# *Heterogeneous and Homogeneous Chiral catalysts for synthesis of chiral drug intermediates*

**Thesis submitted to the Bhavnagar University, Bhavnagar for the Degree of**

**DOCTOR OF PHILOSOPHY**
***in***
**CHEMISTRY**

**By**


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**UNDER THE GUIDANCE OF**

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**September 2007**

*Dedicated to my parents, aunty and loving sisters- Rajal & Toral*

केन्द्रीय नमक व समुद्री रसायन अनुसंधान संस्थान
गिजुभाई बधेका मार्ग, भावनगर- ३६४ ००२

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## CERTIFICATE BY THE GUIDE

This is to certify that the contents of this thesis entitled "**Heterogeneous and Homogeneous Chiral catalysts for synthesis of chiral drug intermediates**" is the original research work of Ms. Kavita Pathak carried out under my supervision.

I further certify that the work has not been submitted either partly or fully to any other University or Institution for the award of any degree.

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**(R. V. Jasra)**
Signature of Co-Guide

# CANDIDATE'S STATEMENT

I hereby declare that the work incorporated in the present thesis is original and has not been submitted to any University / Institution for the award of a Diploma or a Degree. Further, I hereby declare that the results presented in this thesis and the considerations made therein, contribute in general to the advancement of knowledge in Chemistry and on particular topic, entitled **"Heterogeneous and Homogeneous Chiral catalysts for synthesis of chiral drug intermediates"**

(Kavita Pathak)

Signature of the candidate

# PERFACE

The work embodied in the present thesis comprises of six chapters. In chapter 1, the brief introduction of chiral homogeneous and heterogeneous asymmetric catalysis, with special emphasis on '*Privileged chiral ligands*'-BINOL and salen. Concise discussion on Asymmetric C-C bond forming reactions of carbonyls and oxidative kinetic resolution of racemic alcohols using chiral BINOL and salen based metal complexes under homogeneous/heterogeneous reaction conditions. This chapter also concludes with the scope and objective of present work. Chapter 2 describes synthesis and physicochemical characterization of mesoporous materials MCM-41 and SBA-15 and used them as supports for immobilization of chiral BINOL. The immobilized chiral BINOL was used as heterogeneous catalyst in Ti-catalyzed asymmetric diethylzinc addition to aldehydes. Chapter 3 consists of immobilization of chiral BINOL on mesoporous materials SBA-15 and MCF of relatively large pore size and used as active catalysts for asymmetric diethylzinc addition to aldehydes. However, Chapters 4, 5 and 6 belong to the synthesis of chiral recyclable salen based metal complexes. Chapter 4 includes synthesis of a new chiral polymeric Zn(salen) catalyst and used as a heterogeneous catalyst in asymmetric phenylacetylene addition to carbonyls. However, Chapter 5 and 6 include synthesis of chiral dimeric and polymeric Mn(III) salen complexes respectively. These complexes were used as recyclable catalysts in oxidative kinetic resolution of racemic secondary alcohols. Each chapter describes references and methods which are related to work for sake of convenience.

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Last but not the least; I am thankful to the Almighty, who has provided me sound health and strength to complete this work. What I am and what I would be I owe to the Almighty for leading me the path of success.

KAVITA PATHAK

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# List of Abbreviations

| | |
|---|---|
| ee | Enantiomeric excess |
| BINOL | 2,2'-dihydroxy 1,1'-binaphthyl |
| BINAP | 2,2'-bis(Diphenylphosphanyl)-1,1'-binaphthyl |
| TADDOL | α,α,α',α'-Tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol |
| DIOP | (4,5-bis(Diphenylphosphinomethyl)-2,2-dimethyl-1,3-dioxolane) |
| LDH | Layered double hydroxides |
| Co-PT | Copolymerization technique |
| MOF | Metal organic frameworks |
| 3D | Three dimensional networks |
| $ScCO_2$ | Supercritical carbon dioxide |
| $Et_2Zn$ | Diethylzinc |
| $H_8$-BINOL | 5,5',6,6',7,7',8,8'- Octahydro-1,1'-binaphthyl |
| KR | Kinetic resolution |
| $\Delta G^{\#}$ | Gibbs free energy of activation |
| OKR | Oxidative kinetic resolution |
| PhIO | Iodosylbenzene |
| $PhI(OAc)_2$ | Iodobenzene diacetate |
| MCM-41 | Mobile crystalline material |
| SBA | Santa Barbara amorphous |
| MCF | Mesocellular foam |
| NMR | Nuclear magnetic resonance |
| SEM | Scanning electron microscopy |

| | |
|---|---|
| TEM | Transmission electron microscopy |
| XRPD | Powder X-ray diffraction |
| FT-IR | Fourier transform infrared |
| $^{13}C$ CP MAS | Cross polarization magic angle spinning |
| ESI-MS | Electron spray ionization mass spectrum |
| HPLC | High pressure liquid chromatography |
| GC | Gas chromatography |
| LC | Thin layer chromatography |
| MW | Molecular weight |
| *m/z* | Mass to charge ratio |
| *J* | Coupling constant (in NMR spectroscopy) |
| TMS | Trimethylsilyl |
| HMDS | Hexamethyldisiloxane |
| TEOS | Tetraethoxysilane |
| TMSCl | Trimethylsilyl chloride |
| NMAPTES | *N*-methyl-3-aminopropyltriethoxysilane |
| CTAB | Cetyltrimethylammonium bromide |
| $CH_2Cl_2$ | Dichloromethane |
| MeOH | Methanol |
| DCE | Dichloroethane |
| EtOAc | Ethyl acetate |
| THF | Tetrahydrofuran |
| rt | Room temperature |

# *Chapter -1*

## *Introduction*

## 1.1. Consequence/ Relevance of Catalysis: Asymmetric Catalysis

Catalysis is the key process for chemical transformations. Most industrial synthesis and nearly all biological reactions require catalysts. Today, catalysis is one of the most important unit-operation in environment protection. A well-known example of this is the catalytic converter for automobiles used to prevent emissions of $NO_x$ and $SO_x$. Catalytic reactions were already used in antiquity, although the underlying principle of catalysis was not recognized at those times. For example, the fermentation of sugar to ethanol and the conversion of ethanol to acetic acid are catalyzed by enzymes (biocatalysts). However, the systematic scientific development of catalysis only began about 200 years ago, and its importance is growing with each passing day.[1,2] The term "catalysis" was introduced as early as in the year 1836 by Berzelius to explain various decomposition and transformation reactions. He assumed that catalysts possess special powers that can influence the affinity of chemical substances.

Catalysis remains a strategic field of chemistry because of its implication in many fields, which include industry, energy, environment, and life science. Whether it is homogeneous or heterogeneous (or even enzymatic), catalysis is primarily a molecular phenomenon since it involves the chemical transformation of molecules into other molecules. Limited natural resources and growing demand for enantio-pure compounds in the life science render catalysis as an indispensable tool, which has stimulated an increased interest specially in asymmetric catalysis.[3,4] Catalytic asymmetric synthesis (more frequently referred as asymmetric catalysis) is defined as an enantioselective transformation controlled by a chiral catalyst. In most of the cases, chiral catalyst is a metal complex with a chiral ligand.

Control over the absolute stereochemistry of a transformation is one of the most recent and most studied aspect in homogeneous catalysis, which is regarded as one of the major challenges in contemporary organic synthesis.[5] Therefore, the use of a catalytic amount of a chiral complex capable of transferring its chirality to prochiral substrates during a reaction appears to be an appealing approach for the preparation of enantio-pure compounds. (*Prochiral substrates are achiral molecules which can be converted to chiral molecules in a single step*). Asymmetric catalysis allows single chiral information embedded in a chiral catalyst to be reproduced a large number of times. Thus, it provides the most economic way to accomplish an asymmetric synthesis since, in principle, one molecule of chiral catalyst can create millions of chiral molecules (chiral multiplication). This is the same way "Nature" utilizes enzymes in biological systems. Consequently, asymmetric synthesis is now increasingly applied in the manufacture of pharmaceuticals, health products for human and animal consumption, agrochemicals, fungicides, pheromones, flavors, and fragrances. Particularly, asymmetric catalysis[6,7] is of growing significance to a sustainable modern society, in which environmental protection is of increasing interest.[8] Justifiably, the Noble prize for chemistry in 2001 was awarded to **William S. Knowles** & **Ryoji Noyori** and **K. Barry Sharpless** for their outstanding works on metal catalyzed asymmetric hydrogenation and asymmetric oxidation reactions respectively.[9-11] Their works had a very great impact on academic research and the development of new drugs and materials and are used in many industrial syntheses of drugs and other biologically active compounds.

In nature, life depends on molecular chirality, as many biological functions are inherently dissymmetric. This is understandable because the building blocks of life forms

*viz.,* sugars and proteins are chiral in nature. Hence, most physiological phenomena arise from highly precise molecular interactions in which chiral host molecules recognize two enantiomeric guest molecules in different ways. There are numerous examples of enantiomer effect, which are frequently dramatic, to the extent enantiomers often smell and taste differently. The structural difference between the enantiomers can be serious with respect to the actions of synthetic drugs. Chiral receptor sites in the human body interact only with drug molecules having the proper absolute configuration,[12-14] resulting in marked differences in the pharmacological activities of enantiomers (**Figure 1.1**).

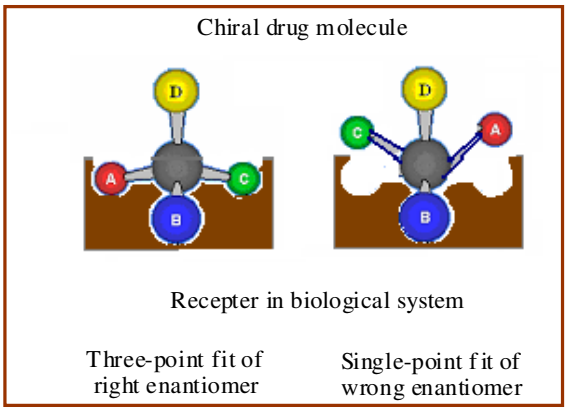



**Figure 1.1** Graphical representation of the drug action based on the hypothesis of "three point fit" of chiral drug molecule to complementary enzyme binding site.

**GLOBAL SALES** of single-enantiomer compounds as drug reached $8.57 billion in year 2004 and would be expected to reach $14.94 billion by the end of 2009, growing annually by 11.4%, according to the Frost & Sullivan survey (**Figure 1.2**). By 2009, the share of the market realized through traditional technology would drop to 41%. The share of chemocatalysis would rise to 36% and the share of biocatalysis to 22%. The use of

catalysis in industrial applications, both chemical and enzymatic, is supposed to increase further in the coming years.[15]

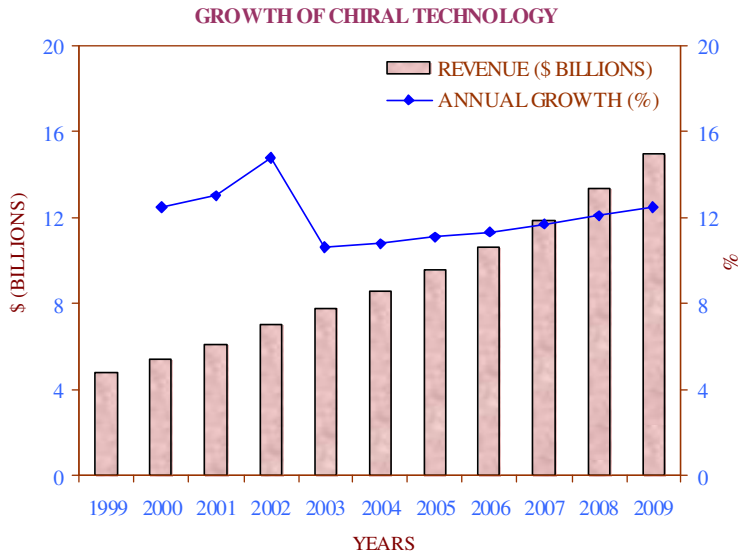



**Figure 1.2** Global Sales of chiral technology over the years with Percentage growth and revenue

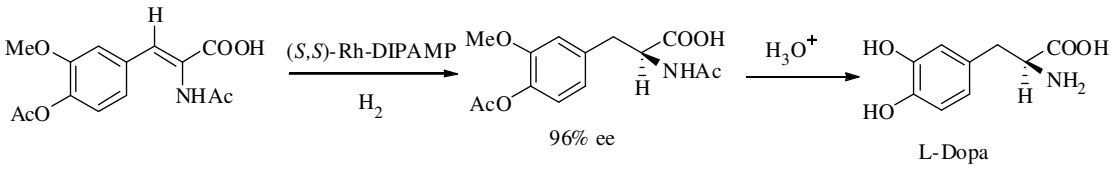
Today, pharmaceuticals and vitamins, agrochemicals, flavors and fragrances and other functional materials are increasingly produced as enantiomerically pure compounds. The reason for this is the often superior performance of the pure enantiomers and/or because regulations demand the evaluation of both enantiomers of a biologically active compound before its approval, for the commercialization of clinical drugs. The regulation to screen single enantiomers was introduced as guideline by the Food and Drug Administration in the U.S in 1992,[16] this has led the pharmaceutical industries to compulsorily consider each enantiomer as different chemical entity for their in vivo activity. As a fall out of this trend chirality was keenly followed in other areas of research activity as well.

## 1.2. Relevance of Asymmetric Catalysis in Different Areas

### 1.2.1. Pharmaceuticals

There is a considerable trend towards enantio-purity in chiral synthetic drugs. In general chiral drugs were (in some cases even now) administered, as racemates. In many cases only one enantiomers is active (eutomer) whereas, the other enantiomers is either less potent with no side effects or bear different and/or undesirable activity (distomer).[17] The most well known and tragic example of the drug where the distomer caused serious side effects is thalidomide, which was sold in 1960's as a racemate. Unfortunately, it was unknown at that time that although the *R*-enantiomer is an effective sedative, the *S*-enantiomer is highly teratogenic and caused fetal abnormalities. Recently however, thalidomide is emerging as a treatment for cancer and inflammatory diseases.[18]

For many applications of chiral compounds, the racemic forms will no longer be accepted as drug. As a consequence, the importance of enantioselective synthesis in general and of enantioselective catalysis in particular has increased. As a result, catalytic asymmetric synthesis provides, in principle, a most efficient route to pharmaceutical products.[19,20] Industrial interest in the application of enantioselective catalysts started in earnest in the mid-sixties when the first publication of successful enantioselective transformations using homogeneous metal complexes were published. Knowles and co-workers at Monsanto reported the first commercially successful synthesis of L-DOPA-a drug for treating Parkinson's disease, using Rh-DIPAMP catalyst (**Scheme 1.1**). Monsanto commercialized this process in the early 1970s,[21] and is a landmark in industrial catalytic asymmetric synthesis and in the process it triggered a number of other industrial based research.

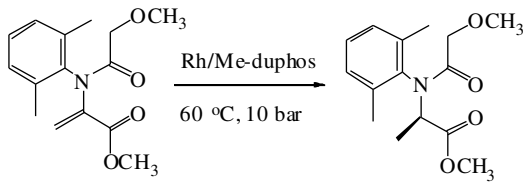



**Scheme 1.1** Synthesis of L-DOPA using chiral Rh- DIPAMP catalyst

### 1.2.2. Agrochemicals

The phenomenon of enantioselecitivity in biological activity is universal. It is also exhibited by agrochemicals that act on living organisms as plants, insects and fungi. The biological properties of chiral agrochemicals are often strongly related to the absolute configuration.[22] The chiral switch from the racemate to an enriched form is not only attractive for pharmaceuticals but is also an important strategy for agrochemicals.[23]

As a result, the technical synthesis of pure or enriched enantiomers is of growing importance in the modern agrochemical industry. The molecular mechanisms of action are completely analogous to those encountered with drugs. Here also the desirable effect will reside predominantly in one enantiomer (the eutomer), while the other enantiomer (the distomer) will either constitute unnecessary isomeric ballast or exhibit undesirable side effect.[24] The application of the herbicides, insecticides and fungicides is a large-scale operation comprising thousands of tons. Therefore, by using single enantiomer chemicals, the chemical burden on the environment can be reduced at least by 50%. An outstanding example of this is a chiral Rh/Me-duphos complex catalyzed large scale production of (*R*)-metalaxyl: a potent fungicide, reported by Blaser et al.[25] (**Scheme 1.2**).

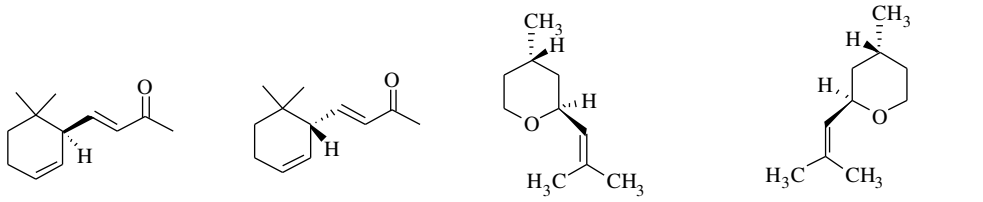



96% ee

**Scheme 1.2** Intermediate for (*R*)-metalaxyl (fungicide)

### 1.2.3. Flavors and Fragrances

One of the first indications that enantiomers might have different odors came in 1874, when two essential oils containing either (1*R*,2*S*,4*R*)-(+)-borneol (Borneo-camphor oil from *Dryobalanops aromatica*) or the enantiomeric (1*S*,2*R*,4*S*)-(-)-borneol (Ngai-camphor oil from *Blumea balsamifera*) were found to have different odors; Borneocamphor oil had a weak camphor-like odor, unpleasantly peppery, while Ngai-camphor oil had an odor of camphor or turpentine.[26] Therefore, two enantiomers may differ in taste, aroma or bioactivity and consequently (**Figure 1.3**), one of them may display the desired effect while the other may not or may even display a detrimental effect.[27]




(*R*)-α-ionone
Fruity-respberry like odor

(*S*)-α-ionone
Cedar-wood like odor

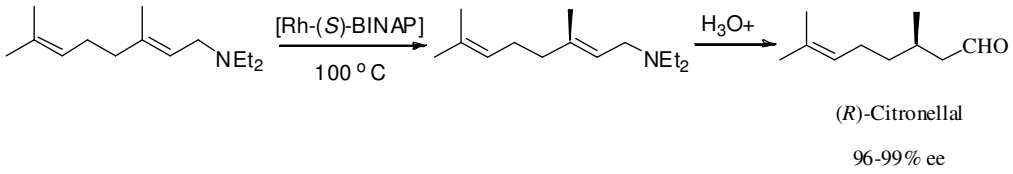
(*4S,2S*)-(+)-trans-rose oxide
herbal rose, citrus (bitter peel)

(*4R,2R*)-(-)-trans-rose oxide
herbal (minty) fruity

**Figure 1.3** Enantioselectivity in taste and odor perception

In the food industry there is an increasing consumer demand for "natural ingredients" as opposed to "synthetic additives." Natural ingredients are products extracted from natural sources or produced by natural process as fermentation, involving

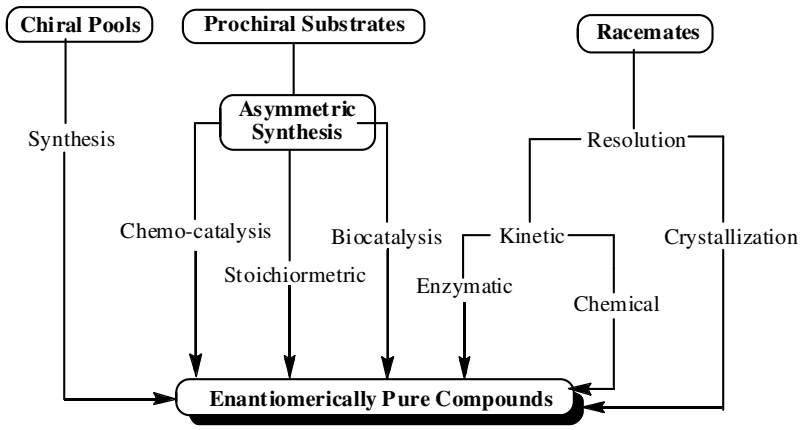
a minimum or no chemical steps. Since the term natural is often synonymous with enantiomerically pure, there is an increasing demand for enantioselective synthesis in the flavors and fragrance industry.[28] Among the most successful example of this is the synthesis of intermediate for (–)-menthol and (*R*)-citronellal using Noyori's Rh-BINAP catalyst[29] (**Scheme 1.3**).




**Scheme 1.3** Synthesis of (*R*)-citronellal using Rh-(*S*)-BINAP

## 1.3. Synthesis Routes to Enantiomerically Pure Products

Discovery of truly efficient methods to achieve desired compound in optically pure form has been a major challenge for chemists in academia and industry. There are several ways to obtain optically pure compounds. The three fundamental strategies start from chiral pools (naturally occurring optically pure compounds), a racemate (mixture of all possible stereoisomers of one chiral compound), or a prochiral substrate (**Scheme 1.4**).




**Scheme 1.4** Sources of enantiopure compounds.

As depicted in **Scheme 1.4**, there are many approaches for the preparation of enantiopure compounds, the most obvious being the chemical modification of enantiopure compounds derived from resources such as fermentation and agriculture. A disadvantage of this approach is the limited diversity of the starting materials and the often difficult accessibility to the opposite enantiomer.[30] The more challenging approach is, however, to introduce the optical activity, which may be achieved by resolving a racemate or by asymmetric synthesis. The latter involves the introduction of asymmetric center in a prochiral substrate. The resolution of racemates is another important and widely used method to obtain enantio-pure compounds, particularly on industrial scale,[31] this can be achieved by crystallization, classical resolution, chiral chromatography and kinetic resolution of racemic organic compound. Catalytic asymmetric synthesis, in contrast, is more recent and the development of practical methods is based on last 30 years of research.[6]

### 1.3.1. Chiral Pool

The term *Chiral pool* refers to chiral building blocks originating from natural products for the construction of the final molecule. These include monosaccharides and fragments thereof, amino acids and hydroxy acids, terpenes and alkaloids **(Figure 1.4)**.[32] These compounds can either occur naturally as pure enantiomer or can be obtained *via* microbial synthesis using a fermentation process or can be synthesized from chiral or prochiral starting materials. This approach is very often used in the early phases of drug development but, depending on the commercial availability of the starting material, it can also be used for large-scale products. Therefore, use of the chiral pool is restricted to the synthesis of chiral compounds with commercial availability of the starting material.[33]

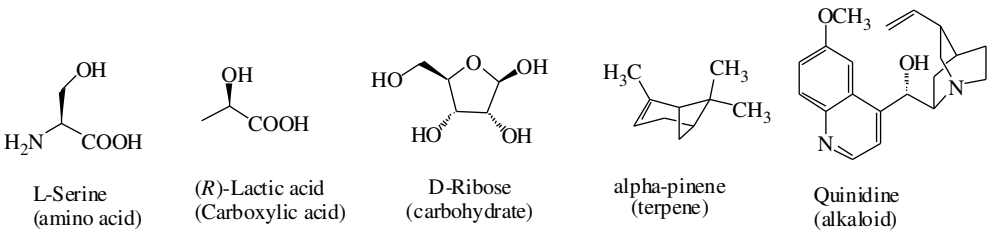



**Figure 1.4** Examples of naturally occurring chiral molecules

### 1.3.2. Racemate Resolution

Leuis Pasteur developed this method when he separated the enantiomers of potassium tartrate deposited in barrels filled with maturing wines.[34] In this methodology, the starting material is an equimolar mixture of the enantiomers, which is called racemate or racemic mixture. The resolution of racemates still constitutes the main method for the industrial synthesis of pure enantiomers. The resolution of racemates can be achieved by crystallization (preferential crystallization and diastereomer crystallization), kinetic resolution (chemical or biological) and by chromatographic separations.

#### 1. Crystallization

Crystallization is widely practiced on an industrial scale for the resolution of racemic compound to achieve the desired enantiomer in high optical purity and yield. This strategy is broadly implemented in two different ways *viz.,* preferential crystallization and diastereomer crystallization.

##### (a) Preferential Crystallization

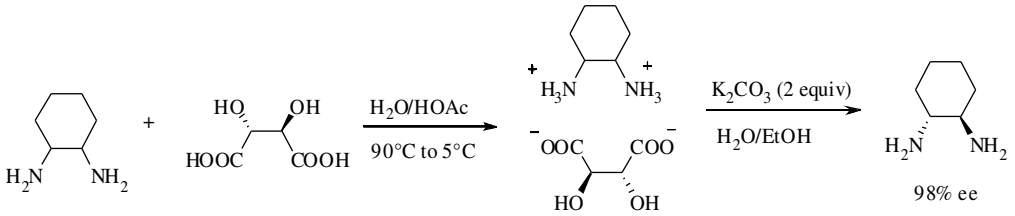
Preferential crystallization has been successfully employed to obtain enantiomers from racemates, is said to be a simple and useful method for large scale chiral separation and is achieved by providing a small amount of one enantiomer as seed crystals in a racemic supersaturated solution.[35] Racemates exist in the forms of racemic compounds,

racemic solid solutions, and conglomerates. However, only conglomerates, which are defined as mechanical mixtures of crystals of both enantiomers, can be optically resolved by preferential crystallization.[36]

**(b) Diastereomer Crystallization**

It is widely used for the industrial synthesis of pure enantiomer. If the racemate is truly racemic, a homogeneous solid phase of the two enantiomers co-existing in the same unit cell, these can be separated *via* diastereomer crystallization. This generally involves interaction of the racemate with an optically pure acid or base (generally referred as resolving agent) to form a mixture of diastereomeric salts which is separated by crystallization.[37] The most commonly used resolving agents are based on natural products such as L-(+)-tartaric acid, D(-)-camphorsulfonic acid and various naturally occurring alkaloids as a base.

A pertinent example is the separation of the enantiomers of 1,2-diaminocyclohexane with L-(+)-tartaric acid (**Scheme 1.5**). The resulting chiral amine is used in the preparation of Jacobsen's catalyst.[38]




**Scheme 1.5.** Resolution of trans-1,2-cyclohexanediamine with L-(+)-tartaric acid

**2. Kinetic Resolution**

Kinetic resolution (KR) is based on the principle that one of the two enantiomers undergo selective reaction in the presence of an optically active catalyst or reagent *i.e.,* a chiral acids or base or a chiral metal complex or a biocatalyst such as an enzyme or

microorganism.[39,40] This is illustrated as follows: in which R and P refers to reactant and product respectively.

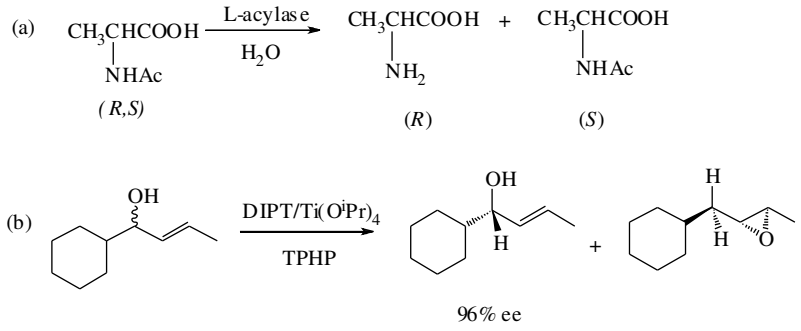
$$R_R \xrightarrow[\text{Chiral catalyst}]{k_R} P_R$$

$$R_S \xrightarrow[\text{Chiral catalyst}]{k_S} P_S$$

$$k_{rel} = \frac{k_{fast}}{k_{slow}} = e^{\Delta\Delta G^{\ddagger}/RT}$$

The subscript points to the nature of the enantiomer. Kinetic resolution occurs when $k_R \neq k_S$, *i.e.,* when the catalytic rate constants for both the reactions are different. In a catalytic kinetic resolution, the relative rates of the reaction for the substrate enantiomer (typically expressed as $k_{rel}$) are dictated by the magnitude of $\Delta\Delta G^{\#}$. This corresponds to the difference in the energies between the diastereoisomeric transition states in the selectivity determining step of catalytic reaction.[41] The energy difference, manifested as a relative rate difference, represents a constant and unrelenting differential pressure upon the two enantiomers. This process should continue until the last molecule of more reactive enantiomer is swept away and one is left with a substance possessed of absolute enantiomeric purity. This concept of being able to achieve absolute enantiomeric purity in kinetic resolutions by removal of the last molecule of the fast reacting enantiomer has attracted chemists to use it as a tool for the preparation of optically active compounds.

**Scheme 1.6** shows two examples, the enzymatic kinetic resolution of racemic *N*-acetylamino acids and the chemical kinetic resolution of a secondary allylic alcohol, developed by Chibata et al.[42] and Sharpless et al.[43] respectively.




**Scheme 1.6** Catalytic kinetic resolution by: (a) biological agent, (b) chemical agent.

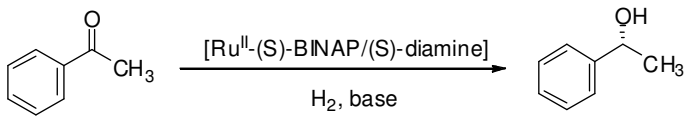
### 3. Chiral Chromatography (HPLC)

An emerging technology for the separation of racemates includes chiral high performance liquid chromatography (HPLC) using simulated moving bed technology.[44] This technique relies on the use of the stationary phase to resolve enantiomers contained in a mobile phase.[45] While crystallization of diastereomeric adducts can be applied on any scale, separation *via* HPLC is probably the most important in the early phase of product development and is restricted to rather small-scale (100 kg to tonnes), for high-value products. In reality, the large solvent volume, long separation times and relatively high cost of the chiral chromatographic supports often limits the scale at which chromatographic separations can be operated.

## 1.3.3 Asymmetric Synthesis Starting from Prochiral Substrates

Asymmetric synthesis has grown enormously in importance since Emil Fischer first noted its existence over one hundred years ago. Asymmetric synthesis takes advantage of the fact that the inclusion (stoichiometric, substoichiometric or catalytic) of a chiral reagent or auxiliary in a synthetic transformation can cause a new chiral center to be preferentially generated with high enantiospecificity.[46,47] However, catalytic

asymmetric synthesis in which a chemocatalyst usually a chiral transition metal complex or a biocatalyst such as an enzyme, is used has clear advantages over the reagents and auxiliaries approach since a catalytic amount of chiral material can produce large quantities of enantiomerically enriched or enantiopure products.[48] Therefore, the chirality is amplified rather than transferred (**Scheme 1.7**).




**Scheme 1.7** Asymmetric hydrogenation of aromatic ketone using chiral Ru catalyst

## 1.4. Privileged Chiral Ligands

The increasing demand of chiral drugs in their high enantiomeric purity led the research to search for highly efficient synthetic processes. Many strategies that include chemical and biochemical processes have been reported in the literature,[6] where chiral ligand based metal complex mediated asymmetric synthesis is of prime importance due to its inherent flexibility in terms of fine tuning the catalyst structure based on specific requirement. In this direction some of the 'privileged chiral ligands'[9] that exhibit high selectivity for a wide range of substrates and over a broad spectrum of reactions are; BINOL (2,2'-dihydroxy 1,1'-binaphthyl), salen (salicyledine ethylenediamine), BINAP (2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl), derivatives of tartaric acid, bis(oxazoline), pybox, derivatives of cinchona alkaloids, and the Duphos (bis-phosphine) ligands (**Figure 1.5**). Metal complexes of these chiral ligands have been applied to a

broad range of asymmetric transformations in which some of the transformations are extremely important to industrial applications.

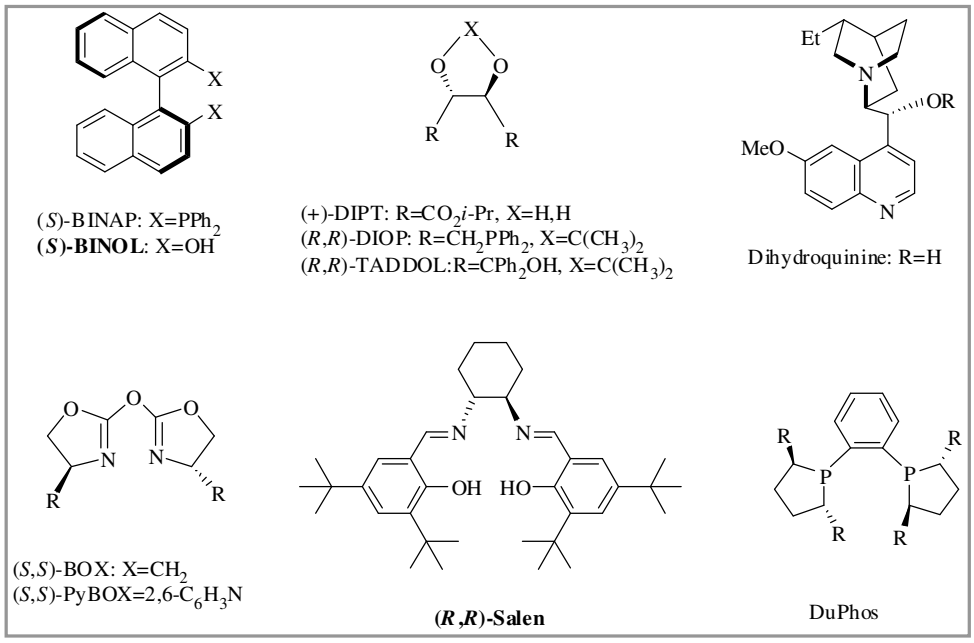
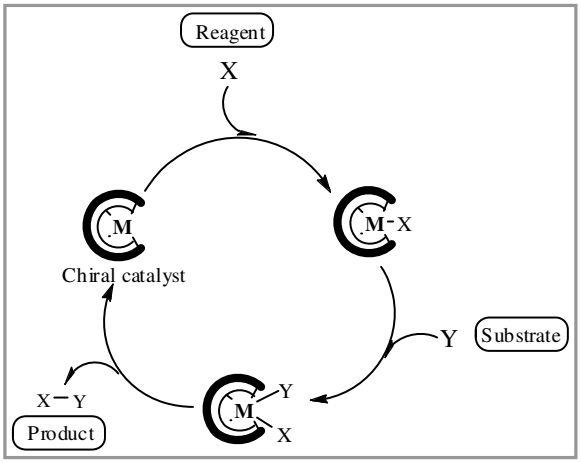



**Figure 1.5** Family of privileged ligands.

The rationale to design a suitable chiral ligand is based on the requirements of stereoselectivity, higher reaction rates, atom economy, cost efficiency, operational simplicity, environmental friendliness, low-energy consumption and preferably readily recyclable. These requirements are many a time difficult to meet, largely due to the insufficient knowledge of the catalytic cycle (**Scheme 1.8**). Thus, asymmetric catalysis is an integrated chemical approach in which maximum chiral efficiency can be obtained only by combination of suitable molecular design of catalyst with proper reaction conditions.[48]




**Scheme 1.8** Catalytic cycle

As a result, there is a difficulty to rationally design a chiral catalyst. Nevertheless, theoretically, only a small amount of the often-expensive chiral catalyst would be needed and the desired enantiomer of the product would be directly formed. The chiral ligands that modify intrinsically achiral metal atoms must possess suitable three-dimensional structure and functionality to generate sufficient reactivity and the desired stereoselectivity. The chiral catalyst can permit kinetically precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules. Certain well-designed chiral metal catalysts not only accelerate the chemical reactions repeatedly but also differentiate between diastereomeric transitions states (TSs) with accuracy of 10 $KJmol^{-1}$.

Among the various 'privileged chiral ligands', metal complexes based chiral BINOL[49,50] and salen[51,52] have found extensive applications in various catalytic asymmetric transformations homogeneous and heterogeneous reaction conditions. This thesis is mainly focused on these distinct classes of chiral ligand systems.

### 1.4.1. BINOL

BINOL (2,2'-dihydroxy- l,1'-binaphthyl) is the best known representative of axially chiral molecules[53] and was first prepared as racemate in 1873 by von Richter.[54] The synthesis of enantiomerically pure (*R*)- or (*S*)- BINOL was carried out by using enzymatic or chemical resolution of racemic BINOL and direct stoichiometric or catalytic oxidative coupling of β-naphthol.[50] However, the enantiomeric BINOL was first recognized as a ligand for metal-mediated catalysis in 1979 by Noyori for the reduction of aromatic ketones and aldehydes.[55] Since, then the enantiomeric BINOL has become among the most widely used ligands with various metal ions for both stoichiometric and catalytic asymmetric reactions.

BINOL has occupied a prominent position in lieu of its ability to form highly enantioselective catalysts with main group elements,[56] transition metals[57] and rare earth elements.[58] A broad spectrum of heterobimetallic complexes containing BINOL that are multifunctional in nature have also been reported.[59] Modifications of the BINOL skeleton aimed at changing its steric as well as electronic properties has proven to be necessary and effective thereby affecting the reaction environment by influencing the properties of the metal center in several catalytic asymmetric reactions.[60] Due to the easy maneuverability of BINOL skeleton, it has been extensively studied in various metal-catalyzed asymmetric transformations. The two most important class of reactions are asymmetric C-C bond formation reactions of carbonyls,[50] *e.g.,* Allylation reaction using organotin reagent, Dialkylzinc addition (alkylation), Diels-Alder reaction, Nitro-aldol reaction, Cyanosilylation reaction and asymmetric Oxidation reactions.[49, 61,62]

### 1.4.2. Salen

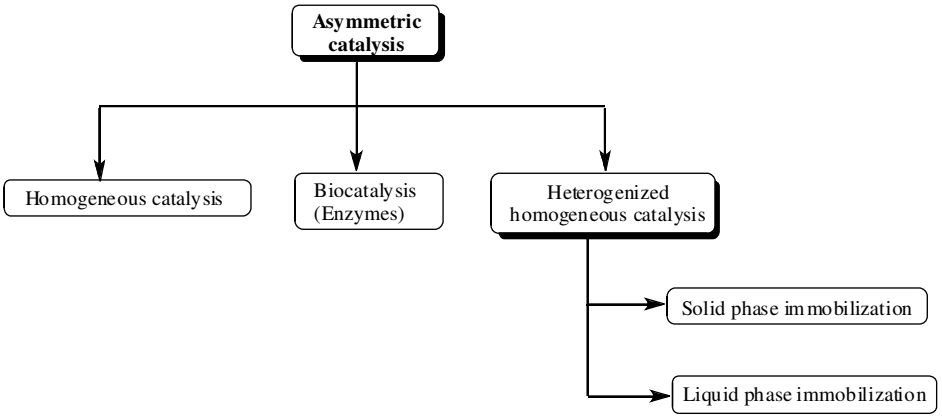
Hugo Schiff described the condensation between an aldehydes and an amine leading to a Schiff base (salen) in 1864.[63] Chiral versions of this tetradentate bis(imine) ligand are accessed simply by using chiral 1,2-diamines as chiral source. Schiff base ligands are able to coordinate metals through imine nitrogen and another group, usually linked to the aldehyde. Chiral salen ligands are among the most synthetically accessible structural entity for asymmetric catalysts, and their structures are readily tuned both sterically and electronically.

Since the past decade, chiral salen metal complexes have emerged as versatile catalysts for a broad range of industrially and academically relevant reactions. Salen motif came into highlight once when Mn(salen) was successfully used to catalyze the asymmetric epoxidation of non-functionalized alkenes in 1991.[64] Subsequent to this various metal complexes of salen ligand have displayed remarkable activity and in a wide variety of catalytic asymmetric reactions *e.g.,* asymmetric Epoxidation reaction, Ring opening of epoxides and other various nucleophilic substitution reactions to carbonyls like asymmetric Cyanosilylation, Diels-Alder reaction, Dialkylzinc addition and Cycloproponation reaction.[9,51,65] Chiral Mn(salen)-catalyzed asymmetric Epoxidation and Co-catalyzed Hydrolytic kinetic resolution processes are currently practiced on an industrial scale.[52]

## 1.5. Classification of Asymmetric catalysis

Asymmetric catalysis can be classified in three broad categories (**Scheme 1.9**):

1. Homogeneous asymmetric catalysis; where catalyst and reagents are present in the same phase.
2. Heterogeneous asymmetric catalysis; where catalyst and reagents are present in different phases. Mostly this class of catalysis is pursued by using solid catalysts prepared by the heterogenization of well known homogeneous catalysts.
3. Biocatalysis; where either free enzymes or whole cell or microbes are used as catalyst.




**Scheme 1.9** Classification of Asymmetric catalysis

### 1.5.1. Homogeneous Asymmetric Catalysis

According to the nature of the catalyst, homogeneous catalysts can further be divided into nucleophilic (Lewis bases,[66] Brønsted bases,[67] biological[68]), electrophilic (Lewis acids,[69] Brønsted acids[70]) and coordination catalysts[9] (transition metal complexes). Enzymes are still considered to be the most efficient homogeneous catalysts due to their high activity and specificity. As a consequence, biocatalysis recently started to find an increasing number of applications in organic chemistry.[68,71] However, in general synthetic organic chemists are not well trained and equipped with reaction conditions used in enzyme catalysis which largely comprised of fermentation technology.

This has led intense activity for developing organic and/or metal based catalysis where reactions can be carried out in familiar reaction-setups. In the last decades huge advances in terms of activity and selectivity have been achieved in transition metal catalysis,[5] resulting in a large diversity of possible reactions, some of which can only be performed using coordination catalysis.

Homogeneous metal catalyzed asymmetric synthesis has made impressive progress during the last decades[6,7] and chemists involved in the pioneering breakthroughs in asymmetric catalysis were awarded Nobel Prize of Chemistry in 2001.[11] These studies marked a new era in coordination chemistry, in which metal catalysts, due to their activity and selectivity, started to be considered *chemists' enzymes*, thereby reducing the gap between chemo- and bio-catalysis.

The field of asymmetric catalysis has been dominated for a long time by homogeneous catalysis because of their key features, such as:

- Higher selectivity and activity.
- Operation under milder reaction conditions.
- Reaction reproducibility.
- Accessible mechanistic insight.
- Easier structural modification of the catalyst.

However, homogeneous asymmetric catalysts are often expensive and their separation and recycling is troublesome. Despite the fact that there are couple of enantioselective homogeneous catalyst being used on commercial scale[19] some of the potential chiral homogeneous catalysts find difficult for acceptability in industry due to their inherent shortcomings, *viz.,* (i) complicated work-up of the reaction mixture, (ii)

preparation of the pure products not contaminated with catalysts or constituents thereof, (iii) isolation of the valuable catalyst or its constituents, which can be achieved only with high technical complexity and expenditure. The most feasible way to circumvent this problem is to '*heterogenize*' the homogeneous catalyst, by means of immobilization, anchoring, or encapsulation on an inorganic (zeolites or mesoporous materials) or organic (polymeric) solid support.[72-74]

### 1.5.2. Heterogeneous Asymmetric Catalysis

In recent years, significant developments in the area of solid-phase chemistry has resulted in enormous progress being made in interdisciplinary research on stereoselective heterogeneous catalysis.[75] The potential advantages of heterogeneous catalysis, such as easy separation, efficient recycling, minimization of metal traces in the product, and an improved handling and process control, that finally result in overall lower costs are well known. Furthermore, in some cases heterogeneous catalysts are even more selective than their homogeneous counterparts,[76] this is generally attributed to the confinement effect of the support. The confinement effect essentially originates from the pore and surfaces of the support that are not inert thus might influence the active catalyst through various weak interactions to impart higher enantioselectivity during the catalytic process.[77] Heterogenization of homogeneous catalyst also takes into account of the principles of green chemistry where the industry requires to make all necessary efforts to minimize wastes, particularly those of substances that contain noxious transition metals typically present in metallic catalysts.[73]

Two main strategies have been employed for the heterogenization of chiral homogeneous catalysts.

[1] Solid phase immobilization: The homogeneous catalyst is heterogenized by anchoring it onto a solid support (*e.g.,* an inorganic material or polymer) *via*, (i) a covalent bonding; (ii) adsorption; (iii) ion-pair formation; (iv) encapsulation or (v) entrapment.

[2] Liquid phase immobilization: the homogeneous catalyst is confined in one of the liquid phase in a two-phase system (*e.g.,* aqueous phase, fluorous phase, supercritical carbon dioxide ($ScCO_2$) or ionic liquid) and the other phase is used for delivery and/or removal of reactants and products.

Besides, so-called a ''self-supported strategy'' has also been reported where dimeric or polymeric form of the monomeric homogeneous catalyst is employed which is either insoluble in the reaction medium or can be easily precipitated out in order to have effective product-catalyst separation.[74,78-80] Out of these, the most effective method is the heterogenization of homogeneous catalyst onto a solid support by covalent grafting method as it prevents/minimizes leaching of the active catalyst which is often associated with heterogenization of the homogeneous catalytic system.[73]

### 1.5.2.1. Solid Phase Immobilization

Immobilization of chiral catalyst occurs by covalent or non-covalent attachment of the chiral ligand, the metal, or the preassembled complex to the support (**Figure 1.6**). The ligand can even be synthesized on the support, thus allowing the efficient synthesis and screening of a library of ligands.[81] The choice of a suitable support plays an important, although not fully understood, role and remains a challenge. Numerous

problems can occur during the immobilization of a homogeneous catalyst that diminishes its performance. Therefore, it is important to account the following parameters:

- Interactions between the support and the metal–ligand complex that can adversely affect the activity and selectivity.
- The optimal geometry of the catalyst, which is crucial for high enantioinduction, should not be disturbed by the support.
- The stability of the linkage between the catalyst and the support so that the active catalyst is not leached during catalytic process.
- Accessibility to the active site should be unhindered.
- Optimum distribution of catalytic sites in order to prevent de-activation of active catalyst through formation of catalytically inactive dimmers and polymers (often occur in homogeneous system *e.g.,* formation of catalytically inactive μ-oxo species of Fe and Co during catalytic oxidation reaction). On the other hand too much of site isolation may hamper cooperative process which often enhance the activity and selectivity of the catalyst during the reaction.[82]

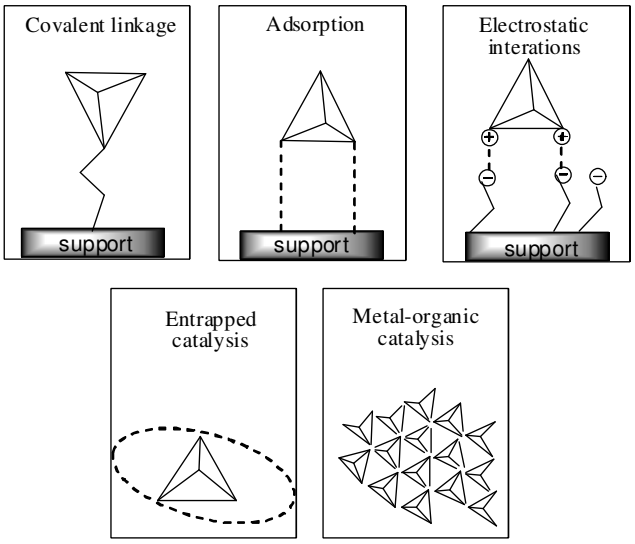



**Figure 1.6** Strategies for immobilization of chiral homogeneous catalyst

**[i] Covalently Immobilized Catalysts**

A classical method to immobilize a chiral homogeneous ligand or its metal complex is copolymerization with a monomer, or its covalent linkage to a suitable support, such as functionalized polymers, inorganic solids, carbon nanotubes, etc. The most important parameters that influence the activity and selectivity of the immobilized metal complex include structural modification of the chiral ligand, length and flexibility of the linker, catalyst loading, accessibility of the active catalyst center, choice of the solvent and the temperature at which catalytic reaction is conducted.[74]

**(a) Covalent Immobilization on Polymeric Resins** (Anchored to Polymers by SPS)

The success of the solid-phase synthesis (SPS) of peptides developed by Merrifield in the 1960s was the driving force for the vigorous research activity in the covalent attachment of chiral ligand onto a functional polymer. This approach greatly facilitated the reaction workup and the product purification.[83,84] The strategy quickly became popular to prepare supported reagents, scavengers, and catalysts. Besides Merrifield resins (poly(styrenedivinylbenzene)- polymers), other resins such as JandaJEL (polystyrene polymers containing a tetrahydrofuran-derived crosslinker),[85] TentaGel (polystyrene-poly(ethyleneglycol-$OC_2H_4$-$NHCOC_2H_5$),[86,87] and other PS-PEG (polystyrenepolyethyleneglycol) resins[88] have also been employed successfully for anchoring metal–ligand complexes.

Song et al.[89] immobilized the Trost ligand after suitable modifications. In the key modification, the cyclohexyldiamine moiety was replaced by a pyrrolidinediamine unit so as to allow facile anchoring of the ligand onto the support. The care was taken to instill

minimal disturbance to the catalytically active site (**Figure 1.7**). He used different types of organic supports and found that the choice of support greatly influence the activity and selectivity of the core catalyst. The JandaJEL-supported ligand gave excellent results (ee; 98%) comparable to those obtained in homogeneous catalyst in Pd-catalyzed desymmetrization, while polystyrene-bound catalyst was less active. The high activity of the JandaJel resins was attributed to the structure of the resin which is derived from long and flexible, tetrahydrofuran-derived cross-linkers. Therefore, the resin swells in the organic solvents thereby gives greater degree of flexibility to the attached complex and creates an atmosphere close to the homogeneous condition.

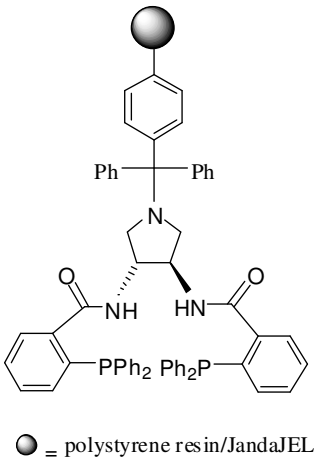



**Figure 1.7** Chiral modified Trost ligand immoblized on organic polymer

Yang et al.[90] chose an amide linkage in proximity to the catalytically active site to anchor a modified BINOL through its 3,3'-position to a polystyrene resin (**Figure 1.8**). Clearly higher ee values were obtained at full conversion in the Ti-catalyzed addition of diethylzinc to aldehydes with supported ligand than with the homogeneous BINOL (benzaldehyde: 97 versus 91.5% ee, respectively). This is one of the rare examples where

the support material had a positive effect of the polymer due to its proximity to the catalytically active site, thus resulting in an increased conformational rigidity of the metal complex. This is contrary to the popular belief that rigidity in the complex can cause loss in enantioselectivity.

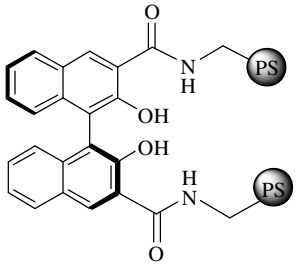



**Figure 1.8** Chiral BINOL immobilized on polystyrene resin through its 3,3' position

**(b) Covalent Immobilization by Copolymerization**

Copolymerization of suitable monomers allows for the introduction of the chiral information into the backbone of the heterogeneous catalyst. Radical polymerization of vinyl modified ligands with styrene and divinylbenzene[91] (**Figure 1.9**) or polymerization of amines with isocyanates to polyurethanes[92] are commonly used methods. In this method, the accessibility of the active site, which depends heavily on the degree of cross-linkage in the copolymer, is crucial for the activity and selectivity of the final catalyst. In general, the swelling ability of the copolymer in organic solvents decreases as the degree of cross-linkage increases.

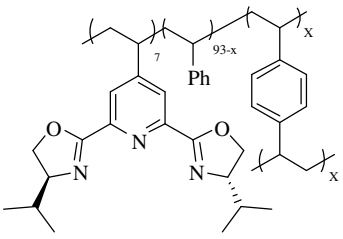



**Figure 1.9** Copolymerization of chiral Pybox using AIBN (azobisisobutyronitrile).

On the other hand, a functional polymer is synthesized at first and then chirally modified to synthesize the supported chiral ligand. For example, the opening of enantiomerically pure epoxides immobilized on a copolymer with different amines gave a series of immobilized amino alcohols. These ligands were successfully used in the Ru-catalyzed asymmetric transfer hydrogenation of acetophenone.[93]

The unique polarity of the organic polymer supports and their conformational, textural, and geometric factors may lead to an increase in the stability of the catalyst with enhanced enantio and regioselectivity due to the steric hindrance. However, compared to inorganic supports, the use of functionalized polymers can encounter some limitations: (i) the surface area of organic polymers is usually low compared to the inorganic supports, which results into a decrease in the interfacial contact between the supported complex and the substrates; (ii) possible side reactions with the polymer backbone may occur during the reaction; and (iii) as in the case of sophisticated inorganic supports, the preparation of the functionalized polymer backbone can require dedicated organic synthesis.[74]

**(c) Covalent Immobilization on Inorganic Supports**

The application of inorganic materials as heterogeneous supports offers a number of advantages like their rigid structure do not allow the aggregation of active catalysts; they do not swell, and are insoluble in organic solvents. The last two properties are interesting in regard to their application as stationary chiral phases in a continuous process. In addition, inorganic supports possess better thermal and mechanical stability under catalysis conditions. Moreover, the structure of the support needs to be such that the active sites are well dispersed on its surface and that these sites are easily accessible.

Generally, this requires the support to have a reasonably high surface area (typically >100 $m^2g^{-1}$) and appropriate pore size (*i.e.,* >20 Å) to allow easy diffusion of the reactants to the active sites.[94]

Among inorganic materials such as silica, zeolite, alumina, zirconia, ZnO, clay, zeolites and other mesoporous materials (pore size between 2 and 50 nm), which are characterized by their high surface area and easily accessible pores, have been extensively used for covalent immobilization of asymmetric catalysts.[73,95-97] Various types of zeolites and mesoporous silica like MCM-41 ("Mobile Crystalline Material", ordered hexagonal, usually 30–40 Å pore diameter; its very high porosity renders it less mechanically stable than other inorganic materials),[97] MCM-48 (ordered cubic), Grace332 (ca. 19 Å ), USY ("Ultra stabilized zeolite Y", 12–30 Å), SBA-15 ("Santa Barbara Amorphous ordered hexagonal, 46–300 Å ),[97], MCF (Mesocellular foam; 100-500 Å)[98] and nonporous silica such as Carbosil have been used successfully for the covalent immobilization of asymmetric catalysts.

Liu et al.[99] reported immobilization of Ru–(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (TsDPEN) catalyst on amorphous silica gel, mesopores of MCM-41 and SBA-15 for asymmetric transfer hydrogenation of ketones (**Figure 1.10**). Excellent conversion (>99%) with enantioselectivity (ee; 98%) were achieved with silica base catalyst. The silica-gel catalyst was reused in multiple catalytic runs without loss of activity.

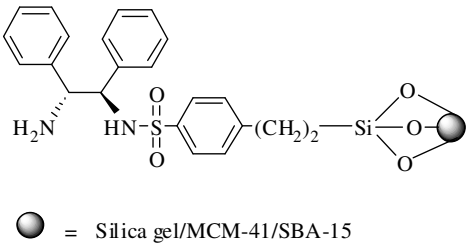



**Figure 1.10** Immobilization of chiral TsDPEN on different inorganic supports

**[ii] Non-Covalently Immobilized Catalysts**

There are various strategies by which chiral metal complexes can be immobilized without covalent bonding. Non-covalent immobilization has advantage that it reduces overall synthetic steps (sometimes!) for the heterogenization of a chiral catalyst. Mainly following strategies are used:

**(a) Immobilization by Adsorption**

The simple physisorption of a chiral ligand or metal–ligand complex on a support through van der Waals interactions is an attractive approach, since it renders a synthetic modification of the chiral ligand unnecessary.[74] However, this concept has only had limited success, because the complexes are only weakly bound. Therefore, the optimization of the reaction conditions, especially the choice of the right solvent, is a difficult task. The stability can be improved significantly if the chiral metal–ligand complex is immobilized by hydrogen bonding on a polar support such as silica. A cationic complex can be also bound by a surface-supported counterion, in this case no modification of the ligand structure is necessary[100] (**Figure 1.11**).

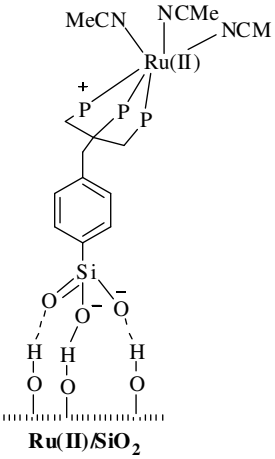



**Figure 1.11** Ru(II) complex on silica

**(b) Immobilization by Ion-Exchange**

Ion exchange between a chiral, cationic metal–ligand complex and an acidic resin represents an elegant method for immobilization through electrostatic interactions. Moreover, ion exchange is the only method that allows the direct immobilization of the metal itself. Layered materials, such as cationic clays (*e.g.,* hectorite, montmorillonite), anionic clays (hydrotalcite), possess suitable properties to support catalysts, such as large surface area, high ion exchange capacity, swelling, and intercalation. The immobilization of homogeneous catalysts in the interlayer space of inorganic layered compounds has been investigated extensively.[101] Intercalation of clays with metal complexes containing chiral ligands is believed to be a promising way to prepare the heterogeneous asymmetric catalyst. Cationic chiral catalysts can be easily intercalated into the interlayer of cationic clays by cation exchange. Intercalation of cationic clays have been used to design heterogeneous asymmetric catalysts for various asymmetric transformations, *e.g.,* Epoxidation, Diels-Alder reaction and Hydrogenation.[73]

Kureshy et al.[102] reported the intercalation of dicationic chiral Mn(III) salen complex into the interlayers of montmorillonite clay for asymmetric epoxidation (**Figure**

**1.12**). Good to excellent enantioselectivity (ee; 99%) has been achieved with four times recyclability of the supported catalyst without leaching of the metal complex.

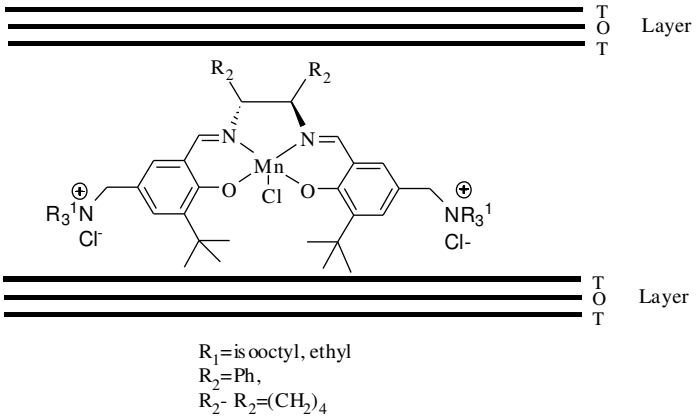



**Figure 1.12** Immobilization of Chiral Mn(III) salen in clay by cationic exchange

The hydrotalcite-like layered double hydroxides (LDHs) are the well-known anionic clays, which have been successfully applied in a broad spectrum of organic reactions.[103] However; few examples of the incorporation of chiral catalysts into the interlayer of LDH were reported. Choudary et al.[104] synthesized two heterogeneous enantioselective catalysts, LDH-proline and LDH-BINOL, by co-precipitation method. These organo-LDHs exhibit high catalytic activity but low enantioselectivity for asymmetric transformations.

**(c) Encapsulation**

Molecular sieves with 3-D channel systems may provide site isolation as well as shape selectivity. Encapsulation within the cages of tridirectional large-pore zeolites is generally known as “ship in a bottle” (SIB), where a big-sized catalyst is assembled in side the micropores through small-sized catalyst precursors. The SIB approach alludes to a methodology to immobilize homogeneous complexes in which the host-guest

interaction not chemical (neither ionic nor covalent bonding), but physical.[105] The term SIB was probably coined by Herron, who reported the synthesis of several types achiral salen-metal complex encapsulated within zeolites.[106] This situation can easily occur in tridirectional zeolites having rigid structures with well defined cages and cavities that are interconnected through smaller windows.

Zeolites are aluminosilicates having crystal structure defined by empty channels and cavities of strictly regular diameter called micropores. These micropores allow mass transfer from the exterior to the interior of the zeolite particles, provided that the size of the diffusing molecules is smaller than the dimensions of the micropores. This method brings no changes to the chemical properties of the immobilized catalyst except for the steric confinement of porous supports.[107] Sabatier et al.[108] encapsulated Mn-*trans*-(*R,R*)-1,2-*bis*(salicyideneamino)-cyclohexane complex within the pores of zeolite Y by this ship-in-bottle method (**Figure 1.13**).

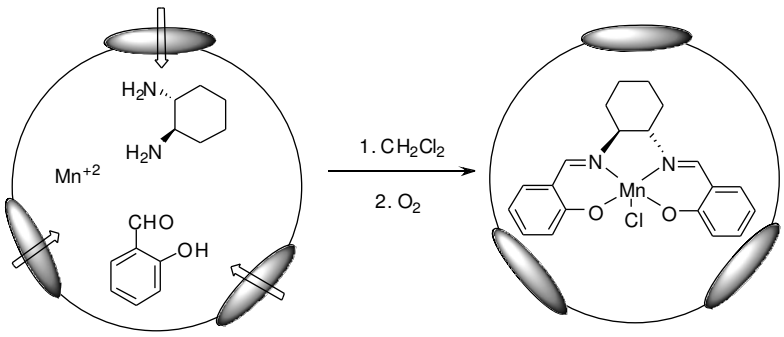



**Figure 1.13** Immobilization of Mn(III) salen in Zeolite Y by encapsulation

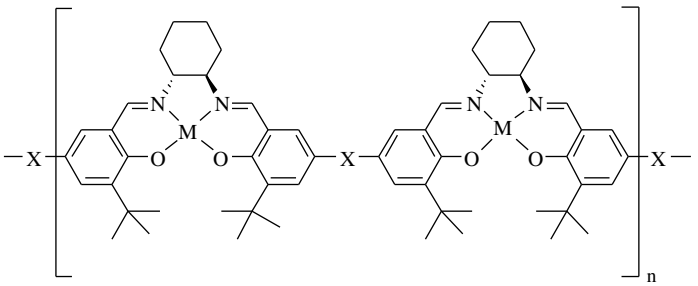
### (d) Polymers Formed *in situ* by the Suspension Co-PT (Copolymerization Technique)

Various approaches for heterogenization of homogeneous catalyst have been described in the preceding sections are well documented in the literature. All of

these approaches are interesting but demand additional modifications to the structure of the catalyst or require the reaction to be carried out in the presence of some reagents which often result in the loss of activity and selectivity.

An insoluble polymer that contains the active complex can be prepared by copolymerization or by co-precipitation of ligand monomers or by self-polymerization of bifunctional-monomers. Much of this type of study involved chiral salen metal complex.[74] Poly-salen-Mn catalysts having methylene or methylene-oxy-methylene (**Figure 1.14**) as linking motifs were developed by Yao et al.[109] The catalysts were tested for the asymmetric epoxidation of styrene and chromene derivatives with excellent enantioselectivities, and the catalysts could be recycled effectively four times.

Kureshy et al.[80] synthesized chiral polymeric Mn (salen) complex with 12 salen units and used in asymmetric epoxidation of non-functionalized alkenes. These complexes were used as homogeneous catalyst during the catalytic run. However, the catalyst was easily separated from reactants and products by simple precipitation technique using non-polar solvent. The precipitated complex can be used directly without activation for subsequent catalytic runs. Five such repeat runs were reported be successfully accomplished.




X= $CH_2$ or $CH_2OCH_2$ or $CH_2CCH_2$

**Figure 1.14** Structures and Linking Motifs of the Poly-salen catalysts using the Co-PT method

**(e) Chiral Metal–Organic Catalysts**

In the recent years, the chemistry of hybrid solids constructed from organic linkers and metal nodes has received much recent attention, owing to the propensity of incorporating and fine-tuning desired properties *via* judicious choices of their building blocks.[110] The design and synthesis of chiral porous materials based on metal-organic frameworks (MOF) by connecting metal nodes with chiral bridging ligands that have orthogonal functionalities. Two complementary strategies have been successfully utilized to synthesize catalytically active chiral MOFs. In the first approach, the primary functional groups are linked by metal-connecting units to form extended networks whereas the orthogonal secondary chiral groups can then be used to generate asymmetric catalytic sites by coordinating to a secondary metal center. In the second approach, the primary functional groups are used to generate robust transition metal precatalysts which are then linked by the metal nodes to form porous extended networks via the secondary functional groups. The catalytically active chiral porous solids have been used for highly enantioselective asymmetric catalysis by both Lewis acids and group 8 metal complexes. The present complementary synthetic strategies have thus led to ideal heterogeneous asymmetric catalysts in which both the catalytic sites and the secondary environments around them are identical throughout the solid. In comparison to other immobilization approaches, this strategy allows the synthesis of heterogeneous asymmetric catalysts with higher catalyst loading and more accessible catalytic centers. Their performance is comparable to or better than that of the parent catalysts, they are easy to separate and reuse, and there is minimum leaching of the catalyst.

Wu et al.[111] introduced catalytically porous metal–organic network using axially chiral bridging ligand (*R*)-6,6'-dichloro-2,2'-dihydroxy-1,1'-binaphthyl-4,4'-bipyridine, which contains the bipyridyl primary functionality and orthogonal chiral 2,2'-dihydroxy secondary functionality, was used to construct homochiral porous MOFs (**Figure 1.15**). This metal organic chiral auxiliary was used in asymmetric diethylzinc addition to aldehydes. High enantioselectivity (ee; 93%) was achieved under heterogeneous reaction conditions.

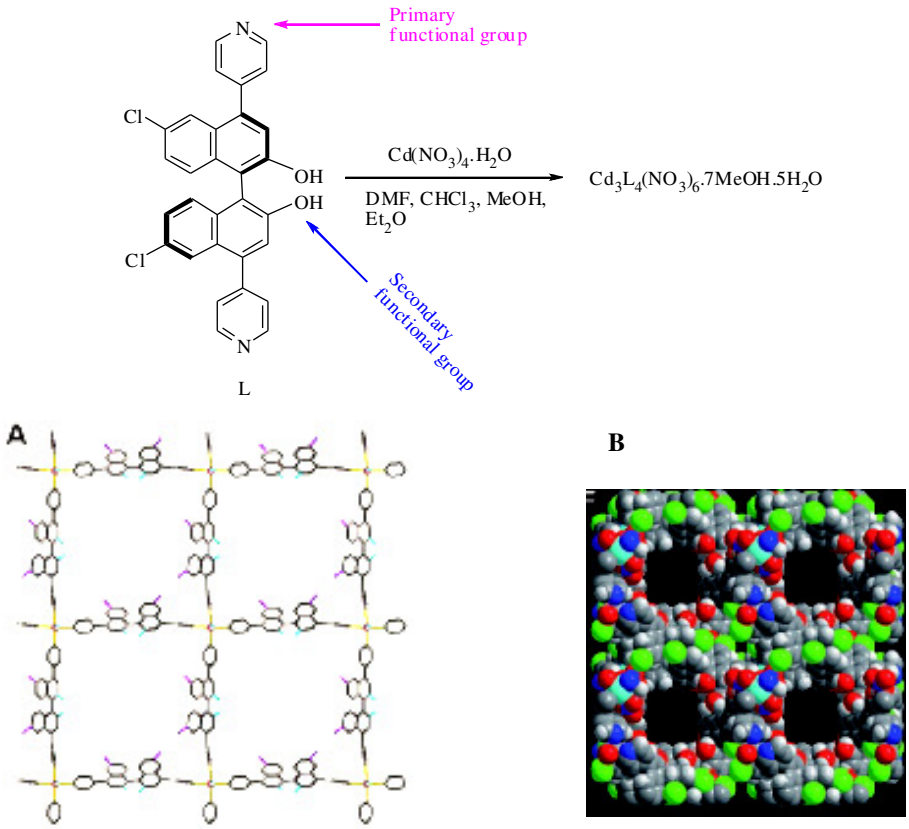



**Figure 1.15** Chiral MOF

### 1.5.2.2. Liquid Phase Immobilization

The immobilization of catalytically active organometallic complexes onto organic or inorganic polymers by covalent or non-covalent interactions, besides these approaches,

the use of novel reaction media (aqueous biphasic systems, ionic liquids, supercritical fluids and fluorous systems) in which homogeneous catalysts can effectively operate and then be easily recovered by simple phase separation is currently attracting considerable interest. Research in this last field is also stimulated by the unusual selectivity and increased activities which are sometimes observed for catalytic reactions.[74] This class of immobilization refers that the chiral homogeneous catalyst is confined in one of the liquid phases in a two-phase system (*e.g.,* aqueous phase, fluorous phase, supercritical carbon dioxide ($ScCO_2$) or ionic liquid) and the other phase is used for delivery and/or removal of reactants and products. In recent years, many works have been devoted using this type of immobilization using various chiral metal based complexes based on salen and BINOL scaffolds. Some of the examples are listed below:

**(a) Supercritical Carbon dioxide ($ScCO_2$) Containing Phase**

The supercritical state of $CO_2$ is easily achievable at moderate pressures (73.8 bar) and temperatures (31°C) as compared to other gases. The supercritical fluid state has interesting properties in catalysis including disappearance of the liquid-gas interphase, a fast gas-like molecular diffusion, and liquid-like solubility.[112] In general; the solubility of compounds in supercritical fluids depend strongly on the pressure, temperature, and additives, particularly in the vicinity of the supercritical state conditions. Therefore, the reactants, products, and catalysts can be easily separated by pressure or temperature changes according to the phase diagram of a particular mixture. For example, vanadyl salen complexes was reported to catalyze the stereoselective epoxidation of allylic alcohols with *tert*-butyl hydroperoxide in supercritical $CO_2$.[113]

**(b) Fluorous Containing Phase**

The flurous biphasic system is one of the most useful systems that gained considerable interest for immobilization of chiral homogeneous catalyst. In this type of immobilization the chiral ligand is modified by perfluroalkyl chain to make flurous ligand and used of flurous liquid as transfer medium. There are many reports on recoverable chiral ligands by liquid–liquid fluorous technique involving BINAP, BINOL, salen and chiral phase-transfer catalyst tethered with long perfluoroalkyl chains.[114] Pozzi et al.[115] reported Mn(salen) complex derived from chiral amines having perfluorooctyl substituents in the *ortho*- and *para*-positions of the phenolic moieties and used in asymmetric epoxidation terminal alkenes using molecular oxygen and pivalaldeyde under FB (fluorous biphasic) conditions (**Figure 1.16**).

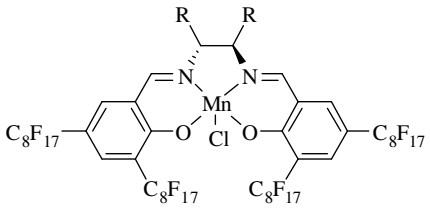



**Figure 1.16** First-generation fluorous chiral salen ligands.

**(c) Ionic Liquid**

Ionic liquids are organic salts which are liquid at room temperature. Ionic liquids became alternative solvent for catalysis and have attracted considerable attention as 'Green reaction media'.[116,117] The most widely used ionic liquids are derivatives from *N*,*N*'-dialkylimidazolium or *N*-alkylpyridinium with an inorganic anions such as $PF_6^-$, $BF_4^-$, or even $Cl^-$.They have reasonably good thermal stability and have sufficient ability to dissolve most organic compounds. Nonvolatile and immiscibility with some organic

solvents such as alkanes and ethers makes these solvents as recoverable Green solvent. For this reason, ionic liquids are considered as a suitable homogeneous reusable catalytic media reaction.

Tethering functional groups to ionic substructures gives rise to task-specific ionic liquids (TSILs),[118] these compounds combine the properties of the anchored organic groups with the solubility behavior of ionic liquids. Anchoring transition metal containing substructures led to catalytic TSILs with enhanced ionophilicity,[119] which improves catalyst re-usability.[120,121] As an example of this vanadyl salen complex has been modified by appending in peripheral positions of the ligand an *N*-methylimidazolium tag that should increase the "ionophilicity" of the salen catalyst[122] (**Figure 1.17**). This complex has been used in asymmetric cyanosilylation of benzyldehyde. However, enantioselectivity was inferior as compared to unmodified vanadyl salen complex.

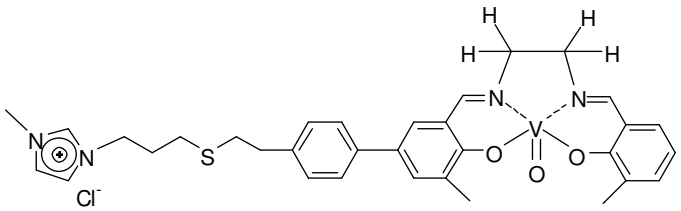



**Figure 1.17** Chiral vanadyl salen complex attached to imadazolium tag

### 1.5.3. Biocatalysts

Biocatalysts (Enzymes) are still considered to be the most efficient homogeneous catalysts due to their high activity and specificity. Enzymes are protein molecules of colloidal size [*e.g.,* poly (amino acids)]. Some of them act in dissolved form in cells, while others are chemically bound to cell membranes or on surfaces. Enzymes can be

classified somewhere between molecular homogeneous catalysts and macroscopic heterogeneous catalysts.

Enzymes are the driving force for biological reactions. They exhibit remarkable activities and selectivity. For example, the enzymes catalyze decomposition of hydrogen peroxide $10^9$ times faster than inorganic catalysts. The enzymes are organic molecules that almost always have a metal as the active center. Often the only difference to the industrial homogeneous catalysts is that the metal center is ligated by one or more proteins, resulting in a relatively high molecular mass. Some of the factors that account for the significance of enzymes are, (i) they are chemo-, regio-, and stereoselective, and environment friendly, (ii) Because of the mild conditions under which they operate, enzymatic reactions are affected to a lesser extent by side reactions (*viz.* isomerization, racemization, epimerization, and rearrangement of molecules) as compared to nonenzymatic processes.[68]

Apart from high selectivity, the major advantage of enzymes is that they function under mild conditions, generally at room temperature in aqueous solution at pH values near 7. Their disadvantage is that they are sensitive, unstable molecules which are destroyed by extreme reaction conditions. They generally function well only at physiological pH values in very dilute solutions of the substrate. Enzymes are expensive and difficult to obtain in pure form. Only recently enzymes, often in immobilized form, have been increasingly used for reactions of non-biological substances. With the increasing importance of biotechnological processes, enzymes will also grow in importance in pharmaceuticals.[123]

## 1.6. Asymmetric C-C Bond Forming Reactions

Recently, asymmetric catalysis has evolved into a rapidly growing; forefront area of chemical research. Of particular importance is to develop asymmetric catalysts mostly for C-C bond forming reactions.[47,65] There are various asymmetric C-C bond forming reactions studied extensively with various chiral catalysis.[49,124] Highly valuable chiral products can be synthesized through C-C bond formations that are important drug intermediates and key ingredients in natural products. Some the important C-C bond formations are Aldol reaction, Diels-Alder and Hetero Diels-Alder reaction, Cyclopropanation, Allylation of carbonyls with organotin reagents, Cyanosilylation of carbonyls and asymmetric Alkylation and Alkynylation of carbonyls using diorganozinc reagents.

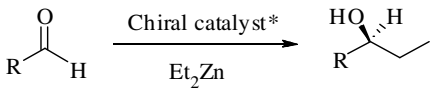
In recent years, much research has been devoted on catalytic asymmetric C-C bond formations using various chiral 'privileged' ligands.[51] Chiral products obtained by asymmetric C-C bond formation reactions are important chiral intermediates for pharmaceuticals and vitamins, agrochemicals, flavors and fragrances and functional materials.

### 1.6.1. Asymmetric Addition of $Et_2Zn$ to Aldehydes (Asymmetric Alkylation)

Nucleophilic addition of organometallic reagents to carbonyl substrates constitutes one of the most fundamental operations in organic synthesis.[125] The use of organozinc chemistry, in place of conventional organolithium or -magnesium chemistry, has been developed into an ideal protocol for the catalytic enantioselective alkylation of aldehydes, leading to a diverse array of optically pure secondary alcohols.[126,127] Optically active secondary alcohols are important intermediates for the synthesis of many naturally

occurring compounds, biologically active intermediates and materials such as liquid crystals.[128,129] The asymmetric addition of dialkylzinc as a reagent to alkylation of benzaldehyde has become an archetypical reaction for evaluating the activity of newly developed chiral catalysts.[130] A plethora of chiral ligands *e.g.,* β-amino alcohols, BINOL, oxazoline have been reported to be catalytically active towards this reaction, with ranging from medium to excellent.

Since the first report of enantioselective addition of diethylzinc to benzyldehyde catalyzed by (*S*)-leucinol in 1984,[131] studies on homogeneous and heterogeneous catalytic enantioselective addition of organozinc compounds to aldehydes (**Scheme 1.10**) have received enormous attentions.[72]




**Scheme 1.10** Asymmetric addition of $Et_2Zn$ to prochiral aldehyde

The catalytic asymmetric addition of diethylzinc to aldehydes utilizing BINOL-Ti complex is an efficient catalyst under homogeneous system,[132-134] but heterogenization of asymmetric catalytic system has inherent advantage of easy recovery, product separation from the reaction mixture and re-use of the expensive chiral catalyst.[135,136] This strategy also narrows the gap between homogeneous and heterogeneous catalysis. In this direction, some attempts have been made for heterogenization of chiral BINOL on various supports which are described below.

### 1.6.2. Heterogenization of Chiral BINOL for Asymmetric Addition of $Et_2Zn$ to Aldehydes

A number of recoverable catalysts of chiral BINOL on to various supports have been investigated on support materials such as polymers, dendrimers, monolayer protected Au cluster, ionic liquids and fluorous biphasic system as attractive alternatives to the corresponding homogeneous systems for asymmetric dialkylzinc addition to aldehydes. However, immobilization of BINOL on siliceous support has been scarcely studied for this reaction.

#### [i] Organic Polymers as Supports

The use of organic co-polymers as support for chiral auxiliaries/complexes allows one to conjugate a controllable flexibility of the polymeric matrix with the possibility to fine tune the physical properties such as polarity, ability to swell, morphology etc. of the material by suitable combination of co-monomers and cross linkers. A large amount research have been carried out using organic polymer as supports for immobilization of chiral BINOL and used in privileged C-C bond formation reaction. Some of contributions are listed below.

Yang et al.[90] reported the synthesis of polymer supported BINOL ligand (**Figure 1.18a**) by connecting functionalized BINOL to Merrifield type resin through amide bond. The resulting heterogenized chiral auxiliary was employed in Ti-catalyzed diethylzinc addition to aldehydes. The reaction carried out in $CH_2Cl_2$ at 0 °C, gave the product in high enantioselectivity (ee; 99%). The results showed that the polymer-supported catalyst was substantially more enantioselective than its homogeneous analogue. Dong et al.[137] reported the polymeric BINOLs in which BINOL moieties were connected through imine bonds (**Figure 1.18b**). Another type of polymer supported BINOL was reported by

Lipshutz et al.[138] (**Figure 1.18c**). The BINOL and substituted BINOLs tethered at 7 and 7' positions were attached via the linkage to polystyrene resin using simple acetalization.

Jayaprakash et al.[139] reported soluble polystyrene supported BINOL and used in Ti-catalyzed asymmetric diethylzinc addition to benzaldehyde. The reaction demonstrated high ee (84%) under heterogeneous reaction conditions (**Figure 1.18d**).

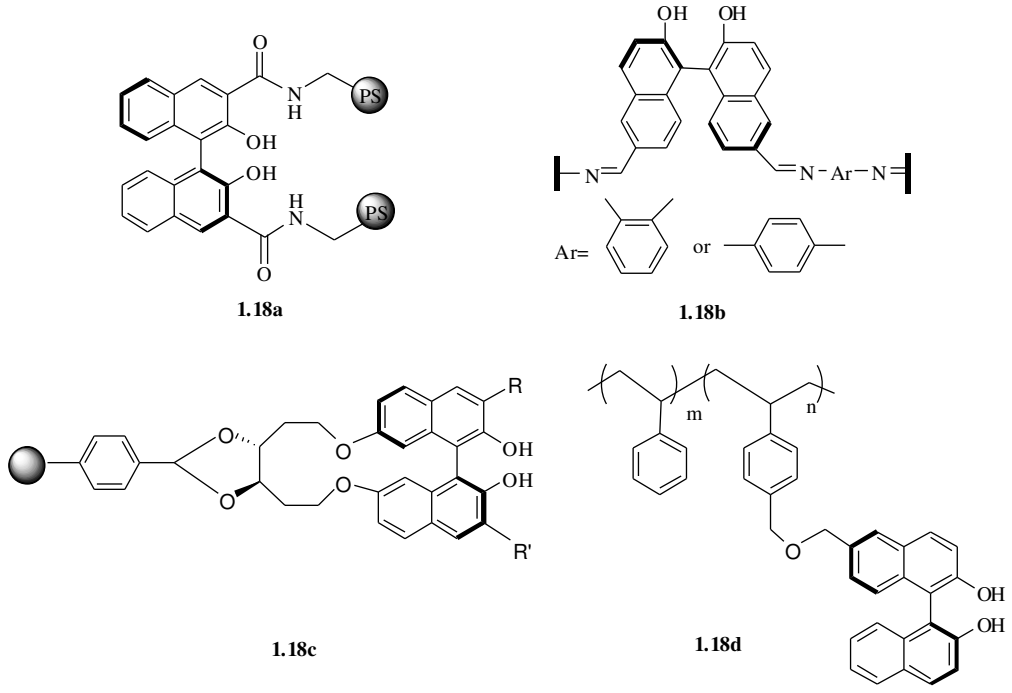



**Figure 1.18** Polymer-supported chiral BINOL

Other notable work on polymer supported chiral BINOL was reported by Moreau et al.[140,141] using cross-linking polymerization technique (**Figure 1.19**). The reaction demonstrated high conversion (99%) with enantioselectivity (up to 78%) under heterogneous reaction conditions.

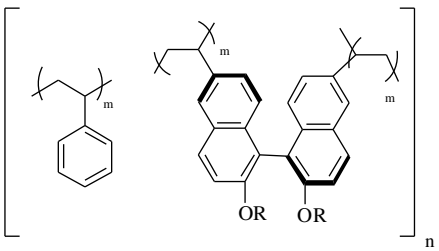



**Figure 1.19** Polymer -supported BINOL using cross-linking polymerization technique

Recently, Harada et al.[142] reported the new method for the immobilization of chiral BINOL-Ti complex using aggregation phenomenon (**Figure 1.20**). The insoluble polymer aggregates were used in asymmetric diethylzinc addition to aldehydes. High enantioselctivity (ee; 84%) was achieved in the case of 1-naphthaldehyde with 3 reuse experiments.

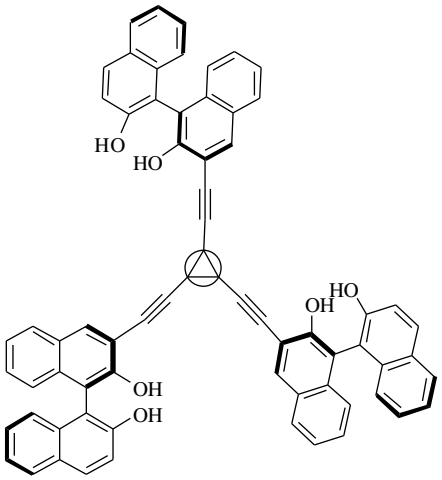



**Figure 1.20** Immobilization of BINOL using aggregation phenomenon

**[ii] Dendrimers as Supports**

Dendrimers are highly branched macromolecules which have precisely defined nano-sized molecular structures. Since the pioneering work of van Koten et al.[143] reported in 1994, dendritic catalysts have become a subject of intensive research,[144] such novel catalysts can be used under homogeneous conditions and be readily recovered *via* simple precipitation or nanofiltration methods. Compared to the linear soluble polymeric chiral catalysts, the dendrimer architecture might offer better control of the disposition of the catalytic species than soluble polymer-based catalysts. Although a number of dendritic catalysts have been described, so far relatively few reports on catalytic asymmetric catalysis employing chiral dendritic catalysts are available.

Few dendritic BINOL ligands[145-148] have been prepared and used them as heterogeneous chiral catalysts in asymmetric ethylation of aldehydes (**Figure 1.21**).

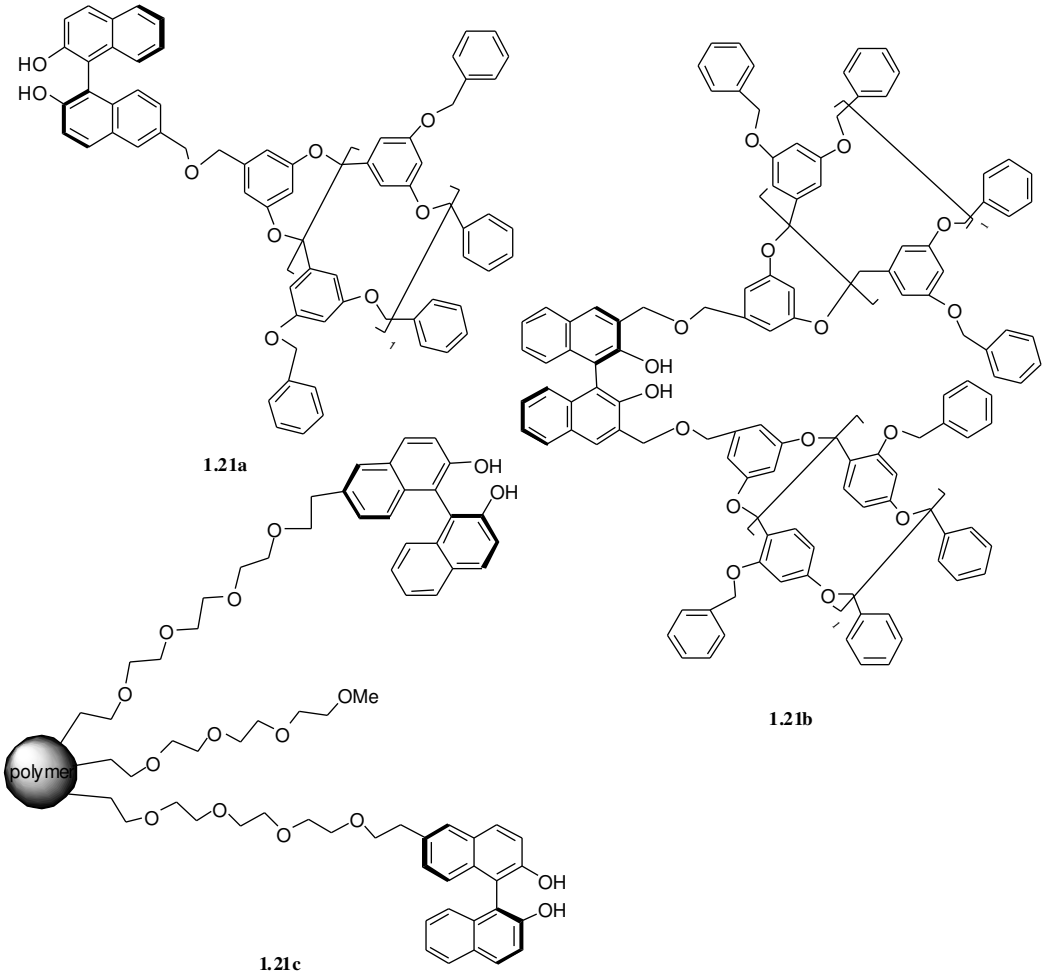



**Figure 1.21** Dendritic BINOL ligands

Other remarkable work on Monolayer-protected metal clusters (MPCs) of Au as support for immobilization of chiral BINOL was reported by Marubayashi et al.[149] (**Figure 1.22**). The synthesized BINOL-functionalized MPC gave high enantioselctivity (86%) in the case of benzyldehyde at -10 $^{o}$C.

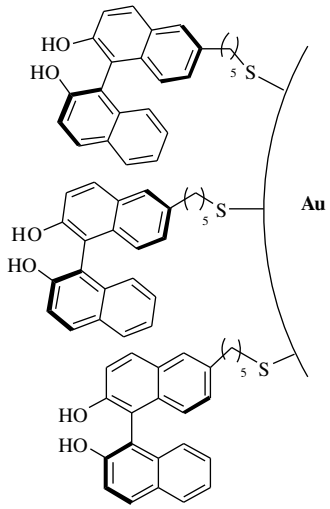



**Figure 1.22** Chiral BINOL on Au-cluster

**[iii] Use of Ionic Liquids**

Gadenne et al.[150] reported an (*S*)-BINOL containing imidazolium salt as a chiral auxiliary in the asymmetric addition of diethylzinc to benzaldehyde and showed similar catalytic properties as the non-ionic counterpart (**Figure 1.23**). The ionic substructure allows convenient recovery of the ionic compound after the reaction and can be considered as a ligand recovery vehicle. The easy-to-handle (*S*)-BINOL functionalized imidazolium salt was re-used for three reaction cycles.

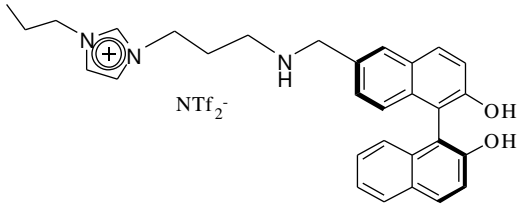



**Figure 1.23** (*S*)-BINOL functionalized with imidazolium tag

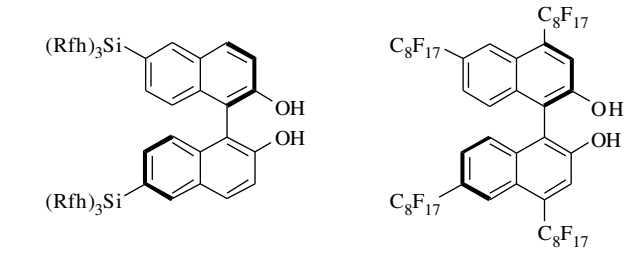
**[iv] Use of Fluorous System**

Fluorous technique is novel separation and immobilization technique that is attracting current interest in organic synthesis. Fluorinated or highly fluorinated solvents such as perfluoroalkanes are called 'fluorous solvents'. These are immiscible with typical organic solvents and water at ambient temperature. However, these organic and fluorous two phases are miscible when the temperature is elevated.

Compounds that have highly fluorinated carbon chains or perfluoroalkyl chains are dissolved in fluorous solvents.[151-154] Horvath and Ravai in 1994 introduced an innovative technique called 'fluorous biphase catalysis' approach to catalysis.[155] In this technique a metal complex bearing one or more highly fluorinated ligands is dissolved in a fluorous solvent and this solution is mixed with substrates in an organic solvent. The catalytic reaction is then affected under biphasic conditions. In a significant variant, warming renders the organic and fluorous phases miscible and the reaction occurs under homogeneous conditions. In either case, the organic phase contains the pure products, and the fluorous phase contains the catalyst at room temperature. Therefore, fluorous chiral ligands that are reusable have a potential to afford catalytic systems that fit the needs of the researchers.[114]

Nakamura et al.[156] synthesized fluorous chiral BINOL (FBINOL) (**Figure 1.24a**) and used as ligand in Ti-catalyzed asymmetric addition of diethylzinc to aromatic aldehydes in an organic and FC-73 ($CF_3(CF_2)_4CF_3$) biphase system. High enantioselectivity was achieved (up to 91%) with three times reuse. Tian et al.[157] (**Figure 1.24b**) reported BINOL substituted at the 4,4'; 6,6' and 4,4',6,6' positions with perfluoroalkyl groups and used in fluorous biphasic system for asymmetric diethylzinc

and triethyl aluminium addition to aldehydes. Enantioselectivity up to 79% has been achieved with more than eight times of reuse.



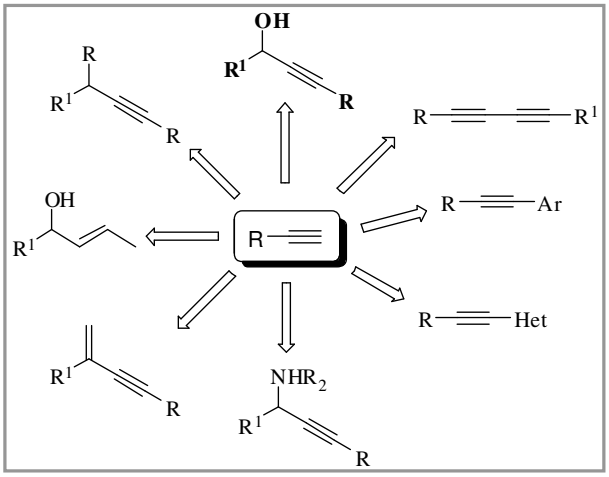

Rfh=$C_6F_{13}CH_2CH_2$- or $C_8H_{17}CH_2CH_2$-

**1.24a** **1.24b**

**Figure 1.24** Fluorous chiral BINOL (FBINOL)

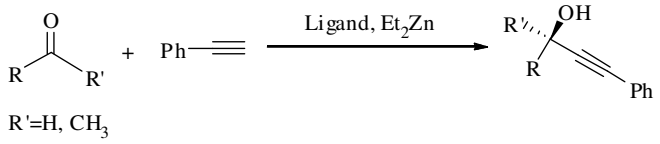
### 1.6.3. Asymmetric Phenylacetylene Addition to Carbonyls (Asymmetric Alkynylation)

The addition of nucleophiles to carbonyl substrates or imines is an important and established process in organic synthesis,[158] because new stereogenic centers and C-C bonds are formed in a single step. However, in the case of the stereo-selective catalytic version of this reaction, only a limited set of nucleophiles such as enolsilanes, allylstannanes, silanes or boranes, and dialkylzinc reagents can be used,[159] these nucleophiles have been extensively applied in the total synthesis natural products or in the preparation of useful bioactive intermediates. But they have clear disadvantages in that they are often not commercially available, difficult to prepare, and exhibit severe environmental and safety problems. In recent years alkynes have emerged as promising nucleophiles for selective and mild C-C bond forming reactions[160] (**Scheme 1.11**).




**Scheme 1.11** Alkynes used for various C-C bond formation reactions

Among the nucleophilic reactions of alkynyl-metal reagents, the addition to carbonyls is particularly useful because the resulting *secondary/tertiary* propargylic alcohols are versatile precursors to many organic molecules including natural products and pharmaceutical compounds.[161-163] This nucleophilic addition produces a new C-C bond with concomitant creation of a stereogenic center in a single transformation (**Scheme 1.12**).




**Scheme 1.12** Asymmetric phenylacetylene addition to carbonyls.

The acetylene and hydroxyl functions of the propargylic alcohol products can be used to construct very diverse molecular structures. Tan and co-workers[164] and Jiang and co-workers[165] reported asymmetric alkynylzinc addition to activated ketones for the synthesis of Efavirenz, a drug for AIDS treatment.

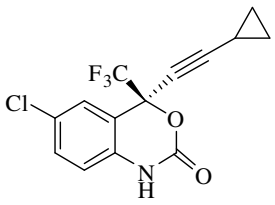



**Figure 1.25 Efavirenz**, the reverse transcriptase inhibitors for the treatment of AIDS.

### 1.6.3.1. Asymmetric Alkynylation of Carbonyls using Chiral Nitrogen Containing Ligands

There are various chiral nitrogen-containing ligands like amino alcohols, pyridyl and alkaloids that have been extensively studied in asymmetric alkynylation of carbonyls. The active chiral catalysts or reagents in the alkynylzinc additions are often generated *in situ* from the reaction of the chiral ligands with the metal precursors. Highly enantioselective catalytic as well as stoichiometric amino alcohols have been developed for these additions. Cinchonidine and pyridyl ligands containing a hydroxyl group have also shown promising results. Amine or pyridyl ligands without a hydroxyl group cannot provide good stereocontrol for the alkynylzinc additions.[161] Niwa et al.[166] reported the first example of a catalytic asymmetric addition of an alkynylzinc reagent to an aldehyde by using the enantiomerically pure amino alcohols and amines. Various chiral nitrogen containing ligands have been evaluated for asymmetric alkynylation of carbonyls (**Figure 1.26**).

Recently, Chen et al.[167] reported asymmetric phenylacetylene addition to ketones using chiral Schiff-base amino alcohol. Excellent (ee; 95%) has been achieved using 1 mol% catalyst loading at -18 $^{o}$C (**Figure 1.26j**).

Besides that, recent attempts to improve the activity and enantioselectivity of the asymmetric alkynylation lead to the development of other nitrogen containing ligands including sulfonamides[168-170] and oxazolines.[171]

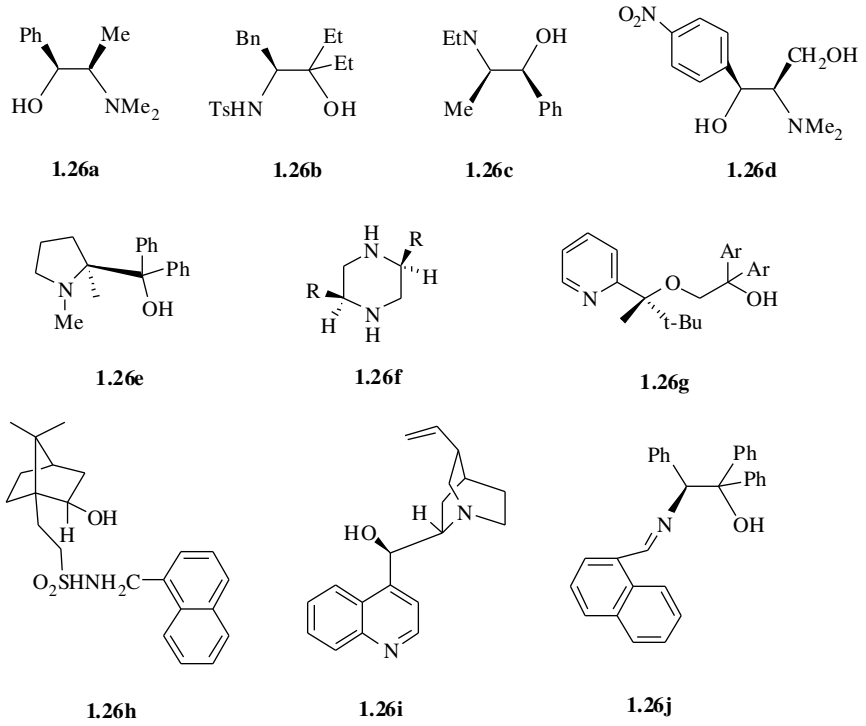



**Figure 1.26** Chiral Nitrogen-containing ligands used in asymmetric alkynylation of carbonyls

### 1.6.3.2. Asymmetric Alkynylation of Carbonyls using Chiral 1,1'-Binaphthyl Ligands

The combinations of chiral BINOL with various metal salts have been widely used in asymmetric catalysis. High enantioselectivity has also been discovered for BINOL and its derivatives in the alkynylzinc additions to aldehydes. The research groups of Pu[172] and Chan[173] were independently working on the use of BINOL for the asymmetric alkynylzinc additions (**Figure 1.27a**). They found that BINOL in

combination with $Ti(O^iPr)_4$ could effect the highly enantioselective alkynylzinc additions to aldehydes.

Previous studies revealed that chiral catalysts derived from 5,5',6,6',7,7',8,8' octahydro-1,1'-bi-2-naphthyl ligands ($H_8$BINOL) exhibited higher efficiency and enantioselectivity for many asymmetric transformations than those using BINOL ligand, probably due to the steric and electronic modulations in the binaphthyl backbone.[174] The use of $Ti(O^iPr)_4$-$H_8$BINOL catalysts in asymmetric alkynylation was also studied.[175] (**Figure 1.27b**). Various aldehydes were converted to the corresponding propargylic alcohols with very good enantioselectivity (ee; 96%) and yields. The system was also applicable to aliphatic aldehydes and moderate to good ee were obtained in most cases.

Lu et al.[178] reported asymmetric phenylacetylene addition to aldehydes using chiral ligands derived from combination the structure of 1,1'-binaphthyl and amino alcohols. Excellent (ee; 90%) was achieved for the reaction of *o*-bromobenzyldehyde. However, vary low enantioselectivity was observed with aliphatic aldehydes (**Figure 1.27c & Figure 1.27d**). Further 3,3'-substituted chiral binaphthyl ligands were also used in asymmetric phenylacetylene addition to aldehydes even without use of titanium complex.[176,177] High enantioselectivity (80-94%) was achieved with range of aromatic aldehydes (**Figure 1.27e & Figure 1.27f**).

Anther interesting work has been reported by Li et al.[179] using chiral BINOL-salen ligand for enantioselective alkyne additions to aromatic aldehydes. Excellent enantioselectivity (ee; 9'7%) was achieved without addition of $Ti(O^iPr)_4$ (**Figure 1.27g**).

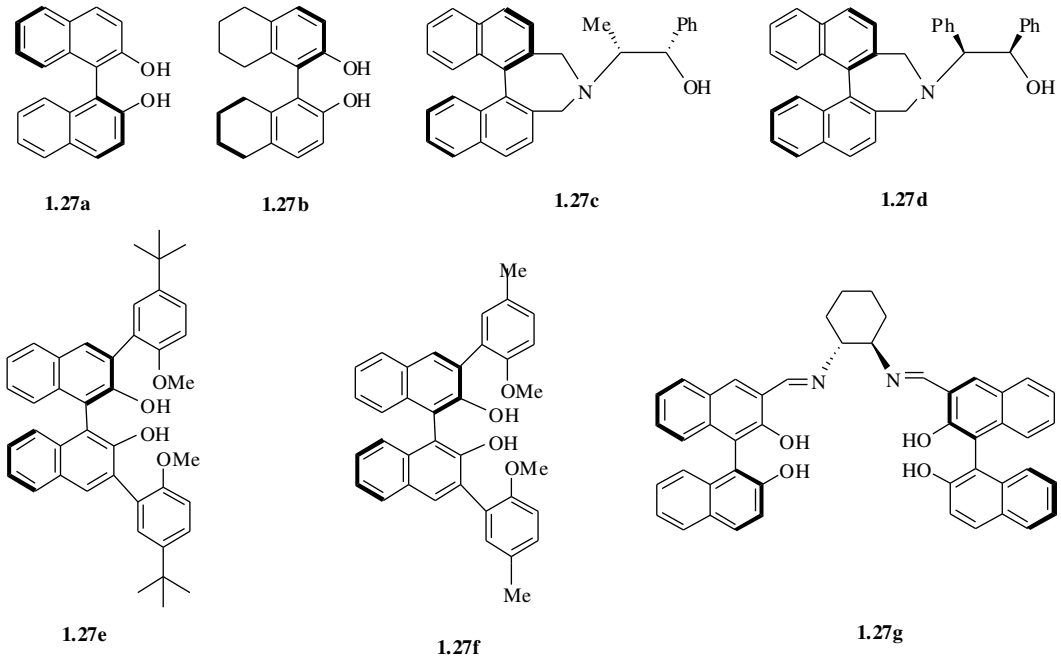
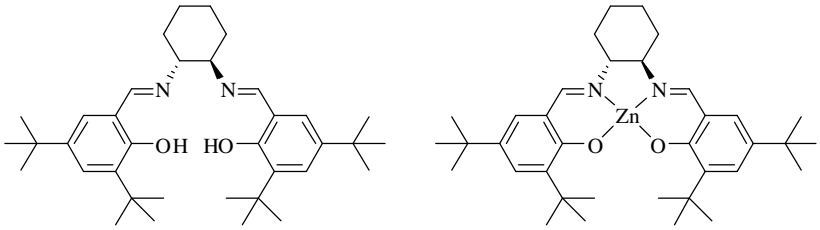



**Figure 1.27** Chiral 1,1'- Binapthyl based ligand used in asymmetric alkynylation

### 1.6.3.3. Asymmetric Alkynylation of Carbonyls using Chiral Salen Ligands

The chiral salen ligand system plays a distinct role in asymmetric catalysis that impart high levels of enantioselectivity in many diverse organic transformations.[9,52] Besides, it can also behave as a bifunctional Lewis acid-Lewis base catalyst. In this direction, Zn(salen) complexes were used earlier in asymmetric diethylzinc addition to aldehydes reported by Cozzi et al.[180] and Kozlowski et al.[181] In 2003, Cozzi[182] reported enantioselective alkynylation of ketones by Zn(salen) complex as catalyst at room temperature (**Figure 1.28b**). Corresponding chiral *tertiary* propargylic alcohol was obtained in 61% ee and 72% yield. High enantioselectivity (up to 81%) was achieved while using various alkynes to different ketones.




**1.28a** **1.28b**

**Figure 1.28** Chiral salen ligand and Zn (salen) complex

## 1.7. Kinetic Resolution of Racemic Compounds

Among the numerous synthetic methods that are capable of producing chiral substances with high enantiomeric excess values, kinetic resolution (KR) has the distinction of being the oldest. KR is also unique among the available methodologies because it allows the preparation of samples that are enantiomerically pure, well beyond the assay limits of modern analytical techniques.[183] Another distinction of KR is that, it can be applied to virtually every class of chiral substrates and can be used in combination with all methods of enantioselective synthesis. The definition of KR according to the 1996, IUPAC recommendation follows: "The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, solvent, etc.)".[184]

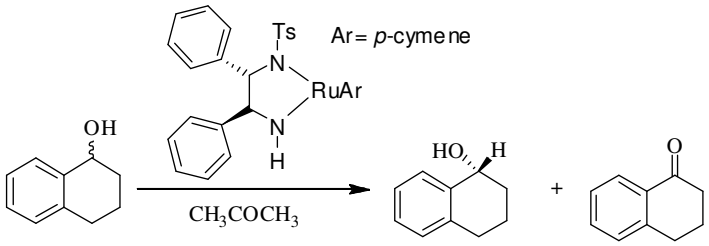
For the production of enantiomerically pure substances, KR is generally regarded as a poor cousin to asymmetric synthesis. Kinetic resolution (KR) suffers from the disadvantage that at least half of the starting material is lost. There is one striking advantage KR holds over asymmetric synthesis. The enantiomeric excess (ee) realized in asymmetric synthesis simply a consequence of the energy difference $\Delta\Delta G^{\#}$ between two

diastereomeric transition states; the only way to improve the % ee is to increase that energy difference (see section 1.3). KR too depends on there being an energy difference between diastereomeric transition states, but the manner in which that energy difference is expressed is unique to kinetic resolutions. The energy difference, manifested as a relative rate difference, represents a constant and unrelenting differential pressure upon the two enantiomers. This process should continue until the last molecule of more reactive enantiomer is swept away and one is left with a substance possessed of absolute enantiomeric purity. This concept of being able to achieve absolute enantiomeric purity in kinetic resolutions by removal of the last molecule of the fast reacting enantiomer has attracted chemists to use it as a tool for the preparation of optically active compounds.

### 1.7.1. Oxidative Kinetic Resolution (OKR) of Racemic Secondary Alcohols

Although excellent catalytic enantioselective methods exist for a variety of oxidation processes such as epoxidation,[185,186] dihydroxylation,[187,188] and aziridination,[189] there are relatively few catalytic enantioselective examples of ubiquitous alcohol oxidation.[190-192] There has been considerable interest in kinetic resolutions that are based on the oxidation of a chiral secondary alcohol to a prochiral ketone, as the (achiral) product of the reaction can usually be recycled to the racemic starting material by simple hydride reduction. In principle, product recycling allows improved material recovery with greater efficiency. In this direction, enzyme-catalyzed kinetic resolution through selective reaction towards one of the enantiomers has been extensively studied.[71,193-196] In recent years, attempts were made for the development of versatile chiral catalysts for non-enzymatic kinetic resolution. A recent advance in this regard is the catalytic oxidative kinetic resolution of secondary alcohols.

The first broadly applicable method for kinetic resolution of alcohols was reported by Noyori and co-workers using chiral Ru catalyst for benzylic alcohols (**Scheme 1.13**) in the presence of acetone as the ultimate stoichiometric hydride acceptor,[197] this reaction is essentially the reverse of the Noyori hydrogenation of ketones, a transformation that employs the same catalyst in the presence of isopropanol as the stoichiometric hydride donor.



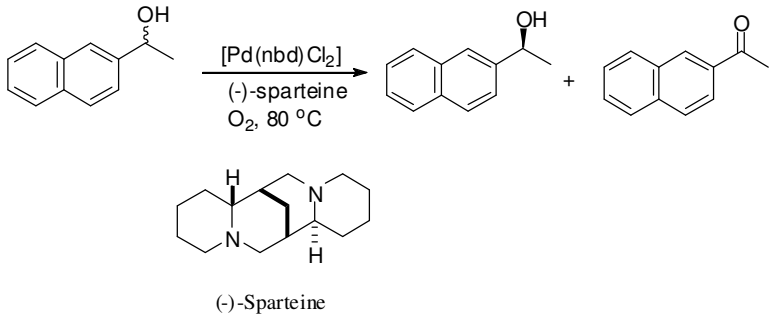

**Scheme 1.13** Chiral Ru(II) catalyzed oxidative kinetic resolution of racemic 1,2,3,4-tetrahydronaphthyl alcohol

Various chiral metal complexes as catalysts have been evaluated for OKR of racemic secondary alcohols which are discussed in details below:

### 1.7.2. Oxidative Kinetic Resolution (OKR) of Racemic Secondary Alcohols using Chiral Metal Complexes as Catalysts

Pd-catalyzed kinetic resolution of secondary alcohols that uses naturally occurring diamine [(–)-sparteine] as chiral auxiliary and molecular oxygen as a terminal oxidant has been reported.[198-201] The use of molecular oxygen in combination with a catalytic metal complex has exceptional advantages for applications in organic synthesis. This is partly due to the favorable economics associated with molecular oxygen and the formation of environmentally benign byproducts in the oxidation manifold (water and $H_2O_2$).

Excellent enantioselectivity (>99%) of chiral secondary alcohols were achieved with Pd-(–)-sparteine as catalyst (**Scheme 1.14**).




(-)-Sparteine

**Scheme 1.14** Pd-(–)-sparteine catalyzed oxidative kinetic resolution 1-Naphthylalcohol

Nishibayashi et al.[202] reported oxidative kinetic resolution of racemic secondary alcohols by using acetone as a hydrogen acceptor in the presence of a catalytic amount of [$RuCl_2(PPh_3)$(ferrocenyloxazolinylphosphine)] (**Figure 1.29**) which proceeds effectively to recover the corresponding alcohols in high yields with an excellent . Optically active 1-indanol in good yield with high enantioselectivity (ee; up to 94%) was also achieved with turnover frequency (TOF) that exceeds 80,000 $h^{-1}$.

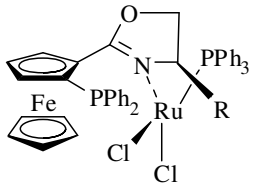
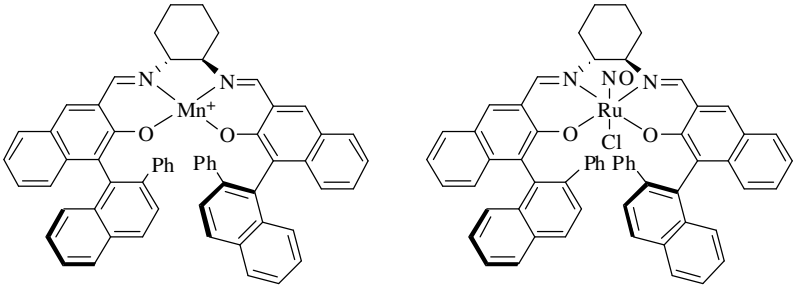



**Figure 1.29** $RuCl_2(PPh_3)$(ferrocenyloxazolinylphosphine) complex

Katsuki and co-workers[203] have reported the use of BINOL-derived Mn(salen) complexes as catalysts with PhIO as an oxidant, however, only low yields and moderate enantioselectivity were achieved. Later, the same group reported BINOL-derived

Ru(salen) complexes[204] in the photo-induced aerobic oxidation of racemic secondary alcohols. In this system though alcohols with high enantioselectivity was achieved, the reaction time was too long (**Figure 1.30**).




**1.30a** **1.30b**

**Figure 1.30** BINOL-derived Mn(salen) and Ru(salen) complexes

Xia et al.[205,206] have reported OKR of racemic secondary alcohols with chiral Mn(salen) catalysts with excellent enantioselectivity using iodobenzene diacetate ($PhI(OAc)_2$) as an oxidant in the presence of bromide salts in water-organic solvent system (**Figure 1.31**). The bromide salt is required for the activation of $PhI(OAc)_2$ to carry out the oxidative kinetic resolution of alcohols in the presence of water-organic solvent system. High enantioselectivity (>99%) of chiral secondary alcohols was achieved using $PhI(OAc)_2$ as an oxidant and KBr as an additive.

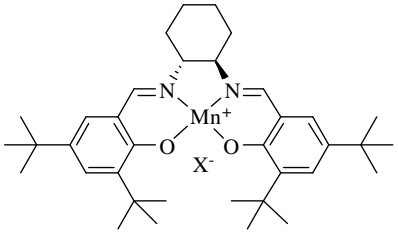



**Figure 1.31** Chiral Mn(III) salen complex

## 1.8. Summary of the Work done in the Present Thesis

With the state-of-the-art in asymmetric catalysis as described in preceding sections, the present thesis deals with two different strategies for achieving recyclable chiral catalysts based on BINOL and salen ligands. Suitably designed ligands were complexed with appropriate metal ions and were used as recyclable chiral catalysts for asymmetric C-C bond forming reactions and oxidative kinetic resolution of racemic secondary alcohols.

**(A)** Silica based chiral recyclable catalysts:

- Immobilization of chiral BINOL on mesoporous silicas with varying pore size and their use as catalysts in asymmetric addition of diethylzinc to aldehydes.

**(B)** Non-silica based chiral recyclable catalysts:

- Chiral dimeric/polymeric metal salen complex as recyclable catalysts for asymmetric addition of phenylacetylene to carbonyl compounds and oxidative kinetic resolution of racemic secondary alcohols.

**(A) Silica based Chiral Recyclable Catalysts**

Inorganic silica supports have many advantages over organic polymers due to their superior mechanical & thermal stability and less polymer swelling characteristics thus avoiding structural changes which normally take place in organic polymers during recovery and re-use steps in catalysis.[73] The ordered mesoporous materials[97,98] are potentially promising supports for immobilizing the homogeneous catalysts for chiral synthesis on two accounts. Firstly, the pore size distribution of ordered mesopores is uniform and in the range of 2–20 nm that can accommodate or assemble various chiral

molecules/catalysts; therefore, the mesopores could act as a nanoreactor for chiral synthesis. The molecular size of most fine chemicals and pharmaceutical compounds fall in this range. Secondly, the hydrothermal stability of silica materials is good enough since the chiral synthesis is usually carried out under mild reaction conditions. Moreover, the pore size and inner environment of the pore can be chemically modified to fine tune the confinement effect for improved.[73]

**Chapter 2**: ***Immobilization of chiral BINOL on mesoporous silicas (MCM-41 and SBA-15) and their use as catalysts in asymmetric addition of diethylzinc to aldehydes.***

This chapter deals with the immobilization of chiral BINOL on inorganic solid supports such as MCM-41 and SBA-15 (**Figure 1.32,** *the figure given in parenthesis represents the serial number of the ligand/catalyst synthesized for the present study*), their use as catalysts in an important C-C bond formatting reaction-asymmetric addition of diethylzinc to aldehydes. The characterization of immobilized ligands was done by microanalysis, XRPD, FT-IR, $^{13}C$ CP MAS and $N_2$ sorption studies. We also minimized undesired catalytic activity on the silica surface by the capping of free hydroxyl groups present on silica surface with trimethylsilyl (TMS) groups[207] by treating these with hexamethyldisiloxane (HMDS) at reflux temperature. The active heterogeneous catalysts for enantioselective addition of diethylzinc to various aldehydes were generated *in situ* by the interaction of silica-bound BINOL and $Ti(O^iPr)_4$. SBA-15 immobilized ligands, which have larger pore size than MCM-41 gave better results by facilitating the diffusion of reactants and the products. The catalyst **SBA-BINOL-CAP(4)** with capping of free silanol moiety with TMS groups was found to be more active with better (ee; up to 81%). The regeneration of the catalyst was effectively carried out by washing with 10%

HCl in methanol. After washing, the regenerated catalyst with fresh reactants worked well up to two cycles with the retention of enantioselectivity.

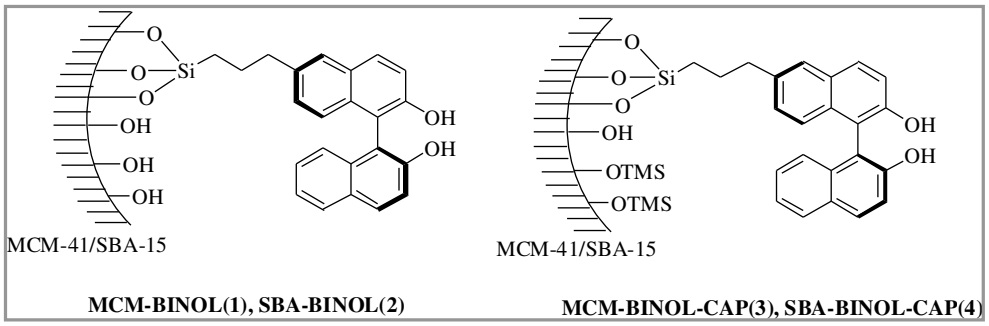



**Figure 1.32** Chiral BINOL immobilized on MCM-41 and SBA-15

**Chapter 3**: ***Immobilization of chiral BINOL on large pore sized mesoporous silicas (SBA-15 and MCF) and their use as catalysts in asymmetric addition of diethylzinc to aldehydes***

We have seen earlier that the pore size of the support has significant impact on the activity and enantioselctivity in asymmetric addition of diethylzinc to aldehydes. Hence, we synthesized silica supports with larger pore sizes. We also visualized that if we increase the distance between the catalyst and walls of the support by way of increasing the length of the linkage there could be increase in enantioselectivity and reactivity by creating catalyst environment more akin to homogeneous system. Accordingly, we synthesized chiral BINOL ligand immobilized onto larger pore size SBA-15 and MCF silica and used them as chiral solid auxiliary in Ti-promoted asymmetric addition of diethylzinc to aldehydes under heterogeneous reaction conditions. For the present work, we have synthesized the siliceous SBA-15 of large pore diameter (7.5 nm) by using amphiphillic triblock copolymer P123 as a structure-directing agent, while for MCF (mesocellular foam) synthesis; mesitylene was used as a swelling agent. MCF[98] is a novel mesoporous material with unique advantages

as a solid support for catalysts. MCF has a surface area of 500–800 $m^2/g$, and a 3-dimensional pore structure with ultra large, cell-like pores (23–42 nm) that are connected by windows of 9–22 nm. Such a pore structure would minimize any steric effects associated with the immobilization of bulky molecules, and facilitate the diffusion of large substrates. To increase linkage length, *N*-methyl-3-aminopropyltriethoxysilane (NMAPTES) was used as a reactive surface modifier. After successful surface modification, modified chiral BINOL ligand was immobilized on surface modified silicas to give supported ligands. We have also modified the accessible free silanol sites of the silicas with TMS groups to give desired supported ligands **SBA-BINOL-CAP(5)** and **MCF-BINOL-CAP(6)** (**Figure 1.33**).

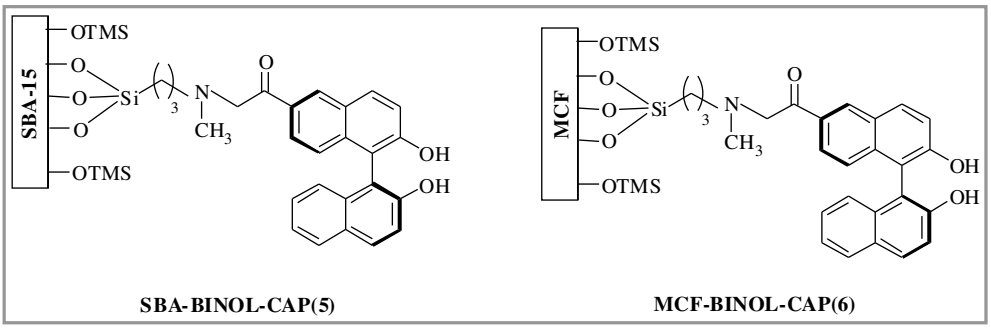



**Figure 1.33** Chiral BINOL immobilized on SBA-15 and MCF

Excellent conversion (99%) with high chiral induction (up to 94% ee) was achieved in the case of benzaldehyde with catalyst **MCF-BINOL-CAP(6)**. The overall performance was better for large pore sized MCF based catalyst than SBA-15 based catalyst. We presume that the better performance of the MCF-supported catalyst might be due to the relatively large pore size that allows increased accessibility of the substrates

and reactants and minimize the diffusional limitation. Hence, chiral BINOL immobilized on silica-SBA-15 and MCF gave higher ee values in the asymmetric alkylation of aldehydes than MCM-41 based catalysts. Moreover, immobilized chiral catalysts could be recycled in multiple catalytic runs with retention of enantioselectivity.

**(B) Non-Silica based Chiral Recyclable Catalysts**

An alternate strategy to achieve the virtues of heterogeneous catalyst while still performing reactions under homogeneous condition was also accomplished by tuning the solubility of catalyst. This was achieved by way of increasing the molecular weight of the catalyst with increase in active catalytic sites (copolymerization technique) so that the catalysts would be insoluble in non polar solvent like hexane.[78-80] With such catalysts, the catalytic runs were conducted under homogeneous condition (the catalysts are soluble in the reaction media) and the catalyst was easily retrieved from the reaction medium by precipitating it out upon the addition of hexane followed by filtration. This methodology avoids several synthetic steps needed for making the ligand suitable for its immobilization on to solid supports. We have synthesized dimeric and polymeric salen based metal complexes for their use as recyclable catalysts in the asymmetric phenylacetylene addition to the carbonyl compounds and oxidative kinetic resolution of racemic secondary alcohols.

**Chapter 4**: ***Chiral polymeric Zn(salen) complex as recyclable catalyst for asymmetric phenylacetylene addition to carbonyl compounds.***

The fourth chapter of the thesis deals with synthesis of new polymeric Zn(salen) complex **Polycy-Zn(7) (Figure 1.34)** that was employed in the enantioselective phenylacetylene addition to aldehydes and ketones to produce corresponding chiral secondary propargylic alcohols with yields (up to 96%) and (ee; up to 72%) and *tertiary* propargylic alcohols with yields (up to 79%) and (ee; up to 68%) at room temperature. This complex was derived from poly[(*R, R*)-*N, N*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine}cyclohexene-1,2-diamine].[80] The interesting feature of this novel polymeric Zn salen complex lies in its inherent tendency to get precipitated in a non-polar solvent

system like n-hexane due to its higher molecular weight and lower solubility. We have recovered the catalyst, which worked well up to four cycles with marginal loss in reactivity due to some physical loss during post work up process with retention of  of propargylic alcohols.

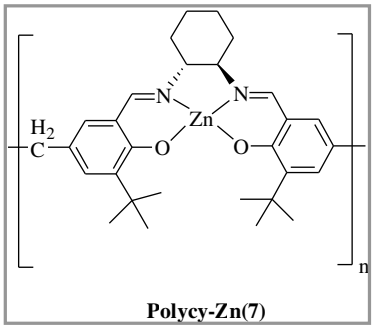



**Figure 1.34** Chiral **polycy-Zn(7)** complex

**Chapter 5**: ***Chiral dimeric Mn(III) salen complexes as recyclable catalysts for oxidative kinetic resolution of racemic secondary alcohols.***

The fifth chapter of the thesis deals with oxidative kinetic resolution (OKR) of racemic alcohols catalyzed by chiral dimeric Mn(III) salen complexes as recyclable catalysts. OKR is potentially attractive method to achieve optically active alcohols together with corresponding carbonyl compounds. However, BINOL-derived Ru(salen) and Mn(salen) complexes earlier used for the enantioselective oxidation of racemic secondary alcohols showed moderate success.[202,203] Recently Xia et al.[204,205] reported OKR of racemic secondary alcohols with chiral Mn(salen) catalysts with excellent enantioselctivity in homogeneous conditions. However, recyclable catalyst based on salen ligand for OKR of racemic alcohols has not been reported so far in the literature.

Chiral dimeric Mn(III) salen complex **Dimercy-MnCl(8)** was synthesized according to the reported procedure,[78] while changing counterion with OAc [**Dimercy-MnOAc(9)**] and **Dimerdph-MnCl(10)** complex (**Figure 1.35**) were synthesized and characterized by various physico-chemical techniques. These complexes were used in oxidative kinetic resolution of racemic secondary alcohols using $PhI(OAc)_2$ as an oxidant and KBr as an additive at room temperature. Various racemic secondary alcohols have been studied in this present work. Excellent enantioselectivity (ee; up to 99%) of chiral secondary alcohols was achieved in 30-60 minutes. The effect of solvents, additives and catalysts loadings on activity and enantioselectivity of the catalytic system was also studied. The catalysts were easily recovered by precipitation and were re-used up to five times with some loss of activity while there was no loss of enantioselectivity in the product.

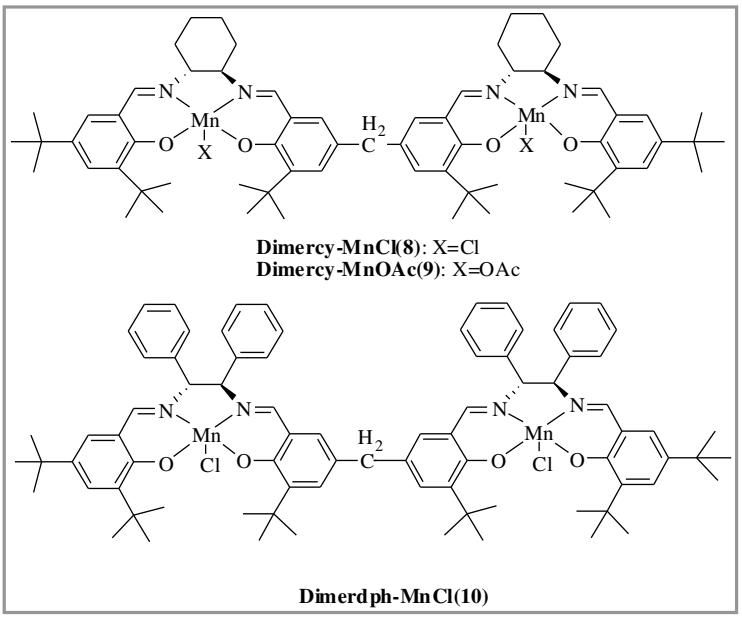



**Figure 1.35** Chiral dimeric Mn(III) salen complexes.

**Chapter 6**: ***Easily recyclable chiral polymeric Mn(III) salen complexes for oxidative kinetic resolution of racemic secondary alcohols.***

We have earlier studied the performance of recyclable dimeric Mn(III) salen complexes used in oxidative kinetic resolution of aldehydes. In this chapter, we have used chiral polymeric Mn(III) salen complexes (**Figure 1.36**) as an effective and easily recyclable catalysts for oxidative kinetic resolution of racemic secondary alcohols at room temperature using $PhI(OAc)_2$ as an oxidant. Chiral polymeric complexes **Polycy-MnCl(11)** and **Polydph-MnCl(13)** were synthesized according to previously reported procedure,[80] while complex **Polycy-MnBr(12)** was synthesized and characterized by various physicochemical methods. High chiral purity (ee; >99%) was achieved for the oxidative kinetic resolution of racemic secondary alcohols with 0.6 mol% catalyst loading in 60 minutes in the presence of various additives in water/organic solvent mixture at room temperature. The catalyst was easily recycled for successive five catalytic experiments.

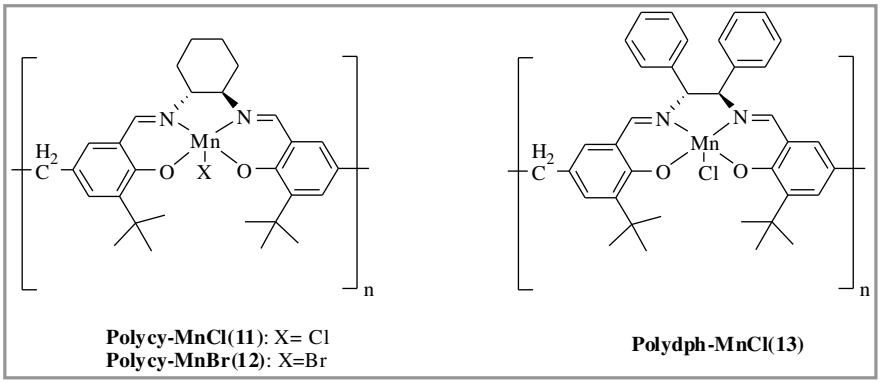



**Figure 1.36** Chiral polymeric Mn(III) salen complexes.

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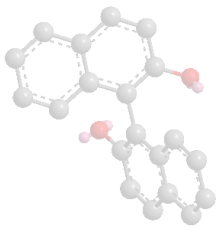


# Chapter -2

## Immobilization of Chiral BINOL on Mesoporous Silicas (MCM-41 and SBA-15) and their use as Catalysts in Asymmetric Addition of Diethylzinc to Aldehydes.

## 2.1. Introduction

Chiral ligands embodying the binaphthyl framework such as BINOL and BINAP have earned a prominent status due to their versatility in catalytic asymmetric reactions.[1,2] Chiral BINOL based metal complexes are extensively studied catalysts for various asymmetric transformations under homogeneous reaction conditions.[3-5] In recent years, heterogenization of homogeneous catalysis has attracted considerable attention because it greatly simplifies the separation of the catalyst from the reaction mixture and allows the efficient recovery and re-use of the expensive chiral catalyst.[6-8]

The asymmetric addition of dialkylzinc to aldehydes is one of the most important and vigorously pursued areas in the asymmetric C-C bond formation that afford chiral secondary alcohols as synthetically and pharmaceutically useful compounds.[9,10] A plethora of chiral ligands including β-amino alcohols, TADDOL and BINOL have been extensively reported to be catalytically active towards this reaction, with enantioselectivity ranging from mediocre to excellent.[11] Due to its economic importance of catalytic asymmetric addition of $Et_2Zn$ to aldehydes, immobilized version of homogeneous catalysts has attracted intense research activity in recent years.[8] In this direction, some attempts have been made for the heterogenization of chiral BINOL on organic polymers by grafting it onto polymer back bone,[12-15] cross-linking co-polymerization,[16-18] dendrimers,[19-21] monolayer protected Au cluster,[22] ionic liquid[23] and fluorous biphasic system[24-26] for their use as catalyst in $Et_2Zn$ addition reaction.

Ordered mesoporous solids like MCM-41 and SBA-15, with their well-defined uniform mesopores and facile surface modification, are potential materials for heterogenization of valuable chiral homogeneous catalyst.[27,28] Various ligand systems

such as β-amino alcohols based N-alkylnorephedrine, ephedrine and proline immobilized on inorganic supports have also been investigated for enantioselective addition of $Et_2Zn$ to aldehydes.[29-33] Immobilization of BINOL on inorganic siliceous supports has been reported scarcely for other reactions.[34,35] However, the literature was devoid of any report utilizing chiral BINOL on inorganic support as catalyst for dialkyzinc addition to aldehydes.

In this chapter, we are reporting here, the immobilization of chiral BINOL ligand covalently bonded to mesoporous silica such as MCM-41 and SBA-15. The active heterogeneous catalyst for enantioselective addition of $Et_2Zn$ to various aldehydes were generated in situ by the interaction of bonded BINOL ligand with $Ti(O^iPr)_4$. The study deals with (a) strategy to support chiral BINOL on mesoporous silicas, (b) catalytic activity of these supported catalysts, (c) minimizing undesired catalytic activity on the silica surface by capping of free hydroxyl groups of silica surface with TMS groups,[36] and (d) regeneration of the expensive chiral catalyst.

## 2.2. Experimental

### 2.2.1. Materials & Methods

Cetyltrimethylammonium bromide (CTAB) (s.d. Fine Chem. Ltd., India), sodium silicate solution (Kadvani Chemicals, India) were used as received. Tetraethyl orthosilicate (TEOS), triblock organic copolymer ($EO_{20}$-$PO_{70}$-$EO_{20}$) Pluronic P123, benzaldehyde, *m*-methoxybenzaldehyde, *p*-fluorobenzaldehyde, $Et_2Zn$ (1 M in hexane), $Ti(O^iPr)_4$ and hexamethyldisiloxane (HMDS) were purchase from Aldrich Chemical and used without further purification. (*S*)-BINOL was purchased from Fluka. All catalytic

experiments were carried out under an atmosphere of dry nitrogen. All the solvents used in the present study were purified by the known methods.[37]

### 2.2.2. Synthesis of Mesoporous Silica

#### 2.2.2.1. Synthesis of Siliceous MCM-41

A highly ordered hexagonal siliceous MCM-41 was synthesized according to the modified procedure of Das et al.[38] by hydrothermal crystallization method. The sodium silicate (27.34% $SiO_2$ and 8.05% $Na_2O$) was used as a silica source and CTAB as a template. In a typical synthesis, CTAB was dissolved in warm (40-45 $^oC$) de-ionized water and to this solution; the required quantity of sodium silicate solution was added while stirring. The pH of the mixture thus obtained was adjusted to 10 with 1:1 $H_2SO_4$: $H_2O$ v/v followed by vigorous stirring. The resulting gel was placed in Teflon Parr high-pressure reactors for crystallization at 110 $^oC$ for 144 h. The solid was filtered, washed thoroughly with de-ionized water till the pH was 7-8. It was air dried at room temperature and calcined in air at 550 $^oC$ for 6 h.

#### 2.2.2.2. Synthesis of Siliceous SBA-15

Highly ordered mesoporous SBA-15 was synthesized using a procedure reported by Zhao et al.[39] under hydrothermal conditions using a triblock organic copolymer as a template. In a typical synthesis, 12 g of triblock, poly(ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) ($EO_{20}$-$PO_{70}$-$EO_{20}$) (Pluronic P123, mw 5800) was dispersed in 90 g of double-distilled water to which 360 g of 2 M aqueous HCl was added under stirring at ambient temperature (25-30 °C) for 1 h. Finally, 27 g of silica source TEOS was added to the homogeneous solution under stirring to form a gel at 313 K for 24 h, and this was allowed to stand for crystallization under static hydrothermal conditions at

373 K for 48 h in a Teflon Parr reactor. The crystallized product was filtered off, washed with warm distilled water, dried at 383 K, and finally calcined at 813 K in air for 6 h to remove the template. The calcined SBA-15 was characterized by powder XRD analysis.

### 2.2.3. Synthesis of Chiral Ligand Precursors

The synthesis of chiral ligand precursors is described as follows.

#### 2.2.3.1. (*S*)-2-Hydroxy-2'-pivaloyloxy-1,1'-binaphthyl (2)

The compound **2** was synthesized according to the procedure.[40] (*S*)-BINOL **1** (4.0 g, 14.0 mmol), $(C_2H_5)_3N$ (5.9 mL, 42.0 mmol) and pivaloyl chloride (1.68 g, 14.0 mmol) were taken in $CH_3CN$ (45 mL) at 0 °C. The mixture was allowed to warm till it reached rt at which it was stirred for 6h. Crude mixture was dissolved in diethyl ether and washed with aq. 1N HCl (20 mL), saturated aq. $NaHCO_3$ (20 mL) and brine. Organic phase was dried over anhydrous $Na_2SO_4$ and filtered. Evaporation of the solvent afforded the desired product that was purified by column chromatography (silica gel, n-Hexane/EtOAc (60:40)) to give **2** (Yield; 4.96 g, 96%); IR (KBr): 3414, 2969, 1720, 1509, 1280, 1154, 813 $cm^{-1}$; $^1H$ NMR((200 MHz, $CDCl_3$): δ 0.75 (s, 9H), 5.08 (s, 1H), 7.01 (d, *J*= 8.4 Hz, 1H), 7.15–7.34 (m, 6H), 7.46 (t, *J*= 5.8 Hz, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 8.8 Hz, 1H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 27.31, 39.59, 115.10, 119.0, 122.69, 123.94, 124.37, 125.4, 126.50, 127.10, 127.54, 128.28, 128.76, 129.18, 129.89, 131.13, 131.55, 133.05, 134.37, 134.51, 149.19, 152.65, 178.66 ppm; Anal. calcd for ($C_{25}H_{22}O_3$): C, 81.08; H, 5.95, Found: C, 80.91; H, 5.90%. $[\alpha]_D^{27}$=-54.5 (c=0.5,THF)

**2.2.3.2. (*S*)-6-Bromo-2-hydroxy-2'-pivaloyloxy-1,1'-binaphthyl (3)**

The compound **3** was synthesized according to the reported procedure.[40] To a solution of **2** (4 g, 10.8 mmol) in $CH_3CN$ (50 mL) was added bromine (1.10 mL, 21.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h, quenched with aqueous $Na_2SO_3$ and extracted with diethyl ether. The organic phase was washed sequentially with saturated aq. $NaHCO_3$, aqueous 1N HCl, brine and dried over anhydrous $Na_2SO_4$. After removal of the solvent **3** was obtained as white solid (Yield, 3.92 g, 98%); IR (KBr): 3404, 2969, 1720, 1494, 1152, 815, 489, 422 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 0.76 (s, 9H), 5.13 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 7.20–7.35 (m,5H), 7.48 (td, *J*1 = 7.2 Hz, *J*2 = 1.2 Hz, 1H), 7.75 (d, *J* = 8.8 Hz, 1H), 7.92 (m, 2H), 8.04 (d, *J* = 8.8 Hz, 1H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 27.32, 39.59, 115.36, 118.15, 119.0, 120.26, 122.66, 126.22, 127.14, 128.41, 129.24, 130.17, 130.72, 131.81, 133.0, 133.78, 134.07, 134.90, 135.1, 149.16, 153.0, 178.61 ppm; Anal. calcd for ($C_{25}H_{21}O_3Br$): C, 66.82; H,4.67, Found: C, 66.12; H, 4.50%; $[\alpha]_D^{27} = 5.99$ (c=0.52, THF).

**2.2.3.3. (*S*)-6-Bromo-2,2'-dihydroxy-1,1'-binaphthyl (4)**

A mixture of **3** (3.5 g, 7.78 mmol), KOH (1.3 g, 23 mmol), THF (25 mL) and water (10 mL) was stirred for 16 h at ambient temperature under $N_2$. The reaction mixture was diluted with EtOAc and the organic phase was washed with aqueous 1N HCl (25 mL), saturated aq. $NaHCO_3$, and brine in that order. The organic phase was then dried over $Na_2SO_4$ and concentrated in vacuum to give **4** as a yellow solid. (Yield; 2.8 g, 98%); IR (KBr): 3476, 3401, 1587, 1496, 1144, 816, 749, 421 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 4.94 (s, 1H), 5.04 (s, 1H), 6.99 (d, *J* = 8.0 Hz,1H), 7.05 (d, *J* = 7.2 Hz, 1H), 7.25–7.37 (m, 5H), 7.48 (t, *J* = 5.8 Hz, 1H), 7.82–7.85 (m, 2H), 7.93 (d, *J* = 8.6 Hz, 1H),

8.0 (s, 1H) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$): δ 111.05, 112.11, 118.25, 118.91, 119.85, 124.20, 124.65, 126.3, 127.98, 128.65, 130.10, 130.61, 131.11, 132.40, 132.65, 133.10, 133.65, 133.9, 153.0, 153.5 ppm; Anal. calcd for ($C_{20}H_{13}O_2Br$): C, 65.76; H, 3.56, Found: C, 65.60; H, 3.45%; $[\alpha]_D^{27}$= 6.35 (c=0.55, THF).

**2.2.3.4. (*S*)-6-Bromo-2,2'-dimethoxy-1,1'-bi-naphthyl (5)**

To a solution of **4** (2.5 g, 6.84 mmol) in anhydrous acetone (80 ml) were added anhydrous $K_2CO_3$ (2.83 g, 20.5 mmol) and methyl iodide (2.91 g, 20.5 mmol) at room temperature and the mixture was refluxed for 18 h under dry reaction condition. The solvent was completely removed under vacuum and the residue was dissolved in $CH_2Cl_2$ (80 ml) and $H_2O$ (70 ml). The aqueous layer was further extracted with $CH_2Cl_2$ (3 x 20 ml). The combined organic layer was dried over anhydrous $Na_2SO_4$. After the removal of the solvent the pale yellow product was washed with methanol to get **5** as white solid (Yield; 2.34g, 87 %); IR (KBr): 2933, 1586, 1492, 1265, 1251, 807, 749 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 3.75 (s, 6H), 6.94 (d, *J*=9.2 Hz, 1H), 7.11 (d, *J*=9.2 Hz, 1H), 7.18-7.27 (m, 3H), 7.47 (d, *J*=9 Hz, 2H), 7.84 (d, *J*=6.6 Hz, 1H), 7.89 (d, *J*=5.7 Hz, 1H), 7.95 (d, *J*=10.8 Hz, 1H), 8.01 (d, *J*=2.8 Hz, 1H) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$): δ 57.3, 110.1, 111.3, 117.1, 118.2, 123.8, 124.0, 125.7, 127.1, 128.3, 129.5, 129.8, 130.2, 130.6, 130.8, 131.3, 132.3, 152.1, 152.7 ppm; Anal. Calcd. ($C_{22}H_{17}BrO_2$): C, 67.17; H, 4.33, Found: C, 67.02; H, 4.30%; $[\alpha]_D^{27}$= 48.1 (c=0.5, $CHCl_3$)

**2.2.3.5. (*S*)-6-(1-Propyltrimethoxy silane)-2,2'-dimethoxy-1,1'-binaphthyl (6)**

Magnesium turnings (0.92 g, 38 mmol), 65 ml of dried and degassed THF and a crystal of iodine were allowed to react with **5** (2 g, 5.8 mmol) in 15 ml of THF under dry and argon atmosphere for 30 min at ambient temperature followed by its gentle refluxing

for 9 h. The resulting mass was cooled to room tempreture and a solution of 3-chloropropyltrimethoxysilane (1.15 gm, 1 equivalent in 25 ml of dry THF) was added drop-wise over a period of 40 min. The reaction mixture was then refluxed for 12 h and the solvent was distilled out completely under an inert atmosphere. Dry toluene (30 ml) was added to the resulting residue that was stirred for 2 h and filtered under inert atmosphere to afford **6** in solution. The compound **6** is highly moisture sensitive; hence an aliquot from the above solution was taken for spectroscopic characterization, while rest of the solution was directly used for subsequent synthesis. $^{1}$H NMR (200 MHz, $CDCl_3$): δ 0.92 (broad t, *J*= 7, 2H), 0.75-0.85 (m, 2H), 1.84 (broad t, *J*= 7Hz, 2H), 3.56 (s, 9H), 3.75 (s, 6H), 6.95 (d, *J*= 9Hz, 1H), 7.02 (d, *J*= 9Hz, 1H), 7.17-7.35 (m, 3H), 7.42 (d, *J*= 3.8 Hz, 1H), 7.48 (d, *J*= 3.5Hz, 1H), 7.84 (d, *J*= 8.5Hz, 1H), 7.88 (d, *J*= 9Hz, 1H), 7.95 (d, *J*= 9Hz, 1H), 8.0 (d, *J*= 2Hz, 1H) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$): δ 7.4, 8.7, 26.9, 47.8, 50.9, 51.3, 114.9, 115.8, 124.0, 125.6, 125.9, 126.7, 126.8, 127.0, 127.5, 127.8, 128.5, 128.6, 129.1, 129.4, 130.0, 130.2, 130.4, 130.5, 149.9, 150.1 ppm; Anal. Calcd. ($C_{28}H_{32}O_5Si$) : C, 70.58; H, 6.72, Found: C, 70.12; H, 6.44%.

**2.2.4. Immobilization of Modified BINOL (6) on Mesoporous Silicas (7, 7')**

Calcined MCM-41/SBA-15 (1.8 g) was added to the above-synthesized solution of **6** and the suspension was allowed to stir at reflux temperature under argon atmosphere for 48 h. After cooling, the powder was collected by filtration, washed successively with dry toluene, and then dried under vacuum. Dried material was subjected to soxhlet-extraction with $CH_2Cl_2$ for 24 h. Finally the sample was dried under vacuum at 45-50 $^{o}$C. Yield; 1.85 g; IR (KBr): 3439, 2959, 2857, 2358, 1635, 1439, 1251, 1084, 964, 807, 796, 689, 558, 461 $cm^{-1}$; Anal. Found: C, 5.0; H, 0.88%.

**2.2.4.1. Removal of the Protecting Groups (MCM-BINOL(1), SBA-BINOL(2))**

2,2'-Dimethoxy-1,1'-bi-naphthalene supported silicas **7** and **7'** (2.0 g) was taken in dried $CH_2Cl_2$ (20 ml) and cooled to -78 $^oC$. $BBr_3$ (3ml, 3.0 mmol, 1M solution in $CH_2Cl_2$) was added to the cooled suspension drop-wise with continuous stirring for 2 h. After that the reaction mixture was brought to room temperature, stirred for additional 2 h and an aqueous saturated solution of $NaHCO_3$ was slowly added to it. The resulting solid was filtered off, washed successively with water, acetone and $CH_2Cl_2$, and finally dried at 55 $^oC$ under vacuum for 10 h. Yield; 1.93 g, IR (KBr): 3418, 2959, 2358, 1636, 1383, 1231, 1076, 963, 800, 579, 454 $cm^{-1}$; Anal. Found: C, 6.7; H, 0.51%.

**2.2.4.2. End-capped of Silanol groups (Trimethylsilylation) (MCM-BINOL-CAP(3), SBA-BINOL-CAP(4))**

In an extremely dry condition, a suspension of **7/7'** (0.5 gm), $(CH_3)_3SiCl$ (TMSCl) (10 gm), and $((CH_3)_3Si)_2O$ (HMDS) (15 gm) were refluxed overnight with stirring under argon atmosphere. The volatiles were stripped on a rotary evaporator and the dry powder was washed 2 or 3 times with 10 ml dry acetone by centrifugation and finally dried under vacuum at 75-80 $^oC$ for 6 h. Material recovery was >98%. After successful TMS capping of compound **7** & **7'**, resulting compounds were demethylated using 1M $BBr_3$, to get desired compounds **MCM-BINOL-CAP(3), SBA-BINOL-CAP(4)** (**Scheme 2.1**). IR (KBr): 2963, 2361, 1627, 1236, 1085, 840, 457 $cm^{-1}$; Anal. Found: C, 9.92; H, 2.35%.

**2.2.5. General Procedure for Enantioselective Addition of $Et_2Zn$ to Aromatic Aldehydes**

Immobilized ligands (8 mol %) dried under vacuum for 6 h at 110 $^oC$ was taken in 2 ml dry toluene and was stirred with $Ti(O^iPr)_4$ (1.5 mmol) for 2h at room temperature

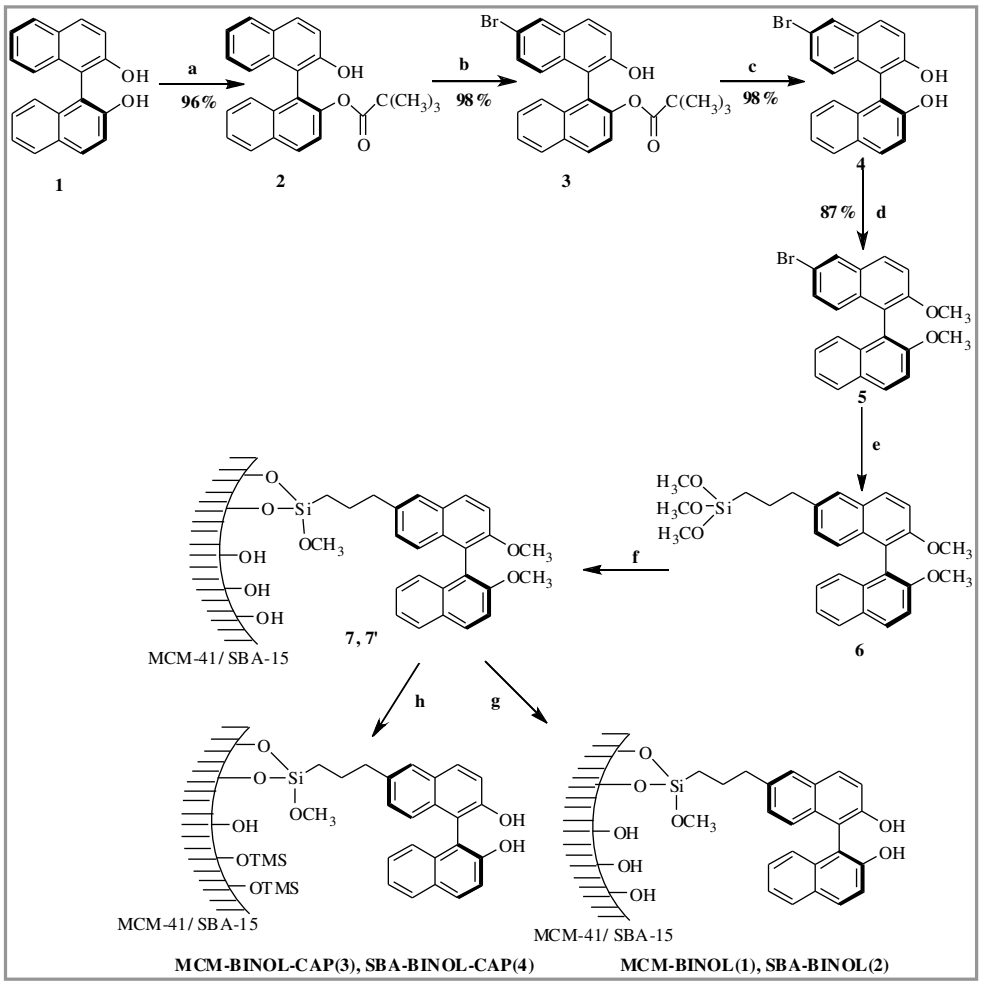
under an argon atmosphere. To the above suspension a solution of $Et_2Zn$ (1 M solution in hexane, 3.0 mmol) was added, cooled to 0 $^oC$, added appropriate aromatic aldehyde (1.0 mmol) and the resulting mixture was stirred for 24 h at 0 $^oC$. The progress of the catalytic reaction was monitored on HPLC. After completion of the reaction, the immobilized catalyst was filtered off from the reaction mixture, washed with toluene, dried under vacuum and kept for reuse experiments. The filtrate and combined washings were quenched with saturated $NH_4Cl$ solution (10 ml), washed with water and dried over anhydrous $Na_2SO_4$. It was filtered and concentrated to provide colorless oil, which was analyzed on HPLC chiralcel OD column to determine the optical purity.

## 2.3. Results and Discussion

### 2.3.1. Synthesis and Characterization of Immobilized Chiral BINOL

In order to retain the flexibility of the free BINOL and to develop the catalyst system akin to the structure that was used under homogeneous condition, we synthesized **MCM-BINOL(1), SBA-BINOL(2)** and **MCM-BINOL-CAP(3), SBA-BINOL-CAP(4)** according to the steps shown in (**Scheme 2.1**). Thus monoesterification of **1** was achieved leading to the formation of compound **2** in excellent selectivity. Bromination of **2** yielded exclusively mono-brominated product with the bromine attached on $6^{th}$ position of the non-esterified naphthyl moiety **3**. The brominated product on saponification afforded (*S*)-6-monobromo-1, 1'-bi-2-naphthol **4**. Protection of hydroxyl groups of **4** with $CH_3I$ under basic condition, yielded (*S*)-6-bromo-2, 2'-dimethoxy-1, 1'-bi-naphthyl **5**. To achieve covalent grafting to mesoporous silica, the compound **5** was treated with $Mg/I_2$ and 3-chloropropyltrimethoxysilane to get *O*-methylated BINOL with a silanol arm **6.** The

compound **6** was then refluxed with calcined MCM-41/SBA-15 in toluene to afford **7/ 7'**. Demethylation of compounds **7** and **7'** afforded **MCM-BINOL(1)** and **SBA-BINOL(2)** respectively. Also, silica matrix bears many hydroxyl groups that may possibly react with Ti metal ions to create non-chiral catalyst sites on silica support. Therefore, in order to understand the role of hydroxyl groups belonging to silica's compounds **7** and **7'** were capped with TMS groups and then demethylated to give solid ligands **MCM-BINOL-CAP(3)** and **SBA-BINOL-CAP(4)**.




**Scheme 2.1** The synthetic route for the anchoring of BINOL with functional groups onto silica surface: reagents and conditions–(a) Pivaloyl chloride, $Et_3N$, $CH_3CN$, 0 °C; (b) $Br_2$, $CH_3CN$, 0 °C, 3 h; (c) KOH, $H_2O$, THF, rt, 24 h; (d) $CH_3I$, $K_2CO_3$, acetone, 18 h; (e) (i) $Mg/I_2$, THF, reflux, 9 h; (ii) Chloropropyltrimethoxysilane, toluene, reflux, 12 h; (f) calcined MCM-41/SBA-15, toluene, 48 h; (g) $BBr_3$, $CH_2Cl_2$, -78 °C; (h) (i) HMDS, reflux, 12h; (ii) $BBr_3$, $CH_2Cl_2$, -78 °C

The characterization of the mesoporous silicas supported ligands were accomplished by various physico-chemical techniques. The grafted amount of chiral auxiliary was found to be 16-18 mg/100mg of solid support calculated from elemental analysis and thermal gravimetric data. **Figure 2.1** and **2.2** show FT-IR spectra of immobilized ligands on mesoporous silica. The characteristic bands of $CH_2$ for aliphatic C-H stretching vibrations at 3000-2900 $cm^{-1}$ and bands at ~1465 and 1454 $cm^{-1}$ due to C=C stretching vibration of the attached BINOL group implying that the modified BINOL was covalently grafted to the mesoporous silicas. Further, the FT-IR spectra for **MCM-BINOL-CAP** and **SBA-BINOL-CAP** showed remarkable reduction in the intensity of –OH band at ~3432 $cm^{-1}$ due to the capping of -Si-OH with TMS (**Figure 2.1(c)** & **2.2 (c')**).

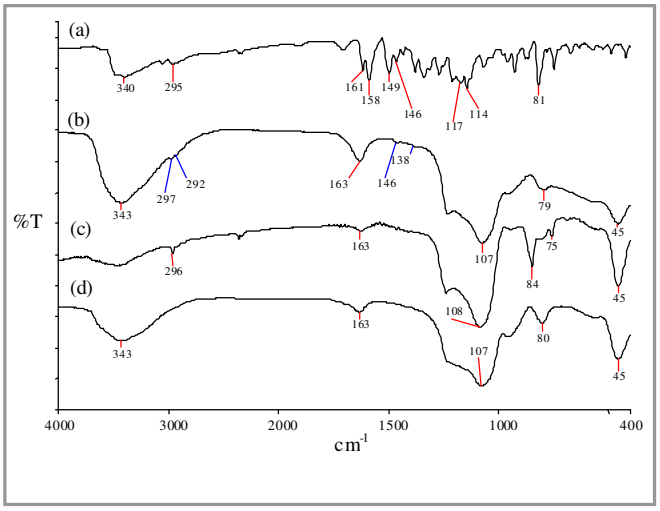



**Figure 2.1** FT-IR Spectra of ligand **4** (a), ligand **MCM-BINOL(1)** (b), ligand **MCM-BINOL-CAP(3)** (c), calcined MCM-41(d).

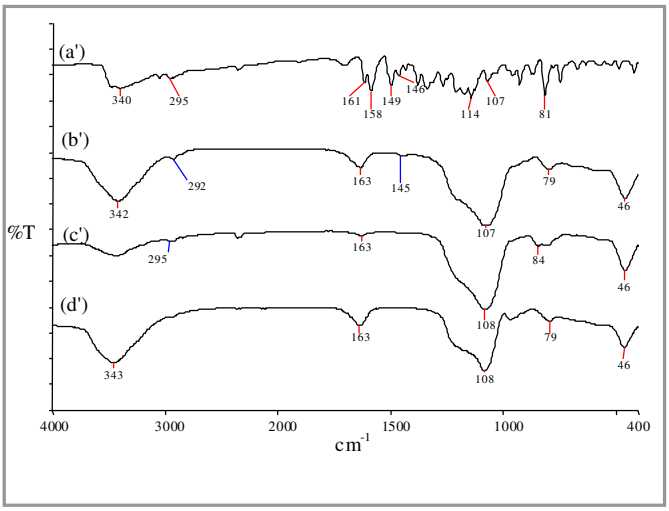



**Figure 2.2** FT-IR Spectra of ligand **4** (a'), ligand **SBA-BINOL(2)** (b'), ligand **SBA-BINOL-CAP(4)** (c'), calcined SBA-15 (d')

$^{13}$C CP MAS NMR spectra of immobilized modified BINOL on SBA-15 peaks in the range δ = 8-35 ppm due to the propyl group of silanol arm and δ = 109-155 ppm aromatic carbons due to naphthyl groups of BINOL respectively, additionally support our view of successful anchoring of BINOL on mesoporous silicas[15] (**Figure 2.3**).

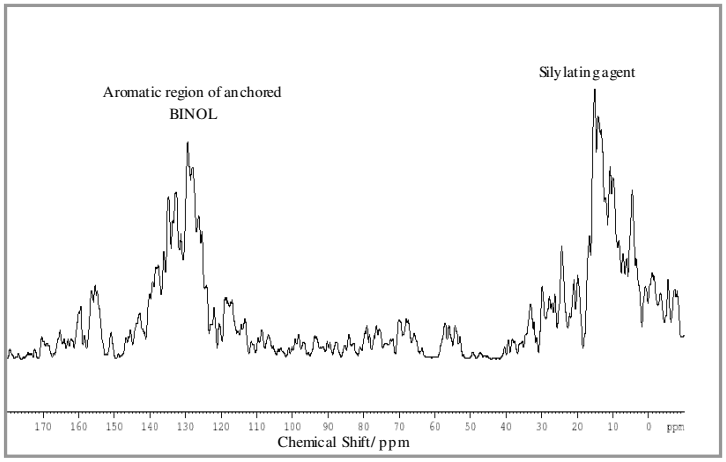



**Figure 2.3** $^{13}$C MAS NMR spectra of ligand **SBA-BINOL(2)**

The degree of orderness and mesoporous structure of all siliceous and modified mesoporous materials were determined by powder X-ray diffraction (XRPD). **Figure 2.4 & 2.5** show powder XRD patterns of MCM-41 and SBA-15 samples respectively. The XRPD patterns of siliceous MCM-41 and SBA-15 show characteristic low angle reflections of hexagonal space group (*p6mm*) mesophase (**Figures. 2.4** & **2.5**, (a) & (a')). After immobilization of chiral auxiliary confirmed structure hexagonal space group (*p6mm*) of inorganic supports remain preserved after immobilization and even after successive reuse experiments.

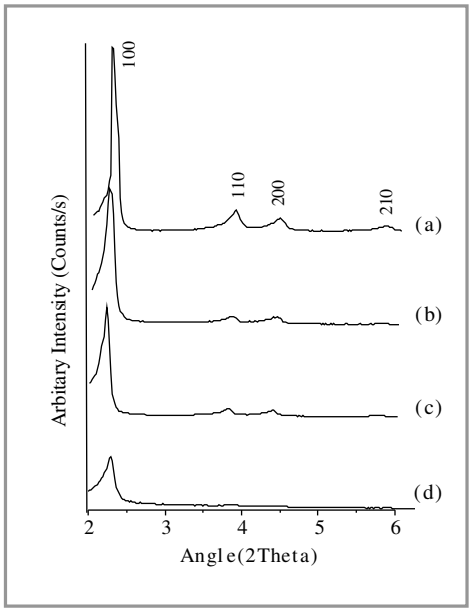



**Figure 2.4** XRPD patterns of calcined MCM-41 (a), ligand **MCM-BINOL(1)** (b), ligand **MCM-BINOL-CAP(3)** (c), reused catalyst (d)

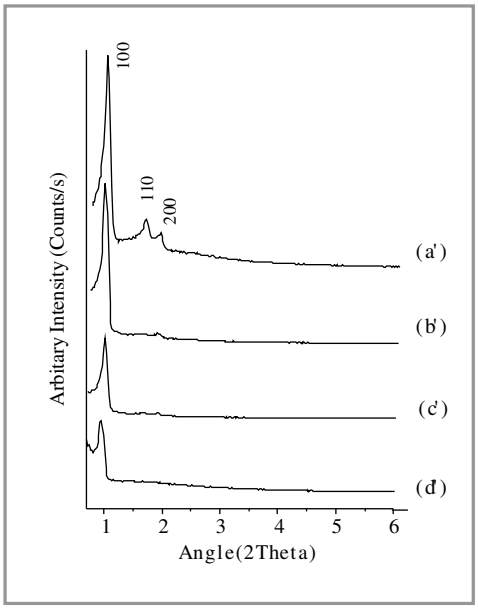



**Figure 2.5** XRPD pattern of calcined SBA-15 (a'), ligand **SBA-BINOL(2)** (b'), ligand **SBA-BINOL-CAP(4)** (c'), reused catalyst (d')

The textural characteristics of this supported chiral ligand were accomplished by $N_2$ sorption study. Typical adsorption and desorption isotherm (type IV) were retained

after immobilization of the organic functions on the surface, the conservation of the same type of isotherms indicates that the structure of the inorganic surface remain intact after modification (**Figures 2.6 to 2.9**). However, a decrease in BET surface area ($S_{BET}$), total pore volume and BJH average pore diameter were observed that can attributed due to the presence of chiral BINOL auxiliary in the mesopores that partially blocks the adsorption of nitrogen molecules (**Table 2.1**).

**Table 2.1** Textural characterization of mesoporous silica and immobilization of BINOL during various synthetic steps.

| Compound | BET surface area ($m^2/g$) | Total Pore volume ($cm^3/g$) | BJH Pore Diameter (Å) |
|---|---|---|---|
| MCM-41 | 998 | 0.9875 | 35 |
| **MCM-BINOL(1)** | 864 | 0.6142 | 29 |
| **MCM-BINO-CAP(3)** | 842 | 0.5142 | 26 |
| SBA-15 | 797 | 1.1327 | 68 |
| **SBA-BINOL(2)** | 493 | 0.6768 | 63 |
| **SBA-BINOL-CAP(4)** | 443 | 0.5667 | 59 |

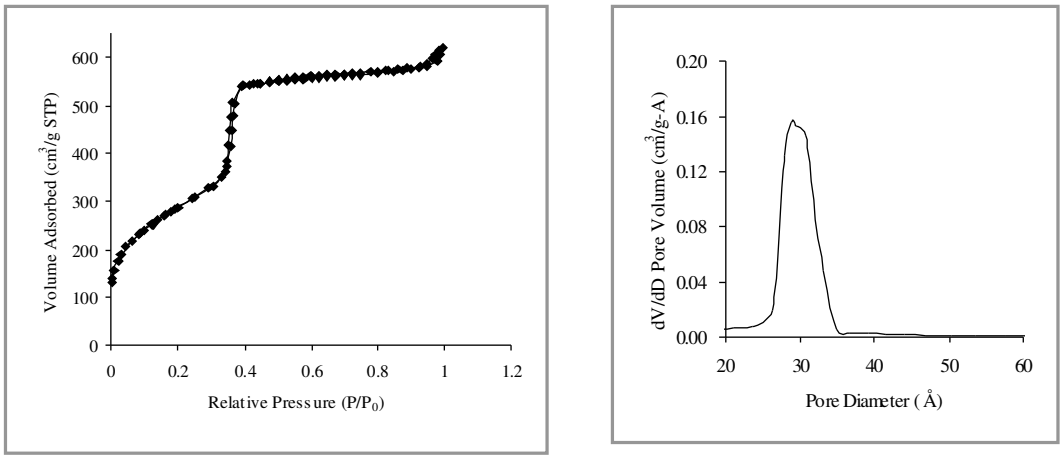



**Figure 2.6** $N_2$ Adsorption-desorption isotherm and pore diameter and relative pore volume of calcined MCM-41

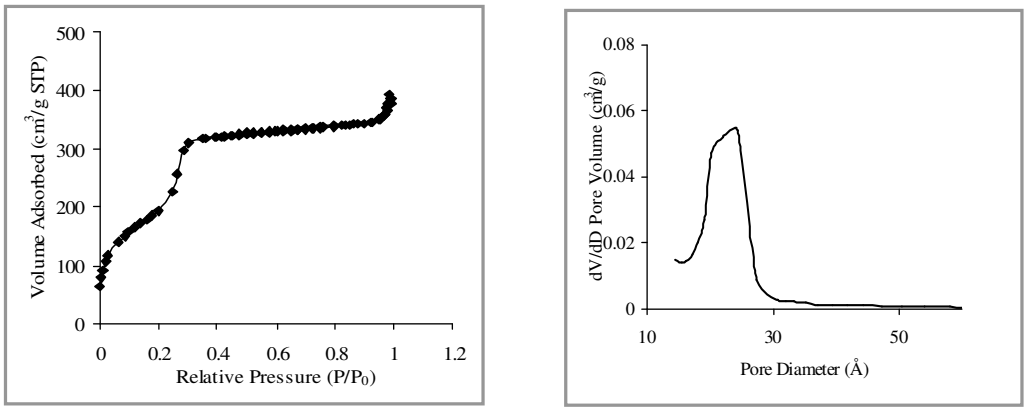



**Figure 2.7** $N_2$ Adsorption-desorption isotherm and pore diameter and relative pore volume of immobilized **MCM-BINOL-CAP (3)**

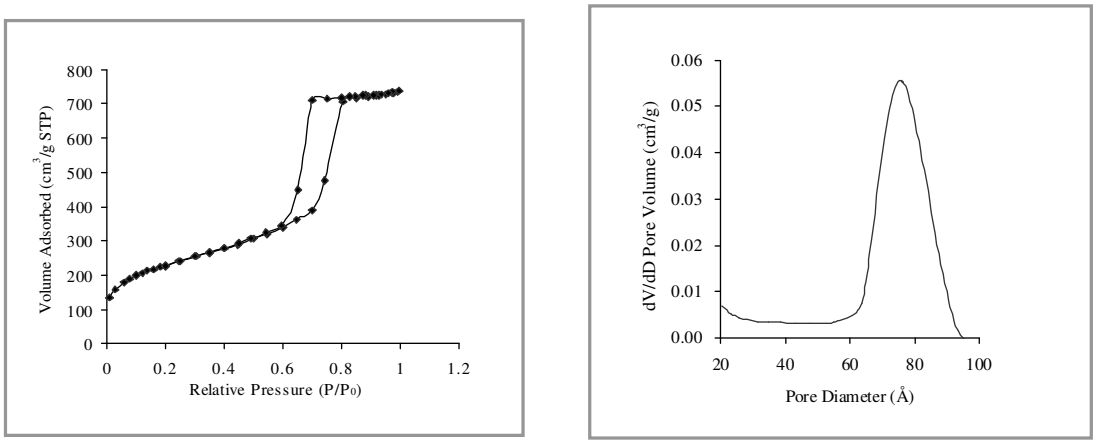



**Figure 2.8** $N_2$ Adsorption-desorption isotherm and pore diameter and relative pore volume of calcined SBA-15

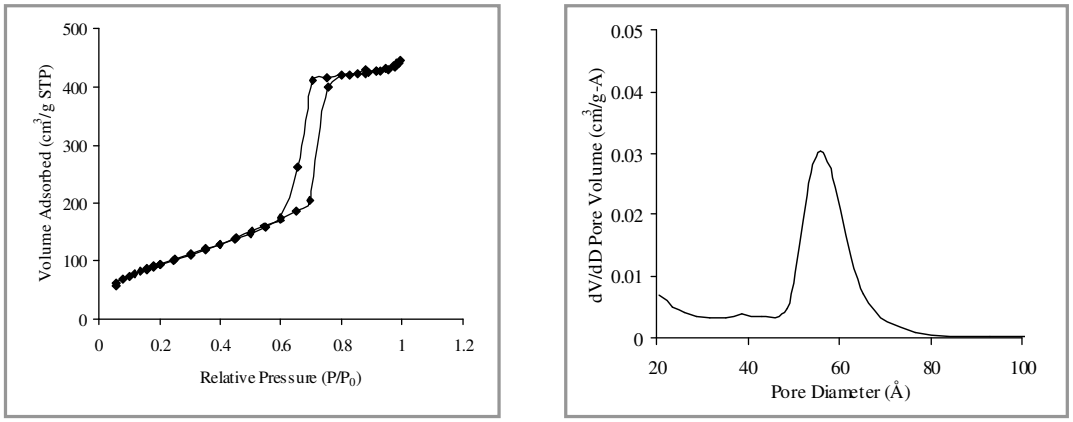



**Figure 2.9** $N_2$ Adsorption-desorption isotherm and pore diameter and relative pore volume of immobilized **SBA-BINOL-CAP (4)**

SEM micrographs (**Figure 2.10)** revealed that MCM-41 and SBA-15 samples consist of small agglomerates whose morphology did not change in the supported catalysts **MCM-BINOL-CAP(3)** and **SBA-BINOL-CAP(4)**.

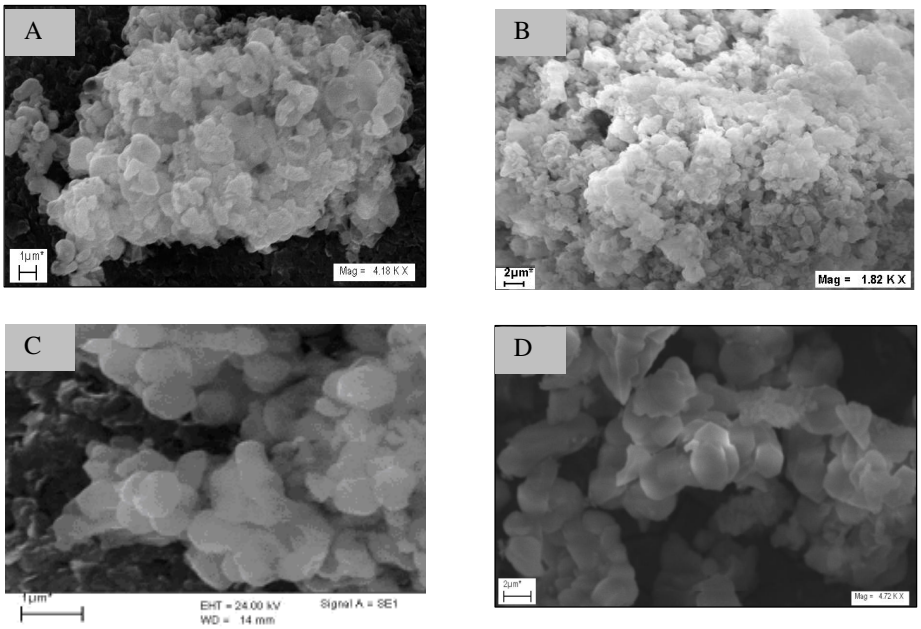



**Figure 2.10** SEM micrograph of MCM-41 and SBA-15 samples calcined MCM-41(A), **MCM-BINOL-CAP(3)** (B), calcined SBA-15(C), **SBA-15-BINOL-CAP(4)**(D)

TEM micrographs of purely siliceous SBA-15 showed 2D hexagonal symmetry. (**Figure 2.11** (A)). The ordered mesoporous structure of support was remained preserved on immobilization of chiral BINOL and also after reused of the supported catalyst. (**Figure 2.11** (B) & (C)).

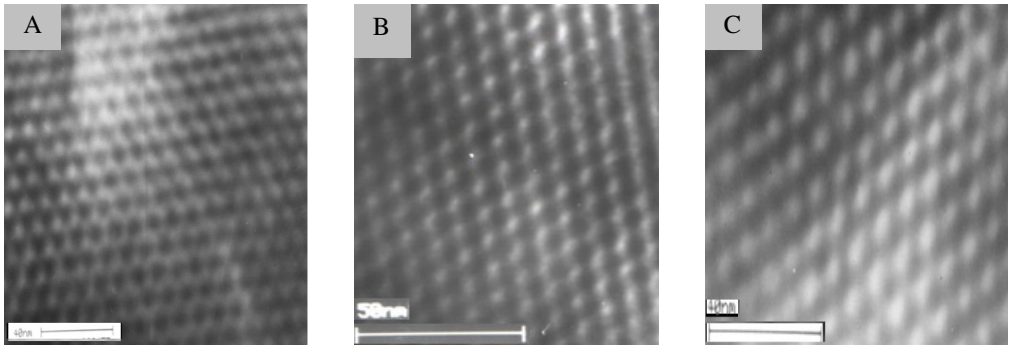



**Figure 2.11** TEM images of calcined SBA-15 (A), ligand **SBA-BINOL-CAP(4)** (B), reused **SBA-BINOL-CAP(4)** (C)

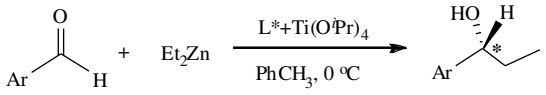
### 2.3.2. Enantioselective Addition of $Et_2Zn$ to Aldehydes

Enantioselective addition of $Et_2Zn$ to various aldehydes like benzaldehyde, 3-methoxybenzaldehyde and 4-fluorobenzaldehyde was carried out using immobilized chiral modified BINOL-Ti complex generated in situ to give respective secondary alcohols (**Table 2.2**). To compare the catalytic efficacy of immobilized catalyst, we used ligand **4** as catalyst precursor under homogeneous condition by keeping other reaction parameters constant for the enantioselective addition of $Et_2Zn$ to various aldehydes to give excellent conversion (95-99%), selectivity (95-100%) and enantioselectivity (88-89%) for the secondary alcohols (entries 1, 6, 11) in 7 h. However, when the same reaction was conducted with MCM-41 immobilized ligand **MCM-BINOL(1)** under heterogeneous condition, a conversion of (78-88%) with selectivity (80-89%) and enantioselectivity (37-45%) was obtained for the respective secondary alcohols (entries 2, 7, 12) in 24 h. The longer reaction time under heterogeneous condition was possibly due to the slow diffusion of reactants to the catalytic sites in mesopores of silica.

SBA-15 immobilized ligand **SBA-BINOL(2)** however gave conversion up to 94% with high selectivity 92% and good enantioselectivity 69% in the product 1-phenyl-

1-propanol using benzaldehyde as a substrate (entry 4). This improvement over MCM-41 based catalyst was attributed to the bigger pore size of the SBA-15 support facilitating the diffusion of reactants. Significant improvement in conversion (82-98%), selectivity (87-99%) and enantioselectivity (ee; 51-81%) (entries 3, 5, 8, 10, 13, 15) were observed when TMS-capped silicas (**MCM-BINOL-CAP(3)** & **SBA-BINOL-CAP(4)**) were used as catalyst precursor for the addition of diethyl zinc with various aldehydes under heterogeneous reaction condition. The over all performance was better for larger pore sized SBA-15 supported catalyst **SBA-BINOL(2), SBA-BINOL-CAP(4)** than MCM-41 based catalyst **MCM-BINOL(1)**, **MCM-BINOL-CAP(3)**. Highest enantioselectivity (ee; 81%) was achieved with ligand **SBA-BINOL-CAP(4)** (entry 5) with conversion and selectivity nearly similar to homogeneous catalytic system**.** The catalytic activity of the TMS capped silica without a chiral ligand showed only 10 % conversion of the product under the similar reaction conditions (entry 16). This residual activity of the silica is possibly causing a reduction of the enantioselectivity.[32]

**Table 2.2** Enantioselective addition of $Et_2Zn$ to aromatic aldehydes using (*S*)-BINOL-Ti complexes[a]




| Entry | ArCHO | L* | Conversion[b] (%) | Selectivity[c] (%) | Ee[d] (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5CHO$ | **4** | 99 | 100 | 89 |
| 2 | | **MCM-BINOL(1)** | 82 | 88 | 45 |
| 3 | | **SBA-BINOL(2)** | 90 | 92 | 62 |
| 4 | | **MCM-BINOL-CAP(3)** | 94 | 92 | 69 |
| 5 | | **SBA-BINOL-CAP(4)** | 98 | 99 | 81 |
| 6 | *m*-$OCH_3C_6H_4CHO$ | **4** | 95 | 95 | 88 |
| 7 | | **MCM-BINOL(1)** | 78 | 80 | 37 |
| 8 | | **SBA-BINOL(2)** | 82 | 87 | 51 |
| 9 | | **MCM-BINOL-CAP(3)** | 76 | 80 | 58 |
| 10 | | **SBA-BINOL-CAP(4)** | 86 | 90 | 70 |
| 11 | *p*-$FC_6H_4CHO$ | **4** | 97 | 98 | 89 |
| 12 | | **MCM-BINOL(1)** | 88 | 89 | 41 |
| 13 | | **SBA-BINOL(2)** | 90 | 91 | 57 |
| 14 | | **MCM-BINOL-CAP(3)** | 90 | 93 | 63 |
| 15 | | **SBA-BINOL-CAP(4)** | 96 | 98 | 78 |
| 16[e] | $C_6H_5CHO$ | **TMS capped SBA-15** | 10 | - | - |

[a]Reactions were carried out with 8 mol % of **4** for 7 h (entry 1, 6, 11) under homogeneous and immoblized ligands for 24 h under heterogeneous reaction conditions using 1.5 mmol $Ti(O^iPr)_4$, 3.0 mmol $Et_2Zn$ and 1.0 mmol substrate in 2 ml toluene at 0 °C. [b]Determined by $^1H$ NMR spectroscopy. [c]%Selectivity: 100 ([*R*] + [*S*]) / ([*R*] + [*S*]+[$PhCH_2OH$]). [d]Determined by HPLC using Daicel Chiralcel OD column. [e]Reaction performed with TMS capped surface SBA-15 without ligand 24 h. Configuration of all products is *S*.

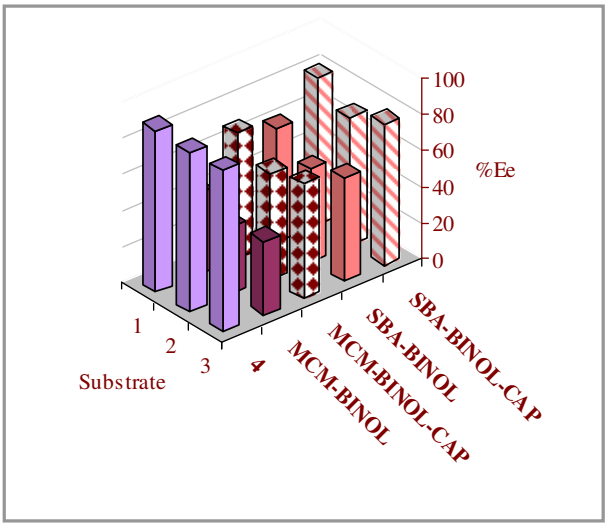



**Figure 2.12** 3D view showing % ee versus substrates (1) benzaldehyde, (2) *m*-methoxybenzaldehyde (3) *p*-fluorobenzaldehyde with BINOL catalyst

### 2.3.3. Recycling Study

After the first use of immobilized catalysts **MCM-BINOL-CAP(3)**, **SBA-BINOL-CAP(4)** was filtered before quenching the reaction mixture by $NH_4Cl$ solution. Recovered catalyst was washed with toluene and dried under vacuum at 110 $^oC$ for 4-5 h for reuse. In the second run, with catalyst **MCM-BINOL-CAP(3)** the conversion was decreased markedly (from 90 to 60 %) and similarly with catalyst **SBA-BINOL-CAP(4)** (from 98 to 67 %), (**Table 2.3**, catalytic run 1, 2) probably due to the blockage of catalytic sites with the reactants. Therefore, the recovered catalyst was washed sequentially with 10% HCl in MeOH, $H_2O$ and finally with acetone under centrifugation,[41] this treatment resulted in restoration of activity and selectivity of the immobilized catalyst. The hexagonal porosity of the dried material was intact as confirmed by XRPD analysis (**Figure 2.4d, 2.5d'**) and TEM image (**Figure 2.11C**). The catalytic system worked well for two more repeat catalytic experiments with some loss in

activity for the enantioselective addition of $Et_2Zn$ to benzaldehyde (**Table 2.3**, catalytic run 3, 4). This approach simplifies the recovery of chiral auxiliaries, and can be transposed to the re-use of other functional organic compounds.

**Table 2.3** Recycling data for addition of $Et_2Zn$ to benzaldehyde as representative substrate using immobilized ligand with $Ti(O^iPr)_4$ as catalyst[a].

| Catalytic run | $L^*$ + $Ti(O^iPr)_4$ | Conversion (%) | Ee (%) |
|---|---|---|---|
| 1 | **MCM-BINOL-CAP(3)** | 90 | 62 |
| | **SBA-BINOL-CAP(4)** | 98 | 81 |
| 2 | **MCM-BINOL-CAP(3)** | 60 | 58 |
| | **SBA-BINOL-CAP(4)** | 67 | 76 |
| 3[b] | **MCM-BINOL-CAP(3)** | 85 | 60 |
| | **SBA-BINOL-CAP(4)** | 94 | 80 |
| 4[b] | **MCM-BINOL-CAP(3)** | 77 | 59 |
| | **SBA-BINOL-CAP(4)** | 89 | 78 |

[a]Using 8 mol % ligand at 0 °C, reaction time- 24 h. [b]After washed with 10% HCl in MeOH, $H_2O$ and acetone.

## 2.4. Conclusion

In summary, mesoporous silica-supported BINOL has been synthesized which could be used to generate Ti-BINOL complex. These silica supported chiral catalyst were used for the enantioselective addition of $Et_2Zn$ to aldehydes to achieve moderate conversions for the secondary alcohols under heterogeneous reaction condition. The TMS capped catalyst **SBA-BINOL-CAP(4)** with larger pore size gave excellent conversion (98%) with higher enantioselectivity (ee; up to 81%) in product 1-phenyl 1-propanol. The reuse of expensive chiral BINOL based catalyst was effectively worked out by washing

the used catalyst with 10% HCl in methanol and the regenerated catalyst was used for further catalytic runs with the retention of enantioselectivity.

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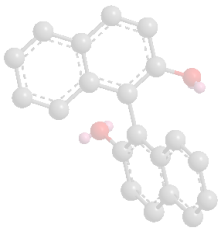

# *Chapter -3*

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## *Immobilization of Chiral BINOL on Large Pore sized Mesoporous Silicas (SBA-15 and MCF) and their use as Catalysts in Asymmetric Addition of Diethylzinc to Aldehydes*

## 3.1. Introduction

We have earlier studied the immobilization of chiral BINOL on MCM-41 and SBA-15 silica and used them as solid chiral auxiliaries in asymmetric addition of $Et_2Zn$ to aldehydes. Subsequent to our observation that pore size of the support plays a crucial role for obtaining higher reactivity and enantioselectivity, we synthesized silica supports with still larger pore sizes. We also visualized that if we increase the distance between the catalyst and walls of the support by way of increasing the length of the linkage there could be an increase in enantioselectivity and reactivity by creating catalyst environment more akin to homogeneous system. Therefore, we synthesized chiral modified BINOL ligand immobilized onto larger pore size SBA-15 and MCF (mesocellular foam) using *N*-methyl-3-aminopropyltriethoxysilane (NMAPTES) as a reactive surface modifier. The solid chiral auxiliaries were used in Ti-promoted asymmetric addition of diethylzinc to aldehydes under heterogeneous reaction conditions. The siliceous SBA-15of large pore diameter (7.5 nm) was synthesized by using amphiphillic triblock copolymer P123 as a structure-directing agent,[1] while for MCF synthesis; mesitylene was used as a swelling agent. MCF[2-4] is a novel mesoporous material with unique advantages as a solid support for catalysts. MCF has a high surface area of 500–800 $m^2/g$, and a 3-D pore structure with ultra-large-cell-like pores (23–42 nm) that are connected by windows of 9–22 nm. Such a pore structure would minimize any steric effects associated with the immobilization of bulky molecules, and facilitate the diffusion of large substrates. The supported catalyst systems were studied under a variety of reaction conditions with varying substrates. Excellent conversion (99%) with high chiral induction (up to 94% ee) was achieved in the case of benzaldehyde. The heterogeneous chiral auxiliary was also

used for various small to bulkier aldehydes to achieve good to excellent enantioselecitivity (ee, 65-91%). The MCF supported BINOL catalyst could be reused in several catalytic runs without significant drop of enantioselecitivity.

## 3.2. Experimental

### 3.2.1. Materials & Methods

Poly-(ethylene oxide)-poly (propylene oxide)-poly (ethylene oxide)block copolymer (Pluronic 123, MW: 5800), tetraethoxysilane (TEOS), 1,3,5-trimethylbenzene (TMB), benzaldehyde, *o*-methylbenzaldehyde, *m*-methoxybenzaldehyde, *p*-methyl benzaldehyde, *p*-fluorobenzaldehyde, 1-naphthyldehyde, *trans*-cinnamaldehyde, MAPTES, $Et_2Zn$ (1 M in hexanes), $Ti(O^iPr)_4$ and HMDS were purchase from Aldrich Chemicals and used without further purification. (*S*)-BINOL was purchased from Fluka. All experiments were carried out under an atmosphere of dry nitrogen. All the solvents used in the present study were purified by the known methods[5] and stored over activated 4 Å molecular sieves.

### 3.2.2. Synthesis and Surface Modification of Mesoporous Silica

#### 3.2.2.1. Synthesis of Siliceous SBA-15 of Large Pore Size

Highly ordered mesoporous SBA-15 of large pore diameter was synthesized using a modified procedure reported by Zhao et al.[1] under hydrothermal conditions using a triblock organic copolymer as a template. In a typical synthesis, 12 g of Pluronic P123 ($EO_{20}$–$PO_{70}$–$EO_{20}$) (mw 5800) was dispersed in 90 g of double-distilled water to which 360 g of 2 M aqueous HCl was added under stirring at ambient temperature 303 K for 1 h. Finally, 27 g of silica source TEOS was added to the homogeneous solution under

stirring to form a gel at 383 K for 24 h, and this was allowed to stand for crystallization under static hydrothermal conditions at 383 K for 48 h in a Teflon Parr reactor. The crystallized product was filtered off, washed with warm distilled water, dried at 383 K, and finally calcined at 813 K in air for 6 h to remove the template. The calcined SBA-15 was characterized by powder XRD.

**3.2.2.2. Synthesis of Siliceous MCF**

Siliceous MCF was synthesized according to procedure reported by Stucky et al.[2] Triblock copolymer P123 (8 g, 0.0014 mol) was dispersed in 60 g of double-distilled water stirred for 3 h at room temperature. After a solution of 1,3,5 trimethylbenzene (TMB) (11.42 g, 0.1 mol) was added slowly to a stirred solution and stirred for 30 min at room temperature. Then 300 g of 2 M aqueous HCl was added under stirring at ambient temperature (25–30 $^{o}$C) for 1 h. Finally, silica source TEOS (18.8 g, 0.09 mol) was added to the homogeneous solution under stirring to form a gel at 100 $^{o}$C for 24 h, and then allowed to stand for crystallization under static hydrothermal conditions at 110 $^{o}$C for 48 h in a Teflon Parr reactor. The crystallized product was filtered off, washed with warm distilled water, air-dried at 35 $^{o}$C. Calcination at 550 $^{o}$C for 6 h.

**3.2.2.3. Synthesis of *N*-Methylaminopropyl Functionalized SBA-15 (4) and MCF (4')**

The predried calcined silicas (3.5 g) and MAPTES (1.8 mL, 7.2 mmol) was refluxed in toluene (30 mL) under a nitrogen atmosphere for 5-6 h. The solids were filtered, washed successively with toluene and acetone and dried at 100 $^{o}$C under vacuum for 4-5 h. **4**: IR: $\nu$ = 3450, 2925, 1088, 795, 461 cm$^{-1}$; Elemental analysis: found (wt %): C 8.26, H 1.2, N 0.35. **4'**: IR: $\nu$ = 3454, 2929, 1085, 798, 460 cm$^{-1}$; Elemental analysis: found (wt %): C 9.52, H 2.10, N 0.43.

### 3.2.3. Modification and Immobilization of Chiral BINOL

#### 3.2.3.1. (*S*)-2,2'-Dimethoxy-1,1'-binaphthyl (2)

The compound **3** was synthesized according to the reported procedure.[6] To a solution of **1** (5 g, 17.4 mmol) in anhydrous acetone (160 ml) were added anhydrous $K_2CO_3$ (7.2 g, 52.2 mmol) and methyl iodide (7.38 g, 52.2 mmol) at room temperature and the mixture was refluxed for 18 h under dry condition. The solvent was completely removed under vacuum and the residue was dissolved in $CH_2Cl_2$ (160 ml) and $H_2O$ (140 ml). The aqueous layer was further extracted with $CH_2Cl_2$ (3 x 40 ml). The combined organic layer was dried over anhydrous $Na_2SO_4$. After the removal of the solvent the pale yellow product was washed with methanol to get **2** as white solid (Yield; 4.6 g, 87 %); IR (KBr): ν = 2969, 2870, 1585, 1494, 1259, 1087, 799 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 3.77 (s, 6H), 6.94 (d, *J*= 9.2 Hz, 1H), 7.11 (d, *J*= 9.2 Hz, 1H), 7.18-7.27 (m, 3H), 7.47 (d, *J*= 9 Hz, 2H), 7.84 (d, *J*= 6.7 Hz, 1H), 7.89 (d, *J*= 5.7 Hz, 1H), 7.95 (d, *J*= 10.8 Hz, 1H), 8.01 (d, *J*= 2.8 Hz, 1H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 57.3, 110.1, 111.3, 117.1, 118.2, 123.8, 124.0, 125.7, 127.1, 128.3, 129.5, 129.8, 130.2, 130.6, 130.8, 131.3, 132.3, 152.1, 152.7 ppm; LC-MS: m/z 315 ($M^+$ + H); Anal. Calcd. for ($C_{22}H_{18}O_2$): C, 84.05; H, 5.57, Found: C, 83.9; H, 5.53%; $[\alpha]_D^{27}$ = +110.5 (c=0.5, $CHCl_3$).

#### 3.2.3.2. (*S*)-6-Chloro acetyl- 2,2'-dimethoxy-1,1'-binaphthyl (3)

A mixture of **2** (3 gm, 9.5 mmol), anhydrous $AlCl_3$ (1.26 g, 9.8 mmol) and $CH_2Cl_2$ (60 ml) was stirred at 0 °C for 15 min in an argon atmosphere. Chloro acetyl chloride (1.1 ml, 9.8 mmol) was added drop wise in the reaction mixture and the resulting brown reaction mixture was warmed to room temperature and stirred magnetically for 18-20 h. The reaction mixture was quenched with aqueous 1 N HCl (150 ml) and extracted

with $CH_2Cl_2$ (75 ml). The organic extract was dried over anhydrous $Na_2SO_4$. After the removal of the solvent the residue was purified by column chromatography over silica gel using *n*-Hexane/EtOAc (98:2) to get **3** as light yellow solid. (Yield; 1.82 gm, 60 %); IR (KBr): ν = 2921, 2847, 1689, 1591, 1462, 1262, 1173, 1062, 806, 748, 678 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 3.75 (s, 6H), 4.72 (s, 2H), 7.19 (d, *J*= 8.8 Hz, 1H), 7.28 (d, *J*= 9Hz, 1H), 7.17-7.35 (m, 3H), 7.42 (d, *J*= 3.8 Hz, 1H), 7.48 (d, *J*= 3.5Hz, 1H), 7.84 (d, *J*= 8.5Hz, 1H), 7.88 (d, *J*= 9Hz, 1H), 7.95 (d, *J*= 9Hz, 1H), 8.02 (d, *J*= 2Hz, 1H) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 46.6, 56.8, 114.7, 115.0, 115.4, 117.7, 124.1, 124.9, 125.7, 126.5, 127.1, 127.6, 128.7, 129.5, 129.8, 130.2, 130.6, 130.8, 131.3, 132.3, 157.8, 174.1, 196.5 ppm; LC-MS: m/z 392 ($M^+$ + H); Anal. Calcd. for ($C_{24}H_{19}O_3Cl$): C, 73.75; H, 4.87, Found: C, 73.71; H, 4.84%; $[\alpha]_D^{27}$= +26.7 (*c* 0.5, $CHCl_3$).

### 3.2.3.3. Immobilization of (3) onto *N*-Methylaminopropyl Functionalized SBA-15 and MCF

The *N*-methylaminopropyl functionalized silicas **4/ 4'** (2.0 g) and modified chiral BINOL ligand **3** (3 mmol) were allowed to stir at reflux temperature under a nitrogen atmosphere for 24 h. After cooling, the powder was collected by filtration, washed successively with dry toluene, and then dried under vacuum. Dried material was subjected to soxhlet-extraction with dichloromethane for 24 h. Finally the samples **5/5'** were dried under vacuum at 45-50 $^oC$ for 4-5 h.

### 3.2.3.4. Removal of the Protecting Groups (SBA-BINOL-6 & MCF-BINOL-6')

Removal of protecting groups was carried out with 1 M $BBr_3$ in $CH_2Cl_2$ using procedure described in experimental section 2.2.4.1.

**SBA-BINOL-6:** IR: ν = 3435, 2952, 2856, 1637, 1472, 1088, 807, 693, 459 $cm^{-1}$; Elemental analysis: found (wt %): C 8.71, H 0.75, N 0.39; **MCF-BINOL-6':** IR: ν =

3429, 2962, 2858, 1620, 1470, 1089, 808, 691, 461 $cm^{-1}$; Elemental analysis: found (wt %): C 9.22, H 0.79, N 0.42.

**3.2.3.5. TMS Modification of BINOL-Immobilized SBA-15 and MCF (SBA-BINOL-CAP-(5) and MCF-BINOL-CAP-(6))**

TMS modification was carried out using procedure described in experimental section 2.2.4.2.

**SBA-BINOL-7:** IR: ν = 2972, 2850, 1641, 1476, 1080, 845, 804, 691, 460 $cm^{-1}$; Elemental analysis: found (wt %): C 10.20, H 1.30, N 0.38.

**MCF-BINOL-7:** IR: ν = 2961, 2858, 1647, 1473, 1074, 846, 800, 695, 460 $cm^{-1}$; Elemental analysis: found (wt %): C 11.57, H 1.42, N 0.40; $^{13}C$ CP MASS: $\delta$ 0.6 ($Me_3SiO$-), 8, 17, 28, 39, 60, 122, 132, 144, 153, 170 ($CH_2NH$-) ppm.

**3.2.4. General Procedure for Asymmetric Addition of $Et_2Zn$ to Aldehydes**

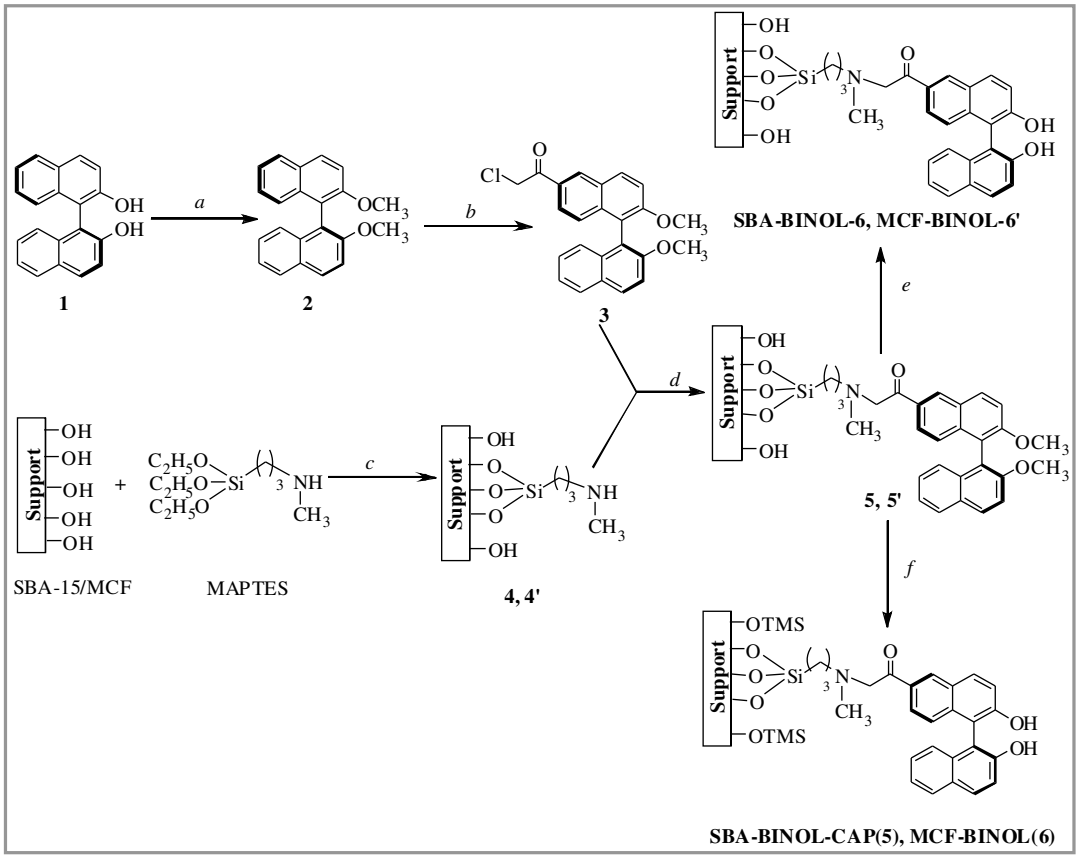
Supported ligand (0.05 mmol) was dried under vacuum for 6 h at 110 $^oC$ then taken in 2 mL dry $CH_2Cl_2$ and was stirred with $Ti(O^iPr)_4$ (1.5 mmol) for 2h at room temperature under a nitrogen atmosphere. To the above suspension a solution of $Et_2Zn$ (1 M solution in hexane, 3.0 mmol) was added, cooled to 0 $^oC$, aldehyde (1.0 mmol) was added drop wise in the resulting mixture was allowed to stir at 0$^oC$ for 15 h. The progress of the catalytic reaction was monitored on HPLC. After completion of the reaction, the supported catalyst was filtered off from the reaction mixture, washed with $CH_2Cl_2$, dried under vacuum and kept for reuse experiments. The filtrate and combined washings was quenched with saturated $NH_4Cl$ solution (10 mL), washed with water and dried over anhydrous $Na_2SO_4$. It was filtered and crud product was analyzed on HPLC Chiralcel OD column to determine the optical purity.

## 3.3. Results and Discussion

### 3.3.1. Synthesis and Characterization of Immobilized BINOL

To retain the flexibility of chiral BINOL ligand by way of increasing the chain length between the support and BINOL, chloro acetyl group was introduced at $6^{th}$ position on one of its naphthyl ring. This new modified chiral BINOL ligand was heterogenized on surface modified mesoporous silica having large pore diameter according to the method illustrated in **Scheme 3.1**. The hydroxyl groups of (*S*)-BINOL **1** was protected with $CH_3I$ under basic condition yielded compound **2.** The *O*-methylated BINOL **2** was treated with chloroacetyl chloride with anhydrous $AlCl_3$ in dichloromethane at 0 $^oC$ afforded 6-chloroacetyl 2,2'- dimethoxy- 1,1'-binapthyl **3** in 60% yield after column purification.

In this study, we have selected two relatively large pore size mesoporus silica. The surface modification of these two different pore sized silica was achieved by NMAPTES as a reactive surface modifier. After successful surface modification, compound **4** and **4'** were refluxed with modified chiral BINOL ligand **3** in toluene for 24 h to get **5** and **5'** which on demethylation afforded supported ligand **SBA-BINOL-6** and **MCF-BINOL-6'**. Further, silica matrix bears hydroxyl groups that may react with Ti metal ions to create non-chiral catalyst sites on silica support. We modified the accessible free silanol sites of the **5** and **5'** by treating with hexamethyldisiloxane (HMDS) at reflux temperature for 12h followed by demethylation with 1 M $BBr_3$ in $CH_2Cl_2$ to afford supported ligands **SBA-BINOL-CAP(5)** and **MCF-BINOL-CAP(6)**.




**Scheme 3.1** The immobilization of chiral BINOL onto silica surface; reagents and conditions: *a*: $CH_3I$, $K_2CO_3$, acetone, reflux, 18 h, 87%; *b*: Cl-$CH_2COCl$, anhydrous $AlCl_3$, $CH_2Cl_2$, 0 °C, 4 h, 60%; *c* and *d*: toluene, reflux, 24 h; *e:* $BBr_3$, $CH_2Cl_2$, -78 °C; *f*: (*i*) HMDS, reflux, 12h; (*ii*) $BBr_3$, $CH_2Cl_2$, -78 °C.

The characterizations of the mesoporous silica's supported ligands were accomplished by various physico-chemical techniques. The elemental analysis of supported chiral ligands based on the wt% of N demonstrated that the loading of the chiral ligands was 22-24 mg/gm respectively. **Figure 3.1** shows representative $^{13}C$ CP MAS spectra of functionalized SBA-15 **4** and supported ligand **SBA-BINOL-6,** which showed peaks 63, 41, 28, 9 ppm due to the surface modification by MAPTES[7], 120-155 ppm for aromatic carbons due to naphthyl groups of BINOL and 170 ppm ($CH_2$-NH group) further confirmed the successful attachment of BINOL on silica.

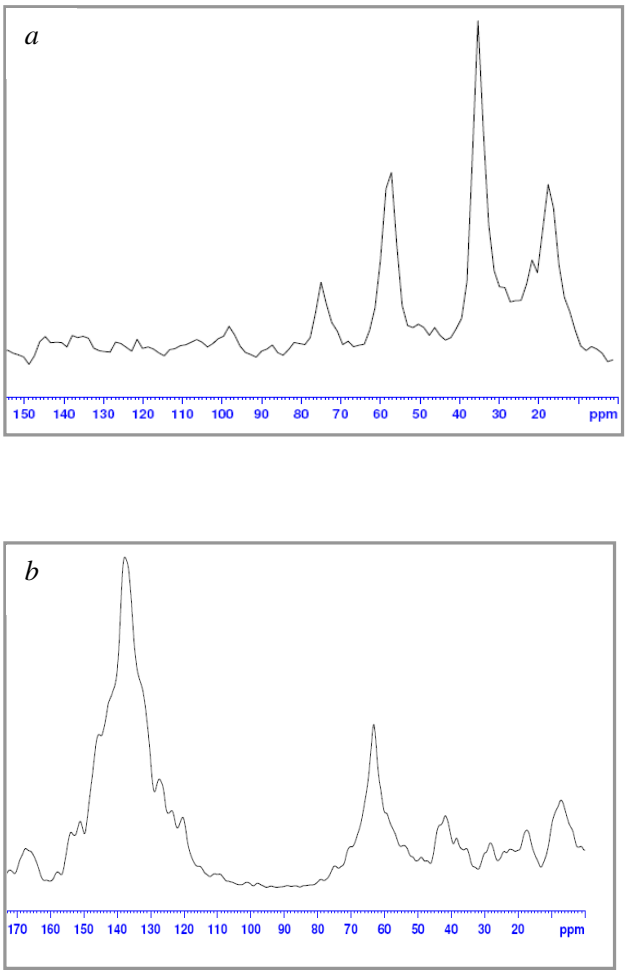



**Figure 3.1** $^{13}C$ CP MAS NMR spectra of **4** (*a*), supported ligand **SBA-BINOL-6** (*b*)

FT-IR spectra of heterogenized ligands were in good agreement with the expected chemical structure of the organic moieties (**Figure 3.2**). New peaks at 2952, 2856 (C-H stretching vibrations), 1637 (C-N vibration), 1472 (C=C stretching vibration) $cm^{-1}$ in comparison with the inorganic supports before grafting, indicate the formation of the organic-inorganic hybrid ligands. Moreover, FT-IR spectra illustrated significant decrease in free Si-OH stretching at ~3400 $cm^{-1}$ after silanol capping with TMS groups on siliceous supports.

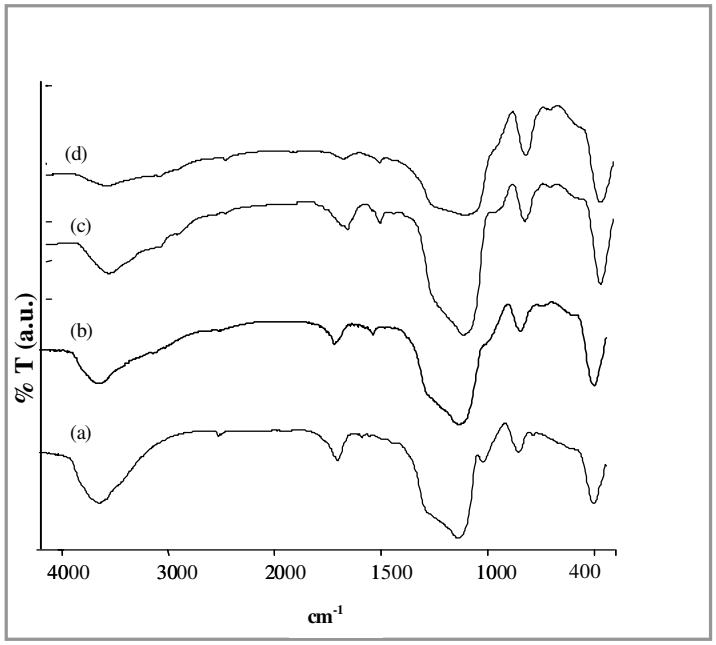



**Figure 3.2** FT-IR spectra of pristine MCF (a), **4'** (b), supported ligand **MCF-BINOL-6'** (c), supported ligand **MCF-BINOL-CAP(6)** (d)

The powder XRD patterns of pristine SBA-15 show a very intense peak assigned to reflection at (100) and two additional peaks with low intensities at (110) and (200) reflections, which can be indexed for a hexagonal unit cell (**Figure 3.3**). It is observed that on functionalization with MAPTES, the intensities of all of the peaks of decrease marginally with a little shift toward lower $2\theta$ values. These peaks did not change significantly after the attachment of modified chiral BINOL unit **3** to functionalize the silica, suggesting that the structure of silica do not collapse after chiral BINOL is supported on surface of silica.

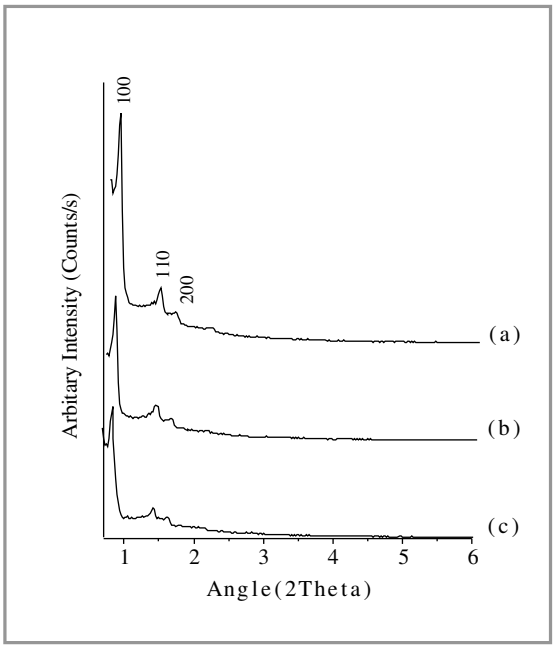



**Figure 3.3** XRPD patterns of calcined SBA-15 (a), *N*-methyl-3-aminopropyl functionalized SBA-15 **4** (b), **SBA-BINOL-CAP(5)** (c)

**Figure 3.4** & **3.5** show $N_2$ sorption isotherms and pore size distribution curves of pristine silica and supported ligands. Unmodified SBA-15 and MCF exhibit a reversible type IV adsorption-desorption isotherm, characteristic of a mesoporous solids. Pristine MCF shows steep hystereses of type H1 at high relative pressures (**Figure 3.5**), which exhibit capillary condensation and evaporation and have large pore sizes with narrow size distributions.[2] The isotherms of the functionalized SBA-15 and MCF samples show a lower $N_2$ uptake, pointing to a decrease in the specific surface area and pore volume (**Table 3.1**). This effect is more pronounced for the trimethylsilylated samples **SBA-BINOL-CAP(5)** and **MCF-BINOL-(6)**, for which $S_{BET}$ decreased more than 49% and $V_p$ decreased more than 45%. The height of the capillary condensation step and the $p/p_0$ coordinate of the inflection point slightly decrease, indicating changes in pore size

distribution due to grafting of the internal silica surface with the organic species. This is confirmed by comparing the pore size distributions (PSD) of the pristine and modified silica materials.

**Table 3.1** Textural parameters of samples taken from nitrogen adsorption data

| Sample | $S_{BET}$ ($m^2.g^{-1}$) | $\Delta S_{BET}$ [a] (%) | $V_p$ ($cm^3.g^{-1}$) | $\Delta V_p$ [b] (%) | $d_{BJH}$ (nm) |
|---|---|---|---|---|---|
| SBA-15 | 745 | - | 1.25 | - | 7.5 |
| **4** | 600 | -20 | 0.98 | -22 | 7.2 |
| **SBA-BINOL-6** | 435 | -28 | 0.65 | -34 | 6.9 |
| **SBA-BINOL-CAP(5)** | 237 | -46 | 0.32 | -51 | 6.7 |
| MCF | 635 | - | 2.20 | - | 14.0 |
| **4'** | 545 | -15 | 1.84 | -17 | 13.2 |
| **MCF-BINOL-6'** | 410 | -25 | 1.10 | -41 | 11.0 |
| **MCF-BINOL-CAP(6)** | 217 | -48 | 0.52 | -53 | 9.5 |

[a]Variation of surface area in relation to parent mesoporous material. [b]Variation of total pore volume in relation to parent mesoporous material.

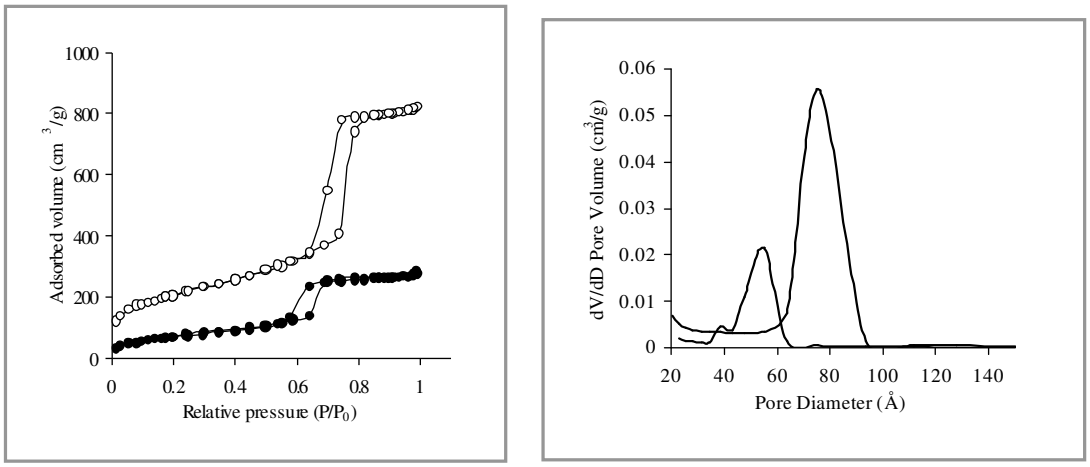



**Figure 3.4** Overlay of $N_2$ Adsorption-desorption isotherms and pore diameter and relative pore volume of calcined SBA-15 and **SBA-BINOL-CAP(5)**

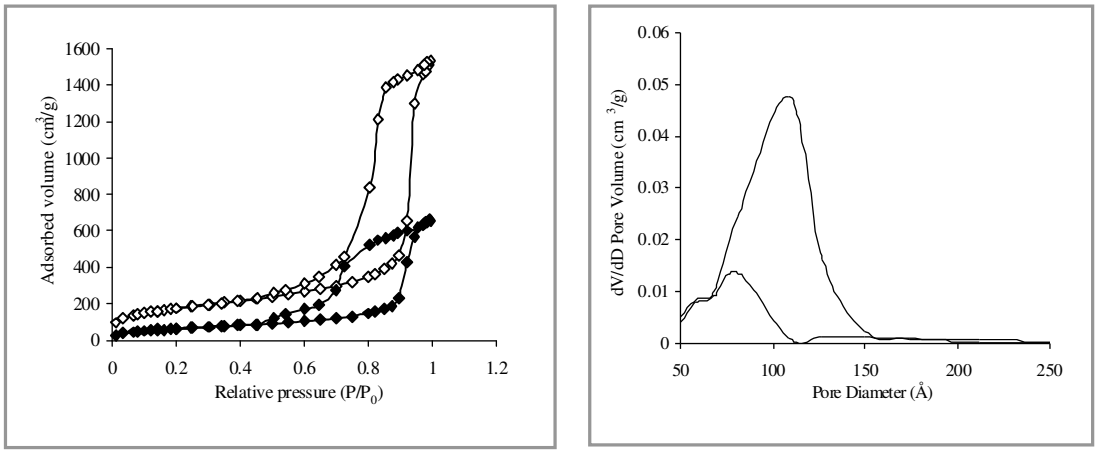



**Figure 3.5** Overlay of $N_2$ Adsorption-desorption isotherms and pore diameter (desorption branch) and relative pore volume of calcined MCF and **MCF-BINOL-CAP(6)**

**Figure 3.6** shows TEM micrographs of pristine MCF and immobilized **MCF-BINOL-CAP(6).** It is revealed that a disordered array of silica struts, which is the characteristic structural feature of the MCF. TEM analyses indicate that the phase transition from the undulated SBA-15-type, ordered structure with *p6mm* symmetry to the strut like MCF structure. So, it is revealed that MCF has ink-bottle-type pores, in which large spherical cells (bodies of the ink bottles) are interconnected by narrower windows (bottlenecks).[2a] Thus structure of mesoporous support was unaffected by immobilization of chiral modified BINOL.

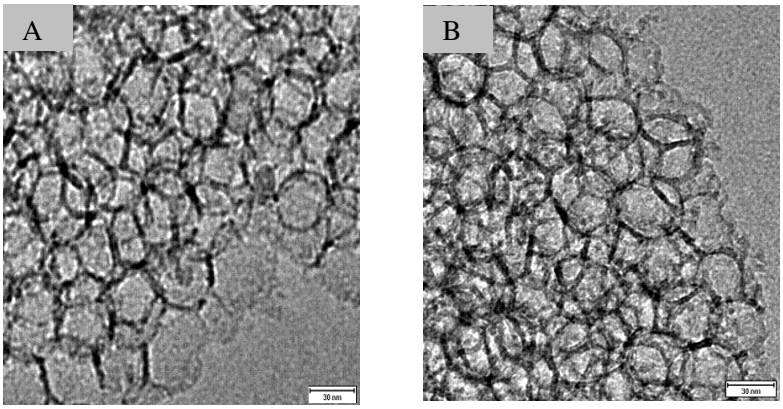



**Figure 3.6** TEM images of of calcined **MCF** (A), supported ligand **MCF-BINOL-CAP(6)** (B)

### 3.3.2. Asymmetric Addition of $Et_2Zn$ to Aldehydes

Asymmetric addition of $Et_2Zn$ to benzaldehyde was carried out using Ti complex of (*S*)-BINOL **1** as catalyst under homogeneous reaction condition. Excellent conversion to 1-phenyl-1-propanol with high *ee* (92%) was achieved in 7 h (**Table 3.2**, entry 1) using $CH_2Cl_2$ as solvent. When **SBA-BINOL-6** and **MCF-BINOL-6'** were screened for its activity towards the addition of diethylzinc to benzaldehyde under the similar reaction conditions, to give (92-95%) conversion with enantioselecitivity (ee; 70-72%) (**Table 3.2**, entries 2, 3). Passivation of the free SiOH moieties on the silica surface with TMS (**SBA-BINOL-CAP(5)** and **MCF-BINOL-(6))** significantly improved conversion (99%) with excellent enantioselecitivity (ee, 88- 94 %) of chiral 1-phenyl-1-propanol (entries 3, 4).

Several common factors which are known to affect the enantioselecitivity of the catalyst system such as choice of solvent and reaction temperature have been studied using *in situ* generated Ti-complex of immobilized ligands **SBA-BINOL-CAP(5)** and **MCF-BINOL-(6)** as catalysts and benzaldehyde as a substrate. Consequently, the use of

toluene and diethyl ether as solvent gave good conversion (90-98%) with enantioselecitivity (80-87%) (**Table 3.2**, entries 6-9) nevertheless, results obtained with the use of $CH_2Cl_2$ are better for the present catalytic system. When reaction was conducted at lower temperature (-20 $^oC$) in $CH_2Cl_2$, the enantioselecitivity increased only marginally but conversion slowed down significantly. Moreover, the selectivity was found to be lower when the reaction was carried out at room temperature (**Table 3.2**, entries 12, 13). The catalytic activity of the TMS capped MCF without a chiral ligand was checked under the same reaction conditions that gave 15 % conversion and the product obtained was found to be racemic. This shows that silica surface itself is benign for imparting enantioselecitivity.

**Table 2**. Chiral BINOL-Ti catalyzed asymmetric addition of diethylzinc to benzaldehyde under various reaction conditions.[a]

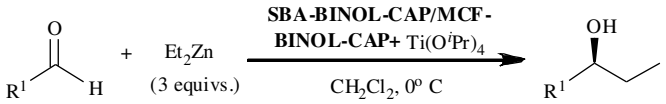
| Entry | Ligand | Solvent | Temperature ($^{o}$C) | Conversion[b] (%) | Selectivity[d] (%) | Ee[e] (%) |
|---|---|---|---|---|---|---|
| 1 | **1** | $CH_2Cl_2$ | 0 | 99 | >99 | 92 |
| 2 | **SBA-BINOL-6** | $CH_2Cl_2$ | 0 | 92 | 92 | 70 |
| 3 | **MCF-BINOL-6'** | $CH_2Cl_2$ | 0 | 95 | 96 | 72 |
| 4 | **SBA-BINOL-CAP(5)** | $CH_2Cl_2$ | 0 | 97 | 98 | 88 |
| 5 | **MCF-BINOL-CAP(6)** | $CH_2Cl_2$ | 0 | 99(97)[c] | >99 | 94 |
| 6 | **SBA-BINOL-CAP(5)** | Toluene | 0 | 96 | 98 | 84 |
| 7 | **MCF-BINOL-CAP(6)** | Toluene | 0 | 98 | 99 | 87 |
| 8 | **SBA-BINOL-CAP(5)** | Diethyl ether | 0 | 90 | 93 | 80 |
| 9 | **MCF-BINOL-CAP(6)** | Diethyl ether | 0 | 93 | 95 | 83 |
| 10 | **SBA-BINOL-CAP(5)** | $CH_2Cl_2$ | -20 | 71 | 73 | 89 |
| 11 | **MCF-BINOL-CAP(6)** | $CH_2Cl_2$ | -20 | 74 | 75 | 91 |
| 12 | **SBA-BINOL-CAP(5)** | $CH_2Cl_2$ | rt | 98 | 62 | 82 |
| 13 | **MCF-BINOL-CAP(6)** | $CH_2Cl_2$ | rt | 99 | 65 | 86 |
| 14 | **TMS capped MCF** | $CH_2Cl_2$ | 0 | 15 | - | - |

[a]Reactions were carried out with 0.05 mmol of ligand **1** (homogeneous reaction condition) for 7 h and 0.05 mmol of supported chiral ligand (heterogeneous reaction condition) using 1.5 mmol $Ti(O^{i}Pr)_4$, 3.0 mmol $Et_2Zn$ and 1.0 mmol substrate in 2 mL solvent for 15 h. [b]Determined by $^{1}$H NMR spectroscopy of crude products. [c]Isolated yield. [d]% Selectivity: 100 ([*R*] + [*S*]) / ([*R*] + [*S*] + [$PhCH_2OH$]). [e]Determined by HPLC using Daicel Chiralcel OD column.

Scope of supported chiral BINOL ((**SBA-BINOL-CAP(5)** and **MCF-BINOL-(6))** for their use in asymmetric addition of $Et_2Zn$ was further extended to various other aldehydes in $CH_2Cl_2$ under heterogeneous condition. The active chiral catalyst was generated *in situ* by the interaction of supported BINOL ligand with in dichloromethane. Smaller to bulkier aldehydes like *o*-methyl benzaldehyde, *m*-methoxy benzaldehyde, *p*-methyl benzaldehyde, *p*-fluoro benzaldehyde, 1-naphthaldehyde and *trans*-cinnmaldehyde gave respective chiral secondary alcohols in excellent conversion and ee (**Table 3.3**). However, the substituents on benzaldehyde derivative had some influence on the reactivity and enantioselectivity, *p*-substituted aldehydes showed better reactivity (**Table 3.3**, entries 5-8) with respect to conversion and ee than *o*-substituted aldehyde (entries 1, 2) with supported catalysts. This is probably due to the strong steric effect of the *ortho*-substitutents which may deteriorate the coordination of the substrate to the chiral catalyst thus lowering the reactivity, although activity and selectivity was found to be very good to excellent for different substrates in terms of their steric and electronic features with both catalysts. Best enantio-induction (ee, 91-94%) with high yields (95-97%) of respective secondary alcohols was obtained for benzaldehyde and 1-naphthyldehyde with catalyst **MCF-BINOL-(6)** (**Table 3.2** & **3.3**, entries 5 & 10 respectively). The overall performance was better for large pore sized MCF based catalyst than SBA-15 based catalyst (**Figure 3.7**). We presume that the excellent performance of the MCF-supported catalyst might be due to the relatively large pore size which allows better accessibility of the substrates and reactants and minimize the diffusional limitation. Hence, chiral BINOL immobilized on relatively large pore size mesoporous silica-SBA-15and MCF gave higher ee values in asymmetric addition of

diethylzinc to aldehydes with the modification of supports by organosilane like TMS groups enhanced the catalytic activity due to deactivation of free SiOH groups which is quite match with earlier reports.[8,9]

**Table 3.3** Supported chiral BINOL-Ti catalyzed asymmetric addition of $Et_2Zn$ for smaller to bulkier aldehydes[a]




| Entry | $R^1$ | Supported ligand | Conversion[b] (%) | Selectivity[d] (%) | Ee[e] (%) |
|---|---|---|---|---|---|
| 1 | *o*-$CH_3$ | **SBA-BINOL-CAP(5)** | 87 | 85 | 62 |
| 2 | | **MCF-BINOL-CAP(6)** | 94 | 95 | 65 |
| 3 | *m*-$OCH_3$ | **SBA-BINOL-CAP(5)** | 90 | 91 | 78 |
| 4 | | **MCF-BINOL-CAP(6)** | 93 | 96 | 80 |
| 5 | *p*-$CH_3$ | **SBA-BINOL-CAP(5)** | 90 | 92 | 82 |
| 6 | | **MCF-BINOL-CAP(6)** | 98 | 99 | 87 |
| 7 | *p*-F | **SBA-BINOL-CAP(5)** | 92 | 95 | 82 |
| 8 | | **MCF-BINOL-CAP(6)** | 98 | 99 | 89 |
| 9 | 1-Naphthyl | **SBA-BINOL-CAP(5)** | 90 | 93 | 85 |
| 10 | | **MCF-BINOL-CAP(6)** | 98(95)[c] | 96 | 91 |
| 11 | *t*-$C_6H_5CH$=CH | **SBA-BINOL-CAP(5)** | 78 | 88 | 78 |
| 12 | | **MCF-BINOL-CAP(6)** | 86 | 93 | 86 |

[a]Reactions were carried out with 0.05 mmol of supported chiral ligand using 1.5 mmol $Ti(O^iPr)_4$, 3.0 mmol $Et_2Zn$ and 1.0 mmol substrate in 2 mL $CH_2Cl_2$ for 15 h. [b]Determined by $^1H$ NMR spectroscopy of crude products. [c]Isolated yield. [d]% Selectivity: 100 ([*R*] + [*S*]) / ([*R*] + [*S*] + [$PhCH_2OH$]). [e]Determined by HPLC using Daicel Chiralcel OD column.

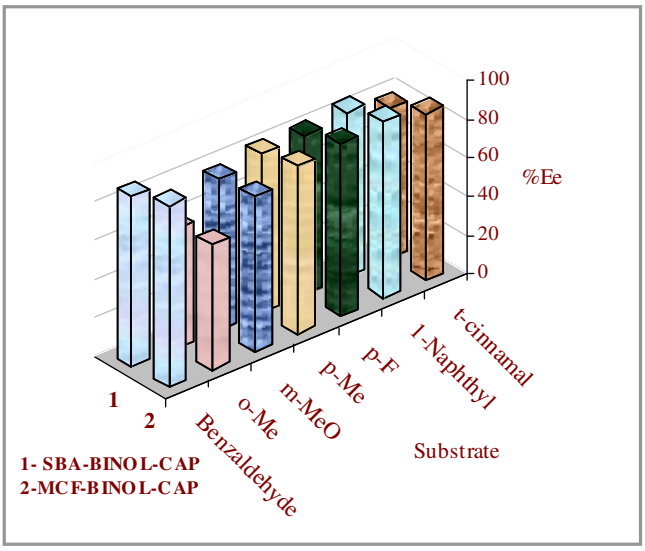



**Figure 3.7** 3D view showing %Ee versus substrate using immobilized **SBA-BINOL-CAP(5)** and **MCF-BINOL-CAP(6)** catalysts

### 3.3.3. Recycling study

The supported chiral catalyst **MCF-BINOL-CAP(6)** was taken as representative candidate for recycling experiments (**Table 3.4**). The supported catalyst was readily recovered before quenching the reaction mixture by $NH_4Cl$ solution. The recovered catalyst was washed with $CH_2Cl_2$ and dried under vacuum at 110 $^oC$ for 5-6 h and kept in desiccators for further use. The supported catalyst was reused in multiple catalytic runs. However, in the fifth reuse experiment there was notable decreased in the conversion and enantioselecitivity probably due to the blockage of catalytic sites with the reactants. Therefore, the catalyst recovered after 5$^{th}$ run was washed sequentially with 10% HCl in MeOH, $H_2O$ and finally with acetone under centrifugation.[10] The regenerated ligand thus obtained was used for the next catalytic run with the fresh supply of Ti. We observed that the above treatment restored the activity and enantioselecitivity of the catalyst for another 3 successive reuse cycles.

**Table 3.4** Recycling data for asymmetric addition of diethylzinc to benzaldehyde using **MCF-BINOL-CAP(6)** with as catalyst[a]

| Catalytic Run | Conversion (%) | Ee (%) |
|---|---|---|
| 1 | 99 | 94 |
| 2 | 98 | 93 |
| 3 | 98 | 92 |
| 4 | 73 | 85 |
| 5[b] | 97 | 93 |
| 6 | 98 | 94 |
| 7 | 98 | 94 |

[a]Using 0.06 mmol of  in 15 h at 0 °C. [b]After washed with 10% HCl in MeOH, $H_2O$ and acetone and reloaded with Ti metal.

## 3.4. Conclusion

In summary, we have described the heterogenization of chiral BINOL on robust large pore sized siliceous SBA-15 and MCF as supports. The new assembled heterogeneous organic-inorganic hybrid moiety was used in Ti-promoted asymmetric addition of diethylzinc to aldehydes. The supported catalyst systems were studied under a variety of reaction conditions with varying substrates. Excellent conversion (99%) of 1-phenyl-1-propanol with high chiral induction was achieved (ee; up to 94%) in the case of benzaldehyde. The heterogeneous chiral auxiliary was also used for various small to bulkier aldehydes to achieved good to excellent enantioselecitivity (ee, 65-91%). The MCF supported BINOL catalyst could be reused in several catalytic runs without significant drop of enantioselecitivity. The enantioselecitivity of the reaction was strongly influenced by pore size of the support with changing the environment around the catalytic sites by the modification of support with TMS groups.

## 3.5. References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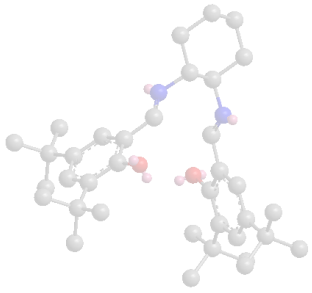
# Chapter -4



## Chiral Polymeric Zn(salen) Complex as Recyclable Catalyst for Asymmetric Phenylacetylene Addition to Carbonyl Compounds.

## 4.1. Introduction

Chiral salen complexes have become a matter of recent interest[1,2] because of their wide applications as catalysts in various asymmetric transformations *viz.* epoxidation[3,4] cyclopropanation,[5] aziridination,[6] Knoevenagel condensation,[7] and selective hydrogenation.[8]

Enantioselective alkyne addition to carbonyl compounds is one of the efficient routes for synthesis of optically active propargyl alcohols.[9-11] Chiral propargyl alcohols are versatile building blocks for asymmetric synthesis and have diverse synthetic applications as important pharmaceutical intermediates.[12-17] Various chiral ligands such as amino alcohols,[18] sulfonamides,[19] binaphthols[20] and oxazolidine[21] have been used for the synthesis of chiral propargyl alcohols. In recent years, Zn(salen) complexes have been used in asymmetric addition of organometallic reagent to carbonyl compounds.[22-25] as it can behave as a bifunctional Lewis acid-Lewis base catalyst. However, the catalyst stability, product and catalyst separation remains troublesome with these homogeneous systems. Keeping in mind that chiral catalysts are expensive their reusability is highly advantageous for their industrial application. To overcome these problems one way is to increase the molecular weight of the catalyst so that it has lower solubility in some of the non-polar organic solvents, facilitating product isolation and catalyst recovery by precipitation method, which in turn makes the post reaction work-up much convenient.[26,27]

In this chapter, we have synthesized polymeric salen ligand for the synthesis of new polymeric Zn(salen) complex as an effective catalyst for enantioselective phenylacetylene addition to aldehydes and ketones to synthesize corresponding chiral

secondary and *tertiary* propargylic alcohols in single step. Unlike its monomeric version the catalytic system worked well up to four times with retention of enantioselecitivity.

## 4. 2. Experimental

### 4.2.1. Materials & Methods

All aldehydes were purchased from Aldrich and used as received. $Et_2Zn$ (1M solution) and phenylacetylene (Aldrich), acetophenone, *o*-methylacetophenone, *o*-bromoacetophenone, *p*-methylacetophenone, *p*-methoxyacetophenone, *p*-fluoroacetphenone, 1'-naphthacetophenone, 3-Methyl butane 2-one purchased from Across (Belgium). 2-*tert*-Butyl-phenol was purchased from Aldrich. All reactions were carried out under dried argon atmosphere. The (1*R*,2*R*)-(-)-cyclohexanediamine was resolved from the technical-grade *cis-trans* mixture according to procedure.[28] All the solvents used in the present study were purified by the known methods.[29]

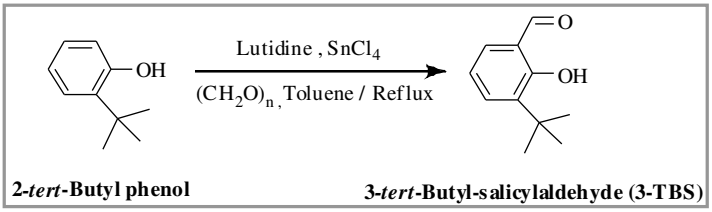
### 4.2.2. Synthesis of Chiral Ligand Precursors

The synthesis of chiral ligand precursors is described as follows.

#### 4.2.2.1. 3-*tert*-Butyl-salicyaldehyde (3-TBS)

2, 6-lutidine (4.3 mL, 0.041 mol), $SnCl_4$ (5.2 mL, 0.020 mol), 2- *tert*-Butyl phenol (10 g, 0.67 mol) was taken in toluene (200 ml). The resulting mass was stirred at 25 °C under nitrogen for 1 h followed by the addition of paraformaldehyde (8.0 g, 0.26mol). The mixture was heated under reflux for 8 h and the reaction progress was monitored by TLC. The reaction mixture was allowed to cool to 25 °C and water (200 ml) and diethyl ether (200 ml) was added. The resulting emulsion was filtered through a pad of celite and the layers were separated. The organic layer was washed with water, brine, and dried

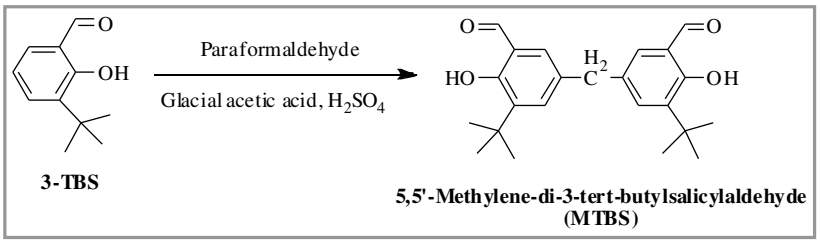
over anhydrous $Na_2SO_4$, and then concentrated. The crude product was purified by flash column chromatography on silica gel (Hexane: EtOAc.) to afford the title compound as a pale yellow oil[28] (**Scheme 4.1**) (10.6 g, 90% yield), IR (KBr): 2958, 1612, 1653, $cm.^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 9H), 6.87 (t, 1H), 7.38(d, 1H), 7.52 (d, 1H), 9.84(s, 1H ), 11.77(s, 1H) ppm; Anal. Calcd. For ($C_{11}H_{14}O_2$): C, 74.15; H,7.87, Found: C,74.05 ; H, 7.79%.




**Scheme 4.1** Synthesis of 3-TBS

**4.2.2.2. 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde (MTBS)**

3-*tert*-Butyl salicylaldehyde (0.12 mol) was treated with a solution of paraformaldehyde (0.06 mol) in glacial acetic acid (16 ml) and sulphuric acid (2 ml) under nitrogen. The resulting solution was allowed to heat to 90°C with stirring for 24 h. The reaction mixture was poured into cold water and allowed to stand overnight. The deposited dark brown solid was extracted with petroleum ether (3×15 ml). The organic phase was dried over anhydrous sodium sulphate. The dark brown compound was purified by silica gel column chromatography using hexane–ethyl acetate as eluent to yield **MTBS** as a solid (**Scheme 4.2**) (30.9 g, 70%). M. P. 99-100°C; $^1H$ NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 9H, methyl), 3.93 (s, 2H, methylene), 7.14 (d, 2H, aromatic, *J*m = 2.14), 7.37 (d, 2H, aromatic *J*m = 2.14), 9.82 (s, 2H, HCO), 11.72 (s, 2H, OH) ppm; $^{13}C$ ($CDCl_3$, 50 MHz): δ 197.6, 160.3, 139.3, 135.1, 131.6, 121.1, 40.7, 35.3, 29.7 ppm; Anal. Calcd for ($C_{23}H_{28}O_4$): C, 74.97; H, 7.66, Found: C, 74.80; H, 7.58%.




**Scheme 4.2** Synthesis of 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde (MTBS)

#### 4.2.2.3. Poly[(*R,R*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine} cyclohexene 1,2 -diamine] (A)

5,5'-methylene-di-3-*tert*-butylsalicylaldehyde **C** (0.002 mol) was dissolved in methanol and 1*R*,2*R*-(-)-cyclohexanediamine (0.002 mol) was added under cold condition and the resulting mixture was refluxed for 6-8 h. After cooling a partial removal of the solvent from the reaction mixture precipitated out the desired chiral ligands high yield. This ligand was recrystallized with ethanol and characterized by micro analysis, IR, $^1$H NMR and Vapour Pressure Osmometry (VPO). $M_n$= ~5400, n = ~12; Yield. 84% (**Scheme 4.3**); IR (KBr): 1620 ν(H-C=N) cm$^{-1}$; $^1$H NMR ($CDCl_3$, 200MHz): δ 1.36 (s, 18H, *t*- butyl), 1.87 (m, 8H, cyclohexane), 3.29 (bm, 2H, asymmetric), 3.68 (s, 2H, methylene), 6.74 (d, 2H, aromatic, $J_m$ = 2Hz), 7.05 (d, 2H, aromatic, $J_m$ = 2Hz), 8.21 (s, 2H, azomethine), 13.77 (bs, 2H, OH) ppm. $^{13}$C ($CDCl_3$, 50 MHz): δ 24.9, 30.0, 33.8, 35.4, 41.1, 73.0, 119.1, 130.1, 130.9, 137.7, 159.2, 166.1 ppm; Anal. Calcd. for ($C_{29}H_{40}N_2O_2$): C, 77.64; H, 8.98; N, 6.24, Found: C, 77.52; H, 8.93; N, 6.20%.

#### 4.2.2.4. Characterization of Polymeric Zn(salen) complex (Polycy-Zn(7))

IR (KBr) 2953, 2914, 2863, 2342, 1630, 1435, 1325, 1273, 1253, 1075, 835, 785, 532 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): δ 1.39 (s, 8H, *t*-butyl), 1.89 (m, 8H, cyclohexene),

3.35 (bm, 2H, asymmetric), 3.72 (s, 2H, methylene), 6.75 (d, 2H, aromatic, $J_m$ = 2Hz), 7.1 (d, 2H, aromatic, $J_m$ = 2Hz), 8.25 (s, 2H, azomethine) ppm; $^{13}$C NMR (50 MHz, $CDCl_3$): δ 24.9, 30.0, 33.8, 35.6, 42.1, 73.0, 118.5, 129.1, 133.1, 138.4, 158.8, 170.5 ppm; Anal. Calcd. For ($C_{37}H_{38}N_2O_2Zn$): C, 73.72; H, 6.31; N, 4.65, Found: C, 73.10; H, 6.25; N, 4.63%.

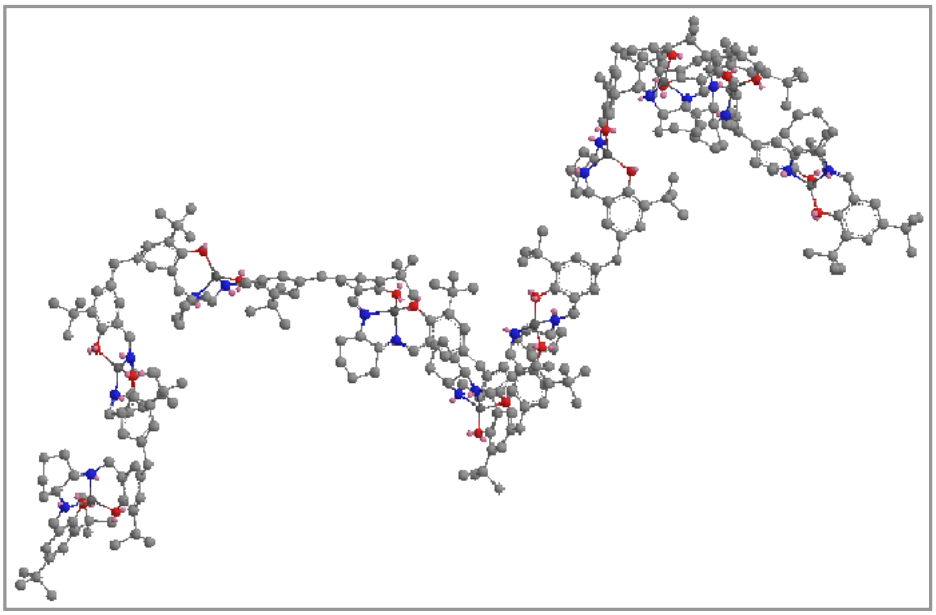


**Figure 4.1** Energy minimized structure of polymeric Zn (salen) complex

### 4.2.3. General Procedure for Asymmetric Addition of Phenylacetylene to Aldehydes

A flame dried 10-ml two necked round bottom flask was flushed with dry argon and charged with polymeric salen ligand (0.025 mmol, 10 mol %) in dry toluene (2 ml) at room temperature. To the above stirring solution, 1 M solution of $Et_2Zn$ (0.50 mmol, 2 equiv.) was added drop wise and the mixture was allowed to stir for 12 h at room temperature. Phenylacetylene (0.53 mmol, 2.1 equiv.) was added and stirred for 1h, and then aldehyde (0.25 mmol) was added. The resulting mixture was stirred at room temperature till the reaction was complete (20 h). Finally the salen complex was

precipitated out from the reaction mixture by the addition of hexane, which was further washed with hexane and dried under vacuum for re-use experiments. The filtrate was quenched with water and extracted with diethyl ether. The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated. The residue was subjected to column chromatography on silica gel eluted with 5-10% ethyl acetate in hexane. The ee values of products were measured by HPLC using a chiral column. The configurations of products were assigned by comparison with the sign of specific rotation of the known compounds.[20a]

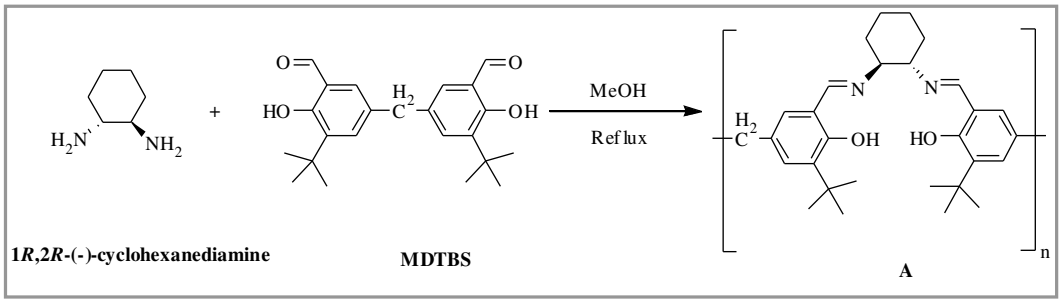
**4.2.4. General Procedure for Asymmetric Addition of Phenylacetylene to Ketones**

A flame dried 10-ml two necked round bottom flask was flushed with dry argon and charged with polymeric salen ligand (0.025 mmol, 10 mol %) in dry toluene (2ml) at room temperature. To the above stirring solution, 1 M solution of $Et_2Zn$ (0.75 mmol, 3 equiv.) was added drop wise and the mixture was allowed to stir for 12 h at room temperature. Phenylacetylene (0.75 mmol, 3 equiv.) was added and stirred for 1h, and then ketone (0.25 mmol) was added. The resulting mixture was stirred at room temperature till the reaction was complete (60 h). Finally the salen complex was precipitated out from the reaction mixture by the addition of hexane, which was further washed with hexane and dried under vacuum for re-use experiments. The filtrate was quenched with water, extracted with diethyl ether and dried with anhydrous sodium sulfate, filtered and concentrated. The residue was subjected to column chromatography on silica gel eluted with 5-10% ethyl acetate in hexane. The ee values were measured by HPLC using a chiral column.

## 4.3. Results and Discussion

### 4.3.1. Synthesis and Characterization

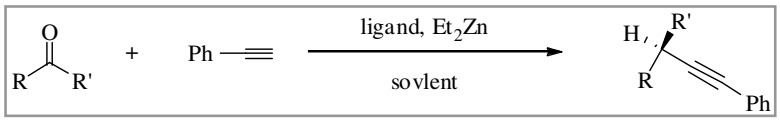
Polymeric salen ligand was synthesized by condensation of mono tartrate salt of 1*R*, 2*R*-(-)-diaminocyclohexane with 5, 5 ethylene-di-3-*tert* butyl salicylaldehyde in 1:1 molar ratio in methanol (**Scheme 4.3**). $^{1}$H NMR and IR showed the absence of aldehyde group in the ligand**.** The number of repetitive units and average molecular weight of the polymeric ligand as measured by vapour pressure osmometry was ~5400 (n =12).




**Scheme 4.3** Synthesis of chiral polymeric salen ligand **A**

### 4.3.2. Asymmetric Phenylacetylene Addition to Aldehydes and Ketones

The polymeric salen ligand was used for *in situ* generation of polymeric Zn salen catalyst for enantioselective phenylacetylene addition to various aldehydes/ketones in two steps: (1) treatment of polymeric salen ligand with $Et_2Zn$ in toluene at room temperature (2) addition of phenylacetylene, an aldehyde/ketone to give chiral secondary / *tertiary* propargylic alcohols at room temperature.




**Scheme 4.4** Asymmetric phenylacetylene addition to carbonyls

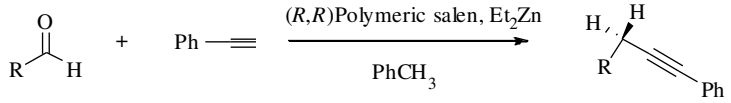
In order to confirm the probable structure of polymeric Zn salen complex as active recyclable catalyst, we have isolated the complex from the reaction mixture by removing the solvent under reduced pressure and subsequent recrystallization in $CH_2Cl_2$ gave yellow solid. (Data given in experimental section 4.2.3.).

From the data in **Table 4.1**, it can be seen that the present catalytic protocol is quite general for the range of substrates used in the present study. However, the substituents on benzaldehyde derivatives had some influence on the yield and ee of the product. For example *p*-methyl benzaldehyde among aldehydes substrate gave higher yield (96%) and good ee (72%) (**Table 4.1**, entry 6). On the other hand the substrates with bulky substituents e.g., 1-naphthaldehyde and 2-naphthaldehyde (**Table 4.1**, entry 8 and 9) gave good yield but moderate enantioselectivity. We have also screened the efficacy of this ligand as active pre catalyst with aliphatic aldehydes to achieve good yield (80-88%) with moderate enantioselecitivity. While with ketone substrates, *p*-methoxy acetophenone fared best with 79% yield and 68% ee for the corresponding *tertiary* propargyl alcohol (**Table 4.2**, entry 17). The absolute configuration of the major enantiomer of the addition product is same as the absolute configuration of the chiral source moiety of the polymeric ligand used as the catalyst precursor.

To compare these results with that of monomeric Jacobsen catalyst, the enantioselective addition of phenylacetylene to benzaldehyde and acetophenone was conducted under our standard reaction condition in toluene which gave 85% yield with 56% ee in the case of benzaldehyde (**Table 4.1**, entry 1) while the yield was found to be 71% with ee 51% (**Table 4.2**, entry 12) in case of acetophenone. The remarkable improvement in the performance of polymeric zinc complex over

monomeric complex may be due to the presence of 12 active catalytic centers on it that may have some beneficial influence on each other.

**Table 4.1** Asymmetric addition of phenylacetylene to aldehydes using **Polycy-Zn(7)** complex[a]




**1a-j** **2** **3a-j**

| Entry | RCHO | Products | Yield[b] (%) | Ee[c] (%) |
|---|---|---|---|---|
| 1[d] | $C_6H_5CHO$ (**1a**) | **3a** | 85 | 56 |
| 2 | $C_6H_5CHO$ (**1a**) | **3a** | 88 | 61 |
| 3 | *o*-$CH_3C_6H_4CHO$ (**1b**) | **3b** | 84 | 62 |
| 4 | *o*-$OCH_3C_6H_4CHO$ (**1c**) | **3c** | 82 | 54 |
| 5 | *m*-$OCH_3C_6H_4CHO$ (**1d**) | **3d** | 89 | 60 |
| 6 | *p*-$CH_3C_6H_4CHO$ (**1e**) | **3e** | 96 | 72 |
| 7 | *p*-$OCH_3C_6H_4CHO$ (**1f**) | **3f** | 90 | 67 |
| 8 | 1-naphthylCHO (**1g**) | **3g** | 85 | 64 |
| 9 | 2-naphthylCHO (**1h**) | **3h** | 81 | 58 |
| 10 | $(CH_3)_2CH$-$CH_2CHO$ (**1i**) | **3i** | 80 | 51 |
| 11 | $C_6H_{11}CHO$ (**1j**) | **3j** | 87 | 58 |

[a]10 mol% polymeric salen ligand used $Et_2Zn$ (2 equiv.), phenylacetylene (2.1 equiv.), aldehyde(1equiv.), toluene (2 ml), 20 h, room temperature. [b]Isolated yield. [c]The ee values were determined by HPLC using chiralcel OD column. The absolute configurations were assigned by comparison to literature values. [d]Reaction was carried out using 10 mol% Jacobsen salen ligand.

Ketones proved less reactive than aldehydes and the reaction took longer time to complete (60 h) at room temperature. The over all reactivity and enantioselectivity of catalytic system with all the aldehydes used in the present study was quite superior to those of ketones as shown in **Figure 4.1** & **4.2**.

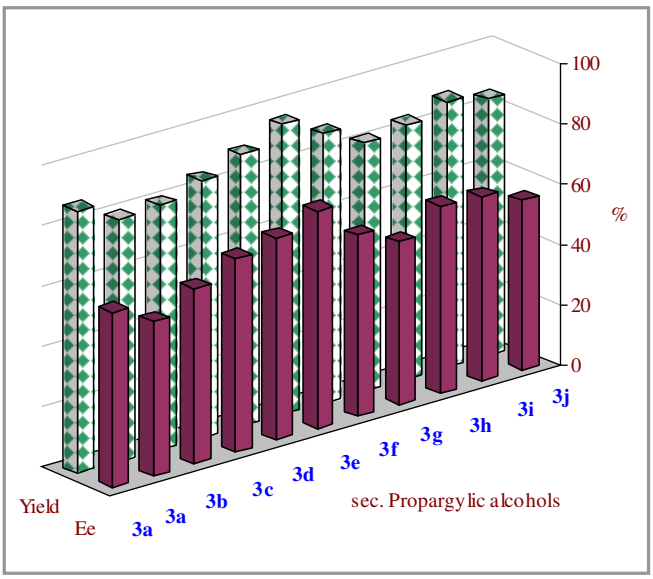
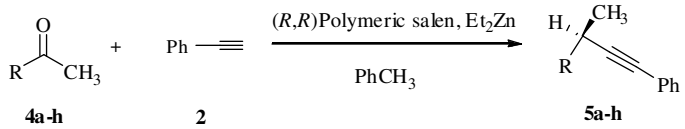



**Figure 4.1** 3D view showing % ee and yield of secondary propargylic alcohols

**Table 4.2** Asymmetric addition of phenylacetylene to ketones using **Polycy-Zn(7)** complex[a]




| Entry | Ketones | Products | Yield[b] (%) | Ee[c] (%) |
|---|---|---|---|---|
| 12[c] | $C_6H_5COCH_3$ (**4a**) | **5a** | 71 | 51 |
| 13 | $C_6H_5COCH_3$ (**4a**) | **5a** | 75 | 55 |
| 14 | *o*-$CH_3C_6H_5COCH_3$ (**4b**) | **5b** | 62 | 57 |
| 15 | *o*-$BrC_6H_5COCH_3$ (**4c**) | **5c** | 68 | 63 |
| 16 | *p*-$CH_3C_6H_5COCH_3$ (**4d**) | **5d** | 72 | 65 |
| 17 | *p*-$OCH_3C_6H_5COCH_3$ (**4e**) | **5e** | 79 | 68 |
| 18 | *p*-$FC_6H_5COCH_3$ (**4f**) | **5f** | 70 | 54 |
| 19 | 1-naphthyl$COCH_3$ (**4g**) | **5g** | 63 | 61 |
| 20 | $(CH_3)_2CH\ COCH_3$ (**4h**) | **5h** | 74 | 52 |

10 mol% poly salen ligand used $Et_2Zn$ (3 equiv.), phenylacetylene (3 equiv.), ketone (1equiv.), toluene (2 ml), 60 h, room temperature. [b]Isolated yield. [b]The ee values were determined by HPLC using chiralcel OD column. The absolute configurations were assigned by comparison to literature values. [c]Reaction carried out using 10 mol% Jacobsen salen ligand.

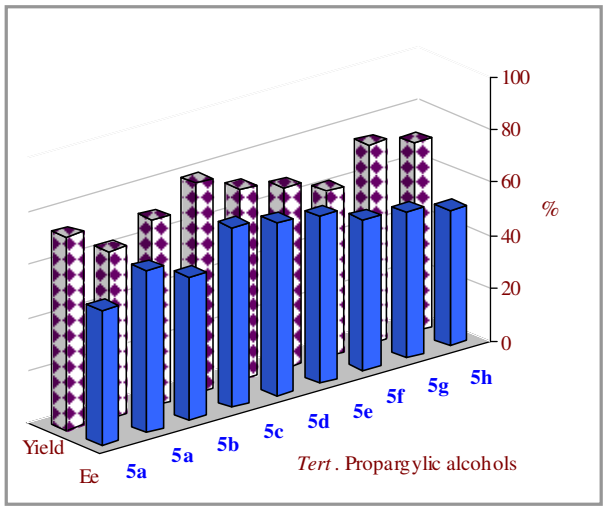



**Figure 4.2** 3D view showing % Ee and yield of *tertiary* propargylic alcohols

### 4.3.3. Effect of Solvents, Temperature and Catalyst loading in Enantioselective Addition of Phenylacetylene to Carbonyls

It has been reported in literature that enantioselective addition of phenylacetylene to aldehydes and ketones depends on various parameters such as solvent, temperature and catalyst loading.[23] For this purpose, we have selected polymeric salen ligand **B** catalyzed enantioselective addition of phenylacetylene to benzaldehyde and acetophenone as model reaction to optimize the reaction condition and data are presented in **Table 4.3** & **4.4**. Of all the solvents used (**Table 4.3**, entries 21-24 & **Table 4.4**, entries 28-31) toluene was found to the best for this addition reaction (**Table 4.3**, entry 21 & **Table 4.4**, entry 28). On conducting the catalytic reaction at 0 $^{o}$C, the reaction did not proceed at all (**Table 4.3**, entry 27 & **Table 4.4**, entry 34). Upon increasing the reaction temperature from room temperature to 50 $^{o}$C, fast conversion was observed (**Table 4.3**, entry 26 & **Table 4.4**, entry 33) but there was a significant drop in enantioselectivity. Further, the effect of loading of chiral polymeric salen ligand (10mol% – 20mol %) on product yield and enantioselectivity was also studied, but there

is no significant improvement in the performance of the catalytic reaction (**Table 4.3**, entry 25 & **Table 4.4**, entry 32).

**Table 4.3** Effect of solvent, temperature and catalyst loading in enantioselective phenylacetylene addition to benzaldehyde using polymeric (Zn) salen complex[a]

| Entry | T ($^oC$) | Solvent | Yield[b] (%) | Ee[c] (%) |
|---|---|---|---|---|
| 21 | rt | Toluene | 88 | 61 |
| 22 | rt | $CH_2Cl_2$ | 75 | 52 |
| 23 | rt | $Et_2O$ | 60 | 33 |
| 24 | rt | THF | 63 | 38 |
| 25[d] | rt | Toluene | 82 | 57 |
| 26 | 50 | Toluene | 90 | 35 |
| 27 | 0 | Toluene | - | - |

[a]10 mol% polymeric salen ligand, $Et_2Zn$ (2 equiv.), phenylacetylene (2.1 equiv.), benzyldehyde (1equiv.), toluene (2 ml), 20 h, [b]Isolated yield. [c]Determined by HPLC using chiralcel OD column. The absolute configurations were assigned by comparison to literature values. [d]20 mol% polymeric ligand.

**Table 4.4** Effect of solvent, temperature and catalyst loading in enantioselective phenylacetylene addition to acetophenone using polymeric (Zn) salen complex[a]

| Entry | T ($^oC$) | Solvent | Yield[b] (%) | Ee[c](%) |
|---|---|---|---|---|
| 28 | rt | Toluene | 75 | 55 |
| 29 | rt | $CH_2Cl_2$ | 67 | 49 |
| 30 | rt | $Et_2O$ | 60 | 45 |
| 31 | rt | THF | 43 | 20 |
| 32[d] | rt | Toluene | 62 | 51 |
| 33 | 50 | Toluene | 80 | 30 |
| 34 | 0 | Toluene | - | - |

[a]10 mol% polymeric salen ligand,$Et_2Zn$ (2 equiv.), phenylacetylene (2.1 equiv.), acetophenone (1equiv.), toluene (2 ml), 60 h, [b]Isolated yield. [c]The ee values were determined by HPLC using chiralcel OD column. The absolute configurations were assigned by comparison to literature values.[d]20 mol% polymeric ligand

### 4.3.4. Recovery and Recycling of Catalyst

The interesting feature of this novel polymeric Zn salen complex rests in its inherent tendency to get precipitated out in a non-polar solvent like hexane due to its higher molecular weight and lower solubility in the reaction medium. In a post catalytic run, we have precipitated the catalyst by the addition of hexane to the reaction mixture. The solid thus recovered was thoroughly washed with hexane and dried in a desiccator. The recovered catalyst worked well up to four cycles but with gradual loss in reactivity due to the physical loss during post work up process. However, enantioselectivity of the product propargylic alcohols was retained (**Table 4.5**). Besides, the catalytic system proved to be most efficient recyclable salen system so far reported[23] for the synthesis of chiral propagylic alcohols.

**Table 4.5** Data for asymmetric phenylacetylene addition to benzaldehyde and acetophenenone with recycled **Polycy-Zn(7)**catalyst

| Catalytic cycle | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Yield (%) | 88(75) | 85 (70) | 80(67) | 79 (61) |
| Ee (%) | 60 (55) | 59 (55) | 59(54) | 58(54) |

10 mol% polymeric salen ligand used $Et_2Zn$ (2 equiv.), phenylacetylene (2.1 equiv.), aldehyde (1equiv.), 20 h. Result in parenthesis are for ketone (1 equiv.) used $Et_2Zn$ (3 equiv.), phenylacetylene (3 equiv.), toluene (2 ml), 60 h, rt.

## 4.4. Conclusion

In conclusion, we have developed the recyclable polymeric Zn salen complex for enantioselective addition of phenylacetylene to various aldehydes and ketones to produce corresponding chiral secondary and *tertiary* propargylic alcohols in high yields (up to 96%) with good enantioselectivity (ee; 72%) at room temperature as compared to

Jacobsen's Zn(salen) complex with an added advantage of four times reuse with retention of enantioselectivity.

## 4.5. References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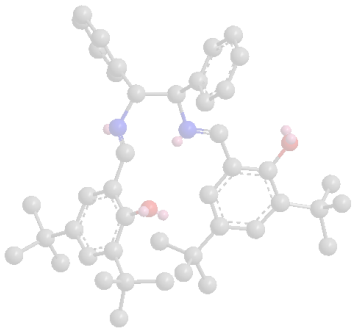
# Chapter -5

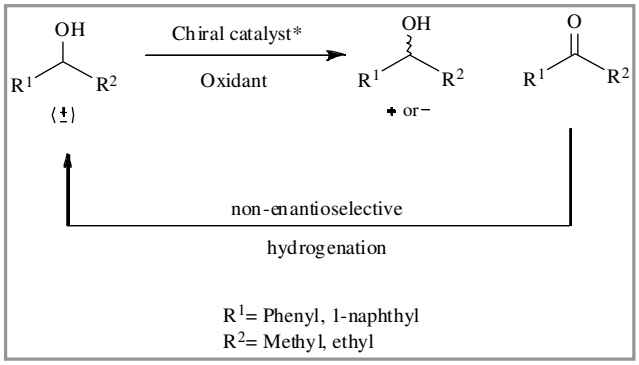


## Chiral Dimeric Mn(III) salen Complexes as Recyclable Catalysts for Oxidative Kinetic Resolution of Racemic Secondary Alcohols.

## 5.1. Introduction

After the successful utilization of chiral polymeric Zn salen complex in the asymmetric phenylacetylene addition to carbonyls, we further explored the use of chiral dimeric/polymeric salen system in another important organic transformation-enantioselective oxidation of alcohols.

The oxidation of alcohols to carbonyl compounds is one of the most fundamental organic transformations with significant biological and mechanistic interest.[1,2] With readily available efficient methods for the oxidation of alcohols,[3-11] oxidative kinetic resolution (OKR) of racemic alcohols is potentially attractive method to achieve optically active alcohols together with corresponding carbonyl compounds (**Scheme 5.1**). This strategy is so powerful that entire racemic secondary alcohol may be converted to single enantiomer of the alcohol of desired chirality by simply nonenantioselective hydrogenation of ketone obtained as a result of OKR.




**Scheme 5.1** Oxidative kinetic resolution of racemic secondary alcohols

Optically active alcohols are extremely important starting materials and key intermediates in the production of chiral building blocks for the synthesis of pharmaceutically important and biologically active compounds.[12] Toward this goal,

enzyme catalysts were extensively used for kinetic resolution through selective oxidation of one of the enantiomers.[13-17] Recently, several effective non-enzymatic catalysts for the OKR of racemic alcohols have been studied.[18-23] Katsuki and co-workers have reported the use of BINOL-derived Ru(salen) complexes as catalysts in the photo-induced aerobic oxidation of racemic secondary alcohols.[24] In this system though alcohols with high enantioselectivity was achieved, the reaction time was too long. Later, the same group reported enantioselective oxidation of racemic alcohols using BINOL-derived Mn(salen) complexes as catalysts with PhIO as an oxidant[25], however, only low yields and moderate enantioselectivity were achieved.

Recently, Xia et al have reported OKR of racemic secondary alcohols with chiral Mn(salen) catalysts with excellent enantioselectivity.[26] However, the catalyst stability, product and catalyst separation remained difficult for this homogeneous system. As chiral catalysts are expensive, their reusability is highly advantageous. Surprisingly, recyclable catalyst based on salen ligand for OKR of racemic alcohols was not so far reported in the literature. Although, chiral dimeric Mn salen complexes have been extensively used as recyclable catalysts in asymmetric epoxidation reaction in the literature.[27-30]

In this chapter, we have synthesized chiral dimeric Mn(III) salen complexes **Dimercy-MnCl(8).**[27a] Also complex **Dimercy-MnOAc(9)** was synthesized when the counterion $Cl^-$ from **Dimercy-MnCl(8)** was replaced with $OAc^-$. Besides, its diphenyl version-**Dimerdph-MnCl(10)** was synthesized by taking chirally pure diphenylethylene diamine as in place of chirally pure cyclohexanediamine. All the three complexes were characterized by appropriate physico-chemical techniques. These complexes were then used in oxidative kinetic resolution of racemic secondary alcohols using iodobenzene

diacetate ($PhI(OAc)_2$) as an oxidant and KBr as an additive at room temperature. Various racemic secondary alcohols were studied in this present work. The catalyst **Dimercy-MnCl(8)** was easily recovered by precipitation by adding non-polar solvent and re-used up to five times with some loss of activity while there was no loss of enantioselectivity in the product. The effect of solvents, additives and catalysts loadings on activity and enantioselectivity of the catalytic system was also studied.

## 5. 2. Experimental

### 5.2.1. Materials & Methods

$PhI(OAc)_2$, tetraethtylammonium bromide, tetrabutylammonium bromide, KBr, LiBr and NaBr were purchased from Across Organics, Belgium. Hexylpyridinium bromide was prepared according to the known procedure.[31] 2,4-di-*tert*-Butyl phenol, 1-phenyl-2-propanol and (±)-menthol were purchased from Aldrich, while other alcohols used in the present study were prepared by the reduction of corresponding ketones with $NaBH_4$. All the solvents used in the present study were purified by the known methods.[32]

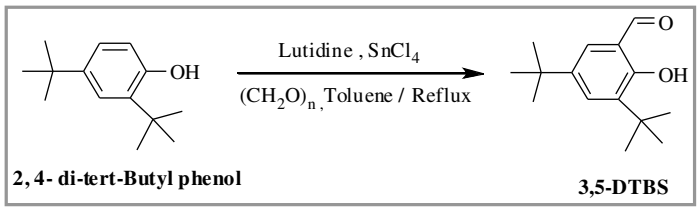
### 5.2.2. Synthesis of Chiral Dimeric salen Ligands

The synthesis of chiral dimeric salen ligands is described as follows.

#### 5.2.2.1. 3,5-di-*tert*-Butyl salicylaldehyde (3,5-DTBS)

2, 6-lutidine (4.3 mL, 0.041 mol), $SnCl_4$ (5.2 mL, 0.020 mol), 2, 4- di-*tert*-Butyl phenol (10 g, 0.67 mol) was taken in toluene (200 ml). The resulting mass was stirred at 25 °C under nitrogen for 1 h followed by the addition of paraformaldehyde (8.0 g, 0.26mol). The mixture was heated under reflux for 8 h and the reaction progress was monitored by TLC. The reaction mixture was allowed to cool to 25 °C and water (200

ml) and diethyl ether (200 ml) was added. The resulting emulsion was filtered through a pad of celite and the layers were separated. The organic layer was washed with water, brine, and dried over anhydrous $Na_2SO_4$, and then concentrated. The crude product was purified by flash column chromatography on silica gel (Hexane: EtOAc= 95:05) to afford the title compound as a yellow solid (**Scheme 5.2**). IR (KBr): 2958, 1612, 1653 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.34 (s, 18H), 6.89 (t, 1H), 7.40 (d, 1H), 7.54 (d, 1H), 9.89 (s, 1H), 11.80 (s, 1H), ppm; Anal. Calcd. For ($C_{14}H_{19}O_2$): C, 76.68; H, 7.7, Found: C, 76.60; H, 7.79%.




**Scheme 5.2** Synthesis of 3,5-DTBS

**5.2.2.2. 5,5'-Methylene-di-3-*tert*-butylsalicylaldehyde (MTBS)**

The compound was synthesis according to the procedure described in experimental section 4.2.2.2.

**5.2.2.3. *N*-2-Hydroxy-3,4-di-*tert*-butyl-benzaldehyde)-1-amino-2-cyclohexeneimine (A)**

The mono tartrate salt of (1*R*,2*R*)-(-)-cyclohexane diamine (0.0112mol) and anhydrous $K_2CO_3$ (0.0225mol) were dissolved in 15 ml of distilled water with stirring. Ethanol (6ml) was added and the resulting cloudy mixture was heated to reflux at 70-80 °C for 2 h. The solvent was removed completely and the liberated diamine was extracted with $CHCl_3$ (4x5ml). The free diamine thus obtained was stirred with **3,5-DTBS** (0.0022 mol in 20ml $CHCl_3$) for 48 h at 0 $^oC$. Removal of the solvent gave yellow colored compound (**A**) (**Scheme 5.3**). $^1H$ NMR ($CDCl_3$,

200MHz): δ 1.24 (s, 9H), 1.41 (s, 9H), 1.58-2.25 (m, 11H, 2H exchangeable with $D_2O$), 3.35 (1H), 6.89 (s, 1H), 7.26 (s, 1H), 8.42 (s, 1H), 13.73 (b, 1H, exchangeable with $D_2O$) ppm; $^{13}C$ NMR ($CDCl_3$, 50 MHz): δ 25.1 25.8, 26.0, 30.0, 31.0, 34.0, 35.2, 55.3, 77.3, 118.3, 126.5, 127.5, 140.0, 142.7, 158.63, 166.1 ppm; Anal. Calcd. for ($C_{21}H_{34}N_2O$): C, 76.31; H, 10.37; N, 8.48, Found: C, 76.26; H, 10.30; N, 8.40%; MS (ESI): *m/z* = 331.37 $[M+H]^+$.

**5.2.2.4. *N*-(2-Hydroxy-3,5-di-*tert*-butyl benzaldehyde)-1-amino-1,2-diphenyl ethaneimine (B)**

3,5-di-*tert*-butyl salicylaldehyde (**3,5-DTBS**) (0.001mol) dissolved in 10 ml $CHCl_3$ reacted slowly with 0.001mol of 1*R*,2*R*-(-)-1,2-diphenylethylenediamine in 50 ml of cold $CHCl_3$; the reaction mixture was stirred for 48 h at 0 °C. The progress of the reaction was checked on TLC using a hexane:ethyl acetate (9:1) mixture. The reaction was concentrated under cold condition by vacuum evaporation to get viscous liquid (**B**) (**Scheme 5.4**). IR (KBr): 3448, 2958, 2868, 1626, 1598, 1453, 1414, 1391, 1250, 1175, 1047, 880 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200MHz): δ 1.29 (9H, s), 1.47 (9H, s), 1.66 (2H, s, br), 4.29-4.44, (q, 1H), 4.72 (d, 1H), 6.87-7.30 (bs, 12H, aromatic), 8.46 (s, 1H, H-C=N), 13.60 (s, 1H, OH exchangeable with $D_2O$) ppm; Anal. Calcd. for ($C_{29}H_{36}N_2O$): C, 81.32; H, 8.40; N, 6.53, Found: C, 81.25; H, 8.36; N, 6.48%; MS (ESI): *m/z* = 429.30 $[M+H]^+$.

**5.2.2.5. 5,5-Methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N'*-(3',5'-di-*tert*-butyl salicylidene)]-1,2-cyclohexanediamine] (1A)**

Compound **A** (0.002 mol) in $CH_2Cl_2$ and 5,5-methylene-di-3-*tert*-butyl salicylaldehyde (**MTBS**) (0.001 mol) in ethanol were refluxed for 6-8 h. The resulting solution on concentration precipitated out the desired chiral ligand (**1A**) (**Scheme 5.3**).Yield 85%. IR (KBr): 1620 ν(H-C=N) $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 200

MHz): δ 1.23 (s, 18H), 1.40 (s, 36H), 1.54-2.0 (m, 16 H), 3.22 (s, 4H), 3.68 (s, 2H), 6.74 (s, 4H), 7.05 (s, 4H), 8.21 (s, 4H), 13.69 (bs, 4H exchangeable with $D_2O$) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 23.3, 24.8, 28.3, 29.4, 31.6, 34.9, 35.4, 40.2, 42.2, 65.1, 69.4, 121.3, 125.0, 127.1, 128.4, 128.8, 137.1, 138.2, 139.2, 139.5, 157.3, 161.4 ppm; Anal. Calcd for ($C_{65}H_{92}O_4N_4$): C, 78.58; H, 9.34; N, 5.64, Found: C, 78.26; H, 9.30; N, 5.47%.

**5.2.2.6. 5,5-Methylene di-[(*R,R*)-{*N*-(3-*tert*-butyl salicylidine)-*N'*-(3',5'-di-*tert*-butyl salicylidene)]-1,2-diphenylethylenediamine] (1B)**

Compound **B** (0.002 mol) in $CH_2Cl_2$ and 5,5-methylene-di-3-*tert*-butyl salicylaldehyde (**MTBS**) (0.001 mol) in ethanol were refluxed for 6-8 h. The resulting solution on concentration precipitated out the desired chiral ligand (**1B**) (**Scheme 5.4**). Yield 85%.; IR (KBr): 1620 ν(H-C=N) $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 1.24 (18H, s,), 1.46 (36H, s,), 3.87 (2H, s,), 4.65 (4H, s,), 6.77–7.60 (28H, m), 8.32 (4H, s), 13.63 (4H, bs) ppm; $^{13}C$ NMR (50 MHz, $CDCl_3$): δ 29.4, 31.4, 34.9, 40.2, 76.4, 117.8, 118.4, 126.3, 127.9, 128.2, 131.2, 137.0, 137.4, 139.6, 139.9, 157.9, 166.8 ppm; Anal. Calcd for ($C_{81}H_{96}O_4N_4$): C, 81.78; H, 8.14; N, 4.71, Found: C, 81.42; H, 7.80; N, 4.54%.

**5.2.3. Synthesis of Chiral Dimeric Mn(III) salen Complexes**

The synthesis of chiral dimeric Mn(III) salen Complexes is described as follows.

**5.2.3.1. 5,5-Methylene di-[(*R,R*)-{*N*-(3-*tert*-butylsalicylidine)-*N'*-(3',5'-di-*tert*-butyl salicylidene)}-1,2-cyclohexanediaminato(2-) manganese(III) chloride] Dimercy-MnCl(8)**

The chiral dimeric schiff base **1A** (1 gm, 0.001 mol) was dissolved in 40 ml $CH_2Cl_2$:$CH_3OH$ (1:1) and $Mn(CH_3COO)_2 \cdot 4H_2O$ (0.48 gm, 0.002 mol) was added to it in an inert atmosphere. The reaction mixture was refluxed for 8 h and the reaction was

monitored by TLC using hexane:ethyl acetate (6:4) as the mobile solvent. The reaction mixture was cooled to room temperature; lithium chloride (0.25 gm, 0.006 mol) was added, and the mixture was stirred for 5 h in air and filtered. The solvent was removed from the filtrate and the residue was extracted with dichloromethane. The organic layer was washed with water and brine and dried over sodium sulphate. After partial removal of the solvent the desired complex **Dimercy-MnCl(8) (Scheme 5.3)** was precipitated upon the addition of petroleum ether (40-60). (0.91 gm Yield 90%); IR (KBr): 3431 (br), 2947 (s), 2866 (s), 1612 (s), 1538 (s), 1475 (sh), 1435 (s), 1388 (m), 1342 (s), 1309 (s), 1285 (sh), 1238 (sh), 1201 (m), 1170 (m), 1100 (w), 1030 (m), 940 (w), 833 (m), 780 (w), 731 (w), 690 (w), 568 (s), 475 (w) $cm^{-1}$; UV-Vis ($CH_2Cl_2$) $\lambda_{max}(\varepsilon)$: 250 (50000), 266 (49960), 345 (47540), 420 (41460), 451(41040), 510(36060); Anal. Calcd. for ($C_{65}H_{92}Cl_2Mn_2N_4O_6$): C, 67.81; H, 8.06; 4.87, Found: C, 67.60; H, 8.02; N, 4.83%; MS (ESI): *m/z* = 1187 $[M + H_2O]^+$; $[\alpha]^{25}_D$ = - 50.4 (c = 0.12, $CH_2Cl_2$).

**5.2.3.2. 5,5-methylene di-[(*R*,*R*)-{N-(3-tert-butyl salicylidine)-N'-(3',5'-di-tert-butyl salicylidene)}-1,2-cyclohexanediaminato(2-) manganese(III) acetate] Dimercy-MnOAc(9)**

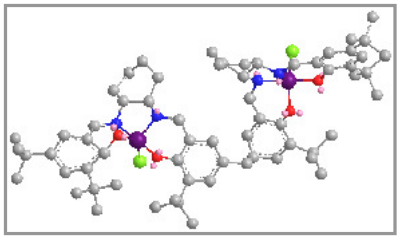
The dimeric Schiff base **1A** (1 gm, 0.001 mol) was dissolved in $CH_2Cl_2$ (15 ml) while $Mn(CH_3COO)_2 \cdot 4H_2O$ (0.48 gm, 0.002 mol) was taken in $CH_3OH$ (5 ml) and the two solutions were mixed and refluxed under an inert atmosphere for 5-8 h. The reaction mixture was allowed to cool to room temperature and a slow stream of air was allowed to pass through the reaction mixture for 2 h. The mixture was filtered and the solvent was removed from the filtrate. The residue thus obtained was extracted with dichloromethane (3 x 15ml). The combined extracts were washed with water (3 x 10 ml) and the organic layer was dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced

pressure and the crude product thus obtained was recrystallized with petroleum ether/$CH_2Cl_2$ to get the desired complex **Dimercy-MnOAc(9)** as brown powder (0.95 gm, yield 94%) (**Scheme 5.3**). IR (KBr): 3426 (br), 2951 (s), 2865 (s), 1612 (s), 1537 (s), 1477 (sh), 1432 (s), 1389 (m), 1341 (s), 1310 (s), 1271 (sh), 1252 (sh), 1201 (m), 1173 (m), 1102 (w), 1028 (m), 928 (w), 835 (m), 780 (w), 748 (w), 691 (w), 567 (s), 477 (w), 418 (w) $cm^{-1}$; UV–vis ($CH_2Cl_2$): $\lambda_{max}$ ($\varepsilon$) 242 (50000), 264 (49956), 323 (47535), 418 (41450), 436 (41032), 512 (36058); Anal. calcd. for ($C_{69}H_{94}Mn_2N_4O_8$) (1216): C, 68.09; H, 7.73; N 4.60, Found: C, 67.98; H, 7.69 N, 4.58 %;; MS (ESI): *m/z* = 1234 $[M + H_2O]^+$; $[\alpha]_D^{25}$ = -174 (c= 0.12, $CH_2Cl_2$).

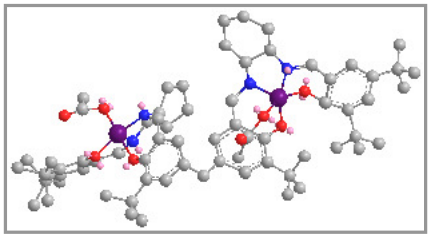
**5.2.3.3. 5,5-methylene di-[(*R*,*R*)-{N-(3-tert-butyl salicylidine)-N'-(3',5'-di-tert-butyl salicylidene)}-1,2-diphenylethylene diaminato(2-) manganese(III) chloride] Dimerdph-MnCl(10)**

The dimeric Schiff base **1B** (1.2 gm, 0.001 mol) in $CH_2Cl_2$ (15 ml) was stirred under reflux with $Mn(CH_3COO)_2 .4H_2O$ (0.48 gm, 0.002 mol) in $CH_3OH$ (5 ml) under an inert atmosphere for 8–10 h. The reaction mixture was cooled to room temperature. Lithium chloride (0.25 gm, 0.006 mol) was added and the mixture was stirred for a further 4 h while exposed to air. The mixture was filtered and the solvent was removed from the filtrate. The evaporation residue was extracted with dichloromethane (3 x 10 ml) and washed with water (2 x 10 ml), brine and dried over anhydrous $Na_2SO_4$. The solvent was removed under reduced pressure and the crude product thus obtained was recrystallized with petroleum ether to get the desired complex **Dimerdph-MnCl(10)** as solid brown powder (1.0 gm, yield 90%) (**Scheme 5.4**). IR (KBr): 3434 (br), 2954 (s), 2867 (s), 1608 (s), 1535 (s), 1456 (sh), 1428 (s), 1388, 1311 (s), 1250 (s), 1172 (m), 1026 (w), 918 (w), 850 (w), 698 (w), 554 (s) $cm^{-1}$; UV–vis: ($CH_2Cl_2$): $\lambda_{max}$ ($\varepsilon$) 242 (5239), 323

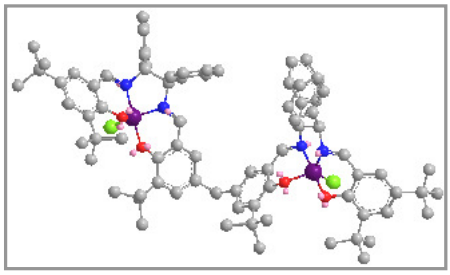
(73078), 440 (23548), 508 (8265), 538 (6608); Anal. calcd. for ($C_{81}H_{92}Cl_2Mn_2N_4O_4$) (1364.5) : C, 71.21; H, 7.03; N 4.10, Found: C, 71.35; H, 6.90; N, 3.95%; MS (ESI): *m/z* =1382.5 $[M + H_2O]^+$; $[\alpha]_D^{25}$ = -128 (c= 0.14, $CH_2Cl_2$).



**Dimercy-MnCl(8)**



**Dimercy-MnOAc(9)**



**Dimerdph-MnCl(10)**

**Figure 5.1** Energy minimized structure of Dimeric Mn(III) salen complexes

### 5.2.3.4. Characterization of Recycled Catalyst: Dimercy-MnCl(8)

The catalyst was recovered after its 3rd consecutive reuse in OKR of 1-phenylethanol. The recovered catalyst was characterized by IR, elemental analysis, UV and ESI-MS analysis: IR (KBr): 3427 (br), 2952 (s), 2860 (s), 1611 (s), 1535 (s), 1470 (sh), 1432 (s), 1392 (m), 1336 (s), 1310 (s), 1283 (sh), 1242 (sh), 1200 (m), 1170 (m), 1100 (w), 1030 (m), 945 (w), 836 (m), 785 (w), 732 (w), 690 (w), 562 (s), 470 (w) $cm^{-1}$; Anal. calcd. for ($C_{65}H_{88}Cl_2Mn_2N_4O_4$) (1169): C, 67.80; H, 8.05; N 4.85, Found: C, 66.67; H, 7.85; N, 4.70%; UV–vis ($CH_2Cl_2$): $\lambda_{max}$ (ε) 253 (50000), 260 (49960), 343 (47540), 422 (41460), 455 (41040), 513 (36060); MS (ESI): *m/z* = 1187 $[M + H_2O]^+$

**5.2.3.5. Procedure for the Oxidative Kinetic Resolution of Racemic Secondary Alcohols Catalyzed by Chiral Dimeric Mn(III) salen Complexes**

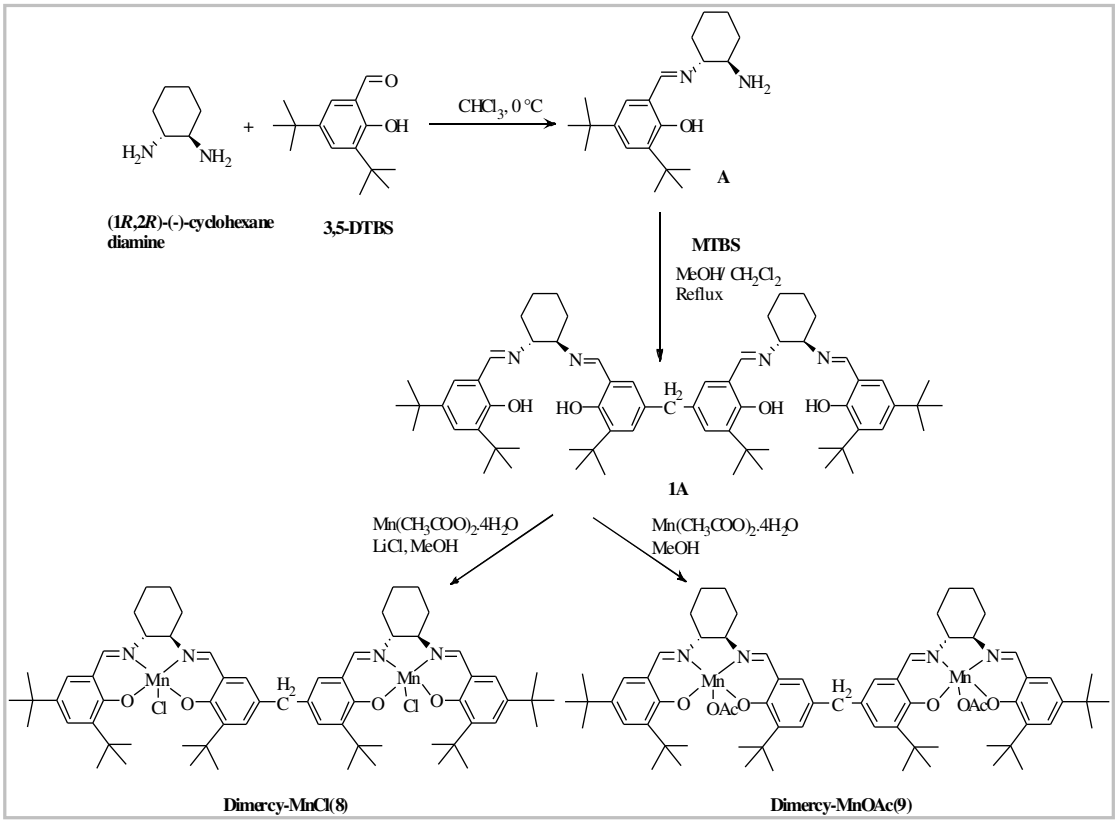
In a typical procedure, a mixture of the substrate (1 mmol), catalyst (0.02 mmol, based on monomeric salen unit), additive (0.04 mmol, 4 mol %), $CH_2Cl_2$ (1 ml) and water (2 ml) was stirred in a 10 ml glass vial for 10 minutes at room temperature. The oxidant $PhI(OAc)_2$ (0.7 mmol) was then added and the system was magnetically stirred for mentioned time at room temperature. Progress of the reaction was monitored on GC/ HPLC using suitable chiral columns. After the desired level of oxidation was achieved, the catalyst was precipitated out by the addition of n-hexane, which was removed by filtration. The recovered catalyst was washed with diethyl ether (3 x 5 ml), dried under vacuum and kept in desiccator for recycling experiments. The filtrate and washings were combined, washed with brine, dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure.

## 5.3. Results and Discussion

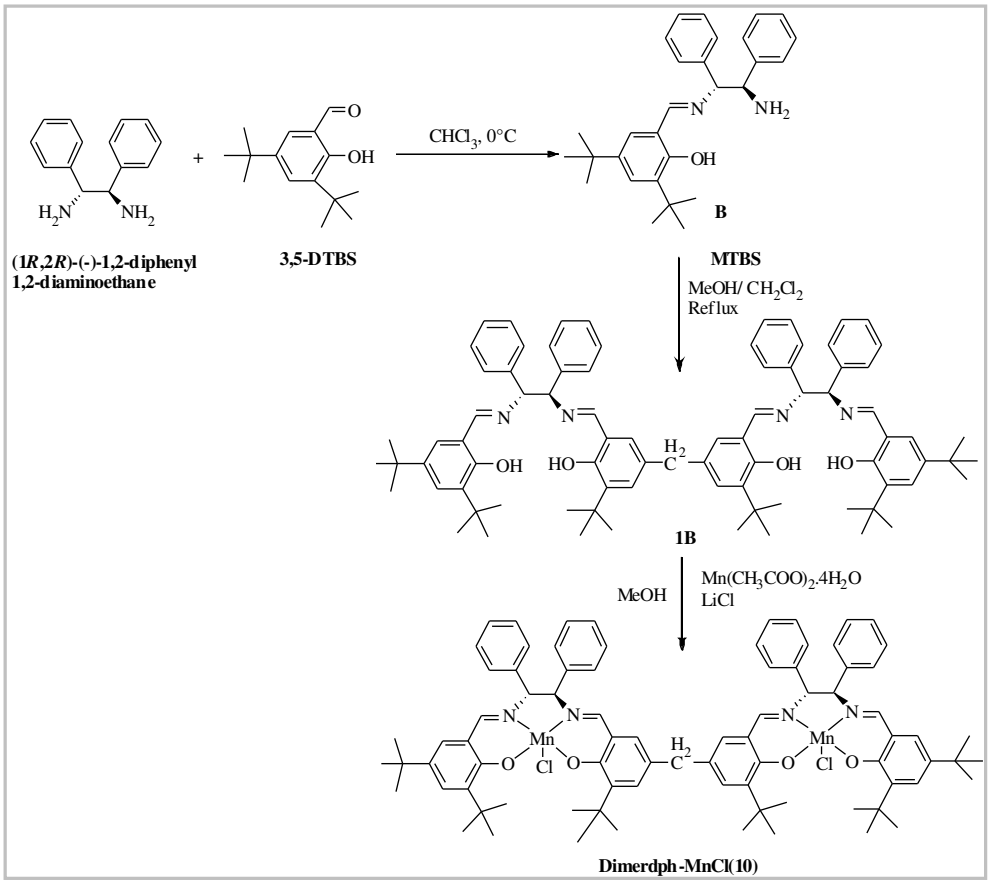
### 5.3.1. Synthesis and Characterization of Chiral Dimeric Mn(III) salen Complexes

Chiral dimeric Mn(III) salen complexes **Dimercy-MnCl(8)**, **Dimercy-MnOAc(9)** and **Dimerdph-MnCl(10)** were synthesized by the synthetic strategy shown in **Scheme 5.3 & 5.4**. Accordingly, condensation of chiral amines with 3,5- di-*tert*-butyl salicylaldehyde in a 5:1 molar ratio in $CHCl_3$ at low temperature to get **A** and **B**. Free amines function of **A** and **B** were then condensed further with **MTBS** to get chiral dimeric ligands **1A** and **1B** respectively. Dimeric Schiff base **1A and 1B** were then interacted with manganese(II) acetate followed by their air oxidation. In the case of complex **Dimercy-MnOAc(9),** LiCl was not used. Complexes were characterized by

NMR, microanalysis, conductance, optical rotation, UV–Vis. and IR spectroscopy and data are given in experimental section 5.2.3.




**Scheme 5.3** Synthesis of dimeric Mn(III) salen complexes **Dimercy-MnCl(8)** and **Dimercy-MnOAc(9)**.




**Scheme 5.4** Synthesis of dimeric Mn(III) salen complex **Dimerdph-MnCl(10)**

### 5.3.2. Oxidative Kinetic Resolution (OKR) of Racemic Secondary Alcohols

Dimeric Mn(III) salen complexes were screened for their efficacy as catalysts in oxidative kinetic resolution of racemic secondary alcohols. It has been reported earlier that bromide salts play distinctive role for the activation of both PhIO[33] and $PhI(OAc)_2$[26] for the oxidation of various alcohols to give ketones whereas others halide ions were only marginally active. Therefore, these catalysts (5 mol %, based on monomeric salen unit) were examined for the OKR of racemic 1-phenylethanol as a representative substrate with KBr as an additive using $PhI(OAc)_2$ as an oxidant at room temperature (**Table 5.1**). We observed that catalyst **Dimercy-MnCl(8)** gave high enantioselectivity (ee, 95%)

(**Table 5.1**, entry 1) and changing the counter ion from $Cl^-$ with $OAc^-$ (complex **Dimercy-MnOAc(9)** did not alter conversion and ee significantly (**Table 5.1**, entry 2). Whereas complex **Dimerdph-MnCl(10)** was less effective catalyst than complex **Dimercy-MnCl(8)** as evidenced by low ee and $k_{rel}$ values obtained for the alcohol (entry 3). To check the efficiency of complex **Dimercy-MnCl(8)** in the kinetic resolution of 1-phenylethanol, catalytic run was performed with 2 mol% catalyst. This low catalyst loading significantly improved enantioselectivity (ee, 99%). However, further reduction in the catalyst loading from 2 mol% to 0.2 mol% (entry 5) resulted in 48% conversion and 90 % ee with longer reaction time (60 minutes).

In kinetic resolutions, enantiomers of racemic substrate react at different rates to form a product and these relative rates of reaction is typically expressed as $k_{rel} = k_{fast}/k_{slow}$. The $k_{rel}$ values are generally considered to be more useful for the evaluation and especially comparison of the efficacy of kinetic resolution catalysts.[34]

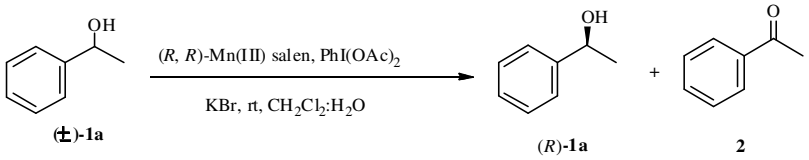
$$k_{rel} = \frac{\ln (1\text{-}c)\ (1\text{-}ee)}{\ln (1\text{-}c)\ (1\text{+}ee)}$$

Where ee is the enantiomeric excess of the secondary alcohol and c is the conversion of secondary alcohol.

In order to compare the reactivity of dimeric Mn(III) salen complex **Dimercy-MnCl(8)** with its monomeric counterpart**,** we have conducted the OKR of 1-phenylethanol as a representative substrate with monomeric Mn(III) salen complex using KBr as an additive (**Table 5.1**, entry 6). It has also been observed from the kinetic profile that the formation of the corresponding ketone increased linearly up to 5 minutes, after which a significant increase is not observed (**Figure 5.2**). Therefore, the initial rate

constants $K_{obs}$ were determined from the data in this time range for the complex **Dimercy-MnCl(8)** and monomeric Mn(III) salen complex that gives $K_{obs}$ values = 46x $10^{-2}$ M/h and 30x $10^{-2}$ M/h respectively.

**Table 5.1** OKR of 1-phenylethanol with Mn(III) salen complexes.[a]




| Entry | Catalyst | Catalyst loading (mol %) | Time (min) | Conversion[b] (%) | Ee[c] (%) | $k_{rel}$[d] |
|---|---|---|---|---|---|---|
| 1 | **Dimercy-MnCl(8)** | 5 | 30 | 58 | 95 | 19 |
| 2 | **Dimercy-MnOAc(9)** | 5 | 30 | 55 | 91 | 21 |
| 3 | **Dimerdph-MnCl(10)** | 5 | 30 | 60 | 78 | 7 |
| 4 | **Dimercy-MnCl(8)** | 2 | 30 | 62 | 99 | 20 |
| 5 | **Dimercy-MnCl(8)** | 0.2 | 60 | 48 | 90 | 59 |
| 6 | **Monomercy-MnCl (Jacobsen catalyst)** | 2 | 30 | 60 | 97 | 18 |

[a]Reactions were carried out at room temperature in mentioned time. [b]Determined by GC analysis using dodecane as an internal standard. [c]Determined by HPLC using Chiralcel OD column. [d] $k_{rel}$ represents an average of at least two experiments.

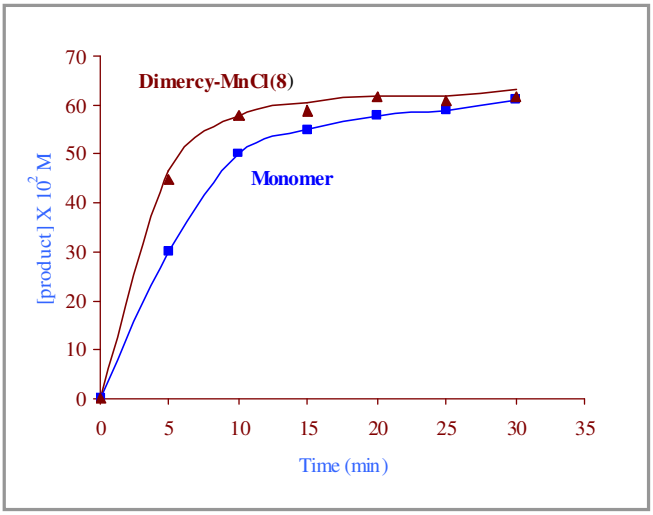
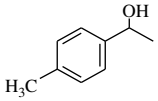
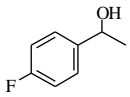
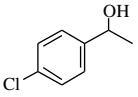
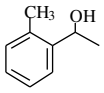
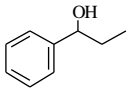
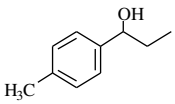
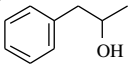
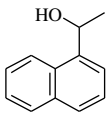
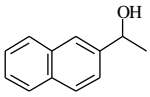
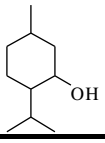



**Figure 5.2** Time dependent plot of OKR of 1-phenylethanol at rt, [catalyst: **Dimercy-MnCl(8)**] = 0.66x$10^{-2}$M, [1-phenylethanol] = 33.0x$10^{-2}$M, [KBr] = 1.3x$10^{-2}$M, [oxidant] = 23.0x$10^{-2}$M.

The scope of OKR of various other racemic secondary alcohols was investigated with catalyst **Dimercy-MnCl(8)** (2 mol%) by using KBr (4 mol%) as an additive (**Table 5.2**). In general racemic 1-phenylethanol with substituents at the *para*-position were enantioselectively oxidized to the respective ketones (conversion, 59-67%) to yield remaining alcohol in high chiral purity (ee, 95-97%) in 30 minutes (**Table 5.2**, entries 7, 8 and 9) and these results are comparable with earlier reported procedure with monomeric (Jacobsen Mn(salen)) complex.[26] The $k_{rel}$ values are very sensitive towards the conversion for a given ee, however, a selectivity factor as low as 11 allows the isolation of unreacted alcohol in 97% ee with quite reasonable 31% recovery (**Table 5.2**, entry 8). However, substituents at the *o*-position of the phenyl group (**Table 5.2**, entry 10) or extension of alkyl chain (from R'=$CH_3$ to R'=$CH_2CH_3$) (**Table 5.2**, entries 11, 12) severely effected ee's and $k_{rel}$ values presumably due to the steric hindrance caused by the substituted group which, does not allow close contact of the substrate with chiral centers bearing catalytically active metal center of the complex. On the other hand, 1-phenyl-2-propanol gave good results in terms of enantioselectivity (ee, 89%) (Entry 13). Other bulkier secondary alcohols like 1-naphthylethanol and 2-naphthylethanol gave good enantioselectivity (73-85%) but the reaction was slower (**Table 5.2**, entries 14, 15). Remarkably, (±)-menthol exhibited high $k_{rel}$ value with very good enantioselectivity (ee, 92%) (Entry 16). Here it is worth mentioning that (*R*, *R*) form of the catalyst selectively oxidized *S* form of the alcohols to produce respective ketones leaving behind remaining alcohol enriched with *R* configuration.

**Table 5.2** Oxidative kinetic resolution (OKR) of various secondary alcohols using **Dimercy-MnCl(8)** catalyst [a]

| Entry | (±)Alcohol | Time (min) | Conversion[b] (%) | Ee[c] (%) | $k_{rel}$[d] |
|---|---|---|---|---|---|
| 7 |  | 30 | 59 | 95 | 19 |
| 8 |  | 30 | 67(31)[e] | 97 | 11 |
| 9 |  | 30 | 60 | 96 | 17 |
| 10 |  | 60 | 15 | 9 | 4 |
| 11 |  | 30 | 57 | 25 | 2 |
| 12 |  | 30 | 49 | 14 | 2 |
| 13 |  | 30 | 64 | 89 | 9 |
| 14 |  | 80 | 50 | 73 | 15 |
| 15 |  | 60 | 52 | 85 | 22 |
| 16 |  | 30 | 51 | 92 | 53 |

[a]Reactions were carried out using 2 mol% **Dimercy-MnCl(8)**, KBr (4 mol%), racemic secondary alcohols (1 mmol), $PhI(OAc)_2$ (0.7 mmol) in 1 ml $CH_2Cl_2$+ 2 ml $H_2O$ at room temperature in mentioned time. [b]Determined by GC analysis using dodecane as an internal standard. [c]Determined by HPLC using Chiralcel OD/OB column. [d]Selectivity factor $k_{rel}$ represents an average of at least two experiments. [e]Isolated yield of enantioenriched secondary alcohol.

### 5.3.3. Effect of Solvent Systems and Additives in OKR of Racemic 1-Phenylethanol

Solvent plays critical role in the OKR of secondary alcohols[27]. In view of this, the effect of solvents was carried out using catalyst **Dimercy-MnCl(8)** for the OKR of 1-

phenylethanol as a representative substrate and the results are summarized in **Table 5.3**. In the case of $H_2O$ alone as a solvent (**Table 5.3**, entry 17) and KBr as an additive a conversion of 47% with 36% ee for 1-phenylethanol was obtained, possibly due to only partial solubility of the catalyst **Dimercy-MnCl(8)** in the alcoholic substrate.

**Table 5.3** OKR of 1-phenylethanol using catalyst **Dimercy-MnCl(8)** in various solvent systems.[a]

| Entry | Solvent system | Time (min) | Conversion[b] (%) | Ee[c] (%) | $k_{rel}$[d] |
|---|---|---|---|---|---|
| 17 | $H_2O$ | 30 | 47 | 36 | 3 |
| 18 | $H_2O$+Toluene | 30 | 63 | 98 | 16 |
| 19 | $H_2O$+DCE | 30 | 60 | 96 | 17 |
| 20 | $H_2O$+$CHCl_3$ | 30 | 64 | 82 | 7 |
| 21 | $H_2O$+$CH_2Cl_2$ | 30 | 62 | 99 | 20 |
| 22 | $H_2O$+Ethyl acetate | 30 | 43 | 17 | 2 |

[a]Reactions were carried out using 2 mol% complex- **Dimercy-MnCl(8)**, KBr (4 mol%), 1-phenylethanol (1 mmol), $PhI(OAc)_2$ (0.7 mmol) in 1 ml organic solvent + 2 ml $H_2O$ at rt in mentioned time. [b]Determined by GC analysis using dodecane as an internal standard. [c]Determined by HPLC using Chiralcel OD column. [d]Selectivity factor $k_{rel}$ represents an average of at least two experiments.

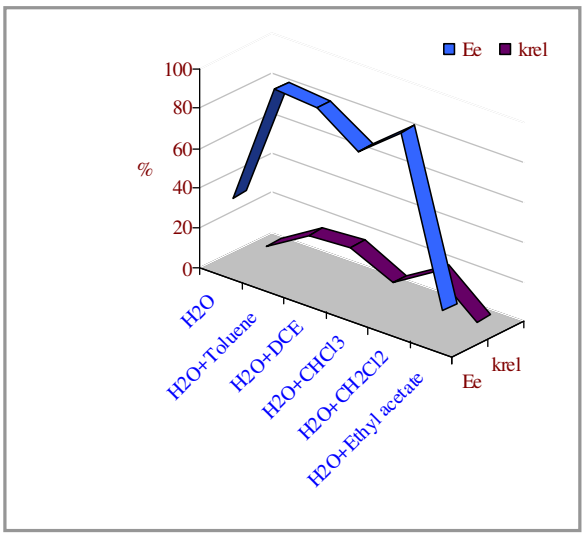
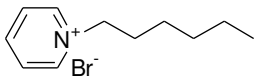



**Figure 5.3** 3D view showing ee and $k_{rel}$ versus different solvent systems for OKR of 1-phenylethanol using **Dimercy-MnCl(8)**

Solvents like toluene, 1, 2-dichloroethane and chloroform when mixed with water, gave high enantioselectivity (82-98%) in the case of 1-phenylethanol (**Table 5.3**, entries 18-20), while ethyl acetate gave poor results (Entry 22). Out of all the solvent systems studied, the $CH_2Cl_2$: Water:: 1:2 was found to be the solvent of choice (**Table 5.3**, entry 21) (**Figure 5.3**). Further, we studied the effect of various additives on the efficacy of OKR of 1-phenylethanol using complex **Dimercy-MnCl(8)** as a catalyst (**Table 5.4**). The phase transfer catalysts like tetraethyl ammonium bromide and tetrabutyl ammonium bromide as additives gave moderate to high enantioselectivity (ee, 59-95%) with conversions (50-64%) (**Table 5.4**, entries 23, 24). While bromine salts like hexylpyridinium bromide, NaBr and LiBr exhibited better enantioselectivity (ee, 92-97%) (**Table 5.4**, entries 25, 26 and 27). Surprisingly Cetyltrimethylammonium bromide (CTAB) as phase transfer catalyst gave very poor results (Entry 28). On carrying out OKR of 1-phenylethanol in the absence of an additive the enantioselectivity of the reaction dropped considerably (**Table 5.4**, entry 29), inferring that presence of bromide ion is required for the activation of $PhI(OAc)_2$ to carry out the oxidative kinetic resolution of alcohols in the presence of water-organic solvent system. These observations are in consonance with earlier report[26].

**Table 5.4** OKR of 1-phenylethanol using catalyst **Dimercy-MnCl(8)** in presence of various additives[a]

| Entry | Additives | Time (min) | Conversion[b] (%) | Ee[c] (%) | $k_{rel}$[d] |
|---|---|---|---|---|---|
| 23 | $N(C_2H_5)_4Br$ | 30 | 64 | 95 | 11 |
| 24 | $N(C_4H_9)_4Br$ | 30 | 50 | 59 | 7 |
| 25 |  | 30 | 61 | 92 | 12 |
| 26 | NaBr | 30 | 56 | 93 | 9 |
| 27 | LiBr | 30 | 64 | 97 | 13 |
| 28 | CTAB | 60 | 39 | 16 | 2 |
| 29[e] | - | 60 | 5 | <1 | 1 |
| 30 | KCl | 60 | 8 | 1 | 1 |

[a]Reactions were carried out using 2 mol% complex- **Dimercy-MnCl(8)**, additive (4 mol%), 1-phenylethanol (1 mmol), $PhI(OAc)_2$ (0.7 mmol) in 1 ml $CH_2Cl_2$ + 2 ml $H_2O$ at rt in mentioned time. [b]Determined by GC analysis using dodecane as an internal standard [c]Determined by HPLC using Chiralcel OD column. [d]Selectivity factor $k_{rel}$ represents an average of at least two experiments [e]Reaction was carried out in absence of additive.

### 5.3.4. Recovery and Recycling of Catalyst

Dimeric Mn(III) salen complex has an inherent tendency to get precipitated out in non-polar solvents like n-hexane due to its higher molecular weight. Therefore, after the completion of catalytic run the catalyst **Dimercy-MnCl(8)** was recovered by the addition of n-hexane to the reaction mixture. The recovered catalyst was washed thoroughly with n-hexane and diethyl ether, dried and reused for the subsequent OKR runs of 1-phenylethanol as a representative substrate by adding fresh reactants. **Table 5.5** represented the recycling of complex **Dimercy-MnCl(8)** for oxidative kinetic resolution of 1-phenylethanol. From the data presented in Table 5 it is evident that the catalyst **Dimercy-MnCl(8)** worked well for five cycles with retention of enantioselecitivity. To

check the stability of the catalyst during the OKR we characterized the recovered catalyst (after 3rd reuse) by IR, UV and ESI-MS analysis and the data are given in experimental section. It is evident from these data that the catalyst remained unchanged during the course of OKR of 1-phenylethanol used as model substrate.

**Table 5.5** OKR of 1-phenylethanol with recycled **Dimercy-MnCl(8)** complex [a]

| Catalytic run | Time (min) | Conversion[b] (%) | Ee[c] (%) |
|---|---|---|---|
| 1 | 30 | 62 | 99 |
| 2 | 30 | 60 | 98 |
| 3 | 30 | 58 | 99 |
| 4 | 30 | 57 | 99 |
| 5 | 30 | 55 | 98 |

[a]2 mol% complex, KBr (4 mol%), 1-phenylethanol (1 mmol), $PhI(OAc)_2$ (0.7 mmol) in 1 ml $CH_2Cl_2$ + 2 ml $H_2O$ at rt. [b]Determined by GC analysis using dodecane as an internal standard. [c]Determined by HPLC using Chiralcel OD column.

## 5.4. Conclusion

In conclusion, we have demonstrated that chiral dimeric Mn(III) salen complexes can be successfully used as recyclable chiral catalysts for the oxidative kinetic resolution of racemic secondary alcohols using $PhI(OAc)_2$ as an oxidant. Excellent enantioselecitivity (ee; up to 99%) of chiral secondary alcohols was achieved in 0.5 h. Effect of different solvent systems and additives in OKR of racemic 1-phenylethanol has been studied with chiral dimeric Mn(III) salen catalyst. Catalyst **Dimercy-MnCl(8)** was recovered easily and reused up to five times with the retention of enantioselecitivity.

## 5.5. References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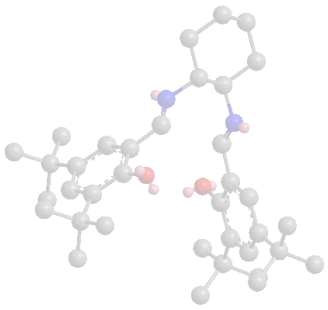
# Chapter -6



## Easily Recyclable Chiral Polymeric Mn(III) salen Complexes for Oxidative Kinetic Resolution of Racemic Secondary Alcohols

## 6.1. Introduction

In the preceding chapter, we presented the results based on our studies on the performance of recyclable dimeric Mn(III) salen complexes used in oxidative kinetic resolution of alcohol. This chapter deals with use of chiral polymeric Mn(III) salen complexes as an effective and easily recyclable catalysts for oxidative kinetic resolution (OKR) of racemic secondary alcohols at room temperature. Chiral polymeric complexes **Polycy-MnCl(11)**[1], **Polycy-MnBr(12)** and **Polydph-MnCl(13)**[1] were synthesized and characterized by various physicochemical methods. High chiral purity (ee; >99%) was achieved for the OKR of racemic secondary alcohols with 0.6 mol% catalyst loading in 60 minutes in the presence of various additives in water/organic solvent mixtures at room temperature. The catalyst was easily recycled for successive five catalytic experiments without lose of enantioselectivity.

## 6.2. Experimental

### 6.2.1. Materials & Methods

$PhI(OAc)_2$, tetraethylammonium bromide, tetrabutylammonium bromide, KBr, LiBr and NaBr were purchased from Across Organics, Belgium. Hexylpyridinium bromide was prepared according to the known procedures.[2] The (1*R*,2*R*)-(-)-cyclohexanediamine was resolved from the technical-grade *cis/trans* mixture according to the reported procedure.[3] 2-*tert*-butyl-phenol, 1-phenyl-2-propanol and (±)-menthol were purchased from Aldrich, other racemic alcohols, *viz.*, 4-fluorophenylethanol, 4-chlorophenylethanol, 4-methylphenylethanol, 2-methylphenylethanol, 1-phenyl-1-propanol, 1-(4-methylphenyl)-1-propanol and 1-(2-naphthyl)ethanol were prepared by

reduction of the corresponding ketones with $NaBH_4$. All the solvents used in the present study were purified by the known methods.[4]

### 6.2.2. Synthesis of Chiral Polymeric salen Ligands

The synthesis of chiral polymeric salen ligands is described as follows according to the **Scheme 6.1**.

#### 6.2.2.1. 5,5'-Methylene-di-3-tert-butylsalicylaldehyde (MTBS)

The compound 5,5'-Methylene-di-3-tert-butylsalicylaldehyde was synthesized according to the procedure described in the experimental section 4.2.2.2.

#### 6.2.2.2. Poly[(*S,S*)-*N,N'*-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine} cyclohexene 1,2 -diamine] (A)

The ligand **A** was synthesized according to the procedure described in experimental section 4.2.2.3.

#### 6.2.2.3. Poly [(*R,R*)-*N,N'*-bis{3-(1,1-dimethylethyl)-5-methylene salicylidine} 1,2-diphenyl-1,2- ethylenediamine] (B)

5,5'-methylene-di-3-*tert*-butylsalicylaldehyde **(MTBS)** (0.002 mol) was dissolved in $CH_3OH$ and 1*R*,2*R*-(+)-1,2-diphenyldiamine (0.002 mmol) was added at cold condition and the resulting mixture was refluxed for 6-8 h. Partial removal of the solvent precipitated out the desired chiral ligand **B** which was characterized by micro analysis IR, $^1$HNMR and Vapour Pressure Osmometry (VPO). $M_n$= 5200, n = ~10. M. P. 220°C. Yield 85%. IR (KBr): ν(H-C=N) 1630 $cm^{-1}$; $^1$H NMR ($CDCl_3$, 200MHz): δ 1.34 (s, 18H, *t*-butyl), 3.66 (s, 2H, asymmetric), 4.64 (s,2H, methylene), 6.67 (d, 2H, aromatic), 7.03 (d, 2H, aromatic), 7.13 (bs, 10H, phenyl), 8.22 (s, 2H, azomethine), 13.56 (bs, 2H, OH) ppm; $^{13}$C($CDCl_3$, 50 MHz): δ 29.9, 35.4, 40.9, 80.6, 119.0, 128.1, 128.6, 128.9, 130.4,

130.8, 131.0, 137.7, 140.3, 159.2, 167.4 ppm; Anal. Calcd. for. ($C_{37}H_{40}N_2O_2$): C, 82.83, H, 6.90, N, 4.82, Found: C, 82.75, H, 6.85, N, 4.76%.

### 6.2.3. Synthesis of Chiral Polymeric Mn(III) salen Complexes

The synthesis of chiral polymeric Mn(III) salen Complexes is described as follows:

#### 6.2.3.1. Poly [(*R,R*)-*N,N'*-bis{3-(1,1-dimethylethyl)-5-methylene salicylidine} cyclohexene-1,2-diaminato -manganese(III) chloride] Polycy-MnCl(11)

Chiral Schiff base **A** (0.001mol) was dissolved in $CH_2Cl_2$ while manganese acetate (0.002mol) was taken in $CH_3OH$ and the two solutions were mixed and refluxed under an inert atmosphere for 8-10 h. The reaction mixture was cooled to room temperature; solid lithium chloride (0.006mol) was added and was further stirred for 5 h, while exposed to the air and filtered. The solvent was removed from the filtrate and the residue was extracted with $CH_2Cl_2$. The organic layer was washed with water, brine and dried over anhydrous $Na_2SO_4$. The solvent was partially removed and the desired complex **Polycy-MnCl(11)** was precipitated on addition of petroleum ether (40-60) which was filtered and dried. Yield 90%; IR (KBr): 3431 (br), 2947 (s), 2865 (s), 1612 (s), 1538 (s), 1421 (sh), 1388 (m), 1342 (s), 1309 (s), 1285 (sh), 1238 (sh), 1201 (m), 1170 (m), 1100 (w), 1030 (m), 940 (w), 833 (m), 780 (w) $cm^{-1}$; UV-Vis ($CH_2Cl_2$) $\lambda_{max}(\varepsilon)$: 196(3092), 206(3778), 218(4904), 224(4618), 238(16116), 248(16823), 260(18545), 278(16782), 290(16243), 326(14187), 412(4527), 416(4517), 424(4513), 484(1932), 602(516) nm; Anal. Calcd. for ($C_{29}H_{39}ClN_2O_3Mn$): C, 62.87; H, 7.09; N, 5.05, Found: C, 62.80; H, 7.03; N, 5.02%; $[\alpha]_D^{30}$ = + 188 (c = 0.05, $CH_2Cl_2$). Configuration (*S*); $\Lambda_M$ (MeOH): 4 mho $cm^{-1}$ $mol^{-1}$.

**6.2.3.2. Poly [(*R,R*)-N,N-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidine} cyclohexane-1,2-diaminato (2-) manganese (III) bromide] Polycy-MnBr (12)**

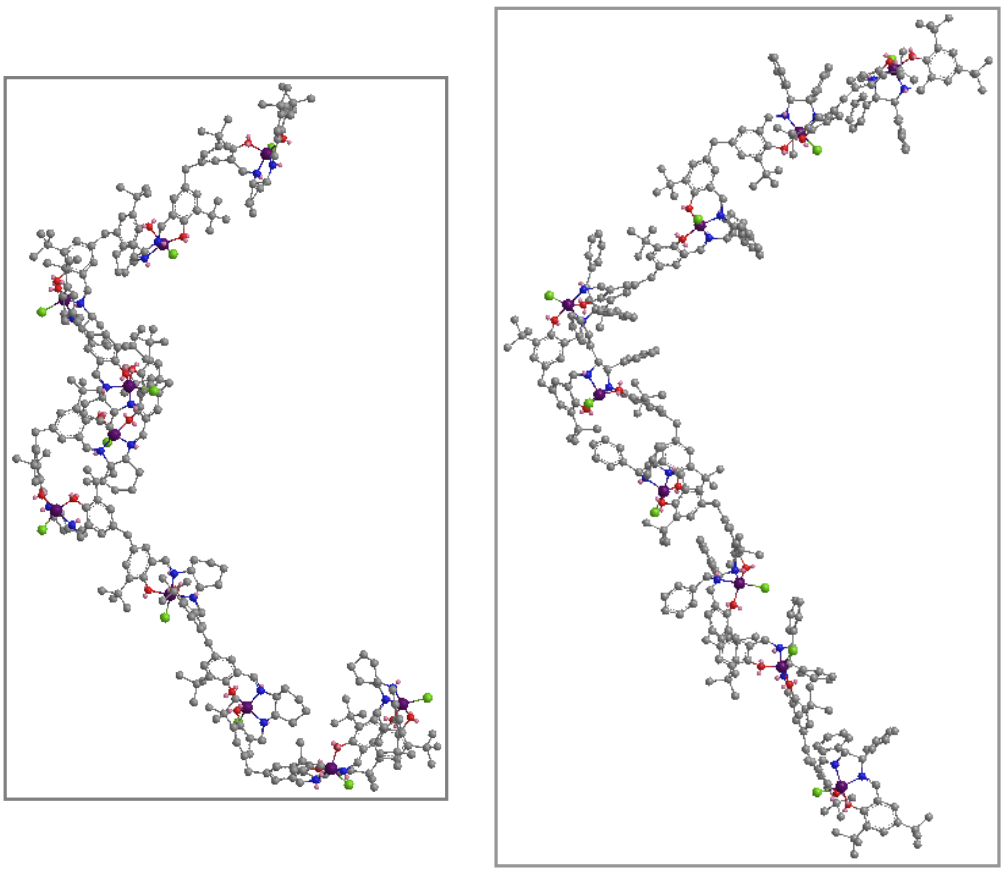
Chiral Schiff base **A** (0.001 mmol) was dissolved in $CH_2Cl_2$ (10 ml) while $Mn(OAc)_2$ (0.002 mmol) was taken in $CH_3OH$ (5 ml) and the two solutions were mixed and refluxed under an inert atmosphere for 10-12 h. A slow stream of air was allowed to pass through the reaction mixture for an additional 1 h. Under vigorous stirring, 2 ml of a saturated aqueous solution of NaBr (0.002 mmol) was added and the suspension was allowed to cool to room temperature and stirred for 4 h. After addition of 10 ml of $CH_2Cl_2$ to the reaction mixture, the mixture was washed three times with 10 ml of water and once with 10 ml NaBr (aq). The organic layer was dried over anhydrous $Na_2SO_4$ and the recrystallization of the crude product was done with petroleum ether/$CH_2Cl_2$ to yield the desired complex as brown powder in 94% yield. IR (KBr): 3428 (br), 2943 (s), 2868 (s), 1614 (s), 1536 (s), 1422 (sh), 1389 (m), 1344 (s), 1310 (s), 1283 (sh), 1238 (sh), 1200 (m), 1174 (m), 1106 (w), 1033 (m), 942 (w), 838 (m) $cm^{-1}$; Anal. Calcd. for ($C_{29}H_{39}BrN_2O_3Mn$): C, 58.19; H, 6.52; N, 4.68, Found: C, 58.12; H, 6.48; N, 4.65%;

$[\alpha]_D^{25}$ = -228 (c= 0.05, $CH_2Cl_2$).

**6.2.3.3. Poly [(*R,R*)-*N,N'*-bis{3-(1,1-dimethyl ethyl)-5-methylene- salicylidine}1,2-diphenyl-1,2 ethane diaminato manganese(III) chloride] Polydph-MnCl(13)**

Chiral Schiff base **B** (0.001mol) was dissolved in $CH_2Cl_2$ while manganese(II) acetate (0.002mol) was taken in $CH_3OH$ and the two solutions were mixed and refluxed under an inert atmosphere for 8-10 h. The reaction mixture was cooled to room temperature; solid lithium chloride (0.006mol) was added and was further stirred for 5 h, while exposed to the air and filtered. The solvent was removed from the filtrate and the residue was extracted with $CH_2Cl_2$. The organic layer was washed with water, brine and

dried over anhydrous $Na_2SO_4$. On partial removal of the solvent, the desired complex **Polydph-MnCl(13)** was precipitated on addition of petroleum ether (40-60) Yield 90%; IR (KBr): 3446 (br), 2957 (s), 2869 (s), 1605 (s), 1536 (s), 1456 (sh), 1418 (s), 1388 (m), 1346 (s), 1309 (s), 1285 (sh), 1238 (sh), 1201 (m), 1170 (m), 1100 (w), 1030 (m), 940 (w), 831 (m), 780 (w), 731 (w) $cm^{-1}$; UV-Vis ($CH_2Cl_2$) $\lambda_{max}(\varepsilon)$: 206(3658), 220(4851), 238(16342), 242(16881), 264(179755), 266(17674), 280(17485), 296(17168), 316(15602), 328(15602), 416(4695), 412(47416), 448(5011), 490(2248) nm; Anal. Calcd. for ($C_{37}H_{40}ClN_2O_3Mn$): C, 69. 91, H, 5.86, N, 4.07, Found: C, 69.86, H, 5.83, N, 4.04%; $[\alpha]_D^{30}$ = + 793 (c = 0.0.6, $CH_2Cl_2$). Configuration (*R*); $\Lambda_M$ (MeOH): 6 mho $cm^{-1}$ $mol^{-}$



**Polycy-MnCl(11)** **Polydph-MnCl(13)**

**Figure 6.1** Energy minimized structures of Polymeric Mn(III) salen complexes

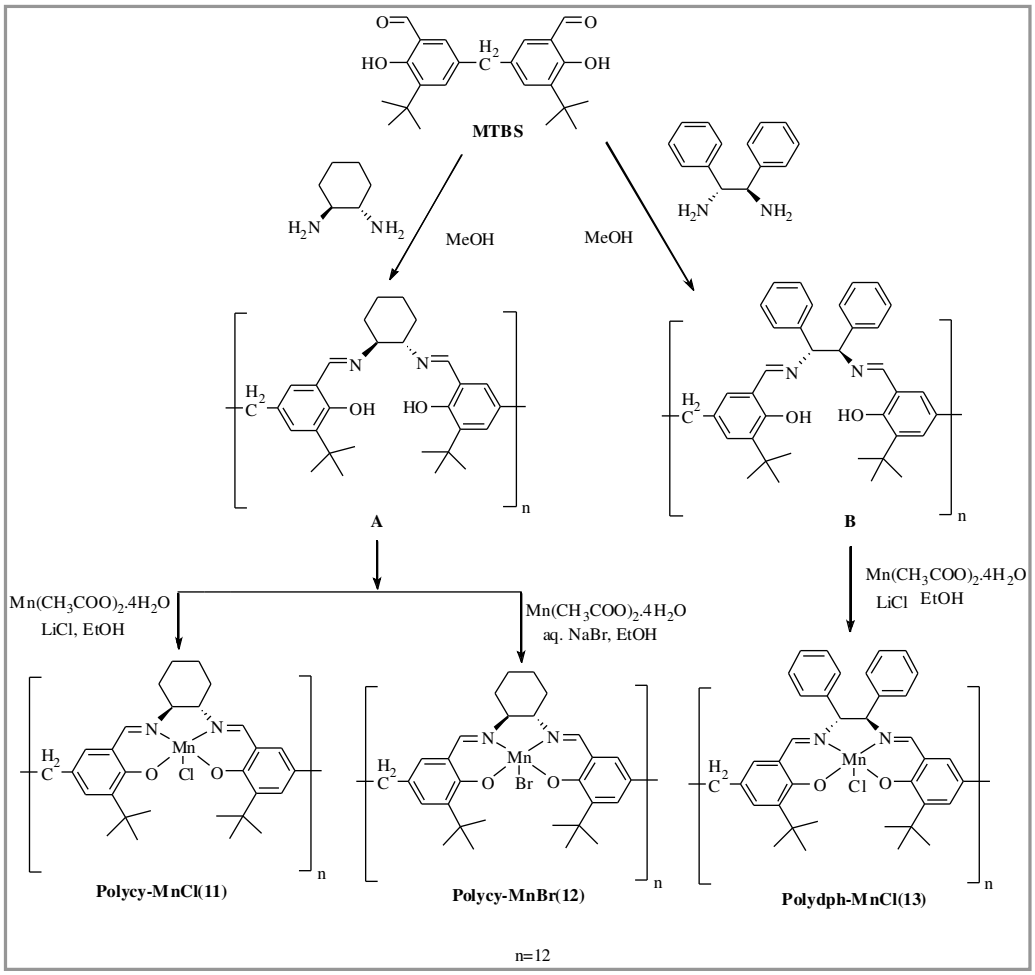
#### 6.2.3.4. General Procedure for the Oxidative Kinetic Resolution of Racemic Secondary Alcohols

A mixture of the substrate (1 mmol), chiral polymeric Mn(III) salen complex (0.006 mmol, 0.6 mol %), additive (0.012, 1.2 mol %), $CH_2Cl_2$ (0.3 ml) and water (0.6 ml) was stirred in a 5 ml tube for 10 minutes at room temperature. The oxidant $PhI(OAc)_2$ (0.7 mmol) was then added and the system was stirred for (60-120 minutes) at room temperature. After the desired conversion was achieved, n-hexane was added to the reaction mixture. The catalyst thus precipitated was filtered off, the mixture of product and chirally enriched alcohol was extracted by diethyl ether. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated under reduced pressure. Conversion and ee values were determined by performing GC and HPLC analysis.

## 6.3. Results and Discussion

### 6.3.1. Synthesis and Characterization of Chiral Polymeric Mn(III) salen Complexes

Chiral polymeric complexes were synthesized as described in **Scheme 6.1.** Accordingly, condensation of chiral amines with **MDTBS** to get chiral polymeric ligands **A** and **B.** Polymeric schiff base **A** and **B** were then interacted with manganese (II) acetate followed by their air oxidation to get **Polycy-MnCl(11)** and **Polydph-MnCl(13) complxes respectiviely.** In the case of complex **Polycy-MnBr(12),** aq. NaBr was added before air oxidation. Complexes were characterized by NMR, microanalysis, conductance, optical rotation, UV–Vis. and IR spectroscopy and data are given in experimental sections 6.2.2. and 6.2.3.




**Scheme 6.5** Schematic representation of synthesis of chiral polymeric Mn(III) salen complexes

### 6.3.2. Oxidative Kinetic Resolution (OKR) of Racemic Secondary Alcohols

Chiral polymeric Mn(III) salen complexes (2 mol %, based on monomeric salen unit) were used for OKR of racemic 1-phenylethanol with $PhI(OAc)_2$ as an oxidant using KBr as an additive at room temperature and the results are summarized in **Table 6.1**. The complex **Polycy-MnCl(11)** was found to be the better catalyst in terms of excellent enantiomeric excess (98%) with a $k_{rel}$ value of 17 (**Table 6.1**, entry 1). Changing the counter ion from $Cl^-$ to $Br^-$ (complex **Polycy-MnBr(12)**) did not improve the ee of the

product (entry 2). On the other hand, complex **Polydph-MnCl(13)** was less effective catalyst as evidenced by low ee of the alcohol (entry 3). Therefore, the chiral polymeric Mn(III) salen complex **Polycy-MnCl(11)** was studied in detail for optimization of reaction parameters and its applicability to catalyze OKR of different racemic secondary alcohols. We first examined the influence of catalyst loading using 1-phenylethanol as a representative substrate. Increasing the catalyst loading from 2 mol% to 5 mol%, there was no improvement in enantioselection of the reaction (ee, 94%) (entry 4). A catalyst loading of 0.6 mol% gave results (ee, 96%) similar to those achieved with 2 mol% catalyst loading but the reaction time was increased from 15 minutes to 60 minutes (entry 5). Further reduction in catalyst loading to a level of 0.2 mol% caused reduction in the enantioselection of the product alcohol in oxidative kinetic resolution (ee, 91%) (entry 6).

In order to compare the reactivity of polymeric Mn(III) salen complex **Polycy-MnCl(11)** with its monomeric counterpart, we have conducted OKR of 1-phenylethanol as a representative substrate with Jacobsen's monomeric Mn(III) salen complex as catalyst using KBr as an additive. Kinetic profile for both the complexes showed linear increase in the product formation up to 10 minutes after which no significant increase was observed (**Figure 6.1**). Therefore, the initial rate constants $K_{obs}$ were determined from the data in this time range for the **Polycy-MnCl(11)** and monomeric complex that gives $K_{obs}$ values $36 \times 10^{-2}$ M/h and $24 \times 10^{-2}$ M/h respectively. This enhanced $K_{obs}$ value can be attributed to the more number of catalytically active sites present in the polymeric complex **Polycy-MnCl(11)** which may not be working in isolation.

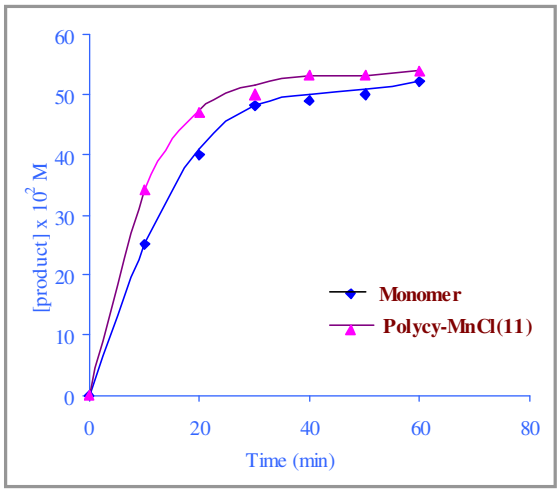



**Figure 6.1** Time dependent plot of oxidative kinetic resolution of 1-phenylethanol at rt, [catalyst **Polycy-MnCl(11)**] = $0.80 \times 10^{-2}$M, [1-phenylethanol] = $111.0 \times 10^{-2}$M, [KBr] = $1.3 \times 10^{-2}$M, [oxidant] = $77.6 \times 10^{-2}$M

To check the efficiency of complex **Polycy-MnCl(11)** with optimized catalyst loading (0.6 mol%), the OKR of other racemic secondary alcohols, viz., 4-fluorophenylethanol, 4-chlorophenylethanol, 4-methylphenylethanol, 2-methylphenylethanol, 1-phenyl-1-propanol, 1-(4-methylphenyl)-1-propanol, 1-phenyl-2-propanol, 1-(2-naphthyl)ethanol and menthol was performed with KBr as an additive using $PhI(OAc)_2$ as an oxidant in $CH_2Cl_2$:$H_2O$ solvent system (**Table 6.1**). It can be observed from **Table 6.1** that 1-phenylethanol with substituents at the *p*-position favor high enantioselectivity (ee, >99%) with (51-63%) conversion (**Table 6.1**, entries 7-9) in 60 minutes. However, the reaction was sluggish (only 11% conversion in 120 minutes) for *o*-substituted 1-phenylethanol with poor enantioselection (ee, 5%) (**Table 6.1**, entry 10). Further, when the R' group of the substrate was changed from methyl to ethyl, the enantioselectivity of the reaction was severely affected (ee's, 10-23%) (**Table 6.1**, entries

11, 12). On the other hand, 1-phenyl-2-propanol gave good results in terms of enantioselectivity (83%) (Entry 13). Bulkier secondary alcohols like 2-naphthylethanol took long time (80 minutes) to affect ee up to 76% (entry 14). Noticeably, menthol exhibited high enantioselectivity (ee; 94%) with high $k_{rel}$ value (Entry 15).

**Table 6.1** OKR of racemic secondary alcohols using chiral polymeric Mn(III) salen complexes.[a]

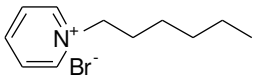
| Entry | Catalysts | Catalyst loading (mol %) | Substrate | Time (min) | Conversion[b] (%) | Ee[c] (%) | $k_{rel}$[d] |
|---|---|---|---|---|---|---|---|
| 1 | **Polycy-MnCl(11)** | 2 | 1-phenylethanol | 15 | 62 | 98 | 17 |
| 2 | **Polycy-MnBr(12)** | 2 | 1-phenylethanol | 15 | 56 | 95 | 25 |
| 3 | **Polydph-MnCl(13)** | 2 | 1-phenylethanol | 15 | 52 | 88 | 29 |
| 4 | **Polycy-MnCl(11)** | 5 | 1-phenylethanol | 15 | 60 | 94 | 15 |
| 5 | **Polycy-MnCl(11)** | 0.6 | 1-phenylethanol | 60 | 53 | 96 | 48 |
| 6 | **Polycy-MnCl(11)** | 0.2 | 1-phenylethanol | 90 | 49 | 91 | 118 |
| 7 | **Polycy-MnCl(11)** | 0.6 | 4-fluorophenylethanol | 60 | 63 | >99 | 19 |
| 8 | **Polycy-MnCl(11)** | 0.6 | 4-chlorophenylethanol | 60 | 51 | 92 | 53 |
| 9 | **Polycy-MnCl(11)** | 0.6 | 4-methylphenylethanol | 60 | 60 | 93 | 15 |
| 10 | **Polycy-MnCl(11)** | 0.6 | 2-methylphenylethanol | 120 | 11 | 5 | 2 |
| 11 | **Polycy-MnCl(11)** | 0.6 | 1-phenyl-1-propanol | 60 | 50 | 23 | 3 |
| 12 | **Polycy-MnCl(11)** | 0.6 | 1-(4-methylphenyl)-1-propanol | 60 | 42 | 10 | 2 |
| 13 | **Polycy-MnCl(11)** | 0.6 | 1-phenyl-2-propanol | 60 | 55 | 83 | 13 |
| 14 | **Polycy-MnCl(11)** | 0.6 | 1-(2-naphthyl)ethanol | 80 | 52 | 76 | 11 |
| 15 | **Polycy-MnCl(11)** | 0.6 | menthol | 60 | 48 | 94 | 398 |

[a]All reactions were carried out at room temperature in mentioned time. [b]Determined by GC analysis using an internal standard. [c]Determined by HPLC using chiralcel OD/OB column. [d]Selectivity factor $k_{rel}$ was determined using equation, $k_{rel} = \ln[1 - c(1 - ee)]/\ln[1 - c(1 + ee)]$ (where c is the conversion of secondary alcohol and ee is the enantiomeric excess of secondary alcohol), The data represents an average of at least three experiments.

### 5.3.3. Effect of Solvent Systems and Additives in OKR of Racemic 1-Phenylethanol

The choice of solvent and additives has a significant effect on the activity and the enantioselectivity of the chiral Mn(III) salen complexes.[5] We have further studied the effect of the solvent and additives on the activity of oxidative kinetic resolution taking 1-phenylethanol as a representative substrate using complex **Polycy-MnCl(11)** as catalyst (**Table 6.2**). In the case of $H_2O$ alone as a solvent (**Table 6.2**, entry 16) with KBr as an additive a conversion of 57% with 35% ee for 1-phenylethanol was obtained in 60 minutes, possibly due to some solubility of catalyst **Polycy-MnCl(11)** in the alcoholic substrate. Solvents like toluene, 1, 2-dichloroethane and chloroform in combination with $H_2O$, resulted good to excellent enantioselectivity (83-94%) in the case of 1-phenylethanol (**Table 6.2**, entries 17-19), while ethyl acetate gave poor results (entry 20). On conducting the reaction in the solvent system of $CH_2Cl_2$:$H_2O$ using different bromide salts *viz.*, NaBr, LiBr and hexylpyridinium bromide as an additive, the system exhibited high enantioselectivity (87-91%) (**Table 6.2**, entries 21-23). Considering the biphasic nature of the above reaction system, it was pertinent to study the effect of a phase transfer catalyst like tetraethyl ammonium bromide or tetrabutyl ammonium bromide in oxidative kinetic resolution of 1-phenylethanol in $CH_2Cl_2$:$H_2O$ solvent system. The presence of phase transfer catalyst gave moderate to high enantioselectivity (58-93%) (**Table 6.2**, entries 24, 25). However, when the reaction was conducted using KCl as an additive or in the absence of an additive, oxidative kinetic resolution reaction did not proceed at all (entries 26, 27). These observations suggested that the presence of bromide ion is desirable for oxidative kinetic resolution to take place.[5]

**Table 6.2** Effect of solvent systems and additives in OKR of 1-phenylethanol using chiral **Polycy-MnCl(11)**[a].

| Entry | Solvent system | Additives | Time (min) | Conversion[b] (%) | Ee[c] (%) |
|---|---|---|---|---|---|
| 16 | $H_2O$ | KBr | 60 | 57 | 35 |
| 17 | $H_2O$+Toluene | KBr | 60 | 55 | 92 |
| 18 | $H_2O$+DCE | KBr | 60 | 61 | 94 |
| 19 | $H_2O$+$CHCl_3$ | KBr | 60 | 47 | 83 |
| 20 | $H_2O$+Ethyl acetate | KBr | 60 | 39 | 14 |
| 21 | $H_2O$+$CH_2Cl_2$ | NaBr | 60 | 49 | 91 |
| 22 | $H_2O$+$CH_2Cl_2$ | LiBr | 60 | 58 | 87 |
| 23 | $H_2O$+$CH_2Cl_2$ |  | 60 | 60 | 90 |
| 24 | $H_2O$+ $CH_2Cl_2$ | $N(C_2H_5)_4Br$ | 60 | 56 | 93 |
| 25 | $H_2O$+ $CH_2Cl_2$ | $N(C_4H_9)_4Br$ | 60 | 48 | 58 |
| 26 | $H_2O$+$CH_2Cl_2$ | KCl | 120 | 5 | 1 |
| 27[d] | $H_2O$ | - | 120 | 7 | <1 |

[a]Reactions were carried out using 0.6 mol% polymeric Mn(III) salen complex- **Polycy-MnCl(11)**, KBr (1.2 mol%), racemic secondary alcohols (1 mmol), $PhI(OAc)_2$ (0.7 mmol) in 0.3 ml $CH_2Cl_2$+ 0.6 ml $H_2O$ at rt in mentioned time. [b]Determined by GC analysis using an internal standard. [c] Determined by HPLC using chiralcel OD column. [d]Reaction was carried out in absence of additive.

### 5.3.4. Recycling of Catalyst

Just like dimeric salen complex used in the previous chapter the polymeric Mn(III) salen complex too had lower solubility in the catalytic reaction media hence in the post catalytic run (OKR of 1-phenylethanol as a representative substrate) the complex was precipitated out easily by the addition of hexane to the reaction mixture. The precipitate was then separated from the reaction mixture by simple filtration. While the product and other reactant were recovered from the filtrate the solid was washed thoroughly with hexane, dried and kept in desiccator for re-use experiments. The results

are shown in **Table 6.3**. It is evident that the catalyst **Polycy-MnCl(11)** worked well up to five repeat experiments with small decrease in reactivity due to some physical loss during post work up process but with retention of enantioselectivity in reuse experiments. To the best of our knowledge polymeric Mn(III) salen complex is the most efficient recyclable catalyst for the oxidative kinetic resolution of racemic secondary alcohols.

**Table 6.3** Recycling data of chiral **Polycy-MnCl(11)** complex for OKR of 1-phenylethanol as a representative substrate[a].

| Catalytic cycle | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Time(min) | 60 | 60 | 60 | 60 | 60 |
| Conversion[b] (%) | 52 | 51 | 48 | 45 | 43 |
| Ee[c] (%) | 96 | 96 | 95 | 95 | 95 |

[a]0.6 mol% polymeric Mn(III) salen complex- **Polycy-MnCl(11)**, KBr (1.2 mol%), 1-phenylethanol (5 mmol), $PhI(OAc)_2$ (3.5 mmol) in 1 ml $CH_2Cl_2$+ 2 ml $H_2O$ at rt. [b]Determined by GC analysis using an internal standard. [c]Determined by HPLC using chiralcel OD column.

## 6.4. Conclusion

In summary, we can concluded that chiral polymeric Mn(III) salen complex as an effective catalyst in oxidative kinetic resolution of various racemic secondary alcohols. High chiral purity (ee; >99%) was achieved for the oxidative kinetic resolution of racemic secondary alcohols with 0.6 mol% catalyst loading in 60 minutes. These results are superior than chiral dimeric Mn(III) salen complexes studied in previous section (ee; 99%) using 2 mol% catalyst loading. Moreover polymeric Mn(III) salen catalyst was recycled up to five times with retention of enantioselecitivity.

## 6.5. References

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## Conclusions and Future Outlook

The demand, especially from the pharmaceutical industry, for the production of enantiomerically pure compounds, has continued to increase. There are several approaches to obtain chiral compounds including chiral resolution, chemical derivatization and asymmetric catalysis. Asymmetric catalysis is one of the most attractive methods, because plentiful prochiral substrates can be transformed to chiral compounds with controlled absolute configuration catalyzed usually by a small amount of chiral catalysts. Homogeneous asymmetric catalysis has made great progress in the last few decades. However, most of the homogeneous asymmetric catalysts have not been industrialized yet. One of the major problems is due to the difficulty in the separation and recycling of the chiral catalysts. Recently, heterogeneous asymmetric catalysis has attracted much attention for its potential advantages, such as the easy purification of products, separation and recycling of chiral catalysts, isolation of catalytic centers, and continuous reaction via a fix-bed reactor.

For that purpose, '*Privileged*' Chiral ligands- BINOL and salen have been studied under heterogeneous reaction conditions in two most important asymmetric transformations-Asymmetric C-C bond forming reactions and Kinetic resolution of racemic compounds. In order to achieve, heterogenize system, we adopted two strategies- one is immobilization on silica and second one is self supported catalyst using co-polymerization technique. In first strategy, we have immobilized chiral BINOL on mesoporous silica of varying pore size like MCM-41, SBA-15 and MCF and used as

heterogeneous catalyst in Ti-catalyzed asymmetric addition of $Et_2Zn$ to aldehydes. We can conclude from this study that large pore size silica support enhances catalytic activity and enantioselectivity in reaction.

In next strategy, We have synthesized chiral dimeric and polymeric salen based metal complexes and used them as heterogeneous catalysts in asymmetric phenylacetylene addition to carbonyls and oxidative kinetic resolution of racemic secondary alcohols. Excellent results in terms of enantioselectivity have been achieved with these catalysts using low catalyst loading. These catalysts can be recyclable several times without lose of activity.

These results should encourage further research with these recyclable BINOL and salen base metal complexes in other important asymmetric transformations under heterogeneous reaction conditions. Moreover, the design and preparation of more selective and highly enantioselecitive heterogeneous catalyst system can be synthesize using this two distinct strategies. Nevertheless, use of these chiral heterogeneous catalysts on large scale to get more value addition in asymmetric catalysis is still untouched, which means that a lot remains to be explored and developed in this field of research.

## LIST OF PUBLICATIONS

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3. Enantioselective addition of diethylzinc to aldehydes using immobilized chiral BINOL–Ti complex on ordered mesoporous silicas.
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A. Bhatt**, K. Pathak**, R. V. Jasra, R. I. Kureshy, N. H. Khan, S. H. R. Abdi*, R. V. Jasra.
***Journal of Molecular Catalysis A: Chemical*** (Under communication) **2007**.

## PAPERS PRESENTED IN CONFERENCE/ SYMPOSIUM

1. Best Paper presentation in **TAGRSM-2003** organized by **Indian Chemical society Vadodara Chapter** on 23rd Feb. 2003, entitled, "Homochiral Dimeric Mn (III) Salen complex-catalysed enantioselective epoxidation of non-functionalized alkenes using NaOCl as oxidant".
R. I. Kureshy*, N. H. Khan, S. H. R. Abdi, S. Singh, **K.Pathak,** R. V. Jasra.

2. A poster entitled "Supported catalyst for alkylation through addition of diethyl zinc" was presented in **National workshop on advances in catalysis at Loyola Collage, Chennai** during January 6-7, 2004
**K. Pathak**, A. Bhatt, S. H. R. Abdi*, R. V. Jasra

3. A poster entitled "Immobilization of Chiral BINOL on MCM-41 for the Synthesis of Chiral Catalyst for Nitro-Aldol Reaction" was presented in

**National workshop on advances in catalysis at Loyola Collage, Chennai** during January 6-7, 2004
A. Bhatt, **K. Pathak**, S. H. R. Abdi*, R. V. Jasra

4. A poster entitled "Asymmetric addition of diethylzinc to aldehydes using Ti (IV) Binol complex anchored on MCM-41**"** was presented at **17th National symposium on catalysis, organized by Catalysis society of India & CSMCRI, Bhavnagar** during January 18-20, 2005
**K. Pathak**, A. Bhatt, S. H. R. Abdi*, R. V. Jasra.

5. A poster entitled "An efficient heterogeneous catalyst for enantioselective Henry reaction" was presented at **17th National symposium on catalysis,** January 18-20, 2005 **organized by Catalysis society of India & CSMCRI, Bhavnagar**
A**.**Bhatt**, K. Pathak**, S. H. R. Abdi*, R. V. Jasra

6. A poster entitled "Catalytic asymmetric alkylation of aldehydes using varied pore size mesoporous silicas incorporating covalently bonded BINOL-Ti as heterogeneous catalyst" has been presented in **11th symposium on Modern Trends in Inorganic Chemistry (MTIC-XI) Indian Institute of Technology, New Delhi** during 8-10 Dec. 2005.
**K. Pathak**, A. Bhatt, S. H. R. Abdi*, R. V. Jasra.

7. A paper entitled "Immobilization of BINOL-Ti complex on ordered mesoporous silica: Heterogeneous catalysts for production of optically active secondary alcohols" was presented in Fourth Gujarat Research Scholars Meet (FAGRSM) **Indian Chemical society Vadodara Chapter** held at M. S. University, Vadodara on 22 rd Jan. 2006.
**K. Pathak**, A. Bhatt, S. H. R. Abdi*, R. V. Jasra.

8. A poster entitled "Oxidative kinetic resolution of secondary alcohols catalyzed by recyclable chiral dimeric Mn(III) salen catalyst" was presented in **18th National symposium on catalysis,** April 16-18, 2007 **organized by Catalysis Society of India & IIP, Dehradun**
**K. Pathak**, S. H. R. Abdi*, R. I. Kureshy, N. H. Khan R. V. Jasra

## INTERNATIONAL CONFERENCE

1. A poster entitled "Synthesis, characterization of Ti (IV) Binol complex anchored on MCM-41 as effective catalyst for asymmetric addition of diethyl zinc to aldehydes." was presented in 9th National conference on "BIOACTIVE HETEROCYCLES AND DRUG DISCOVERY PARADIGM" **[One Day International Symposium on Recent Trends in Drug Discovery]** during 8 - 10th January, 2005 Organized by Indian Society of Chemists & Biologists, Central Drug Research Institute, Lucknow at Saurashtra University, Rajkot, (Gujarat) India.
   **K. Pathak**, S. H. R. Abdi*, A. Bhatt, R. V. Jasra.