CHAPTER I

INTRODUCTION

1.1 Chirality and importances in living

Chiral molecule is a type of molecule which has no symmetry plane in their three-dimensional chemical structure. Each of its configurations is the mirror image of the other and they cannot be superimposed.[*1*] Both configurations which are called **enantiomers** are identical in constitution, physical properties, for example, boiling point, melting point, refractive index, density, as well as chemical properties in any achiral environments.(Figure 1.1) However, they differ in the three-dimensional arrangement of atoms and chemical properties when in contact with chiral environment such as chiral reagents. In addition, each of the enantiomers with equal concentration can rotate the plane of polarized light in the opposite directions but to an equal angle. In any living organisms, many of metabolic pathways mostly involved in several mechanisms which consist of any chiral molecules such as enzymes and protein. Proteins (and their constituent amino acids), which control most processes within biological systems, and the nucleic acids DNA and RNA which are responsible for holding the information necessary for proteins to be synthesized. For this reason, if a chiral compound interacts with a protein to induce a specific response in a biological organism, it is likely that its enantiomer will either not interact or produce a completely different response. This principle is very vital in any of chemical industries, for example, agrochemical, perfume industry, especially in pharmaceutical industry involving chiral drugs.[*2*] A number of chiral molecules and their different effects are shown in Figure 1.2.

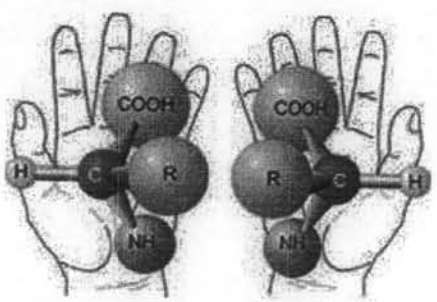


Figure 1.1 The amino acid in two enantiomeric forms which are mirror images of each other and not superimposable

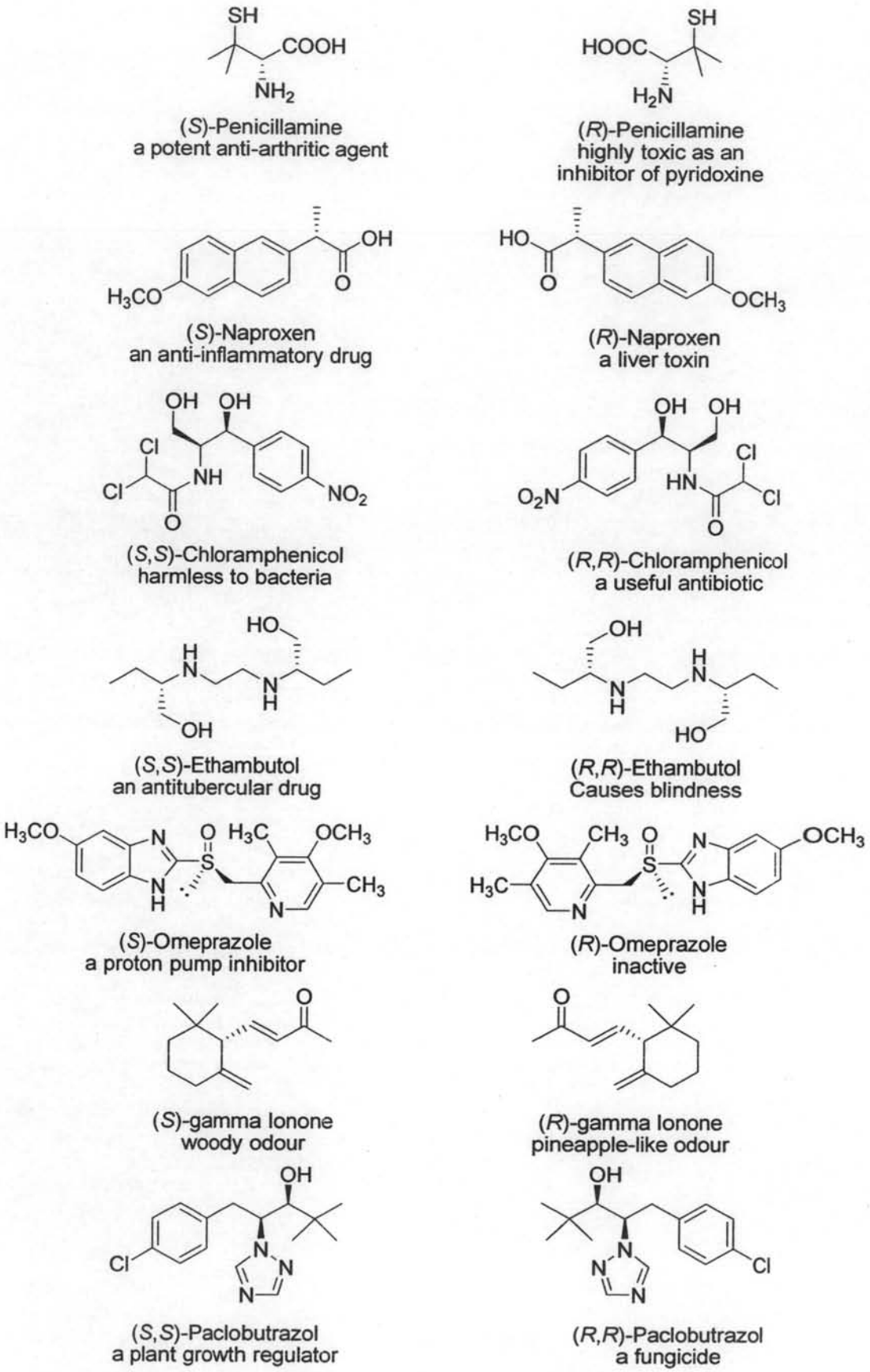


Figure 1.2 Enantiomeric molecules and their different activities

It would be desirable to obtain single enantiomers. The resolution of each enantiomers and the synthesis of pure single enantiomers which have been called 'asymmetric synthesis' have become an area of interest among many researchers.[*3*,4]

1.2 Resolution : one of the classical methods for obtaining single enantiomers

Resolution may be considered a classical method for obtaining enantiomerically pure products.[1] The procedure is based on the principle to derivatize both enantiomers (*R* and *S*) which have the same physical properties are with a naturally occuring enantiomerically pure compound (either *R* or *S*). The resulting two compounds are related as diastereomers. Both of the diastereomers have non-superimposable structures and are **not** mirror images to each other. They have entirely different physical properties. These new compounds may be separated, most commonly by crystallization but also by chromatography, and then separately treated to liberate the two enantiomers. The overall process of classical resolution is depicted in Figure1.3 which represents substrate to be resolved by **S** and the resolving agent by **A***.

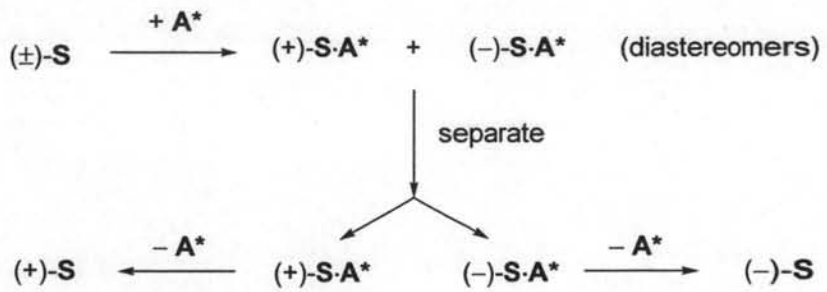


Figure 1.3 The diagram of overall resolution process

The resolving agent is recovered unchanged after this procedure and can be reused repeatedly. This method often provides the most cost-effective way to obtain enantiomerically pure compound on a large scale. The disadvantage of this method is the limit of percentage yield from the amount of desired enantiomer in the mixture before resolution. If the resolution is started from the mixed solution of 50 : 50 R : S which is called a racemic mixture, the maximum %yield of either of the desired enantiomer is only 50 %. The efficiency of this method is therefore low. A principle, referred to in the next topic as asymmetric synthesis, offers a much higher efficiency.

1.3 Asymmetric synthesis

An asymmetric synthesis was defined [1] as "a synthesis in which an ensemble of substrate molecules is converted to a new stereogenic unit such that the possible stereoisomers are formed in unequal amounts". The ultimate goal of asymmetric synthesis is achievement of the highest proportion of the desired enantiomer as possible. An important parameter to indicate the degree of enantioselection is called "enantiomeric excess (*ee*)". This value is generally reported in the percentage of enantiomeric excess (%*ee*) which can be calculated by equation (1)

$$\%ee = \frac{|R-S|}{R+S} \times 100 \qquad (1)$$

The known methods of asymmetric synthesis have been conveniently classified in several approaches.[1,5-6] One of these is divided into four major classes which is summarized in Figure 1.4.

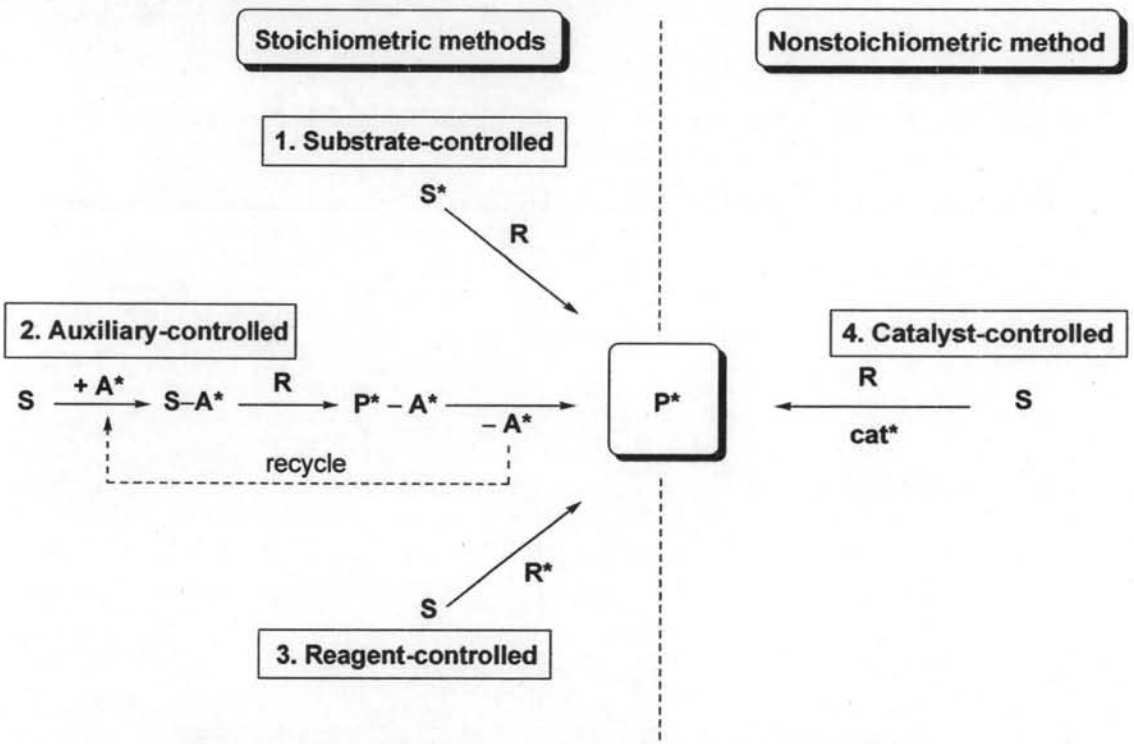


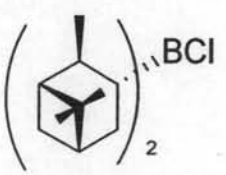
Figure 1.4 Four major classes of asymmetric synthesis

The original method is substrate-controlled. In this first generation of asymmetric synthesis, an optically pure product is obtained from the reaction between a substrate which contains any stereogenic units in the molecule, may be from natural product or the prior step of synthesis, and an achiral reagent. The induction from the stereogenic unit already present in the starting molecule causes an optically active

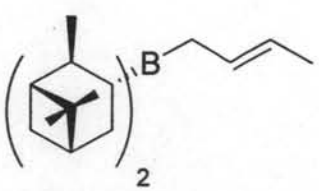
product with some new stereogenic units. However, one of the disadvantages of this method is the control of enantioselectivity in the new stereogenic unit because the old stereogenic unit is a part of the new product. It is hard to modify the available group for selectivity improving.

The second method is auxiliary-controlled. Starting from an achiral substrate, an enantiomerically pure auxiliary is necessary to be introduced to the substrate in the first step to form an optically pure substrate-auxiliary intermediate. The next step is, in principle, similar to the substrate-controlled method. The good selectivity of a new stereogenic center is formed by an induction from the chirality already present in the molecule, in this case from the auxiliary. The last step of the sequence is the removal of auxiliary moiety to get the desired enantiomerically rich product. The advantage of this method is the convenience in selecting a type of suitable auxiliary for the best selectivity. In addition, the changing of opposite enantiomers of the auxiliary leads to the opposite enantiomer of the desired product in the same enantioselectivity. One of the disadvantages of this method is, however, the requirement of at least two additional steps in the reactions arising from an attachment and a removal of a chiral auxiliary. These steps, more often than not, can affect the overall yield of the desired product.

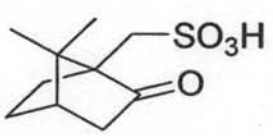
The third method is reagent-controlled. In this strategy, a non-chiral starting material is treated by an optically active reagent to afford a chiral product. However, there are still a relatively limited numbers of chiral reagents although many chiral reagents have been developed for various specific asymmetric reactions, for instance, (-)-Ipc_2BCl for asymmetric reduction and (*S*)-camphorsulphonic acid for asymmetric protonation(Figure 1.5).



(-)-Ipc_2BCl



(*E*)-crotylborane



(*S*)-camphorsulphonic acid

Figure 1.5 Some examples of chiral reagents

The three methods described above are stoichiometric method, *i.e.*, all reaction steps which involve compounds from the "chiral pool" require a stoichiometric amount of chiral substances. Actually, the acquisition of chiral substances in a large

amount for stoichiometric process, especially in fine-chemical industries, is rather dissipating. This is a major drawback for these three methods.

The less expensive and more effective method is to utilize a catalyst-controlled strategy. This class of asymmetric reaction, which includes many enzyme-catalyzed transformations, is clearly seen very attractive and is the subject of intensive research at the present time. By definition, the catalyst can be recovered unchanged at the end of the reaction and in many cases only a small quantity (5 mol% or less) is required to achieve a reasonable rate of conversion and an efficient asymmetric induction. The possibility of using only a catalytic amount of enantiomerically pure compound obviously has great attractions for large-scale industrial use where cost is critical.

1.4 Chiral catalysts in catalytic asymmetric synthesis

Chiral catalysts can be categorized into 2 main classes. The first is a purely organic compound which does not contain any metals called an "organocatalyst". Organocatalysts are usually small molecules. They are robust, and commercially available in reasonable quantities, making them inexpensive and readily obtainable. They are stable to moisture and oxygen, making inconvenient air sensitive techniques unnecessary. Unfortunately, organocatalysts often require high loadings to be effective, and may be difficult to separate from the resultant reaction mixture.[7] Organocatalysts may be obtained from some commonly available natural products or amino acids, such as (*L*)-proline, quinine, quinidine, and chinconine. They are also from synthetic organic compounds, such as urea and thiourea derivatives (Figure 1.6).

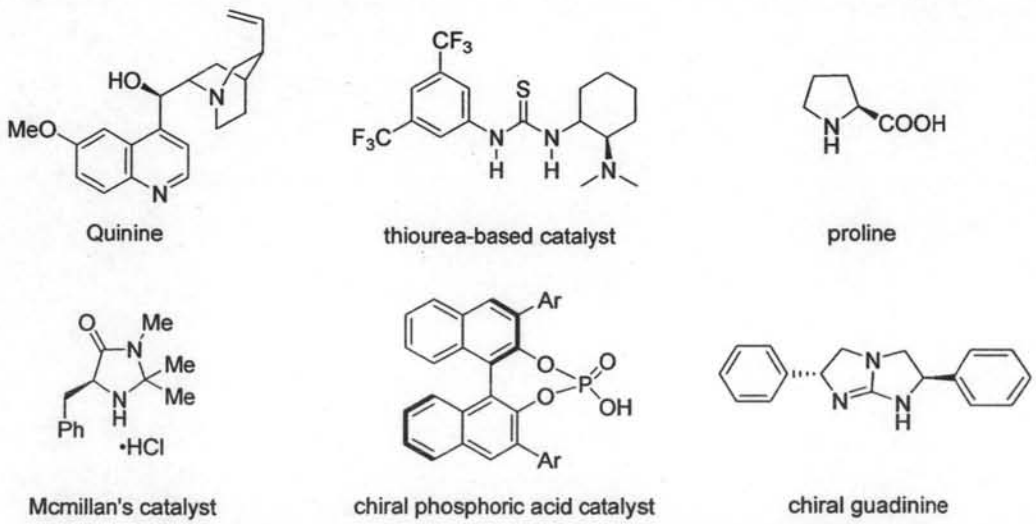


Figure 1.6 Some examples of common organocatalysts

The mechanism of asymmetric induction by an organocatalyst may be from a temporary covalently-bound interaction between an organocatalyst and reactants in the catalytic cycle. One of the obvious examples is an enantioselective Mannich reaction using (*L*)-proline as an organocatalyst. (*L*)-proline reacts with a ketone by covalent bond to form an enantiopure enamine intermediate which is an asymmetric nucleophile to proceed through an enantioselective addition and be further hydrolyzed back to the initial (*L*)-proline in the catalytic cycle.[*8*] (Figure 1.7)

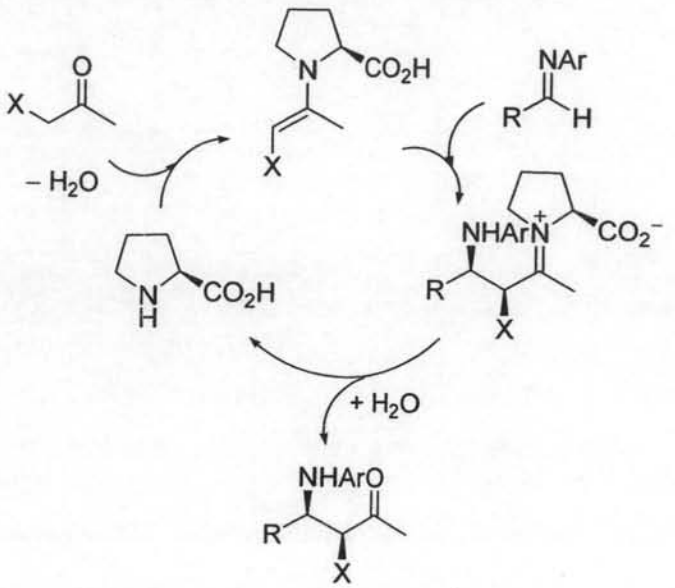


Figure 1.7 A plausible catalytic cycle of (*L*)-proline catalyzed Mannich reaction

The other mechanism of organocatalyzed reaction is an asymmetric induction between organocatalyst molecule and reactants *via* intermolecular forces such as hydrogen bond or dipole-dipole interaction. A good example is Michael reaction between *trans*-β-nitrostyrene and a malonate catalyzed by thiourea bifunctional catalyst.[*9*] (Figure 1.8)

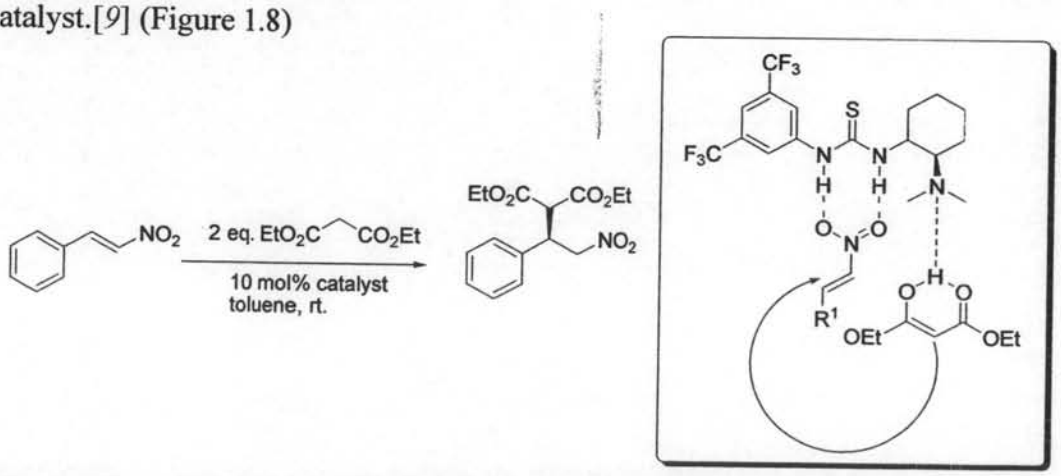


Figure 1.8 Michael reaction between *trans*-β-nitrostyrene and diethyl malonate catalyzed by thiourea bifunctional catalyst.

The other class of chiral catalysts is chiral organometallic catalyst. The asymmetric induction affects from any chiral ligands which are attached to metal centers. Since metals can act as either Lewis acids or Lewis bases, the development of the catalyst efficiency can be achieved by changing of metal for better coordination from any chiral ligands and functional groups of reactants. The type or structure modification of chiral ligands is also a method for reactivity or enantioselectivity improvement.[*10*] There is a number of literatures reported highly successful utilization of metal-chiral ligand catalysts for various enantioselective reactions.[*11-12*] These include, for example, Michael reaction, hydrogenation, Strecker reaction, *etc.*. One of the advantages of chiral organometallic catalysts over organocatalysts is the catalyst loading percentage. Many of the chiral-organometal-catalyzed reactions can be achieved in an excellent enantioselectivity even with less than 1 mol% catalyst loading, sometimes even as low as 0.05 mol%.[*13*] Many classes of chiral ligands are well-known and widely used in asymmetric synthesis, examples of which are as shown in Figure 1.9.

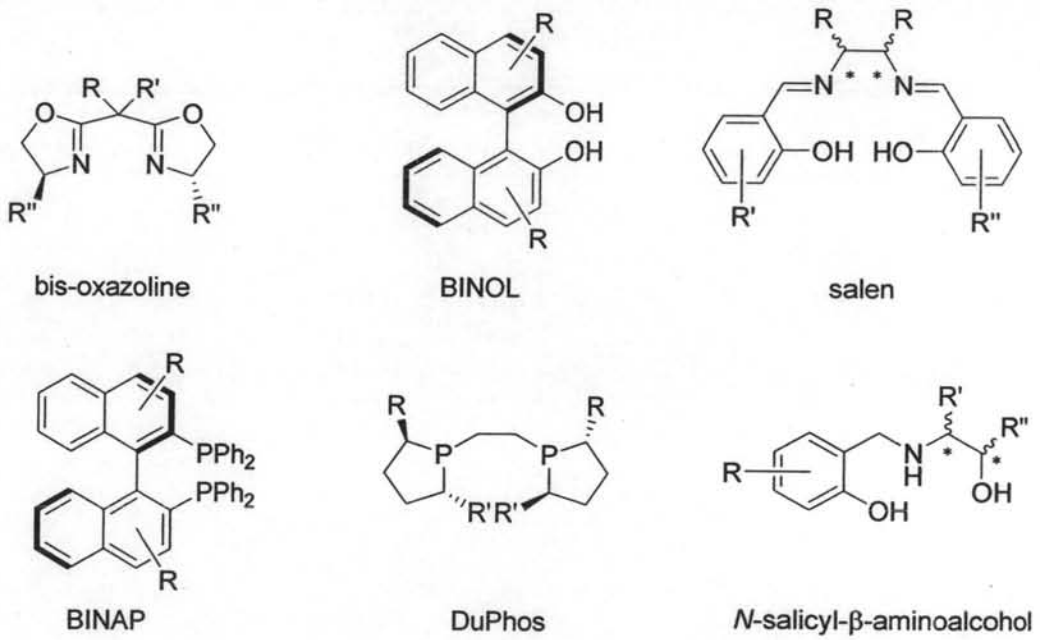


Figure 1.9 Some of well-known chiral ligands

1.5 *N*-Salicyl-β-aminoalcohol as chiral ligands

Simple transformations, such as α-amino acid reductions, allow entry to other classes of compound that are also useful as the source of chiral centers, as with α-

amino aldehyde and β-1,2-amino alcohols. 1,2-Amino alcohols and their derivatives have long been used as chiral auxiliaries and chiral ligands in organic synthesis.[*14*] *N*-salicyl-β-aminoalcohols constitute a group of 1,2-amino alcohol derivatives which are recently favored among many researchers because of the ease in the synthesis, structure modification, and the low cost of reactants. The ligands can be synthesized by reduction of a Schiff's base which was prepared from salicylaldehyde and a chiral-β-aminoalcohol. (Figure 1.10) In addition to the use of the amino alcohols, there are many literatures that also reported the use of the ligand in Schiff's base form which could be synthesized in the same way.

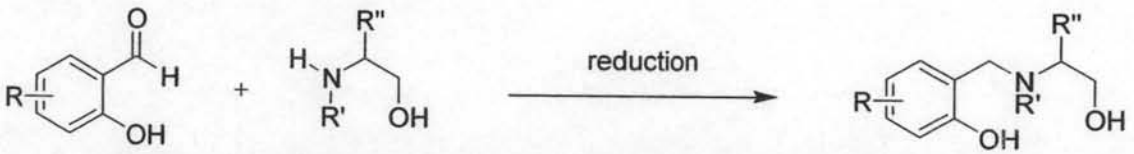


Figure 1.10 Synthesis of *N*-salicyl-β-aminoalcohols

In 2006, Feng [*15*] reported the use of *N*-salicyl-β-aminoalcohols in Schiff's base form which were complexed with Cu(II) from $Cu(OTf)_2$ in the highly enantio- and diastereoselective hetero-Diels-Alder reaction of Brassard type diene **1** with aldehydes. The best result was obtained from the use of ligand **2** which was derived from (1*R*,2*S*)-1-amino-2-indanol with an adamantanyl group at the 3-position of the phenolic ring of the salicyl moiety. The corresponding 5-methyl-containing α,β-unsaturated δ-lactone derivatives **3** was afforded in moderate yields, high enantioselectivities (up to 99 %*ee*), and excellent diastereoselectivities (up to 99:1 anti/syn) (Figure 1.11).

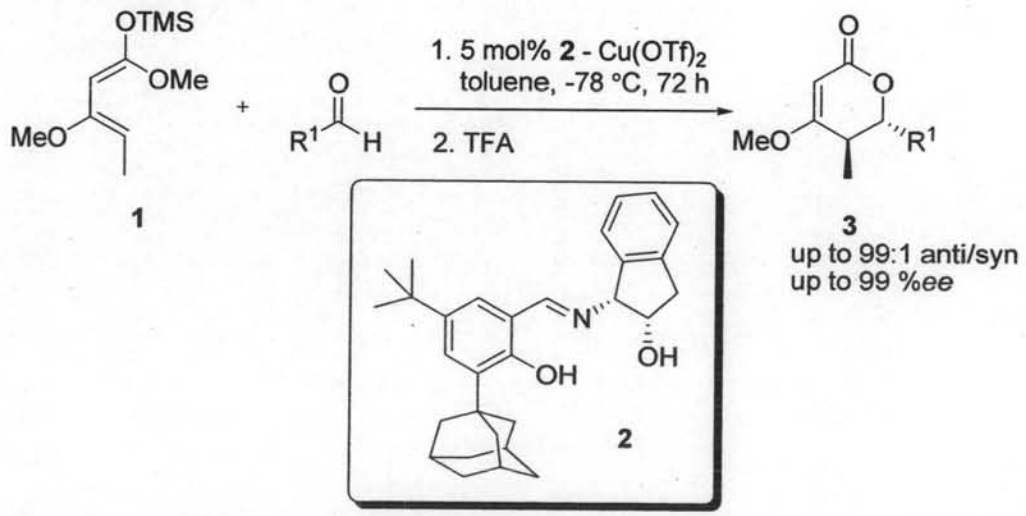


Figure 1.11 The highly enantio- and diastereoselective hetero-Diels-Alder reaction of Brassard type diene

In 2006 Trost [*16*] had reported a direct catalytic asymmetric Mannich-type reaction *via* a dinuclear zinc catalyst **4**. A broad array of hydroxyacetylated aromatics **5**, including phenyl, 2-furyl, 1-naphthyl, and 2-naphthyl, have been shown to react well. In addition, the reactions focused on the use of enolizable imines **6**. With *N*-diphenylphosphinoyl imine, the reactions are *anti* selective with enantiomeric excesses ranging from 83 to 99%, except for the reaction of the 2-methoxy-2'-hydroxyacetylbenzene. With the *N*-Boc-imines, the reactions were *syn* selective with enantiomeric excesses from 90 to 94% (Figure 1.12).

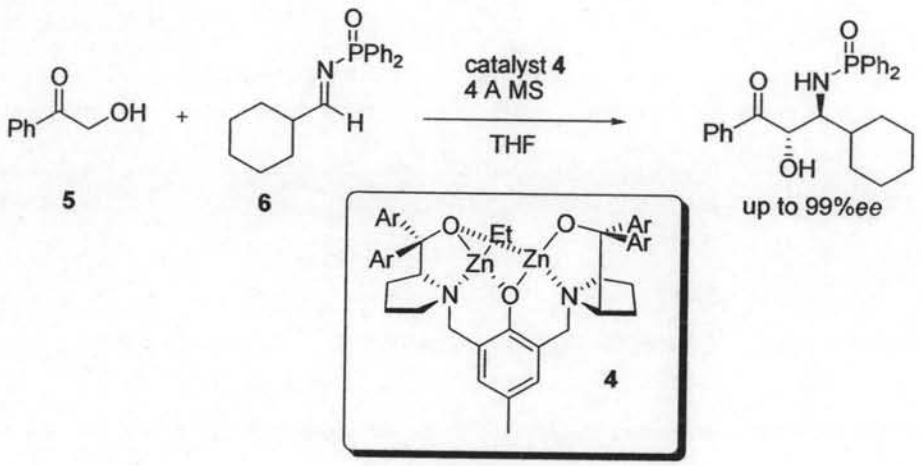


Figure 1.12 A direct catalytic asymmetric Mannich-type reaction *via* a dinuclear zinc catalyst

Examples of asymmetric oxidation using Schiff's base of *N*-salicyl-β-aminoalcohols have been reported since 1998.[*17*] Ellman demonstrated that a complex between ligand (*S*)-**7** and $VO(acac)_2$ in catalytic asymmetric oxidation of *t*-butyl disulfide **9** could afford the corresponding sulfinate ester (*R*)-**10** with an enantioselectivity up to 82 %*ee*.[*18*] Problems arose in a large-scale production of the product since that aminoalcohol in opposite configuration for the production of ligand (*R*)-**7** was not readily available. Moreover, the condition required a toxic solvent, chloroform. Nevertheless, in 2003, Ellman [*19*] had released a report on an employment of ligand **8** in the synthesis of *tert*-butanesulfinamide under which the scalability problems of the previous syntheses were overcome. The key step was the catalytic asymmetric oxidation of the inexpensive di-*t*-butyl disulfide starting material. The new homogeneous reaction conditions utilize an inexpensive chiral ligand prepared in a single step from commercially available *cis*-1-amino-indan-2-ol.

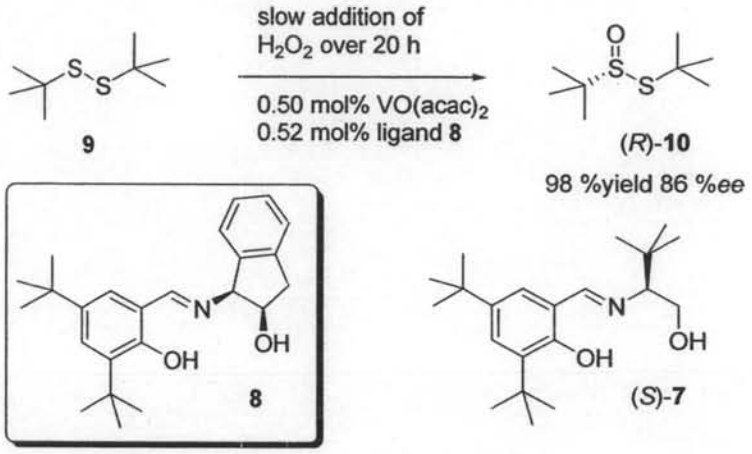


Figure 1.13 Catalytic asymmetric oxidation of *t*-butyl disulfide

In 2005, a report by Toste [*20*] revealed a vanadium-catalyzed method for the oxidative kinetic resolution of α-hydroxyesters, using oxygen as the terminal oxidant. Catalyst **11** is generated *in situ* from vanadium(V) tri-*iso*-propoxyoxide in combination with a tridentate ligand derived from 3,5-di-*tert*-butylsalicylaldehyde and (*S*)-*tert*-leucinol. The reaction allows for the enantioselective synthesis of both aromatic and aliphatic secondary alcohols, including those containing olefins and alkynes. Moreover, the catalyst systems based on tetradentate salen-type ligands failed to produce either efficient or selective oxidation catalysts. (Figure 1.14)

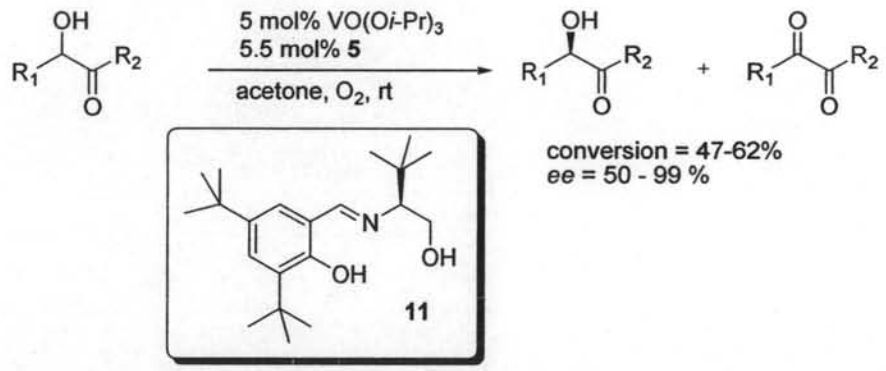


Figure 1.14 Vanadium-catalyzed asymmetric oxidation of α-hydroxy esters using molecular oxygen as stoichiometric oxidant

Recently, Chen [*21*] also reported a highly enantioselective aerobic oxidation of α-hydroxyphosphonates **12** catalyzed by chiral vanadyl(V) methoxides **13** bearing *N*-salicylidene-α-aminocarboxylates at ambient temperature with selectivity factors ranging from 3 to >99 (Figure 1.15).

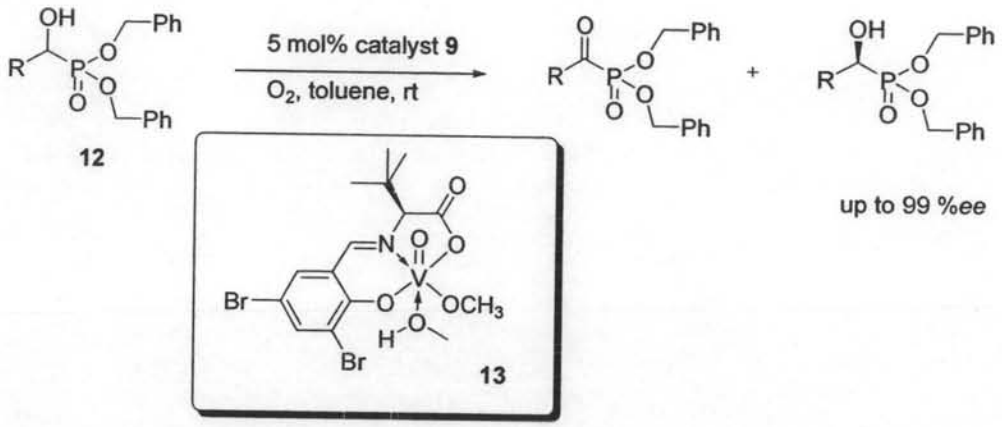


Figure 1.15 Highly enantioselective aerobic oxidation of α-hydroxyphosphonates **12** catalyzed by chiral vanadyl(V) methoxides **13** bearing *N*-salicylidene-α-aminocarboxylates

Enantioselective cyanosilylation of aldehyde catalyzed by Schiff's base of *N*-salicyl-β-aminoalcohol was achieved since 1993 by Oguni. [*22*] The catalyst (*S*)-**14** was the most efficient catalyst for a variety of aldehydes **15** (aromatic, heteroaromatic, α,β-unsaturated, and nonconjugate aliphatic aldehydes). Enantioselectivities of products **16** vary in the range of 20-96 %*ee*. Absolute configurations of products are (*R*)-isomer (Figure 1.16). A transition-state structure which corresponded with the product configuration had been proposed (Figure 1.17).

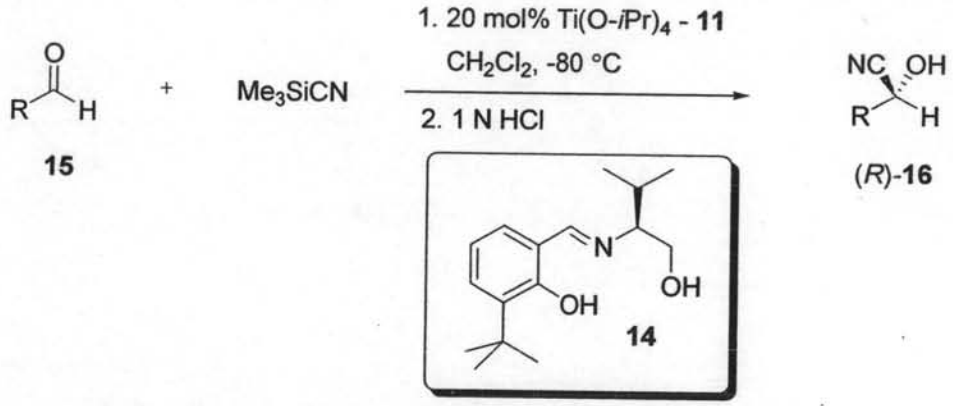


Figure 1.16 Enantioselective cyanosilylation of aldehyde

In addition, Zhang also reported a highly enantioselective cyanosilylation of aldehydes catalyzed by *N*-salicyl-β-aminoalcohol-titanium complexes in 2004.[*23*] In the presence of 5 mol% of **17**-Ti(O-^{i}Pr)$_4$ complex catalyst, the aromatic, conjugated, heteroaromatic, and aliphatic aldehydes **18** were converted to their corresponding trimethylsilyl ethers of cyanohydrins (*S*)-**19** in 90-99 %yields with up to 94 %*ee* under mild conditions (Figure 1.18). A working model was proposed (Figure 1.19).

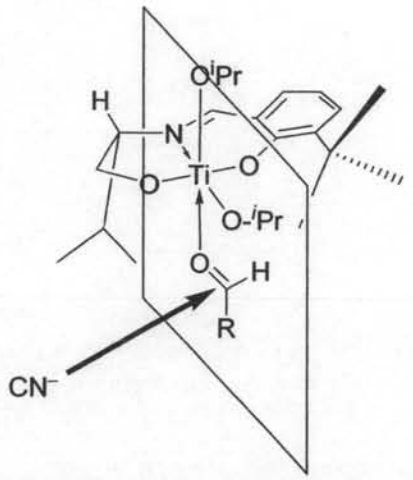


Figure 1.17 A proposed transition-state which led to the formation of (*R*)-**16**

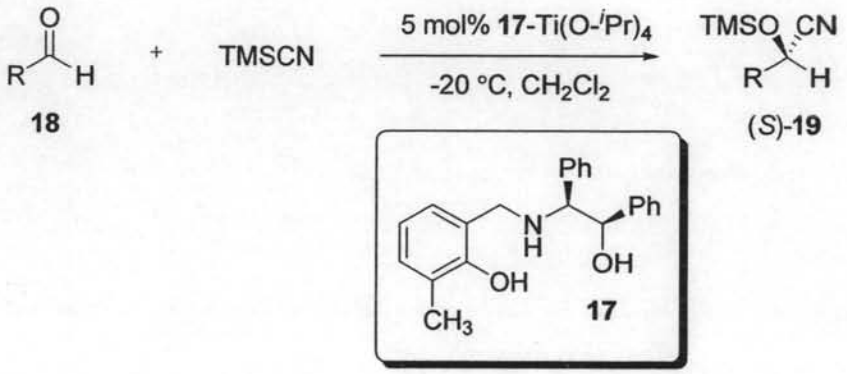


Figure 1.18 Highly enantioselective cyanosilylation of aldehydes catalyzed by *N*-salicyl-β-aminoalcohol-titanium complexes

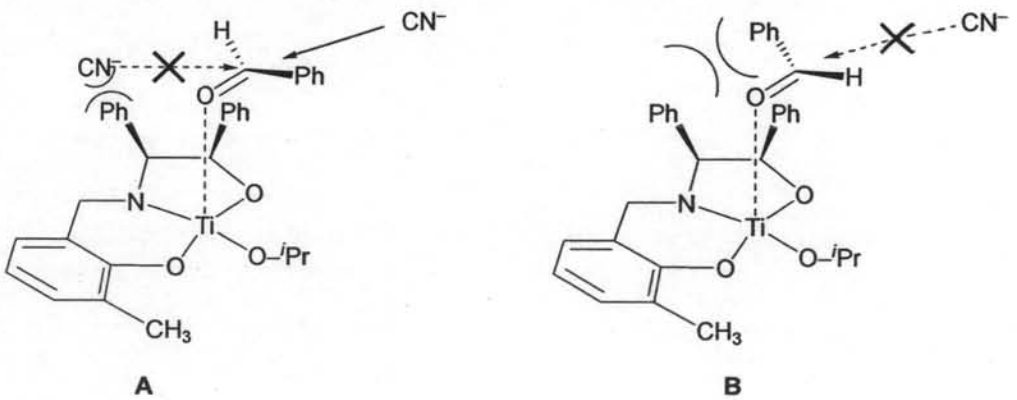


Figure 1.19 Proposed working model for asymmetric cyanosilylation of benzaldehyde

In 1999, an efficient enantioselective ring opening of meso aziridines **20** by $TMSN_3$ using tridentate Schiff's base chromium complex **21** derived from 1-amino-2-indanol was reported by Jacobsen.[*24*] The enantioselectivities were up to 94 %*ee* (Figure 1.20).

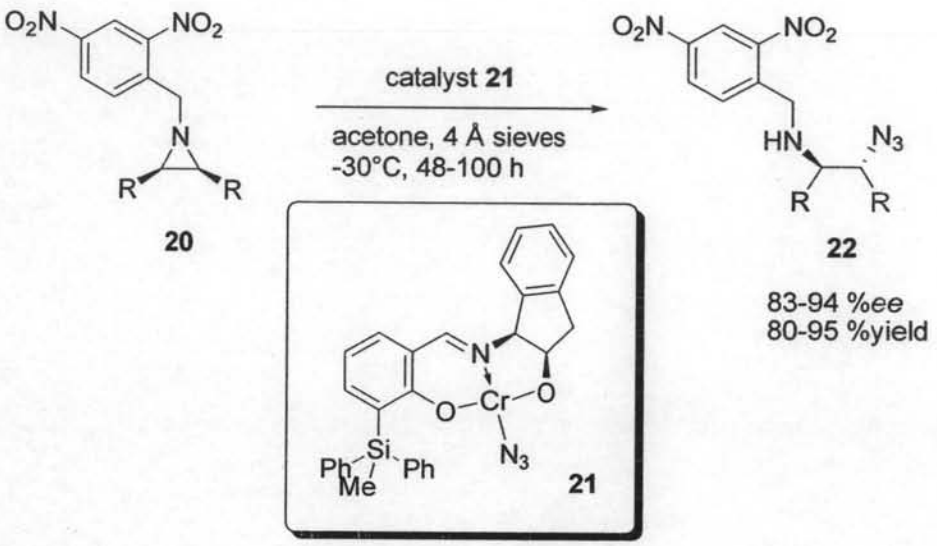


Figure 1.20 An enantioselective ring opening of meso aziridines by $TMSN_3$

For asymmetric Michael reaction catalyzed by metal complexes of *N*-salicyl-β-aminoalcohol ligands and some metals, it was firstly reported by Narasimhan in 2001. Ligands **23** and **24** which were complexed with $LiAlH_4$ as heterobimetallic catalysts were shown to be effective in Michael reaction between diethyl malonate and cyclohexenone in moderate %yield and %*ee*. In addition, they also reported the enantiomer switching phenomenon of products from using $LiAlH_4$: ligand ratio of 1:1 to 1:2 (Figure 1.21). [*25-26*]

In Narasimhan's work, the effect of the R groups on the salicyl and the amino alcohol moieties has not been thoroughly investigated. Only isopropyl, isobutyl, *sec*-butyl, and benzyl groups were studied. In 2004, Vilaivan and Srikaenjan [*27*] had achieved a systematic study on structure-activity relationship on the efficiency of the heterobimetallic catalysts derived from $LiAlH_4$ and *N*-salicyl-β-aminoalcohol ligands in an asymmetric Michael addition. A series of ligands with a variation of groups on the salicyl and aminoalcohol moieties have been prepared. These ligands have been employed in a Michael reaction between cyclic α,β-unsaturated ketones

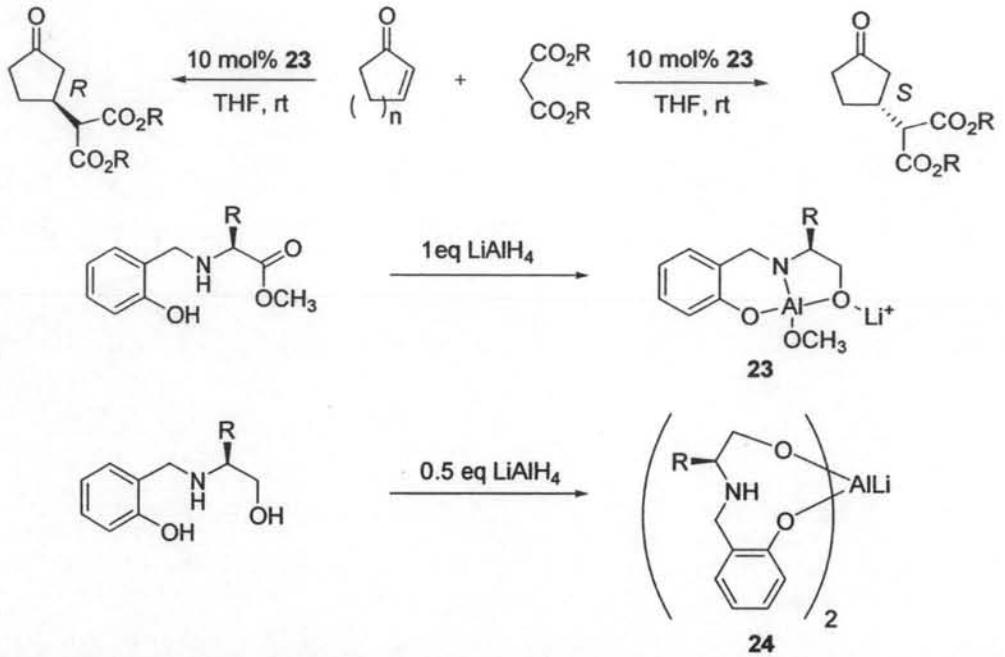


Figure 1.21 Michael reaction of malonate ester to enone catalyzed by Li-Al-*N*-salicyl-β-aminoalcohol complexes

and malonates. Furthermore, other classes of ligands, for instance, other groups of aminoalcohols such as C_2-symmetrical amino alcohols have also been studied. The best result was obtained from using ligand **25** which was synthesized from salicylaldehyde and (*S*)-*t*-leucinol. The highest enantioselectivity observed was 88 % from the reaction between 2-cyclohexen-1-one and di-*t*-butylmalonate using 10 mol% $LiAlH_4$ and 10 mol% **25** as an asymmetric catalyst. The absolute configuration of the product was determined to be (*R*). Moreover, the metal : ligand ratio of 1:1 led to higher enantioselectivities than when the 1:2 ratio was administered. This result is in contrast with what was previously reported by Narasimhan[*25-26*] (Figure 1.22).

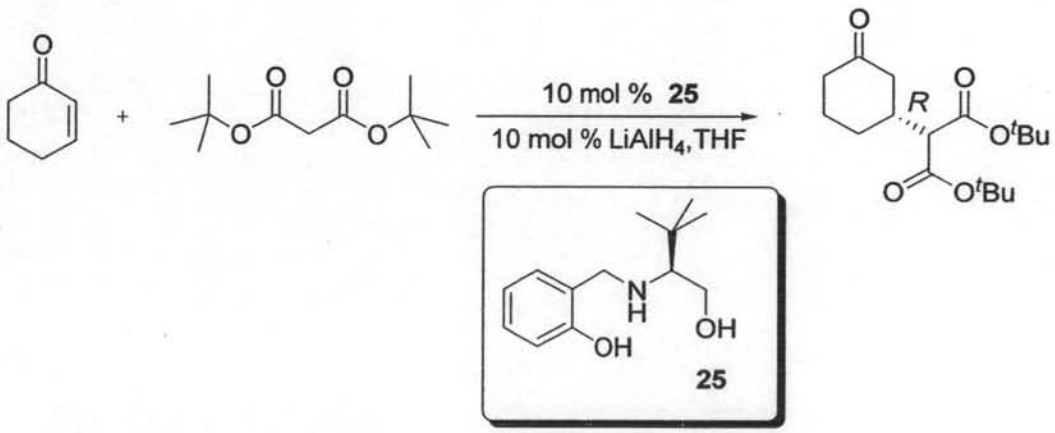


Figure 1.22 Michael reaction of di-*t*-butylmalonate to 2-cyclohexen-1-one catalyzed by a complex between $LiAlH_4$ and ligand **25**

Recently, Vilaivan and coworkers[*28*] reported that *N*-salicyl-β-amino alcohols **26**, derived from (*S*)-phenylalaninol, were evaluated as the best ligand for catalytic asymmetric Strecker reactions. *N*-Benzhydrylaldimines derived from aromatic and aliphatic aldehydes have been shown to react with TMSCN in the presence of 10 mol% of Ti-**26** complex to give the Strecker products in excellent yields and in up to > 98%*ee*. The absolute configuration of the product was (*S*). The presence of isopropanol as a protic additive is essential to ensure good conversion and reaction rate (Figure 1.23).

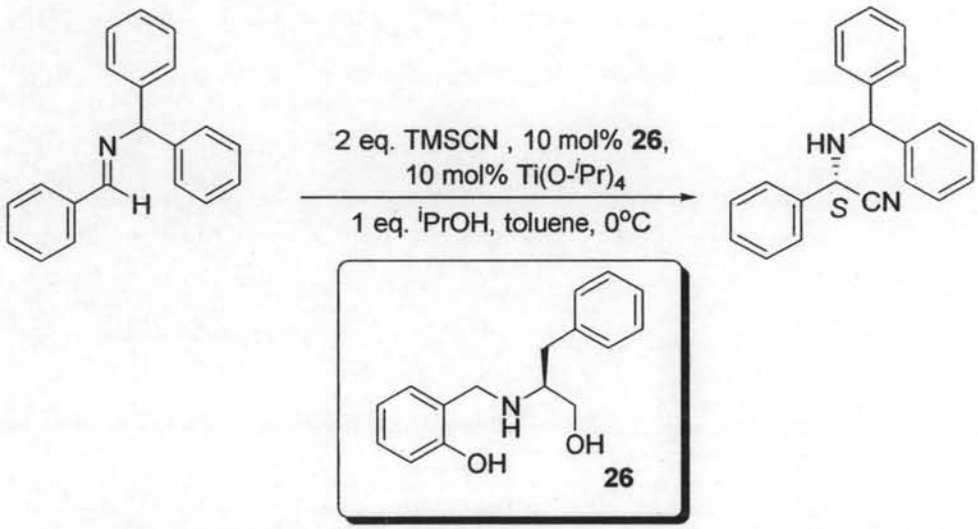


Figure 1.23 Enantioselective Strecker reaction between *N*-benzhydrylaldimine and trimethylsilylcyanide catalyzed by a complex between $Ti(O\text{-}^{i}Pr)_4$ and ligand **26**

Furthurmore, Vilaivan and coworkers [*29*] were the first to discover that heterobimetallic complexes between *N*-salicyl-β-aminoalcohol and $LiAlH_4$ could be an asymmetric catalyst for hydrophosphonylation of aldehydes. The bulkiness of substituents on the salicyl and β-amino alcohol moieties plays a significant role in the induction of enantioselectivities. The catalyst from ligand **27** is the most efficient in the reaction between aliphatic or aromatic aldehydes and diethylphosphite to give the corresponding α-hydroxyphosphonate in moderate yields (59-89 %) and moderate enantioselectivities (32-72 %*ee*) (Figure 1.24).

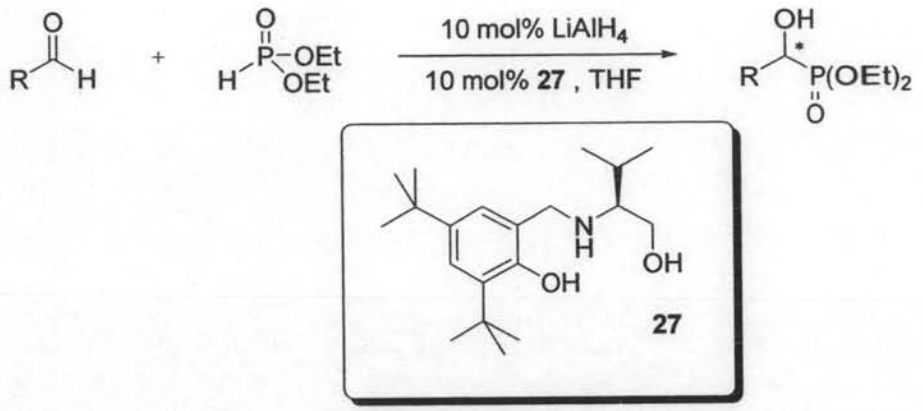


Figure 1.24 Asymmetric hydrophosphonylation reaction between various aldehydes and diethylphosphite catalyzed by heterobimetallic complex of $LiAlH_4$ and ligand **27**

1.6 Amino alcohol ligands containing naphthyl groups

A few examples of amino alcohols containing a naphthyl group have been reported as efficient chiral ligands in asymmetric reactions. In 2001 Chan and coworkers[*30*] reported the use of optically active aminonaphthol **28** which was obtained by condensation of 2-naphthol, benzaldehyde, and (*S*)-methylbenzylamine followed by *N*-methylation. Ligand **28** was found to catalyze an enantioselective ethylation of aryl aldehydes to secondary alcohols with high enantioselectivities (up to 99.8%) at room temperature (Figure 1.25).

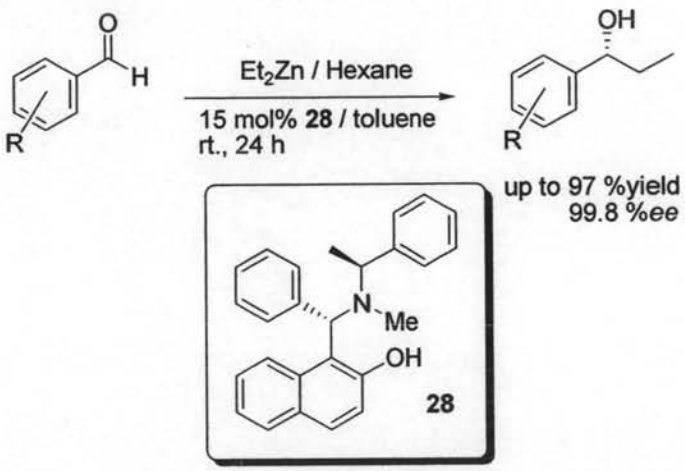


Figure 1.25 Enantioselective addition of diethylzinc to aryl aldehyde in the presence of chiral aminonaphthol

In addition, with the same ligand, in 2003 Chan and coworkers[*31*] also reported an enantioselective alkenylation of various aldehydes with high *ee* values (up to 98 %*ee*), which provide a practical method for the synthesis of chiral (*E*)-allyl alcohols (Figure 1.26).

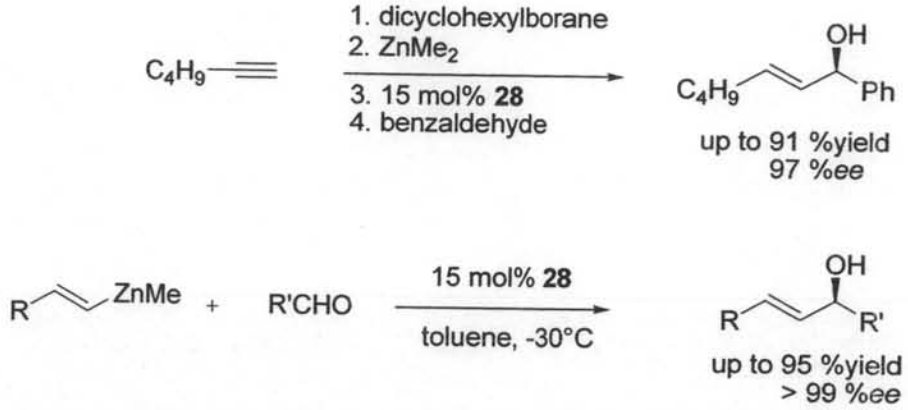


Figure 1.26 Enantioselective alkenylation of various aldehydes in the presence of chiral aminonaphthol

Furthurmore, in 2005, the same group of researchers demonstrated that a new chiral tertiary aminonaphthol ligand **29** could serve as a highly efficient ligand for the asymmetric catalytic phenyl transfer to aromatic aldehydes. As a result, a variety of chiral diarylmethanols was prepared in high *ee* values (up to 99%).[*32*] They also reported using ligand **28**, bearing a phenyl group at a new stereogenic center in the reaction leading to 89 %*ee* of the product, the maximum *ee* observed in this case. Compared to **28**, ligand **29** which bears a 1-naphthyl group at a new stereogenic center, afforded the best *ee* of up to 99 %. From the data, they surmised that the attachment of a bulkier group at a new stereogenic center should favor a selection of a conformationally more restricted transition state, which should be beneficial for stereochemical induction. (Figure 1.27) Their discussion relied mainly on a steric hindrance and the difference of electronic effect, either of phenyl and naphthyl group, on stereochemical induction was not mentioned.

As discussed earlier, several literatures have demonstrated that metal complexes derived from chiral *N*-salicyl-β-aminoalcohol ligands constitute an important class of catalysts with high potentials for asymmetric induction in various catalytic asymmetric reactions. However, the most bulky substituent on the aminoalcohol moiety which has been synthesized thus far is the *t*-butyl group. Naphthyl groups, or other bulky groups which not only are considered sterically hindered, but also possess the origin of a large electronic effect because their 10-π electron systems offer themselves as potential new group to investigate. Perhaps, some interactions which is non-existing in aliphatic substituents, such as π-π stacking interactions, can assist in pertaining the rigidity of the transition state and promote an improved face selectivity in catalytic asymmetric reactions.

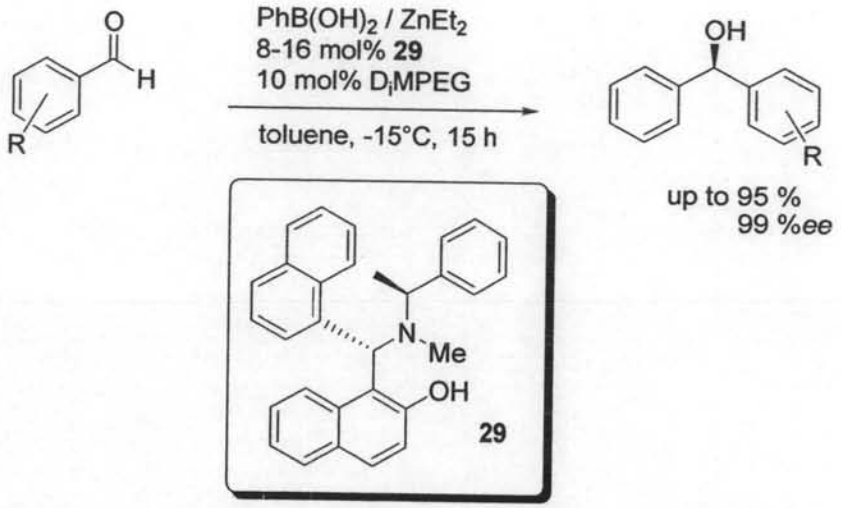


Figure 1.27 Catalytic asymmetric phenyl transfer to aromatic aldehydes

In light of this basis, we chose to focus on the synthesis of optically active *N*-salicyl-β-naphthyl aminoalcohol ligands. In addition, their potentials as chiral ligands in various asymmetric reactions would be investigated. A key intermediate in the synthesis is enantiopure α-naphthylglycinol which has been synthesized by several methods. A review on α-naphthylglycinol synthetic pathways will be discussed in the next topic.

1.7 Several methods of α-naphthylglycinol synthesis pathways: Literature reviews

The retrosynthetic diagram of α-naphthylglycinol is shown in Figure 1.28.

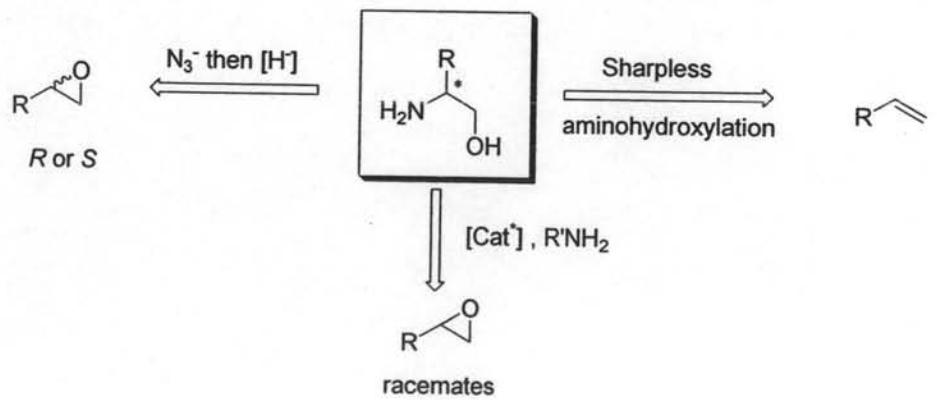


Figure 1.28 The retrosynthetic analysis of naphthyl beta amino alcohol (R = 1- or 2-naphthyl)

A method to synthesize α-naphthylglycinol is Sharpless asymmetric aminohydroxylation of vinyl naphthalene which was reported in 1998 by Sharpless and coworkers.[*33*] *N*-boc-2-naphthylglycinol was synthesized in high %*ee* (up to 98 %) and moderate yields (70 %). The control of enantioselectivity could be achieved by changing a chiral ligand to the opposite enantiomers (Figure 1.29).

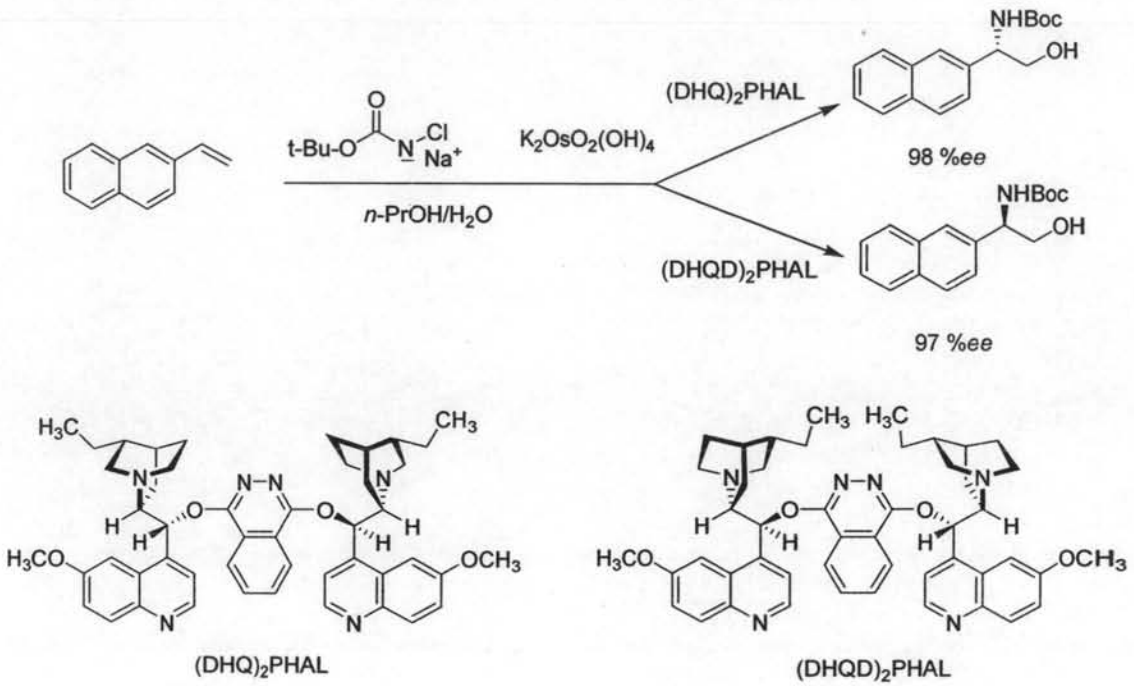


Figure 1.29 Sharpless aminohydroxylation of 2-vinylnaphthalene

Recently, in 2004 Bartoli and coworkers reported the synthesis of optically active phenylglycinol derivatives from racemic *trans*-aromatic epoxides and anilines *via* aminolytic kinetic resolution (AKR) catalyzed by chromium salen catalyst **30**.[*34*] The process affords enantioenriched *anti*-β-aminoalcohols in up to 99 %*ee*. However, naphthyl oxiranes have not been the reactant of this resolution (Figure 1.30).

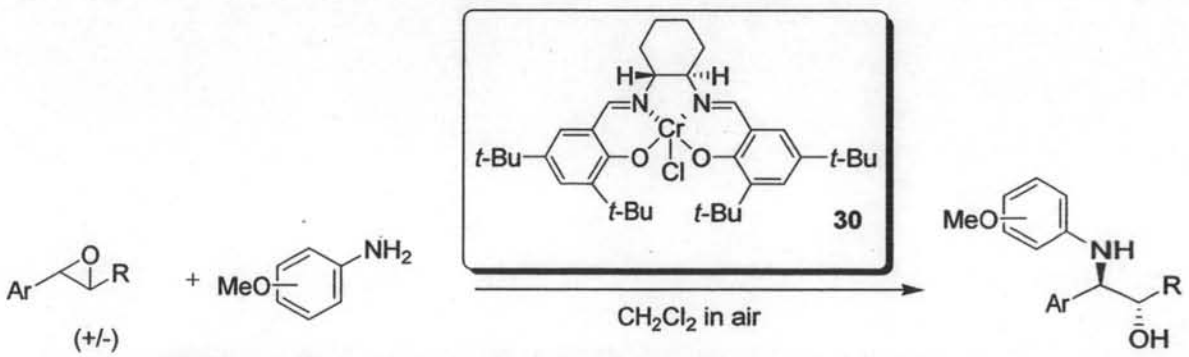


Figure 1.30 Asymmetric aminolysis of aromatic epoxides

Within the same year, Bartoli's group reported another aminolytic kinetic resolution of racemic terminal epoxides using carbamates as the nucleophile catalyzed by cobalt(III) salen complex **31**. This provided a practical and straightforward method for the synthesis of both aliphatic and aromatic *N*-Boc- or *N*-Cbz-protected 1,2-amino alcohols in almost enantiomerically pure form (> 99 %*ee*). (Figure 1.31)[*35*] In case of racemic styrene oxide, the corresponding *N*-Boc-amino alcohol was afforded in 90 % and the enantioselectivity was 99.9 %. Racemic naphthyl oxiranes have not been tested with this resolution either. The most interesting point of this aminolytic kinetic resolution is the regioselectivity. Only products from the β-attack, the less partially positively-stabilized and sterically hindered position, of terminal epoxides were investigated in all cases. The protected aminoalcohol from this method can be conveniently deprotected to the corresponding aminoalcohols.

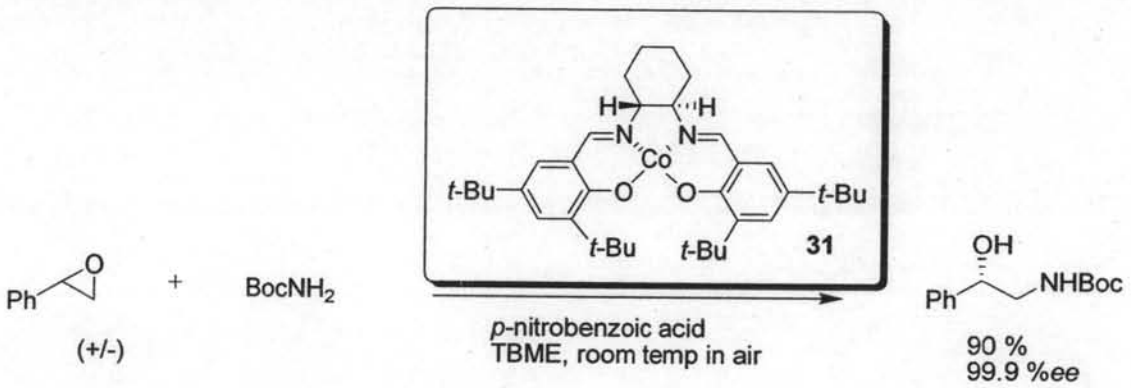


Figure 1.31 Aminolytic kinetic resolution of racemic styrene oxide with $BocNH_2$ catalyzed by cobalt(III)salen complex

The other potential method for the synthesis of α-naphthylglycinol is a ring-opening of optically active naphthyloxirane with an azide ion, followed by reduction. The retrosynthetic analysis is shown in Figure 1.32. There are several methods available for the synthesis of the pre-requisited oxirane.

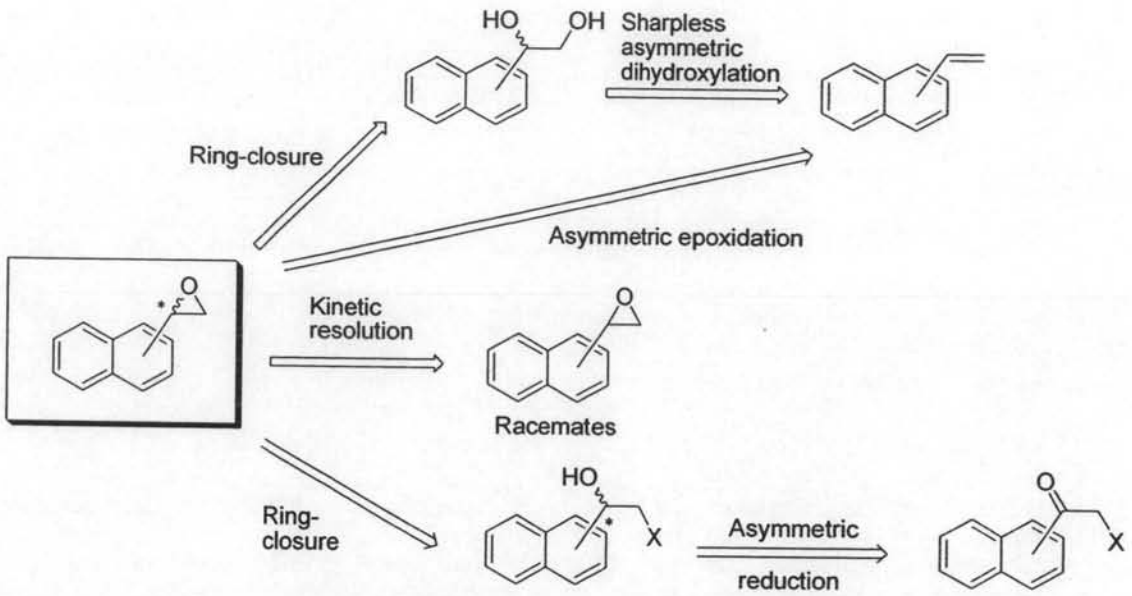


Figure 1.32 Retrosynthetic analysis of chiral naphthyl oxiranes

1.7.1 Asymmetric dihydroxylation

In 1998 Rawal and coworkers [*36*] reported the synthesis of (*R*)-2-(naphthalen-1-yl)oxirane from 1-vinylnaphthalene by Sharpless asymmetric dihydroxylation, followed by cyclization to the epoxide. Enantioselectivity was up to 96 % (Figure 1.33).

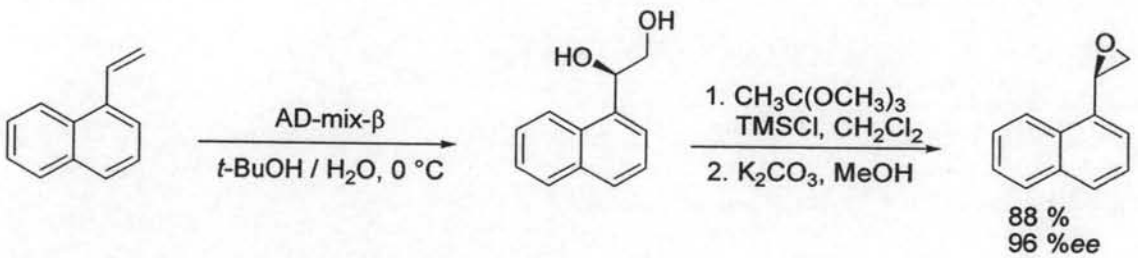


Figure 1.33 Sharpless asymmetric dihydroxylation of 1-vinylnaphthalene followed by cyclization to (*R*)-2-(naphthalen-1-yl)oxirane

1.7.2 Asymmetric epoxidation

The catalysts in asymmetric epoxidation of alkene can be categorized into several groups. The first is chiral porphyrin derivarives. In 1997 Kodadek[*37*] reported the synthesis of (*R*)-2-(naphthalen-2-yl)oxirane from 2-vinylnaphthalene by asymmetric epoxidation catalyzed by chloromanganese(III) derivative of chiral D_4-symmetric porphyrins. LiClO has been used as a terminal oxidant and dicyclohexyl imidazole as the axial ligand in a phase transfer system. The yield and enantioselectivity were moderate (Figure 1.34).

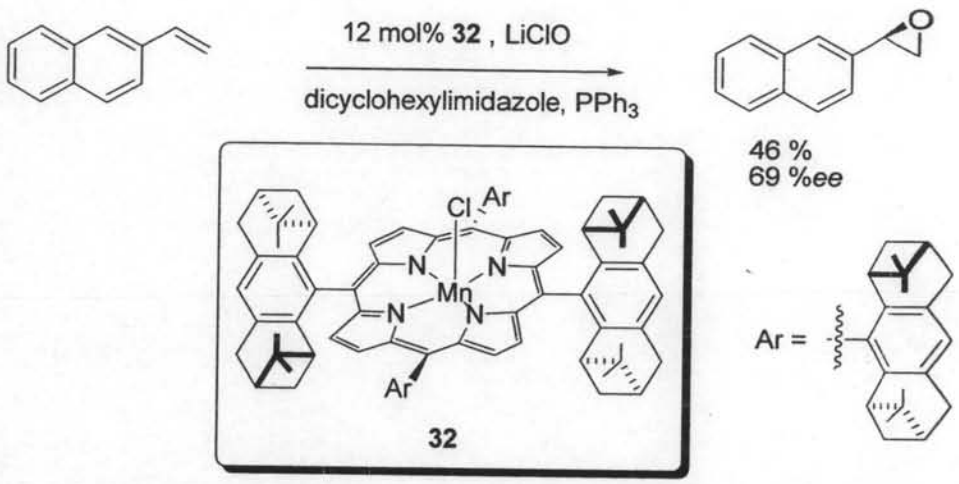


Figure 1.34 Asymmetric epoxidation of 2-vinylnaphthalene to (*R*)-2-(naphthalen-2-yl)oxirane catalyzed by chloromanganese(III) derivative of chiral D_4-symmetric porphyrins

In addition, in 2001 Che and coworkers[*38*] had demonstrated an asymmetric epoxidation of vinylnaphthalene by the use of 2,6-dichloropyridine *N*-oxide (Cl_2pyNO) as a terminal oxidant with a D_4-symmetric chiral dichlororuthenium(IV) porphyrin **33** as catalyst. The enantioselectivity of (*R*)-2-(naphthalen-2-yl)oxirane slightly increased from using of the previous porphyrin catalyst to 72 % (Figure 1.35).

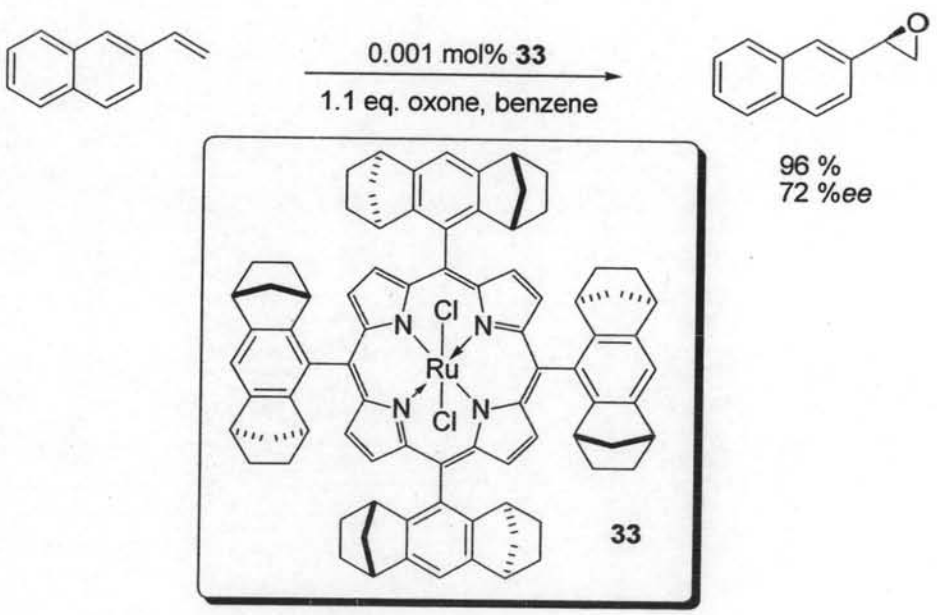


Figure 1.35 Asymmetric epoxidation of 2-vinylnaphthalene to (*R*)-2-(naphthalen-2-yl)oxirane catalyzed by D_4-symmetric chiral dichlororuthenium(IV) porphyrin

After that, in 2002 [*39*] the same research group reported the use of catalyst **33** which was encapsulated in highly ordered mesoporous molecular sieves (MCM-41 and MCM-48) for asymmetric alkene epoxidation with the same procedure of the prior report. This method slightly improved the enantioselectivity of (*R*)-2-(naphthalen-2-yl)oxirane from 72 to 77 %*ee*.

The next group of chiral catalyst in asymmetric epoxidation of alkene is chiral ketone which was firstly developed by Shi and coworkers. In 1999 [*40*] they reported using a pseudo C_2 symmetric ketone **34** as a catalyst for asymmetric epoxidation of 2-vinylnaphthalene. However, the asymmetric induction ability was efficient with only electron deficient alkenes such as enones. The enantioselectivity of (*R*)-2-(naphthalen-2-yl)oxirane from this method was quite low (54 %). Nevertheless, in 2001[*41*] the same group reported a utilization of chiral dioxirane derived from **35** as a new catalyst. The enantioselectivity of (*R*)-2-(naphthalen-2-yl)oxirane had been improved to 84% (Figure 1.36).

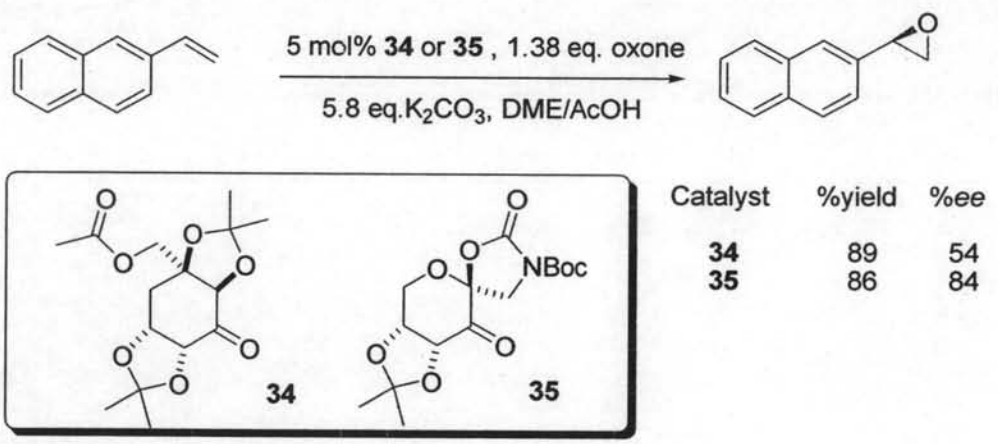


Figure 1.36 Asymmetric epoxidation of 2-vinylnaphthalene to (*R*)-2-(naphthalen-2-yl)oxirane catalyzed by chiral ketone catalyst

The last group of chiral ligand is salen-based. In 1990 Jacobsen and coworkers [*42*] reported enantioselective epoxidation of unfunctionalized olefins catalyzed by (Salen)manganese complex **36**. The reactions were carried out in air with iodomesitylene as oxygen atom source. In the case of 2-vinylnaphthalene, enantioselectivity is 78 %. The absolute configuration of the corresponding product which was implied from the sign of optical rotation value was (*S*) (Figure 1.37).

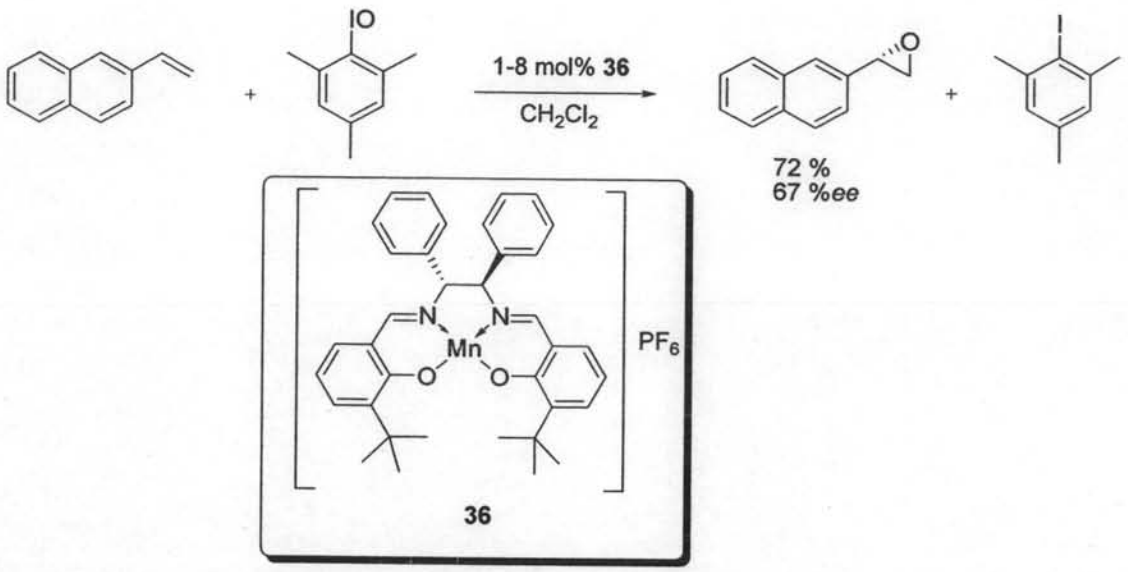


Figure 1.37 Asymmetric epoxidation of 2-vinylnaphthalene catalyzed by (Salen)manganese(III) complex

From all of the reviews discussed above, the synthesis of chiral naphthyl oxirane by asymmetric epoxidation of the corresponding alkene is only moderately effective and the enantioselectivity of the oxiranes appeared to be relatively low.

1.7.3 Kinetic resolution of racemic oxirane

1.7.3.1 The principle of kinetic resolution[*1*]

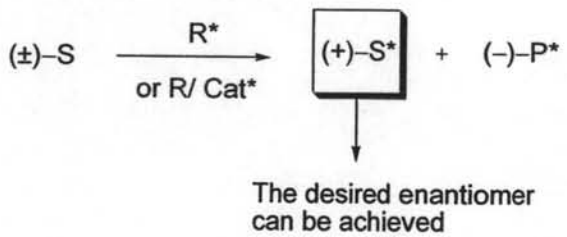


Figure 1.38 A diagram of classical kinetic resolution

Kinetic resolution is a conventional procedure to separate a racemic mixture of chiral compounds or achiral compounds containing equivalent enantiotopic groups. This kind of resolution is based on a fact that the rate of reaction of an enantiomer in a racemic mixture or an enantiotopic group in an achiral compound is different from that of the other when the reaction is performed under an unsymmetrical environment, developed by another chiral reagent or chiral catalyst which cooperates with the achiral reagent. From Figure 1.38, one enantiomer ((-)-S) may react faster whereas the

other, (+)-S, may react adequately more slowly or not at all. When the resolution has proceeded to completion, an enrichment of the enantiomer which reacted more slowly, (+)-S, can be achieved. Simultaneously, a new enriched product, (-)-P, is obtained. However, it is not possible for the maximum yield of a desired enantiomer or a new enriched product from classical resolution to exceed 50%. This is a disadvantage of this method.

A new enriched product, (-)-P, can be afforded in more than 50% yield under certain circumstances known as a dynamic kinetic resolution (DKR).[*43*] A pair of enantiomers need to be interconvertible with each other *via* a chemical equilibrium. When (-)-S which reacts with a reagent faster are converted to (-)-P, the decreasing amount of (-)-S is compensated by a conversion from (+)-S, which reacts with chiral reagent or catalyst more slowly than (-)-S, *via* a chemical equilibrium. Hence, the yield of (-)-P from DKR can up to 100% as maximum yield in principle (Figure 1.39).

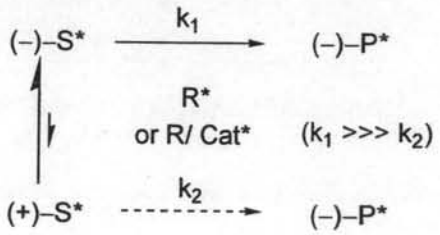


Figure 1.39 A diagram of dynamic kinetic resolution (DKR)

1.7.3.2 Kinetic resolution of racemic oxiranes

In 2002 Jacobsen and coworkers reported hydrolytic kinetic resolution (HKR) of a variety of racemic terminal epoxide catalyzed by (Salen)cobalt(III) complex **37**.[*44*] In case of styrene oxide, using only 0.8 mol% of catalyst and 0.55 equivalent of H_2O afforded the enriched styrene oxide in 44 %yield and > 99 %*ee* after 72 hours. Simultaneously, the enriched diol was obtained in 42 %yield and 98 %*ee*. However, applications of HKR to naphthyloxirane substrates has not been reported (Figure 1.40).

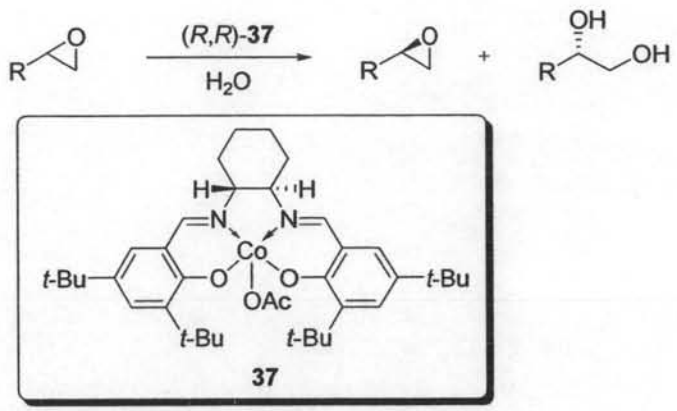


Figure 1.40 A hydrolytic kinetic resolution (HKR) of terminal epoxide

1.7.4 Asymmetric reduction of α-haloacetophenone or α-sulfonyloxy acetophenone

The synthesis of chiral non-racemic oxirane *via* asymmetric reduction of ketones bearing and α-leaving group is an efficient and well-known method with precedent reports including the use of chiral auxiliaries, chiral reagents, or chiral catalysts. Asymmetric reduction by chiral borane reagents and catalysts were consecutively developed and reported by Cho. In 2001 [*45*] they reported a facile synthesis of optically active styrene oxide derivatives, including 1- and 2-naphthyloxirane, by asymmetric reduction of substituted 2-(*p*-toluenesulfonyloxy)acetophenone with (-)-*B*-chlorodiisopinocampheylborane (Ipc_2BCl). In case of 1- and 2-naphthyloxirane, only moderate enantioselectivities were obtained (65 % and 72 % for 1- and 2-naphthyloxirane, respectively) (Figure 1.41).

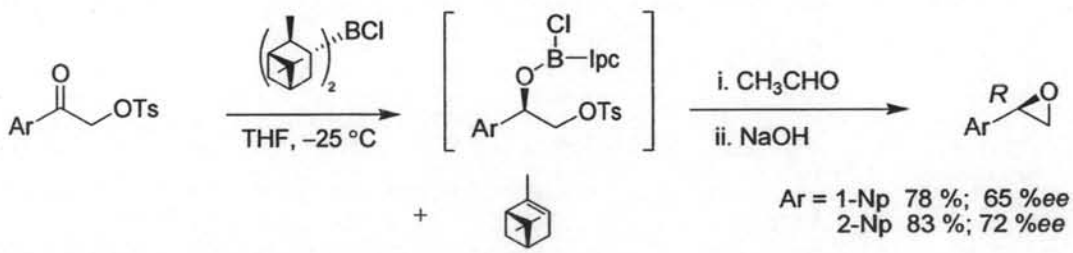


Figure 1.41 Asymmetric reduction of substituted 2-sulfonyloxyacetophenones with (-)-*B*-chlorodiisopinocampheylborane (Ipc_2BCl)

Later in the same year they also revealed a synthesis of optically active 1,2-diol monosulfonates and terminal epoxides *via* oxazoborolidine **38** as catalyst in asymmetric borane reduction of α-sulfonyloxy ketone. [*46*] (*S*)-2-(naphthalen-2-

yl)oxirane was synthesized by this method in very high yield (97 %) and enantioselectivity (100 %*ee* based on optical rotation analysis) (Figure 1.42).

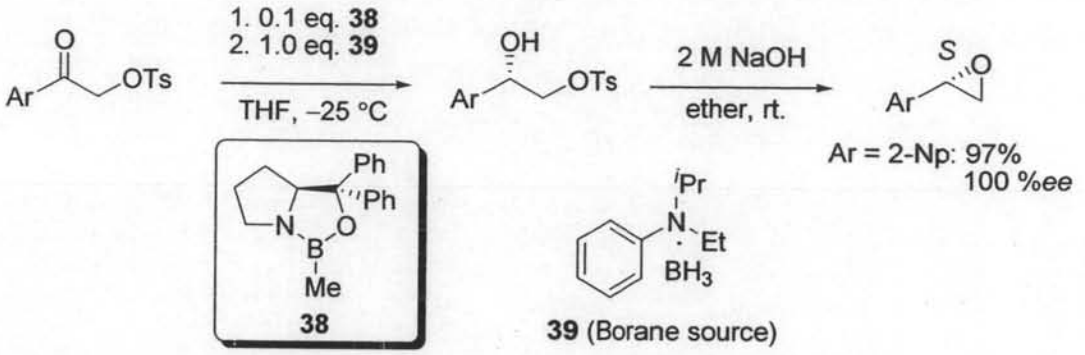


Figure 1.42 Asymmetric reduction of 2-sulfonyloxyacetophenones catalyzed by oxazoborolidine

Furthermore, in 2003, they reported a facile synthesis of enantiopure 1,2-diols and terminal epoxides from catalytic asymmetric reduction of chiral β-ketosulfides using the same oxazoborolidine **38** as catalyst and *N*-ethyl-*N*-isopropylanilineborane **39** as the borane source.[*47,48*] (*S*)-2-(naphthalen-2-yl)oxirane was also synthesized in 93 %yield and 99 %*ee* (Figure 1.43).

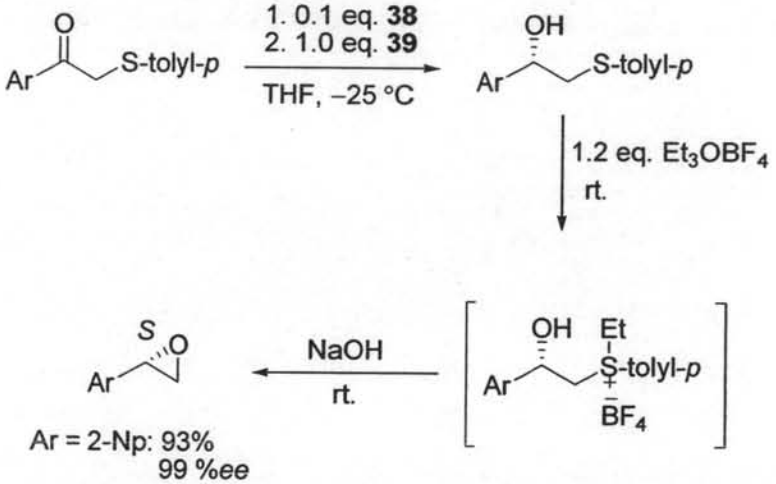


Figure 1.43 Asymmetric reduction of β-keto *p*-tolylsulfides catalyzed by oxazoborolidine

Recently, enantioselective reduction of representative 2-(bromoacetyl)- and 2-(chloroacetyl)benzofurans with (-)-Ipc_2BCl was reported by Zaidlewicz and coworkers.[*49*] The range of enantioselectivity of the corresponding (*R*)-halohydrin was between 92 to 98 %*ee* when the leaving group was chlorine. The enantioselecitvities were drastically decreased when bromine was used as a leaving group (73 to 88 %*ee*) (Figure 1.44).

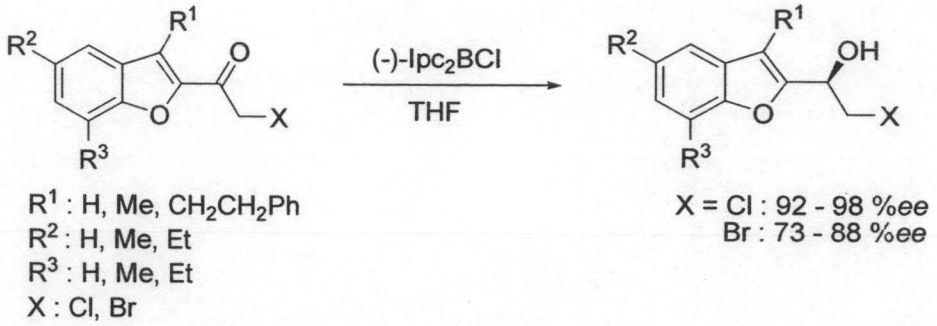


Figure 1.44 Enantioselective reduction of representative 2-(bromoacetyl)- and 2-(chloroacetyl)benzofurans with (-)-Ipc_2BCl

Asymmetric reductions of α-chloroacetophenone derivatives by chiral rhodium or ruthenium catalyst have been developed continuously since 2002.[*50-53*] Noyori and coworkers[*54*] reported the synthesis of optically active styrene oxides *via* a formation of optically active 2-chloro-1-phenylethanols generated by reductive transformation of ring-substituted 2-chloroacetophenones catalyzed by a well-defined chiral Rh complex, Cp*RhCl[(*R*,*R*)-Tsdpen] **40**. The optically active alcohols with up to 98%*ee* are obtainable from the asymmetric reduction of acetophenones (Figure 1.45).

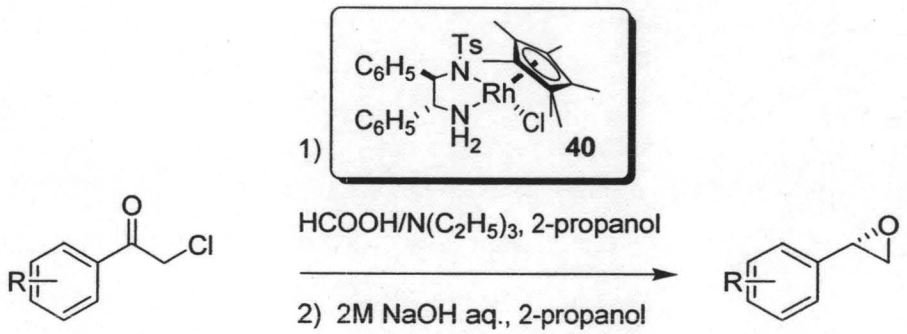


Figure 1.45 Synthesis of optically active styrene oxide *via* reductive transformation of 2-chloroacetophenones with chiral rhodium catalyst

More recently, Wills and coworkers[*55*] have demonstrated the use of the reverse-tethered ruthenium (II) catalyst **41** for asymmetric transfer hydrogenation reaction of 2-chloroacetophenone derivatives. The absolute configuration of the major enantiomer was (*R*) with 97 %*ee* as the highest (Figure 1.46).

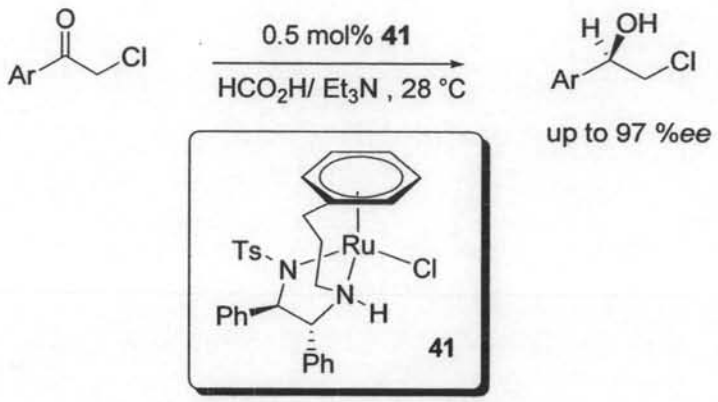


Figure 1.46 Asymmetric transfer hydrogenation using of the reverse-tethered ruthenium(II) as catalyst

1.8 Objectives of this research

The objectives of this research are to prepare two chiral *N*-salicyl-β-naphthylaminoalcohols which are anticipated to be synthesized from the corresponding chiral 1- and 2-naphthylglycinols. In the course of the synthesis, it is aimed to develop efficient methodologies for chiral naphthyl oxirane and chiral naphthyl glycinol synthesis. Emphasis will be made by focusing on convenient and effective methods employing commercially available reagents. In addition, we will focus on evaluating the efficiency of the newly synthesized ligands in some known catalytic asymmetric reactions, such as Strecker reaction, Michael addition, and hydrophosphonylation of aldehydes catalyzed by heterobimetallic catalysts.