ASYMMETRIC HYDROXYLATIONS OF OLEFINS, REDUCTIONS OF KETONES AND ORGANIC TRANSFORMATIONS USING HETEROGENEOUS CATALYSIS

A Thesis

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in

CHEMISTRY

By

PRODEEP PHUKAN

Division of Organic Chemistry : Technology

National Chemical Laboratory

Pune - 411 008, INDIA

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ॐ

.....To my Parents

राष्ट्रीय रासायनिक प्रयोगशाला (वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद) पुणे - 411 008.

NATIONAL CHEMICAL LABORATORY (COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH) PUNE 411 008. (INDIA)

Dr. A. Sudalai
Organic Chemistry: Technology

Tel & Fax: 91-020-393614
E-mail: sudalai@dalton.ncl.res.in

CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Asymmetric Hydroxylations of Olefins, Reductions of Ketones and Organic Transformations Using Heterogeneous Catalysis**" by Mr. Prodeep Phukan was carried out under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.

A Sudalai

(Dr. A. Sudalai)
Research Guide

CONTENTS

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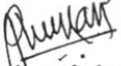
I thank Director, NCL for allowing me to present my work in the form of a thesis and CSIR, New Delhi for the award of research fellowship for the last five years.



(Pradeep Phukan)

GENERAL REMARKS

1. All melting points and boiling points temperatures are in centigrade scale.
2. The compound numbers, scheme numbers and reference numbers given in each chapter refers to that particular chapter only.
3. All solvents were distilled prior to use. Petroleum ether refers to the fraction collected in the boiling range 60-80 °C.
4. Organic layers were dried over anhydrous sodium sulfate.
5. TLC analyses were carried out on glass plates using silica gel; GF-254 and the plates were developed by iodine stain.
6. In case where chromatographic separations were done, SiO_2 was used as the stationary phase.
7. The IR spectra were recorded on Perkin-Elmer spectrophotometer 683 B or 1605 FT-IR and absorptions are expressed in cm^{-1}.
8. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker WH-90, Bruker AC-200 or MSL-300 instruments using trimethylsilane as the internal standard. The following abbreviations were used. S = singlet, d = doublet, t = triplet, q = quartet, m = multiplate, bs = broad singlet and dd = doublet of doublet.
9. The mass spectra were recorded on Finingan MAT-1020-B-70eV mass spectrometer.
10. The optical rotations were carried out on JASCO-181 digital polarimeter at 25 °C using sodium D light.
11. Elemental analyses were done in Carlo ERBA EA110B instrument.

GLOSSARY

Ac	Acetyl
AD	Asymmetric Dihydroxylation
AA	Asymmetric Aminohydroxylation
Ar	Aryl
Bp	Boiling point
DHQ	Dihydroquinine
DHQD	Dihydroquinidine
DMSO	Dimethyl sulfoxide
DMF	Dimethyl formomide
equiv.	Equivalent
Et	Ethyl
EtOH	Ethanol
EtOAc	Ethylacetate
ee	Enantiomeric excess
g	Grams
h	Hours
IR	Infra Red
mL	Milliliter
NMR	Nuclear Magnetic Resonance
Me	Methyl
MeOH	Methanol
mg	Milligrams
min	Minutes
mp	Melting point
M^+	Molecular ion
MS	Mass spectrum
Pd/C	Palladium (10 %) on carbon
Pet. ether	Petroleum ether
Ph	Phenyl
Py	Pyridine
PTSA	*p*-Toluene sulfonic acid
RB or rb	Round bottom flask
RT of rt	Room temperature
THF	Tetrahydrofuran
TLC	Thin layer chromatography

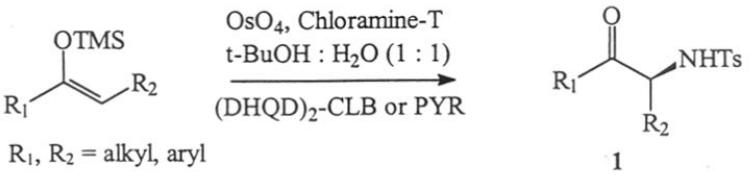
ABSTRACT

The thesis entitled " **Asymmetric Hydroxylations of Olefins, Reductions of Ketones and Organic Transformations Using Heterogeneous Catalysis**" is divided into five chapters as follows.

CHAPTER I

OsO_4 - Catalyzed Amination of Silyl Enol Ethers : Enantioselective Synthesis of α-Amino Ketones

The synthesis of enantiomerically pure α-amino alkyl or aryl ketones is of wide interest in that it provides a direct route to the synthesis of biologically active β-amino alcohols, heterocyclic compounds and unnatural amino acids[1]. Literature search reveals that a few direct methods are available for the preparation of *racemic* amino ketones but no method is known for the synthesis of chiral amino ketones. Chapter I describes a direct method of amination of silyl enol ethers using Sharpless asymmetric aminohydroxylation[2] conditions to provide optically pure α-amino ketones (**1**) (Scheme-1).



R_1, R_2 = alkyl, aryl

1

Scheme-1

CHAPTER II

Synthesis of Optically Active Amino Acids Using Asymmetric Aminohydroxylation

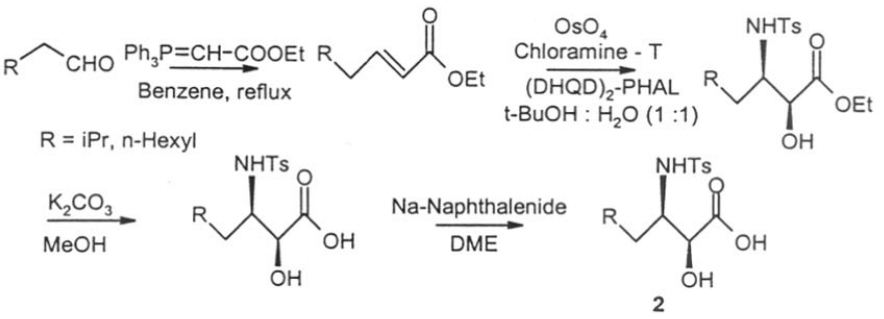
The OsO_4 catalyzed asymmetric aminohydroxylation (AA) of olefins has become the most powerful method for the preparation of a wide variety of enantiomerically pure aminoalcohols[2]. Direct and one pot introduction of both amino

and hydroxyl functionalities make this process more practical. In this chapter this synthetic methodology is applied to synthesize amino acids. This chapter is further divided into two sections.

Section A :

Enantioselective Synthesis of α-Hydroxy β-Amino Acids : Key Intermediate for Aminopeptidase Inhibitor

In recent years syn-β-amino-α-hydroxy acids (**2**) have received considerable attention as crucial component of peptidomimetic protease inhibitors. For instance (2S,3R)-β-amino-α- hydroxy unit has been found in amastatin[3] and a marine natural product microginin[4] which inhibits angiotensin-converting enzyme. Several multistep syntheses are known for the synthesis of this moiety. Here a very short route is described for the synthesis of two such compounds (Scheme 2).



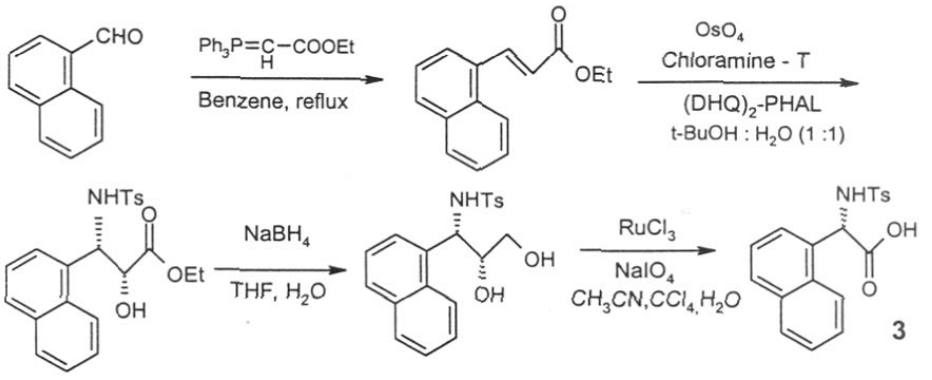
Scheme - 2

Section B :

A Short and Efficient Synthesis of Enantiomerically Pure Naphthyl Glycine

1–Naphthyl glycine (**3**) is a representative example of aryl glycines, an important class of non-proteinogenic aminoacids. Aryl glycines are present in many biologically active compounds such as cephalosporins or nocardicins. Moreover they have potential interest as chiral building blocks or as precursors of chiral ligands for asymmetric synthesis. Most of syntheses of naphthyl glycine (**3**) are either not stereoselective or based on chiral auxiliary approach in which the chiral inductor cannot be recovered. Some other syntheses are also reported involving Sharpless asymmetric epoxidation. This section provides a short and efficient synthesis of enantiomerically

pure naphthyl glycine employing asymmetric aminohydroxylation as key step (Scheme 3).



Scheme 3

CHAPTER III

Chiral Cyclic Sulfate : Versatile Synthon for the Synthesis of Adrenergic Blockers

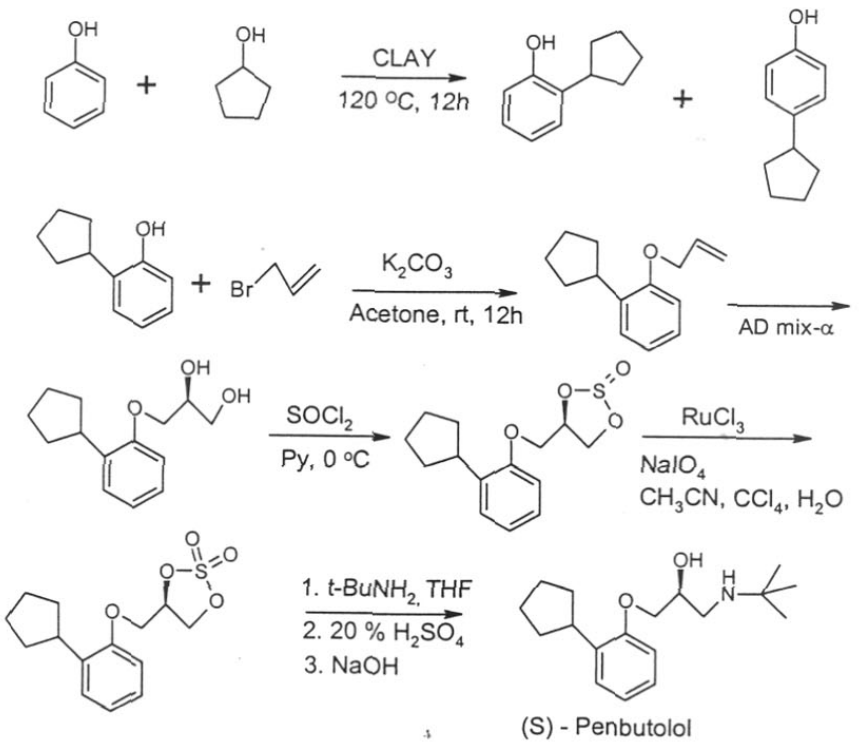
With the new synthetic developments of the enantiomerically enriched diol, their stereoselective transformations are of contemporary interest and are widely used for the total synthesis of a variety of naturally occurring and biologically active molecules[5]. These diols can be converted to chiral cyclic sulfates, which can be opened with a variety of nucleophiles in a regio and stereoselective manner to give optically active product[6]. Application of this strategy is described in this chapter to get enantiomerically enriched amino alcohols. This chapter is divided into two sections.

Section A

Asymmetric Synthesis of β-Adrenergic Blocker, (S)–Penbutolol

Although racemic β-blockers have been used over two decades, there is now a great deal of concern about enantiomerically pure isomers which are having higher affinity to the β- receptors. (S)–penbutolol is one of those drugs whose synthesis is not

much known. This section describes the synthesis of (S)–penbutolol starting from phenol by employing asymmetric dihydroxylation as a key steps (Scheme 4).

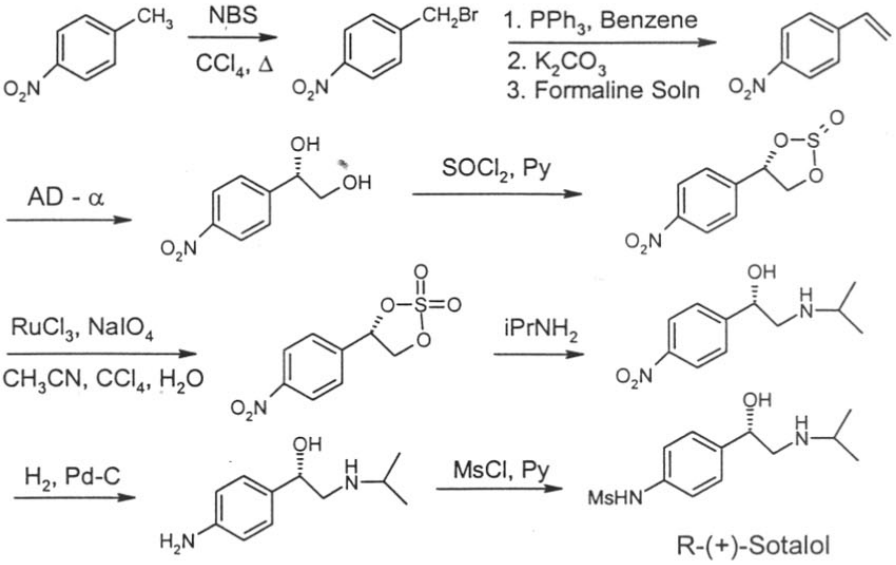


Scheme 4

Section B :

Asymmetric Synthesis of Antiarrhythmia Agent *d*-Sotalol

Reentrant ventricular arrhythmia is a major factor for most cases of sudden cardiac death. *Class III* antiarrhythmia compounds such as R-(+)–Sotalol effectively control such arrhythmia and these drugs are in various stages of clinical trials. In the past few years considerable progress was made in the preparation of R-(+)–Sotalol by chiral chromatographic separation, chiral homogeneous hydrogenation etc. This section describes the enantioselective synthesis of R-(+)–Sotalol using asymmetric dihydroxylation process (Scheme 5).



Scheme 5

CHAPTER IV

Transfer Hydrogenation of carbonyl compounds using transition metal catalysts

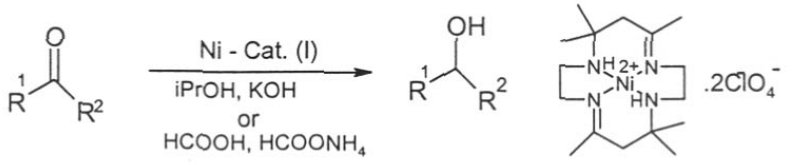
The reduction of multiple bonds with the aid of hydrogen donor in the presence of a catalyst is known as transfer hydrogenation[7]. In comparison with catalytic reduction using molecular hydrogen, transfer reduction using H-donors such as ammonium formate, isopropanol, etc. has real and potential advantages since it avoids the risks and constraints associated with high pressure reactors. In this chapter several homogeneous, heterogeneous and chiral catalysts have been synthesized and screened for transfer hydrogenation of carbonyl compounds. This chapter is divided into three sections.

Section A :

Chemoselective Transfer Hydrogenation of Carbonyl Compounds Catalyzed by Homogeneous Macrocyclic Nickel (II) Complex

Compounds of most of the elements from the second transition series in the periodic table are suitable for catalytic reduction. Both salts and complexes of Pd, Pt, Ru, Ir, Rh, Fe, Ni, and Co have been used as catalysts for the transfer of hydrogen from

molecular hydrogen or hydrogen donors to organic substrates. Most of the complexes reported contain the triphenyl phosphine moiety . This section describes the synthesis of



R_1, R_2 = alkyl, aryl, H

Ni - Macrocyclic Complex (I)

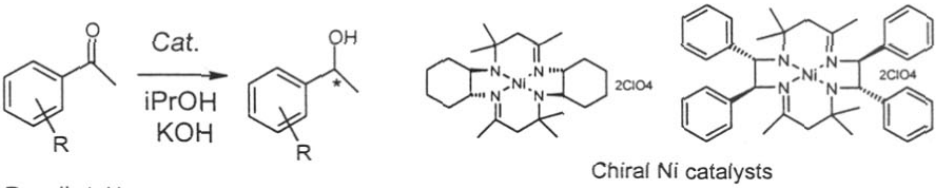
Ni complex (I) and its remarkable catalytic activity for the chemoselective reduction of carbonyl compounds (Scheme 6).

Scheme 6

Section B :

Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Chiral Macrocyclic Nickel Complex

The interest over the development of new chiral catalyst is increasingly growing in recent years and many Rh and Ru based catalysts have been developed for asymmetric transfer hydrogenation[9]. But Ni based catalyst is not studied so far for asymmetric transfer hydrogenation. This section contains a study on various Ni based chiral complex for asymmetric transfer hydrogenation of carbonyl compounds (Scheme 8).



R = alkyl, H

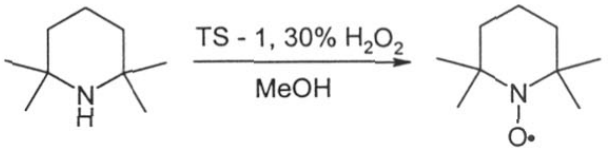
Chiral Ni catalysts

Scheme 8

Section A :

Oxidation of Secondary Amines with 30 % H_2O_2: Use of Zeolites in the Synthesis of Nitroxyl Radicals

Nitroxyl radicals are compounds containing the >N-O group which has one unpaired electron.[11] These radicals have wide range of applications in the field of organic, polymer as well as in biochemical field. In this section a single step preparation of nitroxide radicals is presented using a heterogeneous catalytic system titanium silicate (TS-1) and aq. H_2O_2 for the synthesis of these radicals (Scheme 9).

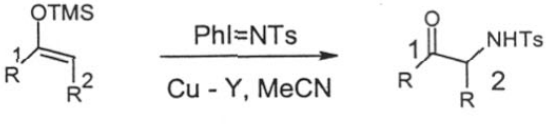


Scheme- 9

Section B :

Cu–Exchanged Y–Zeolite: an Efficient Catalyst for the Synthesis of α-Aminoketones.

The amination of carbonyl compounds is an important reaction because of its potential applications for the synthesis of heterocyclic compounds and unnatural amino acids. Among the many methods available for the synthesis of amino ketones , use of PhI=NTs is found to be a good aminating reagent. The aziridination of enol silanes reported by Evans could afford the α-tosylamino ketones in the presence of various copper salt as catalyst[12] under homogeneous conditions. Here we are employing Cu–exchanged Y–zeolite, a heterogeneous catalyst for this transformation (Scheme 10).

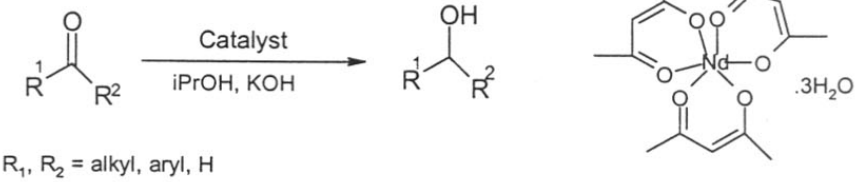


Scheme 10

Section C

Heterogeneous Catalytic Transfer Hydrogenation of Carbonyl Compounds

Of all the methods available for addition of hydrogen to organic compounds, heterogeneous catalytic transfer reactions have been relatively underutilized. Catalysts derived from Rh, Ru, Pd, Ni, Ir, Pt, Co are known to promote hydrogenation process. These catalysts are generally in the form of finely divided metals, as metals supported on carbon or skeletal metals like Raney Ni[8]. This section constitutes a study using Rh and Ru exchanged Clay as well as Ru on alumina for heterogeneous transfer hydrogenation process. Moreover, another catalyst $Nd(acac)_3.3H_2O$, which is not studied so far, is also screened for this purpose. Interestingly, this catalyst shows higher activity in a heterogeneous manner for transfer hydrogenation with the aid of



R_1, R_2 = alkyl, aryl, H

Catalyst : (a).M-Clay (M = Ru, Rh); (b). Ru-Al_2O_3 ; (c) $Nd(acac)_3.3H_2O$

isopropanol as hydrogen donor (Scheme 7).

Scheme 7

CHAPTER V

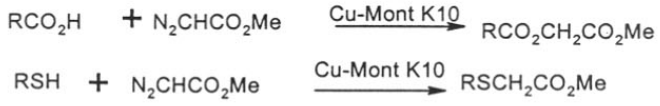
Organic Transformations Using Heterogeneous Catalysis

Zeolites and clays are aluminosilicates finding numerous applications in many areas of catalysis generating intense interest in industrial and academic laboratories[10]. Reusability and recyclability make these catalysts more useful particularly in the industrial scale. As catalyst, these materials exhibit appreciable acid activity with shape selective features. In addition, these materials can act as support for a variety of catalytically active metals. Use of these catalysts for various organic transformations are investigated in this chapter which is further divided into three sections.

Section C :

Cu-Exchanged Montmorillonite K10 Clay Mediated Insertion Reaction of Methyldiazoacetate into Thiols, Acids, and Alcohols.

The reaction of methyl diazoacetate with a variety of aromatic and aliphatic acids and thiols catalyzed by Cu–Mont K10 has been studied. The study has resulted in the development of a convenient methodology for the synthesis of β-acid esters and β-thio esters respectively (Scheme 11).



Scheme 11

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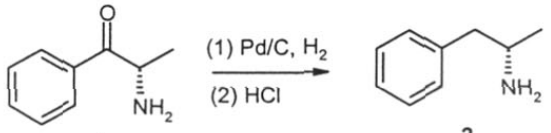
CHAPTER I

OsO_4 - Catalyzed Amination of Silyl Enol Ethers : Enantioselective Synthesis 0f α-Amino Ketones

1. 1. Introduction

Synthesis of α-amino ketones is of general interest in that it provides a direct route to a large variety[1] of biologically significant compounds. Moreover, due to the presence of both nucleophilic and electrophilic centers, these α-amino ketones can be used for the construction of nitrogen-containing heterocycles[2]. Some optically active amino ketones such as cathinone ((-)-(2S)-2-amino-1-phenyl-1-propanone), **2**, is found



1 2

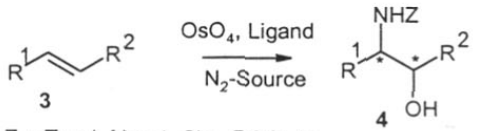
Scheme 1

in natural products. Cathinone is the main active constituent of the products extracted from the fresh leaves of "*catha edulis*" [3] which was found in several countries of East Africa and Arabian Peninsula. The biological activity of cathinone is analogous to that of amphetamine, **2** (Scheme 1), especially on the cardiovascular system[4] and metabolism of dopamine[5].

1.1.1. Asymmetric Aminohydroxylation (AA) : A Review

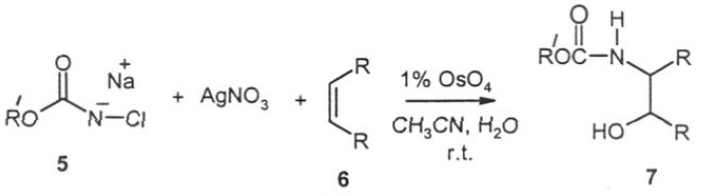
Among all catalytic asymmetric processes, asymmetric aminohydroxylation is the most versatile as it facilitates a single step introduction of two functional groups *viz* amino and hydroxyl functionality to an olefinic bond. This process where olefins (**3**) undergo vicinal addition of an amino (protected) and a hydroxyl group (**Scheme 2**) can obviously be considered as an extension of the asymmetric dihydroxylation (AD)

process[6]. The remarkable feature of this catalytic process is that it proceeds with a good to efficient regio- and enantioselectivity to furnish β-amino alcohols **4**. The resulting β-amino alcohols are an important structural element in biologically active compounds as well as the starting point in the design of many chiral ligands.[7]



Scheme 2

Indeed, the osmium catalyzed or palladium-mediated aminohydroxylation of alkenes has been known for 20 years.[8] According to the original protocol alkenes can be converted into racemic, N-tosyl-protected β-aminoalcohols in the presence of catalytic amount of osmium tetroxide using chloramine-T as the nitrenoid source and water as the hydroxyl source.[9] However, unlike the AD process, the aminohydroxylation of unsymmetrical alkenes can lead to two regioisomeric products, which was a drawback in the early stages of its development.[10, 11] Moreover, the direct reaction of osmium tetroxide with the alkene could not be completely suppressed, and diols were sometimes observed as side products.

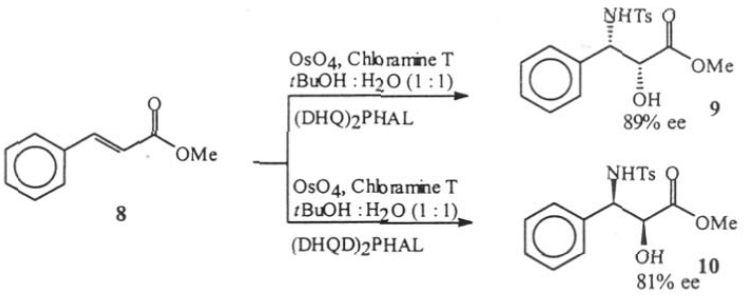


Scheme 3

In a later stage of development, vicinal oxyamination was achieved by using N-chloro-N-argentocarbamates[11] (Scheme 3). N-Chloro-N-argento carbomates are generated in situ by reaction of the corresponding N-chlorosodio carbomates **3** with $AgNO_3$ in acetonitrile. But the use of this methodology was limited only because this process involves the generation of silver salt.

Since the discovery of the catalytic AD in 1987, there have been numerous attempts by the Sharpless group to render the old catalytic aminohydroxylation process

asymmetric.[12] Recently Sharpless *et. al.* reported that the important chiral β-hydroxyamino unit can be synthesized directly from olefins in enantiomerically enriched form (**Scheme 4**).[13] The new osmium catalyzed asymmetric process is exemplified by the synthesis of the enantiomers of the taxol side chain from methyl cinnamate.[14]



Scheme 4

The new process otherwise relies on a simple combination of the phthalazine ligands (Fig.1) of the AD reaction and the conditions of the old, but efficient, osmium catalyzed aminohydroxylation from the 1970's. Other than the asymmetric induction, the most dramatic effect of the cinchona alkaloid ligand is on the regioselectivity. Another positive effect of the ligand is its ability to suppress the formation of diol byproduct, which in the absence of ligands is substantial. But the increase of temperature above 25°C leads to the formation of diol. The process in the present form leads to only modest enantioselectivities (33-81% ee) but enantiomeric purity near 100% can often be reached by recrystallization. Both MeCN : H_2O and *t*BuOH : H_2O (1 : 1) are used as solvents. Although the rate is faster in case of MeCN, *t*-BuOH gave better enantioselectivity.

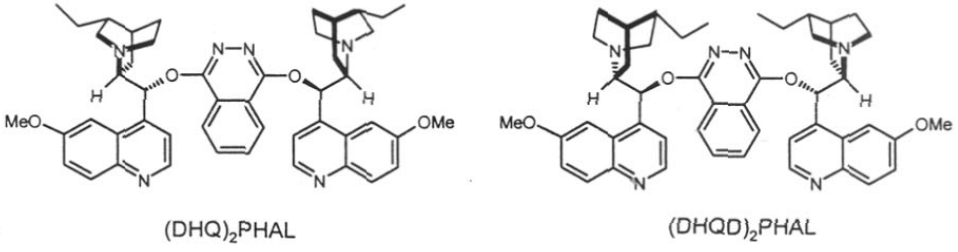
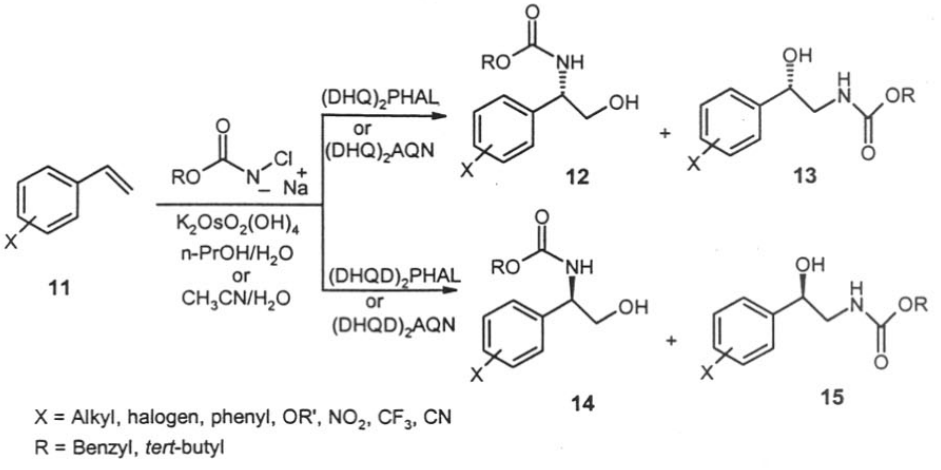


Fig.1

Two features of the asymmetric aminohydroxylation (AA) process are surprising: Even strongly electron deficient olefins such as dimethyl fumarate react rapidly and with good ee values (77%), whereas in the AD reaction dimethyl fumarate reacts extremely slowly and with less than 40% ee. *cis*-Disubstituted olefins and symmetrical compounds, which give achiral meso diols in the AD, appear to be promising substrates in AA reaction.

Use of smaller substrates proved to be a better choice in this sulfonamide based AA process[15]. Both yield and selectivity can be improved by the use of chloramine-M in *n*-PrOH : H_2O (1:1) solvent system. Use of this combination of reagent gave better yield (49-76 %), enantio (66-95%) - as well as regioselectivity (90:10).

Although this sulfonamide based AA process efficiently gives chiral N-protected amino alcohols, the scope of this process is limited due to its poor substrate selectivity. Styrene type olefins, which are the best substrate for AD process, are very poor substrates for this approach. The replacement of sulfonamides by carbamates[16] greatly improves the AA in both scope and selectivity. Under this new modified conditions styrenes become the best substrate for AA process like AD reaction. Moreover, they also obey the same face selection rule established for the AD reaction[6] (Scheme 5).

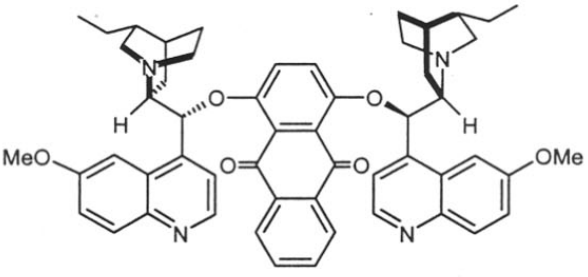


Scheme 5

This procedure led to high selectivity and yield in case of substrates like methyl cinnamate. But styrenes give both the regioisomers. The regioselectivity is seen to be

highly dependent on the nature of the styrene as well as the choice of ligand, solvent, and ligand-solvent combination[16b]. Phthalazine ligands such as $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ in *n*-PrOH (alcoholic solvents) favor the benzylic amine (**12, 14**) over the benzylic alcohol regioisomer (**13, 15**). In acetonitrile, the ratio of benzylic amine to benzylic alcohol (**12/13**) decreases significantly and sometimes reverses.

The use of anthraquinone (AQN) ligand[17] (Fig2) instead of PHAL ligand favour this reversal of regioselectivity and when used in conjunction with the CH_3CN/H_2O solvent system but enantioselectivity drops significantly even to the extent of zero.

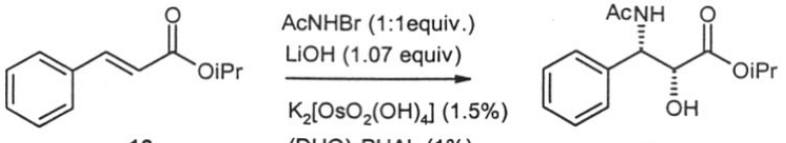


$(DHQ)_2AQN$

Fig.2

Another notable observation is that the use of *tert*-butyl carbamate instead of benzyl carbamate under same reaction conditions gives unsatisfactory results. Substantial diol formation and low yields were observed. Best result were obtained while 2:1 ratio of n-PrOH/water with little more amount of ligand and $K_2OsO_2(OH)_4$.

In the third stage of development of AA process N-bromoacetamide is used as nitrogen source[18] (Scheme 6). This methodology also can be applied to all kinds of



16 **17**

Scheme 6

molecules including styrenes. Regioselectivity of the aminoalcohol formation is reversed from that delivered by the carbamate version of AA process. In this case percentage of benzylic alcohol isomer is more prominent and even more when AQN

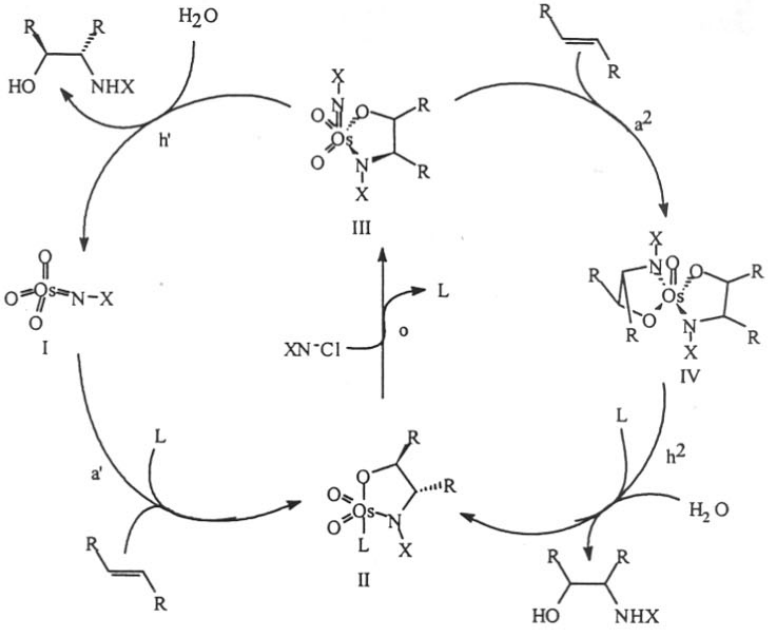
ligand is used. One positive point of this amide process is that one equivalent of the aminating agent is needed whereas in other case three equivalents are necessary.

Irrespective of the regiochemical outcome the face selection rule follows that for the AD reaction. $(DHQD)_2PHAL$ directs addition to the β-face and $(DHQ)_2PHAL$ directs addition to the α-face. For *trans*-olefins it is now the DHQ series that generally gives higher ee values, whereas the inverse of the situation for the AD reaction. One feature of the AA process of styrenes is that benzylic amide were found with higher asymmetric induction than the benzylic alcohols. The AA process shares with the AD three desirable features. The first is simplicity: Only catalytic amounts of both OsO_4 and chiral ligands are required. The reactions are performed at close to room temperature with commercially available reagents and are not influenced by water or oxygen and the products can be often isolated by filtration of the crude reaction mixture. The second feature is the crucial functional group transformations AA and AD provide to a variety of organic compounds. For example, the products obtained by the AA process can be easily transformed into precursors for α,β-diaminoacids.

1.1.2. Mechanism of AA reaction

The **Scheme 7** shows the proposed mechanism involving the key intermediate complexes in this catalytic system.[15] The intermediate in these reactions is the imino-osmium species (I) which is continuously regenerated by the reaction of OsO_4 and the nitrogen donor. Like the AD process, there is substantial evidence that at least two catalytic cycles are operative in the AA system. Both the cycles proceed via three steps *viz.* addition (a), reoxidation (o) and hydrolysis (h). Experiments with sulfonamide derivatives suggest that both electronic and steric factors on the organic substituent play an important role in the stereoselectivity and rate of the reaction. The smaller substituent is thought to allow a better fit of the ensemble into the binding pocket of the catalyst in the transition state of the irreversible step (step a'). However, the effect of the ligand on selectivity are only possible when turnover occurs in the first cycle (a^1, o, h^1, repeat). If the reaction proceeds via the ligand independent second cycle (a^2, h^2, o, repeat), the ligand selectivity features lost. Involvement of this cycle results almost no enantio- or regioselectivity. In general, catalysis in the second cycle proceeds with much slower

turnover rates since the osmium (VI) bisazaglycolates (IV) are often slow to hydrolyze (h^2), which is necessary before reoxidation (o) can occur.



Scheme 7

1.1.3. Reaction Conditions of AA Reaction

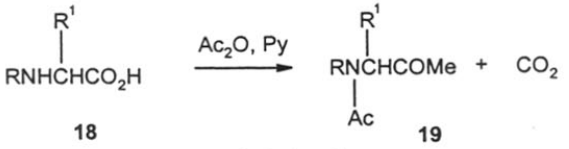
Asymmetric aminohydroxylation of olefins does not involve any special technique and presence of water or oxygen causes no problem. It can be considered as one of the easiest metal catalyzed reaction to perform. Generally, the reaction is carried out in a solvent mixture containing 50% water. Most common non-aqueous solvent used for this purpose is *t*-butanol, *n*-propanol and acetonitrile. Both regioselectivity and enantioselectivity is dependent on ligand, ligand-substrate combination, solvent and solvent – water ratio. Usually reaction is performed using 2-4 mole % of Os reagent and 5-mole % of the ligand. When sulfonamide or carbamate is used as nitrogen source, three equivalents of the reagent are used to maintain the 1st catalytic cycle and to suppress the formation of diol. But 1 equivalent of n-bromoacetamide is enough to

of the unwanted *p*-toluene sulfonamide byproduct can be reduced. Although in all the cases the solvent-water ratio is 1:1, in case of aa of styrenes using *t*-alkyl carbamate-based chloramine salt the occurrence of 2nd cycle and diol formation become more prominent when 1:1 water –alcohol mixture is used. For best result 2:1ratio of *n*-propanol/water is preferred alongwith 6 mol % of the ligand and 4 mol % of the os reagent.

1.1.4. Review of Literature on Synthesis of α-Amino Ketones

Various methods of preparing racemic α-amino ketones are available in the literature and new routes for their synthesis continue to be devised. Some of the important synthetic routes so far known are described below.

The Dakin – West reaction[19] is one of the oldest known methods for the synthesis of α-amino ketones (Scheme 8). In this method an α-amino acid **18** is directly converted into the corresponding α-acetylamino alkyl methyl ketone **19** by the action of acetic anhydride in the presence of a base such as pyridine. The same methodology was later modified by Evans[20] to get δ-aminolevulinic acid.



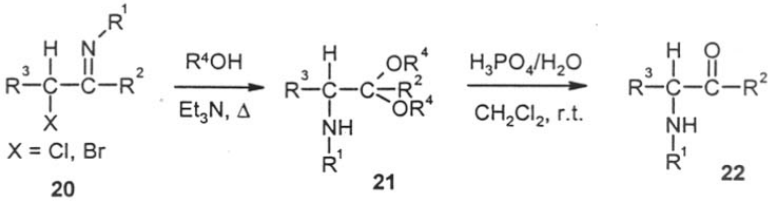
18 **19**

Scheme 8

Another method of obtaining amino ketone is reduction of corresponding nitrile or azidoketone. Reduction of acyl cyanides with zinc-acetic acid in the presence of excess of acetic anhydride leads to n-acetyl aminoketone.[21] α-Azido ketone can also be reduced with h_2, pd/c to get the corresponding amino ketone.[22]

Kimpe's approach (1982)[23]

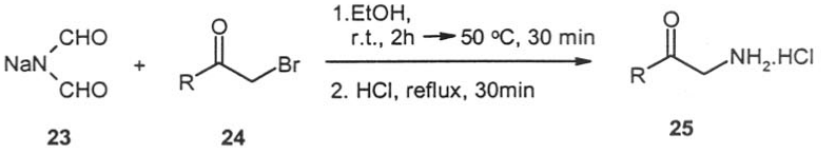
Kimpe and coworkers reported the conversion of secondary α-haloketimines **20** into α-alkylamino acetals **21** by reaction with anhydrous alcohols in the presence of triethylamine. The α-alkylamino acetal was further hydrolyzed by aqueous phosphoric acid (in two-phase system with dichloromethane) at room temperature to yield α-alkylamino ketone **22** (scheme 9).



Scheme 9

Yinglin's approach (1990)[24]

Yinglin *et. al.* have synthesized α-amino ketones **25** in high yield by treating bromomethyl ketones, **24** with sodium diformylamide, **23** in ethanol followed by treatment with hydrochloric acid (Scheme 10).



Scheme 10

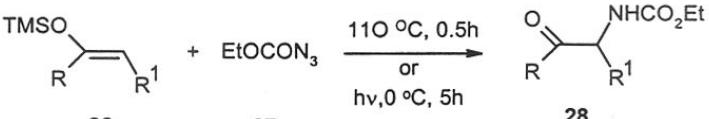
Many other methods are known in the literature for the synthesis of N-protected racemic α-amino ketones[25, 26].

Amination of enolate is well known process and this concept is widely applied for the enantioselective synthesis of amino acids.[27] Generally, in this procedure a chiral auxiliary is N-acylated followed by enolisation of the adduct. Amination of the chiral enolate and subsequent cleavage of the auxiliary gives the optically pure amino acid. But this strategy was restricted only in case of amino acid synthesis as the attachment of

chiral auxiliary was the prerequisite of the process. Detachment of the chiral auxiliary results in the formation of amino acids. Although this method is well exploited in case of amino acid synthesis, it was applied only for the synthesis of racemic amino ketones. Following are the reports available in the literature.

Tardella's approach (1983)[28]

Synthesis of α-amino ketone from silyl enol ether was first reported by Tardella et. al.. Thermolysis or photolysis of ethyl azidoformates in enol trimethylsilane results in N-ethoxy carbonyl α-amino ketones (Scheme 11).

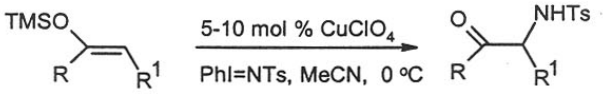


26 27 28

Scheme 11

Evans's approach (1991)[29]

The aziridination of enol silanes reported by Evans could afford the α-N-tosylamino ketones employing (N-(*p*-toluenesulfonyl)imino)phenyl iodinane, PhI=NTs, as nitrene precursor in the presence of various copper salts as catalyst.

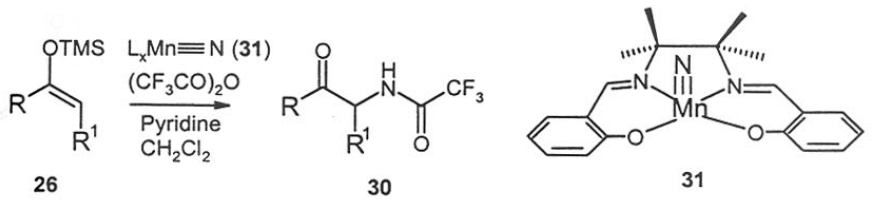


26 29

Scheme 12

Carreira's approach (1996)[30]

Carreira and coworkers recently developed a shift base nitridomanganese complex as nitrogen transfer reagent for the aminohydroxylation of alkenes. Amination of silyl enol ethers with this complex in combination with trifluoroacetic anhydride results in protected aminoketones (Scheme 13).



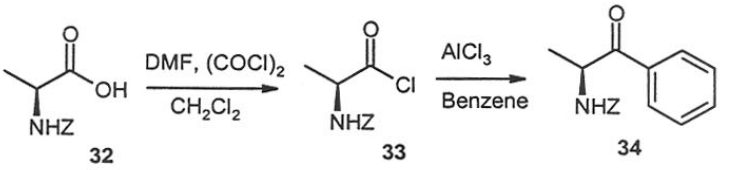
26 30 31

Scheme 13

Although the syntheses of racemic amino ketones are well documented in the literature, methods for the synthesis of optically pure amino ketones are rare. Almost all the syntheses start from optically active materials or by resolution techniques. Known methods for the synthesis of optically pure amino ketones are described below.

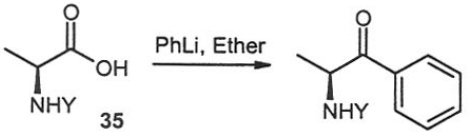
Rapoport's approach (1981)[1]

Rapoport et. al. reported the synthesis of optically active α-amino ketones starting from N-acylated amino acids. The synthesis was achieved by Friedal-Craft's acylation and arylmetallo reactions (Scheme 14).



32 33 34

Z = CO_2CH_2Ph, $CO_2C_2H_5$



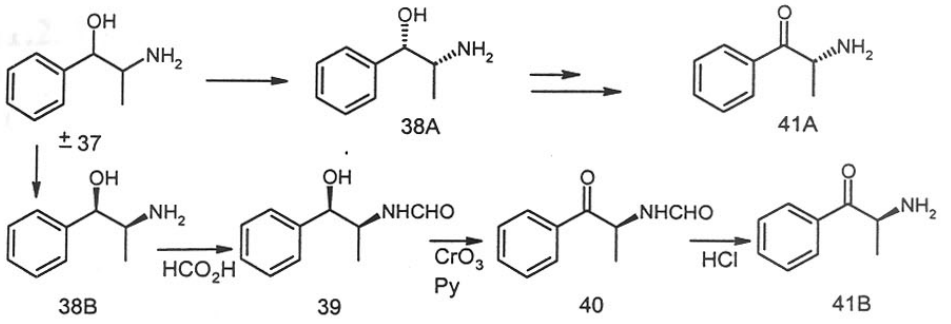
35 36

Y = CO_2Et, SO_2Ph

Scheme 14

Berrang's approach (1982)[3]

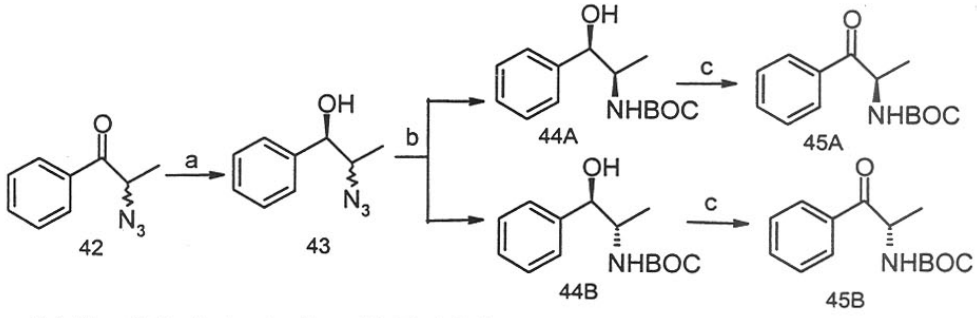
The preparation of the optical antipodes of α-aminopropiophenone (cathinone) from norephedrine **37** was reported by Berrang. Norephedrine was resolved into its (+) and (-) antipodes with *O,O*-dibenzoyl-d-tartaric acid. Each isomer was then converted into cathinone (Scheme 15).



Scheme 15

Besse's approach (1994)[31]

Synthesis of both the enantiomers of cathinone with more than 95% ee was described by these authors via microbiological reduction of 2-azido-1-phenyl-1-propanone (Scheme 16).



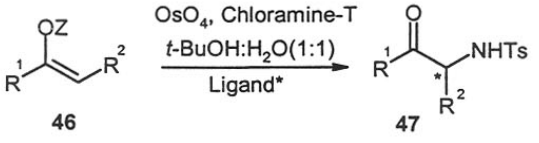
(a) Microbiological reduction with R-glutinis
(b) (i) 10% Pd/C, H_2, $(Boc)_2O$, EtOAc (ii) Column Chromatography.
(c) PCC

Scheme 16

1.2. Present Work

Objective

Although many methods are available for the synthesis of racemic amino ketones, there is paucity in the literature for the synthesis of optically pure aminoketones. Efforts are on for newer synthetic methods as these α-amino ketones in optically pure form can be used as drugs or drug intermediates. α-Amination of enolates in an enantioselective fashion is known for decades but its applicability is limited to the synthesis of optically active α-amino acids. Sharpless asymmetric dihydroxylation and aminohydroxylation processes catalyzed by OsO_4 became the most important tool nowadays for asymmetric synthesis because of its simplicity and wide range of applicability. The objective of the present investigation is to apply Sharpless asymmetric oxyamination process to develop new methodology for the synthesis of optically pure α-amino ketones (Scheme 17).



Z = TMS, TBDMS
R^1, R^2 = aryl, alkyl, or cycloalkyl

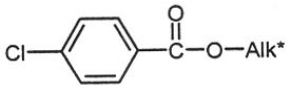
Scheme 17

1.3. Results and Discussion

According to earlier reports[28, 29] aziridination of silyl enol ethers result in the formation of α-amino ketones. Later Carreira[30] showed that the nitridomanganese complex on reaction with olefins gives amino alcohol, which could also be used to synthesize α-amino ketones from silyl enol ethers. In a similar way, extension of the Sharpless asymmetric amino hydroxylation methodology on silyl enol ethers provided the synthesis of α-amino ketones in enantiomerically pure form.

Preparation of silyl enol ethers was first carried out by refluxing the substrate in DMF with triethylamine and trimethylsilyl chloride[32]. But longer reaction time and aqueous work up render the method impractical. Sometimes, during work up some part of the product goes back to ketone, which is very difficult to separate, as boiling point of the ketone and the silyl enol ether are very close. Moreover, in case of acyclic ketones such as propiophenone this method yields a mixture of *cis-* and *trans-* isomer. To avoid these difficulties, most of the silyl enol ethers (both TMS and TBDMS ethers) are prepared by using LDA in THF. The IR spectrum of silyl enol ethers showed the presence of a band near 1650 cm^{-1} corresponding to the double bond and absence of carbonyl peak at 1700 cm^{-1}. ^1H NMR spectrum showed the presence of singlet at 0.1 δ corresponding to trimethyl silyl functionality. In case of TBDMS ether there is an additional broad singlet at 1 δ corresponding to *t*-BuSi group. Even, TLC can very easily ascertain the formation of silyl enol ether. It appears as a wide white spot (slowly darkens later) moving with the solvent front in pet. ether.

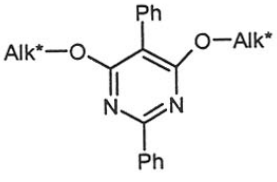
Asymmetric aminohydroxylation of the enol ethers **46** was done in presence of various chiral ligands such as DHQD-CLB, DHQD-PYR and DHQ-PYDZ (Fig. 3) to furnish aminoketone **47**. These three ligands were prepared according to the literature procedure.[33-35]



CLB-Ligand

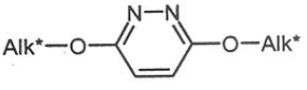
48

Alk* = DHQ or DHQD



PYR-Ligand

49



PYDZ-Ligand

50

Fig.3

DHQD-CLB was prepared by treating *p*-chlorobenzoyl chloride with dihydroquinidine and triethylamine in dichloromethane at 0 °C. Ligand **49** was synthesized by condensation reaction of 4,6-dichloro-2,5-diphenylpyrimidine and two equivalent of dihydroquinidine in presence of KOH in argon atmosphere with azeotropic removal of water for 6 h. The ligand **50** was prepared also in the same way by treating 3,6-dichloropyridazine with dihydroquinine in presence of KOH in toluene.

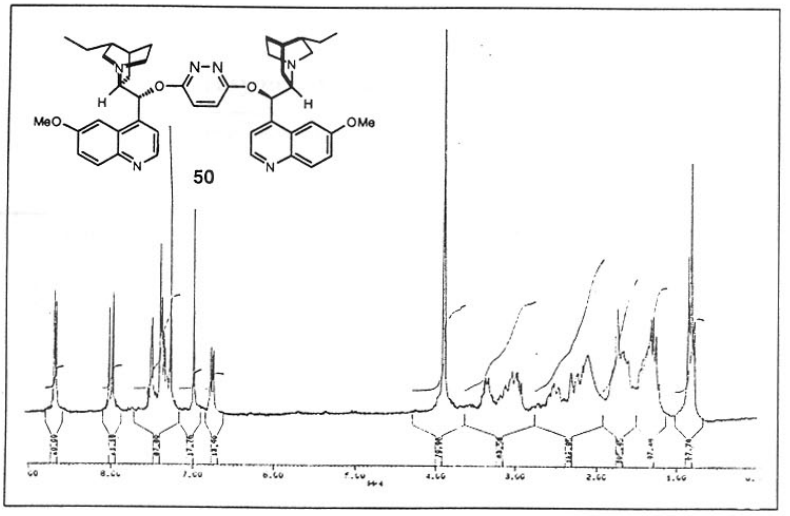


Fig. 4. ^{1}H NMR of compound (DHQ)$_2$-PYDZ, 50

The bis-alkaloid ligands formed were characterized by IR ^{1}H NMR and mass spectra. IR spectra showed the disappearance of hydroxyl group at 3400 cm^{-1} and ^{1}H NMR showed the characteristic 9-O-substituted proton at 6.9 δ confirming the formation of the ether linkages. Moreover, the methoxy group of the alkaloid also appears at 3.9 δ. 3,6-Dichloropyridazine was prepared according to literature procedure.[36] 3,6-Pyridazine diol was synthesized by treating maleic anhydride with hydrazine hydrochloride in water at boiling. Interesting feature of this diol is that it shows a band in IR spectra at 3250 cm^{-1} and also at 1672 cm^{-1}. This is because the compound exists in both ketone and enol form. This diol was further converted to 3,6-dichloropyridazine refluxing in $POCl_3$. Purification of this compound was achieved by sublimation. ^{1}H NMR spectrum of 3,6-dichloropyridazine shows one singlet at 7.5 δ.

Asymmetric aminohydroxylation of various silyl enol ethers was carried out using ligands **48**, **49** and **50**. **Table 1** shows the yield and enantiomeric excess of the various aminoketones. All the reactions were performed in *t*-BuOH/H_2O (1:1) using chloramine-T trihydrate as co-oxidant as well as aminating agent at *ca.* 25 °C. The molar ratio of substrate : OsO_4 : ligand : Chloramine-T is 1 : 0.001 : 0.002 : 3.

Table 1 : OsO_4 - catalyzed asymmetric aminohydroxylation of silyl enol ethers.

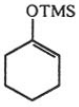
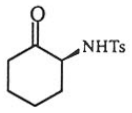
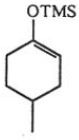
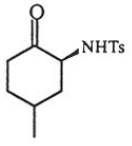
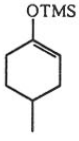
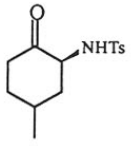
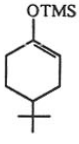
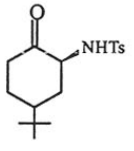
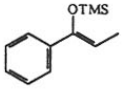
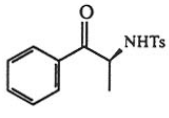
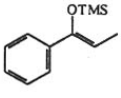
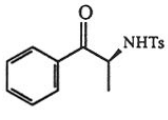
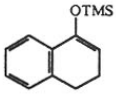
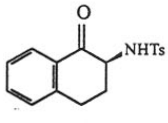
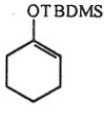
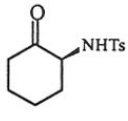
Expt. No.	Silyl enol ether **46**	Chiral Ligand	α - Amino Ketone **47**	t (min)	Yield[b] (%)	ee[c] (%).
1.		$(DHQD)_2$-CLB		15	35	92
2.		$(DHQD)_2$-CLB		15	38	72
3.		$(DHQD)_2$- PYR		15	40	86
4		$(DHQD)_2$-CLB		15	34	76
5.		$(DHQD)_2$-CLB		120	41	70
6.		$(DHQD)_2$- PYR		120	45	85
7.		$(DHQD)_2$-CLB		10	28	76
8		$(DHQD)_2$CLB		15	50	90

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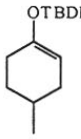
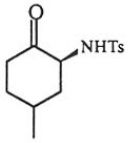
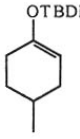
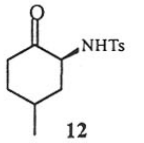
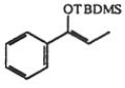
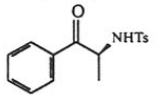
Table 1 contd...

Expt. No.	Silyl enol ether **46**	Chiral Ligand	α - Amino Ketone **47**	t (min)	Yield[b] (%)	ee[c] (%)
9		$(DHQD)_2CLB$		15	49	77
10		$(DHQ)_2PYDZ$		15	47	95
11		$(DHQD)_2CLB$	**12** 	150	54	76

a: Molar ratio of silyl enol ether : OsO_4 : chiral ligand = 1 : 0.01 : 0.02 ; temp 25°C ; b : isolated yield after chromatographic purification and crystallization ; c : % ee was determined by chiral HPLC analysis : chiral CEL - AC - 40 F column.

As can be seen from Table 1, the amination of silyl enol ethers took place rapidly (<20min) in most of the cases studied. The reaction proceeded rapidly to completion as indicated by the distinct color change from dark green to dark brown. Reaction rate is slower in case of aliphatic enol ethers. In case of cyclic systems, due to the strain in the ring, reaction proceeds at a faster rate. The crude reaction mixture was purified by column chromatography and crystallized from $CHCl_3$. Although purification method for all the compounds are very simple, sometimes *p*-toluene sulfonamide, the side product formed in the reaction makes the purification difficult, especially when sulfonamide and the product elute together in column chromatography. In that case sulfonamide can be eliminated from the mixture simply by stirring in large amount of pet ether. Sulfonamide being insoluble in pet-ether will precipitate out from the solution. Work up of reaction mixture involving tetralone is a bit cumbersome due to the formation of highly colored material. A second chromatographic run was necessary for this purpose.

Initial experiments were done using trimethylsilyl enol ether as starting material. But yields were low which may be due to the instability of silyl enol ethers. That is why *t*-butyl dimethylsilyl enol ethers were prepared and reactions were repeated. Use of TBDMS ethers improves yield although it did not improve enantioselectivity. Both

Chiral ligands, $(DHQD)_2$-CLB and $(DHQD)_2$-PYR, performed almost to the same extent in inducing enantioselectivity as has been found in the case of 1-trimethylsilyloxy -4-methylcyclohex-1-ene. Improvement of enantioselectivity was achieved by using $(DHQ)_2$-PYDZ ligand.

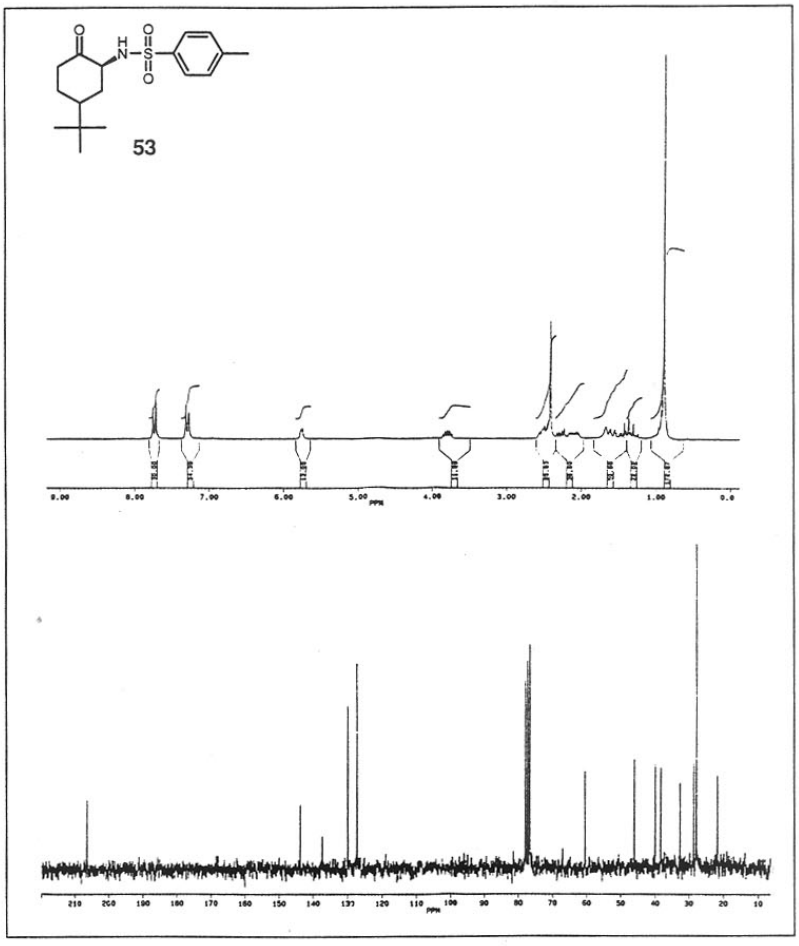


Fig 5. ^1H and ^{13}C NMR of compound 53

Characterization of the product was done using IR, ^1H NMR, ^{13}C NMR, Mass spectra and elemental analysis. IR spectra showed a band at 3290 cm^{-1} indicating the presence of NH- functionality. A signal at 1690 cm^{-1} indicated carbonyl functionality. Presence of NH- and Ts- functionality can easily be make out from ^1H NMR. There is a

doublet (sometimes-broad singlet) at 5.8 δ in ^{1}H NMR spectrum indicating the presence of NH proton. Methyl group of *p*-tolyl sulfonyl functional group appears at 2.4 δ. The CH-proton attached to N-functionality appears at around 3.75 δ in ^{1}H NMR. Aromatic protons of tosyl group appear as two doublets at 7.3 δ and 7.7 δ. In ^{13}C NMR spectra of these compounds, the tertiary carbon attached to N-Ts of compound **54** appears at 53.3 δ and in case of other cyclic compounds it appears at 60 δ. Carbonyl carbon appears at 200 δ.

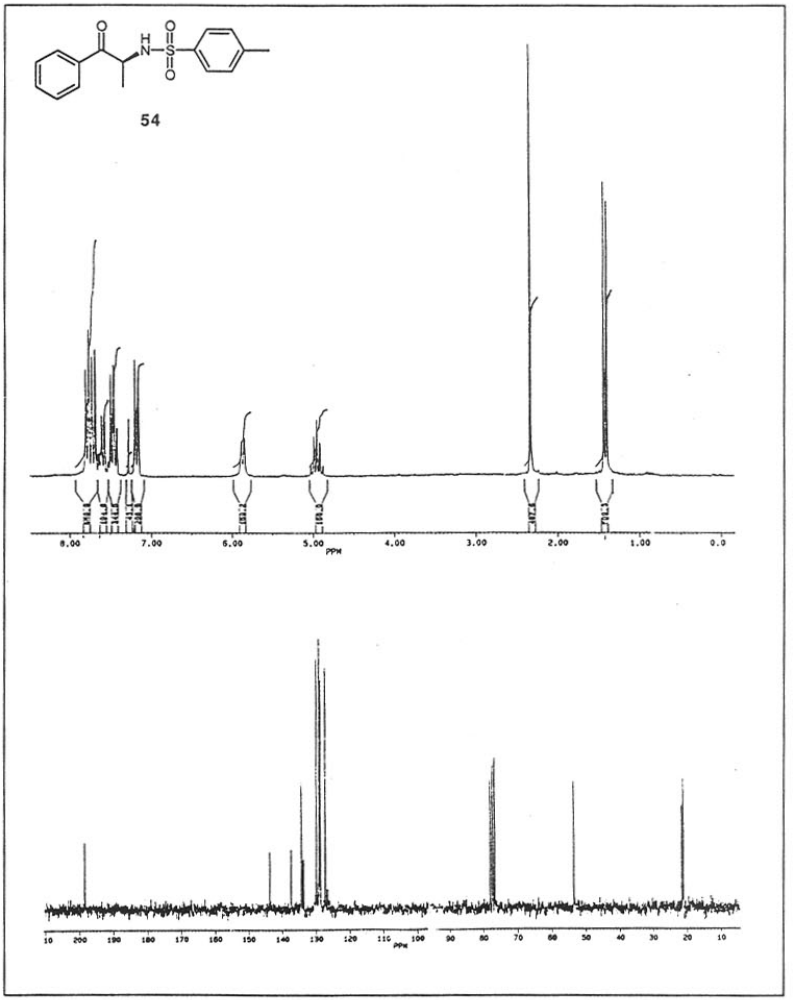


Fig 6 ^{1}H and ^{13}C NMR spectrum of compound 54

Enantiomeric excess of the α-amino ketones was determined by HPLC using Macherey Nagel CEL-AC 40 F column. The mobile phase was 96 % ethanol-water. Initially the racemic compounds were injected to get proper separation of the two enantiomers. Racemic aminoketones were prepared by $Cu(OTf)_2$ catalyzed aziridination of silylenol ether employing (N-(*p*-toluenesulfonyl)imino) phenyliodinane, PhI=NTs as nitrene precursor as reported by Evans *et. al.*[29] Enantiomer excess, ee was determined by using following formula.

$$\% \text{ ee} = \frac{|A_1 - A_2|}{A_1 + A_2}.100 = |\%A_1 - \%A_2|$$

where A_1 and A_2 are the area or % area of the two peaks in the HPLC chromatogram. For example, HPLC chromatogram of compound 51 shows two peaks at 20.60 min (minor) and 23.0 min (major) has area percentage 4.21% and 95.78 % respectively. The enantiomeric excess is

$$\% \text{ ee} = \frac{|4.21 - 95.78|}{4.21 + 95.78}.100$$

$$= 91.58 \approx 92\ \%$$

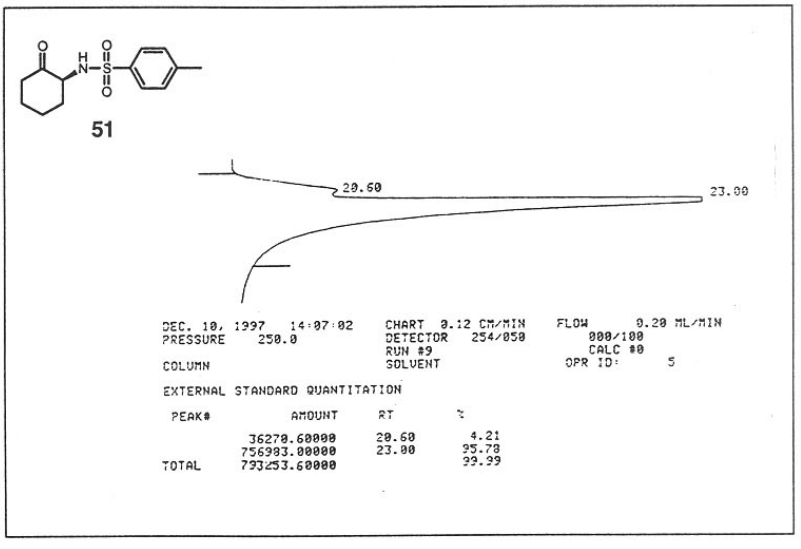
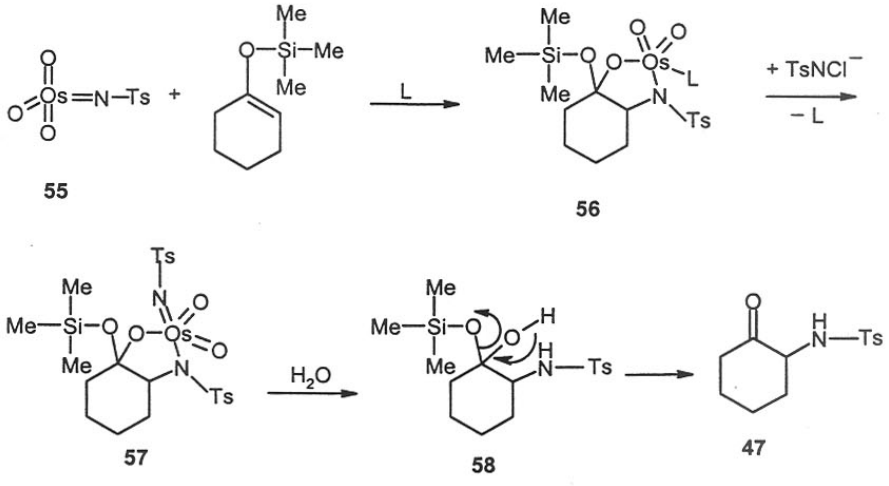


Fig 5. HPLC chromatogram of compound 51

1.4. Mechanism

In analogy with the mechanism of oxiamination discussed in the introductory section, the probable mechanistic pathway for the formation of aminoketone can be depicted in the Scheme 18. The imino osmium species 55 reacts with the silyl enol ether to form the species 56. Displacement of the ligand L by TsNCl produces the species 57. Hydrolysis of the species 57 regenerates the species 55 and forms the unstable amino alcohol 58, which upon subsequent elimination of Me_3SiOH generate the α-amino ketone 47.



Scheme 18

1.4. Conclusion

Various α-amino ketones were synthesized in enantiomerically pure form in a catalytic way. The enantiomeric excesses range from 70 – 95 % and yields are in the range of 28 % to 50 %. The ligands DHQD-CLB and DHQD-PYR gave almost same enantioselectivity, but use of DHQ-PYDZ ligand showed better result. Use of tms-ethers resulted lower yield of α-amino ketones improvement of yield was achieved by using more stable TBDMS-ethers. Reaction rate for cyclic silyl enol ethers is faster than that of acyclic one, which may be due to the strain associated with the cyclic ring.

1.7. Experimental section

All solvents were distilled before use. Compounds were purified by flash chromatography over silica gel (230-400 mesh). IR spectra were recorded on a Perkin - Elmer 137 E spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on 200 MHz and 300 MHz instruments using TMS as internal standard. The mass spectra (MS) were recorded on automated Finnigan MAT 1020C mass spectrometer using ionization energy of 70 eV. The optical rotations were carried out on JASCO-181 digital polarimeter at 25°C using sodium D light. HPLC analyses were performed by using Waters HPLC system consisting of pump model 510, UV detector model 481, model 730 data module and Rheodyne injector. Chiral analyses were done using Macherey Nagel CEL - AC - 40 F (4.0mm x 25 cm) column.

Preparation of 1-trimethylsilyloxy-cyclohex-1-ene,

To a solution of 6.28 g (7.3 mL, 58 mmol) of chlorotrimethyl silane and 11.7 g (16.2 mL, 116 mmol) triethyl amine in 20 mL of DMF was added 4.74 g (5 mL, 48 mmol) of cyclohexanone. The resulting mixture was refluxed for 8h and cooled. The reaction mixture was further diluted with 50 mL of pet ether and washed with three 50 ml portions of cold aqueous $NaHCO_3$ solution. The organic layer was washed with cold brine, dried over Na_2SO_4 and the solvent evaporated. The residue was distilled under reduced pressure (15 mm) to get 5.1 g pure trimethyl silyl enol ether.

Yield	:	5.1 g (62 %)
bp.	:	70-71 °C /15 mm
IR (neat cm^{-1})	:	2910, 1640, 1395, 1240, 1170
^{1}H NMR (200 MHz, $CDCl_3$), δ ppm	:	0.53 (s, 9H), 1.75 (m, 4H), 1.95 (m, 4H), 4.75 (t, J=5.4 Hz, 1H)

General procedure for the synthesis of TMS and TBDMS-enol ethers using LDA

Ketone (40 mmol) in dry THF (5 mL) was added to a stirred solution of lithium diisopropylamide (LDA) (prepared in situ by addition of *n*-butyl lithium (45 mmol) to diiospropylamine (55 mmol) in dry THF) under nitrogen atmosphere at –78 °C over

10min. The solution was stirred for further 1h. Thereafter, chlorotrimethyl silane or *t*-butyldimethyl chlorosilane (70 mmol) was added over 5 min. The solution was allowed to warm to room temperature and after stirring for 1h, the solvent was evaporated in vacuo. Dry pet. ether (100 mL) was added and lithium chloride removed by filtration. Evaporation of the filtrate followed by column chromatographic purification on neutral alumina or distillation gave the pure product.

1-Trimethylsilyloxy-4-*t*-butylcyclohex-1-ene

Yield	:	83%
bp.	:	75-77 °C/15mm
IR (neat cm^{-1})	:	2920, 1665, 1395, 1250.
^1H NMR	:	0.25 (s, 9H), 1.3 (m, 1H), 1.65 (m, 4H), 2.05(m, 2H)
(200 MHz, $CDCl_3$), δ ppm		4.80(m, 1H).

1-Trimethylsilyloxy-4-methylcyclohex-1-ene

Yield	:	85 %
IR (neat cm^{-1})	:	2920, 1660, 1395, 1260, 1180.
^1H NMR	:	0.2 (s, 9H), 1.3 (m, 1H), 1.9 (s, 9H), 1.7 (m 4H),
(200 MHz, $CDCl_3$), δ ppm		2.05(m, 2H), 4.85 (t, J = 2.7 Hz, 1H).

1-trimethylsilyloxy-1-phenylprop-1-ene

Yield	:	89 %
IR (neat cm^{-1})	:	2920, 1665, 1395, 1250.
^1H NMR	:	0.2 (s, 9H), 1.8 (d, J=8.1Hz, 3H), 5.35 (q, J=5.4, 1H),
(200 MHz, $CDCl_3$), δ ppm		7.25(m, 3H), 7.50(m, 2H).

1-Trimethylsilyloxy-1-tatralene

Yield	:	80 %
IR (neat cm^{-1})	:	2900, 1645, 1600, 1395, 1250.
^1H NMR	:	0.6 (s, 9H), 2.1-2.8 (m, 4H), 5.0 (t, J=5.4, 1H), 6.8-
(200 MHz, $CDCl_3$), δ ppm		7.4(m, 4H).

1-(*t*-Butyldimethyl)silyloxycyclohex-1-ene

Yield	:	85 %
IR (neat cm^{-1})	:	2900, 1665, 1390, 1240
^1H NMR (200 MHz, $CDCl_3$), δ ppm	:	0.15(s, 6H), 1.0 (s, 9H), 1.7 (m, 4H), 1.95(m, 4H), 4.8 (m, 1H).

1-(*t*-Butyldimethyl)silyloxy 4-methylcyclohex-1-ene

Yield	:	85 %
IR (neat cm^{-1})	:	2900, 1650, 1440, 1390, 1240, 1170.
^1H NMR (200 MHz, $CDCl_3$), δ ppm	:	0.15(s, 6H), 0.95(bs, 12H), 1.3(m, 1H), 1.7(m, 4H), 2.1(m, 2H), 4.85(m, 1H).

1-(*t*-butyldimethyl)silyloxyprop-1-ene

Yield	:	83 %
IR (neat cm^{-1})	:	2900, 1645, 1600, 1395, 1250.
^1H NMR (200 MHz, $CDCl_3$), δ ppm	:	0.2 (s, 6H), 0.9 (s, 9H), 1.75 (d, J=8.1 Hz), 5.25(q, J=5.4, 1H), 7.2 (m, 3H), 7.5 (d, 2H).

Preparation of 9-(*O*-Dihydroquinidinyl)*p*-chlorobenzoate, $(DHQD)_2CLB$

A flame dried 100 mL RB flask was charged with dihydroquinidine (0.652 g, 2 mmol), triethyl amine (0.42 ml, 3 mmol) and dichloromethane (10 mL) under argon atmosphere and cooled to 0 °C with stirring. *p*-Chlorobenzoyl chloride (0.493 g, 1 mmol) in CH_2Cl_2 (3 mL) was added dropwise and allowed to stir overnight at 0 °C. The reaction was monitored by tlc (15h). Water was added (15 mL) and extracted with ether (4 x 15 mL), washed with brine (15 mL), dried over anhydrous sodium sulfate and concentrated to yield a brown solid which was further purified by recrystallization from a mixture of ether : pet.ether (1 : 1) to furnish a white crystalline solid (0.81 g).

Yield	:	91 %
mp	:	113-115 °C
IR (Nujol, cm^{-1})	:	ν_{max} 2925, 2860, 1629, 1470, 1385, 1272
$[\alpha]_D^{25}$	:	- 33.5°(c 0.9, EtOH)

^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.85 (t, J=6 Hz, 3H), 1.2-15 (m, 8H), 1.5-1.9 (s, 1H), 2.0-2.7 (m, 6H), 2.9-3.2 (m, 4H), 3.4 (q, J = 8.1 Hz, 1H), 3.9 (s, 3H), 6.75 (d, J = 5.4 Hz, 1H), 7.0 (s, 2H), 7.35 (m, 4H), 7.5 (d, J=2.7Hz, 2H), 8.0 (d, J=9.4 Hz, 2H), 8.7 (d, J = 5.4 Hz, 2H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 11.9, 23.0, 25.2, 25.8, 26.5, 37.0, 49.8, 50.5, 55.6, 59.5, 74.0, 101.2, 118.7, 121.8, 127.0, 127.5, 128.6, 129.5, 130.0, 131.2, 132.2, 133.3, 143.6, 144.9, 147.5, 158.0, 165.0.
Elemental analysis	:	Calculated for $C_{27}H_{30}N_2O_3$: C, 75.35; H, 6.97; N, 6.51, Found : C, 74.81; H, 6.80; N, 6.96.

Preparation of 4,6-bis(9-*O*-Dihydroquinidinyl)-2,5-diphenyl pyrimidine

A suspension of dihydroquinidine (0.978 g, 3 mmol), 4,6-dichloro-2,5-diphenyl pyrimidine (0.421 g, 1.4 mmol) and potassium hydroxide (0.252 g, 4.5 mmol) in toluene (20 mL) was stirred at reflux with azeotropic removal of water for 6 h. The reaction mixture was diluted with water (20 mL), extracted with EtOAc (4 x 20 mL) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to furnish a crude product as light yellow syrup. It was purified by flash column chromatography over deactivated silica gel using a mixture of EtOAc : methanol (99 : 1). The solvent was evaporated under reduced pressure to afford a colorless solid (0.83g).

Yield	:	0.83 g (65 %)
mp	:	116-118 °C
IR (Nujol, cm^{-1})	:	ν_{max} 2935, 1622, 1390, 1235
$[\alpha]_D^{25}$	:	- 234.5°(c 1.4, EtOH)
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 0.82 (t, J = 8 Hz, 3H), 1.28 (m, 10H), 1.62 (m, 6H), 2.0 (bs, 2H), 2.3 (m, 2H), 2.55 (m, 2H), 3.1 (m, 6H), 3.86 (s, 6H), 6.95 (m, 4H), 7.65-7.1 (m. 14H), 8.05 (d, J = 9 Hz, 2H), 8.74 (d, J = 4.5 Hz, 2H),

Preparation 3,6-pyridazine-diol:

Hydrazine hydrochloride required for this purpose was made by passing HCl gas through hydrazine hydrate for around 12 h. Hydrazine hydrochloride precipitated out was filtered and dried by suction.

To a boiling solution of 7.5 g (0.07 mol) of hydrazine hydrochloride in 50 ml of water was added in one lot 6.8 g (0.07 mol) of maleic anhydride, with stirring. The mixture was maintained at boiling point for 3h. The reaction mixture was kept at room temperature overnight. 3,6-Pyridazinediol precipitated out was filtered and dried in air.

Yield	:	6.2 g (80 %)
Mp	:	300-301°C (lit[37] 299.5-300 °C)
IR (Nujol, cm^{-1})	:	3250, 2922, 2852, 1672, 1578, 1404, 1316, 1212.
Analysis	:	$C_4H_4N_2O_2$ requires, C, 42.86; H, 3.57; N, 25.00; Found: C, 41.78; H, 3.77; N, 25.37

Synthesis of 3,6-dichloropyridazine:

3,6-Pyridazine diol (5 g) was refluxed in 60 ml of freshly distilled phosphorous oxychloride for 5h. Excess reagent was distilled in vacuo and cooled residue poured into ice. Ammonium hydroxide (28%) was added till the suspension was slightly alkaline (litmus). The light brown solid was filtered off and dried in vacuo. The combined filtrate was extracted with chloroform and solvent removed to get another lot of the product. The crude material was further sublimed to get the pure product as white solid.

Yield	:	4.9 g (74 %).
Mp	:	68-69 °C (lit[36]. 68-69 °C).
^1H NMR (200 MHz, $CDCl_3$)	:	7.5 (s, 2H)

Preparation of 3,6-bis(9-*O*-dihydroquinyl)pyridazine, $(DHQ)_2PYDZ$

A suspension of dihydroquinine (0.978 g, 3 mmol), 3,6-dichloropyridazine (0.207 g, 1.4 mmol) and potassium hydroxide (0.252 g, 4.5 mmol) in toluene (20 ml) was stirred at reflux with azeotropic removal of water for 6h. The reaction mixture was

diluted with water (20 ml), extracted with EtOAc (4 x 20 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to furnish a crude product as light yellow syrup. It was purified by flash column chromatography over deactivated silica gel using a mixture of EtOAc : methanol (99 : 1). The solvent was evaporated under reduced pressure to afford a colorless solid (0.73 g).

Yield	:	0.73 g (63 %)
mp	:	114-116 °C
IR (Nujol, cm^{-1})	:	ν_{max} 2930, 1620, 1380, 1231
$[\alpha]_D^{25}$	:	- 78.8°(c. 0.9, EtOH)
^1H NMR (200 MHz, $CDCl_3$)	:	δ 0.83 (t, J = 8 Hz, 6H), 1.6-1.25 (m, 12H), 1.7 (bs, 2H), 1.88 (m, 2H), 2.7-2.5 (m, 8H), 3.28 (q, J = 8.25 Hz, 2H), 3.88 (s, 6H), 6.78 (d, J = 6.25 Hz, 2H), 7.0 (s, 2H), 7.37 (m, 4H), 7.47 (d, J = 2.5 Hz, 2H), 8.0 (d, J = 9 Hz, 2H), 8.67 (d, J = 4.5 Hz, 2H),
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 12.22, 23.08, 25.53, 26.38, 27.55, 37.62, 50.3, 51.11, 55.9, 60.24, 77.03, 102.14, 118.8, 121.56, 122.05, 128.0, 131.83, 144.87, 145.03, 147.65, 158.03, 161.1.
Elemental analysis	:	Calculated for $C_{44}H_{52}N_6O_4$: C,72.52; H, 7.14; N, 11.54, Found : C, 72.32; H, 7.18; N, 11.42

Typical procedure for the asymmetric aminohydroxylation of silyl enol ethers

A mixture consisting of $(DHQD)_2CLB$ (10mg, 0.02 mmol) in 20 mL of t-butanol : H_2O (1:1), and OsO_4 (20 μL of 0.5 molar solution in toluene, 0.01 mmol) was stirred for 2 min. To this solution, chloramine - T (570 mg, 2.5 mmol) was added and stirred for 2 min., followed by the addition of the silyl enol ether (1mmol). Pale green colour was formed immediately and turned to dark brown after 10 minutes. The progress of the reaction was monitored by TLC. After additional 5 min. stirring the reaction was quenched by the addition of sodium metabisulfite. The two layers were separated. The aqueous layer was extracted with ethyl acetate. The combined organic

layer was washed with brine, dried over anhydrous sodium sulphate and solvent was distilled off under reduced pressure. The crude product was purified by flash chromatography (8 - 10 % ethyl acetate : pet ether) to give the pure product. Chiral analysis was done by using 96 % ethanol - water with detector wavelength fixed at 210 nm.

2 - (N - (p -Tolylsulfonyl)amino)cyclohexanone, 51

Yield	:	50 %
mp.	:	139-140 °C (Lit.[29] 133-135 °C)
$[\alpha]_D$	:	-10°(c 0.5, $CHCl_3$) (Ligand: DHQD-CLB)
IR ($CHCl_3$, cm^{-1})	:	3290, , 1695, 1585, 1350, 1310, 1265, 1160, 1090, 815, 740, 670.
^1H NMR (300 MHz, $CDCl_3$),	:	δ 1.5 (m, 3H, ring CH), 1.8 (m, 1H, ring CH), 2.0 (m, 1H, ring CH), 2.2 (dt, 1H, ring CH) 2.35 (s, 3H, Ar-CH_3), 2.5 (m, 2H, ring CH), 3.7 (m, 1H, CHN), 5.75 (d, J =6.2 Hz, 1H, NH), 7.25 (d, J = 9.4 Hz, 2H, Ar-H) 7.7 (d, J = 9.4 Hz, 2H, Ar-H).
^{13}C NMR (200 MHz, $CDCl_3$),	:	δ 21.43, 23.88, 27.44, 36.76, 40,72, 60.60, 126.87, 129.75, 136.98, 143.55, 205.61.
MS : m/z (% rel intensity)	:	239(68), 211(20), 155(83), 154(41), 139(23), 133(12), 111(17), 97(12), 91(100), 90(63), 84(42), 83(33), 73(7).
Analysis	:	$C_{13}H_{17}NO_3S$ requires C, 58.43; H, 6.37; N, 5.24; S, 11.985 %. Found: C, 58.34; H, 6.3; N, 5.3; S, 11.91 %.
Chiral HPLC		Retention times: 20.60 (minor) and 23.00 (major). Flow rate: 0.2 ml/min

2 - (N - (p - Tolylsulfonyl)amino) - 4 – methylcyclohexanone, 52

Yield	:	49 %
mp	:	99 - 100 °C
$[\alpha]_D$		+22.5°(c 0.5, $CHCl_3$), (Ligand DHQ-PYDZ)
IR ($CHCl_3$, cm^{-1})	:	3280, 1695, 1590, 1400, 1320, 1220, 1160, 1090, 920, 810, 740, 660

^{1}H NMR (200MHz, $CDCl_3$),	:	δ 1.0 (d, J = 8.1 Hz, 3H, ring-CH_3), 1.15-1.35 (m, 2H, ring CH), 1.6-1.7(bs, 1H, ring CH), 1.9-2.0 (m, 1H, ring CH), 2.25-2.35 (m, 1H, ring CH), 2.4 (s, 3H Ar-CH_3), 2.4 -2.5 (m, 2H, ring CH), 3.75 (m, 1H, CHN), 5.75 (d, J= 5.4 Hz, 1H, NH), 7.3 (d, J = 9.2 Hz, 2H, Ar-H), 7.7 (d, J = 9.2 Hz, 2H, Ar-H).
^{13}C NMR (200MHz, $CDCl_3$),	:	δ 20.9, 21.74, 31.0, 35.45, 39.97, 44.75, 59.89, 127.22, 129.98, 137.22, 143.8, 206.31.
MS : m/z (% rel. intensity)	:	281(M^+, 6), 237(8), 224(51), 216(51), 155(88), 133(9), 126(26), 98(81), 91(100), 81(29), 70(14), 65(37), 55(15).
Aanalysis	:	$C_{14}H_{19}NO_3S$ requires C, 59.79 ; H, 6.76 ; N, 4.98; S, 11.39 %. Found: C, 59.73; H, 6.8; N, 4.85; S, 11.36 %.
Chiral analysis	:	Retention times: 18.5 (minor) and 21.2 (major). Flow rate: 0.5 ml/min

2 - (N - (p - Tolylsulfonyl)amino) - 4 - *tert*-butylcyclohexanone, 53

Yield	:	34 %
mp		120 – 121 °C
$[\alpha]_D$		-11.4°(c 0.5, $CHCl_3$) (Ligand: DHQD-CLB)
IR ($CHCl_3$, cm^{-1})	:	3290, 1700, 1600, 1340,1290, 1160, 1090, 980, 920, 810, 760, 670.
^{1}H NMR (200MHz, $CHCl_3$)	:	δ 0.9(s, 9H, tBu), 1.25-1.5(m, 2H, ring-CH), 1.55-1.7(m, 1H,ring CH), 2.05-2.15(m, 1H,ring CH) 2.2-2.35(m, 1H, ring CH), 2.4(s, 3H, Ar-CH_3), 2.45 -2.6(m, 2H, ring CH), 3.75(m, 1H, CHN), 5.75(bd, J = 5.4 Hz, 1H,NH), 7.25(d, J = 9.2 Hz, 2H, Ar-H), 7.75(d, J = 9.2Hz, 2H, Ar-H).
^{13}C NMR ($CDCl_3$, 50.3MHz),	:	δ 21.7, 27.8, 28.6, 32.6, 38.3, 39.9, 46.0, 60.4, 127.3, 129.9, 143.8, 206.4.
MS : m/z (% rel. intensity)	:	323(M^+, 3), 266(54), 238(22), 210(25), 172(9), 155(49), 140(17), 123(24), 110(17), 91(100), 82(20), 77 (7), 65

(36), 57 (70), 55 (49).

Analysis : $C_{17}H_{25}NO_3S$ Requires C, 63.16; H, 7.74; N, 4.33; S, 9.91 %. Found: C, 63.23; H, 7.84; N,4.38; S, 9.82%.

Chiral analysis : Retention time: 17.80(minor), 21.37(major)
Flow rate: 1 ml/min.

2 - (N - (p - Tolylsulfonyl)amino) propiophenone, 54

Yield : 54 %

mp : 115 –116 °C (Lit.[29] 112-114 °C)

$[\alpha]_D$ - 17°(c 1, $CHCl_3$) (Ligand: DHQD-CLB)

IR ($CHCl_3$, cm^{-1}) : 3280, 1670, 1590, 1400, 1345, 1220, 1160, 1090, 960, 860, 750, 700, 660

^1H NMR (200MHz, $CDCl_3$), : δ 1.4 (d, J = 8.1 Hz, 3H, CH_3) 2.3 (s, 3H, Ar-CH_3), 4.95 (m, 1H, CHN), 5.8 (d, J = 8.1 Hz, 1H, NH), 7.15 (d, J = 8.1 Hz, 2H, ArH), 7.45 (t, J = 8.1 Hz, 2H, ArH), 7.55 (t, J = 8.1 Hz,1H, ArH), 7.7 (d, J = 8.1 Hz, 2H, ArH), 7.8 (d, J = 8.1 Hz, ArH).

^{13}C NMR (50.3MHz, $CDCl_3$), : δ 21.0, 21.5, 53.5, 127.2, 128.6, 128.8, 129.0, 129.8, 133.6, 134.2, 137.3, 143.6, 198.4.

MS m/z (% rel. intensity) : 303(M^+,1) 199(10), 198(100), 155(70), 105(33), 91(26), 90(16), 77(9).

Analysis : $C_{16}H_{17}NO_3S$ requires C, 63.36; H, 5.61; N, 4.62; S, 10.561 %. Found : C, 63.35; H, 5.60; N, 4.64; S, 10.57%

Chiral analysis : Retention time: 21.39 (minor); 26.43 (major)
Flow rate: 0.4 ml/min.

2 - (N - (p - Tolylsulfonyl)amino)tetralone, 55

Yield : 28 %

mp : 105-106 °C (Lit.[29] 105 °C)

$[\alpha]_D$: - 6.5°(c 0.5, $CHCl_3$)

IR ($CHCl_3$ cm^{-1}) : 3280, 1690, 1600, 1460, 1400, 1360, 1330, 1295, 1210,

		1165, 1095, 1000, 960, 815, 750, 680
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 2.1 - 2.35 (m, 2H, ring CH), 2.45 (s, 3H, Ar-CH_3), 2.7 (m, 1H), 3.9 (m, 1H, CHN), 6.1 (bs, 1H, NH), 7.2 - 7.35 (m, 4H, ArH), 7.55 (t, J = 6Hz, 1H, ArH), 7.85 (d, J = 8.2 Hz, 2H, ArH), 7.95 (d, J = 8.2 Hz , 1H, ArH)
^{13}C NMR (200 MHz, $CDCl_3$)		δ 21. 47, 28.61, 32. 79, 60. 15, 127.46, 128.13, 128.58, 128.73, 128.89, 129.60, 130.47, 134.63, 143.86, 144.65, 194.37.
MS m/z (% rel. Intensity)	:	315(M^+, 4), 266(11), 160(72), 155(15), 144(26), 130(47), 124(13), 117(40), 115(29), 110(11), 112(22), 91(100), 84(26), 81(13), 77(32), 69(16), 65(46), 60(8), 57(47).
Analysis	:	$C_{17}H_{17}NO_3S$ requires C, 64.762; H, 5.40; N, 4.44, S, 10.16 %. Found : C, 64.70; H, 5.36; N, 4.43; S,10.2 %.
Chiral analysis	:	Retention time: 22.50(minor), 25.40(major). Flow rate: 0.4 ml/min.

Synthesis of racemic amino ketones

The aminating reagent (N-(*p*-toluenesulfonyl)imino)phenyliodinone, PhI=NTs was prepared according to literature procedure.[37]

Preparation of Iodobenzene diacetate, $PhI(OAc)_2$:

Hydrogen peroxide (30%, 7 ml) and acetic anhydride (30.5 ml) was stirred together for 4 h at 40 °C. Iodobenzene (5 g, 24 mmol) was added to the solution which was kept overnight. Some $PhI(OAc)_2$ crystallized out and was filtered off. The filtrate was concentrated to small volume and a second crop obtained. The combined crystals were washed with ether and dried.

Yield : 5.1 g (65 %)

mp. : 156-158 °C (lit.[37] 158 °C).

Preparation of (N-(*p*-toluenesulfonyl)imino)phenyl iodinane, PhI=NTs

Iodobenzene diacetate (3.2 g, 10mmol) was added at 5 °C under argon to a stirred mixture of *p*-toluenesulfonamide (1.71 g, 10 mmol) and KOH (1.4 g, 25 mmol) in methanol (40 ml). The resulting yellow homogeneous solution was then stirred for 30 min at 5 °C anf 3 h at room temp. The mixture was then concetrated under argon (20 ml) and poured on ice (100 g). The precipitated pale yellow solid was filtered off and washed with anhydrous ether (50 ml) to afford crystals of PhI=NTs was then dried under vacuum and stored at 0 °C on dark under argon to avoid decomposition.

Yield : 2 g (55%).

General procedure for the synthesis of racemic amino ketones

To PhI=NTs (250 mg, 0.67 mmol) in 10 mL of dry acetonitrile was added silylenol ether (1.0 mmol) followed by $Cu(OTf)_2$ (0.024 g, 0.067 mmol) at –15 °C. The reaction was allowed to stir at –15 °C for about 2 h and stopped when all the PhI=NTs had been drown into solution. Solvent was evaporated and the crude product was purified by silicagel chromatography using 10-15 % ethylacetate/pet. ether to afford the pure product.

Yield : 60-65 %

1.7. References

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CHAPTER II

Synthesis of Optically Active Amino Acids Using Asymmetric Aminohydroxylation

2.0. General Introduction

Amino acids have been the focus of great interest in all areas of both the physical and life sciences for over 150 years. It is well known that α-amino acids are vital to life itself as the "building blocks" of peptides, proteins, and many other natural products. Beyond this fundamental role, amino acids are used extensively as food additives, agrochemicals, and pharmaceuticals. The recent evaluation in molecular biology and protein engineering technologies have opened vast new perspective for the intelligently designed use and incorporation of amino acids in numerous proteinaceous and non-proteinaceous materials. Major advances in the understanding of enzyme mechanisms, protein conformations and properties related to molecular recognition, protein-nucleic acid interactions amongst countless other important regulatory interactions involving the basic twenty or so proteinogenic amino acids have placed the study of amino acid chemistry at the forefront of modern chemical science. The number of naturally occurring, non-proteinogenic amino acids is rapidly approaching 1,000; the number of non-natural or totally synthetic amino acid could in principle be almost infinite. Amino acids have also been used in organic synthesis as synthetic targets, as source of chiral raw materials and as constituents got reagents and/or catalysts in asymmetric synthesis. With the now routing automated technology to synthesize on solid supports, the possibilities for synthesizing new enzymes, hormones, synthetic immunostimulants, drugs and countless other valuable materials have started to become recognized and represent emerging, exciting and creative fields. The benefits of these efforts will undoubtedly reach far into the future.

Numerous reviews and monographs on the chemistry and biochemistry of the amino acids and their utilization have been appeared in recent years.[1] Detailed discussion about the use of amino acids in the field of pharmaceuticals, agricultural products, the food industry, materials science, molecular biology and protein engineering technologies are accounted in those reports. As application of amino acids

are extensively increasing day by day, their synthetic methods are also appearing very rapidly in recent years.[2] Many amino acids are found to be the crucial constituent of natural products endowed with significant biological activity. For example, α-hydroxy derivatives of β-amino acids are the part of many biomolecules such as amastatin, bestatin, microginin etc. Therefore, construction of amino acid part is an important step towards the synthesis of these biomolecules. Arylglycines are the important constituent of glycopeptide antibiotics, which inhibits bacterial cell-wall biosynthesis. Synthetic D-arylglycins are used as a side chain moiety of semisynthetic penicilins and cephalosporins. The arylglycine side chain aids in the oral absorption of these β-lactam antibiotics.

The importance of amino acids has prompted the development of a multitude of methods for their racemic and asymmetric synthesis. All the amino acids occurring in nature are in the L form and are comparatively cheaper than that of its antipode. Since numerous applications of D-configured amino acids are also started very widely and rapidly, efforts are on to promote the synthetic manipulations more efficient and cost effective.

Enantioselective Synthesis of α-Hydroxy β-Amino Acids : Key Intermediate for Aminopeptidase Inhibitor

2.1.1. Introduction

In recent years, *syn*-α-hydroxy β-amino acids have received considerable attention as the crucial component of peptidomimetic protease inhibitors. For instance, this moiety occurs in important renin inhibitors such as KRI-1230 (**1a**)[3] and KRI-1314[4] (**1b**), in which the absolute stereochemistry of the corresponding acid parts is 2R, 3S.

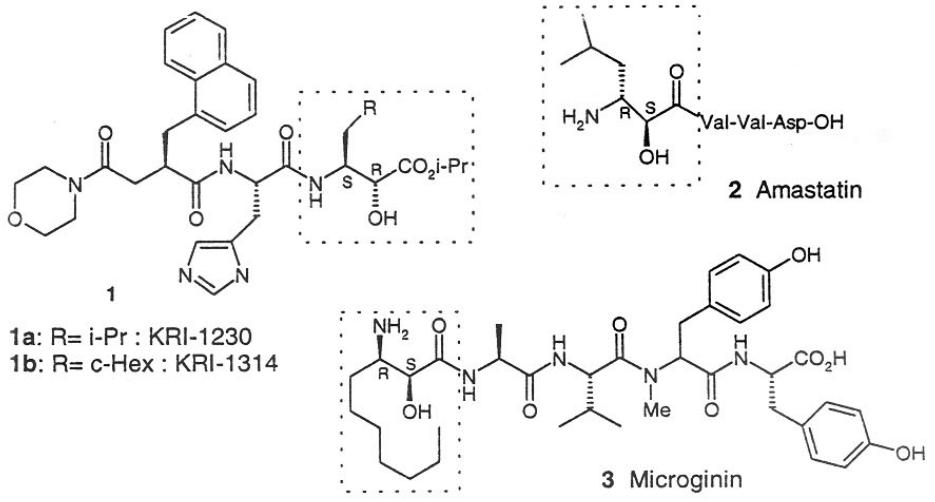
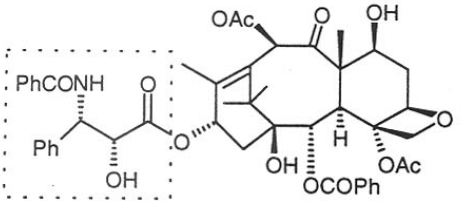


Fig. 1

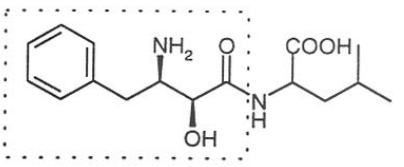
On the other hand, its antipode of the stereochemistry, a (2S, 3R)- -α-hydroxy β-amino acid unit, has also been found in amastatin (**2**)[5] and a marine natural product, microginin (**3**),[6] which was recently isolated from the cultured fresh water blue-green algae

Microcystic aeruginosa and exhibits inhibitory activity toward the angiotensin-converting enzyme (**Fig.1**).

Other most striking examples are provided by the potent anti-neoplastic agent, taxol (**4**)[7] the activity of which depends on the constituent acids having the '*syn*' configuration(**Fig. 2**). Also, bestatin (**5**)[8] (2S, 3R)-3-amino-2-hydroxy-4-phenyl-butanoyl-S-leucine is well known as an immune-response modifier and inhibitor of aminopeptidase B.



4 Taxol



5 Bestatin

Fig. 2

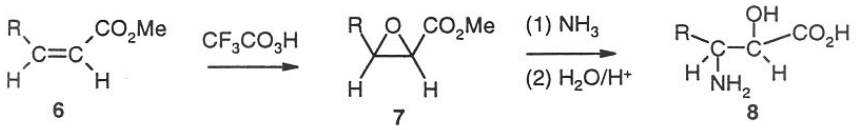
Apart from their intrinsic properties, β-amino acids are useful as intermediates for preparing β-lactams,[9] piperdins,[10] indoliziines,[11] and modified peptides.[12] In view of their promising chemical and pharmaceutical potential, it is no surprise that much effort has been expended in devising enantioselective synthesis of β-amino acids in general.[13]

2.1.2. Review of Literature

Many methods have already been developed for the synthesis of α-hydroxy β-amino acid units. Most of the early studies that used chiral natural products as starting materials were limited in their flexibility of structural modification. Although, more recently, several methods that are applicable to the synthesis of derivatives bearing a variety of side chains have been reported, practical routes for the construction of both their enantiomers starting with common frameworks are still desirable. Following are the methods reported in the literature.

Takita's approach[14]

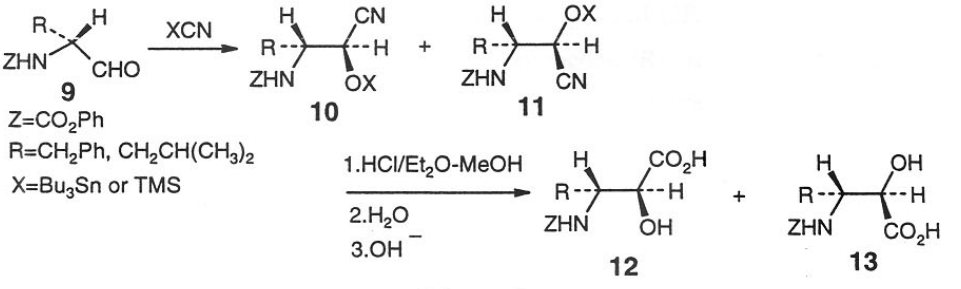
Threo-3-amino-2-hydroxy acids were synthesized from *cis*- and *trans*-2-olefinic acids *via* regiospecific ring-opening of cis-2,3-epoxy-acids by ammonia (scheme 1).



Scheme 1

Herranz's approach[15]

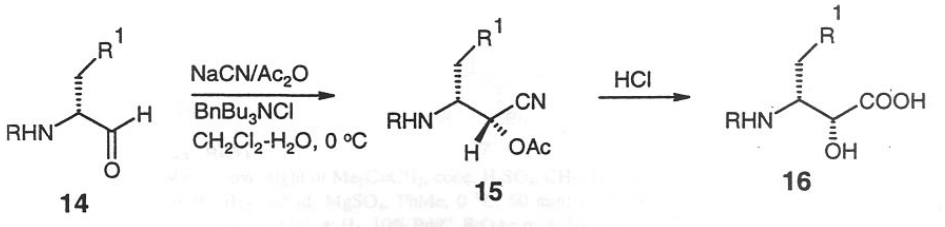
These authors developed a one pot procedure for the stereoselective synthesis of (2R, 3R)-3-amino-2-hydroxy-4-phenylbutanoic acid [(2R, 3R)-AHPBA] and (2S, 3R)-3-amino-2-hydroxy-5-methylhexanoic acid [(2S, 3R]-AHMHA], consisting of reaction of the corresponding N-2-amino aldehyde with (trimethyl silyl)cyanide or (tributyl tin)cyanide followed by hydrolysis of cyano group via the intermediate imidate hydrochloride (scheme 2).



Scheme 2

Terashima's approach[16]

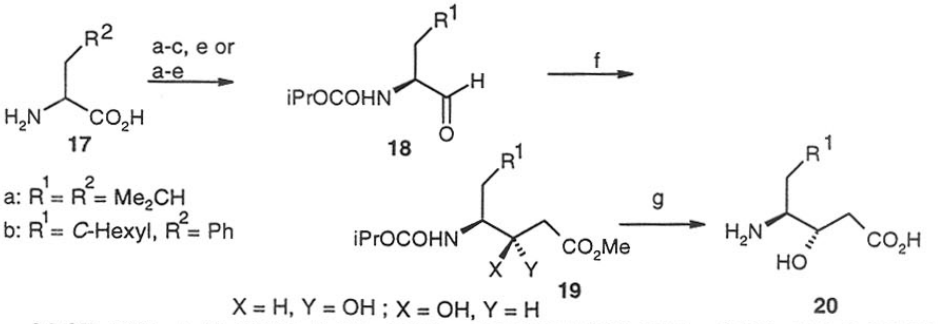
Terashima *et. al.* achieved the synthesis via highly diastereoselective formation of a cyanohydrin acetate (**15**) from an aldehyde (**14**) under phase transfer condition (scheme 3).



Scheme 3

Terashima's approach[17]

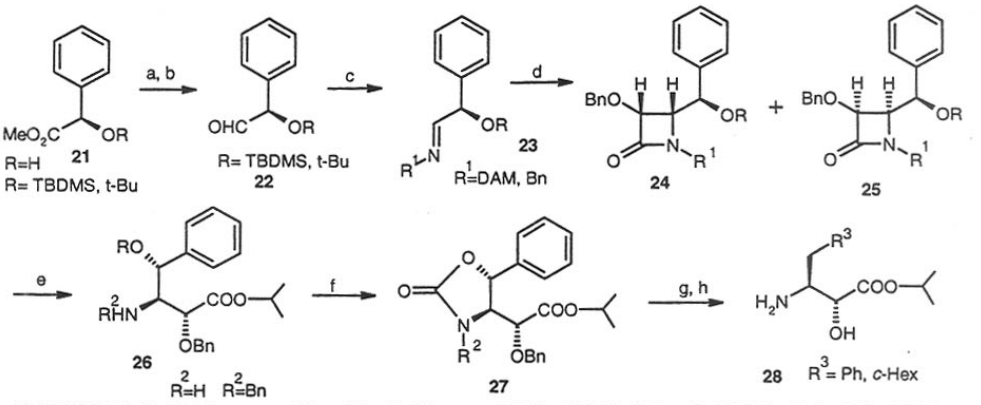
The synthesis of α-hydroxy β-amino acid was accomplished by employing stereoselective aldol reaction of O-methyl-O-trimethylsilyl ketene acetal with (S)-α-amido aldehyde (**18**) in the presence of titanium (IV) chloride (scheme 4).



a: MeOH, $SOCl_2$; **b**: iPrOCOCl, K_2CO_3, CH_2Cl_2 or iPrOCOCl, Et_3N, THF; **c**: $NaBH_4$, LiCl, EtOH, THF; **d**: H_2 (4 atm), $Rh\text{-}Al_2O_3$, MeOH, AcOH; **e**: SO_3, Py, DMSO, Et_3N, PhMe; **f**: CH_2=C(OMe)(OTMS), $TiCl_4$, MS 4A, CH_2Cl_2, -78°C; **g**: (i) 6M HCl, AcOEt, 100°C; (ii) Dewex AG

Scheme 4

In an another method, Terashima[18] had synthesized (2R, 3S) and (2S, 3R)-3-amino-2-hydroxycarboxylic acid derivatives from methyl (R)- and (S)-mandalate. The synthesis was accomplished by featuring the [2+2] cycloaddition reaction of a chiral imine (**23**)with benzyloxyketone. Alcoholysis of the formed 2-azetidinone derivative (**24, 25**) and reductive removal of the mandelate derived benzylic oxygen by way of a 2-oxazolidone derivative to get the amino alcohol (scheme5).

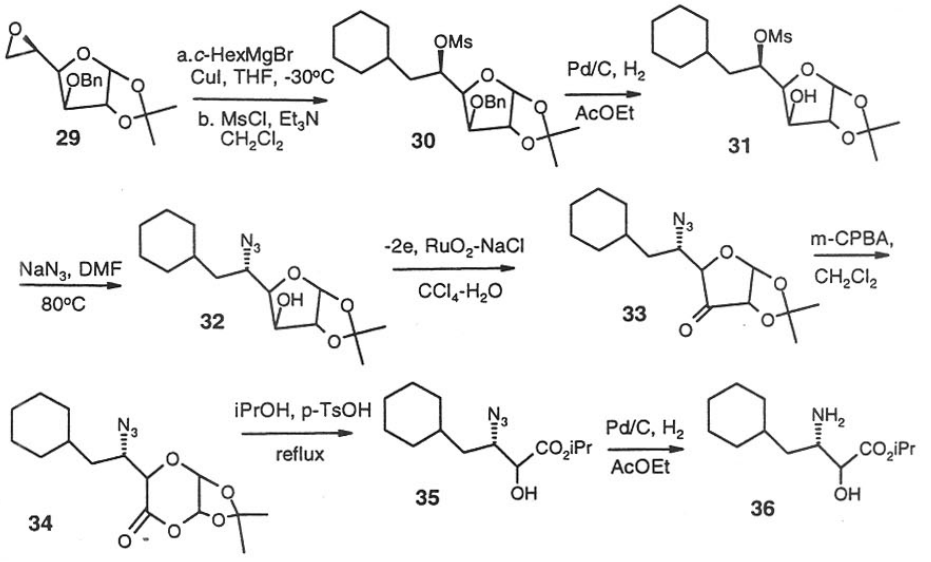


a: TBDMSCl, ImH, DMF, r t, overnight or Me_2C=CH_2, conc. H_2SO_4, CH_2Cl_2, 2 days; **b**: DIBAL, Et_2O-C_6H_6, -78 °C, 20 min; **c**: $DAMNH_2$ or $BnNH_2$, anhyd. $MgSO_4$, PhMe, 0 °C, 50 min; **d**. $BnOCH_2COCl$, Et_3N, CH_2Cl_2,; **e**: HCl, iPrOH, rt; **f**: Cl_3COCl, Py, CH_2Cl_2, O °C; **g**: H_2, 10% Pd/C, EtOAc rt; **h**: H_2(5 atm), 5% $Rh\text{-}Al_2O_3$, AcOH.

Scheme 5

Torii's approach[19]

These authors reported the synthesis of cyclohexylnortatines derived from D-glucose *via* cyclohexylation at C(6) position, azidation at the C(5) carbon and cleavage

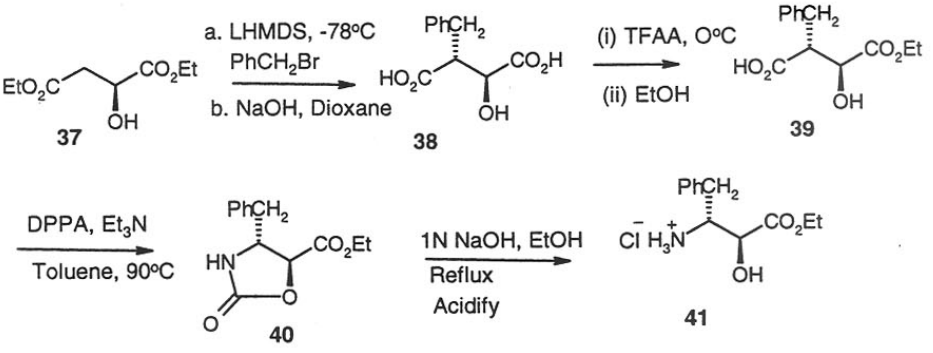


Scheme 6

of the C(2)—C(3) bond by electrooxidation / Bayer- Villiger oxidation sequence (scheme 6).

Norman's approach[20]

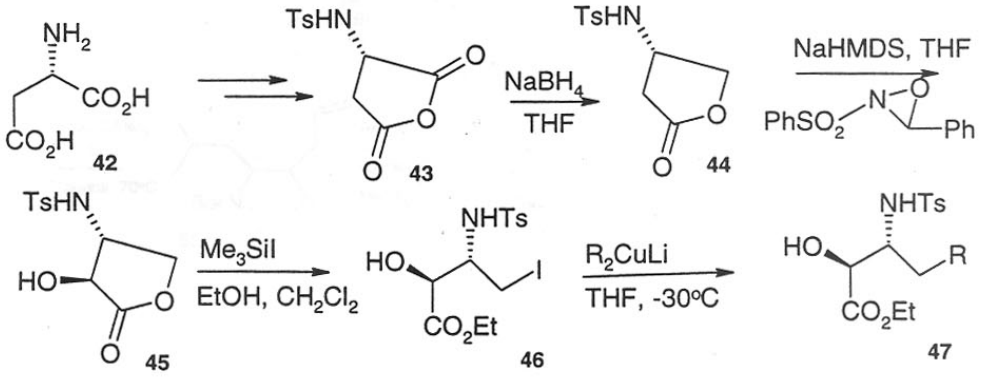
This approach features a stereocontrolled alkylation of diethyl (S)-malete and proceeds through an oxazolidone via a Curtius rearangement (scheme 7).



Scheme 7

Jefford's approach[21]

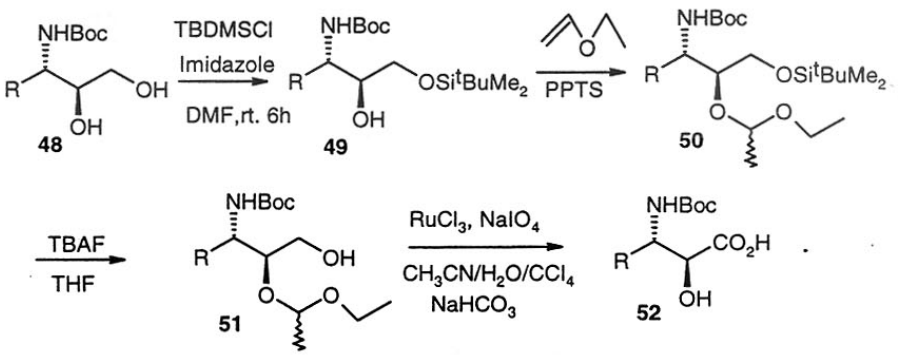
Jefford and coworkers developed a method for the synthesis of 3-amino-2-hydroxy acids from L-aspartic acid by N-tosylation, anhydride formation, reduction, α-hydroxylation, iodoesterification and alkylation followed by saponification and deprotection (scheme 8).



Scheme 8

Reira's approach[22]

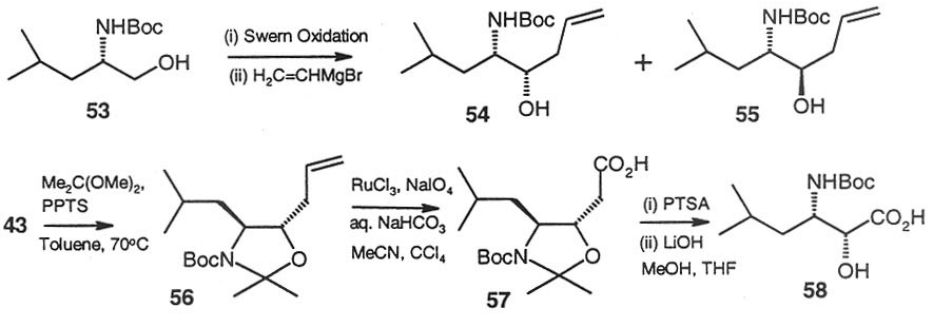
Both *anti-* and *syn*-α-hydroxy-β-amino acid are synthesized in protected form and high enantiomeric purity from readily available anti-N-Boc-1-*tert*-butyldimethylsilyl-3-amino-1,2-diols. The synthesis was achieved by protection of the secondary hydroxyl group (1-ethoxyethyl) followed by desilylation/oxidation of the primary hydroxyl group (scheme 9).



Scheme 9

Datta's approach[23]

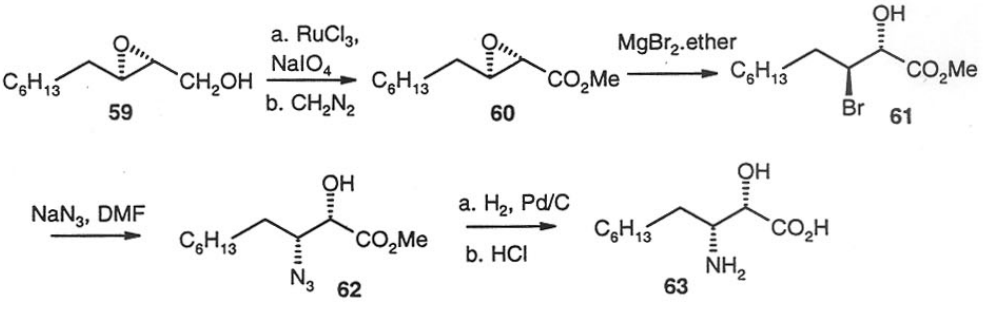
Datta reported the synthesis of the α-hydroxy-β-amino acid via a syn selective Grignard reaction of N-Boc leucinol with vinyl magnesium bromide (scheme 10).



Scheme 10

Righi's approach[24]

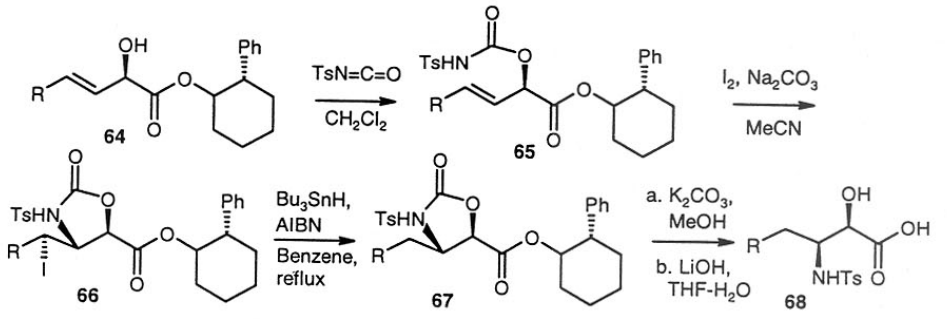
The synthesis (2S, 3R)-3-amino-2-hydroxydecanoic acid was achieved by Righi and coworkers via regio- and stereoselective opening of epoxide (**60**) by $MgBr_2.Et_2O$ as a key step. The azidation of the bromoalcohol (**61**) followed by reduction yielded the amino hydroxy acid (scheme 11).



Scheme 11

Sugimura's approach[25]

Sugimura reported the synthesis of syn-α-hydroxy-β-amino acid via the preparation of trans-4,5-disubstituted 2-oxazolidinone derivative (**66**) by cyclization of allylic carbamates (**65**). The subsequent removal of the iodo group and the protective functionality afforded the required amino acid (scheme 12).



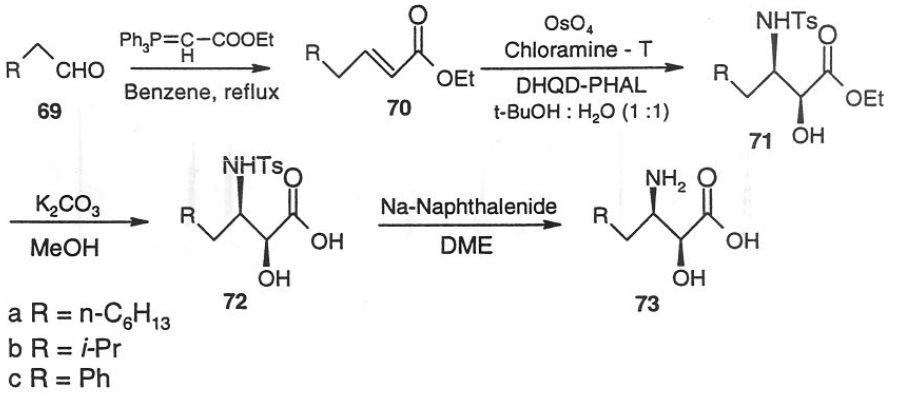
Scheme 12

Most of the above methods for the synthesis of α-hydroxy-β-amino acids deal with the use of chiral starting material, separation of the diasteromers etc. The synthesis involves multiple steps as well as the use of very expensive reagents. Thus there is a scope for a more convenient synthetic route.

2.1.3.Present Work

Objective

Efforts that direct towards the total synthesis of peptidomimetic protease inhibitors continue unabated. Most of the reports described earlier used chiral natural products as starting materials and are limited in their flexibility of structural modification. Although several of the recent methods applicable to the synthesis of derivatives bearing a variety of side chains have been developed, practical routes for the construction of both their enantiomers starting with common framework are still desirable. The objective of the present investigation is to apply Sharpless aminohydroxylation process for the synthesis of these α-hydroxy-β-amino acids to make the synthetic procedure simple involving lesser number of steps (Scheme13).



Scheme 13

2.1.4. Results and Discussion

The synthetic route for the synthesis of α-hydroxy-β-amino acids is depicted in **Scheme 13**. The olefin **70** was prepared by Wittig reaction of corresponding aldehyde with carbethoxymethyl triphenyl phosphorane in benzene at reflux temperature. The IR spectrum shows a sharp peak at 1710 cm^{-1} corresponding to the ester functionality and a peak at 1650 cm^{-1} (less intense than the carbonyl peak) due to the C=C stretching of the olefin. The olefinic protons appear in the ^1H NMR spectrum at 5.8 δ as doublet of doublet and at 6.9 δ as multiplet. The J value for the peak at 5.8 δ (14.9 Hz) indicates

the formation of the *trans*-olefin. In ^{13}C NMR spectrum the olefinic carbon appear at 121.2 and 148.6 δ. The olefin **70** was subjected for aminohydroxylation in presence of DHQD-PHAL as chiral ligand to give the amino alcohol **71**. The IR spectrum of the compound **71** show a peak at 3400 and 3200 cm^{-1} indicating the presence of both OH and NH group. The peak at 1650 cm^{-1} in the IR spectrum disappears. The NH proton appears in the ^1H NMR spectrum at 5.0 δ. The CH proton attached to the NH functionality appears at 3.6 δ as multiplet. The CH_3-protons of the tosyl group appears at 2.4 δ. ^{13}C NMR spectrum indicates the presence of the carbons attached to OH and NH functionality at 61.7 and 71.6 δ respectively (Fig. 3).

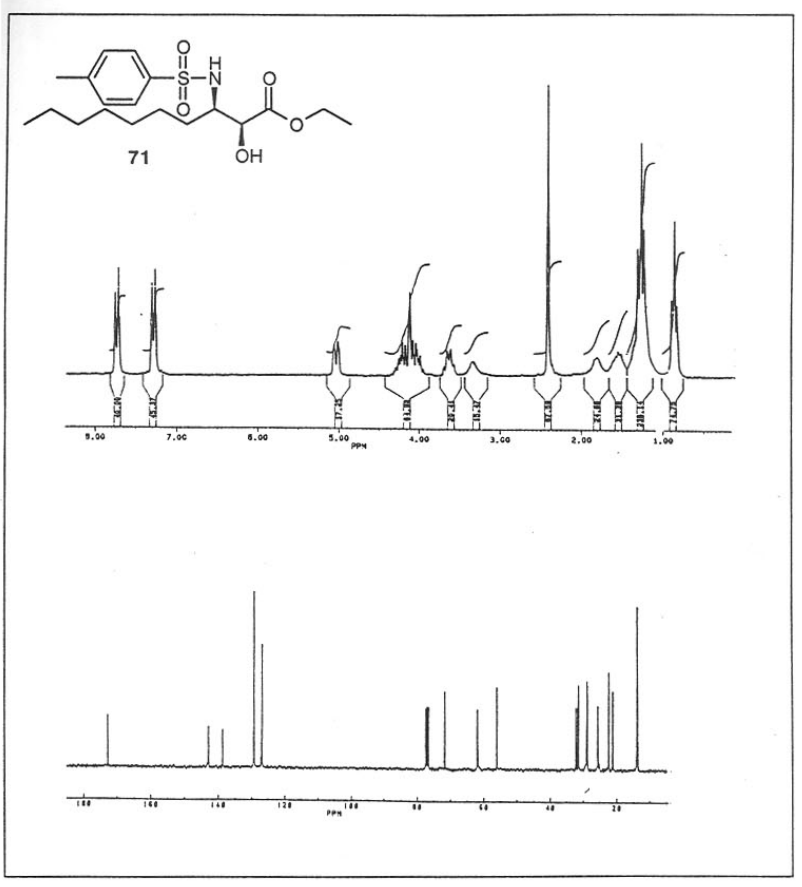


Fig. 3. ^1H and ^{13}C NMR of the compound 71a.

Hydrolysis of the esters **71** was done using K_2CO_3 in methanol to get the acid **72**. IR spectrum shows a broad band at 3400 cm^{-1} indicating the presence of acid functionality. Absence of ethyl of ester functionality in the ^1H NMR spectrum confirms the formation of acid **72**.

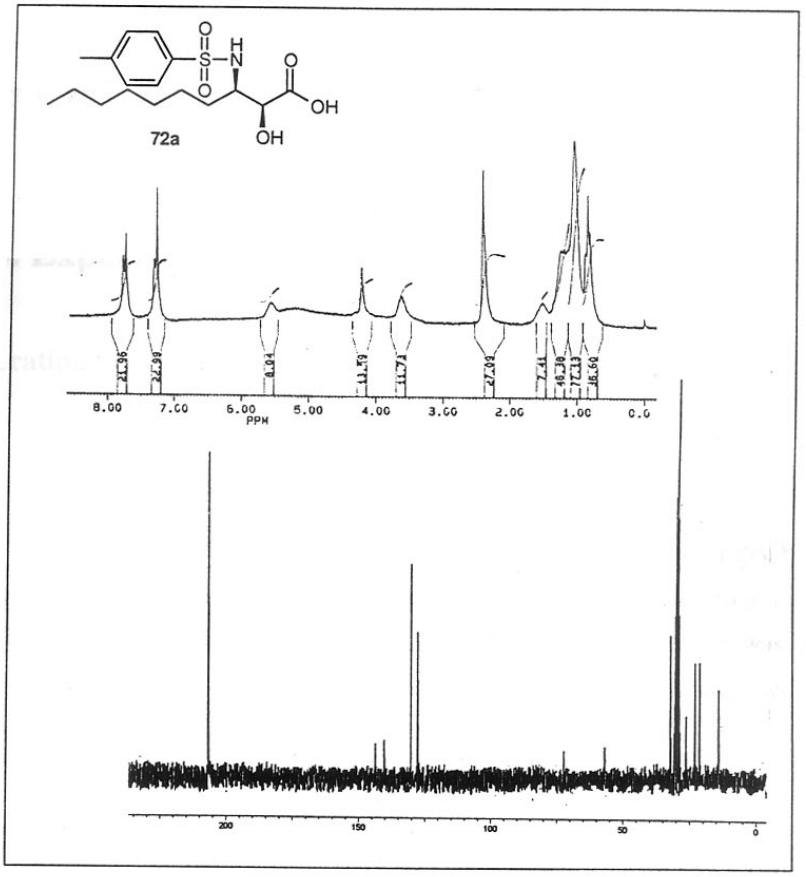


Fig. 4. ^1H and ^{13}C NMR of the compound 72a.

N-Detosylation of the acid **72** was carried out by using sodium naphthalenide to get the (2S, 3R)-3-amino-2-hydroxycarboxylic acid **73** in 76% yield. The IR spectrum of the compound shows the presence of broad band at 3400 cm^{-1} and the ^1H NMR shows the absence of tosyl functionality. The optical purity of the final compounds were determined by comparing the optical rotation of the same reported in the literature. The optical purity of the compounds were found to be >95 %.

2.1.5. Conclusion

A concise synthesis of (2S, 3R)-3-amino-2-hydroxycarboxylic acids (73) is achieved successfully in good yield and optical purity (>95 %) using Sharpless asymmetric aminohydroxylation process. The sequence of highly enantioselective aminohydroxylation and deprotection steps are quite practical for the synthesis α-hydroxy -β- amino acids.

2.1.4. Experimental

Preparation of Carboxymethylenetriphenylphosphonium bromide

$$Ph_3P + BrCH_2COOEt \rightarrow Ph_3{}^{+}PCH_2COOEt\ Br^{-}$$

To a solution of triphenylphosphine (10g, 0.038 mol) in 60 ml of dry benzene was added ethylbromoacetate (6.37g, 0.038 mol) dropwise with stirring at 40°C. Phosphonium bromide salt precipitated slowly. The reaction mixture was stirred overnight; the solid thus formed was filtered and washed with benzene and pet.ether and dried under vacuum.

Yield	:	16g, 98%
m. p.	:	160°C (Lit.[26] 163°C)

Preparation of carbethoxymethyl triphenylphosphorane

$$Ph_3P^{+}CH_2COOEt\ Br^{-}\ \text{aq. NaOH} \rightarrow Ph_3P{=}CHCOOEt$$

To a stirred solution of the above salt (6g) in 100 mL of cold water, aq. NaOH solution was added dropwise, till the solution became alkaline. Precipitated phosphorane was filtered, washed with water and dried. Recrystallization from benzene afforded the desired pure compound.

Yield	:	3.2g. (68%)
m. pt.	:	120°C (Lit.[26] 116-117°C)

General procedure for the preparation of olefin s

To a solution of carbethoxymethyltriphenylphosphorane (2.8g, 8.1 mmol) in benzene (20 mL) 1-octanal (1g, 7.8 mmol) was added. The mixture was stirred at reflux for 2.5h. The solvent removed *in vacuo* and the residual oil was extracted with pet.ether (3x20mL). The pet. ether solution was passed through a pad of silica gel and concentrated to get 1.4g light yellow oil.

Ethyl 3-(n-heptyl) acrylate (70a)

Yield	:	90 %
IR (Neat) cm^{-1}	:	2895, 1700, 1635, 1440, 1250
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.9 (t, J=8.1Hz, 3H), 1.15-1.5 (m, 13H), 2.15 (q, J=8.1Hz, 2H, -$\underline{CH_2}$-CH=C), 4.15 (q, J=8.1Hz, 2H, -O-$\underline{CH_2}$), 5.8 (d, J=14.9 Hz, 1H, =$\underline{CH}$-CO), 6.95 (m, 1H, $\underline{CH}$=C).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.69, 13.95, 22.40, 27.91, 28.93, 31.56, 31.92, 59.53, 121.19, 148.59, 165.91
Mass (m/z, % relative int.)	:	199 (M^+, 4), 153(38), 127(17), 115(17), 110(32), 101(73), 81(50), 73(81), 69(63), 55(100)

Ethyl-3-(2-methylpropyl)acrylate (70b)

Yield	:	92%
IR (Neat) cm^{-1}	:	2900, 1705, 1635, 1445, 1255, 1160
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.9 (d, J=9.1Hz, 6H, CH-$\underline{CH_3}$), 1.25 (t, J=7Hz, 3H, -$CH_2\underline{CH_3}$), 1.65-1.85 (m, 1H), 2.05 (t, J=6.1Hz, 2H), 4.15 (q, J=7Hz, 2H), 5.8 (d, J=15.7Hz, 1H), 6.9 (m, 1H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.13, 22.17, 27.76, 41.33, 59.70, 122.45, 147.52, 166.34

Ethyl-3-benzyl acrylate (70c):

Yield	:	88%
IR (Neat) cm^{-1}	:	2900, 1710, 1640, 1260.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.3 (t, J=6.4Hz, 3H, $-CH_3$), 3.5 (dd, J=8.1Hz, 2.7Hz, 2H, Ph-CH_2), 4.15 (q, J=8.1Hz, -OCH_2), 5.85 (d, J= Hz,), 7.05 (m, 1H), 7.15-7.4 (m, 5H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.6, 38.79, 60.56, 122.75, 126.66, 127.02, 129.05, 138.10, 147.61, 166.73

General procedure for aminohydroxylation of olefins

To a stirred solution of DHQD-PHAL (0.098g, 0.12 mmol, 5 mol %) in 15 mL of t-butanol and 15 mL of water was added. OsO_4 (0.25 ml of 0.2 molar solution in toluene, 0.05 mmol, 2 mol %). After stirring for two minutes, chloramine-T trihydrate (1.72g, 7.6 mmol, 3 mol equivalent) was added, followed by the olefin (2.5 mmol). The reaction was stirred till the green colour changed to yellow (about 2h.). Ethyl acetate (15 mL) and sodium sulfite (1g) were added and stirred for 1h. Organic layer was separated and aqueous layer was extracted with ethyl acetate (3x10 mL). The combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography using 10-15% ethylacetate-pet.ether.

(2S,3R)-Ethyl-2-hydroxy-3-(tosylamino)decanoate (71a)

Yield	:	62%
IR (Neat) cm^{-1}	:	3400, 3220, 2900, 1720, 1450, 1325, 1210, 1165, 1095.
$[\alpha]_D$		+ 30.9°(c 1, MeOH)
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.9 (t, J=7Hz, 3H), 1.25 (m, 13H), 1.5 (m, 1H), 1.75 (m, 1H), 2.45 (s, 3H), 3.35 (bs, 1H), 3.6 (m, 1H), 3.95-4.3 (m, 3H), 5.0 (d, J=10.8Hz, 1H), 7.3 (d, J=8.1Hz, 2H), 7.75 (d, J=8.1Hz, 2H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.60, 20.96, 22.19, 25.46, 28.71, 31.28, 31.43, 32.03, 55.87, 61.76, 71.59, 126.71, 129.11, 138.52, 142.69, 172.66

(2S,3R)-Ethyl-2-Hydroxy-5-methyl-3-(tosylamino)hexanoate (71b)

Yield	:	56%
IR (Neat) cm^{-1}	:	3280, 2950, 1720, 1420, 1340, 1160, 1095.
$[\alpha]_D$	:	+29.6°(c 0.8, $CHCl_3$)
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.70 (d, J=5.4Hz, 3H), 0.8 (d, J=5.4Hz, 3H), 1.1 (t, 1H), 3.3 (t, J=5.4Hz, 3H), 1.5 (m, 1H), 1.7 (m, 1H), 2.4 (s, 3H), 3.3 (bs, 1H), 3.7 (m, 1H), 4.0 (m, 2H), 4.2 (m, 1H), 4.9 (bs, 1H), 7.25 (d, J=5.4Hz, 2H), 7.7 (d, J=5.4Hz, 2H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 14.29, 21.72, 22.33, 22.76, 24.65, 41.33, 54.56, 62.51, 71.83, 82.34, 127.31, 129.78, 138.72, 143.46, 173.41

(2S,3R)-Ethyl-2-hydroxy-4-phenyl-3-(tosylamino)butanoate (71c)

Yield	:	54%
$[\alpha]_D$	:	+26.7°(c, 1, $CHCl_3$)
IR (Neat) cm^{-1}	:	3460, 3275, 1730, 1600, 1490, 1445
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.25 (t, J=7Hz, 3H), 2.50 (s, 3H), 2.65 (dd, J=13.2Hz, 5.4, 1H), 2.97 (dd, J=13.2, 10.00, 1H), 3.4 (bs, 1H), 3.85-4.05 (m, 3H), 5.05 (d, J=10Hz, 1H), 7.10 (d, J=8.0Hz, 2H), 7.25-7.10 (m, 5H), 7.7 (d, J=8.6Hz, 2H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 13.82, 21.53, 38.46, 57.52, 62.49, 70.20, 126.73, 126.92, 128.66, 129.62, 136.99, 138.20, 143.82, 173.22

General procedure for Hydrolysis of esters

To a solution of the ester (1 mmol) in methanol (10 mL) was added K_2CO_3 (0.28g, 2 mmol) in water (3 mL). The solution was stirred for 12h. Washed with ether and acidified with 2N HCl to pH 2. The mixture was extracted with ether (3x10 mL) and the combined organic layer washed with brine, dried over sodium sulfate and evaporated to give **72a-c**.

(2S,3R)-2-Hydroxy-3-(tosylamino)decanoic acid (72a)

Yield	:	85%
m. pt.	:	117-118°C

$[\alpha]_D$	:	+28.4°(c, 1, acetone)
IR (Nujol) cm^{-1}	:	3445, 3250, 1745, 1600, 1495
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.85 (t, 3H), 0.9-1.3 (m, 12H), 2.35 (s, 3H), 3.6 (bs, 1H), 4.2 (d, 1H), 5.6 (bs, 1H), 7.35 (d, J=5.4Hz, 2H), 7.75 (d, J=5.4Hz, 2H)
^{13}C NMR (Acetone d_6 + $CDCl_3$)	:	δ 14.42, 21.51, 23.32, 26.59, 29.84, 31.11, 32.21, 32.47, 57.13, 77.25, 127.93, 130.35, 140.54, 143.48, 206.81

(2S,3R)-2-Hydroxy-5-methyl-3(tosylamine)hexanoic acid (72b)

Yield	:	93%
IR (Nujol)	:	3400, 3250, 2960, 1740, 1600, 1440, 1320
m. pt.	:	141-143°C
$[\alpha]_D$	:	+32.4°(c, 1, acetone)
^{1}H-NMR (200 MHz , Acetone d_6 + $CDCl_3$)	:	δ 0.75 (t, J=6.2Hz, 3H), 0.8 (d, J=6.2Hz, 3H), 1.1-1.2 (m, 1H), 1.4-1.6 (m, 2H), 2.40 (s, 3H), 3.7 (m, 1H), 4.20 (d, 1H), 5.0 (bs, 1H), 7.25 (d, J=5.4Hz, 2H), 7.7 (d, J=5.4Hz).
^{13}C NMR (Acetone d_6 + $CDCl_3$)	:	δ 20.22, 21.24, 23.73, 39.86, 53.89, 70.68, 126.5, 129.2, 138.4, 143.2, 172.7

(2S,3R)-2-Hydroxy-5-phenyl-3-(tosylamino)pentanoic acid (72c)

Yield	:	83 %
m. pt.	:	184-186 °C
$[\alpha]_D$	:	+ 26.7°(c 0.4, acetone)
IR (Nujol) cm^{-1}	:	3450, 3250, 2940, 1760, 1600, 1460, 1320, 1255
^{1}H-NMR (200 MHz, $CDCl_3$)	:	2.4 (s, 3H), 2.55 (dd, J=13H, 54, 1H), 2.90 (t, J=13.0, 10.4, 1H), 4.05 (s, 1H), 3.85 (m, 1H), 6.50 (m, 1H), 7.05-7.25 (m, 5H), 7.35 (d, J=8.0Hz, 2H), 7.8 (d, J=8Hz, 2H)
^{13}C NMR (Acetone d_6 + $CDCl_3$)	:	21.32, 38.44, 58.89, 70.50, 127.33, 127.72, 129.38, 130.10, 130.38, 138.69, 140.24, 143.66, 173.92

General procedure for deprotection of (2S,3R)-2-Hydroxy-3-(tosylamino) acids

To a sodium naphthalenide solution, prepared from naphthalene (1g, 8 mmol) and Na (0.17 g, 7.7 mmol) in DME (10 mL) with stirring for 1h at room temperature, was added a solution of acid **72a** (g, mmol) in DME (5 mL) at 0 °C under argon. After 1 h, 15 mL of water was added to the reaction mixture. The organic layer separated and washed twice with water. The aqueous layer was extracted with ether to remove excess naphthalene. Evaporation of the aqueous layer gave the crude product, which was purified crystallyzation from EtOH : H_2O (4:1) to give **73a** as white solid.

Yield	:	75%
$[\alpha]_D$	:	- 5.1°(c 1, 1N HCl)(Lit[21] +6, 1N HCl)
IR (Nujol) cm^{-1}	:	3400, 3250, 1745, 1600, 1490
^{1}H-NMR (200 MHz, D_2O)	:	δ 0.7 (t, J=7Hz, 3H), 1.1-1.3 (m, 10H), 1.45 (m, 1H), 1.6 (m, 1H), 3.3 (m, 1H), 3.95 (d, J=3.7Hz, 1H).

(2R,3S)-3-Amino-2-hydroxy-5-methyl hexanoic acid (73b)

Yield	:	79%
$[\alpha]_D$	:	+25.8°(C, 1, AcOH) (Lit[27a]. +26.9, C, 0.32, AcOH)
^{1}H-NMR (200 MHz, D_2O)	:	δ 0.90 (d, J=6.2, 3H), 1.0 (d, J=6.2Hz, 3H), 1.3-1.45 (m, 2H), 1.65 (m, 1H), 3.25 (m, 1H), 4.05 (d, J=2.7Hz, 1H).

(2S,3R)-3-Amino-2-hydroxy-4-phenylbutanoic acid (73c)

Yield	:	73%
$[\alpha]_D$	:	+28.6°(c 0.7, 1N HCl) (Lit.[27b] +29.5 (1N HCL)
^{1}H-NMR (200 MHz, D_2O)	:	δ 2.65 (dd, J=15.2Hz, 8.2, 1H), 2.86 (dd, J=15.2Hz, 8.1, 1H), 3.80 (s, 1H), 7.25 (m, 5H)

A Short and Efficient Synthesis of Enantiomerically Pure Naphthylglycine

2.2.1. Introduction

1-Naphthylglycine is a representative example of the arylglycines, an interesting and important class of nonproteinogenic amino acids.[2a] The isolation of arylglycines from natural sources is rare but has increased in frequency over the past 25 years. For example, *m*-hydroxy- and 3′, 5′-dihydroxyphenylglycine were isolated from latex.[28] Arylglycines are present in many biologically active compounds such as vancomycins.[2d] In many cases, arylglycines are used as chiral ligands for asymmetric synthesis.

Apart from the interesting naturally occurring arylglycines, there are also a number of unique synthetic arylglycines. Synthetic D-arylglycines are used as side chain moiety of mainy antibiotics. Synthetic antibiotic cephalexin, cefadroxil and amoxicillin contain phenylglycines as a side-chain constituents.[2d] An interesting application of naphthyl glycine is in the field of chiral separation. 1-Naphthylglycine was used as chiral stationary phase for the seperation of enantiomers by HPLC.[29]

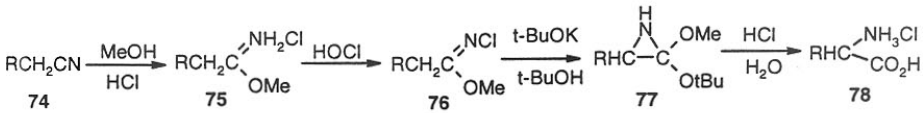
Numerous approaches for the synthesis of arylglycines are appearing in recent years. Due to their simplicity and wide applicability, these substances have become challenging synthetic target to obtain in optically pure form.

2.2.2 Review of Literature

Although numerous methods are reported in the literature for the synthesis of arylglycines, a very few reports are available for the synthesis of naphthylglycine. Moreover, initial reports on the synthesis of napthylglycine were not stereoselective. The reports for the synthesis of naphthyl glycine are briefly discussed below.

Baumgarten's approach[30]

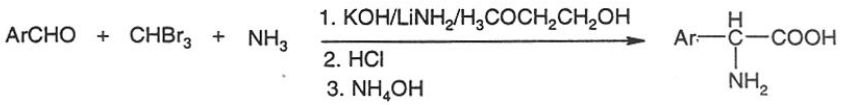
Baumgarten reported the synthesis of racemic naphthyl glycine from alkyl acetamides. Substituted alkyl acetamides (**75**) were halogenated on nitrogen with hypochlorous acid; the resulting N-chloro-imino-esters (**76**) were subjected to base catalyzed rearrangement, to get the aziridine (**77**). Subsequent acid hydrolysis of the intermediates gave the α-amino acid (scheme 14).



Scheme 14

Compere's approach[31]

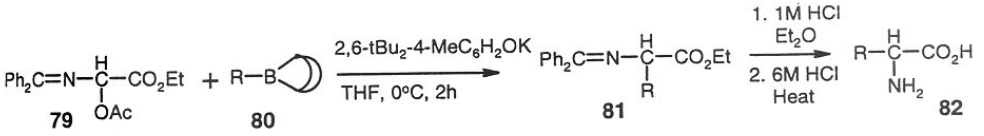
They reported a one-pot synthesis of racemic amino acid by treating aryl aldehydes with bromoform and ammonia in presence of a base (scheme 15).



Scheme 15

O'Donnell's approach[32]

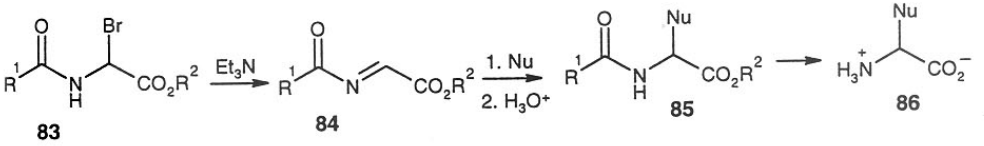
O'Donnell reported the synthesis of racemic naphthylglycine by the reaction of acetate (**79**) with organoboranes to provide naphthylglycine (scheme 16).



Scheme 16

Bretschneider's approach[33]

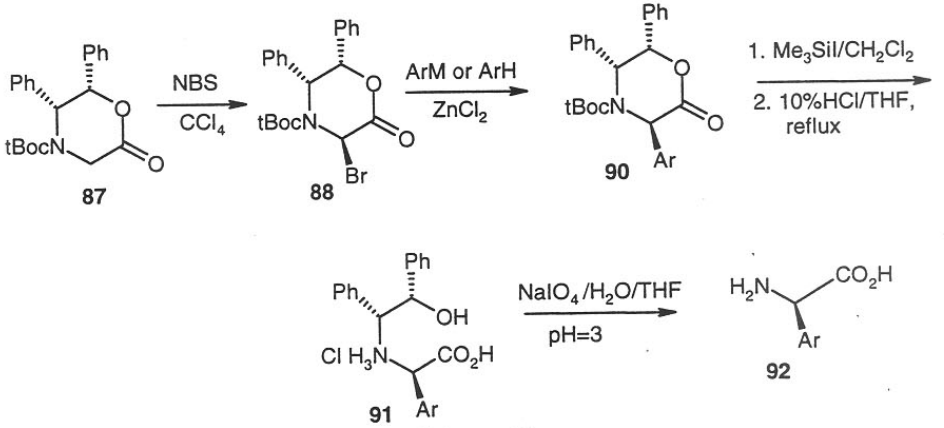
The reaction of N-acylamino-2-bromoacetate (**83**) with higher order mixed cuprate, trimethylsilyl enol ethers and β-dicarbonyl compounds lead to napthlyglycine (scheme 17).



Scheme 17

Williams' s approach[34]

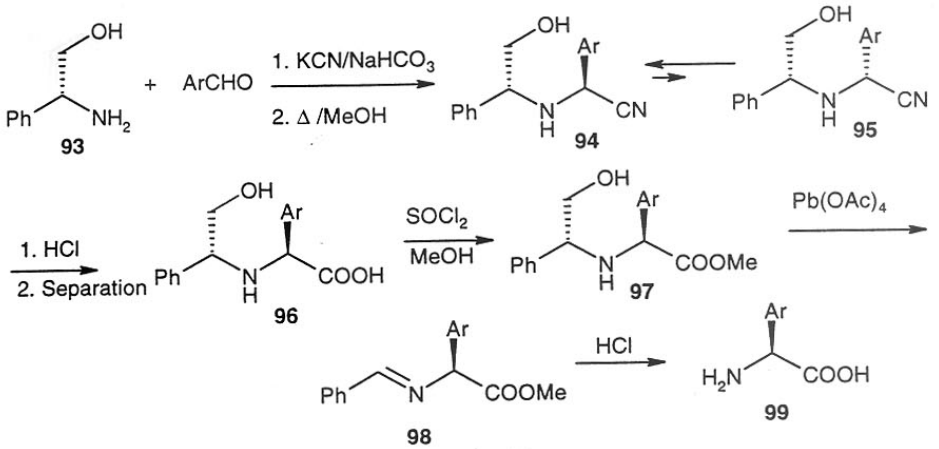
Williams's approach involves either cuprate or Friedel-Craft coupling to chiral bromoglycenate (**88**) to furnish compound (**90**). Removal of *t*-Boc group and susequent treatment of the resulting hydroxy acid (**91**) with $NaIO_4$ gave aminoacid (**92**) (scheme 18).



Scheme 18

Inaba's approach[35]

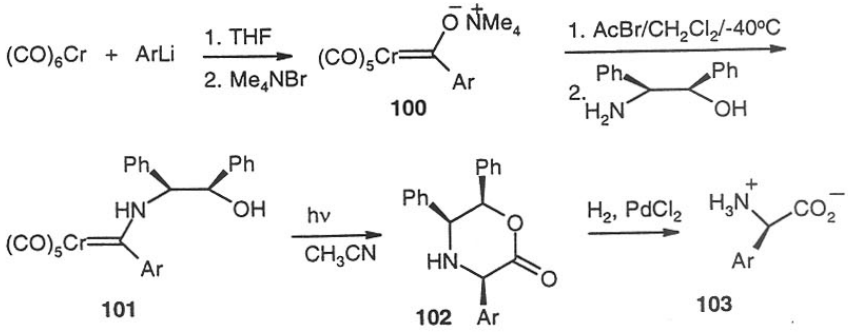
α-Amino acids including naphthylglycine were synthesized via the α-amino-carbonitriles given by Strecker reaction of (R)-2-aminophenylethanol with aldehyde and HCN (scheme 19).



Scheme 19

Vernier's approach[36]

Photolysis of [(amino)(aryl)carbene]chromium complexes having the optically active aminoalcohol (1R,2S)-(-)-or (1S, 2S)-(+)-2-amino-1,2-diphenylethanol as the amino group produces aryl substituted oxazinones. Facile separation of diastereomers followed by mild reductive cleavage produced several arylglycines (scheme20).

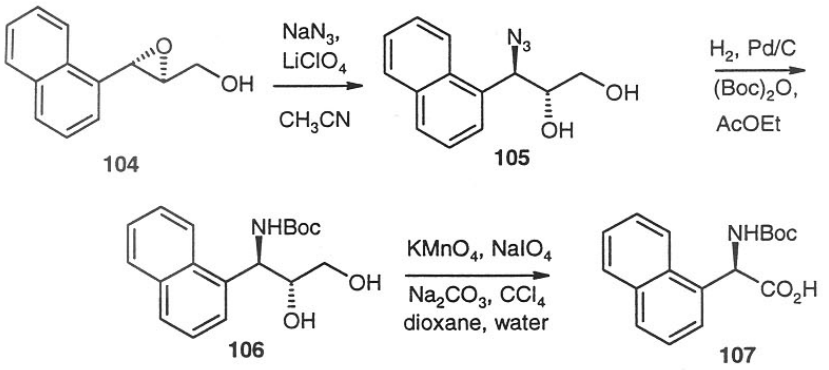


Scheme 20

Riera's approach[37]

Riera had developed a stereoselective synthesis of enantiomerically pure 1-naphthylglycine using Sharpless epoxidation as key step. Regioselective and

stereospecific ring-opening of the corresponding epoxy alcohol **104** with NaN_3 and subsequent hydrogenation in presence of $(Boc)_2O$ afforded the N-Boc-3-(1-naphthyl) propane-1,2-diol **106**. The diol was further oxidized to the protected α-amino acid (scheme 21).

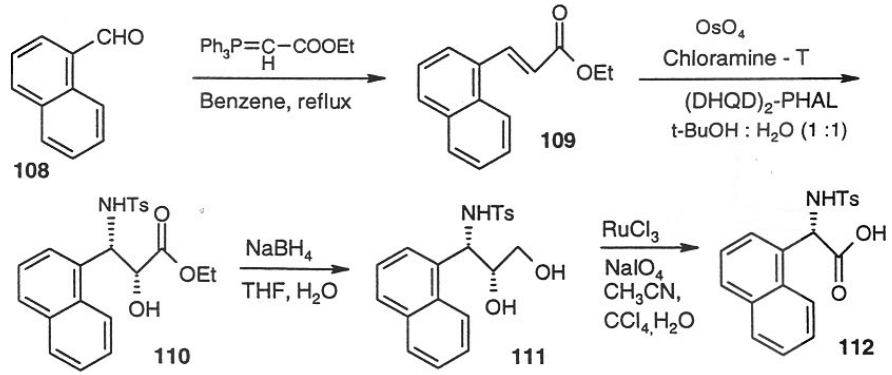


Scheme 21

2.2.3. Present Work

Objective

Most of the syntheses of naphthylglycine as described above are either not stereoselective[30-33] or based on a chiral auxiliary approach[34-36] in which the chiral inductor cannot be recovered. A more practical approach with lesser number of steps for the synthesis of naphthylglycine is strongly desired for further studies. Sharpless asymmetric aminohydroxylation is the most efficacious method in recent years for the synthesis of aminoalcohols. The objective of the present investigation is to apply Sharpless methodology for the synthesis of naphthylglycine which will be more practical with less number of steps (Scheme 22).



Scheme 22

2.2.4. Results and Discussion

The synthetic route for the synthesis of naphthylglycine is depicted in **scheme 22**. The olefin **109** was prepared by Wittig reaction of naphthaldeyde with carbethoxymethyl triphenylphosphorane in benzene at reflux temperature. The IR spectrum showed a strong peak at 1700 cm^{-1} corresponding to the ester functionality and a peak at 1640 cm^{-1} (less intense than the carbonyl peak) due to the C=C stretching of the olefin. The olefinic proton (α- to the carbonyl group) appears in the ^1H NMR spectrum at 6.55 δ as doublet. Another olefinic proton (at benzylic position) appears at

8.55 δ. The J value of the doublets (15 Hz) suggests the compound to be E- olefin. The olefin **109** was subjected for aminohydroxylation in presence of DHQD-PHAL as chiral ligand to give the amino alcohol **110**. The IR spectrum of the compound **110** showed a band at 3400 cm^{-1} confirming the presence of OH and NH functionalities. The NH proton appears in the ^1H NMR spectrum at 5 δ. The CH proton attached to the NH functionality appears at 4.1 δ as a multiplet. The CH_3-protons of the tosyl group appears at 2.25 δ. ^{13}C NMR spectrum indicates the presence of the carbons attached to OH and NH functionality at 62.01 and 73.35 δ respectively (Fig 5).

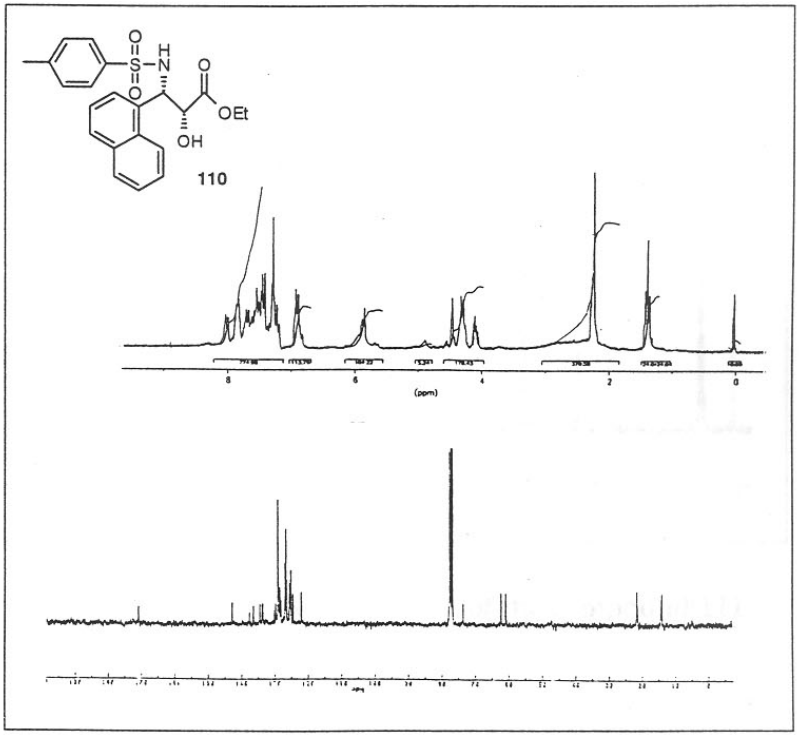


Fig. 5. ^1H and ^{13}C NMR spectra of the compound 110

The amino alcohol **110** was then reduced with $NaBH_4$ in THF-H_2O mixture to get the diol **111** in 83 % yield. Absence of the triplet and the quartet (corresponding to the ethyl group) in the ^1H NMR spectrum ensures reduction. The protons corresponding to the CH_2 group appears in the ^1H NMR spectrum at 3.5 δ. In ^{13}C NMR spectrum the CH_2 carbon appears at 54.45 δ (Fig 6).

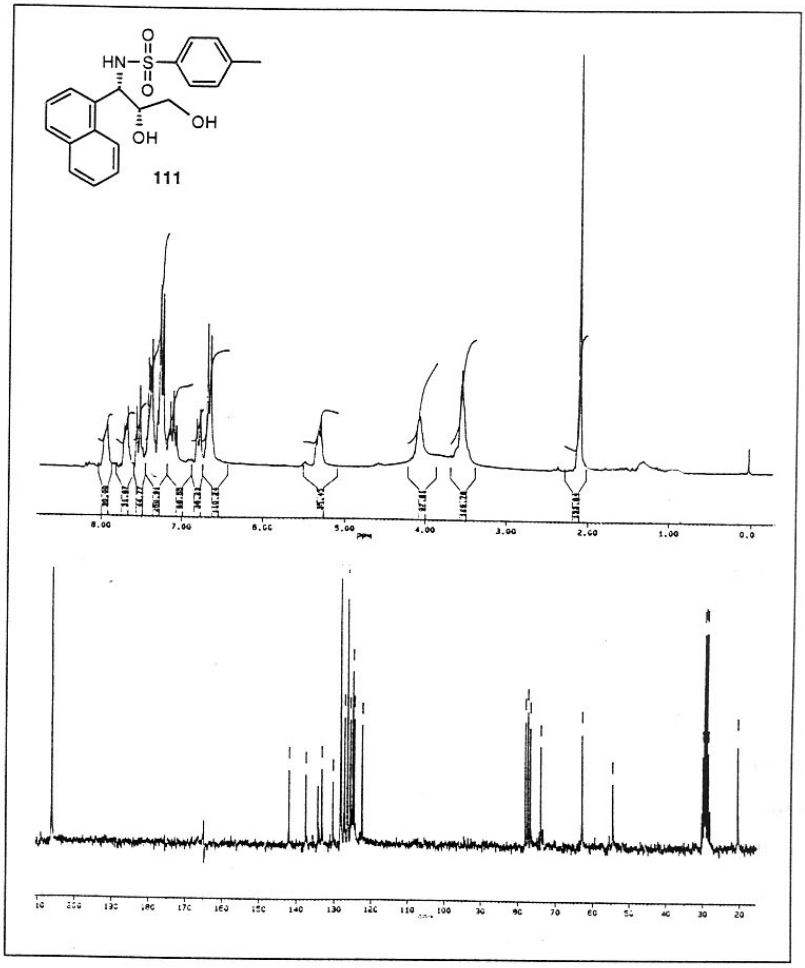


Fig. 6. ^{1}H and ^{13}C NMR spectra of the compound 111

Oxidation of the compound **111** was carried with $NaIO_4$ in presence of $RuCl_3.3H_2O$ as catalyst in a mixture of solvent CCl_4, MeCN and H_2O to get the N-tosyl naphthylglycine **112**. A broad peak at 3200-3550 cm^{-1} indicates the presence of acid group. The carbonyl group appears at 1720 cm^{-1} in the IR spectrum. The CH_2 protons of **111** disappear in the ^{1}H NMR spectrum after the reaction. The CH proton α- to the acid group appears at 5.75 δ as doublet in the ^{1}H NMR spectrum. The NH-proton also comes at 5.05 δ as doublet (Fig. 7).

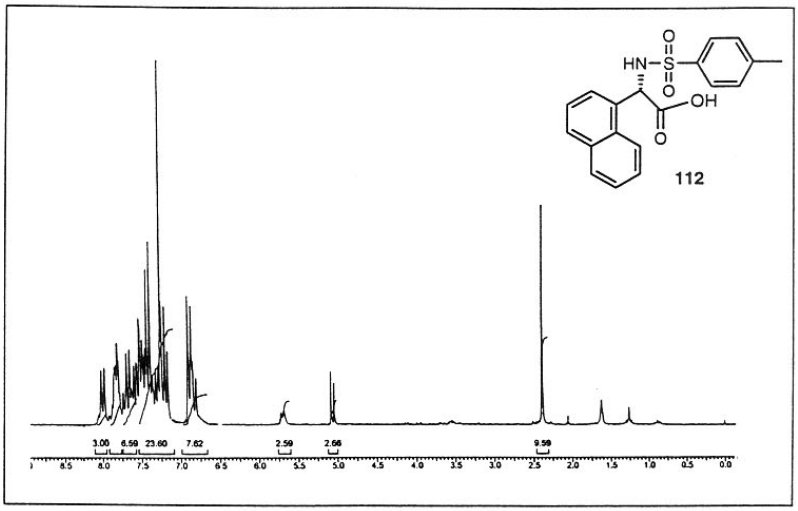


Fig. 7. ^{1}H NMR spectrum of the compound 112

2.2.5. Conclusion

The asymmetric synthesis of naphthyl glycine with >95 % optical purity was successfully achieved *via* Sharpless asymmetric aminohydroxylation. This strategy can be further extended for the synthesis of other aryl glycines. This synthetic method involves lesser number of steps. Furthermore, the steps involved are efficient, easy to operate and economically viable.

2.2.6. Experimental

Preparation of Ethyl-3-(naphthyl acrylate), 109

To a solution of carbethoxymethyltriphenylphosphorane (2.3g, 6.6 mmol) in benzene (15 mL), naphthaldehyde (1g, 6.4 mmol) was added. The mixture was stirred at reflux for 3 h. Solvent was removed in vacuo and the residual oil was extracted with pet.ether (3x10mL). The pet.ether solution was passed through a pad of silica gel and concentrated to afford light yellow oil.

Yield	:	86%
IR (Neat) cm^{-1}	:	2950, 1700, 1640, 1290, 1240, 1160, 1040, 770
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.4 (t, J=7Hz, 3H), 4.4 (q, J=7Hz, 2H), 6.55 (d, J=15.5Hz, 1H, =CH—C(O)-), 7.4-7.65 (m, 3H), 7.75 (d, J=8Hz, 1H), 7.95 (d, J=8Hz, 2H), 8.25 (d, J=8Hz, 1H), 8.55 (d, J=15.5Hz, 1H, =CH-Ar).

Preparation of (2R,3S)-Ethyl-2-hydroxy-3-naphthyl-3(tosylamino)propanoate, 110

To a stirred solution of DHQD-PHAL (0.112g, 0.14 mmol, 5 mol %) in 15 mL of t-butanol and 15 mL of water was added OsO_4 (0.29 ml of 0.2 molar solution in toluene, 0.06 mmol, 2 mol %). After stirring for two minutes, chloramine-T trihydrate (1.96 g, 8.6 mmol, 3 mol equivalent) was added, followed by the olefin **109** (0.65g, 2.9 mmol). The reaction was stirred till the green colour changed to yellow (about 2h.). Ethyl acetate (15 mL) and sodium sulfite (1g) were added and stirred for 1h. Organic layer was separated and aqueous layer was extracted with ethyl acetate (3x10 mL). Combined organic layer was washed with brine, dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography using 10-15% ethylacetate-pet.ether as eluent.

Yield	:	0.77 g (65 %)
m. p.	:	117-119°C
$[\alpha]_D$	:	+30.7°(c 1.2, MeOH)
IR (Nujol) cm^{-1}	:	3420, 3315, 2920, 1725, 1595, 1455, 1370, 1300
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.4 (t, J=5.5Hz, 3H), 2.25 (s, 3H), 4.1(m, 1H), 4.3 (m, 2H), 4.45(m, 1H), 5.9 (m, 1H), 6.9 (d, J=8.3 Hz, 2H), 7.15-8.1 (m, 9H).
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 13.98, 21.24, 60.57, 62.01, 73.35, 121.92, 124.38, 124.38, 124.99, 125.14, 125.32, 125.45, 126.30, 126.48, 126.79, 128.03, 128.35, 128.90, 129.59, 133.50, 134.34, 136.31, 142.72, 170.63.

Analysis : $C_{22}H_{23}NO_5S$ requires C, 63.92; H, 5.57; N, 3.39; S, 7.75. Found: C, 63.72; H, 5.64; N, 3.29; S, 7.67.

Preparation of (2S,3S)-Tosylamino-3-(1-naphthyl)-1,2-propanediol (111)

To a solution of the amino alcohol **110** (200 mg, 0.48 mmol) in THF (5 mL) was added a solution of $NaBH_4$ (0.18g, 4.8 mmol) in water (2 mL) at 0°C. After being stirred at room temperature for 3 h., the mixture was diluted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The crude material was eluted with 40% EtOAc/pet. ether through silica gel (230-400 mesh) to get 0.15g. (83%)of the diol **111**.

Yield : 0.15 g (83%)

m. p. : 136-137°C

$[\alpha]_D$: +35.4°(c 0.7, MeOH)

IR (Nujol) cm^{-1} : 3400, 2920, 1460, 1375, 1340, 1150.

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.1 (s, 3H), 3.55 (b, 2H), 4.05 (b, 1H), 5.3 (m, 1H), 6.7 (d, J=8.1Hz, 1H), 6.8 (d, J=8.1Hz, 1H), 7.1 (t, J=8.1Hz, 1H), 7.25 (d, J=8.1Hz, 2H), 7.45 (m, 2H), 7.55 (d, J=8.1Hz, 1H), 7.65 (m, 1H), 7.9 (b, 1H)

^{13}C-NMR (Acetone d_6 + $CDCl_3$) : δ 20.363, 54.45, 62.75, 73.82, 122.41, 124.54, 124.91, 125.02, 125.61, 126.36(x2), 127.18, 128.17, 128.29(x2), 130.31, 133.28, 334.30, 137.51, 141.97

Analysis : $C_{20}H_{21}NO_4S$ requires C, 64.69, H, 5.66, N, 3.77, s, 8.62 Found: C, 64.76, H, 5.60, N, 3.69, s, 8.65

Synthesis of (S)-N-Tosyl-1-naphthylglycine (112)

To the stirred solution of diol (0.1g, 0.27 mmol) in CCl_4 (3 mL), CH_3CN (3 mL) and H_2O (4 mL) were added $NaIO_4$ (0.057g, 0.27 mmol) and $RuCl_3$ (0.005g, 0.003 mmol). Stirring was allowed to continue for 2h. Then, 10 mL of 1M $NaHCO_3$ solution and 25 mL of ethyl acetate was added. The solution was acidified with 1M HCl. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated. The crude

product was purified by column chromatography using 95% EtOAc/pet. ether as eluent to afford 0.68 g of the solid product.

Yield	:	0.068 g (71%)
m. p.	:	200-201 °C
$[\alpha]_D$	:	+144.9° (c 0.6, MeOH) [Lit[37](for N-Boc-D-1-naphthylglycine) -147.7° (c 1, MeOH)]
IR (Nujol) cm^{-1}	:	355-3200, 2960, 1720, 1680, 1395, 1160.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.4 (s, 3H), 5.05 (d, J=8 Hz, 1H), 5.75 (d, J=8 Hz, 1H), 6.8 (m, 2H), 7.1-8.1 (m, 9H).
Analysis	:	$C_{19}H_{17}NO_4S$ requires C, 64.22; H, 4.79; N, 3.94 %. Found: C, 64.64; H, 4.64; N, 3.89 %.

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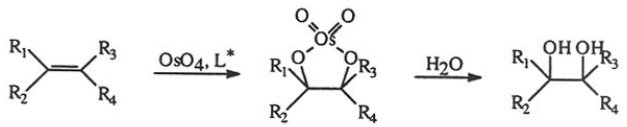
CHAPTER III

Chiral Cyclic Sulfate : Versatile Synthon for the Synthesis of Adrenergic Blockers

3.0. General Introduction

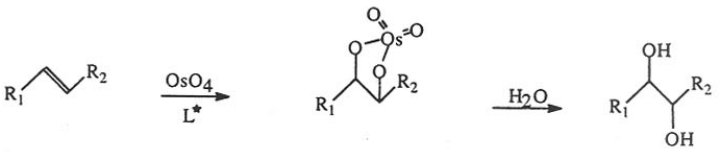
3.0.1. Osmium Tetroxide Catalyzed Asymmetric Dihydroxylation (AD) of Olefins

Osmium tetroxide (OsO_4) catalyzed asymmetric dihydroxylation of olefins is, perhaps, the most reliable and selective transformations in organic chemistry (**Scheme 1**).[1] The property of stereospecifically embedding two hydroxyl groups in the olefin framework accounts for its popularity in organic synthesis. Criegee's noted discovery[2] of dramatic acceleration of the reaction by adding pyridine as the ligand into the reaction mixture led to the discovery of most effective ligands for this reaction which proceed *via* the ligand acceleration effect.[3]



Scheme 1

Criegee showed in his pioneering work on the stoichiometric reaction of OsO_4 with olefins that pyridine accelerates the reaction considerably[2, 4] (**Scheme 2**).



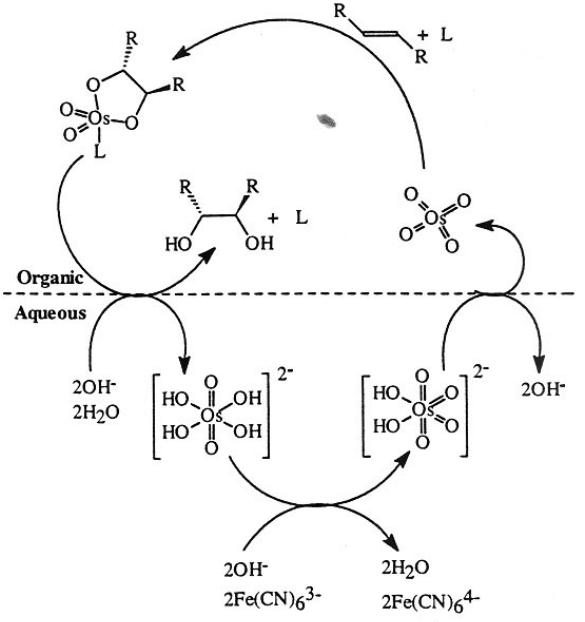
Scheme 2

However, the cost consideration makes the stoichiometric osmylation uneconomical. Not surprisingly, catalytic variants of the reaction, which employ

relatively inexpensive reagents for the reoxidation of the osmium (VI) glycolate products, greatly enhance its synthetic utility.

Initial efforts by Sharpless and Hentges[5] to induce enantioselectivity in the osmylation with chiral pyridine derivatives failed due to the low affinity of these ligands for OsO_4. It was found that the binding constant of a ligand is extremely sensitive to the steric hindrance near the reacting center. Consequently, quinuclidine derivatives were used instead of pyridines for further investigations due to their intrinsically higher affinity for OsO_4.[5, 6]

Apart from the cinchona alkaloid catalyzed AD, there are number of recent methods employing chiral monodentate ligands[7] and bidentate diamine ligands.[8] Despite the good to excellent enantioselectivities that can be obtained with diamine ligands, a serious drawback results from their bidentate nature, they form very stable chelate complexes with the Os(VI) glycolate products and as a consequence prevents *in situ* recycling of the Os and the ligand. Thus, all the reactions involving bidentate ligands are stoichiometric in both OsO_4 and the chiral ligand.[8]



Scheme 3

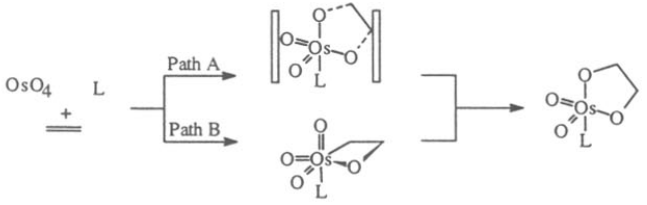
Initially, the AD using derivatives of cinchona alkaloids were performed under stoichiometric conditions,[5] but in 1987 Marko and Sharpless[9] found that the process became catalytic when N-methyl morpholine N-oxide (NMO) was employed as co-

oxidant. Kwong[10] showed that the reaction can be performed under two-phase conditions with K_3FeCN_6 as the stoichiometric re-oxidant (**Scheme 3**). Under these conditions there is no oxidant other than OsO_4 in the organic layer, in contrast to the homogeneous NMO condition. Later, Amberg[11] found that the rate of reaction can be accelerated considerably by methane sulfonamide addition. Due to this sulfonamide effect, most AD reactions can be carried out at 0°C rather than at room temperature, which normally has a beneficial influence on the selectivity.

The discovery of the ligands with two independent cinchona alkaloid units by Hartung and Crispino[12] attached to a heterocyclic spacer has led to a considerable increase in both the enantioselectivity and the scope of the reaction. Due to these improvements, it is now possible to obtain high enantioselectivities with a broad range of alkenes. However the enantioselectivities in the case of *cis* and terminal olefins was far from satisfactory.

3.0.1.1. Mechanism of AD Reaction

The Os catalyzed AD reaction has been the center of extensive mechanistic investigations and two different mechanisms have been suggested. Boseken and Criegee originally proposed a concerted [3+2] pathway[2] (**Scheme 4**, path A), while Sharpless *et. al.* suggested a stepwise reaction which is initiated by a [2+2]-like addition[4] of the olefin across an Os=O bond (path B), followed by rearrangement of the resulting osmaoxetane intermediate to the glycolate product.



Scheme 4

But based on observations and nonlinear Eyring relationship between ee and temperature it was established that the stepwise [2+2]-like mechanism is operative.[13]

The mechanism for the reoxidation process in presence of $K_3Fe(CN)_6$ is already discussed as in the **scheme 3**.

Recent ligand structure-activity studies[14] have showed light on the origin of the enantioselectivity on the AD reaction and demonstrated the importance of an enzyme-like binding pocket present in the dimeric cinchona alkaloid ligands. The cinchona alkaloid backbone is ideally suited for providing high ligand acceleration as well as enantioselectivity and the relationship between ligand structure and activity.[15]

3.0.1.2. Reaction Conditions

The AD reaction is performed in a solvent mixture containing 50% water, and is best carried out under heterogeneous conditions with three equivalents of both K_3FeCN_6 and K_2CO_3 in order to avoid the second catalytic cycle.[10] Optimization studies have revealed that a 1 : 1 mixture of water and *t*-butanol is the solvent system of choice, and less polar solvents can result in inferior enantioselectivities. The olefin concentration in the solvent mixture is usually 0.1 M. While the reaction is normally run under basic conditions (K_2CO_3, pH 12.2, aqueous layer), it is possible to buffer the system with three equivalents of $NaHCO_3$. Buffering of the reaction does not affect the ee, but it can have a beneficial effect on the yield when base-sensitive substrates such as esters or base sensitive products (in case of allyl bromide) are used.[16] Normally the reaction is performed with three equivalents of K_3FeCN_6 as the reoxidant, but the use of peroxodisulfate gives good results with comparable reaction rates to the original conditions.[17]

Usually, the reaction is performed with very small amounts of the key intermediates. Only 0.2 mol % of Os-reagent added to the reaction mixture and 1 mol% of the ligand are sufficient for most olefinic substrates. Terminal, 1,1-disubstituted and *trans*-1,2-disubstituted as well as trisubstituted olefins can be regarded as the standard substrates for the AD reaction. Since these substrates require very similar reaction conditions, it is possible to use a premix of all the reactants called AD-mixes.[18] These AD-mixes are commercially available and can be readily prepared. The currently recommended contents in 1Kg of AD-mix are as follows : K_3FeCN_6, 699.6 g, K_2CO_3, 293.9 g, $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$, 5.52 g, and $K_2OsO_2(OH)_4$, 1.04 g. The standard AD procedure calls for 1.4 g of this AD mix per millimole of olefin. It should

be noted that 1 equivalent of $MeSO_2NH_2$ should be employed for all substrates other than terminal alkenes to enhance hydrolysis of the osmate(VI) ester and hence the rate of catalytic turnover especially in the case of tetrasubstituted olefins, enol ethers, electron deficient olefins etc.[11, 19] For large scale reaction it is advisable to recover the ligand by extraction with 3% aqueous H_2SO_4.

In a recent study of the scope of the AD reaction, the chemoselectivity in the reaction of sulfur containing olefins with OsO_4 was investigated.[20] It was found that sulfides, disulfides and certain dithianes are unaffected under the AD conditions and this considerably broadens the scope of this reaction, since sulfur containing functional groups are commonly used in organic synthesis.[20, 21]

3.0.2. Chiral Cyclic Sulfate as Synthon

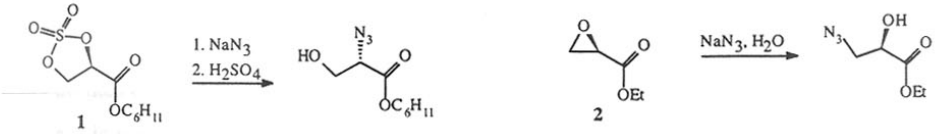
Epoxides have played a significant role in organic synthesis,[22] in recent years, presumably due to their high reactivity as well as simultaneous protection of the adjacent functionalized carbon atom for nucleophilic attack. They are usually superior to their acyclic counterparts because of their cyclic nature, which renders the competing elimination process stereoelectronically unfavourable. The similar properties are shared by the cyclic sulfates also. Although the chemistry of cyclic sulfates has been known for a long time, the synthetic utilization of these classes of compounds are not found in the main stream of organic chemistry unlike the epoxides.

3.0.2.1. Reactivity of Cyclic Sulfate

Cyclic sulfate (1,3,2-dioxathiolane-2,2-dioxide) is more reactive than its precursor cyclic sulfite (1,3,2-dioxathiolane-2-oxide). The high reactivity of cyclic sulfates has been attributed to the ring strain. It has been speculated that the possible cause of ring strain might be due to angle strain, partial double bond character between ring oxygen and sulfur due to 2p(O)-3d(S) orbital interaction or 1,3-nonbonding interactions between the ring oxygen and the exocyclic oxygen.[23] In addition to the ring

strain, the good leaving ability of the $ROSO_3^-$ moiety makes the five membered cyclic sulfate very reactive towards various reagents.

The reactivity of cyclic sulfates and epoxides towards nucleophiles are similar in nature but very different in selectivity. For example, cyclic sulfate **1** reacts with sodium azide in acetone : water to give preferentially the α-azide substituted product whereas the epoxyester **2** gives exclusively the β-substituted product[24] (**Scheme 5**)



Scheme 5

3.0.2.2. Reaction with Electrophiles

Cyclic sulfites and cyclic sulfates of 1,2-glycols are hydrolysed easily with acids to give glycol. On the other hand, tetramethyl-1,3,2-dioxathiolane-2,2-dioxide underwent after protonation and ring opening, a rapid pinacol type rearrangement to afford pinacolone in good yield.[25]

Ethylene sulfites also reacts with certain metal carbonyls in which sulfur functions as an electron donor.[26] In the case of cyclic sulfite or sulfate containing a C=C double bond, smooth addition of electrophiles proceeds in good yield.

3.0.2.3. Reaction with Nucleophiles

Nucleophilic reactions of cyclic sulfites and sulfates are perhaps the most commonly studied reactions and are well known for their high reactivity.[27] In many cases, the nucleophilic substitution reactions of certain cyclic sulfates are far superior to their epoxide counterparts.

O-Nucleophiles

Water acts as a nucleophile in the presence of strong acid for 1,3,2-dioxathiolane 2-oxide to give a tetraco-ordinate intermediate, which in turn undergoes a fast ring opening to give glycol.[28] Reaction of ethylene sulfite with sodium methoxide give ethyleneoxide and sodium methyl sulfite as major products suggesting that the

methoxide ion attacks at sulfur site only. In contrast, phenolate reacts with ethylene sulfite predominantly at the C-center to yield aryl 2-hydroxyethyl ether.[28]

Cyclic sulfates of aliphatic 1,2-diols are powerful alkylating agents towards a series of O-nucleophiles. For example, cyclic sulfates react readily with carboxylates to furnish the corresponding alkylated products in high yields.[29]

S-Nucleophiles

Ethylene cyclic sulfites as well as sulfates react with thiophenolates similar to phenolates but the product arising from the reaction of thiophenolate and ethylene cyclic sulfate is unstable and readily hydrolyses to give β-(phenylthio)ethanol.[30] The reaction proceeds with complete inversion at the stereogenic center.

Halide Nucleophiles

Cyclic sulfites of di- and meso- hydrobenzoin react with dry hydrogen chloride in dioxane on heating to form the *threo* and *erythro* chlorohydrin respectively with the extrusion of sulfur dioxide.[31] Substituted cyclic sulfates undergo ready nucleophilic displacement at the carbon center furnishing high yield of halosubstituted products.[29b, 32] Unsymmetrically substituted cyclic sulfates usually give a mixture of regioisomers during nucleophilic displacement.[24]

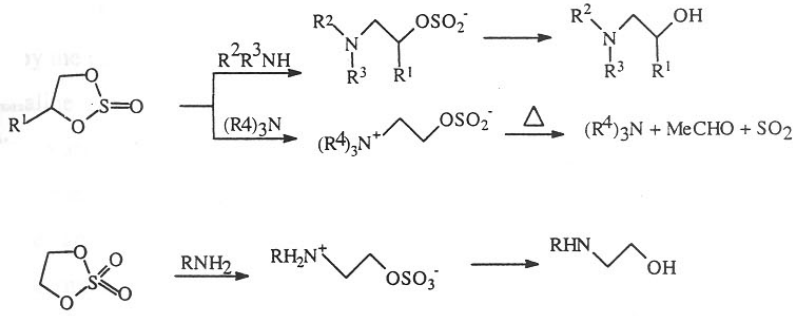
C-Nucleophiles

Depending upon the reaction conditions, phenylmagnesium bromide with ethylene sulfite gives 3-23 % of ethyl bromohydrin and 42-60 % yield of diphenyl sulfoxide. Recently, Rebiere and Kagan[33] have reported the reaction of several organometallic compounds with chiral cyclic sulfites, which lead to the formation of optically active sulfones.

Unlike the β-hydroxysubstituted ethylene derivatives, generated under the similar nucleophilic substitution reactions of epoxides, the corresponding sulfate moiety is still a leaving group and can serve as such under certain conditions. Thus, the reaction of sodium salt of dimethyl malonate with cyclic sulfates afforded cyclopropane derivatives.[29b] The reaction of anion generated from ethyl 1,3-dithiane-2-carboxylate with BuLi in THF gave the ring opened product.[25, 34]

N-Nucleophiles

The reaction of nitrogen nucleophiles with cyclic sulfates and sulfates is the most extensively studied.[27, 35] The parent cyclic sulfite reacts with primary and secondary amines to give β-aminoalcohols, whereas , the reaction of tertiary amine resulted in sulfitibetaines, which decomposes to give acetaldehyde (**Scheme 6**).



Scheme 6

Recently, various methods are reported in the literature in respect to the use of this concept of opening of chiral cyclic sulfites and sulfates with N-nucleophile for the asymmetric synthesis of biologically active molecules.[36]

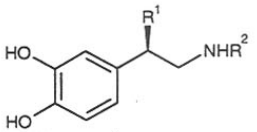
H-Nucleophiles

Gao and Sharpless have reported the nucleophilic ring opening of a few cyclic sulfates using hydride as nucleophile.[37] For example, tartarate cyclic sulfate gave 55% yield of optically pure maleic ester when treated with sodium cyanoborohydride in THF at pH 4-5 at 60 °C.[24]

3.0.3. Adrenergic receptors

Adrenoreceptors play a vital role in the control of the automatic nervous system. The adrenergic system is divided into two branches,[38] *viz.*, α and β on the basis of the ways in which the neurotransmitters noradrenaline, **1** and adrenaline, **2** control bodily function, particularly in the cardiovascular system.

The first successful drugs were β-agonists and β-antagonists designed to treat asthma and *angina pectoris*, respectively, but they were also found to be effective treatments for hypertension, glaucoma, heart failure, anxiety and obesity. The α-agonist noradrenaline is the transmitter released at nerve endings by stimulation of adrenergic nerves while adrenaline, the β-agonist, is a circulating hormone released by the adrenal gland in response to stress.

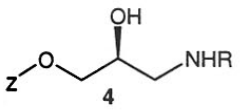


1. R^1 = OH, R^2 = H
2. R^1 = OH, R^2 = Me
3. R^1 = H, R^2 = H

Fig.1. Neurotransmitters

Noradrenaline accelerate heart rate and constricts blood vessels in situation where adrenaline accelerates heart rate while relaxing blood vessels. These catecholamines induce a variety of biological responses in mammalian systems mainly in smooth muscle, the central nervous system and the control metabolism.[39]

The main class of β-adrenergic ligands are based on the structure of three neurotransmitters noradrenaline (**1**), adrenaline (**2**) and dopamine (**3**) (Fig 1). Initially, aryl ethanolamines such as pronethalol [(2-(isopropylamino)-1-(2-naphthyl) ethanol] was tried for treatment of anigma but it was dropped due to its severe side effect. It was found that compounds containing an aryloxy propanolamine nucleus performs best as β-adrenergic agent (Fig. 2). The essential features of the series are: (i) an aromatic or heterocyclic ring **Z** ; (ii) an oxypropanol unit containing the secondary alcohol in S-configuration[40]; and (iii) a secondary amine bearing a bulky substituent **R** particularly isopropyl and t-butyl[41] group.



a Propranolol: Z=1-naphthyl
b: Penbutolol:
Z=2-cyclopentyl phenyl

Fig. 2. β-Blockers

Apart from the above features another important point is that an ortho substitution, particularly a bulky substituent in the aromatic ring exerts a profound effect on the agonism exhibited by β-antagonists.[42] But disubstitution in ortho position nullify the activity.

In the present work we have made use of the chemistry of ADH and cyclic sulfates for the synthesis ofoptically active drugs. Section A deals with the asymmetric synthesis of (S)-Penbutolol. Section B deals with the asymmetric synthesis of d-Sotalol.

Asymmetric Synthesis of β-Adrenergic Blocker, (S)-(-)–Penbutolol

3.1.1. Introduction

β-Adrenergic blocking agents (β-blockers) are important drugs widely used for the treatment of hypertension and *angina pectoris*.[43] Most of the β-blockers possess a gerneral structure $ArOCH_2CH(OH)CH_2NHCH(CH_3)_2$ and have been used in the form of racemic mixtures.[44] Three fundamental goals of cardiovascular drugs are the lowering of blood pressure (antihypertensive), return of the heart to rhythmic beating (antiarrhythmics) and the general improvement of the heart muscle tone (cardiotonics).[45] Biochemically, the mechanism of action involves the adrenergic system in which the hormonal system provides the communication link between the sympathetic nervous system and involuntary muscle.[46] Propranolol is the first successful drug[47] having anti-anginal and antihypertensive effect. The discovery of propranolol prompted the synthesis of many thousands of compounds containing an aryloxy propanolamine nucleus (Fig 2). Some of them are having ortho substitution in the aromatic ring such as penbutolol.

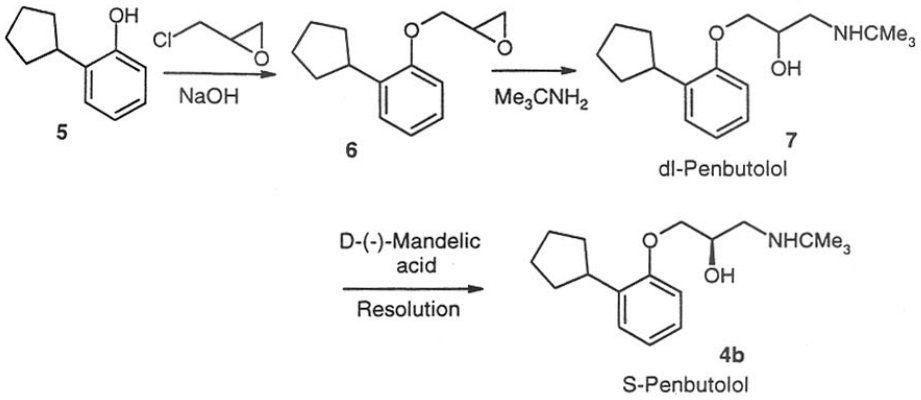
Although (*S*)-isomers are known to be much more effective (50-500 fold) than the (R)-isomers,[44b, 48] these antihypertensive drugs are sold as racemic mixtures. To avoid unnecessary stress, or in some cases toxicity to an organism caused by the (R)-isomers, the administration of optically pure (*S*)-isomers are desirable. (*S*)-penbutolol being the representative of these β-adrenergic blocking agents.

3.1.2. Review of Literature

Various preparative methods of the optical isomers of these β-blocking agents have been reported. Almost all the syntheses are starting from optically active materials or by resolution techniques. Most of the syntheses reported in the literature are concerned with the synthesis of (S)-propranolol, which involves the use of 1-naphthol as one of the starting material. But the synthesis of penbutolol is less common in the literature. Some of the important asymmetric synthetic routes reported are discussed below.

Haertfelder's approach[49]

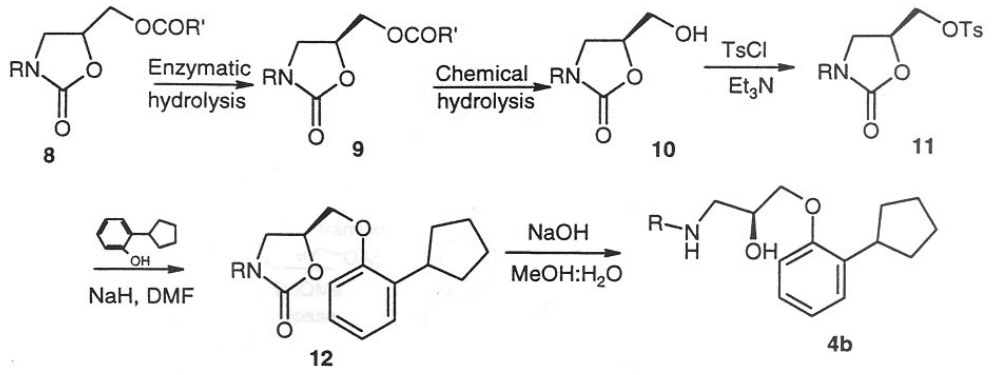
Haertfelder *et. al.* discovered and studied the pharmacological properties of penbutolol. Penbutolol was prepared by reaction of 2-cyclopentylphenol **5** with epichlorohydrin to give **6** in basic medium followed by reaction of **6** with *tert*-butylamine to dl form of penbutolol **7** which was resolved with D-(-)-mandelic acid (scheme 7).



Scheme 7

Watanabe's approach[50]

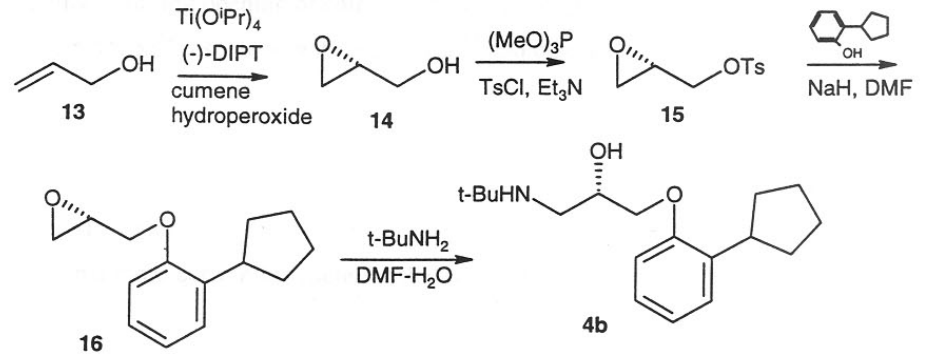
These authors reported the synthesis of β-blockers from (S)-5-hydroxymethyl-3-alkyloxazolidinone (alkyl = *t*-Bu or *i*-Pr) via the route as depicted in the scheme 8. Oxazolidone was prepared via enzymatic hydrolysis.



Scheme 8

Sharpless et al. (1989)[51]

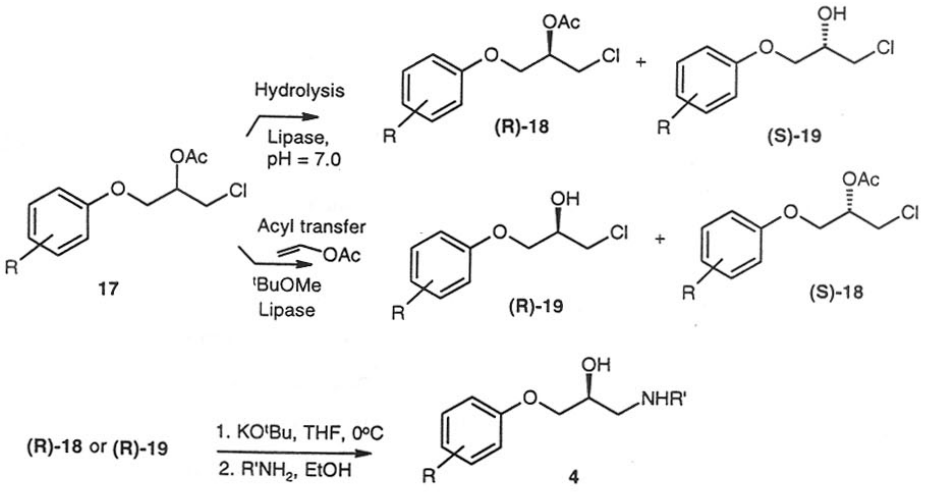
Sharpless had prepared a series of crystalline arene sulfonate derivatives of enantiomerically enriched glycidol. A very high regioselectivity was observed in the reaction of these compounds with nucleophiles such as amines. This methodology was applied to the synthesis of β-adrenergic blocking agent. (**Scheme 9**).



Scheme 9

Schneider's approach[52]

Optically active chlorohydrin derivatives **18** and **19** of both enantiomeric series were prepared *via* both enzymatic hydrolysis and acyl transfer reactions catalyzed by lipase. The resulting building blocks were further transformed into the corresponding β-blockers in high enantiomeric purity (scheme 10).



Scheme 10

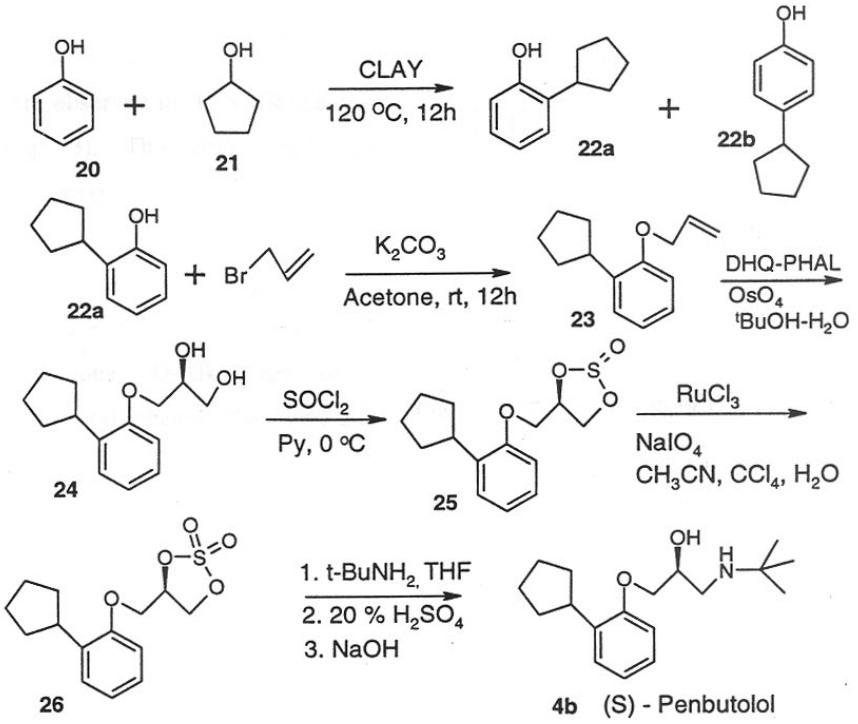
Many other methods are available for the synthesis of propranolol (Fig 2; Z = 1-naphthyl) via ring opening of chiral epoxide with isopropylamine[53], asymmetric transfer hydrogenation[54] resolution with biocatalyst[55] and others.[56]

All the reported methods for the synthesis of this class of compounds suffer from one or the other drawbacks such as use expensive enzymes and resolving agents, low yields, more number of steps or low optical purity etc. Hence there is a need to develop a more convenient route for the asymmetric synthesis of this important class of compounds.

3.1.3. Present work

Objective

Although racemic β-blockers have been used over two decades, there is now a great deal of concern about enantiomerically pure isomers having higher affinity to β-receptors. As described in the preceding section, a few reports are available in the literature for the synthesis of penbutolol although many methods are available for the synthesis of propranolol. One of the reasons may be the ease of availability of 2-cyclopentyl phenol, which is expensive. Most of the methods reported involve the use of the glycidyl ether as the key intermediate for the synthesis. To explore the chemistry of chiral cyclic sulfite and sulfate and to develop a new general route for the synthesis of penbutolol which will be high yielding, experimentally simpler we have undertaken the synthesis of penbutolol starting from phenol (scheme 11).



Scheme 11

3.1.4. Results and Discussion

The present synthetic route employed for the synthesis of (S)-penbutolol is depicted in the **scheme 11**. 2-Cyclopentylphenol was synthesized by alkylation of phenol with cyclopentanol in presence of montmrillonite K10 clay at 120 °C without any solvent. Interestingly, the reaction proceeds with 62% yield and remarkable ortho-selectivity (68%). In general, alkylation with $AlCl_3$ as catalyst, para products predominate. But in this case ortho selectivity is found to be higher. Another experiment was also carried out, where alkylation of phenol was done with cyclohexanol using same procedure. But in this case both ortho and para-isomers were formed in almost equal amount. The reason for the ortho selectivity for cyclopentanol in comparison to cyclohexanol is due to less bulkiness of cyclopentyl group. The structure of the cyclopentyl phenols was confirmed by ^1H NMR spectra.

In case of *ortho*-product, four distinct signal in the aromatic region were observed in ^1H NMR spectrum (Fig. 3). The *ortho* and *para* cyclopentylphenols were separated by column chromatography using pet. ether as eluent. *Para* substituted product elutes first followed by the *ortho* one. O-Alkylation of 2-cyclopentyl- phenol **22a** with allyl bromide in presence of K_2CO_3 in acetone gave 2-cyclopentylphenyl allyl ether **23**. The olefinic CH_2 protons appear at 5.5 δ as doublet of doublet in ^1H NMR spectrum. CH proton of olefin comes at 6.1δ as multiplet. The O-CH_2 protones appear as broad doublet at 4.5 δ in ^1H NMR spectrum. The CH and CH_2 carbons appear at 112.06 δ and 116.89 δ respectively in the ^{13}C NMR spectrum. The quaternary carbons in the aromatic ring attached to the cyclopantyl group and oxygen appear at 132.42 δ and 153.43 δ respectively in the ^{13}C NMR spectrum. The compound **23** was subjected to Sharpless asymmetric dihydroxylation using DHQ-PHAL as chiral ligand in *t*-BuOH:H_2O (1:1) as solvent. The IR spectrum shows a band at 3400 cm^{-1} indicating the presence of OH functionality. The terminal CH_2 protons appear at 3.8 δ in the ^1H NMR spectrum as

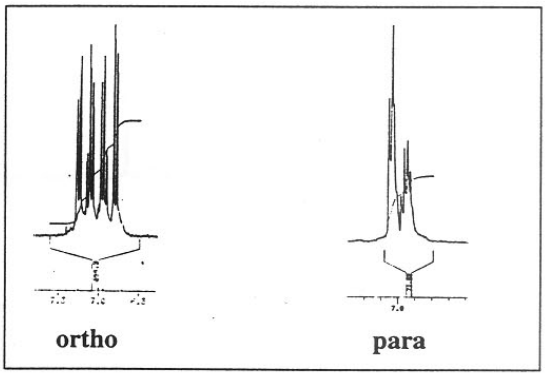


Fig.3. Aromatic region of cyclopentyl phenols

multiplet. The CH proton apears at 4.1 δ as multiplet. The O- CH_2 protons display as doublet at 4.05 δ in ^{1}H NMR spectrum. The terminal CH_2 and the CH carbons appear at 64.29 δ and 71.18 δ respectively in the ^{13}C NMR spectrum (Fig.4).

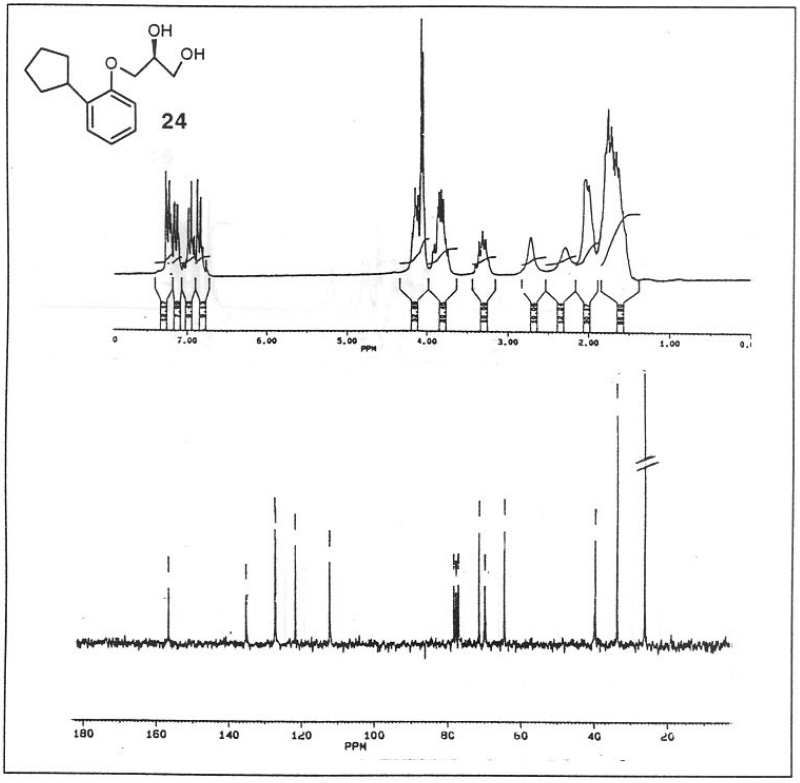


Fig. 4. ^{1}H and ^{13}C NMR spectra of compound 24

The diol **24** was converted to cyclic sulfite **25** using thionyl chloride in pyridine in 93% yield. The IR spectrum of cyclic sulfite **25** showed the absence of hydroxyl groups (3400 cm^{-1}) and the appearance of a strong band at 1235 cm^{-1} characteristic of cyclic sulfites. ^{1}H NMR spectrum of the cylic sulfite **25** showed the presence multiplets at 4.1δ 4.4 δ, 4.7 δ, 4.9 δ, 5.35 δ indicating the presence of a diastereomeric mixture. In ^{13}C NMR spactrum there are two small signals corresponding to the carbons at 67.09 δ and 69.01 δ (Fig 5).

The cyclic sulfite **25** on treatment with *t*-butylamine in DMF at reflux is expected to give the desired compound penbutolol **4b**. In this connection, Lohray *et. al.* reported the ring opening of cyclic sulfite with LiN_3 in DMF.[57] However, in our case, by

following the same procedure, reaction did not proceed at all. The reaction was further tried in toluene and THF as solvents. Here again, the reaction failed.

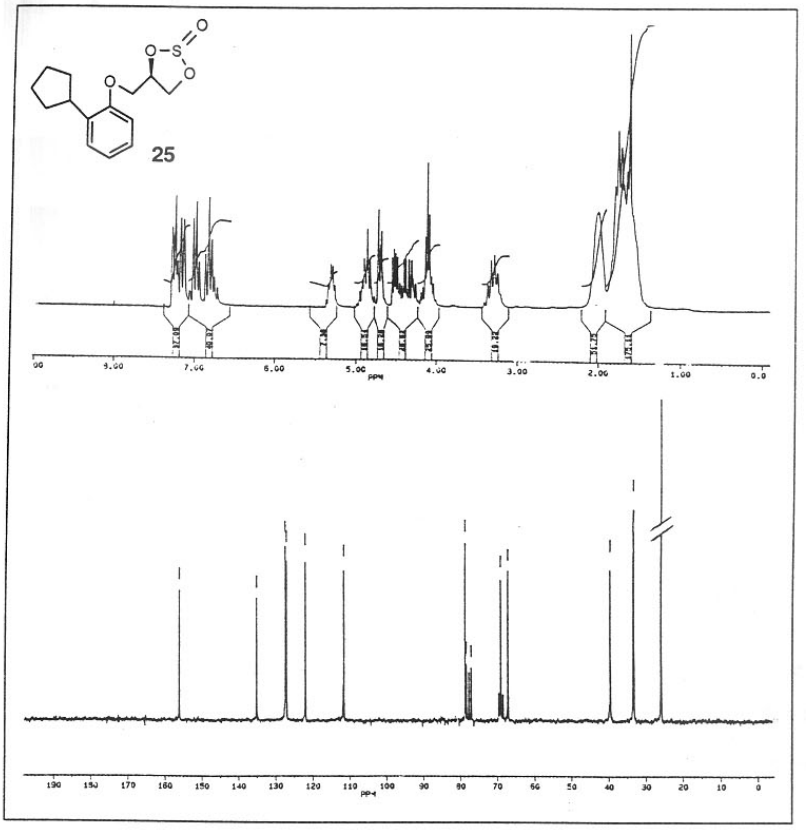


Fig. 5. ^{1}H and ^{13}C NMR spectra of cyclic sulfite 25

Hence, the cyclic sulfate **25** was then oxidized to cyclic sulfate **26** using sodium periodate in presence of catalytic amount of $RuCl_3$. The formation of cyclic sulfate was confirmed by NMR. ^{1}H NMR spectrum showed the disappearance of the diastereomeric multiplets and presence of other two multiplets (4.9 δ and 5.35 δ). In ^{13}C NMR spectrum two small signals also disappeared (Fig 6).

The cyclic sulfate **26** was subjected to reaction with *t*-butyl amine in dry THF. The reaction mixture was first acidified with 20 % sulfuric acid and then basified with 20 % NaOH to get the required compound penbutolol **4b** in 72 % yield.

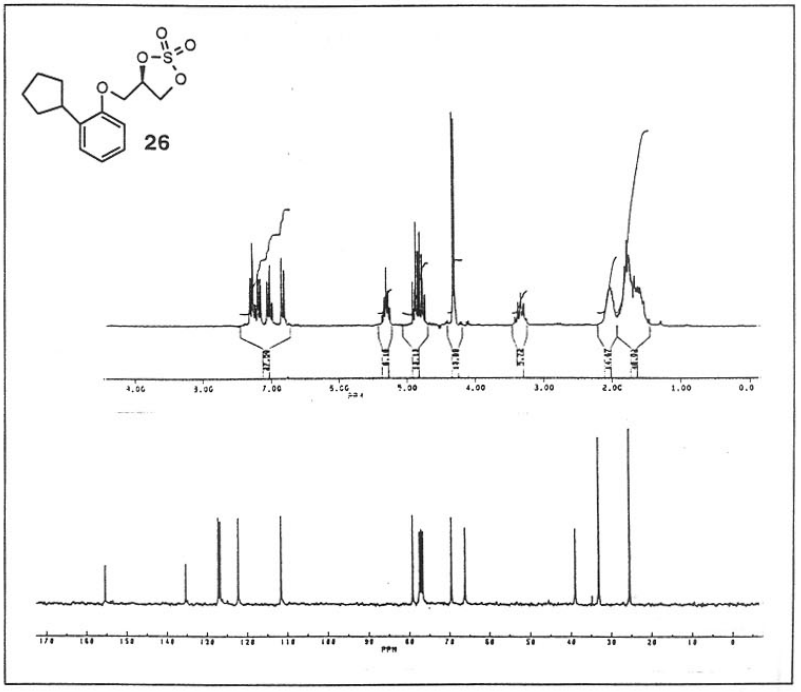
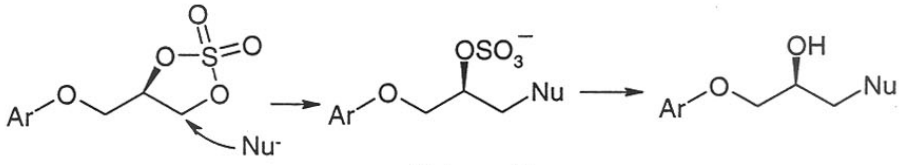


Fig. 6. ^{1}H and ^{13}C NMR spectra of cyclic sulfate 26

It is believed that the N-nucleophile (*tert*-butylamine) will react with the cyclic sulfate at the less hindered terminal carbon selectively in a S_N2 pathway under neutral conditions without the help of any catalysts to furnish the chiral β-hydroxybutylamine in good yields (**Scheme 12**).



Scheme 12

The structure of the compound **4b** was confirmed by IR, ^{1}H NRM ^{13}C NMR and MS spectra and elemental analysis. The ^{1}H NMR spectrum shows the presence of two singlets at 1.9 δ and 5.1 δ indicating the presence of *t*-butyl and NH group respectively. The ^{13}C NMR spectrum shows a signal at 25.45 δ which confirms the presence of carbons of *t*-butyl group. The quaternary carbon of *t*-butyl group appears at 57.62 δ in the ^{13}C NMR spectrum (Fig 7). The optical purity of the final product **4b** was

determined by comparing the optical rotation reported in the literature[49b] and was found to be 95 % ee.

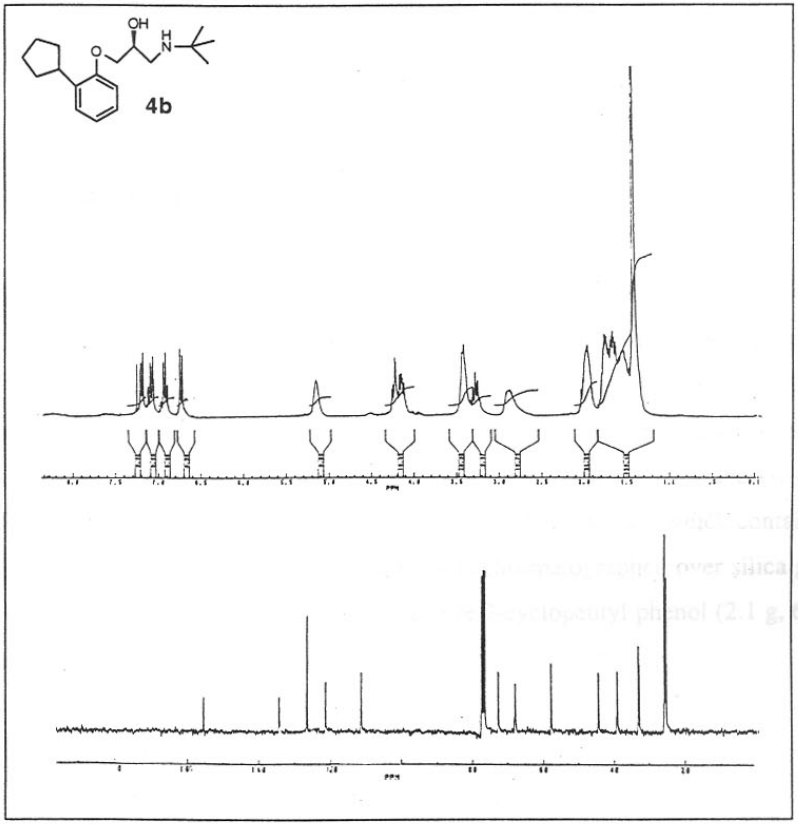


Fig. 7. ^{1}H and ^{13}C NMR spectra of S-Penbutolol 4b

3.1.5. Conclusion

2-Cyclopentylphenol was prepared by the caly catalyzed alkylation of phenol with cyclopentanol in a solvent free condition. In this case the *ortho*-substituted product predominates whereas in case of alkylation with cyclohexanol *ortho-para* components are almost equal. The reason may be ascribed to the steric factor, which is controlling the reaction. 2-Cyclopentylphenol was further transformed into a very useful β-adrenergic blocker (*S*)-penbutolol with 95% optical purity *via* highly efficient Sharpless

asymmetric dihydroxylation. The diol was converted to chiral cyclic sulfate in good yield. The N-nucleophile reacted at the terminal carbon of the cyclic sulfate selectively to furnish the β-hydroxy propylamine in very good yield. This methodology can be further extended for the synthesis of various β-adrenergic blockers with great scope.

3.1.6. Experimental

Preparation of 2-cyclopentylphenol.

Phenol (2 g, 21 mmol), cyclopentanol (2.2 g, 26 mmol) and Montmorillonite K10 (Aldrich USA) (200 mg, 10 wt. % based on phenol) were taken in a 50 ml round bottom flask and heated at 120 ^{0}C for 12 hrs. Dichloromethane was added to the reaction mixture and the catalyst was filtered off. Organic layer was washed with brine and, dried over Na_2SO_4 and evaporated. The crude reaction mixture which contains both 2-cyclopentylphenol and 4-cyclopentylphenol was chromatographed over silica gel (60-120 mesh) using pet ether as eluent to get the pure 2-cyclopentyl phenol (2.1 g, 62%) as colorless oil.

2-Cyclopentyl phenol 22a

Yield	:	62 %
IR (Neat, cm^{-1}),	:	3400, 2910, 1600, 1480, 1290
^{1}H NMR (200 MHz, $CDCl_3$),	:	δ 1.5-2.0 (m, 6H), 2-2.2 (m, 2H), 3.15-3.3 (m, 1H), 4.9 (s, 1H), 6.8 (d, 2H J =8.1Hz), 6.95 (t, 1H, J =8.1Hz), 7.1 (t, 1H, J =8.1Hz), 7.25 (d, 1H, J =8.1Hz)
^{13}C NMR (50 MHz, $CDCl_3$)	:	δ 25.5, 33.1, 39.05, 115.5, 121.04, 126.8, 127.8, 132.42, 153.43
Mass (m/z, % rel. intensity)	:	162 (M^+, 42), 147 (31), 133 (100), 120 (65), 115 (22), 107 (97), 91 (54), 77 (16).

4-Cyclopentylphenol 22b

Yield	:	28 %
IR (Neat, cm^{-1}),	:	3400, 2920, 1600, 1480, 1290

^{1}H NMR (200 MHz, $CDCl_3$),	:	δ 1.2-1.9 (m, 6H), 1.9-2.2 (m, 2H), 3.15 (m, 1H), 4.8 (s, 1H), 6.95 (m, 2H), 7.05 (m, 2H)

2-Cyclohexylphenol

Yield	:	38 %
IR (Neat, cm^{-1}),		3300, 2910, 1610, 1495, 1270
^{1}H NMR (200 MHz, $CDCl_3$),	:	δ 1.1-1.6 (m, 6H), 1.6-2.1 (m, 4H), 2.3 (m, 1H), 4.9 (s, 1H), 6.8 (d, J =8.1Hz 1H), 6.95 (t, J =8.1Hz, 1H), 7.1 (t, J =8.1 Hz, 1H), 7.2 (d, J =8.1 Hz, 1H)

4-Cyclohexylphenol

Yield	:	41 %
IR (Neat, cm^{-1}),		3300, 2910, 1610, 1480, 1285
^{1}H NMR (200 MHz, $CDCl_3$),	:	δ 1.2-1.55 (m, 6H), 1.55-1.8 (m, 4H), 4.1 (m, 1H), 4.8 (s, 1H), 6.9 (m, 2H), 7.3 (m, 2H)

Preparation of Allyl (2-cyclopentylphenyl) ether 23

A mixture of 2-cyclopentylphenol (1.5 g, 9.3 mmol), allyl bromide (2.24g, 18.5 mmol) and potassium carbonate (3.2 g, 23 mmol) in acetone (50 ml) was stirred at room temperature for 12 h (TLC). The mixture was filtered through sintered funnel and the filtrate was evaporated to dryness. The residue was purified by flash chromatography using 1% EtOAc in pet-ether to furnish the allyl phenyl ether as light yellow liquid (1.7 g).

Yield	:	1.7 g (91%)
IR (neat, cm^{-1})	:	2920, 1630, 1390, 1225.
^{1}H NMR (200 MHz, $CDCl_3$,)	:	δ 1.4-1.9 (m, 6H ring CH_2), 1.9-2.15 (m, 2H, ring CH_2), 3.35 (m, 1H, ring CH), 4.5 (bd 2H, OCH_2), 5.15-5.5 (dd. 2H, J=8.1 Hz, $=CH_2$) 6.1 (m, 1H CH=), 6.7-7.05 (m, 2H, ArH), 7.05-7.3 (m, 2H, Ar·H)
^{13}C NMR (50.3 MHz $CDCl_3$)	:	δ 25.76, 35.17, 33.17, 39.59, 69.14, 112.03, 116.89, 120.93, 126.65, 127.0, 134.05, 135.21, 156.73

MS (% rel. intensity) : 202 (M^+, 4), 161 (27), 145 (17), 133 (28), 107 (100), 91 (54), 77 (8)

Procedure for asymmetric dihydroxylation of 23 to get diol 24

A 250 ml round bottom flask was charged with $K_3Fe(CN)_6$ (3.4 g, 10 mmol), K_2CO_3 (1.43 g, 10 mmol) DHQ-PHAL (54 mg, 0.07 mmol) and *t*-BuOH: H_2O (80 ml) and stirred for 5 minutes at room temperature. The flask was cooled to 0 °C and a solution of OsO_4 (0.17 ml of 0.2 M solution in toluene, 0.03 mmol) was added followed by the allyl 2 cyclopentylphenyl ether (0.7 g, 3.5 mmol). The reaction mixture was stirred for 24 hours at room temperature (monitored by TLC). Ethyl acetate (20 ml) and sodium metabisulfite (1g) were added to the mixture and stirred for 1 hour. Two layers were separated out. Organic layer was separated and aqueous layer was extracted with EtOAc (3 ×20 ml). Combined organic layer was washed with brine, dried over sodium sulfate and evaporated to dryness. The crude product was purified by flash column chromatography using EtOH: pet-ether (1:1) to yield the diol **24** as colorless liquid (0.74 g)

Yield : 0.74 g (90%)

$[\alpha]_D$: - 12.3°(c 0.8, MeOH)

IR (neat, cm^{-1}) : 3300-3550, 1600, 1492, 1452, 1242, 1112, 1046.

^1H NMR (200 MHz, $CDCl_3$) : δ 1.4-1.9 (m, 6H), 1.9-2.15 (m, 2H), 2.3 (bs, 1H, OH), 2.7 (bs, 1H, OH), 3.2-3.35 (m, 1H), 3.7-3.9 (m, 2H, -CH_2), 4.05 (d, J=5.4 Hz, 2H, O-CH_2), 4.1-4.25 (m, 1H, -CH-), 6.85 (d, J=8.1 Hz 1H), 7.0 (t, J=8.2 Hz, 1H), 7.15 (t, J=8.1Hz, 1H), 7.25 (d, J=8.1Hz, 1H)

^{13}C NMR (50 MHz, $CDCl_3$) : δ 25.85, 33.35, 39.35, 64.29, 69.58, 71.18, 112.08, 121.49, 126.96, 127.17, 135.16, 156.58

MS (% rel. intensity) : 236 (M^+, 11), 162 (60), 133 (100), 120 (43.1), 107 (47), 91 (21), 77 (4)

Procedure for the preparation of cyclic sulfite 25

The diol **24** (0.5 g, 2.1 mmol) was dissolved in dry pyridine (2 mL) and cooled to 0°C in an ice bath under argon atmosphere. Freshly distilled thionyl chloride (0.46 g, 0.19 mL, 2.2 mmol) was added dropwise and the reaction mixture was stirred for 3 hours. Ice cold water was added to the reaction mixture and extracted with ether. The ethereal layer was washed with dil HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was dissolved in 10 ml of DCM and 2.5 mL aliquot was taken and purified by flash column chromatography using EtOAc : pet-ether (1: 9) to furnish light yellow oil (0.138 g).

Yield	:	0.138 g (93 %)
$[\alpha]_D$	:	+12.05°(c, 0.8, MeOH)
IR (neat)		2930, 1440, 1390, 1235, 1195
^{1}H NMR	:	δ 1.5-1.9 (m, 6H), 1.9-2.1 (m, 2H), 3.3 (m, 1H), 4.1
(200 MHz, $CDCl_3$)		(m, 1H), 4.4 (m, 2H), 4.7 (d, J = 6.4 Hz, 1H), 4.9 (m,1H), 5.35 (m, 1H), 6.85 (d, J= 8.1Hz, 1H), 7.0 (d, J=8.1Hz, 1H) 7.2 (t, J=8.1Hz 1H), 7.3 (d, J=8.1Hz, 1H)
^{13}C NMR	:	δ 25.78, 33.13, 33.19, 39.51, 67.09, 69.01, 78.70,
(50 MHz, $CDCl_3$)		121.95, 127.02, 127.36, 135.12, 156.07.
MS (% rel. intensity)	:	282 (12), 218 (2), 160 (78), 145 (50), 131 (56), 121 (100), 107 (41), 91 94), 77 (6).
Analysis	:	Calcd: C 59.57, H 6.38, S 11.35 %, Found: C 59.94, H 6.42, S 11.31 %.

Preparation of cyclic sulfate 26

The crude cyclic sulfite **25** (≅ 0.41 g, 1.5 mmol) was dissolved in a mixture of 2mL acetonitrile and 2mL CCl_4 and cooled to 0 °C in an ice bath. Sodium periodate (0.47 g, 2.2 mmol) was added to the cold solution followed by $RuCl_3$ (3 mg, 0.014 mmol) and 3 ml of water. The reaction mixture was filtered through a pad of celite and evaporated the solvent. The mixture was extracted with ether and dried over anhydrous sodium sulfate and evaporated to dryness. Purification by flash column

chromatography of the crude product with EtOAc : pet-ether (1: 9) afforded 0.40 g of white solid.

Yield	:	0.4 g (91 %)
Mp	:	89 ^{0}C
$[\alpha]_D$	:	+5.6°(c 1, MeOH)
IR (nujol, cm^{-1})	:	2900, 1445, 1370, 1235, 1195.
^{1}H NMR (200 MHz, $CDCl_3$)	:	δ 1.5-1.95 (m, 6H), 1.95-2.1 (m, 2H), 3.25-3.4 (m, 1H), 4.35 (d, J= Hz, 2H), 5.75-5.95 (m, 2H), 5.3 (m, 1H), 6.75 (d, J= 8.1Hz, 2H), 7.0 (t, J=8.1Hz, 1H), 7.15 (t, J=8.1Hz, 1H), 7.25 (d, J=8.1Hz, 1H)
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 25.29, 32.88, 38.73, 65.95, 69.35, 79.00, 111.44, 122.03, 126.53, 127.03, 135.086, 155.14.
MS (% rel. intensity)	:	298 (M^+, 15), 161 (26), 145 (100), 131 (150), 115 (23), 107 (12), 91 (18), 77 (10)

Procedure for the opening of cyclic sulfate 26 to get 1-(2-cyclopentylphenoxy)-3-[(1,1-dimethylethyl)amino]-2-propanol,[S-Penbutolol], 4b

A 25 ml round bottomed flask was charged with cyclic sulfate (200 mg, 0.67 mmol) in dry THF (10 mL) and freshly distilled t-butyl amine in excess (5 mL) under nitrogen atmosphere. The reaction mixture was refluxed for 8 hours (monitored by TLC). The solvent was evaporated under reduced pressure to get a wine red viscous residue. This residue was treated with 5 mL 20 % H_2SO_4 and 10 mL ether for 12 hours. White precipitate was observed. The reaction mixture (as such) was further treated with 20 % NaOH solution up to pH 10 and stirred for 0.5 hours. The white ppt. disappeared. Thereafter, reaction mixture was extracted with ether (3.20 mL) and then ethyl acetate. The ether layer was discarded and ethyl acetate layer was washed with brine and dried over Na_2SO_4. Removal of ethyl acetate gave almost pure product, which was recrystallized from hot heptane to get 140 mg of S-penbutolol.

Yield	:	0.14 g (72 %)
mp	:	66-68 °C [Lit.[49b] 68-72]

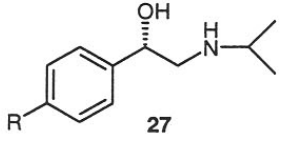
IR	:	3456, 3094, 2980, 2918, 2842, 1600, 1492, 1452, 1380, 1216, 1028, 918,
$[\alpha]_D$	:	-10.9°(c 0.8, MeOH) [Lit.[49b] –11.5° (c 1, MeOH)]
^{1}H NMR (300 MHz)		δ 1.9 (s, 9H), 1.5-1.9 (m, 6H), 1.9-2.1 (m, 2H), 3.3 (m, 1H), 3.45 (m, 2H), 4.1-4.3 (m, 3H), 5.1 (bs, 1H), 6.75 (d, J= , 1H), 6.9 (t, 1H), 7.1 (t, 1H), 7.2 (1H)
^{13}C NMR (75 MHz, $CDCl_3$)	:	δ 25.02, 25.45, 32.69, 38.84, 44.18, 57.62, 72.43, 111.32, 121.24, 126.46, 134.59, 155.21.
MS (% rel. intensity)	:	291 (M^+ 2), 276 (5), 233 (3), 200 (3), 162 (13), 133 (29), 120 (16), 107 (16), 91 (13), 86 (100), 77 (4).

Section B

Asymmetric Synthesis of Antiarrhythmia Agent *d*-Sotalol

3.2.1. Introduction

Reentrant ventricular arrythmia is a major factor for most cases of sudden cardiac death.[58] Class III antiarrhythmia compounds[59] such as *d*-Sotalol [4′-[2-(isopropylamino)-1-hydroxyethyl]methanesulfonanilide], **27a** (**Fig. 8**) effectively control such arrhythmia and this drug is under various clinical trials. The pKa value (8.3) of the sulfonamide is so low, that the molecule exists in the zewitterionic form, thus diminishing the possibility of hydrogen bond donation. As a result of this ionisation sotalol is an extremely hydrophilic compound. It is the only commercially successful β-antagonist to emerge from the aryl ethanolamine series.



27

a: d-Sotalol: R= NHMs ; b: d-Nifenalol R= NO_2

Fig. 8

Another antiarrhythmic drug is nifenanlol, **27b**, which is not much explored so far. Only two reports are there in the literature for the synthesis of this compound.

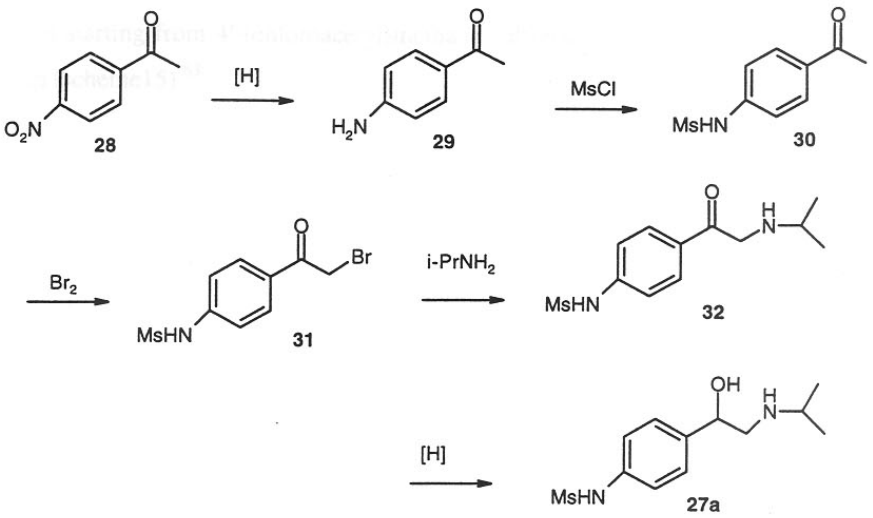
3.2.2. Review of Literature

3.2.2.1. Synthesis of *d*-Sotalol

There are a few reports on the synthesis of *d*-Sotalol involving resolution, chiral homogeneous hydrogenation, CBS reduction etc. The methods reported in the literature are described below.

Larsen's approach[60]

Larsen has synthesized racemic Sotalol from 4-nitroacetophenone. Reduction of 4-nitroacetophenone **28**, mesylation followed by bromination of the resulting compound gave 4′-(bromoacetyl)methanesulfonanilide **31**. Treatment of **31** with isopropyl amine followed by reduction of the carbonyl functionality gave the racemic Sotalol (scheme 13).



Scheme 13

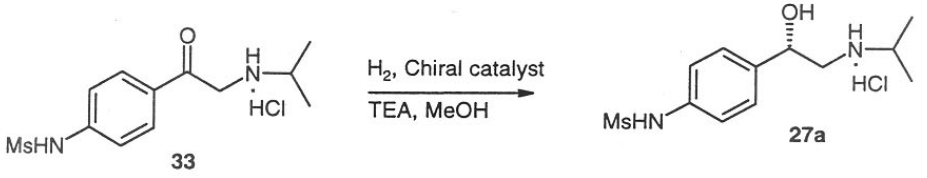
Simon's approach[61]

This group reported the resolution of racemic Sotalol with chiral l-mandelic acid. Racemic Sotalol was mixed with l-mandelic acid in hot isopropanol. On cooling,

an optically enriched fraction of the d-Sotalol-l-mandelate salt was obtained. Acidification of the salt with ethanolic HCl afforded the d-Sotalol.

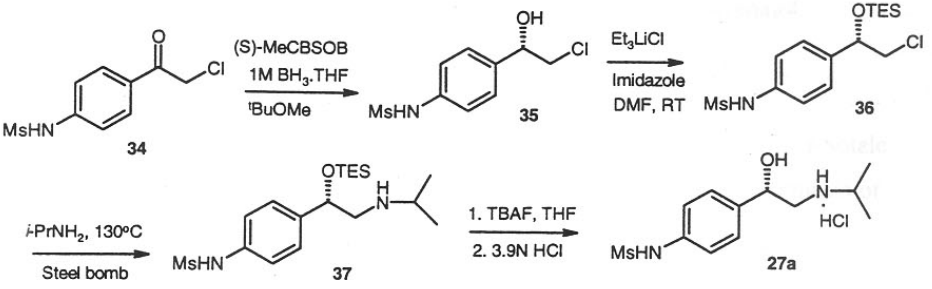
Vmishetti's approach[62, 63]

Asymmetric synthesis of d-Sotalol with 85% optical purity was accompanied by chiral homogeneous hydrogenation of (4-isopropylaminoacetyl)methanesulfonanilide hydrochloride **33** (scheme 14).



Scheme 14

Another chiral synthesis of *d*-Sotalol with 98% optical purity was developed by them starting from 4′-(chloroacetyl)methane sulfonanilide using CBS reduction as key step (scheme15).[63]



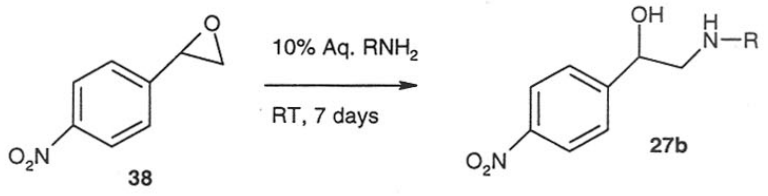
Scheme 15

3.2.2.2. Synthesis of *d*-Nifenalol

There are two reports available in the literature for the synthesis of d-Nifenalol in the literature. These are described below.

Bella's approach[64]

Bella and coworkers synthesized racemic Nifenanlol, **27b** via ring opening of epoxide **38** with primary amine (scheme 16).



Scheme 16

Almirante's approach[65]

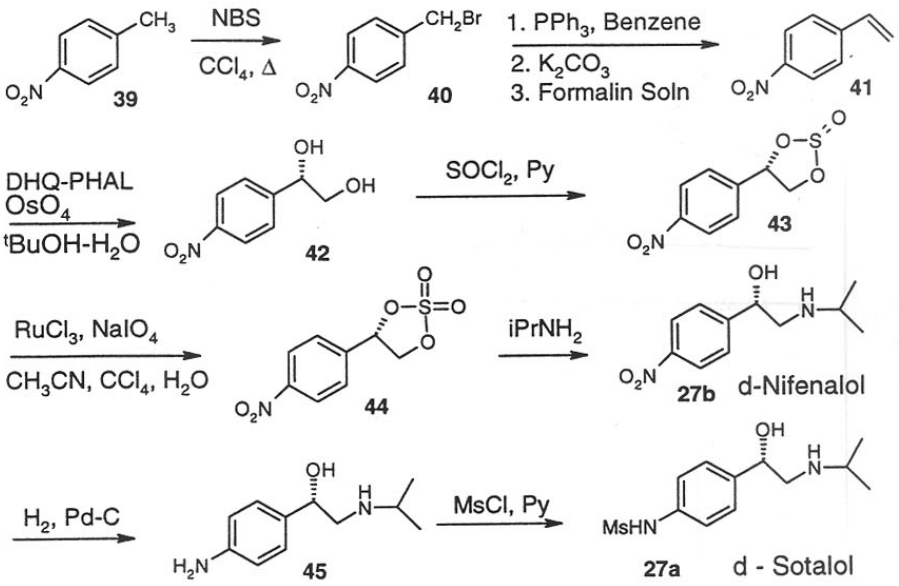
Resolution of nifenalol was achieved by making of the salt by treating with D-(-)-dibenzoyltartaric acid. Fractional crystallization of the salt from ethanol and subsequent treatment of the crystallized salt with alkali give l-(-)-Nifenalol.

Thus, there are a very few methods available for the synthesis of *d*-Sotalol and Nifenalol. Thus it is essential to find a more convenient route for the synthesis of these important β-adrenergic blockers.

3.2.3. Present work

Objective

With the new synthetic developments of the enantiomerically enriched diols, their stereoselctive transformations are of contemporary interest and is widely used for the total synthesis of a variety of naturally occurring and biologically active compounds. It is seen from the above literature search that there are very few reports available for the synthesis of Sotalol and Nifenalol. The objective of the present investigation is to develop a new general route for the synthesis of Sotalol and Nifenalol by applying the chemistry of chiral cyclic sulfate (scheme 18).



Scheme 18

3.2.4. Results and Discussion

The present strategy for the synthesis of Nifenalol and Sotalol is depicted in the **scheme 18**. 4-Nitrostyrene 41 was prepared by following reported procedure.[66] 4-Nitrobenzyl bromide 40 was prepared from 4-nitrotoluene 39 using NBS as brominating

agent in CCl_4 at reflux temperature. Melting point of the compound **40** is matching with the literature data. CH_2 protons of 4-nitrobenzyl bromide appeared at 4.5 δ in ^1H NMR spectrum. 4-Nitrobenzyl bromide was then converted to 4-nitrobenzyltriphenyl phosphonium bromide in 97% yield by treating with triphenylphosphine in benzene at reflux. The phosphonium salt was then treated with aqueous K_2CO_3 to produce phosphorane, which on subsequent treatment with aqueous formalin solution gave 4-nitrostyrene 41 in 79% yield. While preparing styrene **41** it is necessary to wash carefully the phosporane to make it free of base before treating with formalin solution to avoid yield loss due to the formation of 4-nitrototoluene as the side product. ^1H NMR spectrum of **41** shows the characteristic signals of styrene at 5.9 δ (doublet) and at 6.8 δ (doublet of doublet).

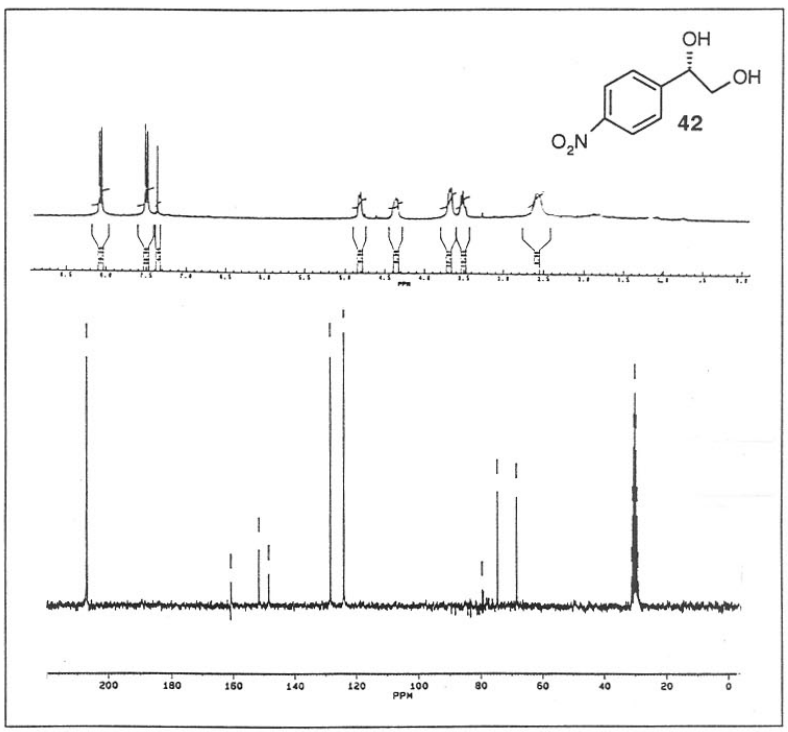


Fig. 9. ^1H and ^{13}C NMR spectra of diol 42

4-Nitrostyrene was subjected to asymmetric dihydroxylation using DHQ-PHAL as chiral ligand to furnish the diol **42**. The IR spectrum of the diol **42** shows a band at

3400 cm^{-1} indicating the presence of hydroxyl functionality. The bands at 1510 cm^{-1} and 1340 cm^{-1} indicate the presence of nitro group in the compound. The CH_2 protons appear in ^1H NMR spectrum as two distinct doublets at 3.5 δ and 3.7 δ. The CH proton appears at 4.8 δ as multiplet (Fig 9).

The diol **42** was transformed into cyclic sulfite **43** using $SOCl_2$ in pyridine in 91% yield. The IR spectrum of cyclic sulfite **43** showed the absence of hydroxyl groups (3400 cm^{-1}) and the appearance of a strong band at 1205 cm^{-1} characteristic of cyclic sulfites. ^1H NMR spectrum of the cyclic sulfite **43** showed the presence of minor multiplets alongwith the major multiplets at 4.4 δ, 4.9 δ, 5.5 δ, indicating the presence of diastereomeric mixture. Similarly, two minor signals corresponding to the signals at 71.67 δ, 79.69 δ are also seen in the ^{13}C NMR spectrum (Fig 10).

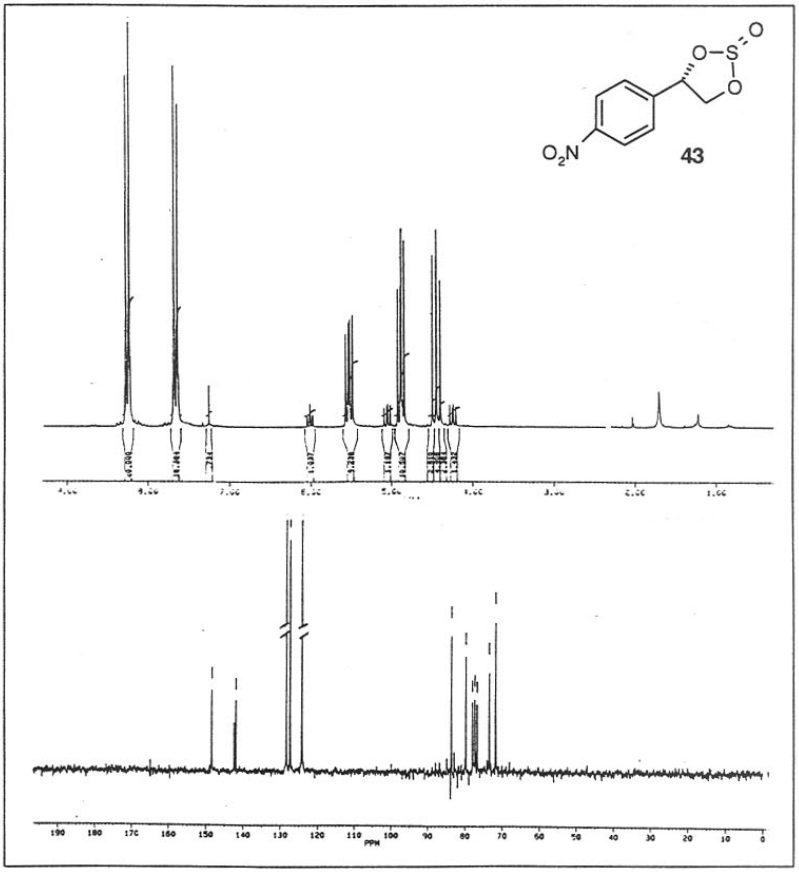


Fig. 10. ^1H and ^{13}C NMR spectra of chiral cyclic sulfite 43

The cyclic sulfite **43** was treated with isopropylamine in DMF at reflux to produce the desired compound nifenalol. Lohray reported the ring opening of cyclic sulfite with LiN_3 in DMF.[57] We followed the same condition to open cyclic sulfite, but reaction did not proceed at all in this case.

Hence, the cyclic sulfite 43 was oxidized with $NaIO_4$ in presence of a catalytic amount of $RuCl_3$ to produce the cyclic sulfate 44. Formation of cyclic sulfate was confirmed by NMR. ^1H NMR showed the disappearance of the diastereomeric multiplets and presence of other three signals (at 4.55 δ, 5.05 δ and 6.0 δ). In ^{13}C NMR two minor signals also disappeared (Fig. 11).

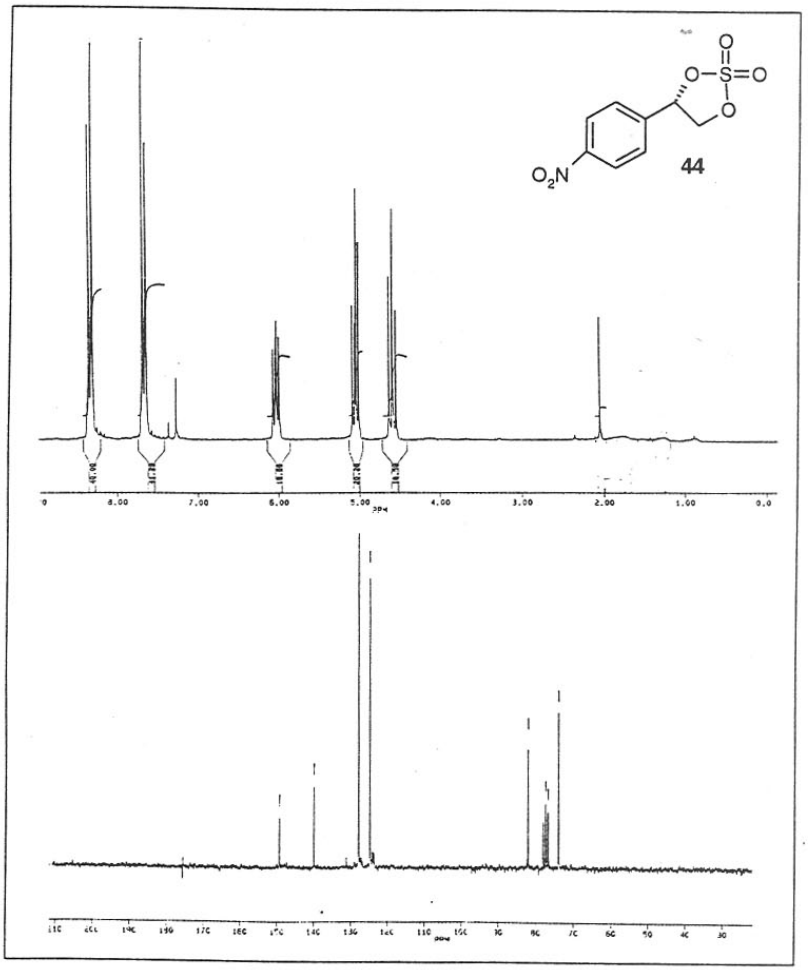


Fig.11. ^1H and ^{13}C NMR spectra of chiral cyclic sulfate 44

The cyclic sulfate **44** was treated with isopropyl amine in THF. After completion of reaction, the reaction mixture was first acidified with 20 % sulfuric acid and then basified with 20 % NaOH to get the required compound nifenalol **27b** in 61 % yield. It is believed that the N-nucleophile (isopropylamine) would react with the cyclic sulfate at the less hindered terminal carbon selectively in a S_N2 pathway under neutral conditions without the help of any catalysts to furnish the chiral β-hydroxypropylamine in good yield. The structure of the compound was confirmed by IR, ^{1}H NMR and MS spectra and elemental analysis. The ^{1}H NMR spectrum shows the presence of a doublet at 1.15 δ and a singlet at 1.8 δ indicating the presence of *i*-propyl and NH group respectively. CH proton of isopropyl group appears at 4.0 δ as multiplet. The signal at 5.0 δ corresponds to the CH proton attached to the OH group (Fig 12).

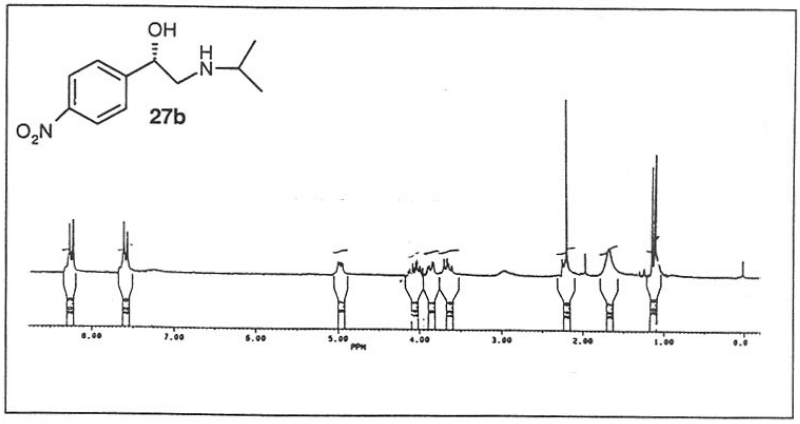


Fig.12. ^{1}H NMR spectrum of nifenalol 27b

Nifenalol was further reduced with H_2/Pd-C in ethanol at 50 psi pressure to furnish the amino compound **46**. The compound was characterized by IR and ^{1}H NMR spectra. The ^{1}H NMR spectrum shows absence of aromatic signals of nifenalol at 7.6 δ and 8.25. Appearance of two doublets at 6.8 δ and 7.0 δ confirms the reduction of NO_2 group to NH_2 group.

The crude product was then treated with methane sulfonyl chloride to produce the final compound d-Sotalol **27a**. The yield of this step is low (40%) and a mixture of product was found due to mesylation of hydroxyl functional groups. However, d-Sotalol was easily separated by column chromatography.

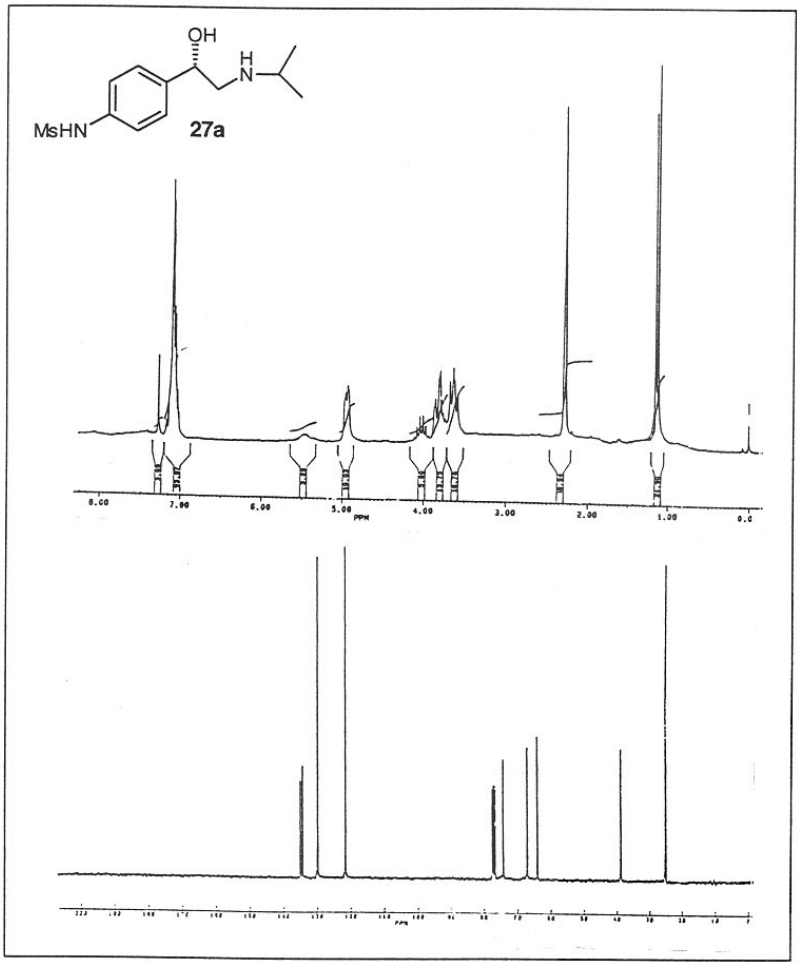


Fig.12. ^{1}H and ^{13}C NMR spectra of d-Sotalol 27a

d-Sotalol was characterized by IR, NMR and elemental analysis. The ^{1}H NMR spectrum shows the presence of isopropyl group indicated by the doublet at 1.1δ and a multiplet at 4.0 δ respectively. The aromatic signals appeared in the ^{1}H NMR of the previous compound disappeared and a multiplet at 7.1 δ is seen in the spectrum. The CH_3 carbons and CH carbon of isopropyl group appear in ^{13}C NMR at 24.84 δ and 63.93 respectively. The CH_3 carbon of mesyl group appears in ^{13}C NMR at 38.58 δ (Fig 13). Optical purity is determined by comparing the optical rotation for the same reported in the literature and found to be 94%.

3.2.5. Conclusion

A simple method is developed for the synthesis of d-Nifenalol and d-Sotalol using Sharpless asymmetric dihydroxylation *via* the cyclic sulfate intermediate. The N-nucleophile reacted at the terminal carbon of the cyclic sulfate selectively to furnish the β-hydroxy propylamine in good yield. Although this procedure is employed sucessfully for the synthesis of nifenalol, further synthetic manipulation for the synthesis of d-Sotalol was rather inefficient since the last step involving mesylation resulted in a mixture of products.

3.2.6. Experimental

Synthesis of 4-nitrobenzyl bromide:

A stirred solution of 4-nitrotoluene (10g, 73 mmol), NBS (15g, 84 mmol) in CCl4 (300 mL) and benzoyl peroxide (1.8g, 7.4 mmol) was heated under reflux for 5h. The reaction mixture was filtered and washed with water, brine solution and dried over Na_2SO_4. Removal of solvent and column chromamtography over silicagel (60-120 mesh) using pet. ether as eluent afforded 13.9g (88%) of 4-nitrobenzyl bromide.

Yield	:	13.9 g (88%)
m. p.	:	97-98°C [Lit. 98-100 °C]
IR (Nujol) cm^{-1}	:	1600, 1460, 1360, 1230, 1100
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 4.5 (s, 2H), 7.55 (d, J=8Hz, 2H), 8.2 (d, J=8Hz, 2H)

Preparation of 4-nitrobenzyl triphenyl phosphonium bromide

4-Nitrobenzyl bromide (4g, 18.5 mmol) and triphenyl phosphine (4.86g, 18.5 mmol) were taken in 30 ml benzene and stirred at 50 °C for 2 h. White precipitate formed was filtered and dried to get 8.6 g. of the triphenyl phosphonium salt.

Yield : 8.6 g (97%)

m. p. : 295-97 °C

Preparation of 4-Nitro styrene, 41

4-Nitrobenzylphosphonium bromide (8.5g, 17.8 mmol) was added slowly to a stirred aqueous 20 % K_2CO_3 (200 ml) solution and stirring was continued for 1h. The purple coloured phosphorane precipitated was filtered off and washed with water to make it free from base. Phosphorane was then treated with 100 mL of 30% formaline solution till colour of phosphorane disappears (15 minutes). The solution was extracted thrice with 3.0 mL portions of chloroform. Combined organic extract was washed with brine, dried over Na_2SO_4 and evaporated to get crude *p*-nitrostyrene. The crude styrene was purified by passing through a column of alumina using pet.ether as eluent.

Yield	:	2.1g. (79%)
IR (Neat, cm^{-1})	:	2942, 1654, 1598, 1514, 1494, 1344, 1320, 1110
^{1}H-NMR ($CDCl_3$, 200 MHz, δ ppm	:	5.5 (d, J=10.8Hz, 1H), 5.9 (d, J=16.7Hz, 1H), 6.7-6.9 (dd, J=10.8Hz, 6.7Hz, 1H), 7.55 (d, J=8.1Hz, 2H), 8.2 (d, J=8.1Hz, 2H)

Synthesis of 4-nitrostyrene diol, 42

A 250 mL round bottom flask was charged with $K_3Fe(CN)_6$ (8.28g, 25 mmol), K_2CO_3 (3.47g, 25 mmol), $(DHQ)_2PHAL$ (0.13g, 0.17 mmol) and t-BuOH:H_2O (1:1) mixture (80 mL) and stirred for 5 minutes at room temperature. The flask was cooled to 0 °C and a solution of OsO_4 (0.4 mL of 0.2 molar solution in toluene; 0.084 mmol) was added, followed by 4-nitrostyrene (1.25g, 8.4 mmol). The reaction mixture was stirred for 40 h. at room temperature (monitored by TLC). Ethyl acetate (50 mL) and sodium metabisulfite (1g.) added to the mixture and stirred for 1h. Organic layer was separated and aqueous layer was extracted with EtOAc (3x20 mL). Combined organic layer was washed with brine, dried over sodium sulfate and evaporated to dryness. The crude product was purified by flash column chromatography using EtOAc:pet. ether (1:1) to yield the diol **42** as a white solid.

Yield	:	1.26g. (82%)
m. p.	:	101-102°C
$[\alpha]_D$	:	+25° (c 0.8, MeOH)
IR (Nujol) cm^{-1}	:	3500-3200, 2920, 1600, 1510, 1460, 1375, 1340, 1275, 1095
^{1}H-NMR ($CDCl_3$, 200 MHz,)	:	δ 2.6 (bs, 1H), 3.5 (d, J=5.4Hz, 1H), 3.7 (d, J=5.4Hz, 1H), 4.4 (bs, 1H), 4.8 (m, 1H), 7.5 (d, J=6.8Hz, 2H), 8.1 (d, J=6.8Hz, 2H).
^{13}C-NMR (Acetone d_6, 50 MHz)	:	δ 68.46, 74.65, 124.01, 128.38, 148.31, 151.52.
Analysis	:	$C_8H_9NO_4$ requires: C, 52.46; H, 4.92, N, 7.65 Found: C, 52.52; H, 4.89; N, 7.60

Synthesis of ethyl(4S)-4-(4-nitrophenyl)-1,3,2-dioxathiolane-2-oxide, 43

The diol (0.7 g, 3.8 mmol) was dissolved in dry pyridine (3 mL) and cooled to 0°C in an ice bath under argon atmosphere. Freshly distilled thionyl chloride (0.47 g, 0.34 mL, 3.9 mmol) was added dropwise and the reaction mixture was stirred for 3 hours. Ice cold water was added to the reaction mixture and extracted with ether. The ethereal layer was washed with dil HCl, saturated sodium bicarbonate solution and with brine successively. The ether extract was dried over anhydrous sodium sulfate and evaporated to dryness. The crude product was dissolved in 10 ml of DCM and 2.5 ml aliquot was taken and purified by flash column chromatography using EtOAc : pet-ether (1: 9) to furnish cyclic sulfite **43** as a white solid (0.16 g).

Yield	:	0.16g. (91%)
m. p.	:	56-58°C
$[\alpha]_D$	:	-41.4 ° (c 1.3, MeOH)
IR ($CHCl_3$) cm^{-1}	:	1600, 1523, 1351, 1316, 1209, 855
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 4.35-4.55 (t, J= 8.1 Hz, 1H), 4.8-4.98 (q, J=8.1 Hz, 1H), 5.45-5.55 (q, J=8.1 Hz, 1H), 7.65 (d, J=9.2 Hz, 1H), 8.25 (d, J=9.2 Hz, 1H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 71.67 (73.35), 79.69 (83.61), 124.10, 127.29, 128.28, 141.85, 148.36.

Mass (m/z, % rel. Intensity)	:	229 (M^+, 1), 165(2), 150(39), 135(93), 118(33), 105(100), 77(79).
Analysis	:	$C_8H_7NO_5S$ requires: C, 41.92, H, 3.05, N 6.11, S=13.97%; Found: C=42.00, H, 3.11, N 5.80, S, 13.88%.

Preparation of ethyl(4S)-4-(4-nitrophenyl)-1,3,2-dioxathiolane-2,2-dioxide, 44

The crude cyclic sulfite (0.71 g, ≅1.5 mmol) was dissolved in a mixture of 3mL acetonitrile and 3mL CCl_4 and cooled to 0 °C in an ice bath. Sodium periodate (0.47 g, 2.2 mmol) was added to the cold solution followed by $RuCl_3$ (3 mg, 0.014 mmol) and 4.5 mL of water. The reaction mixture was filtered through a pad of celite and evaporated the solvent. The mixture was extracted with ether and dried over anhydrous sodium sulfate and evaporated to dryness. Flash column of the crude product with EtOAc : pet-ether (1: 9) resulted 0..59 g of **44** as white solid.

Yield	:	0.59g. (86%)
m. p.	:	139 °C
$[\alpha]_D$	:	-51.5°(c 0.4, MeOH)
IR ($CHCl_3$) cm^{-1}	:	1600, 1530, 1355, 1310, 1230,
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 4.55 (t, J=9.4Hz, 1H), 5.05 (dd, J=5.4Hz, 1H), 6.0 (d,d J=5.4Hz, 1H), 7.65 (d, J=8.1Hz, 2H, Ar-H), 8.35 (d, J=8.1Hz, 2H, ArH).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 73.82, 81.92, 124.54(x2), 127.66(x2), 139.72, 149.10
MS (m/z, % rel. intensity)	:	165(14), 153(27), 150(5), 135(24), 105(100), 77(50)
Analysis	:	$C_8H_7NO_6S$ requires: C 39.18, H 2.86, N 5.71, S 13.06%; Found: C 39.13, H 2.96, N 5.75, S 13.11%.

Reaction of cyclic sulfate with isopropyl amine to produce Nifenanol, 27b

A 25 ml RB flask was charged with cyclic sulfate (300 mg, 1.2 mmol) in dry THF (10 mL) and freshly distilled isopropyl amine in excess (6 mL) under nitrogen

atmosphere. The reaction mixture was refluxed for 10 hours (monitored by TLC). The solvent was evaporated under reduced pressure to get a wine red viscous residue. This residue was treated with 5 ml 20 % H_2SO_4 and 10 ml ether for 12 hours. White precipitate was observed. The reaction mixture (as such) was further treated with 20 % NaOH solution up to pH 10 and stirred for 0.5 hours. The white ppt. disappeared. There after reaction mixture was extracted with ether (3x20 mL) and then ethyl acetate. The ether layer was discarded and ethyl acetate layer was washed with brine and dried over Na_2SO_4. Removal of ethyl acetate gave almost pure product, which was recrystallized to afford 168 mg of R-Nifenalol, **27b**.

Yield	:	0.168g. (61%)
m. p.	:	97-98°C
IR (nujol, cm^{-1})	:	3350, 3245, 2920, 1595, 1530, 1460, 1370, 1340, 1260.
$[\alpha]_D$	:	+ 41.5 ° (c 0.4, 1N HCl) (Lit.[65] +43° (c 2, H_2O)(for Nifenalol hydrochloride)]
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.15 (d, J=7.7Hz, 6H), 1.7 (bs, 1H), 2.35 (b, 1H), 2.95 (bs, 1H), 3.65 (dd, J=7.7Hz, 3.8, 1H), 3.85 (dd, J=7.7, 3.8Hz, 1H), 4.05 (m, 1H), 4.95 (dd, J=5.8, 3.8Hz, 1H, CH), 7.6 (d, J=7.7Hz, 2H), 8.25 (d, J=7.7Hz, 2H).
Analysis	:	$C_{11}H_{16}N_2O_3$ requires: C, 58.93, H, 7.14, N, 12.5 Found: C, 58.58, 7.06, 12.40%

Reduction of nifenanol (27b) to produce 1-(4-aminophenyl)-2-isopropylamino ethanol, 45

A par bottle is charged with 150 mg of nifenanol (150 mg, 0.67 mmol), 10mg of 5% Pd/c and 10 mL of 95% ethanol). The mixture is stirred with H_2 under 50 psi for 2h. The catalyst was filtered and solvent evaporated. Ethyl acetate was added to the crude product, dried over sodium sulfate and evaporated to get 140 mg. of the crude product.

^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.2 (d, J=5.4Hz, 6H), 1.5 (bs, 1H), 2.55 (bs, 1H),

3.6 (m, 1H), 3.8 (m, 1H), 4.0 (m, 1H), 4.95 (m, 1H), 6.8 (d, J=8.1Hz, 2H), 7.0 (d, J=8.1Hz, 2H).

Mesylation of (45) to produce d-sotalol, 27a

1-(4-Aminophenyl)-2-isopropylamino ethanol was dissolved in 3 mL of pyridine, cooled at –20°C (with ice-salt bath), treated dropwise with a solution of mesyl chloride (0.07g, 0.62 mmol) in pyridine (2 mL) and stirred at the same temperature for 1h. The ice-water was added and the mixture was extracted with ethyl acetate. The combined organic extract was washed with brine, dried over Na_2SO_4 and flash column with ethyl acetate/pet ether (95:5) as eluent furnished d-solatol. The resulting product was treated with 1equiv. of 5% HCl the get d-Sotalol hydrochloride.

Yield	:	(67 mg) 40%
m. pt.	:	199-201 °C [Lit.[61] 204 –205 °C]
IR ($CHCl_3$) cm^{-1}	:	3350, 3260, 2960, 2850, 1495, 1210, 1125, 1040.
$[\alpha]_D$	:	+34.6° (c 0.7, H_2O) [Lit.[61] +36° (H_2O)]
^{1}HNMR (200 MHz, $CDCl_3$)	:	δ 1.1 (d, J=6.5Hz, 6H), 1.9 (bs, 1H), 2.3 (bs), 3.65 (m, 1H), 3.0 (s, 3H), 3.8 (m, 1H), 4.0 (m, 1H), 4.95 (m, 1H), 7.1 (m, 4H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 24.84, 38.57, 63.93, 67.48, 74.48, 121. 45, 129.70, 134.18, 134.85.

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CHAPTER IV

Transfer Hydrogenation of Carbonyl Compounds Using Transition Metal Catalysts

4.0 General Introduction

Reduction of organic compounds is important synthetically both in the laboratory and in industry. Transfer hydrogenation is one of the most widely studied reduction process[1] these days due to its potential advantage over conventional hydrogenation process using molecular hydrogen. This process entails hydrogen abstraction from the reagent (hydrogen donor) by means of a catalyst, followed by (or in concert with) hydrogen addition to the unsaturated functional group of the substrate (hydrogen acceptor). This can be generalized as in the scheme 1.

$$DH_2 + A \overset{\text{cat.}}{\rightleftharpoons} D + AH_2$$

DH_2 = hydrogen donor; A = hydrogen acceptor

Scheme 1

Several different substrates have been successfully reduced by transfer hydrogenation in the presence of both heterogeneous and homogeneous catalysts.[1-4] The list of hydrogen acceptors includes ketones, α,β-unsaturated carbonyl compounds, such as α,β-unsaturated acids and esters, imines and nitro compounds.

In comparison with catalytic reduction using molecular hydrogen, transfer reduction is potentially advantageous due to its simplisity. Whereas use of molecular hydrogen needs high-pressure reactors and causes potential hazards due to its high diffusibility and flamability. Additionally, rate and selectivity of the reaction can be favorably affected by selecting the most appropriate hydrogen donor. This process is very well exploited to induce enantioselectivity to prochiral substrates employing chiral catalyst, thus providing new route to accomplish an asymmetric process.[1b, 5] This expands the potential of asymmetric H-transfer and makes it more versatile than asymmetric catalytic hydrogenation. Transfer hydrogenation particularly its asymmetric

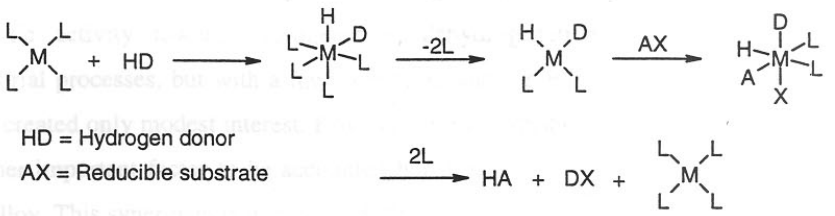
version is rapidly growing in recent years. The discovery of more active catalysts and more efficient hydrogen donors has given the possibility of new opening.

4.0.1. Types of Catalysts

Catalysts play a very important role in any kind of transformation. Types of catalysts used for transfer hydrogenation processes are discussed accordingly below.

4.0.1.1. Homogeneous Catalysts

Compounds of most of the elements from the second transition series in the periodic table are suitable for catalytic homogeneous reductions. Both salts and complexes of Pd, Pt, Ru, Ir, Rh, Fe, Ni and Co have been used as catalysts for the transfer of hydrogen from molecular hydrogen or hydrogen donors to organic substrates. Generally, the most active catalysts are to be found in the salts and complexes of Rh, Ru and Pd, although extensive effort have been made to find catalysts from among the less expensive metals. The catalytic activity of the transition metal salts and complexes is the result of a delicate balance of valance states and strengths of chemical bonds.[6] No catalytic activity is observed if the hydrogen donor and the transition metal form a stable compound. In a similar way, there is no catalytic activity if reaction between hydrogen donor and the transition element cannot occur. For transfer of hydrogen to the substrate to occur, the hydrogen source must be accommodated by the transition metal. Also the bond between the transition metal and the organic substrate is equally important criterion in this case. Thus, catalytic activity depends on a balance of energies with regard to the binding of the substrate to the metal and the desorbing of any resulting reduced substrate. The process can be depicted as in the scheme 2.



Scheme 2

Here, HD is a hydrogen donor and AX is a reducible organic substrate. Oxidative additions and eliminations lead to the formation of a reduced species HA and regeneration of the catalyst ML_4. The activity of the catalyst depends on the existence of free coordination sites on the central metal or on the possibility of producing a vacant site by loss of a ligand. Therefore, the coordination number of the metal complex should be less than the maximum possible, or for saturated complexes, the ligand-metal bond strength should be such that dissociation is possible or that ligand displacement by solvent, hydrogen donor, or substrate hydrogen acceptor can occur. Because of wide choice of ligands, extensive modification of homogeneous catalysts is possible, but the final catalytic activity is a result of a delicate balance of factors and small changes of structure can lead to large change in activity. Some types of compounds bond strongly to the central metal atom and thus deactivate the catalyst. Some sulfur compounds, CO, O_2, hydrogen halides are the most common catalyst poison.

It is important to note that a good number of the homogeneous catalysts reported in the literature[1] are complexes containing phosphine ligand. This is simply because of better coordination ability of phosphorous with the central metal atom. The metal complex is better stabilized through $p\pi$-$d\pi$ bonding and hence show better catalytic activity.

4.0.1.2. Heterogeneous Catalysts

The most active catalysts for heterogeneous transfer reduction are based on palladium metal. Catalysts may be pure bulk metal, finely divided, dispersed on various carriers, as with palladium on carbon, $Pd/CaCO_3$, $Pd/BaSO_4$, and Pd/asbestos or be of a porous or skeletal type. Less versatile catalysts are derived from Ni, Rh, Ru, Pt, Ir, Os and Co, again as finely divided metals, as metals supported on carbon (charcoal) or as skeletal metals like Raney Ni. Alloys of many metals have been investigated for catalytic activity toward hydrogenation, dehydrogenation and hydrogenolysis in industrial processes, but with a few exceptions such as Pd-Ru and Ni-Cu, these alloys have created only modest interest. However, the synergistic effects of mixed catalysts is another important factor to be accounted but in this case physical mixing is preferred not alloy. This synergism is due to the different activities of each of two mixed catalysts

to intermediates produced during catalytic process and not the effect of one catalyst on the other.

Sometimes, pure finely divided (black) metals prove to be more active than supported ones. For example, Pd black is proven to be superior than any of the supported Pd catalysts such as Pd/C, Pd/asbestos etc. in many reduction process.[1,7] But it is not true for each and every catalyst. For instance, Rh, Pd, Pt supported on charcoal was found to be superior for dehydrogenation than the pure metal itself.[8] So activity of catalyst is dependent on the state of the metal itself. Also in many cases impurity present in the support can also alter substantially the characteristic of catalyst. For example, chloride ions present as impurity in many supports can activate[9] or deactivate[10] the catalyst. The exceptional role of palladium in hydrogen transfer reactions appears to be due, at least in part, to general mobilizing action for hydrogen-carbon bonds. For instance, palladium is much more effective than rhodium or platinum in causing rearrangements during regular catalytic hydrogenation of substituted cyclohexenes.[11]

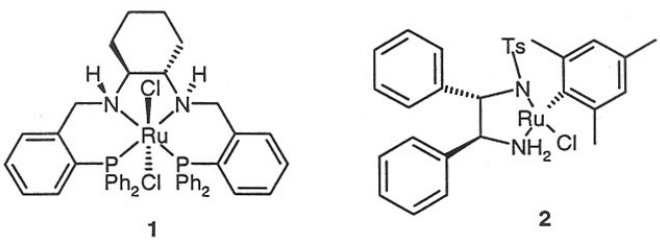
The major factor that need to be considered in the preparation of a heterogeneous catalyst are (a) the type of metal salt to be reduced to metal, (b) the kind of reducing agent used, (c) procedures adopted for washing the prepared catalyst and (d) the purity and physical state of the supporting material. A catalyst prepared in two different ways may or may not have the same catalytic activity. Slight variation of preparative method may have dramatic effect on the property of the catalyst.

The most common mode of deactivation of heterogeneous catalyst is absorption of gases or deposition of foreign elements such as S, P, N, Hg (or their compounds) on the active sites of the catalyst. Even oxygenated compounds may also deactivate the catalyst. Of course, not all S, P and N compounds are poison although sulfur containing compounds are avoided in catalytic reduction.

In most cases homogeneous catalysts show better reactivity than its heterogeneous counterpart. Generally heterogeneous catalyst need more reaction time and higher temperature to achieve same performance of homogeneous one. The main advantage of heterogeneous catalyst is it can be reused several times for the same type of reaction before its activity is noticeably diminished.

4.0.1.3. Asymmetric Catalysts

Asymmetric transfer hydrogenation became one of the rapidly growing subjects in recent years. This process is quite advantageous as enantioselective synthesis of chiral alcohol can be achieved with high optical purity without the use of molecular hydrogen. Using some transition metal and lanthanoid complexes along with 2-propanol, enantioselective reduction was carried out,[5, 12] but the processes were unsatisfactory due to low catalytic activity and insufficient enantioselectivity. Later, this area was extensively developed by Noyori.[1b] Both mono- polynuclear Ru(II), Rh(I) and Ir(I) complexes with chiral phosphorous and nitrogen ligands have been successfully employed to promote transfer hydrogenation. Among them, Ru complexes (Fig. 1) are most common and widely used in recent years. Chiral phosphine ligands, which are most popular in asymmetric hydrogenation, are observed to be less effective for transfer hydrogenation. Ligands containing nitrogen as donor atoms are more effective for this application. Two important features of these ligands are: (a) several of them have a C_2-symmetry axis; (b) each class has stereocenter (s) in close proximity to the nitrogen atom.



1 2

Fig-1

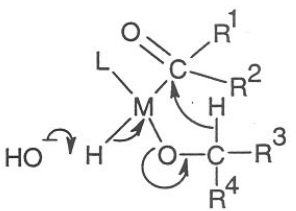
When the ligand coordinates to the metal, the substituents at the stereogenic centers provide an efficient shielding to the metal ion from two opposite directions and should therefore have a distinct effect on the stereochemical course of the reaction occurring within the coordination sphere.[13]

4.0.2. Hydrogen donors

Hydrogen donor can, in principle, be any organic compound whose oxidation potential is sufficiently low so that the hydrogen transfer can occur under mild conditions. At higher temperature, especially in the presence of catalysts, almost any organic compound can donate hydrogen (catalytic cracking), but this has little potential for controlled synthesis. The choice of hydrogen donor is generally determined by the ease of reactrion and availability. The most popular hydrogen donors are alcohols and formic acid. Other than these two, many H-donors are known in the literature.[1a] This includes cyclohexene, cyclohexadiene, indene, tetralin, indoline, tetrahydroquinoline, dihydrofuran, dioxan, ethanol, 2-methoxyethanol, benzyl alcohol, tetrahydrofurfurol, steroids, 1,2-ethandiol, 2,3-butandiol, 1,2-cyclohexanediol, polyvihyl alcohol, ascorbic acid, sugars, phenols, limonene, benzhydrol, hydroquinone, N-benzylaniline, formates, phosphinic acid, sodium phosphinate, sodium terahydroborate and hydrazine. Since dehydrogenation of formic acid derivatives is an irreversible and exothermic process,[1a] this usually overwhelms the energetic requirement of the reduction process. The use of such H-donors is recommended in reactions where unfavorable energetic balances are expected. Secondary alcohols are better H-donors than primary ones and can be successfully employed even in the reduction of ketones, provided they are present in excess.[14] Among secondary alcohols, propan-2-ol is most popular donor, because of its simplicity, cheapness, availability, and the ease of removal of both it and its dehydrogenation product, acetone, from reaction systems.

4.0.3. Promoters

Strong base like KOH or NaOH or sodium alkoxides are commonly used promoters in H-transfer reactions since they often exert a beneficial effect on reaction rates. In the reduction of ketones with propan-2-ol, the base is essential, for their activity. Base is believed to be effective by removing a proton from the reacting complex. **Scheme 3**



Scheme 3

indicates how base promotes the transfer of hydride ion from an alkoxy radical onto an adjoining coordinated ketone.

4.0.4. Effect of temperature and solvent on catalytic transfer hydrogenation

Generally, increase in temperature leads to increased rates of reduction for most systems. However, the other factors such as catalyst, hydrogen donor, hydrogen acceptor, and solvent also have to be taken into account to get the optimal condition. Increase of temperature may lead to unwanted side reactions such as overreduction, isomerization or decomposition of the substrates. At higher temperature the rate of reverse reaction also increase as well. However, reaction conditions for the forward reaction are often different from the reverse reaction and lead to an overall acceleration in the forward reaction.

A correct choice of solvent is an important factor governing the activity of a catalyst in transfer reduction. Most soluble catalysts are either coordinated to ligands or with solvent. Often, a ligand can be displaced by a suitable solvent and the new complexes incorporating solvent molecule may be more or less active than the original complex. Binding by the solvent alters the electron density around the central metal atom and changes its ability to effect oxidative addition. Some metal catalysts are active in solution only after dissociation of one or more ligands leaves the central metal atom with less than its maximum coordination number, thereby facilitating oxidative addition. If solvent molecules displace the original ligands and they do not dissociate from the central metal, then all catalytic activity is lost.

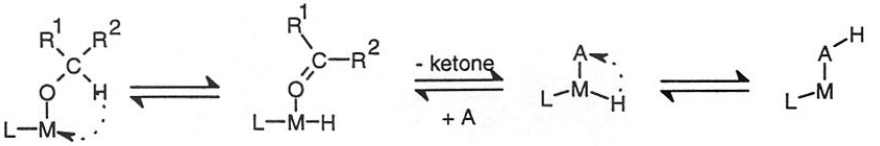
Besides these ligand-displacement mechanisms, catalyst activity may be reduced or destroyed completely if the solvent coordinates to the catalyst better than the hydrogen donor or hydrogen acceptor can do. The coordinate link between the solvent and catalyst should not be stronger than the binding of donor or acceptor.

4.0.5. Mechanism of transfer hydrogenation

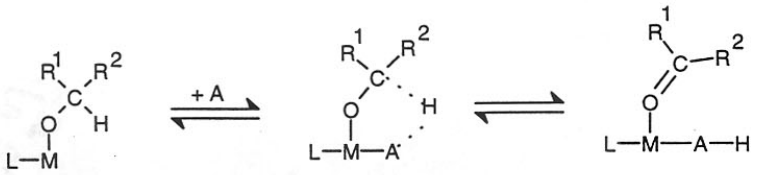
From the mechanistic point of view, two general reaction paths can be taken into consideration for hydrogen transfer[15]: a stepwise process called hydridic route and a concerted process called direct hydrogen transfer (Scheme-4).

The "hydridic route" involves the intermediate formation of a metal hydride derivative by interaction of the catalyst with the hydrogen donor, followed by hydride transfer from the metal to the substrate. The "direct hydrogen transfer" implies that hydrogen is transferred to the substrate in a concerted process where both the H-donor and the H-acceptor are held together in close proximity by the catalyst. A cyclic transition state such as the one proposed to Meerwein-Pondorf-Verley reduction is possibly involved.

Hydridic Route



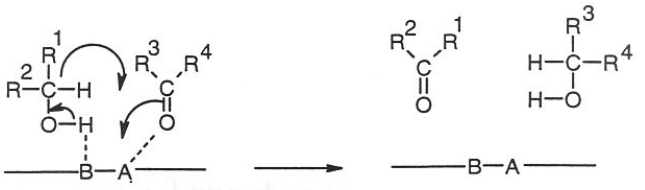
Direct Hydrogen Transfer



L = Ligand A = Hydrogen acceptor

Scheme 4

In case of heterogeneous catalytic transfer reduction using metallic oxides such as MgO/SiO_2, Al_2O_3, Al_2O_3/Na lanthanide oxides etc these catalyst have two active centers, one basic and one acidic. The alcohol (donor) is adsorbed on the basic site (B) and the ketone (acceptor) on an adjacent acidic site (A) and hydrogen is transferred as hydride (Scheme-5).



Scheme 5

Sometimes, donor and acceptor may get adsorbed on two different metal atom of the catalyst surface and hydride transfer takes place in the similar way.

A wide variety of homogeneous and heterogeneous catalysts have been studied for the transfer hydrogenation of organic compounds. In the present study we are trying to investigate some new catalyst for this kind of transformation. This chapter is divided into three sections, which cover homogeneous, asymmetric and heterogeneous catalytic transfer hydrogenations.

Section A

Chemoselective Transfer Hydrogenation of Carbonyl Compounds Catalyzed by Homogeneous Macrocyclic Nickel (II) Complex

4.1.1. Introduction

Although first report on the transfer hydrogenation involved heterogeneous catalyst, homogeneous catalysts become more popular in the later stage. The reasons for this generality are its wide applicability, selectivity and better reactivity than its heterogeneous counterpart. Choice of reaction conditions and catalyst can lead to better selectivity for transfer hydrogenation of different functional groups in presence of the other. Moreover, these catalysts are being modified in several ways to get chiral induction in transfer hydrogenation process.

4.1.2. Review of Literature

Compounds of most of the elements from the second transition series in the periodic table are suitable for catalytic reduction. Both salts and complexes of Pd, Pt, Ru, Ir, Rh, Fe, Ni, and Co have been used as catalysts for transfer hydrogenation. Compared to other metal complexes, ruthenium complexes are widely used for transfer hydrogenation. Table 1 summarizes different transition metal compounds that promote transfer of hydrogen.

Table 1: Different metal compounds used as homogeneous catalyst for transfer hydrogenation.

Ruthenium	Rhodium	Iridium	Osmium and Palladium	Platinum and Nickel	Others
$RuCl_2(PPh_3)_3$,	$RhCl(PPh_3)_3$	$IrHCl_2(CO)(PPh_3)_2$	$OsH(CO)Cl(PPh_3)_3$	$PtCl_2(PPh_3)_2$	$MoH_4(DPE)_2$
$RuH_2(PPh_3)_4$	$RhCl(CO)(PPh_3)_2$	$IrHCl_2(Me_2SO)_3$	$Os(CF_3CO_2(CO)(PPh_3)_2$	$PtCl_2(SnCl_2)(PPh_3)_2$	$FeCl_2(PPh_3)_2$
$RuH_2(CO)(PPh_3)_3$	$RhCl(CO)_2(PPh_3)$	$IrH_2Cl(PPh_3)_3$	$OsHCl(PPh_3)_3$	$PtCl_2/SnCl_2$	$CoCl_2(PPh_3)_2$
$RuH(CO)Cl(PPh_3)_3$	$RhX(PR_3)_2$	$IrHCl_2(PPh_3)_3$		*cis*-$PtCl_2(PEt_3)_2$	$CoH[P(OPh)_3]_2$
$RuH(CF_3CO_2)$	(X=diene, halogen,	$IrH_3(PPh_3)_2$		K_2PtCl_4	
$(CO)(PPh_3)_2$	PR_3 = various	$IrH_5(PPh_3)_3$	$PdCl_2(PPh_3)_2$		$ReCl_5$
$RuCl_2(PPh_3)_4$	phosphines)	$IrX(CO)(PPh_3)_2$	$Pd(OAc)_2$	$NiCl_2(PBu^n{}_3)_2$	
$RuCl_3.3H_2O$	$RhH(CO)(PPh_3)_3$	(X = Cl, Br, I)	$PdCl_2$	$NiCl_2(PPh_3)_2$	
	$RhH(PPh_3)_4$	$IrH(CO)(PPh_3)_3$	$(NH_4)_2PdCl_4$	$Ni[P(oPh)_3]_4$	
	$RhCl_3.3H_2O$	$IrH(CO)_2(PPh_3)_2$			
		$IrCl(C_8H_{12})(PPh_3)_2$			
		Ir(Phen)(COD)Cl			
		$IrH[P(OPh)_3]_4$			

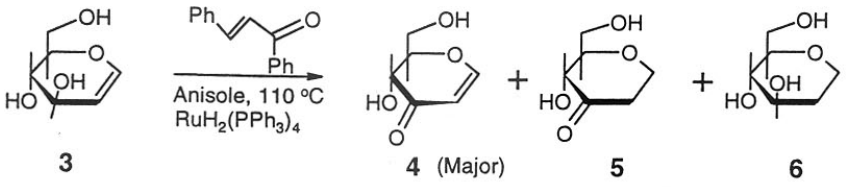
Sasson and coworkers reported the used of $RuCl_2(PPh_3)_3$ as catalyst for transfer hydrogenation of α,β-unsaturated ketones[15, 16]. This catalyst was found to be highly selective to unsaturated bond in the presence of various carbinols at 180 °C in quantitative yield. 1-Phenyl ethanol was found to give the best result as hydrogen source. Saturated ketones are also reduced to alcohol with lower yield *ca.* 60 %. This catalyst is found to promote hydrogen transfer, not only from alcohols, but also from hydrocarbons[16], aldehydes[17], acids[17,18], and amides.[19] $RhCl(PPh)_3$ and $IrCl(CO)(PPh)_3$ are also studied for transfer of hydrogen from aldehydes. They are found to be inferior to Ru-complex. Aldehydes are not good hydrogen donors, as they need very high temperature (200 – 300 °C). Moreover, catalytic decarbonylation of aldehyde[20], which is the major side effect, makes this method less efficient. Formic acid proved to be versatile among these hydrogen donors as it promotes transfer hydrogenation efficiently at lower temperature.[17] Most of the complexes of Ru, Rh, Ir, Pt are studied for this reaction.[18] Addition of alkali metal formates increases the degree of reduction.[18] The mixture of formic acid and lithium format reduces octene-1 to octane quantitatively even at 40 °C in presence of $RhCl(PPh_3)_3$.

Various alcohols have been studied for the transfer hydrogenation of olefins and other functional groups. Primary alcohols are studied for donating hydrogen to acetylene in presence of $RuH(CF_3CO_2)(CO)(PPh_3)_2$ and $Os(CF_3CO_2)(CO)(PPh_3)_2$.[21] These catalysts are found to promote oligomerisation of various acetylenes. Under suitable conditions, methanol can act as hydrogen donor towards organic substrates especially for reduction of ketones to alcohols. Smith and coworker[22] have studied various complexes of Rh, Ir, Ru, and Os for transfer reduction using methanol as donor. $RuCl_2(PPh_3)_3$ has been found to be most effective among all the complexes studied. α, β-Unsaturated ketones are also reduced effectively to corresponding ketones under same conditions. Descotes[23] studied the catalytic activity of $RuCl_2(PPh_3)_3$ and $RuH_2(PPh_3)_4$ for transfer of hydrogen from polyvinyl alcohol to chalcone and found to give good yield at 140 °C in DMF. Imai and coworkers[24] studied various catalysts of Ru, Rh and Pt for transfer of hydrogen from alcohol to cycloolefins and $RhH(PPh_3)_4$ has the highest catalytic activity. Iridium (I) complexes were found to promote hydrogen transfer from ethanol to diphenyl acetylene to give *trans*-stilbene.[25] Ethylene glycol can also act as hydrogenating agent. Various chalcones were found to reduced when refluxed in ethylene glycol in presence of $RuCl_2(PPh_3)_3$[26] in good yield.

Alcohols particularly primary alcohols are used for most of the methods discussed above and reactions were performed at higher temperature to achieve transfer reduction. Addition of catalytic amount of base such as KOH can accelerate the reaction rate. Zassinovich[27] achieved reduction of various ketones using 2-propanol as hydrogen donor, with a catalytic amount of KOH in presence of several Rh complexes. They found that the reaction is very effective at 82 °C (*i.e.* at reflux temperature of 2-propanol) to give quantitative yield of alcohols from ketones. Later it was found that similar result could also be achieved by using Ir[28] and Ru[29] complexes. Transfer hydrogenation of imines also can be achieved in 2-propanol in presence of K_2CO_3 using $RuCl_2(PPh_3)_3$.[30] This method has an advantage that it does not require high temperature. The ruthenium hydride complexes such as $[RuHCl(PPh_3)_3]$ and $[RuH_2(PPh_3)_4]$ are found to catalyze transfer hydrogenation of ketones and imines by propan-2-ol.[30a] Interestingly, the dihydride complex $[RuH_2(PPh_3)_4]$ could catalyze the transfer hydrogenation without base. Although primary alcohols are good hydrogen donors, the side product aldehyde formed in the reaction can poison the catalyst.[30, 31] Aldehyde formed from dehydrogenation of alcohol deactivate the catalyst via decarbonylation. But in case of secondary alcohols decarbonylation does not take place and hence catalytic activity does not decline during the course of reaction.

Not only alcohols but many other compounds such as amine can also act as hydrogen donor for transfer hydrogenation. Imai[32] has shown that cyclic amines such as indoline, tetrahydroquinoline, piperidine etc. can be used as donor for reducing nitro compounds to corresponding amino compounds. Nitro compounds were effectively reduced in presence of $RuCl_3.H_2O$ or $RuCl_3.3H_2O$ at 80 °C in toluene. Other catalysts such as $RuCl_2(PPh_3)_3$, $RhCl(PPh_3)_3$, $RhH(PPh_3)_4$, $FeCl_3.2H_2O$, $CoCl_2.6H_2O$, $RuH_2(PPh_3)_4$ hardly catalyze the reaction. $PdCl_2$ and $PdBr_2$ can also promote this reaction with lower yield.

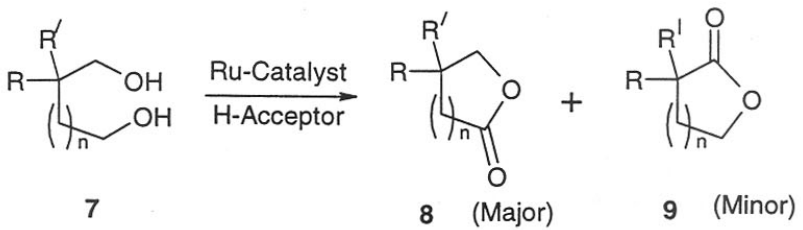
Since alcohols are very good hydrogen donors, this chemistry can very well be applied for the oxidation of alcohols in presence of a suitable hydrogen acceptor. Descotes [33] applied this method to oxidize various glucides in presence of $RuCl_2(PPh_3)_3$ and $RuH_2(PPh_3)_4$, and chalcone as hydrogen acceptor. Similarly, Glucal, (1,5-anhydro-1,2-dideoxy-D-arabinose-1-enitol, 3) can be oxidized regiospecifically on the allylic carbon by hydrogen transfer with chalcone and $RuH_2(PPh_3)_4$[34] (scheme-6).



Scheme 6

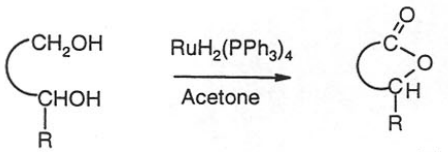
Other competitive processes (hydrogenation, isomerisation) also occur alongwith hydrogen transfer.

In another process, 1,4- and 1,5-diols are converted to γ- and δ-lactones respectively in presence of an hydrogen acceptor such as α,β-unsaturated ketones.[35] Yoshikawa reported regioselective dehydrogenation of unsymmetrically substituted 1,4- and 1,5- diols catalyzed by Ru-complex to give predominantly β-substituted γ-lactones or γ-substituted δ-lactones respectively. Among the Ru-complexes examined, $RuH_2(PPh_3)_4$ was the most active and selective catalyst. The main factor for controlling regioselectivity is the steric constraints produced by the substituent(s) of a diol at the coordination step of alkoxy group to ruthenium (scheme-7).



Scheme 7

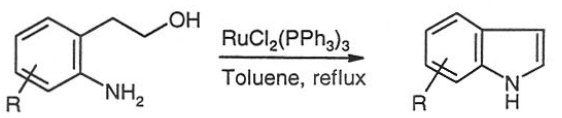
Similar result was also reported by Taki[36], where γ- and δ-lactones were synthesized by catalytic dehydrogenation using $RuH_2(PPh_3)_4$ in presence of acetone hydrogen acceptor (Scheme 8). Primary alcohols are oxidized chemoselectively in the presence of secondary one to give the corresponding lactones. Although the reaction goes without hydrogen acceptor, addition of hydrogen acceptor enhances the rate remarkably to give quantitative yield.



10 11

Scheme 8

Watanabe and coworkers utilized transfer hydrogenation process for the synthesis of various indole derivatives from 2-aminophenethyl alcohol in presence of $RuCl_2(PPh_3)_3$ catalyst (scheme 9).[37]



12 13

Scheme 9

Molybdenum complexes are also known for transfer hydrogenation. Tatsumi *et. al.* studied the catalytic activity of various Mo-complexes such as $Mo(N_2)(DPE)_2$, $MoH_4(DPE)_2$, $MoH_4(DPE)_2$, *trans*-$Mo(CO)(N_2)(DPE)_2$, *cis*-$Mo(CO)_2(DPE)_2$ (DPE = diphenyl phosphino ethane).[38] Reaction was carried out in benzene at reflux using various alcohols. *Sec*-alcohols such as 1-phenyl ethanol and 2-propanol gave best result. $Mo(N_2)(DPE)_2$ was found to be most effective among all these complexes.

Ni complexes are very rarely studied for transfer hydrogenation. Iyer[39] *et. al.* reported the use of $NiCl_2(PPh_3)_2$ for transfer hydrogenation of various aldehydes and ketones to corresponding alcohols in 2-propanol with catalytic amount of KOH. Although yields are good the reaction time is longer as compared to other catalyst. Interestingly double bond was not affected during reduction of the carbonyl group. Recently, use of $Ni[P(Oph)_3]_4$ was also reported by Iyer.[40] In this case, they had used acetic acid in combination of ammonium formate for transfer hydrogenation of various functional groups.

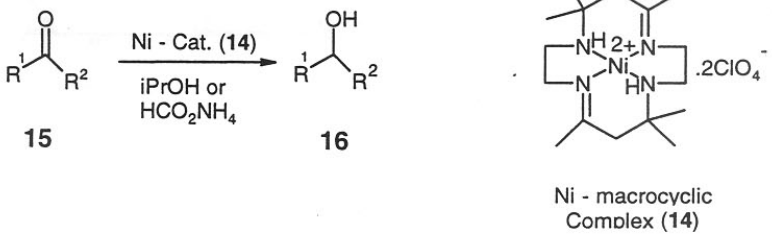
Ru, Rh and Ir complexes are found very effective for transfer hydrogenation process is studied but complexes of other metals such as Mo, Co, Ni are rarely applied due to slower reaction rate in these cases.

4.1.3. Present Work

Objective

Catalysts reported in the literature are mostly the complexes of expensive metals like Pd, Pt, Ru, Rh etc. Other compounds made of comparatively cheaper metals such as that of Ni, Co etc. are not studied extensively. Also, a good number of complexes used for transfer hydrogenation are phosphines. There is paucity of the literature about the use of nonphosphine complexes such as macrocyclic complexes particularly that of nickel.

The chemoselective reduction of organic compounds is synthetically important, both in the laboratory and in industry. Chemoselective reduction of the organic functional groups can be accomplished by classical Meerwein-Ponndorf-Verley reductions. However, the use of aluminium isopropoxide in stoichiometric amounts under drastic conditions often leads to many side products. Most of the catalysts exhibit poor selectivity in product distribution. Therefore, it assumes great importance to have effective control over selectivity in such reactions. In this section, we intend to study macrocyclic complex of Ni for this purpose (scheme 10). We have chosen the simplest macrocyclic complex 14 that can be synthesized very easily from the commercially available starting materials.



Scheme 10

4.1.4. Results and Discussion

Nickel complex **14** was synthesized according to literature procedure[41] by adding perchloric acid dropwise to a solution of ethylene diamine in acetone and the

solution was stirred at room temperature. White crystalline material precipitated out was filtered and dried. The ligand was complexed with nickel by reacting with $Ni(OAc)_2.4H_2O$ in methanol at 60 °C for 1h. The complex was characterized by IR, ^1H NMR and elemental analysis. A band at 3166 cm^{-1} in the IR indicates the presence of NH functionality. The presence of C=N bond is indicated by a band at 1660 cm^{-1}. The bands in the IR spectrum at 1454 cm^{-1} and 1102 cm^{-1} can be inscribe to C-N bond of the complex. Methyl groups attached to the C=N bond appears in the ^1H NMR spectrum at 2.1 δ as a singlet. Other four methyl groups appear at 1.3 δ as singlet. CH_2-Protons attached to the N-atom appears as two multiplets centered at 2.6 and 2.7 δ.

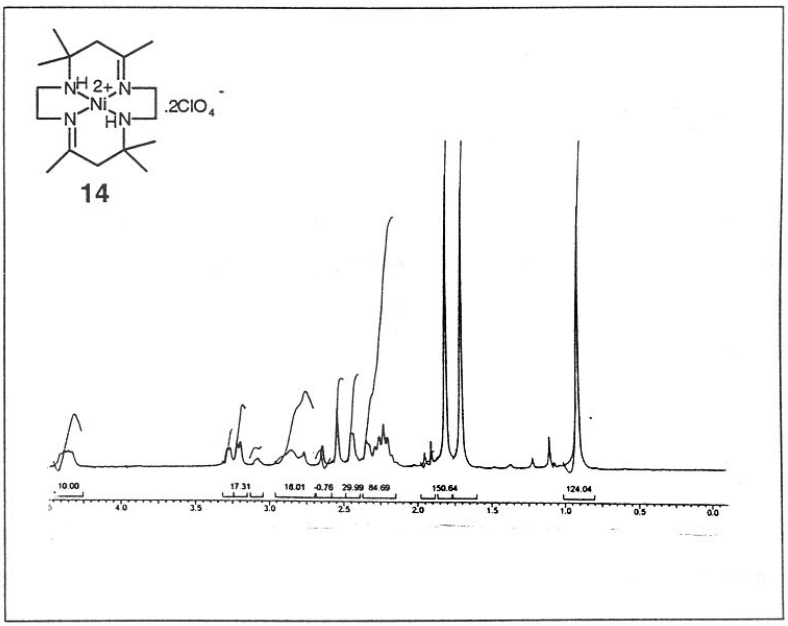


Fig.2.^{1}H NMR spectrum of complex 14

Isopropanol is a very good hydrogen donor particularly in presence of base and Rh,[27] Ir,[28] Ru[29] and Ni[39] catalysts. Initially, a systematic study for the catalytic evaluation of catalyst **14** was undertaken using 2-propanol because of its potential advantages over other donors. The results are summarized in **Table 1**.

Table 1: Transfer hydrogenation of various carbonyl compounds using catalyst 14 in isopropanol at reflux.

Entry	Substrate	t/h	Product[a]	Yield[b] (%)
1	Acetophenone	30	1-Phenylethanol (**17**)	78
2	4-Methylacetophenone	24	1-(4-Methylphenyl)ethanol (**18**)	73
3	4-Chloroacetophenone	24	1-(4-Chlorophenyl)ethanol (**19**)	71
4	Cyclohexanone	24	Cyclohexanol (**20**)	56
5.	Octanal	24	1-Octanol (**21**)	61
6	Cinnamaldehyde	30	Cinnamyl alcohol (**22**)	53
7	Benzaldehyde	24	Benzyl alcohol (**23**)	71
8	4-Chlorobenzaldehyde	24	4-Chlorobenzyl alcohol (**24**)	74
9	4-Nitrobenzaldehyde	36	4-Nitrobenzyl alcohol (**25**)	52
10	4-Cyanobenzaldehyde	36	4-Cyanobenzyl alcohol (**26**)	56

a. Numbers in parentheses refer to compound number; b. isolated yield after chromatographic purification.

The carbonyl compounds were refluxed in isopropanol in presence of KOH (10 mol %). 2 mol % of Nickal catalyst (based on the carbonyl compound) was used. Reaction does not proceed in the absence of KOH. Both aliphatic and aromatic carbonyl functions are reduced without affecting C=C, C-Cl, NO_2 and C≡N groups. However, it takes longer time (>24 h) to achieve good yield of the alcohol. In order to achieve better control over rate and specificity, reactions were carried out using various hydrogen sources. The results are summarized in **Table 2.** It is surprising to note that neither ammonium formate nor formic acid is useful as H-source for ketone reduction. Even at higher temperature (117 °C in case of *n*-butanol) reaction does not proceed (**table 2, entry 5**). However, a dramatic rate enhancement has been observed in the ketone reduction when a combination of both formic acid and ammonium formate are used together as H-source. The catalyst is not soluble in alcohol in absence of base. Addition of base solubilizes the catalyst in alcohol (in case of 2-propanol/KOH). The color of the solution become wine red after addition of base and yellow color of the complex disappears. The occurrence of reaction only in presence of catalyst suggests that the base is playing a vital role in abstracting the proton from the donor by a mechanism similar to that depicted in **Scheme 3.**

Table 2: Transfer hydrogenation of various carbonyl compounds to corresponding alcohols using catalyst 14 and various hydrogen donors.

Entry	Substrate	Hydrogen donor	Temp. (°C)	t/h	Yield[a] (%)
1	Acetophenone	^{i}PrOH	82	30	NR
2	Acetophenone	^{i}PrOH + KOH	82	30	78
3	Acetophenone	MeOH + HCO_2NH_4	65	24	NR
4.	Acetophenone	EtOH + HCO_2NH_4	80	24	NR
5	Acetophenone	n-BuOH + HCO_2NH_4	117	24	NR
6	Acetophenone	98 % HCO_2H	100	24	NR
7	Acetophenone	98% HCO_2H + HCO_2NH_4	100	2.5	94
8	Acetophenone	85%HCO_2H + HCO_2NH_4	100	2.5	94
9	Acetophenone	60% HCO_2H + HCO_2NH_4	100	10	NR
10	4-Methyl acetophenone	85% HCO_2H + HCO_2NH_4	100	2.5	91
11	4-Chloro acetophenone	85% HCO_2H + HCO_2NH_4	100	2.5	90
12	Cyclohexanone	85% HCO_2H + HCO_2NH_4	100	7	73

a. Isolated yiekd after chromatographic purification; NR = no reaction.

This observation was noted earlier by Vol'pin[18] where alkali metal formates accelerate the rate of hydrogen transfer from formic acid in presence of various ruthenium complexes. In that case rate enhancement was noted and reaction proceeds well in absence of alkali metal formate. But in the present case reaction proceed only in presence of ammonium formate with appreciable rate. Triethyl amine also well known to accelerate the rate of decomposition of formic acid.[18a] Wagner[18a] showed that a 3:1 adduct between formic acid and tertiary amine bases (**Fig.3**) forms after addition of tertiary amines to formic acid which further activates formic acid. This activated formic acid very easily decomposes at 90 – 120 °C in presence of cuprous chloride and noble metals to give H_2, CO_2 and the tertiary amine back.

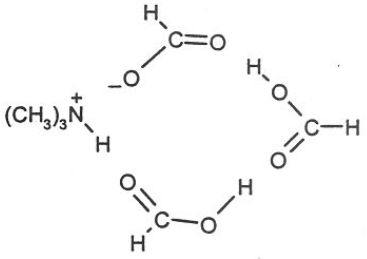


Fig. 3. Formic acid-Me_3N adduct

We assume that ammonium formate may be helping in a similar way in the decomposition of formic acid and transfer hydrogenation occurs via nickel hydride formation. Interestingly, water does not create any problem in this case. This reaction goes very well in presence of water (85% formic acid, **Table2**). Excellent results were obtained by using 85% formic acid along with ammonium format. But further increase of water content (60% formic acid, **entry 6, Table** 2) led to no reaction at all.

Yields are good for all types of ketones and aldehydes, although acyclic ketones and aliphatic aldehydes gave lower yield. Interestingly this catalyst reduces only the carbonyl group. Other groups such as double bond, chloro, nitro and cyano groups were not affected. 4-Chlorobenzaldehyde, 4-nitrobenzaldehyde and 4-cyanobenzaldehyde reduced to corresponding benzyl alcohols but yields are found to be low. Although both 2-propanol/KOH and formic acid/ammonium formate promote transfer hydrogenation, reaction time for formic acid is much less than that of 2-propanol. Yields are also better in case of formic acid system.

All products were characterized by IR, ^{1}H NMR and mass spectrometry. In IR presence of a broad band at around 3300 cm^{-1} and absence of carbonyl peak at around 1700 cm^{-1} indicate clearly the occurrence of reduction.

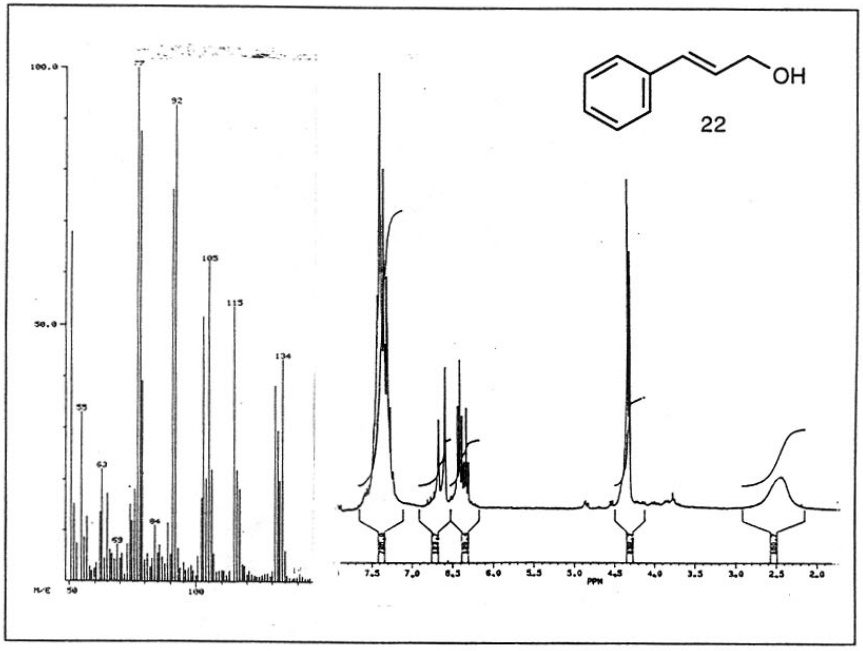


Fig. 4. ^{1}H NMR and Mass spectra of compound 22

In case of acetophenones, ^{1}H NMR shows a doublet at around 1.5 δ and a multiplet at around 4.8 δ indicating the presence of CH_3 and CH group in alcohol. In case of benzyl alcohols, the reduced product of aromatic aldehydes, CH_2 group appears at around 4.6 δ as singlet. Formation of cinnamyl alcohol is indicated by a band at 3400 cm^{-1} in the IR spectrum. The olefinic proton of cinnamyl alcohol appears at 6.3-6.5 δ in ^{1}H NMR spectrum in the form of two triplet (proton attached to CH_2 group) and another proton (attached to phenyl ring) appears as a doublet at 6.6 δ (**Fig.4**). The bands at 1580 cm^{-1} and 1340 cm^{-1} in the IR spectrum of **25** indicate the presence of nitro group in the reduced product of 4-nitrobenzaldehyde (Fig 5).

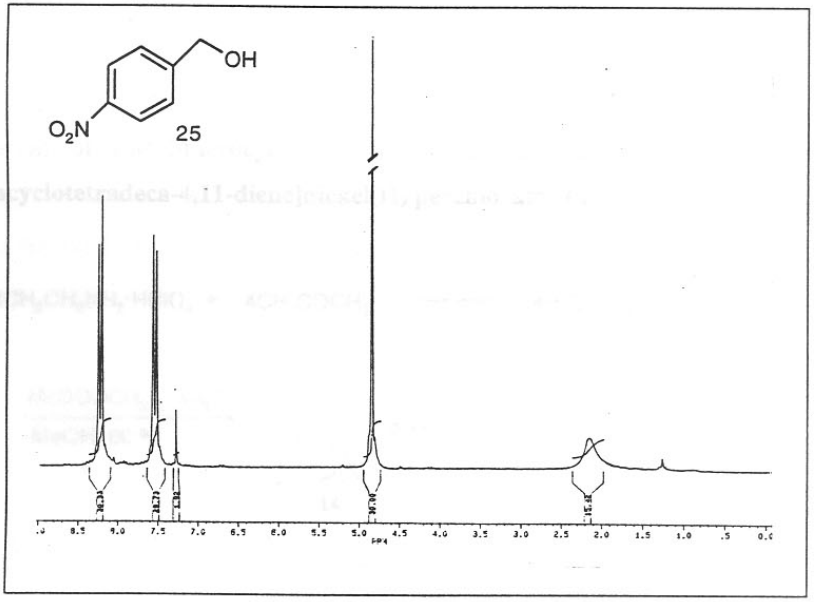


Fig. 5. ^{1}H NMR spectrum of compound 25

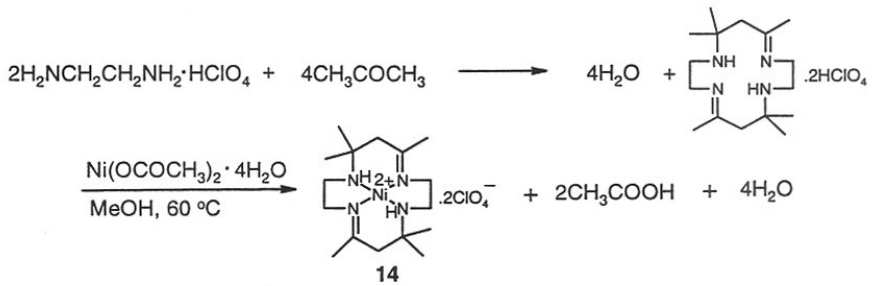
Formation of 4-nitrobenzyl alcohol was further confirmed by the aromatic pattern in the ^{1}H NMR spectrum (AB-quartets at 7.5 δ and 8.2 δ) and M^+ peak (153) in the mass spectrum. The C≡N stretching vibrations of 4-cyanobenzaldehyde appears at 2225 cm^{-1} in the IR indicating the presence of cyanide group. Two doublet of at 7.4 δ and 7.6 δ in ^{1}H NMR and M^+ peak at 133 in mass spectra confirms the formation of 4-cyanobenzyl alcohol.

4.1.5. Conclusions

The macrocyclic complex 14 promotes transfer hydrogenation very efficiently in 2-propanol and formic acid. In both the cases, promoter *viz.* KOH or ammonium formate as the case may be, is necessary for reduction to occur. 2-Propanol, formic acid or ammonium format alone cannot promote transfer hydrogenation. Reduction occurs in formic acid system at a faster rate as compared to 2-propanol system. Yields are also better in case of formic acid. Yields are lower in case of aldehydes as compared to ketones. This catalyst selectively reduces the carbonyl functionality. Other groups such as chloro, nitro, cyano and double bond are not at all affected during reduction process.

4.1.6. Experimental

Preparation of the Macrocyclic complex [(5,7,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradeca-4,11-diene]nickel(II) perchlorate (14)



Scheme 11

To 125 mL of acetone in a 500 mL beaker is added 5g (83.3 mmol) of ethylenediamine. The solution is stirred while 11.96 mL of 70% perchloric acid (83.3 mmol) was added slowly from a dropping funnel over a 10-minute period. The solution becomes hot and an orange-red color developed. After the solution allowed to come to room temperature, white crystalline material was precipitated out and filtered off and dried in vacuum over P_2O_5. The white material was treated with excess of nickel diacetate tetrahydrate in methanol at 60 °C for one hour. The solution was cooled

rapidly in the refrigerator and the yellow crystals are filtered and washed with methanol followed by washing with diethyl ether and finally dried in vacuo.

Yield	:	49 %
IR (Nujol) cm^{-1}	:	3166, 2920, 2854, 1660, 1556, 1464, 1454, 1380, 1102
^{1}H-NMR (200 MHz, D_2O)	:	δ 1.3 (s, 12H), 2.05 (s, 6H), 2.2 (s, 1H), 2.6 (m, 2H), 2.75 (m, 2H), 3.2 (bs, 1H), 3.6 (m, 2H), 3.7 (m, 2H).
Analysis	:	$C_{16}H_{32}N_4Cl_2O_8Ni$ requires C, 35.71; H, 5.95; N, 10.41%; Found: C, 35.86; H, 5.89; N, 10.59 %

General procedure for transfer hydrogenation of carbonyl compounds

Method A: (In propan-2-ol)

A mixture of acetophenone (0.5 g, 4.17 mmol), nickel catalyst **14** (0.045 g, 0.084 mmol 2 mol %) and KOH (25 mg, 0.446 mmol, 10 mol %) in propan-2-ol (10 mL) was refluxed for 30 h. Solvent was removed and the product was dissolved in ether. The ether layer was washed with brine, dried over anhyd. Na_2SO_4 and evaporated. Crude product chromatographed on silicagel using 3% EtOAc-pet ether to get colorless oil.

Method B: (In formic acid)

A mixture of acetophenone (0.5 g, 4.17 mmol), nickel catalyst **14** (0.045 g, 0.084 mmol 2 mol %) and ammonium formate (0.53 g, 8.3 mmol, 2 mol equiv) in formic acid (10 mL) was refluxed for 2.5 h. Formic acid was distilled off under reduced pressure and the product was dissolved in ether, washed with brine, dried over anhyd. Na_2SO_4 and evaporated. Crude product was chromatographed on silicagel using 3% EtOAc-pet ether to get colorless oil.

Method C: (In alcohol)

A mixture of acetophenone (0.5 g, 4.17 mmol), nickel catalyst **14** (0.045 g, 0.084 mmol 2 mol %) and ammonium formate (1.31 g, 20.8 mmol, 10 mol %) in formic acid (10 mL) was refluxed for 12 h.

Reaction was monitored by TLC. No product formation was observed.

1-Phenyl ethanol (17) :

Yield	:	78 %
IR (Neat) cm^{-1}	:	3400-3100, 2900, 1420, 1330, 1170, 1030
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.5 (d, J=7.3Hz, 3H), 2.4 (bs, 1H), 4.85 (q, J=6Hz, 1H), 7.2-7.45 (m, 5H).
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 25.15, 70.27, 125.33, 127.32, 128.51, 145.84
MS (m/z, % rel. intensity)	:	122 (M^+, 58), 107(98), 91(10), 79(100)

1-(4-Methylphenyl)ethanol (18) :

Yield	:	73 %
IR (Neat) cm^{-1}	:	3500-3150, 2920, 1510, 1435, 1360, 1070, 1010, 895
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.5 (d, J=7.4Hz, 3H), 2.1 (bs, 1H), 2.4 (s, 3H), 4.9 (q, J=7.4Hz, 1H), 7.2 (d, J=9.2Hz, 2H), 7.3 (d, J=9.2Hz, 2H).
MS (m/z, % rel. intensity)	:	136 (M^+, 29), 121(97), 103(10), 91(100), 77(62), 65(23).

1-(4-Chlorophenyl)ethanol (19) :

Yield	:	71%
IR (Neat) cm^{-1}	:	3500-3100, 2950, 1590, 1410, 1290, 1200, 1060, 1010
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 1.5 (d, J=6.7Hz, 3H), 2.1 (bs, 1H), 4.85 (q, J=7.41Hz), 7.3 (m, 4H).
MS (m/z, % rel. intensity)	:	156 (M^+, 21), 141(100), 111(22), 107(29), 91(5), 77(38).

Cyclohexanol (20) :

Yield	:	56 %
IR (Neat) cm^{-1}	:	3500-3050, 2950, 1440, 1335, 1040, 950.
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.85-1.3 (m, 5H), 1.45 (m, 1H), 1.65 (m, 2H), 1.8 (m, 2H), 2.8 (s, 1H), 3.5 (m, 1H).
MS (m/z, % rel. intensity)	:	100 (M^+, 4), 82(45), 71(34), 67(48), 57(100), 54(32).

1-Octanol (21) :

Yield	:	58 %
IR (Neat) cm^{-1}	:	3500-3000, 2850, 1445, 1030
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 0.85 (t, 3H), 1.2-1.35 (m, 10H), 1.6 (m, 2H), 3.6 (t, 6.8, 2H)
MS (m/z, % rel. intensity)	:	130 (M^+, 1), 112(6), 97(7), 84(100), 70(36), 56(6)

Cinnamyl alcohol (22) :

Yield	:	53 %
IR (Neat) cm^{-1}	:	3500-3100, 2990, 2850, 1620, 1430, 1060, 990
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.5 (bs, 1H), 4.35 (d, J=5.4Hz), 6.3-6.5 (m, 1H), 6.6-6.75 (d, J=13.5Hz, 1H), 7.2-7.6 (m, 5H).
Mass (m/z, % rel. intensity)	:	134 (M^+, 44), 115(54), 105(62), 92(93), 77(100), 63(22), 55(33).

Benzyl alcohol (23) :

Yield	:	77 %
IR (Neat) cm^{-1}	:	3500-3100, 3000, 2440, 1195, 1000
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 3.0 (bs, 1H), 4.65 (s, 2H), 7.2-7.45 (m, 5H).
MS (m/z, % rel. intensity)	:	108 (M^+, 75), 91(30), 79(100), 63(23).

4-Chlorobenzyl alcohol (24) :

Yield	:	76 %
IR (Neat) cm^{-1}	:	3400-3100, 2990, 1580, 1430, 1350, 1070
^{1}H-NMR (300 MHz, $CDCl_3$)	:	δ 1.8 (bs, 1H), 4.7 (s, 2H), 7.2-7.35 (m, 4H)
MS (m/z, % rel. intensity)	:	142 (M^+, 11), 125(4), 113(8), 107(24), 77(78), 51(100), 31(60), 29(81)

4-Nitrobenzyl alcohol (25) :

Yield	:	52 %
m. p.	:	91-92 (Lit. 92-94)
IR (Nujol) cm^{-1}	:	3500-3300, 2850, 1485, 1435, 1360, 1330
^{1}H-NMR (200 MHz, $CDCl_3$)	:	δ 2.1 (bs, 1H), 4.85 (s, 2H), 7.5 (d, J=8.1Hz, 8.2 (d,

J=8.1Hz, 2H)

MS (m/z, % rel. Intensity) : 153 (M^+, 37), 136(30), 124(20), 77(16), 51(35), 39(21), 30(100).

4-Cyanobenzyl alcohol (26)

Yield : 56 %

IR (Neat) cm^{-1} : 3500-3200, 2225, 1600, 1395, 1120, 1030

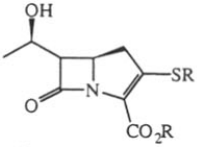
^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.95 (bs, 1H), 4.7 (s, 2H), 7.4 (d, J=9Hz, 2H), 7.6 (d, J=9Hz, 2H)

MS (m/z, % rel. Intensity) : 133 (M^+, 19), 116(6), 104(87), 77(60), 51(100), 39(55), 31(56), 29(74)

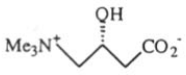
Asymmetric Transfer Hydrogenation of Ketones Catalyzed by Chiral Macrocyclic Nickel Complex

4.2.1. Introduction

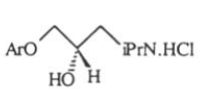
Asymmetric reduction of C=O and C=N bonds forming chiral alcohols and amines, respectively, is among the most fundamental organic transformations.[42] In response to an increasing demand for optically active secondary alcohols in the areas of pharmaceuticals and advanced materials, a series of asymmetric reductions of prochiral aromatic ketones have been developed.[43] Asymmetric reduction of functionalized ketones has resulted in the industrial production of synthetic intermediates of antibiotics, β-lactams and carbapenems,[44] antibacterial levofloxacin,[45] pantolactone, β-blockers carnitine (a vitamin like substance) etc. (**Figure 6**).



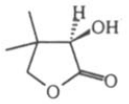
Carbapenems



Carnitine



β-Blockers



(*R*)-Pantolactone

Fig. 6

4.2.2. Review of Literature

Considerable amount of work has been done on stoichiometric asymmetric reduction,[46] for example reduction with chiral boron reagents, reductions with chiral modifications of lithium aluminium hydride, reductions with chiral dihydropyridine reagents, addition of chiral nucleophiles to aldehydes and ketones, stereoselective alkylation reaction of chiral metal enolates, the aldol addition reaction and asymmetric synthesis *via* chiral oxazolines.

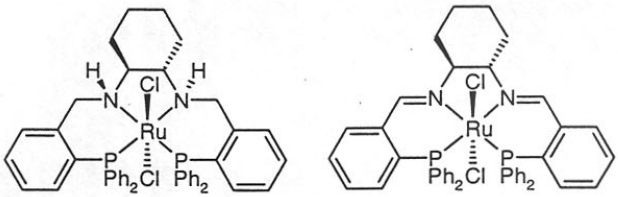
There are two basic ways by which enantioselective hydrogen transfer can be achieved : enantioface selection by means of a chiral catalyst on achiral (or often referred to as prochiral) substrate or enantiomer selection (often referred to as kinetic resolution) of a chiral racemic compound. The chiral catalyst can be substituted as well by the combination of an optically active hydrogen donor with an achiral catalyst.

4.2.2.1. Chiral ligands for asymmetric hydrogen transfer

The chiral ligands employed in asymmetric hydrogen transfer reactions are basically the same that have been shown to be capable of spectacular enantioselectivities in asymmetric hydrogenation.[47] Chiral phosphines are surely the most popular ligands in asymmetric catalysis and they have been employed in hydrogen transfer since the very beginning with Ru, Rh, and Ir catalysts. It should be noted that unlike asymmetric hydrogenation, in the field of enantioselective hydrogen transfer reactions the frequently used chiral ligands contain nitrogen as the donor atom, not phosphorous.[48]

Certain chirally modified Rh(I), Ir(I) and Ru(I) complexes promote asymmetric reduction in refluxing 2-propanol. Initial attempts were made with phosphine based Ir[49,50], Rh[50] and Ru[51] complexes but optical purity was moderate only. Chiral shift base complexes were also studied for this purpose. Krasik and Alper[52] studied Ru-complexes generated *in situ* from $[Ru(C_6H_6)Cl_2]_2$ and chiral shift bases derived from (1R, 2R)-diaminocyclohexane for transfer hydrogenation of alkyl aryl ketones by 2-propanol. But optical purity was only up to 40%. Noyori et al[53] later developed another type of chiral

Ru(II) catalysts which effect a highly enantioselective reaction of aromatic ketones at room temperature (**Fig. 7**).



(S,S)-**1** (S,S)-**27**

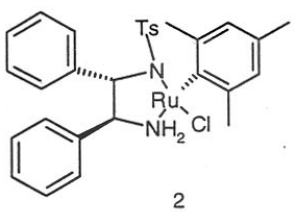
Fig. 7

The catalytic reduction of acetophenone derivatives proceeds from r.t. to 45 °C using 2-propanol as hydrogen donor in presence of catalyst **1** and $(CH_3)_2CHOK$ as cocatalyst in high yield and up to 97% ee. However, the ligand **27** is much less effective due to lake of a NH function.

Chiral β-amino alcohols are found to be better ligand than phosphine based ligands. Noyori[54] had studied the effect of various chiral β-amino alcohols in combination of $[RuCl_2(\eta^6\text{-arene})]_2$ for asymmetric transfer hydrogenation. The presence of a primary or secondary amine end in the amino alcohols is crucial for the catalytic activity. Thus, the combined system consisting of $[RuCl_2(\eta^6\text{-hexamethylbenzene})]_2$ and (1S,2S)-1,2-dimethyl-2-(N-methylamino)ethanol gave the best result with 92% ee in refluxing propane-2-ol in the presence of KOH.

Lemaire[55] studied various C_2-symmetric diamins as ligand for Ru-catalyzed asymmetric transfer hydrogenation of ketones. But results were not promising as the optical purity was only moderate.

N-Tosylated ethylenediamine is found to be an excellent catalyst for asymmetric transfer hydrogenation.[1b] Noyori[56] introduced this type of complexes (**Fig.8**) which is much more reactive than the previously reported azaaromatic[5], phosphine[29, 30] or imine based[52] complexes.

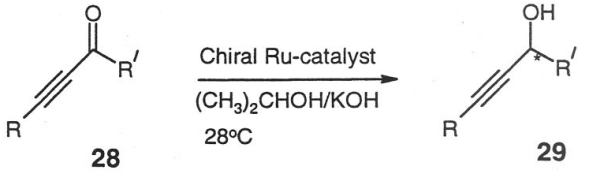


2

Fig.8. Noyori's (S,S)-Ts-DPEN based Ru-catalyst.

This ligand while heating with $[RuCl_2((\eta^6\text{-mesitylene})]_2$ give the chiral complex (R)-RuCl[(1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH-(C_6H_5)NH_2](η^6-mesitylene([*S*,*S*]) which catalyze transfer hydrogenation in propan-2-ol at room temperature with 97% ee and 95% yield.

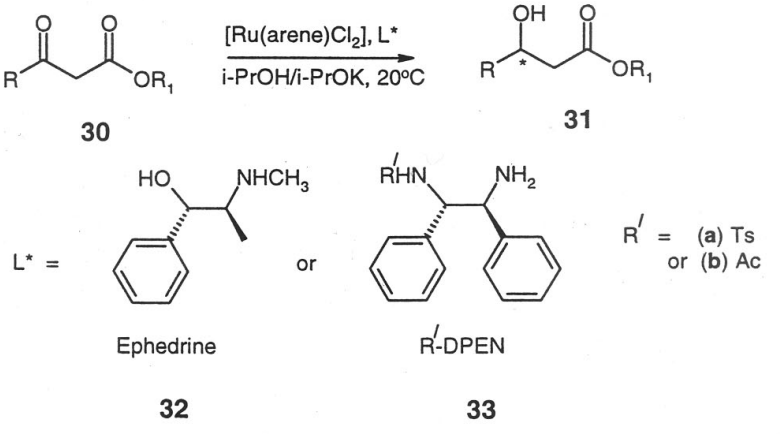
The same Ru complex can also promote asymmetric reduction of ketones to secondary alcohols in the presence of HCOOH-Et_3N effectively with an ee of 98%.[57] The ligation of the S,S-configurated nitrogen ligand induces the R-configuration at the Ru center.[56, 58] Ts-DPEN catalyst is found to be most effective catalyst for the transfer hydrogenation so far. This ligand in combination of Ru-complex can even induce transfer reduction of acetylenic ketones to propergylic alcohols with high selectivity and enantiomeric purity (ee > 99%) (scheme 12).[59]



28 **29**

Scheme 12

Everaere[60] utilized this ligand in combination with $[RuCl_2(\eta^6$ arene$)]_2$ for transfer hydrogenation of β-ketoesters to the corresponding alcohols at 20 °C in ee ranging from 36-94%. He also studied ephedrine ligand and found it to be equally good as Ts-DPEN in this case (Scheme 13).



30 **31** **32** **33**

Scheme 13

Transfer hydrogenation of alkylaryl ketones as well as dialkylketone with isopropanol catalyzed by Ru complexes of chiral phosphinooxazolines[61] (**Fig.9**) were found to proceed with excellent turnover at a substrate/catalyst mole ratio of 1000 : 1 to yield products with upto 94% ee.

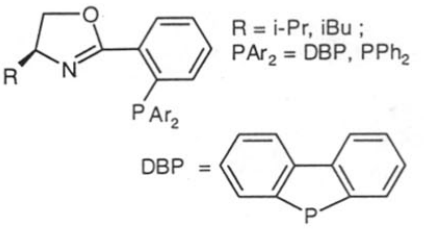


Fig.9. Chiral Phosphinooxazolin

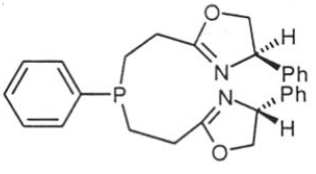


Fig.10. Jiang's ligand

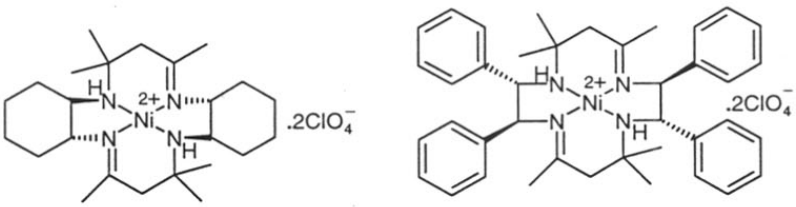
New chiral NPN-type tridentate ligands containing two oxazoline rings and one phosphine (Fig.10) have been reported recently and their Ru(II) complexes show high reactivity and enantioselectivity in the transfer hydrogenation of both aryl alkyl and dialkyl ketones (ee upto 92% in the case of dialkyl ketones).[62]

Chiral ferrocenic secondary diamines also studied for transfer hydrogenation.[63] Although the ligands were highly reactive even at –30 °C moderate chiral induction is resulted.

4.2.3. Present Work

Objective

Due to the importance and synthetic utility of chiral secondary alcohols as is evident from the preceding section, the synthesis of these alcohols from prochiral ketones by transfer hydrogenation technique has received considerable attention. Most of the studies reported in the literature use the complexes of ruthenium. To the best of our knowledge nickel based catalyst have not been tried so far. In **section A** of this chapter we report that Ni-based macrocyclic complex is very effective in promoting transfer hydrogenation of carbonyl compounds particularly in formic acid in presence of ammonium formate. The objective of the present investigation is to make the chiral macrocyclic complexes **36** and **37** (**Fig. 11**) by modifying the complex **14** and to apply these chiral catalysts for the asymmetric synthesis of secondary alcohols via transfer hydrogenation.



36 **37**

Fig. 11. Chiral Macrocyclic Nickel Complex

4.2.4. Results and Discussion

The complexes **36** and **37** were prepared by following the same procedure employed for complex **14**. But in this case the ligand did not precipitate out from the solution. After addition of perchloric acid to the solution of diamine in acetone the mixture was stirred for 2h. Sodium sulfate was added to it and filtered. The organic layer was evaporated and the product was complexed with Ni in methanol at 60 °C. The complexes were characterized by IR, ^{1}H NMR and elemental analysis. These compounds show a strong broad band at 3286 cm^{-1} in their IR spectra due to the N-H vibration. The C=N stretching mode occurs as strong sharp band at 1693 cm^{-1}. The

bands in the IR spectrum at 1456 cm^{-1} and 1094 cm^{-1} can be inscribe to C-N bond of the complex. ^1H NMR of the complex **36** shows multiplets in the region of 3.6 δ and 4.4 δ. The CH protons attached to the N-atom appears as multiplet at 4.5 δ in ^1H NMR.

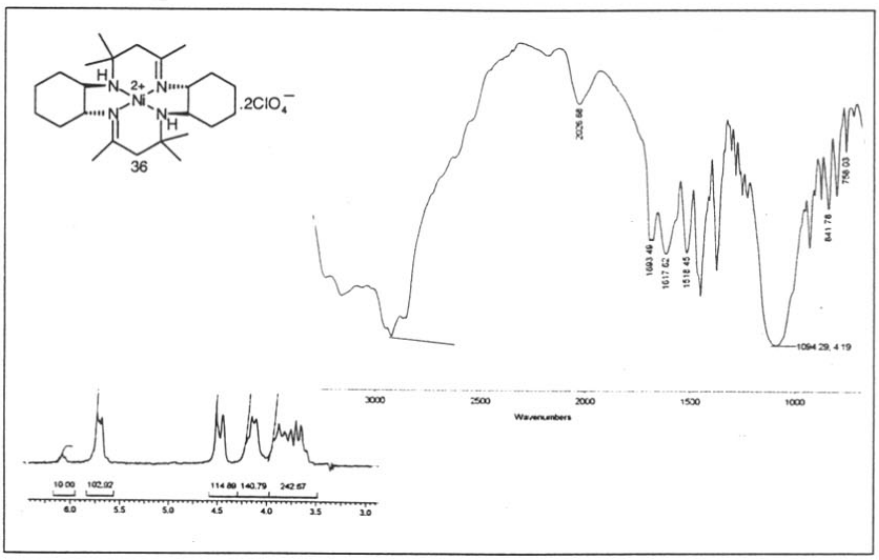
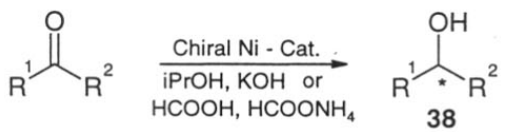


Fig.12. ^1H NMR and IR spectra of the complex 36.

Reactions were carried out in propan-2-ol and KOH as well as formic acid and ammoinum format (Scheme **14**). Most of the experiments were done with chiral catalyst **36** in 2-propanol and KOH.



Scheme 14

Table.3 shows the results obtained from asymmetric transfer hydrogenation of various ketones to get secondary alcohols. Reaction rates are slow similar to the catalyst **14**. As we have seen in the preceding section rate of reaction is faster in case of formic acid-ammonium formate system, reactions are also studied using similar condition. But the results are not promising.

Table 3 : Asymmetric transfer hydrogenation of various ketones using catalyst 36 and 37 to get secondary alcohols.

En-try	Substrate	Cata-lyst	H-donor	t/h	Yie-ld[a] (%)	$[\alpha]_D$	ee[b] %	Config-uration[c]
1	Acetophenone	**36**	^iPrOH + KOH	28	74	+5.3[d] (c 1 $CHCl_3$)	13	R
2	Acetophenone	**36**	HCO_2H + HCO_2NH_4	3	90	+6.7 (c 1 $CHCl_3$)	16	R
3	4-Methyl acetophenone	**36**	^iPrOH + KOH	30	74	+7.4[e] (c 0.6, $CHCl_3$)	14	R
4	4-Chloro acetophenone	**36**	^iPrOH + KOH	30	70	+5.5[f] (c 0.9, Et_2O)	11	R
5	Propiophenone	**36**	^iPrOH + KOH	36	64	+2.8[g] (c 1 $CHCl_3$)	10	R
6	Acetophenone	**37**	^iPrOH + KOH	30	75	+11.6 (c 1.1 $CHCl_3$)	28	R
7	Acetophenone	**37**	HCO_2H + HCO_2NH_4	2.5	88	+12.1 (c 0.8 $CHCl_3$)	29	R

a: isolated yield after chromatographic purification; b: ee' s are determined by comparing rotation with the authentic sample; c: the configuration of the alcohol was assigned by comparing the sign of optical rotation of the authentic sample; d: Lit[64] $[\alpha]_D$ +42.8 (neat); e: Lit[65] $[\alpha]_D$ + 56.0 (neat); f: Lit[66] $[\alpha]_D$ +49.7 (c 2, Et_2O); g: Lit[67] $[\alpha]_D$ +28.1 (neat).

The optical purity of the samples was determined by comparing optical rotation from the literature data. Similarly the configuration of the sample was determined by comparing the sign of optical rotation of the same reported in the literature. Since optical induction by catalyst **36** was quite low, we modified the catalyst to make another catalyst **37**. Reactions were tried for acetophenone in both 2-propanol-KOH and formic acid-ammonium formate. Although optical yields are improved as compared to the results obtained in case of catalyst **36**, still the optical yields are not very good. In both cases use of formic acid gave a marginal improvement of optical yield.

The secondary alcohols formed in the reaction were characterized by IR and ^1H NMR spectra. In IR spectrum, presence of a broad band at around 3300 cm^{-1} and absence of carbonyl peak at around 1700 cm^{-1} indicate clearly the occurrence of

reduction. In case of acetophenones, ^{1}H NMR shows a doublet at around 1.5 δ and a multiplet at around 4.8 δ indicating the presence of CH_3 and CH group in alcohol.

4.2.5. Conclusion

The present work has attempted to project the use of chiral nickel macrocyclic complex for asymmetric transfer hydrogenation to synthesize optically active secondary alcohols from the corresponding prochiral ketones. However, the ee's obtained are low which are nevertheless useful in the case of asymmetric transfer hydrogenation to show the scope, potential and prospects of this useful method. We believe that a suitable molecular architecture of chiral nickel complex coupled with appropriate selection of reaction conditions will lead to an efficient asymmetric ketone reduction displaying wide scope. The present work also describes the scope of macrocyclic nickel complexes for asymmetric transfer hydrogenation reactions, for the first time.

4.2.6. Experimental

Preparation of catalysts 36 and 37

(Representative procedure for **36**)

To 50 mL of acetone in a 100 mL beaker was added 2g (17.5 mmol) of 1,2-diaminocyclohexane. The solution was stirred while 2.52 mL of 70% perchloric acid (17.5 mmol) is added slowly from a dropping funnel over a period of 5-minute. The solution become hot and and wine-red color was developed. The solution was dried over Na_2SO_4 and solvent evaporated. The crude material was treated with excess of nickel diacetate tetrahydrate in methanol at 60 °C for two hour. The solution was concentrated and cooled rapidly in the refrigerator and thereafter kept at room temperature for two days. The yellow crystals are filtered and washed with methanol and diethyl ether and dried in air. The catalyst was kept in the desiccator.

Yield : 2.5 g (44%).

IR (nujol, cm^{-1}) : 3336, 3286, 2925, 2870, 2026, 1693, 1518, 1456,

1094.

$[\alpha]_D$	:	- 15.0 (c 1, acetone)
^1H NMR (200 MHz, $CF_3COOH + D_2O$)	:	δ 3.6-4.0 (m, 20 H), 4.05-4.3 (m, 10 H), 4.4-4.6 (m, 8H), 5.75 (m, 2H).
Analysis	:	$C_{24}H_{44}N_4Cl_2O_8Ni$ requires C, 44.6; H, 6.81; N, 8.67 %; Found C, 44.52; H, 6.89; N, 8.52 %;

Catalyst 37

It was prepared on 1.4 mmol scale following the similar procedure employed for catalyst **36**.

Yield	:	0.24 g (40%).
IR (nujol, cm^{-1})	:	3150, 1670, 1600, 1540, 1450, 1340, 1070.
$[\alpha]_D$	:	-64.3 (c 1, acetone)
^1H NMR (200 MHz, $CF_3COOH + D_2O$)	:	1.35 (s 12h), 2.1 (s, 6H), 2.2 (s 4H), 4.2 (m, 2H), 7.25 (m 20H)
Analysis	:	$C_{40}H_{48}N_4Cl_2O_8Ni$ requires C, 57.02; H, 5.7; N, 6.65 %; Found C, 56.89; H, 5.90; N, 6.49 %

General procedure for transfer hydrogenation of ketone.

A mixture of acetophenone (0.5 g, 4.17 mmol), nickel catalyst **36** (0.054 g, 0.083 mmol 2 mol %) and KOH (25 mg, 0.446 mmol, 10 mol %) in propan-2-ol (10 mL) was refluxed for 24 h. Solvent was removed and the product was dissolved in ether, washed with brine, dried over anhyd. Na_2SO_4 and evaporated. Crude product was chromatographed on silicagel using 3% EtOAc-pet ether to get colorless oil.

Method B: (In formic acid)

A mixture of acetophenone (0.5 g, 4.17 mmol), nickel catalyst **36** (0.054 g, 0.083 mmol 2 mol %) and ammonium formate (0.53 g, 8.3 mmol, 2 mol equiv) in

formic acid (10 mL) was refluxed for 2.5 h. Formic acid was distilled off under reduced pressure and the product was dissolved in ether, washed with brine, dried over anhyd. Na_2SO_4 and evaporated. Crude product was chromatographed on silicagel using 3% EtOAc-pet ether to get colorless oil.

1-Phenyl-1-propanol (39)

Yield	:	64 %
IR (neat cm^{-1})	:	3400-3100, 2920, 1590, 1435, 1360, 1040
$[\alpha]_D$	:	+2.8 (c 1 $CHCl_3$) [Lit[67] $[\alpha]_D$ 28.1 (neat)]
^1H NMR (200 MHz, $CDCl_3$)	:	0.9 (t, J= 4.2 Hz), 1.75 (m, 2H), 2.3 (s, 1H), 4.5 (m, 1H), 7.3 (m, 5H).

Heterogeneous Catalytic Transfer Hydrogenation of Carbonyl Compounds

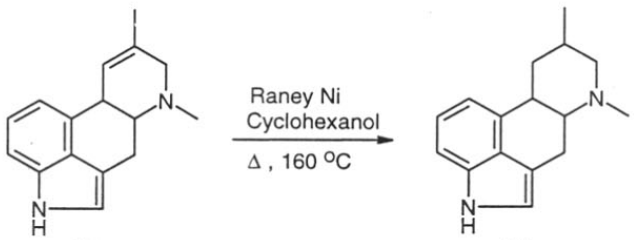
4.3.1. Introduction

Of all the methods available for addition of hydrogen to organic compounds, heterogeneous catalytic transfer reactions have been relatively underutilized. This lack of popularity can be attributed to meager success gained in this area. Another reason for the underutilization of transfer reduction has been the very successful exploitation of molecular hydrogen and hydrides for reduction of organic compounds. But due to ease of separation, purification of reaction mixture and recyclability heterogeneous catalytic methods always has potential advantage over its homogeneous counterparts.

4.3.2. Review of literature

Several heterogeneous catalysts have been used for transfer hydrogenation purpose. These include Pd/C, Pd(black) Pd/asbestos, Pd/$BaSO_4$, Pd/$CaCO_3$, Pd/Pb/C, Pd/Hg/C, Reney Ni, Pt/C, Pt(black), Rh/C, Rh(black), Ru/C, Ru(black), Ir/C, Ir(black), Pd/Ru, Ni/Cu, Os(black), Co(black), Fe(black), MgO/SiO_2, MgO, Al_2O_3, Lanthanide oxides, In, Co/Mo/Al_2O_3, and modified Zirconia. Hydrogen donors used for this purpose are hydrocarbons (such as d-limonine, d-phellandrene, cyclohexene, (+)-1-p-menthene, tetralin, vinylcyclohexene, 1,4-cyclohexadiene, 1,3-cyclohexadiene), alcohols (such as propan-2-ol, cyclohexanol, pentan-3-ol, 1-butanol, benzyl alcohol, allyl alcohol), amines (such as indoline, piperidine, tetrahydroquinoline, N-

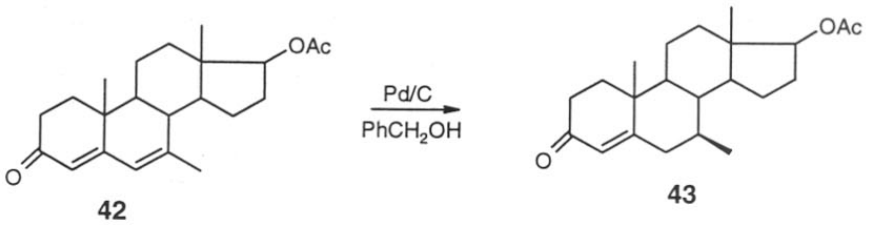
benzylaniline, hydrazine), acids (such as formic acid and phosphinic acid), and salts (such as triethylammonium format, tri-*n*-butylammoinum format, sodium phospinate, sodium format, ammoinum format).[1a] Transfer reduction of carbon-carbon multiple bond is studied very extensively. Among many catalysts used, Pd- catalysts and Raney Ni give best result for transfer reduction. But Raney nickel is less productive for olefins.[68] More successful uses of Raney nickel are reported for conversion of alcohols[68] and amines.[69] For example, norborneol has been reduced in 100% yield with propan-2-ol as hydrogen donor. Stereoselective conversion of agroclavine, **40** (Scheme 15) to 8,9-dihydroagroclavine, **41** was effected in 1 h at 160 °C when cyclohexanol was used as hydrogen donor in presence of Raney nickel.



40 **41**

Scheme 15

The addition of Lewis acid, such as $AlCl_3$ and $FeCl_3$ to Pd/C catalyst can promote reduction.[70] The olefinic bond in a wide range of α,β-unsaturated carbonyl compounds has been reported to undergo heterogeneous catalytic hydrogen-transfer reduction.[2] Mostly, hydrocarbon donors and Pd/C were used and gave good yields. Trialkylammonium formats also have good hydrogen donating ability for these reactions.[71] Several alcohols have been examined as hydrogen donors for the reduction of unsaturated steroids,[72] but only benzyl alcohol gave acceptably selective reduction. For example, 7-methyl-6-dehydrotestosterone acetate can be selectively reduced to 7-methyltestosterone (scheme16) in 90% yield.[73] This reduction appears to proceed through addition of hydrogen to the less hindered α-face of the steroid molecule to induce chiral reductions.



42 43

Scheme 16

The effectiveness of catalytic transfer hydrogenation of aromatic nitro compounds to the corresponding amino compounds is well studied. Utilization of unsaturated hydrocarbons as hydrogen donor has the drawback that the reaction is very slow.[2] But use of triethylammonium formate alongwith formic acid in presence of 5% Pd/charcoal gave good result.[74] Most of the catalyst used for the transfer reduction of nitro compounds are of Pd and Ni.[1a] Fe(III) catalyst also used for this purpose in combination of hydrazine as hydrogen donor.[75] Chemoselective transfer hydrogenation of nitroarenes, aldehydes and ketones with propan-2-ol catalyzed by nickel stabilized zirconia ($Zr_{0.8}Ni_{0.2}O_2$) is reported by Sudalai *et. al.* recently.[76] Nitro group is reduced selectively in presence of carbonyl group. The carbonyl functionality is reduced without affecting the double bond.

The N=N double bond of azo compounds can be reduced readily to give hydrazo compounds, but the latter are readily hydrogenolyzed. Reductive cleavage of azobenzene is reported using Pd catalysts such as 10% Pd/C, 5% Pd/asbestos to give aniline.[77] Recently, Sudalai *et. al.*[78] reported the reduction of azo compounds without cleavage of the N=N bond. Reaction was done in ethanol at reflux using hydrazine hydrate as hydrogen donor in presence $NaHCO_3$ and hydrated zirconia as catalyst. But the use of ammonium formate as hydrogen donor in presence of Pd/C reductive cleavage occurs.[79] Oximes can also be reduced to amines under same condition.[79]

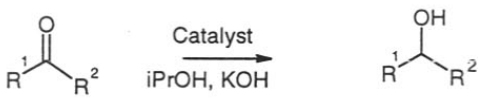
A wide variety of heterogeneous catalysts have been reported for hydrogen-transfer reduction of carbonyl compounds.[1a] With transition metal catalysts, such as Ru, Os, and Ir blacks, cyclohexanones were reduced to cyclohexanols using propan-2-ol as hydrogen donor.[80] Long reaction time is the major drawback of this reactions although conversion is quantitative. Similar results were reported for Raney nickel also.[68] Successful reduction of quinones with a range of hydrogen donors has been reported.[81] Treatment of quinones with Pd/C and one of the hydrogen donors, cyclohexene,

phosphinic acid, or sodium phosphinate in benzene, ethanol, or tetrahydrofuran rapidly (5-60 min) yields the corresponding hydroquinones. Minatchev[82] reported the use of lanthanide oxides for the transfer of hydrogen from butanol to acetone and diisopropyl ketone and from 2-octanol to cyclohexanol. The later reaction was the most selective.

4.3.3. Present Work

Objective

As discussed above, catalysts derived from Rh, Ru, Pd, Ni, Ir and Pt are used for hydrogenation process. Recently, metal exchanged clays are found to be very effective catalyst for numerous organic transformations.[83] Objective of the present investigation is to examine the feasibility of such catalysts for transfer hydrogenation process. Ru- and Rh-exchanged Montmorillonite K10 clay is chosen and the results were compared with that of Ru on alumina. Also, there is a report on lanthanide oxides as heterogeneous catalyst for transfer hydrogenation, but no study was known further. So the purpose of this investigation is also to undertake a study for the transfer hydrogenation using complex of Nd such as $Nd(acac)_3.3H_2O$ under heterogeneous condition (**Scheme 17**).



Catalyst : (a) M-Clay (M = Ru, Rh); (b) $Ru\text{-}Al_2O_3$; (c) $Nd(acac)_3.3H_2O$

Scheme 17

4.3.4. Results and Discussion

Ru- and Rh- exchanged clays were prepared by stirring Mont K10 clay (4%) in 0.002 M aqueous solution of the metal chloride at room temparature for 24 h. The catalyst was filtered, washed with distilled water and dried in oven at 110 °C. Metal content in the catalyst was determined by EDX method. Ru- and Rh content was found to be 0.54% and 0.51% respectively in the sample. Ru on alumina was obtained from Aldrich chemicals, USA. This catalyst was activated by passing hydrogen gas at 270 °C before use.

$Nd(acac)_3.3H_2O$ was prepared according to literature procedure.[84] A solution of aqueous ammonium acetyl acetonate was added to a solution of $NdCl_3$ at pH 6.5. Most

critical factor is the pH of the solution during the addition of the ammonium acetyl acetonate. Because during addition pH may go beyond 7 and in that case its more likely for the formation of $Nd(OH)_3$. Control of pH is the most important factor for the synthesis of the complex. The complex was characterized by elemental analysis.

Transfer hydrogenation reactions were carried out in propan-2-ol at 82 °C and KOH as promoter. **Table 4** summarizes the result of transfer hydrogenation of various ketones and aldehydes to corresponding alcohols using Ru-clay, Rh-clay and Ru-Al_2O_3 as catalysts.

Table 4. Transfer hydrogenation of carbonyl compounds using propan-2-ol as hydrogen donor and Ru- & Rh catalysts.

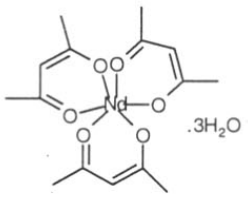
Entry No	Substrate	Ru-Clay (0.54%)		Rh-Clay (0.51%)		Ru-Al_2O_3 (2%)	
		Reaction time (h)	Yield[a] (%)	Reaction time (h)	Yield[a] (%)	Reaction time (h)	Yield[a] (%)
1.	Acetophenone	48	64	48	66	36	74
2.	4-Methyl acetophenone	48	65	48	64	36	74
3.	4-Chloro acetophenone	48	63	48	63	36	72
4.	Cyclohexanone	48	56	48	59	36	63
5.	Octanal	–	–	–	–	36	61
6.	Benzaldehyde	–	–	–	–	36	67

(83) Isolated yield after chromatographic purification

In each case, catalyst used was 5 wt % based on the substrate. Rate of reaction in case of Ru- and Rh- clay catalyzed reactions is slower than that of Ru-Al_2O_3. It may be because of more loading of Ruthenium on alumina (2%). Since the mode and state of preparation of the two catalysts is different, comparison cannot be done for these catalysts. Ru-clay and Rh-clay showed almost the same activity. The reaction proceeds via the mechanism as depicted in the **scheme-5**.

Effectiveness of neodimium catalyst **44** was examined in propan-2-ol as hydrogen donor at reflux temperature and KOH as promoter. The amount of catalyst used for each reaction was 2 mole % and KOH used was 5 mole % (based on the substrate).

Table 5 shows the results of the transfer hydrogenation reactions of various carbonyl compounds using $Nd(acac)_3.3H_2O$. Rate of reaction and yield is better than that of Ru- and Rh- catalyst studied here. Reaction does not proceed without KOH (**entry1, Table 5**) in propan-2-ol. But by the addition of KOH, reaction proceeds well with good yield.



44, $Nd(acac)_3.3H_2O$

Fig. 12

Table 5. Transfer hydrogenation of carbonyl compounds with $Nd(acac)_2.3H_2O$

Entry No	Substrate	H-Donor	t/h	Product	Yield[a] (%)
1.	Acetophenone	Propan-2-ol	24	No reaction	–
2.	Acetophenone	Propan-2-ol/KOH	24	1-Phenylethanol	81
3.	4 –Methyl-acetophenone	Propan-2-ol/KOH	20	1-(4-Methylphenyl)-ethanol	76
4.	4 –Chloro-acetophenone	Propan-2-ol/KOH	20	1-(4-Chlorophenyl)-ethanol	74
5.	Cyclohexanone	Propan-2-ol/KOH	24	Cyclohexanol	63
6.	1-Tetralone	Propan-2-ol/KOH	24	1-Tetralol	67
7.	Citral	Propan-2-ol/KOH	24	3,7-Dimethyloctanol	60
8.	Octanal	Propan-2-ol/KOH	24	Octyl alcohol	61
9.	Benzaldehyde	Propan-2-ol/KOH	16	Benzyl alcohol	74
10.	4-Methoxy-benzaldehyde	Propan-2-ol/KOH	10	4-Methoxybenzyl alcohol	76
11.	Acetophenone	HCO_2H	12	No reaction	–
12.	Acetophenone	HCO_2H / HCO_2NH4	12	No reaction	–
13.	Acetophenone	Propan-2-ol/KOH (With recovered catalyst)	24	1-Phenylethanol	50

a. Isolated yield after chromatographic purification.

Addition of KOH is essential for this reaction which helps to abstract the proton from the donor (**Scheme 3**). Reaction was attempted in formic acid as well as formic acid and ammonium formate. Reaction did not proceed in either case. It was observed that color of the catalyst changes (violet to white) after refluxing in formic acid. Catalyst must have got deactivated in acidic condition at higher temperature. Nd-catalyst can be easily seperated by simple filtration from the reaction mixture. Reusability of the Nd-catalyst **44** was also checked in the case of acetophenone (**entry 14, Table 5**). Reactivity had gone down to almost half in the second run of experiment. Olefinic bond was also reduced with this catalyst. It was found that both the olefinic bond of citral was reduced. No selectivity was observed in this case.

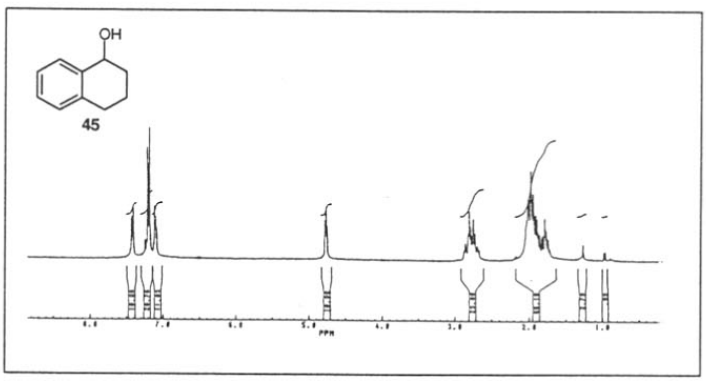


Fig.13. ^{1}H NMR spectrum of compound 45

Products formed in the reaction were characterized by IR and ^{1}H NMR spectra. In IR spectrum presence of a broad band at 3300 cm^{-1} and absence of carbonyl peak at 1700 cm^{-1} indicate clearly the occurrence of reduction. In case of reduction of acetophenones, ^{1}H NMR spectrum shows a doublet at 1.5 δ and a multiplet at 4.8 δ indicating the presence of CH_3 and CH group in alcohol. In case of banzyl alcohols, the reduced product of aromatic aldehydes, CH_2 group appears at 4.6 δ as singlet. In case of reduction of citral no signal was found in the olefinic region in ^{1}H NMR spectrum.

4.3.5. Conclusion

Various carbonyl compounds underwent transfer hydrogenation in presence of Ru-clay, Rh-clay, Ru-Al_2O_3 and $Nd(acac)_3.3H_2O$. Reaction rate is very slow in case of metal exchanged clays. Ru-Al_2O_3 showed better reactivity than M-clay catalysts, which may be due to more loading of Ru on alumina. These three catalysts gave poor result than other Ru and Rh catalyst reported in the literature. Neodemium catalyst gave the best result among all the four catalyst studied in this work. Reactivity of $Nd(acac)_3.3H_2O$ decreases almost to half on its reuse. This catalyst does not show any activity in formic acid, which may be due to decomposition of the catalyst in acidic medium. The Nd-catalyst does not show any selectivity towards double bond and the carbonyl functionality.

4.3.6. Experimental

Preparation Ru-Mont K10 and Rh-Mont K10 clay catalyst

A mixture containing $RuCl_3$ (0.06 g) (or $RhCl_3$) and clay (5 g) in distilled water (150 mL) was stirred vigorously at room temperature for 24 h. It was centrifuged and the clay was washed repeatedly with distilled water until the discarded filtrate was free from Cl^- ions. Finally the clay was dried at 110 °C for 12 h. Metal content in the clay was determined by electron dispersion X-ray spectrophotometer.

Ru-content in the clay = 0.54 %
Rh-content in the clay = 0.51 %

Procedure for the preparation of $Nd(acac)_3.3H_2O$ (44)

$NdCl_3$ (5 g) was dissolved in minimum amount of dil. HCl and pH was adjusted to 5.0. A solution of ammonium acetyl acetonate was prepared by adding con. NH_4OH in 50 mL of water to 15 mL of acetyl acetone. This solution was added dropwise to $NdCl_3$ with stirring. The pH of the solution was maintained at 6.5. The mixture was stirred overnight. The precipitate was filtered and washed with water, dried in vacuo for 1 day and kept in desiccator for one day.

Yield : 8 g (75 %)

Analysis : Calculated for $C_{12}H_{21}O_9Nd$: C, 31.79; H, 4.63. Found C, 31.36; H, 4.57%

Procedure of transfer hydrogenation using Metal exchanged clay

(Representative procedure for acetophenone)

A mixture of acetophenone (0.5 g, 4.16 mmol), Ru-clay (25 mg, 5 wt%) and KOH (12 mg, 0.2 mmol) in propan-2-ol (10 mL) was refluxed for 48 h. Catalyst was filtered and solvent removed. The product was dissolved in ether, washed with brine dried over anhyd. Na_2SO_4 and evaporated. The crude product was chromatographed on silicagel using 3 % EtOAc-pet ether as eluent to get colorless oil.

Yield : 0.325 g (64%)

Procedure for transfer hydrogenation using $Nd(acac)_3.3H_2O$

(Representative procedure for acetophenone)

A mixture of acetophenone (0.5 g, 4.17 mmol), $Nd(acac)_3.3H_2O$ (0.038 g, 0.083 mmol 2 mol %) and KOH (12 mg, 0.2 mmol) in propan-2-ol (10 mL) was refluxed for 24 h. Catalyst was filtered and solvent removed. The product was dissolved in ether, washed with brine dried over anhyd. Na_2SO_4 and evaporated. Crude product chromatographed on silicagel using 3 % EtOAc-pet ether to get colorless oil.

Yield : 0.41 g (81 %)

1-Tetralol (45)

Yield	:	67 %
IR (Neat) cm^{-1}	:	3500-3100, 2860, 1430, 1200, 1050, 1020
^{1}H-NMR (200 MHz, $CDCl_3$)	:	1.7-2.1 (m, 5H), 2.65-2.9 (m, 2H), 4.75 (t, 1H, J=6.8), 7.1 (d, J=6.8Hz, 1H), 7.2 (m, 2H), 7.2 (d, J=6.8Hz, 1H)

3,7-Dimethyloctanol (46)

Yield	:	60 %
IR ($CHCl_3$) cm^{-1}	:	3500-3100, 2940, 1440, 1340, 1055.

^{1}H-NMR (200 MHz, $CDCl_3$) δ	:	0.9 (m, 9H), 1.1-1.2 (m, 4H), 1.4-1.55(m, 2H), 1.65 (m, 2H), 3.2-3.4 (m, 2H).

4-Methoxybenzyl alcohol (47)

Yield	:	76 %
IR ($CHCl_3$) cm^{-1}	:	3500-3200, 2910, 1595, 1490, 1240
^{1}H-NMR (200 MHz, $CDCl_3$) δ	:	2.1 (bs, 1H), 3.7 (s, 3H), 4.6 (s, 2H), 6.9 (d, J=8.3Hz, 2H), 7.25 (d, J=8.3Hz, 2H)

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CHAPTER V

Organic transformations using heterogeneous catalysis

5.0. General Introduction

Zeolites and clays are aluminosilicates finding numerous applications in many areas of catalysis generating intense interest in industrial and academic laboratories[1]. Reusability and recyclability make these catalysts more useful particularly in the industrial scale. As catalyst, these materials exhibit appreciable acid activity with shape selective features. In addition, these materials can act as support for a variety of catalytically active metals.

5.0.1. Zeolites

Zeolites are porous crystalline, hydrated aluminosilicates, having highly ordered rigid 3-dimensional infinite framework. Zeolite may be represented by the general formula[2] $M_{x/n}[(AlO_2)_X(SiO_2)_Y].zH_2O$ where M is a cation of valance n, z is the number of water molecules and the ratio y/x usually has the value of 1-5 depending upon the structure, the sum (x + y) is total number of tetrahedron in the unit cell. The cations M are often group I or II or rare earth ions. Moreover, the cations are mobile and may be usually exchanged. The central atom of the tetrahedron in the zeolite lattice can be replaced by a large number of trivalent and tetravalent atoms[3], which results in altered lattice constants and can therefore be monitored by X-ray diffraction. The nature and extent of incorporation affect the catalytic properties.

The zeolite lattice contains cavities of varying diameters depending on the type of zeolite. The framework of zeolite contains channels and interconnected voids, which are occupied by the cation and water molecules. The cations are quite mobile and may usually be exchanged by other cations. Zeolites can be classified based on their pore size. Barrar[4] and Sand[5] have classified zeolites into three groups based on their effective pore diameter *viz* small pore, medium pore and large pore zeolites. In the case of small pore zeolites, the diameter of the cavity is 4.1 A°. This is formed by eight SiO_4 tetrahedra. This category includes zeolite A, Erionite, Chabazite and Rho. All medium pore zeolites are called Pentasil zeolite, having a ten atom ring system with a tubular

diameter of 5.6 A°. This includes all ZSM-5, ZSM-11, ZSM-22, ZSM-23, ZSM-48, TS-1, TS-2, VS-1, VS-2, silicalite and Theta-1. The third category is the large pore zeolite, which contain 12 to 20 member ring having pore diameter in the range 7.4-100 A°. Faujasite, X- and Y-zeolites, Mordenite, ZSM-12, Omega, Offretite MCM-41, MCM-48 etc. are falling into this category.

The physical and chemical properties of zeolites offer a vast number of options for the tailoring of catalyst for specific reaction within the constraints that the structure must be accommodating the reactants. In addition, the combination of activity and shape selectivity in the zeolite catalysts is an important factor in organic synthesis. The acid strength and the number of acidic sites can be adjusted in a controlled manner during synthesis and/or by subsequent metal (cation) exchange.

The most important application of zeolites is in reactions catalyzed by proton acids and Lewis acids where the change from a homogeneous to heterogeneous procedures bring advantages in respect of easy separation and disposability, reusability, environment friendliness, etc. Zeolites are used in almost all types of organic transformations, viz., alkylation, acylation, halogenation, nitration, isomerization, rearrangements, cyclization, oxidation etc. The interface of synthetic organic chemistry and zeolite induced transformation has acquired an enhanced degree of attention and activity in the last decade.

5.0.2. Clays

Clays are predominantly composed of hydrous phyllosilicates, referred to as clay minerals. These are hydrous silicates of Al, Mg, K and Fe. Clay minerals are extremely fine crystals or particles, often colloidal in size and usually plate like in shape. Many clay mineral crystals carry an excess negative electric charge owing to internal substitution by lower valent cations and thereby increase internal reactivity in chemical combination and ion - exchange.

Clays are classified according to the relative number of tetrahedral and octahedral layers. Most common clays used for catalytic reactions are montmorillonite and kaolinite. Most commonly, the modification of clays is done either by exchanging the cations present in the clay with any other suitable cations like Fe, Zn, Pd, Cu, Ru, Rh, Ce, etc. or by increasing the interlamaller space by pillaring.

Due to ease of availability and cheapness of clays over zeolites clays are becoming one of the most widely used catalysts in recent years. Most of the organic transformations are carried out successfully using various clays as catalyst. Organic transfromations carried out are alkylation, acylation, halogenation, nitration, rearrangements, cyclization, oxidation, protection and deprotection etc.

This chapter deals with the application of various zeolites, metal-exchanged zeolites and clays for organic transformations such as N-H oxidation, α-amination of carbonyl compounds and carbene insertion reactions.

Oxidation of Secondary Amines with 30 % H_2O_2: Use of Zeolites in the Synthesis of Nitroxyl Radicals

5.1.1. Introduction

Interest in the chemistry of nitroxides has been stimulated in recent years by their application as probes in materials[6], spin labels in biochemistry[7], for organic synthesis[8], and more recently as contrast agents in magnetic resonance imaging[9] or electron spin resonance imaging[10] and in polymer chemistry.[11]

Nitroxyl radicals are compounds containing the >NO group which has one unpaired electron.[12] The structure of this fragment can be conceived as a superposition of two resonance structures (Fig.1).

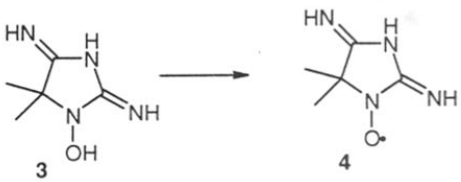
Fig. 1. Nitroxyl radical

5.1.2. Review of Literature

Nitroxyl radicals are very well known in the literature because of its wide synthetic utility. There are many methods for the synthesis of nitroxides reported in the literature.[12] Some of the important methods are briefly discussed below.

(a) By dehyrogenation of hydroxyl amines

In 1901, Piloty and Schwerin[13] prepared the first organic nitroxyl, *porphyrexide* (**4**), by treating 1-hydroxy-2,4-diamino-5,5-dimethylimidazolidine (**3**) with potassium ferricyanide (scheme 1).

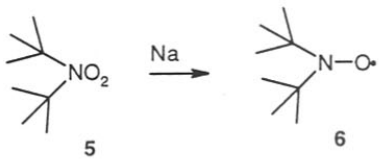


Scheme 1

Several nitoxyl radicals were prepared later by using the same reagent.[14] Many other reagents are known for oxidation of hydroxylamine such as air[15] $KMnO_4$, silver oxide, flourine, mercuric oxide[16], lead (IV) oxide[17], nickel peroxide[18], ammoniacal silver oxide or hydrogen peroxide[19] and periodate[20] to produce nitroxyl radical.

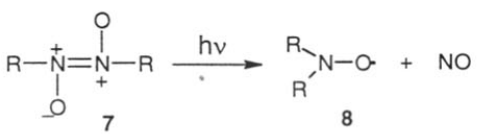
(b) By reduction of nitro compounds

Di-*t*-butylnitroxyl (**6**) was obtained by reduction of 2-nitro-2-methylpropane [$(CH_3)_2CNO_2$] with metallic sodium or by the polarographic technique (scheme 2).[21] Similar strategy of reduction was used by employing Grignard complex[22] and LAH[23] also.



Scheme 2

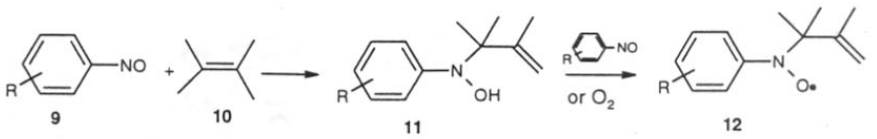
(c) By reduction of nitroso compounds



Scheme 3

The formation of nitroxyls by photolysis of substituted nitrosobenzene derivatives was reported(scheme 3).[24] The process of nitroxyl formation is due to the disproportionation of the nitroso compound dimer on irradiation.

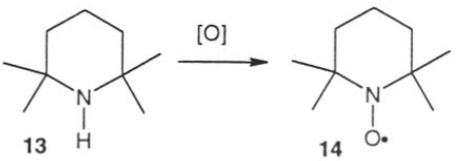
Several nitroxyl radicals have been prepared by this procedure.[25] The formation of nitroxyls upon irradiation or thermolysis of alkyl nitriles proceeds via intermediate nitroso compounds.[26] Alkenylarylnitroxyls **12** can be obtained in solution by reaction of nitrosoarenes with suitable olefins at room temperature (scheme 4). The hydroxylamine derivative **11** formed as intermediates are oxidized to the nitroxyls by oxygen or excess of nitosoarene.[27]



Scheme 4

(d) By oxidation of amines

The preparation of nitroxides by amine oxidation, more recent than the dehydrogenation of hydroxylamine, is currently more widely used and is particularly useful in the preparation of cyclic dialkyl nitroxides (scheme 5).



Scheme 5

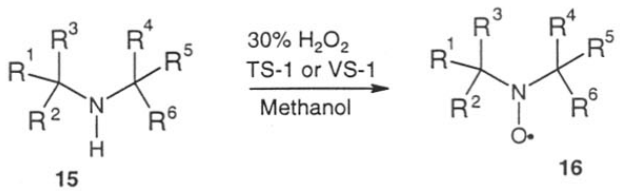
Among the oxidizing agents used to prepare nitroxides are hydroperoxides[28], hydrogen peroxide with cerium[29], silver oxide[30], alkaline solutions of hydrogen peroxides[31], lead(IV)-oxide[32], various peracids[33], pertungstate ion[34], benzoyl peroxide[35] and oxone.[36]

Many more methods are known for the synthesis of nitroxides. Most of the methods are homogeneous method. Therefore, there is a scope for the development of new heterogeneous method for this transformation.

5.1.3. Present work

Objective

Importance of nitroxides is rapidly increasing due to their wide applicability in many areas of chemistry. Synthesis of these compounds become equally important and many new methods are to be developed for betterment of yield and practicability of the process. Most of the methods reported in the literature use reagents, particularly peracids, which are toxic, commercially expensive, highly explosive, and are not suitable for commercial production. Moreover, yields of the nitroxides are very low especially for oxazolidine nitroxides. Other disadvantages are (a) all the reported catalytic methods are homogeneous; (b) some methods generate large amount of inorganic salts as wastes creating problems for disposal. For these reasons it is necessary to develop new process, which will involve heterogeneous catalyst so that recyclability of the catalyst and waste reduction make the process economically more viable. Hydrogen peroxide is well known to oxidize primary amines to nitrones with quantitative yield.[37] The objective of the present investigation is to extend this concept for the synthesis of nitroxides using Ti and V-containing silicates as heterogeneous catalysts and aqueous hydrogen peroxide as oxidant (scheme 6).



15 16

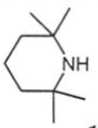
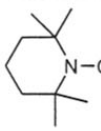
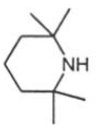
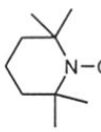
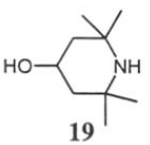
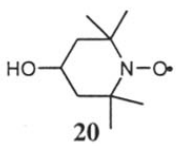
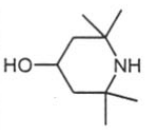
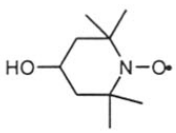
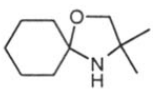
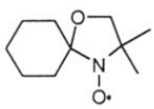
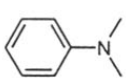
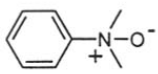
Scheme 6

5.1.4. Results and discussion

2-Spirocyclohexyl-4,4-dimethyl oxazolidine was synthesized following the literature procedure.[38] It was characterized by IR and ^{1}H NMR spectra. IR spectrum shows a band at 3250 cm^{-1} indicating the presence of NH functionality. The two methyl groups appear at 1.15 δ in ^{1}H NMR spectrum as a singlet. The protons of CH_2 group attached to O-atom appears at 3.55 δ as singlet.

Oxidation of various α, α′-tetrasubstituted secondary amines were performed with 30% H_2O_2 as oxidant in presence of Ti and V-containing silicates (TS-1 and VS-1) catalysts. **Table 1** shows the result of oxidation of various secondary amines with 30 % H_2O_2 in the presence of TS-1 and VS-1 as catalysts.

Table 1: Oxidation of various secondary amines with 30 % H_2O_2 in presence of TS-1 and VS-1 as catalysts.

Expt No	Substrate	Cat.	Product	Solvent	Temp °C	Time h	Yield
1	 **17**	TS-1	 **18**	MeOH	60	12	82
2		VS-1		MeOH	60	12	85
3	 **19**	TS-1	 **20**	MeOH	60	18	71
4		VS-1		MeOH	60	18	71
5	 **21**	VS-1	 **22**	MeOH	60	12	78
6	 **23**	VS-1	 **24**	MeOH	60	8	72

Both the catalysts TS-1 and VS-1 catalyze the oxidation of secondary amines very efficiently in good yield. We tried the same reaction with the tertiary amine **23**. Interestingly the reaction goes well to give N-oxide **24**.

Nitroxides were characterized by IR, MS, ESR and ^{1}H NMR spectra. IR spectra of the N-oxides shows a sharp band at 1378 cm^{-1} which is ascribed by the vibration of N—O group. These radicals are better characterized by ESR spectra. ESR spectrum of compound **20** in chloroform shows three signals (Fig. 2). The g-value was found to be 2.0056 and hyperfine coupling constant was 15, which are the typical of nitroxide radicals.

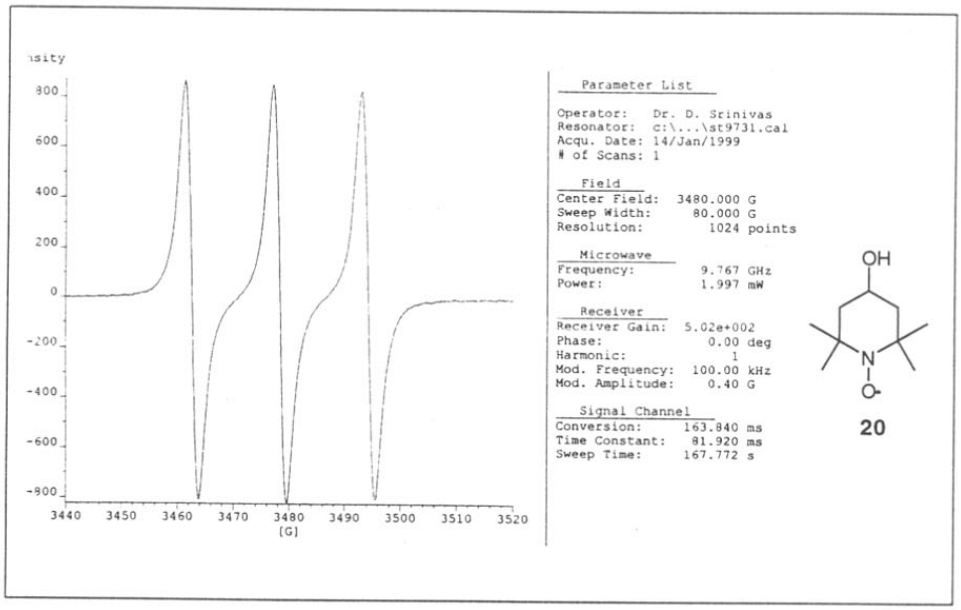


Fig.2. ESR spectrum of the compound 20 in chloroform

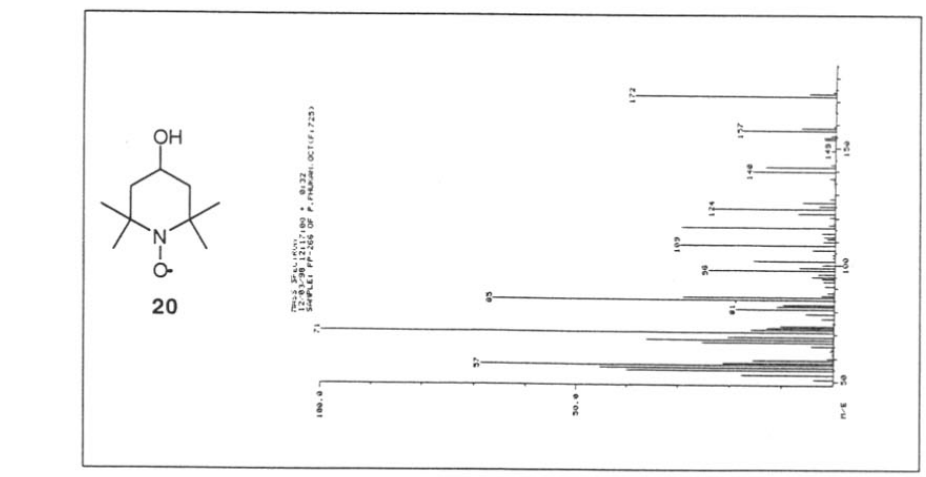


Fig. 3. Mass spectrum of the compound 20

Unlike radicals **18**, **20** and **22**, ^{1}H NMR spectrum of the N-oxide **24** could be recorded. ^{1}H NMR spectrum of **24** shows a singlet at 3.5 δ indicating the presence of CH_3 protons of the compound. (A broad signal appeared at 4 δ in the ^{1}H NMR spectrum of **24** is due to moisture in the sample). Mass spectrum of **24** confirms the structure indicated by the presence of molecular ion peak at 137 (Fig. 4).

The physical characteristics of the two class compounds are different. For example, the nitroxide **18** is sparingly soluble in water whereas the N-oxide **24** is highly water-soluble. Moreover, **18** needs less polar solvent than **24** to purify by column chromatography.

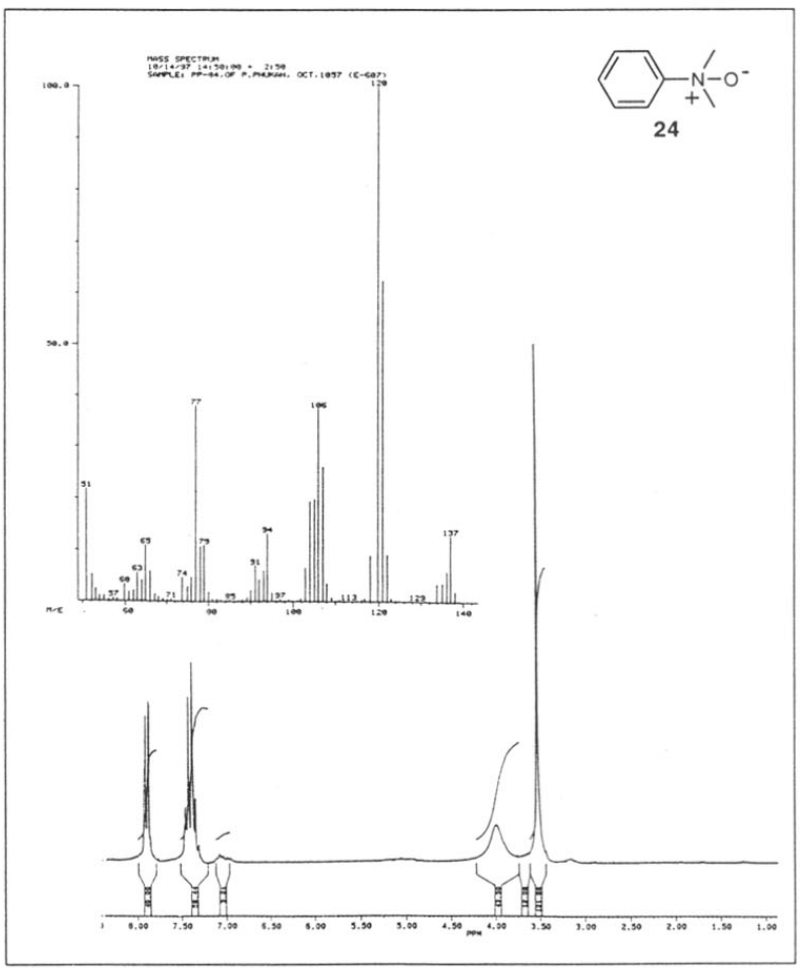


Fig. 4. ^{1}H NMR and Mass spectra of the compound 24

The oxidation of 2,2,6,6-tetramethylpiperidine, **17** was carried out using VS-1 under different reaction conditions as described in the **Table 2**. The progress of the reaction was monitored by GC. Analysis was done by using CP sil 5B column (0.5mm ID) keeping oven temperature at 60 °C for 4 min and increasing to 240 °C in 10 min. Injector was kept at 250 °C and detector temperature was maintained at 275 °C throughout the analysis. It is seen from the Table-2 that the best result was obtained by using methanol as solvent with 4 molar equivalent of hydrogen peroxide at reflux temperature for 12 h. Reaction proceeds with the same conversion at room temperature also. But the rate of reaction is very slow (30 h). Reduction of amount of hydrogen peroxide to 1.5 molar equivalent led to low conversion. Use of acetonitrile at various conditions did not produce better result. Result of experiment in *tert*-butanol is also not promising.

Table 2: Oxidation of 2,2,6,6-tetramethylpiperidine with H_2O_2 over VS-1 as catalyst

Expt No	Amount of 30 % H_2O_2[a]	Solvent	Temp (°C)	Time (h)	% Conv. by GC[b]
1	4 mole equiv.	MeOH	60	12	91.6
2	1.5 mole equiv.	MeOH	60	3	27.13
	1.5 mole equiv.	MeOH	60	6	40.43
3	4 mole equiv.	MeOH	25	30	90.0
4	4 mole equiv.	MeCN	25	3	27.7
5	4 mole equiv.	MeCN	80	4	28
6	3 mole equiv.	MeCN	80	18	17.2
7	1.5 mole equiv.	MeCN	80	3	55.3
	1.5 mole equiv.	MeCN	80	10	52.6
8	4 mole equiv.	t BuOH	25	3	26.7
	4 mole equiv.	t BuOH	25	8	28.4

Reaction Conditions: N-H (250mg), VS-1(50-200mg), Solvent (4mL); a = Molar equivalent is based on amount of N-H compound; b = **Column**: CP sil 5 B, 0.5 mm ID **Oven**: 60°C, 4 min & 240°C, 10 min, **Ramp rate**: 12°/min, **Inj** : 250°C, **Det** : 275°C, **Flow rate:** 20mL/min

A study was undertaken to screen some other heterogeneous catalysts to perform the same transformation. **Table 3** incorporates the results of experiments undertaken using heterogeneous catalysts such as Cu on alumina, Cu on Y-zeolite, $CuO\text{-}Cr_2O_3$, and

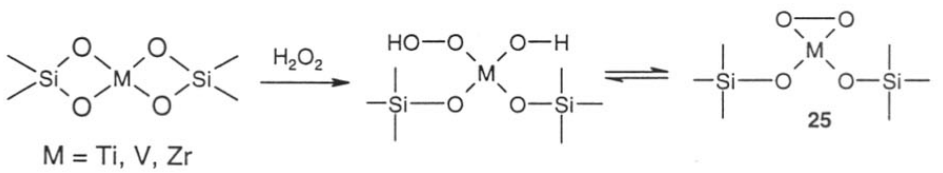
Ru on alumina. It was found that none of the catalysts gave good result in the N-H oxidation. The homogeneous catalyst Re_2O_7, which is becoming very effective catalyst for various oxidation reactions in recent years, is also examined. But the yield of N-oxide was very poor.

Table 3: Oxidation of 2,2,6,6-tetramethylpiperidine over heterogenous catalyst

Expt No	Catalyst	Oxidant (1.5 equiv)	Solvent	Temp (°C)	Time (h)	% Conv. (GC)
1	$Cu\text{-}Al_2O_3$	TBHP	MeCN	80	6	0.97
2	Cu-Y	TBHP	MeCN	80	3	0.43
3	$2CuO.Cr_2O_3$	30 % H_2O_2	MeCN	80	3	3.6
4	$Ru\text{-}Al_2O_3$	TBHP	MeCN	80	3	0.25
5	Re_2O_7	30 % H_2O_2	MeOH	60	3	10.3
	-do-	30 % H_2O_2	MeOH	60	12	11.6

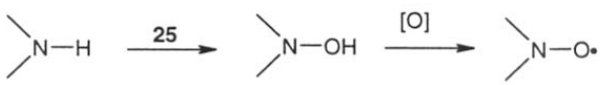
All conditions are similar to the conditions given for the table 2.

Mechanistically, it can be rationalized that a stable metal-peroxo species[40], **25** (scheme 7) forms due to the interaction of the metallo-silicate and hydrogen peroxide under liquid phase condition.



Scheme 7

The Ti(μ-O_2) species **25** oxidizes the N-H bond to generate in situ hydroxylamine which subsequently undergoes further oxidation resulting in the formation of N-oxide (scheme 8).



Scheme 8

5.1.5. Conclusion

Various α α′-tetrasubstituted secondary amines were efficiently oxidized to nitroxyl radical efficiently using zeolite catalysts and 30% hydrogen peroxide as oxidant. Among all the catalysts studied in this set of experiments, VS-1 was found to be the best catalyst for this transformation. Both TS-1 and VS-1 produce similar result although a marginal improvement of yield was achieved by using VS-1. Use of four molar equivalent of 30% H_2O_2 afforded the best result with 91% conversion. The easy separation of catalyst from the reaction mixture makes the procedure very efficient for large-scale production. This process is environmentally friendly and no poisonous or toxic by product was formed.

5.1.6. Experimental

General procedure for the oxidation of amines

A mixture of 2,2,6,6-tetramethylpiperidine (0.5 g, 3.5 mmol), 30 % H_2O_2 (1.6 mL, 0.14 mmol) and 50 mg of VS-1 were taken in 10 mL of methanol and refluxed for 12 h (TLC). Sodium metabisulfite (0.5 g) was added to the reaction mixture and stirred for 0.5 h to destroy excess of hydrogen peroxide. The reaction mixture is then filtered through a pad of celite and methanol was evaporated. Thereafter, the reaction mixture was extracted with DCM and the organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation of the solvent and chromatography of the crude product with 10-15 % EtOAc-pet. ether gave 0.47 g of 2,2,6,6-tetramethylpiperidine-1-oxyl, **18**.

2,2,6,6-Tetramethylpiperidine-1-oxyl, 18

Yield	:	0.47 g (85 %)
m.p.	:	36-38 °C (Lit. 36-38 °C)
IR (Neat) cm^{-1}	:	3400, 2925, 2845, 1460, 1375
Mass (m/z, rel. int.)	:	156 (M^+, 34), 139 (23), 122 (18), 85 (76), 71 (100)

4-Hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl, 20

Yield	:	71%
m.p.	:	68-69 °C (Lit. 69-70 °C)
IR (Neat) cm^{-1}	:	3406, 2960, 2900, 2856, 1462, 1378,
Mass (m/z, rel. int.)	:	172 (M^+, 39), 157(18), 140(16), 124(23), 109(30), 85(65), 71(100), 57(69).
a_N	:	15.87
g-Value	:	2.0056

Synthesis of 2-Spirocyclohexyl-4,4-dimethyl oxazolidine

A solution of cyclohexanone (2 g, 20 mmol), 2-amino-2-methyl propan-1-ol (9.1 g, 100 mmol) and *p*-toluenesulfonic acid (20 mg) in dry toluene was refluxed for 6 h with continuous water removal by means of a Dean-Stark apparatus. Excess of 2-amino-2-methyl propan-1-ol and toluene were removed under reduced pressure and the crude reaction mixture was chromatographed with 10-15 % EtOAc/ pet. ether to get 2.34 g of colorless oil.

Yield	:	2.34 g (68%)
IR ($CHCl_3$) cm^{-1}	:	3250, 2940, 1460, 1230, 1120
^{1}H-NMR (200 MHz, $CDCl_3$)	:	1.15 (s, 6H), 1.4-1.85 (m, 10H), 2.3 (m, 1H), 3.55 (s, 2H)

2-Spirocyclohexyl-4,4-dimethyl-oxazolidine-1-oxyl, 24

Yield	:	78%
m.p.	:	55-57 °C (Lit.[39] 57-58 °C)
IR ($CHCl_3$) cm^{-1}	:	2964, 2876, 1696, 1462, 1378, 1274, 1190, 924.
Mass (m/z, rel. int.)	:	184 (M^+, 1), 168 (1), 147(2), 129(7), 100(100), 87(41.5), 73(29)

N,N-Dimethylaniline N-oxide, 24

Yield	:	72%
IR (Neat) cm^{-1}	:	3400, 3000, 1580, 1475, 1430, 1205, 960, 860, 740
^{1}H-NMR (200 MHz, $CDCl_3$)	:	3.05 (s, 6H), 4.0 (bs, 2H), 5.05 (s, 1H), 7.4 (q, J=8.3Hz, 3H), 7.95 (d, J=7.3Hz, 2H)
Mass (m/z, rel. int.)	:	137 (M^+, 13), 120(100), 106(38), 91(7), 77(38).

Section B

Cu–Exchanged Y–Zeolite: an Efficient Catalyst for the Synthesis of α-Aminoketones

5.2.1. Introduction

The amination of carbonyl compounds is an important reaction because of its potential as a synthetic method for a variety of biologically active compounds[41] and unnatural amino acids.[42] The resulting α-amino ketones are important reagents because they possess both nucleophilic and electrophilic centers, which are useful in the construction of nitrogen containing heterocycles.[43]

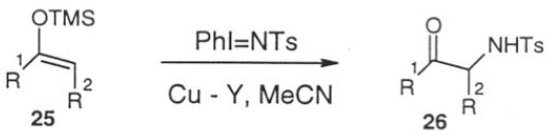
5.2.2. Review of Literature on Synthesis of α-Amino Ketones

Various methods for the synthesis of α-amino ketones available in the literature have been reviewed in **Chapter I**.

5.2.3. Present work

Objective

Among the many methods available for the synthesis of α-amino ketones, use of N-(*p*-toluenesulfonyl)imino)phenyliodinane, PhI=NTs is found to be good aminating reagent. The aziridination of enol silanes reported by Evans[44] could afford the α-N-tosylamino ketones in the presence of various copper salts as catalysts. This method uses the homogeneous condition, which always associated with many disadvantages including tedieus workup procedures. As a part of our investigation of metal exchanged catalysts, we intended to develop a new procedure using heterogeneous copper catalyst such Cu-Y zeolite for this particular transformation (scheme 9).



Scheme 9

5.2.4. Results and discussion

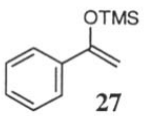
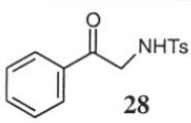
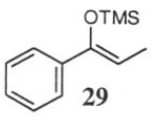
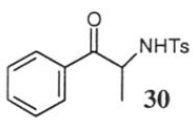
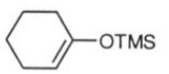
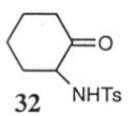
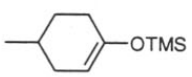
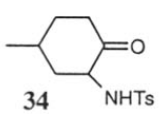
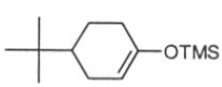
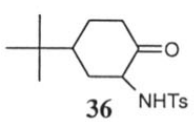
Preparation of silyl enol ethers was carried out by following a very convenient procedure reported recently by Lin.[45] A mixture of the substrate, KI, triethylamine and trimethylsilyl chloride in DMF and pet. ether was stirred for 5 min and allowed to stand for 10 h. The pet. ether layer was separated and usual work up gave the required silyl enol ether in very good yield. The IR spectrum of silyl enol ethers showed the presence of a band near 1640 cm^{-1} corresponding to the double bond and absence of carbonyl peak at 1700 cm^{-1}. ^1H NMR spectrum showed the presence of singlet at around 0.2 δ corresponding to trimethyl silyl functionality. Even, TLC can very easily ascertain the formation of silyl enol ether. It appears as a wide white spot (slowly darkens later) which moves with the solvent front in pet. ether.

Copper exchanged zeolite-Y (Cu-Y) was prepared by stirring Y-zeolite in a aqueous solution of $CuNO_3$ at 80 °C. At higher temperature solution become black and

the required catalyst will not be formed. Copper content in the zeolite was determined by electron dispersion X-ray spectrophotometer and found to be 11.6 %.

The amination reactions were carried out by adding the catalyst to a mixture of the silyl enol ether and PhI=NTs in dry acetonitrile at room temperature under inert atmosphere. It is very important to note that the reaction should be performed in an absolutely dry condition. Otherwise, yield will be low. Table 4 shows the result of amination of various silyl enol ethers.

Table 4. Amination of various silyl enol ethers with PhI=NTs in presence of Cu-Y

Expt. No.	Silyl enol ether	α - Amino Ketone	Time (h)	Yield[a] (%)
1	 **27**	 **28**	3	60
2	 **29**	 **30**	3	63
3	 **31**	 **32**	2	54
4	 **33**	 **34**	2	52
5	 **35**	 **36**	2	48

a: Isolated yield after chromatographic purification

The Cu-Y zeolite catalyzes efficiently the amination of silyl enol ethers to furnish the α-amino ketones at room temperature. Yields are lower in case of cyclic substrates than that of acyclic one. But the rate of reaction is faster in case of cyclic system due to strain in the ring.

Characterization of the product was done using IR, ^{1}H NMR and ^{13}C NMR spectra. IR spectrum showed a peak at 3250 cm^{-1} indicating the presence of NH-functionality. A peak at around 1700 cm^{-1} indicated carbonyl functionality. The presence of NH- and Ts- functionality can easily be confirmed from ^{1}H NMR spectra. There is a broad singlet (sometimes t - double) at 5.7 δ in ^{1}H NMR spectrum indicating the presence of NH proton. Methyl group of *p*-tolyl sulfonyl functional group appears at 2.35 δ. The CH-proton attached to N-functionality appears at 4.45 δ as a doublet in ^{1}H NMR spectrum. In ^{13}C NMR spectra of these compounds, the tertiary carbon attached to N-Ts of compound appears at 48.64 δ. Carbonyl carbon appears at 192.69 δ.

The catalyst was recovered by simple filtration and successfully reused without affecting the yield and selectivity for compound **27**.

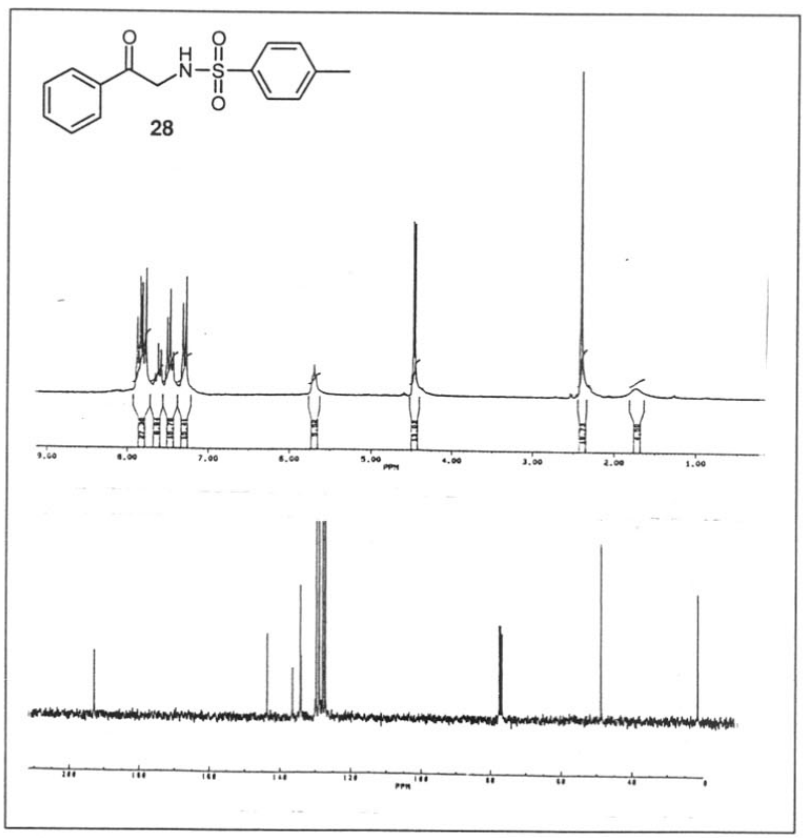


Fig. 5. ^{1}H and ^{13}CNMR spectra of the compound 28

5.2.5. Conclusion

A new heterogeneous catalytic method has been developed for the synthesis of amino ketones from silyl enol ethers using PhI=NTs in the presence of copper exchanged Y-zeolite as catalyst. The methodology is attractive due to the ease of separation of the catalyst from the reaction mixture and the scope of reusability of the catalyst.

5.2.6. Experimental

Synthesis of Cu-exchanged Y zeolite

Zeolite Na-Y (5g) was stirred in 200 mL of 0.1 molar solution of Copper (II) acetate at room temperature for 8 h. The catalyst was filtered washed with distilled water several times, dried first by suction and then at 300 °C in a furnace. This procedure is repeated for three times. Finally the resulted Cu-Y catalyst is calcined at 540 °C for 12 h. The copper content in the zeolite was analyzed through electron probe microanalysis on a EDX detector and found to be 11.6 %.

General procedure for the preparation of silyl enol ethers

To a solution of KI (1.14 g, 6.9 mmol) in DMF (10 mL), pet. ether (5 mL), triethyl amine (2 g, 20 mmol), acetophenone (2 g, 17 mmol), was added chlorotrimethylsilane (2.05 g, 19 mmol) at room temperature. The flask was sealed immediately, stirred for 5 min and kept for 10 h. Pet. ether layer was separated and the DMF layer was washed with pet. ether. The combined organic layer was washed with cold brine, dried over sodium sulfate and evaporated to get the crude product. The crude product was purified either by vacuum distillation or by alumina column.

1-Trimethylsilyloxy-1-phenylethylene

Yield : 2.9 g (90%)

b.p. : 88-90 °C/10 mm (Lit.[46a] 82 °C/5 mm)

IR (Neat, cm^{-1})	:	2920, 1640, 1395, 1260.
^1H NMR (90 MHz, $CDCl_3$)	:	δ 0.2 (s, 9H), 4.35 (d, J= 2.7Hz), 4.85 (d, J=2.7 Hz), 7.2 (m, 3H), 7.4 (m, 2H).

General procedure for α-amination of silyl enol ethers:

To a stirred mixture of PhI=NTs (0.25g, 0.67 mmol) and **1**-styrenyloxy-trimethylsilane (0.19 g, 1mmol) in dry acetonitrile (10 ml) in a two neck round bottom flask, Cu-Y catalyst (25 mg) was added under nitrogen atmosphere (a slow stream of nitrogen was allowed to flow out while adding the catalyst). The reaction was allowed to stirr for 3h. Turbidity goes down to minimal during reaction. Solution was filtered through celite and evaporated. The crude material was chromatographed using 10% EtOAc-pet.ether to get the pure product.

α-Amino-N-*p*-toluene sulfonyl acetophenone

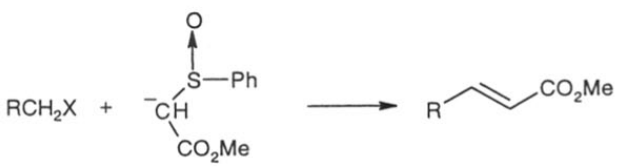
Yield	:	121 mg (63 %)
m. p.	:	113-114 (Lit.[46b] 113-114)
IR ($CHCl_3$) cm^{-1}	:	3250, 1700, 1345, 1290, 1215, 1160, 1095, 780, 750, 680
^1H-NMR (200 MHz, $CDCl_3$)	:	δ 2.35 (s, 3H), 4.45 (d, J=4.1Hz, 2H), 5.7 (bs, 1H), 7.3 (d, J=8.1Hz, 1H), 7.45 (t, J=8.1Hz, 1H), 7.65 (t, J=8.1Hz, 1H), 7.8 (d, J=8.1Hz), 7.85 (d, J=8.1Hz, 1H)
^{13}C-NMR (50 MHz, $CDCl_3$)	:	δ 21.27, 48.64, 127.04(x2), 127.74(x2), 128.78(x2), 129.64(x2), 133.87, 134.12, 143.52, 192.69

Other experimental data resemble with the data given in the **Chapter I**.

Cu-Exchanged Montmorillonite K10 Clay Mediated Insertion Reaction of Methyldiazoacetate into Thiols, Acids, and Alcohols

5.3.1. Introduction

Insertion of carbenes into aliphatic C-H and polar X-H bonds have been used increasingly for the synthesis of carbo- and heterocycles.[47] Aryl or alkyl thioesters are important compounds in organic synthesis as they can be used for the synthesis of biologically active compounds such as $\Delta^{\alpha,\beta}$ butenolides[48], α-methylene lactones and cyclic ketones via alkylative elimination.[49] Sulfoxide elimination have become widely used for introduction of double bond especially alpha to the carbonyl group. The facile elimination of α-sulfinyl carbonyl compounds to their αβ-unsaturated derivative suggested a one-pot olefin synthesis (scheme 10).[49]



Scheme-10

While any sulfoxide anion can be used, high temperature is required for thermal elimination. On the other hand, presence of an α-electronegative substituent such as α,β-unsaturated esters makes the elimination more facile.

Recently, polyunsaturated compounds having β-oxa, γ-oxa, β-thia and γ-thia substituent have found to possess antimalarial and neutrophil stimulatory activity.[50]

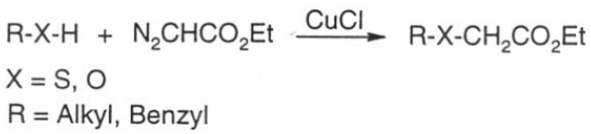
Despite the importance of various oxa and thia compounds, synthesis of these compounds particularly using heterogeneous catalyst is yet to be explored.

5.3.2. Review of Literature

Reaction of alcohols and thiols is being studied since long time.[51] Reaction of alcohol does not proceed without catalyst. The reaction of thiols without catalyst was studied by Miller and Freytag.[52] Thiophenol react with ethyl diazoacetate to form ethyl phenyl diazoacetate whereas aliphatic thiols did not react even at 80 °C. Literature reports for the above insertion reactions are discussed below.

Saegusa's approach[53]

The reaction of thiols and alcohols with diazoacetate by copper compounds such as cupric chloride was examined. Reaction of thiols proceeds well with 85 % yield but with alcohols the yields are low. The yield of insertion to n-BuOH is 15% and maximum conversion was obtained for benzyl alcohol (49 %) (Scheme11).



Scheme 11

Teyssie's approach[54]

Teyssie and coworkers studied Rh-catalyzed insertion reaction of diazoacetate into alcohols, water and weak acids. Catalysts chosen for this experiment are $Rh_2(OAc)_4$, $RhCl_3.3H_2O$ and $RhCl(PPh_3)_3$. $Rh_2(OAc)_4$ was found to be the best choice with 88 % of the adduct for ethanol, 80 % yield for water and 93 % yield for acetic acid. The reactant was used as solvent also for these reactions.

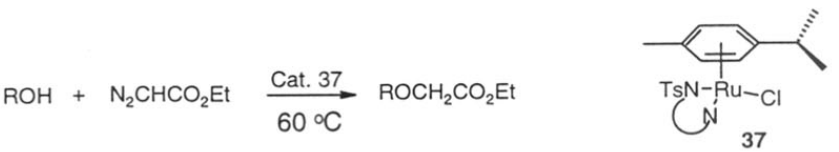
In another report[55] the same group reported the reaction of ethyl diazoacetate with phenol, thiophenol, marcaptans and amines in presence of rhodium acetate. They reported 70 % yield for butanethiol, 90 % for phenol and 92 % yield for thiophenol. Reactions were carried out either neat or in solution (benzene, DME).

Easten's approach[56]

Rhodium acetate was used as catalyst for insertion of *tert*-butyldiazoacetate for the synthesis of polyunsaturated β-oxa fatty acids. Various alcohols derived from naturally occurring polyunsaturated fatty acids were subjected to the reaction in DCM at room temperature to get the β-oxa fatty acids in 38-48 % yield.

Demonceau's approach[57]

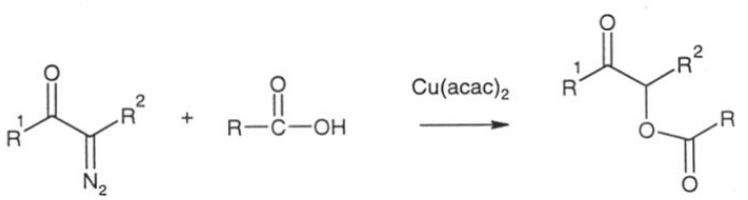
Demonceau and coworkers achieved the insertion reaction of diazoesters into alcohol in presence of various ruthenium complexes. Insertion reaction take place regioselectively to O-H bond in case of allyl alcohol (scheme 12).



Scheme 12

Shimada's approach[58]

They reported the synthesis of α-acyloxy ketones via the insertion reaction of various acids with diazoketones in presence of $Cu(acac)_2$ as catalyst (scheme 13). The treatment of diazo compounds with a carboxylic acid (1.2 equiv) in the presence of $Cu(acac)_2$ (0.1 equiv) at room temperature afforded the corresponding ketoesters in good yields.



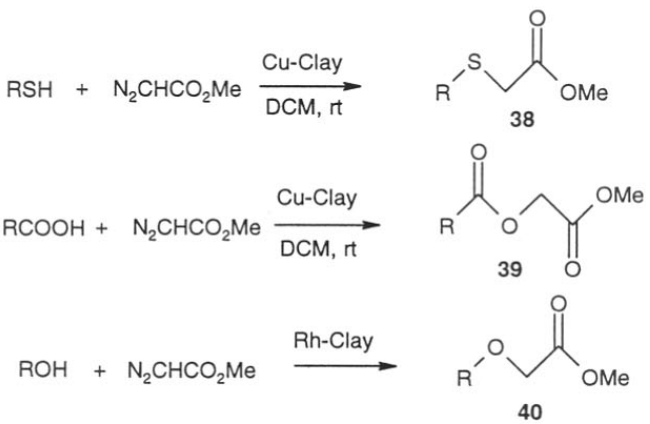
Scheme 13

All of the above methods use different homogeneous catalyst to carry out these transformations. So, there is scope for development of heterogeneous catalyst for this method.

5.3.3. Present work

Objective

It is seen from the above literature survey that there are few reports regarding carbene insertion to the O-H bond and S-H bond involving Cu, Rh and Ru compounds. All the methods involve homogeneous condition involving various metal salts or complexes. It is well known that use of heterogeneous catalyst for any organic transformation has potential advantage over its homogeneous counterpart. There is no report on the use of heterogeneous catalyst for this kind of transformation. Metal exchanged clays are used very extensively for many organic transformations in recent years. The objective of the present investigation is to study the effect of metal exchanged clay as heterogeneous catalyst to achieve insertion reaction of carbene into X—H bond (scheme 14).



Scheme 14

5.3.4. Results and Discussion

The present approach to carry out the insertion reaction of diazoester into alcohols, thiols and acids is schematically showen in the **scheme 14**. Metal exchanged clays were prepared by stirring clay in an aqueous solution of metal salt at room temperature as described in the chapter 4 (section C). Initially, reactions were tried in benzene at reflux temperature. Later it was found that the reactions go well in DCM at

room temperature. Table 5 shows the results of reaction of various thiols, acids and alcohols with methyl diazoacetate in presence of Cu- and Rh-clay as catalysts.

Table 5. Reaction of methyldiazoacetate with acid, thiols and alcohols in presence of M-exchanged clay as catalysts.

Entry No	Substrate	Solvent	Catalyst	Temp.	Time (h)	Yield (%)
1	Thiophenol	benzene	Cu-Clay	80	6	84
2	Thiophenol	benzene	-	80	10	79
3	Thiophenol	DCM	Cu-Clay	25	8	82
4	Butanethiol	DCM	Cu-Clay	25	10	73
5	Ethyl-2-marcaptoacetate	DCM	Cu-Clay	25	8	75
6	Crotonic acid	DCM	Cu-Clay	25	5	95
7	Crotonic acid	DCM	_	25	6	91
8	Cinnamic acid	DCM	Cu-Clay	25	5	96
9	2-Phenylbutyric acid	DCM	Cu-Clay	25	5	92
10	Ethanol	DCM	Cu-Clay	25	12	NR
11	Ethanol	Benzene	Cu-Clay	80	12	18
12	Ethanol	_	Rh-Clay	25	24	46
13	Ethanol		Rh-Clay	60	12	63
14	Ethanol	_	_	60	12	NR
15	Ethanol	_	_	80	12	NR
16	n-Butanol		Rh-Clay	60	12	62
17	Benzyl alcohol		Rh-Clay	60	12	67

It is seen from the table that thiols and acids react at a faster rate than alcohols. Although thiols and acids undergo insertion very efficiently in the presence of Cu-Clay catalyst in DCM at room temperature, reaction did not proceed in case of alcohols. Then alcohols were subjected to the reaction in presence of Rh-clay in DCM at room temperature. But yields were found to be very low. Then the same reaction was done using the alcohol as solvent as well as reactant. In that case yields were improved, and increase of temperature to 60 °C increased the yield up to 67%. In case of thiophenol

and acid reaction proceed well in absence of catalyst although the rate of reaction is slower.

The products were characterized by IR, NMR and mass spectrometry. IR spectrum shows a strong broad band at 1700 cm^{-1} indicating the presence of the carbonyl functionality. Methyl protons appear at 3.8 δ in the ^1H NMR spectrum.

In case of methyl-2-(n-butylthio)acetate, **38b** the protons of CH_2 group attached to the carbonyl and S-atom appear at 3.2 δ as singlet in the ^1H NMR spectrum. The protons of CH_2 group attached to the other CH_2 group and S-atom appear at 2.6 δ in the ^1H NMR spectrum as triplet. Other two CH_2 groups appear at 1.4 δ and 1.6 δ (Fig. 6).

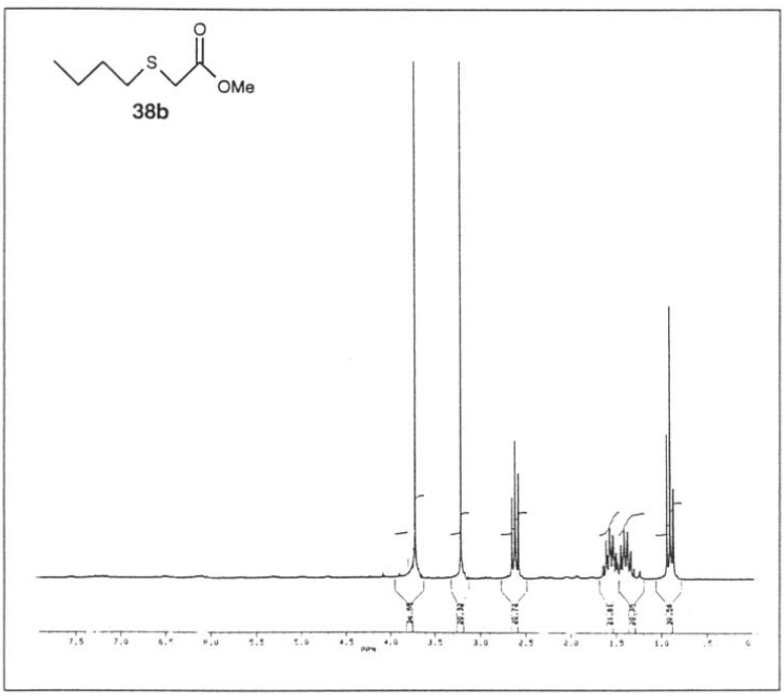


Fig. 6. ^1H NMR spectrum of compound 38b

In case of methoxymethyl crotonate, **39a** the CH proton attached to the CH_2 group appears in the ^1H NMR spectrum at 7.1 δ. Other CH proton appears at 5.95 δ as doublet of doublet (Fig.7).

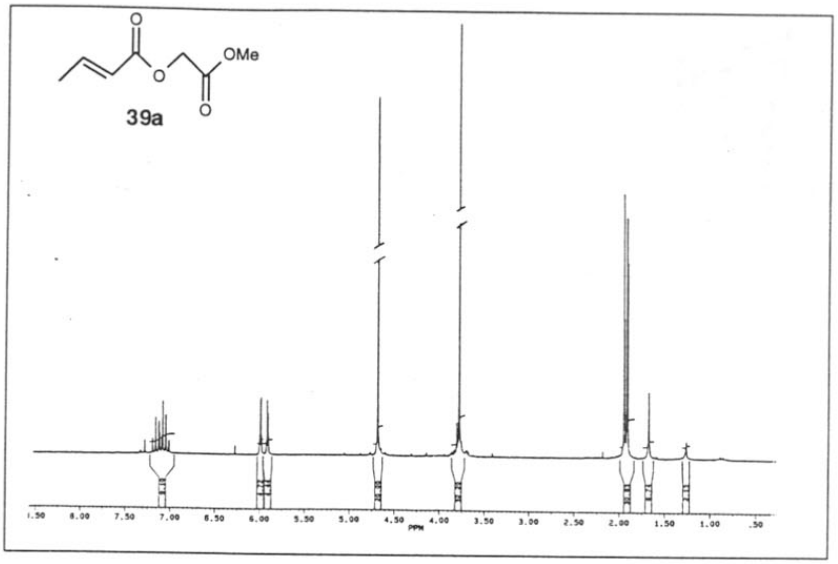


Fig. 7. ^{1}H NMR spectrum of compound 39a

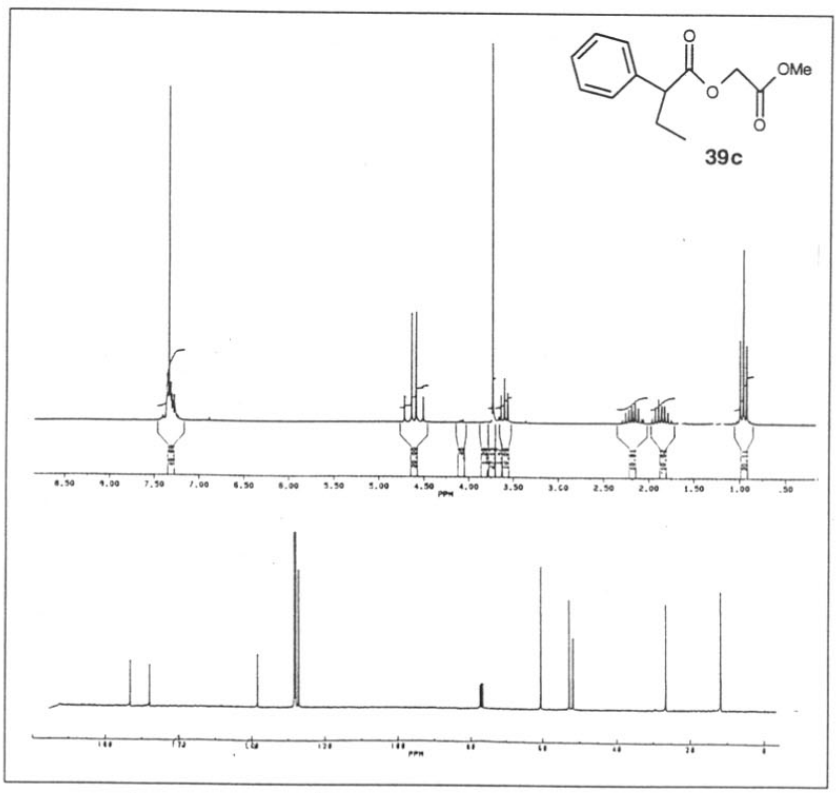


Fig.8. ^{1}H NMR and ^{13}C NMR spectra of compound 39c

In case of methoxymethyl(2-phenyl butanoate), **39c** two multiplets are seen in the ^{1}H NMR spectrum at 1.85 δ and 2.2 δ due to the nonequivalent protons of the CH_2 group at 2-position of butyric acid group (Fig.8).

In case of benzyloxymethylacetate, **40c** all CH_2 protons come together at 4.65 δ in the ^{1}H NMR spectrum (Fig. 9).

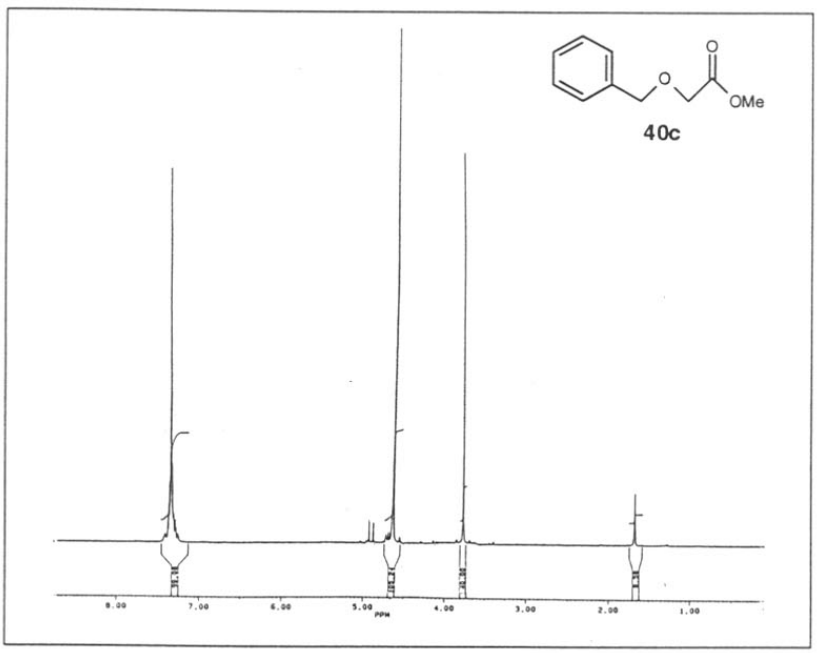
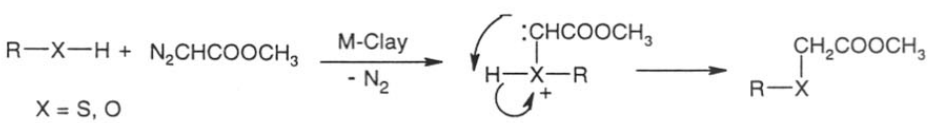


Fig. 9. ^{1}H NMR spectrum of compound 40c

The catalytic pathway for the above reactions can be explained by the fact that the carbene formation is accelerated by the metal catalyst. The carbene first coordinated to the heteroatom **X** to produce the intermediate ylide which further gets rearranged to give the inserted product (scheme15).



Scheme 15

5.3.5. Conclusion

Metal exchanged clays efficiently catalyze the insertion reaction of methyl diazoacetate into X-H bond of thiols, acids and alcohols. Selectivity in insertion into S-H of thiols and O-H of acids is much higher that O-H insertion. Cu-Clay catalyst can efficiently promote the insertion reaction in case of thiols and acids but not effective for O-H insertion. Rh-Clay is found to be effective for O-H insertion at 60 °C in the presence of excess alcohol without any solvent. The method is convenient and easy to perform and useful for large-scale reaction.

5.3.6. Experimental

General procedure for reaction of methyl diazoacetate with acid and thiols

To a mixture of thiophenol (0.5 g, 4.5 mmol) and 25 mg (5 wt %) of Cu-Clay in 5 mL of DCM, methyl diazoacetate (0.86 g, 6.8 mmol) was added dropiwese at room temperature and stirred till the reaction is complete (TLC). Catalyst was filtered and DCM evaporated. The crude product was chromatographed with pet. ether as eluent to get 0.7 g of **38a** as colorless oil.

Methyl-2-(phenylthio)acetate, 38a

Yield	:	84 %
IR (Neat) cm^{-1}	:	1720, 1570, 1420, 1260, 1150, 995
^{1}H-NMR (200 MHz, $CDCl_3$)	:	3.7 (s, 2H), 3.8 (s, 3H), 7.25-7.5 (m, 5H)
Mass (m/z, rel. int.)	:	182 (M^+, 67), 151(2), 123(100), 109(49), 77(31)

Methyl-2-(n-butylthio)acetate, 38b

Yield	:	73 %
IR (Neat) cm^{-1}	:	3000, 1720, 1425, 1270, 1130, 1005
^{1}H-NMR (200 MHz, $CDCl_3$)	:	0.9 (t, J=6Hz, 3H), 1.4 (m, 2H), 1.55 (m, 2H), 2.6 (t, J=6Hz, 2H), 3.2 (s, 2H), 3.75 (s, 3H)

Mass (m/z, rel. int.) : 162 (M^+, 21), 132(6), 103(30), 89(59), 74(91), 61(64), 55(100)

Methyl-2-(carbethoxymethylthio)acetate38c

Yield : 75 %

IR (Neat) cm^{-1} : 1720, 1705, 1635, 1330, 1290, 1120, 1050

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.9 (t, J=7Hz, 3H), 2.9 (s, 2H), 2.95 (s, 2H), 3.3 (s, 3H), 3.8 (q, J=7Hz, 2H)

Methylaceto crotonate, 39a

Yield : 91%

IR ($CHCl_3$, cm^{-1}) : 2990, 1710, 1440, 1270, 1140

^{1}H-NMR (200 MHz, $CDCl_3$) : 3.8 (s, 3H), 4.75 (s, 2H), 5.95 (dd, 1H), C=CH-CO-J=14.6), 7.1 (m, 1H, C-CH=)

Methylaceto cinnamate, 39b

Yield : 90%

IR ($CHCl_3$) cm^{-1} : 2990, 1700, 1610, 1420, 1295, 1150

^{1}H-NMR (200 MHz, $CDCl_3$) : 3.8 (s, 3H), 4.8 (s, 2H), 6.55 (d, J=16.2Hz, 1H), 7.40 (m, 3H), 7.55 (m, 2H), 7.8 (d, J=16.2Hz, 1H), (Ph-CH=C) (C=CH-CO-)

Mass (m/z, rel. int.) : 220 (M^+, 2), 189(3), 131(5), 113(100), 91(82), 77(13)

Methylaceto(2-phenyl) butanoate, 39c

Yield : 91%

IR (Neat) cm^{-1} : 2920, 1730, 1480, 1370, 1140

^{1}H-NMR (200 MHz, $CDCl_3$) : 0.95 (t, J=7.3Hz, 3H), 1.85 (m, 1H), 2.2 (m, 1H), 3.6 (t, J=7.3Hz, 1H), 3.7 (s, 3H), 4.6 (dd, J=15.8Hz, 2H), 7.3 (m, 5H)

^{13}C-NMR (75 MHz, $CDCl_3$) : 11.62, 26.42, 51.62, 52.70, 60.39, 126.94, 127.73, 128.20, 138.24, 167.74, 172.96

Mass (m/z, rel. int.) : 236 (M^+, 6), 205(2), 146(29), 119(56), 104(5),

91(100), 85(6), 77(9), 65(5), 57(16)

Ethoxymethylacetate, 40a

Yield	:	63 %
IR (Neat) cm^{-1}	:	2980, 1720, 1220, 1140, 1030
^{1}H-NMR (200 MHz, $CDCl_3$)	:	1.05 (t, J=5.4 Hz, 3H), 4.05 (q, J=5.4 Hz, 2H), 4.65 (s, 2H), 3.8 (s, 3H)

n-Butoxymethylacetate, 40b

Yield	:	62 %
IR (Neat) cm^{-1}	:	2980, 1720, 1395, 1240, 1130, 1005
^{1}H-NMR (200 MHz, $CDCl_3$)	:	0.9 (t, J=5.4 Hz, 3H), 1.45 (m, 2H), 1.6 (m, 2H), 4.0 (t, J=6Hz, 2H), 4.65 (s, 2H), 3.85 (s, 3H)

Benzyloxymethylacetate, 40c

Yield	:	67 %
IR (Neat) cm^{-1}	:	3000, 1720, 1595, 1240, 1110, 1040, 980
^{1}H-NMR (200 MHz, $CDCl_3$)	:	3.8 (s, 3H), 4.65 (s, 4H), 7.35 (m, 5H)

5.4. References

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