CHAPTER I
INTRODUCTION

1.1 Definition of chirality

Chirality, or handedness, is an interesting property in numerous branches of science and medicine. In the terms of chemistry, chirality usually refers to molecules. A chiral (handed) molecule is one that is non-superimposable on its mirror image (i.e., molecules that do not possess a plane or center of symmetry). Most chiral organic molecules contain one or more stereogenic centers, which are carbon atoms bonded to four different groups. Two mirror images of a molecule that cannot be superimposed onto each other are referred to as enantiomers or optical isomers. When present in a symmetric environment, enantiomers have identical chemical and physical properties such as melting point, solubility, and NMR spectra. This is a reason why enantiomers cannot be separated or distinguished by conventional separation or analytical methods including chromatography and spectroscopy, but differences occur when they are in the presence of other chiral molecules or objects. One chiral object that interacts differently with the two enantiomers of a chiral compound is circularly polarized light: An enantiomer will absorb left- and right-circularly polarized light to differing degrees. This phenomenon is called optical activity. Furthermore, molecular chirality plays a major role in many areas of chemistry because of its application to stereochemistry in inorganic chemistry, organic chemistry, physical chemistry, biochemistry, and supramolecular chemistry. Example of a chiral molecule containing a chiral center (the carbon atom), with the two enantiomers are shown in Figure 1.1.

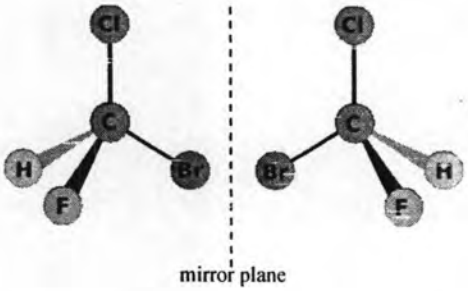
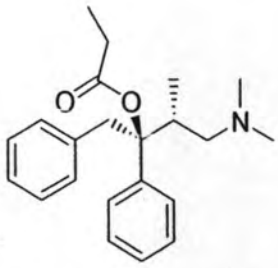


Figure 1.1 The two enantiomers of bromochlorofluoromethane

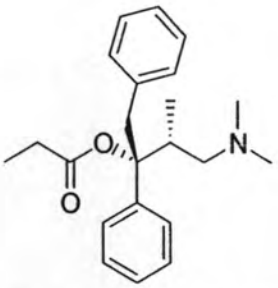
1.1.1 Origin of life: the chirality problem

Because the difference between right and left hands is always known and not difficult to observe, many pairs of enantiomers are assigned as right- and left-handed. A mixture of equal amounts of the two enantiomers (left- and right-handed forms) is said to be a racemate or racemic mixture and has a net rotation of plane-polarized light of zero. Without a chiral environment, a chemical reaction that makes a chiral product will always yield a racemate. The separation of a racemate into the pure enantiomers is called a chiral resolution. An organic chemist will usually use a ready-made homochiral substance from a living organism to separate racemic compounds into their enantiomers. The reaction products of the R and L enantiomers with an exclusively right-handed substance R′ that is R-R′ and L-R′ (called diastereomers), are not mirror images. So they have different physical properties, e.g. solubility in water, thus they can be separated. The maximum yield obtained from this resolutions is 50%.

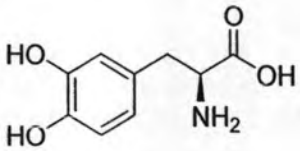
Chirality is a character of many molecules from nature. Among such substances, small molecules or macromolecules, occur in unichiral form. For example, chiral α-amino acids and the peptides and proteins containing them, sugars and their polysaccharides, steroids, antibiotics, and many other compounds from nature are unichiral. Another important aspect of many chiral molecules from nature is their homochirality. This means that related chiral molecules in the same chemical class usually have the same sense of chirality. For example, with rare exceptions α-amino acids occurring in nature consistently have the L configuration; similarly, monosaccharides are of the D configuration. Thus, both unichirality and homochirality are typical for compounds from nature: most of them occur in enantiomerically homogeneous form, and closely related molecules usually have the same sense of chirality. Biological molecules in living organisms such as proteins and enzymes have a chiral property so they usually respond to different enantiomers in different ways. That is the reason why different enantiomers of chiral compounds often taste and smell differently and have different effects as drugs. There are many examples of pharmaceuticals and other chemical compounds where the desired biological property is related to the absolute configuration (Figure 1.2).[1]



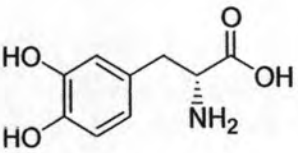
(2*R*,3*R*)-dextropropoxyphene (**1**)



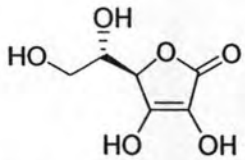
(2*R*,3*S*)-levopropoxyphene (**2**)



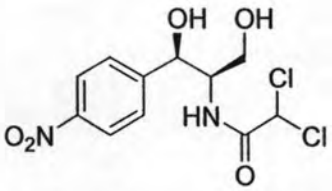
levodopa (**3**)



dextrodopa (**4**)



L-(-)-ascorbic acid (**5**)



D-(-)-chloramphenicol (**6**)

Figure 1.2 Structure of the optically active compounds having different biological activities [1]

Many biologically active molecules are chiral. Different enantiomers of these compounds often exhibit unequal or even different activities. For example, the propoxyphene families, only the dextro-isomer (dextropropoxyphene, (2*R*,3*R*)-(**1**)) has an analgesic effect with a morphine-like action in the body. An optical isomer of dextropropoxyphene, the levo-isomer (levopropoxyphene, (2*R*,3*S*)-(**2**)) appears to use only an antitussive effect (cough suppressants). Levodopa (**3**) or L-DOPA is moderately effective against the loss of natural dopamine and is used in treatment of Parkinson's disease, the enantiomeric dextrodopa (**4**) or D-DOPA is biologically inactive. Another example, ascorbic acid, is a sugar acid with antioxidant properties. The L-enantiomer of ascorbic acid (**5**) is also known as vitamin C which is an essential nutrient for a large number of higher primate species. It is widely known as the vitamin whose deficiency causes scurvy in humans and it is also widely used as a food additive. The opposite D-enantiomer has no physiological significance. Chloramphenicol (**6**) is a bacteriostatic antimicrobial. Only D-(-)-threo isomer has a

high antibacterial activity. It can be seen that drug molecules are usually chiral and the enantiomers have different effects on biological entities. Since many molecules in the bodies of living organisms are chiral, there is often a marked difference in the effects of the two enantiomers on living organisms including human beings.

The separation of each chiral form of a compound is often a critical step in producing enantiomerically pure molecules. This procedure is notably important in the drug and pharmaceutical industry. Due to potential side-effects of the other enantiomer, many chiral drugs must be made with high enantiomeric purity. There are several strategies for the preparation of enantiopure compounds. The first method is the separation of a racemic mixture into its isomers, a process called chiral resolution. Louis Pasteur in his pioneering work was able to isolate the isomers of tartaric acid because they crystallize from solution as crystals each with a different symmetry (conglomerates). Moreover, the use of chiral column chromatography and enzymes can also separate a racemate into its components, the pure enantiomers. Another method is enantioconvergent synthesis. This procedure is the synthesis of one enantiomer from a racemic precursor molecule utilizing both enantiomers. Nowadays, new techniques typically using asymmetric syntheses play an important role in the synthesis of chiral compound that yield a majority of desired isomer. Although a process for separation of a racemic mixture into its isomers, namely chiral resolution, is an effective and important tool in the production of optically active drugs, one major disadvantage of chiral resolution of racemates compared to direct asymmetric synthesis of one of the enantiomers is that only 50% of a desired enantiomer is obtained.

1.2 Asymmetric synthesis

Asymmetric synthesis is an important organic synthesis in the field of pharmaceuticals because different enantiomers or diastereomers of a molecule often have different biological activity. The synthesis of chiral compound as a single enantiomer is one of the most active areas of chemical research. Mainly, there are three methods of asymmetric synthesis.

1.2.1 Chiral pool synthesis

Chiral pool synthesis is the easiest approach. It starts the synthesis of a enantiopure compound from a readily available enantiopure substances and using achiral reagents which maintain its chirality to obtain the desired molecule. In general, the built-in chirality is usually preserved in the remainder of the reaction sequence. This strategy is especially attractive for target molecules having similar chirality to relatively inexpensive naturally occurring building blocks such as a sugar or amino acid, which are common chiral starting materials. However, the number of possible reactions the molecule can undergo are restricted, and tortuous synthetic routes with attendant losses in yield may be required. Also, this approach requires a stoichiometric amount of the enantiopure starting materials, which may be rather expensive if not naturally occurring. In this period of time, it may be not easy to find a suitable enantiopure starting material and other techniques may prove more useful.

1.2.2 Asymmetric induction

Commonly, many strategies in chiral synthesis is asymmetric induction which prefers the formation of one enantiomer or diastereomer over the other as a result of the influence of a chiral feature present in the substrate, reagent, catalyst or environment. There are serveral types of inductions.

Internal asymmetric induction

This type of induction makes use of a chiral center bound to the reactive center through a covalent bond and remains so during the reaction. The starting material is often derived from chiral pool synthesis.

Asymmetric induction can also take place intramolecularly when given a chiral starting material. This chirality transfer can be exploited, especially when the goal is to make several consecutive chiral centers to give a specific enantiomer of a specific diastereomer.

Relayed asymmetric induction

This strategy is the introduction of chiral information by the use of a special synthons called chiral auxiliary which forms an adduct to the starting materials and physically blocks the other trajectory for attack, leaving only the desired trajectory open. Assuming the chiral auxiliary is enantiopure, the different trajectories are

diastereomeric therefore not equivalent. In the last step of reaction, it will be removed in a separate chemical reaction.

External asymmetric induction

In external asymmetric induction, chiral information is introduced in the transition state through a chiral reagent or catalyst. This approach of asymmetric synthesis is economically most desirable.

1.2.3 Asymmetric catalysis

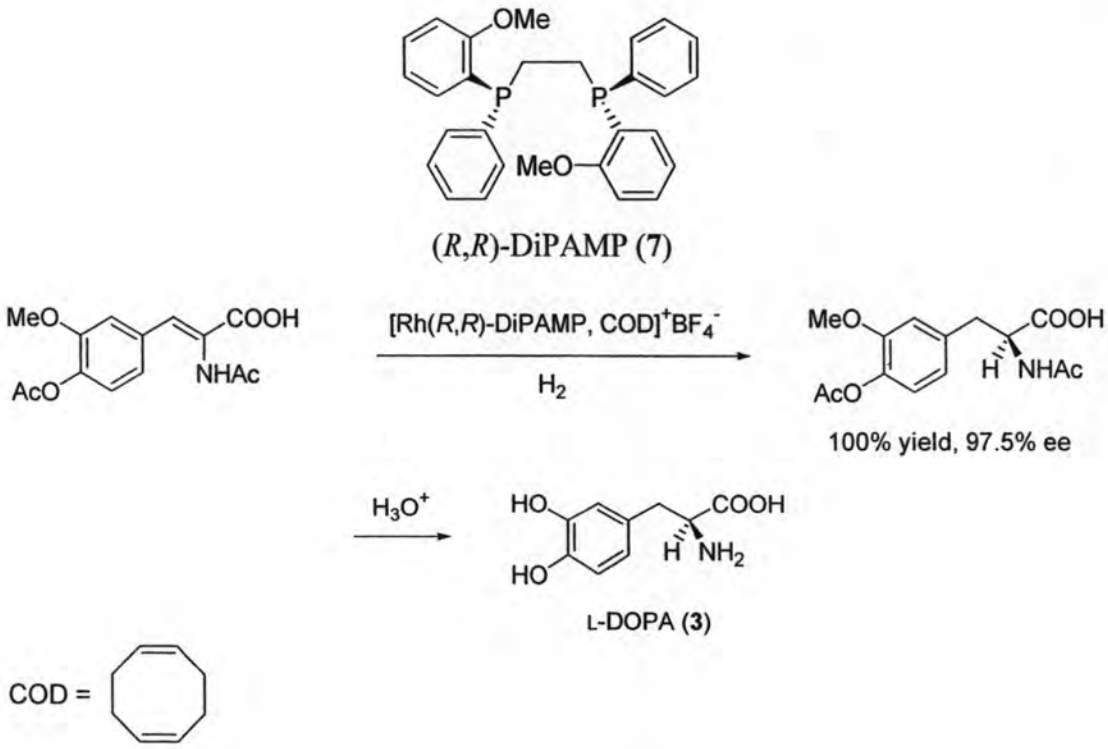
This concept is the introduction of chirality into nonchiral reactants by the use of chiral catalysts. It is an important development in organic synthesis using small amounts of chiral, enantiomerically pure (or enriched) catalysts promote reactions and lead to the formation of large amounts of enantiomerically pure or enriched products.[2-5] Generally, there are three different kinds of chiral catalysts employed:

Metal ligand complexes derived from chiral ligands

Chiral ligands are molecules specially adapted for asymmetric synthesis. The ligands are an enantiopure organic compounds which can combine with one or more metal centers by chelation to form chiral catalysts. These catalysts engage in a chemical reaction and transfers its chirality to the reaction product which as a result also becomes chiral. In an ideal reaction one equivalent of catalyst can turn over many more equivalents of reactants, which enables the synthesis of a large amount of chiral compounds from achiral precursors with the aid of a very small (often expensive) amount of chiral ligand. Elegant works in this field were pioneered by William S. Knowles, Ryoji Noyori, and K. Barry Sharpless (Nobel Prize in Chemistry 2001).

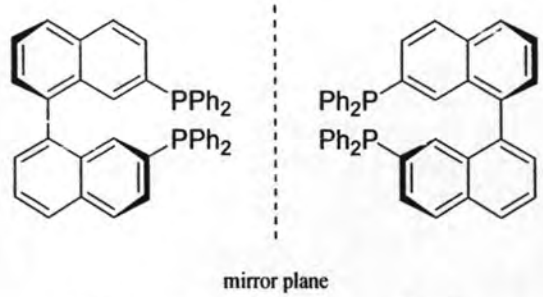
In 1968, [6] Knowles replaced the achiral triphenylphosphine ligands in Wilkinson's catalyst [chlorotris(triphenylphosphine)rhodium(I)] by the chiral phosphine ligands P(Ph)(Me)(Propyl) thus creating the first asymmetric catalyst. The phosphine first used by Knowles in an asymmetric hydrogenation was not enantiomerally pure, yet it produced a mixture in which there was 15% more of one enantiomer than the other (15% ee). Although this excess was modest and hardly of any practical use, the result proved that it was in fact possible to achieve catalytic asymmetric hydrogenation based on this principle.

In an example of the first asymmetric synthesis using a chiral catalyst on industrial scale, Knowles' aim was to develop an industrial synthesis of the amino acid L-DOPA (**3**), which had proved useful in the treatment of Parkinson's disease. The ligand later used in Monsanto's industrial synthesis of **3** was the diphosphine ligand (*R*,*R*)-DiPAMP (**7**). A rhodium complex of this ligand catalyzed hydrogenation of an enamino acid to give a mixture of enantiomers of DOPA in 100% yield. The enantiomeric excess of the desired L-product was as high as 97.5% **3**. Thus Knowles had in a short time succeeded in applying his own basic research and that of others to create an industrial synthesis of a drug. This was the first truly useful catalytic asymmetric synthesis. Similar reactions has been succeeded by many others. The synthesis of **3** is as shown in Scheme 1.1.



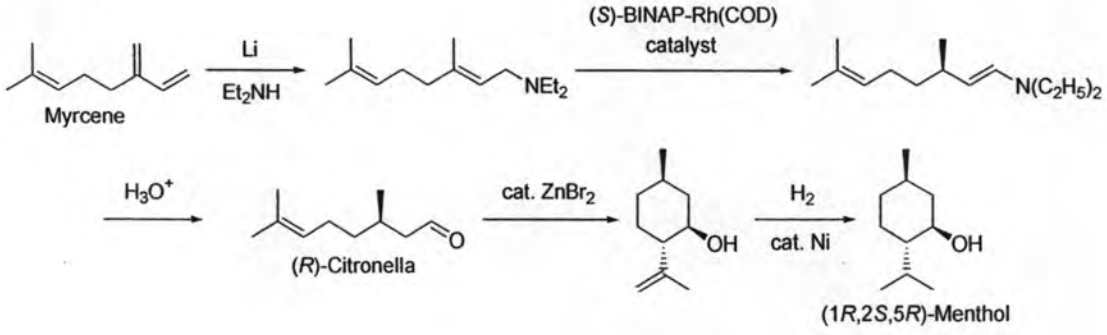
Scheme 1.1 The industrial synthesis of L-DOPA developed by Knowles and co-workers [5]

In 1980, [7] Noyori and co-workers published on the synthesis of both enantiomers of the diphosphine ligand BINAP (**8**). This ligand, in combination with rhodium, catalyzes the synthesis of certain amino acids with an enantiomeric excess of up to 100%.



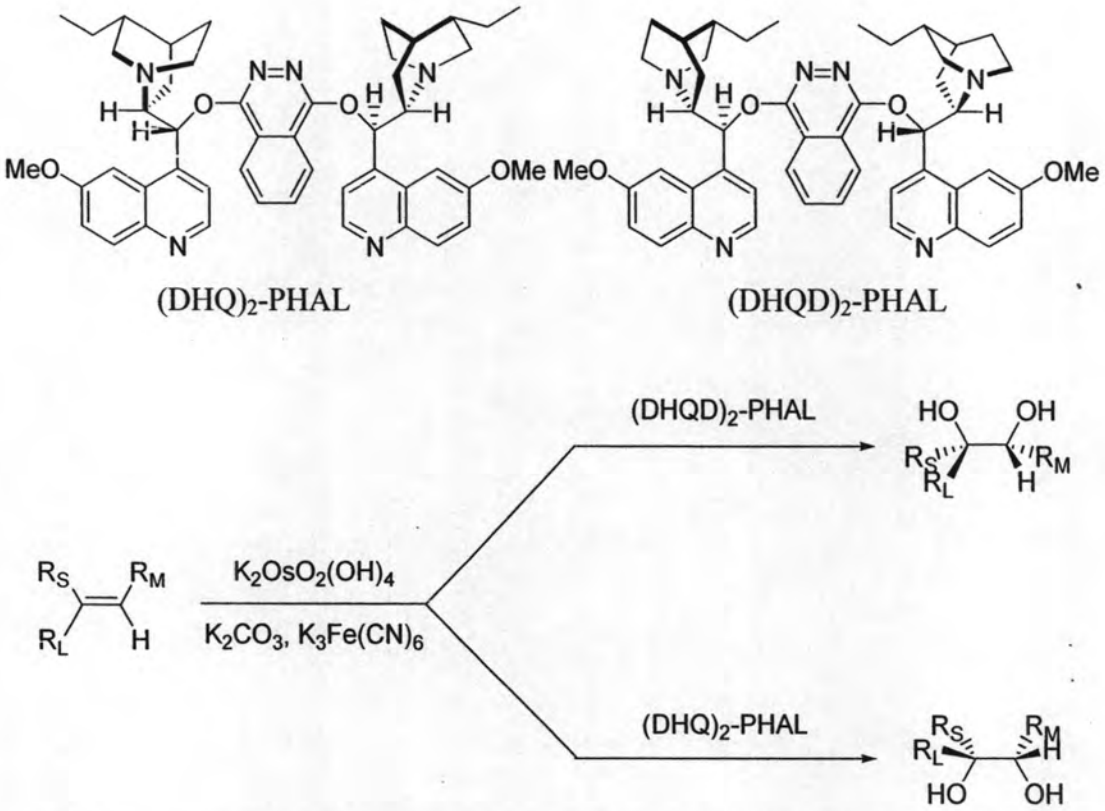
(*S*)-**8** (*R*)-**8**

The early 1980s, (-)-menthol has been manufactured as a single enantiomer (94% ee) by Takasago International Co. on a scale of 400,000 tonnes per year in the presence of a chiral (*S*)-**8**-rhodium complex. The complex catalyze the enantioselective hydrogenation of the functionalized allylic amine in a highly enantioselectivity. This process was also developed by a team led by Noyori (Scheme 1.2).[5]



Scheme 1.2 The synthetic method of (-)-menthol on industrial process by using a chiral (*S*)-**8**-rhodium complex [5]

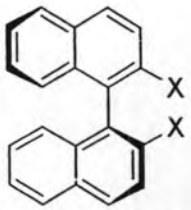
The other part of that Nobel prize concerned the Sharpless asymmetric dihydroxylation (also called the Sharpless bishydroxylation). This reaction is the chemical reaction of an alkene with osmium tetroxide in the presence of a chiral quinine ligand to form a vicinal diol which is important in organic synthesis.[8-10] It is ordinary practice to perform this reaction using a catalytic amount of osmium tetroxide, which after reaction is regenerated with either potassium ferricyanide [11,12] or *N*-methylmorpholine *N*-oxide (Scheme 1.3).[13,14] This dramatically reduces the amount of the highly toxic and very expensive osmium tetroxide needed. These four reagents are commercially available premixed ("AD-mix"). The mixture containing $(DHQ)_2$-PHAL is called AD-mix-α, and the mixture containing $(DHQD)_2$-PHAL is called AD-mix-β.[15]



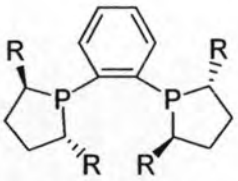
R_L = Largest substituent; R_M = Medium-sized substituent; R_S = Smallest substituent

Scheme 1.3 The synthetic of optically active vicinol diol by using Sharpless asymmetric dihydroxylation [15]

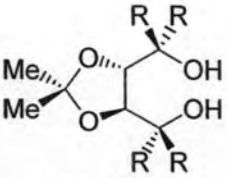
At the present day, many of chiral ligands have been prepared and tested, but only several compound classes have been found to have a general scope. Therefore, These ligands are called privileged ligands (Figure 1.3).[16,17] Important members depicted below are BINAP (**8**), BINOL (**9**), DuPhos (**10**), TADDOL (**11**), DIOP (**12**), bis(oxazoline) or BOX (**13**), all available as enantiomeric pairs. Other members are Salen (**14**) and the cinchona alkaloids (**15**). Many of these ligands possess C_2 symmetry which limits the number of possible reaction pathways and thereby increasing enantioselectivity.



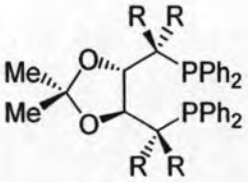
X = PPh_2 ; BINAP (**8**)
X = OH ; BINOL (**9**)



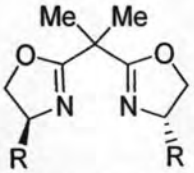
DuPhos (**10**)



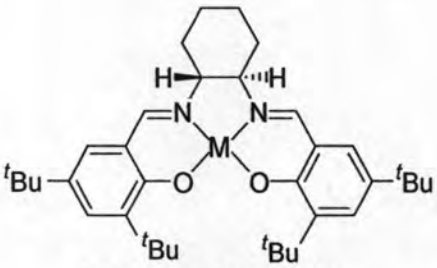
TADDOL (**11**)



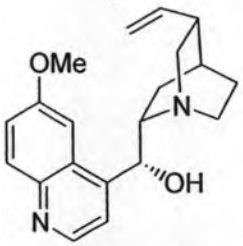
DIOP (**12**)



Bis(oxazoline) (**13**)



Salen complexes (**14**)



Cinchona alkaloid derivatives (**15**)

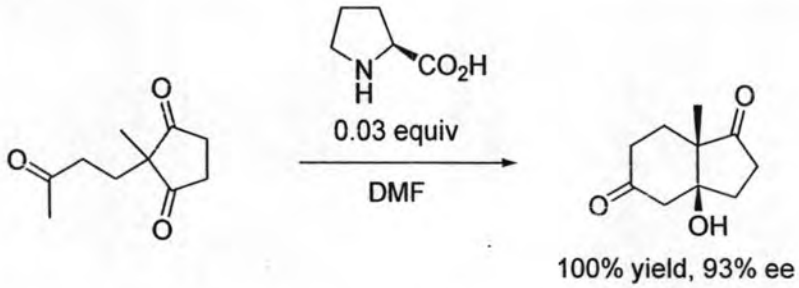
Figure 1.3 Example of privileged chiral ligands and catalysts [16,17]

Chiral organocatalysts

Attempt to avoid the use of heavy metal in the synthesis of optically active compounds having biological activity especially in pharmaceutical manufacturers is important, so chemists try to search for an alternative way to produce enantiopure compounds. The convenient way should be the use of a chiral ligand which can both accelerate a reaction as well as induce the enantioselectivity. In organic chemistry, the term organocatalysis (a concatenation of the terms "organic" and "catalyst") refers to a form of catalysis, whereby the rate of a chemical reaction is increased by an organic catalyst referred to as an "organocatalyst" consisting of carbon, hydrogen, sulfur and other nonmetal elements found in organic compounds.[18-22] If the organic molecule is chiral, it may react preferentially with the substrate of a certain chirality. Indeed, many chiral organocatalysts are an adaptation of chiral ligands (which together with a metal center also catalyze asymmetric reactions) and both concepts overlap to some degree. Because of their similarity in composition and description, they are often

mistaken as a misnomer for enzymes due to their comparable effects on reaction rates and forms of catalysis involved. A main advantages of organocatalysis, there is no need for metal-based catalysis thus making a contribution to green chemistry.

A pioneering asymmetric organocatalysis reaction developed in the 1970s by teams of Hoffmann-La Roche [23] and Schering AG [24] that sums it all up is the Hajos-Parrish-Eder-Sauer-Wiechert reaction shown in the reaction equation below (Scheme 1.4).



Scheme 1.4 The Hajos-Parrish-Eder-Sauer-Wiechert reaction: proline catalyzed asymmetric aldol reaction [23,24]

In this reaction, naturally occurring chiral proline is the chiral catalyst in an asymmetric aldol reaction. The starting material is an achiral triketone and it requires just 3% of proline to obtain the reaction product, an optically active bicyclic ketol in 93% enantiomeric excess. It has been used extensively as a tool in steroid synthesis.

At the present day, organocatalysts for asymmetric synthesis can be grouped in several classes and the figures are as shown in Figure 1.4.[18-24]

- Biomolecules: notably proline, phenylalanine, the cinchona alkaloids, certain oligopeptides.
- Synthetic catalysts derived from biomolecules. Examples of proline derivatives are McMillan imidazolidinones and the CBS catalyst
- TADDOLS
- Derivatives of BINOL such as NOBIN
- Triazolium salts as next-generation Stetter reaction catalysts
- Organocatalysts based on thioureas

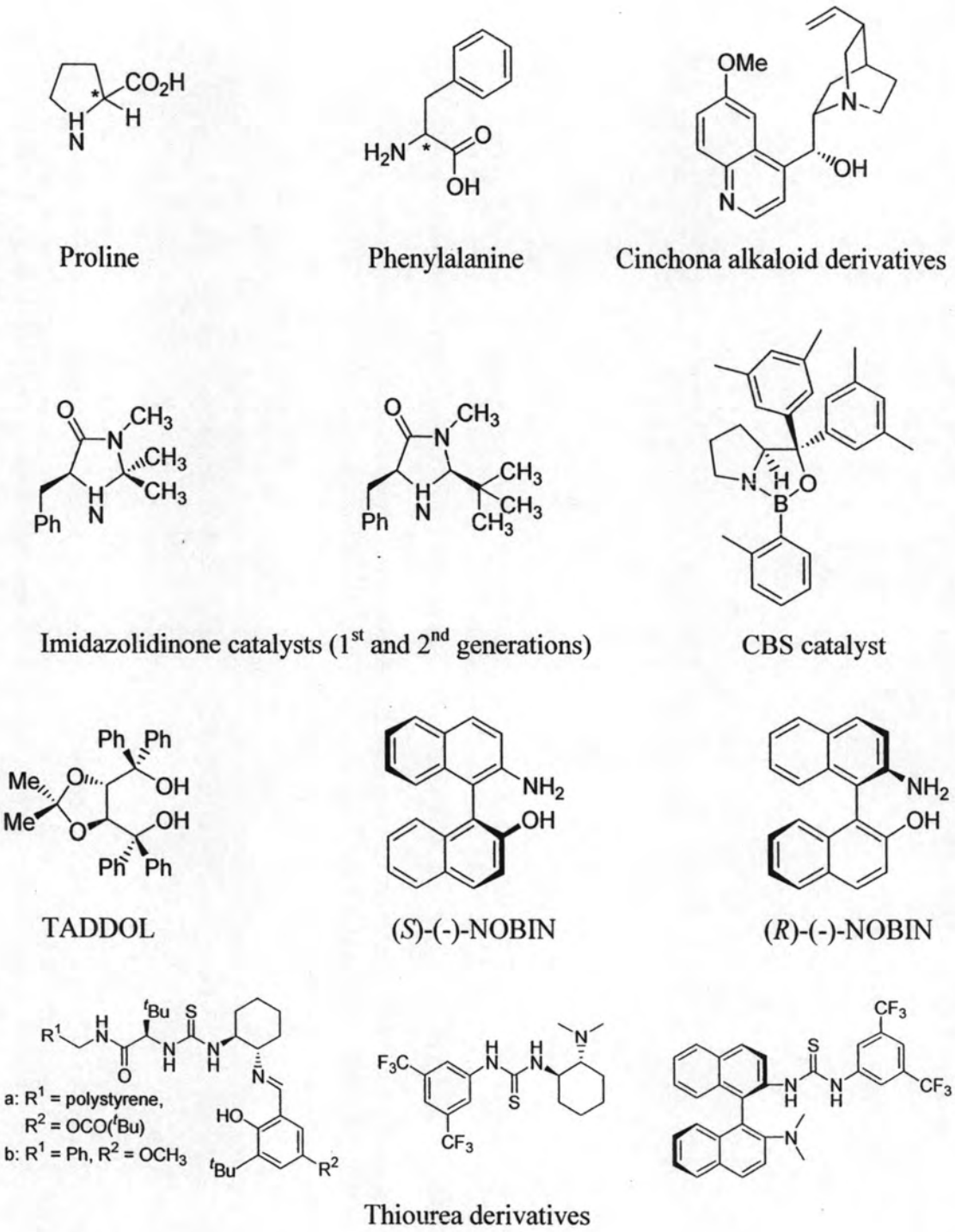


Figure 1.4 Some examples of organocatalysts used for asymmetric synthesis [18-24]

Biocatalysts

Biocatalysis can be defined as utilization of natural catalysts, such as enzymes, to perform chemical transformations on organic compounds. Both enzymes that have been more or less isolated or enzymes still residing inside living cells are employed for this task.[25-27] The employment of enzymes and whole cells have been

important for many industries for centuries. The most obvious usages have been in the food and drink businesses where the production of wine, beer, cheese etc. is dependent on the effects of the microorganisms. More than one hundred years ago, biocatalysis was employed to do chemical transformations on non-natural man-made organic compounds, and the last 30 years have seen a substantial increase in the application of biocatalysis to produce fine chemicals, especially for the pharmaceutical industry.

Selectivity in organic synthesis is necessary to obtain a high yield of a specific product. There are a large range of selective organic reactions available for most synthetic needs. However, there is still one area where organic chemists are struggling, and that is when chirality is involved, although considerable progress in chiral synthesis has been achieved in recent years.

The most important advantage of biocatalysts in asymmetric synthesis are that enzymes display three major types of selectivities:

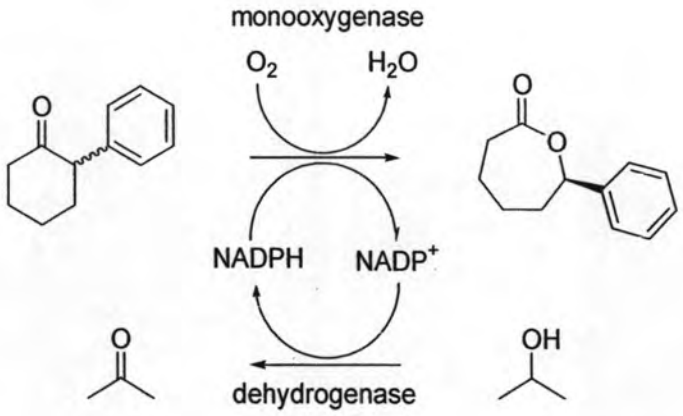
- **Chemoselectivity:** Since the purpose of an enzyme is to act on a single type of functional group, other sensitive functionalities, which would normally react to a certain extent under chemical catalysis, survive. As a result, biocatalytic reactions tend to be cleaner and laborious purification of product(s) from impurities emerging through side-reactions can largely be left out.
- **Regioselectivity and diastereoselectivity:** Due to their complex three-dimensional structure, enzymes may distinguish between functional groups which are chemically situated in different regions of the substrate molecule.
- **Enantioselectivity:** Since almost all enzymes are made from L-amino acids, enzymes are chiral catalysts. As a consequence, any type of chirality present in the substrate molecule is recognized upon the formation of the enzyme-substrate complex. Thus a prochiral substrate may be transformed into an optically active product and both enantiomers of a racemic substrate may react at different rates.

Another important advantage of biocatalysts are that they are environmental friendly, being completely degraded in the environment. Furthermore, the enzymes act under mild conditions, which minimizes problems of undesired side-reactions such as decomposition, isomerization, racemization and rearrangement, which often plague traditional methodology. These reasons, and especially the latter, are the major reasons why synthetic chemists have become interested in biocatalysis. This interest is mainly due to the need to synthesize enantiopure compounds as chiral building blocks

for drugs and agrochemicals. The use of biocatalysis to obtain enantiopure compounds can be divided into two different methods. The first one is kinetic resolution of a racemic mixture and the other is biocatalyzed asymmetric synthesis.

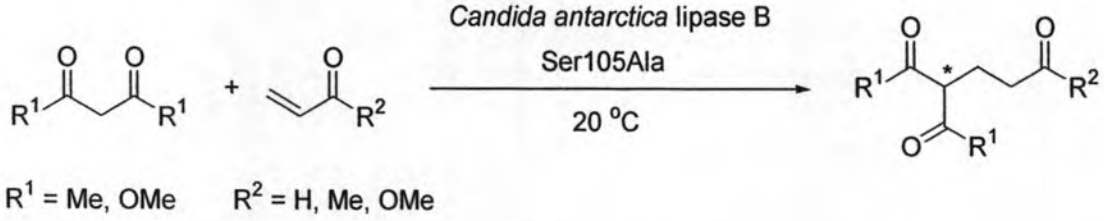
1. Kinetic resolution of a racemic mixture: In kinetic resolution of a racemic mixture, the presence of a chiral object (the enzyme) converts one of the enantiomers into product at a greater reaction rate than the other enantiomer. The maximum yield in such kinetic resolutions is 50%, since a yield of more than 50% means that some of wrong isomer also has reacted, giving a lower enantiomeric excess. Therefore, such reactions must be terminated before equilibrium is reached. If it is possible to perform such resolutions under conditions where the two substrate-enantiomers are racemizing continuously, all substrate may in theory be converted into enantiopure product. This is called dynamic resolution.

2. Biocatalyzed asymmetric synthesis: In biocatalyzed asymmetric synthesis, a non-chiral unit becomes chiral in such a way that the different possible stereoismers are formed in different quantities. The chirality is introduced into the substrate by influence of enzyme. The biocatalytic Baeyer-Villiger oxidation is example of a biocatalytic reaction with a so-called Baeyer-Villiger monooxygenase or BVMO. In one study [28] the enzyme purification issue is addressed and a special thermally stable monooxygenase is isolated from a specific *E. coli* strain. This enzyme converts racemic 2-phenylcyclohexanone with oxygen to the corresponding (*R*)-lactone with 50% chemical yield and 94% enantiomeric excess with in a biphasic system of water and hexane. The NADPH cofactor is regenerated in each catalytic cycle by action of a second dehydrogenase enzyme which consumes isopropanol as a sacrificial catalyst (Scheme 1.5).



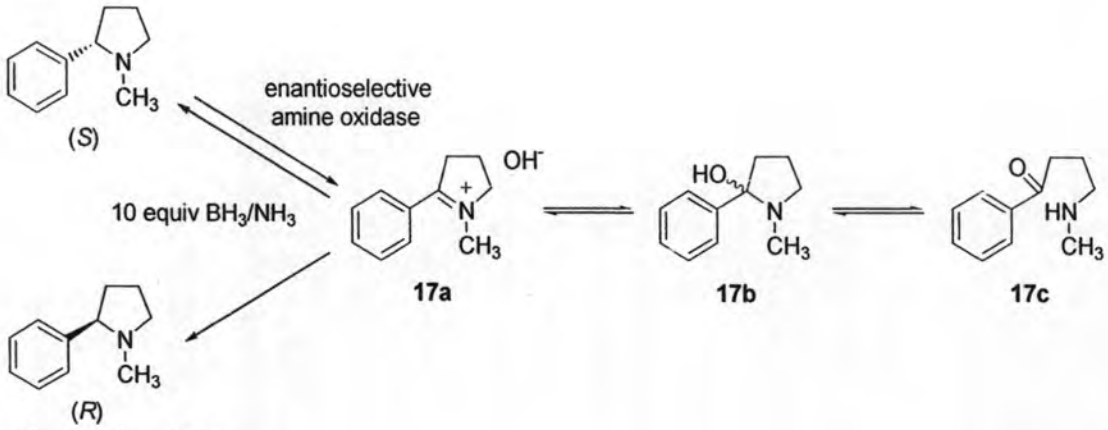
Scheme 1.5 The example of asymmetric Baeyer-Villiger oxidation by using enzyme monooxygenase as a biocatalyst [28]

The another example of a biocatalytic reaction, a specially designed mutant of *Candida antarctica* was found to be an effective catalyst for the Michael addition of acrolein with acetylacetone at 20 °C in the absence of additional solvent (Scheme 1.6).[29]



Scheme 1.6 Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated carbonyl compounds catalyzed by a *C. antarctica* lipase B mutant [29]

In one study demonstrates how racemic nicotine (**16**) can be deracemized in a one-pot procedure concerning a monoamine oxidase isolated from *Aspergillus niger* which is able to oxidize only the amine *S*-enantiomer to the imine **17** and involving an ammonia/borane reducing which can reduce the imine **17** back to the amine **16**.[30] In this way the *S*-enantiomer will contineously be consumed by the emzyme while the *R*-enantiomer accumulates. It is even possible to stereoinvert pure *S* to pure *R*.



(±)-nicotine (**16**)

Scheme 1.7 Deracemization of racemic nicotine **16** with an enantioselective amine oxidase in combination with ammonia borane as the reducing agent [30]

1.3 Chiral ligands containing soft donor atom

1.3.1 Hard and soft acid and base (HSAB) principle

In early 1960s, [31] Ralph G. Pearson introduced the HSAB principle as an attempt to combine inorganic and organic reaction chemistry. This concept also known as the Pearson acid base concept, is widely used in chemistry for explaining stability of compounds, reaction mechanisms and pathways. It assigns the terms 'hard' or 'soft', and 'acid' or 'base' to chemical species. The heart of this theory is that *soft* acids react faster and form stronger bonds with *soft* bases, whereas *hard* acids react faster and form stronger bonds with *hard* bases. The classification in the original work was mostly based on equilibrium constants for reaction of two Lewis bases competing for a Lewis acid. Hard acids and hard bases applies to species which are small atomic/ionic radius, have high charge states (oxidation state) (the charge criterion applies mainly to acids, to a lesser extent to bases), possess high electronegativity, and are weakly polarizable. Moreover, hard acids and hard bases tend to have energy low-lying HOMO (bases) or energy high-lying LUMO (acids). Examples of hard acids are: H^+, alkali ions, Ti^{4+}, Cr^{3+}, Cr^{6+}, BF_3. Examples of hard bases are: OH^-, F^-, Cl^-, NH_3, $CH_3CO_2^-$, CO_3^{2-}. The affinity of hard acids and hard bases for each other is mainly ionic in nature. Soft acids and soft bases applies to species which are large atomic/ionic radius, have low or zero charge states, possess low electronegativity, and are strongly polarizable. In addition, soft acids and soft bases tend to have energy

high-lying HOMO (bases) and energy-low lying LUMO (acids). Examples of soft acids are: CH_3Hg^+, Pt^{4+}, Pd^{2+}, Ag^+, Au^+, Hg^{2+}, Hg_2^{2+}, Cd^{2+}, BH_3. Examples of soft bases are: H^-, R_3P, SCN^-, I^-. The affinity of soft acids and bases for each other is mainly covalent in nature. The examples of hard and soft acids and bases, in part are summarized in Table 1.1.[32]

Table 1.1 Hard and soft acids and bases [32]

acids				**bases**			
hard		**soft**		**hard**		**soft**	
hydronium	H^+	mercury	CH_3Hg^+, Hg^{2+}, Hg_2^{2+}	hydroxyl	OH^-	hydride	H^-
alkali metals	Li^+, Na^+, K^+	platinum	Pt^{4+}	alkoxide	RO^-	thiolate	RS^-
titanium	Ti^{4+}	palladium	Pd^{2+}	halogens	F^-, Cl^-	halogens	I^-
chromium	Cr^{3+}, Cr^{6+}	silver	Ag^+	ammonia	NH_3	phosphine	PR_3
boron trifluoride	BF_3	borane	BH_3	carboxylate	$CH_3CO_2^-$	thiocyanate	SCN^-
carbocation	R_3C^+	P-chloranil		carbonate	CO_3^{2-}	carbon monoxide	CO
		bulk metals	M^0	hydrazine	N_2H_4	benzene	C_6H_6
		gold	Au^+				

Borderline cases are also identified: borderline acids are trimethylborane ($B(CH_3)_3$), sulfur dioxide (SO_2), ferrous (Fe^{2+}), cobalt (Co^{2+}), and lead (Pb^{2+}) cations. Borderline bases are: aniline ($C_6H_5NH_2$), pyridine (C_6H_5N), nitrogen (N_2), azide (N_3^-), bromine (Br^-), nitrate (NO_2^-), and sulphate (SO_3^{2-}) anions.

Chiral ligands containing soft donor atoms such as phosphorus (P) or sulfur (S) complexed with transition metals ion, for example palladium (Pd), zinc (Zn) or copper (Cu) could catalyze the asymmetric nucleophilic additions to carbonyl compounds, [33-36], polarized double bond, [37-41] imines [42,43] or induce asymmetric nucleophilic attack such as hydrogenation reaction, [44-46] asymmetric allylic alkyllation.[47-49] There are many examples of the such ligand groups

developed for catalytic asymmetric synthesis including BINAP (**8**), DuPHOS (**10**) and its derivative (**18**), peptide-based phosphine ligand (**19**), N-S ligand (**20**), γ-amino thiol ligand (**21**), and also N-P ligand (**22**), etc. (Figure 1.5)

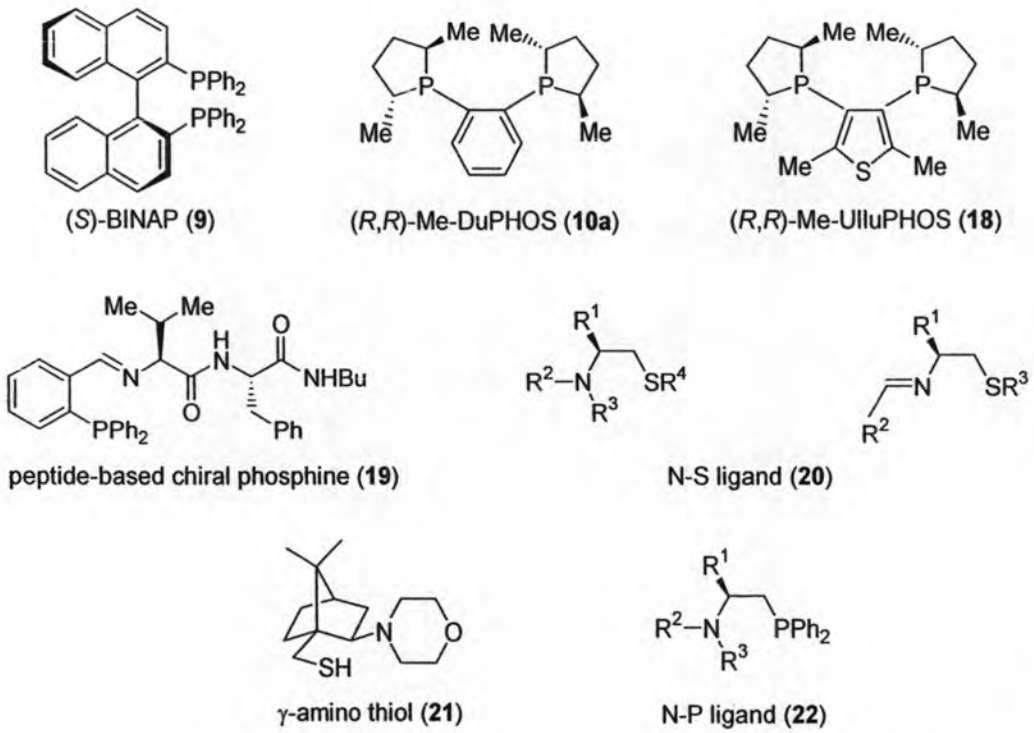


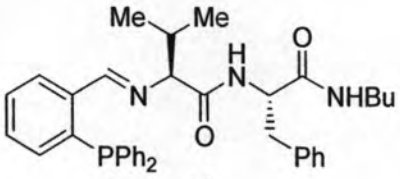
Figure 1.5 Examples of chiral ligands containing soft donor atoms used for asymmetric synthesis

1.3.2 Chiral phosphorus-containing ligands

Chiral phosphorus-based ligands are the most common and useful in organic syntheses. For example, the pioneering work in asymmetric hydrogenation by Knowles, Kagan, and Noyori has been recognized with the Nobel and Wolf Prizes. Introduction of chiral phosphorus ligands is the key for their work. Many pharmaceutical companies, a variety of fine chemical companies, several technology-service and metal companies have developed commercial chiral phosphorus ligands or use them for practical applications. The first successful attempts of homogeneous metal-catalyzed asymmetric transformations involving chiral phosphorus ligands were obtained in the hydrogenation of carbon-carbon double bonds. The coordination of mono- and then diphosphines to transition metal centers has opened up routes to a large number of examples of enantioselective hydrogenations of prochiral substrates containing C=C, C=O and C=N bonds.[50-52] After the introduction of the very

efficient bidentate DIOP ligand by Kagan in 1971, [53,54] this field has mainly been driven by the use of bidentate ligands, especially C_2-symmetrical diphosphines associated to ruthenium, rhodium and iridium metal centers, which make possible the enantioselective hydrogenation of a variety of substrates such as dehydroamino acids, acrylic derivatives, ketones, imines, enamides, enecarbamates, and so on. At the moment there is a variety of chiral ligand containing phosphorus as a soft donor atom used for various asymmetric syntheses.

Asymmetric synthesis of carbonyl compounds using nucleophilic addition to conjugated double bond (Michael addition) is one of the useful method in organic synthesis. Hoveyda *et al.* [37-39] reported the use of peptide-based phosphine ligand (**19**) in asymmetric dialkylzinc addition to cyclic enones [37] in the presence of $(CuOTf)_2{\cdot}C_6H_6$ to obtain the corresponding Michael adducts in 71-98% yield and 62-98% ee (Scheme 1.8).



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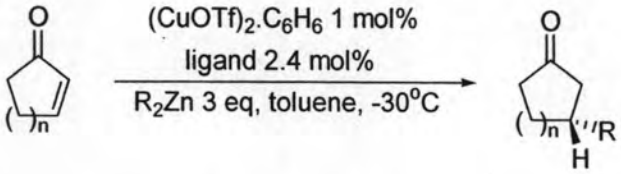
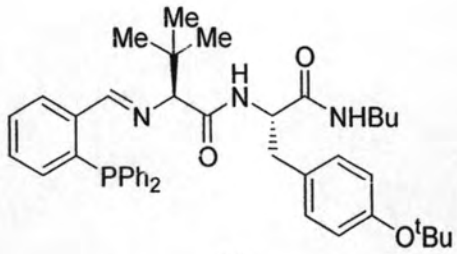


Scheme 1.8 Asymmetric synthesis of carbonyl compounds using dialkylzinc addition to cyclic enones [37]

Moreover, Hoveyda and co-worker also studied using a modified peptide-based phosphine ligand (**23**) to catalyze the same reaction for aliphatic enones.[38] The γ-ethyl ketone products was obtained in 42-93% yield and up to 95% ee was observed (Scheme 1.9).



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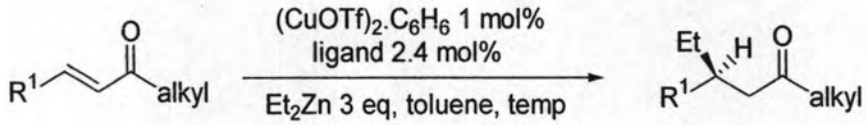
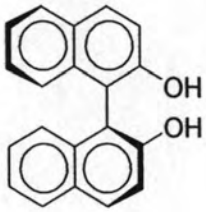
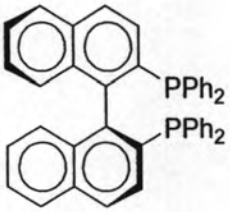


Scheme 1.9 Asymmetric synthesis of carbonyl compounds using diethylzinc addition to aliphatic ketones [38]

Binaphthol or BINOL (**9**) is a chiral ligand utilized for various catalytic asymmetric syntheses.[55] Functionalized the oxygen atoms of **9** with another functional groups such as diphenylphosphine would bring to ligand **8** employed to be catalyst in organic synthesis.

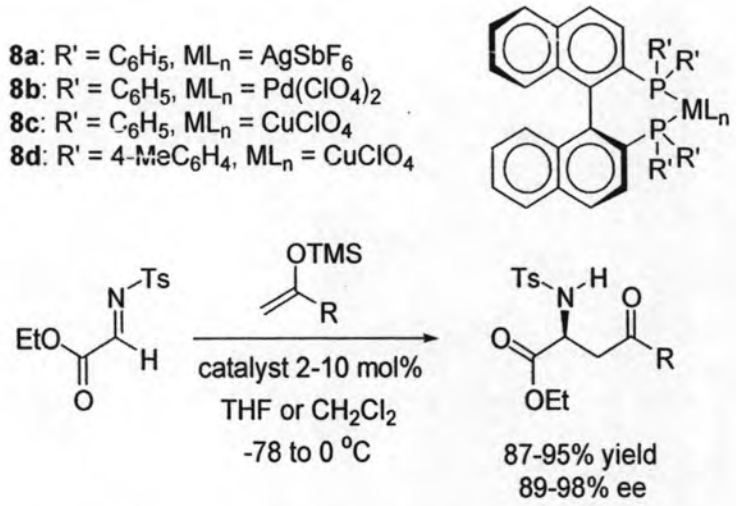


(*S*)-BINOL (**9**)



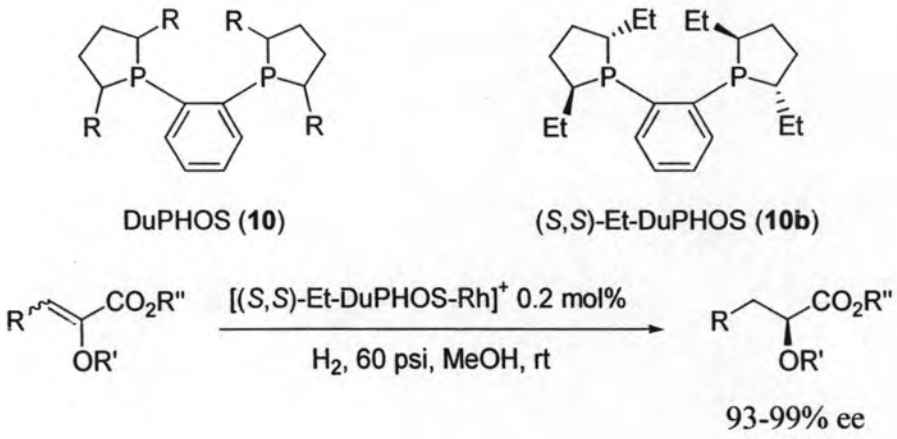
(*S*)-BINAP (**8**)

There were many examples of BINAP's derivatives to catalyze the synthesis of α-, β-amino acids as well as β-lactam from α-imino esters.[43] For example, the synthesis of α-amino acids using enolsilane as a nucleophile in the presence of chiral bis-phosphine ligands (**8a-8d**) complexed with various Lewis acids gave the optical products in 87-95% yield and 89-98% ee (Scheme 1.10).



Scheme 1.10 The synthesis of α-amino acids using enolsilane as a nucleophile in the presence of **8** complexed with various Lewis acids [43]

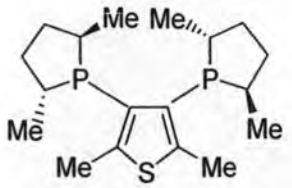
DuPHOS (**10**) is such ligand group possessing two phosphorus atoms as well as BINAP. There were some reports concerning about the employing DuPHOS family such as (*S*,*S*)-Et-DuPHOS (**10b**) complexed with rhodium metal to catalyze asymmetric hydrogenation of enol ester double bond.[44] The products were produced in *S* as a major isomer with excellent enantiomeric excess (93-99%) (Scheme 1.11). The obtained products could be functionalized to give α-hydroxy ester or 1,2-diol, which are useful in organic synthesis.



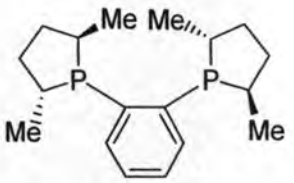
Scheme 1.11 Asymmetric hydrogenation of enol ester double bond employing **10b** complexed with rhodium metal [44]

A substitution of benzene ring in DuPHOS with a thiophene ring would lead to a novel ligand, namely (*R*,*R*)-UlluPHOS (**18**).[46] When this ligand was used for

catalytic asymmetric hydrogenation it was found that **18** complexed with Rh and Ru metal could accelerate the same reaction with faster than the original ligand (**10a**).



(*R*,*R*)-Me-UlluPHOS (**18**)



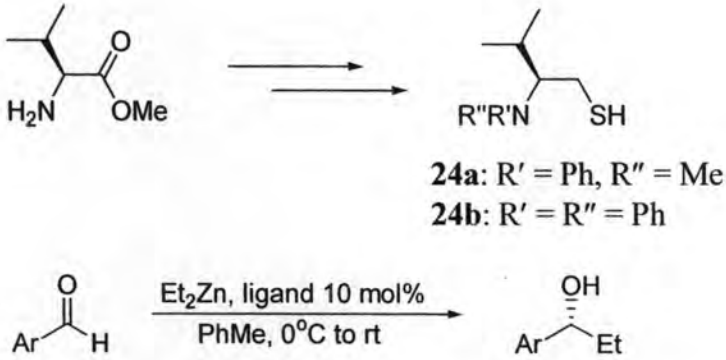
(*R*,*R*)-Me-DuPHOS (**10a**)

1.3.3 Chiral sulfur-containing ligands

Due to the high coordination ability of the sulfur atom to most transition metals, asymmetric sulfur ligands have also been developed for enantioselective catalysis in the last 20 years. The sulfur atom is considered as a soft atom and forms strong bonds with soft metals (such as palladium). Sulfur ligands are poor σ-donor and poor π-acceptor ligands, as a particularity contributing to the metal-sulfur bond strength. This is one of the differences between sulfur and phosphine ligands, which are better σ-donors and π-acceptors. The *trans*-effect of the sulfur ligands, even if it was found lower than that of the phosphine ones, is higher compared to those of the nitrogen- and oxygen-containing ligands. Moreover, sulfur-containing compounds are easily available, and they are also highly stable, allowing easy storage and handling, especially compared to phosphine derivatives. Furthermore, these sulfur ligands open new possibilities over other chelates because a new stereogenic center is formed at the sulfur by coordination to the metal. However, the control of this new chiral center is not always feasible due to its low inversion barrier (10-15 kcal/mol) when this value approaches 30-35 kcal/mol for the phosphorus atom.[56,57] It is noticeable that, in the case of sulfoxides, this inversion barrier is higher (35-45 kcal/mol). The close vicinity of the chiral center to the transition metal may however lead to interesting results in terms of enantiofacial discrimination. A wide diversity of chiral sulfur-containing ligands is easily available either directly from the chiral pool or by facile modifications of other heteroatomic ligands for a comparison of their coordinating ability and efficiency to perform asymmetric catalysis. There are many numbers of asymmetric catalytic reactions performed in the presence of sulfur-containing ligands reported.[58,59] Most of them report the asymmetric formation of new carbon-carbon bonds and in particular the nucleophilic allylic substitution, probably due to the

affinity of the sulfur atom for a strong coordination to palladium. Other examples are found in which asymmetric Diels-Alder or hetero-Diels-Alder cycloadditions, Heck-type reactions, asymmetric conjugated additions, and various additions to carbonyl bonds. Moreover, chiral sulfur-containing complexes have also been successfully used for asymmetric reductions of carbonyl groups or carbon-carbon double bonds. Herein, the nucleophilic additions to unsaturated double bonds including carbonyl bond will be described in relation to the structure of the S- containing ligand used.

In 1998, Anderson and co-worker tried to use novel chiral ligands (**24**) modified from L-valine derivatives having the chelating of S-N atoms for catalytic asymmetric diethylzinc addition to aromatic aldehydes.[33] It was found that the use of chiral ligand containing stereogenic nitrogen (**24a**) could reduce the reaction time and also induce the enantioselectivity with higher's ee compared to the corresponding chiral ligand containing symmetrical nitrogen (**24b**). Both of them gave the optical products in 56-91% yield with 52-82% ee, *R* isomer as a major isomer (Scheme 1.12).



Scheme 1.12 Catalytic asymmetric diethylzinc addition to aromatic aldehydes using chiral ligands **24a** and **24b** [33]

Moreover, Anderson *et al.* [33] compared the experimental results between the use of chiral amino alcohol ligands and the corresponding chiral amino thiol compounds in the same reaction. They found that chiral amino thiols showed better results in terms of catalytic property and also the enantioselectivity compared to the similar chiral amino alcohols. Furthermore, there was a variety of structural S-N ligand revealing the high to excellent efficiency for catalytic asymmetric diethylzinc addition to benzaldehyde (Figure 1.6).

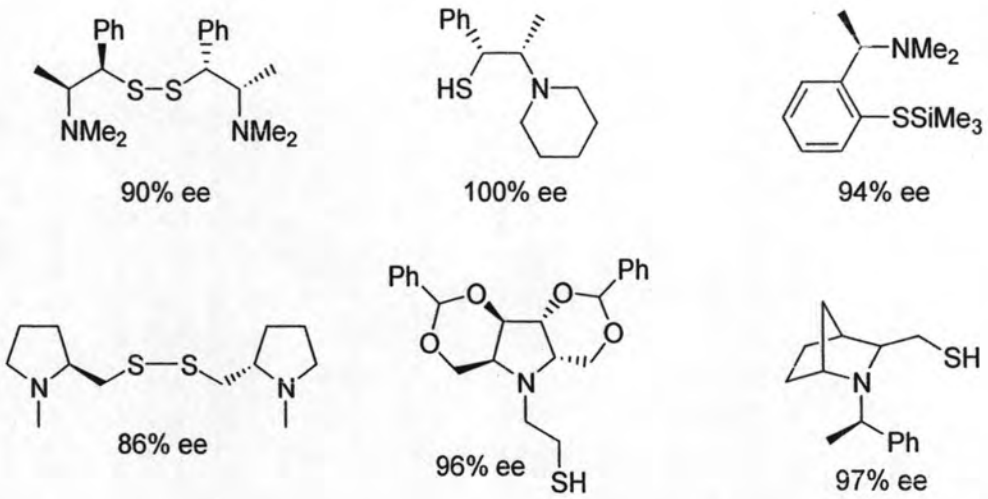
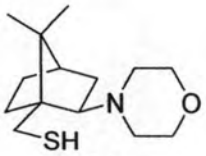


Figure 1.6 A variety of structural S-N ligand for catalytic asymmetric diethylzinc addition to benzaldehyde showing the high to excellent efficiency selectivity [33]

Asymmetric arylation reaction to produce secondary alcohols was successful when camphor derivative, a novel γ-amino thiol (**21**) was used as a catalyst.[36] The addition of aryl groups came from $Ar'B(OH)_2$ to various aromatic aldehydes in the presence of Et_2Zn could obtain diarylmethanol in 73-98% yield with up to >99.5% ee was observed (Scheme 1.13).



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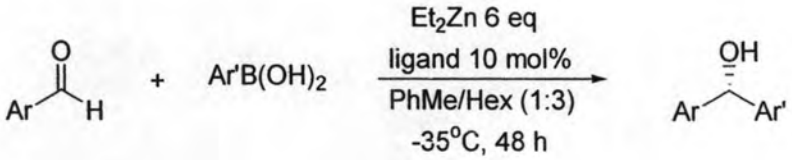


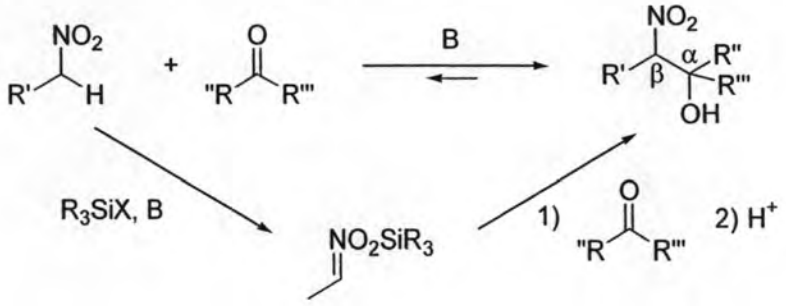
Scheme 1.13 Asymmetric arylation reaction catalyzed by **21** in the presence of Et_2Zn [36]

The details described above showed the effective chiral ligands containing soft donor atoms in asymmetric syntheses. Interestingly, these ligands could induce the enantioselectivity of the many types of nucleophilic additions. It is a design powerful chiral ligands possessing soft donor atoms which could be further developed and investigated their use in catalytic asymmetric syntheses, for example the nitro-aldol

(Henry) reaction or other reactions involving nucleophilic addition to carbonyl compounds, imines, or polarized double bonds.

1.4 Nitro-aldol (Henry) reaction

Among the various carbon-carbon bond forming reactions, one of the most powerful carbon-carbon bond-forming process in organic chemistry, namely the nitro-aldol or Henry reaction has long been known since its discovery in 1985.[60] The reaction is one of the classical named reaction in organic synthesis consisting of the coupling of the nucleophile generated from a nitroalkane bearing alpha hydrogen with a carbonyl compound (electrophile) of an aldehyde or ketone in the presence of a base. It involves a reactive nitronate species, which can be generated *in situ* as part of the catalytic cycle through the action of a suitable catalyst. Alternatively, preformed nitronates, particularly silyl nitronate species, can be used (Scheme 1.14).[60-63]

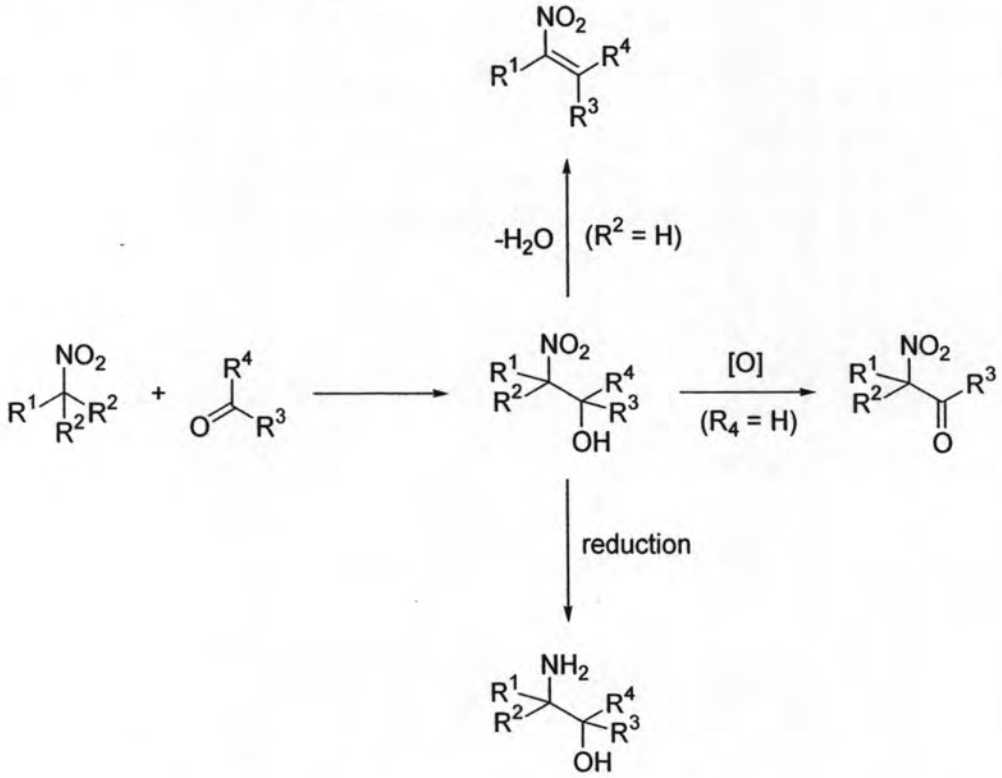


Scheme 1.14 Direct catalytic nitro-aldol reaction and its variant using trialkylsilyl nitronates [60-63]

Hence, to obtain better yields and stereoselectivity of nitro-aldol products, it is necessary to carefully control the basicity of the reaction medium. Furthermore, the products formed in the reaction may undergo base catalyzed elimination of water to give α-nitroalkenes, [64] which readily polymerize. This elimination is difficult to avoid when aryl aldehydes are used.

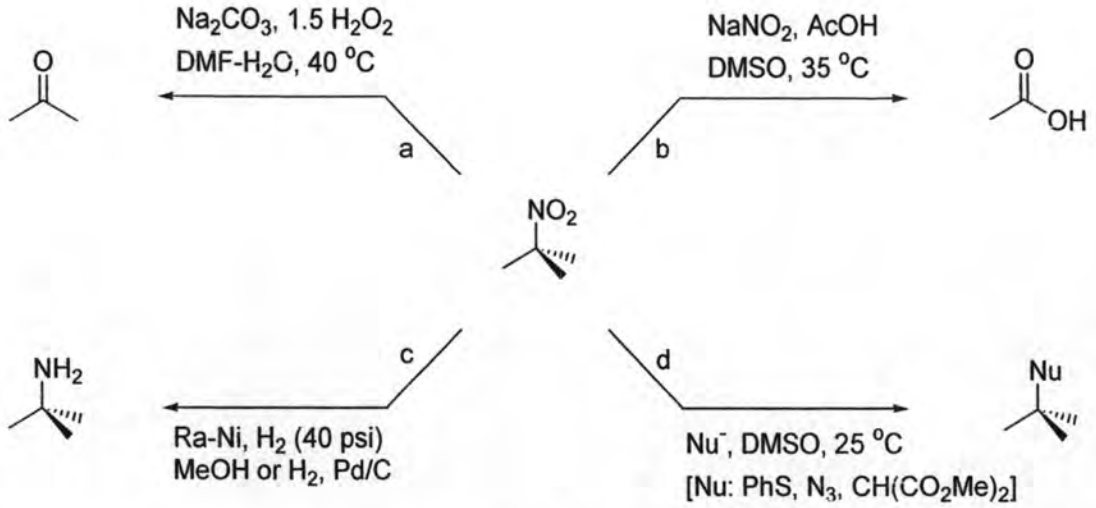
Moreover, in more complex synthetic ventures, the nitro-aldol reaction will facilitate the joining of two molecular fragments, under mild conditions, with the formation of two asymmetric centers at the new carbon-carbon juncture. The resulting product of this reaction is a β-nitroalcohol, which is a versatile intermediate in synthetic organic chemistry, providing efficient access to valuable functionalized

structural motifs such as 1,2-amino alcohols by reduction. Furthermore, nitroalcohol adducts are subjected either to subsequent dehydration reactions to afford conjugated nitroalkenes, which are important building blocks in synthesis, [65] or to oxidation of the carbinol group to provide the corresponding ketone, so stereogenicity at either alpha carbon or beta carbon or at both positions is lost. Typically, the transformations will follow thereby depending on the requirements and overall goal of the multi-step synthetic plan (Scheme 1.15).[66]



Scheme 1.15 The typical transformations of the β-nitroalcohol [66]

For many other applications, however, in which the newly formed beta carbon and/or alpha carbon stereocenters are retained in the target molecules, control of the configuration at those stereocenters is crucial during the nitro-aldol reaction. In particular, the nitro group offers versatile routes to other functionalities. The CH-NO_2 moiety in a nitro-aldol product can thus be converted (Scheme 1.16) [67] into the corresponding ketone, aldehyde or carboxylic acid [68] through Nef oxidation [69] (paths a [70] and b [71]), into an amino compound [72] through reduction (path c), [73] or into other derivatives through substitution of the nitro group by various carbon and heteroatom-centred nucleophiles (path d).[74]

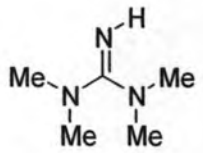


Scheme 1.16 The nitro group as a versatile source of other compound families [67]

1.4.1 Symmetric nitro-aldol reaction

Nitro-aldol reactions may be catalyzed or promoted by many different sets of conditions or catalysts. The classical reaction is routinely performed by use of homogeneous basic catalysts such as organic bases, inorganic bases, quaternary ammonium salts as well as protic, aprotic solvents or solventless conditions have been used to name a few. The types of conditions, which are employed for the reaction will largely depend on the type of functionality present, the solubility of the reactants and the ease to which the nitronate is generated. If the nitro compound is relatively inexpensive, then large excess may be employed so that a high concentration may be maintained and the reaction will progress to completion. On the other hand a large excess of aldehyde may result in competing aldol condensations as well as epimerization. The firrst catalysts of choice for promoting nitro-aldol reactions were variations of either alkoxides or hydroxides in alcoholic or aqueous solvent systems.[75] Such strong bases were normally used to promote reactions between relatively simple substrates bearing limited functionality. In Figure 1.7, 1,1,3,3-tetramethylguanidine (TMG, **25**) has been used to effectively promote the reaction in solvents such as diethyl ether and tetrahydrofuran, while amines such as triethylamine or diisopropylethylamine have been utilized in alcoholic solvents.[76-78] More recently the cyclic analogs of TMG, the bicyclic guanidines **26a** and **26b**, including the polymer-linked **26c**, have been evaluated and appear to be useful additions to the already growing number of achiral nonionic bases which are known to catalyze or promote the nitro-aldol reaction.[79] In developing new promoters for the nitro-aldol

reaction, many investigators cite the need to avoid side reactions such as dehydration to the nitroalkene, normal aldol by-products, epimerization of centers remote from the nitro functionality and the formation of by-products as a result of the Nef-type reactions.



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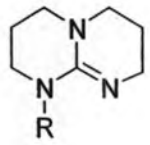
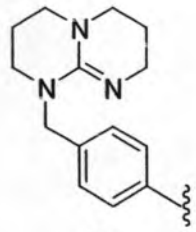


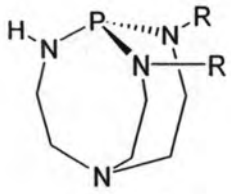
26a: R = H
26b: R = Me



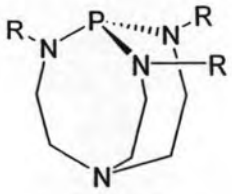
26c

Figure 1.7 The organic bases were used to promote nitro-aldol reaction

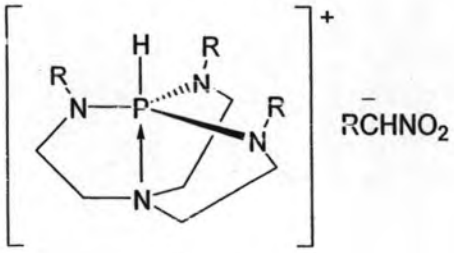
Verkade has developed a series of proazaphosphatranes **27a-27c** which efficiently promote nitro-aldol reactions with ketones as well as aldehydes (Scheme 1.17).[80] Using ketones as substrates, the typical competitive side reaction is self-condensation of the carbonyl substrate. Since the proazaphosphatranes exist as the putative protonated complex **27d**, the competing side-reaction involving ketone self-condensation is suppressed thereby allowing respectable yields of ketone-derived nitroalcohols. For optimal results, Verkade's reagent system includes magnesium sulfate as a Lewis-acid type activator for the carbonyl group.



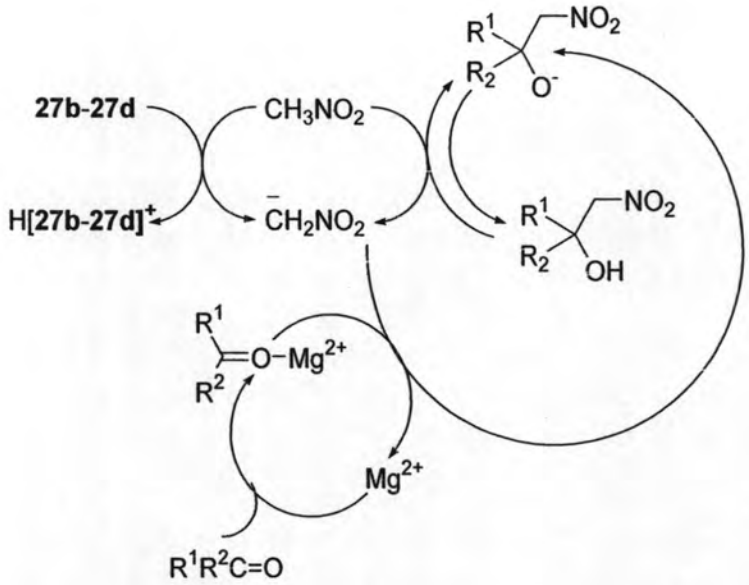
27a: R = ^{i}Pr



27b: R = ^{i}Pr
27c: R = Me

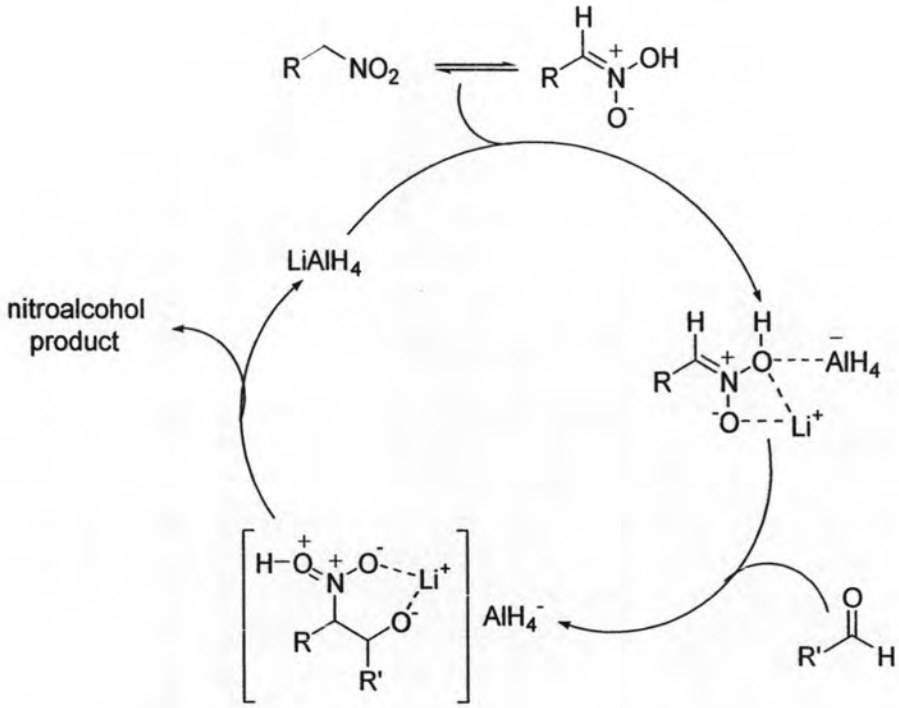


27d



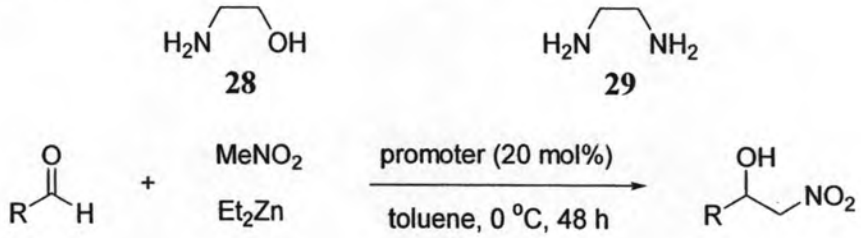
Scheme 1.17 A series of proazaphosphatranes and their mechanism for nitro-aldol reactions [80]

Lithium aluminum hydride (10 mol%) in tetrahydrofuran has been reported to catalyze the nitro-aldol reaction between a variety of aromatic and aliphatic aldehydes and simple nitroalkanes such as nitromethane, nitroethane or nitropropane.[81] The reaction times vary from 2-8 h while the isolated yields range from 71% to quantitative. A proposed catalytic mechanism for the $LiAlH_4$-catalyzed reaction is detailed in Scheme 1.18. At first glance, the presence of moisture and adventitious base such as lithium hydroxide would immediately become suspect in the actual promotion of the reaction rather than $LiAlH_4$. In order to rule out promotion by moisture and basic impurities, the workers used carefully-dried solvents and performed control reactions with LiOH (10 mol%) in THF although the purity of the $LiAlH_4$ was not determined (Scheme 1.18).



Scheme 1.18 Reaction mechanism of nitro-aldol reaction promoted by $LiAlH_4$ [81]

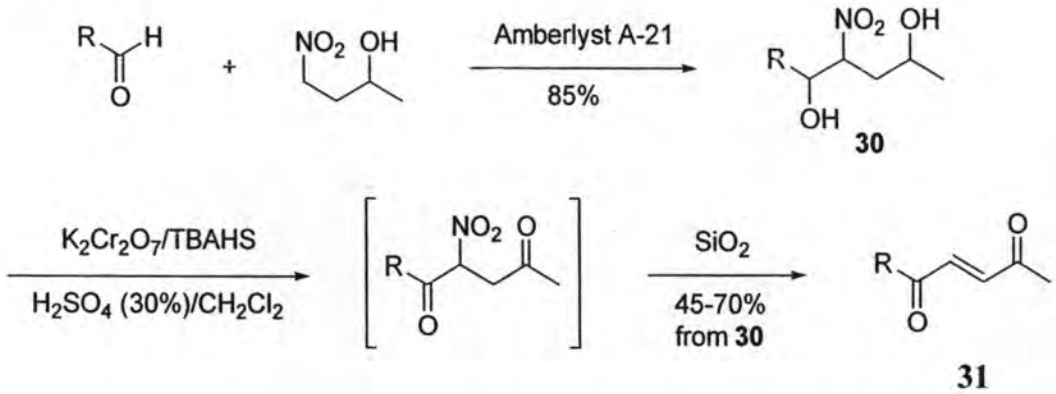
Interestingly, nitro-aldol reactions of nitroalkanes could be initiated with diethylzinc in the presence of catalytic amount of amino alcohols or diamines as promoters.[82] The suitable promoters 1,2-diaminoethanol (**28**) or 1,2-diaminoethane (**29**) could promote the reaction to afford the corresponding nitro-aldol adducts without the addition adduct of diethylzinc to various aldehydes with 49-88% yield (Scheme 1.19).



Scheme 1.19 Nitro-aldol reactions with a variety of aldehyde in the presence of promoters **28** or **29** [82]

Ballini has employed Amberlyst A-21 under solvent free conditions for the preparation of nitrodiols (**30**) from a series of aldehydes and 4-nitro-2-butanol (Scheme 1.20). The nitrodiols were utilized as substrates for the preparation of *E*-α,β-

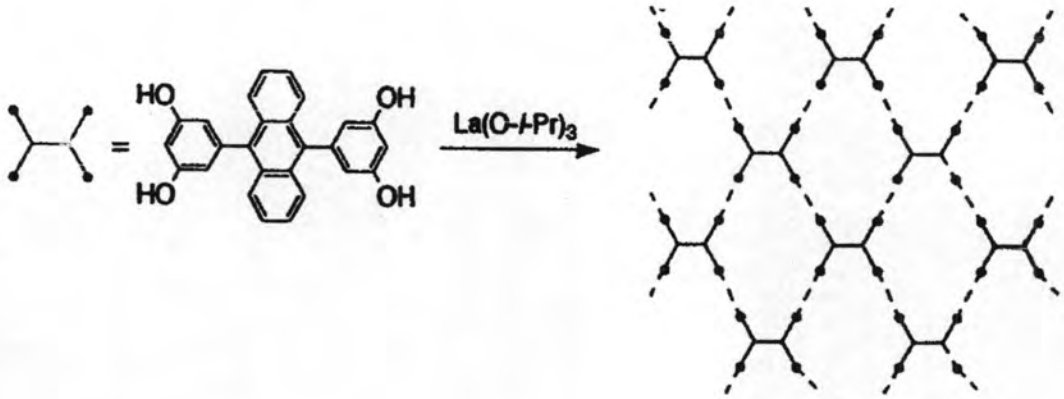
unsaturated-γ-dicarbonyl compounds (**31**) through modified chromic acid oxidation.[83]



Scheme 1.20 The preparation of nitrodiols by using Amberlyst A-21 under solvent free conditions [83]

Nitro-aldol reactions may be run under aqueous conditions in order to avoid the use of organic solvents and their associated environmental concerns. Ballini and co-workers have reported the use of cetyltrimethylammonium chloride as a phase-transfer agent for condensations in water containing sodium hydroxide.[84] Although the reactions are conducted under aqueous conditions, the protocol requires an extractive workup with ether prior to purification of the products. Solvent free conditions have been employed when using microwave irradiation with promotion by ammonium acetate [85] as well as powdered potassium hydroxide.[86]

The heterogeneous catalyst has the consistency of being easily removed upon completion of the reaction thereby simplifying the subsequent purification steps. Nitro-aldol reaction was also developed by using a heterogeneous catalyst derived from admixture of lanthanum trisisopropoxide and the anthracene bisresorcinol results in the formation of an amorphous La^{3+} coordination polymer or La host 'network' (**32**). The La host was found to catalyze the condensation of hydrocinnamaldehyde and nitromethane in benzene although no yields were reported.[87] Catalysis by the La host is presumed to be attributed to the Lewis acid effect by La ions coordinated to the nitronate species while the metal ions are 'immobilized' in the polyphenoxide network.



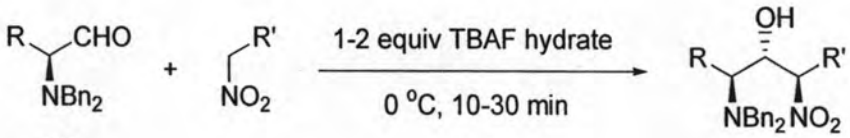
32

Figure 1.8 A heterogeneous catalyst derived from admixture of lanthanum trisisopropoxide and the anthracene bisresorcinol [87]

1.4.2 Asymmetric nitro-aldol reaction

1.4.2.1 Chiral pool synthesis

In 1996, Hanessian *et al.* reported the development of a stereocontrolled version of the nitro-aldol reaction by using an efficient method for the synthesis of nitroalcohols from chiral, non-racemic α-amino aldehydes with high *anti-anti* diastereoselectivity as exemplified in Scheme 1.21.[88]



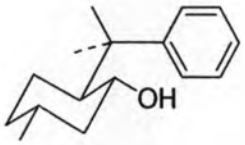
33

Scheme 1.21 Condensations of *N,N*-dibenzyl α-amino aldehydes (**33**) with nitroalkanes mediated by tetrabutylammonium fluoride [88]

From Scheme 1.21 the condensation of *N,N*-dibenzyl α-amino aldehydes (**33**), which are readily accessible from α-amino acids, undergo facile tetrabutylammonium fluoride (TBAF)-mediated condensations with nitroalkanes to give nitro-aldol products in high yields and good stereoselectivities. This affords rapid and stereoselective access to acyclic molecules containing differentiated nitrogen-containing functionality as well as diverse end groups.[88] These, in turn, provide ready access to 1,3-diamino-2-alcohols which are important substructures in medicinally important compounds.

1.4.2.2 Asymmetric induction

There are examples of the stereoselective nitro-aldol reaction using substrates containing a chiral auxiliary, namely (1*R*)-8-phenylmenthol (**34**) to synthesis (2*S*,3*R*)-3-amino-2-hydroxy-5-methylhexanoic acid (**35**), which is the *N*-terminal amino acid of amastatine, a tetrapeptide which has been found to inhibit leucine aminopeptidase and aminopeptidase A.[89]



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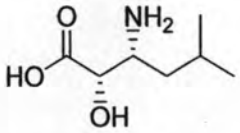
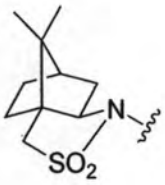
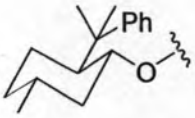


(2*S*,3*R*)-**35**

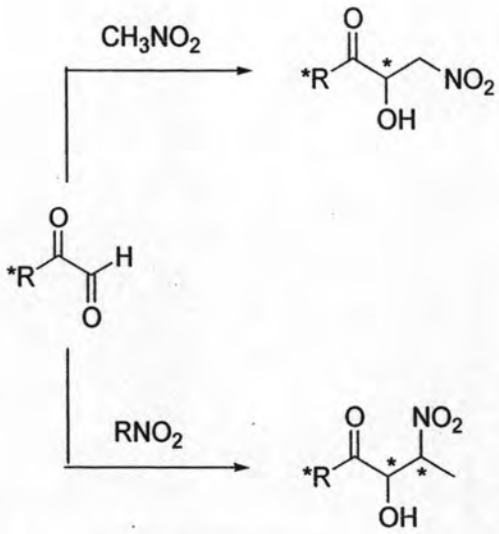
Asymmetric nitro-aldol reactions by using asymmetric induction were also reported by Jurczak *et al.*, [90,91] They used chiral derivatives of glyoxylic acid as starting materials (**36**) to examine their applicability in the addition of **36** to nitromethane and two other simple nitro compound of type. They found that *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam (**36a**) and (1*R*)-8-phenylmenthyl glyoxylate (**36b**) react stereoselectively with simple nitro compounds giving diastereoisomeric nitroalcohols with high asymmetric induction. The glyoximide **36a** is shown to be a highly efficient chiral inducer, superior to glyoxylate **36b**. In all cases, the absolute (2*S*) configuration at the center bearing the hydroxyl group and the relative *syn* configuration for the major diastereoisomers were determined (Scheme 1.22).



R* = **36a**



36b



Scheme 1.22 Asymmetric nitro-aldol reactions by using chiral derivatives of glyoxylic acid as starting materials [90,91]

1.4.2.3 Asymmetric catalysis

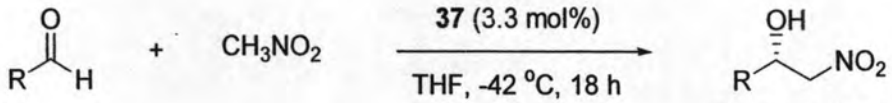
The first asymmetric version of the nitro-aldol reaction was reported by Shibasaki *et al.* in 1992.[92] Since then, interest in this area has been expanded upon considerably and various reports have been continuously appearing in the literature on development of various metal and nonmetal based catalysts for the asymmetric nitro-aldol reaction.

- **Metal based chiral catalysts**

Rare earth–BINOL complexes

The first example of a catalytic asymmetric nitro-aldol reaction was reported by Shibasaki who utilized (*S*)-(-)-binaphthol **9** in conjunction with a lanthanum alkoxide (Scheme 1.23).[92] Enantiomeric excesses of 73-90% were obtained with the chiral binaphthol/rare earth protocol (**37**). They observed that rare earth alkoxides are sufficiently basic due to the low ionisation potential (ca. 5.4-6.4 ev) and electronegativity (1.1-1.3) of the rare earth elements. During this study, it was observed that optically active rare earth alkoxides such as $La_3(O\text{-}^tBu)_9$ promote the nitro-aldol reactions with ee up to 90%. These authors suggested that the first step of the reaction is the ligand exchange between the binaphthol and nitromethane.

37

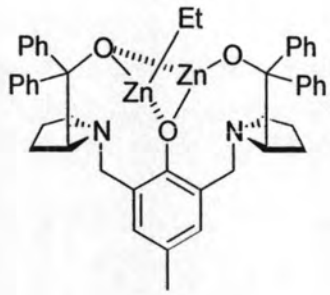


79-91% yield
73-90% ee

Scheme 1.23 Nitro-aldol reactions catalyzed by a heterodimetallic ambifunctional catalyst [92]

Zinc(II)-based catalysis

Trost *et al.* reported the development of a novel type of asymmetric catalyst, which involves a dinuclear zinc complex center with a chiral C_2-symmetric semi-azacrown ligand present in **38** is straightforward from proline and is amenable for structural and electronic tuning. This catalyst has been successfully applied in enantioselective, direct aldol reactions involving various ketone nucleophiles and aldehyde electrophiles.[93-95] The catalyst is prepared by treating phenol with two equivalents of diethylzinc wherein three equivalents of ethane evolve. They revealed the use of a new class of dinuclear zinc complex **38** for the asymmetric nitro-aldol reaction in Scheme 1.24.[96,97]



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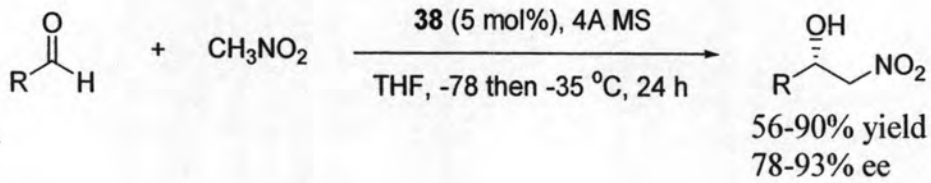
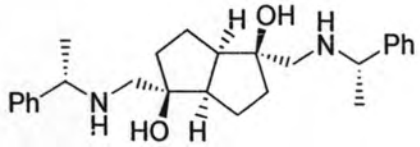


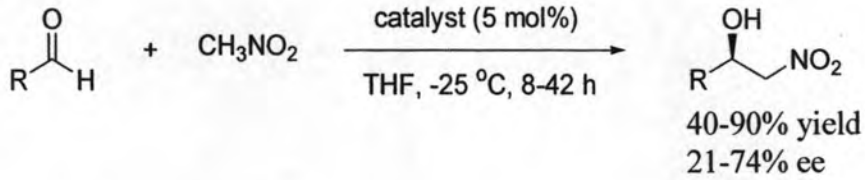
Scheme 1.24 Trost's dinuclear Zn complex's performance in catalytic asymmetric nitro-aldol reactions [96,97]

This catalyst system, which apparently functions along a route of cooperative activation, similar to Shibasaki's catalyst, efficiently converts a-branched aldehydes to the corresponding β-nitroalcohol (up to 93% ee). However, the yields and enantioselectivities were lower with unbranched aldehydes. By using a lower temperature and more equivalents of nitromethane, researchers were able to increase the selectivity, although their attempts to improve the selectivity by modification of the ligand with phenols of different pKa value were not successful.

Other Zn-centred bifunctional metal complexes with applications in catalytic nitro-aldol methodology have been documented as displaying somewhat more limited results.[82,98,99] In 2004, Lin *et al.* employed the complex formed upon admixture of Et_2Zn and the dimeric chiral amino alcohol ligand **39** has been reported to produce nitro-aldol products with low to moderate enantioselectivities (Scheme 1.25).[98]

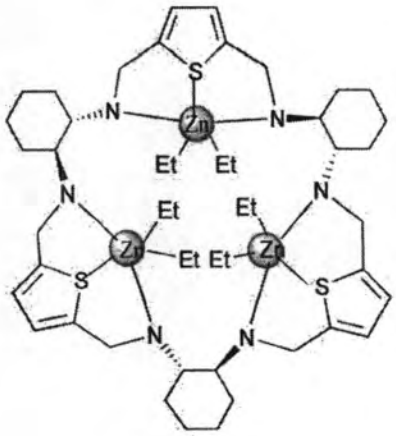


39 (mole ratio): Et_2Zn/**39** = 2/1



Scheme 1.25 A synthetic amino alcohol dimer as a ligand for the Zn-catalyzed nitro-aldol reaction [98]

In the same context, Martell [100] has reported catalysis of the nitro-aldol reaction between nitromethane and benzaldehyde by a trinuclear zinc complex (**40**) obtained from a trimeric thioaza macrocyclic ligand and diethylzinc to provide 68% yield and 75% ee (Scheme 1.26). Unfortunately, no data for assessment of substrate generality are available.



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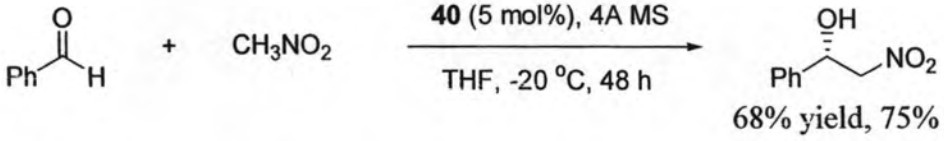
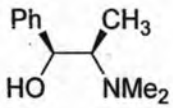


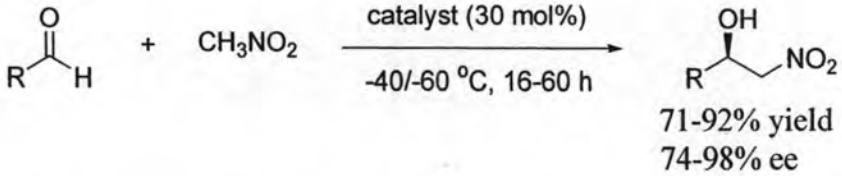
Scheme 1.26 Thioazacrown ligands for the Zn(II)-mediated nitro-aldol reaction between benzaldehyde and nitromethane [100]

Furthermore, Palomo and co-workers have described a practical system that combines a simple Zn(II) salt, a chiral amino alcohol ligand and an amine base

(Scheme 1.27).[101] In this design, the acid and the basic centers, which are presumed concurrently to activate the electrophilic aldehyde and the pronucleophilic nitroalkane, respectively, are not integrated in the same molecular entity. This distinguishing feature facilitates straightforward screening of different combinations of metal salts, amine bases and chiral ligands. Among the chiral amino alcohols tested, *N*-methylephedrine [(+)-NME] (**41**) showed the best results, regularly giving ee values above 90% for all aliphatic aldehydes tested and slightly below 90% for aromatic aldehydes. Of practical importance, essentially quantitative recovery of the chiral amino alcohol used is easy to carry out from the crude reaction product by simple acid/basic workup.



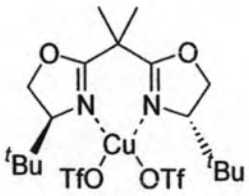
41 (mole ratio): $Zn(OTf)_2/{}^iPr_2EtN/$**41** = 1/1/1.5



Scheme 1.27 Enantioselective nitro-aldol reactions catalyzed by the commercially available triad system $Zn(OTf)_2$/DIPEA/*N*-methylephedrine [101]

Copper-based catalysis

Chiral complexes of copper, particularly Cu(II)-bis(oxazoline) complexes, have found wide application in the general context of catalytic asymmetric transformations.[102] The first application of these type of organometallics to the asymmetric nitro-aldol reaction was reported by Jørgensen [103] and involves reactions between nitromethane and α-keto esters in the presence of chiral Cu(II)-BOX complexes (**42**) and triethylamine as the co-catalyst, working at room temperature (Scheme 1.28). The newly formed quaternary stereocenter is obtained with selectivities generally above 90% for aliphatic and electron-poor aromatic aldehydes, but significantly lower ee values are attained with neutral or electron-rich aromatic congeners.



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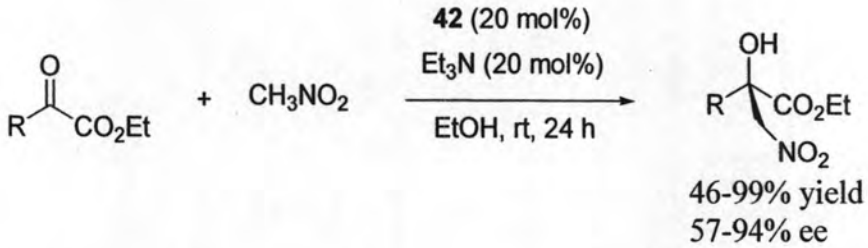
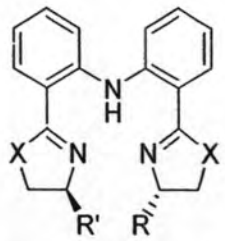


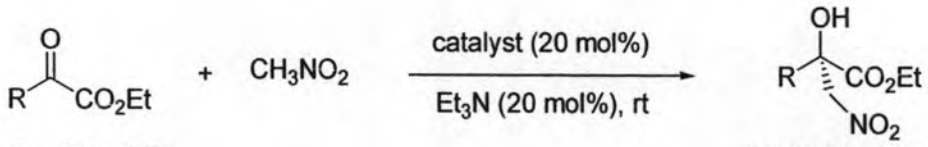
Scheme 1.28 Nitro-aldol reactions between α-keto esters and nitromethane catalyzed by Cu(II)-BOX complex and triethylamine base, affording tertiary alcohols [103]

In a related work, Du has reported [104,105] the use of tridentate bis(oxazoline) and bis(thiazoline) ligands **43** in combination with $Cu(OTf)_2$ salts as catalysts, providing the corresponding (*R*)-configured nitro alcohol products with somewhat inferior selectivity (Scheme 1.29). The best suited catalyst incorporates the bis(thiazoline) ligand bearing *tert*-butyl substituents (X = S, R′ = ^{t}Bu, ee values up to 70%). The complex formed from the same type of ligands (20 mol%) and $ZnEt_2$ (50 mol%) also promoted the reactions in hexane at 0 °C, but predominantly affording products of opposite configuration.[105] Interestingly, in the latter instance, the bis(oxazoline) ligands with R′ = benzyl gave the best results, providing fairly good selectivities (up to 85% ee values).



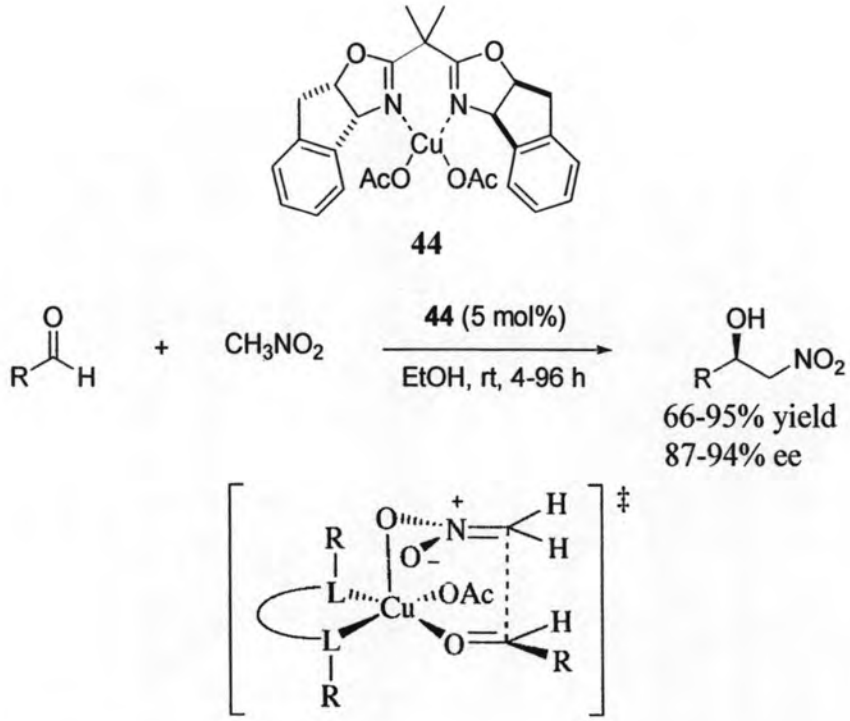
R′ = ^{i}Pr, ^{t}Bu, Ph
X = O, S

43 (mole ratio): $Cu(OTf)_2$/**43** = 1/1



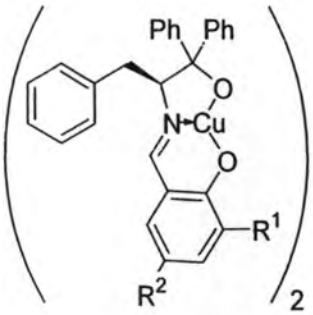
Scheme 1.29 Tridentate bis(oxazoline) ligands for Cu(II)-catalyzed nitro-aldol reactions of α-keto esters [105]

A more efficient Cu(II) catalyst, which is active at loading levels of 5 mol%, has been described by Evans for nitroaldol reactions between nitromethane and aldehydes (Scheme 1.30).[106] The method is quite general for a range of both aliphatic and aromatic aldehydes and works under very mild reaction conditions (EtOH, room temperature). The catalyst design required a weakly acidic metal complex bearing moderately basic charged ligands that would facilitate deprotonation of nitroalkanes, and the $Cu(OAc)_2$-BOX complex **44** was found to fulfill the requirements best. A transition state model involving a Jahn-Teller effect on copper coordination and positioning of reactants in the most favorable orientations according to steric and electronic considerations has been proposed. Copper is thus coordinated both to the nitronate and to the aldehyde carbonyl, producing a preferential boat conformation that correctly predicts the observed stereochemistry.



Scheme 1.30 Bifunctional $Cu(OAc)_2$-BOX catalyst for broad-scope enantioselective nitro-aldol reactions developed by Evans, together with the proposed transition state model [106]

Other Cu(II) catalysts for the nitro-aldol reaction that apparently work on an activation principle similar to that described by Evans have also been described. Zhou has reported a Cu(II) dinuclear complex **45** bearing chiral imino alcohol ligands.[107] The dimeric nature of the catalytic complex was demonstrated by X-ray structure determination. Unfortunately, while good chemical yields were obtained, enantioselectivities were only modest, particularly with aliphatic aldehydes (typically 45-64% ee values). On the other hand, Pedro has described catalysis of the nitro-aldol reaction between nitromethane and *o*-anisaldehyde by complexes formed from camphor-derived iminopyridine ligands and $Cu(OAc)_2$.[108] Again, under reaction conditions similar to those developed by Evans, good yields but modest selectivities were obtained. The best result was obtained with complex **46**, which gave a product with 86% ee (Figure 1.9).



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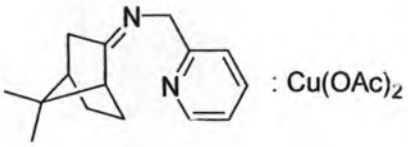
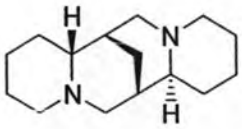


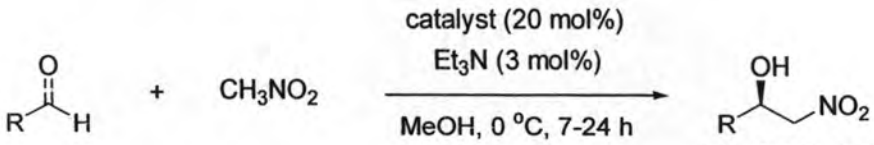
46

Figure 1.9 Catalytic Cu(II)-imine complexes tested against the nitro-aldol reaction [107,108]

Chiral Cu(II)-diamine complexes have also very recently been shown to act as useful catalysts in nitro-aldol reactions reported by Maheswaran and co-worker.[109] In view of the well known stereochemical biases of Cu(II)-sparteine complexes, and their conformational rigidity, complexes of both $CuCl_2$ and $Cu(OAc)_2$ with (-)-sparteine, (**47**) were screened against nitro-aldol reactions between nitromethane and a range of representative aromatic and aliphatic aldehydes. Interestingly, while the $Cu(OAc)_2$-(-)-sparteine complex was able to catalyze the reaction without any need for external base, essentially racemic products were obtained. On the other hand, the $CuCl_2$-(-)-sparteine complex alone was inefficient in promoting the reaction, but a smooth reaction took place in the presence of a small quantity of triethylamine, with ee values in the 80's (Scheme 1.31).



47 (mole ratio): $CuCl_2$/**47** = 1/1

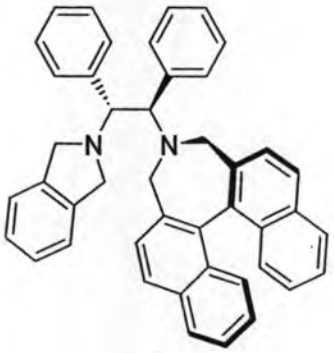


60->95% yield
73-97% ee

Scheme 1.31 A combined Cu(II)-(-)-sparteine/Et_3N catalytic system for nitro-aldol reactions of nitromethane [109]

The authors found the quantity of triethylamine added to be very influential: an increase in the amount of triethylamine base beyond the 3 mol% level lowered the enantioselectivity. Also noteworthy is the requirement for methanol as soivent, since other solvents such as dichloromethane or THF gave poor results. The experimentally observed differences between the complexes derived from $Cu(OAc)_2$ and from $CuCl_2$ were explained on the basis of the significant differences in the bond angles and torsion angles around the copper(II) site as determined in the solid state.

Recently, Arai *et al.* had designed and synthesized a chiral diamine ligand (**48**).[110] The newly developed chiral diamine ligand **48** was utilized in the $Cu(OAc)_2$-catalyzed nitro-aldol reaction. This complex showed a highly efficient catalyst, giving the various nitro-aldols product in high yield with over 90% ee (up to >99%) in the presence of 5 mol% of the **3**-$Cu(OAc)_2$ complex under *n*-propyl alcohol as a solvent at room temperature (Scheme 1.32).



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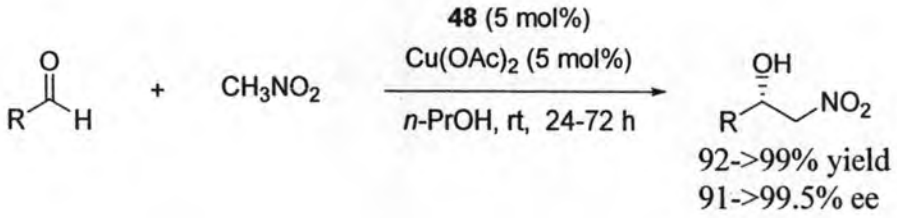
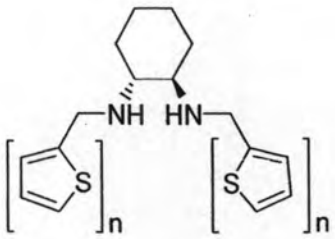


Scheme 1.32 Highly efficient chiral diamine ligands for Cu-catalyzed nitro-aldol reactions [110]

One of the chiral sulfur-containing ligands, chiral diamino-bis(thiophene) compound (**49**) is an effective ligand reported by Bandini *et al.* to apply in the palladium-catalyzed asymmetric allylic alkylation and also in zinc-catalyzed asymmetric transformations.[111]



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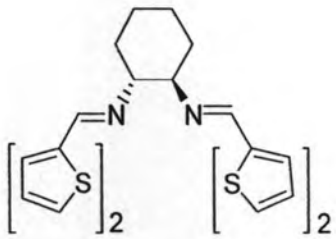


50

The same group explored the potential use of bis-amino systems in the copper catalyzed condensation of nitromethane to the benzaldehyde. From a survey of reaction parameters they were interested to find bis-amino system containing mono- (n = 1) and oligothiophene (n = 2) superior to the bis-imino analogous (**50**) for producing the nitro-aldol adduct. A variety of aldehydes including aromatic, aliphatic, heteroaromatic and α,β-unsaturated compounds were examined for the generality of the method with 5 mol% of **49** (n = 2)/$Cu(OAc)_2$ in the presence of ethanol as a solvent at 0 °C. This catalyst gave the nitro-aldols product with excellent levels of stereoinduction (81-99% ee, 17 examples).[112] Moreover, the suitable crystals for X-ray diffraction studies showed the expected distorted square planar geometry of the copper center was observed with the non-bounded oxygen of the acetate groups occupying vacant apical coordination sites. The two bithiophene arms are parallel to each other and oriented in opposite directions (Figure 1.10).

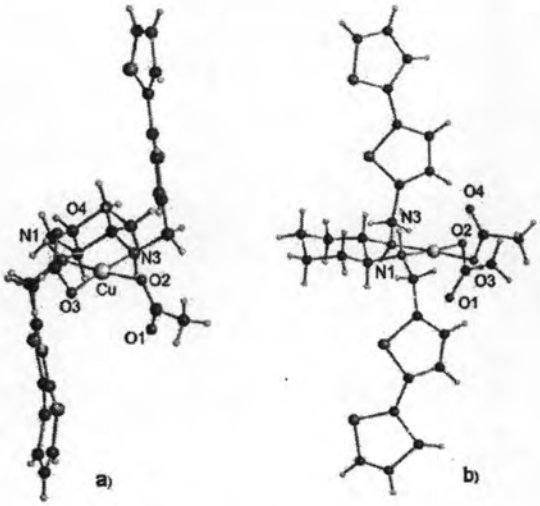
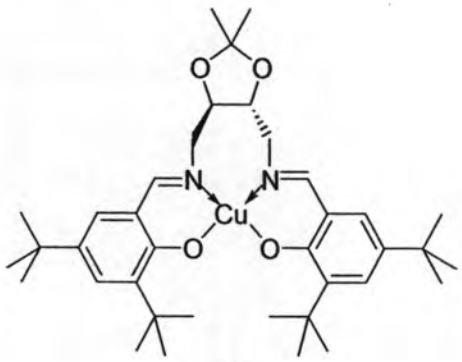


Figure 1.10 Molecular structure of (±)-**49** (n = 2)/$Cu(OAc)_2$. The (*S*,*S*)-enantiomer is shown; (**a**) front view; (**b**) side view [112]

Recently, a novel and facile enantioselective nitro-aldol reaction has been developed using a tetradentate copper complex (**51**) derived from D-tartaric acid. With the optimized reaction conditions, the complex **51** was used to catalyze the addition of nitromethane to a variety of aldehydes to give β-nitroalkanols in moderate to high enantioselectivities (45-84% ee) and 40-79% yield under the indicated time (Scheme 1.33). It is the first reported use of tartaric acid derivatives in the catalytic enantioselective nitro-aldol reaction.[113]



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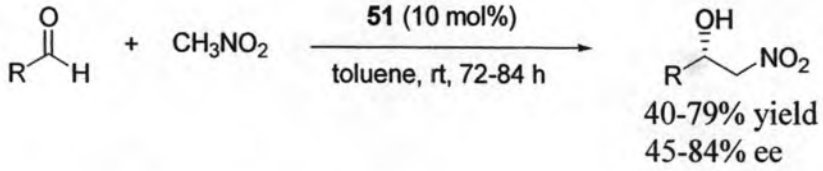
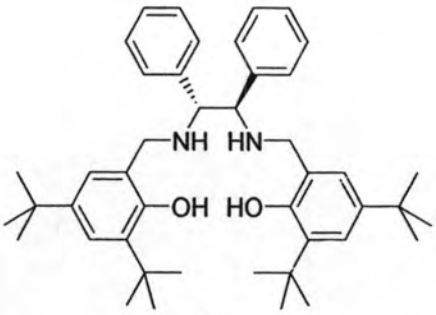


Scheme 1.33 Asymmetric nitro-aldol reactions of nitromethane with various aldehydes catalyzed by complex **51** [113]

After an innovative system for high-throughput screening of catalyst efficiencies, new chiral tetrahydrosalen ligands for Cu(I)-mediated nitro-aldol reactions were identified by Feng *et al.*.[114] Complexes formed from **52** 10 mol% and $(CuOTf)_2 \cdot C_7H_8$ 5 mol% were found to be very active catalysts for nitro-aldol reactions between nitromethane and several aldehydes (Scheme 1.34).



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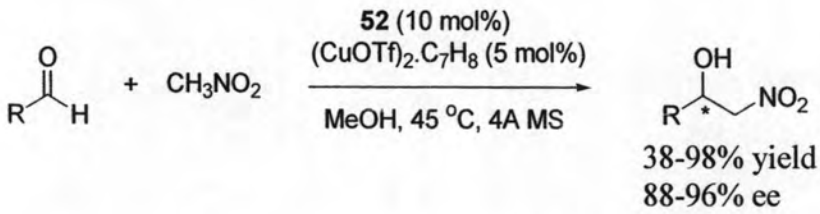
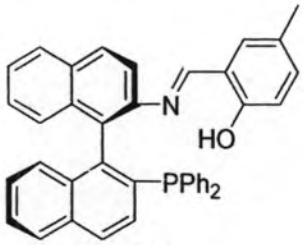


Scheme 1.34 Asymmetric nitro-aldol reaction of various aldehydes with nitro compound catalyzed by Cu(I)-**52** complex [114]

Under optimal reaction conditions, a variety of aromatic, heteroaromatic, aliphatic, and enal aldehydes were found to be suitable substrates giving the corresponding nitro-aldol adducts in moderate to high yields (up to 98%) with excellent enantioselectivities (up to 96% ee).

Another example of Cu(I)-catalyzed enantioselective nitro-aldol reaction was revealed by Shi and Jiang.[115] They developed a new chiral phosphine-salen type ligand **53** and applied for the asymmetric synthesis. The ligand was found to be a fairly effective chiral ligand for Cu(I)-promoted enantioselective nitro-aldol reactions of aromatic aldehydes with nitromethane to give the corresponding adducts in moderate enantioselectivities (65-80% ee) and moderate to good yields (28-87% yield) were as shown in Scheme 1.35.



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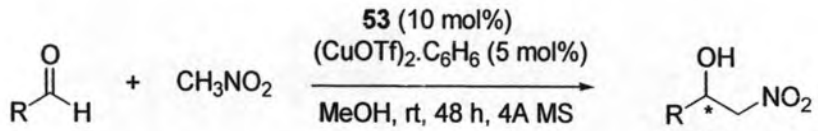
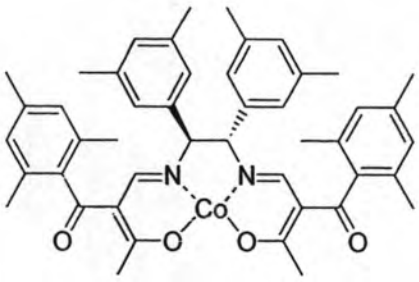


28-87% yield
65-80% ee

Scheme 1.35 Asymmetric nitro-aldol reaction of aromatic aldehydes with nitromethane catalyzed by Cu(I)-**53** complex [115]

Other metal-based catalysts

Yamada and co-workers have found Co(II)-ketoimine and Co(II)-Salen complexes to be good catalysts of the nitro-aldol reaction in the presence of 1 mol equivalent of Hünig's base (Scheme 1.36). Catalyst **54** in combination with stoichiometric diisopropylethylamine (DIPEA), for instance, afforded the corresponding nitro-aldol products with very high yields and enantioselectivities, usually in the 73-92% range for an array of aliphatic and aromatic aldehydes.[116]



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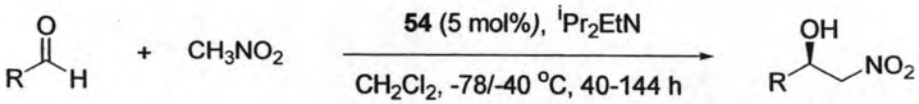
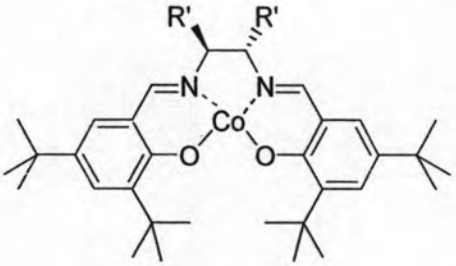


72->99% yield
73-92% ee

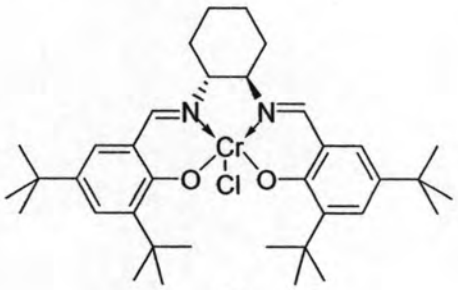
Scheme 1.36 Co-based enantioselective catalytic nitro-aldol reaction using imino-enol ligands [116]

Structurally similar complexes **55a** and **55b** are also promoters of the reaction, although their aldehyde scope seems to be somewhat more limited.[117]



55a: R′ = $(CH_2)_4$
55b: R′ = Ph

Furthermore, Skarżewski *et al.* used chiral chromium(III)-salen-type complex (**56**) to catalyze the enantioselective nitro-aldol reaction. Following the literature precedent, [116,117] they examined the reaction of nitromethane with various aromatic aldehydes, trans-cinnamaldehyde, and cyclohexanecarbaldehyde in dichlorimethane in the presence of stoichiometric amounts of DIPEA and salen-CrCl (2 mol %) to give the corresponding adducts in 40-76% ee and in moderate to good yields (14-98% yield) were as shown in Scheme 1.37.[118]



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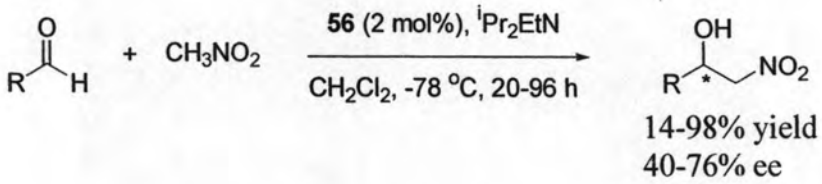
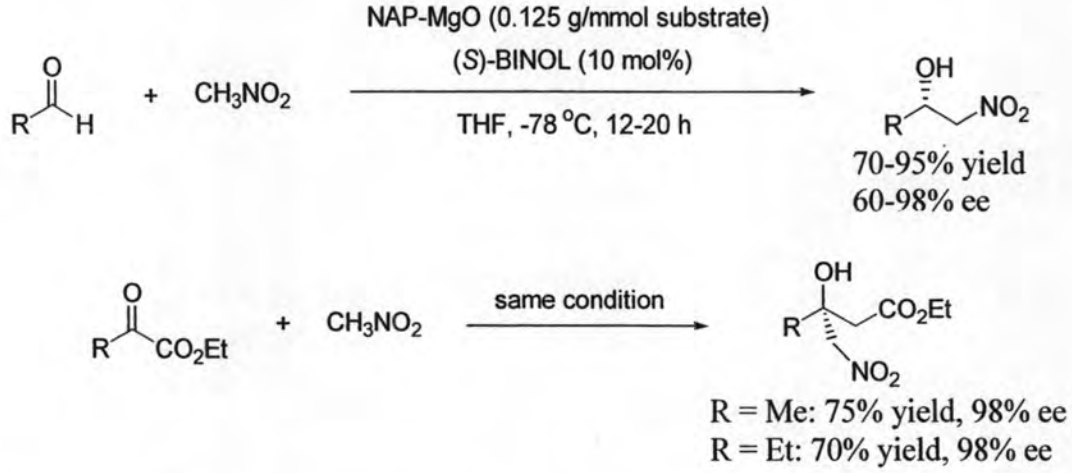


Scheme 1.37 Enantioselective nitro-aldol reactions catalyzed by **56** complex [118]

Heterogeneous catalysis

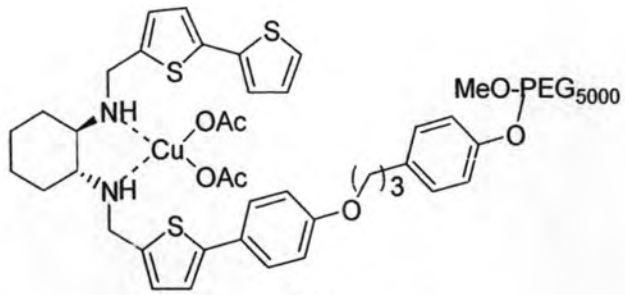
Using nanocrystalline magnesium oxide (NAP-MgO) as a heterogeneous catalyst with defined shape and size, Choudary has reported enantioselective nitro-

aldol reactions involving BINOL as the catalytic chiral ligand (Scheme 1.38).[119] The reactions between nitromethane and a range of aromatic and aliphatic aldehydes at -78 °C were reported to proceed with high yields and selectivities fluctuating between 60% and 98% ee. The heterogeneous catalytic system is equally effective in promoting nitro-aldol reactions of α-keto esters, giving rise to tertiary alcohols in a remarkable 98% ee.



Scheme 1.38 Enantioselective nitro-aldol reactions triggered by a nanocrystalline MgO-BINOL system [119]

Because the combination of C_2-symmetric diaminobithiophenes (**49**, n = 2) with $Cu(OAc)_2$ smoothly promoted the condensation of nitromethane with a variety of aldehydes in excellent enantiomeric excess.[112] Furthermore, the use of a new poly(ethylene glycol)-modified **57**-$Cu(OAc)_2$ complex, reported by Bandini, could catalyze the same reaction in a base-free condition with a highly enantioselectivity (up to 93% ee) and excellent conversions (Scheme 1.39). Finally, unique properties of preformed complex allowed the reusability of the entire organometallic species for several iterations without any significant loss in activity (recoverable up to 5 times).[120]



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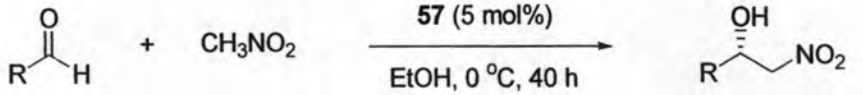


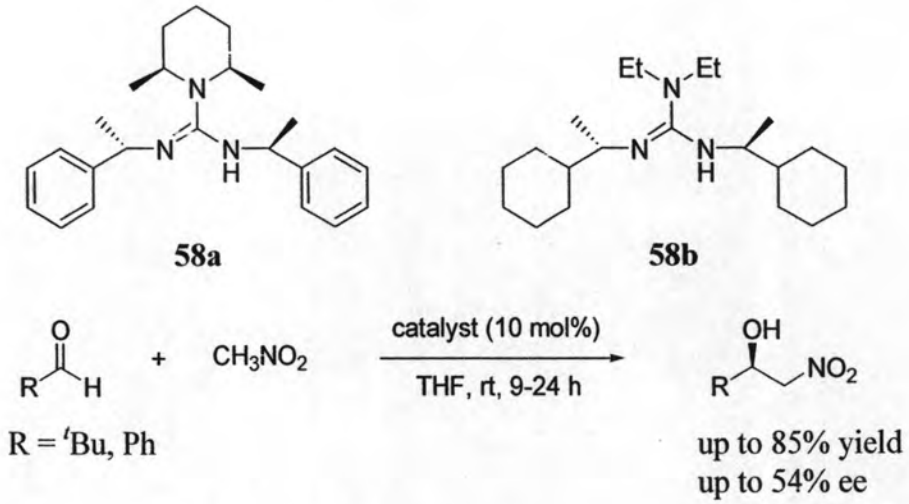
65-90% yield
83-93% ee

Scheme 1.39 Catalytic enantioselective nitro-aldol reaction by using MeO-PEG$_{5000}$-**57**-Cu(OAc)$_2$ complex [120]

- **Organocatalytic nitro-aldol reaction**

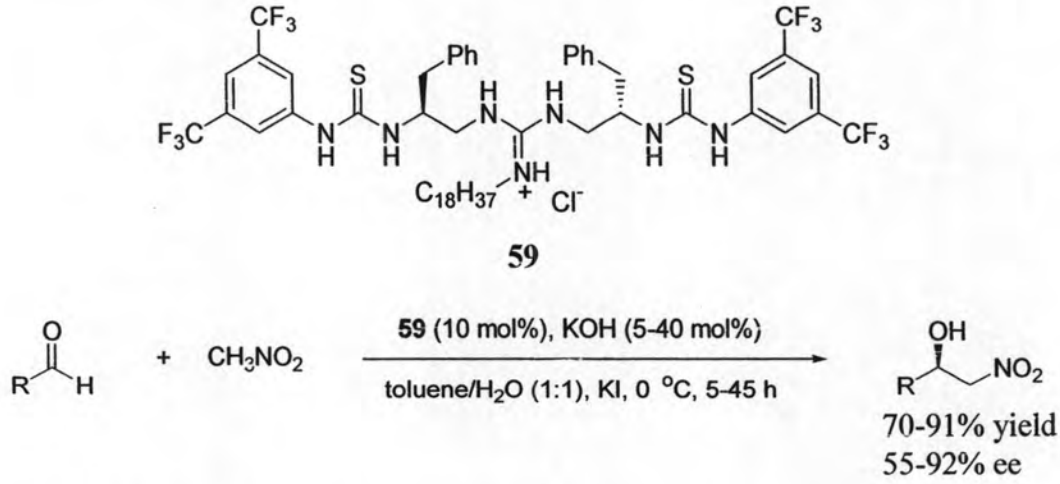
Guanidine derived organocatalysts

The search for small organic molecules capable of promoting a chemical transformation catalytically (organocatalysis) has attracted considerable attention over the last few years.[18] In this context, some selected organocatalysts have demonstrated high chemical and stereereochemical efficiency in nitro-aldol reactions. Common requirements for these organocatalysts structures for achieving good performance appears to be the presence of: (1) a basic unit (or, alternatively, an external base will be required as co-catalyst), (2) some unit capable of binding the nitro (or nitronate) group either through hydrogen bonding or through purely electrostatic interactions, and (3) some unit capable of forming a hydrogen bond with the acceptor carbonyl. In 1994 Nájera *et al.* reported the first organocatalytic asymmetric nitro-aldol reaction using enantiomerically pure guanidines with C_1 and C_2 symmetry, such as **58a** and **58b**, and their application to the reactions between nitromethane and both isovaleraldehyde and benzaldehyde in THF at room temperature (Scheme 1.40).[121] While the yields were generally good, only modest enantioselectivities were observed. Although enantiomeric excess not higher than 54% was achieved in the reaction, this brought forward a new concept to the asymmetric nitro-aldol reaction.



Scheme 1.40 Chiral guanidine species as organocatalysts for the nitro-aldol reaction [121]

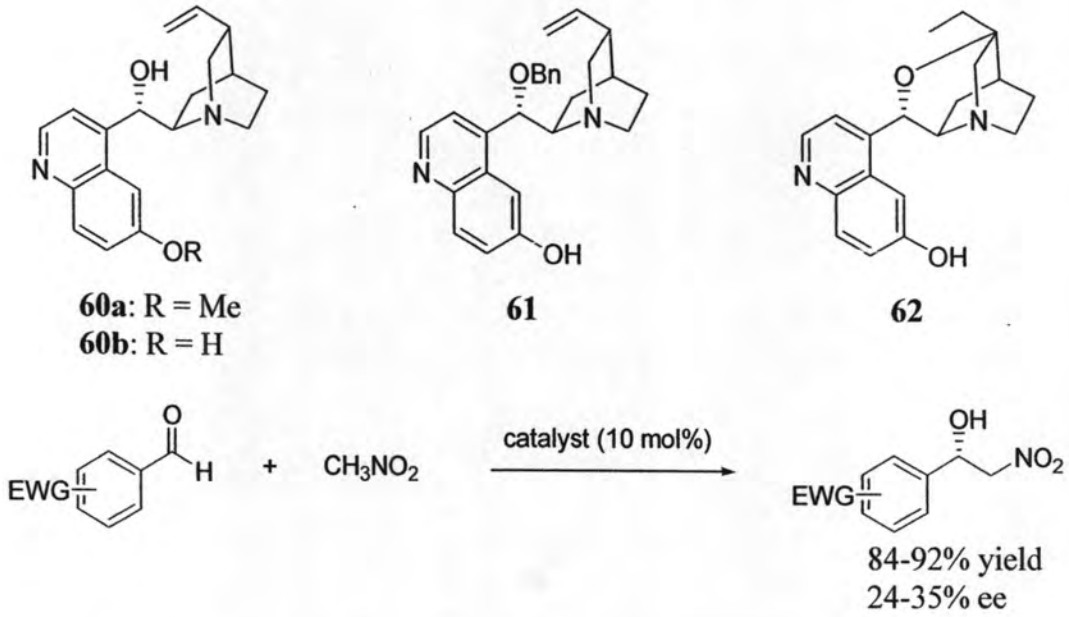
Through the integration of a quaternized guanidine unit and a thiourea unit in the same catalyst molecule, and by working under phase transfer catalyst (PTC) with the assistance of KOH base, Nagasawa has reported an improved catalyst for the nitro-aldol reaction (Scheme 1.41).[122,123] Under the optimal conditions, 10 mol % of the octadecyl substituted catalyst **59** in the presence of KI as additive in a biphasic system of toluene and aqueous KOH promotes condensation between nitromethane and aliphatic α-branched aldehydes in 70-91% yield and 82-92% ee. However, for aliphatic unbranched aldehydes the ee was much lower (55%).



Scheme 1.41 Guanidinium-thiourea molecule as an efficient bifunctional PTC catalyst for nitro-aldol reactions between nitromethane and aldehydes [122,123]

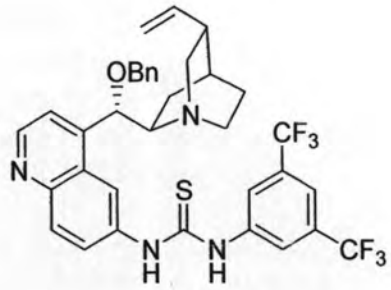
Cinchona alkaloid derived organocatalysts

In general, cinchona alkaloids are known to act as a chiral Brönsted base by creating an effective asymmetric environment. In 2005, Hiemstra *et al.* introduced cinchona derived bifunctional catalysts **60**, **61**, and **62** for a reaction between activated aromatic aldehyde and nitromethane (Scheme 1.42).[124]



Scheme 1.42 A simple cinchona derivative as efficient organocatalyst for nitro-aldol reactions of activated aromatic aldehydes [124]

In an attempt to improve this catalyst, these authors envisioned that replacement of the phenol moiety with a better hydrogen bond donor could result in a more powerful and more enantioselective catalyst. Thus, in a modification, stable catalyst **63** as an efficient catalyst for nitro-aldol reactions of nitromethane, providing very high yields (90-99%) and ee values in the 85-95% range for a series of aromatic aldehydes (Scheme 1.43).[125]



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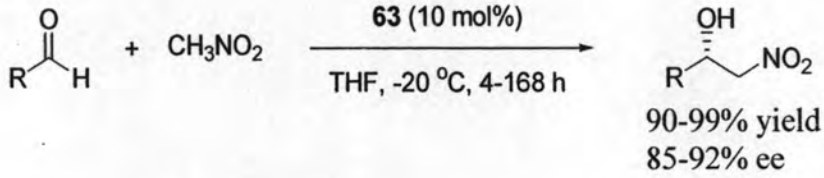
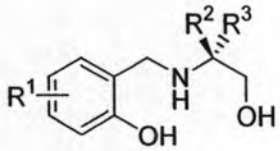


Scheme 1.43 A bifunctional amine-thiourea organocatalyst derived from cinchona alkaloids and its performance in nitro-aldol reactions [125]

1.5 Objectives of this research

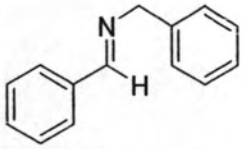
The simple tridentate *N*-salicyl-β-amino alcohols (**64**) derived from condensation between salicylaldehyde and an appropriate amino alcohol followed by reduction with $NaBH_4$ were investigated for their effectiveness as ligands in various asymmetric syntheses including asymmetric Strecker reactions, [126,127] related asymmetric cyanosilylation of aldehydes, [128] and enantioselective borane reduction of ketones as followed.[129]



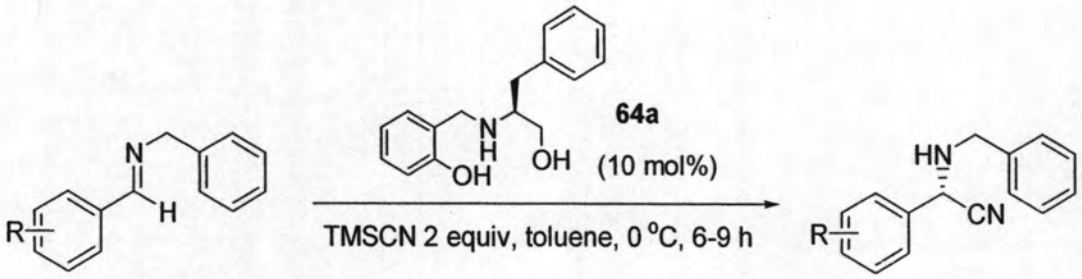
64

1.5.1 Asymmetric Strecker reaction

Vilaivan *et al.* reported an enantioselective Strecker reaction that was catalyzed by titanium-*N*-salicyl-β-aminoalcohol complexes.[126,127] Under the optimized condition obtained from using *N*-benzylidenebenzylamine (**65a**) as a substrate model in the presence of 10 mol% of titanium-*N*-salicyl-β-aminoalcohol (**64a**) complex gave the corresponding α-aminonitriles (**66**) in good to excellent yield (84->99%) and moderate to high enantioselectivity (44-81%) with (*S*)-configuration (Scheme 1.44).[126]



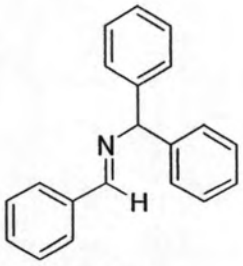
65a



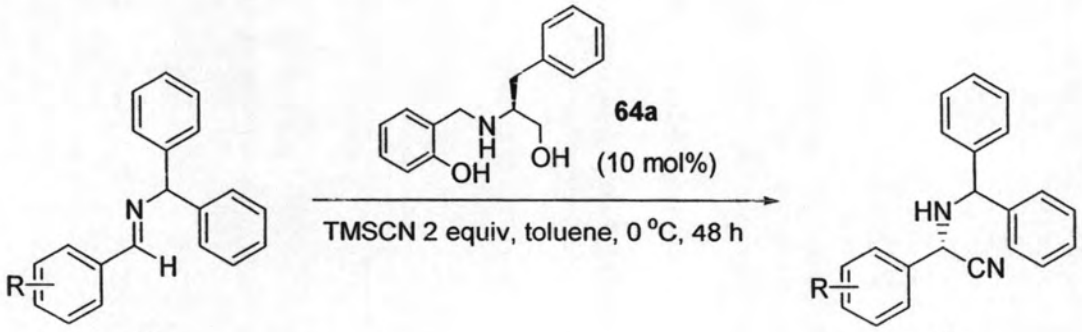
65 **66**

Scheme 1.44 The enantioselective Strecker reaction of imines **65** as substrate catalyzed by titanium-*N*-salicyl-β-aminoalcohol complexes [126]

To improve the enantioselectivity of the Strecker product, *N*-benzhydrylimine (**67a**) was used as substrate. Under the optimized condition, 10 mol % of **64a** could provide very high conversion (97->99%) and ee values in the 90-98% range for a series of aromatic aldehydes (Scheme 1.45).[127]



67a

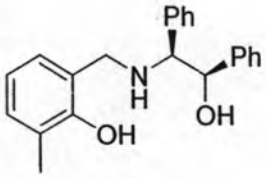


67 **68**

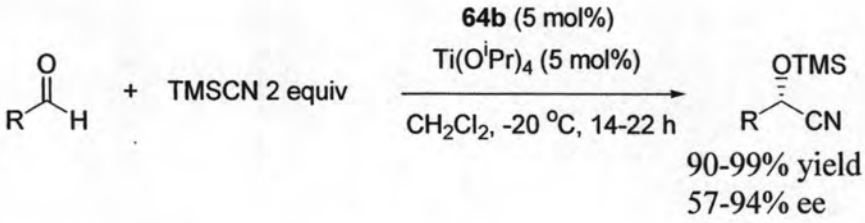
Scheme 1.45 A highly enantioselective Strecker reaction of imines **67** as substrate catalyzed by titanium-*N*-salicyl-β-aminoalcohol complexes [127]

1.5.2 Asymmetric cyanosilylation of aldehydes

Similar to the asymmetric Strecker reaction, cyanosilylation of aldehydes were also reported by Feng *et al.*.[128] A chiral tridentate amino alcohols ligand (**64b**) derived from salicylaldehyde complexed with $Ti(O^iPr)_4$ have been employed to catalyze the addition of trimethylsilylcyanide to a variety of aldehyde under the optimal condition. The corresponding cyanosilylether adducts were obtained in 90-99% yield and 57-94% ee (Scheme 1.46).



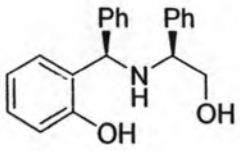
64b



Scheme 1.46 Asymmetric cyanosilylation of aldehydes catalyzed by the Ti(IV)-(**64b**) complex [128]

1.5.3 Asymmetric borane reduction of ketones

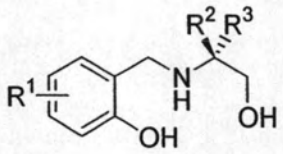
Recently, Lee disclosed the used of tridentate chiral ligand **64c** for the enantioselective reduction of various ketones with borane in toluene at 25 °C to produce the corresponding secondary alcohols. Interestingly, the presence of **64c**, 99% ee value was obtained by asymmetric reduction of ethyl benzoylacetate under the optimized condition.[129]



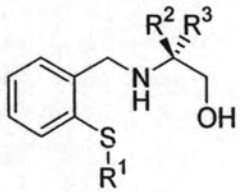
64c

From the application of the simple tridentate chiral amino-alcohols (**64**) in asymmetric synthesis described above, we envisage an expansion of applications of derivatives of such ligands to other types of asymmetric reactions involving a wider

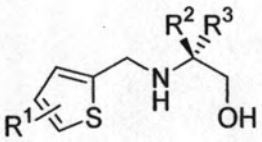
range of metal ions. It was therefore proposed that substitution of one or more of the hard oxygen atoms of **64** with a soft donor atom such as sulfur would lead to ligands such as **69** and **70** having affinities for copper. These ligands should be applicable for synthetically useful copper-catalyzed asymmetric reactions, whose ligands are largely dominated by chiral bis(oxazolines) [102] and diamines.[130]



64



69



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