.

selective potassium channel activator drugs.[138] As shown in Table 41, high conversion (>99%) was obtained for all chromenes (Entries 1–8) in a short reaction time, over the complex catalysts **221b** and **222b**, which induced 98–99% ee for 6-cyano-2,2-dimethylchromene. More importantly, although the catalysts were recycled several times with some loss of activity, the ee values remained unaltered.

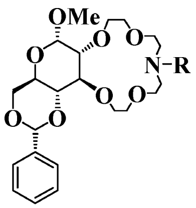


In 2004, Bakó et al. described the asymmetric epoxidation of chalcone in the presence of glucose- and mannose-based lariat ether catalysts **223** and **224**, respectively.[575] Crown ether **223f** proved to be an effective catalyst under phase transfer conditions, as shown in Table 42, in which the yield and the enantioselectivity were significantly affected by *N*-substituents. For example, the lowest ee values (ca. 8–11% ee) were achieved in the case of catalysts **223b**, **223c**, and **223i** containing an *n*-butyl group, a benzyl group, and a diphenylphosphinobutyl *N*-substituent, respectively. The catalysts **223f** (γ-hydroxypropyl substituent) and **223d** (β-hydroxyethyl substituent) showed the best results with 92% ee and 81% ee, respectively, but only 41% ee was detected using δ-hydroxybutyl derivative (**223h**). This proposed that the length of the chain connecting hydroxy group to nitrogen atom played an important role in the asymmetric induction and that the optimal chain length was three carbon atoms as in the case of **223f**. Crown ethers (**224**) containing a mannopyrano side unit could also be used in the above reaction with moderate enantioselectivity.

Table 42. Epoxidation of Substituted Chalcones by *t*-BuOOH in the Presence of Catalyst 223f at Room Temperature[a]

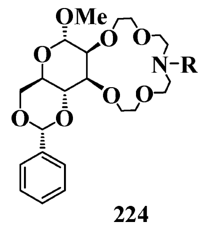
Entry	Substrate	Yield (%)	ee (%)
1		78	73
2		62	81
3		53	82
4		57	80
5		82	47
6		61	66
7		57	77
8		38	79
9		29	27
10		66	77
11		77	3
12		64	76
13		82	42

[a] Adapted from ref 575 with permission. Copyright 2004 Georg Thieme Verlag.



a: R=H
b: R=Bu
c: R=Ph
d: R=(CH$_2$)$_2$OH
e: R=(CH$_2$)$_2$OCH$_3$
f: R=(CH$_2$)$_3$OH
g: R=(CH$_2$)$_3$OCH$_3$
h: R=(CH$_2$)$_4$OH
i: R=(CH$_2$)$_4$P(O)Ph$_2$

223



a: R=(CH$_2$)$_2$OH
b: R=(CH$_2$)$_3$OH
c: R=(CH$_2$)$_3$OCH$_3$
d: R=Ts
e: R=H

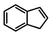
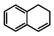
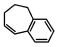
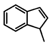
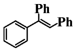
224

3.4.2. Fluorous Biphase Systems (FBS)

Chemical inertness of perfluorocarbons fluids (composed of only C and F, or C, F, and O, or C, F, and N) has bestowed very low solvent interactions with almost all the organic compounds. However, perfluorocarbons possess some peculiar physicochemical properties, such as thermo- and pressure-controlling miscibility with common organic solvents. Perfluorocarbons are almost immiscible in the solvents such as acetonitrile or toluene at room temperature under atmospheric pressure, thus forming a two-phase system, in which the catalyst soluble in the fluorous phase is segregated from reagents and products during the whole process. Since the phase miscibility can be sharply increased with the increase of temperature and pressure, the system will work under homogeneous conditions during the reaction stage but will be restored to two-phase at the end of the reaction. This imposes some potential advantages on perfluorocarbons catalysts over classical homogeneous ones, such as easily effective separation and recycling of the catalyst.[554] Enantioselective transformations were recognized as an extremely interesting domain for the application of FBS at a very early stage of evolvement.[556] It was suggested that, besides helping the recovery and reuse of precious chiral reagents or catalysts, the unique solvation environment and possibly positive effects on the selectivity of reactions provided by perfluorocarbons might have been unforeseen.[576]

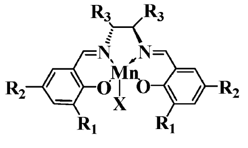
Substantiation of these hypotheses calls for experimental data, which, consequently, requires the synthesis of chiral metal complexes suited to FBS. Perfluoroalkylated tetradentate ligands are suitable for the preparation of catalysts used in the FBS catalysis, on the condition that fluorine loading is higher than 60% (wt %).[37,577−580] The present results also confirm that the classification of perfluorocarbons into special solvents or normal organic solvents could be finely tuned by a slight difference in the fluorine content of perfluorocarbons. The empirical rule of F ≥ 60% is a crucial criterion to define the FBS system in the case of tetradentate ligands and can also be conveniently applied for other classes of compounds.[581] C_2-nitrogen-based ligands were chosen as the most promising candidates to develop efficient and selective fluorous chiral catalysts by Pozzi,[582] who synthesized four substituted salen catalysts (**225**) containing perfluorinated alkyl chains, effective for the enantioselective epoxidations carried out under biphasic (fluorous/organic) conditions. The catalyst could be readily recovered from the fluorous layer by phase separation techniques. As shown in Table 43, a high enantioselectivity up to 90% ee was obtained for indene substrate with acceptable recycling numbers of the catalyst; however, for other substrates only low ee values were achieved, even if those substrates were structurally close to indene as in the cases of dihydronaphthalene and benzosuberene. Low levels of enantioselectivity were tentatively ascribed to inadequate electronic insulation of the metal site from the strong electron-withdrawing effect of perfluoroalkyl substituents and to low steric hindrance imposed by perfluoroalkyl substituents locating in 3,3′- and 5,5′-positions of ligands. The second generation of fluorous salen-Mn(III) complexes including **225e** and **225f** was thus synthesized, in which the 3,3′-positions of the ligands are occupied by *tert*-butyl substituents and perfluoroalkyl-substituted aryl moieties attached to the 5,5′-positions. Note that the biaryl frame offers an additional flexibility in salen ligands. The overall number of R_F ponytails can be increased to the criterion by seeking the preferential solubility in perfluorocarbons, and the proper spacers can be inserted between perfluoroalkyl substituents and the core structure of the ligand, to tune the electron-withdrawing effect finely. The biaryl frame is also expected to exert some impact on the three-dimensional structure of the catalyst and to generatemore steric hindrance, further enhancing the enantioselectivity. Nowadays, it is widely accepted that the fluorine content of at least 60 wt % is a basic requirement for a catalyst or reagent to achieve the preferential solubility in perfluorocarbons. However, the behaviors of **225e** (56.9%F) and **225f** (57.9%F) showed an interesting exception to this rule, as reported recently.[583]

Table 43. Asymmetric Epoxidation of Various Alkenes Catalyzed by Chiral Salen-Mn Complexes under Fluorous Two-Phase Conditions[a,b]

Entry	Substrate	Catalyst	Yield (%)	ee (%)	Cycle number
1		**225c**	83	92	n.d.
2		**225c**	73	89	1
3		**225d**	77	90	n.d.
4		**225d**	75	92	1
5		**225c**	70	10	n.d.
6		**225c**	70	9	1
7		**225d**	70	13	n.d.
8		**225d**	61	10	1
9		**225f**	77	50	n.d.
10		**225f**	67	49	1
11		**225f**	63	45	2
12		**225f**	19	40	3
13		**225c**	92	7	n.d.
14		**225d**	91	12	n.d.
15		**225f**	92	68	n.d.
16		**225f**	92	66	1
17		**225f**	83	64	2
18		**225f**	43	60	3
19		**225f**	91	58	n.d.
20		**225f**	87	53	1
21		**225f**	76	40	2
22		**225f**	45	25	3
23		**225f**	98	77	n.d.
24		**225f**	99	77	1
25		**225f**	82	76	2
26		**225f**	42	57	3
27		**225f**	98	87	n.d.
28		**225f**	96	85	1
29		**225f**	92	83	2
30		**225f**	80	71	3

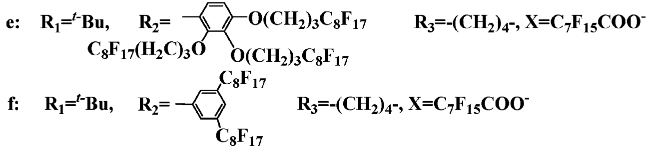
[a] Adapted from ref 582 with permission. Copyright 1999 Wiley-VCH. [b] n.d.: not determined.

In summary, the FBS approach offers several distinct advantages over other heterogeneous catalysis systems, such as remarkably increased stability of the catalyst against leaching, relatively high activity, easy separation, and effective recycling, but wide industrial use of this system is hampered by possible environmental drawbacks resulting from the use of perfluorocarbons and by the high cost of the ligands used in FBS.



225

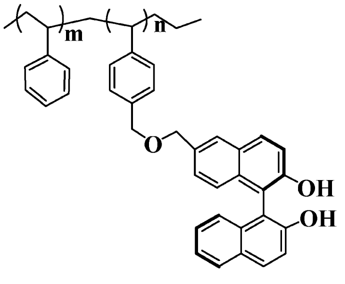
a: R_1=H, R_2=C_8F_{17}, R_3=-$(CH_2)_4$-, X=Cl
b: R_1=H, R_2=C_8F_{17}, R_3=Ph, X=Cl
c: R_1=C_8F_{17}, R_2=C_8F_{17}, R_3=-$(CH_2)_4$-, X=Cl
d: R_1=C_8F_{17}, R_2=C_8F_{17}, R_3=Ph, X=Cl



3.5. Other Heterogeneous Systems

3.5.1. Supported BINOL Systems

With the growing importance of polymer-supported catalysts, considerable attention has been focused on the use of both soluble and insoluble macromolecules, such as chiral 1,1′-bi-2-naphthol (BINOL) for the immobilization of a range of asymmetric catalysts.[584,585] Very recently, Jayaprakash et al. succeeded in anchoring the enantioselective epoxidation catalysts onto the polymeric ligands containing BINOL.[586] The resulting polymer-supported La–BINOL and Yb–BINOL catalysts were employed to catalyze the epoxidation of chalcone and benzalacetone (see Table 44). In all cases, chiral La and Yb complexes generated from the ligands **226** and **227** were found to produce epoxides with a high enantioselectivity and could be reused many times with almost a constant high level of enantioselectivity. Additives such as Ph_3P=O and Ph_3As=O bound strongly to the central lanthanum ion and facilitated the de-oligomerization of oligomeric species to a catalytically superior monomeric complex, which could restrict the active sites sterically, thereby resulting in an enhanced selectivity.



226

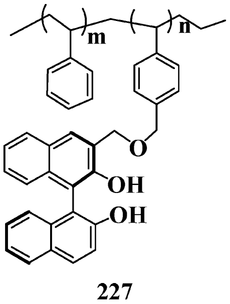


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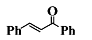
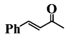
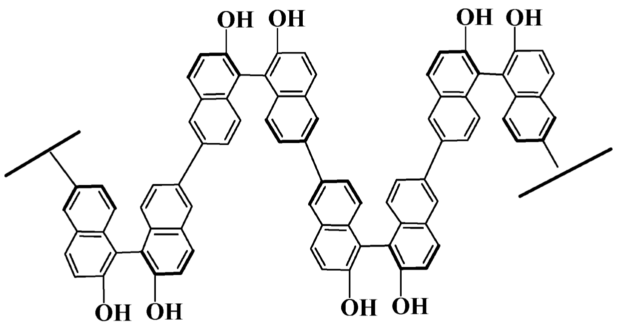
Table 44. Asymmetric Epoxidation of Enones over Polymer-Supported La–BINOL and Yb–BINOL and Ph_3P=O (15 mol %) as the Additive[a–g]

Entry	Substrate	Oxidant	Catalyst	Time (h)	Yield (%)	ee (%)
1[a]		CMHP	**La-226**	22	30	65
2		CMHP	**La-226**	20	96	98
3		TBHP	**La-226**	20	97	83
4[a,b]		CMHP	**La-226**	20	61	62
5[b]		CMHP	**La-226**	67	88	85
6[c]		CMHP	**La-226**	67	91	84
7		TBHP	**La-226**	18	86	82
8[a,d]		TBHP	**Yb-226**	23	62	86
9		TBHP	**Yb-226**	24	59	87
10[b]		TBHP	**Yb-226**	38	49	82
11[d]		TBHP	**Yb-226**	20	58	91
12[b,d]		TBHP	**Yb-226**	22	44	91
13[a,d]		TBHP	**Yb-226**	22	52	84
14[d]		TBHP	**Yb-227**	24	48	84
15		TBHP	**Yb-227**	22	69	88
16[b]		TBHP	**Yb-227**	22	48	85
17[e]		TBHP	**Yb-227**	18	90	88
18[b,e]		TBHP	**Yb-227**	18	62	89
19[e,f]		TBHP	**Yb-227**	36	60	88

[a] Without Ph_3P=O. [b] Reused one time. [c] Reused one time with 4 Å MS. [d] With 4 eq water. [e] With Ph_3P=O (7.5 mol %). [f] Reused in the third time. [g] Table adapted from ref 584 with permission. Copyright 2000 The American Chemical Society.

In 2003, polymer-supported chiral BINOL ligands **228**–**231** were applied to coordinate with Yb–$(O\text{-}^iPr)_3$ or La–$(O\text{-}^iPr)_3$ producing the epoxidation catalysts.[587] In the presence of additives such as water and PPh_3=O, the catalysts afforded epoxides in good yield with a moderate enantioselectivity of up to 73% ee. The presence of a large polymer architecture around catalytic sites renders the catalyst an enhanced stability. Ligand **229** was also found to be rather effective in affording the products in high yields with good selectivity. Ligand **230** exhibited enhanced selectivity in the asymmetric epoxidation of enones catalyzed by zinc complex, due to a synergic effect between adjacent catalytic sites.[355] La–BINOL complex with a ratio of metal to ligand of 2:3 yielded the chalcone epoxide in 95% yield and 35% ee value. The use of a 1:1 complex generated at 40 °C with an additive of 15 mol % PPh_3=O resulted in enhanced selectivity up to 62% ee, consistent with the observations made by Shibasaki et al.[241] Further increasing the additive concentration decreased the selectivity.



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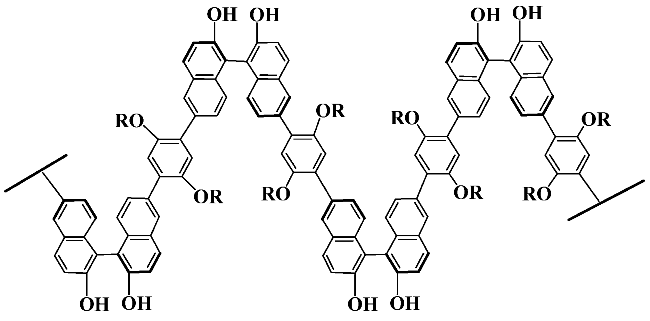
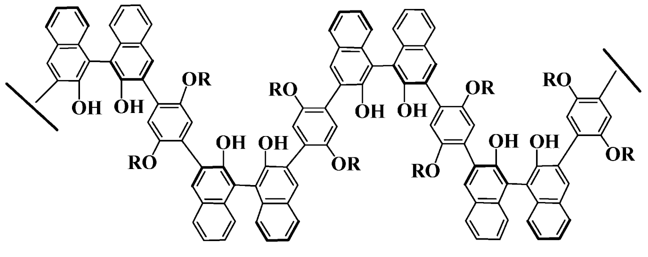
3.5.2. Polyamino Acids Catalysis Systems

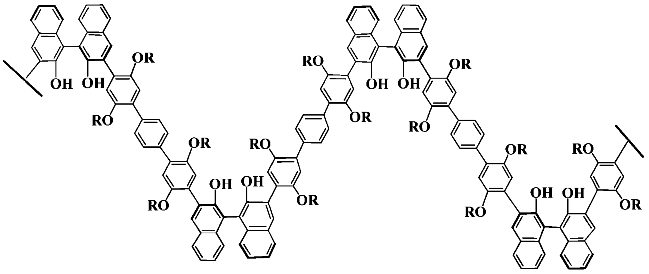
The work published by Juliá et al. in the early 1980s expanded the usefulness of polyamino acids as the heterogeneous catalysts, particularly for the asymmetric epoxidations.[588–600] Subsequently, the catalytic properties of various oligopeptides were carefully investigated. From those studies, it was established that increasing the α-helix structure enhanced the stereoselectivity in the oxidation, while



229



230 R=n-C_6H_{13}



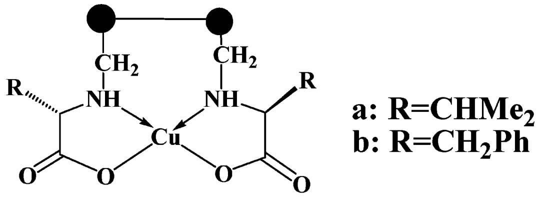
231 R=n-C_6H_{13}

greater β-pleated sheet structure deteriorated the optical purity of the product. Lasterra-Sánchez further expanded the range of substrates epoxidizable in this manner and initiated a study to elucidate both the action mode and the reaction mechanism.[253,601,602] The development of the polyleucine catalyst has made a notable advance, enabling the practical application for the asymmetric epoxidations. The first improvement was indebted to the use of 1,3-diaminopropane as an initiator of the polymerization. However, the key advance lies in the immobilization of polyleucine on cross-linked aminomethylpolystyrene (CLAMPS), which was first carried out by Itsuno et al. in 1990.[603] This CLAMPS polymer, prepared from impure *N*-carboxyanhydrides, was robust and induced an improved enantioselectivity, distinctly revealing the great impact of the amino end of the polymer on the enantioselectivity. Although the parts of the polymer far from the amino end could have very little effect on the enantioselectivity, they were not unimportant and probably were responsible for setting up the correct chiral architecture.[604]

In 1999, Geller et al. reported the asymmetric epoxidation of α,β-unsaturated ketones catalyzed by a robust, readily recycled, highly active catalyst, namely, polyleucine adsorbed onto silica, which showed a significantly higher activity than the nonadsorbed polyleucine.[594] Recycled catalyst still exhibited equally high catalytic activity comparable to a freshly prepared one, with a considerably high level of ee of ≥93%. Furthermore, the workup procedure for recycling the catalyst was very simple, such that the loss of catalyst was minimized. In general, the yields were higher with silica-supported polyamino acid catalyst than those obtained with unmodified polyleucines.

3.5.3. Polymer-Supported Amino Acid Cu(II) Complexes

Although considerable success has been achieved in the asymmetric epoxidation of special substrates, such as styrene or cis/trans-alkenes using homogeneous chiral porphyrins and salen complexes as demonstrated amply by Collman, Jacobsen, and others,[98,121,605−607] no notable success has been reported in the epoxidation of simple straight-chain aliphatic terminal olefins.[393,608] In 2003, Valodkar et al. made a report regarding the asymmetric epoxidation of aliphatic terminal olefins catalyzed by polymer-supported amino acid Cu(II) complexes **232**−**234** using *m*-chloroperbenzoic acid as the oxidant, for which the maximal ee value was obtained at the temperatures 25−40 °C.[609] Neither the cross-linking density (6−8%) of the polymer backbone nor the nature of amino acid (L-valine or L-phenyl alanine) had any major influence on the enantioselectivity. High conversion and moderate enantioselectivity were observed for the epoxidation of 1-octene, 1-hexene, 2-methyl-1-pentene, and 4-methyl-1-pentene. For the catalytic epoxidation of 1-octene as the model substrate over **232**, even after three cycles the catalyst still exhibited high conversions (96−98%) with a slight decrease of enantioselectivity from 32 to 27% ee along with the increase of cycles. The reaction was sensitive to the temperature, and the observed enantioinduction could be interpreted in terms of the trajectory of olefin accessible to the active catalyst.



232 8%●-[(L-PA)$_2$Cu]

233 8%●-[(L-Val)$_2$Cu]

234 6%●-[(L-Val)$_2$Cu]

3.5.4. Nanocrystalline MgO

The heterogenization of homogeneous catalysts represents a complicated conceptual transfer from molecular chemistry to surface metallorganic chemistry, eventually to achieve a single-site catalyst with the retention of activity and enantioselectvity. In 2004, Choudary et al. successfully evolved a single-site catalyst from a complex system based on nanocrystalline MgO, since the nanomaterial holds a well-defined shape and size.[610] Nanosized heterogeneous catalysts afforded chiral epoxy ketones with moderate to good yields and impressive enantioselectivities for the asymmetric epoxidation of chalcones coming from the Claisen-Schmidt condensation of benzaldehydes and acetophenones. And nanocrystalline MgO (NAP−

Table 45. Homogeneous and Heterogeneous Catalyst Systems

		unfunctionalized substituted olefin							functionalized substituted olefin								
		acyclic olefin				cyclic olefin			allylic alcohol				nitro alkene	enyne	α,β-carbonyl compd	alde-hyde	enol ester
		terminal	di-	tri-	tetra-	di-	tri-	tetra-	terminal	di-	tri-	tetra-					
		Homogeneous Catalyst Systems															
Sharpless	Ti								E	E	E						
	V								H	H	E	M					
porphyrin	Fe	E	L														
	Ru	S	S			S											
	Mn	L															
	Mo		L			L											
Salen	Mn	E	E	H		E	H	E						E	E		M
	Cr	S	H			S											
	Co	M	S														
	Pd	S															
	Ru	M	M			S											
BINOL	La														E		
	Yb														E		
	Sm														E		
	Gd														H		
	Ca														S		
carbonyl compd	simple ketone	L	H				S			S							
	polyhydroxyl ketone	S	E	E		H	E			H	H			E	E		H
	aldehyde		H	H		L	S			S							
iminium salts			S	M		S	S			M							
others	W/Mo	L	S														
	Li														S		
	Mg														H		
	Zn												S		E		
	Ru	S	H			M											
	MTO		M				L										
	Ni	M	L		M												
	sulfoniumylide		M													E	
		Heterogeneous Catalyst Systems															
Sharpless	Ti								H	H	S						
	Ta								H	H							
	Co									H							
porphyrin	Ru	S	S			S								S			
Salen	Mn	E	H	H		E	H										
	Cr	S	S			M											
PTC	PTC	M				E									E		
	FBS	H		H		H	H										
others	BINOL														H		
	polyamino acid														E		
	amino acid Cu	M															
	nano MgO																E
	KF/alumina														M		

[a] Blank: not reported; L: ee < 30%; M: 30% < ee < 60%; S: 60% < ee < 85%; H: 85% < ee < 95%; E: ee > 95%.

MgO) was found to be more active than both MgO (NA-MgO) prepared conventionally and commercial MgO (CM-MgO) in the condensation and epoxidation reactions. In this case, the ee value of the product was determined to be 90% for NAP−MgO, 60% for NA-MgO, and 0% for CM-MgO, respectively. The high enantioselectivity of NAP−MgO could be assigned to the presence of electron-withdrawing groups on either of the two aromatic rings in chalcone, which facilitated the formation of resonance-stable oxyanion.

3.5.5. TBHP+KF/Alumina

Although some metal-containing heterogeneous catalysts can be used for the epoxidation of electron-deficient alkenes,[611] the reactions are commonly carried out with hydroperoxides in the presence of a base.[612] Basic solids have been hardly used in the oxidation reactions,[613] and, so far, two systems have been developed to activate the oxidant with a solid base. Hydrotalcites are able to activate hydrogen peroxide by the abstraction of a proton and to generate hydroperoxide anion acting as the nucleophilic reagent for the epoxidation of electron-deficient alkenes.[614,615] Importantly, this system uses hydrogen peroxide as the oxidant, which is preferred in industry. The other system uses KF/alumina as a solid base to activate anhydrous alkyl hydroperoxides.[616,617] In 2001, Fraile et al. reported the application of two heterogeneous systems, i.e., H_2O_2+hydrotalcite and TBHP+KF/alumina in the epoxidation of two chiral alkenes bearing different electron-withdrawing groups, derived from D-glyceraldehyde.[618] The results showed that, for the epoxidation of these chiral alkenes, the system of H_2O_2+hydrotalcite presented some drawbacks, such as the generation of byproducts and the low diastereoselectivity; however, the system of TBHP+KF/alumina was highly efficient and selective with the advantage of easy workup, leading to a de of up to 50%.

4. Conclusions

This review has systematically summarized the existing homogeneous and heterogeneous catalytic systems for the asymmetric epoxidations. Although much progress has been made in recent decades, from a practical viewpoint the results cited in this review are still far from satisfaction. In many systems, there is still a large space to improve the enantioselectivity and chemoselectivity of the asymmetric epoxidations. Since chiral epoxides are very important building blocks for the synthesis of enantiomerically pure complex molecules, in particular of biologically active compounds and pharmaceuticals, more attention will still be paid to the progress of this field. Generally, in this field the heterogenization of homogeneous chiral catalysts and the development of highly efficient chiral catalysts derived from inexpensive raw materials via a convenient route will be prospective. Additionally, more detailed understanding of the mechanism should be addressed in the future, to design highly efficient catalysts for required individual reactions.

5. Appendix: A Cross-Referenced Table

Table 45 is a summary of homogeneous and heterogeneous catalyst systems.

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