CHAPTER I

INTRODUCTION

1.1 What causes chirality?

Chirality is a fundamental symmetry property of three-dimensional objects. An object is chiral if it cannot be superimposed upon its mirror image. In a chemical context, chirality is applied to the three-dimensional structure of molecules. Many compounds may be obtained in two different forms in which the molecular structures are constitutionally identical but differ in the three-dimensional arrangement of atoms such that they are related as mirror images. In such a case the two possible forms are called enantiomers and are said to be enantiomeric with each other. To take a simple example, the amino acid alanine can be obtained in two forms (**1**) and (**2**) which are clearly related to each other as mirror images.

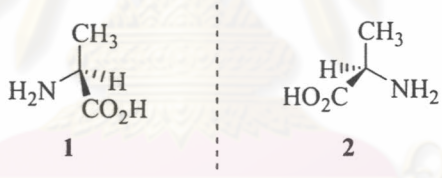


Figure 1. The amino acid alanine in two enantiomeric forms (**1**) and (**2**).

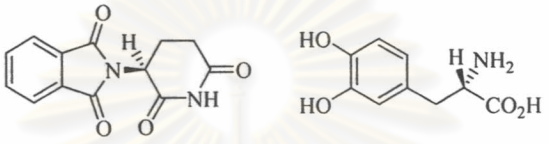
Enantiomers have identical chemical and physical properties, such as melting point, solubility, chromatographic retention time, IR and NMR spectra. There are two properties in which enantiomers do differ and these are the direction in which they rotate the plane of polarized light and their interactions with other chiral molecules.

1.2 The biological significance of chirality: need for asymmetric synthesis

Chirality is a characteristic of nature. Compounds that occur in nature are optically active because living organisms tend to produce only a single enantiomer of a given molecule. Optical activity of these molecules arises from the inherent chirality of enzymes that are responsible for their production. Receptor sites in biological systems, which are also optically active, have the ability to differentiate between two enantiomers of a specified molecule. Therefore, the two enantiomers of a biologically

active chiral compound should interact differently with its receptor sites which is also chiral.

A good example is the drug thalidomide (**3**) for which both enantiomers have the desired sedative effect but the (-)-enantiomer (shown here) also cause foetal deformities. Unfortunately the drug was used clinically as an equal mixture of the two enantiomers during 1960 and have led to several deformation of newly born children during that period.[*1*]



(3) (4)

Figure 2. The drug thalidomide (**3**) and DOPA (**4**).

Another interesting example is the case of DOPA (**4**) used in the treatment of Parkinson's disease. The active drug is the achiral compound dopamine formed from (**4**) by decarboxylation, but this cannot cross the 'blood-brain barrier' to reach the required site of action. However, the 'prodrug' (**4**) can, and is then decarboxylated by an enzyme called dopamine decarboxylase. The enzyme, however, is specific and only decarboxylates the (-)-enantiomer of (**4**) (the form shown here). It is therefore essential to administer DOPA as the pure (-)-enantiomer otherwise there would be a build up of (+)-(**4**) in the body, which could not be metabolized by enzymes, to a dangerous level.[*1*]

Although it would be desirable to use all biologically active compounds as pure active stereoisomer, this would be prohibitively expensive in some cases. However, it has now become necessary to synthesize and evaluate all the possible isomers of a new biologically active compound before it is put into use.

1.3 Methods of asymmetric synthesis

Asymmetric synthesis is a method for construction of one or more new chiral center. It may be defined as a synthesis in which an achiral unit in an ensemble of substrate molecules is converted to a chiral unit such that the possible stereoisomers are formed in unequal amounts. Asymmetric synthesis aims to achieve the highest possible proportion of the desired enantiomer. An important parameter to describe the

degree of enantioselectivity achieved is called enantiomeric excess (*ee*). The enantiomeric excess was calculated by equation (1).

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

% *ee* = percent enantiomeric excess

R = the amount of *R* enantiomer *S* = the amount of *S* enantiomer

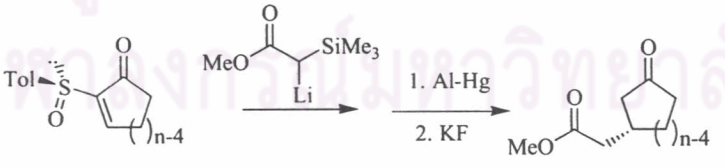
The known methods for asymmetric synthesis can be conveniently divided into four major classes, depending on how this influence is exerted, as follows:

1.3.1. First generation asymmetric synthesis or chiral substrate-controlled

The formation of the new steriogenic unit occurs by reaction with an achiral reagent at diastereotopic site controlled by a stereogenic unit already present in the substrate molecule as shown in scheme **1**.

Scheme 1. Chiral substrate controlled.

An example is the asymmetric Michael addition of ester enolate ions to butenoid sulfoxide (*S*)-(+)-**5** which proceeded smoothly in a non-chelate mode to form, after reductive cleavage of the sulfinyl group, the 1,5-dicarbonyl adduct (*S*)-(+)-**6** in 70-95 % *ee*.[*2*]



5a, n=5
5b, n=6

(*S*)-(+)-**6a** n=5, 70 % *ee*
(*S*)-(+)-**6b** n=6, 95 % *ee*

Figure 3. Asymmetric Michael addition of ester enolate ions to butenoid sulfoxide (*S*)-(+)-**5**.

1.3.2. Second generation asymmetric synthesis or chiral auxiliary-controlled

This approach is similar to the first generation method in that the control is also achieved intramolecularly by a chiral group in the substrate. The difference is that the directing group called "chiral auxiliary" is now deliberately attached to an achiral substrate in order to direct the reaction and can be removed once it has served its purpose.

Scheme 2. Chiral auxiliary controlled.

An example is a highly stereoselective Michael addition of the camphor-derived tetrahydropyran(camTHP*)-desymmetrized glycinamide **7** to a nitro olefin as the Michael acceptor in the presence of 2.0 equiv. of lithium hexamethyldisilazide (LHMDS). Then, removal of the camTHP* protecting group was achieved by acid hydrolysis to give the corresponding Cbz-protected (-substituted glutamic acid derivative) in 60 % yield. Subjection of this product to standard hydrogenolysis conditions afforded the open form glutamide which cyclized on heating to the pyroglutamic acid derivative **9**.[*3*]

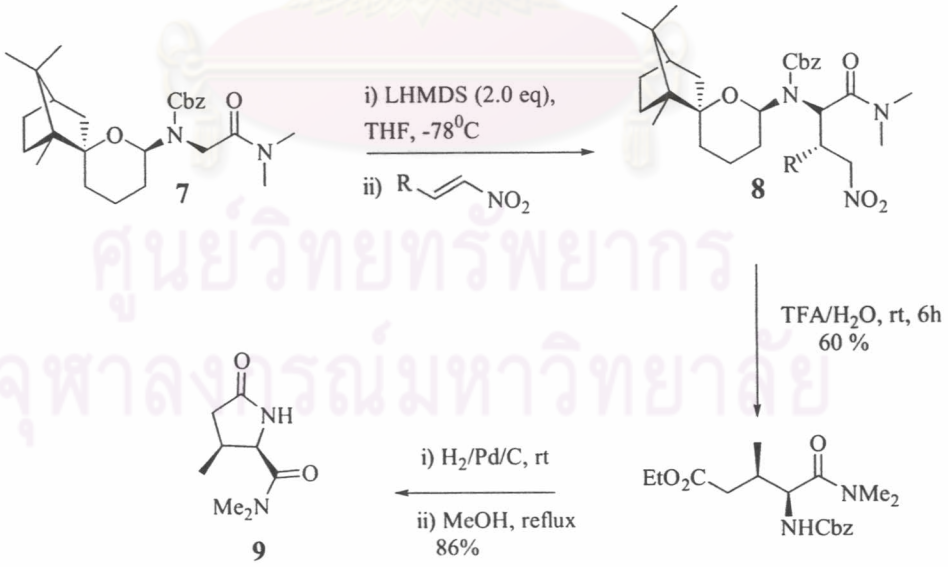
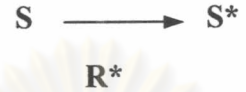


Figure 4. Asymmetric Michael addition of camTHP*-desymmetrized glycinamide **7** to reactive nitro olefins.

1.3.3. Third generation asymmetric synthesis or chiral reagent controlled

Although the second-generation methods have proved very useful, the require two extra steps to attach and then remove the chiral auxiliary is an unattractive feature. This can be avoided by using a third-generation method in which an achiral substrate is directly converted to the chiral product by the use of a chiral reagent.



Scheme 3. Chiral reagent controlled.

An example is conjugate addition of the copper azaenolate to an equimolar amount of cyclohex-2-enone and to cyclopent-2-enone gave, after hydrolysis (ammonium chloride-ammonia), an optically active product in enantiomeric excess ranging from 17 to 75 %. The amino ethers used as a chiral auxiliary can be recovered in 50-80 % yield.[*4*]

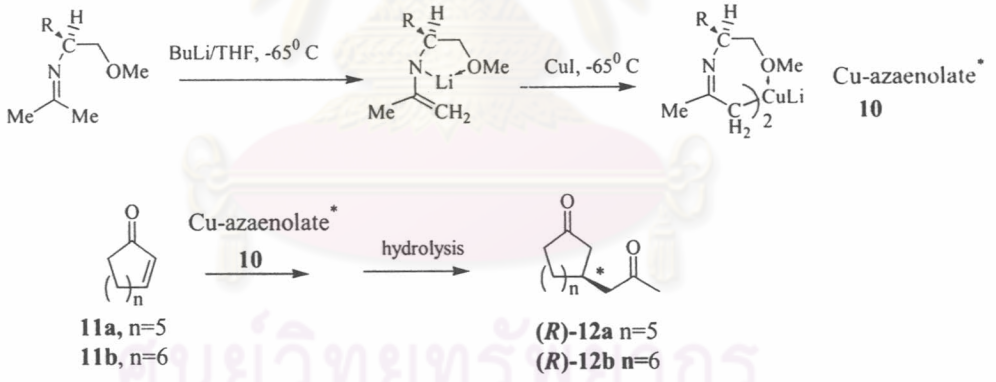


Figure 5. The conjugate addition of the copper azaenolate to an equimolar amount of cyclohex-2-enone and cyclopent-2-enone.

1.3.4. Fourth generation asymmetric synthesis or chiral catalyst controlled

In each of the previously mentioned types of asymmetric synthesis an enantiomerically pure compound must be present in stoichiomeric amounts, although in some case it could be recovered for reuse. The final refinement, in the fourth generation methods is to convert an achiral substrate to the chiral product directly with the help of a chiral catalyst. Again the control here is intermolecular:

$$S \xrightarrow[\text{cat*}]{} P^*$$

Scheme 4. Chiral catalyst controlled.

For example, the conjugate addition of isopropyl 2-cyanopropionate to ethyl vinyl ketone catalyzed by the chiral pincer palladium complex give isopropyl 2-cyano-2-methyl-5-oxoheptanoate with high enantioselectivity (up to 83 % *ee*).[5]

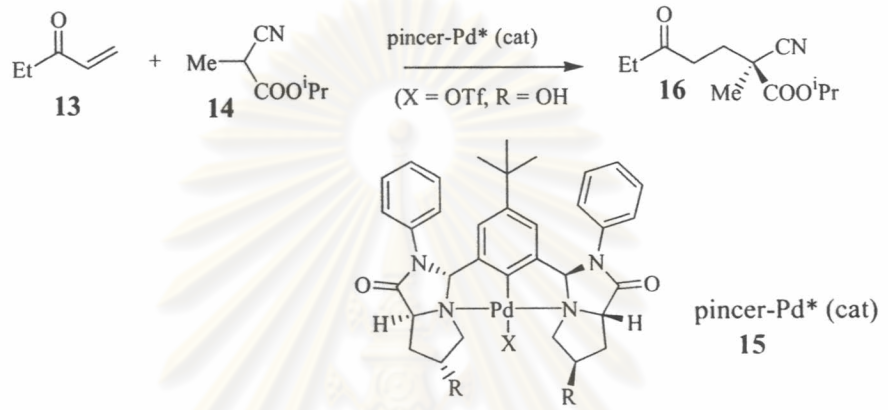
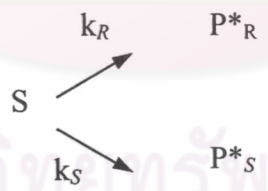


Figure 6. The conjugate addition of isopropyl 2-cyanopropionate to ethyl vinyl ketone.

1.4 Mechanistic considerations



Most diastereoselective and enantioselective reactions are based on a kinetic phenomenon: if the rate constant k_R of the reaction leading to the *R* product is greater than k_s leading to the *S* product, then the product with configuration *R* at the new stereogenic center will predominate, and vice versa.

The enantiomeric or diastereomeric ratio is simply the ratio of the rate constants.

$$\frac{[P^*_R]}{[P^*_S]} = \frac{k_R}{k_S}$$

The Arrhenius equation gives the relationship between the rate constant and the activation energy.

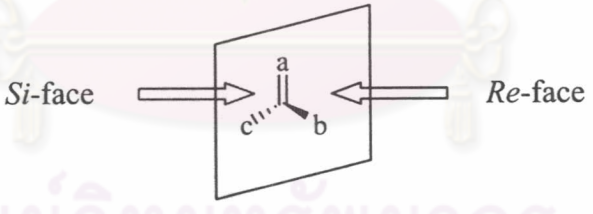
$$k_R = Ae^{(-E_R/RT)}, \qquad k_S = Ae^{(-E_S/RT)}$$

$$\therefore \quad \frac{[P^*_R]}{[P^*_S]} = e^{-(E_R - E_S/RT)} = e^{-\Delta E/RT}$$

In other words, the greater the difference in the activation energy of the two pathways, the greater the selectivity. When the activation energy of the reaction giving the *R* product is the same as that of the reaction to the *S* product, there is no selectivity, and the ratio is 1:1. The difference in activation energy need not be very large to obtain high diastereo- or enantioselectivity: at 300 K a difference of 2 kcal.mol^{-1} (8.4 kJ.mol^{-1}) gives a ratio of 96:4.[*1*]

It is important to note the dependence of the selectivity achieved on the reduce reaction temperature will generally lead to increased selectivity (but also to slower rate).

In this topic consider in more detail the nature of this difference in activation energy. The transition states leading to the *R* and *S* products are diastereomeric, and therefore *non*-equivalent, and of different energies. The key step involves preferential addition form the *Re* or *Si* face to a trigonal carbon, which is usually unsaturated.



Group priority : a>b>c

1.5 Asymmetric Michael addition reaction

Asymmetric Michael addition to α,β-unsaturated systems is one of the fundamental carbon-carbon bond-forming process in organic chemistry and offers an extremely powerful tool for synthesis of highly functionalized organic molecules. Since this reaction often leads to the formation of a stereogenic center, considerable effort has been devoted to the development of efficient stereoselective methods. The products of Michael addition reaction can have biological and pharmaceutical

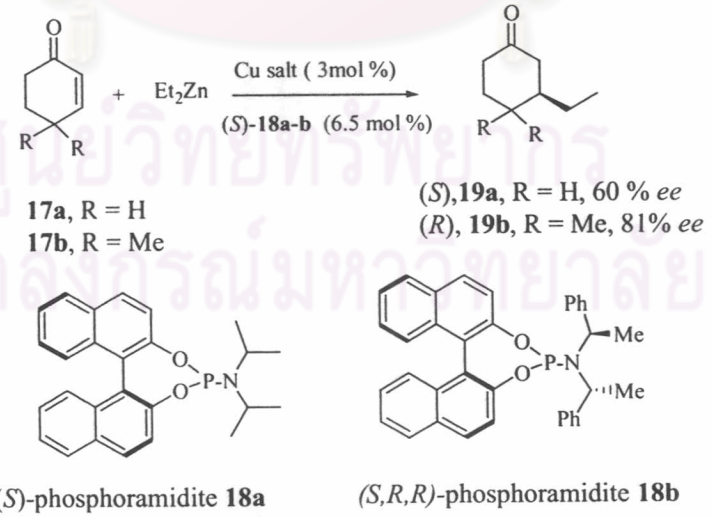
activities, for example, alkaloids, pyrethroid, flavanoid, and amino acid. In this topic, asymmetric Michael reaction will be discussed in more detail.

1.5.1 Asymmetric Michael addition reactions catalyzed by monometallic catalyst

In the past few years, asymmetric Michael addition has been a subject of intense investigation.[*6*] Most favorite methods for asymmetric Michael addition reaction employed chiral Lewis acids consisting of a metal ion and a chiral ligand. Examples of chiral ligands developed for asymmetric Michael addition reactions; include binaphthol, BINAP, phosphoramidite, amino alcohol, diamine, salen, oxazoline and other ligands. The metals used include copper (Cu), aluminium (Al), nickel (Ni), cobalt (Co) and rhodium (Rh). For convenience, this topic will be subdivided according to the type of ligand/catalyst rather than the type of nucleophiles.

1.5.1.1 Phosphoramidite ligands

In 1996, Feringa reported that asymmetric Michael addition of diethylzinc to enone catalyzed by copper-phosphoramidite **18a** was achieved in high yield and enantioselectivity (60-80 %).[*7*] Recently they have developed the use of phosphoramidite **18b** in the same reaction with high yield and enantioselectivity up to 94 %.[*8*]



(*S*)-phosphoramidite **18a** (*S,R,R*)-phosphoramidite **18b**

Figure 7. The asymmetric Michael addition of diethylzinc to enone.

In 2003, they reported an enantioselective 1,4-addition of arylboronic acid to enone catalyzed by rhodium-phosphoramidite complexes. They found that ligands

22a and **22b** provide high enantioselctivity, and (*S*)-3-phenylcyclohexanone (*S*)-**23** was obtained quantitatively with *ee* up to 98 %. The same catalyst was efficient for several enones and arylboronic acid substrates.[*9*]

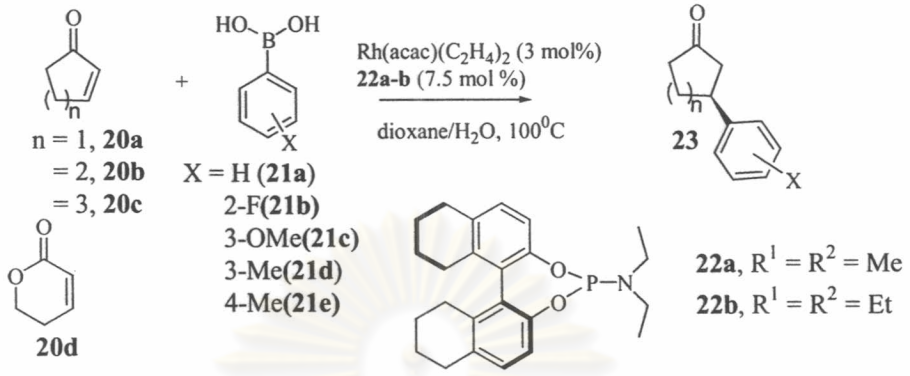


Figure 8. The enantioselective 1,4-additions of arylboronic acids to enone.

They also reported an asymmetric conjugate addition of potassium organotrifluoroborates to various enones catalyzed by rhodium-phosphoramidite complexes. An excellent enantioselectivity and high conversion were achieved.[*10*]

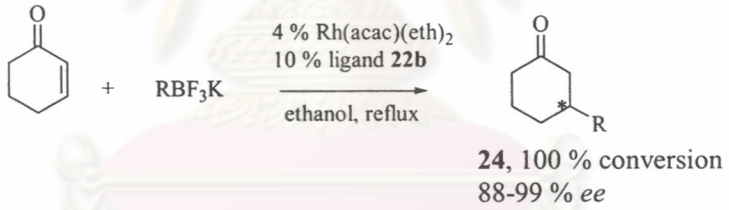


Figure 9. The asymmetric conjugate addition of potassium organotrifluoroborates to various enones.

In 2003, Zhou reported a copper-catalyzed conjugate addition of Et_2Zn to enones using spiro phosphoramidite ligand **26a-c** with high enantioselectivity. The catalyst was efficient for both cyclic and acyclic enones. By using ligand (*R,R,R*)-**26c**, the reaction of cycloheptenone and Et_2Zn afforded 3-ethylcycloheptanone with 97 % *ee*. The reaction of cyclopentenone provided 3-ethylcyclopentanone in 44 % *ee*. In the case of chalcones, the ligand with larger R groups afforded conjugate addition product with high *ee*.[*11*]

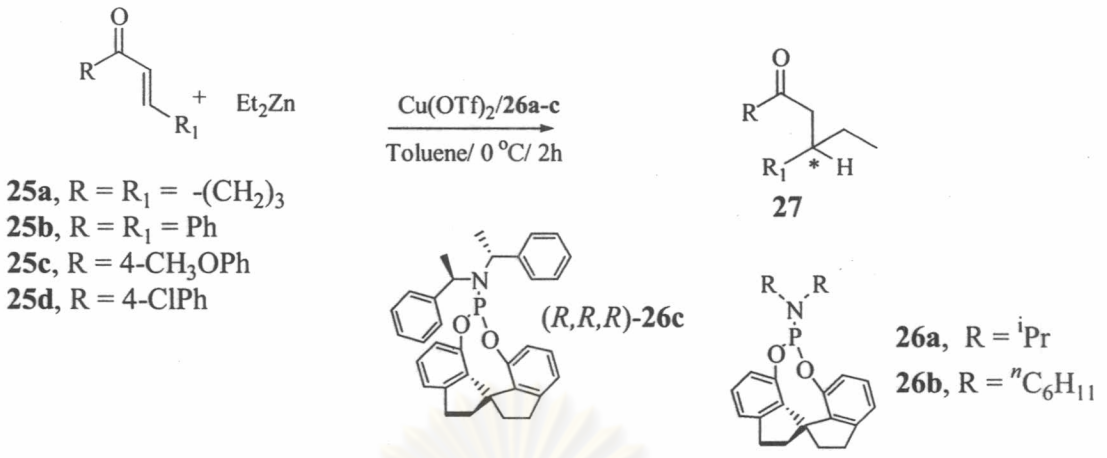


Figure 10. Conjugate addition of Et_2Zn to enones using spiro phosphoramidite ligand.

In 2004, Ojima reported a copper-catalyzed asymmetric conjugate addition of diethylzinc to nitroalkenes. The reactions performed using new chiral monodentate phosphoramidite ligands proceeds with high yield and excellent enantioselectivity (up to 99 %).[*12*]

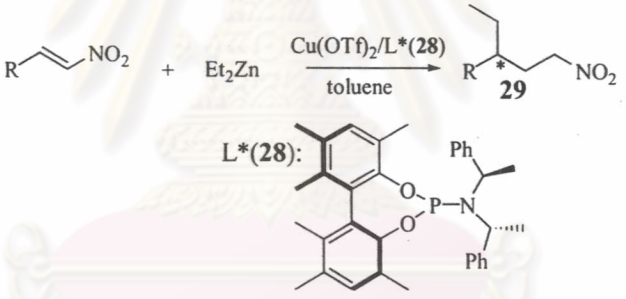


Figure 11. Asymmetric conjugate addition of diethylzinc to nitroalkenes.

1.5.1.2 Phosphorus and sulfur based-ligands

In 2000, Hayashi reported an asymmetric conjugate addition of arylboronic acids (**31**) to nitroalkenes (**30**) catalyzed by rhodium-(*S*)-BINAP (**32**) with high yield (73-89 %) and high enantioselectivity (up to 82-99 %). The reaction of 1-nitrocycloalkene proceeds with high diasterioselectivity giving the thermodynamically less stable *cis* isomer preferentially. Treatment of the *cis*-enriched mixture with sodium bicarbonate in refluxing ethanol caused *cis-trans* equilibration to give the thermodynamically more stable *trans* isomer.[*13*]

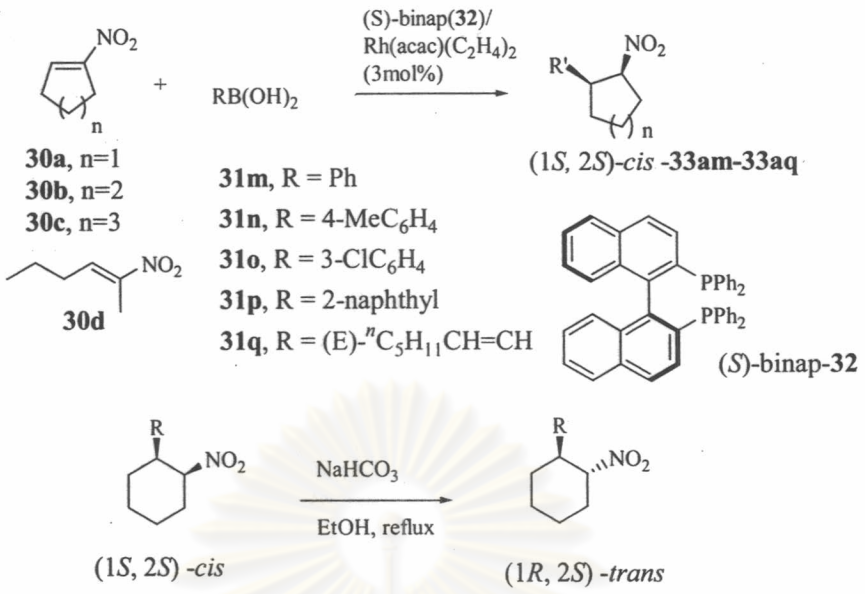


Figure 12. The asymmetric conjugate addition of arylboronic acids **31** to nitroalkenes **30**.

In 2001, Oi reported that highly enantioselective 1,4-addition of organosiloxanes to α,β-unsaturated carbonyl compounds was catalyzed by a chiral rhodium complex generated form $[Rh(cod)(MeCN)_2]BF_4$ and (*S*)-BINAP (**32**). Both (*E*)- and (*Z*)-1-alkenyl group as well as aryl groups could be introduced enantioselectively into β-position of variety of ketones, esters, and amides.[*14*]

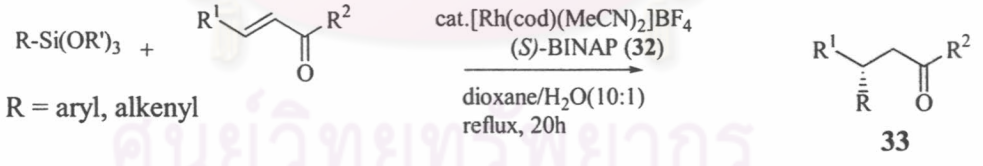


Figure 13. A highly enantioselective 1,4-addition of organosiloxanes to α,β-unsaturated carbonyl compounds.

In 2004, Arink reported that enantioselectives up to 83 % have been obtained in the conjugate addition reactions of diethylzinc to Michael accepters catalyzed by copper (I) aminoarenethiolates **34**. For cyclic enones, Et_2Zn reagents afford better results than Grignard reagent, whereas the opposite is true for acyclic enones.[*15*]

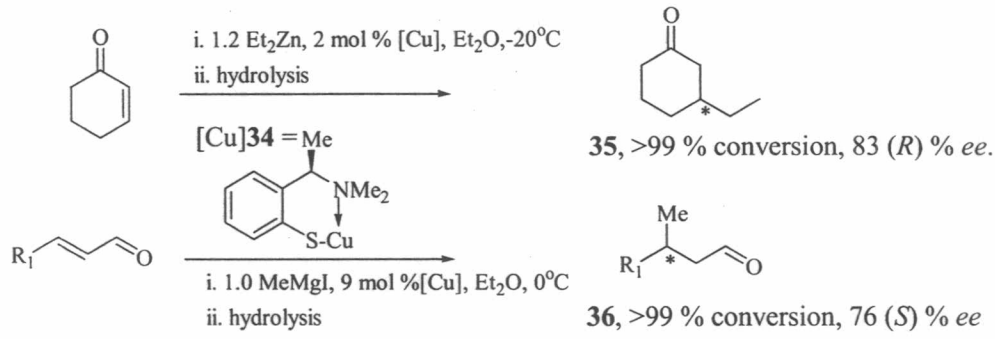


Figure 14. Conjugate addition of diethylzinc to Michael accepters catalyzed by well-defined (chiral) copper (I) aminoarenethiolates.

1.5.1.3 Nitrogen based ligand

In 2001, Kim and Ahn reported that tripodal oxazoline compounds are a new class of potentially useful chiral ligands for the asymmetric Michael reaction of phenylacetate ester and methyl acrylate that involve potassium (^{t}BuOK) complexes. The enantioselectivity of reaction achieved was up to 82 %.[*16*]

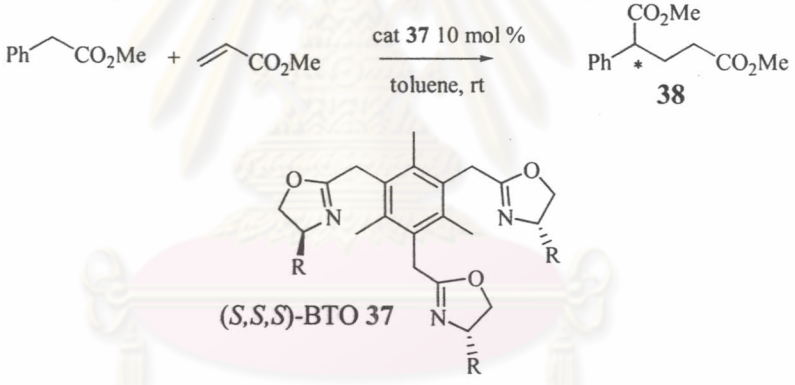
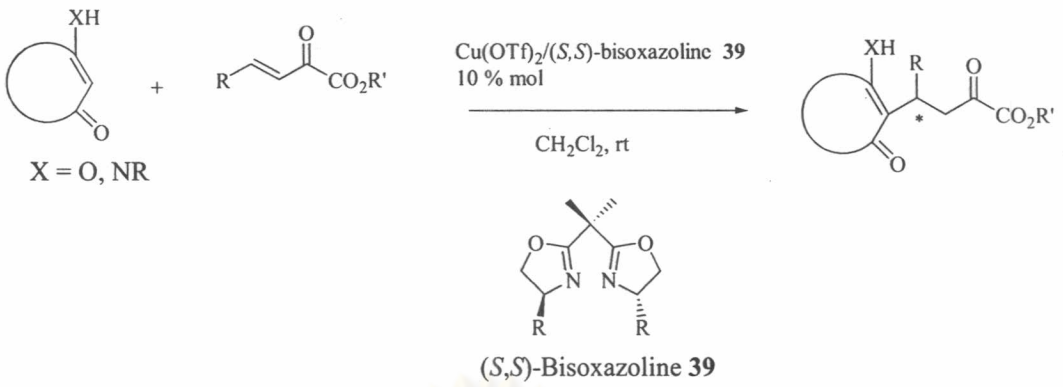


Figure 15. Asymmetric Michael reaction of phenylacetate esters and methyl acrylate.

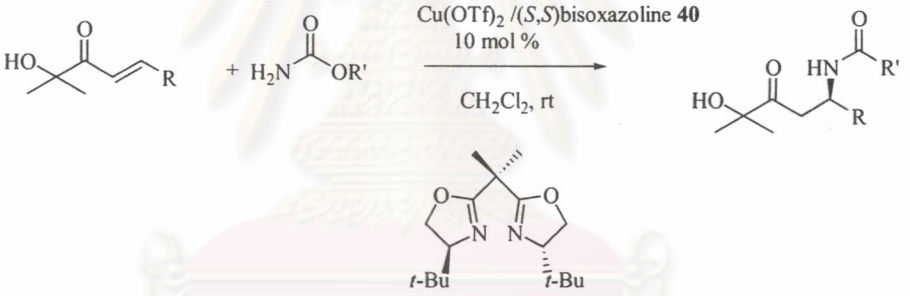
In 2003, Melchiorre and Jφrgensen have developed a novel base-free catalytic asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds and enamines catalyzed by chiral bisoxazoline-copper (II) complexes. The addition to a number of unsaturated 2-ketoesters proceeded smoothly using various 1,3-dicarbonyl compound and quantitative yields and up to 92 % *ee* was obtained. The reaction was extended to cyclic enamines as Michael donors, and these also afforded practically quantitative yields and up to 98 % *ee*.[*17*]



(*S*,*S*)-Bisoxazoline **39**

Figure 16. Asymmetric Michael reaction of cyclic 1,3-dicarbonyl compounds and enamines.

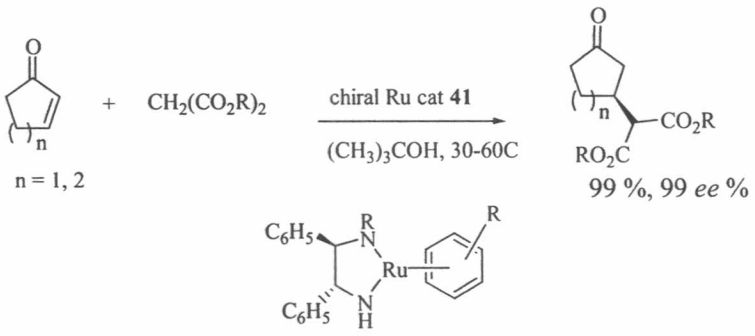
Very recently, Palomo have found that $Cu(OTf)_2$-bis(oxazoline) complex **40** can catalyze asymmetric conjugate addition of carbamates to α-hydroxy enone. Both high enantioselectivity (up to 99 %) and high yield were obtained.[*18*]



(*S*,*S*)-Bisoxazoline **40**

Figure 17. Asymmetric conjugate addition of carbamates to α-hydroxy enones.

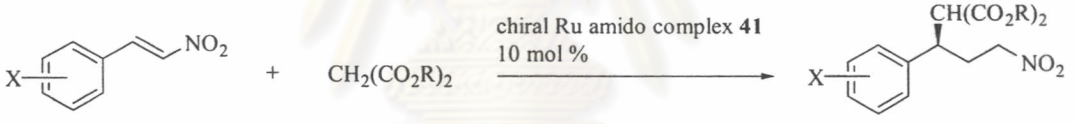
In 2003, Watanabe developed an asymmetric Michael reaction of enones and dialkyl malonates using chiral diamine ruthenium complexes **41**. This reaction gave excellent yield and enantioselectivity (up to 99 % *ee*).[*19*]



chiral Ru complex **41**

Figure 18. Asymmetric Michael reaction of enone and dialkyl malonate using chiral diamine ruthenium complexes **41**.

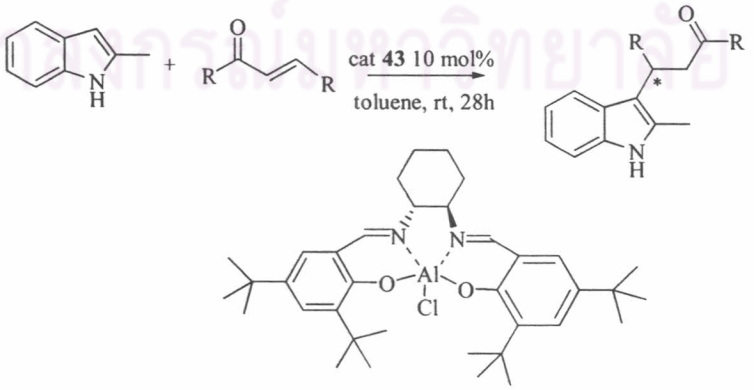
In addition, they found that the Michael addition of 1,3-dicarbonyl compounds to nitroalkenes was also catalyzed by the same chiral Ru amido complexes **41**. The reaction proceeds smoothly to provide the corresponding Michael adducts in high yields and with excellent *ee*.[*20*]



42, 93-99 %, 93-98 % *ee*

Figure 19. The Michael addition of 1,3-dicarbonyl compounds to nitro alkens.

In 2003, Bandini reported that the development of Al-salen complex **43** use catalyst of Friedel-craft reaction of indole to α,β-unsaturated ketone. The product, β-indolyl ketones, were obtained in high yield and enantioselectivity (up to 89 %).[*21*]



Al-salen complex **43**

Figure 20. The Friedel-craft reaction of indole to α,β-unsaturated ketone.

1.5.1.4 Oxygen based ligands

In 2001, Kumaraswamy found that a novel calcium-BINOL complex was an efficient catalyst for asymmetric Michael addition reactions of enones and enals. High yield but moderate enantioselectivity was obtained. It was proposed that this inexpensive monometalic catalyst functions not only as a Lewis acid but also as a Brønsted base.[*22*]

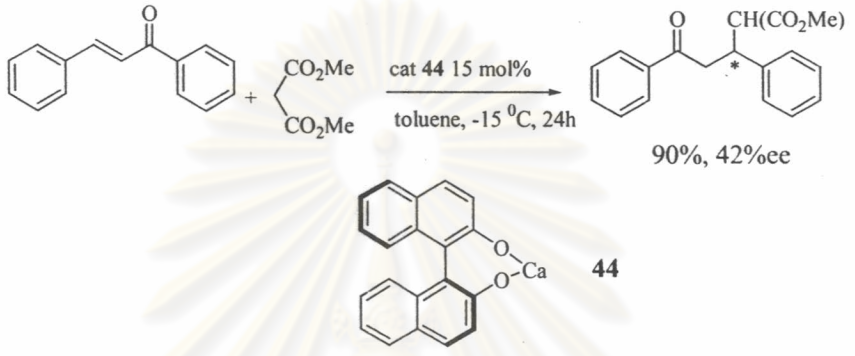


Figure 21. Asymmetric Michael addition reactions of dimethyl malonate to enones and enals.

1.5.1.5 Alkene-based ligands

In 2003, Hayashi reported the preparation of a C_2-symmetric chiral diene ligand and its successful use as a ligand for rhodium-catalyzed asymmetric 1,4-addition of organoboron reagents to enones. The enantioselectivities observed here are among the highest for the rhodium-catalyzed asymmetric 1,4-addition, the selectivity being over 90 % *ee* in most of the reactions examined for several cyclic and acyclic enones and for aryl- and alkenylboron reagents.[*23*]

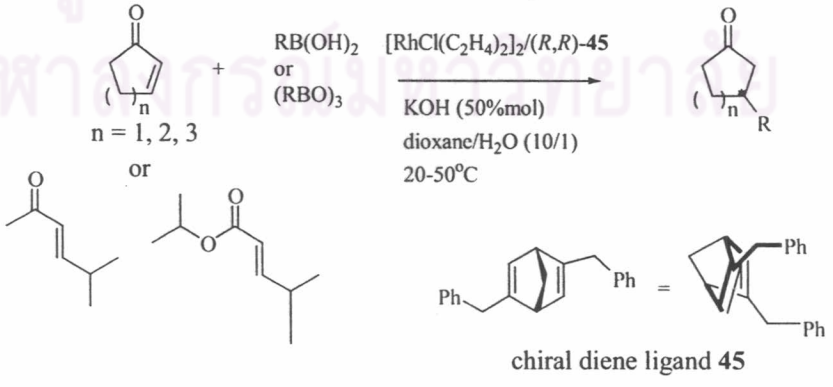


Figure 22. Asymmetric 1,4-addition of organometallic reagents to enones.

1.5.2 Asymmetric Michael addition catalyzed by organocatalyst

In 1996, Yamaguchi reported that L-Proline rubidium salt can catalyze the asymmetric Michael addition of malonate anions to prochiral enones and enals. This method could be applied to a wide range of substrates to give adducts with a predictable absolute configuration: (*S*)-adducts form (*E*)-enones/enals and (*R*)-adducts form (*Z*)-enone. High enantiomeric excess were attained when di-*tert* butyl malonate was added to (*E*)-enones in the presence of CsF. The stereochemistry of the Michael reaction indicates that asymmetric induction took place *via* enantioface discrimination involving the acceptor α-carbon atom rather than the β-carbon atom.[*24*]

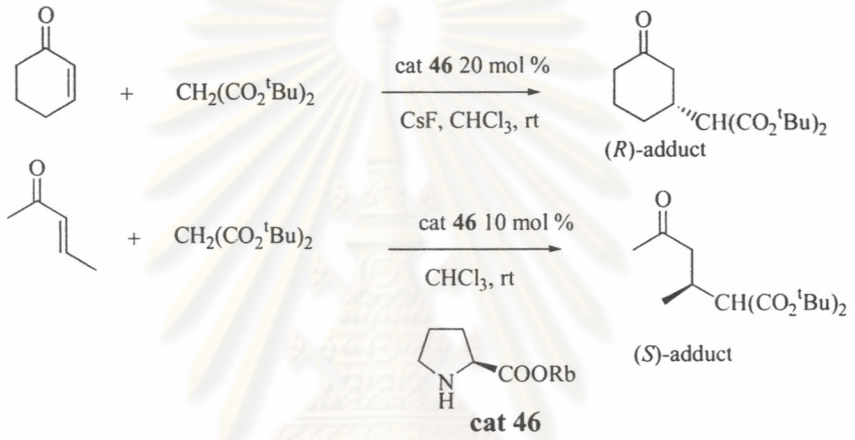


Figure 23. L-Proline rubidium salt (**46**) catalyzed the asymmetric Michael addition of malonate anions to prochiral enones and enals.

In 2003, a thiourea **47** catalyzed asymmetric Michael addition of diethylmalonate to various nitroolefins with high enantioselectivity (81-93 %) was reported. Interestingly, this reaction was also successfully performed without solvent. [*25*]

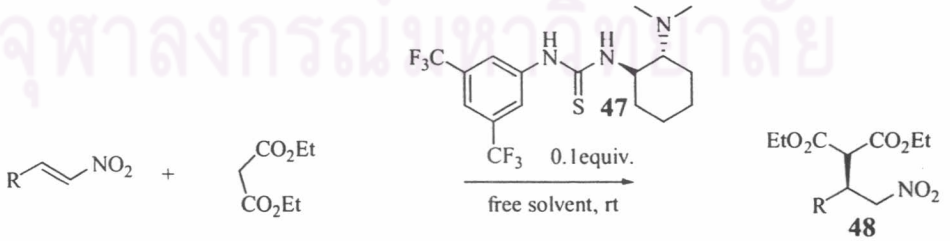


Figure 24. Thiourea **47** catalyzed Michael addition of diethyl malonate to various nitroolefins.

In 2003, Jφrgensen and Melchiorre presented the development of the organocatalytic direct enantioselective Michael addition of aldehyde to vinyl ketone

using chiral amines **49** as the catalyst leading to optically active substituted 5-ketoaldehyde. Moderate enantioselectivity was achieved (up to 79 %).[*26*]

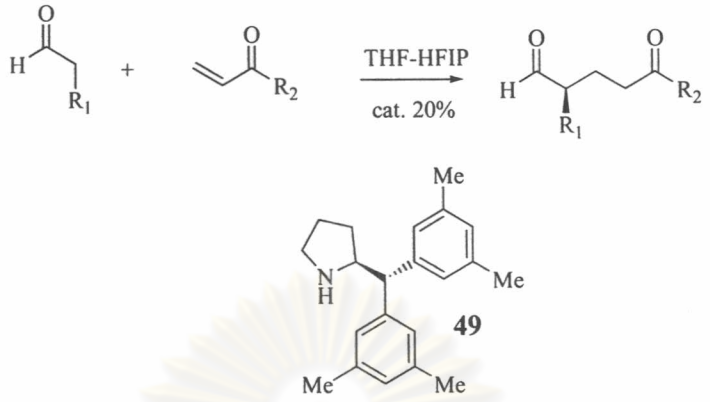


Figure 25. Michael addition of aldehyde to vinyl ketone using chiral amine **49** as the catalyst leading to optically active substituted 5-ketoaldehyde.

1.5.3 Asymmetric Michael addition catalyzed by heterobimetallic complexes

The use of heterobimetallic complexes for asymmetric synthesis were first reported by Shibasaki.[*27*] They usually consist of two metal components in which one metal acts as Lewis acid and the other acts as a Lewis base. For example, in an Al-Li-BINOL complex reported by Shibasaki, the aluminium and lithium were Lewis acid and Lewis base, respectively. Most of the reported heterobimetallic complexes focused on only a few major classes of ligands namely BINOL, salen, and amino alcohols, with aluminium, lanthanoids and alkali metals being used for asymmetric Michael reaction.

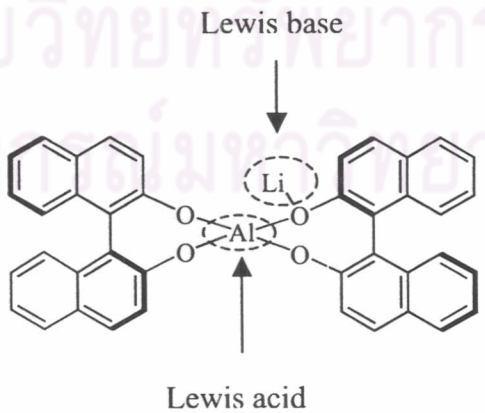


Figure 26. Structure of heterobimetallic complex.

1.5.3.1 BINOL ligands

In 1995, Shibasaki developed an (*R*)-LPB ($LaNa_3$ tris((*R*)-binaphthoxide)) catalyst **50** as the first heterobimetallic catalyst for asymmetric Michael reaction. The Michael adduct were obtained in excellent yield and enantioselectivity (80-90 %).[*27*]

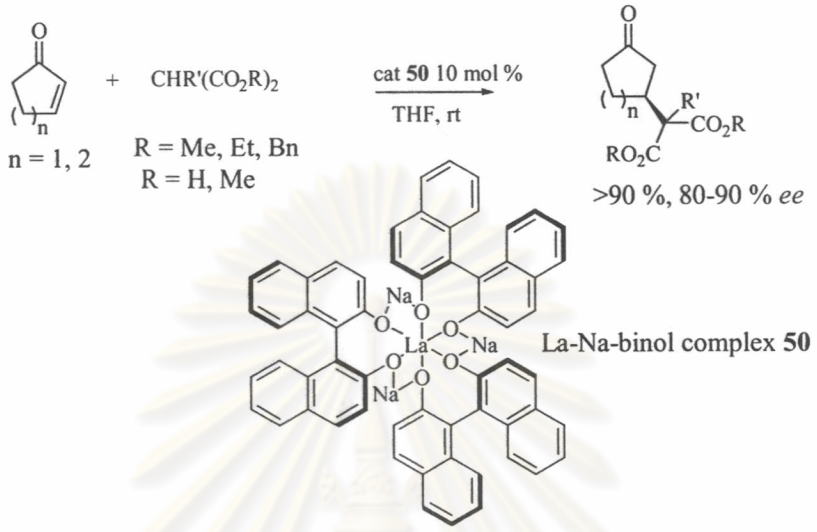


Figure 27. (*R*)-LPB **50** catalyzed asymmetric Michael reaction.

In 1996, they reported another heterobimetallic asymmetric catalyst **51** consisting of lithium aluminium hydride and BINOL for asymmetric Michael reaction of dialkyl malonates to enones. The catalyst (10 mol %) provided high yields of Michael adducts **52** in 91 to 99 % *ee*. The catalyst was also effective for tandem Michael-aldol reaction in the present of 10 mol % of Al-Li-(*R*)-BINOL complex (**51**) gave the three-component coupling product **53** in 82 % yield. Although **53** was a mixture of diastereomers, its oxidation gave the corresponding diketone derivative **54** as a single isomer in 89 % *ee*.[*28,29*]

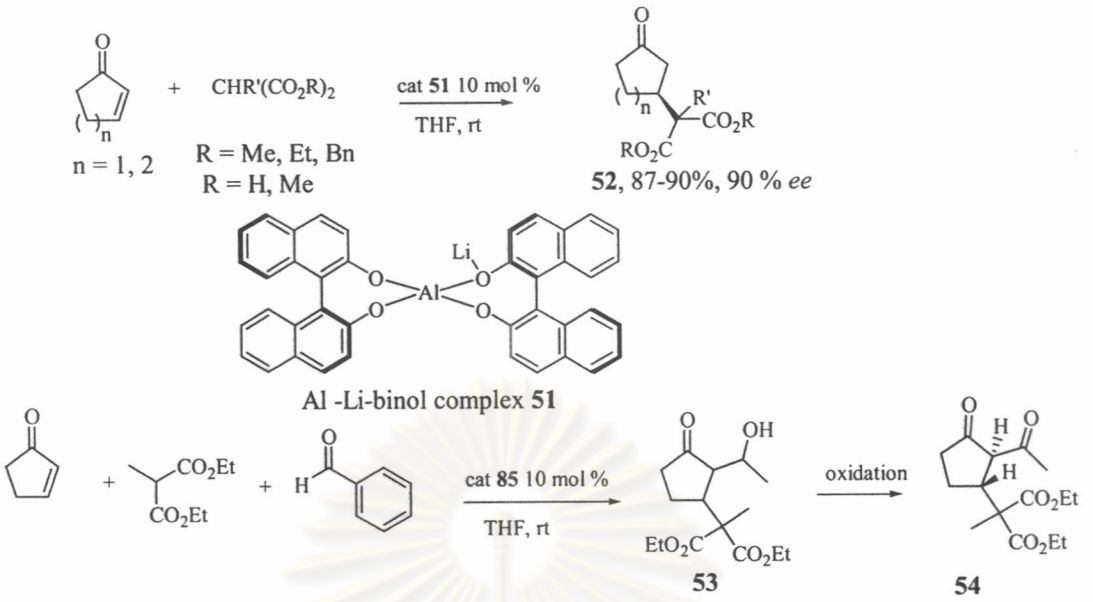


Figure 28. Asymmetric Michael reaction of dialkyl malonate to enone and tandem Michael-aldol reaction of cyclopent-2-enone, dialkyl malonate and benzaldehyde.

They also found that Ga-Na-BINOL(GaSB) **55** was an effective catalyst for asymmetric Michael reaction. High yield and excellent enantiomeric excess were obtained.[*29*]

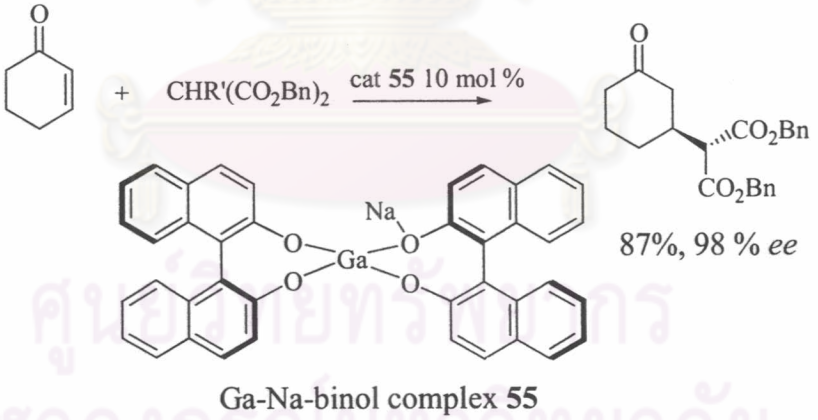


Figure 29. Ga-Na-BINOL(GaSB) **55** as catalyst for asymmetric Michael reaction.

In 1998, Shibasaki reported that the multifunctional catalyst (*R*)-LPB (LaK_3 tris((*R*)-binaphthoxide)) **56** could catalyze the Michael addition of nitromethane to chalcones with excellent enantioselectivity.[*30*]

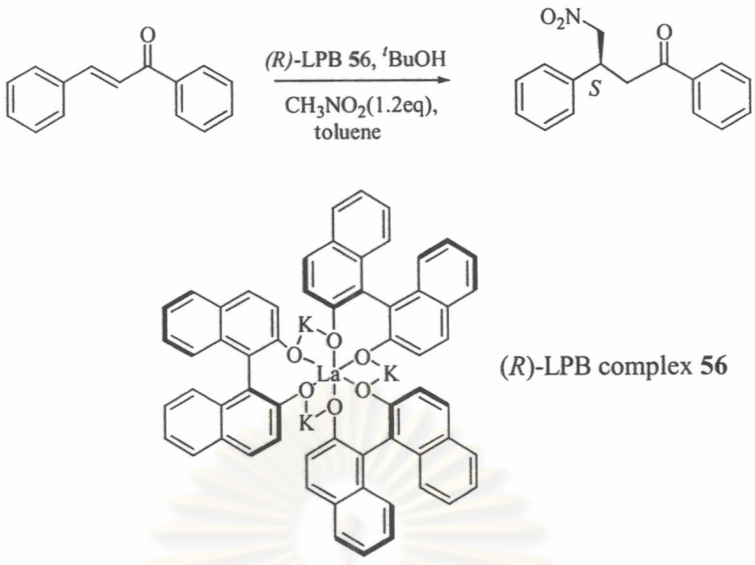


Figure 30. The multifunctional catalyst (*R*)-LPB (**56**).

In 2000, the same group have successfully developed a stable, storable, and reusable La-linked-BINOL complex **57** for the asymmetric Michael reaction (up to > 99 % *ee*) with broader generality compared to any reported catalysts. Even after 4 weeks of storage, this powdered complex **57** was still highly effective in the catalytic asymmetric Michael reaction. Furthermore, recovering and recycling of the complex **57** has been accomplished, and the recovered catalyst **57** still retain its high activity even after the fourth cycle.[*31*]

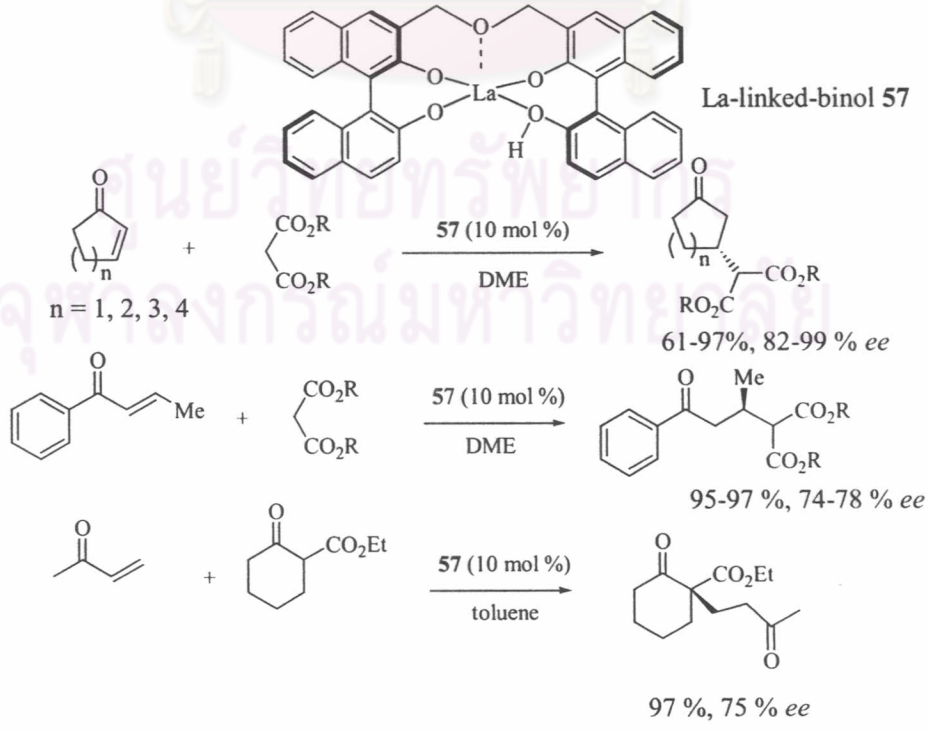


Figure 31. La-linked-BINOL complex **57** catalyzes the asymmetric Michael reaction.

In addition, Sasai reported that catalytic asymmetric Michael reaction of cyclic enone with Horner-Wadsworth-Emmons reagents proceeded efficiently in the presence of an aluminium-lithium-BINOL complex. The catalyst must be activated by addition of an alkali metal reagent such as NaO^{t}Bu.[*32*]

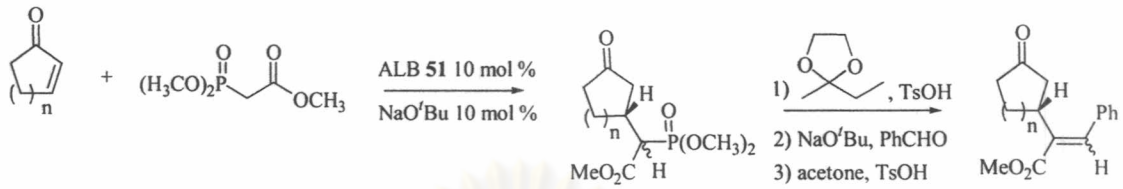


Figure 32. Asymmetric Michael reaction of cyclic enone with Horner-Wadsworth Emmons reagents.

In 2001, Sasai and Jayaprakash reported a synthesis of a soluble polymer containing BINOL residues. Titanium-BINOLate and Al-Li-bis(binaphthoxide) **58** were generated form this polymer and applied to asymmetric addition of Et_2Zn to benzaldehyde and asymmetric Michael addition reactions, respectively. In both cases, the products were obtained in high yield and enantioselectivity.[*33*]

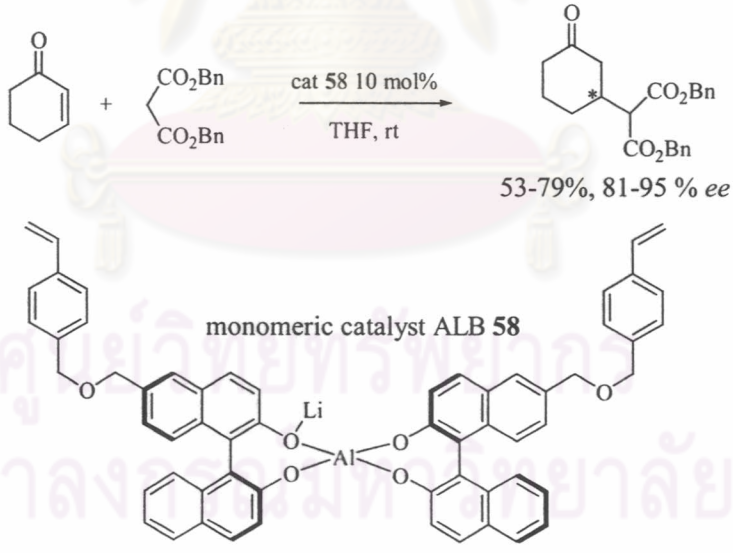


Figure 33. Asymmetric Michael addition of dibenzyl malonate to enone catalyzed by polymer Al-Li-bis(binaphthoxide) catalyst **58**.

In 2002, Shibasaki reported a highly practical and efficient procedure for the large-scale (up to 6 mol scale) synthesis of enantiomerically pure (*R*)-**59** using an (*R*)-Al-Li-bis(binaphthoxide) complex (**51**)-catalyzed asymmetric Michael reaction was developed. Under a highly concentrated condition, the Michael reaction was catalyzed

efficiently by 0.1 mol % of ALB complex (**51**) with 0.09 mol % of KO^{t}Bu and MS 4 A° to completion in 24 h. In addition, the improved work-up procedure made it possible to isolate the pure product **59** in up to 95 % yield and >99 % *ee* without chromatographic separation.[*34*]

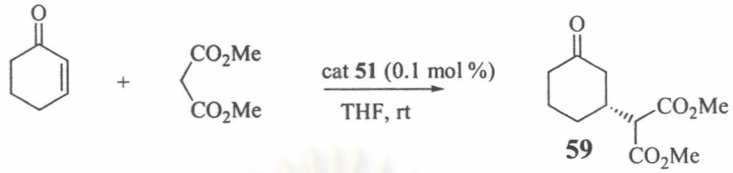


Figure 34. (*R*)-Al-Li-BINOL complex (**51**)-catalyzed asymmetric Michael reaction of diethyl malonate and enones in large scale.

In 2003, they successfully developed a general catalytic asymmetric Michael reaction of acyclic β-keto esters to cyclic enones, in which asymmetric induction occurs (up to 92 % *ee*) at the β-position of the accepter, using the novel La-NR-linked-BINOL complexes (**60a,** R = H, **60b**, R = Me). In addition, they demonstrated that the heteroatom linker in linked-BINOL could tune the catalyst electronically and sterically. In general, the NMe ligand **60b** was suitable for the combination of both small enones and β-keto esters, and the NH ligand **60a** was suitable for bulkier substrate. The usefulness of the Michael product was demonstrated by the synthesis of the key intermediate **61** of (-)-tubifolidine and (-)-19,20-dihydroakuammicine.[*35*]

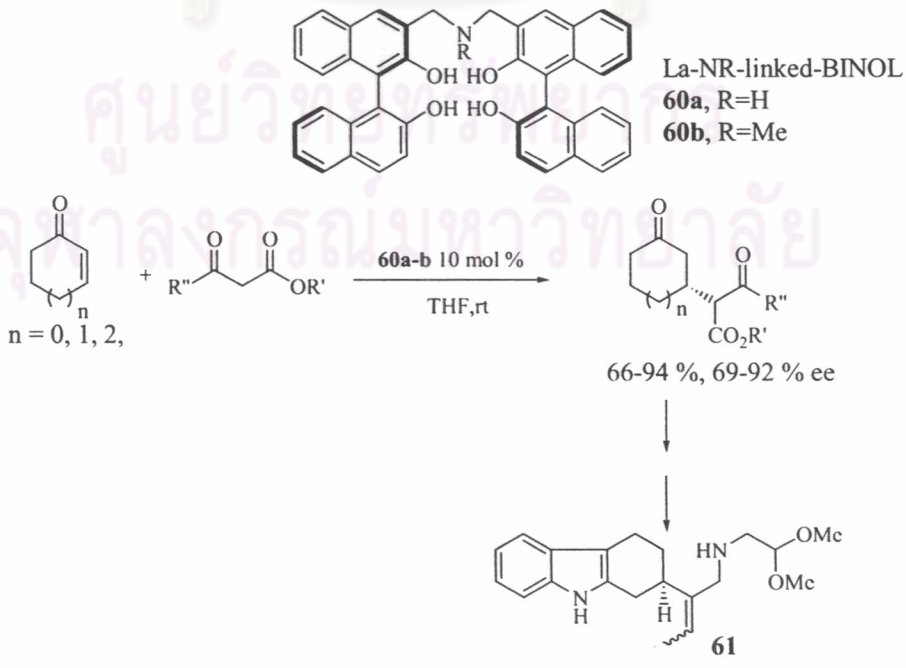


Figure 35. Asymmetric Michael reaction of acyclic β-keto esters to cyclic enones.

1.5.3.2. Salen ligands

In 2001, Jha and Joshi reported a new aluminium-sodium heterobimetallic complex **62** derived form a chiral salen ligand. The catalyst was found to catalyze the Michael reaction of dialkyl malonate to cycloalkene to give the Michael adduct in high yield and up to 58 % enantioselectivity.[*36*]

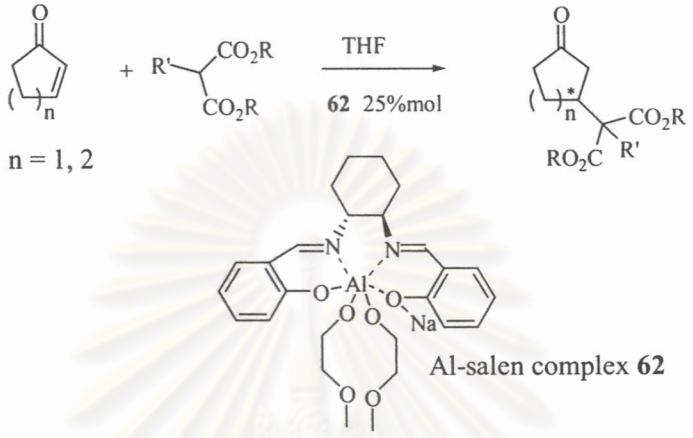


Figure 36. Aluminium-sodium heterobimetallic complexes derived form chiral salen ligand.

1.5.3 3. Chiral amino alcohol ligands

In 1997, Sundararajun and Manickam reported a synthesis of lithium-aluminium heterobimetallic complex **63**, that effectively catalyzed asymmetric Michael addition reaction of alkyl malonates to several cyclic and acyclic enones with high yield and enantioselectivity (94 %).[*37*]

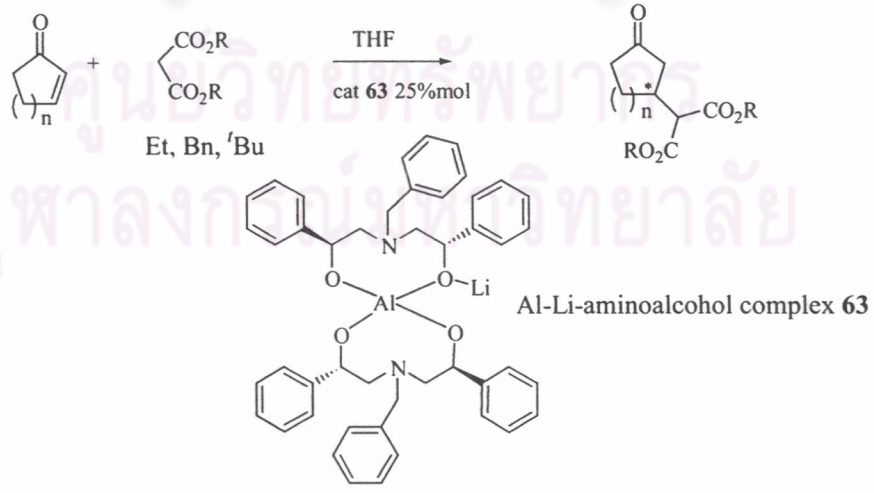
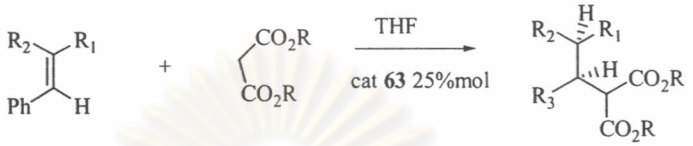


Figure 37. Asymmetric Michael addition of alkyl malonate to several cyclic and acyclic enones catalyzed by Al-Li-amino alcohol complex **63**.

Recently, they reported the synthesis of the heterobimetallic catalyst **63**. The complex **63** was characterized by ^{1}H, ^{13}C, ^{27}Al, and ^{7}Li NMR spectral data. Also, the complex **63** when used in catalytic amounts accelerates Michael addition of malonates and thiophenols to a variety of α,β-unsaturated compounds like aldehydes, cyano and nitro compounds. The results obtained have high yield but no enantioselectivity was observed.[*38*]



R_1 = Me, R_2 = NO_2 Et, Bn, ^{t}Bu
R_1 = CN, R_2 = CO_2Et
R_1 = H, R_2 = NO_2

Figure 38. Michael addition of malonic ester and thiophenols to a variety of α,β-unsaturated compounds like aldehydes, cyano and nitro compounds catalyzed by complex **63**.

In addition, they reported the synthesis of the polymer supported amino ligand (Figure **39**). The resulting insoluble polymers containing chiral lithium and aluminium active centers **(64)** were quite effective for asymmetric Michael addition of nitro compounds, thiols, and amines. Under optimized reaction conditions, the Michael adducts were obtained in good yield and high enantiomeric excess.[*39*]

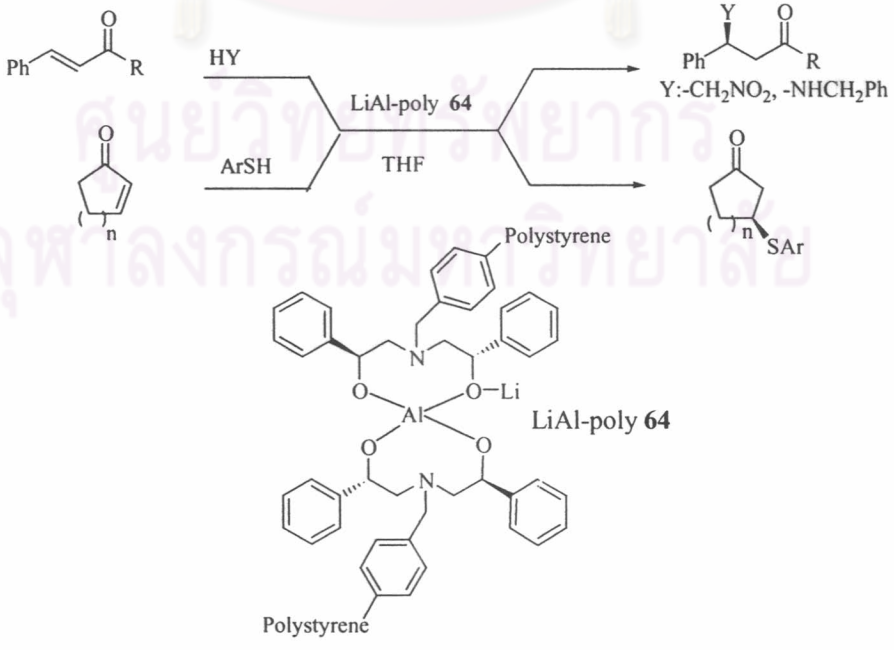


Figure 39. Michael addition of malonic ester to enone catalyzed by complexes **64**.

In 2001, Narasimhan and co-workers reported the preparation of other heterobimetallic complexes of chiral amino alcohol ligands **65** and **66** form shiff bases and $LiAlH_4$ (Figure **40**). They were shown to be effective catalysts in the Michael addition reactions of diethyl malonate and cyclohexenone (65-80 % yield, 37-84 % *ee*). They reported that different lithium aluminium hydride ($LiAlH_4$):ligand ratio of 1:1 and 1:2 provided the Michael adducts with different stereochemistry.[*40,41*]

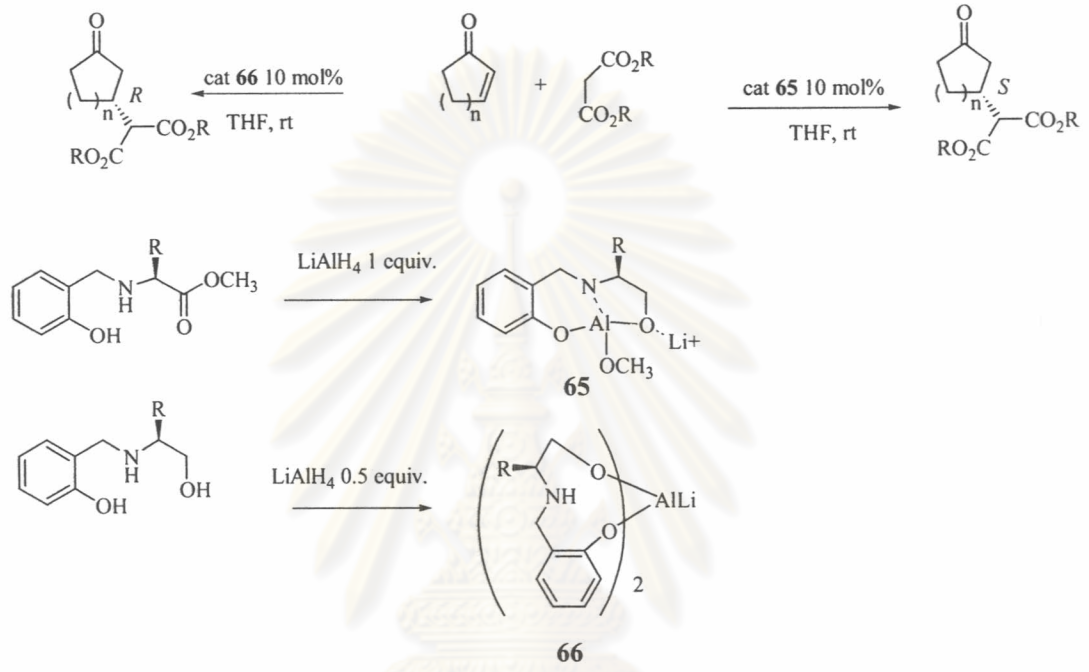


Figure 40. Michael addition of malonic ester to enone catalyzed by Li-Al-*N*-salicyl-β-amino alcohol complexes.

At the same time, Vilaivan has found that complexes of *N*-salicyl-β-amino alcohol ligands and metals, such as $Ti(O^iPr)_4$ and $LiAlH_4$, were effective for asymmetric Strecker and Pudovik reactions.[*42-44*] *N*-Salicyl-β-amino alcohol ligands were interesting because they possess small structure, low molecular weight, and are very easy to synthesize. Although Narasimhan and co-workers studied complexes of $LiAlH_4$ and *N*-salicyl-β-amino alcohol ligands for asymmetric Michael reaction, they have not studied effect of R group on salicyl moiety to enantioselectivity in details. In addition, our preliminary results indicated that the different lithium aluminium hydride ($LiAlH_4$): ligand ratio of 1:1 and 1:2 were found to have no effect to the configuration of the Michael adducts. It is therefore interesting to study this reaction in further details knowing that we can adaptive prepare a good variety of *N*-salicyl-β-amino alcohols ligands.

1.5.4 Applications of asymmetric Michael addition reaction

Asymmetric Michael addition reaction could apply to catalytic asymmetric syntheses of biologically significant compounds, such as (+)-coronafacic acid, (+)-coronatine, 11-deoxy-$PGF_{1\alpha}$, tubifolidine, tubifoline, and (-)-strychnine.

In 1997, Ichihara reported that asymmetric total syntheses of (+)-coronafacic acid and (+)-coronatine, phytotoxins isolated form *Pseudomonas syringae* Pathovars, was accomplished. The chiral ester intermediate was prepared by using catalytic asymmetric Michael reactions promoted by Al-Li-bis[(*S*)-binaphthoxide] complex (ALB **51**).[*45*]

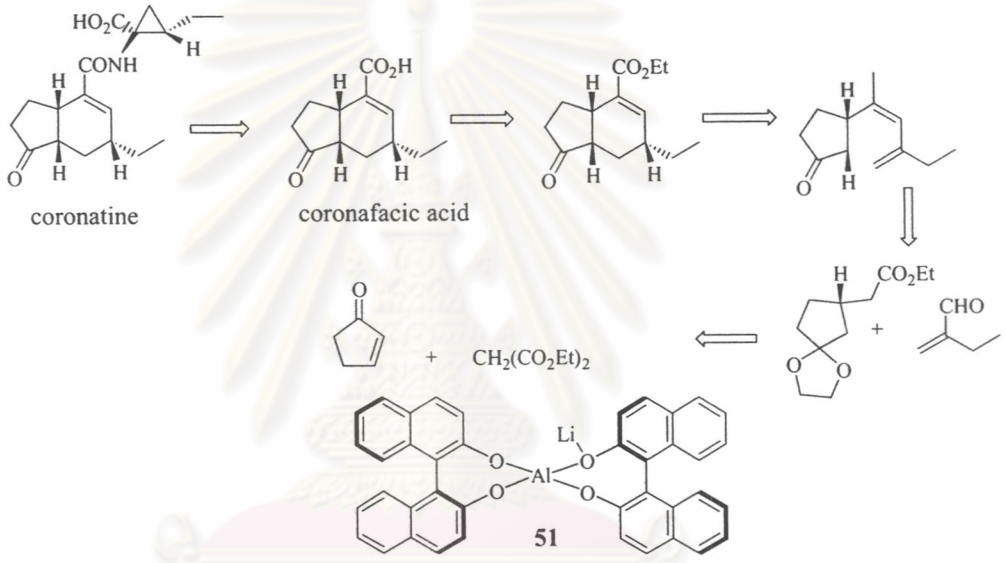


Figure 41. Asymmetric total syntheses of (+)-coronafacic acid and (+)-coronatine.

In 1998, Shibasaki reported that a catalytic asymmetric synthesis of 11-deoxy-$PGF_{1\alpha}$ has been achieved by using cascade Michael aldol reaction as a key step. The cascade reaction was efficiently promoted by a catalytic use of Al-Li-bis[(*S*)-binaphthoxide] complex (ALB **51**).[*46*]

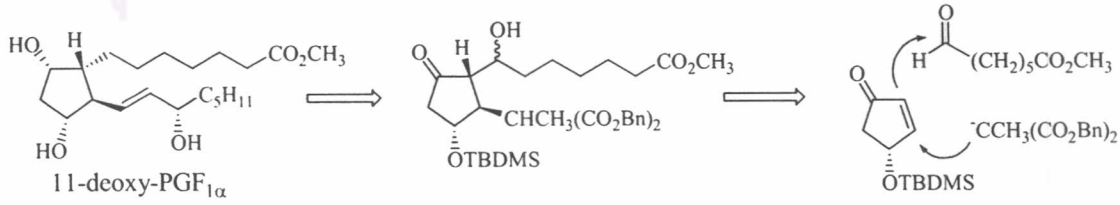


Figure 42. Asymmetric total synthesis of 11-deoxy-$PGF_{1\alpha}$.

Recently, they reported a catalytic asymmetric synthesis of the tubifolidine and tubifoline which is the flagship compound of the family of *strychnos* alkaloids,

which constituted an important group of architecturally complex and widely distributed monoterpenoid indole alkaloid. A highly practical catalytic asymmetric Michael addition of dimethyl malonate to cyclohexenone, as well as a one-pot construction of the ABDE ring systems using DDQ, were involved as key step.[*47*]

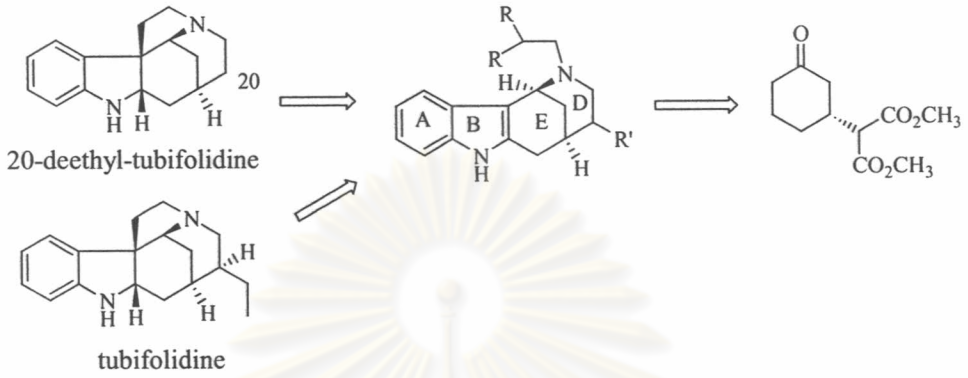


Figure 43. Asymmetric total synthesis of tubifolidine and tubifolidine.

In 2002, they reported a new entry for the synthesis of (-)-strychnine, which is the flagship compound of the family of *strychnos* alkaloids, form easily accessible optically pure Michael adduct, which was synthesized by the catalytic asymmetric Michael reaction.[*48*]

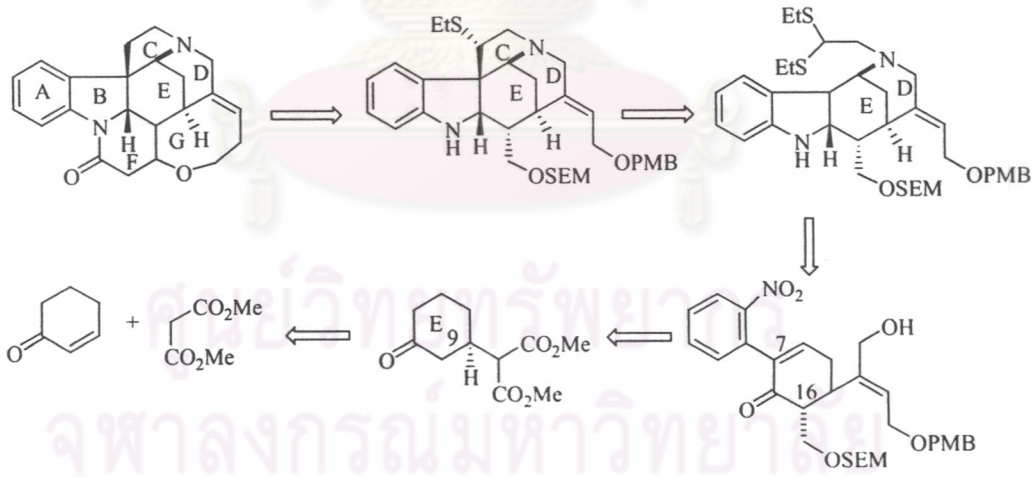


Figure 44. Asymmetric total synthesis of (-)-strychnine.

1.6 Objectives of this research

The objectives of this research are to prepare structurally diverse chiral *N*-salicyl-β-amino alcohol ligands and their heterobimetallic complexes and to evaluate their efficiency in catalyzing asymmetric Michael addition between dialkyl malonates and cyclic enones in order to obtain a structure-activity relationship profile and to develop a simple and reliable protocol for performing the Michael reaction and evaluating the enantioselectivity of the reaction.