CHAPTER I

INTRODUCTION

1.1 General background in asymmetric synthesis

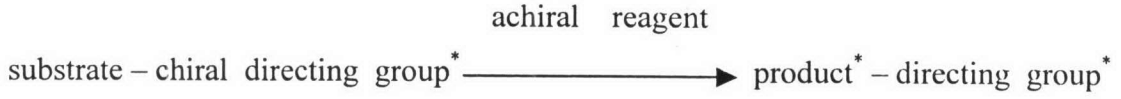
A wide range of biological and physical functions are generated through precise molecular recognition that requires the matching of their structural arrangements and geometrics. A variety of metabolic functions occur through enzymes, receptors, and other natural binding sites that recognize substrates with specific chiral geometry. In pharmaceuticals, usually only one of the possible stereoisomers shows the desired biological activity, while the others are inactive or even cause undesired side effects.

In the past, the classical resolution of racemates was the primary method used to obtain optically active compounds. Other methods involving transformations or derivatizations of available natural chiral compounds such as amino acids and carbohydrates were later developed. The use of various types of asymmetric reactions for the synthesis of enantiomerically enriched chiral compounds is currently of growing importance in organic chemistry and in the chemical industry at large.

An asymmetric synthesis usually involves a formation of a new stereogenic center in the molecule under the influence of a chiral group ultimately derived from a naturally occurring chiral compound. These synthesis may be classified into the following four classes, depending on how the chiral influence is exerted.[1]

a) First-generation or substrate-controlled method

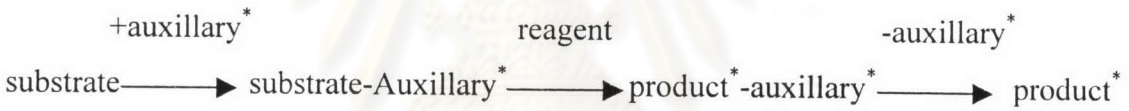
In this case, an asymmetric reaction is directed intramolecularly by a stereogenic enviroment that is presented in the chiral substrate. The formation of a stereogenic unit most often occurs by an achiral reagent reacts at a diastereotopic site controlled by a nearby stereogenic center. The overall process becomes:



The main drawback of this method is the need for an enantiomerically pure chiral starting material. The method does not produce a chiral product from an achiral substrate but merely add an addition stereogenic center to an already enantiomerically pure substrate.

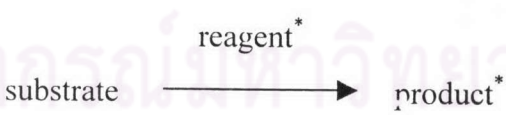
b) Second-generation or auxillary-controlled method

This approach is similar to the first-generation method in that the asymmetric control is achieved intramolecularly by a chiral group in the substrate. The difference is that the directing group, called "the chiral auxillary", is deliberately attached to an achiral substrate in order to direct the reaction and then removed from the molecule afterwards.



c) Third-generation or reagent-controlled method

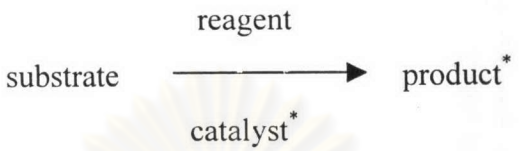
Although the second-generation method was proved to be very useful, the need to attach and remove the chiral auxillary is an unattractive feature. It can be evaded by using a third-generation method in which an achiral substrate is converted to the chiral product by chiral reagent:



Comparing with the earlier methods, this control is intermolecular. This attractive procedure is limited by the availability of the effective chiral reagents.

d) Fourth-generation or catalyst-controlled method

In the previous three classes, an enantiomerically pure compound is required in stiochiometric amounts, although in some cases it could be recovered. The fourth-generation is to use a chiral catalyst to direct the conversion of an achiral substrate to a chiral product with an achiral reagent. This control is intermolecular.



Asymmetric catalysis is the method for synthesizing optically active compound that uses small amount of chiral catalyst. It can produce natural and unnatural chiral materials in a large scale. Asymmetric catalysis is four-dimensional chemistry. The high efficiency that these reactions provide can be obtained through an optimized combination of suitable three dimensional structure mechanism.

1.2 Salens and their asymmetric catalytic properties

Salen (Figure 1.1), a tetradentate ligand is easy to synthesize and can form complexes with various transition metal ions. Many salen derivatives and their metal complexes have thus been synthesized and characterized, and gradually, their value as catalysts has become recognized. The development of chiral salen metal complexes and catalysts in the last decade has stimulated a very rapid growth in the chemistry and application of these species.[2]

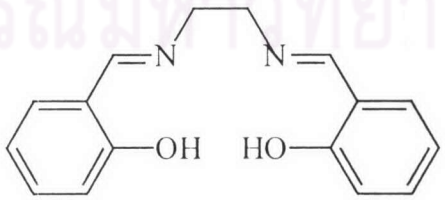
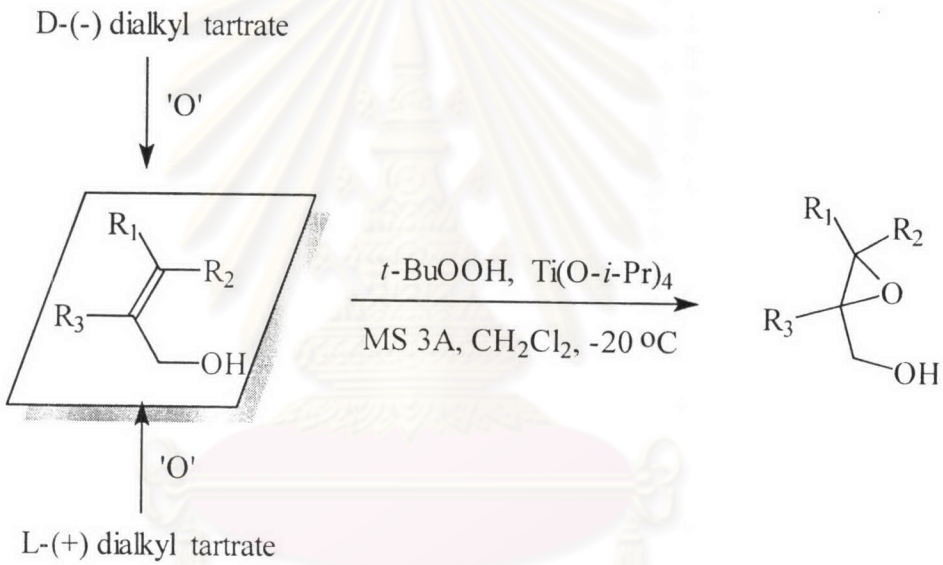


Figure 1.1 The structure of salen.

1.2.1 Asymmetric epoxidation by catalytic process

In 1980, Katsuki and Sharpless discovered asymmetric epoxidation of allylic alcohols with *t*-butyl hydroperoxide (TBHP) as an oxygen donor in the presence of tetraisopropoxytitanium ($Ti(O\textit{i}\text{-}Pr)_4$) and tartaric acid diethyl ester (DET) or the corresponding diisopropyl ester (DIPT).[3] The reactions gave epoxy alcohols with predictable absolute configurations. A variety of primary allylic alcohols were epoxidized in higher than 90% ee and in 70-90 % yield by using this catalytic system in CH_2Cl_2. The reaction was normally performed at low temperature (-30 to 0 °C) with 3 A or 4 A molecular sieves added to avoid catalyst deactivation by removing coexisting water molecules.



In 1990, Jacobsen and his group reported that chiral(salen) manganese (III) complex was an effective catalyst for the enantioselective epoxidation of unfunctionalized olefins.[4] The reactions were carried out in the air with iodosylmesitylene as an oxidant in the presence of 1-8 mol % Mn(salen) complex. As illustrated in Table 1.1, epoxidation with the chiral Mn(III) salen complex afforded high enantioselectivity with a wide range of substrate substitution patterns, as monosubstituted, disubstituted and trisubstited prochiral olefins (Figure 1.2). The best results were achieved with *cis*-disubstituted alkenes.

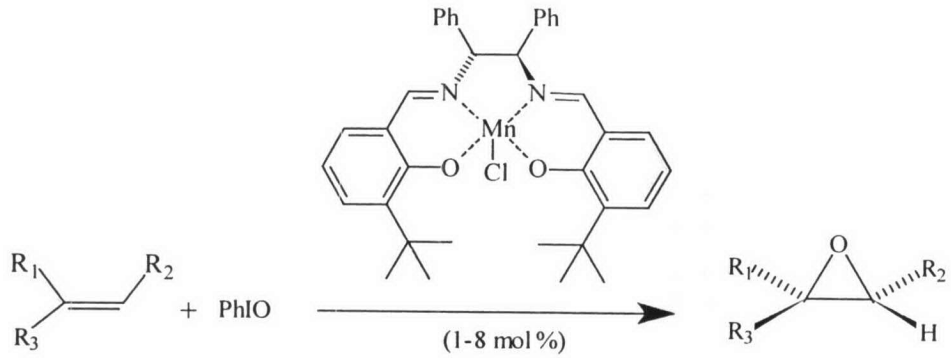
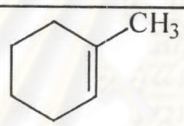
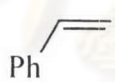
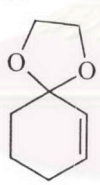
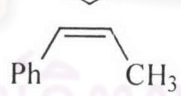
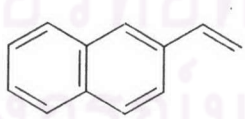
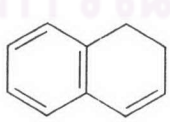
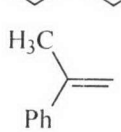


Figure 1.2 Catalytic enantioselective epoxidation of unfunctionalized olefin by Mn(III) chiral salen complex.

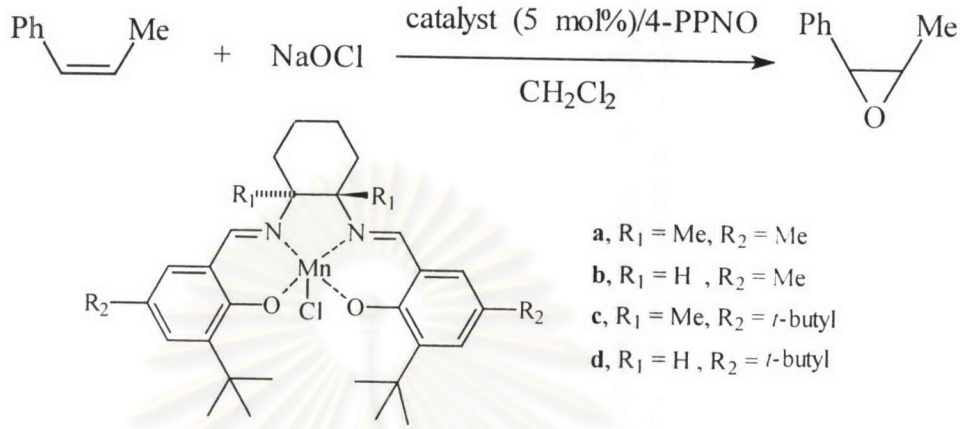
Table 1.1 Asymmetric epoxidation of representative olefins by Mn(salen) complex

Entry	olefin	% yield	% ee
1		50	59
2		75	57
3		72	67
4		52	93
5		73	84
6		72	78
7		36	30

The effect of subtituent on the aromatic ring of Jacobsen's ligand was also investigated.[5] Salen manganese complexes with a second set of *t*-butyl

groups para to the hydroxy substituent on salen gave the best results on enantioselectivity (Table 1.2).

Table 1.2 Asymmetric epoxidation of *cis*-β-methylstyrene with catalysts **a-d**



Entry	Catalyst	% yield	% ee
1	**a**	54	49
2	**b**	87	80
3	**c**	56	55
4	**d**	81	92

The influence of additive on the reaction rate, yield, and enantioselectivity of the Mn(salen) epoxidation was recognized.[6] Amine *N*–oxide was found to be the best axial coligands that help to stabilize the manganese(V)-oxo complex intermediate. Recently, Jacobsen was able to impressively substantiate the importance of additives by synthesizing the (salen) Mn complex containing a pyridine *N*-oxide unit (Figure 1.3).[7] The presence of PPNO appeared to have no influence on the reactivity of this complex.

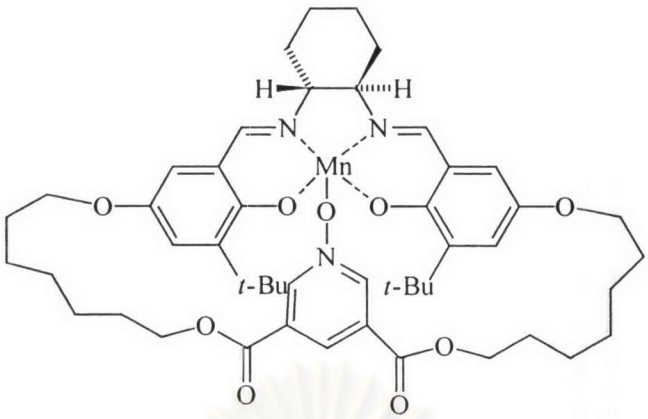
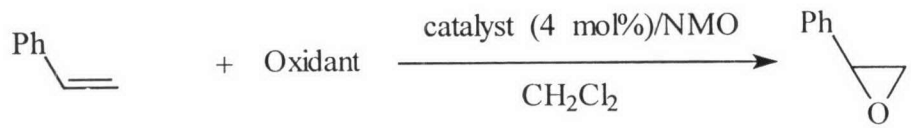
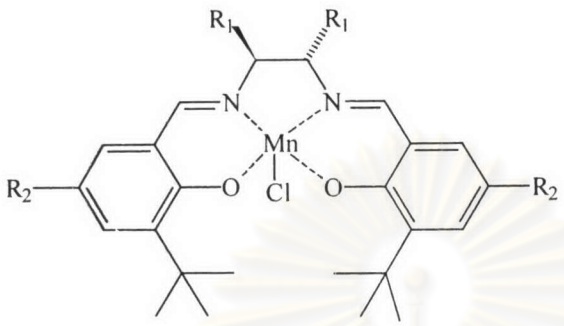


Figure 1.3 The Mn complex containing a pyridine *N*-oxide unit.

Jacobsen examined the epoxidation reaction of styrene in organic solvent such as dichloromethane in the presence of Mn(salen) complex by nonaqueous terminal oxidants: monoperoxyphthalate (MMPP) or *m*-chloroperbenzoic acid (*m*-CPBA) in order to allow lower the epoxidation temperature and hence improve its enantioselectivity.[8] As shown in Table 1.3, both MMPP and *m*-CPBA epoxidized styrene at -78 °C in the presence of catalysts **e**-**g**. Whereas the reactions using MMPP were impractically slow, epoxidation with *m*-CPBA was remarkably rapid even at –78 °C, with complete conversion of styrene to the corresponding epoxide within 30 min. Enantioselectivity was also improved significantly at -78 °C, exceeding 80% ee in the presence of catalyst **f** or **g**.

Table 1.3 Asymmetric epoxidation of styrene with catalysts **e-g**





e, R_1 = -(C_4H_8)-, R_2 = *t*-Butyl
f, R_1 = Ph, R_2 = Me
g, R_1 = Ph, R_2 = OSi(*i*-Pr)$_3$

Entry	Catalyst	Oxidant	Temp(°C)	% yield	% ee
1	**e**	*m*-CPBA	0	97	46
2	**f**	*m*-CPBA	0	98	65
3	**f**	MMPP	0	70	70
4	**g**	*m*-CPBA	0	53	63
5	**e**	*m*-CPBA	-78	94	59
6	**f**	*m*-CPBA	-78	99	83
7	**f**	MMPP	-78	75	80
8	**g**	*m*-CPBA	-78	88	86

Katsuki and his colleagues had developed another ligand design by the introduction of two extra stereogenic axes in place of the *t*-butyl groups at the ortho positions to the oxygen atoms (Figure 1.4).[9] Katsuki also studied the enantioselective epoxidation of unfunctionalized olefins with this Mn complex, but generally lower asymmetric induction than that of Jacobsen's complexes was observed.

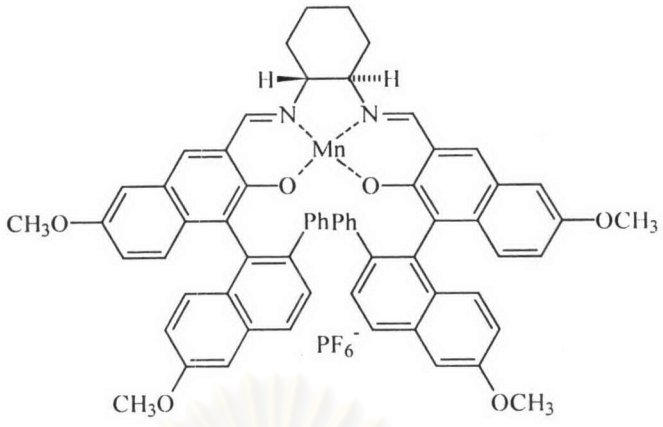


Figure 1.4 The Katsuki's Mn complex.

Mukaiyama group developed a system that uses dioxygen as an oxidant in combination with reactant.[10] The best reactant proved to be pivaldehyde, which was converted to the carboxylic acid. The manganese complexes were used as catalyst (Figure 1.5) and moderate enantioselectivity was obtained. For example; dihydronaphthalene afforded epoxide in 70% yield with 64% ee in the presence of 8 mol% of catalyst.

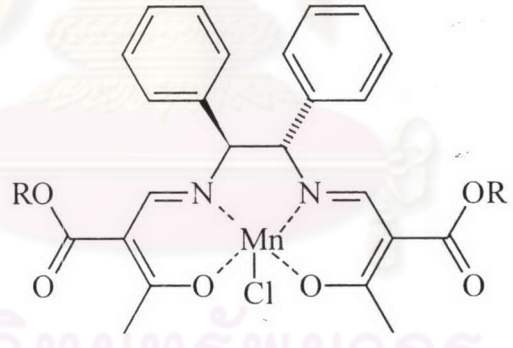
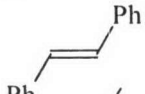
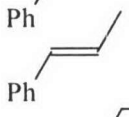
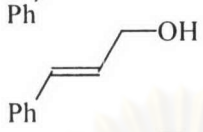
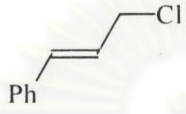
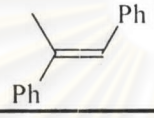


Figure 1.5 The Mukaiyama's catalyst.

Shi and his group reported a highly effective and mild asymmetric epoxidation for *trans*- and trisubstituted olefins using a fructose-derived ketone as a catalyst and oxone as an oxidant.[11] As illustrated in Table 1.4, enantioselectivity was very high in many cases. A variety of functional groups in the olefin substrates can be tolerated and high enantioselectivity was obtained from the epoxidation of unfunctionalized *trans*-olefins.

Table 1.4 Asymmetric epoxidation of olefins by fructose-derived ketone

Entry	olefin	% yield	% ee
1		73	>95
2		81	88
3		60	84
4		61	93
5		73	92

1.2.2 Other asymmetric reaction with chiral salen complexes

Jacobsen discovered hydrolytic kinetic resolution using chiral Co(III) (salen) complex presenting a highly attractive method for accessing terminal epoxides in high enantiomeric purity (Figure 1.6).[12] 3-Chlorostyrene oxide was prepared in greater than 99% ee by this kinetically selective hydrolysis. The resolution was performed successfully on both racemic and enantiomerically enriched epoxides that was obtained from an asymmetric epoxidation.

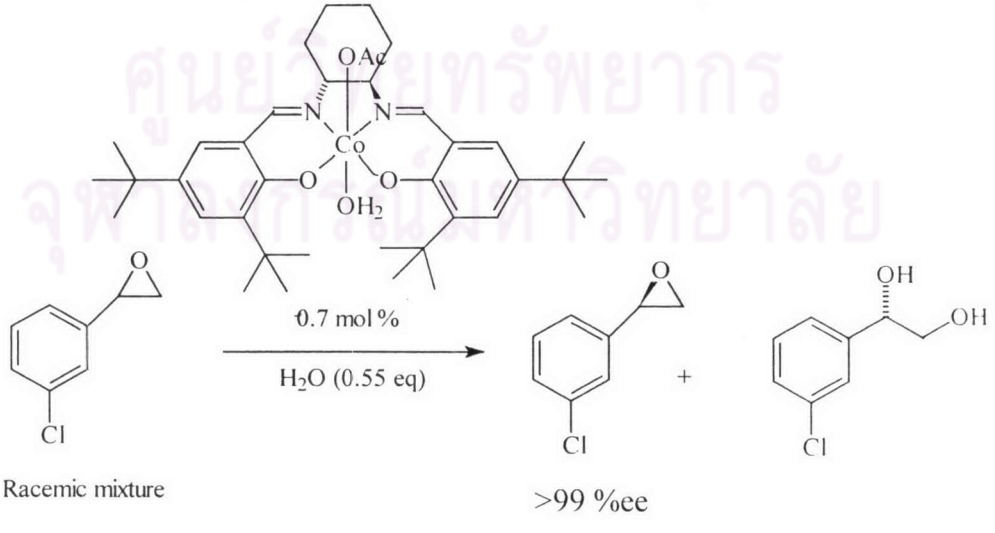


Figure 1.6 Catalytic hydrolytic kinetic resolution of terminal epoxide by Co (III) chiral salen complex.

The asymmetric nucleophilic ring opening of epoxide by benzoic acid with chiral metal-salen complex was reported.[13] First, the first-row transition metal complexes derived from the commercially available Jacobsen's ligand were screened. Several metal complexes can catalyze epoxide decomposition, but only the Co(II) complex mediated clean ring-opening reaction to produce and achieve the highest enantioselectivity (Figure 1.7). Furthermore, the rate, enantioselectivity and yield of the reaction were also found to improve with an addition of one equivalent of *i*-Pr_2NEt. Although the ring-opening reaction with carboxylic acid can be affected using a Co(II) complex, it appeared that reactive species is in fact a Co(III) complex. The optimized reaction conditions for several meso epoxides were shown in Table 1.5.

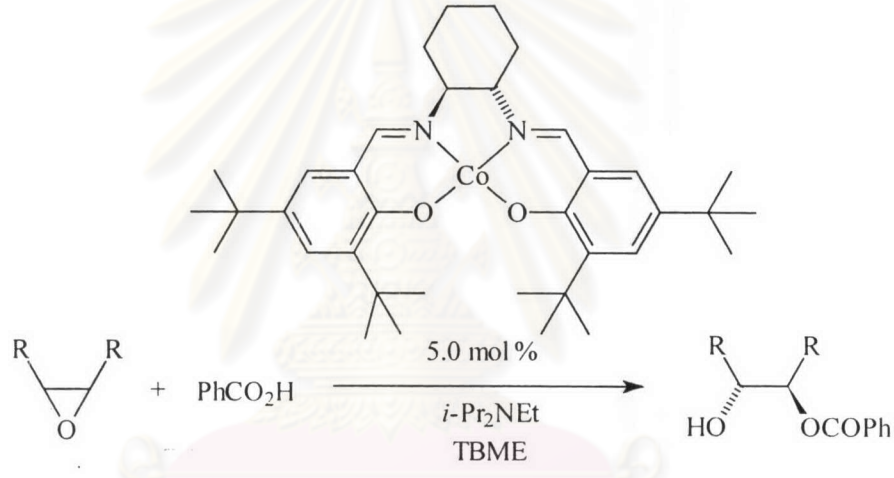
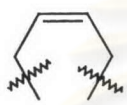
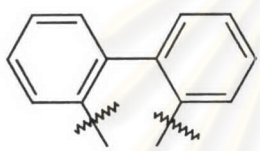
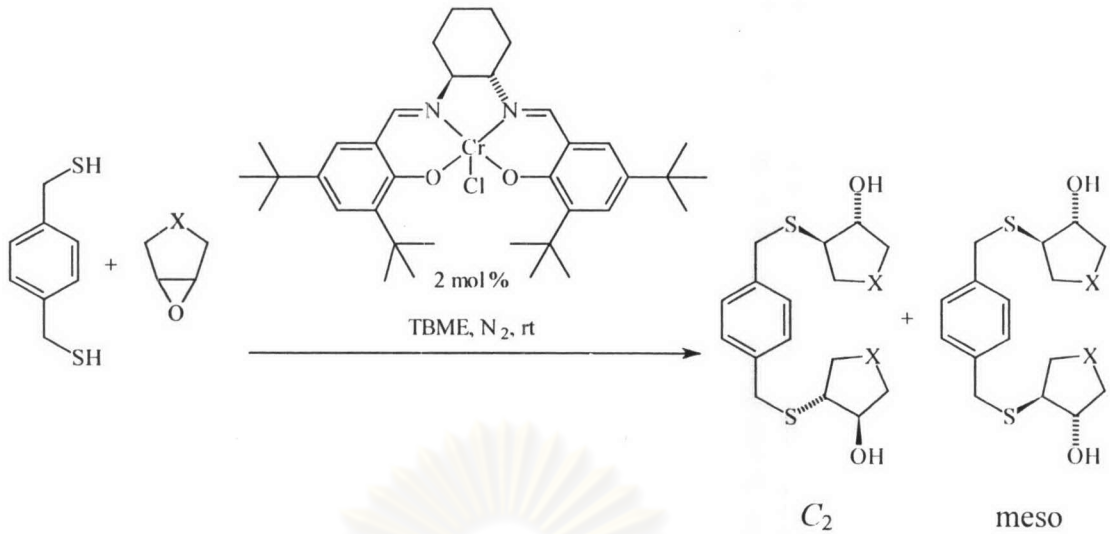


Figure 1.7 Asymmetric nucleophilic ring opening of epoxide by benzoic acid with Co(II) chiral salen complex.

Table 1.5 Asymmetric nucleophilic ring opening of epoxide by benzoic acid catalyzed by Co(II) chiral salen complex

Entry	R	Catalyst loading (mol %)	Temp (°C)	% yield	% ee
1	$-(CH_2)_4-$	2.5	0-4	98	77
2	$-(CH_2)_3-$	5.0	RT	52	55
3	$-(CH_2)_5-$	5.0	RT	77	65
4	Me	2.5	0-4	97	73
5	Ph	5.0	RT	92	92
6		5.0	RT	95	71
7		5.0	RT	96	93

Jacobsen reported that chiral(salen) Cr (III) complex was an effective catalyst for the asymmetric ring opening of epoxide by bifunctional thiol (Figure 1.8).[14] They chose the *p*-xylene thiol as the dithiol derivatives to evaluate in the double asymmetric ring opening strategy. As shown in Table 1.6, cyclohexene oxide underwent reaction with dithiol in the presence of the catalyst to afford the corresponding bishydroxysulfide in 85% ee and 95% yield. The ring-opening of cyclopentene oxide afforded an excellent yield and the highest enantioselectivity (93% ee). These products led to a preparation of β-hydroxythiol that can serve as a chiral pool for synthesis of compounds of potentially biological interest or as ligands for asymmetric catalysis. Moreover, they found that careful exclusion of air from the reaction medium was critical for preventing a formation of disulfide byproducts.



C_2 meso

Figure 1.8 Asymmetric ring opening of epoxide by bifunctional thiol.

Table 1.6 Asymmetric ring opening of epoxide by bifunctional thiol catalyzed by chiral(salen) Cr (III) complex

Entry	X	time, h	% yield	C_2:meso	% ee of C_2
1	CH_2CH_2	24	95	1.8:1	85
2	N-BOC	72	84	2.1:1	89
3	O	96	69	2.2:1	91
4	CH_2	24	95	2.8:1	93

Chiral(salen) Cr (III) complex had been introduced in the asymmetric ring opening of epoxide by $TMSN_3$.[15] The reactions of a variety of meso epoxides with $TMSN_3$ were screened using 2 mol % catalyst (Table 1.7). Five-membered ring epoxides underwent ring-opening with very high enantioselectivity, while six-membered ring and acyclic substrates were slightly less effective.

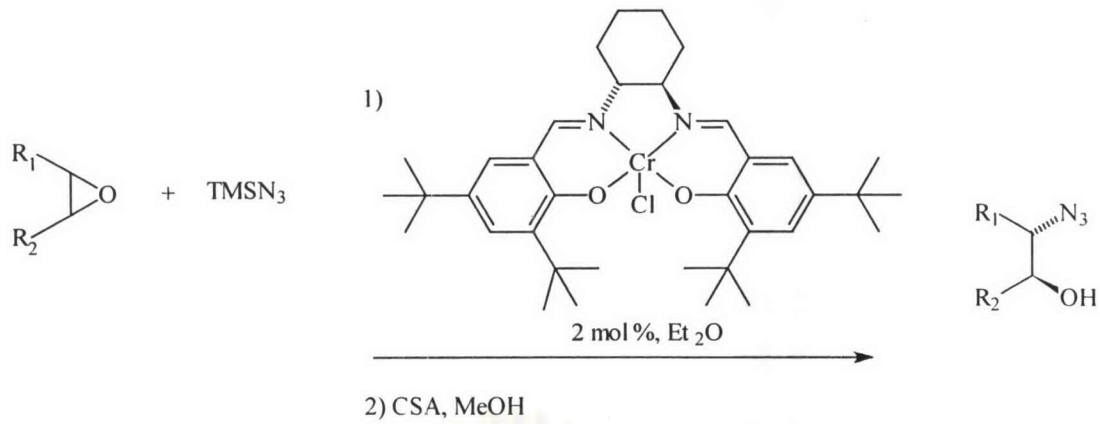
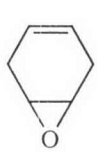
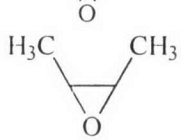


Figure 1.9 Asymmetric ring opening of epoxide by $TMSN_3$ catalyzed by chiral(salen) Cr(III) complex.

Table 1.7 Asymmetric ring opening of meso epoxide by $TMSN_3$

Entry	Epoxide	Time, h	% yield	% ee
1		18	80	88
2		28	80	94
3		18	80	98
4		36	80	95
5		16	90	95
6		46	72	81
7		30	65	82

Jacobsen discovered that the asymmetric hetero-Diels-Alder reactions between aldehydes and 1-methoxy-3-[(trimethylsilyl)oxy]buta-1,3-diene in the presence of 2 mol% Cr(salen) afforded high % ee of dihydropyranones (Figure 1.10).[16] The scope of the asymmetric condensations of butadiene with aldehydes catalyzed by Cr(salen) complex was proven to be quite broad (Table 1.8). Although enantioselectivity in excess of 90% was obtained in only one case, several of the dihydropyranone products could be recrystallized to gain more enantiomeric purity.

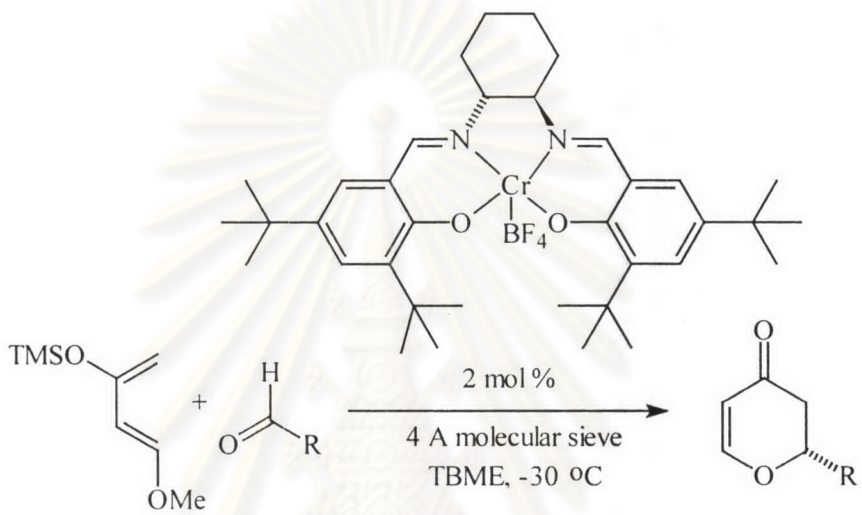


Figure 1.10 Asymmetric hetero-Diels-Alder reaction catalyzed by Cr(III) salen.

Table 1.8 Asymmetric hetero-Diels-Alder reaction between aldehydes and buta-1,3-diene

Entry	R	Temp (°C)	% yield	% ee
1	Ph	-30	85	87
2	C_6H_{11}	-20	71	93
3	*n*-C_5H_{11}	-40	86	83
4	2-furyl	-10	89	76
5	*(E)*-PhCH=CH	0	65	70
6	*p*-$BrC_6H_4CH_2$	-30	67	79
7	*p*-$ClC_6H_4CO_2CH_2$	-20	92	83

Jacobsen and coworkers used chiral Al(salen) complex in the addition of cyanide to imines (the Strecker reaction) that constitutes one of the most direct and viable strategies for the asymmetric synthesis of α-amino acid derivatives (Figure 1.11).[17] A variety of metal complexes of the readily available Jacobsen's ligand was screened for the addition of TMSCN to *N*-allylbenzaldimine. The best result was obtained with Al complex. As a result, they evaluated the reaction of a series of imine with HCN in the presence of 5 mol % of chiral Al(salen) complex. Only imines derived from aromatic aldehydes gave satisfactory results.

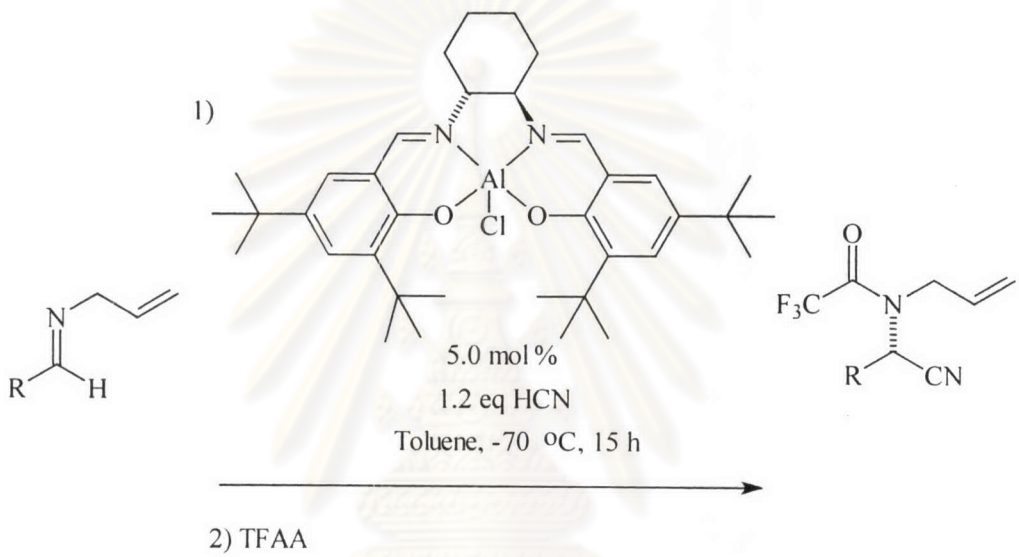


Figure 1.11 Addition of hydrogen cyanide to *N*-allyl benzaldimine.

Table 1.9 Asymmetric Strecker reaction of imines

Entry	R	% yield	% ee
1	Ph	91	95
2	*p*-$CH_3OC_6H_4$	93	91
3	*p*-$CH_3C_6H_4$	99	94
4	*p*-ClC_6H_4	92	81
5	*p*-BrC_6H_4	93	87
6	1-Naphthyl	95	93
7	2-Naphthyl	93	93
8	Cyclohexyl	77	57
9	*t*-Butyl	69	37

North and his colleagues used the optically active Ti(salen) catalyst in the enantioselective trimethylsilylcyanation of benzaldehyde to produce (*S*)-2-phenyl-2-trimethylsilyloxyacetonitrile in an excellent yield (>99 %) with 86 %ee (Figure 1.12).[18] The catalyst was active at room temperature and at very high substrate to catalyst ratio in contrast to previous reports on this reaction.

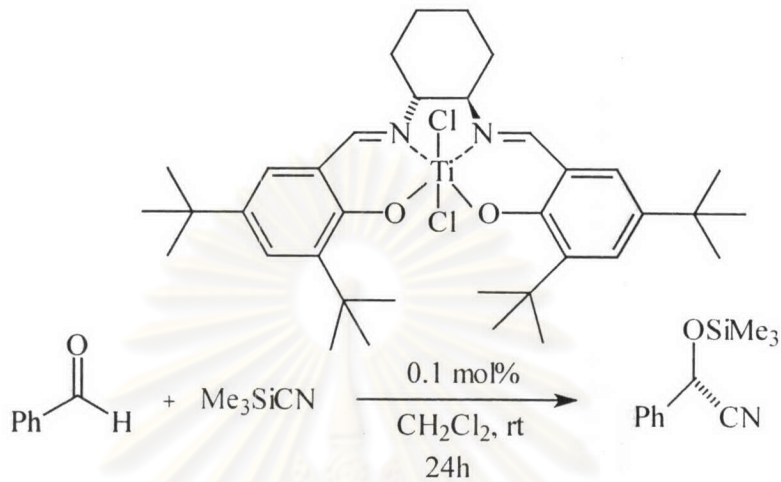


Figure 1.12 Enantioselective trimethylsilylcyanation of benzaldehyde.

1.2.3 Asymmetric reaction with chiral salen complexes in heterogeneous system

Heterogeneous catalysis is a major tool for industrial synthesis. Heterogeneous asymmetric catalysis can be accomplished in liquid-liquid, liquid-solid or gas-solid phases. The covalent attachment of homogeneous catalyst to insoluble supports has been widely studied as an attractive strategy for extending the practical advantage of heterogeneous systems. The benefits of heterogeneous catalysis include simplified product purification, facilitation of catalysis recycle and the possible adaptation of the immobilized catalyst for continuous-flow process. Heterogeneous catalysts which can provide high enantioselectivity for certain reactions would be an important development.

The syntheses of the first polymer-supported chiral Mn(salen) complexes along with their applications as recyclable asymmetric catalysts were reported by Sivaram[19] and Minotolo.[20] Monomeric Jacobsen-type units which containing two polymerizable vinyl groups were copolymerized with divinylbenzene to give crosslinked polymers (Figure 1.13).

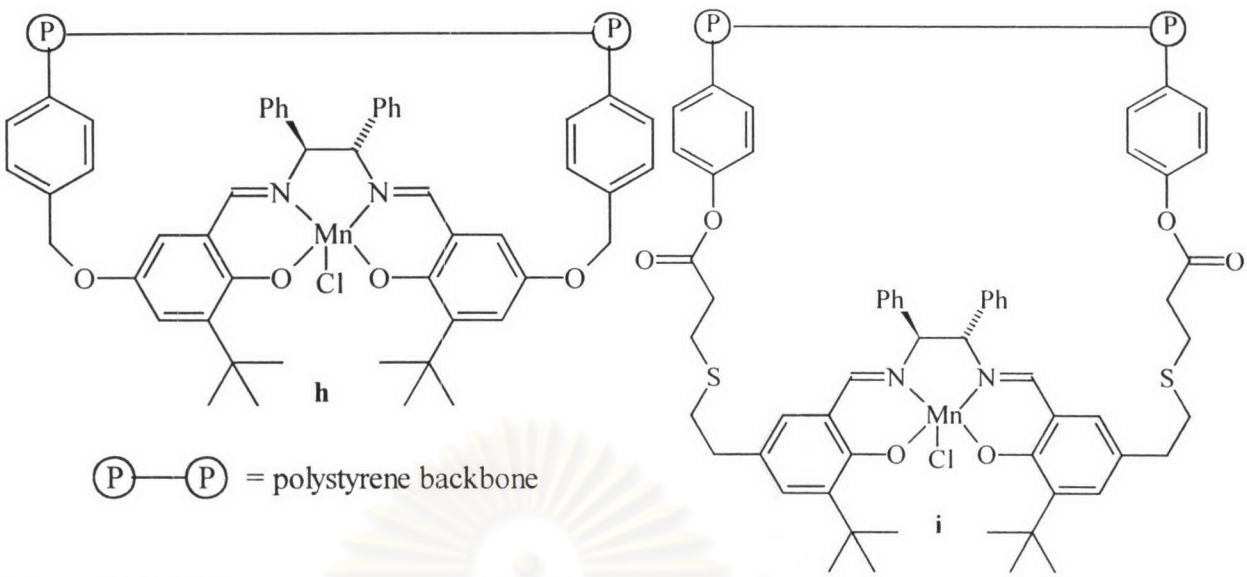


Figure 1.13 Polymer-supported chiral Mn(salen) complexes.

The insoluble salen complex **h** can catalyze epoxidation reaction of unfunctionalized alkene in good yield (65-72 %) but low enantioselectivity (1-26 %ee). The best results were achieved with *cis*-disubstituted alkenes. Catalyst **i** gave higher enantiomeric excess than **h** (14-62 %ee) because of the more flexible spacers between the active site and the polymer backbone.

Jacobsen and his colleagues reported a synthesis of polystyrene-bound chiral Co(salen) complexes and their catalytic activities in the hydrolytic kinetic resolution of terminal epoxides.[21] It gave enantiomeric enriched epoxides (>99 %ee) and diol (>92% ee). This catalyst was able to be recycled five times with no apparent loss of reactivity or selectivity (Figure 1.14).

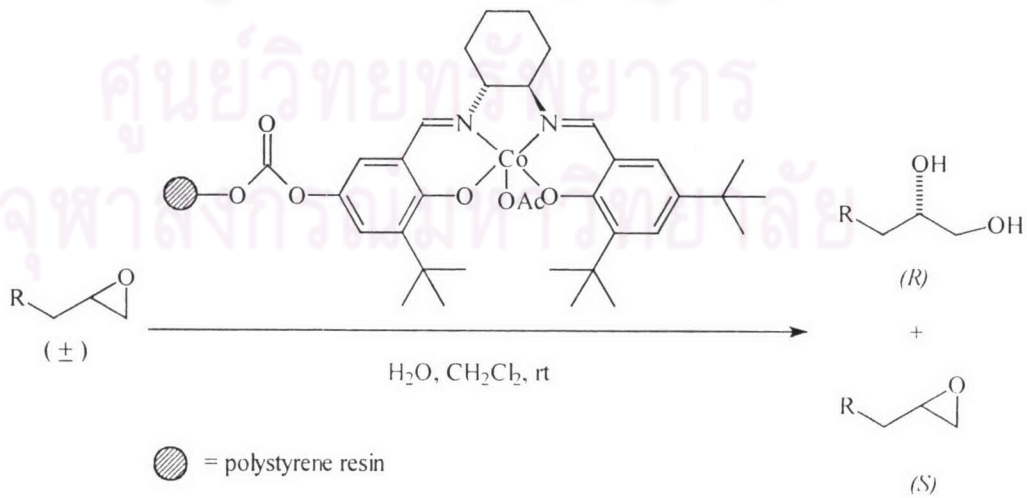
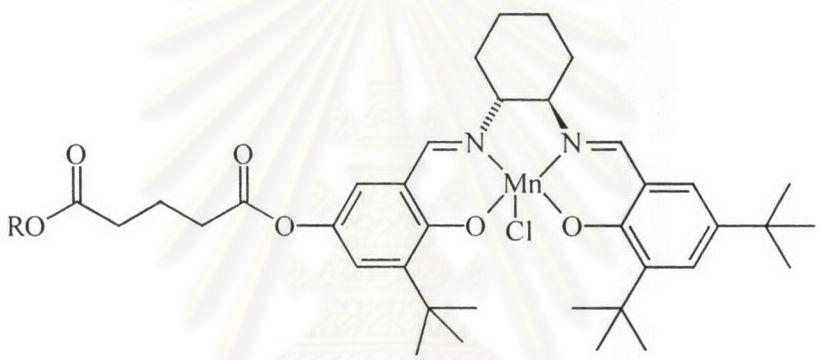


Figure 1.14 Hydrolytic kinetic resolution of terminal epoxides catalyzed by polystyrene-bound chiral Co(salen) complexes.

Janda and coworker synthesized both soluble and insoluble polymer-supported chiral(salen)-Mn complexes and studied their use in asymmetric epoxidation reactions.[22] Poly(ethylene glycol) monomethyl ether (MeO-PEG) and non-crosslinked polystyrene (NCPS) were used as soluble supports while *J*anda*J*el and Merrifield resins served as insoluble supports. Each polymer was linked to the salen catalyst through a glutarate spacer. The best results were obtained with the epoxidation of *cis*-β-methylstyrene, as the enantioselectivity obtained with each polymer-bound catalyst (86-90 %ee) was equivalent to that achieved with the commercially available Jacobsen's catalyst (88 %ee). The soluble catalysts can be recovered by precipitation with suitable solvents while the insoluble catalysts were filtered from the reaction mixture (Figure 1.15).



R = MeO-PEG 5000, NCPS, *J*anda*J*el resin, Merrifield resin

Figure 1.15 Soluble and insoluble polymer-supported chiral(salen)-Mn complexes.

1.3 Catalysts containing glycol chain

Trost showed that the synthesized asymmetric ligand containing glycol chain was an effective catalyst for nucleophilic substitution reaction of allyl ester.[23] He proposed that glycol chain was chosen for its synthetic simplicity and structural flexibility for the tentacle to reach out into solution to coordinate a cation, the counterion of nucleophile. It could enhance both enantioselectivity and reaction rate. For example, the time to complete the reaction of the starting material for the cyclohexenyl ester (Figure 1.16) dropped from 16 h at 40 °C with the standard ligand with no glycol chain unit to only 2 h with the ligand containing glycol units (99 %yield, 99 %ee).

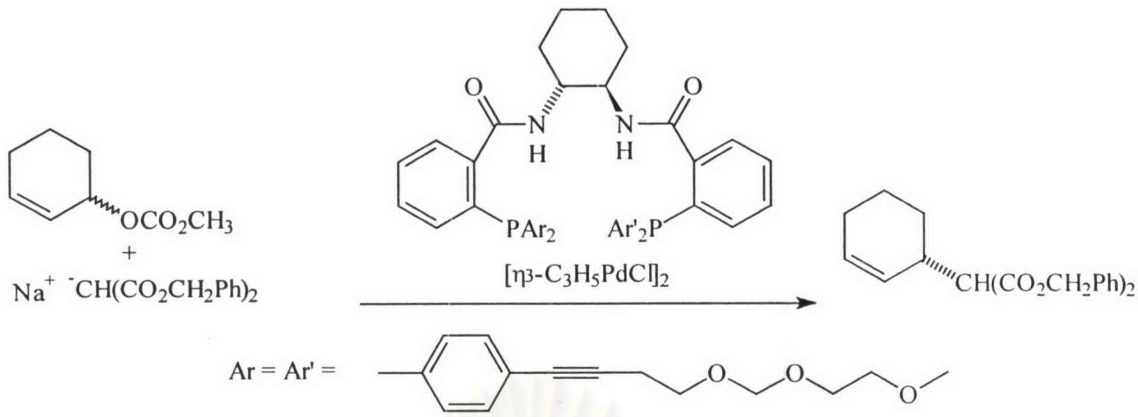


Figure 1.16 Nucleophilic substitution reaction of the cyclohexyl ester.

Bergbreiter and his colleagues introduced poly(ethylene glycol) chain attaching a Pd catalyst for Heck reaction.[24] This catalyst was recycled three times by precipitation with cold ether while loss of reactivity could not be observed.

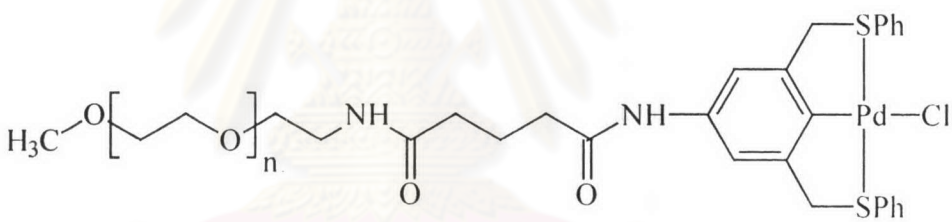


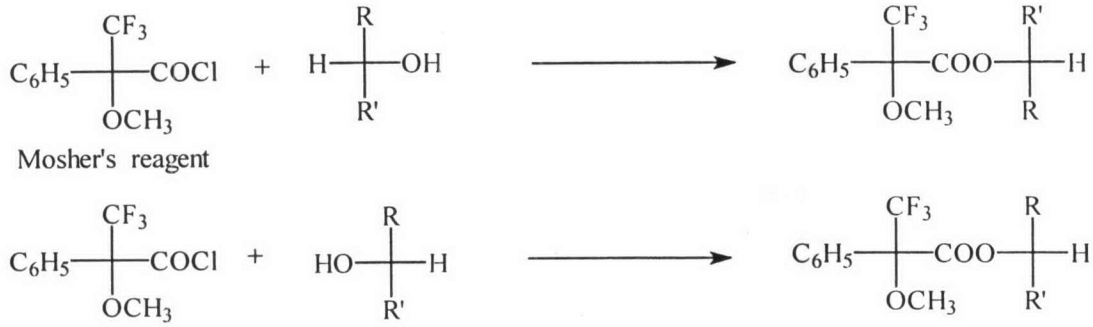
Figure 1.17 The structure of poly(ethylene glycol)-supported Pd catalyst.

1.4 Determination of enantiomeric excess by method of nuclear magnetic resonance

The two enantiomers in racemic mixture can be distinguished by nuclear magnetic resonance (NMR) with various methods as follows:[25]

1) Conversion of enantiomers to diastereomeric compounds

This method is appropriate for the determination of enantiomeric excess of alcohols and amines. For example, a mixture of diastereomeric esters or amides is prepared from a reaction with optically active 3,3,3-trifluoro-2-phenyl-2-methoxypropionyl chloride (Mosher's reagent), the ratio of the diastereomeric products will correspond to the ratio of the starting enantiomers.



With their different chemical shifts of atoms or groups in the ^{1}H-NMR or ^{19}F-NMR spectrum, the integration of the probing signals will reflect the ratio of both enantiomers in the original sample.

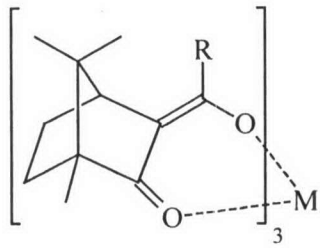
2) Use of chiral solvents

Enantiomeric excess may also be determined by dissolving the sample in an optically active solvent and running the NMR spectrum of this solution. The chemical shifts are affected by hydrogen bonds, dipole-dipole interactions or the interaction of charge-transfer type between the examined compound and the solvent. It is desirable that the solvent has a high magnetic anisotropic group in the vicinity of the stereogenic center such as an aromatic ring. The chiral 2,2,2-trifluoro-1-phenylethanol was an example of a suitable solvent for this purpose.

3) Use of chiral shift reagents

The use of chiral shift reagents in the determination of enantiomeric purity by NMR spectroscopy has several advantages over the preceding methods.

Chiral lanthanide shift reagents can be used with a variety of compounds rather than just alcohols or amines. The magnitude of the difference in chemical shifts is usually much higher than using a chiral solvent. Among the most frequently used chiral shift reagents are the chiral complexes of europium or praseodymium (Figure 1.18).



M = Eu or Pr

R = CF_3, $CF_3CF_2CF_2$

Figure 1.18 Chiral shift reagents.

A typical experiment is simply adding a chiral shift reagent into a mixture of enantiomers and obtaining NMR spectrum. Some signals shift to higher values and split into two signals of which their intensities correspond to the proportion of both enantiomers.

The difference in chemical shifts of both enantiomers in the presence of chiral shift reagent cannot be simply explained. It is assumed that there exists either a difference in the equilibrium constants between (+) and (-) enantiomers upon interacting with the chiral shift reagent, or simply different chemical environments of the resulting diastereomeric complexes.

4) Other methods

Radioactively labeled compounds are used frequently for the determination of enantiomeric purity of compounds of biological origin. Another method is the kinetic resolution, (chemically or enzymatic) based on different rates of reaction of enantiomers with chiral reagents. Enzymatic methods utilizing kinetic resolution depend on the availability of enzymes which react with one enantiomer selectively in the presence of a large excess of the other. Finally, the gas chromatographic method can also be used to determine the diastereomeric ratio of the products from a reaction of a mixture of enantiomers with a chiral reagent. An optically active stationary phase can also be used to separate the enantiomers directly, although generally affords poorer resolution.

1.5 Remarks to the present research

Chiral metal-salen complexes showed promising catalytic properties in many asymmetric reactions including epoxidation of alkenes, ring-opening of epoxides and Strecker reaction. There were reports that the catalyst containing glycol chain enhanced enantioselectivity, reaction rate and facilitated of catalyst recycling.

In the present, two types of ethylene glycol chains, ethylene glycol monomethyl ether and diethylene glycol monomethyl ether, were incorporated into the salen unit in order to investigate the effect of the ethylene glycol chain on the catalytic properties in the enantioselective epoxidation reaction of alkenes. Factors affecting the catalytic properties such as solvent, temperature, amount of catalysts and oxidizing agent were also explored.