CHIRALLY MODIFIED SILICAS FOR SEPARATION AND ASYMMETRIC CATALYSIS

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

DOCTOR OF PHILOSOPHY

in

CHEMISTRY

By

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This thesis is dedicated to My beloved father, who passed away nine months ago, My mother, sister, brother and my fiancée, for their love, support and sacrifices. I will forever be indebted to them.

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. I further declare that the results presented in the thesis and the considerations made therein, contribute in general to the advancement of knowledge in Chemistry and in particular to entitled **"Chirally Modified Silicas For Separation And Asymmetric Catalysis"**

Place: Bhavnagar
Date: 06/04/2009

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This is to certify that the contents of this thesis entitled "**Chirally Modified Silicas For Separation And Asymmetric Catalysis**" is the original research work of **Mr**. **Vishal Jitendrabhai Mayani** carried out under my supervision at Discipline of Inorganic Materials & Catalysis, Central Salt and Marine Chemicals Research Institute (Council of Scientific and Industrial Research - CSIR), Bhavnagar, Gujarat.

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.

Place: Bhavnagar **(S. H. R. Abdi)**

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PREFACE

The work embodied in the present thesis comprises of five chapters. Chapter 1 describes brief introduction of importance of chiral compounds and its separation using different techniques such as chiral pool, resolution through racemates, chiral chromatography and asymmetric catalysis. The main focus of our work based on separation of racemic mixture using chiral chromatography and heterogeneous asymmetric catalysis. We have developed different techniques of separation using chiral stationary phase, chiral ligand exchange stationary phase, enantiomer self-disproportionation and heterogeneous asymmetric Henry reaction during work. Chapter 2 includes the synthesis of a new chiral stationary phase (CSP) covalently bonded to the mesoporous semi crystalline material M41S. These as synthesized (*S*)-amino alcohol-silica were used as chiral selector for the chromatographic separation of mandelic acid, 2,2'dihydroxy-1,1'-binaphthalene (BINOL), cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid. Chapter 3 consists of synthesis and characterization chiral stationary phase used in chiral ligand exchange stationary phase which is one of the promising and potent techniques for the resolution of racemates. In the present thesis, we have demonstrated its utility in the resolution of mandelic acid, diethyl tartrate and BINOL. Chapter 4 presents a new phenomenon of enantiomer self-disproportionation for the separation of non racemic mixture using achiral silica. Chapter 5 contains the utilization of chiral copper complex of amino alcohol covalently bonded on modified silica as heterogeneous catalyst for an important asymmetric C-C bond formation reaction *viz.* nitroaldol (Henry) reaction. Henry reaction is one of the classical named reactions in organic synthesis for the preparation of valuable building blocks such as 1,2-amino alcohols and α-hydroxy carboxylic acids.

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VISHAL J. MAYANI
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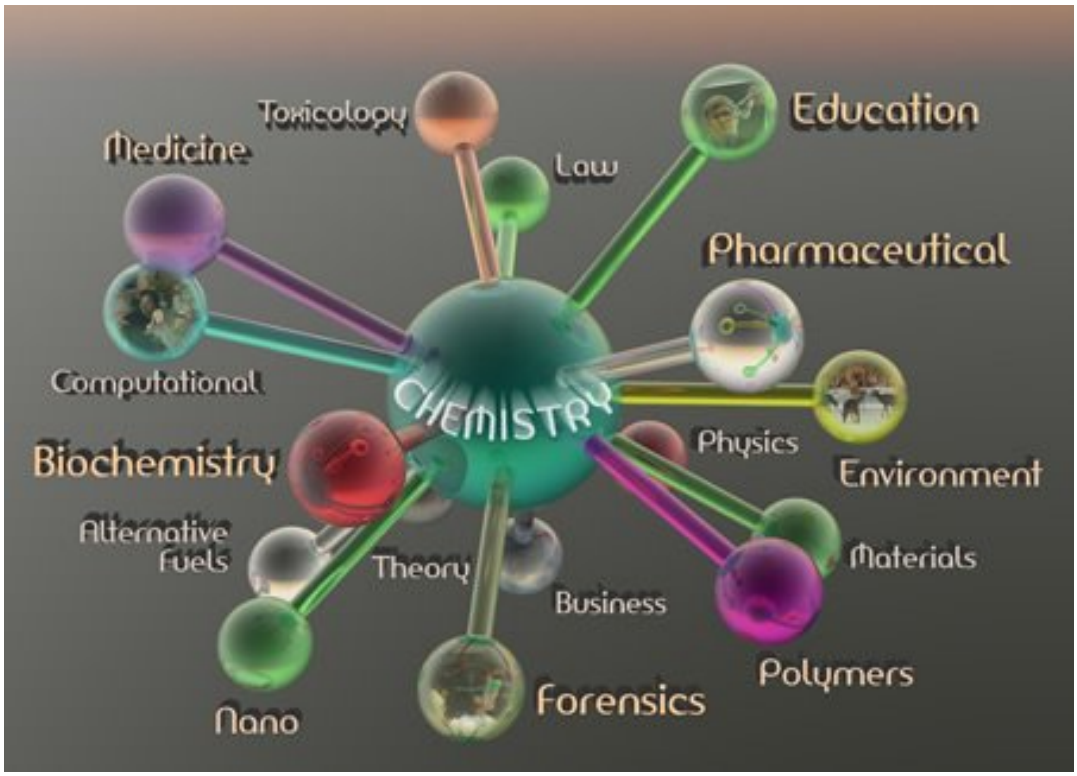
LIST OF ABBREVIATIONS

AGP	:	α_1-acid glycoprotein
APTS	:	3-Aminopropyltriethoxy Silane
BET	:	Brunauer-Emmett-Teller
BINOL	:	2,2'-dihydroxy- 1,1'-binaphthalene
BJH	:	Barrett-Joyner-Halenda
CLES	:	Chiral Ligand Exchange Stationary Phase
CNCR	:	Cyanochromene Oxide
CP-MAS	:	Cross Polarization Magic Angle Spinning
CSP	:	Chiral Stationary Phase
CTAB	:	Cetyltrimethylammonium Bromide
DNBP	:	Dinitrobenzoylphenyl
DRUV-Vis	:	Diffuse Reflectance Ultraviolet-Visible
ee	:	Enantiomeric Excess
EIR	:	Extractant Impregnated Resign
ESD	:	Enantiomer Self-disproportionation
FTIR	:	Fourier Transform Infrared
GC	:	Gas Chromatography
HAS	:	Human albumins
HIC	:	Hydrophobic Interaction Chromatography
HKR	:	Hydrolytic Kinetic Resolution
HPLC	:	High Performance Liquid Chromatography
ICP-AES	:	Inductively Coupled Plasma – Atomic Emission Spectrometry

j	:	Coupling Constant
LCMS	:	Liquid Chromatography – Mass Spectroscopy
m/z	:	Mass to Charge Ration
M41S (MCM-41)	:	Mobil's Crystalline Material
MCFs	:	Meso Cellular Foams
MPLC	:	Medium Pressure Liquid Chromatography
NMR	:	Nuclear Magnetic Resonance
PXRD	:	Powder X-Ray Diffraction
rt	:	Room Temperature
SBA-15	:	Santa Barbara Amorphous
SEM	:	Scanning Electron Microscopy
SMB	:	Simulated Moving Bed
SSR	:	Steady State Recycling
TEM	:	Transmission Electron Microscopy
TEOS	:	Tetraethyl Orthosilicate
TGA	:	Thermo-gravimetric Analysis
TMS	:	Tetramethyl Silane



CHAPTER 1

INTRODUCTION

1.1. CHIRALITY

The term chiral is used to describe an object that is non-superimposable (Figure 1.1) on its mirror image. As human hands are perhaps the most universally recognized example of chirality: The left hand is non superimposable mirror image of the right hand; no matter how the two hands are oriented, it is impossible for all the major features of both hands to coincide. This difference in symmetry becomes obvious if someone attempts to shake the right hand of a person using his left hand, or if a left-handed glove is placed on a right hand.

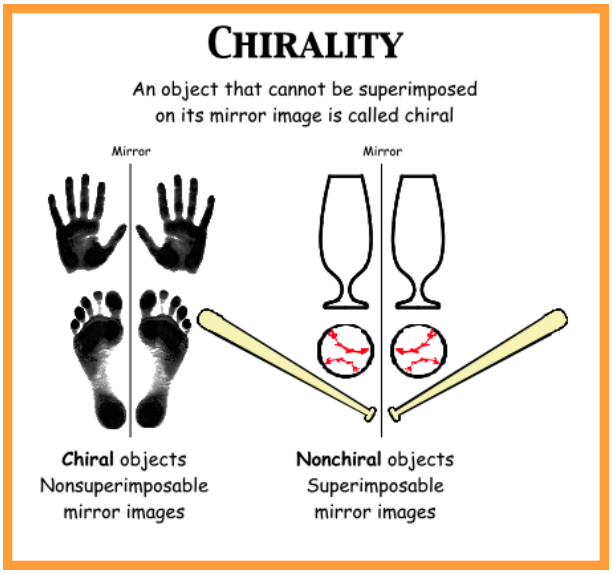


Figure 1.1 Non superimposable and Superimposable mirror images.

In 1815, the French physicist Jean Baptiste Biot for the first time reported phenomenon of '*chirality'* in a molecule [1]. However, in 1848, Louis Pasteur pioneered the first chiral separation, which laid the foundation for stereochemistry [2]. Because of the hemihedral features on the crystals of racemic sodium ammonium tartrate, he was able to separate the mirror image crystals of the isomers by the use of a magnifying glass and tweezers. Characterization of the physical properties of individual enantiomers led Pasteur to hypothesize that the enantiomers have different three-dimensional arrangements and they are mirror-images of each other at the

macroscopic and microscopic levels [3]. He further, advanced the field by studying the influence of one chiral compound upon another and introduced the technique of resolution via diastereoisomer formation. This separation of enantiomers by diastereomer formation is the basis of many modern chromatographic separations especially chiral chromatographic separations.

In 1874, the Dutch physical chemist Jacobus Hendricus Van't Hoff [4] and the French chemist Achille Le Bel [5] independently theorized that the molecular basis of chirality that was first observed by Pasteur was actually due to an asymmetric carbon. The asymmetric carbon proposed by Van't Hoff had the correct tetrahedral shape, whereas Le Bel proposed as a square pyramid. It is interesting to note that Pasteur's discovery of spontaneous enantiomeric resolution applies only to rare cases in which each isomer crystallizes separately and in a recognizable morphologic form. For more than a century, spontaneous resolution as well as diastereomeric separation and differential enzymatic reactivity were the only methods employed for enantiomeric separations.

1.2. IMPACT OF CHIRALITY IN DIFFERENT FIELDS

Chirality is central to all life forms both at molecular level as well as at macro level, and is clearly visible for instance in the shapes of shells and our own hands. Most biomolecules and life-building blocks are chiral such as amino acids, sugars, nucleic acids and hormones. In our planetary life form, these biomolecules exist in only one of the two possible enantiomeric forms, e.g. amino acids in the L-form and sugars in the D-form. It would not be an exaggeration if one says that the biodiversity that we see in the nature is manifestation of chirality. Because of chirality, living organisms show different biological responses to different enantiomers of drugs, pesticides, flavors and fragrance and taste [6]. The nature clearly recognizes that the

use of a catalyst (in the form of an enzyme) is the only way to perform biochemical reactions efficiently and in a precise manner as per the demand of the life form under moderate conditions. Metal based asymmetric catalysis is therefore in a sense mimic biological system, if not exactly in shape, in performance. The recent extraordinary progress in the area of chiral catalysis has given a range of conceptual breakthroughs in chemical sciences and benefited organic synthesis, not only in laboratories but also in industries. The growth of this fundamental technology has provided enormous economic potential in the manufacturing of variety of chemicals (Figure 1.2).

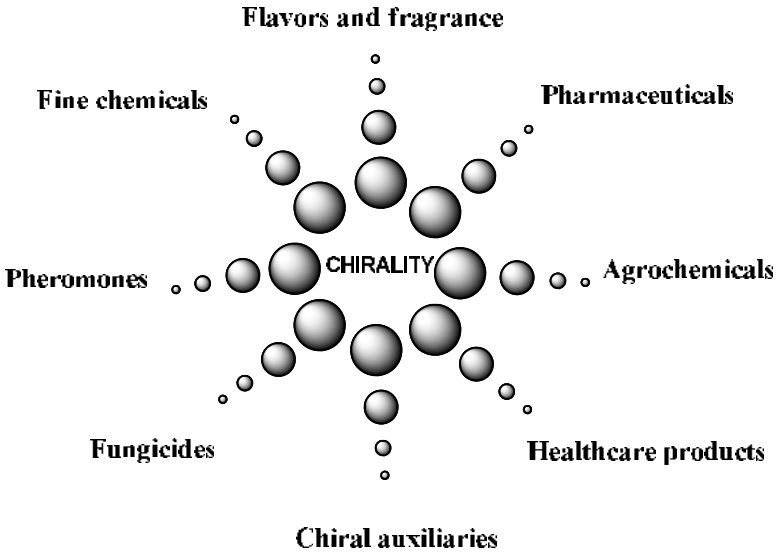


Figure 1.2 Area where chirality has utmost Influence.

1.2.1. Pharmaceuticals

Modern pharmaceutical industry is now well informed about the role of chiral molecules [7,8]. The heightened interest on this aspect of drug molecules is due to the fact that different enantiomers of a chiral drug molecule may have different pharmacological activities, as well as different pharmacokinetic and pharmacodynamic effects on the human body [9]. The body being remarkably chiral

selective, one enantiomer may produce the desired therapeutic activities, while the other may have adverse effects, or at best inactive. A landmark, though tragic episode occurred during 1960's when a racemic drug of *n*-phthalyl-glutamic acid imide (Thalidomide) was marketed as a sedative for the treatment of morning sickness in pregnant ladies. (Figure 1.3) Later, it was discovered that the therapeutic activity of Thalidomide resided exclusively in the (*R)*-(+)-enantiomer and the (*S)*-(+)-enantiomer was teratogenic. Unfortunately this fact was known only after several hundred births took place with organelles [10].

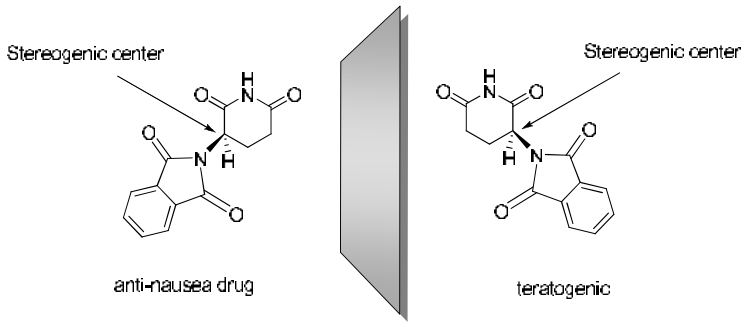


Figure 1.3 Two different isomers of thalidomide.

The above tragedy came as an eye-opener. It is rather strange and sad that a well known three-point-fit drug action model discovered as early as in 1894 by E. Fischer was ignored for so long. In this model, the arrangement of atoms in three dimensional spaces of a drug molecule decides the degree of interaction with the receptor site, which is invariably chiral. Chiral receptor sites in the human body interact only with drug molecules having the compatible configuration [11-13], resulting in marked differences in the pharmacological activities of enantiomers. Figure 1.4 give the schematic representation of this phenomenon where, one form of enantiomer of the drug interacts strongly through its three different binding groups (A, B, and C) with the respective binding sites (A', B' and C') of an enzyme. While, the other form of the enantiomer can have only weak interaction with the enzyme site, possibly because of the structural differences between the binding groups and the enzyme binding sites.

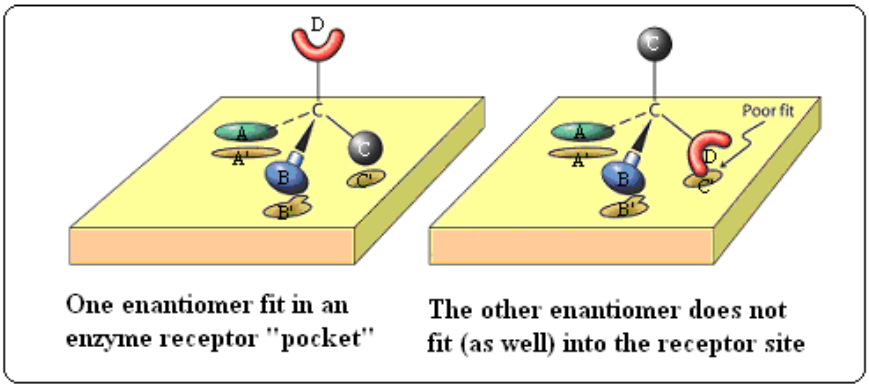


Figure 1.4 Graphical representation of the three-point fit model for enzyme receptor.

Due to the desirable and undesirable drug action of "right" and "wrong" enantiomer respectively [14-15], drug regulatory authorities consider the two enantiomers of a chiral compound as different entity all together. In 1992, the U.S. Food and Drug Administration (FDA) issued a guideline for chiral drugs that only therapeutically active enantiomer should be marketed while all pharmacological and pharmacokinetic data on each enantiomer of the drug should be studied separately and the data based on them should be made available for scrutiny [16]. In addition, an elaborated justification for marketing a racemate of chiral drugs should be given to regulatory authorities. Presently, a majority of commercially available drugs are both synthetic and chiral. However, a large number of chiral drugs are still marketed as racemic mixtures [17,18]. For instance, a variety of 2-arylmethylpropionic acids (profens) (Figure 1.5) are being widely used as non-steroidal anti-inflammatory drugs for the relief of acute and chronic rheumatoid arthritis and osteoarthritis, as well as for other connective tissue disorders and pains [19,20]. All of these drug molecules bear a chiral center and in majority of the cases it is the (*S*)-form which is more active. Though, it is not established as yet that (*R*)-form has any adverse effect, it is not advisable to load the body with less active or inactive chemical(s). Barring a few

countries where only active enantiomer is marketed, rest of the world still sell this over-the-counter drug in the racemic form.

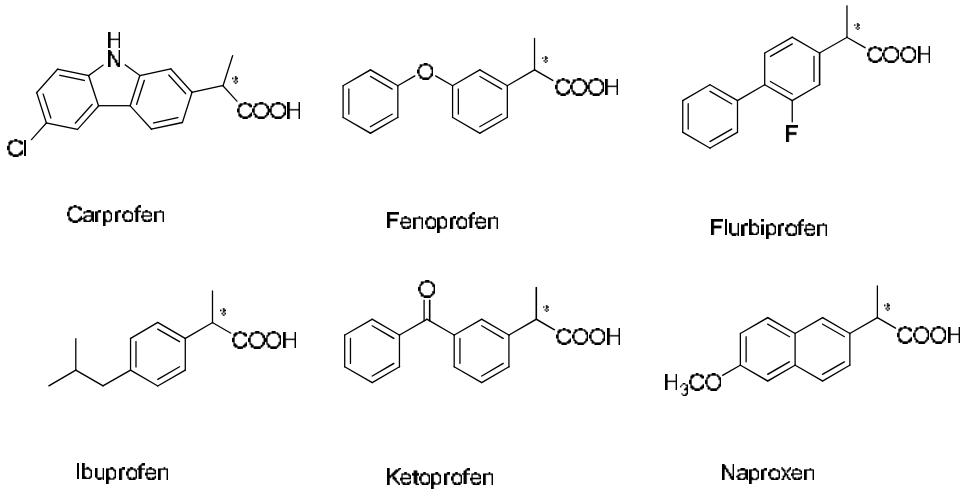


Figure 1.5 Structures of racemic 2-arylmethyl propionic acids (profens).

1.2.2. Flavors and Fragrances

Flavors and fragrances are integral parts of foods and beverages as taste and smell are most fundamental sensors in living beings. Both have reflective effect on the consumers. In Nature there are plenty of examples where, different enantiomers of a chiral flavor and fragrance molecule display different characteristics in the form of taste, smell and bioactivity. For example the figures 1.6 & 1.7, show the enantiomer of *trans*-rose oxide and Nirvanolide which smell and taste differently [21-23]. Another important example of the chiral natural flavoring compound is carvone, where (*S*)-form has odor like caraway seeds, while the (*R*)-enantiomer has odor like spearmint leaves (Figure 1.8).

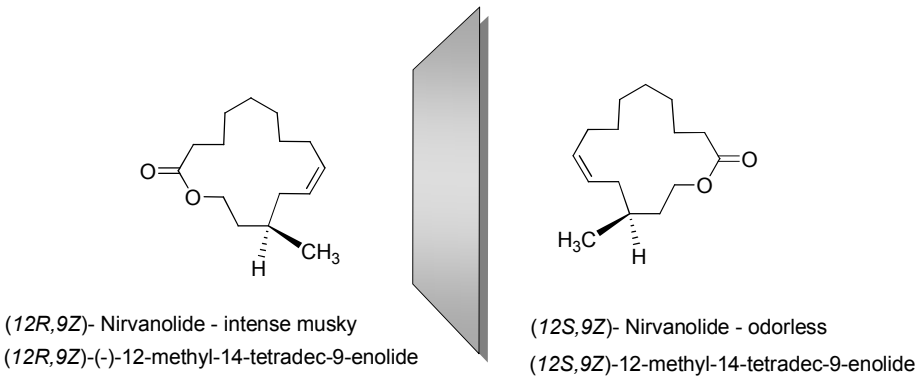


Figure 1.6 Enantiomers of Nirvanolide.

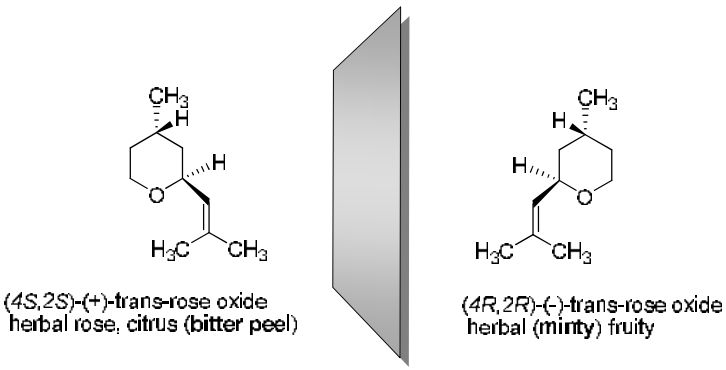


Figure 1.7 Enantiomer of *trans*-rose oxide**.**

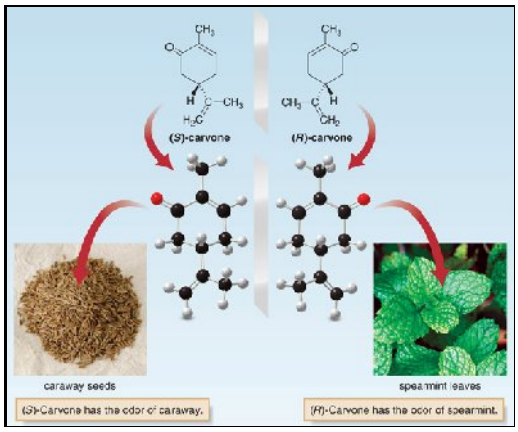


Figure 1.8 Two different enantiomers of carvone.

1.2.3. Agrochemicals

The case of synthetic chiral agrochemicals is no different. They are still marketed as racemic mixtures, despite the fact that, the desired biological activity

resides in only one form of the enantiomer. For example, synthetic pesticides *viz.* pyrethroid insecticides, aryloxypropanoate herbicides and triazole fungicides are chiral and their desired activity is shown by only one enantiomer. A representative example of 2-aryloxypropanoic acids is shown in Figure 1.9. [24].

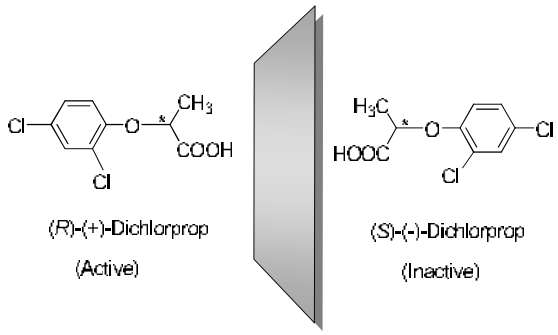


Figure 1.9 Activity of dichlorprop enantiomers.

1.3. ROUTES TO OBTAIN ENANTIOMERICALLY PURE PRODUCTS

Now that we know the importance of having chiral compounds in their enantiomerically pure form, the next question arises "what are the means and methods are available at our disposal to synthesize them". Last 3 decades have seen intense R&D activity in this area of research both in academia and industry with multipronged approaches. Broadly speaking optically active materials can be obtained by making use of chiral pool, separation of racemates and asymmetric synthesis (Figure 1.10).

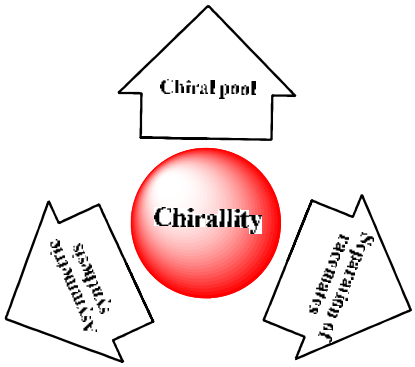


Figure 1.10 Different routes to achieve enantiomerically pure products.

Fermentation and use of microbes to synthesize chiral compounds in their optically pure form constitutes one of the earliest methods. Even now, fermentation technology is a leading technology practiced in many industries to manufacture chirally pure drugs. Many complex microbial metabolites, such as like L-amino acids, vitamins and hormones can be synthesized from inexpensive raw materials such as sucrose. However, this method provides only one form of the chiral molecule and if other form is required one will have to look for other methods or feed stocks.

Other known methods for achieving chirally pure compounds are separation of inexpensive racemic compound through classical resolution, asymmetric catalysis and chiral chromatography. Racemates separation has been used for more than a century to manufacture of chirally pure enantiomers and till now represents the key method for commercial-scale synthesis. Asymmetric catalysis is very recent and the development of practical methods is based on slightly over 30 year's research. Chiral chromatography is relatively new field where chiral selector is used to resolve the enantiomer from a racemic mixture.

1.3.1. Chiral Pool

Many abundantly available natural products are chiral and can be transformed into desired chiral molecule in a matter of few synthetic steps without disturbing the chiral center. Such natural products are termed as chiral pool. The natural products are having very high chiral purity hence; there is no requirement of additional purification. This process has several advantages for the large scale application such as; these are inexpensiveness, easily available in chirally pure natural products. Typically, trade availability of chiral pool falls in the range of 10^2-10^5 tonnes per annum. A wide range of amino acids, hydroxy acids, carbohydrates and their derivatives, terpenes, alkaloids are obtained largely from the natural resources. Some

of the representative examples of chiral pool are; Ascorbic acid, (+)-calcium pantothenate, anhydrous dextrose, ephedrine hydrochloride, (-)-carvone, (+)-limonene, mannitol, monosodium glutamate, norephedrine hydrochloride, quinidine sulphate, L-lysine, quinine sulphate, sorbitol, L-threonine and L-tryptophan [25].

1.3.2. Racemate Resolution via Crystallization

The resolution of racemates still constitutes the main method for the industrial synthesis of pure enantiomers. Methods for their resolution are classified as follows:

- Preferential crystallization
- Diastereomeric crystallization
- Catalytic kinetic resolution
- Chromatography

1.3.2.1. Preferential Crystallization

Preferential crystalization is widely practiced on an industrial scale. It is particularly attractive method for when it is accompanied by spontaneous *in situ* racemization, which allows for a theoretical yield of 100%. In general, such a process is known as crystallization induced asymmetric transformation, also referred as deracemization. The success of preferential crystallization depends on the fact that the two enantiomers crystallize at different rates.

An elegant example of deracemization has been reported by Okada and coworkers [26]. In this process, the two enantiomers of the 1,4-benzodiazepinooxazole (epimerization) is taken in a solution, (Figure 1.11) and when the solution is allowed to stand at ambient temperature, one of the enantiomers crystallizes out in a yield of more than 50%.

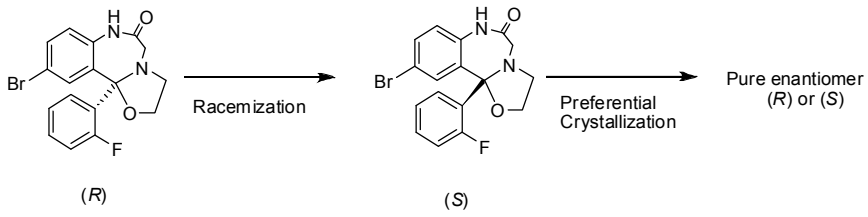


Figure 1.11 Asymmetric transformation of a racemate.

1.3.2.2. Diastereomeric Crystallization

Diastereomeric crystallization is yet another method which is used on commercial scale to achieve target enantiomer in optically pure form. In this process, by reason not well understood as yet, a homogeneous solid phase of the two enantiomers co-existing in the same unit cell and preferentially crystallizes as diastereomer in the presence of an optically pure resolving agent. The diastereomeric salts which thus formed are resolved by simple crystallization with 50 percent yield.

(*RS*)-A + **(*S*)-B** ⟹ **(*R*) A (*S*) B** + **(*S*) A (*S*) B**

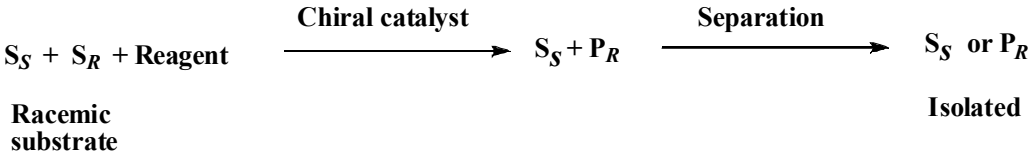
Racemic Mixture — **Resolving agent** — **Diastereomer**

Using this process D-(-)-phenyl-glycine-an intermediate for antibiotic is produced at 1000 t/a scale with the use of camphor sulphonic acid as a chiral resolving agent.

1.3.2.3. Catalytic Kinetic Resolution

The reaction between a racemic/prochiral substrate and a reagent often react at different rates in the presence of a chiral catalyst. In such cases with little a care in balancing stoichiometry, using suitably designed chiral catalyst and tuning of other reaction parameters, it is possible to discriminately transform only one enantiomer out of racemic substrate into a product. The remaining enantiomer in its high optical purity can then easily be separated due to the difference in physical parameters between the substrate and the product. This process is now known as catalytic kinetic

resolution [27]. The first example of kinetic resolution was displayed by Noyori et al. with the use of a chiral metal complex (Rh-BINAP) as catalysts for the enantioselective isomerization of the chiral allylic alcohols to the analogous prostaglandin intermediates [28].



1.3.2.4. Chromatography:

History of chromatography

The **history of chromatography** spans from the mid-19th century to the 21st century. **Chromatography**, term was coined from "color writing". It was used in the first decade of the 20th century, primarily for the separation of plant pigments such as chlorophyll. The first true chromatography is attributed to Russian botanist Mikhail Semyonovich Tsvet, who used columns of calcium carbonate for separating plant pigments.

Chromatography began to take its modern form following the work of Archer John Porter Martin and Richard Laurence Millington Synge during 1940s and 1950s. They laid out the principles and basic techniques of partition chromatography, and their work spurred the rapid development of several types of chromatography methods now know as paper chromatography, gas chromatography, and high performance liquid chromatography. Since then, the technology has advanced rapidly. The chromatographic technique is very popular among analytical tool in **R & D centers**, **pharmaceutical company, hospitals, law enforcement, environmental agencies** and **production units.**

Chromatography terms

Some of the frequently used terminology in chromatography

- The **analyte** is the substance that is to be separated during chromatography.
- **Analytical chromatography** is used to determine the existence and possibly also the concentration of analyte(s) in a sample.
- A **bonded phase** is a stationary phase that is covalently bonded to the support particles or to the inside wall of the column tubing.
- A **chromatogram** is the visual output of the chromatograph. In the case of an optimal separation, different peaks or patterns on the chromatogram correspond to different components of the separated mixture. (Figure 1.12)

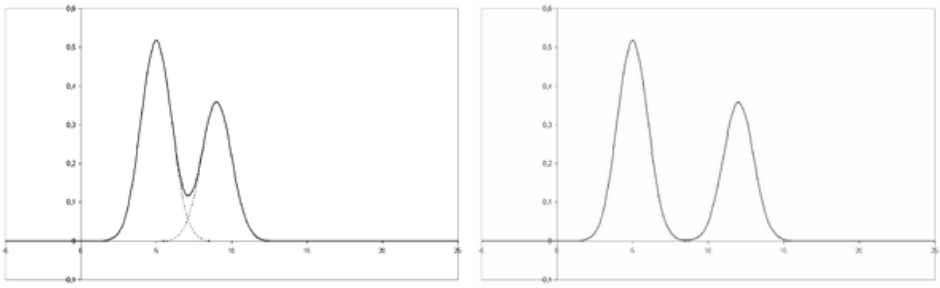


Figure 1.12 Chromatogram of mixture of components with different chromatographic condition.

X-axis gives the retention time and Y-axis gives a signal whose area depends on the substance response to various detectors. By comparing with standard sample the area of the signal is proportional to the concentration of the specific analyte separated.

- A **chromatograph** is equipment that enables a sophisticated separation e.g. gas chromatographic or liquid chromatographic separation.
- **Chromatography** is a physical method of separation in which the components to be separated are distributed between two phases, one of which is stationary

(stationary phase) while the other (the mobile phase) moves in a definite direction in order to analyze, identify, purify and/or quantify.

- The **effluent** is the mobile phase leaving the column.
- An **immobilized phase** is a **stationary phase** which is immobilized on the support particles, or on the inner wall of the column tubing.
- The **mobile phase** is the phase which moves in a definite direction through a stationary phase. It may be a liquid (LC), a gas (GC), or a supercritical fluid (supercritical-fluid chromatography, SFC).
- **Preparative chromatography** is used to purify substances in sufficient quantities for further use. In analytical scale, the quantity of samples is very small typically in mg level and individual compounds which leave column are not recovered.
- The **retention time** is the characteristic time it takes for a particular analyte to pass through the system (from the column inlet to the detector) under set conditions.
- The **sample** is the matter analyzed in chromatography. It may consist of a single component or it may be a mixture of components.
- The **solute** refers to the sample components in partition chromatography.
- The **solvent** refers to any substance capable of dissolving other substance, and especially the liquid mobile phase in LC.

1.3.2.4.1. Types of Chromatography

[1]. ADSORPTION CHROMATOGRAPHY

Adsorption chromatography is probably one of the oldest types of chromatography around (Figure 1.13). It utilizes a mobile liquid or gaseous phase that

is adsorbed onto the surface of a stationary solid phase. The equilibration between the mobile and stationary phase accounts for the separation of different solutes.

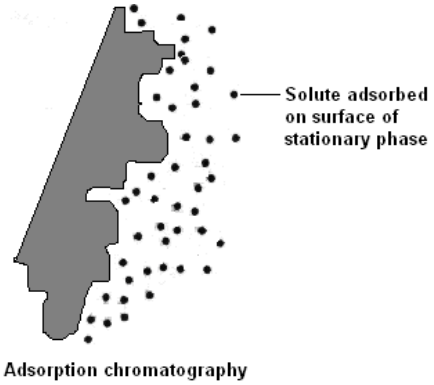


Figure 1.13 Graphical presentation of adsorption chromatography.

[2]. PARTITION CHROMATOGRAPHY

This form of chromatography is based on a thin film of a liquid stationary phase coated on the surface of a solid support (Figure 1.14). Solute equilibrates between the mobile phase and the stationary liquid and due to the difference in partition co-efficient for different compounds separation takes place.

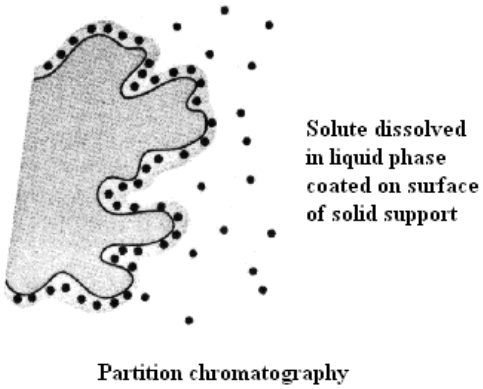


Figure 1.14 Graphical presentation of partition chromatography.

[3]. ION EXCHANGE CHROMATOGRAPHY

In this type of chromatography an anionic or cationic resin (the stationary solid phase) is used to effect separation. (Figure 1.15). Here, solute ions of the opposite charge in the mobile liquid phase are attracted to the resin by electrostatic forces and the degree of the force would decide the order of elution of various components present in the solution.

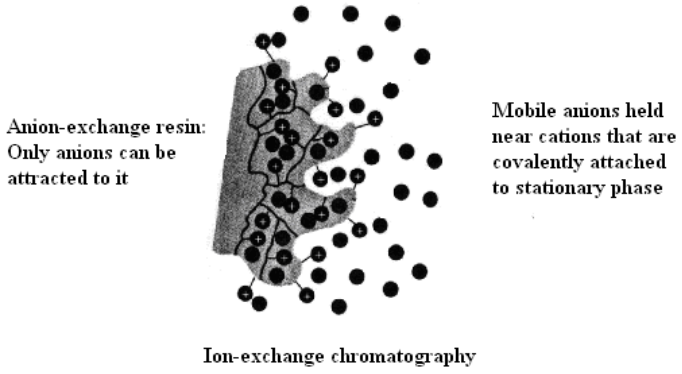


Figure 1.15 Graphical presentation of Ion exchange chromatography.

[4]. MOLECULAR EXCLUSION CHROMATOGRAPHY

Also known as gel permeation or gel filtration, this type of chromatography lacks an attractive interaction between the stationary phase and solute (Figure 1.16). The liquid or gaseous phase passes through a porous gel which separates the molecules according to its size. The pores are normally small and exclude the larger solute molecules, but allow smaller molecules to enter the gel, causing them to flow through a larger volume. This causes the larger molecules to pass through the column at a faster rate than the smaller ones.

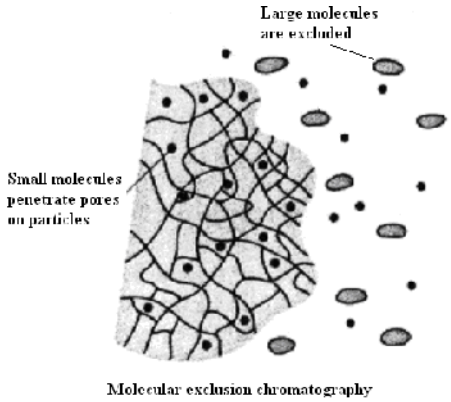


Figure 1.16 Graphical presentation of molecular exclusion chromatography.

[5]. AFFINITY CHROMATOGRAPHY

This is the most selective type of chromatography employed thus far. It utilizes the specific interaction between one kind of solute molecule and a second molecule that is immobilized on a stationary phase (Figure 1.17). For example, the immobilized molecule may be an antibody to some specific protein. When solutes containing a mixture of proteins are passed through such stationary phase, only the specific protein is reacted to the antibody present on the stationary phase leaving other proteins in mobile phase which is washed. The bound protein is later extracted by changing the ionic strength or pH of the mobile phase.

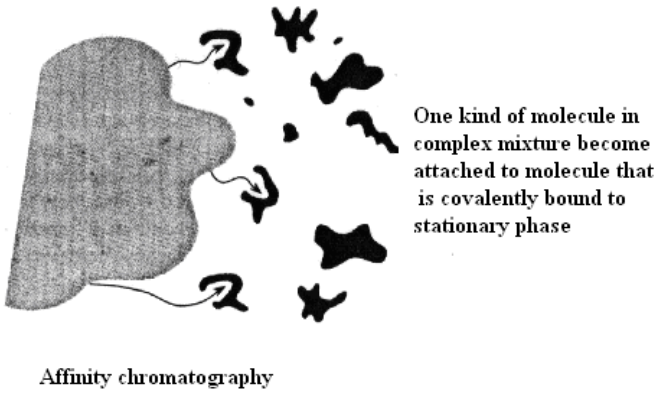


Figure 1.17 Graphical presentation of affinity chromatography.

1.3.2.4.2. Classification of Chromatography through Different Techniques

(A). LIQUID CHROMATOGRAPHY (LC)

Liquid chromatographic separation is based on interaction and differential partition of the sample between the mobile liquid phase and the stationary phase. The commonly used chromatographic methods can be roughly divided into the following groups, not necessarily in order of importance [29-33]:

- Normal phase
- Reversed phase

Normal phase chromatography

Normal phase chromatography is a chromatographic technique that separates analytes based on adsorption to a stationary phase surface chemistry and by polarity, here a polar stationary phase and a non-polar, non-aqueous mobile works effectively for separation of analytes which are readily soluble in non-polar solvents. Use of more polar solvents as mobile phase will decreases the retention time of the analytes, whereas more hydrophobic solvents tend to increase the retention time. Very polar solvents in a mixture lead to deactivation of stationary phase by creating a stationary bound water layer on the stationary phase surface.

Reversed phase chromatography

Reversed phase chromatography uses as non-polar stationary phase and an aqueous, moderately polar mobile phase. To make stationary phase non-polar usually RMe_2SiCl, where R is a straight chain alkyl group such as $C_{18}H_{37}$ or C_8H1_7, is used to modify silica. With these stationary phases retention time is lower for molecules which are more non-polar, while polar molecule elute readily. It is possible to increase retention time by adding more water to the mobile phase.

(B). GAS CHROMATOGRAPHY (GC)

Gas chromatography is applicable to volatile samples that are transported by a carrier gas through the stationary phase (usually silica coated with various oils) of the column where separation takes place by the sorption/desorption process. Samples for gas chromatographic analysis are normally low molecular weight compounds that are volatile and stable at high temperature. Currently, separation by the silica packed column is rapidly being replaced by the capillary column that provides improved resolution and analysis speed.

(C). THIN-LAYER CHROMATOGRAPHY (TLC)

Thin-layer chromatography is the simplest of all the commonly used chromatographic techniques. In TLC separation is based on migration of the sample spotted on a plate coated with a thin layer of stationary phase (usually silica/alumina). The edge of the spotted side of the plate is then placed in a closed chamber having a mixture of solvents (mobile phase) which travel upward by capillary action. Once the solvent reaches a defined distance from the bottom, the plate is taken out of the chamber and the spots can be detected by techniques include fluorescence, UV and sprays (universal and specific) for compounds that are not naturally colored. This technique very convenient to monitor the progress of organic reactions, however it is not as accurate or sensitive as HPLC or GC [34-35].

(D). PAPER CHROMATOGRAPHY

Paper chromatography was the first analytical chromatographic technique developed supposedly using papyrus (Pliny). It was first published by Runge in 1855 [36] and consists of a solvent moving along filter or blotting paper. The interaction between the components of the sample, the solvent, and the paper, results in separation of the components. Most modern paper chromatography is partition

chromatography [37], where the cellulose of the paper used as inert support, and water adsorbed (hydrogen bonded onto the hydroxyl groups of the cellulose) becomes the stationary phase [38].

(E). HYDROPHOBIC INTERACTION CHROMATOGRAPHY ("HIC")

This technique is especially developed for amino acids that contain hydrocarbon side-chains and are not charged; therefore these cannot be purified by the same principles involved in ion-exchange chromatography. These hydrophobic ("water-hating") amino acids are usually buried away inside of the protein folds. These hydrophobic amino acids can bind on a support which contains immobilized hydrophobic groups. It should be noted that these HIC supports work by a "clustering" effect; no covalent or ionic bonds are formed or shared when these molecules associate [38].

(F). CAPILLARY ELECTROPHORESIS

Capillary electrophoresis uses a small fused silica capillary that has been coated with a hydrophilic or hydrophobic phase to separate biomolecules, pharmaceuticals and small inorganic ions. A voltage is applied and the analytes migrate and separate according to their charge under the specific pH conditions, as also happens for electrophoresis. The capillary can also be used for isoelectric focusing of proteins. The use of salt or vacuum mobilization is no longer required [39-43].

(G). COLUMN CHROMATOGRAPHY

Column chromatography consists of a column of particulate material such as silica or alumina that has a solvent passed through it at atmospheric or low pressure. The separation can be liquid/solid (adsorption) or liquid/liquid (partition). The

columns are usually glass or plastic with sinter frits to hold the packing. Most systems rely on gravity to push the solvent through [38].

(H) CHIRAL CHROMATOGRAPHY

Chiral Chromatography is a branch of chromatography that is oriented towards the exclusive separation of chiral substances. Certain stereo-isomers that differ only in the spatial arrangement of their atoms and in their capacity for rotating the plane of polarized light are termed optically active or chiral compounds and the individual isomers are called enantiomers. Enantiomeric separations are achieved in chiral chromatography by the judicious use of chiral stationary phases. The mobile phase can be a gas or liquid giving rise to chiral gas chromatography and chiral liquid chromatography respectively. Chiral selectivity is usually achieved by employing chiral stationary phases, although, in chiral liquid chromatography, chiral mobile phases have been successfully employed. For any chiral separation, the stationary phase must be chosen in such a way so that the spatial arrangement of its composite atoms increases the probability or proximity of interaction differing significantly between the two enantiomers meant to be separated.

1.3.2.4.3. Chiral Stationary Phases

Great efforts have been devoted to the development of better methodology for enantioselective chromatography during the past decade, and have resulted in new chiral stationary phases, pioneered by Pirkle [44]. Chiral agents were derivatized and immobilized on the surface of the support (silica gel mostly) and served as the *in situ* chiral discriminators during the chromatographic process.

1.3.2.4.4. Enantioseparation through Chiral Stationary Phase

Since the main work in the present thesis comprises the development of chiral organic-inorganic hybrids for separation of enantiomers and catalysis, it is pertinent to

deal these subjects in a little more detail. It is evident from the literature that during the last two decades there has been a steep increase in the number of chiral pharmaceuticals sold in their enantiomerically pure form rather than their racemic form [45-48]. Optically pure compounds are beneficial in other fields also, *e.g.,*bio-chemicals, pesticides, aroma, flavor and fragrance chemicals, dyes, pigments, liquid crystals, non-linear optical materials and polymers as well [7, 49, 50-52]. Separation of chiral molecules is required to be done as two enantiomers of a racemic compound have different pharmacological activities in many instances. In order to discern these differing affects, the biological activity of each enantiomer [53,54] needs to be studied separately. This has contributed significantly to the requirement of enantiomerically pure compounds particularly in pharmaceutical industry [55,56] and thereby the need to have chiral chromatography [57]. Attempts have been made in the past for the development of chiral stationary phases using β-cyclodextrin [58, 59], notably DAICEL phases [60,61], crown ether [29,30], antibiotics [31] on silicas for HPLC [29-33], MPLC [62], GC [63,64], capillary electrophoresis [39-43] and chiral ligand exchange chromatography (CLEC) [65-68].

A conventional classification of types of chiral stationary phases are:

- Chiral affinity by proteins (serum albumin, α_1-acid glycoprotein, ovomucoid and chymotrypsin).
- Stereoselective access to helical chiral polymers (derivatized or free polysaccharides).
- Steric interactions between π-donor π-acceptor type of chiral aromatic amide groups (Pirkle).
- Host-guest interactions inside chiral cavities (cyclodextrins, crown ethers and imprinted polymers).

- Ligand exchange (copper ions complexed with chiral moieties).

(P). PROTEIN IMMOBILIZED ON SILICA GEL

One of the most attractive types of chiral stationary phases for pharmaceutical analysis involves the use of protein immobilized on to the surface of silica gel, or other support, as the chiral discriminator. Many small chiral biomolecules have shown stereoselective affinity to serum albumin, α_1-acid glycoprotein, ovomucoid and α-chymotrypsin [69].

(Q). POLYSACCHARIDE DERIVATIVES

Polysaccharides such as cellulose and amylose consist of D-glucose units linked by 1-4 glucosidic bonds, forming the natural polymers with a highly ordered helical structure (Figure 1.18). The three hydroxyls on each glucose unit can be derivatized to form strands around the chiral glucose. The derivatized glucose unit can act as a chiral site discriminating between enantiomers that interact differently with the strands. Resolution can sometimes be achieved with unsupported natural cellulose, but the immobilized version has proven far better. The acetate ester, benzoate ester, or phenylcarbamate derivatives of glucose have shown better performance.

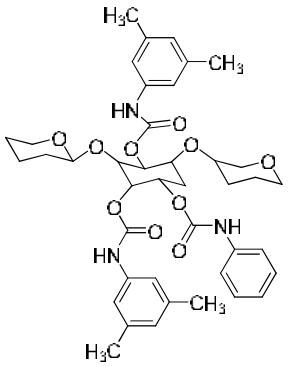


Figure 1.18 Illustrates the structure of a glucose unit of the amylose based stationary phase, derivatized with dimethylphenylcarbamate.

(R). CHIRAL CAVITY

Another general strategy for chiral discrimination on a stationary phase is creation of chiral cavities, in which stereoselective guest-host interactions govern the resolution. The first important consideration for retention and chiral recognition in such stationary phases is the proper fit of the molecule to the chiral cavity in terms of size and shape. This category of stationary phases includes crown ethers [29,30], imprinted polymers and cyclodextrins [58,59]. A majority of commercially available chiral columns are indeed based on suitably derivatised α-, β- an γ-cyclodextrins. (Fig. 1.19)

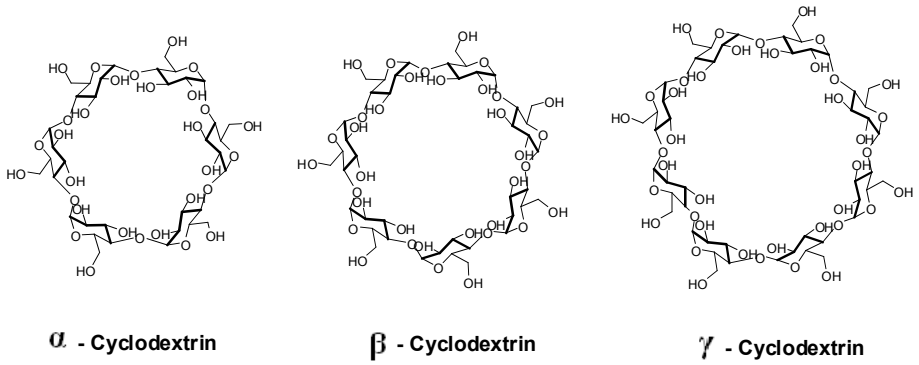


Figure 1.19 Cyclodextrins are macrocyclic molecules containing 6, 7 and 8 glucopyranose units (α-, β-, γ- cyclodextrin respectively).

(S). π-DONOR π-ACCEPTOR - PIRKLE TYPE

Historically, this type of π-donor π-acceptor - pirkle type chiral stationary phase proceeded from all the others types described here (Table 1.1). The pioneering work of Pirkle [70,71] had such an impact on the field that the whole category of donor-acceptor type stationary phases was named after him. The structure of these types of stationary phases is based on single strands of chiral selectors, connected via amidic linkage onto aminopropyl silica as shown in Figure 1.20.

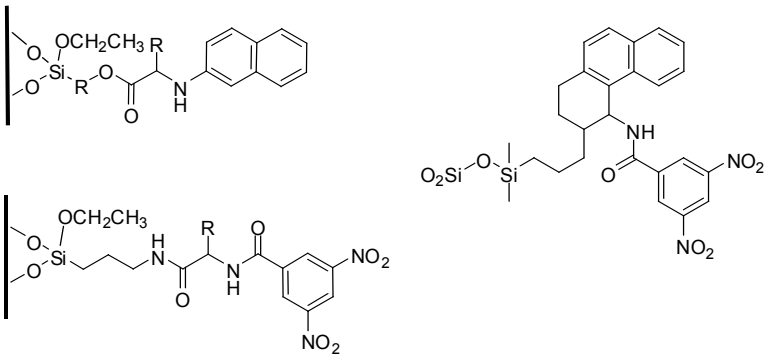


Figure 1.20 Chiral selectors connected via amidic linkage onto aminopropyl silica.

(T). CHROMATOGRAPHY MEMBRANES

Chromatography membranes are designed for separation tasks in laboratory and industrial applications. They are built-in membrane systems such as plate and frame, spiral-wound module, hollow fiber module, and tube-in-shell module.

Table 1.1 The analyte-CSP interactions, leading to the formation of diastereomeric complexes with different stationary phase.

Type	Description	Example	Mode (modifier)
1	Pirkle-type (π-donor / π-acceptors)	DNB-henylglycine, DNB-leucine, naphthylalanine	Normal phase (polar)
2	Attractive interactions followed by inclusion (derivatized cellulose)	Chiralcel OA, OB, OD, OF, OJ	Normal phase (polar)
3	Inclusion (cyclodextrins, polyacrylates, polyacrylamides, crown ethers)	Cyclobond I, II, III; Chiralpak OP, OT; Chiralcel CR	Reversed phase (aqueous acetonitrile or methanol)
4	Ligand exchange	Proline, hydroxyproline	Reversed phase (aqueous buffers)
5	Proteins	Albumin, glycoprotein	Reversed phase (aqueous buffers)

(T). CHIRAL LIGAND EXCHANGE STATIONARY PHASE

Chiral ligand exchange stationary phase is one type of stationary phase where metal ion is involved. In which some organic moiety such as amino alcohol treated

with copper salt anchored on silica which leads to the reversible complex formation [49]. Chiral analyte takes part in ligand exchange process and gives separation (Figure 1.21).

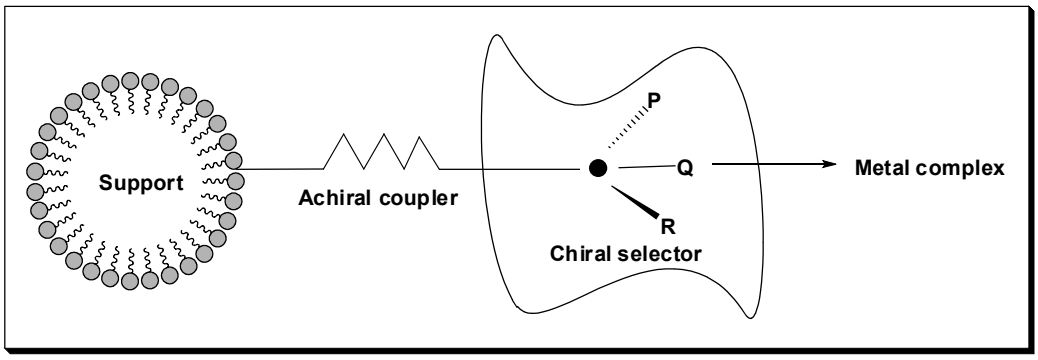


Figure 1.21 General diagram of chiral stationary phase.

1.3.2.4.5. Chiral Separations Analyte-Chiral Stationary Phase Interactions

Diastereomeric analyte-CSP Complexes Formation

The chiral analytes, 2-arylmethylpropionic acids, that are being studied in this research all possess a chiral center. Three separate interactions are required between the enantiomers and the CSP, and these interactions may be attractive or repulsive and they may be single point (e.g., hydrogen bonding) or multipoint (e.g., dipole stacking and π-π interactions). At least one of these interactions must be stereochemically dependent. Figure 1.22 shows the formation of diastereomeric analyte-CSP complexes which follows the Three Point Rule: three simultaneous interactions between the analyte enantiomers and CSP (Table 1.2). Diastereomeric complexes are also formed by diffusion of analyte enantiomers into a chiral matrix. Even though no bonding interactions are invoked, the analyte enantiomers are in a chiral environment. Here, chiral recognition should occur, would be entirely steric in origin. Such conditions are equivalent to a stationary phase containing chiral cavities, for example cyclodextrin.

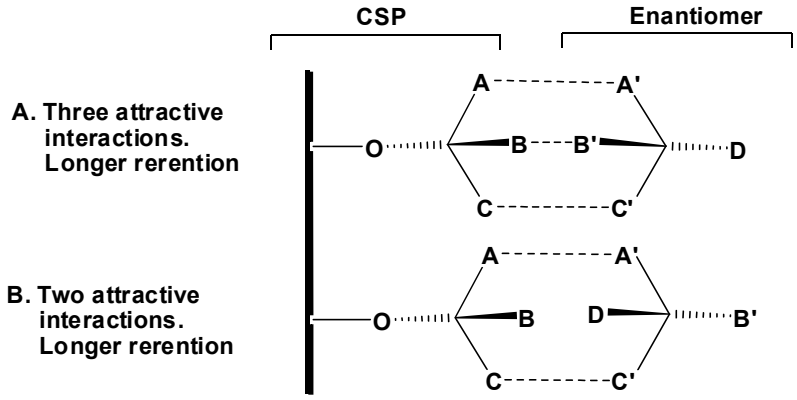


Figure 1.22 Three Point Model for the formation of the diasteromeric analyte-CSP complexes: (a) more stable and more retained and (b) less stable, hence elutes first.

Some analyte-CSP interactions are illustrated in Figure 1.23. Hydrogen bonding (a high energy form of dipole-dipole interaction) is the most important interaction for the majority of the CSPs.

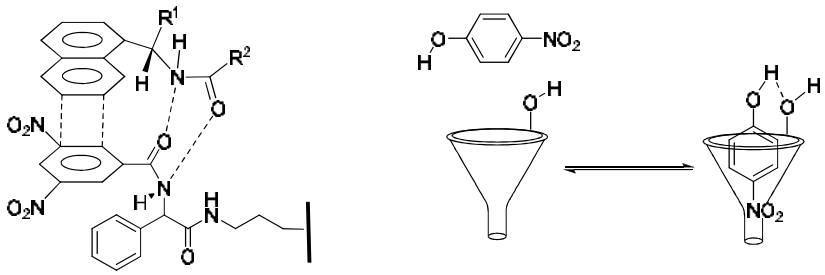


Figure 1.23 Analyte-CSP interactions: (a) π-π interactions between the phenyl moieties of the analyte (donor) and CSP (acceptor) (-----) and dipole-dipole stacking (↔); and (b) inclusion and hydrogen bonding formation between analyte and cyclodextrin CSP.

A hydrogen bond is formed when an acidic proton is in close proximity with an electron pair donor or a hydrogen bond acceptor group such as oxygen (in alcohols, carboxyl, carbonyl, and ethers), a nitrogen atom (primary and secondary amines), a halogen, and a sulfur atom (thiol groups). Hydrogen bonds are nearly linear, asymmetrical and equal to the distance between the proton donor and acceptor atoms.

Table 1.2 gives a summary of various intermolecular attractions between analyte and CSP for diastereomeric complexes formation

Table 1.2 A summary of intermolecular attractions between analyte and CSP for diastereomeric complexes formation.

Sr. No.	Interaction Type	Relative Strength	Working Distances
1	Hydrogen bond	Very Strong	Long range
2	π-Electron Donor-Acceptor	Strong	Moderately long range
3	Ion - Dipole	Strong	Short range
4	Dipole - Dipole	Moderately Strong	Short range
5	Dipole - Induced Dipole	Weak	Very short range
6	London Dispersion Forces	Very Weak	Extremely short range

Some of the commercially available chiral HPLC columns are listed in Table 1.3

Table 1.3 Commercially Available Chiral HPLC Columns.

Sr. No.	Polysaccharide Derivative	Trade Name	Distributor
1	Cellulose triacetate (coated on silica gel)	Chiralcel OA	Daicel
2	Cellulose tribenzoate (coated on silica gel)	Chiralcel OB	Daicel
3	Cellulose trisphenylcarbamate (coated on silica gel)	Chiralcel OC	Daicel
4	Cellulose tris(3,5-dimethylphenylcarbamate (coated on silica gel)	Chiralcel OD Chiralcel OD-R	Daicel
5	Cellulose tris(4-chlorophenylcarbamate) (coated on silica gel)	Chiralcel OF	Daicel
6	Cellulose tris(4-methylphenylcarbamate) (coated on silica gel)	Chiralcel OG	Daicel
7	Cellulose tris(4-metylbenzoate) (coated on silica gel)	Chiralcel OJ	Daicel
8	Cellulose tricinnamite (coated on silica gel)	Chiralcel OK	Daicel
9	Amylose tris(3,5-dimethylphenylcarbamate (coated on silica gel)	Chiralpak AD	Daicel
10	Amylose tris [(S)- phenylethylcarbamate) (coated on silica gel)	Chiralpak AS	Daicel

1.3.2.4.6. Enantiomer Self-disproportionation Chromatography

Most recently discovered phenomenon of enantiomer self-disproportionation (**ESD**) is a process in stereochemistry describing the separation of a non- racemic mixture of enantiomer in an enantioriched fraction and a more racemic fraction as a result of the "*heterochiral"* or "*homochiral"* aggregates. Enantiomers may be separated without the amplification of any external element of chirality.

In the present study, a new chiral stationary phase (CSP) was synthesized based on (*S*)-1-anilino-3-propyl-2-propanol covalently bonded to the mesoporous semi-crystalline material M41S. This was achieved by the interaction of (*S*)-epichlorohydrin with 3-aminopropyl triethoxysilane, which was then immobilized on M41S followed by epoxide ring opening with aniline. Thus, synthesized (*S*)-amino alcohol-silica and its copper complexes were used as a chiral stationary phase and chiral ligand exchange stationary phase respectively for the chromatographic separation of mandelic acid, 2,2'-dihydroxy-1,1'-binaphthalene, cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid.

1.3.3. Asymmetric Synthesis

A chemical transformation which gives a wide-ranging of enantio pure organic substances from achiral precursors is known as asymmetric synthesis. This route should convert substrate into the desired product with desired chirality quantitatively with enantio-selectivity in minimum possible time, in high atom and cost efficiency, operational simplicity, eco-friendly manner and should consume lower. Conventional asymmetric synthesis uses a stoichiometric amount of a chiral compound. Though it is convenient for reactions at smaller to medium scale, it is practical only if the expensive chiral auxiliary intentionally attached to a substrate or reagent is readily

recyclable. These requirements are ideal and desirable but, practically difficult to achieve. To do away with expensive chiral auxiliary, which is required in stoichiometric amount, it is desirable to have a chiral catalyst instead. However, all the virtues described above are still difficult to achieve in a planned manner, mostly due to the insufficient knowledge of the catalytic cycle (Figure 1.24).

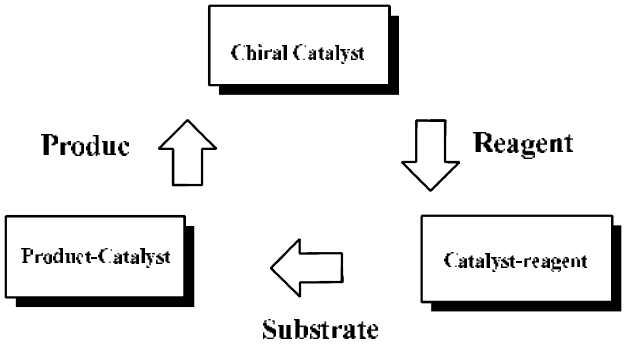


Figure 1.24 Catalytic cycles.

In chiral catalyst therefore, ligand design is extremely important and a well designed catalyst in an extremely small amount can produce millions of chirally pure molecules, and thus neutralize the high cost of the catalyst. Hence, for a highly active and enantioselectivity chiral catalyst following parameters are decisive.

- ✶ Chiral catalysts lead to a very high selectivity because the purification of mixtures of enantiomers is expensive.
- ✶ Its turn-over number / frequency should also be very high for high product yield.
- ✶ Chiral catalyst should ideally be recyclable and reusable for several cylces without loses of activity in order to minimize its high cost.

Several well-designed and developed asymmetric metal complexes not only speed up the chemical reactions but also distinguish between diastereomeric transitions states (TSs) with accuracy of 10 kJ mol^{-1}.

Asymmetric catalysis is presently used in practically all organic transformations where chirally pure products are required. However, the present thesis would be restricted to asymmetric nitroaldol reaction.

1.3.3.1. Asymmetric Nitroaldol Reaction (Henry Reaction)

Asymmetric catalysis, in short span of thirty years has established itself as a viable alternative to conventional organic synthesis, resolution of racemic mixture and biochemical processes [72,73]. Some of the well known and important metal catalyzed enantioselective reactions are hydrogenation, epoxidation and C-C bond formation reactions.

Among the various organic transformations, the nitroaldol reaction is one of the classical C–C bond forming named reactions in organic synthesis. Reaction between carbonyl functionality and nitroalkane is known as nitroaldol reaction (Figure 1.25). Essentially the coupling of the nucleophile generated from a nitroalkane with a carbonyl electrophile is a widely used transformation since its discovery in 1895 [74]. The resulting product of this reaction is a β-hydroxy nitroalkane, which is a versatile intermediate in the synthesis of drugs and biologically active compounds. However, the wide applicability of this transformation, until recently, was impaired due to the unavailability of suitable catalysts for imparting a definite stereochemistry to the newly generated stereogenic centers.

Figure 1.25 Asymmetric nitroaldol reaction.

The first asymmetric version of the Henry reaction was reported by Shibasaki in 1992 [74]. Since then, interest in this area has expanded considerably and various reports are regularly appearing in the literature on the development of various metal and nonmetal based catalysts under homogeneous system [75]. In homogeneous system, separation of product and recycling of catalyst is tedious. Therefore, we conducted heterogeneous version of asymmetric nitroaldol reaction.

1.3.3.2. Heterogeneous Asymmetric Nitroaldol Reaction of Aldehydes Using Nitromethane as Neucleophile

In homogeneous asymmetric catalysis, reagents and catalyst are found in the same phase. Homogeneous metal catalyzed asymmetric synthesis has made impressive progress during the last several decades [76-78] and chemists involved in the revolutionary breakthroughs in asymmetric catalysis were awarded Nobel prize of chemistry in 2001 [79]. These studies marked a new direction in coordination chemistry, in which metal catalysts, due to their activity and selectivity, started to be considered as chemist's enzymes, thereby, reducing the gap between chemo- and bio-catalysis. The field of asymmetric catalysis has been focused for a long time by homogeneous catalysis because of their key advantages, such as:

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

However, potential homogeneous asymmetric catalysts are finding it difficult to get acceptability in industry due to their inherent shortcomings, *viz.,* (i) complex work-up procedure of the reaction mixture; (ii) preparation of the products free from catalyst/degraded catalyst residue; (iii) isolation of the valuable catalyst or its constituents, which can be achieved only with high technical complexity and expenditure. The most practical way to obviate these problems is to "*heterogenize*" the homogeneous catalyst, by means of immobilization, anchoring, or encapsulation on an inorganic or organic solid support [80-82].

This generated increasing interest from both industrial and academic researchers over the last few decades to find ways for economical processes [83, 84]. Among them, the Cu-catalyzed Henry reaction performed at room temperature has received much attention in recent years [85, 86]. We have recently reported copper complexes of (*S*)-amino alcohol supported silicas and used them as chiral ligand exchange stationary phase to resolve racemic compounds [87, 88]. Looking at the structural features of this material we also explored the catalytic ability of this solid supported copper complex for asymmetric nitroaldol reaction.

1.4. SUMMARY OF THE WORK DONE IN THE THESIS

The present work describes the synthesis of chirally modified silicas and their use as chiral stationary phases for column chromatographic separation of racemates using mild pressures by means of chiral stationary phase (CSP) and chiral ligand exchange stationary phase (CLESP). In the process of studying chromatographic separations, we came across an interesting phenomenon of enantiomer self-disproportionation chromatography for the separation of "*non-racemic"* mixtures using "*achiral"* mesoporous semi-crystalline material and standard silica. Further, we have

also studied the utility of these materials in catalytic asymmetric nitroaldol reaction under heterogeneous conditions. Accordingly, the present work is organized in the following chapters.

Chapter 2

Synthesis and characterization of (*S*)-amino alcohol modified M41S as effective material for the enantioseparation of racemic compounds:

In chapter 2, a new chiral stationary phase (CSP) was synthesized based on (*S*)-1-anilino-3-propyl-2-propanol covalently bonded to the mesoporous semi-crystalline material M41S. This was achieved by the interaction of (*S*)-epichlorohydrin with 3-aminopropyl triethoxysilane, which was then immobilized on M41S followed by epoxide ring opening with aniline. Thus, synthesized (*S*)-amino alcohol-silica was used as a chiral selector for the chromatographic separation of mandelic acid, 2,2'-dihydroxy-1,1'-binaphthalene (BINOL), cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid. Excellent chiral separation (ee, >99%) was obtained in the case of mandelic acid. (*S*)-amino alcohol-silica was found to be stable under our chromatographic separation conditions and was reusable. We checked its separation performance for three successive repeat experiments where it showed no sign of deterioration. To the best of our knowledge this is the first report concerning the use of (*S*)-amino alcohol supported on to silica as column packing material to separate different racemates using moderate pressure column chromatography.

Chapter 3

Synthesis and characterization of mesoporous silica modified with chiral auxiliaries for their potential application as chiral stationary phase:

Chapter 3 deals with the synthesis of chiral ligand exchange stationary phase. Chiral ligand exchange chromatography (CLEC) is emerging as a potent technique for the resolution of racemic amino acids, peptides and hydroxyl acids. In this context some of the CSPs prepared by silica modified with chiral chelating agents can be easily converted into their metal complex counter parts, which in turn can be used as material for CLEC. The present work describes the preparation of CSP and CLEC for the resolution of mandelic acid as model compound. In view of the above we have synthesized (*S*)-amino alcohol-supported SBA-15 and standard silica for the chromatographic separation of mandelic acid and other racemate. Besides, the aminoalcohol moiety generated on solid supports was complexed with copper ion to give chiral copper complexes covalently bonded on to SBA-15 and standard silica. These supported metal complexes were used as CLEC to resolve racemic mandelic acid, BINOL and diethyl tartrate. These chirally modified silica materials are stable under ambient conditions and can be repeatedly used for the resolution of racemates under moderate pressure column chromatography. Therefore these materials have potential for their application as stationary phase in chiral HPLC and CLEC.

Chapter 4

Enantiomer self-disproportionation of chiral compounds on achiral ordered mesoporous silica M41S and regular silica gel as a stationary phase:

Chapter 4 includes the new phenomenon of enantiomer self-disproportionation. Enantiomer self-disproportionation (ESD) is a process in

stereochemistry describing the separation of a non- racemic mixture of enantiomer in an enantioriched fraction and a more racemic fraction as a result of the "*heterochiral"* or "*homochiral"* aggregates formation. Enantiomers may be separated without the use of any external element of chirality. This phenomenon was first reported by; Soloshonok et al. in the separation of enantiomers of particularly fluorinated organic compounds on a regular silica gel as a stationary phase. We observed this phenomenon of enantiomer self-disproportionation in non-fluorinated and commercially important chiral compounds *viz.,* mandelic acid and stilbene oxide while purifying non-racemic mixture of these compounds on two achiral stationary phases namely regular silica gel and ordered mesoporous silica M41S using different solvents. For a detailed and systematic study on this phenomenon mandelic acid was selected as a model candidate for compounds having extensive "*hydrogen bonding"*, while stilbene oxide was selected for compounds having nonbonding interactions mostly through phenyl ring related *"π–π interactions"*. In both the cases, initial fractions obtained were more racemic than the original ee of the sample (76.1%) but some of the later fractions showed ee > 99%.

Chapter 5

Heterogeneous material for catalytic asymmetric nitroaldol reaction:

Chapter 5 deals with the heterogeneous asymmetric nitroaldol reaction using chiral metal complex of amino alcohol modified silica. Important C–C bond forming reactions, such as nitroaldol or Henry reaction is one of the classical named reactions in organic synthesis for the preparation of valuable building blocks such as 1,2-amino alcohols and α-hydroxy carboxylic acids. The Cu-catalyzed Henry reaction performed at room temperature has received much attention in recent years [85,89,90]. Since we

synthesized copper complexes of (*S*)-amino alcohol on supported silicas for their use in chiral ligand exchange chromatography [88], it was pertinent to utilize this copper complex as heterogeneous catalyst for asymmetric nitroaldol reaction as well. The solid chiral Cu(II) complex of amino alcohol was a most suitable catalyst for the nitroaldol reaction, providing different *"nitroalcohols"* with moderate to excellent enantioselectivities (ee > 99%) for different aromatic, aliphatic and acyclic aldehydes. Various reaction parameters like solvent and temperature varied in order to optimize the reaction condition. Besides, we also examined the role of different chiral imines (base) as additives and found that (*S*)-*N*-(2-methoxybenzylidene)-1-phenylethanamine is most suitable additive with this heterogeneous catalytic system providing some of the products like (*S*)-1-(4-bromophenyl)-2-nitroethanol in ee's more than 99%. This catalyst is worked well up to three cycles without loosing its catalytic activity and enantioselectivity.

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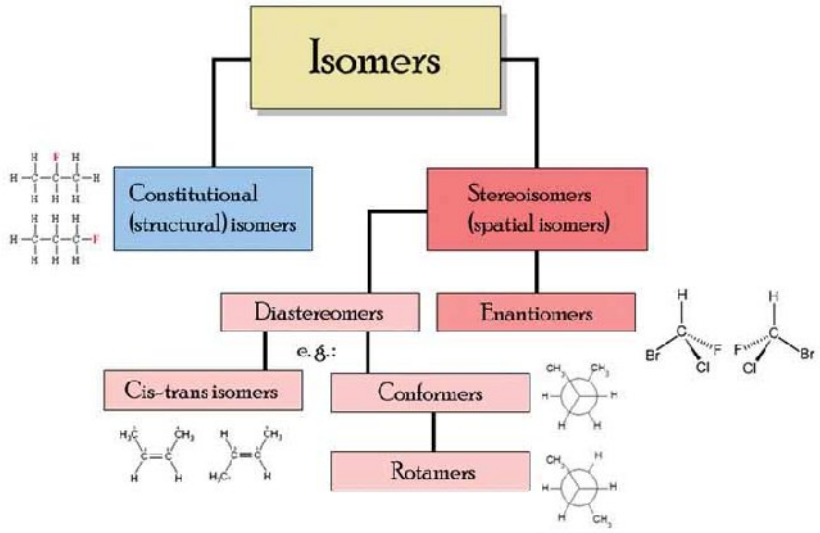

CHAPTER 2

Synthesis and Characterization of (*S*)-amino alcohol Modified M41S as Effective Material for the Enantioseparation of Racemic Compounds

2.1. INTRODUCTION

Separation of chiral molecules is required in many areas of research. As enzymes and other biological receptor molecules possess chiral centers, enantiomers of a racemic compound may interact with them in a different manner. Consequently, two enantiomers of a racemic compound have different pharmacological activities in many instances. In order to discern these differing effects, the biological activity of each enantiomer [1,2] needs to be studied separately. This has contributed significantly to the requirement of enantiomerically pure compounds particularly in pharmaceutical industry [3,4] and thereby the need to have chiral chromatography [5]. Attempts have been made in the past for the development of chiral stationary phases using β-cyclodextrin [6,7] notably DAICEL phases [8,9], crown ether [10,11], antibiotics [12] on silicas for HPLC [10–14], MPLC [15], GC [16,17], capillary electrophoresis [18–22] and chiral ligand exchange chromatography (CLEC) [23–27].

Conventionally amorphous silica is used to support a chiral selector molecule. However, mesoporous semi-crystalline materials (M41S) possess ordered pore structure, a large pore volume and high surface area besides thermal stability and mild acidity. These attributes make these materials a promising candidate for use in chromatography [28]. Ironically, mesoporous silica is seldom used as support for chromatographic applications though its use as catalyst support is well known. In the present study, the (*S*)-amino alcohol-silica **1** was synthesized using mesoporous silica M41S. This was achieved by the interaction of (*S*)-epichlorohydrin **2** with 3-aminopropyl triethoxysilane **3**, which was then immobilized on M41S followed by epoxide ring opening with aniline (Figure 2.1). Thus, synthesized (*S*)-amino alcohol-silica **1** was used as a chiral selector for the chromatographic separation of mandelic acid, 2,2'-dihydroxy- 1,1'-binaphthalene, cyanochromene oxide, diethyl tartrate and

2-phenyl propionic acid. Excellent chiral separation (ee, 99%) was obtained in case of mandelic acid. (*S*)-amino alcohol-silica **1** worked very well up to three repeat experiments without loss in separation performance. To the best of our knowledge, this is the first report concerning the use of (*S*)-amino alcohol-silica **1** as column packing material to separate different racemates.

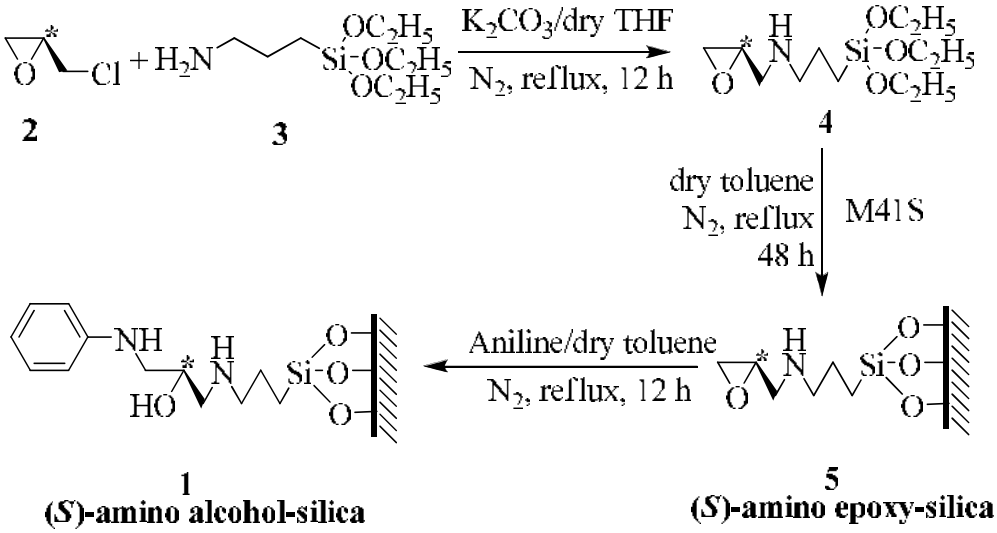

Figure 2.1 Synthesis of the immobilized (*S*)-amino alcohol-silica **1**.

2.2. EXPERIMENTAL

2.2.1. Materials and Methods

Racemic epichlorohydrin, sodium silicate solution, aniline, 2,4-di-*t*-butyl phenol, racemic 2,2'-dihydroxy-1,1'-binaphthalene (Aldrich, USA), 3-aminopropyl triethoxysilane, racemic mandelic acid, 1*R*,2*R*-(-)-1,2-diaminocyclohexane, racemic diethyl tartrate (Fluka, USA), cetyltrimethylammonium bromide, cobalt acetate (s.d. fine chem. Ltd., India) para formaldehyde, racemic 2,6-dimethyl pyridine (National Chemicals, India), stannous chloride (Merck, Germany), racemic 2-phenyl propionic acid (Across organics, Belgium) were used as received. Anhydrous K_2CO_3 (Rankem, India) was used after heating at 80 °C for 3 h. Cyanochromene oxide was synthesized by the reported method [29]. All the solvents used in the present study were purified

by known method [30]. The (*S*)-epichlorohydrin was obtained by the enantioseparation of racemic epichlorohydrin using Jacobsen Co (III)-salen complex as a catalyst under hydrolytic kinetic resolution (HKR) conditions. The purity of the resolved (*S*)-epichlorohydrin was checked on chiral GC column (CHIRALDEX trifluoroacetyl derivatives GTA-type) and by optical rotation. Jacobsen's catalyst was prepared by the known method [31–33]. Synthesis of a highly ordered hexagonal siliceous M41S was carried out by modified hydrothermal crystallization method [34–37].

2.2.2. Synthesis of Siliceous MCM-41

A highly ordered hexagonal siliceous MCM-41 was synthesized according to the modified procedure of Das et al. [34] by hydrothermal crystallization method. The sodium silicate (27.34% SiO_2 and 8.05% Na_2O) was used as a silica source and cetyltrimethylammonium bromide (CTAB) as a template. The composition of the precursor gel used for MCM-41 synthesis was as; 1 SiO_2: 0.33 Na_2O: 0.5 CTAB: 74H_2O. In a typical synthesis, CTAB was dissolved in warm (40-45 °C) de-ionised 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 10.5-11.0 with 1:1 H_2SO_4: H_2O v/v followed by vigorous stirring. The resulting gel was placed in a Teflon Parr high-pressure reactor for crystallization at 110 °C for 144 h. The solid was filtered, washed thoroughly with de-ionised water till the pH was 7-8. It was air dried at room temperature and calcined in air at 550 °C for 6 h.

2.2.3. Preparation of Nano Silica (MCM-41)

Typical synthesis of ordered MCM-41 silica particles were introduced to illustrate the situation of controlling the size of particles. The synthetic condition was both stirring with an extremely low surfactant concentration at 80 °C (353 K).[38-40]

Typically, the synthesis preparation of nano silica (MCM 41) was as follows:

- 3.5 ml of 2M NaOH solution was mixed with 480 ml of double distilled water.
- 1.0 gm of surfactant was added to the solution with heating (80 °C) and stirring.
- When the solution become homogeneous, 5 ml of tetraethoxy silane (TEOS) was dropped in slowly, giving rise to white slurry.
- After 2h, the resulting product was filtered, washed with distilled water, dried at ambient temperature and followed by calcinations in air at 550 °C (823 K) for 4 hours.

2.2.4. Synthesis of Immobilized (*S*)-Amino Alcohol-Silica 1

Immobilized chiral ligand **1** and its precursors were synthesized as per the scheme given in Figure 2.1.

2.2.4.1. Synthesis of chiral (2'S)-N-(2',3'-epoxypropyl)-3-(aminopropyl)-triethoxy-silane 4

A highly dry and inert condition was maintained throughout the reaction using freshly dried reagents and apparatus. Typically, to a stirred suspension of anhydrous potassium carbonate (0.705 g, 5.1 mmol) in THF (5 ml), *S*-(+)- epichlorohydrin **2** (0.2 ml, 2.557 mmol) and 3-aminopropyl triethoxysilane **3** (0.598 ml, 2.557 mmol) were added at room temperature. The reaction mass was then refluxed (65–66 ◦C) for 12 h, filtered under inert atmosphere. Solvent from the filtrate was removed by the dry nitrogen draft; yield (0.674 g, 95%). As the compound **4** was highly moisture sensitive, an aliquot from the above semisolid was taken for spectroscopic characterization, while rest of the material was directly used for the preparation of **5** without further purification. LCMS: 278 $[M+H]^+$, 302 $[M + Na]^+$. ^1H NMR (200 MHz, $CDCl_3$): δ 0.63 (t, J = 7.90, 2H), 1.22 (t, J = 6.97, 3H), 1.48–1.63 (m, 2H), 1.85

(br s, NH), 2.67 (t, *J* = 7.28, 2H), 2.77 (d, *J* = 3.96, 1H), 2.82–2.88 (m, 1H), 3.55 (d, *J* = 5.53, 1H), 3.69 (q, *J* = 6.93, 13.95, 2H), 3.82 (q, *J* = 6.99, 13.93, 2H,); ^{13}C NMR spectroscopy (50 MHz, $CDCl_3$): δ (8.48, 18.86, 27.64, 45.47, 47.99, 52.61, 52.99, 58.97); FTIR (KBr): 3410, 2926, 1653, 1445, 1075, 776, 696 cm^{-1}; CHN analysis data C/H ratio calculated: 5.29, found: 5.21, C/N ratio calculated: 10.29, found: 12.42, Optical rotation $[\alpha]_D^{27}$ = +43.7º (C = 0.35, tetrahydrofuran).

2.2.4.2. Synthesis of (S)-amino epoxy-silica 5

To a solution of **4** (0.709 g, 2.557 mmol) in toluene (15 ml) was added calcined and freshly activated (at 250 °C) M41S (2 g) under an inert atmosphere and the resulting suspension was refluxed for 48 h with stirring. After cooling, the powder was collected by filtration, washed successively with dry toluene and then dried under vacuum. The dried material was subjected to Soxhlet-extraction with toluene for 10 h followed by drying the sample under vacuum [37]. FTIR (KBr) 458, 577, 801, 1078, 1634, 2359, 2936, 3413 cm^{-1}, Solid reflectance UV–vis: 230, 245, 290 nm.

2.2.4.3. Synthesis of (S)-amino alcohol-silica 1

Under dry and inert atmosphere, aniline (455 µl, 5 mmol) was added to a suspension of **5** (2.5 g) in dry toluene (15 ml). The suspension was refluxed with stirring for 12 h. The reaction mixture was cooled to room temperature and the solid was filtered, washed repeatedly with dry toluene and subjected to the Soxhlet-extraction with toluene and 2-propanol (70:30) for 10 h. Finally the sample was dried under vacuum at 40 °C. Solid-state ^{13}C CP–MAS NMR (50 MHz), δ ppm 137 (aromatic carbons originated from aniline), 77–68 and 37–21 (alkyl carbons from epichlorohydrin modified aminopropyl chain), FTIR (KBr) 461, 554, 702, 801, 961, 1082, 1445, 1499, 1600, 1630, 2361, 2937, 3429, 3776 cm^{-1}, CHN analysis (Found)

C: 12.76, H: 2.14, N: 1.90% (C/N = 6.71, C/H = 5.96), diffuse reflectance UV–vis: 230, 245, 290 nm.

2.2.5. Column Chromatography

Slurry of (*S*)-amino alcohol-silica **1** in *n*-hexane and 2- propanol (9:1) was packed in a 260 mm × 16 mm glass column using medium pressure (0.5 kp/cm^2) of nitrogen at room temperature. The analyte solution in 2-propanol/*n*-hexane (1:1) was loaded on thus packed column that was equilibrated for 1 h. Each fraction of the size 4ml was collected at the pressure mentioned above, which were subjected to HPLC analysis using an appropriate chiral column.

2.3. RESULTS AND DISCUSSION

2.3.1. Characterization

The preparation of immobilized chiral (*S*)-amino alcohol-silica **1** is depicted in Figure 2.1. The species **2** was synthesized by hydrolytic kinetic resolution (HKR) of racemic epichlorohydrin using Jacobsen Co (III)-salen complex as a catalyst and was characterized for its chemical and chiral purity by GC using GTA column, ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$ and optical rotation [31–33]. The interaction of **2** in THF with 3-aminopropyl triethoxysilane gave **4**, which was fully characterized by ^{1}H, ^{13}C NMR, FTIR and optical rotation before it was anchored on calcined M41S to form (*S*)-amino epoxy-silica **5**.

The ring opening of the epoxy species **5** was done with aniline in toluene to get **1**. The loadings of chiral organic moiety in compound **5** and **1** were found to be 22.5% and 25.6%, respectively, as determined from the weight loss measured by thermo-gravimetric analysis carried out in the temperature range between 50 and 800ºC (Figure 2.2).

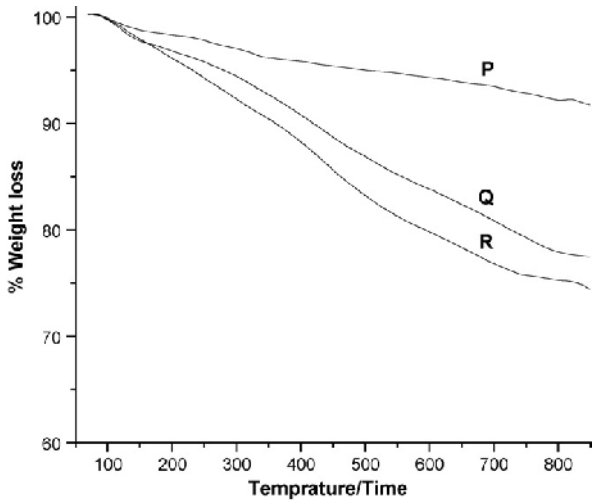

Figure 2.2 TGA curve of calcined M41S (P), (*S*)-amino epoxy-silica **5** (Q) and (*S*)-amino alcohol-silica **1** (R).

The X-ray diffraction pattern of M41S expectedly [34–37] showed (Figure 2.3) hexagonal lattice with a major peak assigned to reflection corresponding to plane (100) and two additional peaks with lower intensity corresponding to reflections from (110) and (200) planes. It was observed (Figure 2.3) that upon surface functionalization of M41S with organic moieties viz., epoxy and amino alcohol in **5** and **1**, the intensity of all of peaks decreased marginally with a small shift toward lower 2θ value.

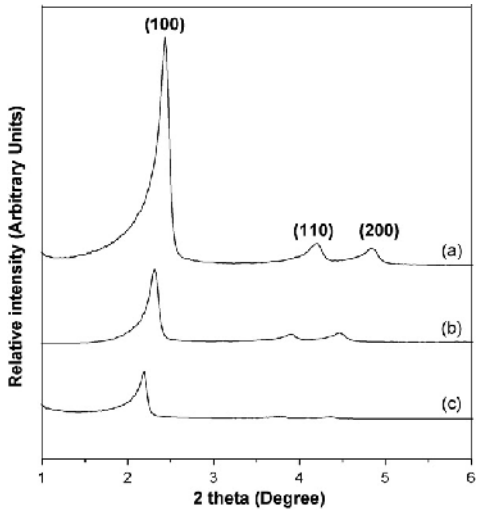

Figure 2.3 Powder X-ray diffraction pattern of calcined M41S (a), (*S*)-amino epoxysilica **5** (b) and (*S*)-amino alcohol-silica **1** (c).

This could be due to the presence of ligand inside the pores that cause an increased in the amount of scattering power within the pores, resulting in overall loss of intensity due to phase cancellation between pore walls and the guest ligand [41]. However, the presence of major reflections corresponding to M41S even after surface functionalization shows that the mesoporous M41S structure is retained.

The FTIR spectra (Figure 2.4) of M41S showed the characteristic band at 1082 cm^{-1} of Si-O-Si and 3435 cm^{-1} for the Si-OH bond. After immobilization of **4** (Figure 2.1) on M41S surface, an additional band appeared at 2936 cm^{-1} due to $\nu(CH_2)$ of propyl arm belonging to silylation agent in **5** (Figure 2.4). However, after carrying out ring opening reaction with aniline (**1** in Figure 2.1), new band due to ν(C−N) and ν(C=C) of aromatic ring appeared at 1499 cm^{-1} and 1600 cm^{-1}, respectively, along with broad band centered around 3429 cm^{-1} with enhanced intensity due to merging of ν(C−N), ν(O−H) along with Si-O-Si bands confirming the formation of supported (*S*)-amino alcohol **1**.

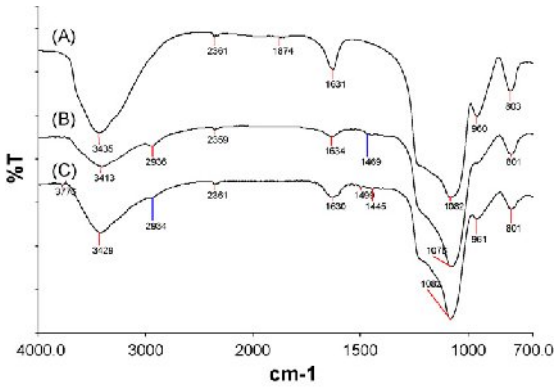

Figure 2.4 FTIR spectra of calcined M41S (A), (*S*)-amino epoxy-silica **5** (B) and (*S*)-amino alcohol-silica **1** (C).

The presence of organic moiety in **1** was further confirmed by solid state (CP-MAS) ^{13}C NMR that showed peaks both in aromatic and aliphatic regions corresponding to carbons originating from aniline and epichloroydrin modified aminopropyl silane (Figure 2.5). Scanning electron microscopy (Figure 2.6) and

Transmission electron microscopy (Figure 2.7) confirm the expected particle morphology with their size of around 1 μm.

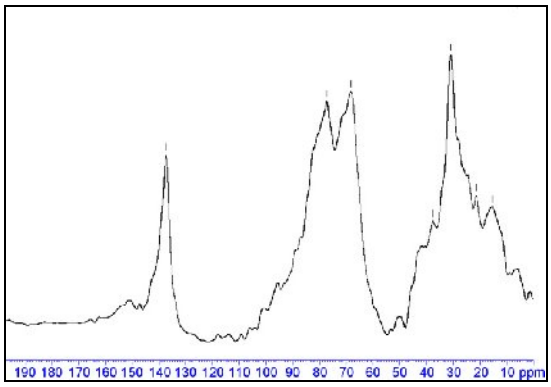

Figure 2.5 Solid-state ^{13}C CP–MAS NMR spectra of (*S*)-amino alcohol-silica **1.**

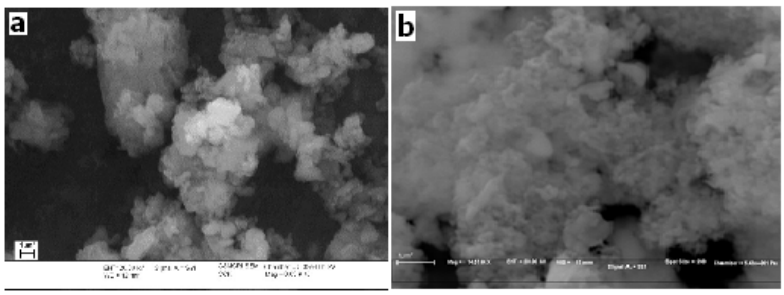

Figure 2.6 Scanning electron microscopy (SEM) images of calcined M41S**.**

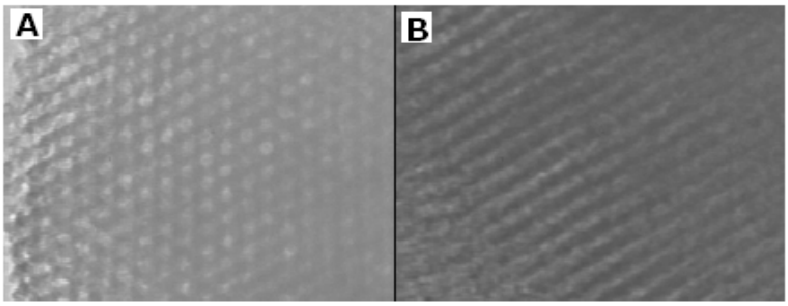

Figure 2.7. Transmission electron microscopy (TEM) images of calcined M41S.

The total pore volume of the sample was estimated from the amount of N_2 adsorption at relative pressure of about 0.995. N_2 adsorption–desorption isotherm of M41S of IV type is also confirmed the well ordered mesopores. The primary mesopore volume *V*p was calculated from the slope of a linear portion of the *t*-plot in

the pressure range above the pressure of nitrogen condensation in primary mesopores. The data on BET surface area, pore diameter, total pore volumes obtained are summarized in Table 2.1. A large decrease in BET surface area was observed (1064–771 m^2/g) upon functionalization of modified M41S represented as **5** in Figure 2.1.

Table 2.1 Physico-chemical data of M41S, (*S*)-amino epoxy-silica **5** and (*S*)-amino alcohol-silica **1.**

Compound	BET surface area, m^2/g	Total pore volume (cm^3/g)	BJH pore diameter (Å)	Wall thickness (Å)
M41S	1064	0.942	35.4	6.31
Compound **5**	771	0.625	32.4	11.51
Compound **1**	680	0.512	30.1	16.46

Similarly, reduction in the mesoporous diameter from 35 to 32 **Å** and in pore volume from 0.942 to 0.625 cm^3/g was also observed (Table 2.1). Moreover, further decrease in BET surface area 771 to 680 m^2/g in pore diameter from 32 to 30 **Å** and pore volume from 0.625 to 0.512 cm^3/g was observed upon ring opening reaction with aniline (**1**, Figure 2.1) indicates that the internal pores of the M41S are occupied by the amino alcohol and structure of the mesopore is maintained after modification (Figure 2.8).

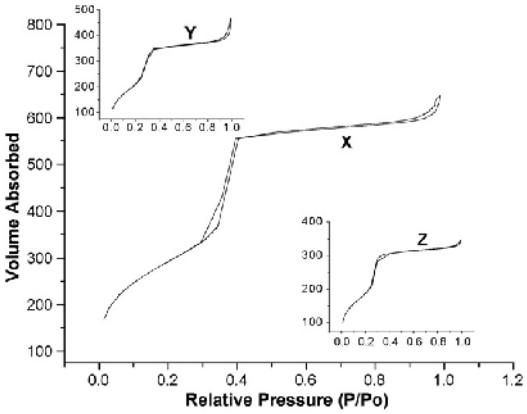

Figure 2.8 Nitrogen adsorption–desorption isotherms of M41S (X), (S)-amino epoxy-silica **5** (Y) and (S)-amino alcohol-silica **1** (Z).

The solid reflectance UV–vis spectrum of the immobilized (*S*)-amino epoxy-silica **5** shows ligand charge transfer band at 230, 260 and 330 nm. After formation of (*S*)-amino alcoholsilica **1** the spectrum remains similar with an increase in the intensity of all the bands showing the presence of amino alcohol covalently bonded to M41S (Figure 2.9).

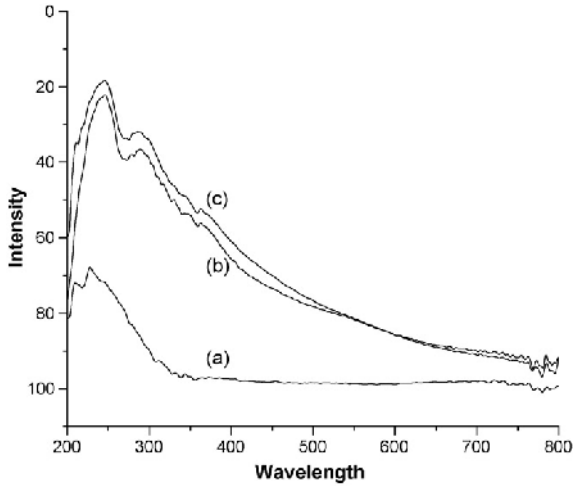

Figure 2.9 Solid reflectance UV-vis spectra of calcined M41S (a), (S)-amino epoxysilica **5** (b) and (S)-amino alcohol-silica **1** (c).

2.3.2. Chiral Resolution of Racemic Mixtures Using Chiral Stationary Phase

The separation activity of the (*S*)-amino alcohol-silica **1** for enantioseparation of racemic mandelic acid (Figure 2.10) was carried out by medium pressure column chromatography by varying the amount of (*S*)-amino alcohol-silica **1** as well as that of analyte as shown in Table 2.2. Mandelic acid (30 mg) in the form of slurry in *n*-hexane/2-propanol (9:1) was loaded on column packed with **1** (2 g). The excellent enantioseparation of (*R*)-(−)-mandelic acid in some of the fraction with ee up to 99.4% was achieved (entry 1). The ee of mandelic acid was determined by HPLC using chiralcel OD column and the HPLC chromatogram of racemic and resolved mandelic acid is shown in Figure 2.11, respectively.

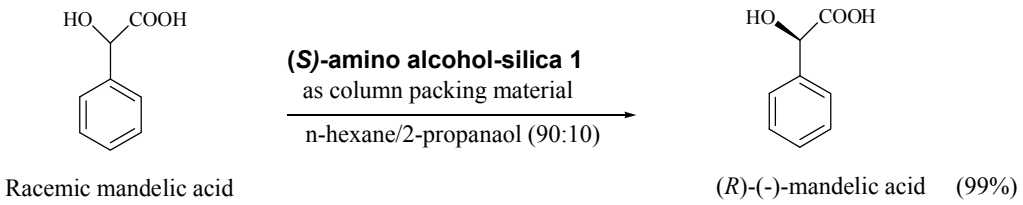

Figure 2.10 Chiral separation of racemic mandelic acid.

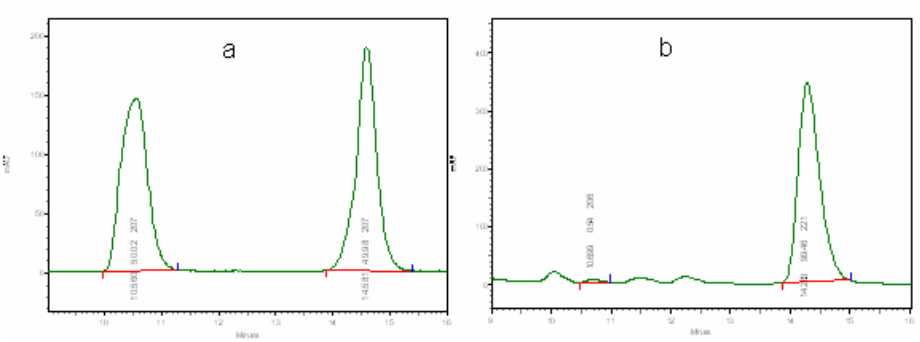

Figure 2.11 HPLC chromatogram of racemic mandelic acid (a), HPLC chromatogram of (R)-(-) mandelic acid (b) after column chromatography carried out on Chiralcel OD column using n-hexane/2-propanol (80/20) mobile phase at 0.5 ml/min flow rate.

After the 30 fractions of 4ml each the chiral stationary phase **1** was washed with 2-propanol to retrieve the (*S*)-mandelic acid (recovery, 9 mg; ee, 47.3%). Table 2.3 and Figure 2.12 show the elution profile and the amount of mandelic acid obtained after separation. For the sake of convenience in weighing we have combined the fractions 1–13, 14–22 and 23–30 which were found to be 4, 5 and 11 mg with ee 4.2, 53.2 and 95.6%, respectively. As a result 11 mg of (*R*)-(−)-mandelic acid with ee >95% was recovered which is >72% of the (*R*)-enantiomer present in 30 mg of the racemic mandelic acid. In all >96% of the mandelic acid was recovered at the end of chromatographic separation.

Table 2.2 Separation of mandelic acid varying amount of mandelic acid and packing material**.**

Entry	Amount of mandelic acid[a] (mg)	Column packing material 1(g)	Eluent[b]	% ee max[c]	Repeat experiment[d]
1	30	2.00	Hex/IPA = 9:1	99.4	1st
2	30	1.90	Hex/IPA = 9:1	99.0	2nd
3	30	1.87	Hex/IPA = 9:1	98.8	3rd
4	30	2.00	Hex/IPA = 9:1	99.3	-
5	10	2.00	Hex/IPA = 9:1	98.5	-
6	10	M41S[e]	Hex/IPA = 9:1	-	-

[a] Separation by HPLC, using chiralcel OD column, eluent n-hexane/2-propanol=9:1 at 220 nm, mandelic acid loaded on column after dissolving in 2-propanol/n-hexane. [b] Hex = n-hexane, IPA = 2-propanol. [c] Enantiomeric Excess of (*R*)-(-)-mandelic acid determined by the comparison of HPLC profile with authentic samples [d] Reuse of chiral stationary phase for chromatographic separation of fresh racemic mandelic acid. [e] 2 g M41S as column packing material

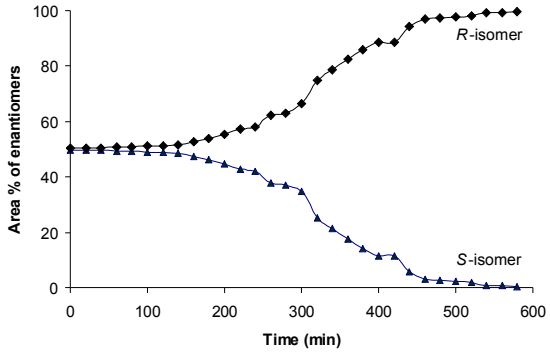

Figure 2.12 Elution profile from the medium pressure column chromatography (Table 2.3).

After completion of one chromatographic run the column material was subjected to the Soxhlet-extraction with toluene and 2-propanol (70:30), dried under vacuum and reused for another separation experiment with fresh racemic mandelic acid under the condition used for first separation experiment. The data for two repeat use of the recovered column material **1** (Table 2.2; entries 2 and 3) show that the material is stable and retain the enantioseparation capability under the separation

conditions used and drying the column material under vacuum. Furthermore, even 2 g of column packing material and 10 mg of analyte are sufficient to achieve similar results (Table 2.2 entry 5). In a control experiment for the chromatographic separation of racemic mandelic acid (10 mg) using calcined M41S (2 g) as packing material was carried out (Table 2.2, entry 6) but, no chiral separation was affected. It is therefore concluded that the chiral separation occurred due to the modification of M41S with chiral amino alcohol. (*S*)-amino alcohol-silica **1** (2 g) was further explored for carrying out the resolution of other racemic compounds viz. 2,2'-dihydroxy-1,1'-binaphthalene, cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid under optimized reaction conditions and data is given in Table 2.4. Of all compounds used, better chiral separation was achieved with 2-phenyl propionic acid (entry 10).

Table 2.3 Data for separation of racemic mandelic acid with elution of n-hexane/2-propanol=9:1 by medium pressure column chromatography[a]

Fractions	Time (min)	Area % of (*S*)-(-)-mandelic acid[b]	Area % of (*R*)-(-)-mandelic acid[b]	Weight of fractions (g)	ee (%)
1	0	49.74	50.26		
2	20	49.74	50.26		
3	40	49.68	50.32		
4	60	49.31	50.69		
5	80	49.25	50.75		
6	100	48.96	51.04		
7	120	48.68	51.32		
8	140	48.29	51.71		
9	160	47.22	52.78		
10	180	46.17	53.83		
11	200	44.79	55.21		
12	220	42.93	57.07		
13	240	42.12	57.88	0.004[c]	4.2
14	260	37.91	62.09		
15	280	36.96	63.04		
16	300	34.77	66.23		

17	320	25.06	74.95		
18	340	21.24	78.76		
19	360	17.55	82.45		
20	380	14.08	85.92		
21	400	11.64	88.36		
22	420	11.44	88.56	0.005[d]	53.2
23	440	5.85	94.15		
24	460	3.23	96.77		
25	480	2.54	97.46		
26	500	2.25	97.75		
27	520	1.73	98.27		
28	540	0.77	99.23		
29	560	0.74	99.26		
30	580	0.36	99.64	0.011[e]	95.6
Total weight of fractions 1-30				0.020	
Recovery after washing column with 2-propanol				0.009[f]	47.3
Total recovery				0.029	

[a] Mandelic acid loading 30mg, Flow rate 0.2 ml/min and amount of each fraction is 4ml at 0.5 kp/cm^2 pressure. [b] Area % is calculated through HPLC Chromatogram. [c] weight obtained by combining fractions 1-13. [d] weight obtained by combining fractions 14-22. [e] weight obtained by combining fractions 23-30. [f] weight obtained after washing the column with 2-propanol after retrieving fractions 1-30.

Table 2.4 Data for separation of different compounds by medium pressure column chromatography[a]

Entry	**Name of compound (racemic)**	**Amount of analyte[f] (mg)**	**Column packing material 1 (g)**	**Eluent[g]**	**% ee max**	**Absolute config.[h]**
7	BINOL[b]	10	2.0	Hex/IPA = 8:2	19.5	*R*
8	CNCR[c]	10	2.0	Hex/IPA = 9:1	3.8	*3S,4S*
9	Diethyl Tartrate[d]	10	2.0	Hex/IPA = 8:2	11.5	*2R, 3R*
10	2-phenyl Propionic acid[e]	10	2.0	Hex/IPA= 9.5:0.	33.5	*S*

[a] All the experiments were conducted under the same condition unless otherwise stated. Temperature (27 °C), amount of sample m = 0.0100 ± 0.0001 g, column diameter d = 16 mm, length = 260 nm, Enantiomeric excess was determined by HPLC analysis by mentioned columns. (l = 25 cm, d = 0.46 cm). [b] Chiralpak AD column, eluent n-hexane/2-propanol=8:2 at 254 nm. [c] Cyanochromene oxide(CNCR) chiralcel OD column, eluent n-hexane/2-propanol=9:1 at 254 nm. [d] Chiralpak AD column, eluent n-hexane/2-propanol=9:1 at 220 nm. [e] Chiralcel OD column, eluent n-hexane/2-propanol/Formic acid =98:2:1 at 254 nm. [f] Analyte loaded on column after dissolving in 2-propanol/n-hexane.[g] Hex = n-hexane, IPA = 2-propanol. [h] The absolute configuration were determined by the comparison of HPLC profile with authentic samples.

2.4. CONCLUSIONS

A new chiral (*S*)-amino alcohol covalently bonded on modified M41S was synthesized and used to separate different racemic compounds such as mandelic acid, 2,2'-dihydroxy- 1,1'-binaphthalene, cyanochromene oxide, diethyl tartrate, and 2-phenyl propionic acid. Excellent chiral separation (ee, 99%) in case of mandelic acid was achieved. The enantioseparation system worked very well up to three separation cycles without loss in separation performance. We are in the process of making large pore size silica material suitably modified with a chiral auxiliary in anticipation of better separation for bigger racemic molecules.

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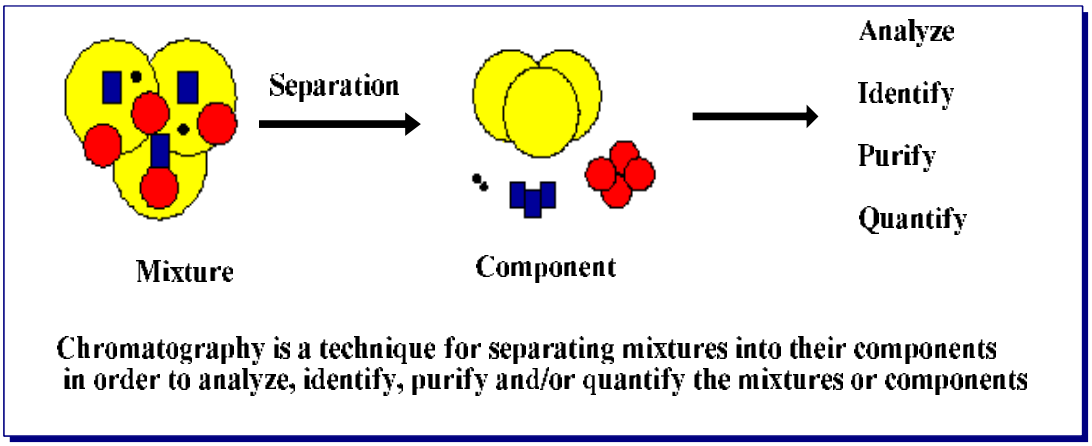

CHAPTER 3

Synthesis and Characterization of Mesoporous Silica Modified with Chiral auxiliaries for their Potential Application as Chiral Stationary Phase

3.1. INTRODUCTION

In chapter 2, we have explained the use of mesoporous semi-crystalline silica material (M41S) modified with chiral amino alcohol as effective chromatographic material for the enantioseparation of racemic compounds [1]. Another material of this class of silica is SBA-15 [2-4], which has higher surface area and larger pore size and volume than M41S. At the same time SBA-15 is a well-ordered material with good thermal stability, hence it holds promise as chromatographic material. Traditionally, standard silica is used for the chromatographic separations hence, it would be proper to compare the efficacy of chirally modified standard silica as against mesoporous silica SBA-15.

Consequently, we have chirally modified SBA-15 and standard silica to use them as materials for CSP and CLEC. Accordingly we have synthesized (*S*)-amino alcohol-supported SBA-15 and standard silica for the chromatographic separation of mandelic acid and other racemate. Besides, the aminoalcohol moiety generated on solid supports can be easily complexed with copper ion to give copper complex covalently bonded on SBA-15 and standard silica which would have all the features of chiral ligand exchange chromatography. Therefore, we also synthesized here copper complexes of (*S*)-amino alcohol-supported silicas and used them as CLEC to resolve racemic mandelic acid, BINOL and diethyl tartarate. Both chirally modified silica materials are stable under ambient conditions and can be repeatedly used for the resolution of racemates under moderate pressure column chromatography. Therefore these materials have potential for their application as stationary phase in chiral HPLC and chiral ligand exchange chromatography.

3.2. EXPERIMENTAL

3.2.1. Materials and Methods

Triblock copolymer poly (ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) pluronic P123, Racemic epichlorohydrin, tetraethyl orthosilicate (TEOS), aniline, 2,4-di-*t*-butyl phenol, copper acetate monohydrate, racemic 2,2'-dihydroxy-1,1'-binaphthalene (Aldrich, USA), 3-aminopropyl triethoxysilane, racemic mandelic acid, 1*R*,2*R*-(−)-1,2-diaminocyclohexane, racemic diethyl-tartrate (Fluka, USA), silica gel H (standard silica, 350 mesh size), cobalt acetate (S.D. Fine Chem. Ltd., India), para formaldehyde, racemic 2,6-dimethyl pyridine (National Chemicals, India), stannous chloride (Merck, Germany) hydrochloric acid (Ranbaxy, India) were used as received. Anhydrous K_2CO_3 (Rankem, India) and standard silica were pre-activated at 100 °C for 3 h before synthetic use. Highly ordered mesoporous SBA-15 was synthesized using a modified hydrothermal crystallization method [2-4]. (*S*)-Epichlorohydrin was obtained by the enantio-separation of racemic epichlorohydrin by way of Jacobsen Co(III)-salen complex as a catalyst under hydrolytic kinetic resolution (HKR) conditions. Enantio-purity of product was analyzed by optical rotation measurement and on chiral GC column (CHIRALDEX trifluoroacetyl derivatives GTA-type). Jacobsen's catalyst was synthesized by reported procedure [5-7]. All the solvents used in the present study were dried by known purification technique [8]. All chemical reactions were carried out under anhydrous conditions using nitrogen atmosphere and oven-dried glassware unless otherwise stated.

3.2.2. Synthesis of SBA-15

Highly ordered mesoporous SBA-15 was synthesized using a modified procedure reported by Zhao et al. [2-3] 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.

3.2.3. Activation of Regular Silica Gel

Regular silica gel H (350 mesh size) was heated at 110 °C for 5 hour to remove moisture contents.

3.2.4. Synthesis of Silica-Supported Copper Complexes of (*S*)-Amino Alcohol 1A'/1B'

Immobilized chiral copper complex **1a'/1b'** and their precursors were synthesized as per the scheme given in Figure 3.1.

3.2.4.1. Synthesis of chiral (2'S)-N-(2',3'-epoxypropyl)-3-(aminopropyl)-triethoxy-silane 4

A highly dry and inert condition was maintained throughout the reaction using freshly dried reagents and apparatus. Typically, to a stirred suspension of anhydrous potassium carbonate (0.705 g, 5.1 mmol) in THF (5 ml), (*S)*-(+)- epichlorohydrin **2** (0.2 ml, 2.557 mmol) and 3-aminopropyl triethoxysilane **3** (0.598 ml, 2.557 mmol) was added at room temperature. The reaction mass was then refluxed (65–66 °C) for 12 h, filtered under inert atmosphere. Solvent from the filtrate was removed by the dry

nitrogen draft; yield (0.674 g, 95%). As the compound **4** was highly moisture sensitive, an aliquot from the above semisolid was taken for spectroscopic characterization, while rest of the material was directly used for the preparation of **5** without further purification. LCMS: 278 $[M+H]^+$, 302 $[M + Na]^+$. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.63 (t, *J* = 7.90, 2H), 1.22 (t, *J* = 6.97, 3H), 1.48–1.63 (m, 2H), 1.85 (br s, NH), 2.67 (t, *J* = 7.28, 2H), 2.77 (d, *J* = 3.96, 1H), 2.82–2.88 (m, 1H), 3.55 (d, *J* = 5.53, 1H), 3.69 (q, *J* = 6.93, 13.95, 2H), 3.82 (q, *J* = 6.99, 13.93, 2H,); ^{13}C NMR spectroscopy (50 MHz, $CDCl_3$): δ (8.48, 18.86, 27.64, 45.47, 47.99, 52.61, 52.99, 58.97); FTIR (KBr): 3410, 2926, 1653, 1445, 1075, 776, 696 cm^{-1}; CHN analysis data C/H ratio calculated: 5.29, found: 5.21, C/N ratio calculated: 10.29, found: 12.42, Optical rotation $[\alpha]_D^{27}$= +43.7º (C = 0.35, tetrahydrofuran).

3.2.4.2. Synthesis of silica-supported (S)-amino epoxy compound 5/5'

Calcined and freshly activated (at 250 ºC) SBA-15/standard silica (2 g) was added to a solution of **4** (0.709 g, 2.557 mmol) in toluene (15–20 ml) under an inert atmosphere and the resulting reaction mixture was refluxed with stirring for 48 h. The solid powder was collected by filtration, washed successively with dry toluene and then dried under vacuum. The dried material was subjected to Soxhlet extraction with toluene for 10 h followed by drying the sample under vacuum.

The number of μ moles of G_1 "*ligand/catalyst/selector"* per m^2 of native silica is calculated by Berendsen de Galen Equation [9-11] as shown below:

$$\alpha_1 = \frac{10^6\, p_1}{S_0\,(100\, C\, n_1 - p_1 M_1}$$

Where,

$\boldsymbol{\alpha_1}$ = No. of μmoles of G_1 per m^2 of native silica (surface coverage of anchored group).

$\mathbf{p_1}$ = Percentage of carbon (wt/wt).

$\mathbf{n_1}$ = No. of carbon atoms per anchored group G_1.

C = Atomic weight of carbon.

$\mathbf{M_1}$ = Molecular weight of anchored group G_1.

$\mathbf{S_0}$ = Specific surface area (m^2/g) of the native silica.

***Characterization data of (S)-amino epoxy-support* 5**

FTIR (KBr): 458, 577, 682, 699, 801, 1078, 1450, 1537, 1553, 1637, 1863, 2359, 2936, 3413 cm^{-1}, CHN analysis (Found) C: 5.13, H: 1.36, N: 1.17% (C/N = 4.39, C/H = 3.77). Solid reflectance UV-vis.: 220, 290, 320, 370 nm. Surface coverage 1.84 μ mols/m^2.

***Characterization data of (S)-amino epoxy-support* 5'**

FTIR (KBr): 463, 804, 1091, 1240, 1465, 1645, 2358, 2982, 3434 cm^{-1}, CHN analysis (Found) C: 4.82, H: 0.80, N: 0.45% (C/N = 10.71, C/H = 6.03). Surface coverage 1.98 μ mols/m^2.

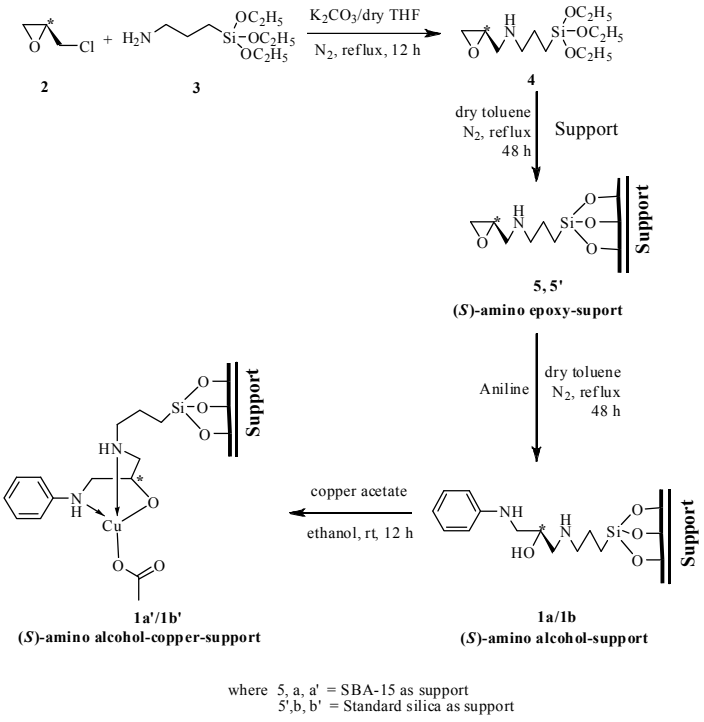

Figure 3.1 Synthesis of the immobilized (*S*)-amino alcohol-support **1a/1b** and (*S*)-amino alcohol–copper-support **1a'/1b'**.

3.2.4.3. Synthesis of silica-supported (S)-amino alcohol 1a/1b

Aniline (455 µl, 5 mmol) was added to a suspension of **5**/**5'** (2.5 g) in dry toluene (15 ml) under dry and inert atmosphere, the mixture was refluxed with stirring for 12 h. The suspension was cooled to room temperature and the solid was filtered, washed repeatedly with dry toluene and subjected to the Soxhlet extraction with toluene and 2-propanol (70:30) for 10 h. Finally the sample was dried under vacuum at 40 °C.

***Characterization data of (S)-amino alcohol-support* 1a**

Solid-state ^{13}C CP–MAS NMR (125 MHz), δ ppm 164 (aromatic C-N) 130-121 (aromatic carbons), 90 (aliphatic C-OH) 84-58 (aliphatic C-N) 38-5 (alkyl carbons); FTIR (KBr): 457, 695, 796, 960, 1079, 1229, 1446, 1499, 1638, 2340, 2361, 2944, 3436 cm^{-1}. CHN analysis (Found) C: 6.23, H: 1.20, N: 1.58% (C/N = 3.94, C/H = 5.19). Diffuse reflectance UV-vis: 225, 240, 290, 375, 370 nm. Surface coverage 1.33 µ mols/m^2.

***Characterization data of (S)-amino alcohol-support* 1b**

FTIR (KBr): 457, 805, 955, 1070, 1388, 1450, 1531, 1646, 2338, 2360, 2979, 3417 cm^{-1}. CHN analysis (Found) C: 6.12, H: 0.94, N: 0.52 % (C/N = 11.77, C/H = 6.51). Surface coverage 1.52 µ mols/m^2.

3.2.4.4. Synthesis of silica-supported copper complex of (S)-amino alcohol 1a'/1b'

(*S*)-amino alcohol-SBA-15 **1a** (2.0 g) and copper acetate monohydrate (0.25 g) were taken in absolute ethanol (40 ml) and the resulting suspension was stirred at room temperature for 12 h. Then the solvent was removed by filtration and the light greenish powder thus obtained was subjected to Soxhlet extraction with 2-propanol for 10 h, filtered and dried under vacuum at 110 °C for 24 h. The dried material was ground well and sieved using 400 mesh (0.037 mm) size test sieves.

***Characterization data of (S)-amino alcohol-copper-support* 1a'**

FTIR (KBr): 460, 805, 968, 1084, 1211, 1454, 1538, 1555, 1646, 2339, 2359, 2952, 3440 cm^{-1}. CHN analysis (Found) C: 6.96, H: 1.83, N: 1.06 % (C/N = 6.56, C/H = 3.80). Solid reflectance UV-vis.: 225, 260, 370, 470, 650 nm. Surface coverage 1.90 μ mols/m^2.

***Characterization data of (S)-amino alcohol-copper-support* 1b'**

FTIR (KBr): 464, 805, 957, 1102, 1251, 1380, 1450, 1535, 1645, 2356, 2981, 3441 cm^{-1}. CHN analysis (Found) C: 6.42, H: 1.00, N: 0.38% (C/N = 16.89, C/H = 6.42). Surface coverage 1.45 μ mols/m^2.

3.2.5. Column Chromatography

The details about the chromatographic setup have been detailed in chapter 2 [1]. Racemic analytes were dissolved separately in the mobile phase (*n*-hexane/2-propanol 90:10, v/v), which were degassed in an ultrasonic bath. The CSPs such as silica-supported (*S*)-amino alcohol **1a**/**1b** and silica-supported copper complex of (*S*)-amino alcohol **1a'**/**1b'** were grounded and sieved using 400 mesh (0.037 mm) size test sieves before use. In a typical chromatographic experiment, the slurry of CSPs in *n*-hexane and 2-propanol (9:1) was packed in a 260 mm X 16 mm glass column using medium pressure (0.5 kp/cm^2) of nitrogen at room temperature and was allowed to saturate and stabilize with the mobile phase for 1 h. The analyte solution in 2-propanol/*n*-hexane was then loaded on thus packed column that was equilibrated for 1 h. Each fraction of the size 4 ml was collected at the pressure mentioned above. The enantiomeric excess of samples was determined by HPLC analysis using a suitable chiral column.

3.3. RESULTS AND DISCUSSION

3.3.1. Characterization

The preparation of immobilized chiral complex of (*S*)-amino alcohol **1a'**/**1b'** is depicted in Figure 3.1. The reactant **2** was synthesized by hydrolytic kinetic resolution of racemic epichlorohydrin using Jacobsen Co(III)-salen complex as a catalyst and was characterized for its chemical and chiral purity by GC using GTA column, ^{1}H NMR using chiral shift reagent Eu(hfc)$_3$ and optical rotation [5-7]. The reaction of **2** in THF with 3-aminopropyl triethoxysilane **3** gave 3-aminopropyl 5,6-epoxy methylene triethoxysilane **4**, which was fully characterized by ^{1}H, ^{13}C NMR, FTIR and optical rotation before it was anchored on calcined SBA-15/standard silica to form amino epoxy-supported silica **5**/**5'**. The ring opening of the epoxy species **5**/**5'** was done with aniline in toluene to get **1a**/**1b** [1]. Copper acetate was used for the complexation of chiral amino alcohol supported on SBA-15 and standard silica to get **1a'** and **1b'** respectively. The loadings of chiral organic moiety in compound **5**, **5' 1a**, **1b**, **1a'** and **1b'** were found to be 16.0, 6.1, 19.6, 10.2, 22.8 and 13.9%, respectively, as determined from the weight loss measured by thermo-gravimetric analysis carried out in the temperature range between 70 and 800 °C (Figure 3.2 and 3.3). This corresponds to 0.083 and 0.062 mol% organic ligand and metal complex in **1a** and **1a'** respectively. ICP analysis of **1a'** showed 0.10 mol% copper metal which is in agreement with the quantity of copper required to be present to form co-ordination compound **1a** (as per thermo-gravimetric analysis (TGA)). While in the case of standard silica, organic ligand **1b** and its copper complex **1b'** was found to be 0.043 and 0.037 mol%, respectively. The surface coverage calculated based on %C for **5**, **5' 1a**, **1b**, **1a'** and **1b'** were found to be 1.84, 1.98, 1.33, 1.52, 1.90 and 1.45 μmol/m^2, respectively.

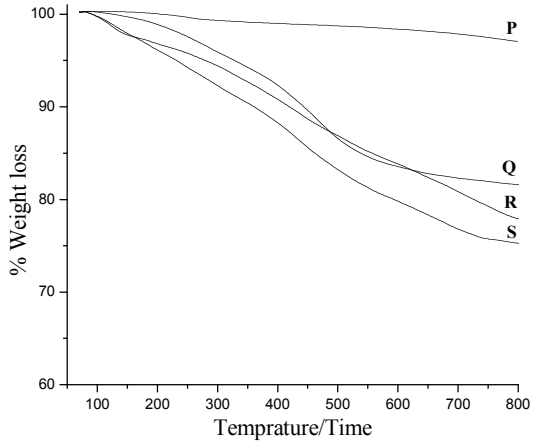

Figure 3.2 TGA curve of calcined SBA-15 (P), (*S*)-amino epoxy-support **5** (Q), (*S*)-amino alcohol-support **1a** (R) and (*S*)-amino alcohol-copper-support **1a'** (S).

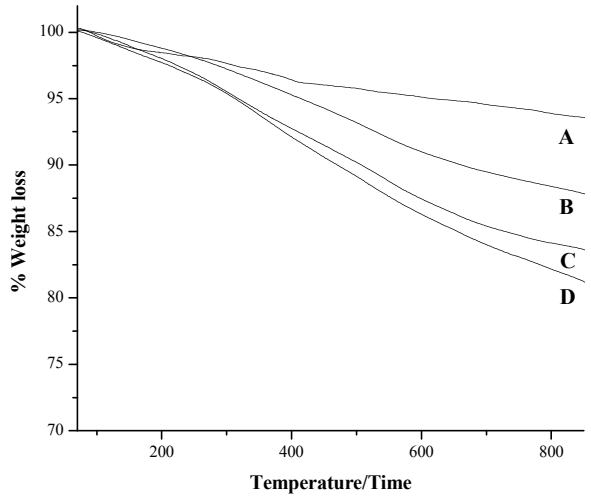

Figure 3.3 TGA curve of calcined standard silica (A), (*S*)-amino epoxy-support **5'** (B), (*S*)-amino alcohol-support **1b** (C) and (*S*)-amino alcohol-copper-suppoert **1b'** (D).

The X-ray diffraction pattern of SBA-15 showed hexagonal lattice with a intense peak assigned to reflection corresponding to plane (100) and two small additional peaks with lower intensity corresponding to reflections from (110) and (200) planes [2-4]. It was observed that upon surface functionalization of SBA-15 with organic moieties viz., epoxy, amino alcohol and its copper complex in **5**, **1a** and **1a'** the intensity of all of peaks decreased marginally with a small shift toward lower

2θ value (Figure 3.4). This may be due to the presence of ligand inside the pores that cause an increased in the amount of scattering power within the pores, resulting in overall loss of intensity due to phase cancellation between pore walls and the guest ligand [12]. However, the presence of major reflections corresponding to SBA-15 even after surface functionalization shows that the mesoporous SBA-15 structure is retained.

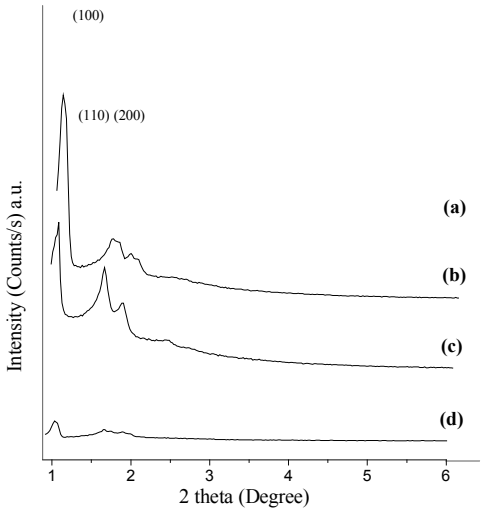

Figure 3.4 Powder X-ray diffraction pattern of calcined SBA-15 (a), (*S*)-amino epoxy-support **5** (b), (*S*)-amino alcohol-support **1a** (c) and (*S*)-amino alcohol-copper-support 1a' (d).

The FTIR spectra of **5**, **1a** and **1a'** showed bands at 2936, 2944 and 2952 cm^{-1}, respectively, due to $\nu(CH_2)$ of propyl arm belonging to silylating agent (Figures 3.5, 3.6, 3.7 and 3.8). This peak was absent in the IR spectra of calcined SBA-15. SBA-15 showed the characteristic band at 1079 cm^{-1} of Si–O–Si and 3438 cm^{-1} for the Si–OH bond. However, after carrying out ring opening reaction with aniline (**1a** in Figure 3.1), a new band due to ν(C–N) and ν(C=C) of aromatic ring appeared at 1446 and 1638 cm^{-1}, respectively, along with a broad band centered around 3436 cm^{-1} with enhanced intensity due to merging of ν(C–N), ν(O–H) along with Si–O–Si bands

suggesting the formation of supported (*S*)-amino alcohol **1a**. On complexation with Cu(II) metal ion the IR band centered around 3462 cm^{-1} due to *v*(O–H) merged with Si–O–Si bands show a decrease in intensity due the coordination with phenolic oxygen to the metal ion. An IR band for *v*(C–O) at 1229 cm^{-1} in **1a** showed a red shift in the frequency of complex **1a'** confirming the formation of copper complex of amino alcohol-supported SBA-15. These observations are in relevant with the earlier reports [13]. Similar trend was observed in FTIR spectra for the copper complex of standard silica-supported (*S*)-amino alcohol **1b'** and its precursors (Figures 3.9 - 3.12).

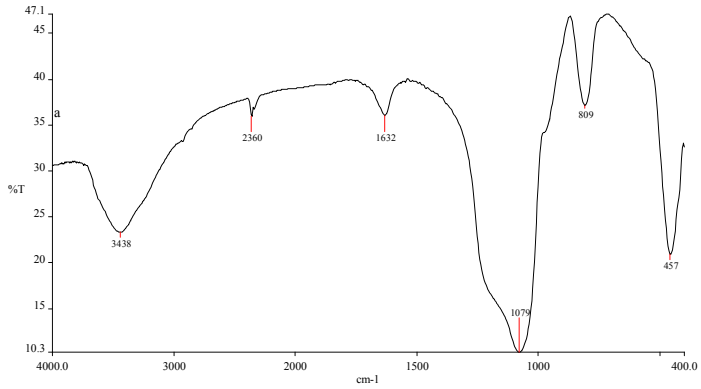

Figure 3.5 FTIR spectra of calcined SBA-15 (a).

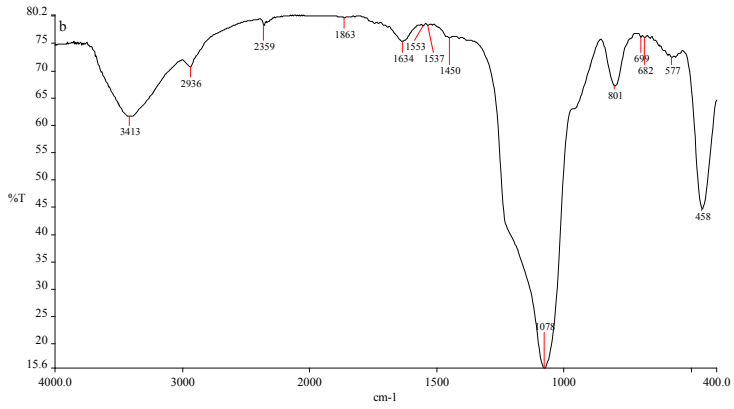

Figure 3.6 FTIR spectra of (S)-amino epoxy-support **5** (b).

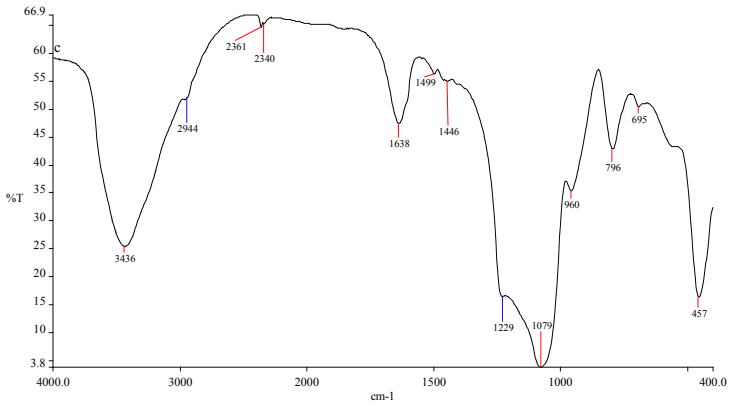

Figure 3.7 FTIR spectra of (S)-amino alcohol-support **1a** (c).

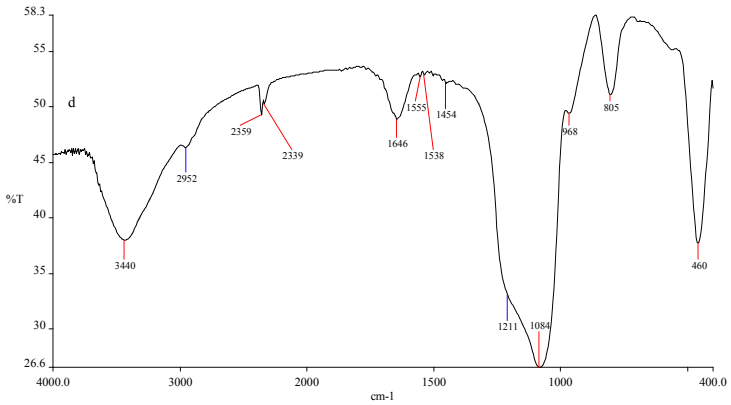

Figure 3.8 FTIR spectra of (S)-amino alcohol-copper-support **1a'** (d).

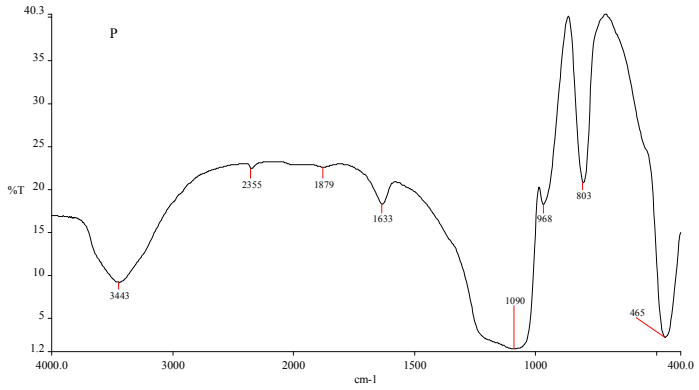

Figure 3.9 FTIR spectra of calcined standard silica (P).

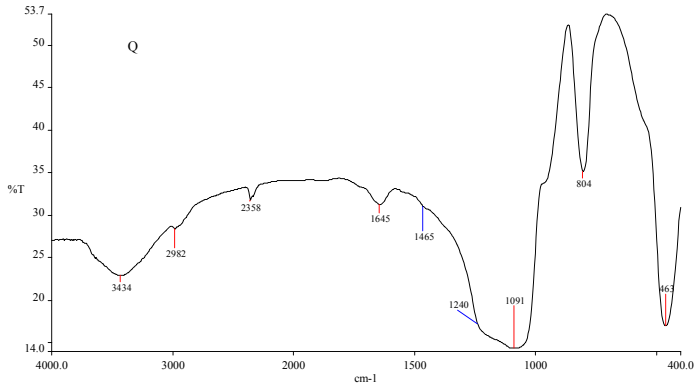

Figure 3.10 FTIR spectra of (S)-amino epoxy-support **5'** (Q).

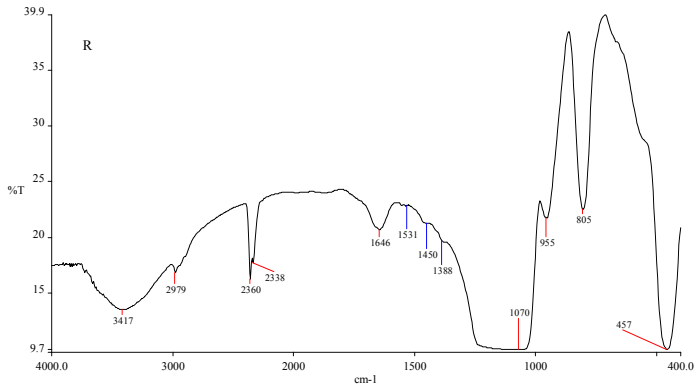

Figure 3.11 FTIR spectra of (S)-amino alcohol-support **1b** (R)

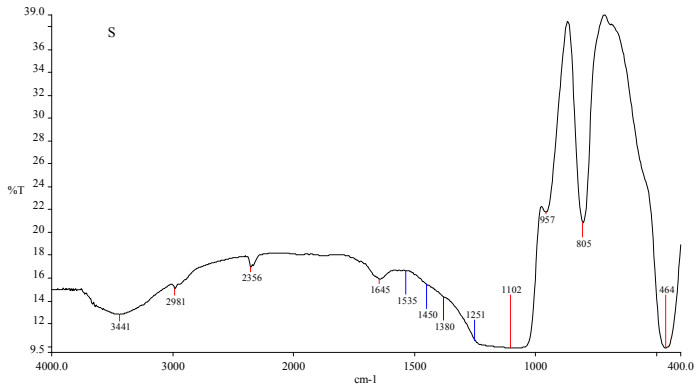

Figure 3.12 FTIR spectra of (S)-amino alcohol-copper-support **1b'** (S).

The presence of organic moiety in **1a** was further confirmed by solid-state (CP-MAS) ^{13}C NMR that showed peaks both in aromatic (164–121 δ ppm) and aliphatic regions (90–82 and 58–13 δ ppm) and is in accordance with the supported ligand structure (Figure 3.13).

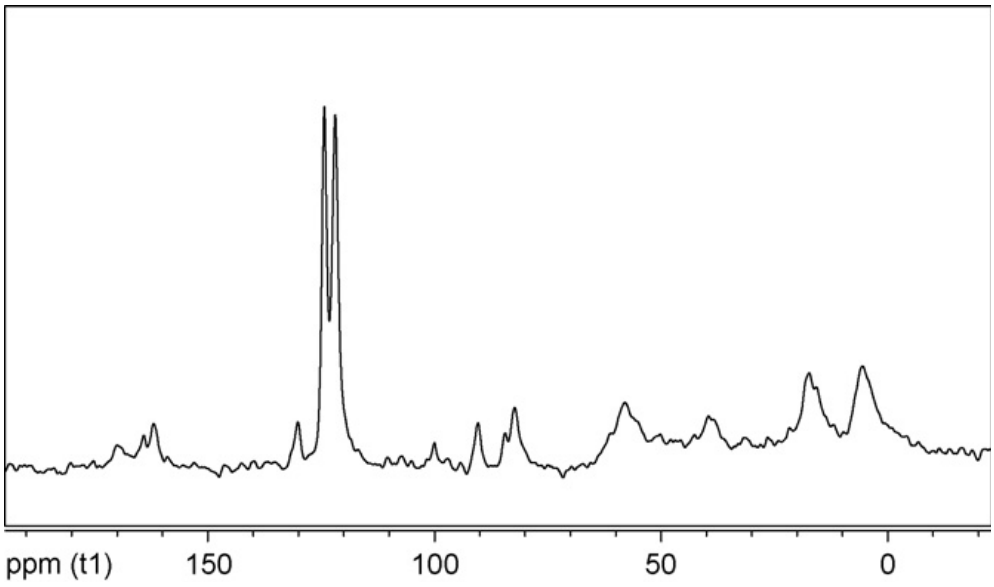

Figure 3.13 Solid-state ^{13}C CP–MAS NMR spectra of (*S*)-amino alcohol-silica **1a**.

SEM micrographs discovered that SBA-15 samples consist of small agglomerates whose morphology does not change in the supported ligand **1a**. TEM micrographs of siliceous SBA- 15 shows hexagonally arranged pore structures when viewed along the pore direction and parallel lattice fringes on a side view (Figure 3.14). Whereas SBA-15 prepared in the acidic medium displayed mesopores of a one-dimensional channel system, proved that SBA-15 has a 2D *p6mm* hexagonal structure. The presence of equidistant parallel fringes exhibits the nature of separation between layers and the unique well-packed arrangement of such monolayers. The ordered mesoporous structure of SBA-15 was unaffected by attaching the chiral ligand **1a**. Unlike SBA-15 based samples SEM images of standard silica and its chirally modified samples showed no crystallinity and no uniformity in pores (Figure 3.15).

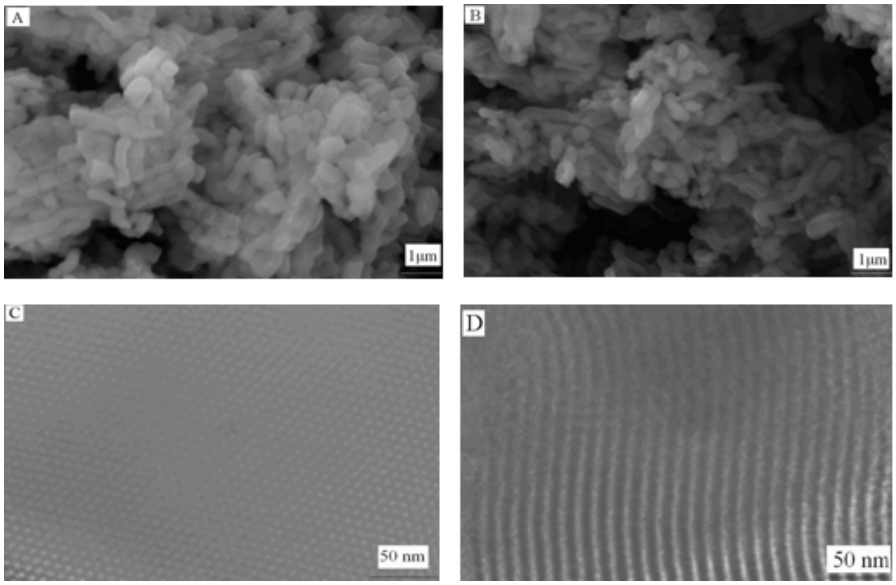

Figure 3.14 Scanning electron microscope (SEM) image of SBA-15 (A), (*S*)-amino alcohol-support **1a** (B) and transmission electron microscope (TEM) image of hexagonal channels of (*S*)-amino alcohol-support **1a** (C) and pore wall of calcined SBA-15 (D).

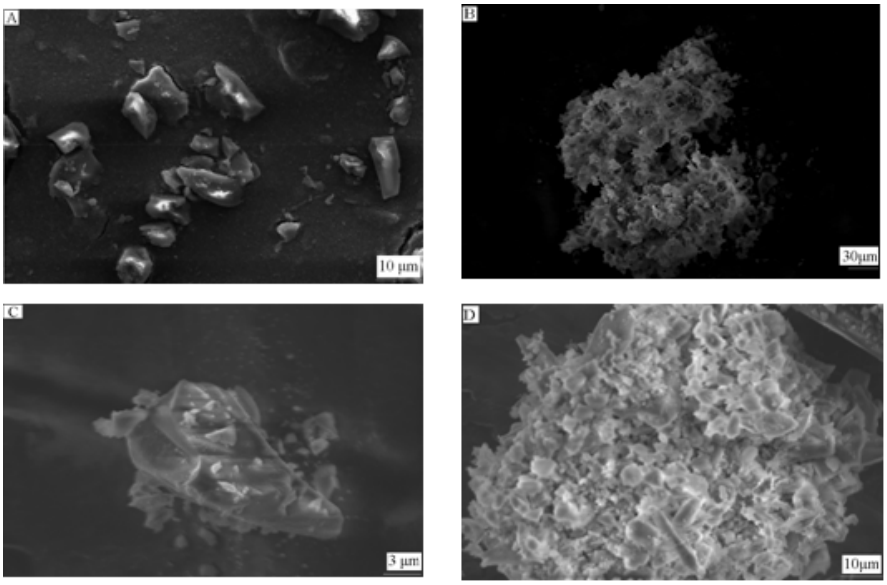

Figure 3.15 Scanning electron microscope (SEM) images of standard silica (A), (S)-amino epoxy-support **5'** (B), (*S*)-amino alcohol-support **1b** (C) and copper complex of (S)-amino alcohol-support **1b'** (D).

The data on BET surface area, pore diameter, total pore volumes obtained are summarized in Table 3.1. A large decrease in BET surface area was observed (from

795 to 429 m^2/g) upon fictionalization of modified SBA-15 represented as **5** in Figure 3.1. Similarly, reduction in the mesoporous diameter from 79 to 74 Å and in pore volume from 1.289 to 0.893 cm^3/g was also observed (Table 3.1). Moreover, further decrease in BET surface area 429–360 m^2/g in pore diameters from 74 to 66 Å and pore volumes from 0.893 to 0.664 cm^3/g was observed upon ring opening reaction with aniline. After complex formation with copper there was only a small decrease in BET surface area (from 360 to 257 m^2/g), pore diameter (from 66 to 61 Å) and pore volume (from 0.664 to 0.508 cm^3/g) (Table 3.1). This indicates that the internal pores of the SBA-15 are occupied by the ligand **5**, **1a** and metal complex **1a'**. A small decrease in BET surface area (from 412 to 372 m^2/g) was observed upon functionalization of standard silica with chiral amino epoxy group **5'**. Similarly, the decrease in pore diameters (from 70 to 67 Å) and pore volumes (from 0.651 to 0.593 cm^3/g) were also observed. Additional decrease in BET surface area, mesoporous diameter and pore volume was affected upon epoxide ring opening reaction with aniline and its subsequent formation of chiral copper complex **1b'** (Table 3.1).

Table 3.1 Physico-chemical data of SBA-15/standard silica supported (*S*)-amino alcohol-copper-support 1a'/1b' and their precursors.

Compound	BET surface area (m^2/g)	Total pore volume (cm^3/g)	BJH pore diameter (Å)
SBA-15	795	1.289	78.9
Compound **5**	429	0.893	73.6
Compound **1a**	360	0.664	66.1
Compound **1a'**	257	0.508	60.8
Standard silica	412	0.651	69.8
Compound **5'**	372	0.593	66.9
Compound **1b**	310	0.520	66.1
Compound **1b'**	306	0.506	62.2

The solid reflectance UV–vis spectrum of the immobilized amino epoxy-support **5** shows ligand charge transfer band at 220, 290, 320 and 370 nm (Figure 3.16).

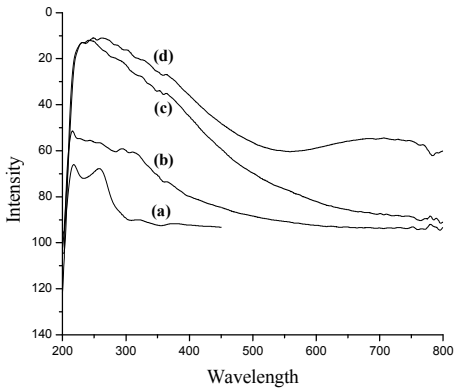

Figure 3.16 Solid reflectance UV-Vis. spectra of calcined SBA-15 (a), (*S*)-amino epoxy-support **5** (b), (*S*)-amino alcohol-support **1a** (c) and (*S*)-amino alcohol-copper-support **1a'** (d).

After formation of amino alcohol-support **1a** the spectrum remains similar with an increase in the intensity of all the bands showing the presence of amino alcohol covalently bonded to SBA-15. After complexation with Cu(II) metal ion a broad d–d band appear near 700 nm which is a characteristic band of copper complex [12] confirming the formation of the complex **1a'.**

3.3.2. Chiral Resolution of Racemic Mixture Using Chiral Ligand Exchange Stationary Phase and Chiral Stationary Phase

In Chapter 2, we demonstrated the use of (*S*)-amino alcohol immobilized on M41S as column-packing material for the resolution of racemic mandelic acid where we achieved excellent chiral purity (ee's, 99%) in some of the fractions was observed [1]. The results observed in the present study with similarly modified SBA-15 was at equivalence with the previously reported [1] M41S material, however, with standard silica we could achieve a maximum of 92% ee in the case of mandelic acid. These

observations clearly indicate that the surface area, pore size and pore distribution of the silica material have pronounced effect on the resolution process. The separation activity of the (*S*)-amino alcohol-support **1a** and its copper complex **1a'** for enantio-separation of racemic mandelic acid, BINOL and diethyl tartrate was carried out by medium-pressure column chromatography by varying the amount of **1a** and as well as that of analyte as shown in Table 3.2.

Mandelic acid (30 mg) in the form of slurry in *n*-hexane/2-propanol (9:1) was loaded on column packed with **1a** (2 g). The enantio-separation of (*R*)-(−)-mandelic acid in some of the fraction with ee up to 98.9% was achieved (Table 3.2, entry 1). After the completion of one chromatographic run the column material was subjected to the Soxhlet extraction with toluene and 2-propanol (70:30), dried under vacuum and reused for another separation experiment with fresh racemic mandelic acid under the condition used for the first separation experiment. Furthermore, similar resolution was achieved with 10 mg of analyte and 2 g of column-packing material (Table 3.2, entry 2).We further explored the separation activity of newly prepared (*S*)-amino alcohol–copper-support **1a'** for the separation of racemic mandelic acid under identical reaction conditions. Excellent chiral separation about (99.52%, ee) (*R*)-(−)-mandelic acid (Table 3.2, entry 3) was achieved. The ee of mandelic acid was determined by HPLC using chiralcel OD column (Figure 3.17).

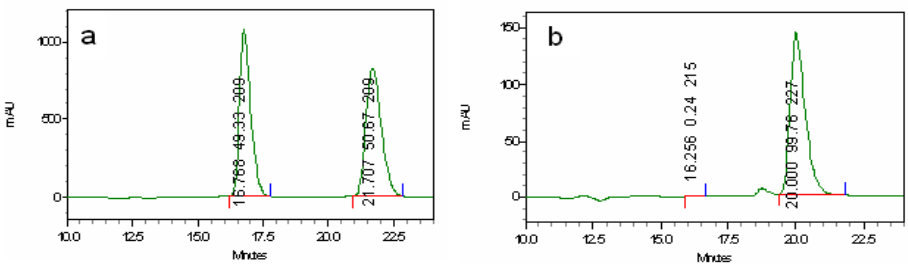

Figure 3.17 HPLC chromatogram of racemic mandelic acid (a), and (*R*)-(-) mandelic acid (b) after column chromatography carried out on chiralcel OD column using complex **1a'** as column packing material.

The same chromatographic experiments were carried out with standard silica immobilized (*S*)-amino alcohol **1b** and its copper complex **1b'** (Table 3.2, entry 4 and 5). Where both the CSPs **1b** and **1b'** gave enantio-separation of mandelic acid with ee~92% which is significantly lower then SBA-15 supported chiral selector and its copper complex. On the basis of this separation result we can say that porosity of the support plays key role in enantio-separation. In a control experiment the chromatographic separation of racemic mandelic acid (10 mg) using calcined SBA-15/standard silica (2 g) as packing material was carried out (Table 3.2, entry 6 and 7) but, no chiral separation was affected.

Table 3.2 Separation of different analytes using two different column packing materials.

Entry[a]	Amount of mandelic acid[b] (mg)	Stationary phases	% ee max[g]	Absolute config[g]	Repeat Experiment[h]
1	30	**1a**	98.9	*R*	1st
2	10	**1a**	99.1	*R*	2nd
3	30	**1a'**	99.5	*R*	---
4	30	**1b**	91.90	*R*	---
5	30	**1b'**	92.48	*R*	---
6	10	SBA-15[e]	---	---	---
7	10	Silica[f]	---	---	---
8(9)	BINOL[c]	**1a (1a')**	15.6(6.5)	*R*	---
10(11)	Diethyl tartrate[d]	**1a (1a')**	9.7(8.1)	*2R,3R*	---

[a] Data given in parenthesis are from compound **1a'**. 2 g of column packing material was used in all the experiments. [b] Separation by HPLC using chiralcel OD column, eluent *n*-hexane/2-propanol=8:2 at 220 nm, mandelic acid loaded on column after dissolving in 2-propanol/*n*-hexane. [c] 10 mg of BINOL, Chiralpak AD column, eluent *n*-hexane/2-propanol=8:2 at 254 nm. [d] 10 mg of diethyl tartrate, Chiralpak AD column, eluent *n*-hexane/2-propanol=9:1 at 220 nm. [e] 2 g SBA-15 was used as column packing material. [f] 2 g standard silica was used as column packing material. [g] Enantiomeric Excess and absolute configuration of resolved compounds was determined by the comparison of HPLC profile with [h] Reuse of chiral stationary phase for chromatographic separation of fresh racemic mandelic acid.

It is therefore concluded that the chiral separation occurred due to the modification of SBA-15/standard silica with chiral amino alcohol. (*S*)-Amino alcohol-support **1a** (2 g) and (*S*)-amino alcohol–copper-support **1a'** (2 g) were further investigated for carrying out the resolution of other racemic compounds viz. 2,2'-dihydroxy-1,1'-binaphthalene and diethyl tartrate under optimized reaction conditions and data is given in (Table 3.2, entry 8–11). Unfortunately, both **1a** and **1a'** gave poor results for the resolution of BINOL and diethyl tartrate.

Table 3.3 Data for separation of racemic mandelic acid with elution of *n*-hexane/2-propanol = 9:1 by medium pressure column chromatography using compound **1a' (1a)**[a] as column packing material.

Fractions	Time (min)	Area % of (S)-(−)-mandelic acid[b]	Area % of (R)-(−)-mandelic acid[b]	Weights of fractions	Ee (%)
1	0	49.89 (44.71)	50.11 (55.29)		
2	20	49.40 (44.32)	50.60 (55.68)		
3	40	50.87 (43.99)	49.13 (56.01)		
4	60	48.86 (43.41)	51.14 (56.59)		
5	80	48.25 (42.71)	51.75 (57.29)		
6	100	47.22 (41.14)	52.78 (58.86)		
7	120	46.17 (40.96)	53.83 (59.04)		
8	140	44.90 (38.24)	55.10 (61.76)		
9	160	43.88 (32.20)	56.12 (67.80)	0.0047 (0.0050)[c]	4.57 (17.40)
10	180	42.93 (25.91)	57.07 (74.09)		
11	200	41.47 (21.22)	58.53 (78.78)		
12	220	40.47 (16.18)	59.53 (83.82)		
13	240	37.04 (14.82)	62.96 (85.18)		
14	260	31.66 (11.67)	68.34 (88.33)		
15	280	26.34 (9.39)	73.66 (90.61)		
16	300	22.72 (7.72)	77.28 (92.28)		
17	320	21.33 (4.81)	78.67 (95.19)		
18	340	16.91 (3.74)	83.09 (96.26)	0.0073 (0.0076)[d]	37.58 (74.34)
19	360	11.16 (3.02)	88.84 (96.98)		
20	380	9.80 (2.55)	90.20 (97.45)		
21	400	6.82 (2.43)	93.18 (97.57)		
22	420	5.95 (2.09)	94.05 (97.91)		
23	440	4.33 (2.01)	95.67 (97.99)		
24	460	3.91 (1.99)	96.09 (98.01)		
25	480	2.43 (1.70)	97.57 (98.30)		
26	500	1.25 (0.82)	98.75 (99.18)		
27	520	0.24 (0.58)	99.76 (99.42)	0.0092 (0.0089)[e]	89.80 (97.56)
Total Weight of fractions 1-27,				0.0212 (0.0215)	
Recovery after washing column with 2-propanol,				0.0079 (0.0081)[f]	40.3 (33.54)
Total recovery,				0.0291 (0.0296)	

[a] Data given in parenthesis are from compound **1a**. 2 g of column packing material was used. Mandelic acid loading 30mg, Flow rate 0.2 ml/min and amount of each fraction is 4ml at 0.5 kp/cm^2 pressures. [b] Area % is calculated through HPLC Chromatogram. [c] Weight obtained by combining fractions 1-9. [d] Weight obtained by combining fractions 10-18. [e] Weight obtained by combining fractions 19-27. [f] Weight obtained after washing the column with 2-propanol after retrieving fractions 1-27.

For the calculation of mass recovery we collected 27 fractions of resolved mandelic acid of 4ml and the chiral stationary phase **1a'** was washed with 2-propanol to retrieve the (*S*)-mandelic acid (recovery, 7.9 mg; ee, 40.3%). For the sake of convenience in weighing we have combined the fractions 1–9, 10–18 and 19–27 which were found to be 5, 7 and 9 mg with ee 4.6, 37.6 and 89.8%, respectively. As a result 9 mg of (*R*)-(−)-mandelic acid with ee > 71% was recovered which is >89.8% of the (*R*)-enantiomer present in 30 mg of the racemic mandelic acid. In all >96.9% of the mandelic acid was recovered at the end of chromatographic separation. The same experiment was carried out for mandelic acid using (*S*)-amino alcohol-support **1a** as column-packing material. Table 3.3 show the elution profile (Figure 3.18) of mandelic acid using (*S*)-amino alcohol–copper-support **1a'** and (*S*)-amino alcohol-support **1a**, respectively. The same comparative study was carried out using chiral stationary phase **1b** and **1b'** with its elution profile (Figure 3.19) for separation of racemic mandelic acid (Table 3.4). It gave (*R*)-mandelic acid with ee >91% in case of **1b** and ee >92% in case of **1b'** with >95 and >98% total recovery of mandelic acid, respectively. Relatively speaking CSP (*S*)-amino alcohol-support **1a**/**1b** has slight edge over CLES (*S*)-amino alcohol–copper-support **1a'**/**1b'** as for enantioseparation of mandelic is concerned. A detailed study with the use of **1a'**/**1b'** as chiral ligand exchange stationary phase for the separation of amino acids is underway and the results would be communicated separately.

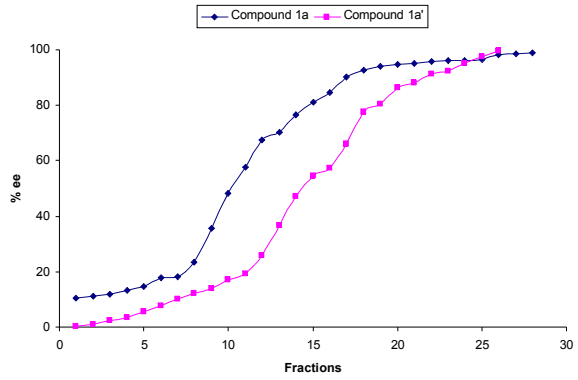

Figure 3.18 Elution profile from the medium pressure column chromatography using (*S*)-amino alcohol-support **1a** and (*S*)-amino alcohol-copper-support **1a'** as column packing material (Table 3.3).

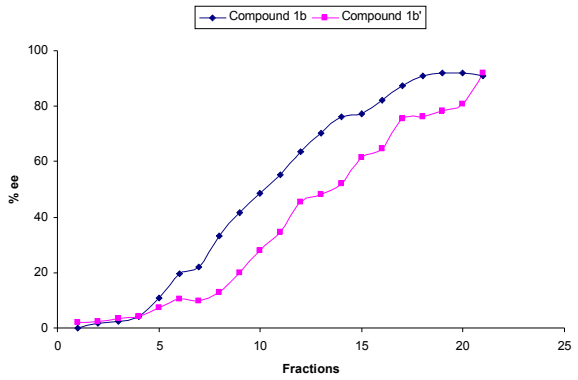

Fig. 3.19 Elution profile from the medium pressure column chromatography using (*S*)-amino alcohol-support **1b** and (*S*)-amino alcohol-copper-support **1b'** as column packing material (Table 3.4).

Table 3.4 Data for separation of racemic mandelic acid with elution of *n*-hexane/2-propanol = 9:1 by medium pressure column chromatography using compound **1b' (1b)**[a] as column packing material.

Fractions	Time (min)	Area % of (S)-(−)-mandelic acid[b]	Area % of (R)-(−)-mandelic acid[b]	Weights of fractions	Ee (%)
1	0	49.01 (49.92)	50.99 (50.08)		
2	20	48.82 (49.07)	51.18 (50.93)		
3	40	48.29 (48.74)	51.71 (51.26)		
4	60	47.96 (47.90)	52.04 (52.10)		
5	80	46.41 (44.54)	53.59 (55.46)		
6	100	44.75 (40.21)	55.25 (59.79)		
7	120	45.08 (39.97)	54.92 (61.03)	0.0047 (0.0048)[c]	5.62 (8.76)
8	140	43.50 (33.37)	56.50 (66.63)		
9	160	40.02 (29.27)	59.98 (70.73)		
10	180	36.10 (25.78)	63.90 (74.22)		
11	200	32.75 (22.06)	67.25 (77.94)		
12	220	27.24 (18.16)	72.76 (81.84)		
13	240	25.90 (14.82)	74.10 (85.18)		
14	260	24.01 (11.88)	75.99 (88.12)	0.0066 (0.0081)[d]	34.42 (55.49)
15	280	19.17 (11.39)	80.83 (88.61)		
16	300	17.57 (8.90)	82.43 (91.10)		
17	320	12.25 (6.34)	87.75 (93.66)		
18	340	11.96 (4.51)	88.04 (95.49)		
19	360	10.91 (4.09)	89.09 (95.91)		
20	380	9.53 (4.05)	90.47 (95.95)		
21	400	3.99 (4.56)	96.01 (95.44)	0.0085 (0.0062)[e]	75.61 (87.47)
Total Weight of fractions 1-20,				0.0198 (0.0191)	
Recovery after washing column with 2-propanol,				0.0096 (0.0094)[f]	37.54 (51.06)
Total recovery,				0.0294 (0.0285)	

[a] Data given in parenthesis are from compound **1b**. 2 g of column packing material was used. Mandelic acid loading 30mg, Flow rate 0.2 ml/min and amount of each fraction is 4ml at 0.5 kp/cm^2 pressures. [b] Area % is calculated through HPLC Chromatogram. [c] Weight obtained by combining fractions 1-7. [d] Weight obtained by combining fractions 8-14. [e] Weight obtained by combining fractions 14-21. [f] Weight obtained after washing the column with 2-propanol after retrieving fractions 1-21.

CONCLUSIONS

New chiral (*S*)-amino alcohol covalently bonded on modified SBA-15/standard silica and its copper complex as CSPs were synthesized and used to resolve different racemic compounds such as mandelic acid, 2,2'-dihydroxy-1,1'-binaphthalene (BINOL) and diethyl tartrate. These materials are simple to handle and affect excellent optical resolution under medium pressure. Chiral separation (ee, 99.5%) in case of mandelic acid was achieved using (*S*)-amino alcohol–copper-support **1a'** as chiral ligand exchange stationary phase. However, (*S*)-amino alcohol-support **1a**/**1b** was still imparted slightly better separation as compared to (*S*)-amino alcohol–copper-support **1a'/1b'** in the case of mandelic acid. Both of these materials performed excellent chiral resolution and are quite stable under our experimental conditions and can be repeatedly used for several separation cycles. Chirally modified SBA-15 with uniform hexagonal pores favors better enantio-separation of racemic mandelic acid as compared to similarly modified standard silica.

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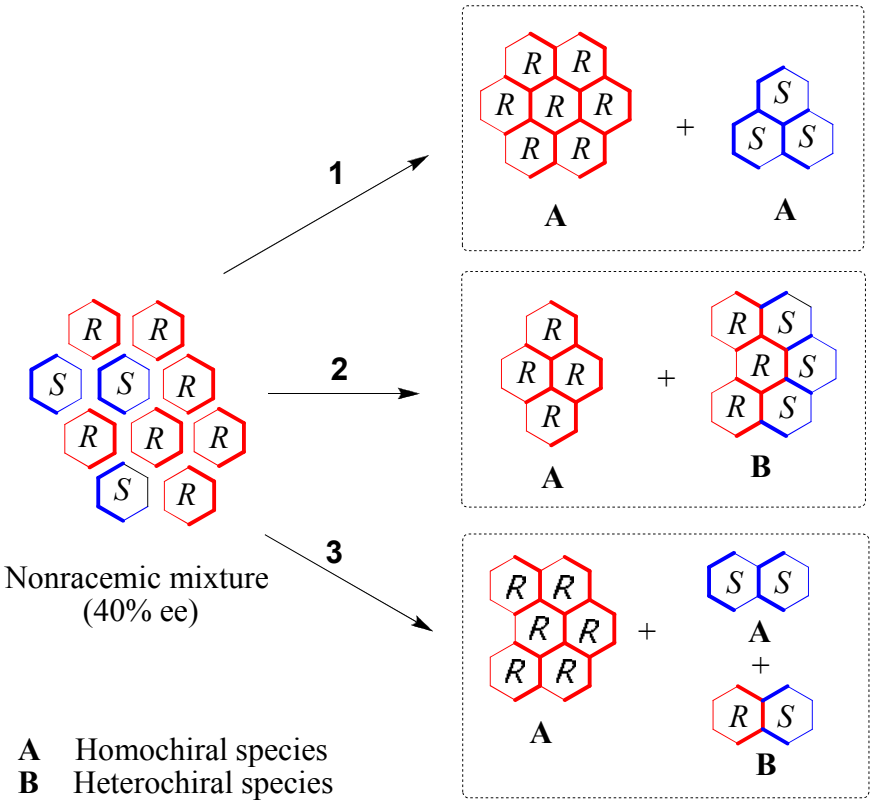


CHAPTER 4

Enantiomer Self-disproportionation of Chiral Compounds on Achiral Ordered Mesoporous Silica M41S and Regular Silica gel as a Stationary Phase

4.1. INTRODUCTION

The optically pure compounds have supreme importance in pharmaceuticals, agrochemicals, fine chemicals, and biochemical research as enantiomers express themselves differently in biological systems. Presently optically active compounds in their high optical purity are mainly obtained through (a) asymmetric synthesis which includes the use of a suitable chiral catalyst, (b) by separation of enantiomers from respective racemic mixtures with the use of various chemical/analytical techniques [1–5]. Application of chiral stationary phases (CSPs) both at analytical and preparative scale is a rapidly growing area to affect the separations of enantiomers in liquid chromatography [6]. Various chiral selectors are already known for CSPs for separations of enantiomers in literature [7–10]. In chapter 2 and 3, we have demonstrated the use of M41S modified with chiral (*S*)-amino alcohol as CSPs to separate various racemic compounds. Excellent chiral separation was achieved in the case of racemic mandelic acid (ee, 99%) on a glass column filled with thus modified M41S at medium pressure [11].

Recently, Soloshonok and coworkers [12–14] have reported a very unusual phenomenon of separation of enantiomer by enantiomer self-disproportionation on a regular silica gel as a stationary phase. He attributed this phenomenon to two distinct modes of intermolecular interaction, i.e., between the enantiomers of a chiral compound. These are homochiral (*R:R*) and heterochiral (*R:S*) associations, which are present in nonracemic solutions and are largely responsible for nonlinear behavior of optical rotation [15,16], UV absorbance [17], and in asymmetric catalysis [18–21]. These associations in a solution, however, create hot spots of internal chirality and thus can be exploited for the optical purification/separation of nonracemic mixtures with the use of relatively inexpensive achiral phase chromatography [22, 23]. The

extent and nature of homochiral and heterochiral associations, though not fully understood, depend on the structural features of the chiral compounds and nature of the solvent.

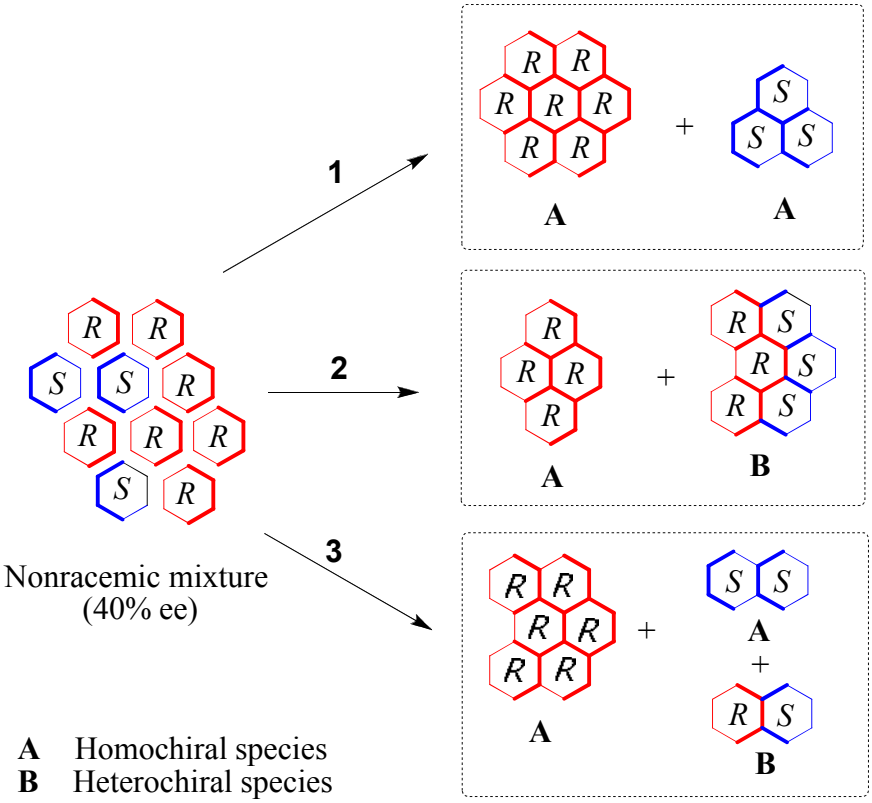


Figure 4.1 Preferential formation of homochiral and heterochiral aggregates of varied molecular weights.

While performing chromatography of such solutions, the nature of achiral stationary phase can also affect the elution pattern. We present, here, our findings on the phenomenon of enantiomer self disproportionation (Figure 4.1) of commercially important chiral compounds as analyte, viz., mandelic acid and stilbene oxide using different solvents with two achiral stationary phases namely regular silica gel and ordered mesoporous silica M41S. While regular silica gel is conventionally used in chromatography, we have explained in chapter 2 the use of M41S in chromatography. M41S is a thermally stable, mesoporous, and semi-crystalline silica material that

possess highly ordered pore structure. Besides, its large pore volume, high surface area, and mild acidity make this material a promising candidate for chromatography [11]. Mandelic acid was selected as a model candidate for compounds having extensive hydrogen bonding, while stilbene oxide was selected for compounds having nonbonding interactions mostly through phenyl ring related π–π interactions.

4.2. EXPERIMENTALS

4.2.1. Materials and Methods

Sodium silicate solution, Trans stilbene oxide (Aldrich, USA), (*R*)-(-)-mandelic acid, (*S*)-(+)-mandelic acid (Fluka, USA), cetyltrimethylammonium bromide and regular silica gel H (350 mesh size) (s. d. fine chem., India) were used as received. All the solvents used in the present study were purified by known methods [24]. (*1R,2R*)-Stilbene oxide was synthesized as per the reported procedure [25]. Synthesis of a highly ordered hexagonal siliceous M41S was carried out by modified hydrothermal crystallization method as described previously [26–28].

4.2.2. Method of Column Chromatography

In a typical optimal conditions of slurry packing system, 2.0 g of freshly calcined M41S of uniform particle size (grounded and sieved using 170 mesh size test sieves)/ regular silica gel (heated for 5 h at 110 °C) was packed in a 260 mm X 16 mm glass column with different eluents using medium pressure (0.5 kp/cm^2) of nitrogen at room temperature. In general, the solution of 0.0100 g of analyte (mandelic acid/stilbene oxide) dissolved in 0.50 ml of eluent was loaded on thus packed column and was equilibrated for 1 h. Following this the column was pressurized at above mentioned pressure and fractions of the size 4.0 ml were collected. The eluent was completely evaporated from each fraction for mass calculations. Different eluents used in the present study are; n-hexane/2-propanol (9:1), n-hexane/diethylether (9:1)

and neat chloroform. Each fraction was subjected to high-performance liquid chromatography analysis (HPLC, CLASS-VP 10A, 20 µl injection loop, PDA detector, Shimadzu) to determine enantiomeric excess (ee) using an appropriate chiral column.

4.3. RESULTS AND DISCUSSION

4.3.1. Characterization

M41S is fully characterized by various characterization methods as shown in chapter 2.

4.3.2. Phenomenon of *"Enantiomer self-disproportionation"*

Enantiomer self-disproportionation (ESD) is a process in stereochemistry describing the separation of a non- racemic mixture of enantiomer in an enantioriched fraction and a more racemic fraction as a result of the "*heterochiral"* or "*homochiral"* aggregates. Enantiomers may be separated without the amplification of any external element of chirality (Figure 4.1).

Conceptually, the association of enantiomers can take place either in homochiral or heterochiral manner with varied degree of aggregation leading to different molecular weights of aggregates which can be separated by a simple achiral chromatographic technique [13]. Figure 4.1 shows graphical presentation of disproportionation phenomenon by taking an arbitrary value of enantiomeric excess (ee) as 40%. If the formation of homochiral association is preferred, we would have situation 1 (see Figure 4.1) where oligomers of both enantiomers with different molecular weights would exist in solution and therefore could be separated without applying external element of chirality. However, if the molecule is capable of forming only dimeric homochiral association (e.g., *SS* or *RR*), these would have identical mass and other physical properties, hence may not be separated. On the other hand, when

heterochiral associations are preferred (Situations 2 and 3 in Figure 4.1), there would always be an excess of one form of enantiomer (e.g., *R* in the present case) along with racemic species, which are different chemical species and therefore may be separated easily on an achiral column.

To understand this phenomenon, we have used two achiral stationary phase-regular silica gel and mesoporous M41S for chromatographic separation of nonracemic mandelic acid and stilbene oxide. These silicas were characterized by various physicochemical techniques like FTIR spectra, powder X-ray diffractions pattern, thermogravimetric analysis, solid reflectance UV–vis spectra, and scanning electron microscopy, which are in agreement with literature values [11, 26, 27]. The nitrogen-sorption study like BET surface area, pore diameter, total pore volumes, and average particle size of achiral stationary phases are summarized in Table 4.1. While M41S was well crystalline mesoporous material having ordered hexagonal array of pores, regular silica gel used was microporous in nature.

Table 4.1 Physico-chemical data of M41S and amorphous silica gel.

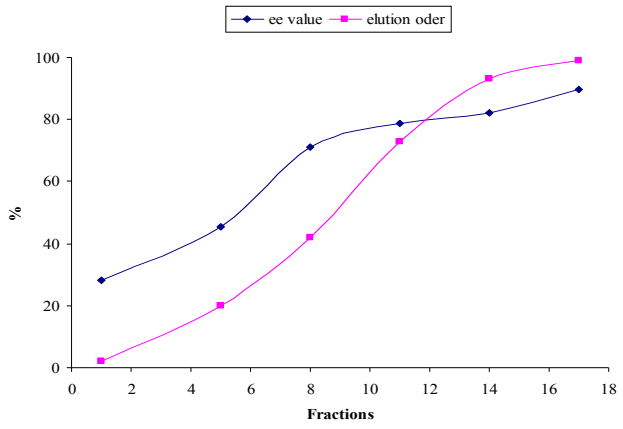
Compound	**BET surface area (m^2/g)**	**Total pore volume (cm^3/g)**	**BJH pore diameter (Å)**	**Average particle size (µm)**
M41S	1064	0.942	35.4	7.2
Regular silica gel	412	0.597	57.7	16.6

These silicas were used as achiral stationary phases for the separation of enantiomers of mandelic acid and stilbene oxide using different eluents. In a typical experiment, 0.0010 g sample of (*R*)-(-)-mandelic acid having 76.1% ee was loaded on column filled with M41S/regular silica gel (2.0 g) using n-hexane/2-propanol (9:1) as a mobile phase. The elution profiles for this sample with M41S and regular silica are presented in Tables 4.2 and 4.3, respectively. In both the cases, initial fractions

obtained were more racemic than the ee of the sample (76.1%) before chromatographic separations. Hence, it can be suggested that the enantiomer self-disproportionation phenomenon through heterochiral molecular association is existent in the case of nonracemic mandelic acid. Interestingly, the extent of enantiomer self-disproportionation was much more pronounced when M41S was used as stationary phase (28% ee for the first fraction to 89.8% ee for the final fraction) than regular silica gel (from ee, 72.8% to 81.2%). It shows that the nature of stationary phase has a strong influence on the phenomenon of enantiomer self-disproportionation.

Table 4.2 Chromatography of (*R*)-(-)-mandelic acid (76.1 % ee) with elution by *n*-hexane/2-propanaol (9:1) using M41S[a] as column packing material[b]

Fraction	ee[c] (%)	Mass (%)
1	28.2	2
5	45.2	20
8	71.2	42
11	78.7	73
14	82.3	93
17	89.8	> 99

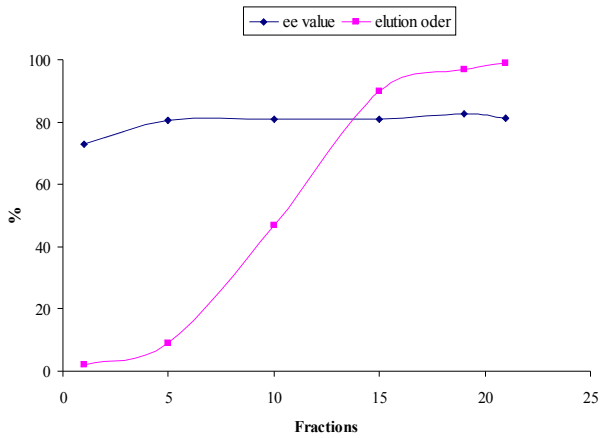


Elution profile

[a]2 g M41S as column packing material. [b]Separation by HPLC, using chiralcel OD column, eluent *n*-hexane/2-propanol (8:2) at 220 nm. [c]Starting % ee of 0.0100 g (*R*)-(-)mandelic acid is 76.1; the ee of samples were determined by the comparison of HPLC profile with authentic samples.

Table 4.3 Chromatography of (*R*)-(-)-mandelic acid (76.1 % ee) with elution by *n*-hexane/2-propanaol (9:1) using regular silica gel[a] as column packing material[b]

Fraction	ee[c] (%)	Mass (%)
1	72.8	2
5	80.6	9
10	81.0	47
15	81.0	90
19	82.6	97
21	81.2	> 99



Elution profile

[a]2 g regular silica gel as column packing material. [b]Separation by HLPC, using chiralcel OD column, eluent *n*-hexane/2-propanol (8:2) at 220 nm. [c]Starting % ee of 0.0100 g (*R*)-(-)-mandelic acid is 76.1; the ee of samples were determined by the comparison of HPLC profile with authentic samples.

We have also studied the influence of starting enantiomeric excess of mandelic acid by taking mandelic acid with different ee values on the phenomenon of enantiomer self-disproportionation both on M41S and regular silica gel as stationary phases (Table 4.4). The difference between lowest ee and highest ee for the chromatographic fractions (Δee) was found to be lower (Δee, 47), when sample of mandelic acid with low ee (18.0%) was subjected to chromatography on M41S. The Δee for mandelic acid with high ee (76.1%) was found to be 61.6 with M41S. However, Δee was much lower when regular silica gel was used as a stationary phase with high ee sample of mandelic acid (Table 4.4, entry 4)

Table 4.4 Self-disproportionation of enantiomers of mandelic acid on achiral M41S (regular silica gel)[a] chromatography[b]

Entry	Starting ee (%)	Eluents[c]	ee (%) min.	ee (%) max.
1(2)	18.0	Hex/IPA	8.0 (16.7)	55.6 (41.0)
3(4)	76.1	Hex/IPA	28.2 (63.5)	89.8 (82.6)
5(6)	Racemic	Hex/IPA	0.1 (0.0)	1.1 (2.2)
7(8)	18.0	Hex/DEE	4.6 (12.8)	22.5 (18.3)
9(10)	76.1	Hex/DEE	28.2 (57.0)	82.3 (89.3)
11(12)	Racemic	Hex/DEE	0.1 (0.1)	2.5 (2.1)
13(14)	18.0	$CHCl_3$	11.2 (18.4)	50.3 (30.5)
15(16)	76.1	$CHCl_3$	78.2 (18.4)	88.5 (81.3)
17(18)	Racemic	$CHCl_3$	0.6 (0.5)	1.06 (1.7)

[a]Data given in parenthesis are from regular silica gel. 2 g of column packing material was used in all the experiments. [b]All the experiments were conducted under the same condition unless otherwise stated. Temperature (27 ◦C), amount of sample m= 0.0100 ± 0.0001 g, column diameter d = 16 mm, length = 220 mm, ee was determined by HPLC analysis by mentioned columns (l=25 cm, d = 0.46 cm). [c]Hex = n-hexane, IPA = 2-propanol, DEE = diethylether. Throughout the experiments the ratios for Hex/IPA and Hex/DEE was (9:1).

To observe the effect of solvent on enantiomer self-disproportionation, same sets of experiments as described in the preceding paragraph were repeated with n-hexane/ diethyl ether (9:1) and neat chloroform as eluents. Although n-hexane/diethyl ether as eluent followed similar pattern of resolution on M41S, highest ee achieved was lower than in the case of n-hexane/2-propanol (Table 4.4, entries 1, 3, 7, and 9). On the other hand, n-hexane/diethyl ether as eluent affected better enantio-enrichment (highest ee obtained was 89.3%) for the mandelic acid with starting ee 76.1% (Table 4.4, entry 10) using regular silica gel as stationary phase. Neat chloroform as an eluent followed similar pattern, (entries 13–16) as n-hexane/2-propanol for both stationary phases. In all the experiments where racemic mandelic acid was subjected to chromatographic separation on both stationary phases, the phenomenon of enantiomer self-disproportionation was not observed (Table 4.4, entries 5, 6, 11, 12, 17, and 18).

To assess the practical usefulness of the phenomenon of enantiomer self-disproportionation, we measured the weight of each fraction for the chromatographic separation of (*R*)-(-)-mandelic acid with initial 76.1% ee using M41S using hexane/2-propanol (9:1) as eluents (Table 4.5).

Table 4.5 Data for separation of (*R*)-(-)-mandelic acid (76.1 % ee) with elution of *n*-hexane/2- propanol (9:1) using M41S[a] as column packing material[b]

Fractions	Area % of (*S*)-(-)-mandelic acid	Area % of (*R*)-(-)-mandelic acid	Weight of fractions (g)	ee[c] (%)
1	35.88	64.12	0.0002	28.24
2	31.77	68.23	0.0003	36.46
3	59.16	40.84	0.0006	-18.32*
4	29.74	70.26	0.0004	40.52
5	27.42	72.58	0.0005	45.16
6	17.43	82.57	0.0007	65.14
7	17.68	82.32	0.0006	64.64
8	14.40	85.60	0.0009	71.20
9	13..51	86.49	0.0011	72.98
10	11.48	88.52	0.0009	77.04
11	10.70	89.30	0.0011	78.60
12	10.17	89.83	0.0009	79.66
13	9.41	90.59	0.0006	81.18
14	8.84	91.16	0.0005	82.32
15	6.94	93.06	0.0004	86.12
16	6.18	93.82	0.0001	87.64
17	5.10	94.90	0.0002	89.80
Total weight of fractions 1-17			0.0100	
column washing with 2-propanol			----	
Total recovery			0.0100	

[a] 2 g M41S as column packing material. [b]Separation by HPLC, using chiralcel OD column, eluent *n*-hexane/2-propanol (8:2) at 220 nm. [c]Starting % ee of 0.0100 g (*R*)-(-)-mandelic acid 76.1; the ee of samples were determined by the comparison of HPLC profile with authentic samples. * (*S*)-(+)-mandelic acid was in excess.

Nearly 47% yield of mandelic acid with ee 83% can be obtained when Fractions 10–17 are combined. Interestingly, Fraction 3 (Table 4.5) showed negative ee (-18.32%) because of the presence of (*S*)-enantiomer of mandelic acid in excess,

most likely as a result of homochiral associations (Figure 4.1, situation 3). Importantly, the recovery of mandelic acid was quantitative at the end of chromatographic separation. The percentage ee of the chromatographed fractions and nonracemic samples (before chromatography) were determined by HPLC using chiralcel OD column. Figure 4.2 represents the HPLC chromatograms of the fraction 17 of Table 4.5 and nonracemic sample of mandelic acid.

On the basis of our experimental results, we tried to understand a possible mechanism for the phenomenon of enantiomer self-disproportionation. Soloshonok and coworkers [12–14] suggested that hydrogen bonding may play crucial role in enantiomer self-disproportionation effect. In the case of mandelic acid too, hydrogen bonding seems to be responsible for hetrochiral and homochiral interactions. It is evident from the packing diagrams of the crystal structures of racemic mandelic acid and its (*S*)-enantiomer (Figures 4.3A and 4.3B, respectively) that the mode of hydrogen bonding significantly differs from each other [29–31]. Although this behavior may not exactly occur in solutions, nevertheless, in a similar manner, it reflects possibility of existence of homochiral and heterochiral agglomerations in solution, the extent of which would depend upon the nature of the solvent. This assumption is further supported by the observations from the fact that the ee obtained for the separation of same analyte was different in different solvents (Table 4.4). The degree of homochiral and heterochiral agglomeration would also depend upon the nature of the molecule. As suggested by Soloshonok [12–14], fluorinated compounds have pronounced effect hence ee of such products should be determined before performing chromatography for the product isolation and purification for those samples where the product formed is not racemic. We suggest that this phenomenon may also exist in compounds other than fluorinated products. Typically, those

compounds which can form intra-/inter-molecular hydrogen bonding among themselves or with the mobile (solvent) and stationary phase should form varying degree of homochiral and heterochiral agglomerations in their nonracemic mixtures.

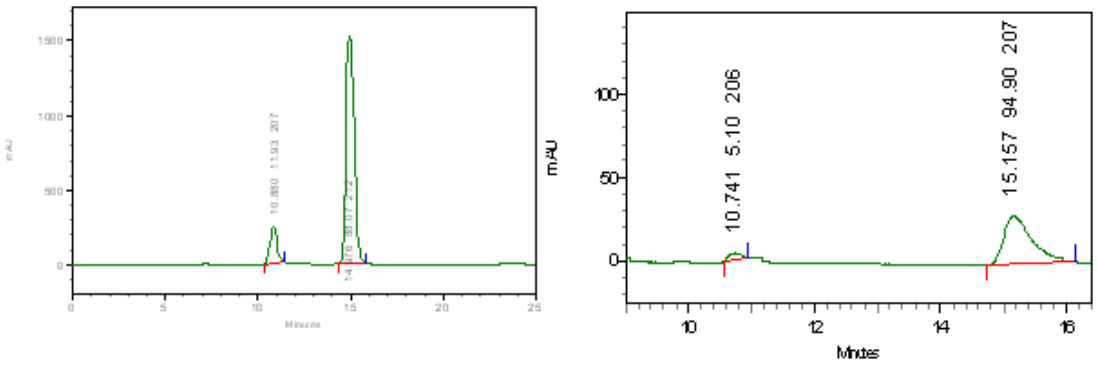


Figure 4.2 HPLC chromatogram of 76.14 % ee (*R*)-(-)-mandelic acid (a), 89.8 % ee (*R*)-(-)-mandelic acid (b) after column chromatography carried out on Chiralcel OD column, hexane/isopropanol (80/20), 0.5 ml/min flow rate using M41S as column packing material.

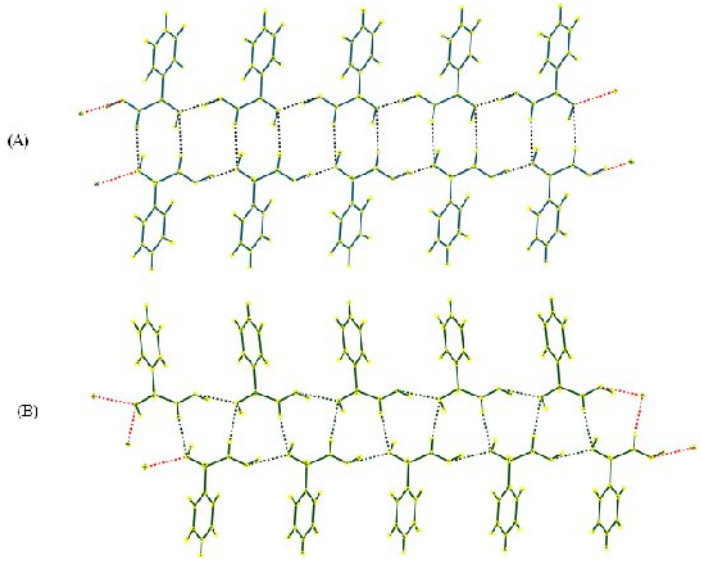


Figure 4.3 Intermolecular associations through hydrogen bonding for Racemic mandelic acid (A) and (*S*)-(+)-mandelic acid (B).

To explore whether the phenomenon of enantiomer self-disproportionation can also occur in molecules lacking hydrogen bonding, we choose stilbene oxide as a

model compound. Accordingly, we carried out enantiomer self-disproportionation chromatography of stilbene oxide with racemic and nonracemic samples (42.9% ee and 23.0% ee) using M41S and regular silica gel as an achiral stationary phase with n-hexane/2-propanol as eluent (Table 4.6). However, the results were impressively notable. It followed similar elution pattern as in the case of mandelic acid (elution pattern is not shown here), where the first fraction was of substantially lower ee and then the ee value increased for the latter fractions. In this case too, enantio-enrichment (Δee, 64.8 and 65.1) was achieved with the mixture having higher starting ee (42.9%) (Table 4.6, entries 1 and 2). On another hand taking lower starting ee (23.0%) of the mixture lower Δee (24.3 and 22.0) was observed (Entries 3 and 4). In the case of stilbene oxide, both M41S and regular silica gel as stationary phase behaved similarly. As in the case of mandelic acid separation, there was no enantio-enrichment for the racemic stilbene oxide after chromatography (entries 5 and 6). Figure 4.4 shows the HPLC chromatogram of stilbene oxide before and after chromatographic separation on achiral stationary phase. The driving force for the enantiomer self-disproportionation phenomenon in the case of stilbene oxide could be attributed to intermolecular π–π staking interactions between the phenyl rings.

Table 4.6 Self-disproportionation of enantiomers of stilbene oxide on achiral M41S (regular silica gel)[a] chromatography[b]

Entry	Starting ee[c] (%)	Eluents[d]	ee (%) min.	ee (%) max.
1(2)	42.9	Hex/IPA	7.2 (5.0)	72.0 (70.1)
3(4)	23.0	Hex/IPA	1.8 (14.0)	26.1 (36.0)
5(6)	Racemic	Hex/IPA	0.2 (0.4)	1.6 (0.8)

[a]Data given in parenthesis are from regular silica gel. 2 g of column packing material was used in all the experiments. [b]Separation by HPLC, using chiralcel OD column, eluent *n*-hexane/2-propanol = 8:2 at 228 nm. [c]0.0100 g (*1R, 2R*)-stilbene oxide; the ee of samples were determined by the comparison of HPLC profile with authentic samples. [d]Hex = *n*-hexane, IPA = 2-propanol. Throughout the experiments the ratio for Hex/IPA was (9:1).

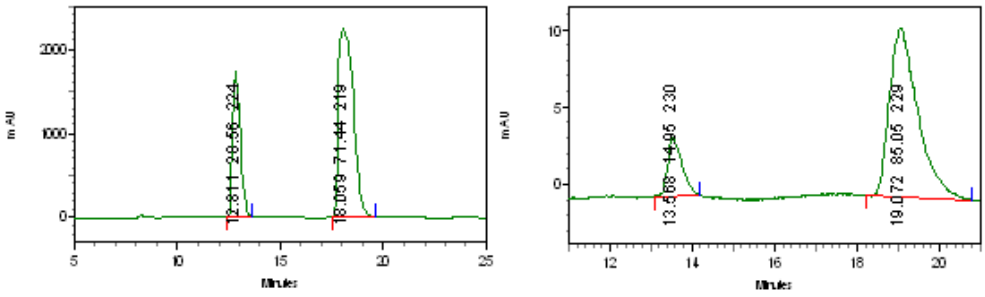


Figure 4.4 HPLC chromatogram of (1*R,2R*)-stilbene (ee, 42.88 %) oxide before chromatography (a), (ee, 70.1 %) after chromatography (b) using regular silica gel as stationary phase.

This phenomenon can be effectively utilized to enhance optical purity of a non-racemic mixture by using inexpensive achiral stationary phase like amorphous or mesoporous and crystalline silica. In further study, we found our results on enantiomer self-disproportionation phenomenon using silica gel as stationary phases and 2,2'-dihydroxy-1,1'-binaphthalene (BINOL), diethyl tartrate, 2-amino 1,2-diphenylethanol and α-methyl benzyl amine of different ee's as analytes (Table 4.7).

Table 4.7 Enantiomer self-disproportionation non racemic mixtures of analytes on achiral silica gel chromatography.[a]

Entry	Analyte	Starting ee[b] (%)	ee (%) min.	ee (%) max.
1	(*R*)-BINOL[c]	67.4	54.9	83.5
2	(*2S,3S*)-Diethyl tartrate[d]	80.1	75.1	84.3
3	(*1S,2R*)-2-amino 1,2-diphenyl ethanol[e]	73.3	68.6	80.6
4	(*R*)-α-methyl benzyl amine[f]	55.9	44.3	94.4

[a] 2 g silica gel as column packing material and Hex = *n*-hexane, IPA = 2-propanol. Throughout the experiments the ratio for Hex/IPA was (9:1). [b] Stating ee's of 0.0300 g of the analyte taken for enantiomer self-disproportionation. [c] BINOL separated by HPLC, using chiralpak AD column, eluent *n*-hexane/2-propanol (6:4) at 230 nm. [d] Diethyl tarttrate separated by HPLC, using chiralpak AD column, eluent *n*-hexane/2-propanol (8:2) at 215 nm. [e] 2-amino-1,2-diphenyl ethanol separated by HPLC, using chiralpak AD column, eluent *n*-hexane/2-propanol (8:2) at 230 nm. [f] α-methyl benzyl amine separated by HPLC, using chiralcel OD-H column, eluent *n*-hexane/2-propanol (8:2) at 210 nm.

And we found excellent enantioseparation of non-racemic mixtures. On the basis of results on hand, we can say that the appearance and enormity of enantiomer self-disproportionation is highly dependant on the optical purity of the starting compounds and the nature of the eluent used.

4.4. CONCLUSIONS

The phenomenon of enantiomer self-disproportionation chromatography was explored for nonracemic mandelic acid and stilbene oxide on achiral mesoporous semicrystaline material M41S and regular silica gel as stationary phase. Both mandelic acid and stilbene oxide exhibited the phenomenon of enantiomer self-disproportionation. Strong hydrogen bonding was attributed to show this effect for the former compound while π-π staking interaction between the phenyl rings could be responsible for the latter. The phenomenon of enantiomer self-disproportionation was also found to be sensitive toward the selection of eluents. This phenomenon can be exploited for the enantio-enrichment of nonracemic compounds of industrial relevance. Besides, it is also important to measure enantiomeric excess of the nonracemic products obtained from asymmetric synthesis before chromatographic purification to assess the true efficacy of asymmetric synthesis (catalysis) protocol. Our study shows that the phenomenon of enantiomer self-disproportionation should further be extended to nonracemic compounds having various other structural types to have deeper understanding of this truly remarkable phenomenon.

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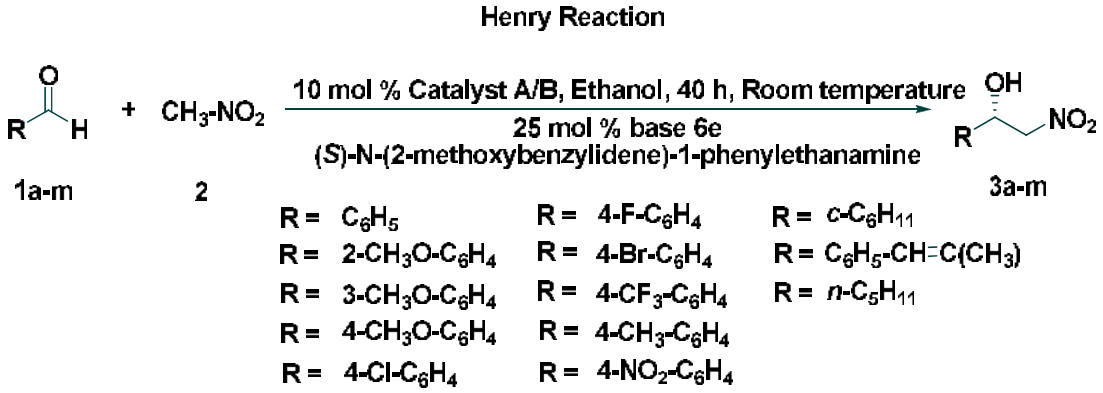


CHAPTER 5

Heterogeneous Material for Catalytic Asymmetric Nitroaldol Reaction

5.1. INTRODUCTION

Discovered in 1895, nitroaldol (Henry) reaction is one of the classical C–C bond forming reactions in organic synthesis [1-9] where the coupling of the nucleophile generated from a nitroalkane takes place with a carbonyl electrophile providing efficient access to valuable building blocks such as 1,2-amino alcohols and α-hydroxy carboxylic acids. However, the wide applicability of this transformation, until recently, was hampered due to the nonavailability of suitable catalysts for imparting a definite stereochemistry to the newly generated stereogenic centers. Shibasaki reported the first asymmetric version of the Henry reaction in 1992 [10-18]. Since then, there is an increased interest in this area of research with various reports appearing in the literature on the development of metal and nonmetal based catalysts for the asymmetric Henry reaction. Many chiral catalyst, using chiral ligands (such as BINOL, [12-16,19] amino alcohol [20,21], bis(oxazoline) [7,8, 22,23], bis(thiazoline) [24], bis(imidazoline) [25, 26], sulfonyl diamine [27], Schiff bases [28-34] with diverse metals (such as Zn [35,36], Sm [37], Cu [38-40], Mg [41-42], Cr [32], La [10,13,39], Li [12,14,19], Na [17], Ag [29, Pd [11, Zr [10], Yb [42], enzymes [1,43] and organocatalyst [44-47] have been developed in past. Among them, the Cu-catalyzed Henry reaction performed at room temperature has received much attention in recent years due to its high catalytic activity and excellent enantioselectivity under homogeneous reaction conditions [28-31,38-40,48-50]. Furthermore, a variety of bases (such as potassium hydroxide [5,44,45], cetyltrimethyl ammonium hydroxide [48], sodium carbonate [39], triethyl amine [39], 2,6-lutidine [27], pyridine [27] and aromatic imines [23] were reportedly used as additives to improve the efficiency of some of the catalysts in nitroaldol reactions.

Homogeneous asymmetric catalysis has made great growth in the last few decades. However, most of the homogeneous asymmetric catalysts have not been commercialized 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 and continuous reaction via a fix-bed reactor [51]. Heterogeneous chiral catalysts prepared through immobilization of the homogeneous catalysts on organic or inorganic supports for asymmetric hydrogenation, epoxidation, Aldol reaction and Diels Alder (D-A) addition have been extensively studied in the past [52-55]. However, heterogeneous chiral catalysts for asymmetric nitroaldol reaction have not been reported except for lone report on heterogeneous chiral lanthanum-lithium-binaphthol complex by Abdi et al [19]. In chapter 3 we described the synthesis of copper complexes of (*S*)-amino alcohol-supported silica and successfully used them as chiral stationary phase and chiral ligand exchange stationary phase for the separation of racemic compounds [56-58]. Herein, we have used this material along with chiral imines as promoter as a truly recyclable heterogeneous catalyst for asymmetric nitroaldol reaction to afford chiral nitro alcohols in good to excellent yields and enantioselectivity.

5.2. EXPERIMENTAL

5.2.1. Materials and Methods

Triblock copolymer poly (ethylene oxide)–poly(propylene oxide)–poly(ethylene oxide) pluronic P123, Tetraethyl orthosilicate (TEOS), 1, 3, 5-trimethyl benzene (TMB), aniline, *(S)-(-)*-α-methyl benzylamine, copper acetate monohydrate (Aldrich, USA), 3-aminopropyl triethoxysilane (Fluka, USA), silica gel H (standard silica, 350 mesh size) (S.D. Fine Chem. Ltd., India), hydrochloric acid

(Ranbaxy, India) were used as received. Different aromatic, aliphatic, α,β-unsaturated aldehydes and alicyclic aldehydes (Aldrich USA, Merck Germany) were used as received for asymmetric nitroaldol reaction. All chemical reactions were carried out under anhydrous conditions using nitrogen atmosphere and oven-dried glassware unless otherwise stated.

5.2.2. Synthesis of 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. [59,60] 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 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.

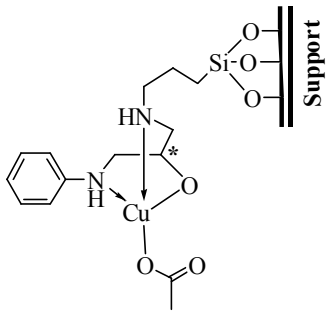
5.2.3. Synthesis of Meso Cellular Foams (MCFs)

Siliceous MCFs was synthesized according procedure reported by Stucky et al. [61,62]. Triblock co-polymer P123 (8 g, 0.0014 mol) was dispersed in 60 g of double distilled water and stirred for 3 hours at room temperature. After a solution of 1, 3, 5-trimethyl benzene (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 2M aqueous HCl was added under stirring at ambient temperature (25-30 °C) for 1 hour. Finally silica source

tetraethoxy silane (TEOS, 18.8 g, 0.09 mol) was added to the homogeneous solution under stirring to form a gel at 100 °C for 24 hours and then allowed to stand for crystallization under static hydrothermal condition at 110 °C for 48 hours in a Teflon parr reactor. The crystallized product was filtered off, washed with warm distilled water, air dried at 35 °C, calcined at 550 °C for 6 hours.

5.2.4. Synthesis of Solid-Supported Copper Complexes of (*S*)-Amino Alcohol A/B

Silica Immobilized chiral copper complex and their precursors were synthesized as per our chapter 2 and 3 (Figure 5.1). Further this catalyst then immobilized on mesoporous solid support MCFs. This both the catalysts have been used for asymmetric nitroaldol reaction.



A = SBA-15 Supported Catalyst
B = MCFs Supported Catalyst

Figure 5.1 Chiral copper complexes for asymmetric nitroaldol reaction.

5.2.5. General Procedure for Preparation of Chiral Imine

Normally, to a stirred solution of aldehyde (8 m mol) in absolute ethanol (10 ml), *(S)-(-)*-α-methyl benzylamine (1.27 ml, 10 mmol) was added at 0 °C temperature. The reaction mixture was then refluxed (78–80 ºC) for 12 h [63]. The completion of the reaction was monitored by high performance liquid chromatography. The residue is concentrated and purified by column chromatography (using neutral silica gel) by using *n*-hexane/EtOAc (90:10). Chiral purity of the imine was checked through HPLC using Chiralcel OD column, *n*-hexane/*i*-PrOH 85:15, 0.8 ml min^{-1}.

5.2.6. Typical Procedure of Asymmetric Nitroaldol Reaction

Asymmetric nitroaldol reactions were carried out in screw cap vials with magnetic stirring with highly dry and inert condition. Silica supported chiral copper (II) complex (63.74 mg, 0.04 m mol) was added to absolute ethanol (1 ml) at room temperature. Reaction mass was stirred after addition of chiral imine as additive (0.1 m mol) and then aldehyde (0.4 m mol) and nitro methane (0.3 ml, 5.5 m mol) were added to the resulting light green solution and stirring continued for 40 h at room temperature. The completion of the reaction was monitored by thin layer chromatography (TLC). The mixture was filtered and washed with dry ethanol and dried over $MgSO_4$ then evaporated in vacuum. The residue was purified by column chromatography by using *n*-hexane/EtOAc (90:10). Enantiomeric excess was determined by HPLC analysis using chiral column OD, OD-H and AD.

5.3. RESULT AND DISCUSSION

5.3.1. Characterization

Chiral complex supported on SBA-15 henceforth designated as catalyst **A** was synthesized and characterized by various physico-chemical and spectral studies according to chapter 3. While characterization of chiral copper complex supported on MCFs are given below.

5.3.1.1. Characterization data of MCFs

FTIR (KBr): 466, 809, 1095, 1634, 2355, 3438 cm^{-1}. Solid reflectance UV-vis.: 220, 260, 340, 360 nm.

5.3.1.2. Characterization data of catalyst B

FTIR (KBr): 463, 806, 1093, 1464, 1515, 1535, 1630, 1725, 1765, 2340, 2361, 2856, 2927, 3438 cm^{-1}. Solid reflectance UV-vis.: 220, 260, 310, 370, 400, 520, 530 nm. CHN analysis (Found) C: 6.12, H: 0.98, N: 0.50 % (C/N = 12.24, C/H = 6.24). Surface coverage 1.41 μ mols/m^2.

The total pore volume of the sample was estimated from the amount of N_2 adsorption at relative pressure of about 0.995. N_2 adsorption–desorption isotherm of MCFs of IV type is also confirmed the well-ordered mesopores. The primary mesopore volume *V*p was calculated from the slope of a linear portion of the *t*-plot in the pressure range above the pressure of nitrogen condensation in primary mesopores. The data on BET surface area, pore diameter, total pore volumes obtained are summarized in Table 5.1. A large decrease in BET surface area was observed (770–298 m^2/g) upon functionalization of modified MCFs. Similarly, reduction in the mesoporous diameter from 119 to 110 Å and in pore volume from 2.299 to 0.819 cm^3/g was also observed (Table 5.1). Moreover, further decrease in BET surface area 298 to 272 m^2/g in pore diameter from 110 to 101 Å and pore volume from 0.819 to 0.689 cm^3/g was observed upon ring opening reaction with aniline indicates that the internal pores of the MCF are occupied by the amino alcohol and structure of the mesopore is maintained after modification (Figures 5.2, 5.3 and 5.4 respectively).

Table 5.1 Physico-chemical data of MCFs and catalyst B

Compound	**BET surface area (m^2/g)**	**Total pore volume (cm^3/g)**	**BJH pore diameter (Å)**
MCFs	770	2.299	119.4
Catalyst **B**	298	0.819	109.7
Recycled Catalyst **B**	272	0.689	101.1

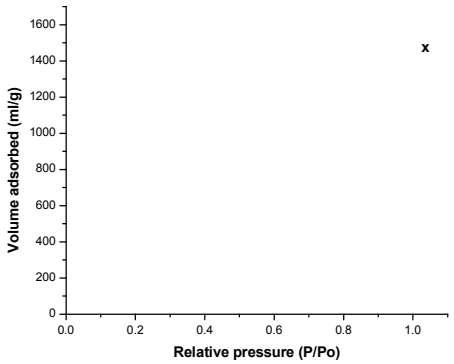


Figure 5.2 Nitrogen adsorption-desorption isotherm of MCFs (X).

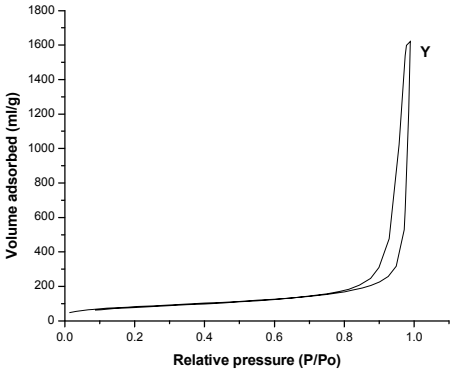


Figure 5.3 Nitrogen adsorption-desorption isotherm of catalyst **B** (Y).

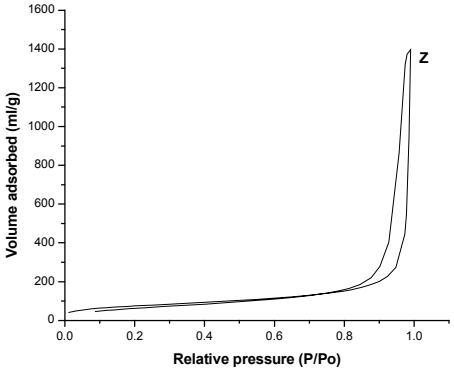


Figure 5.4 Nitrogen adsorption-desorption isotherm of recycled catalyst **B** (Z).

The loadings of chiral copper complex **B** was found to be 13.2% as determined from the weight loss measured by thermo-gravimetric analysis carried out in the temperature range between 70–800 °C (Figure 5.5). Scanning electron

microscopy (Figure 5.6) and Transmission electron microscopy (Figure 5.7) confirms the expected particle morphology of meso cellular foams (MCFs).

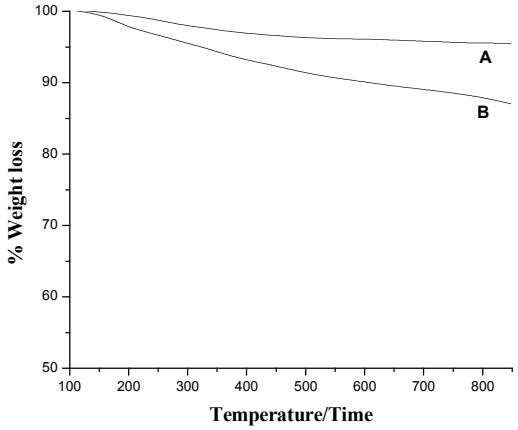


Figure 5.5 TGA curve of calcined MCFs (A), Catalyst **B** (B).

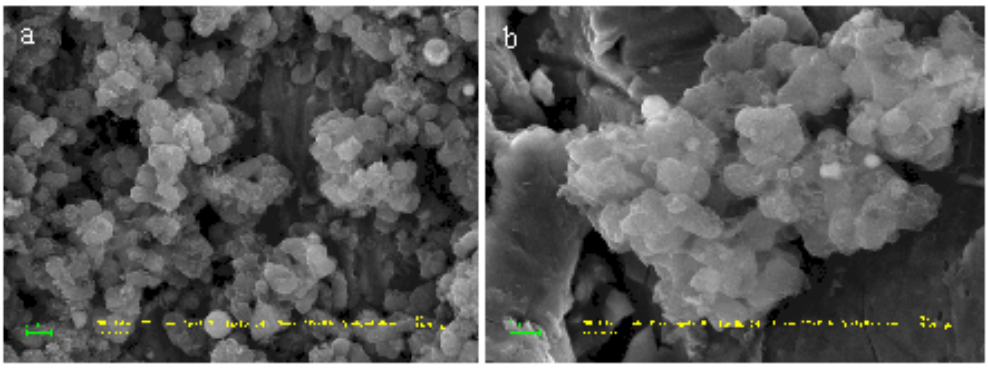


Figure 5.6 SEM images of calcined MCFs (a), Catalyst **B** (b).

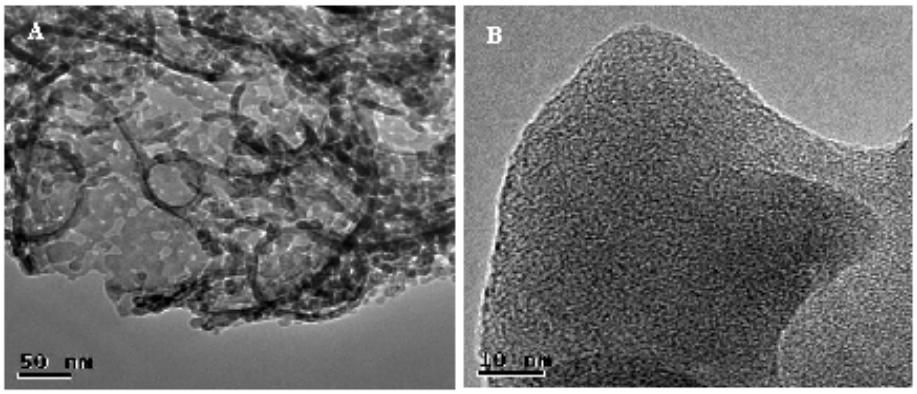


Figure 5.7 TEM images of calcined MCFs (A), Catalyst **B** (B).

The FTIR spectra (Figure 5.8) of MCFs showed the characteristic band at 1095 cm^{-1} of Si-O-Si and 3438 cm^{-1} for the Si-OH bond. On complexation with

Cu(II) metal ion the IR band (Figure 5.9) centered around 3433 cm^{-1} due to υ(O-H) merged with Si-O-Si band show a decrease in intensity due to the co-ordination with phenolic oxygen to metal ion. An additional band appeared at 2927 cm^{-1} due to υ(CH_2) of propyl arm belonging to silylation agent and new band due to υ(C-N) and υ(C=C) of aromatic ring appeared at 1464 cm^{-1} and 1630 cm^{-1}, respectively, confirming the formation chiral copper complex of (*S*)-amino alcohol immobilized on MCFs. After one catalytic cycle the recycled catalyst subjected for FT-IR observation, we found almost similar as fresh catalyst (Figure 5.10).

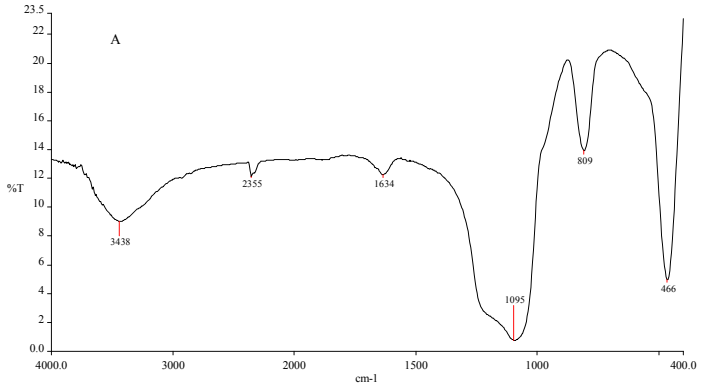


Figure 5.8 FTIR spectra of calcined MCFs (A).

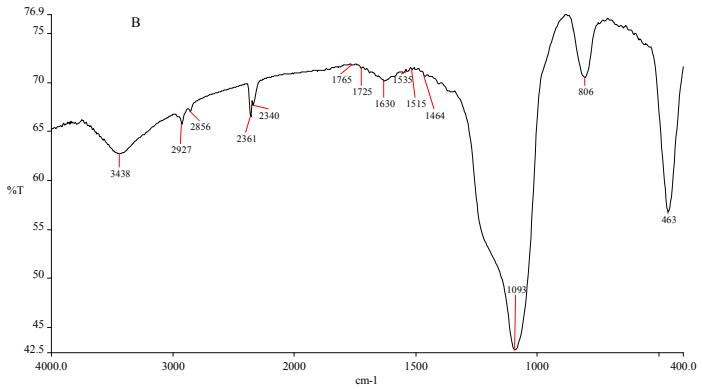


Figure 5.9 FTIR spectra of catalyst **B** (B).

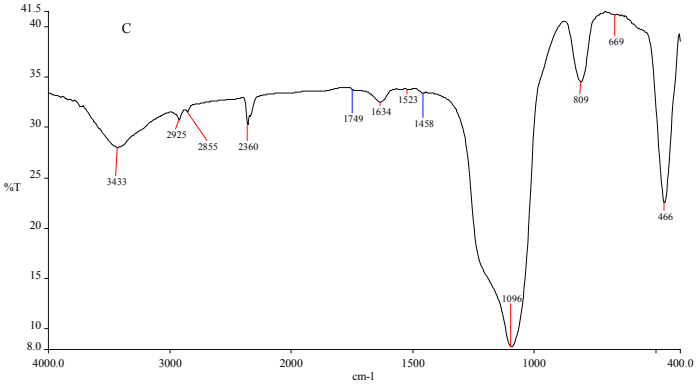
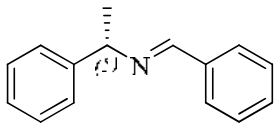


Figure 5.10 FTIR spectra of recycled catalyst **B** (C).

5.3.1.3. Characterization data of chiral imine and 1,2-nitroalcohols

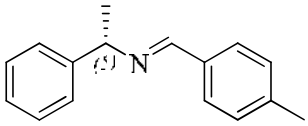
Characterization of chiral imine and 1,2-nitroalcohols were given below.

1. Spectral data of *(S)-N*-benzylidene-1-phenylethanamine 6a:



The name compound was synthesized by using general procedure and purified by column chromatography (9:1, *n*-hexane/EtOAc) to give yellow semi solid (89% yield). FT-IR 2972, 2847, 1885, 1645, 1493, 1450, 1380, 1296, 1071, 908, 754, 696 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.60 (d, J = 7 Hz, 3H), 4.55 (q, J= 6.5, 1H), 7.21-7.25 (m, 2H), 7.32-7.35 (m, 2H), 7.39-7.43 (m, 6H), 8.37 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 24.9, 69.4, 126.7, 126.9, 128.4, 128.5, 128.7, 130.7, 136.5, 145.2, 159.6. Anal. Calcd. For $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 86.02; H, 7.19; N, 6.62. TOF–MS (ESI+): found $C_{15}H_{15}N$ m/z 210 (M^{+}+H). $[\alpha]_D^{27}$ = – 169° (C = 0.16, $CHCl_3$). Chiral purity was determined by HPLC with a Chiralcel OD column (85:15 *n*-hexane: isopropanol, 0.8 ml/min, t_r = 12.4 min).

2. Spectral data of *(S)-N*-(4-methylbenzylidene)-1-phenylethanamine 6b:



The name compound was synthesized by using general procedure and purified by column chromatography (9:1, *n*-hexane/EtOAc) to give colorless sticky oil (95% yield). FT-IR 3431, 2972, 2923, 2854, 2365, 1643, 1586, 1530, 1447, 1369, 1171, 1068, 908, 824, 764 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.57-1.58 (d, *J* = 6.5 Hz, 3H), 2.15 (s, 3H), 4.45-4.51 (q, *J*= 6.5, 13 Hz,1H), 7.33-7.42 (m, 5H), 7.69-7.71 (d, *J*=8.5*,* 2H), 7.80-7.82 (d, *J* = 8.5 Hz, 2H), 8.31 (s, 1H), 8.80 (s, 1H) (Figure 5.11). ^{13}C NMR (125 MHz, $CDCl_3$) 20.9, 24.9, 69.8, 126.6 126.9, 128.5, 128.8, 129.5, 134.87, 144.9, 158.1 (Figure 5.12). Anal. Calcd. For $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.34; H, 6.51; N, 5.98. TOF–MS (ESI+): found $C_{16}H_{17}N$ *m*/*z* 224 (M^++H), 225 (M^++2). $[\alpha]_D^{27}$ = – 284° (C = 0.32, $CHCl_3$). Chiral purity was determined by HPLC with a Chiralcel OD column (85:15 *n*-hexane: isopropanol, 0.8 ml/min, t_r = 12.1 min) (Figure 5.13).

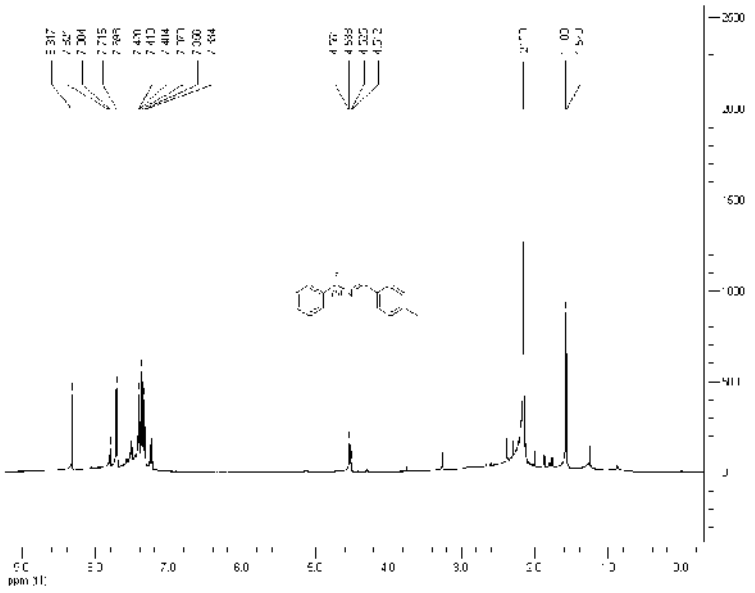


Figure 5.11 ^1H NMR Spectra of *(S)-N*-(4-methylbenzylidene)-1-phenylethanamine **6b**.

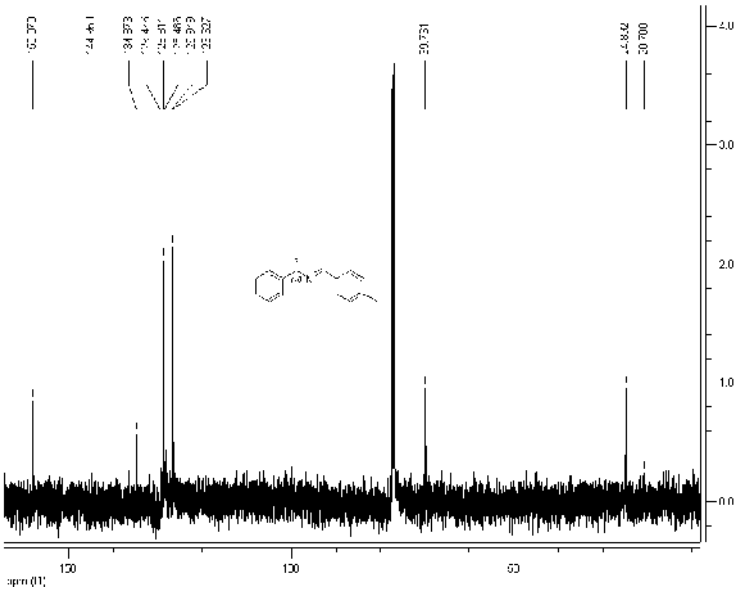


Figure 5.12 ^{13}C NMR Spectra of *(S)-N*-(4-methylbenzylidene)-1-phenylethanamine **6b**.

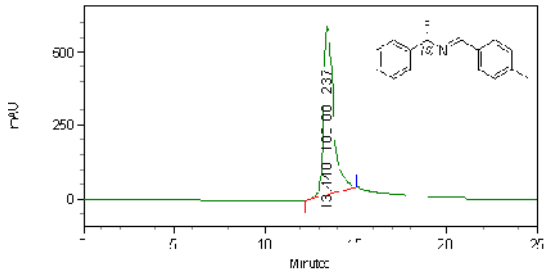
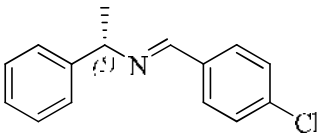


Figure 5.13 HPLC chromatogram of *(S)-N*-(4-methylbenzylidene)-1-phenylethanamine **6b**.

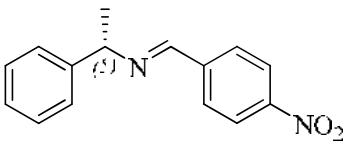
3. Spectral data of *(S)-N*-(4-chlorobenzylidene)-1-phenylethanamine 6c:



The name compound was synthesized by using general procedure and purified by column chromatography (9:1, *n*-hexane/EtOAc) to give a colorless solid (96% yield). FT-IR 2972, 2864, 1806, 1640, 1488, 1449, 1378, 1291, 1082, 908, 763, 635 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ1.59 (d, *J* = 6.5Hz, 3H), 4.45 (q, *J* = 6.5Hz, 1H),

7.24-7.26 (m, 2H), 7.34-7.42 (m, 5H), 7.27 (d, *J* = 8Hz, 2H), 8.32 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 24.8, 69.8, 126.6, 126.9, 128.5, 128.8, 129.5, 134.9, 136.5, 144.9, 158.1. Anal. Calcd. For $C_{15}H_{14}NCl$: C, 73.92; H, 5.79; N, 5.75. Found: C, 73.87; H, 5.74; N, 5.70. TOF–MS (ESI+): found $C_{15}H_{14}NCl$ *m/z* 244 (M^++H), 266 (M^++Na). $[\alpha]_D^{27}$ = – 120° (C = 0.02, $CHCl_3$). Chiral purity was determined by HPLC with a Chiralcel OD column (85:15 *n*-hexane: isopropanol, 0.8 ml/min, t_r = 9.9 min).

4. Spectral data of *(S)-N*-(4-nitrobenzylidene)-1-phenylethanamine 6d:



The name compound was synthesized by using general procedure and purified by column chromatography (9:1, *n*-hexane/EtOAc) to give a orange oil (85% yield). FT-IR 3408, 3066, 3131, 2975, 2929, 2859, 2449, 1710, 1644, 1601, 1523, 1449, 1347, 1220, 1107, 1013, 911, 850, 748 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.58-1.59 (d, *J* = 6.5 Hz, 3H), 4.52-4.56 (q, *J*= 6.5,13.5 Hz, 1H), 7.22-7.25 (m, 1H), 7.32-7.37 (m, 4H), 7.40-7.42 (d, *J* = 7.0 Hz, 3H), 7.70-7.71 (d, *J* = 8.5 Hz, 2H), 8.31 (s, 1H) (Figure 5.14). ^{13}C NMR (125 MHz, $CDCl_3$) 24.8, 69.8, 125.0, 126.6, 126.9, 128.5, 128.8, 129.5, 147.2, 158.1 (Figure 5.15). Anal. Calcd. For $C_{15}H_{14}N_2O_2$: C, 70.85; H, 5.55; N, 11.02. Found: C, 69.55; H, 6.04; N, 10.49. TOF–MS (ESI+): found $C_{15}H_{14}N_2O_2$ *m/z* 254 (M^+), 253 (M^-). $[\alpha]_D^{27}$ = – 221° (C = 0.30, $CHCl_3$). Chiral purity was determined by HPLC with a Chiralcel OD column (85:15 *n*-hexane: isopropanol, 0.8 ml/min, t_r = 14.0 min) (Figure 5.16).

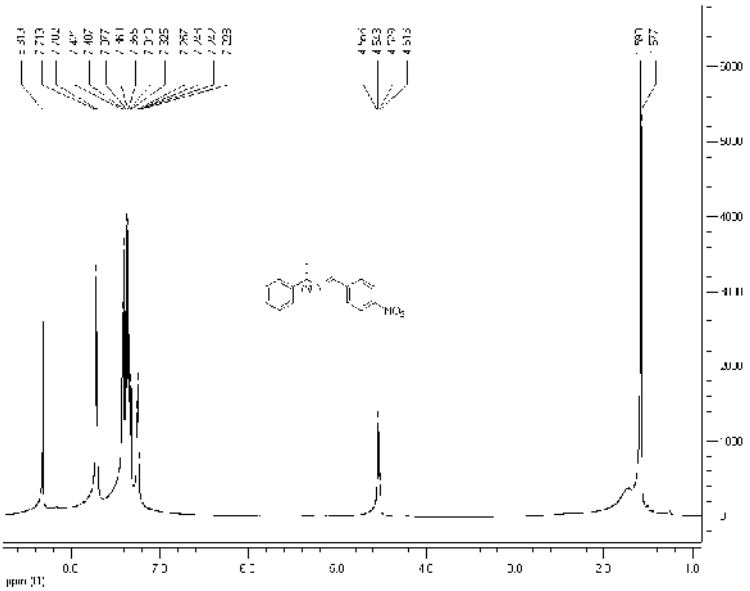


Figure 5.14 ^{1}H NMR Spectra of *(S)-N*-(4-nitrobenzylidene)-1-phenylethanamine **6d**.

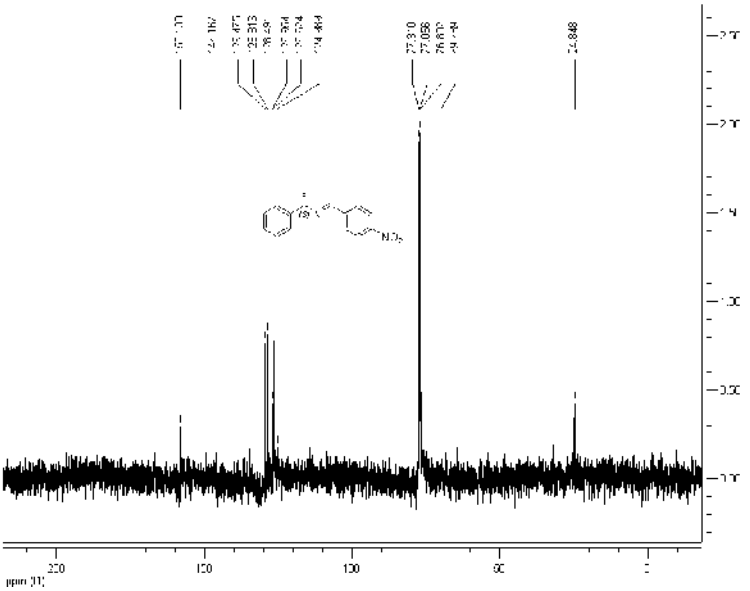


Figure 5.15 ^{13}C NMR Spectra of *(S)-N*-(4-nitrobenzylidene)-1-phenylethanamine **6d**.

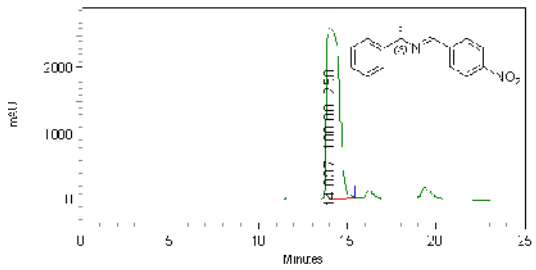
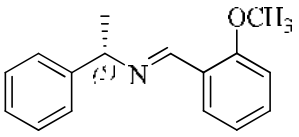


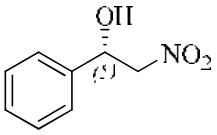
Figure 5.16 HPLC chromatogram *(S)-N*-(4-Nitrobenzylidene)-1-phenylethanamine **6d**.

5. Spectral data of *(S)-N*-(2-methoxybenzylidene)-1-phenylethanamine 6e:



The name compound was synthesized by using general procedure and purified by column chromatography (9:1, *n*-hexane/EtOAc) to give yellow oil (94% yield). FT-IR 2968, 2927, 1879, 1635, 1488, 1379, 1246, 1161, 1046, 835, 761, 468 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ1.59 (d, *J* = 6.5Hz, 3H), 3.83 (s, 3H), 4.55 (q, *J* = 6.5Hz, 1H), 6.86-6.96 (m, 2H), 7.21-7.43 (m, 6H), 8.05 (br s, 1H), 8.82 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) 25.0, 55.5, 70.1, 111.0, 120.8, 124.9, 126.7, 127.7, 128.4, 128.6, 131.8, 136.0, 145.6, 155.5, 158.8. Anal. Calcd. For $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.26; H, 7.12; N, 5.80. TOF–MS (ESI+): found $C_{16}H_{17}NO$ *m/z* 240 (M^++H), 263 (M^++Na). $[\alpha]_D^{27}$ = – 426° (C = 0.4, $CHCl_3$). Chiral purity was determined by HPLC with a Chiralcel OD column (85:15 *n*-hexane: isopropanol, 0.8 ml/min, t_r = 13.4 min).

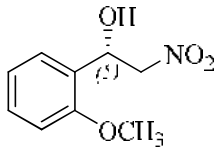
6. Spectral data of (*S*)-1-Phenyl-2-nitroethanol 3a:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give light yellow oil (97% yield). FT-IR 3313, 3032, 2874, 2366, 1874, 1719, 1496, 1454, 1274, 1205, 1079, 1018, 736, 698, 596 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69-2.70 (t, *J* = 2.5 Hz, 1H), 3.02-3.04 (t, *J* = 5.5 Hz, 1H), 3.53 (s, 1H), 3.76-3.77 (t, *J* = 3 Hz, 1H), 7.21-7.28 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) 61.9, 64.4, 126.6, 127.1, 128.1, 129.3, 140.7. Anal. Calcd. For $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 56.03; H, 5.13; N,

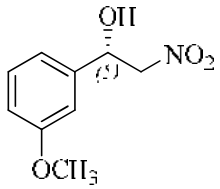
7.96. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 18.7 min, minor enantiomer t_r = 21.8 min. $[\alpha]_D^{27}$ = + 33.2° (C = 1.3, CH_2Cl_2). TOF–MS (ESI+): found $C_8H_9NO_3$ *m/z* 167 (M^+).

7. Spectral data of (*S*)-1-(2-Methoxyphenyl)-2-nitroethanol 3b:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give yellow oil (85% yield). FT-IR 3432, 2925, 2520, 2230, 1994, 1593, 1465, 1243, 1109, 1041, 844, 755, 627 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.95 (s, 1H), 2.77-2.79 (dd, *J* = 2.5, 5.5 Hz, 1H), 3.10-3.12 (dd, *J* = 4, 5.5 Hz, 1H), 3.83-3.84 (t, *J* = 3 Hz, 1H), 3.41 (s, 3H), 7.25-7.34 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 50.4, 51.1, 52.2, 125.3, 128.0, 128.4, 137.4, 169.0. Anal. Calcd. For $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.40; H, 5.60; N, 7.13. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane: 2-propanol, flow 0.8 ml/min) major enatiomer t_r = 15.7 min, minor enantiomer t_r = 18.2 min. $[\alpha]_D^{27}$ = + 34.7° (C = 1.6, CH_2Cl_2). TOF–MS (ESI+): found $C_9H_{11}NO_4$ *m/z* 215 (M^++NH_4).

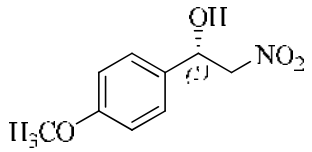
8. Spectral data of (*S*)-1-(3-Methylphenyl)-2-nitroethanol 3c:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give a dark yellow oil (92% yield). FT-IR 3366, 2973, 2932, 2887, 2522, 2361, 2050, 1659, 1559, 1466, 1379, 1307, 1161, 1129, 952, 817, 697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.60 (s, 1H),

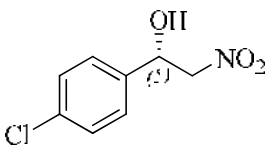
2.72-2.76 (dd, *J* = 2.4, 5.4 Hz, 1H), 3.06-3.10 (t, *J* = 4.8 Hz, 1H), 3.38 (s, 3H), 3.79-3.82 (t, *J* = 3.2 Hz, 1H), 7.26-7.28 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 50.6, 51.3, 52.4, 125.5, 128.2, 128.5, 137.6. Anal. Calcd. For $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.31; H, 5.20; N, 6.80. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 18.2 min, minor enantiomer t_r = 19.6 min. $[\alpha]_D^{27}$ = + 23.7° (C = 2.1, CH_2Cl_2). TOF–MS (ESI+): found $C_9H_{11}NO_4$ *m/z* 197 (M^+).

9. Spectral data of (*S*)-1-(4-Methoxyphenyl)-2-nitroethanol 3d:



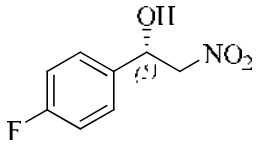
The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give colorless oil (85% yield). FT-IR 3378, 2973, 2660, 2194, 1898, 1655, 1410, 1380, 1307, 1161, 1129, 951, 816 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.032 (s, 1H), 2.80-2.84 (m, 1H), 3.13-3.18 (t, *J* = 5.2 Hz, 1H), 3.46 (s, 3H), 3.81-3.87 (t, *J* = 2.6 Hz, 1H), 7.30-7.32 (d, J = 5.2Hz, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 56.9, 59.4, 121.6, 122.0, 122.7, 123.0, 135.6, 160.2 Anal. Calcd. For $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.32; H, 5.31; N, 7.05. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 15.5 min, minor enantiomer t_r = 23.2 min. $[\alpha]_D^{27}$ = + 18.3° (C = 0.9, CH_2Cl_2). TOF–MS (ESI+): found $C_9H_{11}NO_4$ *m/z* 196 (M^-), 215 (M^++NH_4).

10. Spectral data of (*S*)-1-(4-Chlorophenyl)-2-nitroethanol 3e:



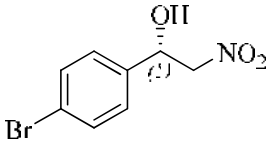
The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give light yellow oil (72% yield). FT-IR 3505, 2839, 2516, 2361, 2151, 1939, 1653, 1543, 1421, 1274, 1134, 1020, 651 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.54 (s, 1H), 4.56-4.75 (m, 2H), 5.51-5.57 (dd, *J* = 3.8, 8.8 Hz, 1H), 7.39-7.43 (d, *J* = 8.4 Hz, 2H), 7.63-7.68 (d, *J* = 8.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 41.5, 51.3, 52.5, 125.5, 128.2, 128.5, 137.6. Anal. Calcd. For $C_8H_8NO_3Cl$: C, 47.66; H, 4.00; N, 6.95. Found: C, 46.90; H, 3.92; N, 6.89. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 17.6 min, minor enantiomer t_r = 21.2 min, $[\alpha]_D^{27}$ = + 17.3° (C = 0.55, CH_2Cl_2).TOF–MS (ESI+): found $C_8H_8NO_3Cl$ *m/z* 224 (M^++Na).

11. Spectral data of (*S*)-1-(4-Fluorophenyl)-2-nitroethanol 3f:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give dark yellow oil (68% yield). FT-IR 3410, 2925, 2855, 2452, 1711, 1558, 1437, 1364, 1225, 1094, 736, 532 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 3.94 (s, 1H), 4.45-4.59 (m, 2H), 5.41-5.43 (dd, *J* = 2.5, 9.5, Hz, 1H), 7.05-7.06 (d, *J* = 8.5 Hz, 2H), 7.36-7.37 (d, *J* = 5.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 62.2, 64.7, 126.9, 127.3, 128.3, 129.4, 129.5, 140.9. Anal. Calcd. For $C_8H_8NO_3F$: C, 51.90; H, 4.36; N, 7.26. Found: C, 51.50; H, 4.22; N, 7.26 .HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 18.6 min, minor enantiomer t_r = 19.4 min. $[\alpha]_D^{27}$ = + 30.6° (C = 0.9, CH_2Cl_2). TOF–MS (ESI+): found $C_8H_8NO_3F$ *m/z* 185 (M^+), 186 (M^++H).

12. Spectral data of (*S*)-1-(4-Bromophenyl)-2-nitroethanol 3g:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give dark yellow oil (73% yield). FT-IR 3399, 2976, 2926, 2016, 1748, 1588, 1490, 1445, 1369, 1261, 1168, 1046, 880, 824, 729, 605 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.39 (s, 1H), 4.40-4.62 (m 1H) 5.37-5.43 (dd, *J* = 3.6, 8.8 Hz, 2H), 7.25-7.28 (d, *J* = 8.2 Hz, 2H), 7.50-7.54 (d, *J* = 8.2 Hz, 2H) (Figure 5.17). ^{13}C NMR (125 MHz, $CDCl_3$) 51.3, 52.4, 125.5, 128.2, 128.5, 137.6 (Figure 5.18). Anal. Calcd. For $C_8H_8NO_3Br$: C, 39.05; H, 3.28; N, 5.69. Found: C, 38.79; H, 3.25; N, 5.70. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 19.1 min, minor enantiomer t_r = 22.2 min (Figures 5.19 and 5.20). $[\alpha]_D^{27}$ = + 27.5° (C = 0.8, CH_2Cl_2). TOF–MS (ESI+): found $C_8H_8NO_3Br$ *m/z* 246 (M^+).

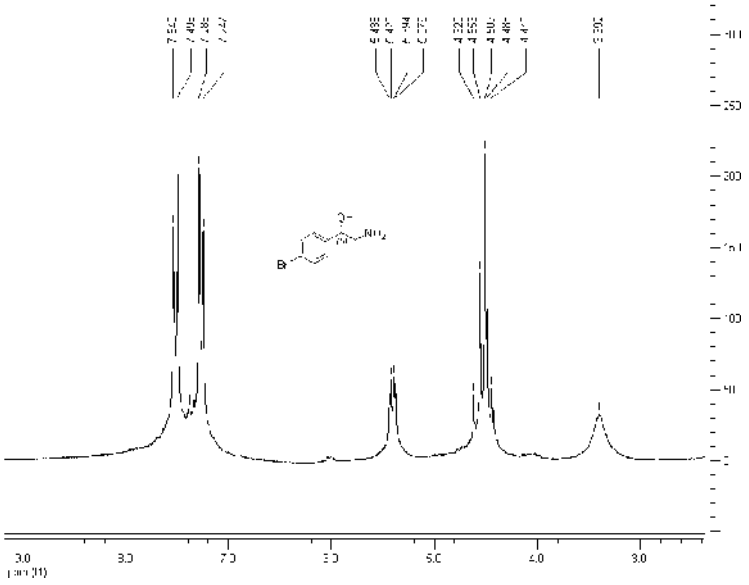


Figure 5.17 ^1H NMR Spectra of (*S*)-1-(4-Bromophenyl)-2-nitroethanol 3g.

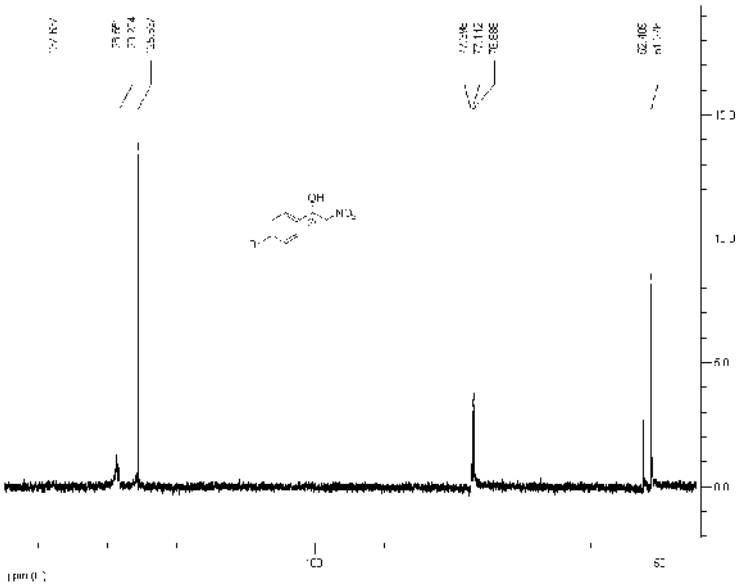


Figure 5.18 ^{1}H NMR Spectra of (*S*)-1-(4-Bromophenyl)-2-nitroethanol 3g.

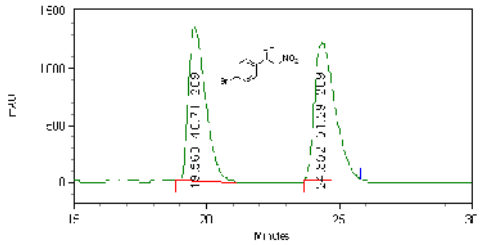


Figure 5.19 HPLC chromatogram racemic 1-(4-Bromophenyl)-2-nitroethanol.

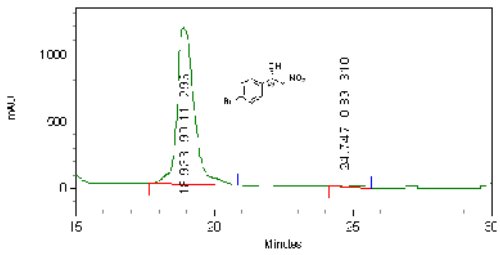
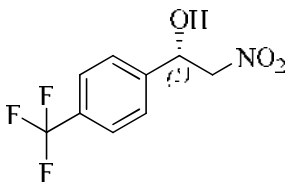


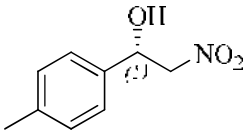
Figure 5.20 HPLC chromatogram of (*S*)-1-(4-Bromophenyl)-2-nitroethanol 3g.

13. Spectral data of (*S*)-1-(4-trifluoromethylphenyl)-2-nitroethanol 3h:



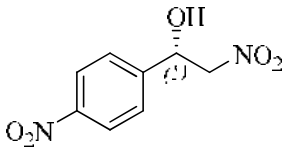
The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give dark yellow oil (72% yield). FT-IR 3504, 3004, 2927, 2341, 2142, 1712, 1627, 1557, 1494, 1436, 1363, 1223, 1126, 1068, 904, 759, 704 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.51 (s, 1H), 4.44-4.47 (m, 1H), 5.39-5.42 (d, *J* = 5.4Hz, 2H), 7.37 (br s, 4H), ^{13}C NMR (125 MHz, $CDCl_3$) 64.9, 127.1, 127.6, 128.48, 128.49, 128.53, 129.76, 140.9. Anal. Calcd. For $C_9H_8NO_3F_3$: C, 45.97; H, 3.43; N, 5.96. Found: C, 45.90; H, 3.41; N, 5.88. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 17.6 min, minor enantiomer t_r = 19.7 min. $[\alpha]_D^{27}$ = + 11.7° (C = 1.0, CH_2Cl_2). TOF–MS (ESI+): found $C_9H_8NO_3F_3$ *m/z* 258 (M^++Na).

14. Spectral data of (*S*)-1-(4-Methylphenyl)-2-nitroethanol 3i:



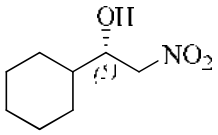
The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give a light yellow oil (85% yield). FT-IR 3399, 3026, 2976, 2925, 2148, 1613, 1561, 1515, 1437, 1375, 1239, 1045, 818, 739, 656 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 2.15 (s, 3H), 3.25 (s, 1H), 4.27-4.31 (m, 1H), 4.51-4.55 (dd, *J* = 6.5, 13 Hz, 2H), 7.69-7.71 (d, *J* = 8.5 Hz, 2H), 7.80-7.82 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 24.88, 69.76, 126.6, 126.9, 128.5, 128.8, 129.5, 134.9, 145.0. Anal. Calcd. For $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.60; H, 6.21; N, 7.38. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 19.6 min, minor enantiomer t_r = 21.3 min. $[\alpha]_D^{27}$ = + 8.1° (C = 1.3, CH_2Cl_2). TOF–MS (ESI+): found $C_9H_{11}NO_3$ m/*z* 183 (M^++2).

15. Spectral data of (*S*)-1-(4-Nitrophenyl)-2-nitroethanol 3j:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give a orange oil (62% yield). FT-IR 3350, 2976, 2361, 2337, 2220, 1644, 1524, 1381, 1346, 1274, 1089, 1049, 879, 751, 671 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.78 (s, 1H), 2.77-2.78 (m, 1H), 3.11-3.13 (t, *J* = 5 Hz, 1H), 3.83-3.84 (t, *J* = 3 Hz, 1H), 7.25-7.34 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) 70.1, 123.8, 124.3, 126.6, 127.2, 128.6, 128.9, 130.5, 157.2. Anal. Calcd. For $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.20. Found: C, 45.19; H, 3.30; N, 13.11. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 14.2 min, minor enantiomer t_r = 19.5 min. $[\alpha]_D^{27}$ = + 20.6° (C = 1.03, CH_2Cl_2). TOF–MS (ESI+): found $C_8H_8N_2O_5$ *m/z* 235 (M^++Na).

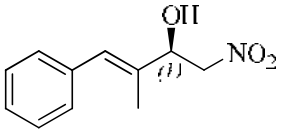
16. Spectral data of (*S*)-1-Cyclohexyl-2-nitroethanol 3k:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give light yellow oil (93% yield). FT-IR 3353, 2973, 2659, 2361, 2030, 1658, 1466, 1379, 1307, 1161, 1129, 952, 817, 772, 649 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.23-1.35 (m, 11H), 3.26 (s, 1H), 3.43-3.45 (t, *J* = 6 Hz, 1H), 3.69-3.73 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 24.9, 25.34, 25.7, 25.9, 28.8, 42.9, 50.0, 58.4. Anal. Calcd. For $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.38; H, 8.39; N, 7.75. HPLC analysis: Chiralcel AD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) major enatiomer t_r = 14.6 min, minor

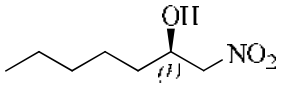
enantiomer t_r = 16.5 min. $[\alpha]_D^{27}$ = + 15.8° (C = 1.4, CH_2Cl_2). TOF–MS (ESI+): found $C_8H_{15}NO_3$ m/*z* 174 (M^++1).

17. Spectral data of (*R*)-3-methyl-1-nitro-4-phenylbut-3-en-2-ol 3l:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give light yellow oil (76% yield). FT-IR: 3392, 2972, 2931, 2360, 1943, 1868, 1741, 1696, 1518, 1461, 1395, 1265, 1125, 952, 871, 817, 668 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.79 (s, 1H), 4.08-4.11(d, *J* = 7.6 Hz, 1H), 4.54-4.57(d, *J* = 6.2 Hz, 1H), 4.90-4.97 (t, *J* = 6.4 Hz, 1H), 6.70 (s, 1H), 7.26-7.46 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) 11.0, 18.4, 58.4, 128.7, 129.6, 130.1, 135.1, 138.3, 149.9. Anal. Calcd. For $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.80. Found: C, 63.63; H, 6.27; N, 6.80. HPLC analysis: Chiralcel OD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) minor enatiomer t_r = 18.4 min, major enantiomer t_r = 20.9 min. $[\alpha]_D^{27}$ = − 9.9° (C = 0.7, CH_2Cl_2). TOF–MS (ESI+): found $C_{11}H_{13}NO_3$ *m*/*z* 208 (M^++H).

18. Spectral data of (*R*)-1-nitroheptan 2-ol 3m:



The name compound was synthesized by using typical procedure and purified by column chromatography (95:5, *n*-hexane/EtOAc) to give light yellow oil (% yield). FT-IR : 3752, 3015, 2858, 2630, 2361, 1741, 1555, 1399, 1358, 1255, 1147, 1072, 848, 545 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (br s, 3H), 1.32-1.86 (m, 8H), 2.29-2.43 (m, 1H), 2.812 (s, 1H), 4.33-4.52 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) 13.7, 18.1, 21.7, 22.3, 31.2, 43.8, 57.9, 93.4, 94.3. Anal. Calcd. For $C_7H_{15}NO_3$: C,

52.16; H, 9.38; N, 8.40. Found: C, 51.39; H, 9.36; N, 8.40. HPLC analysis: Chiralcel AD, (85:15, *n*-hexane:2-propanol, flow 0.8 ml/min) minor enatiomer t_r = 22.3 min, major enantiomer t_r = 27.3 min. $[\alpha]_D^{27}$ = − 9.3° (C = 1.3, CH_2Cl_2). TOF–MS (ESI+): found $C_7H_{15}NO_3$ *m*/*z* 162 (M^++H).

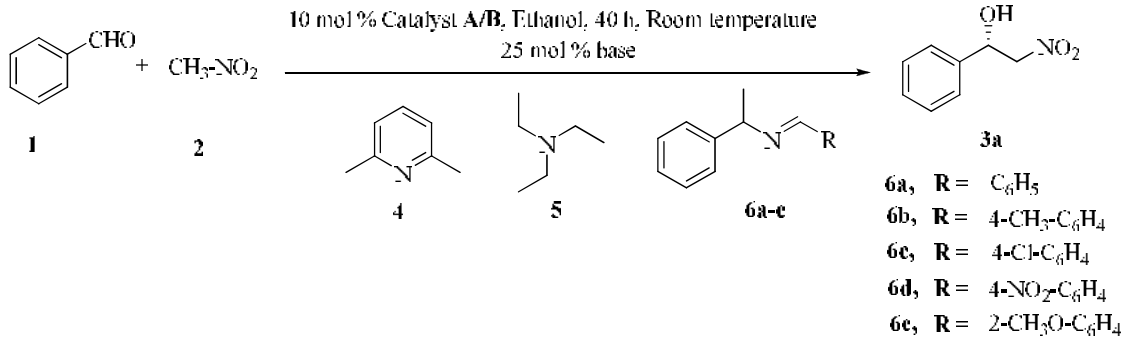
Configuration assignment: The absolute stereochemistry was assigned by comparison of the optical rotation with the literature value [7,8].

5.3.2. Enantioselective Heterogeneous Henry Reaction of Aldehydes

We have presented here the preparation of MCF supported catalyst **B** and its characterization to study the nitroaldol reaction. In the current study we have used these heterogeneous catalysts **A** and **B** to catalyze the nitroaldol reaction for the synthesis of various pharmaceutically important chiral nitro alcohols at room temperature in high yield and chiral purity.

To see the potential of this new reaction, we have used only catalyst **A** and **B** that is SBA-15 and MCF supported copper complex of chiral amino alcohol respectively (Table 5.1, entries 1,2) to know the influence of catalyst and additive. Both of the catalysts **A** and **B**, without additive, giving >90% yield and >75% selectivity. As expected, the possibility of the reaction with respect to both the additive and the catalyst was investigated under the described reaction conditions (Table 5.1). Excellent enantioselectivity was observed with additive bearing both electron-rich and electron-poor substituents (entries 3-9). Hetero-aromatic imine (2,6-lutidine **4**), giving less conversion with poor enantioseparation, was not suitable additive for our experimental condition (entry 3). While triethylamine (**5**) has performed well in productivity but ineffective for enantioselectivity (entry 4).

Table 5.1 Catalytic Study of Mixture of Different Materials on Asymmetric Nitroaldol Reaction[a]



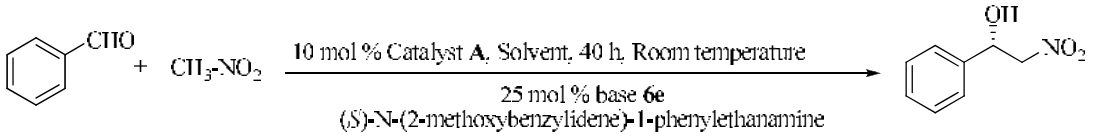
Entry	Materials[b]	Yield[c] (%)	ee[d] (%)
1	Catalyst A	90	75
2	Catalyst B	91	80
3	Catalyst A + 2,6- lutidine (4)	30	---
4	Catalyst A + Triethyl amine (5)	90	19 (*S*)
5	Catalyst A + R = C_6H_5 (6a)	85	72 (*S*)
6	Catalyst A + R = 4-CH_3-C_6H_4 (6b)	96	75 (*S*)
7	Catalyst A + R = 4-Cl-C_6H_4 (6c)	95	77 (*S*)
8	Catalyst A + R = 4-NO_2-C_6H_4 (6d)	92	74 (*S*)
9	Catalyst A + R = 2-CH_3O-C_6H_4 (6e)	97	97 (*S*)
10	SBA-15	---	---
11	MCF	---	---
12	SBA-15 + R = 2-CH_3O-C_6H_4 (6e)	---	---

[a] Reaction conditions: benzaldehyde (0.4 m.mol) with nitromethane (5.5 m.mol) in 1 ml of absolute ethanol for 40h at room temperature. [b] Different mesoporous materials, catalyst **A/B** and chiral additive (imine) were used. [c] Isolated yield by column chromatography. [d] Determined by HPLC using chiralcel OD column 85:15, *n*-hexane:2-propanol, flow 0.8 ml/min.

More significantly, aromatic imines (**6a-6e**) were found to be effective substrates, giving with high to very high yield as well as selectivity (entries 5-9), which were previously not reported. Surprisingly, the addition of *o*-methoxybenzaldehyde (**6e**) gave greater conversion with higher selectivity as compare to other substituted additives (entry 9). Although the role of chiral additive (**6a-6e**) is indistinct, there notable acceleration effects with enhancement of enantioselectivity were found with **6e** in asymmetric nitroaldol reaction. While using chiral imine as additive with catalyst **A**, the reactivity and enantioselectivity notably increases. The reaction was more suitable only with chiral imine **6e**, which was converted to the corresponding adduct in >97% yield with 97% ee (entry 9). We next examined blank experiment using unmodified SBA-15 and MCF as catalyst (Table 5.1). Both of the mesoporous materials are not showing any catalytic activity (entries 10,11). To find the role of chiral imines, we have used SBA-15 and chiral imine **6e,** as catalyst, for asymmetric nitroaldol reaction of benzaldehyde (entry 12). But we did not found any activity of chiral imine alone.

Consequently, we studied the solvent engaged significantly on both the yields and enantioselectivity of the nitroaldol reaction (Table 5.2). Under optimal reaction condition, a variety of solvents *viz.,* toluene, tetrahydrofuran (THF), diethylether (DEE), dichloromethane (DCM) and ethanol were inspected (entries 1-5). The experimental results clearly give the priority of ethanol as solvent in terms of yield and enantioselectivity (entry 5).

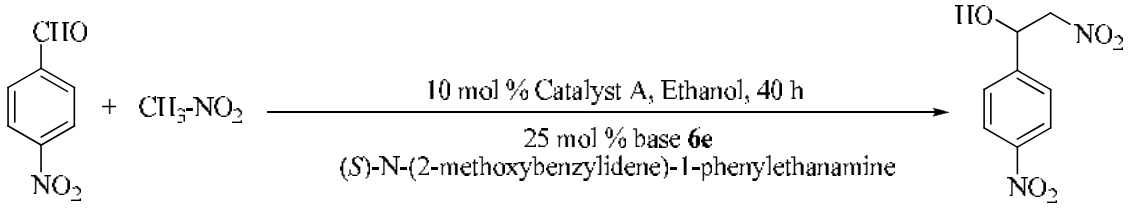
Table 5.2 Effect of Solvent on Asymmetric Nitroaldol Reaction of Benzaldehyde[a]



Entry	Solvent	Yield[b] (%)	ee[c] (%)
1	Toluene	98	19
2	Tetrahydrofuran (THF)	92	28
3	Diethylether (DEE)	95	10
4	Dichloromethane (DCM)	93	22
5	Ethanol	97	97

[a] The reaction was carried with benzaldehyde (0.4 m.mol), nitromethane (5.5 m.mol), 10 mol % of catalyst **A** with 25 mol % of base **6e** in 1 ml of solvent for 40h. [b] Isolated yield by column chromatography. [c] Determined by HPLC using chiralcel OD column, 85:15, *n*-hexane:2-propanol, flow 0.8 ml/min.

Table 5.3 Temperature Effect of Asymmetric Nitroaldol Reaction of 4-Nitro Benzaldehyde[a]



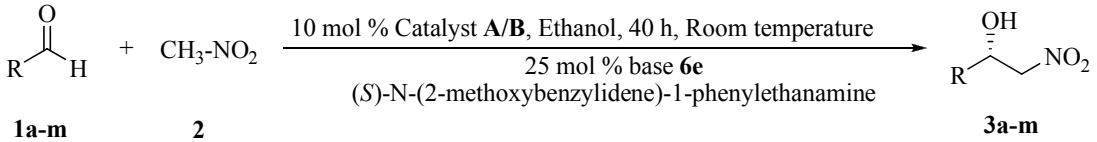
Entry	Temperature	Yield (%)	ee[c] (%)
1	-10◦C	26	38
2	0◦C	40	18
3	0◦C addition then room temperature[b]	60	20
4	Room temperature	62	64

[a] The reaction was carried with *p* -Nitro benzaldehyde (0.4 m.mol), nitromethane (5.5 m.mol), 10 mol % of catalyst **A** with 25 mol % of base **6e** in 1 ml of absolute for 40h. [b] Addition of the reactants were carried out at 0◦C and then reaction mass was stirred at room temperature. [c] Determined by HPLC using chiralcel OD column, 85:15, *n*-hexane:2-propanol, flow 0.8 ml/min.

Nitro aldol reaction can be further studied by lowering the temperature using *p*-nitrobenzaldehyde as substrate. In one case, mixing the reactants and stirring the resulting mass at -10 °C for 40 hrs performed the reaction in Table 5.3 (entry 1). Catalysis separation afforded the corresponding nitro alcohol adduct in 26% yield and 18% ee. When the same reaction was carried out at 0 °C, major rate acceleration was noted with reduction in the enantiomeric excess. (entries 2,3). The reaction is more suitable at room temperature giving rise in conversion as well as in enantiomeric excess is concern (entry 4).

Under the optimal reaction conditions in hand, a selection of different aromatic, aliphatic, α,β-unsaturated aldehydes and alicyclic aldehydes were successfully used as starting material, with the nitroaldol reaction giving the corresponding nitroaldol product in lower to good yields with excellent enantioselectivity as shown by the results compiled in Table 5.4. In general, excellent enantiomeric excesses (5-99% ee) are observed at room temperature for aromatic aldehydes having either electron-withdrawing or electron-donating groups. Under 10 mol % catalyst loading with 25 mol % base addition, range of aldehydes were easily converted to nitro alcohols at room temperature, in most of the cases, the (*S*)-enriched product we found by using catalyst **A** (entries 1-16). For simple benzaldehyde, over 97% ee was obtained when the reaction was carried out at room temperature (entry 1). *o, m* and *p*-methoxybenzaldehyde were converted to the corresponding adduct in 70-92% yield with 69-95% ees (entries 3-5). Moreover alicyclic cyclohexanal was smoothly converted to nitroaldols in good yields with quite high ee (entry 16). Typically, linear and branched aliphatic aldehydes are also suitable substrates, providing nitro alcohol products in good yields and enantioselectivity with reverse configuration. Surprisingly, very different results were obtained in entries 17 and 18.

Table 5.4 Enantioselective Nitroaldol Reaction Catalyzed by Cu(II) Complex of Chiral Amino Alcohol (Catalyst A[a]/B[b])



1a-m **2** **3a-m**

R	C_6H_5	**R**	4-F-C_6H_4	**R**	*c*-C_6H_{11}
R	2-CH_3O-C_6H_4	**R**	4-Br-C_6H_4	**R**	C_6H_5-CH=C(CH_3)
R	3-CH_3O-C_6H_4	**R**	4-CF_3-C_6H_4	**R**	*n*-C_5H_{11}
R	4-CH_3O-C_6H_4	**R**	4-CH_3-C_6H_4		
R	4-Cl-C_6H_4	**R**	4-NO_2-C_6H_4		

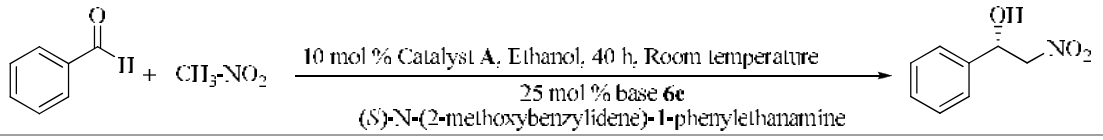
Entry	R	Product (3)	Yield[e] (%)	ee[f] (%)
1 (2)	C_6H_5	3a	97(94)	97(96)(*S*)
3	2-CH_3O-C_6H_4	3b	70	69 (*S*)
4	3-CH_3O-C_6H_4	3c	92	94 (*S*)
5 (6)	4-CH_3O-C_6H_4	3d	85(83)	95(89) (*S*)
7 (8)	4-Cl-C_6H_4	3e	72 (78)	76 (80)(*S*)
9	4-F-C_6H_4	3f	68	30 (*S*)
10	4-Br-C_6H_4	3g	73	99 (*S*)
11 (12)	4-F_3C-C_6H_4	3h	72 (75)	98(78) (*S*)
13 (14)	4-CH_3-C_6H_4	3i	85(86)	5(9) (*S*)
15	4-NO_2-C_6H_4	3j	62	64 (*S*)
16	*c*-C_6H_{11}[c]	3k	93	89 (*S*)
17	C_6H_5-CH=C(CH_3)	3l	76	98 (*R*)
18	*n*-C_5H_{11}[d]	3m	61	92 (*R*)

[a] Reaction conditions: aldehydes (0.4 m.mol), nitromethane (5.5 m.mol), 10 mol % of catalyst **A/B** with 25 mol % of base **6e** in 1 ml of solvent for 40h.[b] value given in parenthesis are for Catalyst **B** [c] Cyclohexyl group. [d] Normal pentyl group. [e] Yield of the corresponding isolated products **3** based on compounds **1.** [f] Determined by HPLC using chiral OD, OD-H and AD columns, the absolute configuration of the products was assigned by comparison with the literature value.

The experimental results in Table 5.4 show the effectiveness of the catalyst **A** [23]. To study the catalytic activity, we have synthesized MCF supported copper complex of chiral amino alcohol as catalyst **B.** In Table 5.4 as parenthesis study, we have used catalyst **B** with chiral additive **6e** under selected reaction condition in asymmetric nitroaldol reaction. Several aldehydes such as benzaldehyde, 4-methoxy benzaldehyde, 4-chlorobenzaldehyde, 4-methylbenzaldehyde and 4-triflouromethylbenzaldehyde have been used for asymmetric nitroaldol reaction and found similar to higher activity and enantioselectivity (Table 5.4, entries 2, 6, 8, 12, 14).

An attempt to reuse the catalytic system was made for the reaction with benzaldehyde, after the product was filtered from the reaction mass and washed with Soxhlet-extraction using toluene. Experiments, with 10 mol% of catalyst **A** and 25 mol% chiral imine **6e**, were repeated four times and a small drop in yield was observed after the fourth repetition (first reuse 97%, second reuse 97% and third reuse 96% fourth reuse 95%) (Table 5.5).

Table 5.5 Catalyst Recycling Data of Enantioselective Nitroaldol Reaction of Catalyst A[a]



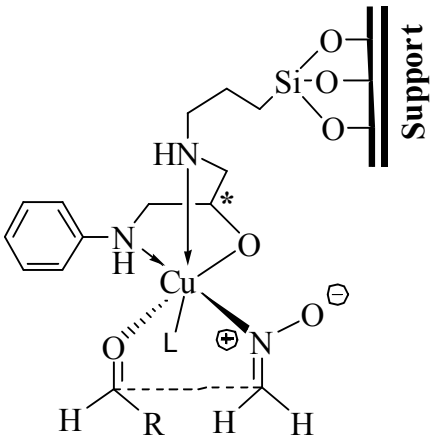
Entry	Catalytic run	Yield (%)	ee (%)
1	1	97	97
2	2	97	97
3	3	96	97
4	4	95	96

[a] The reaction was carried with benzaldehyde (0.4 m.mol), nitromethane (5.5 m.mol), 10 mol % of catalyst **A** with 25 mol % of base **6e** in 1 ml of absolute ethanol for 40h.

Nevertheless, the enantioselectivity of the reaction was preserved (96-97% ee). The recovered catalyst **A** was reused and only a slight decrease of the chemical yields as well as enantioselectivity was observed.

5.3.3. Proposed Mechanism for Asymmetric Henry Reaction.

The proposed mechanism (Figure 5.21) is combination of investigational remarks and description for absolute configuration of some selected products for heterogeneous asymmetric Henry reaction. Here, the silica modified chiral complex that binds the two reaction partners, at the same time, should position the nucleophile, vertical to the ligand phase. While the electrophile, for maximum activation, should be positioned in one of the more Lewis acidic equatorial site in the ligand plane which is in agreement with the reported steric and electronic consideration [26].



L = $OCOCH_3$

Figure 5.21 Proposed Mechanisum for the Henry reaction

5.4. CONCLUSION

In conclusion, we have designed and developed a new valuable multi-tasked chiral copper complex **A/B** and different chiral imine for asymmetric nitroaldol reaction. Ranges of aldehydes (aliphatic, aromatic, alicyclic and α,β-unsaturated aldehydes) were acceptable substrates giving moderate to good enantioselectivity (up to 99% ee) at mild reaction condition (10 mol% catalyst loading, room temperature). All these points contribute to the practicality and usefulness of this catalytic system. The study of the scope of this reaction, the preparation of new ligands and their application to the nitroaldol reaction is currently in progress.

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EXPERIMENTAL METHODS

Enantiomeric excess (ee) and optical purity of products were determined by using programmable high performance liquid chromatography system (HPLC, CLASS-VP 10A, 20 μL injection loop, PDA detector, Shimadzu) using chiral DAICEL columns OD, AD, OD-H and OJ. Gas chromatography (GC 14B, Shimadzu) and automatic polarimeter (Digipol-781, Rudolph Instrument, USA) also used to determine the chiral purity as well as selectivity. Microanalysis of the products was carried out by a CHN analyzer (Perkin-Elmer Series II, 2400). ^{1}H & ^{13}C, solid state ^{13}C cross polarized magic angle spinning (CP-MAS) NMR spectra were recorded on 200 and 50MHz spectrometer (Bruker F113V) and on 500 and 125MHz Spectrometer (Bruker 500 ultrashield), FTIR spectra were completed in KBr/nujol mull (Perkin-Elmer spectrum GX spectrophotometer). Powder X-ray diffraction (PXRD) analyses of the samples were accomplished by a Phillips X'pert MPD diffractometer in 2 theta range (1.5–10) at scan speed of 0.4º s^{-1}. BET surface area was determined from N_2-sorption data measured at 77K using volumetric adsorption set up (Micromeritics ASAP-2010, USA). The BJH pore diameter of the silica samples was determined from the desorption branch of nitrogen adsorption isotherm employing the Barret-Joyner-Halenda (BJH) model. Thermo-gravimetric measurements and microstructure evaluation of these samples were carried out on Mettler Toledo (TGA/SDTA 851e) instrument and scanning electron microscope (SEM) (LEO 1430VP) and transmission electron microscope (TEM, Techai 20, Phillips, The Netherlands). The Cu estimation of complex was determined on an inductive coupled plasma spectrometer (ICP, PerkinElmer, USA; model ICP optima 3300 RL). Based on %C, surface coverage calculation of chemically bonded phase was carried out using Berendsen–De Galan

equation. Splitting patterns were reported as s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad.

Column chromatography

Slurry of 'Chiral stationary phase' in *n*-hexane and 2- propanol (9:1) was packed in a 260 mm × 16 mm glass column using medium pressure (0.5 kp/cm^2) of nitrogen at room temperature. The analyte solution in 2-propanol/*n*-hexane (1:1) was loaded on thus packed column that was equilibrated for 1 h. Each fraction of the size 4ml was collected at the pressure mentioned above, which were subjected to HPLC analysis using an appropriate chiral column.

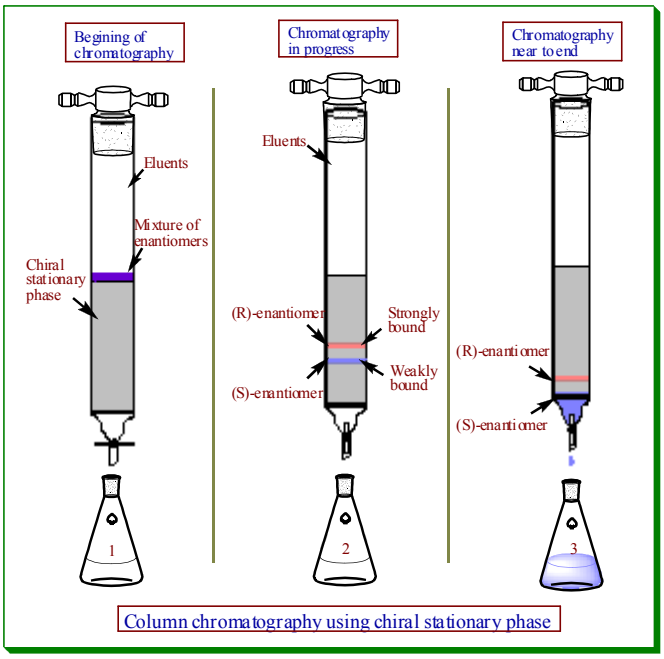

Figure 1 Separation of racemic mixture using chiral stationary phase.

All the supported catalysts were washed thoroughly with ethanol and toluene on a Soxhlet extractor until the washings become colorless to washout the chiral copper complex from surface of the inorganic support.

CONCLUSION AND FUTURE

OUTLOOK

In pharmaceutical industry, majority of commercially available drugs are both synthetic and chiral. A large number of chiral drugs are still marketed as racemic mixtures. Discovery of truly efficient methods to achieve desired compound in enantiomerically pure form has been a major challenge for chemists in both academia and industry. Optically active materials can be obtained by making use of chiral pool, separation of racemates and asymmetric synthesis. Although the role of chiral pool in the production of chiral compounds in their high optical purity is still very popular in industry, its scope is limited as not all kind of compounds in both enantiomeric forms can be obtained through this approach. Separation of racemate is one of the most popular methods used in the industry however, the limiting factors of this approach are; (*a*) maximum theoretical yield is 50%, (*b*) treatment cost of the 50% undesirable enantiomer obtained as byproduct and (*c*) in general high processing cost due to the use of often non-recoverable costly resolving agents. In case of asymmetric synthesis for obvious reasons asymmetric catalysis most attractive in terms of built in flexibility of this approach where a chiral metal complexes can be designed as per the demand of the particular organic transformations. The asymmetric catalysis is still dominated by homogeneous asymmetric catalysis and it has made a great progress in the last few decades. However, a large number of very attractive homogeneous asymmetric catalysis systems are knocking the doors of industries and are denied entry due to the reasons: (*i*) high cost of ligands often more expensive that precious metals, (*ii*) tedious catalyst recovery for its reuse and (*iii*) chances of catalyst/metal contamination in the final product which is a big no-no in pharmaceutical industry. To overcome these issues the most logical approach is to "*heterogenize*" the homogeneous catalyst, by means of immobilization, anchoring, or encapsulation on an inorganic or organic solid support. In the present thesis, I have taken up the

problem of developing recyclable resolving agent and recyclable chiral catalyst for asymmetric nitroaldol reaction. While working on asymmetric catalysis we came across the phenomenon of enantiomer self-disproportionation (ESD) which we judicially employed for the separation of a non-racemic mixture of enantiomer (often in asymmetric catalysis the product are obtained in non-racemic form) without the use of any external element of chirality.

Accordingly in this thesis, we have synthesized (*S*)-amino alcohol-silica as a chiral selector for the chromatographic separation of mandelic acid, 2,2'-dihydroxy-1,1'-binaphthalene (BINOL), cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid. Excellent chiral separation (ee, >99%) was obtained in the case of mandelic acid. This supported ligand when complexed with copper was used as material for chiral ligand exchange chromatography (CLEC) to resolve racemic mandelic acid, BINOL and diethyl tartrate.

We have also worked out our findings on the phenomenon of enantiomer self-disproportionation of commercially important chiral compounds *viz.,* mandelic acid and stilbene oxide with two achiral stationary phases namely regular silica gel and ordered mesoporous silica M41S using different solvents. Mandelic acid was selected as a model candidate for compounds having extensive "*hydrogen bonding"*, while stilbene oxide was selected for compounds having nonbonding interactions mostly through phenyl ring related *"π–π interactions".* In both the cases, initial fractions obtained were more racemic than the original ee of the sample (76.1%). We achieved ee > 99% of (*R*)-(-)-mandelic acid in some of the fractions using enantiomer self-disproportionation technique.

Further, we have studied the heterogeneous asymmetric nitroaldol reaction using as synthesized copper complexes of (*S*)-amino alcohol on supported silicas (the

one we used in chiral ligand exchange chromatography) as catalyst. The solid chiral Cu(II) complex of amino alcohol in presence of some chiral additives showed excellent performance in the nitroaldol reaction, providing different nitroaldols with moderate to good enantioselectivities (ee > 99%).

Based on the analysis of the present work it is felt that the following could be undertaken in future to strengthen and expand the scope of the work:

- To synthesize chiral stationary phases for their use in HPLC based on these materials.
- To prepare large pore size silica material of suitable sizes and modify them with a chiral auxiliary which can find application in the separation of various other structural groups and bigger sized racemic molecules besides the one used in the present thesis.
- To prepare nano-crystalline materials for chromatographic separation of racemates and as support for heterogeneous catalyst.
- The phenomenon of "enantiomer self-disproportionation" should further be extended to non-racemic compounds having various other structural types to have deeper understanding of this truly remarkable phenomenon.
- To study the scope of asymmetric nitroaldol reaction, the preparation of new ligands, additives, solid support and their application to the reaction.
- These results should encourage for further research with metal complexes in other important asymmetric transformation under heterogeneous reaction conditions. Moreover, the design and preparation heterogeneous catalyst system for more selective and highly enantio-pure chiral compounds.

PATENTS/PUBLICATIONS / SYMPOSIA / CONFERENCE / AWARDS

A. PATENTS

1. **U.S. patent Application No. PCT WO/2008/038300**.
   S. H. R. Abdi, R. I. Kureshy, N. H. Khan**, Vishal J. Mayani,** Santosh Agrawal, R. V. Jasra
   Preparation of Organic-Inorganic hybrid chiral Sorbent and process for the preparation thereof.

2. **U.S. patent (Under preparation).**
   S. H. R. Abdi, R. I. Kureshy, N. H. Khan**, Vishal J. Mayani,** H. C. Bajaj
   Heterogeneous hybrid material for asymmetric nitroaldol reaction.

B. RESEARCH PUBLICATIONS:

1. **Tetrahedron Letters 47 (2006) 5277–5279.**
   Rukhsana I. Kureshy, Surendra Singh, Noor-ul H. Khan, Sayed H. R. Abdi, Santosh Agrawal, **Vishal J. Mayani** and Raksh V. Jasra.
   Microwave-assisted asymmetric ring opening of meso-epoxides with aromatic amines catalyzed by a Ti-S-(-)-BINOL complex.

2. **European Journal of Organic Chemistry (2006) 3175–3180.**
   Noor-ul H. Khan, Santosh Agrawal, Rukhsana I. Kureshy, Sayed H. R. Abdi, **Vishal J. Mayani**, and Raksh V. Jasra.
   Asymmetric Synthesis of *O*-Acetyl cyanohydrins by Reaction of Aldehydes with NaCN/KCN Catalyzed by Recyclable Chiral Dimeric Titanium (IV)/Vanadium (V) Salen Complexes.

3. **Journal of Chromatography A, 1135 (2006) 186-193.**
   Vishal J. Mayani, S. H. R. Abdi, R. I. Kureshy, N. H. Khan, Santosh Agrawal, R. V. Jasra.
   Synthesis and characterization of (*S*)-amino alcohol modified MCM-41 as effective material for the chiral resolution of racemic compounds.

4. **Tetrahedron Asymmetry, 17 (2006) 2659–2666.**
   Noor-ul H. Khan, Santosh Agrawal, Rukhsana I. Kureshy, Sayed H. R. Abdi, **Vishal J. Mayani** and Raksh V. Jasra.
   Asymmetric Addition of Trimethysilyl Cyanide to Aldehydes Promoted by Chiral Polymeric Vanadium(V) Salen Complex as an Efficient and Recyclable Catalyst.

5. **Journal of Molecular Catalysis A: Chemical, 264 (2007) 140-145.**
   Noor-ul H. Khan, Santosh Agrawal, Rukhsana I. Kureshy, Sayed H. R. Abdi, **Vishal J. Mayani,** Raksh V. Jasra.

Easily Recoverable Polymeric V(V) Salen Complex for the Enantioselective *O*-Acetyl Cyanation of Aldehydes.

6. **Chirality, 21 (2009) 255–261**
   Vishal J. Mayani, S. H. R. Abdi, R. I. Kureshy, N. H. Khan, Santosh Agrawal, R. V. Jasra.
   Enantiomer self-disproportionation of chiral compounds on achiral ordered mesoporous silica M41S and regular silica gel as a stationary phase.

7. **Journal of Chromatography A, 1191 (2008) 223-230.**
   Vishal J. Mayani, S. H. R. Abdi, R. I. Kureshy, N. H. Khan, Santosh Agrawal, R. V. Jasra.
   Synthesis and characterization of mesoporous silica modified with chiral auxiliaries for their potential application as chiral stationary phase.

8. **Journal of Organic Chemistry, (under communication) 2009.**
   Vishal J. Mayani, Sayed H. R. Abdi*, Noor-ul H. Khan, Rukhasana I. Kureshy and Hari C. Bajaj.
   Heterogeneous Material for Catalytic Asymmetric Nitroaldol Reaction.

9. **Catalysis survey from Asia (Communicated) (2009).**
   S. H. R. Abdi, R. I. Kureshy, N. H. Khan, **Vishal J. Mayani,** H. C. Bajaj
   Asymmetric catalysis in epoxide ring opening and C-C bond formation reactions.

10. **Manuscript under preparation**
    Vishal J. Mayani, Sayed H. R. Abdi*, Noor-ul H. Khan, Rukhasana I. Kureshy and Hari C. Bajaj.
    Enantiomer self-disproportionation of non-fluorinated organic compounds using achiral silica gel chromatography

C. INTERNATIONAL CONFERENCE/ SYMPOSIUM:

1. A paper entitled **"Phenomenon of self-disproportionation of enantiomers in non-racemic mixtures of non-fluorinated organic compounds on achiral silica gel chromatography"** has been accepted (invited) in 238th ACS National Meeting & Exposition, organized by American chemicals society, Washington, DC, USA on August 16-20, 2009.

D. NATIONAL CONFERENCE / SYMPOSIUM:

1. A poster entitled **"Chiral Mn(II) salen covalently bonded to MCM-41 as efficient catalyst for epoxidation of non-functionalized alkene."** has been presented in 17th National Symposium on Catalysis organized by catalysis Society of India & CSMCRI, Bhavnagar (India) during 18-20th January, 2005.

2. A poster entitled **"Recyclable Dimeric Ti (IV) (Salen) Complex-Catalyzed Asymmetric Synthesis of *O*-Acetylcyanohydrin using NaCN"** has been presented in XIth symposium on Modern trends in inorganic chemistry organized by Indian Institute of Technology, New Delhi (India) during 8-10th December, 2005.

3. A poster entitled **"Asymmetric synthesis of *O*-acetyl cyanohydrins from NaCN/KCN, Ac_2O and aldehydes catalyzed by recyclable dimeric salen V(V) complex."** has been presented in 4th All Gujarat Research Scholars' Meet (FAGRSM) organized by Indian Chemical society Vadodara Chapter held at M. S. University Vadodara on 22nd February, 2006.

4. A poster entitled **"Development of organic-inorganic hybrid chiral sorbent for resolution of racemic compounds."** has been presented in 18th National Symposium on Catalysis organized by Catalysis Society of India & IIP, Dehradun (India) during 16-18th April, 2007.

5. A paper entitled **"Chiral polymeric vanadium (V) salen complex as efficient and recyclable catalyst for asymmetric addition of trimethyl silyl cyanide to aldehyde".** has been presented in 18th National Symposium on Catalysis organized by catalysis Society of India & IIP, Dehradun (India) during 16-18th April, 2007.

6. A poster entitled **"Self-disproportionation of chiral molecules**

on totally achiral M41S and silica gel based stationary phase chromatography" has been presented in 13th National workshop on catalysis (CAT WORKSHOP 2008) organized by Catalysis Society of India & IMMT, Bhubaneswar (India) during 18-20th February 2008.

7. A paper entitled **"Enantiomer self-disproportionation of non-racemic mixtures on totally achiral MCM-41 and standard silica gel stationary phase"** has been presented in XXII Gujarat Science Congress (GSC 2008) organized by Catalysis Society of India & Bhavnagar university (India) on 9th March 2008.

8. A paper entitled **"Synthesis and application of multi-functional material"** has been presented in 19th National Symposium on Catalysis (CATSYMP-19) organized by National Chemical Laboratory, Pune (India), under the auspices of Catalysis Society of India, 18-21 January, 2009.

9. A poster entitled **"Silica modified with chiral auxiliaries for their potential application as chiral stationary phase"** has been presented in 19th National Symposium on Catalysis (CATSYMP-19) organized by National Chemical Laboratory, Pune (India), under the auspices of Catalysis Society of India, 18-21 January, 2009.

E. AWARDS:

1. **Senior Research Fellow-2008** (Council of Scientific and Industrial Research, India).

2. **Hindustan Platinum award – 2005** Best poster presentation during 17th National Conference catalysis society of India held at CSMCRI Bhavnagar on 18-20th February 2005.

3. **Hindustan Platinum award – 2008** Best poster presentation during 13th National Workshop, Catalysis society of India held at IMMT Bhubaneswar on 18-20th February 2008.

4. **Best oral poster presentation award** during XXII Gujarat Science Congress (GSC-2008), Indian Chemical society held at Bhavnagar University, Bhavnagar on 9th March 2008.

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(57) Abstract: The present invention provides an organic-inorganic hybrid chiral sorbent for chiral resolution of various racemic compounds viz. racemic mandelic acid, 2- phenyl propionic acid, diethyl tartrate, 2,2'-dihydroxy-1,1 '-binaphthalene (BINOL) and cyano chromene oxide with excellent chiral separation (enantiomeric excess, 99 %) in case of mandelic acid under medium pressure column chromatography. These optically pure enantiomers find applications as intermediates in pharmaceutical industries.

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Enantiomer Self-Disproportionation of Chiral Compounds on Achiral Ordered Mesoporous Silica M41S and Regular Silica Gel as a Stationary Phase

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ABSTRACT Chromatographic behavior of nonracemic mixtures, viz., mandelic acid and stilbene oxide as analytes has been studied in detailed by enantiomer self-disproportionation on achiral ordered mesoporous material M41S and regular silica gel as stationary phases. Enantiomer self-disproportionation gave enhanced separation of analytes. The extent and magnitude of enantiomer self-disproportionation is dependent on the optical purity of the starting non-racemic molecules, presence of intermolecular hydrogen bonding/π–π interactions and the nature of eluents used. The present study and previous literature data suggest that percentage ee of a nonracemic mixture needs to be determined before any chromatographic purification is taken up as enantiomer self-disproportionation phenomenon could occur during purification. The data show that enantiomer self-disproportionation of nonracemic mixtures can be harnessed for its enantioenrichment on inexpensive achiral stationary phases. *Chirality 21:255–261, 2009.* © 2008 Wiley-Liss, Inc.

KEY WORDS: enantiomer self-disproportionation; achiral phase chromatography; M41S; mandelic acid; stilbene oxide; ESD-test

INTRODUCTION

The optically pure compounds have paramount importance in pharmaceuticals, agrochemicals, fine chemicals, and biochemical research as enantiomers express themselves differently in biological systems. Presently optically active compounds in their high optical purity are mainly obtained through (a) asymmetric synthesis which includes the use of a suitable chiral catalyst, (b) by separation of enantiomers from respective racemic mixtures with the use of various chemical/analytical techniques.[1–5] Application of chiral stationary phases (CSPs) both at analytical and preparative scale is a rapidly growing area to affect the separations of enantiomers in liquid chromatography.[6] Various chiral selectors are already know for CSPs for separations of enantiomers in literature.[7–10] Recently, we have reported the use of M41S modified with chiral (*S*)-amino alcohol as CSPs to separate various racemic compounds. Excellent chiral separation was achieved in the case of racemic mandelic acid (ee, 99%) on a glass column filled with thus modified M41S at medium pressure.[11]

Recently, Soloshonok and coworkers[12–14] has reported a very unusual phenomenon of separation of enantiomer by enantiomer self-disproportionation on a regular silica gel as a stationary phase. He attributed this phenomenon to two distinct modes of intermolecular interaction, i.e., between the enantiomers of a chiral compound. These are homochiral (*R:R*) and heterochiral (*R:S*) associations, which are present in nonracemic solutions and are largely responsible for nonlinear behavior of optical rotation,[15,16] UV absorbance,[17] and in asymmetric catalysis.[18–21] These associations in a solution, however, create hot spots of *internal chirality* and thus can be exploited for the optical purification/separation of nonracemic mixtures with the use of relatively inexpensive achiral phase chromatography.[22,23] The extent and nature of homochiral and heterochiral associations, though not fully understood, depend on the structural features of the chiral compounds and nature of the solvent. While performing chromatography of such solutions, the nature of achiral stationary phase can also affect the elution pattern. We present, here, our findings on the phenomenon of enantiomer self disproportionation of commercially important chiral compounds as analyte, viz., mandelic acid and stilbene oxide using different solvents with two achiral stationary phases namely regular silica gel and ordered mesoporous silica M41S. While regular silica gel is conventionally used in chromatography, we have earlier reported the use M41S in chromatography. M41S is a thermally stable, mesoporous, and semi-

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Synthesis and characterization of (*S*)-amino alcohol modified M41S as effective material for the enantioseparation of racemic compounds

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Abstract

A new chiral stationary phase (CSP) was synthesized based on (*S*)-1-anilino-3-propyl-2-propanol covalently bonded to the mesoporous semi-crystalline material M41S. Direct semipreparative enantioseparation of mandelic acid could be achieved using medium pressure chromatography. Partly separated could also be the enantiomers of 2,2′-dihydroxy-1,1′-binaphthalene, cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid. The characterization of CSP was accomplished by microanalysis, cross polarized magic angle spinning (CP-MAS) ^{13}C NMR, powder X-ray diffraction (XRD), FTIR, thermo-gravimetric analysis (TGA), N_2 adsorption–desorption isotherm, scanning electron microscopy (SEM) and solid reflectance UV–vis spectroscopy. Furthermore the stability of CSP was satisfactory as it could withstand three washing and reuse experiments of enantioseparation of mandelic acid without loss in its performance.

Keywords: Enantioseparation; Racemic mandelic acid; 2,2′-dihydroxy-1,1′-binaphthalene; Cyanochromene oxide; Diethyl tartrate; 2-Phenyl propionic acid; Amino alcohol; M41S

1. Introduction

Separation of chiral molecules is required in many areas of research. As enzymes and other biological receptor molecules possess chiral centers, enantiomers of a racemic compound may interact with them in a different manner. Consequently, two enantiomers of a racemic compound have different pharmacological activities in many instances. In order to discern these differing effects, the biological activity of each enantiomer [1,2] needs to be studied separately. This has contributed significantly to the requirement of enantiomerically pure compounds particularly in pharmaceutical industry [3,4] and thereby the need to have chiral chromatography [5].

Attempts have been made in the past for the development of chiral stationary phases using β-cyclodextrin [6,7] notably DAICEL phases [8,9], crown ether [10,11], antibiotics [12] on silicas for HPLC [10–14], MPLC [15], GC [16,17], capillary electrophoresis [18–22] and chiral ligand exchange chromatography (CLEC) [23–27].

Mesoporous semi-crystalline materials (M41S) possess ordered pore structure, a large pore volume and high surface area besides thermal stability and mild acidity. These attributes make these materials a promising candidate for use in chromatography [28]. In the present study, the (*S*)-amino alcohol-silica **1** was synthesized using mesoporous silica M41S. This was achieved by the interaction of (*S*)-epichlorohydrin **2** with 3-aminopropyl triethoxysilane **3**, which was then immobilized on M41S followed by epoxide ring opening with aniline (Fig. 1). Thus, synthesized (*S*)-amino alcohol-silica **1** was used as a chiral selector for the chromatographic separation of mandelic acid, 2,2′-dihydroxy-1,1′-binaphthalene, cyanochromene oxide, diethyl tartrate and 2-phenyl propionic acid. Excellent chiral separation (ee, 99%) was obtained in case of mandelic acid. (*S*)-amino alcohol-silica **1** worked very well up to three repeat experiments without loss in separation performance. To the best of our knowledge, this is the first report concerning the use of (*S*)-amino alcohol-silica **1** as column packing material to separate different racemates.

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Synthesis and characterization of mesoporous silica modified with chiral auxiliaries for their potential application as chiral stationary phase

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Available online 16 February 2008

Abstract

Novel chiral stationary phase (CSP) based on chiral aminoalcohol immobilized on ordered mesoporous silica SBA-15 **1a** and standard silica **1b** and their copper complexes **1a′** and **1b′**, respectively, was synthesized as potential material for chiral ligand exchange chromatography (CLEC). Microanalysis, inductively coupled plasma spectroscopy (ICP), thermo-gravimetric analysis (TGA), cross polarized magic angle spinning (CP-MAS) ^{13}C NMR, Powder X-ray diffraction (PXRD), FTIR, N_2 adsorption isotherm, scanning electron microscopy (SEM), transmitted electron microscope (TEM) and solid reflectance UV–vis spectroscopy were used to characterize these materials. All the chiral stationary phases thus synthesized were used for the separation of different racemic compounds such as mandelic acid, 2,2′-dihydroxy-1,1′-binaphthalene BINOL) and diethyl tartrate by simple medium-pressure column chromatography. Successful enantio-separation of racemic mandelic acid was achieved with all the stationary phases but **1a** and **1b** gave slightly better resolution than their copper complexes **1a′** and **1b′**. Remarkably these materials are stable under the given experimental conditions and can be used repeatedly for several cycles of enantioresolution. It was observed that the porosity and surface area of the stationary phase play an important role in the chiral separation.

Keywords: Chiral ligand exchange chromatography; Chiral stationary phase; Amino alcohol; Copper complex; SBA-15; Standard silica; Mandelic acid; 2,2′-Dihydroxy-1,1′-binaphthalene (BINOL); Diethyl tartrate

1. Introduction

Chirality is a fundamental feature of many natural and bioactive compounds. During the last two decades there has been a steep increase in the number of chiral pharmaceuticals sold in their enantiomerically pure form rather than their racemic form [1–3]. This increase is attributed to the fundamental understanding of chiral molecules where enantiomers have shown different pharmacological activity or toxicity. Owing to this behavior of chiral molecules, it has now become mandatory to resolve their all possible enantiomers in their high optical purity and screen separately their *in vivo* activity for their application in pharmaceutical, medicinal, and other biological sciences. Therefore, separation of enantiomers has become an extremely important and challenging unit operation in the area of asymmetric synthesis. Some of the recent work on chiral resolution include, high performance liquid chromatography (HPLC) [4–8], chiral ligand exchange chromatography (CLEC) [9–12], M41S and SBA-15 based research [13–18], supercritical fluid chromatography (SCF) [19,20], steady state recycling (SSR) [21], extractant impregnated resign (EIR) [22], NMR spectroscopy [23,24], simulated moving bed (SMB) [4,25,26], enantioselective inclusion complexation (EIC) [27], nanoaqueuos capillary electrophoresis [28], self disproportionation of enantiomers (SDC) [29–30]. However, enantioselective chromatography employing chiral stationary phases (CSPs) is a major technique for the separation of enantiomers. There is an incremental growth in the development of new CSPs with focus on better enantioselectivity, stability and capacity for their potential application in industry. Besides, CLEC is also emerging as a potent technique for the resolution of racemic amino acids, peptides and hydroxyl acids [9]. In this context some of the CSPs prepared by silica modified with chiral chelating agents can be easily converted into their metal complex counter parts, which in turn can be used as material for CLEC. The present work primarily deals with the preparation of CSP and CLEC for the resolution of mandelic acid as model compound to test the efficacy of thus developed new CSP and CLEC. Importantly, (*R*)-mandelic acid is a key inter-

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FULL PAPER

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Asymmetric Synthesis of *O*-Acetylcyanohydrins by Reaction of Aldehydes with NaCN/KCN Catalyzed by Recyclable Chiral Dimeric Titanium(IV)/Vanadium(V) Salen Complexes

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Keywords: Cyanohydrins / Catalysis / Dimeric Ti^{IV}/V^{V} salen complexes

The efficient catalytic asymmetric addition of an inexpensive and nonvolatile cyanide source such as NaCN or KCN and acetic anhydride to various aldehydes was catalyzed by recyclable dimeric Ti^{IV} and V^{V} chiral salen complexes at –20 °C. High chiral induction (96% *ee*) in the *O*-acetylcyanohydrin was obtained in the case of 2-fluorobenzaldehyde, and the results achieved with sodium cyanide are quite comparable to those with potassium cyanide. The chiral V^{V} salen complex was found to be the most efficient recyclable catalyst reported so far in the literature, and was better than the Ti^{IV} salen system. Both the catalysts were recovered after the first use and recycled effectively four times.

Introduction

Chiral cyanohydrins are versatile building blocks for pharmaceuticals, agrochemicals and specialty materials bearing optically active multifunctional groups such as amino alcohols, hydroxy acids, and amino acids.[1,2] A number of synthetic methods have been reported for the synthesis of chiral cyanohydrins employing enzymes,[3] synthetic peptides,[4] organocatalysts[5] and metal complexes,[6–11] the latter being the most widely used over the last decades.[6–11] Most of these hydrocyanation reactions utilized trimethylsilyl cyanide (TMSCN) as a source of cyanide to achieve *O*-(trimethylsilyl)cyanohydrins. However, *O*-(trimethylsilyl)cyanohydrins are labile and readily undergo hydrolysis to form cyanohydrins that are prone to racemization. In addition, cyanohydrins are frequently prepared at very low temperatures while using toxic, highly volatile and expensive hydrogen cyanide or trimethylsilyl cyanide. It is therefore advantageous from synthetic and economic points of view to obtain chemically *O*-protected chiral cyanohydrins using an inexpensive and nonvolatile source of cyanide e.g., potassium cyanide or sodium cyanide, under milder conditions. In this direction, very efficient catalysts based on bimetallic Ti–O–Ti and V^{V}=O complexes were reported by Belokon et al. using potassium cyanide as a cyanide source to give high *ee* up to 92% at –42 °C.[12] As chiral ligands are expensive, the recycling of chiral catalysts is highly desirable. Recently, many efforts have been made to develop recyclable metal complexes using organic or inorganic supports[13] and ionic liquids[14] as reaction media where expensive and volatile trimethylsilyl cyanide was used as source of cyanide. We have reported the development of recyclable polymeric and dimeric chiral salen complexes for enantioselective epoxidation and hydrolytic kinetic resolution of terminal epoxides.[15] Herein we are extending the application of dimeric salen ligands by synthesizing titanium(IV) and vanadium(V) complexes **1** and **2**, respectively, for the asymmetric addition of nonvolatile and inexpensive sodium cyanide and potassium cyanide to various aldehydes in the presence of acetic anhydride at –20 °C. Quantitative yield (99%) of *O*-acetylcyanohydrin with high chiral induction (*ee* up to 96%) was achieved in the case of 2-fluorobenzaldehyde. Remarkably, with our methodology, comparable yields and chiral inductions in the products were achieved with sodium cyanide and potassium cyanide. We also observed that the V^{V} salen complex was the most efficient recyclable catalyst reported so far in the literature, and was a better catalyst than the Ti^{IV} salen complex.

Results and Discussion

The synthesis of dimeric salen ligand **1′** (Figure 1) and its precursors was carried out as described in reference.[15a] The complexation of the dimeric salen ligand (**1′**) with $V(O)SO_4 \cdot 5H_2O$ for catalyst **2** (Figure 2) was carried out in ethanol, while catalyst **1** was generated in situ by the interaction of equimolar quantities of the chiral salen ligand with $Ti(OiPr)_4$ (Figure 3). These catalysts, **1** and **2**, were characterized by ^1H NMR, optical rotation, IR, UV/Vis and CHN microanalysis (see data given in Exp. Sect.). The

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Easily recyclable polymeric V(V) salen complex for the enantioselective *O*-acetyl cyanation of aldehydes

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Abstract

A new recyclable polymeric V(V) salen complex **1** derived from poly[(*R*,*R*)-*N*,*N*′-bis-{3-(1,1-dimethylethyl)-5-methylene salicylidene} cyclohexane 1,2-diamine] with vanadyl sulphate was synthesized and characterized by microanalysis, ^{1}H NMR, optical rotation, IR, and UV–vis spectroscopy. The complex **1** was used as catalyst for asymmetric *O*-acetyl cyanation of various aldehydes with KCN as an inexpensive and non-volatile cyanide source and acetic anhydride at −20 °C. High chiral induction (ee, 96%) for *O*-acetylcyanohydrin was obtained in the case of 2-methylbenzaldehyde with added advantage of catalyst recyclability.

Keywords: Asymmetric cyanohydrin; Aldehyde; KCN; Recyclable polymeric salen; Vanadium(V)

1. Introduction

Asymmetric cyanohydrin synthesis is attracting significant interest in recent years largely due to their potential applications in pharmaceuticals, agrochemicals and other fields. Consequently, many efficient and successful synthetic methods have been developed, however, the chiral catalytic method is one of the most attractive strategy where asymmetric addition of a cyanide to the carbonyl group of aldehydes and ketones was affected with the help of a catalyst among enzymes [1], synthetic peptides [2], organocatalysts [3] or transition metal complexes [4]. Most of these hydrocyanation reactions utilize highly volatile, toxic and expensive hydrogen cyanide or trimethylsilyl cyanide (TMSCN) as a source of cyanide to achieve cyanohydrins or *O*-trimethylsilyl cyanohydrins, respectively at a very low temperature. Although less expensive cyanide sources, such as ethyl cyano formate, and benzoyl cyanide, have been used to achieve *O*-protected cyanohydrins [5–11], exploring an inexpensive and non-volatile source of cyanide under milder reaction conditions is still interesting.

In recent years, Belokon et al. have reported some very efficient catalysts based on Ti(IV) and V(V)=O complexes for asymmetric *O*-acetylcyanation of aldehydes using potassium cyanide as a cyanide source to give desired cyanohydrin with ee up to 92% at −42 °C [12]. As chiral catalysts are expensive their recycling is necessary for their commercial exploitation. Recently, many efforts have been made to develop recyclable metal complexes using organic or inorganic supports [13] and ionic liquids [14] but these methods demand major modification in the structure of the catalysts.

We have an ongoing interest in the design and development of recyclable dimeric/polymeric salen complexes [15] as catalysts for various asymmetric organic transformations, herein, we are extending the application of recyclable polymeric salen ligand [15c] for asymmetric *O*-acetyl cyanation of various aromatic aldehydes. The polymeric salen ligand was used to synthesize its vanadium(V) complex **1** that was applied as catalyst with potassium cyanide as an inexpensive and non-volatile source of cyanide to various aldehydes in the presence of acetic anhydride at −20 °C. Quantitative yield (99%) of *O*-acetylcyanohydrins with high chiral induction (ee, up to 96%) was achieved in the case of 2-methylbenzaldehyde. Besides, we have observed that the V(V) salen complex is an efficient recyclable catalyst in term of reactivity and enantioselectivity with added advantages of recyclability.

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Asymmetric addition of trimethylsilyl cyanide to aldehydes promoted by chiral polymeric vanadium(V) salen complex as an efficient and recyclable catalyst

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Abstract—The asymmetric addition of trimethylsilyl cyanide to various aldehydes catalyzed by efficient new vanadyl polymeric salen complexes having 12 repeating salen units was investigated at room temperature. An excellent yield of the trimethylsilylether of cyanohydrins (up to 98%) with high chiral induction (96%) in case of 2-methylbenzaldehyde was achieved in 18 h. The catalyst recovered four times with retention of its performance.

1. Introduction

Chiral cyanohydrins are highly versatile intermediates, which can easily be converted into a wide range of valuable classes of chiral compounds, such as α-amino acids, α-hydroxy acids, β-amino alcohols, vicinal diols, α-hydroxy ketones.[1,2] They also play an important role for the preparation of a wide range of pharmaceuticals, agrochemicals and insecticides.[3] Substantial progress has been made towards the development of efficient methods for the preparation of these compounds, with a growing emphasis on the identification of enantioselective catalytic approaches with practical potential.[4,5] Several useful cyanation reagents have been reported in the literature.[6] Among them trimethylsilylcyanide (TMSCN) seems to be one of the most effective and safe cyanation sources for nucleophilic addition to carbonyl compounds in the presence of a chiral catalyst.[7–10]

Although impressive enantio-induction have been obtained in many cases, issues such as moderate temperature, reaction conditions and recycling of the expensive chiral catalyst need to be addressed for their practical application. Recently, much effort has been made to develop recyclable metal complexes involving multi-step surface modification of the support and its binding with a catalytically active complex using organic or inorganic supports[11] and ionic liquids[12] as reaction media. Our groups have been involved in developing recyclable polymeric and dimeric salen complexes for various asymmetric organic transformations.[13] Herein, we extend the application of a polymeric salen ligand[13c] by synthesizing its vanadium(V) salen complexes **1** and **2** for the asymmetric addition of TMSCN to various aldehydes at room temperature. An excellent yield (98%) of trimethylsilylether of cyanohydrin derivatives with high chiral induction (ee, up to 96%) was achieved in the case of 2-methylbenzaldehyde with catalyst **1**. In all catalytic runs, the (*R*)-form of polymeric V(V) salen complexes converted all aldehydes into (*S*)-cyanohydrins. To the best of our knowledge, V(V) polymeric salen complex **1** is a more efficient, recyclable catalyst for cyanosilylation reaction than the complex **2** and chiral monomeric V(V) salen system.[7b]

2. Results and discussion

Synthesis of polymeric V(V) salen complexes **1** and **2** was carried out by the condensation of the mono tartrate salt of (1*R*,2*R*)-(−)-diaminocyclohexane with 5,5-methylene-di-3-*tert*-butyl salicylaldehyde/5,5-methylene-di-3-methyl

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Microwave-assisted asymmetric ring opening of *meso*-epoxides with aromatic amines catalyzed by a Ti-*S*-(−)-BINOL complex

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Abstract—Catalytic asymmetric ring opening of cyclohexene oxide and *meso*-stilbene oxide with anilines was catalyzed by a Ti-(*S*)-(−)-BINOL complex to afford β-amino alcohols in high yield (up to 95%) and good enantioselectivities (ee up to 55%) under microwave irradiation. The reaction using a microwave was found to be 10 times faster than traditional oil-bath heating with retention of enantioselectivity.

Chiral transition metal complex catalyzed asymmetric ring opening of *meso*-epoxides with aromatic amines[1,2] is of particular interest because the chiral β-amino alcohol products have wide applications in the synthesis of pharmaceutically active compounds[3] and chiral auxiliaries/ligands. In recent years, attempts have been made to ring open *meso*-epoxides with alkyl/aryl amines to generate β-amino alcohols using various lanthanides[4–8] with (*R*)/(*S*)-BINOL, Cr(Salen)[9] and Sc(bipyridine).[10] Microwave irradiation is used for the ring opening of vinyl epoxides and terminal epoxides by NH_4OH,[11,12] thiols,[13] pyrazole and imidazole[14] and amines;[15–17] however, the area of transition metal catalyzed asymmetric epoxide ring opening reactions using microwaves[18] has scarcely been studied, probably due to the difference in activation energy of the two enantiomers involved in the asymmetric reaction which is insignificant in comparison with the energy supplied by microwaves.[19] Consequently, the enantioselectivity of the reactions could be affected in a negative way by the use of microwaves. Recently, Jacobs et al. reported the asymmetric ring opening of epoxides using $TMSN_3$ as the nucleophile under microwave irradiation.[20] As part of our continuing efforts towards asymmetric ring opening of *meso*-epoxides with aromatic amines using Ti-(*S*)-BINOL at ambient temperature,[21] we report for the first time asymmetric ring opening of *meso*-stilbene oxide and cyclohexene oxide with aniline and substituted anilines catalyzed by a Ti-(*S*)-BINOL complex to give enantioenriched *syn*-β-amino alcohols and *trans*-β-amino alcohols in high yields (up to 95%) with up to 55% enantiomeric excess under microwave (MW) irradiation at 60 °C. The enantiomeric excess (ee) was comparable with the values obtained at room temperature.

Complex **1** was generated in situ by the reaction of equimolar quantities of (*S*)-BINOL, $Ti(O^iPr)_4$ and water in dry toluene (Scheme 1). NMR and MS data for complex **1** suggested the existence of a catalytically active dimeric species, which was in equilibrium with the corresponding monomeric species and this observation was in agreement with previous reports.[22,23] In our earlier report on asymmetric ring opening of *meso*-stilbene oxide with aniline at room temperature, we observed that complex **1** was superior in performance to other Ti(IV) complexes and toluene was the solvent of choice.[21] The asymmetric ring opening (ARO) of *meso*-cyclohexene oxide with aniline was carried out using 10 mol % of complex **1** under microwave irradiation as a test reaction in toluene. The asymmetric ring opening under microwave irradiation at 60 °C showed a comparable enantiomeric excess (49% ee, Table 1, entry 3) to that of the reaction conducted at 60 °C in an oil bath (54% ee, Table 1, entry 5). The turnover frequency

Keywords: Microwave irradiation; Ring opening; Epoxides; Aniline; Ti-BINOL complex.
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