SYNTHESIS OF CHIRAL LIGANDS AND THEIR APPLICATION TO ASYMMETRIC HYDROGENATION USING TRANSITION METAL COMPLEXS

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Certificate

This is to certify that, the work incorporated in the thesis entitled **"Synthesis of chiral ligands and their application to Asymmetric Hydrogenation using Transition metal complexes"** submitted by Mr. Sudhindra Hanamant Deshpande for the degree of Doctor of Philosophy, was carried out by the candidate under my supervision, in Chemical Engineering and Process Development, Division, National Chemical Laboratory, Pune-411008, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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I, hereby declare that the thesis entitled **"SYNTHESIS OF CHIRAL LIGANDS AND THEIR APPPLICATION TO ASYMMETRIC HYDROGENATION USING TRNSITION METAL COMPLEX,"** submitted by me for the degree of Doctor of Philosophy to the University of Pune is the record of work carried out by me during the period from December 2006 to September 2013 under the guidance of **Dr. A. A. Kelkar** and has not formed the basis for the award of any degree, diploma, associate ship, fellowship, titles in this or any other University or other institution of Higher learning.

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Sudhindra Hanamant Deshpande

NOVEMBER 2013 **Candidate**

Pune

Dedicated to My Parents,

Wife and Daughters

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November 2013 ***Sudhindra Deshpande***

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Abbreviations

AP	Acetophenone
ATH	Asymmetric transfer hydrogenation
BINAP	2, 2'-bis (diphenylphosphino)- l, l'-binaphthyl
BINAS	Sulphonated 2, 2'-bis (diphenylphosphinomethyl) - l, l'-binaphthylene
BocDi-*t*-butyl dicarbonate	
Bpy	2, 2' bipyridine
Conc.	Concentration
C-T	Concentration-time
CTAB	Cetyltrimethylammonium bromide
Cp*	Pentamethylcyclopentadiene
DABCO	1,4-diazabicyclo[2.2.2]octane
DPEN	1,2-Diphenyl-1,2-ethylenediamine
DMF	N,N-Dimethyl foramide
ee	Enantiomeric excess
Ephedrine	2-Methylamino-1-phenyl-1-propanol
FA-TEA	Formic acid and triethylamine (5:2)
FID	Flame ionization detector
FTIR	Fourier transform infrared
GC	Gas chromatography
GC-MS	Gas chromatography-Mass spectrometry
h	Hour (s)

HPLC	High performance Liquid Chromatography
HR-MS	High Resolution Mass Spectrometer
IPA	Isopropyl alcohol(2-propanol)
LDA	Lithium Di isopropyl amide
min.	minutes
NMP	N-methyl 2-pyrolidone
NMR	Nuclear magnetic resonance
org.	Organic
Ph	Phenyl
ppm	Parts per million
RT	Room temperature
SDS	Sodium dioctyl sulfosuccinate
Skewphos	2,4-bis(diphenylphosphino)pentane
Temp.	Temperature
THF	Tetrahydrofuran
TOF	Turnover frequency
TON	Turnover Number
TPP	Triphenyl phosphine
TsDPEN	N-[-2-amino-1,2-diphenylethyl]-4-methylbenzenesulfonamide
TsCYDN	1R, 2R)-N-(*p*-tolylsulfonyl)-1,2-cyclohexyl –diamine]

Abstract of the thesis

Synthesis of Chiral ligands and their application to Asymmetric Hydrogenation using Transition metal complexes

Chirality[1] (handedness; left or right) is an intrinsic universal feature of various levels of matter. Molecular chirality plays a key role in science and technology. In particular, life depends on molecular chirality, in that many biological functions are inherently dissymmetric. Most physiological phenomena arise from highly precise molecular interactions, in which chiral host molecules recognize two enantiomeric guest molecules in different ways. Enantiomers often smell and taste different. Thus, gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals, and flavors is important. Earlier, enantiomerically pure compounds were obtained by the classical resolution of a racemate or transformation of readily accessible, naturally occurring chiral compounds such as amino acids, tartaric and lactic acids, carbohydrates, terpenes, or alkaloids.[2, 3] Even though stereo selective conversion of a prochiral compound to a chiral product, namely through an asymmetric reaction, is the most attractive approach, practical access to pure enantiomers relied largely on biochemical or biological methods. However the scope of such methods using enzymes, cell cultures, or whole microorganisms is limited because of the inherent single-handed, lock-and-key specificity of biocatalysts. On the other hand, a chemical approach allows for the flexible synthesis of a wide array of enantiopure organic substances from achiral precursors. Of various possibilities, the use of chiral organometallic molecular catalysts would be the most powerful strategy for this purpose.

Asymmetric catalysis is an integrated chemical approach in which the maximum chiral efficiency can be obtained by a combination of suitable molecular design with proper reaction conditions. Using this strategy in last two decades Noyori pioneered the enantioselective hydrogenation of ketones, imines and olefins[4-7], which includes molecular as well as transfer hydrogenation[8-10].

These hydrogenation reactions are a subject of remarkable interest both from academic and industrial point of view. However, safety related to the use of hydrogen as gas is of utmost importance. Also, for functionalized molecules selective hydrogenation of desired functional group is of utmost importance. This has led to the development of Asymmetric Transfer Hydrogenation (ATH), also pioneered by Noyori[8-10], which offers certain advantages over alternative methodologies[11]. ATH is highly selective method and reduces the risks and safety restrictions associated with the use of molecular hydrogen. In ATH cheaper and less hazardous hydrogen donors like formate salts, IPA etc. are used. Furthermore, ATH is accompanying co-products or byproducts that can easily be disposed off and are not associated with any significant environmental issues. The total process is safe, simple, and ecologically friendly.

Various hydrogen donors like formic acid and formate, alcohols etc. are used in ATH. The various properties of the donors and acceptor, the effect of various catalysts, and the use of different solvents etc have been studied in detail. The ATH reactions can be categorized based on the catalyst and ligands used and also by the substrates employed. It is observed that majority of the applications utilize prochiral substrates to get optically active products using chiral catalysts. ATH now has emerged as a powerful, practical and versatile tool for the enantioselective reduction of ketones and imines .The optically active products such as alcohols and amines are common intermediates for pharmaceuticals, biologically active compounds and fine chemicals. The most successful ligands were β amino alcohols and 1, 2 monotosylated diamines in combination with Transition metals like Ru, Rh and Ir.

OBJECTIVE OF RESEARCH

Considering the above facts, the present study was focused on the Asymmetric Transfer hydrogenation reactions of ketones and imines. The hydrogenated products of these substrates viz. chiral alcohols and chiral amines are useful as intermediates in pharmaceutical, agricultural, flavors. The main objective of this work was to develop efficient ligands in combination with transition Metal complex to get high activity and enantioselectivity for ketones and imines. It was also important to study the various parameters affecting activity, enantioselectivity and mechanistic features of these

reactions to develop a deeper understanding. Therefore, following specific topics were chosen for the present work.

- Synthesis of Chiral β amino alcohols having different electronic and steric properties than reported in literature.
- Synthesis of 1, 2 monotosylated diamines having different electronic and steric properties than reported in literature.
- Screening of amino alcohols and 1,2 Monosulfonated diamines ligands using Transition metal complexes in ATH of ketones using 2, propanol, sodium formate as hydrogen donor and study of various reaction Parameters
- Screening of 1,2 Monosulfonated diamines ligands with Transition metal complexes in ATH of ketones using Formic acid: Triethyl amine as hydrogen donor with pH variation, and study of various reaction parameters
- Screening of 1,2 Monosulfonated diamines ligands with Transition metal complexes in ATH of imines using Formic acid: Triethyl amine as hydrogen donor

OUTLINE OF THE THESIS

The thesis will be presented in four chapters, a brief summary of which is given below.

Chapter 1: Introduction and Literature Survey

In this chapter, a detailed survey of the literature on the Asymmetric Transfer hydrogenation reaction is presented. A thorough discussion of the different aspects of the existing literature and the understanding gained from this survey has been presented. Based on the literature reports, specific topics have been chosen for detailed work.

i) **Asymmetric transfer hydrogenation of ketones**: From the literature, it is realized that extensive work has been carried out to understand the role of different catalysts, ligands, hydrogen donors on the activity and enantioselectivity towards desired product. There are reports on the Ruthenium, Iridium and Rhodium catalysts for transfer hydrogenation of ketones. The detailed literature on ATH of ketones using β-amino alcohol ligands is discussed. From the literature, it was clearly seen that amino alcohol structure and substituents significantly affect conversion as well as enantioselectivity, though the exact reasons for the observed effects (steric and electronic) are still not understood

completely. There is a scope to develop and investigate new amino alcohol derivatives (with different steric and electronic properties) as ligands. Also it was found in literature that, although in 2-propanol amino alcohols shows higher activity and enantioselectivity, the reactions are reversible due to unfavorable thermodynamic equilibrium.

It was found from literature that Asymmetric Transfer hydrogenation of ketones with Formic acid: TEA as the hydrogen source in molar ratio 5:2 and 1, 2 Monotosylated chiral diamines in combination with Ruthenium proceeds with truly irreversibility and near complete conversions is obtained. Further rhodium and iridium precatalyst prepared from 1,2 monotosylated chiral diamines also provide comparable enantioselectivity and conversion for unfunctionalized ketones using sodium formate as hydrogen donor in water. The reaction rates in water found are significantly higher than the neat FA: TEA systems. Monotosylated ligands form stable and crystalline complexes with Ru, Rh and Ir metal and Noyori has carried out detailed investigations using TsDPEN (TsDPEN = (1R,2R)-N-(*p*-tolylsulfonyl)-1,2-diphenylethylene-diamine) as a ligand and Ru, Rh and Ir complexes as catalyst precursors. However, there are very few ligands reported in the literature apart from TsDPEN and TsCYDN (TsCYDN =1R, 2R)-N-(*p*-tolylsulfonyl)-1,2-cyclohexyl –diamine].The fact that major numbers of ligands reported are either modification or the derivatives of TsDPEN and TsCYDN ligands. It is clear from literature that it's not with complete success as these ligands gave less activity as well as low ee compare to parent ligands. Kinetic and mechanistic investigation has been done, the systematic study of parametric effects has not been reported because of probably much slower reaction in FA: TEA, and/or in homogeneity of reaction media in water.

ATH of imines was found to be still more challenging even though the imines are more reactive than ketones under FA: TEA systems. There are very few reports on ATH of imines .This describes of TsDPEN as ligand and Ruthenium and Rhodium as metal complex. There are only few reports on study of various parameters such as temperature, formic acid concentrating, substrate concentration, affecting rate and enantioselectivity. Also the mechanistic investigation has been done to study the intermediates in catalytic cycle and mechanism is predicted. The use of different hydrogen donors like FA: TEA, sodium formate has been discussed in literature. .All these reports describe the use of TsDPEN as ligand along with ruthenium and rhodium as metal complex .There are no

reports on ATH of imines using ligands having different steric and electronic properties than TsDPEN.

Chapter 2: Synthesis of chiral amino alcohols and 1, 2 Monosulfonated diamines.

Chiral amino alcohols were synthesized from S methyl lactate, racemic methyl mandalate, benzyl amine and enantiomers of α methyl benzyl amine, which are easily available and cheap.

The amides generated were reduced with the help of sodium borohydride and Lewis acid such as Boron trifluride diethyl etherate to get amino alcohol ligands based on methyl mandalate, methyl mandalate was reacted with enantiomers of α methyl benzyl amine. The amide derivatives, which are mixture of diastereoisomers were crystalized from toluene to get single diastereoisomer. These amide derivatives were reduced with the help of sodium borohydride and Lewis acid such as Boron trifluride diethyl etherate to get amino alcohol ligands based on mandelic acid. The relative and absolute configuration of the resultant amino alcohol was confirmed with X-ray single crystal.

1, 2 monosulfonated vicinal diamines were synthesized .In all 8 ligands were prepared from 1R, 2S norephedrine and its enantiomer 1S, 2R norephedrine. The synthetic methodology used was Mitsunobu reaction and ring opening of activated Aziridine to get regioisomers of various azido sulfonamides. The reduction of this azido sulfonamide with Pd/C or Triphenyl phosphine / water, gives 1, 2 monosulfonated diamines. Structures of the ligands were confirmed with all the spectroscopic data. X-ray single crystal structure of intermediate of ligand 9 is established. A systematic variation in regio and stereo positions of amine and sulfonamide was made and ligands were screened for ATH of ketones and imines.

Chapter 3: Applications of the amino alcohols and 1,2 monotosylated diamines to ATH of ketones

This chapter presents the results and discussion on ATH of ketones using the amino alcohols, and 1, 2 Monosulfonated diamines ligands. Initially amino alcohols along with transition metal complexes such a $[RuCl_2(benzene)]_2$, $[RuCl_{2(}p\text{-cymene })]_2$,

$[RhCl_2(CP^*)_2]_2$ and $[IrCl_2(CP^*)_2]_2$ were used for ATH of acetophenone using 2-propanol as hydrogen donor. The results showed that metal complex ligand combination is important for good activity and enantioselectivity, the results were compared with benchmark ligand like (1R, 2S) ephedrine. Chirality of Hydroxyl group is important and the resultant alcohols have the same configurations as that carbon bearing hydroxyl group.

Parametric effect for ATH of ketone with ligand 4 and $[RhCl_2(CP^*)_2]_2$ was done. However it was found that ATH in 2-propanol using these conditions is highly equilibrium controlled raection, and large variation in ee,(5>%) during the course of reaction was observed.

Therefore, $[RuCl_2(p\text{-cymene})]_2$, and ligand 4 is selected and screening of various ketones was done to expand the scope of ATH reaction. Very good conversions and moderate to good enantioselectivity was observed for various ketones. It was also found that steric and electronic properties of ketones affect the conversion and enantioselectivity.

1,2 Monosulfonated diamines were screened for ATH of acetophenone using sodium formate in water and $[RuCl_2(p\text{-cymene})]_2$, $[RhCl_2(CP^*)_2]_2$ and $[IrCl_2(CP^*)_2]_2$ as transition metal complexes. Excellent activity and very good enantioselcvities was obtained using $[RhCl_2(CP^*)_2]_2$ and ligand 9. It was found that geometry of amine and sulfonamide group should be trans with respect to each other for good activity. Ligands having cis geometry were totally inactive. Based on the results best combination of metal complex and ligand i.e. $RhCl_2(CP^*)_2]_2$ and ligand 9 is selected and screening of various ketones was done to expand the scope of ATH reaction. Excellent conversions(.90%) and enantioselectivity(>80%) for diverse ketones was obtained.

Further, role of co-solvent in ATH was examined using various water miscible solvents like in DMF, methanol. It was found that ATH of acetophenone is accelerated by 2 fold, by using (25%v/v) DMF and methanol co-solvent in water.

Simple procedure for ATH of ketones in methanol with sodium formate as hydrogen source was developed. The X-ray single crystal structure of the Rh-Ligand 9 complex(precatalyst) was established and various parameters affecting conversion and enantioselectivity was done. The parameters studied were i) catalyst preparation procedure ii) source of formate iii) formate concentration iv) temperature v) catalyst

concentration and vi) substrate concentration. It was observed that conversion and enantioselectivity is independent of various catalyst procedure adopted. Out of different formate screened Sodium formate gives optimum conversion and ee and concentration of sodium formate required is more than 2 equivalence (w.r.t acetophenone).It was also found that with increase in substrate concentration conversion increases and more moles of product is formed up to S/C ratio of 300. Beyond which sodium formate concenatrion and by product formation becomes limiting factor.

Finally the results of ATH with ligand 9 were compared with the benchmark ligands like TsDPEN and TsCYDN with $[RhCl_2(CP^*)_2]_2$ and observed that it has comparable activity and enantioselectivity for ATH of acetophenone.

Chapter 4 Application of 1, 2 monotosylated diamines to ATH of ketones and imines using FA: TEA as hydrogen source

In this chapter initial screening of 1,2 monosulfonated diamines(ligand 9)with $RuCl_2$(p-cymene $)]_2$, $[RhCl_2(CP^*)_2]_2$and $[IrCl_2(CP^*)_2]_2$ and FA:TEA for ATH of acetophenone, showed very less activity. Based on literature findings pH variation was done using equal volume of water and ATH of ketone was investigated at different pH, using varying ratio of FA:TEA and equal volume of water. The Results showed that variation in pH along with equal volume of water proved critical for conversion and enantioselectivity. Ru complex which showed less activity in water/ methanol and sodium formate, showed good activity, whereas rhodium complex which were less reactive at low pH showed Drasmatic,improvement in conversion(98%,in 0.5h) and marginal improvement in enantioselectivity.(86% to 96%)

In order to optimize the reaction conditions further various parameters like i) Formate concentration, ii) catalyst concentration iii) effect of temperature iv) effect of substrate concentration was investigated. It was observed that with increase in catalyst concentration conversion increases with no impact on ee. Increase in substrate concentration up to S/C 400 showed increase in conversions. With substrate to catalyst ratio above S/C 500 was not studied as formate concentration becomes limiting factor. To overcome this problem and study effect of substrate concentration at higher S/C. the reactions were carried at 10 mmol concenatrion and S/C ratio of 100-1200 in 20 ml

volume. At this ratio effect of formate concenatrion and catalyst concentration were studied, and found that reaction can be carried out at high S/C ratio 1200, (542, TOF,h^{-1} and TON of 1038).

ATH of imines: The 1,2 monosulfonated diamines ligand synthesized in chapter 2 , were screened for ATH of imines with $[RuCl_{2(}$p-cymene $)]_{2,}$ $[RhCl_2($ CP*$)_2]_2$and $[IrCl_2($ CP*$)_2]_2$ and FA:TEA as hydrogen donor.. Results showed that ligand 9 in combination with $RuCl_2$ $_{(}$p-cymene$)]_2$ provides excellent conversions(99%) and enantioselectivity(93%).Rhodium analogue showed higher activity, with less enantioselectivity and to the best of our knowledge this is the first example of rhodium and unsymmetrical vicinal diamine to the ATH of imines. Based on the results best combination, ($[RuCl_{2(}$p-cymene $)]_{2,}$ and ligand 9) ,different cyclic imines were screened for ATH. The results showed excellent conversions and enantioselectivity for variety of imines and are shown to be comparable with benchmark ligand TsDPEN. Parametric Study was done using ($[RuCl_{2(}$p-cymene $)]_2$ and ligand 9. To the best of our knowledge this is the first example of use of rhodium and unsymmetrical vicinal diamine to the ATH of imines.

To summarize

- New amino alcohol and 1,2 Monotosylated Diamine ligands were synthesized, the synthetic methodology was developed to prepare ligands on gm(s) scale
- ATH of ketones was carried out using Ru, Rh, and Ir complexes with 2-propanol and sodium formate, as hydrogen donor, excellent conversions, were obtained for Ru and Rh, with amino alcohol ligands. For Monotosylated diamine, $[RhCl_2($ CP*$)_2]_2$ ligand 9 proved to be best catalyst system using sodium formate in water as hydrogen donor. pH variation in broad range using FA:TEA was done (4 to 10), and conditions were optimized to get high conversion(>90%) and enantioselectivity(>90%), at high S/ C ratio of 1200.
- ATH of Imines was carried out using Ru, Rh, and Ir complexes with 1,2 monotosylated diamines ligands best results were obtained Ru-Ligand 9 catalyst system (99%, conversion in 1h nd 93% ee) , comparable to benchmark ligand

TsDPEN[12]. Effect of various raection parameters on conversion and ee in ATH of imine was investigated.

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Chapter 1: Introduction and literature survey

1.1 Introduction

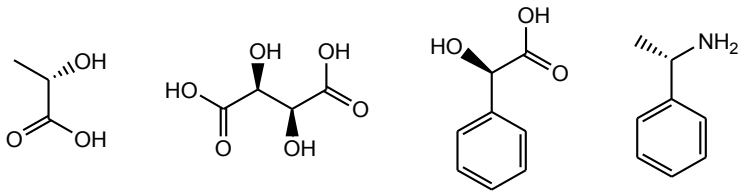
Molecular chirality[1] is pervasive in the chemistry of life and plays a key role in biology as well as in technology. Life itself is dependent on chirality because the interactions of living systems take place almost always with enantiopure compounds. Most physiological phenomena arise from highly precise molecular interactions, in which chiral host molecules recognize two enantiomeric guest molecules in different ways. There are numerous examples of enantiomer effects which are frequently dramatic.

The structural difference between enantiomers can be serious with respect to the actions of synthetic drugs. Chiral receptor sites in the human body interact only with drug molecules having the proper absolute configuration, which results in marked differences in the pharmacological activities of enantiomers. A sad example of the relationship between pharmacological activity and molecular chirality was provided by the tragic administration of thalidomide to pregnant women in the 1960s. (R)-Thalidomide has desirable sedative properties, while its (S)- enantiomer is teratogenic and induces fetal malformations.[2] In spite of this even in the early 1990s, about 90% of synthetic chiral drugs were racemic; that is, equimolar mixtures of both enantiomers, which reflects the difficulty in the practical synthesis of single-enantiomeric compounds. In 1992, the Food and Drug Administration in the U.S. introduced a guideline regarding ™racemic switches, in order to encourage the commercialization of clinical drugs consisting of single enantiomers. Such marketing regulations for synthetic drugs, coupled with recent progress in stereo selective organic synthesis, resulted in a significant increase in the proportion of single-enantiomer drugs. In 2012, nearly one third of drugs marketed were single enantiomers. Thus, gaining access to enantiomerically pure compounds in the development of pharmaceuticals, agrochemicals, and flavors is a very important task.

Discovery of truly efficient methods to achieve this has been a substantial challenge for chemists in both academia and industry. Thus, gaining access to enantiomerically pure compounds is important in the development of pharmaceuticals, agrochemicals, and flavors. For a long time access to highly enantiomerically pure compounds, at least in a practical sense, was thought to be Nature's monopoly and has indeed been accomplished by biological or biochemical transformations.

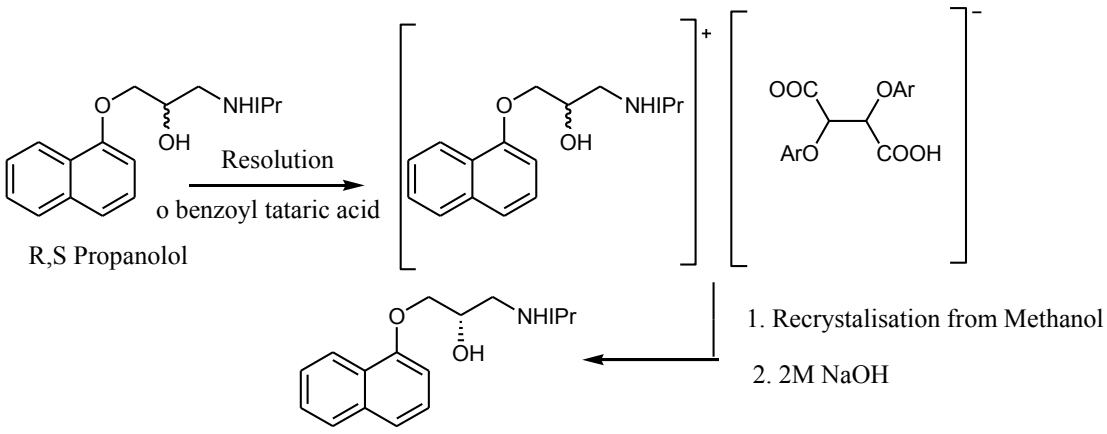
1.1.1 Chiral Resolution:

Earlier, enantiomerically pure compounds were obtained by the classical resolution of a racemate or transformation of readily accessible, naturally occurring chiral compounds such as amino acids, tartaric and lactic acids, carbohydrates, terpenes, or alkaloids[3] (Fig.1.1). The oldest of all the processes is based on the synthesis of the racemic target molecule or intermediate in its synthetic sequence. The material is afterwards resolved with the help of an enantiomerically pure compound. Resolution is an important and still widely used process, mainly for commercial purposes but it suffers from a major drawback, *i.e.* the production of at least 50% of unwanted material. This drawback can sometimes be overcome by recovering/recycling of the unwanted enantiomer of the product. The resolution of racemic propranolol by benzoyl tartrate is shown in Fig.1.2



S Lactic acid, L tartaric aid (R) Mandelic acid S-phenethylamine

1Fig.1.1: Chiral resolving agents



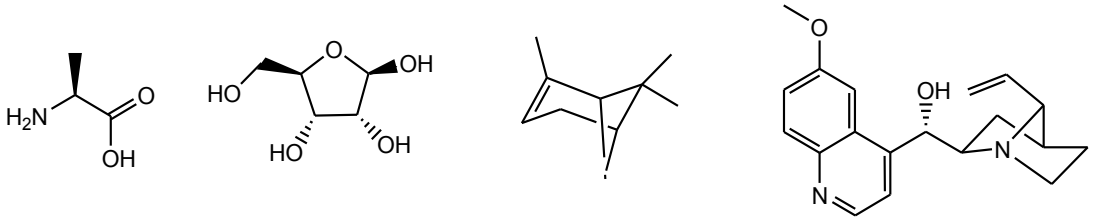
2Fig.1.2: Resolution of (R, S) Propranolol

1.1.1.1 Chiral pool synthesis:

In this case the synthesis of the desired compound is based on a commercially available and enantiomerically pure starting material. Many naturally occurring building blocks are available for this purpose such as carbohydrates, amino acids, terpenes and alkaloids.[4]

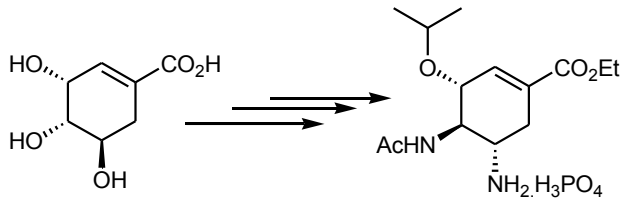
The "chiral pool"(Fig. 1.3) approach strongly limits the possible synthetic strategies due to the still limited availability of appropriate starting materials. Besides this fact, usually only one of the enantiomers of the starting material is naturally occurring further restricting the synthesis.

Costs may also be a problem since unnatural enantiomers which are manmade are usually much more expensive. One of the example of the synthesis of Tamiflu, from shikimic acid is as shown in Fig. 1.4[5]



Amino acid Ribose (carbohydrate) Pienene (Terpenes) Quinine (Alkaloid)

3.Fig.1.3: Chiral pool of naturally occurring compounds



4Fig.1.4: Synthesis of Tamiflu from shikimic acid

1.1.1.2 Asymmetric synthesis:

Asymmetric synthesis involves the introduction of chirality by the action of a chiral reagent, auxiliary or catalyst; which is incorporated in the final product. This process is probably the process of choice, and provides various options in the synthesis of

desired chiral compound. During the last few decades a variety of asymmetric transformation protocols have been developed. Due to its importance, asymmetric synthesis and in particular asymmetric catalysis are treated in more detail in the following sections.

Asymmetric synthesis provides a very efficient methodology for the synthesis of chiral compounds. In order to produce an enantiomerically enriched product at least one part of the reacting system must be chiral itself. Hence, chiral substrates, chiral auxiliaries, chiral reagents or a chiral catalyst can be used to achieve an asymmetric synthesis:

- In the *substrate controlled asymmetric synthesis* a chiral compound is used as a starting material, not necessarily a naturally occurring material. The formation of the new chiral center is induced by the presence of a Stereogenic fragment on the substrate.
- In the *auxiliary controlled asymmetric strategy* an enantiomerically pure compound, chiral auxiliary, is temporarily attached to the starting material. After a diastereoselective reaction the auxiliary is removed, obtaining the product in an enantiomerically pure form.
- In the *reagent controlled asymmetric synthesis* the enantioselectivity is induced by a chiral reagent e.g. base, reducing agent or hydroboration reagent.
- In *asymmetric catalysis* the enantioselectivity is induced by a catalyst, present in sub stoichiometric amounts, the catalyst lowers the activation energy of one diastereomeric transition state and thereby enhances the reaction rate and asymmetry in the product. Asymmetric catalysis is described in more detail below.

A small amount of a well-designed chiral catalyst can produce chiral compound stereo selectively in a large quantity. Of various possibilities, the use of chiral organometallic molecular catalysts would be the most powerful strategy for this purpose. Asymmetric catalysis is an integrated chemical approach in which the maximum chiral efficiency can be obtained with high enantioselectivity. Thus design and development of chiral ligand is the most critical part of asymmetric catalysis. Thus stereo selective conversion of a prochiral compound to a chiral product, namely through an asymmetric reaction, is the most attractive approach.. Therefore asymmetric synthesis only will be useful, if it's carried out in the form of catalysis.

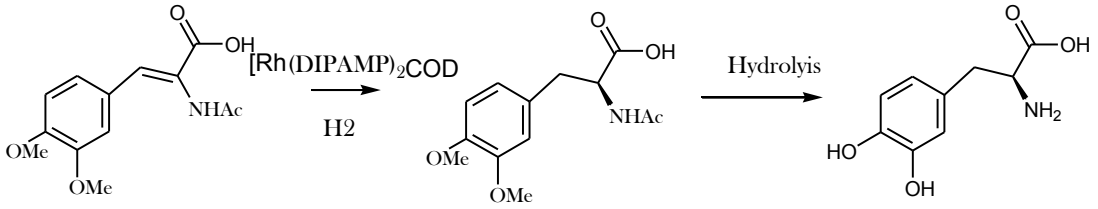
The rapid developments in the asymmetric catalysis (which involves parallel developments in improved synthesis methods for chiral ligands, developments in organometallic and coordination chemistry, instrumentation for better characterization techniques, theoretical analysis including molecular modeling) has led to the development of catalysts for asymmetric reactions including hydrogenation, oxidation, hydroformylation, hydroxylation, aldol reaction. The chiral catalyst can permit kinetically precise discrimination among enantiotopic atoms, groups, or faces in achiral molecules. Certain well-designed chiral metal catalysts not only accelerate the chemical reactions but also differentiate between diastereomeric transition states (TSs) with an accuracy of 10 kJ/mol[6]. In this way, such compact molecular catalysts with a molecular weight less than1000, or 20 A in length or diameter, allow for an ideal method for synthesizing enantiomeric compounds.[6]

The diverse catalytic activity of metal complexes, as well as the virtually unlimited structural variation of the organic ligands, has provided enormous opportunities for the development of symmetric catalysis. By using this technology Noyori et al.[7-13] have developed the enantioselective hydrogenation of prochiral olefins, ketones and imines.[14] The end products obtained such as chiral alcohols, chiral amines being important molecules in fragment, flavors, and agrochemicals.

1.1.2 Enantioselective Hydrogenation:

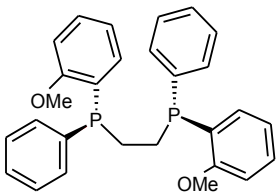
The history of asymmetric hydrogenation goes back to the early 1956 when a heterogeneous catalyst made of palladium deposited on silk was first used to successfully produce chiral hydrogenation products where marginal ees were observed. Later, in 1968, the groups of William Knowles[15] published the first example of asymmetric hydrogenation using a homogeneous rhodium catalyst along with chiral phosphine ligand. Though the enantiomeric excess was low for both of these reactions, it demonstrated that asymmetric hydrogenation was possible using homogeneous metal complex catalysts and led to rapid growth of the field. In 1972, Rh catalyzed hydrogenation of z-acrylamno acids using DIPAMP(Fig 1.5) as chiral phosphorous ligand gave desired product with enantiomeric excess of 90 %.[15] Initial success led to rapid developments in the synthesis of new and improved ligands as well as transition metal complex catalysts for many reactions. Leading academic and corporate R & D Laboratories focused their attention on the development of improved catalysts for asymmetric hydrogenations. The first industrial synthesis using this

technology for the synthesis of L-DOPA, used as drug for Parkinson's disease was achieved by Knowles et al.[15]



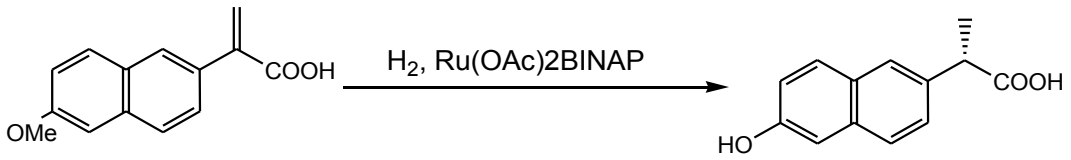
L-DOPA 95% ee

DIPAMP =



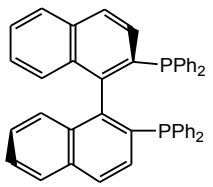
5Fig.1.5: First commercial example of asymmetric hydrogenation of acetaimido cinnamic acid[15]

The field of asymmetric hydrogenation continued to experience significant advances. Henri Kagan[16] developed a new type of chiral ligands called DIOP (C2 symmetric ligands)[17] that allowed chiral information to be transferred to substrates much more effectively.[17] The Asymmetric hydrogenation took major leap; when BINAP[7, 18] was introduced by Noyori. In 1986, Noyori introduced the use of ruthenium-based catalysts for asymmetric hydrogenation of several important types of substrates, which include, prochiral olefins (unsaturated carboxylic acids),[9] β-ketoesters[9-12, 19] and simple ketones.[12] Thus the reduction of various substrates under asymmetric catalytic hydrogenation was made very popular. Typical hydrogenation of unsaturated carboxylic acid is shown in Fig. 1.6



S-Naproxen, 97% ee

[7, 18]BINAP =



6Fig.1.6: Asymmetric hydrogenation using Ru-BINAP complexes

Although, the procedure involved has some difficulty in implementation, for example, it requires special care in the handling of hydrogen which is a highly flammable and explosive gas hence presents considerable hazards. In some cases high pressure is mandatory for the reaction to occur. This involves risks involved in safety and handling of hydrogen. Explosion risks associated with the use requires leak-proof reactors and special electrical connections, detectors etc. All this may not be available with small manufacturer for the synthesis of specialty chemicals. Therefore, there was a necessity for the development of procedure which does not require the use of molecular hydrogen gas as a reactant. It was found that some molecules, such as cyclohexadiene, isopropanol, ammonium formate etc., readily release hydrogen in situ in the presence of a catalyst to form more stable products. The reactions involving such reagents for hydrogenation are referred as catalytic transfer hydrogenation. The catalytic transfer hydrogenation offers certain advantages over alternative methodologies which are as follows:

The hydrogen source is easy to handle (no pressure vessels are necessary).

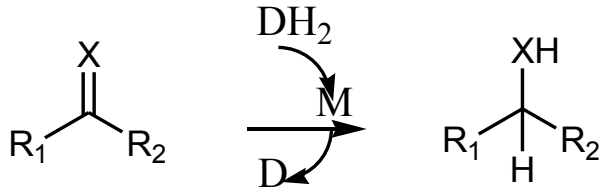
- Possible hazards associated with the handling of molecular hydrogen are eliminated.
- The mild reaction conditions.
- Variations in the choice of donors are also possible.
- Chemo selectivity of multifuctionalised compound is highest with transfer hydrogenation reaction.
- The accompanying co-products can easily be disposed off and some of them can be dehydrogenated back easily.

Thus catalytic transfer hydrogenation process is safe, simple, and ecologically friendly. Aim of the thesis was investigations on asymmetric transfer hydrogenation (ATH) of ketones and imines and hence a detailed literature review on ATH is presented below.

1.1.3 Transfer hydrogenation reaction

1.1.3.1 General background of transfer hydrogenation reaction

Transfer hydrogenation or hydrogen transfer (H-transfer) is defined as “the reduction of multiple bonds with the aid of a hydrogen donor (DH_2) in the presence of a catalyst”, as depicted in Fig.1.7.



X=O/CHR/NHR, M-catalyst, R1/R2=Phenyl/alkyl, DH_2-hydrogen donor, D-byproduct

7Fig.1.7: General transfer hydrogenation reaction

In the above equation, the reaction is catalyzed by a metallic species, M, and the hydrogen transfer takes place either from MDH or by way of metal hydride, MH, formed by elimination of DH. The H is transferred as proton and then D is left out depending on the nature of metal catalyst and hydrogen donor.

1.1.3.2 The concept of Hydrogen donor (DH_2)

The hydrogen donor is characterized by the presence of hydrogen that, under the influence of a suitable promoter, can be mobilized in such a way as to add to an unsaturated functional group in the substrate. At the same time the hydrogen donor is converted to its dehydrogenated counterpart-D (Fig. 1.7). In the large majority of cases the two hydrogens of the donor are non-equivalent and they are transferred sequentially, one as a formal hydride and the other as a formal proton.

In terms of electronegativity, hydrogen occupies a central position in the periodic table. With Pauling's definition of electronegativity,[20] hydrogen, having a value of 2.1, lies between fluoride (4.0) and many metals; which typically have values of about 0.9-l.5. Therefore, in reactions involving hydrogen may appear as a proton, atom, or hydride depending on reagents and conditions. For example, on dissolving gaseous HCl in water, hydrogen is transferred as a proton to water. The reaction of lithium tetrahydroaluminate with a carbonyl group effectively involves the addition of hydride to the carbon of the carbonyl. Many catalytic hydrogenations with molecular hydrogen actually involve atomic hydrogen dispersed in and over the catalyst. In many reductions with hydrogen donors, it may not be easy to decide just how hydrogen is being transferred. For example, formic acid may be regarded as providing proton and a hydride or two hydrogen atoms.[21] However, it is clear that the best hydrogen donor is the compound which contains the hydrogen bonded to the elements or groups with similar electro-negativity. In this respect, formic acid and formates, phosphinic acid and phosphinates, phosphorous acid and phosphites, hydrazine,

hydrides of boron, aluminum, silicon, and tin, alcohols, amines and hydrocarbons are all hydrogen donors in catalytic transfer reduction. Formation of a co-product D is the main drawback of transfer hydrogenation processes when compared with processes such as catalytic hydrogenation. Furthermore, upon losing two hydrogen atoms the hydrogen donor (DH_2) it becomes a hydrogen acceptor that may be in competition with the substrate until equilibrium is reached. Example is where 2-propanol (IPA) is used as the hydrogen source in the transfer hydrogenation of ketones. There is an added advantage when the products of the decomposing donor have large negative enthalpies of formation. Thus, CO_2 from formic acid and N_2, from hydrazine provide added driving force to the reactivity of these substances as hydrogen donors.

1.1.3.3 Historical overview of transfer hydrogenation reaction

The periodic use of unsaturated compounds had been made in the past as hydrogen acceptors in catalytic dehydrogenation reactions. However, few systematic studies were directed toward the reverse process which is called then as catalytic transfer hydrogenation. The knowledge of this basic reaction goes back to the turn of the century, when Knoevenagel[22] first observed that dimethyl 1,4-dihydroterephthalate disproportionate readily in the presence of palladium black to dimethyl terephthalate and hexahydroterephthalate. In the next few decades attention was focused principally on catalytic dehydrogenation reaction. Through the systematic efforts of Braude and Linstead et al.[23] it was observed that catalytic hydrogen transfer from an organic donor molecule to a variety of organic acceptors might be possible under mild conditions in the presence of palladium black. The discovery of reduction of ethylene and acetylene linkages in high yield and purity by refluxing with cyclohexene in THF at 65°C in the presence of palladium black was reported. Subsequent studies established the scope of the reaction by utilizing formate salts as hydrogen donors. It was further shown that carbonyl groups are generally not susceptible to reduction with palladium black and cyclohexene as a hydrogen donor unless part of a potential aromatic system, as is the case with quinones or decalones. The utility of this process for the reduction of carbonyl compounds only became apparent to chemists several years later, when the ability of aluminum alkoxide in promoting hydrogen transfer reactions was reported and established in the form of a synthetic protocol useful for the reduction of ketones to their corresponding alcohols (Meerwein-Pondorf-Verley (MPV) reduction).[24-26] The next milestone was the discovery that some transition

metal complexes which were able to catalyze the H-transfer reduction of ketones homogeneously.[27] The first reports illustrating this property, published in 1967[28], were preceded by preliminary work reporting the Ir-catalyzed reduction of cyclohexanone to alcohols with 2-propanol as a hydrogen donor, which had been almost completely overlooked.[29] However, it was only in the second half of the 1970s with impressive results obtained in catalytic homogeneous hydrogenation that this topic began to attract significant interest. A seminal contribution to the development of this area was provided by the pioneering work of Sasson and Blum,[30-32] who demonstrated that Ru-triphenyl Phosphine complexes had good catalytic activity in the transfer hydrogenation of acetophenone with 2-propanol. Their contributions were shortly followed by the first reports on the asymmetric transfer hydrogenation (ATH) of ketones emerging a new area in asymmetric catalysis.[33] Since then ATH has emerged as a powerful, practical and versatile tool for enantioselective reduction of carbonyl compounds.

The most popular hydrogen donors reported for the transfer hydrogenation reactions are 2-propanol (IPA) and the azeotrpic FA–TEA mixture, which act as solvent at the same time. The formic acid and its salts (sodium, potassium and ammonium formate) are viable hydrogen sources which are soluble in water. The pioneering work carried out by Joo, Sasson and Sinou has attracted the interest in aqueous transfer hydrogenation reaction.[34] Now transfer hydrogenation in water has afforded an effective and green alternative for fast and selective (and enantioselective) hydrogenation. Thus transfer hydrogenation reactions can be carried out using hydrogen sources which are cheap, easily available, generating non-hazardous waste in the reduction. Apart from these merits, the hydrogenation is easy to conduct, requiring mild reaction conditions and often no inert gas protection. The aqueous transfer hydrogenation process provides the use of soluble form of formate and enables easy catalyst/product separation.

1.2 Asymmetric Transfer hydrogenation of ketones (ATH)

The first ATH was reported by Doering et al.[35], who designed an asymmetric version of the Meerwein–Pondorf–Verley reduction of ketones by using an achiral catalyst and a chiral hydrogen source like (-) 2 butanol to achieve 5% ee. In the 1970s, the groups of Ohkubo[36] and Sinou[37] demonstrated the feasibility of using a chiral transition-metal catalyst to achieve ATH by combining $[RuCl_2(PPh_3)_3]$ with a chiral

monophosphine ligand. Since then, several chiral catalytic systems have been developed for ATH, including Pfaltz's Ir(I) dihydrooxazole complexes[38], Genet's chiral diphosphane Ru(II) catalysts[39] etc. However, a significant breakthrough in transition-metal-catalyzed ATH was made by Noyori and co-workers. Ru(II) catalysts bearing monotosylated 1,2-diamines (TsDPEN) were discovered to be highly efficient and enantioselective for the reduction of ketones with isopropyl alcohol (IPA)[40] or FA/Et_3N azeotrope.[41] β-amino alcohols showed ligand acceleration effect in ATH of ketones[42]. Since this discovery, a significant number of new ligands and metal complexes have been reported for the ATH of ketones. Extensive work has been done on ATH reaction which is very well documented in the literature.[43-45] The role of different catalysts, chiral ligands and hydrogen donors on product formation and enantioselectivity towards desired isomer and reaction mechanism has been studied in detail using ruthenium, rhodium and iridium catalysts. For developing a catalytic system for ATH reaction there are three major aspects to be considered: 1) the choice of hydrogen donor, 2) the transition metal source, and 3) the chiral ligand which will enable the process to proceed with good stereo selectivity. Considering these three major aspects the literature on ATH of ketones is presented in the following sections.

1.2.1 Hydrogen Donors Used in ATH

It is found that three versatile hydrogen donating systems have emerged for ATH; many others also work but are less practical:

1) 2-propanol (IPA):[46]- When 2-propanol is used as a reductant; a base such as an alkali metal hydroxide or alkoxide is usually necessary to enable the extraction of hydrogen from the alcohol.[47] The amount of this promoter can vary over a wide range depending on the nature of the catalyst. When IPA is used as the reducing agent, the reaction is reversible in nature and the substrate needs to have an oxidation potential that differs from that of the hydrogen donor.[26] A large excess of the hydrogen donor (IPA) is required to shift the equilibrium to right. For this reason IPA is used in excess and mostly as a solvent for these reactions. The dehydrogenation product of IPA is acetone. IPA is cheap and most of substrates are soluble in it. It can be easily disposed of and readily recycled. The by-product acetone can be readily distilled off from the reaction mixture. Furthermore, in this solvent many catalysts have a long enough lifetimes for high conversions to be obtained, even at reflux. The presence of base can reduce the enantiomeric purity of the alcohol.[42, 48]

2) Formic acid-triethylamine azeotrope (FA-TEA):[49-51] When azeotropic (5:2) mixture of formic acid and triethylamine is used as a hydrogen donor, the reaction is irreversible and kinetically controlled. This gives CO_2 gas as the dehydrogenated product. Hence it is the hydrogen donor of choice for many reactions. However, the inherent acidity of formic acid constitutes a significant drawback to its general use since it may favor a stronger interaction of the hydrogen donor with the catalytic system[41, 43] resulting in complete inhibition or even decomposition of the catalytic species. This renders formic acid incompatible with a large number of the most active hydrogen transfer catalysts and limits its scope as a hydrogen source in the reduction of unsaturated compounds.

3) Formate salts:[34, 52, 53] Recently it was found that the ATH of aromatic ketones is significantly accelerated when the reaction is carried out in neat water with sodium formate as a hydrogen donor. A number of ATH reactions with various catalysts using formate salt in water have been reported[52, 54-56]. The reaction is not reversible. The bi-carbonate salt of corresponding formate is formed as a byproduct.

1.2.2 Catalysts Used in ATH

After the discovery of Noyori's Ru-TsDPEN catalyst complex, a variety of related metal catalysts have been developed and have since been applied to ATH of various ketones. Some lanthanides La[57], Sm[58] in combination with chiral ligands such as naphthol and the amino alcohols have shown high activities and enantioselectivities (over 99 % *ee*) in the reduction of aryl alkyl ketones.[59, 60] Iron based complexes such as Fe-porphyrin are also found to give good catalytic activity in the reduction of ketones.[61] Cu-complexes with chiral bisoxazolines in the presence of Hantzsch esters are able to reduce β-keto esters to α-hydroxyl esters in over 99 % *ee*.[62] Among all the catalysts reported so far, it is found that ruthenium-based catalysts have become the catalysts of choice for the ATH of ketones. Second and third, in popularity behind ruthenium, are rhodium and iridium catalysts, respectively.[63, 64] Although Rh and Ir complexes have been used as catalysts early in the 80s.[65-68] However their performance varies with the choice of chiral ligand. In most cases, the ATH reactions with chiral ligands are performed by reacting the ligands with a metal compound, typically $[RuCl_2(\eta_6\text{-arene})_2]_2$ and $[Cp^*MCl_2]_2$ (M=Rh, Ir). The η^6-arene fragment contributes significantly to the performance of these catalyst through C(sp2)H/πinteraction which stabilizes the transition state. They occupy three out of

six co-ordination sites of Ru in its octahedral environment, leaving two sites for chiral bi-dentate ligand and one site for halide or hydride. The complexes prepared by transition metals as precatalyst and protic ligands (like β-amino alcohol) act as bi-functional scaffolds for anchoring the substrate and transferring the hydride enantioselectively.

1.2.3 Chiral Ligands Used in ATH; an Overview:

A number of ligands of diverse structure have been developed for the synthesis of Ru, Rh and Ir complexes in d^6 and d^8 electronic configurations, which have been used in hydrogen transfer reductions. The ligands differ in the number and type of the donor atom(s) and in symmetry properties. They can be neutral or anionic, depending on whether or not they possess a protonated donor center -XH of appropriate acidity. These ligands contain various combinations of nitrogen, oxygen, phosphorus and sulfur as the donor atoms. They can be bi-dentate, tri-dentate or tetra-dentate. A brief overview of these ligands is presented below.

In 1995 Noyori,[69] published the use of TsDPEN as a ligand for ATH of ketones using 2-propanol as hydrogen donors and Ru as a catalyst. Complete conversion of acetophenone was achieved after nearly 12-24 h and very good ee (95%) was achieved. Noyori also showed the use of Rh and Ir complexes[51] of TsCYDN ligand in ATH of ketones using 2-propanol as a hydrogen donor.

To overcome the long reaction times and irreversibility associated with the use of 2-propanol as discussed, in section the use of FA:TEA azeotrpic mixture was introduced as a hydrogen donor, and it was found that reaction was complete with kinetic control and without having problem of unfavorable thermodynamic balance. Carbon dioxide formed as by-product escapes out of the reaction system. The Conversions were very high (99 %) and enantioselectivities were excellent (98%).[41] However again the reaction time was nearly 24 h.

Noyori introduced β-amino alcohol ligands in combination with Ru-complexes, which provided ligand acceleration effect.[42] It was found that most reactions were found to be complete within very short time of 1h, with very good enantioselectivities. Since then importance of amino alcohols continued to grow, as large number of chiral amino alcohols were synthesized during this period and tested in ATH of Ketones. Especially notable ligands synthesized in include cis-amino indanol by wills[70], azanorboronyl methanol by Anderson[71, 72], Substituted norephedrine (nearly 50

derivatives) by Carpentier.[45, 73, 74] Many chiral pool molecules like, terpenes[75], proline[76-78], and S-Phenethyl amine[79], were explored in the synthesis of chiral amino alcohols for ATH of ketones.

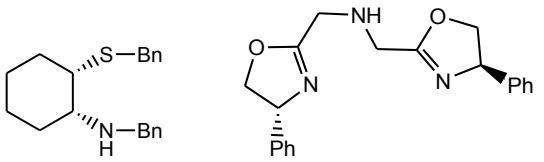
The trend continued till 2004 , when Xiao et al.[54] reported the use of Ru-TsDPEN ligand in water with sodium formate as a hydrogen donor. This was another significant breakthrough in ATH of ketones. This report published, where excellent conversions and very good enantuiosecltvitiy (99% and 94% respectively) was achieved within 1h. Since then the use of sulfonated diamines as ligands really took off. Xiao et al.[80] investigated ATH of ketones with Ru-TsDPEN complex as catalyst and FA:TEA in equal volume of water as hydrogen donor in the pH range of 5-8. They found that the activity was ~ ten fold higher, compared to the reaction in neat FA:TEA.[41] Very soon, in 2005 Xiao et al. showed the use of Rh-TsCYDN[55] in water and sodium formate complete conversions for various ketones were observed within short time of 0.25 h to 1h. In 2008 Rh-TsDPEN and Ir-TsDPENcomplexes[52] were used by Xiao et al. in ATH of various ketones and it was found that in sodium formate and water Rh-TsDPEN complex gave better ee and conversion than corresponding Ru-TsDPEN complex, the two fold increase in activity was observed by Xiao et al.[54] Since then use of sulfonated diamines as ligands in ATH of ketones as well as imines has speeded up. And many modifications in TsDPEN or TsCYDN ligands were attempted, which include structural modification of amino group or replacing the tosyl group by trifluro methyl, methane sulfonyl or naphenesulfonyl group. Along with this preliminary variation in structure of these ligands, the secondary variation like tethering, immobilsation, polymer support is also done for amino alcohols as well as Sulfonated diamines, in order to improve activity as well as longevity. As it can be seen from literature all these modifications are done without disturbing the C_2symmetric backbone of the parent ligand.[81-97] A brief account on these developments is presented in the following sections.

As it was seen from the literature that versatile amino alcohol ligands are prepared and used in ATH of ketones. The preparation of sulfonamide ligands having different electronic and steric properties, (without C2 symmetric backbone) is very scarcely used. The last of this section deals with these unsymmetrical diamines, which have been explored by Wills et al.[98, 99] in 2002 and 2004., and very recently by Ming – Hua,[100] and Roszowski.[77] However, these attempts were not so encouraging as fair to good enentiolselctivyty was observed by using these ligands. Also the use of these

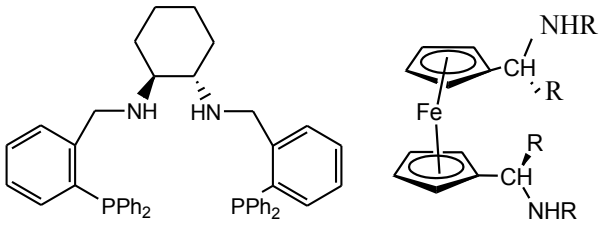
ligands were restricted to Ru complexes, while, Rh and Ir complexes were very less explored. During this period various neutral ligands which include, nitrogen, phosphorous as well as sulfur and nitrogen donor were also prepared and tested for ATH of ketones. A brief account of all these developments with different ligands with special focus on amino alcohol and monosulfonated diamines is presented below.

1.2.3.1 Neutral chiral ligands

A selection of neutral chiral ligands recently reported in the Ru-catalyzed ATH of ketones is shown in **Fig.1.8.** The stereo selectivity of these types of polydentate neutral chiral ligands ranges from good to excellent for ATH of acetophenone, but the catalytic activity varies widely. Ligand L1 showed 80% ee within 1h of reaction.[101] Among these only **[L2]** N, N, N tridentate ligand gives TOF up to 10000 h^{-1}. In contrast to asymmetric hydrogenation, bidentate P-donor ligands give poor activity in transfer hydrogenation of ketones.[102] The chiral tetradentate P_2N_2 ligand **[L3]** which consists of two chelating (one P,P and one N,N) atoms in single ligand also gave *ee* up to 97%[103] (**Fig. 1.8)**.



L1 **L2**

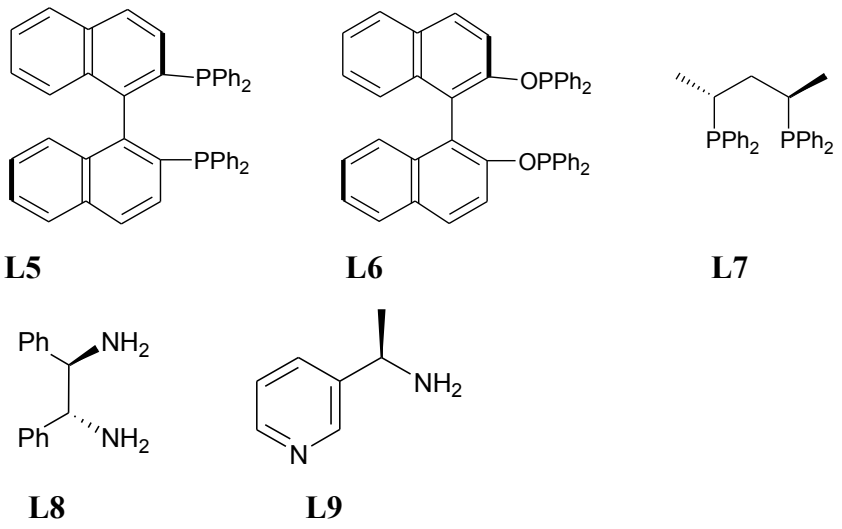


L3 **L4**

8Fig.1.8: Neutral chiral ligands in ATH of ketones

The Ru complex obtained using one chiral C_2-symmetric chelating diamine ligand such as DPEN [L8] and one chiral C_2-symmetric diphosphane ligand such as BINAP [L5], (Fig. 1.9) shows impressive activity and stereo selectivity in the molecular hydrogenation of ketones.[18, 20,9, 11, 13, 104] But it is less efficient in ATH of ketones.[44]

However, recently Morris[45] and Baratta[46] have succeeded in discovering matched pairs of Cooperative P,P and N,N donor ligands, BINOP [L6], Skewphos [L7], DPEN [L8], and amino methyl pyridine [L9] respectively (Fig. 1.9), which provide catalysts of high activity (over 270000 h^{-1}) and enantioselectivity over 85% *ee* in the reduction of acetophenone at 82°C using IPA/KOH as hydrogen donor.[105]



L5 **L6** **L7**

L8 **L9**

9Fig 1.9: Co-operative chiral ligands in ATH of ketones

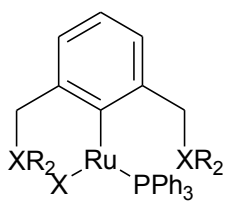
1.2.3.2 Pincer or cyclometalated ligands

The pincer or cyclometalated ligands are polydentate ligands which bind to metal via a carbon-metal bond, stabilized by one or two intramolecular dative heteroatom to metal bonds as shown in **Fig. 1.10 [L10-L12**].[106] The achiral cyclometalated Ru-pincer complex of PCP type gave high catalytic activity, with TOF of 27000-33000 $h^{-1}$for cyclohexanone[107]; but after introduction of chiral P-centers to it as in ligand **[L11]** did not result in high *ee* values.[108] Whereas the chelating chiral diphosphane and aminomethylpyridine ligand such as [L12] internally cyclometalated to a pincer-like coordination with Ru or Os, to give very high stereo selectivity (95% *ee*).[106]

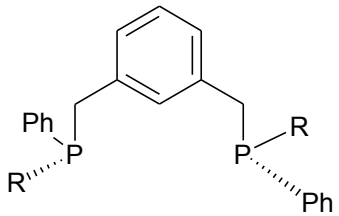
Literature on ATH of acetophenone with Ru-neutral ligand catalyst system is presented in **Table 1.1.**

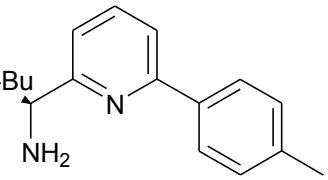
1Table 1.1: ATH of acetophenone using chiral neutral ligands with [Ru(p-cymene)] and 2-propanol as a hydrogen donor

Entry	Ligand used	Temperature, (^{o}C)	Time, (h)	ee, (%)	Ref.
1	L1	RT	1	80	[101]
2	L2	RT	0.08	97	[109]
3	L3	45	7	97	[110]
4	L4	22	1.5	80	[111]
5	L12	82	5	95	[112, 113]
6	L13	28	3	96	[114]



XR2= PPh_2/NMe_2/pCy_2



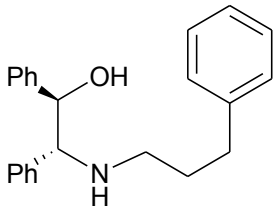


L 10 **L 11** **L 12**

10Fig 1.10: Pincer or Cyclometaled type chiral ligands in ATH of ketones

1.2.3.3 Tethered ligands

As discussed in section 1.2.2, theη^6-arene fragment exerts a marked effect on performance of the catalyst. By connecting the arene fragment to the backbone of the chiral ligand. Wills et al[114, 115] have prepared a new range of ligands which is called as "tethered ligands "as shown in Figure 1.11. It allows a highly organized transition state by locking of the chiral elements by the three coordination sites of the ligand as shown in Fig. 1.11 [**L13**].The lifetime of the catalyst was improved significantly when tethered catalysts are used.[114]

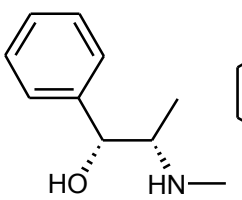


L13

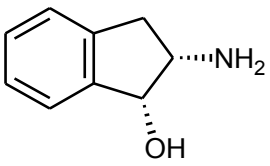
11Fig 1.11: Tethered amino alcohol ligand

1.3 β-amino alcohol ligands

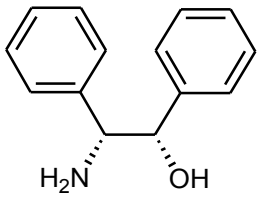
The β-amino alcohols, pioneered by Noyori, which showed ligand acceleration effect compared to tosyl diamines the time when it as introduced. The important amino alcohols are displayed in **Fig. 1.12** Noyori et al.[40, 116] showed that a $RuCl_2(\eta^6\text{-}C_6Me_6)_2]_2$ catalyst along with some simple amino alcohol ligands (in pure enantiomeric form) such as 1,2 phenyl ethanol amine (**L16)**, ephedrine (**L14**) showed high catalytic activity and *ee* (95% conversion and 91% *ee*) in the reduction of acetophenone. This was considered as great ligand acceleration effect over, first reported Ru-TsDPEN ligands[40] which took nearly 15 h for 95% conversion. This speeded up the use of various amino alcohol ligands in ATH of ketones.



L14



L15



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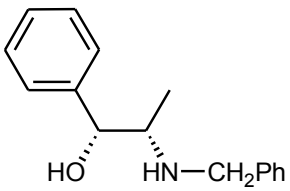
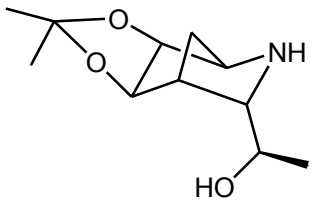
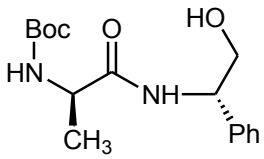


L17



L18



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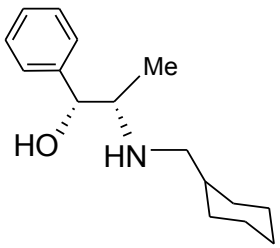
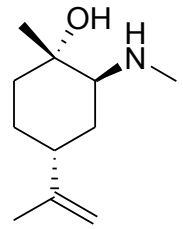
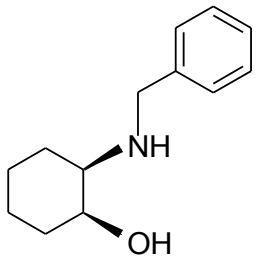


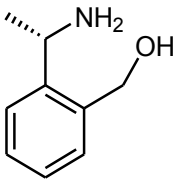
L20



L21



L22



L23

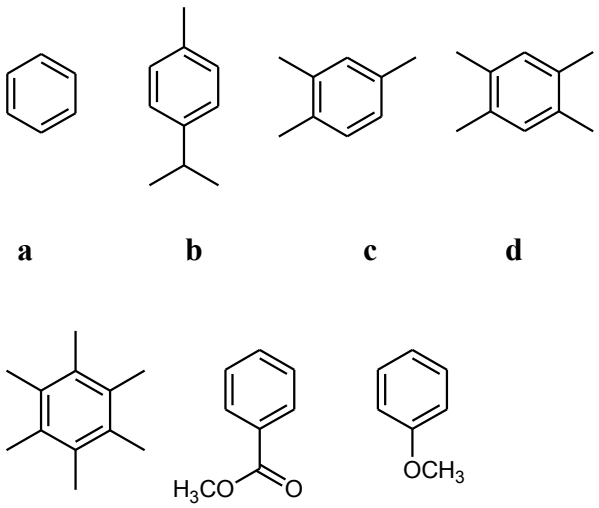
12Fig 1.12: Bench mark amino alcohol ligands

In 1997 Wills et al. [70] used (1R, 2S)-cis -1-aminoindan-2-ol [**L15**] as a ligand in the Ru-catalyzed ATH, which was easily available from one of the metabolite of Merck`s antiviral drug Indianvir. It was found that cis derivative was more active and enantioselective than trans derivative[70] (70% and 23% conversions, respectively).

Andersson et al.[71, 72] have developed 2-azanorboronyl based amino alcohol having rigid backbone attached to nitrogen atom, with primary, secondary and tertiary hydroxyl group. Ligand [**L18**] displayed good to excellent enantioselectivities (85-96% *ee*) in the Ru-catalyzed ATH reaction, of ketones achieving good to excellent enantioselectivities. Easily available prolinol was compared for ATH of ketones which gave poor ee in ATH of ketones. Schoemacker synthesized various N –alkyl derivatives starting from 1R,2S norephedrine using alkylation at amino nitrogen using benzyl bromideand phenbenzyl bromide. Best results (88% conversion of acetophenone with 95% ee) were obtained using (1R, 2S)-N-benzyl-norephedrine as a ligand **L17**). They also synthised ethylene bridged tetradentate ligand from norephedrine. But it was observed that bidentate coordination is desirable even for tetradentate ligand (confirmed by crystal structure) and catalytic activity decreased significantly with tetradentate ligands. For all other alkyl substitution (except methyl)

it was found that activity was slower side (more than 20h for 50% conversion). Ligand **L17** showed excellent enantioselectivity up to 97% at 0^0C.

Carpentier et al.[117-119] made systematic variation in the R2 and R3 position of norephedrine (synthetic methodology is discussed in Section 1.11.1.4.). They also made systematic variation in Ru-Arene complexes and screened various arene groups (Fig. 1.13, **a** to **g**) like Ru-benzene, Ru-*p*-cymene, Ru-hexamethyl, Ru–methyl benzoate as the catalyst precursors, and studied the effect of these complexes in ATH of β-ketoesters using various n-alkylated norephedrine as ligands. Ru benzene and Ru-anisole showed greater activity with **L17**. (187, and 250, TOF, h^{-1}) and increasing the bulk for **c** and **d** in general reduced the activity (<10 TOF, h^{-1}). In general increasing alkyl groups on arene rings; it was found that enenatiselctivity increased. However it was also found that tendency affecting reactivity is not straight forward, both steric and electronic properties of ligand, metal complex and the substrate play important role in getting good activity and enantioselectivity. The substitution in N-alkylated norephedrine, suggested that for substitution at nitrogen with group like -CH_2Ph showed good conversions, (1h, for 100%) but lower than 1S, 1R, ephedrine (0.5 h, 100% conversion), which is N-methylated norephedrine. Schoemacker et al.[120] also observed similar results in their ligand substitution studies.



a **b** **c** **d**

e **f** **g**

13Fig 1.13: Various arene ligands used with Ruthenium

Frost et al.[121] have prepared a series of imino alcohols (based on established amino alcohol backbone of 1.2 phenyl ethanol amine) these imino alcohols were prepared and used in ATH of ketones with Ru-*p* -cymene complexes. It was found that imino alcohols showed good conversion (83%) and ee (96%). The imino alcohols were further reduced to amino alcohols and found that ligand **L20 (Fig. 1.13)** gave best results for transfer hydrogenation of acetophenone (95% conversion and 95% ee) with $[RuCl_2(p\text{-cymene})_2]_2$. Again underlining the importance of secondary nitrogen (-NHR) for achieving high activity and enantioselectivity as mentioned by Noyori[122].

Watts et al.[75] have prepared a series of terpene based amino alcohols and used for transfer hydrogenation of various ketones using $[RuCl_2\ (p\text{-cymene})_2]_2$ as a catalyst. Good to excellent yield with moderate enantioselectivity (up to 71%) was obtained using limonene derived amino alcohol (1S, 2S,4R)-1-methyl-4-(1-methylethenyl)-2-(methylamino)cyclohexane (Fig. 1.13 **L21**). Schaffer's et al.[101] have used 2-aminocyclohexanol derivatives for transfer hydrogenation of acetophenone using $[RuCl_2(p\text{-cymene})_2]_2$ as catalyst. Enantiomers of 2-aminocyclohexanol derivatives were separated by resolution using (R)- and (S)-Mandelic acid. Best results (>90% conversion and up to 96% ee) were obtained using **L 22** Fig. 1.13) as a ligand.

Very recently Zheng et.al used ortholithiation methodology, to synthesize chiral amino alcohols as shown in Fig 1.13 (**L23)**. The major difference observed is that existing amino alcohol ligands are 1, 2 vicinal amino alcohols, while **L23** amino alcohol is having 1,4 backbone.

The ATH of various ketones using $[RuCl_2(p\text{-cymene})_2]_2$ was carried out at -10^oC, for many ketones 99% conversions were observed with good enantioselectivity (67%-92%).[79] it was also found that configuration of the alcohols was opposite to the carbon bearing amino group.

The detailed parametric study by Sun et.al[48] using rhodium cp* and ligand 1R,2S-aminoindanol showed that high substrate to catalyst ratio (S/C 1000, TOF, h^{-1} 2239) , can be employed in ATH of acetophenone. However it was observed that catalyst could be deactivated by high temperature and air atmosphere. Decrease in enantioselevity at higher catalyst and substrate concentration was observed.

The kinetics of the ATH acetophenone to 1-phenyl-ethanol using Ru-catalyst with a (1R,2S)cis-1-amino-2-indanol were determined in a batch reactor with on-line FT-IR spectroscopy.[123] The overall kinetics was found to be in agreement with the proposed mechanism of transfer hydrogenation of ketones by Noyori.[124-126] The equilibrium

constant for the transfer hydrogenation was about 0.19 at 33°C. The enantiomeric excess of the asymmetric conversion was high (92%) and almost no reduction in ee was observed in the course of the reaction.

Besides these representative ligands, there are number of chiral amino alcohol ligands that were reported to be efficient for Transition metal catalyzed ATH of ketones (Ru, Rh, and Ir). Table 1.2 presents the literature on ATH using chiral amino alcohol ligands in detail.

2Table 1.2: Literature survey on ATH using amino alcohol as ligand

A. $RuCl_2(\eta^6C_6Me_6)]_2$ **B.** $[RuCl_2(p\text{-cymene})]_2$ **C.** $[Rh(Cp^*)Cl_2]_2$ **D.** $[Ir(Cp^*)Cl_2]_2$
E. $RuCl_2(benzene)]_2$ **F.** $RhCl_3.H_2O$

Sr no	Cat	Ligand	Substrate	H - donor, base	Reaction conditions			Results		Remarks	Ref
					S: Ru: L: Base	T, °C	Time, h	yield %	*ee* %		
1	**A**	(1S, 2S)2 methyl amino 1,2 di phenyl ethanol	Acetophenone	IPA, KOH	200:1:2:5	28	1	94	92	Activity is decreased with increase in the bulkiness of the arene auxiliary of cat, for threo and erythro series of ligands are studied	42
2	**B**	(1R,2S) cis 1-amino-2indanol	Acetophenone	IPA, KOH	400:1:4:10	RT	1.6	70	91	Cis isomer is more active than Trans isomer	70
3	**C**	(1S,2R) norephedrine	Acetophenone	IPA, KOH	200:1: 4: 4	RT	2	90	84	Patent describing procedure of ATH using Amino alcohol ligands	127
4	**A**	(1S,3R,4R)-2-Azanorbonyl methanol	Acetophenone	IPA, KO^iPr	400 :1 :8 : 10	83	5	92	95	Ru-*p*-cymene gives good ee and conversions	71
5	**E**	(1S,2R) Ephedrine	Acetophenone	IPA, KO^iPr	100 :1 :2 : 6	50	15	85	94	Ru complexes with various arenes are screened and *p*-cymene was found effective.	117
6	**E**	(1R,2S) Ephedrine	β-keto ester	IPA, KO^tBu	400 : 1 :2.2 : 3.3	20	1	86	58	The enantioselectivity of the reaction is studied by molecular modeling using DFT calculations.	128
7	**B**	NH-Benzyl (1*R*,2*S*) norephedrine	Acetophenone	IPA, KO^tBu	400:1:2.2:6	RT	2	91	95	High ee and Conversions are obtained Using specific ratio of Metal and ligand	120

Sr no	Cat	Ligand	Substrate	H - donor, base	Reaction conditions			Results		Remarks	Ref
					S: Ru: L: Base	T, °C	Time,	yield %	*ee* %		
8	**B**	2 -Azanorboronyl derived alcohols	Acetophenone	IPA, KO^{i}Pr	200:1: 4: 5	RT	2	95	95	Structure of the ligand is optimized to get high activity.	72 129
9	**B**	NH-benzyl (1R,2S)norephedrinetethered to silica	Acetophenone	IPA, KO^{t}Bu	166:1:5:12	RT	2	95	88	Constant activity for 1week , in recycle study Patent describing the use of 1(· amino benzyl)-2 naphthol ligand for ATH of aryl alkyl ketone	
10	**B**	1(alpha amino benzyl)-2 naphthol	Acetophenone	IPA, KOH	200:0.5:1:4	RT	2	95	67		
11	**E**	Chiral ferrocenyl amino alcohol	Acetophenone	IPA, KOH	200:1:2 :5	RT	2	94	70	Stereogenic carbon is at α-position with respect to cyclopentadienyl ring	130
12	**B**	Modified -aza norbornyl amino alcohol	Acetophenone	IPA, KOH	100 :1 :4 : 5	RT	2	97	96	Enhanced activity was explained by DFT calculations.	131
13	**B**	(1S,2R) cis amino 2- indanol	Tri fluro methyl acetophenone	IPA, KOH	100 :1 :2 : 5	RT	2	98	91	Inclusion complex with DABCO developed to upgrade *ee* Catalyst is active for 3 successive Recycles. *ee* does not decrease after prolonged exposure of cat in reaction medium.	132
14	**B**	Dendritic ligand of norephedrine	Acetophenone	IPA, KOH	100:1:2.5:5	25	2	70	93		133

Sr no	Cat	Ligand	Substrate	H - donor, base	Reaction conditions			Results		Remarks	Ref
					S: Ru: L: Base	T, °C	Time, h	yield %	*ee* %		
15	**F**	L-norephedrine tethered to a tetramethylcyclopentadienyl gr.	Acetophenone	IPA, KO^{t}Bu	S: C: Base 100:1:5:2.5	RT	4	94	64	Catalyst does not remain stable under reaction conditions. *ee* decreases with time.	115
16	**F**	(1R,2S)-(N-3 cyclohexa-1,4-dienyl-propyl) norephedrine	Acetophenone	IPA, KOH	S: C: Base 200:1:5	28	1	98	54	Ruthenium dimer with tethered complex is prepared.	114
17	**B**	2-azanorbornyl ,2-methanol	Acetophenone	IPA, KOH	500 :1 :2 : 5	RT	1	90	96	The origin of the *ee* was studied by DFT calculations	134
18	**C**	1R,2S amino indanol	Acetophenone	IPA, NaO^{i}Pr	200 :1 :2 : 8	30	1	95	97	Parametric effect done, w.r.t temperature and concentration	48
19	**B**	Ephedrine HCl	Acetophenone	Aq NaF	S: C: formate 40 :1 : 5	RT	2	99	75	First example of ATH in water with ephedrine hydrochloride salt as ligand.	135
20	**B**	Dipeptide ligands derived from amino acid	Acetophenone	IPA, NaOH	100 :0.5 :3 : 1	RT	2	81	80	Smaller R group on amino acid part of ligand gave better conversion.	75
21	**B**	Amino alcohols derived from di-ethyl tartrate	Acetophenone	IPA, KOH	20:1:2:5	RT	12	96	72	N-benzyl substituents give highest 90% *ee*. With $[Ir(COD)Cl]_2$ 72% conv. with only 30% *ee* obtained.	136
22	**B**	Amino alcohols derived from terpenes	Acetophenone	IPA, KO^{t}Bu	100:2:0.5:5	25	72	99	63	The highest *ee* is reported for terpenes based amino alcohol containing a tertiary alcohol moiety.	75

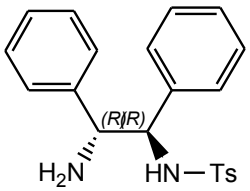
Sr no	Cat	Ligand	Substrate	H - donor, base	Reaction conditions					Remarks	Ref
					S: Ru: L: Base	T, °C	Time, h	yield %	*ee* %		
24	**B**	1S,2R cis amino 2-indanol	PhCOMe	IPA, KO^tBu	400:1:4:10	33	1.5	99	92	Reaction conditions are optimized The kinetics of reaction reported.	123
25	**B**	1R,2S Ephedrine	PhCOMe	Aq NaF	S/C=100 2ml water	40	12	99	73	FA-TEA mixture 1:1 in water gave 45% *ee* with 58% conv in 40h.	137
26	**E**	Amino alcohols from isosorbide	PhCOMe	IPA, KO^tBu	100:1:1.5:1.5	70	21	96	60	Ligands are designed and synthesized from isosorbide, a by-product from the starch industry.	138
27	**B**	Amino alcohol from enantiopure phenyl glycinol	PhCOMe ketones	IPA, KOH	50:1:2:4	25	4	99	82	Bulky substituents on ligand accelerate reductions in IPA, an opposite effect observed in water as bulky group prevent proper access of the substrate to the catalytic species at substrate /water interphase.	139
				or aq. NaF	S/C=50 2ml water	25	24	72	60		
28	**B**	Ephedrine	PhCOMe		40:1:1.2:2	25	4	79	71	Secondary amine was used as additive to increase conversion.	140
29	**E**	Amino alcohol from isosorbide	PhCOMe ketones	IPA, KO^tBu	100:1:2:2	70	21	94	71	Two series of epimer Amino alcohols are easily prepared from isosorbide and isomannide.	138
30	**E**	Amino alcohol from isosorbide	PhCOMe	IPA, KO^tBu	40:1:2:2	25	2	99	70	In ligand synthesis original wedge-shaped structure is retained as it is.	76

The information available on ATH using β-amino alcohol ligands is summarized as follows:

- In general, β-amino alcohols and transition metal complexes produce catalysts with higher activity than tosyl diamine derivatives when 2-propanol is used as a hydrogen donor[40, 42],
- The extent of asymmetric induction is determined primarily by the configuration of hydroxyl carbon bearing hydroxyl group,
- The mono-substitution at nitrogen exerts a positive effect on stereo selectivity. However, there are known exceptions in literature (cis Amino Indanol[70] and others[79]).
- Increase in bulk (ethyl, propyl and t-butyl) substituents attached to nitrogen reduce activity and ee, although -CH_2Ph substitution is exception which showed higher ee.[73]
- Both syn and anti-configured ligands give high enantioselectivity, however, syn isomers show higher activity.[42, 70]
- Both arene ligand coordinated to metal and amino alcohol ligand influence the enantioselectivity but the tendency is not straightforward. High *ee* is obtained only when appropriate arene and chiral amino alcohol auxiliary are combined.[73]
- It is also found that amino alcohols are weakly coordinating ligands and hence the ligand to metal ratio has proved to be critical.
- There are very few reports on use of Rh complexes in ATH of ketones using amino alcohol ligands.

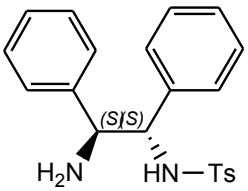
1.4 Monotosylated diamine ligands

The most popular anionic ligands for ATH of ketones and imines are monotosylated diamines (**L24** to **L28)** as shown in Fig 1.14 and reported by Noyori and coworkers in a series of papers initiated in 1995.[14, 40-42, 141] Significant work has been carried out on the ATH of ketones using monotosylated diamine ligands with Rh, Ru and Ir complexes as catalysts with various hydrogen donors like 2-propanol, FA:TEA azeotrope, formate salts in water. Major advantage of ATH using these ligands is that the reaction is not equilibrium controlled and the system is tolerant to wide variety of substituents. From the literature it was observed that most of the work has been carried out using TsDPEN and TsCYDN ligands. Also, during last 2 decades ATH reaction has undergone significant changes based on the type of hydrogen donor used and new knowledge gained over the years. In the recent past ATH in water has taken center stage and now new reports on the synthesis of new monotosylated diamine ligands are appearing in the literature. This prompted us to discuss the literature reports in different sections based on the metal complex as well as hydrogen donor used. Although the literature discussion for ATH of imine is done in the last section, there are some inherent and common references which will appear in this section also.



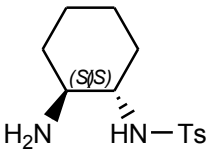
R, R, TsDPEN

L24



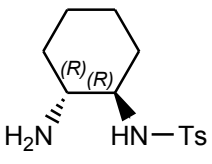
S, S, TsDPEN

L25



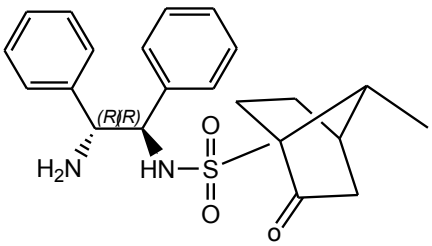
S, S TsCYDN

L26



R, R TsCYDN

L27



R, R CsCYDN

L28

14Fig. 1.14: C2 symmetrical monosulfonated diamine ligands

1.4.1 ATH using different hydrogen donors

1.4.1.1 ATH of ketones with monosulfonated diamines in 2-Propanol

The introduction of TsDPEN ligand with Ruthenium complex by Noyori, in ATH of ketones by using 2-Propanol was successful and gave 95% conversion of acetophenone with 97% ee in 15h reaction time.[40] This was the first report on the ATH of ketones using transition metal complexes and diamine ligands. With Cyclic ketones like Indanone and Tetralone, the ATH using this procedure was sluggish (<50% conversions) although enantioselectivity was excellent for both (>93%). In 1998, Tani et al.[142] showed that extended reaction period of 48 h using Rh-TSDPEN complexes gave fairly good conversion of acetophenone (85%, 97% ee).[51] Cyclic ketones showed less conversion (50%). Ir complexes showed only 36 % conversion and 96% ee.

In 1999, Murata et al.[51] prepared Rh-TsCYDN and Rh-TsDPEN complexes and Rh-TsCYDN showed good conversions (85% and enantioselectivity 97%), but Rh-TsDPEN complex showed only 14% conversion with 2-propanol in 12h. However ATH of α- halo ketones with Rh-TsDPEN complex using 2-propanol, showed very good conversion and enanatioseclctivity[143] (14h, 94% conv , 98% ee). Thus ATH of ketones in 2-propanol using sulfonated diamines showed that the metal ligand combination along with substrate was important for high activity for ATH of ketones in 2-propanol. Some draw backs such as long reaction time and very low conversion for many ketones. The unfavorable thermodynamic equilibrium associated with 2-propanol, was also affecting conversion and enantioselectivity. The detailed literature on ATH of ketones using monotosylated diamine ligands and 2-propanol as hydrogen donor is presented in Table 1.3.

3Table 1.3: Literature survey on ATH of ketones with 2-propanol as hydrogen donor and 1,2 monosulfonated diamine ligands

A. $RuCl_2(\eta^6C_6Me_6)]_2$ **B.** $[RuCl_2(p\text{-cymene})]_2$ **C.** $[Rh(Cp^*)Cl_2]_2$ **D.** $[Ir(Cp^*)Cl_2]_2$
E. $RuCl_2$(benzene)]

Entry	Complex	Ligand	S/C ratio	Time, h.	Conv, %	%ee	Remarks	Ref.
1	B	TsDPEN	200	15	95%	97	1st example of ATH by monosulfonated diamine as ligands , Cyclic ketones like Indanone and Tetralone showed low conversions	40
2	C	TsDPEN	200	48	85	87	The first use of Catalyst C in ATH of ketones with prolonged time, Crystal structure of the catalyst established	142
3	C	TsDPEN	200	12	14	87	Shorter time for complex C with TsDPEN, shows lower activity	51
4	D	TsDPEN	200	12	36	96	Lower activity with Iridium complexes	51
5	C	TsCYDN	200	12	85	87	Complex C showing better activity with TsCYDN , than with TsDPEN , showing Importance of proper metal –ligand combination	51
6	D	TsCYDN	200	12	36	96	Lower activity with Rhodium complexes	51
7	B	TsCYDN	100	12	99	81	Lower activity with Iridium complexes	52

Entry	Complex	Ligand	S/C ratio	Time, h.	Conv, %	%ee	Remarks	Ref.
8	B	TsDPEN	100	14	94	98	ATH of alpha chloro acetophenone	143

1.4.1.2 ATH of ketones with monosulfonated diamines in FA: TEA azeotrope

As discussed in earlier section, the use of 2-propanol as hydrogen source, presented quite a few problems in ATH of ketones such as long reaction times, low activity for various substrates and unfavorable thermodynamic equilibrium causing incomplete conversions and erosion in the ee.[42, 118-120]

The use of FA:TEA azeotropic mixture provided solution to many of these problems. In 1996, use of Ru- TsDPEN complexes by Noyori, with FA:TEA as hydrogen source provided the complete conversion of acetophenone and excellent enantioselectivity (99% and 98% respectively).[41] The reaction proceeded with complete kinetic control and without having any thermodynamic imbalance, as the by-product of FA: TEA being carbon dioxide, driven out of the reaction system thus pushing the equilibrium forward. A variety of ketones were reduced with excellent conversions and enantiosectivity. These included cyclic ketones like Indanone and Tetralone[41] and substrates like methoxy acetophenone. Complete conversions (>99%) and nearly 98% enantiomeric excess was obtained. FA:TEA as a hydrogen donor with many other ligands and metal complex systems (Rh-TsDPEN, Ir-TsDPEN, and Ru-TsCYDN) showed incompatibility and poor conversions[144,145] in case of simple ketones (<10%). However ATH of alpha substituted ketones with Rh-TsDPEN complex using FA:TEA showed moderate conversions and enantioselectivity[146] (59% conv and 94% ee for alpha hydroxyl acetophenone). These results were better than analogues Ru-TsDPEN catalyst under the same reaction conditions (45% conv and 89% ee). Ikariya in 2002,[143] studied the ATH of α−chloro acetophenone using Ru, Rh, Ir complexes. The ATH of α−chloro acetophenone using FA:TEA as hydrogen donor showed excellent conversion in neat FA:TEA (1h, 99% conv, 92% ee) at high S/C ratio of 1000. Ir-TsDPEN showed slightly slower activity (99% in 4h), with much lower ee (71%). The Ru-TsDPEN showed surprisingly lower conversion (36% after 24 h). Though; exact reason for this contrasting behavior for Ru-TsDPEN and Rh-TsDPEN is still not known.

Very recently in 2013 Xiao varied the ratio of FA:TEA from 2.5:1 to 0.2:1.[147] With this change in FA:TEA ratio (or initial pH); depending on the composition, it was observed that it has accelerating effect on ATH of ketones. ATH of acetophenone was completed with 99% conversion within 5 h, with very good enenatiselctivity. For Ru-TsDPEN complex the reaction time in neat FA:TEA azeotrope was around 24 h, at

28^0C and 12 hrs at 40^0C). Rh-TsDPEN complex under similar conditions showed 99% conversion of acetophenone in nearly 80 hours. It was also found in the literature that eanatiselctivity varied in both the cases. Thus Ru-TsDPEN showed very good enenatiselctivity (96%), while Rh-TsDPEN showed 86%ee (in FA:TEA, 0.2:1).[147] Thus the use of FA:TEA was choice as hydrogen donor in ATH of ketones, mainly with ruthenium complexes. This result however did not lead to further advancement in the development of new sulfonamide ligands in ATH of ketones, till the use of these complexes in water and sodium formate was reported by Xiao et al.[54] Table 1.4 presents the literature on the ATH of ketones with monotosylated diamines as ligands and FA:TEA azeotrope as a hydrogen donor.

4Table 1.4: ATH of ketones using FA:TEA azeotrope as hydrogen donor and 1, 2 sulfonated diamine ligands

A. $RuCl_2(\eta^6C_6Me_6)]_2$ **B.** $[RuCl_2(p\text{-cymene})]_2$ **C.** $[Rh(Cp^*)Cl_2]_2$ **D.** $[Ir(Cp^*)Cl_2]_2$
E.$RuCl_2(benzene)]_2$

Entry	Complex	Ligand	Temp. ^0C	S/C ratio	Time, h.	Conv, %	%ee	Remarks	Ref.
1	B	TsDPEN	28	200	24	99	98	First use of FA:TEA by monosulfonated Diamines , reaction proceeds with complete kinetic control and does not any reversibility	41
2	B	TsDPEN	28	200	22	98	98	Comparison with (1R, 2S)TsDPEN, Importance of anti-substitution of amine and sulfonamide groups	99
3	B	TsDPEN	40	100	12	98	97	Use of FA:TEA at higher temperature	52
4	C	TsDPEN	28	200	12	59	94	ATH of alpha hydroxyl acetophenone	146
5	C	TsDPEN	28	200	12	45	89	ATH of alpha hydroxyl acetophenone, showing different behavior For Ru and Rh	146
6	C	TsDPEN	28	1000	1	99	89	In neat FA:TEA ,lower ee, was observed for alpha halo ketones	143
7	D	TsDPEN	28	1000	4	99	71	In neat FA:TEA ,lower ee, was observed for alpha halo ketones	143
8	C	TsDPEN	40	100	16	<1	N/A	Use of , Rh –TsDPEN and azeotrope for ATH of simple ketones ,	52

1.4.1.3 ATH in water using sodium formate as a hydrogen donor

Reactions carried out in water are desirable as water is safe, non-toxic and the system is considered as "green chemistry compatible". In fact; enzyme-catalyzed reactions in nature proceed exclusively in aqueous media. Generally, such reactions may either form homogeneous (i.e.,both catalyst and substrate are soluble in water) or heterogeneous (one of the components being insoluble in water) systems. The substrate and/or the catalyst often have low water solubility and, in contrast, the hydrogen donor can be hydrophilic.

In 2004, Xiao et al. reported excellent results for the ATH of aromatic ketones with Ru-TsDPEN catalyst[54] using sodium formate as the hydrogen source and water as the solvent. In this work Xiao et al. showed that the reaction proceeded much faster in $HCOONa/H_2O$ (complete conversion of acetophenone in 2 h with 94% ee) than inthe FA:TEA azeotrope (complete conversion of acetophenone in 12 h, 98% ee).[41] The explanation for higher activity in water was based on the assumption Ru-TsDPEN was more soluble in the substrate (organic phase) than in water. Various ketones were reduced with excellent conversions and enantioselectivity, (>90% conversion and >90% ee). The ATH was carried out even at higher S/C ratio with very good conversions and ee (>90% and 90% ee).

Soon in 2005, Canivet[144] prepared aqua complexes of various diamine sulfonamide derivatives and used in ATH of ketones. It was found that at 60^0C, these complexes showed very good activity and moderate enantioselectivity (91% conv and 83% ee). It was also found that with increase in temperature by 10^oC sudden decrease in activity is observed.

In 2005, Wu and Xiao[55] showed that Rh-TsCYDN, displayed remarkably enhanced activities and excellent enantioselectivities in the reduction of a wide range of ketones in water. For example, ATH of acetophenone by HCOONa in water afforded almost complete conversions in 15 minutes, with ee of 94%. A quite broad range of ketones was effectively reduced with the Rh-TsCYDN[55]catalysts by HCOONa in water, apart from the simple aromatic ketones which have been successfully reduced with the Ru-TsDPEN catalysts, heterocyclic,functionalized and multi-substituted ketones were all viable substrates with Rh-TsCYDN catalyst system.

Thus ATH is easy to carry out providing the chiral alcohols with excellent ee in a short reaction time for most of the substrates. For example, most of the reactions with Rh-TsCYDN catalyst with HCOONa in water finished within several minutes. Thus, 2-acetyl furan was completely reduced to (R)-1-(2-furyl)ethanol within 5 minutes.[55] Furthermore, it was found that the ATH of ketones can be effectively carried out in the open air with the Rh-TsCYDN catalyst. As presented in earlier sections it is interesting to note that very little reduction was observed with Rh-TsDPEN catalyst in FA-TEA azeotrope as hydrogen donor. The ATH afforded only 45% conversion with 89% ee in 24 h in 2-propanol.[51, 52]

Immediately in 2006, Xiao et al. prepared the camphor sulfonyl analogue of 1,2 diamino cyclohexane(CsCYDN). [148] Iridium complex of these ligand showed very good enantioselectivity compared to their Ru and Rh analogues (>97% conv and 97% ee).[148] Again the ATH of acetophenone was faster with aqueous HCOONa as hydrogen donor. Ir-CsCYDN complexes outperformed Ru-CsCYDN and Rh-CsCYDN, in terms of enantioselectivity. In particular, acetophenone was reduced with 97% conversion and 98% ee in 2.5 h at S:C ratio of 1000.[148] The Ir-CsCYDN catalyst was also found to effective and several ketones were reduced in several hours in water at an S:C ratio of 1000, affording excellent enantioselectivities. The electronic properties and steric effects of the substituents on the ketone impacted the activity as well as enantioselectivity significantly. Thus, faster reduction was observed for ketones with electron withdrawing groups such as Cl, Br, F, CN or NO_2; in contrast, electron donating groups such as methyl or Methoxy necessitated longer reaction times.

In 2008, Xiao et al.[52] used Rh-TsDPEN and Ir- TsDPEN complexes in ATH of ketones. The ATH of acetophenone was completed within 30 minutes (99% conv and 97% ee). Ir analogue showed slightly lower activity and ee (99 % conv and 91 % ee

in 3 h). Xiao et al. showed that with sodium formate and water Rh-TsDPEN complexes were highly active compared to Ru-TSDPEN analogues (99 % conv in 30 min for Rh compared to 99 % conv in 2 h for Ru).[54] Various ketones were hydrogenated with high conversion and ee with Rh-TsDPEN catalyst and it was observed that ketones with electron donating groups or substituents in 'ortho' position generally gave lower conversion. At higher substrate to catalyst concentration, the conversions were variable for ketones like 4-methoxy acetophenone. (17 % conversion at S/C ratio of 1000).

5Table 1.6: ATH of acetophenone using sulfonated diamine ligands and sodium formate as hydrogen donor in water

A. $RuCl_2(\eta^6C_6Me_6)]_2$ B. $[RuCl_2(p\text{-cymene})]_2$ C. $[Rh(Cp^*)Cl_2]_2$

D. $[Ir(Cp^*)Cl_2]$, Hydrogen donor Sodium formate , S/C ratio 100, Temperature 40^0C

Entry	Catalyst	Ligand	S:C	Time. h	Conversion, %	ee,%	Remarks	Ref.
1	B	TsDPEN	100	2	>99	94	Use of water and sodium formate , showed accelerating effect on ATH of ketones using Ru Complexes	54
2	B	TsCYDN	100	2	99	85	Other C2Symmetric ligand (TsCYDN) showing lower enentioslectity	55, 145
3	B	CsCYDN	100	2.5	>99	81	TsCYDN , modified ligand with Camphor sulfonyl derivative	148
4	C	TsDPEN	100	0.5	99	97	Rhodium complexes of TsDPEN showed better activity than Ru-complexes	145
5	C	TsCYDN	100	0.25	>99	95	Rh-TsCYDN , ATH of ketones carried out in open air, highly active catalyst , higher S/C 1000 ratios	55
6	C	CsCYDN	100	0.7	99	99	replacing p-toluene sulfonyl group of TsCYDN, by Camphor sulfonyl group , require more time for ATH of ketone	148

7	D	TsDPEN	100	3	99	93	Iridium analogues showed lower acivity than Rhodium analogues	145
8	D	TsCYDN	100	1	99	92	Different results , than reported by caviet et al.	145
9	D	CsCYDN	100	0.7	98	97	Iridium analogues , highest enantiosectivity for ATH of ketones	148
10	A	TsCYDN	100	2	86	93	Ru-TsCYDN complexes at Higher Temperature 60^0c, sharp decline in conversion , with 100c increase in Temperature	144

All the investigations on successful ATH of ketones in water with sodium formate or FA:TEA hydrogen donors were carried out using TsDPEN and TsCYDN ligands with Ru, Rh and Ir catalyst systems. However because of the success of TsDPEN ligand most of the developments are related with modifying the various substituents on the phenyl ring or varying the sulfonyl groups. These modifications of TsDPEN and TsCYDN ligands have been carried out, for making the ligand water soluble or to make complex water insoluble, or by anchoring to polymer support. Unlike amino alcohols there very few structural modifications done on the sulfonated diamine ligands. In the next section brief account of these developments has been presented.

1.4.1.4 ATH of ketones using FA:TEA in water: Effect of solution pH

Though; excellent results were observed with HCOONa-water system, the reason for low activity of Rh-TsDPEN in FA:TEA system was not understood.

Xiao et al. found out that ATH of ketones can be considerably accelerated by using water[81, 149-155] as a solvent and HCOONa as a hydrogen donor with Ru–(R,R)-PTs-DPEN, (polymer supported TsDPEN) as the catalyst and the catalyst was recycled more than 10 times without loss in enantioselectivity. The hydrogen donor used in this study was HCOONa. However, the reaction was found to be much slower with FA:TEA azeotrope as a hydrogen donor in water. This observation led to importance of pH of the solution (pH of azeotrpic FA:TEA is acidic and that of sodium formate is ~7)

The success of ATH in water by Ru-TsDPEN complexes prompted the need for detailed understanding of ATH in aqueous and organic medium. Xiao et al. carried out the systematic variation in FA:TEA ratio in equal volume of water and obtained similar results to that obtained with sodium formate in water[54], with slightly better enanatioseclctivity (97% vs 94%) with Ru-TsDPEN catalyst. The detailed investigation by Xiao et al.[80] showed that a longer induction was observed in neat FA:TEA mixture till pH 3.9. Above this pH (lower FA:TEA ratios), the rate of reaction increased considerably. The difference in the rates of two reactions was attributed to the initial pH of the reaction mixture. Significant finding of ATH of ketones in aqueous FA:TEA mixture is that the reaction rates vary with initial pH of the solution. Thus it was found that with an increase in pH of the solution from ~ 3.9 to ~4.9, the rate of reaction increased almost 20 times.[80] At lower pH (acidic pH) activity was very low and little reduction occurred, but the pH increased with time

due to decomposition of FA into carbon dioxide (CO_2) and H_2 by the catalyst.[41, 50, 80] Importantly it was observed that the enantioselectivity also varied significantly with a change in pH. Optimal pH values for Ru-TsDPEN catalyst were found to be between pH 5 and 8, which was effectively maintained by a equivolume aqueous solution of FA:TEA in a ratio of 1.2:1. Remarkably, this optimization of the reaction conditions allowed the use of S/C ratios as high as 10,000 with excellent conversions and enantioselectivity (98% conversion, 96 % ee, respectively).[80]

Watanabe and co-workers observed the effect of pH in achiral transfer hydrogenation of carbonyl compounds using Ir Cp*, Ir Cp*methyl pyridine and Ir Cp*bipyidyl complexes.[156-158] Observed variation in activity was attributed to the electron donating ability of these complexes and the dependency on pH and metal complex used. It was observed that increasing basicity of the ligand used, higher was the optimum pH in transfer hydrogenation.

pH will the In 2005, Canivet studied[144] the ATH of ketones with Ru-TsCYDN complexes with different arene system at various pH values. He showed that for Ru-TsCYDN catalyst the optimum pH was 9, acetophenone conversion of 90 % with slightly lower ee (83%) was obtained using Ru(hexamethylbenzene)-TsCYDN catalyst at 60^{o}C. Enantioselectivity was not affected by a change in reaction mixture pH for this catalyst system.

In 2008, Xiao et al.[52] investigated Rh-TsDPEN catalyst with systematic variation of pH with FA:TEA in water (equal volume) system. Results showed dramatic variation in catalytic activity and best results were obtained at nearly neutral pH for Rh-TsDPEN catalyst, and the activity of Rh-TsDPEN catalyst was higher than Ru-TsDPEN catalyst.[54] It was found that optimum window of pH for Ru-TsDPEN complex was 5-8, whereas that for Rh-TsDPEN complex was between 6.5 to 8.5. The overall activity for iridium complex was lower (98% conversion, 3h) and the pH range for optimum activity was 6-8. The ATH carried out with Ir-TsDPEN catalyst in basic pH range showed slower conversions without loss of enantioselectivity (98% in 4h). Thus FA:TEA-water (equal volume), was found to be excellent hydrogen donor system and was applicable to all the transition metal catalysts (Ru, Rh, Ir).

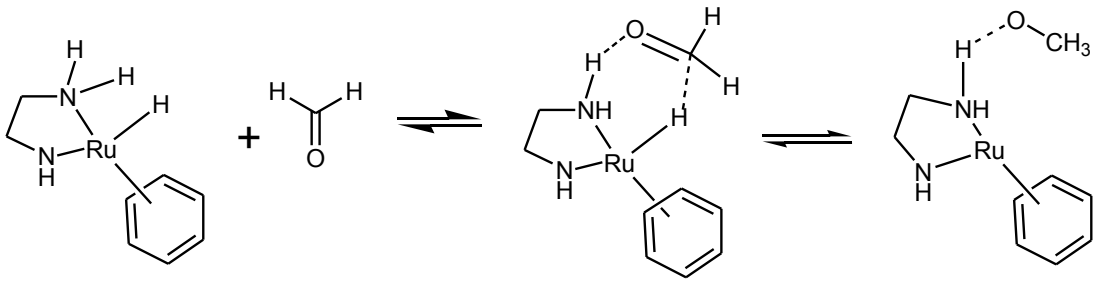
6Table 1.4: ATH of ketones using FA:TEA in water as hydrogen donor and 1,2 sulfonated diamine ligands

A. $[RuCl_2(p\text{-cymene})]_2$ **B.** $[Rh(Cp^*)Cl_2]_2$ **C.** $[Ir(Cp^*)Cl_2]_2$

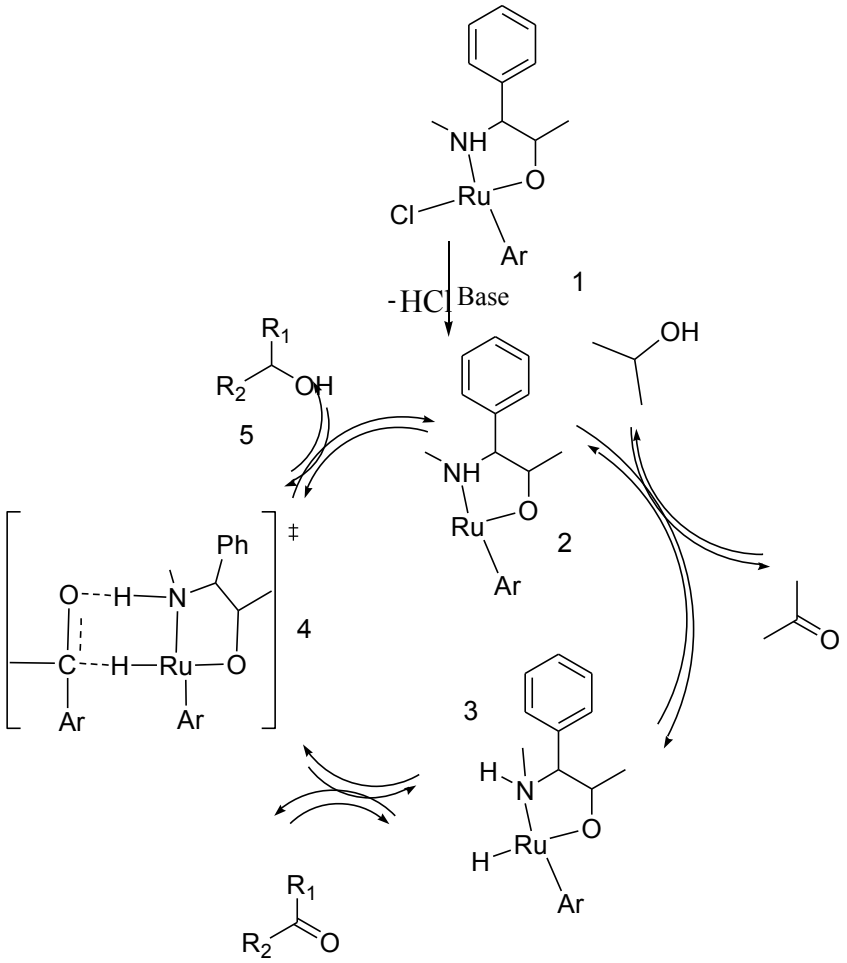
Entry	Complex	Ligand	S/C ratio	Time, h.	Conv, %	%ee	Remarks	Ref.
1	A	TsDPEN	100	1.5	>99	97	pH controlled ATH using various ratios of FA:TEA and equivolume water	52, 80
2	A	TsDPEN	1,000	9	>99	96	pH controlled ATH using various ratios of FA:TEA and equivolume water, high s/c ratio	80
3	A	TsDPEN	5,000	57	98	96	pH controlled ATH using various ratios of FA:TEA and equivolume water high s/c ratio	80
4	A	TsDPEN	10,000	110	98	94	pH controlled ATH using various ratios of FA:TEA and equivolume water high s/c ratio	80
5	B	TsDPEN	100	16	<1	N/A	Rhodium complex inactivity with FA:TEA and equivolume water	52
6	B	TsDPEN	100	24	18	64	Use of , Rh –TsDPEN azeotrope, and equivolume water for ATH of simple ketones ,	52
7	C	TsDPEN	100	24	39	87	Use of , Ir-TsDPEN azeotrope, and equivolume water for ATH of simple ketones	52

1.5 Mechanism of ATH of ketones

In 2000 Noyori et al.[125] Published a seminal work where the fundamental features of the ATH of ketones coined as metal-ligand (M-L) bifunctional catalysis, were proposed. The initial calculations upon this reversible system were performed using formaldehyde as a substrate, and simplified structures of the catalytic complexes,[125] (*i.e.*, RuH(η^6-benzene)(ethylenediamine) or RuH(η6-benzene)(ethanolamine), were used (Fig. 1.15). According to these findings, the substrate does not coordinate directly to the Ru center, but forms a 'C=O**…**H-N' hydrogen-bonded intermediate **C2** with the $[RuCl_2(p\text{-cymene})_2]_2$ complex, which evolves into a six-membered cyclic transition state (TS) **C2**. The hydrogen bond is supported by a so-called "NH effect": the N-H bond in the chelating ligand is markedly more polar when in a complex with $[RuCl_2(p\text{-cymene})_2]_2$. Thus, the six-membered TS results in a transfer of the proton from the NH group to the carbonyl oxygen, and a hydride transfer from Ru to the C=O carbon atom.



15Fig. 1.15: Metal ligand bifunctional theory for transfer hydrogenation of carbonyl compounds[126]

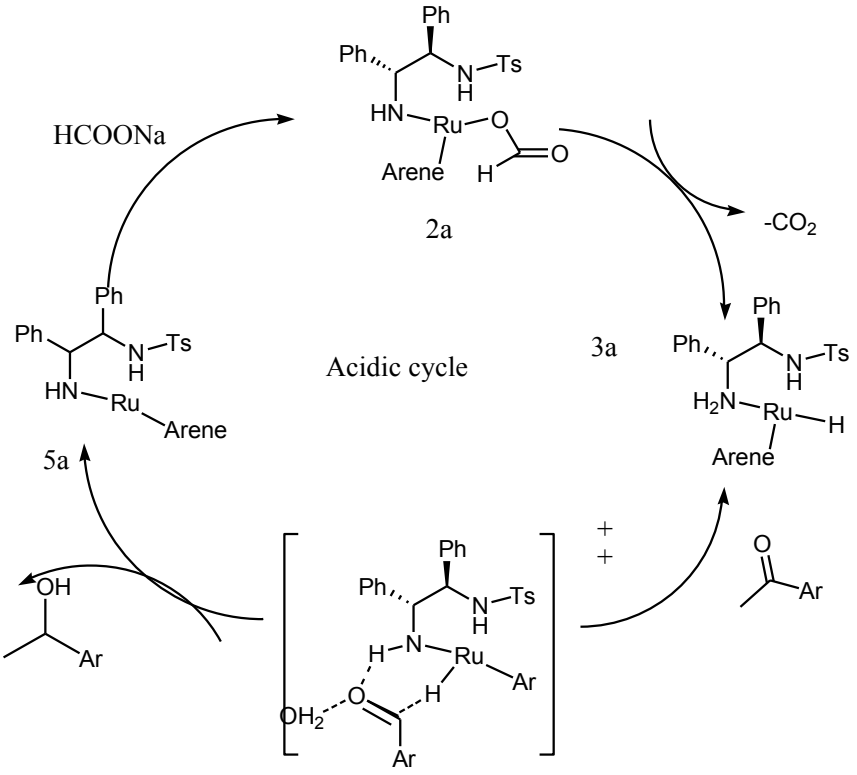


16Figure 1.16: Mechanism of ATH of ketones Carpentier et al. [73, 120, 125, 159]

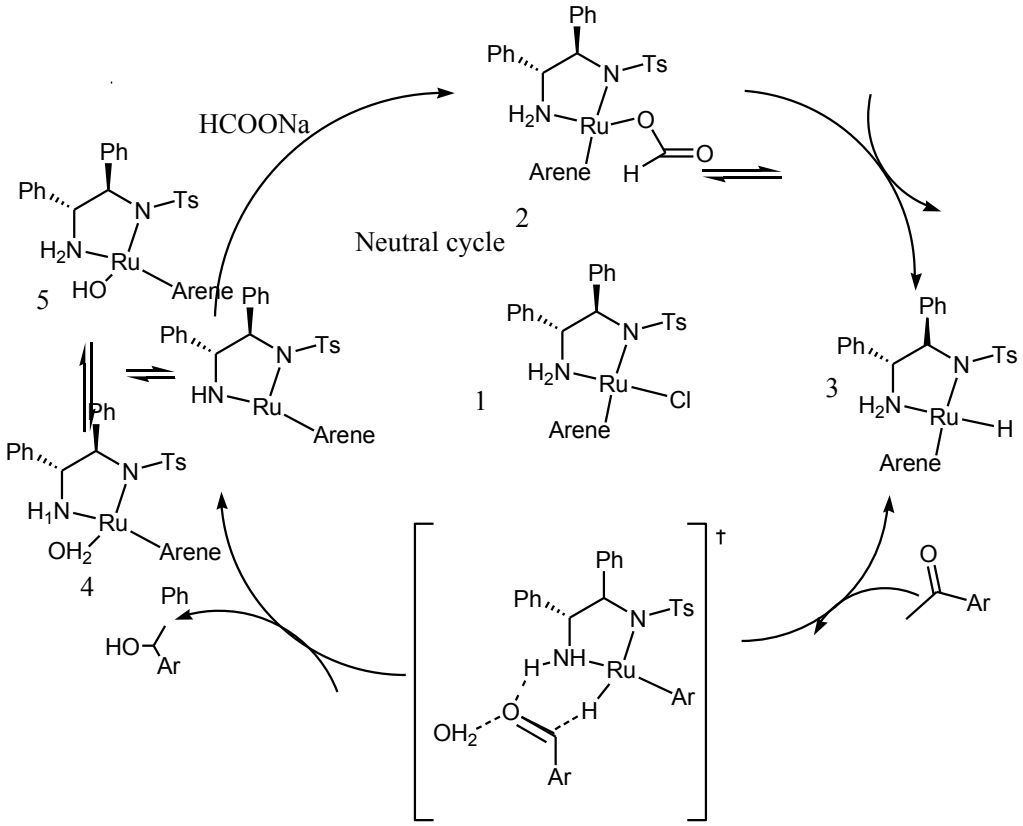
The similar mechanism for ATH by amino alcohols was proposed by many other researchers.[73, 120, 125, 159] (Fig. 1.16) This novel mechanism was also compared with the mechanism of the aqueous ATH which has recently been investigated.[54, 56, 145, 160] by Xiao and co-workers. The mechanism of ATH of acetophenone with sodium formate and Ru-TsDPEN catalyst was studied using nuclear magnetic resonance (NMR) spectroscopy, kinetic and isotope measurements,[56] and density functional theory (DFT) calculations. This showed that two catalytic cycles are likely to operate in the ATH reaction, depending on the solution pH. This is shown in Fig 1.17 and 1.18. Neutral cycle (Fig.1.18) describes ATH under neutral conditions and is more efficient, affording fast rates and high enantioselectivity *via* a water-assisted transition state. Under acidic conditions, Cycle 2 dominates, in which protonation occurs at nitrogen attached to sulfonamide group, (Fig 1.17, acidic cycle, **3a** and **5a**) leading to lower catalytic activity and lower ees. However, higher pH drives the catalyst into an inactive hydroxyl form shown in, neutral cycle (species 4 and 5) thus decreasing the

concentration of active catalyst and hence the reduction in rates, without affecting the ee values. Further details on Cycle 1 under neutral conditions have also been revealed. The Ru-H species is visible in the NMR spectrum; however, the Ru-formato complex could not be detected under either stoichiometric or catalytic reactions.[161] In kinetic studies, it was found that the ATH is first order in both the catalyst and ketone concentrations but is inhibited by CO_2. This evidence points to the rate-limiting step of the ATH reaction being the hydrogen transfer from Ru to ketone. The transition state is similar to that proposed by Noyori and others for non-aqueous systems.[119, 124-126]

Water has been demonstrated to accelerate the ATH[54, 160] and this acceleration can be at least partly traced to its effect on the rate-limiting step mentioned above. Thus, in the stoichiometric reduction of acetophenone by isolated Ru (II)-H, the rate inwet deutarated dichloromethane (CD_2Cl_2) was six times of that in dry CD_2Cl_2. Further insight was gained from DFT calculations[56, 162] which showed that water participates in the transition state of hydrogen transfer, stabilizing it by ~4 kcal mol^{-1} (~17 kJ mol^{-1}) through hydrogen bonding with the oxygen in ketone.[56]



17Figure 1.17: Mechanism of ATH under acidic, medium



18Figure 1.18: Mechanism of ATH under, neutral and basic medium [61, 89]

The lifetime of the Ru catalyst in ATH reactions is remarkably prolonged in the presence of water. Thus, in the presence of water, the Ru-TsDPEN catalyst was stable for up to a few months; in contrast, the catalyst lifetime was significantly shortened when water was removed from the solution.

For instance, the catalyst decomposed in half an hour in diethyl ether. NMR studies indicate that water reacts with the 16-lectron species shown in Fig. 1.18 affording aqua and hydroxyl species (neutral cycle species 4 and 5, Fig 1.19).

This would provide stabilizingcatalytically activeunable species, although the hydroxide will compete with formate for coordination to the metal center under more basic conditions.

Among the catalysts investigated, the Rh-TsDPEN complex appears to outperform Ru-TsDPEN and Ir-TsDPEN complex catalyst for most of the reactions studied, displaying high activity, high enantioselectivity and broad substrate scope.

However, the performance of the catalysts varies with the ligands used, pH of the reaction mixture as well as substrate used[52, 54].

1.6 Modification of tosylated Diamines, with

A variety of approaches have emerged for the immobilization of TsDPEN ligand, offering solid catalysts applicable in heterogeneous ATH of ketones and imines.

This generally involves introduction of a functional group onto the aromatic ring of the diamine ligand, which provides the necessary linkageto the solid material.

Representative ligands are shown in Fig.1.19. Perhaps the first attempt at hetero-genization of TsDPEN (ligand P1)was published in 1998[163].

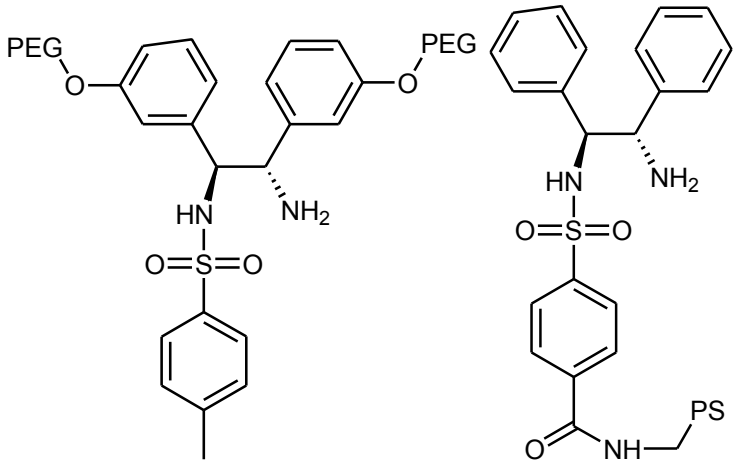
The TsDPEN ligand was functionalized with 4-vinylphenyl group to obtain *N*-[(4-inylphenyl)sulfonyl]-1,2-diphenylethylene-1,2-diamine, which was subsequently copolymerized with styrene (1:10) into a linear polymer (or with styrene and divinylbenzene (1:10:0.5) into a cross-linked polymer.

These two ligands were tested with $[Ru(\eta^6\text{-benzene})Cl_2]_2$, $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ and $[Ir(COD)Cl_2]_2$ precursors in the ATH of acetophenone using iso-propanol as the hydrogen donor. Although the iridium-based catalysts were both more active and selective (up to 94% *ee* at 96% yield after 48 h),

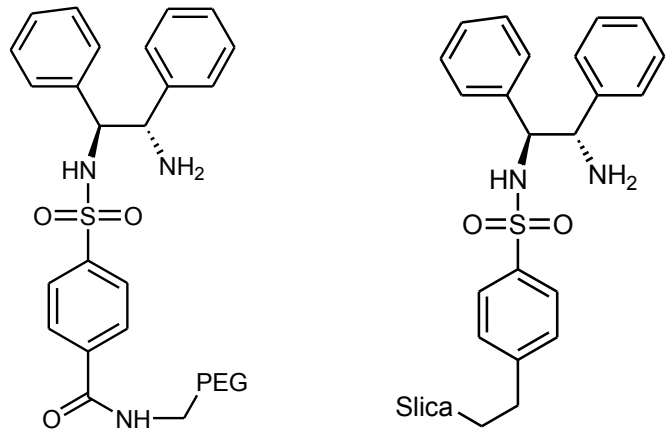
Their stability was disappointingly low. The [Ru(*p*-cymene) $Cl_2]_2$ complex was somewhat more stable (*i.e.*, reusable up to 4 times) but gave significantly lower *ee value*s and was less active. In 1998 Bayston et al.[164] Immobilized TsDPEN to amino methylated polystyrene (PS), with or without polyethylene glycol (PEG) spacer units, creating orange/red polymeric beads. The PEG-containing ligand was used with $[Ru\ (\eta^6\text{-}p\text{-cymene})Cl_2]_2$ in the ATH of acetophenone in neat FA:TEA mixture, and gave (*S*)-1-phenylethanol in 96.7% *ee.* Ligand with PEG spacer unit was more active when co-solvents were used (DMF, CH_2Cl_2), giving the product with > 99% *ee.* However, both the catalysts could e reused only twice.

In 2004, many contributions in the field of heterogeneous ATH with modified sul-fonated diamine ligands appeared. Xiao and co-workers attempted to attach the TsDPEN ligand *via* its phenyl rings to a polyethylene glycol support, creating an immobilized ligand **P3** (PTsDPEN).[81] ATH of acetophenone in neat FA:TEA with $[Ru\ (\eta^6\text{-}p\text{-cymene})Cl_2]_2$,and ligand **P3** gave 94% *ee*. Catalyst could be recycled three times due to rapid loss of catalytic activity. ATH of acetophenone in water using HCOONa as a hydrogen donor with the same catalyst gave 92 % ee in 1 h reaction time.[155]

In 2009, Zhou[165] synthesized new water-soluble chiral aminosulfonamide ligands from (R,R)-1,2-diphenylethylenediamine. The ruthenium catalysts prepared from chiral aminosulfonamide ligands with [Ru (η^6-*p*-cymene)Cl_2]$_2$ were used in the asymmetric transfer hydrogenation of prochiral ketones in water with excellent conversion (100 % conv in 2 h) and enantioselectivities (94% to 98%) without adding any surfactants. The catalysts could be easily recovered and reused several times without loss of enantioselectivity and activity.



P1 P2



P3 P 4

Fig.1.19: Sulfonated diamine ligands immobilized on polymers

1.7 Modification of tosylated diamines without disturbing C2 symmetry.

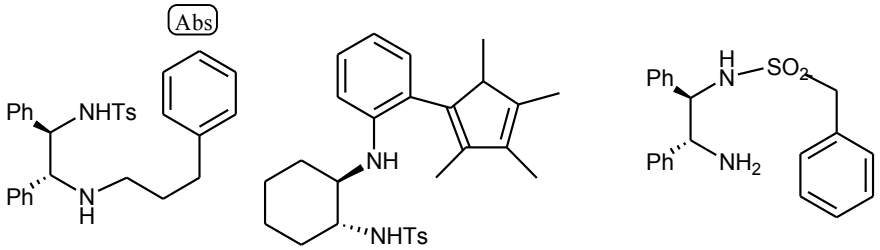
As reported by Noyori[42] and Carpentier et al.[45] the η6-arene fragment exerts a marked effect on performance of the catalyst. By connecting the arene fragment to the back-bone of the chiral ligand Wills et al.[84, 89, 114, 166] have prepared a new range of ligands which they called as "tethered ligands" as shown in Figure 1.20. It allows a highly organized transition state by locking of the chiral elements by the three coordination sites of the ligand **[L29 to L31].** The lifetime of the catalyst was improved signifi-cantly when tethered catalysts were used.[84, 166] Complete conversions were obtained with excellent enanatioseclctivity (96%) in a short time of 3 h for ligand (L**30**).

Tetra methyl TsDPEN derivative (3,3,5,5-TMTsDPEN) (**L35**) was synthesized by Liu[167] and applied in asymmetric transfer hydrogenation of ketones. A variety of para substituted ketones were reduced, but at lower enanatioseclctivity (89% for acetophe-none) compared to Ru-TsDPEN[54] under similar reaction conditions. He proposed that NCCN dihedral angles of chiral ligands could be the reason for lower enantioselectiv-ities of the reaction. Sterk et al. prepared a variety of different sulfonated DPEN lig-ands,[168] which were synthesized from the corresponding arenesulfonylchloride and (1S,2S)-DPEN followed by purification. These ligands were used to reduce variety of activated ketones (alpha keto esters, alpha substituted trifluro methyl ketones) at room temperature using the formic acid–triethylamine azeotrope. Both these examples were with Ru catalyst .

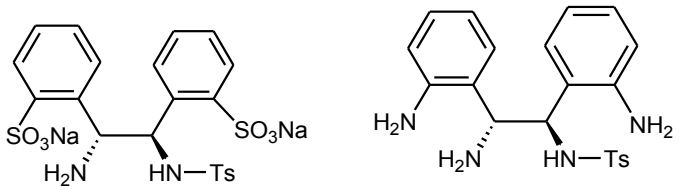
Thus it was observed that small alterations in the structure of diamine ligand led to the development of noteworthy catalytic systems enabling the implementation of ATH in water. This topic has also been reviewed extensively.[63]

In general, the derivatives generally bear a polar functional group which increases the solubility of ligands in water. In 2003, Deng and coworkers disclosed a TsDPEN ligand modification bearing two ortho-sulfonate groups (**L32**) the ligand was easy to prepare and was water-soluble.[169] The initial experiments on the ATH of ke-tones with acetophenone were carried out using $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ complex and (**L32**) with sodium formate as a hydrogen donor and sodium dodecyl sulfate as a surfactant. A range of aromatic ketones were successfully reduced, including α-bromo acetophenone with this system. 1-phenylethanol was obtained in 95% *ee* and the ATH of α-bromo acetophenone in a H_2O/CH_2Cl_2 mixture proceeded with 94% *ee*. However, with FA/TEA azeotrope as hydrogen donor and Ru-TsDPEN catalyst, the

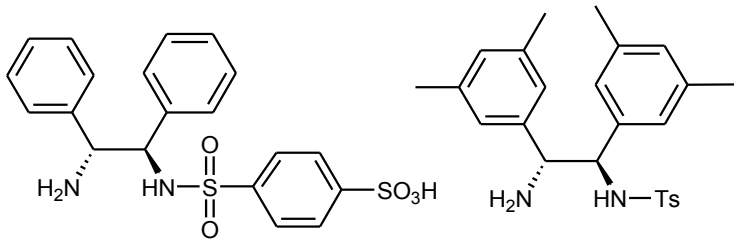
activity was very poor. In 2007, Deng et al introduced an *o,o'*-aminated TsDPEN ligand **L33** for ATH in water. Although the catalyst, formed *in situ* with [Ru(η6-*p*-cymene)Cl_2]$_2$, was not active in the ATH of acetophenone using HCOONa its [Cp*$RhCl_2$]$_2$ analogue gave 97% conversion of acetophenone under identical conditions. Many other aromatic ketones were also reduced using this complex, mostly with excellent enantioselectivity (>95%).



L29 **L30** **l31**



L32 **L33**



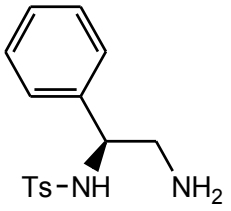
L34 **L35**

19Fig.1 20: Modified sulfonamide ligands with C2 symmetrical diamines

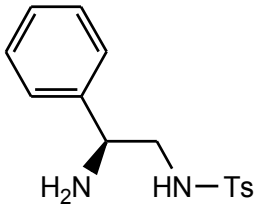
1.8 Unsymmetrical vicinal dimaines in ATH of ketones

After the discovery of TsDPEN ligand by Noyori,[40] in 1995, initial efforts were still concentrated on amino alcohols, because of their ligand acceleration effect.[42] Thus very few unsymmetrical monotosylated diamine ligands have been synthesized and tested in ATH of ketones. The structures of these ligands are presented (Fig.1.21), and the results are presented in Table 1.6.

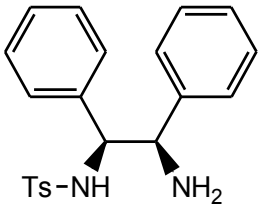
Nearly 7 years after the discovery of TsDPEN, first report on the synthesis of new ligand having different electronic and steric properties appeared in literature. Wills et al. developed various unsymmetrical monotosylated diamines from 1,2-Amino indanol.[98] The ATH of ketones using cis derivative [L42] and $[RuCl_2(p\text{-cymene})_2]_2$ complex gave 96 % conv, 83% ee in 24 h. The conversions and ee, were on lower side compared to Ru- TsDPEN[41] catalyst for various other ketones.



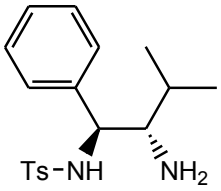
L36



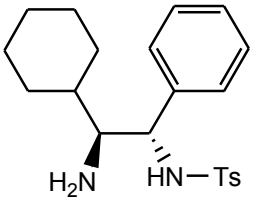
L37



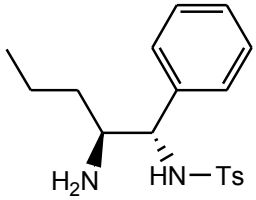
L38



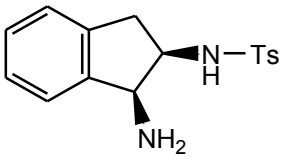
L39



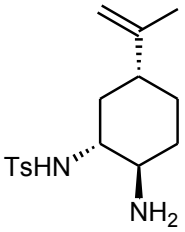
L40



L41



L42



L43

20Fig.1.21: unsymmetrical vicinal diamines synthesized for ATH of ketones

In 2004, Wills etal. synthesized the cis derivative of TsDPEN[99] **(L38)** along with ligands **[L36]**and **[L37]** having only one chiral Centre. Wills et al.[104] proposed that anti-geometry of amino and sulfonamide group was essential for better activity and enantiosectivity. Cis isomer of TsDPEN showed poor conversions (<50%, in more than 2 days) and enantioselectivity. It was observed that enantioselection is decided by configuration of carbon bearing tosyl amide group. Comparison of the activity of [Ru*p*-cymene)$Cl_2]_2$ with ligands **[L36]** or **[L37]** in ATH of acetophenone showed

that ligands in which amine group is attached to the carbon bearing phenyl group is more active in ATH of ketones (95% conversion in 48 h, vs 32% conversion in 220 h). The details of their conversion and ee are presented in the Table 1.6.

After this no major development in structural variations of sulfonated diamine ligands was reported till 2011. In 2011 Xu et al.[100] prepared series of unsymmetrical vicinal diamines[100] using synthesis strategy of chiral auxiliary (the synthesis part is discussed separately in synthetic methodology section). In this report all the ligands synthesized were having trans geometry of amine and sulfonamide. The ligands were used in ATH of ketones. However, Xu et al. observed that, ligand having tosylamide group attached to the carbon bearing one phenyl group and presence of bulky groups like cyclohexyl or isopropyl on the another carbon bearing amino group, **L39** and **L40** is a must for good activity and enantioselectivity (98% in 48 h). The ligand having linear n-propyl group (**L41**) showed no activity in ATH of acetophenone using FA:TEA as hydrogen donor and $[Ru(\eta^6\text{-}p\text{-cymene})Cl_2]_2$ catalyst. However, again it was observed that compared to TsDPEN ligand the activity of these ligands was significantly low. For many ketones the reaction time varied from 2 days to 4 days.

Very recently Roszowski[170] synthesized, unsymmetrical vicinal diamines from limonene. Seven derivatives were synthesized and used in ATH of ketones With $[Ru(p\text{-cymene})Cl_2]_2$, and alpha substituted acetophenone using FA:TEA as hydrogen donor to obtain 100% conversion in 42 h with 93% ee.

7Table 1.7 ATH of acetophenone using unsymmetrical diamines and FA: TEA as hydrogen donor

Catalyst [$RuCl_2$(*p*-cymene)$_2$], S/C ratio 200 ,Temp 28^0C

Entry	Ligand	Time,	Conv, %	%ee	Ref.
1	L36	13 DAYS	46	33	[99]
2	L37	48 h,	95	69	[99]
3	L38	220 h	32	70	[99]
4	L39	40 h	95	97	[100]
5	L40	NA	98	97	[100]
6	L41	-	<10	-	[100]
7	L42	20h	96	83	[98]
8	L43	42h	100	94	[77]

The information available on ATH using monosulfonated diamine ligands is summarized as follows:

- ATH of acetophenone was first reported with Ru-TsDPEN, (95% conv, 97% ee, 15h), ATH of cyclic ketones showed low conversions (<50%), reversibility of reaction in 2-propanol was another problem.[40]
- Ru-TsDPEN showed excellent conversion and ee in FA:TEA, (99% and 98%, respectively). ATH of variety of ketones with (>90% conv and 90% ee).[171] However, longer reaction times (24h), incompatibility with Rh-complexes (for simple ketones)[171] was observed.
- Ligands having syn-substitution of amine and sulfonamide ligands give low enantioselectivity and activity,[99] however, cis isomer of indane mono sulfonamide amine also showed good activity.[98] The configuration of resultant alcohol is determined by the carbon having sulfonamide group.
- Use of sodium formate in water, greatly accelerated the ATH by Ru-TsDPEN, Rh-TsDPEN , and Rh-TsCYDN, various ketones were subjected to ATH in excellent conversions and ee (>95% and 90% respectively).[52, 54, 55]
- Variation in Metal ligand combination, affects conversions and ee to great extent (For, example Rh-TsCYDN is more active than Rh-TsDPEN whereas Ru-TsDPEN is more active than Ru-TsCYDN).[52, 54, 55]
- However because of heterogeneous nature of reaction in water, probably detailed parametric effects were not studied.
- Use of co-solvents like methanol, ethanol and ACN were explored by Xiao et al. Mechanistic studies were performed using DMF as a co-solvent.[56]
- It was also found that equivolume water in variable ratios of FA:TEA had significant impact on conversion and ee.[80] Dramatic changes in conversion and ee in water, with different metal complex with same ligand (Ru-TsDPEN) and Rh-TsDPEN was observed.
- It was also found that unlike amino alcohols, amino sulfonamide ligands form stable crystalline complexes.
- Rh-TsDPEN and Rh-TsCYDN showed very high activity, Other ligands were not explored.

1.9 ATH of imines

1,2,3,4-Tetrahydroquinolines are key structural elements in many natural products and have found broad commercial applications.[172] In particular, optically pure hydroquinolines are commonly present in alkaloids and are required in pharmaceutical and agrochemical synthesis. Representative examples include the bioactive alkaloids (+)-alipinine[173] and augustureine,[174, 175] and the antibacterial drug (S)-flu equine.[174] In recently reported organo catalytic asymmetric reduction reactions of quinolines with the Hantzsch ester as the hydrogen source, excellent enantioselectivities were observed for 2-aryl substituted quinolones.[176, 177] Also $[Ir(COD)Cl]_2$/(S)-SegPhos/I_2 catalyzed ATH of quinolines gave 88% ee.[178] Till now ATH of imines is in the development stage and there are very few reports in literature available which are discussed below.

In 1996, Noyori reported Ru-TsDPEN catalyzed asymmetric transfer hydrogenation of various imines in very efficient way.[14] A preformed chiral Ru-TsDPEN complex, catalyzed the transfer hydrogenation of various cyclic and acyclic imines with FA:TEA azeotrpic mixture. Particularly effective substrates were dihydroisoquinoline derivatives which yielded tetrahydroisoquinolines with high ee. The best results for the reduction were obtained with Ru-TsDPEN catalyst using 5:2 FA:TEA azeotrpic mixture in acetonitrile at 28°C. The reaction led to the product 1-methyl tetrahydro isoquinoline in 95% ee and in quantitative yield. The ATH process was conducted equally well in various aprotic solvents including DMF, DMSO and CH_2Cl_2 but not in ethereal or alcoholic media. Labeling studies with deutarated propan-2-ol indicated that propan-2-ol could not be used as a hydrogen source for this particular catalytic system. This catalytic method was found to be particularly useful for the enantioselective reduction of other 3, 4-dihydroisoquinoline derivatives to corresponding amines with excellent ee.

In 1999, Baker et al.[50] reported the ATH of cyclic and acyclic imines using Rh-TsDPEN complex and FA-TEA as the hydrogen donor. The reaction was very fast and 95 % conversion of imine was observed in just 10 min with 90 % enantioselectivity. Baker synthesized the catalyst precursor from $[Rh(Cp^*)Cl_2]_2$ and TsDPEN and used for ATH of various imines at a substrate/catalyst (S/C) molar ratio of 200:1 using a 5:2 FA:TEA azeotrope as the hydrogen donor at 20°C. The reaction with the 1-methyl-3,4-dihydroisoquinoline proceeded very rapidly and was complete in about 10 min at 20 °C, with an ee value of 99%. The reaction with a higher

substrate:catalyst ratio of 1000:1 proceeded slowly with a slight loss in enantioselectivity. The catalyst exhibited excellent enantioselectivity for ATH of a number of cyclic imines and cyclic sulfonimides.

The research group of Blackmond[179] reported the detailed kinetic studies on the asymmetric transfer hydrogenation of imines with formic acid using Rh-TsDPEN catalyst. They discussed the role of bases like Et_3N and controlled release of FA into the catalytic cycle and showed that the rate behavior strongly depended on the reaction conditions, including the type of solvent and the method of addition of the hydrogen transfer agent. The authors suggested that the reaction protocol involving controlled addition of formic acid gave high yields even at high substrate/catalyst ratio (S/C) 1000.

Wills and co-workers investigated ATH of imines with Ru(benzene)-N'-alkylated TsDPEN catalyst and observed 100 % conversion with 85 % ee in 6 h.[180] The Ru-N'-alkylated complex in some cases gave reduction products of equal or improved ee (95%), relative to the non-alkylated complexes in the reduction of certain cyclic imines.

Deng and co-workers reported the first asymmetric transfer hydrogenation of cyclic imines and iminiums in water.[181] ATH was performed by using sodium formate as the hydrogen source and CTAB as an additive using Ru-TsDPEN as the catalyst. The Sulfonated ligand[181] L31 (Fig.1.20) was subsequently applied to the ATH of imines and iminiums under similar conditions and 93 % conversion with 94 % ee was obtained in 10 h. A variety of cyclic imines (isoquinoline, β-carbolines, *N*-sulfonylimines) were successfully reduced this way, although in the case of some acyclic imines, this catalytic system was found to be unsuitable. Pihko and group investigated ATH of imines with Ru-TsDPEN catalyst and sodium formate as hydrogen donor and $AgSbF_6$ as an additive to improve activity. ATH of cyclic imine was achieved in 90% yield and 99% ee in 16 h reaction time.

Limonene based sulfonated diamine ligand (Fig.1.21, **L43**) was tested for the ATH of imines.This was applied to the reduction of 1-methyl-3,4-dihydro carbolines[77] and the best results were obtained using Ru-L43 catalyst system (100% conversion with 98% ee in 20 h). Various imines were reduced with complete conversion with variable ee (50% to 93%).

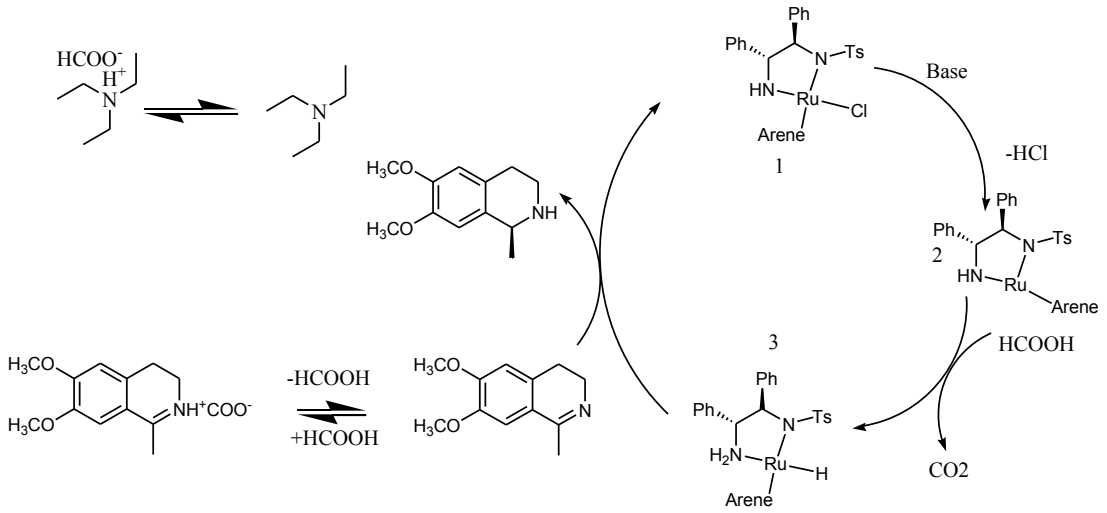
Xiao et al.[182] carried out the ATH of quinolines in water using sodium formate and buffer of pH 5. The pH of solution was maintained at 5 using sodium acetate and

acetic acid buffer. Very good conversions (>90 %) and enantioselectivities (>90 %) in 12 h was obtained using Rh-TsDPEN complex catalyst. The results were better than isoelectronic Ru-TsDPEN and Ir -TsDPEN catalysts.

Very recently in 2013 Kacer et al.[183] investigated ATH of 1-methyl-3,4-dihydroisoquinoline in detail, using FA:TEA azeotrope as hydrogen donor and Ru-TsDPEN complex catalyst. Effect of various reaction conditions like substrate concentration, temperature and substrate-to-catalyst molar ratio, FA:TEA ratio, FA: substrate (1-methyl-3,4-dihydroisoquinoline) molar ratio on the activity and enantioselectivity was investigated in detail. It was found that the FA:TEA ratio along with formic acid to substrate ratio is important in deciding the activity and enantioselectivity. Optimum FA:TEA ratio was found to be 5:2. Conversion decreased with increase in substrate/catalyst ratio to 300 and the optimum substrate to catalyst ratio was found to be S/C 200. Under optimum conditions 96% conversion of 1-methyl-3,4-dihydroisoquinoline with 85 % ee was obtained in 50 min.

1.10 Molecular modeling for mechanism of ATH of imines

Mechanism of ATH of imines has been investigated based on density functional theory (DFT) computational methods.[125, 126, 184] Kacer et al. [194] have proposed transition structures for the ATH of 1-methyl-3,4-dihydroisoquinoline catalyzed by (*S*,*S*)-Ru-TsDPEN. The imine molecule was selected for its simplicity since all $[RuCl_2(p\text{-cymene})]_2$ complex structures were treated "as is" without any simplifications, which resulted in very high hardware demands.[185] In this study ionic mechanism was used for doing calculations. On application of the ionic mechanism (Fig. 1.22), the reaction preferentially affords the (R)-amine product, which is in agreement with the experimental observations. Calculated transition state structures for the hydrogenation of protonated 1-methyl-3,4-dihydroisoquinoline were discussed together with their preceding and following energy minima. Stabilization of the favorable transition state by a CH/π interaction between the η6-p-cymene ligand and the substrate molecule was explored in depth to show that both C(sp2)H/π interactions are more probable than C(sp3)H/π interaction in this molecular system.



21Fig.1.22: Mechanism of ATH of imines 1

Summary:

From the literature it was observed that there are very few reports on ATH of imines. Also the scope of ligands investigated is limited. Major literature reports for ATH of imines were with Ru, Rh and Ir complexes with TsDPEN as a ligand.

The effect of various reaction conditions on the conversion and enantioselectivity has been investigated in detail with Ru-TSDPEN and Rh-TsDPEN complex catalyst.[179, 183]

Very recently ATH of imines was tried with limonene based sulfonamide ligands[170] using $[RuCl_2(p\text{-cymene})_2]$, but with little success. However, TsCYDN, which is highly successful in ATH of ketones using Rh complexes, to the best of our knowledge is not utilized in ATH of imines.

1.11 Methodologies for synthesis of amino alcohols and 1,2 Diamines

From the literature it was clear that, the most promising ligands in ATH of ketones were amino alcohol and monotosylated diamines. It was observed from literature that, there are many chiral amino alcohol ligands synthesized and used in ATH of ketones with different steric and electronic properties. This is because of chiral amino alcohols are prepared easily. The use of structurally versatile monotosylated diamine ligands, are scarcely observed in literature. However in last two years, there are growing number of literature reports describing, the synthesis of the structurally diverse mono sulfonated diamines and their use in ATH of ketones and imines. A brief account of synthetic methodologies used for the synthesis of amino alcohols and monosulfonated diamine which were used as ligands in ATH of ketones and imines is presented below.

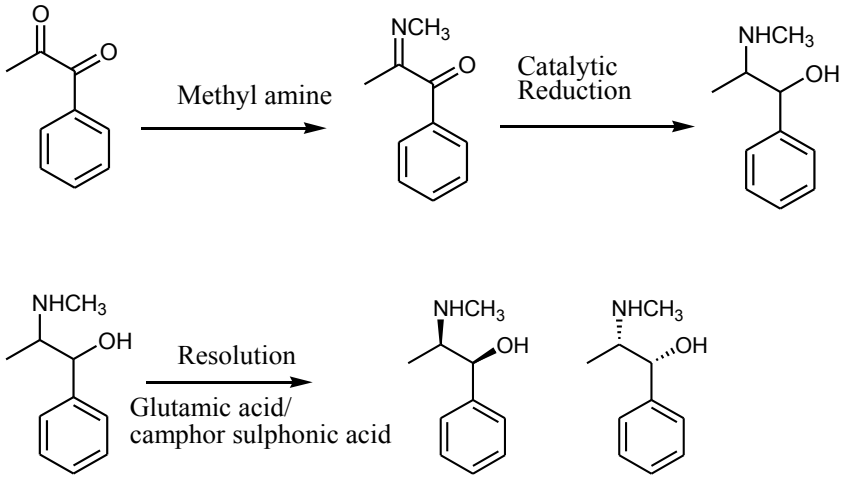
1.11.1 Synthesis of amino alcohols

The vicinal amino alcohol moiety is a common structural component in a vast group of naturally occurring and synthetic molecules. The general methods for preparation of amino alcohols are huge in number. The review of all these methods is beyond the scope of this thesis. Efforts were concentrated to synthesize new amino alcohols having different structural and electronic properties. The general synthetic methodologies which were used in preparation of amino alcohol ligands is briefly discussed. The presence of vicinal amino alcohols and the relative (as well as absolute) stereochemistry is generally important for the catalytic activity used in ATH reactions. Therefore as such, a variety of stereoselctive synthetic methods have been developed. This section however, will focus on methods that have been used and developed for the synthesis of vicinal amino alcohols which are used as ligands in ATH of ketones.

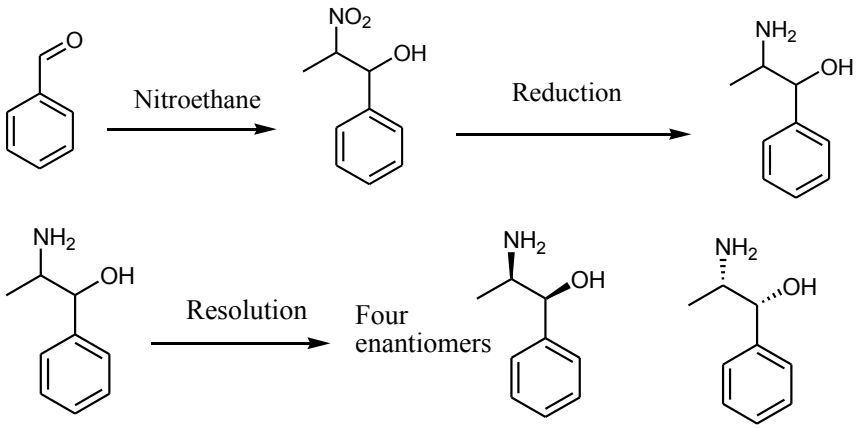
1.11.1.1 The Synthesis of ephedrine and norephedrine

In 1996, Noyori, used the 1,2-phenyl ethanolamine (all four enantiomers), and various derivatives of commercially available ephedrine, having chirality adjacent to the hydroxyl and amine function for ATH of ketones. The Schematic of ephedrine synthesis and norephedrine synthesis is shown in Figs. 1.23 and 1.24.

The 1, 2 di carbonyl compound reacts with methyl amine to give corresponding imine derivative as shown in Fig 1.23.[186, 187] Catalytic reduction of imine and ketone groups followed by chiral resolution gives all four enantiomers of ephedrine (Fig. 1.23). Synthesis of norephedrine derivatives starts with the aldol condensation type reaction of benzaldehe and nitro, followed by reduction and resolution to give four enantiomers of norephedrine. This building block of ephedrine derivatives proved very important in ATH of ketones, as using norephedrine and ephedrine as starting materials nearly 40 chiral amino alcohols have been synthised by Carpentier et al.[119]



22Fig.1.23: Synthesis of ephedrine[186]1S, 2R ephedrine1R, 2S ephedrine



1S, 2R norephedrine , 1R, 2S norephedrine

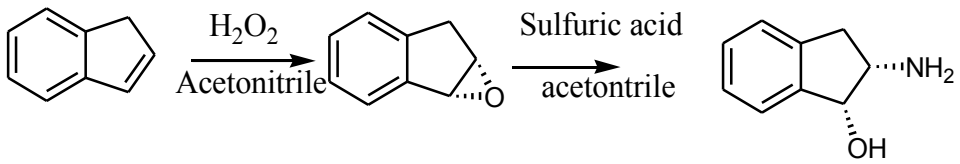
23Fig.1.24: Synthesis of norephedrine

The 1, 2 phenyl ethanol[187] amine and ephedrine in theory gives rise to 4 enantiomers because of the 2 chiral centers. 1, 2 phenyl ethanol amine and it isomers were treated with camphor sulfonic acid or glutamic acid, to get all the 4 enantiomers.

All the enantiomers of ephedrine and norephedrine along with 1,2 phenyl ethanol amine was tested in ATH of ketones using Ru catalysis. Since then many commercial available amino alcohols have been tested in the ATH of ketones. However to study the structure activity relationship and use versatile ligands in ATH, there is need for the development new ligands. These easily available norephedrine isomers are used as building blocks as the primary amine function can easily undergo various functional group transformations, to form structurally versatile amino alcohols.

1.11.1.2 Synthesis of amino indanol

1R, 2S amino indanol[188] is one of the intermediate for the synthesis of Merck antiviral drug Indianvir and is commercially available in both the enantiomeric forms. However it is prepared by using the synthetic methodology presented in Fig.1.25.

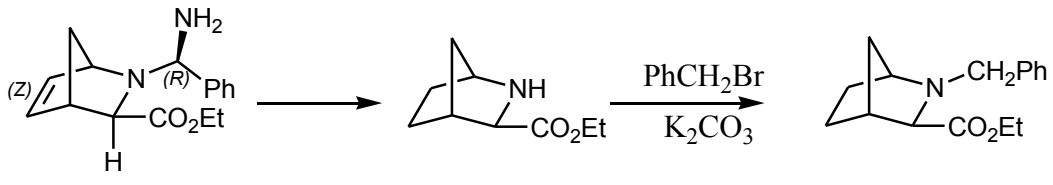


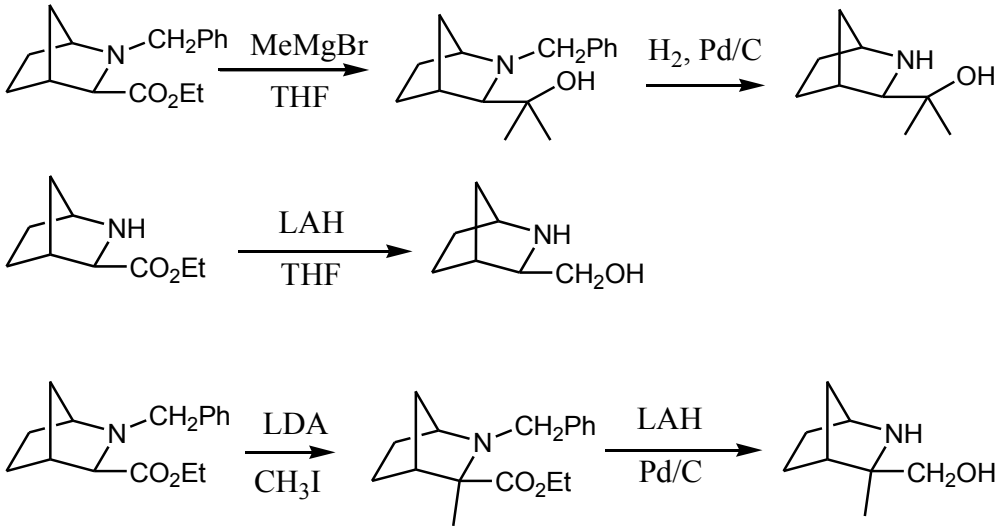
24Fig. 1.25: Synthetic Methodology for Cis amino indanol[189]

This was synthesized from cis indene. Cis indene was treated with hydrogen peroxide to generate cis Indane epoxide, which is isolated by enzymatic resolution as single enantiomer.[189] The ring opening of the epoxide in acetonitrile followed by simple hydrolysis in water gave cis amino indanol.

1.11.1.3 Azabornyl based ligands

Anderson etal[71, 72] developed azabornyl ligands which yielded stericaly rigid amino alcohols. These amino alcohols have secondary nitrogen which is attached to rigid azabornyl ring. The alcohol attached to the carbon which is primary, secondary or tertiary chiral center. The simpler and very common methods like Grignard reaction and LAH reduction were used to synthesize stericaly rigid alcohol. Representative example is shown in Fig.1.26.





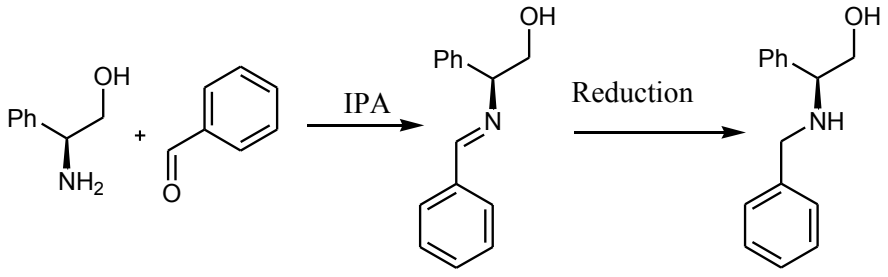
25Fig. 1.26: Synthetic methodology for azanorboronyl ligands

The simple methodologies like N-alkylation, using alkyl bromide and Grignard addition to esters to generate tertiary alcohols was carried out. Use of strong base like LDA was used to alkylation of carbon at α-position.

1.11.1.4 Use of norephedrine in synthesis of amino alcohol ligands

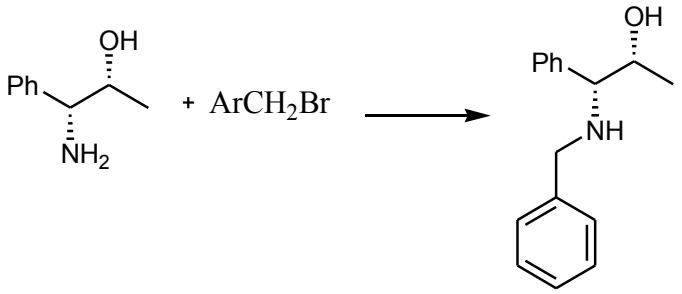
Christopher frost[121] synthised imino alcohols form norephedrine using imine formation procedure in IPA. Also to study different ligands effect based on structure modification, amino alcohol from phenyl glycinol was synthesized using imine formation followed by reduction of the imino alcohol using sodium borohydride.

The scheme is represented in Fig 1.27.



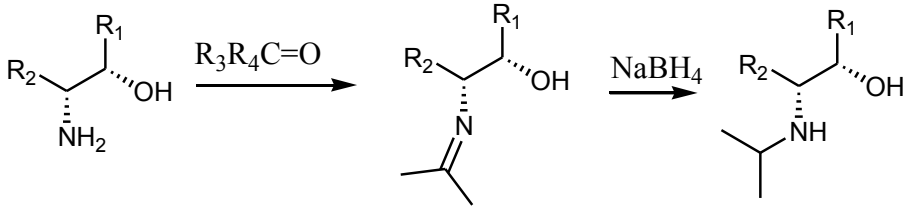
26Fig. 1.27: Amino alcohols from reductive amination phenyl glcinol

Carpentier and Shoemaker[73, 117, 118, 120, 128] synthised various N- alkyl derivatives starting from 1,2-pheethanolamine and 1R,2S-norephedrine using alkylation at amino nitrogen using benzyl bromide and phenbenzyl bromide. Representative example using benzyl bromide is shown in Fig.1.29.



27**Fig.1.28: Amino alcohol modification using N-Alkylation procedures**

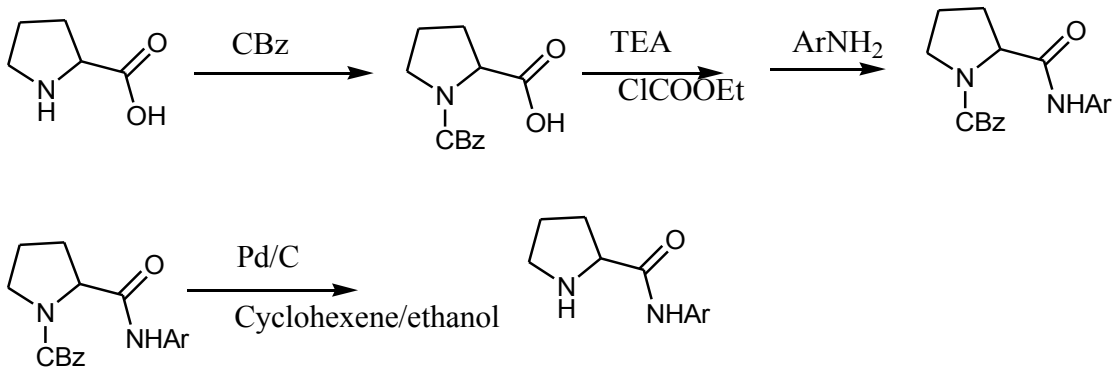
Carpentier et al.[190] used commercially available norephedrine and ethanol amines or synthesizing various new amino alcohol ligands. They used amino function which was subjected to single step reductive amination[190]of various ketones to get N-alkylated amines. Thirty different amino alcohols were prepared by this method (Fig. **1.31**) using various ethanol amines[191, 192] and their activity in ATH of ketone were tested.



28Fig. 1.29: Reductive amination of norephedrine using various ketones

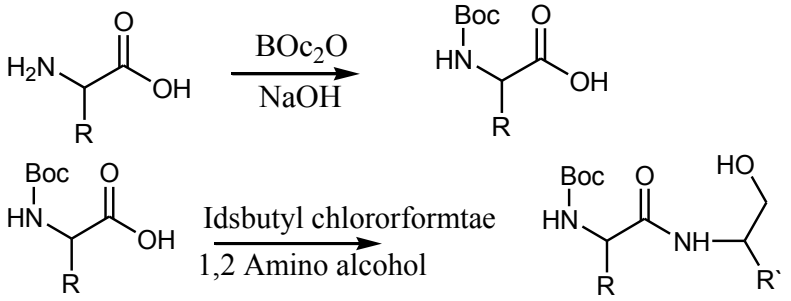
1.11.1.5 Amino acid based ligands

Coupling of amino acids with amines provides simple method for the synthesis of amino alcohols. Many naturally occurring chiral pool molecules like, proline, terpene have been used for the synthesis of chiral amino alcohols. Proline base ligands were synthised by using simple procedure of acid amine condensation with ethyl chloro formate in TEA and THF (**Fig. 1.30**).



29Fig. 1.30: Synthesis of proline based ligands using acid amine coupling

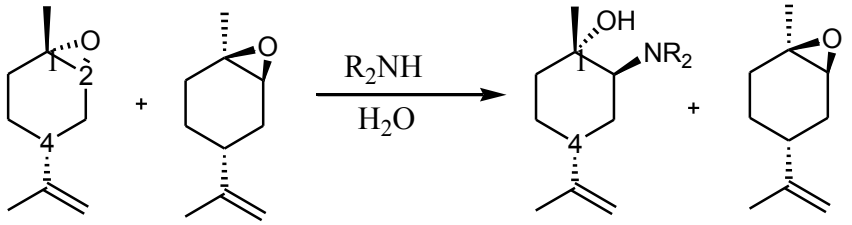
Adolfsson et al.[193] developed modular type peptide ligands using 9 amino acids and 5 amino alcohols. Nearly 45 ligands were synthised using, the simple methodology of acid amine condensation in present of isobutyl chloro formate. The Amine group was protected using BOc anhydride (Fig 1.31).



30Fig 1.31: Synthesis methodology for peptide type ligands from amino acids and amino alcohols.

1.11.1.6 Synthesis of terpene based amino alcohols

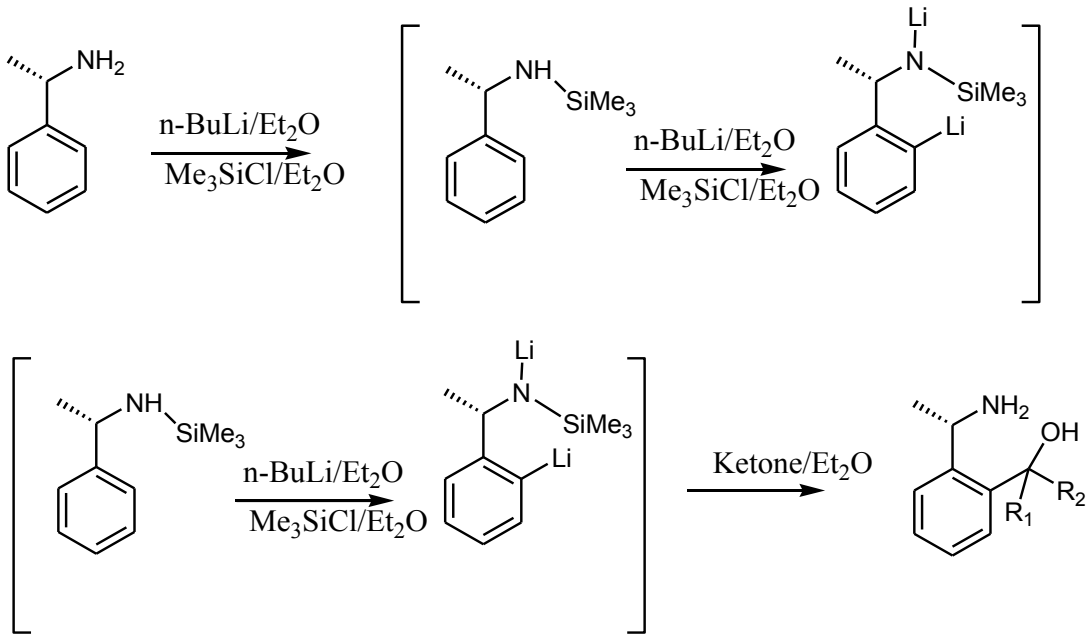
Singaram et al.[194] used the commercially available mixture of cis and trans limonene oxide to synthesize new amino alcohols. They developed and used the kinetic resolution method in which trans limonene oxide undergo nucleophilic ring opening by secondary amines in water (Fig. 1.32) in faster way compared to cis limonene oxide.[195] The unreacted cis limonene oxide was easily separated from trans amino alcohol by distillation.



31Fig. 1.32 Synthesis methodology for terpenes based amino alcohol using kinetic resolution.[195, 196]

1.11.1.7 Use of ortho lithiation from S-Phenethyl amine:

Very recently Zheng et al.[197] used ortho lithiation methodology, for synthesis of chiral amino alcohol from S-Phenethyl amine. The procedure involves the protection amine function by trimtehyl silyl chloride and then ortho ligation with butyl lithium.[198] The reaction of lithiated amine reacts with variety of ketones, giving chiral amino alcohols shown in Fig.1.33.



32Fig 1.33 Synthetic methodology using S-Phenethyl amine and ortho lithiation

Based on the synthetic methodologies reported for enantiopure β amino alcohols it was observed that, the methodologies used was substrate specific, rather than the general method of synthesis. i.e. class of compounds like amino acids, amino

alcohols, ephedrine's, (1,2 phenyl ethanol) are selected and then functional group transformation like, reductive amination, epoxide ring opening or N-Alkylation or acid amine coupling were used to get amino alcohols. Easily available molecules like S-Phenethyl amine, commercially available limonene epoxide, amino acids or amino alcohols like ephedrine are the major dominant substrates.

It was also observed that, chiral resolution and kinetic resolution are also popular methodologies for accessing pure compounds (e.g ephedrine or terpene base amino alcohol).

1.12 Synthetic methodologies from monotosylated diamines:

As discussed in the introduction part, there are very few reports on the synthesis of 1, 2 monotosylated diamines as ligands for ATH of ketones and imines. Most of the ligand modifications have been carried out using TsCYDN and TsDPEN as starting vicinal diamine. Chiral, enantiomerically pure 1,2-diamines (or vicinal diamines) and their derivatives are also used in stereoselctive organic synthesis, for example as chiral auxiliaries, or as metal ligands in catalytic asymmetric synthesis. These utilizations brought about the development of synthetic methods for the preparation[199-205] of aliphatic1,2-diamines in diastereomerically and enantiomerically pure form. The problem of stereo chemical control encountered in their synthesis depends on the number of substituents on the carbon chain. However, the literature review in this section will be restricted to the synthesis of 1,2-diamines (in the monotosylated form); which are used as ligands in ATH of ketones and imines.

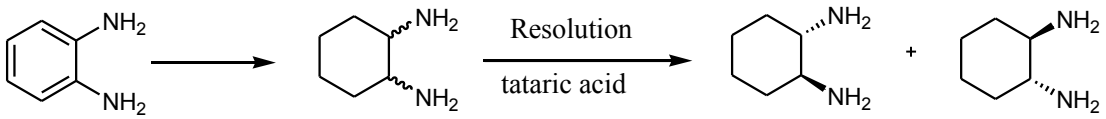
1.12.1 C2 symmetrical 1, 2 diamines

The monotosylated dimaines, which are used as ligands in ATH of ketones and imine, are easily prepared by the simple procedure from 1,2-diamines using p-toluene sulfonyl chloride. However these cannot be done with unsymmetrical vicinal diamines, as the reaction would lead to theoretically 2 regioisomers which are often very difficult to sepate or purify, by normal available methods.

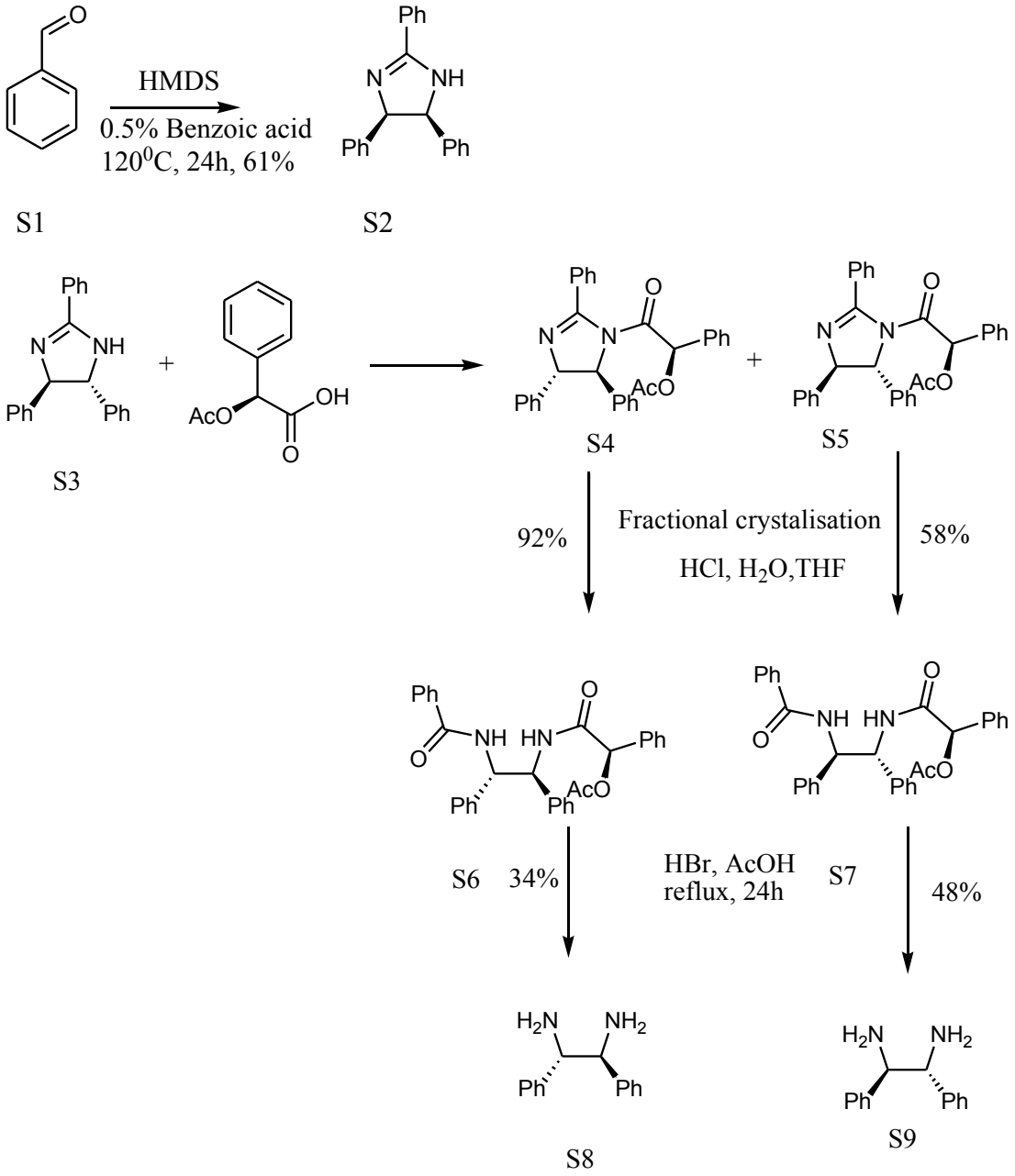
The preparation and isolation or purification of the parent 1,2 diamine compound is the critical step in synthesis of monosulfonated diamines. The 1,2 TsCYDN is prepared easily by reduction of 1,2-phenylene diamine to cyclohexane diamine. The chiral resolution of trans cyclohexane diamine[204, 205] by tartaric acid leads to the formation of diastereomeric salt. The crystallization is carried out using hot water. This procedure gives access to both R,R and S, S, Diamino cyclohexane.[204]

The 1,2 TsDPEN preparations however is slightly tedious, because of trivial synthesis of 1,2 diphenylene ethylene diamine. Condensation of benzaldehe (Fig. 1.35, S1) and HMDS (an ammonia equivalent) in the presence of catalytic amount of benzoic acid leads to the formation of ± isoamairine[206, 207] (Fig.1.35, S2, pl. check). The epimerization of isoamairine is carried out using sodium hydroxide in ethylene glycol to give S3 (Fig1.35).

Acetyl mandelic acid is used to prepare disatereotopic amide of the corresponding iso amairine (S4 and S5). The isolation of single diastereoisomer is done by fractional crystallization (S6 and S7). The subsequent hydrolysis of diastereoisomer with HCl in THF followed by reaction with HBr in acetic acid gave both the enantiomers in pure form with more than 98% purity. The scheme for the preparation of 1,2 diaminocyclohexane and 1,2 DPEN is shown in Fig.1.34 and 1.35 respectively.



33Fig. 1.34Preparation of enantiomers of 1, 2 diaminocyclohexane

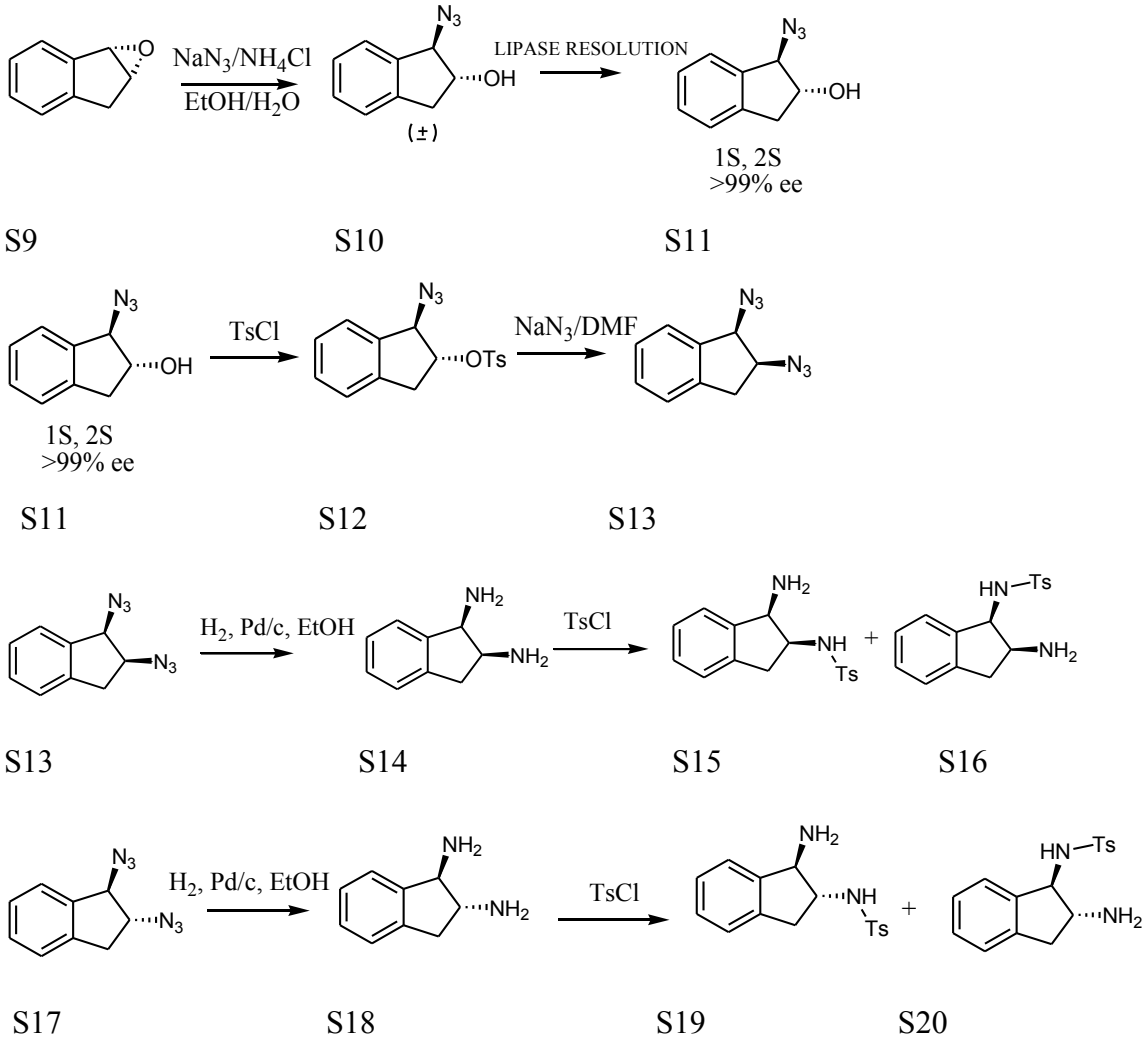


34Fig. 1.35: Synthesis of 1, 2 diamio 1, 2 diphenyl ethane enantiomers

1.12.2 Preparation of monotosylated derivative from indane

TsDPEN and TsCYDN are popular ligands in combination with transition metal complexes (Ru, Rh, Ir) for ATH of ketones and imines. However, there were no reports on the synthesis of monotosylated diamines with modified structure as a ligand in ATH of ketones and imines till 2002. In 2002, wills et al.[188, 189] developed new synthetic methodology for the preparation monotosylated diamine ligand from amino indanol (Fig. 1.36).[98] The racemic azido alcohol was prepared from Cis indene oxide[189] by reaction with ammonium chloride and sodium azide (S10). Enzymatic resolution of the azide with lipase gave pure enantiomeric cis azido alcohol (S11).

Tosylation of cis azido alcohol gives (S12), which is converted to diazido indane by reaction with sodium azide (S13). Reduction of diazido indane (S13 and S17) with Pd/C catalyst gave 1,2 diamino indane amines as the product (S14 and S18). Tosylation of unsymmetrical vicinal diamine (S14 and S18) resulted in regorisomeric monotosylated diamines (S15, S16, S19 and S20), which on column chromatographic purification gave unsymmetrical vicinal diamines S15, S16, S19 and S20 in pure form (in monotosylated forms). The synthetic methodology is presented in Fig. 1.36 below.

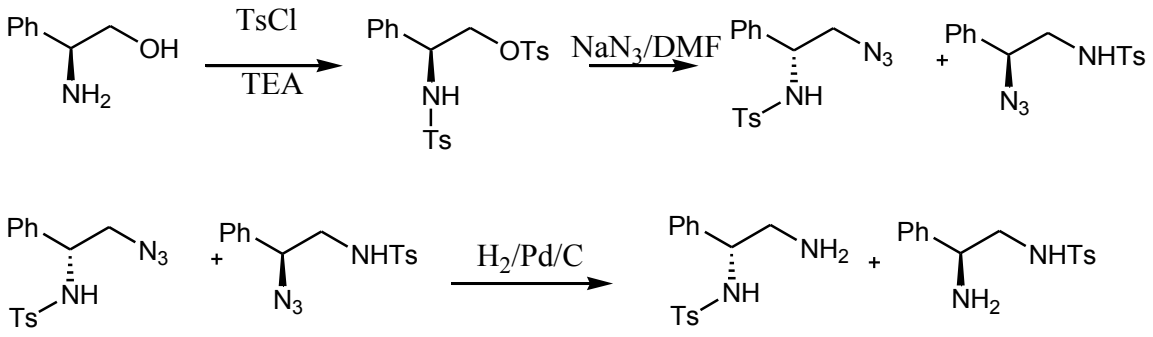


35Fig. 1.36: Synthetic methodologies for unsymmetrical vicinal diamines from Cis indene

1.12.3 Synthesis 1,2 Diamine derivative from amino alcohol

In 2004, Wills et al.[99] synthesized another vicinal diamine from phenyl glycinol and 1,2 Phenyl ethanolamine (Fig.1.37) using the basic functional group transformations like tosylation, ring opening of activated aziridine with sodium azide and subsequent

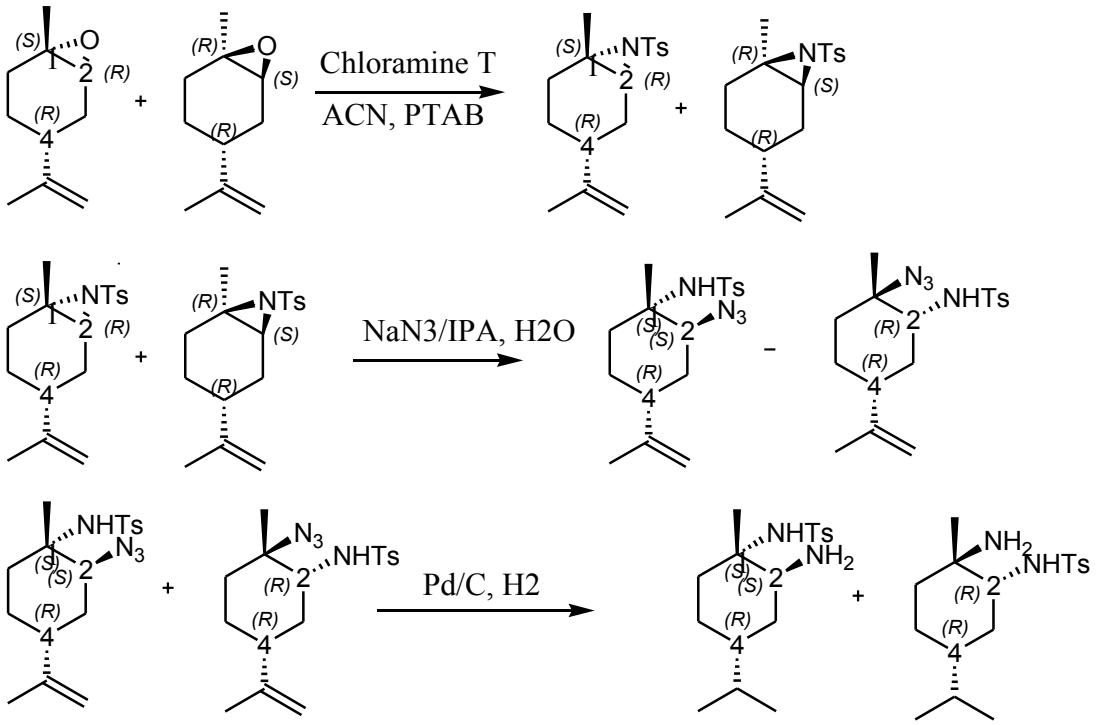
reduction of azide to monotosylated diamines as per the earlier synthesis of indane monosulfonated diamine.[98] Regioisomers of monotosylated dimaine were separated by column chromatography.



36Fig. 1.37: Synthesis methodology for unsymmetrical vicinal diamines from phenyl glycinol

1.12.4 Limonene based sulfonamide ligands:

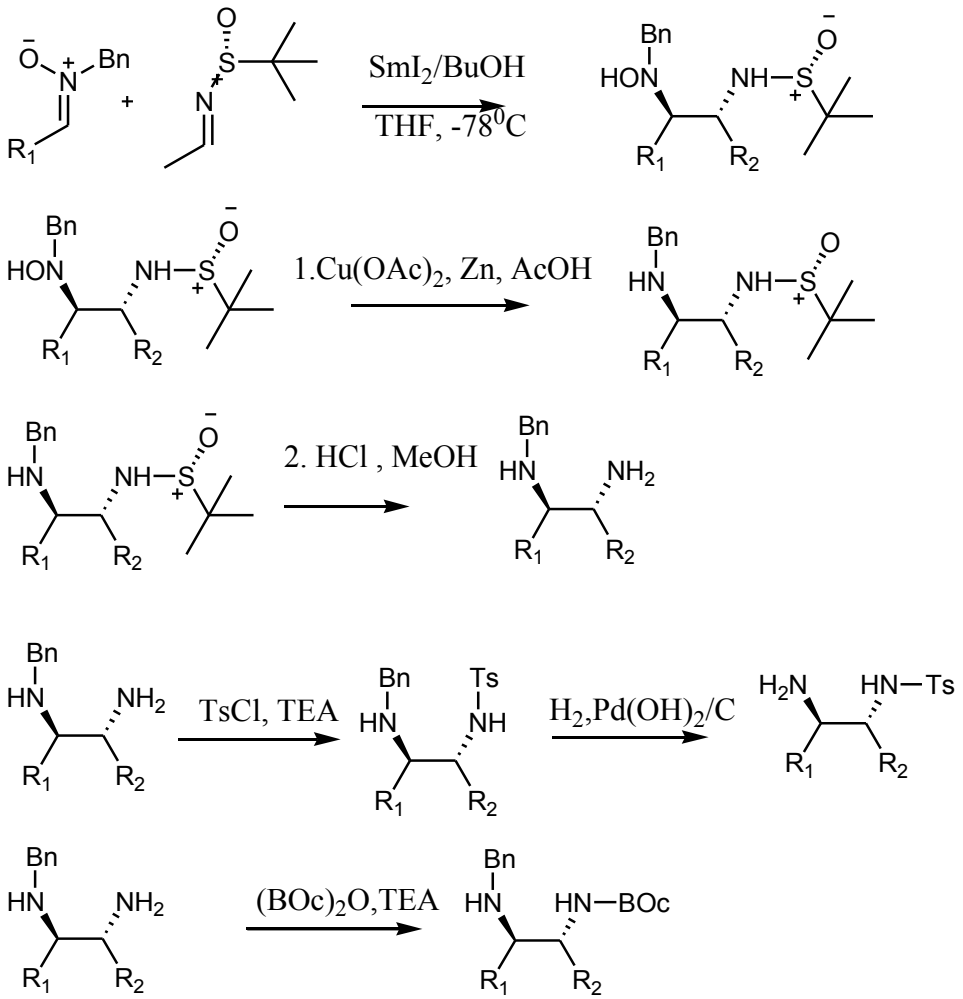
Limonene oxide conversion to corresponding, tosyl aziridine[208] was carried out with PTAB and chloramine T. The ring opening of sulfonamide with sodium azide in 2-propanol and water provides two regioisomers. The ring opening of the epoxide was selective and only trans isomer was reactive with secondary and primary amine while cis limonene oxide remained unreactive.[195] The separation of regioisomers, like in all earlier cases was very difficult at the azido stage, and required column chromatographic purification. The reduction of azido sulfonamide with Pd/C gave respective amino sulfonamide based on limonene. Based on this synthetic methodology (Fig 1.38) seven ligands were prepared and tested for ATH of ketones and imines.



37Fig 1.38: Synthetic methodology for limonene based monosulfonated diamine ligands

1.12.5 Chiral auxiliary approach

Xu et al.[100, 209] used the chiral auxiliary approach to synthesize various diamines using a samarium diiodide induced coupling protocol. In this methodology, chiral N-t-butyl sulfonyl imines were coupled with nitrones. This was the first example of diastereoselective cross coupling of two different imine systems. Excellent enantioselectivity as well as high diastereo selectivity was achieved in this reaction. The modified procedure developed by Xu et al. to generate regioseclitve and stereo selective aminosulfonamide derivatives is as shown in Fig 1.39, This procedure was used to synthesize various unsymmetrical vicinal diamine ligands. These unsymmetrical dimaine ligands were used in ATH of ketones. This method was proved to be highly selective for the formation of trans derivatives of amino and sulfonamide groups. However compounds having cis geometry were not reported using this method. The detailed synthetic methodology is presented in Fig 1.39.



38Fig 1.39: Synthesis of unsymmetrical vicinal diamines using chiral auxiliary

Summary:

From literature it was observed that there are very few reports on the preparation of vicinal symmetrical and unsymmetrical diamines as ligands which are used in ATH of ketones and imines.

Symmetrical amines having C2 axis of symmetry are still widely produced by resolution as shown in the examples. In case of unsymmetrical diamines, in most of the cases chiral building blocks like, limonene, phenyl glycinol and 1,2-phenyl ethanol amine were used. The synthetic methodology used was the functionalization of hydroxyl group to suitable leaving group like O-tosyl group and then react with amine or azido nucleophiles. However, using this methodology it was observed that regioselective ring opening of azidine was difficult to achieve. The result was mixture of regioisomers of amino sulfonamides. This has provided, extra opportunity to test these regorisomeric ligands in ATH of ketones and imines.

Xu et al.[100, 209] developed a versatile cross coupling procedure, using chiral sulfynyl imines and nitrones, giving unsymmetrical diamines in excellent enanatiselcvity and diastereoselctivity. However, this method does not give access to the cis compounds of amine and sulfonamides as cross coupling resulted in only in one diastereoisomer.

SCOPE AND OBJECTIVES OF THE THESIS

Asymmetric Transfer Hydrogenation (ATH) has emerged as a powerful tool for the synthesis of chiral alcohols, amines etc. ATH is highly selective method and reduces the risks and safety restrictions associated with the use of molecular hydrogen. In ATH cheaper and less hazardous hydrogen donors like 2-propanol, formate salts, FA:TEA azeotrope etc are used. Amino alcohols and monotosylated diamines are most investigated ligands for this reaction. In most of the amino alcohols investigated the chiral centers are present on vicinal carbon atoms and in most of the cases chiral backbone is based on ephedrine or norephedrine. Similarly for monotosylated diamines most of the work is carried out using TsDPEN and TsCYDN ligands. Recently there are reports on the synthesis of unsymmetrical diamine ligands starting form cis amino indanol. Thus there is a scope to develop new ligands for ATH reaction. Considering the above facts, the present study was focused on the synthesis of new ligands based on amino alcohol and tosylated diamines and application to Asymmetric Transfer hydrogenation reactions of ketones. Since, 1 2 monosulfonated

diamines are also reported for ATH of imines, new ligands synthesized will also be screened for ATH of imines using FA: TEA source. The hydrogenated products of these substrates viz. chiral alcohols and chiral amines are useful as intermediates in pharmaceutical, agricultural, flavors. The main objective of this work was to develop efficient ligands in combination with transition metal complexes to get high activity and enantioselectivity for ATH of ketones and imines. It was also important to study the various parameters affecting activity, enantioselectivity and mechanistic features of these reactions to develop a deeper understanding. Therefore, following specific topics were chosen for the present work.

- Synthesis of new derivatives of Chiral β-amino alcohols having different electronic and steric properties.
- Synthesis of new 1, 2 monotosylated diamines having different electronic and steric properties.
- Screening of amino alcohols and 1,2 Monosulfonated diamines ligands using transition metal complexes in ATH of ketones using 2-propanol, sodium formate as hydrogen donors. Detailed investigations on the effect of various reaction parameters on activity and enantioselectivity.
- Screening of 1,2 monosulfonated diamine ligands with Transition metal complexes in ATH of ketones using FA:TEA in water as hydrogen donor. Effect of pH on conversion and enantioselctivity using transition metal catalysts and investigations on the effect of various reaction parameters on activity and enantioselectivity.
- Screening of 1,2 Monosulfonated diamine ligands with Transition metal complexes in ATH of imines using FA:TEA as hydrogen donor.

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Chapter 2: Synthesis of chiral, amino alcohols and 1,2 monotosylated diamines.

2.1 Introduction

Asymmetric transfer hydrogenation of prochiral ketones using various hydrogen sources are well documented in the literature. Owing to simplicity of operation and importance of the subject, the reaction has been extensively investigated using various ligands in recent years. A number of ligands with diverse structure have been developed for use in ATH of ketones. The ligands differ in the number and type of the donor atom(s) and in symmetry properties. These ligands contain various combinations of nitrogen, oxygen, phosphorus and sulfur as the donor atoms as discussed in the introduction chapter 1.12.3).They can be bi-dentate, tri-dentate or tetra-dentate. Two important classes of ligands which are popular and successful include amino alcohols and tosylated amines. Noyori et al.[1-3] introduced β-amino alcohol ligands[3] with Ru complex catalyst in 1996; which provided ligand acceleration effect in ATH of ketones. Since then the importance of amino alcohols continued to grow, as large number of chiral amino alcohols were synthesized and investigated for ATH of ketones. Andersson et al[4, 5] synthesized 2-azanorboronyl based amino alcohols as ligands with secondary nitrogen which is attached to rigid azanorboronyl ring. The simpler and very common methods like Grignard reaction and LAH reduction were used to synthesize stericaly rigid alcohols azanorbornyl ligands as shown in the 1.11.3 Van Leeuwen et al.[6, 7] and carpentier et al.[8] synthesized amino ethanol and norephedrine based derivatives. Various N–alkyl derivatives starting from 1R, 2S norephedrine using alkylation at amino nitrogen using benzyl bromide and phenbenzyl bromide were prepared. Frost et.al[9] synthesized amino alcohols from 1,2 phenyl ethanolamine and norephedrine using imine formation procedure in IPA. Also amino alcohols were prepared from Phenyl glycinol via imine formation followed by reduction of the imino alcohol using sodium borohydride. Singaram et al.[10] used the commercially available mixture of cis and trans limonene oxide, to synthesize new amino alcohols. They developed and used the kinetic resolution method in which trans limonene oxide undergoes nucleophilic ring opening by secondary amines in water in faster way compared to cis limonene oxide[10]. The unreacted cis limonene oxide was easily separated from trans amino alcohol by distillation. Schiffer's et al.[11] prepared 2-aminocyclohexanol derivatives by resolution using (R)- and (S)-Mandelic acid.

A variety of amino alcohol ligands have been designed and synthesized for ATH of ketones, with different electronic and steric properties as discusses in the Introduction Chapter and section 1.11,[4, 5, 7, 9, 12-14] but the structurally versatile monosulfonated diamine ligands are less reported and most reports are restricted on modifying the substitution either on sulfonamide group or on the phenyl group without disturbing the C2 symmetric backbone, of TsDPEN or TsCYDN.[15-19] Wills et al.[20] synthesized new unsymmetrical monosulfonated vicinal diamines from phenyl glycinol and 1,2-phenyl ethanolamine, using the basic functional group transformations like tosylation, ring opening of activated aziridine with sodium azide and subsequent reduction of azide to monotosylated diamines as per the earlier synthesis of Indane monosulfonated diamine.[20, 21] Very recently Ming-hua-xu synthesized further analogues of unsymmetrical vicinal diamines[22, 23] and showed that along with one phenyl group attached to carbon bearing the sulfonamide group, a bulky substituent on the carbon bearing amine is needed for high activity and enantioselectivity for ATH of ketones. Chiral auxiliary approach was used to synthesize various diamines using samarium diiodide induced coupling protocol. But the careful observation of these results indicate that there is no clear view on which kinds of substituents are tolerated and in which position.

Symmetrical amines having C2 axis of symmetry are still widely produced by resolution,[24-32] as discussed in the in the section 1.12.. In case of unsymmetrical diamines, as can be seen from the section 1.12, in most of the cases chiral building blocks like limonene, cis indene, phenyl glycinol, 1,2 phenyl ethanol amine[20, 21] were used. The synthetic methodology used was the functionalization of hydroxyl group in to suitable leaving group like o-tosyl group and then react with amine or azido nucleophiles. The result was mixture of regioisomers for amino sulfonamide. These regioisomers were separated by chromatography, and provided, extra opportunity to test these various ligands in ATH of ketones and imines.

Though there are several reports on the synthesis of amino alcohol ligands, the reports on the synthesis of monosulfonated diamine ligands are limited. In the present work we have synthesized amino alcohol ligands from cheap and easily available lactic acid and mandelic acid and unsymmetrical monotosylated diamine ligands from easily available norephedrine. The synthetis protocols were standardized during this work to prepare ligands on gram scale.

2.1.1 Amino alcohol based ligands

From the literature, it was clearly seen that amino alcohol structure and substituents significantly affect conversion as well as enantioselectivity, though the exact reasons for the observed effects (steric and electronic) are still not understood completely.[6, 7, 13] Also, most of the amino alcohol derivatives investigated have chiral centers on adjacent carbon atoms and are mostly derived from ephedrine or norephedrine. Other amino alcohol ligands like cis amino indanol or azabornyl methanol ligands have some rigidity in the structure. Based on the synthetic methodologies used for the synthesis of enantiopure β amino alcohols (used as ligands in ATH of ketones), it was observed that the methodologies used were substrate specific, rather than the general methods of synthesis. Thus compounds like amino acids, amino alcohols norephedrine, 1,2-phenyl ethanol[24, 33, 34] were taken and functional group transformations like reductive amination (of ethanol amines),[35-37] epoxide ring opening[38] or N-alkylation or acid amine coupling were carried out to obtain amino alcohol based ligands. Easily available molecules like s-Phenethyl amine,[39] limonene epoxide,[39, 40] amino acids or amino alcohols like ephedrine are the dominant substrates. It was also observed that, chiral resolution and kinetic resolution were popular methodologies for accessing pure amino alcohol compounds. (e.g. ephedrine[24, 33, 34] or terpenes[10] base amino alcohol)). Ortho lithiation of S-phenethyl amine methodology[39] was also used to synthesize amino alcohol as ligands which are used in ATH of ketones.

However there are seldom reports on use of cheap lactic acid, mandelic acid in the preparation of chiral amino alcohols used as ligands in ATH of ketones. The work carried out on the synthesis of new derivatives of amino alcohol ligands starting from cheap and easily available s-lactic acid and racemic mandelic acid is presented in the following section. Three ligands were prepared starting from S (-) methyl lactate and α-(S)-methyl benzyl amine, α-(R) methyl benzyl amine or benzyl amine as reactants. Typical procedures used for the synthesis and characterization details of ligands prepared are presented below.

2.1.1.1Materials

S-(-)-methyl lactate, racemic and S-methyl mandalate was purchased from local company. Benzyl amine, S-(α)-methyl benzyl amine, R-(α)-methyl benzyl amine and reagents like $NaBH_4$ and BF_3.etherate were purchased BOc protected p-toluene

sulfonamide, TMS azide, DABCO were purchased from sigma Aldrich in India. All the solvents like THF, toluene, methanol were bought from Loba chemicals. Norephedrine was purchased from local company.

2.1.1.2 Analytical Methods:

Ligand synthesis reactions were monitored by LC-MS analysis (Thermo MSQ plus). NMR spectra were recorded on Bruker AV 200 or AV 400 Avance II Machines and reported as parts per million (ppm). FT-IR spectra were recorded using Shimadzu DRS prestige 21 instrument and are reported in cm^{-1}. HR-MS was recorded using Agilent Q-TOF 6520 machine.

2.2 Synthesis of lactic acid based amino alcohol ligands:

Lactic acid based ligands were synthesized as per the scheme shown in **Fig. 2.1**.

For amino alcohols prepared based on S- lactic acid, first S-(-)-methyl lactate, was condensed with different amines such as benzyl amine, α-methyl benzyl amines (R and S) to give secondary amides. These secondary amide derivatives were reduced with the mixture of $NaBH_4$ and Lewis acid such as BF_3.etherate using the procedure developed by Brown[41]. Detailed procedure used for the synthesis of 2-Propanol-1-[(1-phenyl ethyl) amino] [S, S] using S (-) methyl lactate and α-(S)-methyl benzyl amine as reactants is presented below. All other amino alcohols based on lactic acid were prepared using similar procedure.

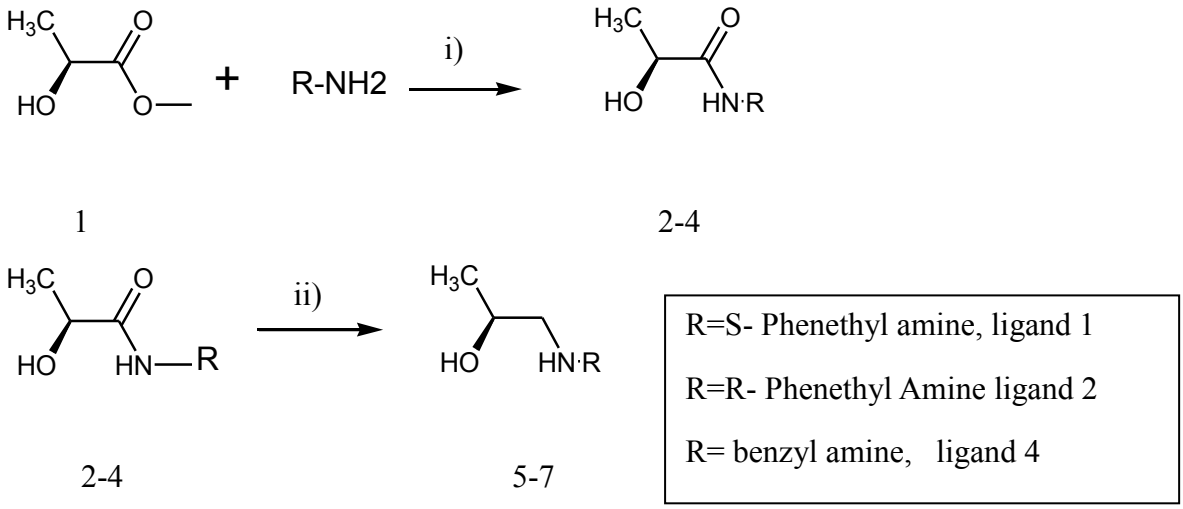


Fig. 2.1: Synthesis of lactic acid based amino alcohol ligands

Reaction conditions: i) Heating at 140^0C ii) $NaBH_4$ and BF_3.etherate in THF

2.2.1 Synthesis of ligand 1 ((S)-1-((S)-1-phenylethylamino) propan-2-ol)

2.2.1.1 Preparation of compound 2 Step 1: (2S)-2-hydroxy-N-((S)-1-phenylethyl) propanamide

S-(-)-methyl lactate 10.4 g (0.1 mol) and α-(S)-methyl benzyl amine 12.1 g (0.1 mol) were taken in a 100 ml round bottom flask and heated at 140^0c for 12 h. The contents were cooled to room temperature. 50 ml ice-cold solution of 1N HCl was added to the flask. The contents were shaken vigorously and aqueous layer was discarded to remove unreacted amine. Toluene (50 ml) was added to the remaining organic layer in the flask. The contents were heated at 70^oC for about 10 minutes to get clear solution. The solution was dried over sodium sulphate and concentrated under reduced pressure using rotary evaporator to get amide derivative. Brown color liquid, Yield of the compound was 16 g (83 %).

Compound 2

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm, 1.43 (d, *J*=7.0 Hz, 3 H) 1.50 (d, *J*=6.8 Hz, 3 H) 4.20 (q, *J*=6.8 Hz, 1 H) 5.11 (q, *J*=7.08 Hz, 1 H) 7.22 - 7.40 (m, 5 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm, 21.3, 21.9, 48.4, 68.4, 126.1, 127.4, 128.7, 143.0, 173.4; FT-IR (neat, cm^{-1})**:** 3383, 3327, 2980, 2877, 1658, 1122**;** HR-MS: measured 193.1103, calculated, 193.1107 difference 2.3 ppm;[α] $^{25}_D$= -27.5(1.0., $CHCl_3$);

2.2.1.2 Preparation of compound 5 (Ligand 1) Step 2: (S)-1-((S)-1-phenylethylamino) propan-2-ol

$NaBH_4$ (3.33 g, 87.6 mmol) was taken in 250 ml round bottom flask containing 100 ml THF (dried over KOH). Amide derivative (4.2 g, 21.8 mmol) was dissolved in 50 ml THF (dried over KOH). The solution was added slowly to $NaBH_4$ solution. The resulting solution was cooled to 0-5 ^oC using ice water bath. Using dropping funnel, BF_3.etherate 10 ml (11.4 gm., 80 mmol) was added carefully to the above solution over a period of 20 minutes, making sure that excessive pressure does not develop. The solution was stirred for 1 hour and allowed to come to room temperature. The solution was refluxed for three hours and after cooling to room temperature 10 ml of 2N HCl was added carefully, followed by 30 ml distilled water, to destroy excess $NaBH_4$ present. The resulting solution was concentrated to ~ 40 ml and extracted with n-hexane (2 x 30 ml). 5N NaOH solution was added to aqueous layer to adjust the pH

to 11-12 and extracted with ethyl acetate (3 x 30 ml). Ethyl acetate layer was dried over sodium sulphate and concentrated to get yellowish liquid **compound 5 (Ligand 1), (**2.5 g, yield: 64 %).

Compound 5 (Ligand 1)

^{1}H NMR (400MHz, CHLOROFORM-d) δ,ppm, 7.34 - 7.19 (m, 5H), 3.71 (d, *J*=6.5 Hz, 1H), 3.62 (dd, *J*=2.8, 5.8 Hz, 1H), 2.50 (dd, *J*=12.0 Hz,3.4Hz 2H), 2.30 (dd, *J*=3.4, 12.0 Hz, 1H), 1.35(d, *J*=6.0 Hz, 3H), 1.06 (d, *J*=6.3 Hz, 3H);^{13}C NMR (101MHz, CHLOROFORM-d) δ ppm. 145.6 128.6, 127.1, 126.5, 66.4, 58.7, 24.1, 20.7;FT-IR Neat (cm^{-1}): 3381, 3309, 2966, 2877, 1454, 1118, 744, 698**,** HR-MS: measured 179.1313, calculated mass, 179.1310 difference 1.7 ppm; [α] $^{25}_{D}$= -17.5 ,(1.0. $CHCl_3$);

2.2.2 Synthesis of compound 6 (Ligand 2)

2.2.2.1 Step 1: Preparation of compound 3 (2S)-2-hydroxy-N-((R)-1-phenylethyl) propanamide

The amide derivative was prepared using S-(-)-methyl lactate compound **1** and α-(R) methyl benzyl amine as reactants and same procedure used for compound 2. Product obtained was yellowish semi solid (15.5 g, yield: 81 %).

Compound 3

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.23 (d, *J*=7.0 Hz, 3 H) 1.53 (d, *J*=6.8 Hz, 3 H) 4.40 (q, *J*=6.8 Hz, 1 H) 5.09 (q, *J*=7.1 Hz, 1 H) 7.20 - 7.39 (m, 5 H)

^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm,20.7, 22.1, 47.3, 67.6, 126.2, 127.3, 128.6, 142.8, 173.9; FT-IR (neat, cm^{-1})**,** 3353, 3329, 2954, 2865, 1663, 1028**;** HR-MS: measured 193.1103, calculated mass, 193.1105 difference 1.1 ppm;[α] $^{25}_{D}$= +97.5(1.0, $CHCl_3$);

2.2.2.2 Preparation of compound 6 (ligand 2) Step 2: 2-Propanol-1-[(1-phenyl ethyl) amino] [S, R]

The ligand was prepared by reduction of compound **3.** Same procedure as used for ligand 1 synthesis is used. Product obtained was yellowish semi solid (2.5 g, yield: 64 %).

Compound 6 (Ligand 2)

^{1}H NMR: δ ppm,1.11-1.14, (d, J = 6.2 Hz,3H), 1.39-1.42, (d, J = 6.6 Hz,3H), 2.23-2.33, (dd, J = 9.6 Hz, 12.2 Hz,1H), 2.58-2.65, (dd, J = 3 Hz, 11.8 Hz,1H) and 2H (N-H and O-H, br, singlet), 3.77-3.80, (m,2H), 7.31-7.41, (m,5H).^{13}C NMR: δ ppm

143.7, 127.5, 126.5, 125.5, 64.7, 56.7, 53.3, 23.2, 19.4;FT-IR (cm^{-1}): 3390,3323, 2924, 1450, 1118, 1064, HR-MS: measured179.1314, calculated mass 179.1310;[α] $^{25}_{D}$= +81.0,(1.0.$CHCl_3$);

2.2.3 Synthesis of compound 7 (ligand 3), (S)-1-(benzyl amino) propan-2-ol

2.2.3.1 Preparation of compound 4. Step 1: (S)-N-benzyl-2-hydroxy propanamide

The amide derivative was prepared using S-(-)-methyl lactate and benzyl amine as reactants and same procedure used for synthesis of . Product was obtained as a yellowish liquid (15 g, yield: 83 %).

Compound 4

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm) 1.46 (d, *J*=6.78 Hz, 3 H), 4.28 (q, *J*=6.8 Hz, 1 H) 4.46 (d, *J*=5.8 Hz, 2 H), 7.23 - 7.40 (m, 5 H);^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm, 21.4 , 43.2 , 68.5 , 127.6 , 127.7 , 128.7 , 137.9 , 174.2 ; FT-IR (neat, cm^{-1})**:** 3383, 3309, 2966, 2877, 1653, 1125;HR-MS: measured 179.0948, calculated mass, 179.0946 diff 1.1 ppm;[α] $^{25}_{D}$= +43.2 ,(1.0.,$CHCl_3$);

2.2.3.2 Preparation of compound 7 (ligand 3) Step 2: (S)-1-(benzyl amino) propan-2-ol

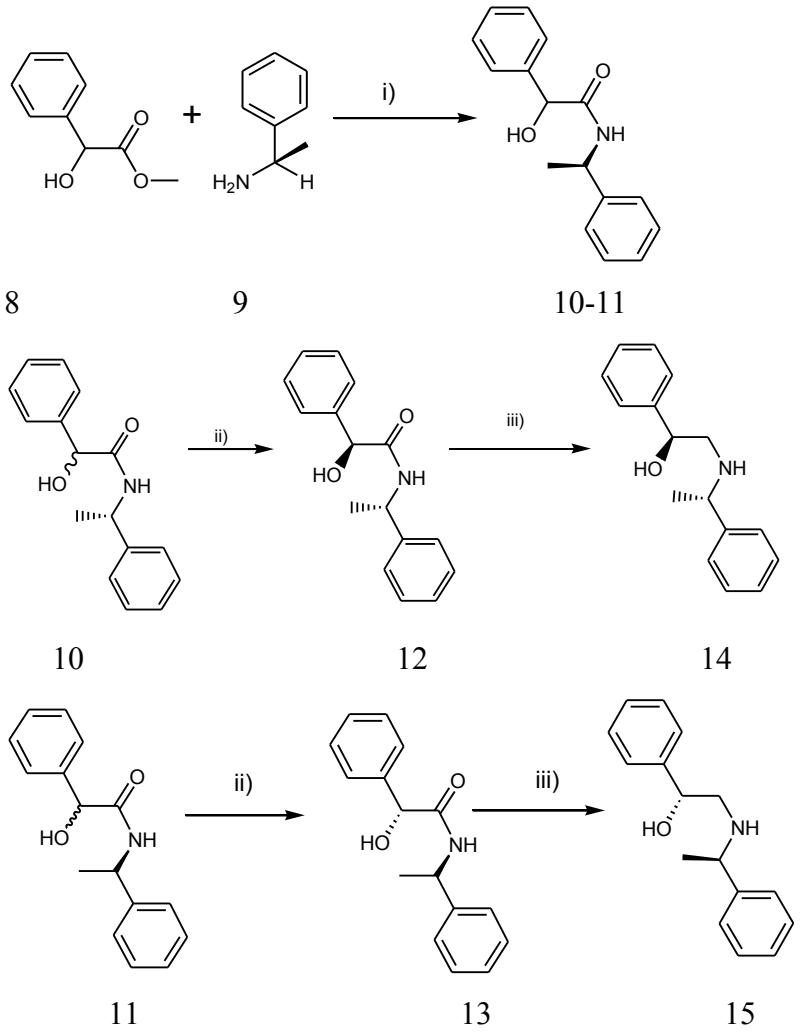
The ligand was prepared by reduction of compound **4.** Same procedure as used for synthesis of compound 2.Product obtained was yellowish liquid (2.7 g, yield: 75 %).

Compound 7 ligand 3

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.46 (d, *J*=6.8 Hz, 3 H), 4.28 (q, *J*=6.8 Hz, 1 H) 4.46 (d, *J*=5.8 Hz, 2 H) 7.23 - 7.40 (m, 5 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 127.4, 127.1, 126.1, 64.6,55.3, 52.6, 19.3;FT-IR(neat,cm^{-1}): 3309, 3029, 2970, 1455, 1110, 1030, 744,;HR-MS: measured mass 165.1154, calculated mass,165.1154; [α] $^{25}_{D}$= +34.9 ,(1.0., $CHCl_3$);

2.3 Synthesis of amino alcohol ligands based on mandelic acid

The synthesis of amide derivative was carried out by the reaction of methyl mandalate (S and R) with alpha methyl benzyl amine (S and R). as per the Fig. 2.2



8 9 10-11

10 12 14

11 13 15

Fig. 2.2: Preparation of mandelic acid based amino alcohols ligands

Reaction conditions: i) heating at 140 ^{0}C, ii) Crystallization using toluene, iii) $NaBH_4$ and BF_3 etherate in THF

The synthesis of amide derivative was carried out by the reaction of methyl mandalate (S and R) with alpha methyl benzyl amine (S and R). However During the reaction it was found that racemization at the alpha carbon of mandelic acid occurs. This leads to diastereotopic (mixture of amides (10 and 11) (Confirmed by NMR analysis). This required purification of diastereo isomers. So it was thought that racemic mandelic acid methyl ester could in principally be used so that synthesis including the separation of amide derivatives could be carried out using cheaper starting material like racemic methyl mandalate instead of chiral methyl mandalate. Few experiments were carried out to standardize the procedure.

Thus condensation of racemic methyl mandalate with (R)-α-methyl benzyl amine was carried out and formation of a mixture of diasteriomers was expected. The mixture of diasteriomers obtained was sticky mass of solid settled at the bottom of the flask. When toluene was added to this sticky mass, it was observed that part of the sticky mass dissolved in the toluene and white crystalline solid was found to be settled at the bottom. HPLC analysis of the toluene layer indicated that the toluene was containing one of the diasteriomer in more quantity. This observation prompted to make us think that separation of the diasteriomers could be carried out using toluene as a solvent. After few trials, procedure was standardized for the separation of diasteriomers. The details are given in detailed procedure mentioned in section 2.5.1. NMR analysis of the white solid showed that the solid obtained was pure single diastereo isomer (compound 12 or 13, depending on the amine used). With this simple technique, we were able to separate pure enantiomers (R,R or S,S) from the mixture of diasteriomers, while other diasteriomer (R,S or S,R) remained in the solution, along with small amount of R,R or S, S isomer. The other diastereoisomer, which was soluble in toluene, could not be isolated in pure form.

Reduction of the purified amide using sodium borohydride in the presence of Lewis acid such as BF_3.etherate (the literature procedure described by Brown[41]) gives required amino alcohol ligand **(compound 14 and compound 15**) (Fig. 2.2). Compounds14 and 15 were characterized by HR-MS; ^{1}H NMR analysis. Compound 14 was characterized by single crystal X-ray analysis (Figure 2.3 for ^{1}H NMR). The single crystal analysis of ligand 4 showed the configuration, relative to the other chiral center which was not disturbed during the reaction. (Fig. 2.4, ORTEP diagram), (single crystal X-ray analysis details are attached in Appendix).

Using this strategy two amino alcohols were prepared starting from racemic mandelic acid (Fig.2. 2).

^{1}H NMR (400MHz, Chloroform-d) δ = 7.34 - 7.18 (m, 10H), 4.55 (dd, *J*=3.6, 8.7 Hz, 1H), 3.74 (d, *J*=6.8 Hz, 1H), 2.72 (dd, *J*=3.8, 12.3 Hz, 1H), 2.64 - 2.36 (m, 3H), 1.36 (d, *J*=6.5 Hz, 3H),

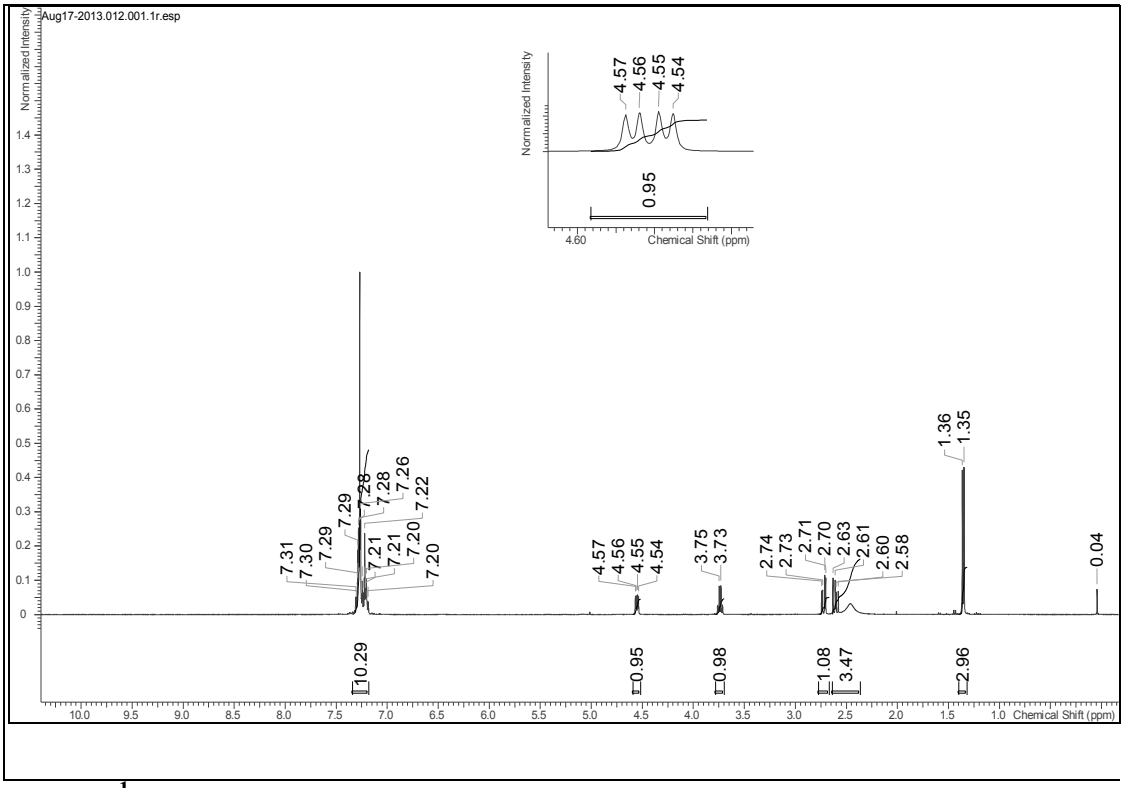


Fig. 2.3:^{1}H NMR of compound 14 (Ligand 4)

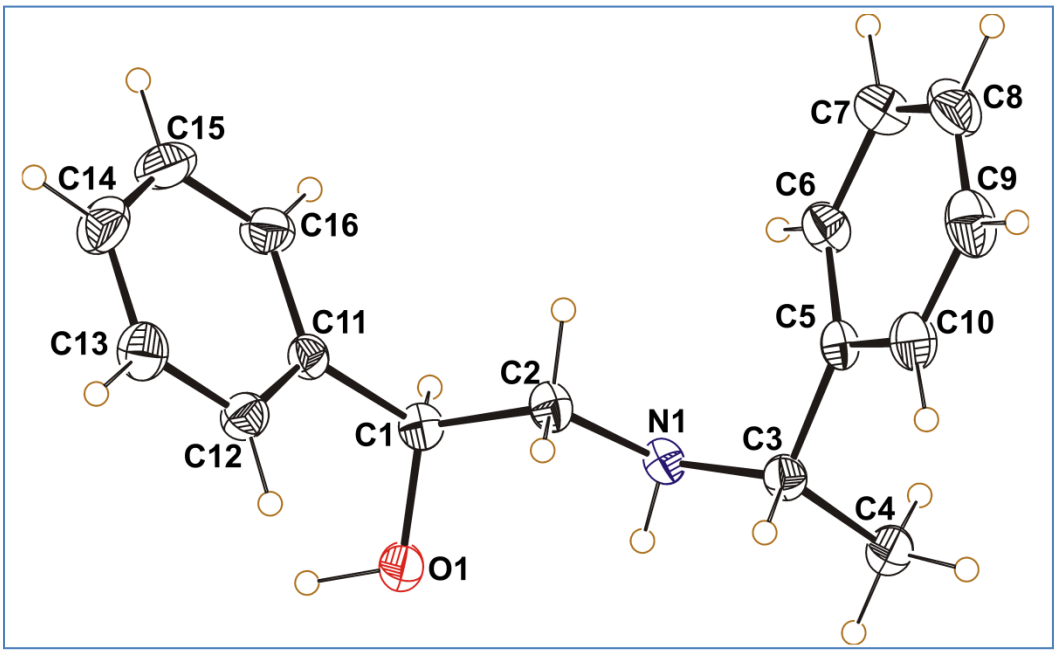


Fig. 2.4: Crystal structure of compound 14 (Ligand 4)

The data has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 645066.

2.3.1 Preparation of Compound12

Step 1: (2S)-2-hydroxy-2-phenyl-N-((S)-1-phenylethyl)acetamide

Methyl mandalate 16.6 g (0.1 mol) and α-(S)-methyl benzyl amine12.1 g (0.1 mol) were taken in a 250 ml round bottom flask and heated at 130^{o}C for 3 hours. The solution was cooled to room temperature and 100 ml of ice-cold solution of 1N HCl was added with stirring. Sticky solid separated on stirring for 15 minutes. Sticky solid (mixture of racemic amide derivatives) was filtered and dissolved in 30 ml warm toluene to obtain clear solution. The clear solution obtained was cooled to 0^{o}C and kept standing for 12 hours to obtain white crystalline solid. White crystalline solid was filtered and washed with toluene. White solid obtained was pure (S, S) (>99% purity) isomer of amide derivative **compound 12** (6.5 g, yield 25.5%).

Compound 12:

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.43 (d, *J*=6.8 Hz, 3 H), 4.98 (s, 1 H) 5.04 (q, *J*=6.3 Hz, 1 H) 7.23 - 7.40 (m, 5 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm; FT-IR(KBr,cm^{-1}): 3383,3203,2989, 1652, 1530, 1060, HR-MS: measured mass 255.1255, calculated mass,255.1259; difference 1.6 ppm [α] $^{25}_{D}$= -82.8 ,(1.0. $CHCl_3$);

2.3.1.2 Preparation of compound 14 (ligand 4)

Step 2: (S)-2-((S)-1-phenylethylamino)-1-phenylethanol

$NaBH_4$ (3.33 g, 90 mmol) was taken in a 250 ml round bottom flask containing 100 ml THF (dried over KOH). Amide derivative (5.2 g, 20.4 mmol) was dissolved in 50 ml THF (dried over KOH) in a separate flask and was added slowly to $NaBH_4$ solution. The resulting solution was cooled to 0-5 ^{o}C using ice water bath. BF_3.etherate 10 ml (11.4 gm, 80 mmol) was taken in dropping funnel and was added carefully to the above solution over a period of 20 minutes, making sure that excessive pressure does not develop. The solution was stirred for 1 hour and allowed to come to room temperature. The solution was refluxed for three hours and after cooling to room temperature, 10 ml of 2N HCl was added carefully followed by 30 ml distilled water, to destroy excess $NaBH_4$ present. The resulting solution was concentrated to ~ 40 ml and extracted with n-hexane (2 x 30 ml). 5N NaOH solution was added to aqueous layer to adjust the pH to 11-12 and the solution was cooled to room temperature to get white crystalline product, which was recrystallized using

methanol to get 3.5 g of the pure product (yield: 71.2 %).,(^{1}H NMR , Fig. 2.3) Toluene solution contained more amount (~20% by NMR) of the other diastereoisomer. Our efforts to isolate it in pure form were not successful.

The separation of diasteriomers by preferential precipitation of one of the isomer from the toluene solution has allowed us to develop easy procedure for the synthesis of (R, R) and (S, S) isomers starting from cheap racemic methyl mandalate as reactant.

Compound 14 (ligand 4)

^{1}H NMR (400MHz, CHLOROFORM-*d*)) δ ppm, 7.34 - 7.18 (m, 10H), 4.55 (dd, *J*=3.6, 8.7 Hz, 1H), 3.74 (d, *J*=6.8 Hz, 1H), 2.72 (dd, *J*=3.8, 12.3 Hz, 1H), 2.64 - 2.36 (m, 3H), 1.36 (d, *J*=6.5 Hz, 3H), ^{13}C NMR: (101 MHz, CHLOROFORM-*d*) , δ ppm 145.3, 142.5, 128.6, 128.4, 127.5, 127.1, 126.5, 125.8, 72.4, 58.5, 55.3, 24.1;FT-IR(KBr, cm^{-1}): 3290, 2920, 1454, 1064,; HR-MS: measured mass 241.1465,calculated mass 241.1467;[α] $^{25}_D$= -44.7,(1.0., $CHCl_3$);

2.3.2. Synthesis of compound 15 (ligand 5)

2.3.2.1 Preparation of compound 13

[((2R)-2-hydroxy-2-phenyl-N-((R)-1-phenylethyl)acetamide

Amide derivative **Compound 13** was prepared by the reaction of racemic methyl mandalate with R-Phenethyl amine using the procedure mentioned in synthesis of compound 12 **(6.4g, Yield 25%)**

Compound 13

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.46 (d, *J*=6.8 Hz, 3 H), 4.96 (s, 1 H) 5.03 (q, *J*=6.3 Hz, 1 H) 7.20 - 7.41 (m, 5 H); ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 170.1, 145.1 142.7, 128.6, 128.4, 127.5, 127.1, 126.5, 125.8, 72.4, 64.5, 24.1;FT-IR(KBr,cm^{-1}): 3383,3203,2989, 1652, 1530, 1060, ;HR-MS: measured mass 255.1255, calculated mass, 255.1259; difference 1.6 ppm [α] $^{25}_D$= +84.9 ,(1.0. $CHCl_3$);

2.3.2.2 Preparation of Compound 15 (ligand 5)

Step 2: (R)-2-(R)-1-phenylethylamino)-1-phenylethanol

The ligand was prepared by the reaction compound 13 using the procedure mentioned for compound 14.(Ligand 40 . White crystalline product obtained was recrystallized using methanol to get 3.5 g of the pure product (yield: 71.2 %).

Compound 15

1H NMR: δ=1.42-1.45, 3H (d, J=6.6 Hz), δ =2.21, 2H (br, singlet), δ= 2.62-2.68, 1H (dd, J=8.5 Hz, 12.2 Hz), δ= 2.72-2.83, 1H (dd, J=3.8 Hz, 12.2 Hz), δ=3.77-3.86, 1H (q, J=6.8 Hz), δ= 4.59-4.65, 1H (dd, J=3.8 Hz, 8.4 Hz), δ=7.30-7.37, 10H (multiplet)^{13}C NMR: (δ in ppm) 145.3, 142.5, 128.6, 128.4, 127.5, 127.1, 126.5, 125.8, 72.4, 58.5, 55.3, 24.1;FT-IR(KBr, cm^{-1}): 3290, 2920, 1454, 1064, 703;HR-MS: measured mass 241.1464,Target mass 241.1467 difference 1.2 ppm;[α] $^{25}_{D}$= +46.3 ,(1.0. $CHCl_3$);

Thus in this section synthesis of amino alcohol based ligands was carried out using cheap and easily available compounds like lactic acid and mandelic acid. The structures of five ligands prepared are presented in Figure 2.5.

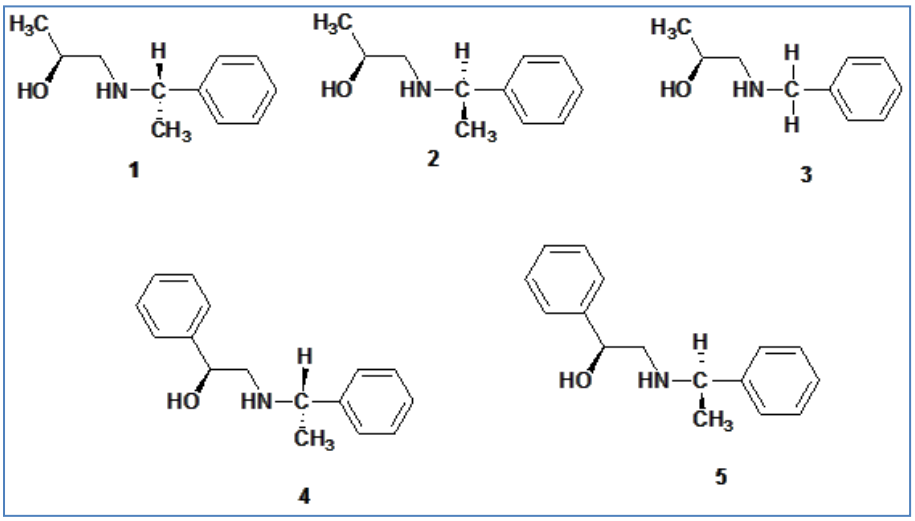
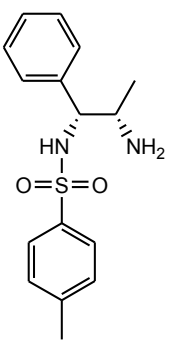


Fig. 2.5: Various amino alcohols synthesized

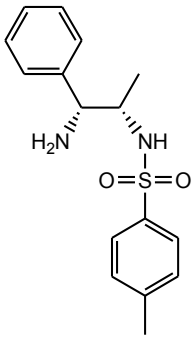
2.4 Synthesis of 1, 2 monotosylated unsymmetrical diamine ligands

From literature section(1.12) it was observed that there are very few reports on the preparation of vicinal symmetrical and unsymmetrical diamines as ligands which are used in ATH of ketones. Symmetrical amines having C2 axis of symmetry are still widely produced by resolution as discussed in the literature section.[22, 24, 33, 34] For the synthesis of unsymmetrical diamine ligands (1.12) chiral building blocks like, limonene[10] Phenyl glycinol, 1,2-phenyl ethanol amine[20, 21] have been used. The synthetic methodology used involved functionalization of hydroxyl group in to a suitable leaving group like o-Tosyl group and then reacting it with amine or azido nucleophiles. The result was mixture of regioisomers for amino sulfonamides, which were separated by column chromatography. This provided, opportunity to test various regioisomers, as ligands in ATH of ketones and imines.

In the present work unsymmetrical vicinal diamine ligands have been prepared starting from cheap and easily available enantiomers of norephedrine. We have prepared four pairs of unsymmetrical vicinal diamine ligands which have different stereo and regio positions of amine and sulfonamide groups as shown in Fig.2.6. The ligands 6 -9 and ligands 10-13 are enantiomers of each other respectively. The work described here presents two methodologies developed for synthesis of ligands. The methodology used for the synthesis Ligand 6, ligand 7 is presented separately. For ligand 8 and ligand 9; combined methodology for synthesis and purification is adopted which is described in detail.



6



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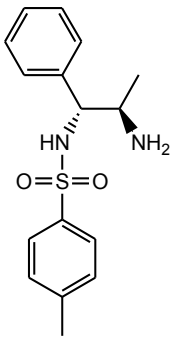

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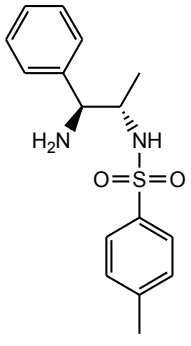

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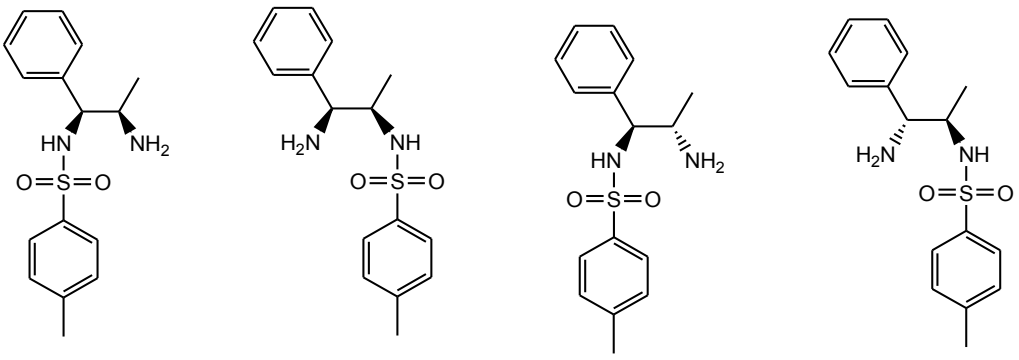


10 11 12 13

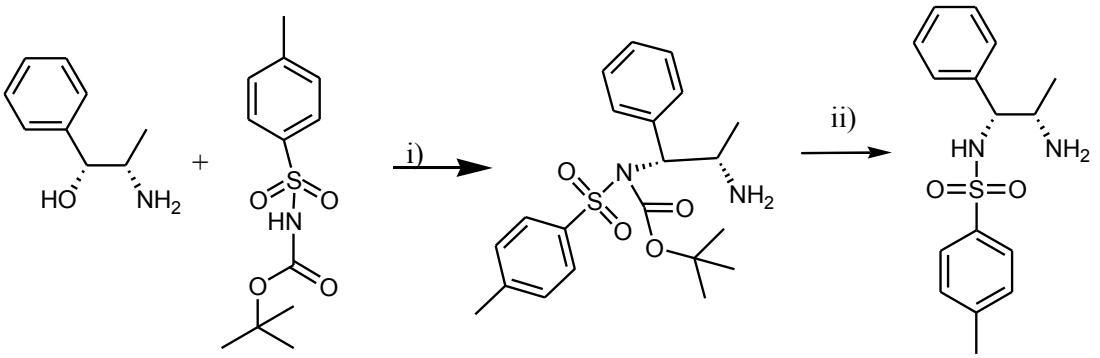
Fig.2.6: Various monosulfonated diamine ligands synthesized

2.4.1 Synthesis of compound 18 (ligand 6) and 18 a (ligand 10)

Mitsunobu reaction[42] is useful reaction for converting the hydroxyl group in to various functional groups by using a wide variety of nucleophiles. Both inter and intra versions of Mitsunobu reaction are well documented in the literature.[43] Replacement of Hydroxyl group of 1R, 2S norephedrine by *p*-Toluene sulfonamide could be the easiest approach to synthesize, amino sulfonamide ligands. However, it is well known that under Mitsunobu conditions triphenyl phosphine reacts with *p*-toluene sulfonamide to form $TsN{=}PPh_2$.[44] Use of alkylated sulfonamides would result in tertiary sulfonamides which are not useful in ATH of ketones and imines. However use of N-acyl Sulfonamide discovered by the same group provided excellent opportunity to use BOc protected sulfonamide[44] as nucleophile in Mitsunobu Reactions. N-BOc sulfonamide was easily prepared in high yield by the addition of t-butanol to commercially available p-toluene sulfonyl isocyanate.

1R, 2S norephedrine and its enantiomer 1S, 2R norephedrine were used as key starting materials and scheme shown in Fig. 2.7 is followed to generate the compound **18.** The reaction of N-BOc sulfonamide with 1R, 2S norephedrine under Mitsunobu conditions was carried out (Fig.2.7). It was expected that the reaction will proceed with the inversion of configuration, at hydroxyl carbon, based on Mitsunobu reaction mechanism. ^{1}H NMR spectrum however, showed the coupling constant of the vicinal hydrogen to be 4 Hz (Fig.2.8). Thus indicating that the sulfonamide and amine geometry to be cis with respect to each other. The probable cause for this could be, NH_2 group adjacent to hydroxyl group forming intermediate aziridine with inversion of configuration. The intermediate aziridine ring opening is caused by the N-BOc

sulfonamide again with inversion of configuration to get the compound 18 (efforts for isolation of the intermediate 17 failed, during the isolation 17 was partially getting converted to 18). Similar observation for Mitsunobu reaction of amino alcohols and ephedrine was reported by Jules Freedman and others.[45, 46] This approach got the first target of amino sulfonamide ligands, with cis geometry. The yield obtained in this reaction was moderate, due to difficulty in ring opening of inactive aziridine without Lewis acid catalyst.



16 17 (intermediate) 18

Fig.2.7: Synthesis of compound 18 (ligand 6)

Reaction conditions: i) DEAD, Triphenyl phosphine in DCM, ii) 4N HCl in Dioxane

2.4.2 Preparation of compound 18 (ligand 6)

In a 3 necked 100 ml round bottom flask 1R, 2S norephedrine (3.0g,20 mmol), triphenyl phosphine (5.2 g, 20 mmol) and of BOc protected *p*- toluene sulfonylamide(5.42 g,20 mmol) were stirred in dichloromethane, (50ml) and the solution was cooled to 0-5^{0}C. To this solution DEAD (3.46 g, 20 mmol) was added slowly over a period of 15 mins. The solution was brought to room temperature and stirred for another 6 h. After 6 h of stirring, reaction mass was washed with 1N HCl (10ml) in water (40 ml). 4N HCl in dioxane (20 ml) was added and the reaction mixture was heated at 50^0 for 2 h. The reaction mass after heating was evaporated to near dryness and dichloromethane (50 ml) and water (50 ml) was added to it. The layers were shaked vigorously and DCM layer was discarded. Aqueous layer was neutralized slowly using dilute NaOH (4N), by drop wise addition to the aqueous layer till the pH was 7. The white solid precipitated was allowed to digest overnight at room temperature and then filtered using sintred glass crucible. The precipitate was

washed 2-3 times using water (10 ml) and was dried in oven at 60^0C. White solid was crystalized from toluene to get pure sulfonamide Ligand, 2 g, (Yield 32.8 %) ligand **6.**

(**Compound 18) ligand 6**

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.52 (d, *J*=8.0 Hz, 2H), 7.14 (dd, *J*=1.6, 4.9 Hz, 3H), 7.11 - 7.01 (m, 4H), 4.20 (d, *J*=4.0 Hz, 1H), 3.20 - 3.13 (m, 1H), 2.33 (s, 3H), 0.95 (d, *J*=6.5 Hz, 3H) ^{13}C NMR (101MHz, CHLOROFORM-d) δ ppm, 142.9, 137.5, 137.2, 129.2, 128.1, 127.6, 127.4, 127.0, 62.6, 51.0, 21.5, 20.7FT-IR(KBr, cm^{-1}) 3574, 3358, 2878,1599,1323,1162;HR-MS calculated Mass: 304.1245, measured Mass: 304.1254 Difference 2.7 ppm;[α] $^{25}_D$= -64.2 (1.0,CHCl3);

2.4.2.1 Preparation of compound 18a (Ligand 10)

The compound **18a** was prepared by using the same procedure presented in the earlier for compound 18 using 1S, 2R norephedrine as the starting material.

(**Compound 18a) ligand 10**

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.52 (d, *J*=8.0 Hz, 2H), 7.14 (dd, *J*=1.6, 4.9 Hz, 3H), 7.11 –6.98 (m, 4H), 4.21 (d, *J*=4.0 Hz, 1H), 3.20 - 3.15 (m, 1H), 2.31 (s, 3H), 0.95 (d, *J*=6.5 Hz, 3H) ^{13}C NMR (101MHz, CHLOROFORM-d) δ = 142.8, 137.5, 137.2, 129.2, 128.1, 127.6, 127.4, 127.0, 62.6, 51.0, 21.5,20.7;FT-IR(KBr,cm^{-1}) 3572, 3364, 2878,1599,1323,1160;HR-MS calculated Mass: 304.1245, measured Mass: 304.1249 Difference 1.3 ppm;[α] $^{25}_D$= +62.7 (1.0,CHCl3);

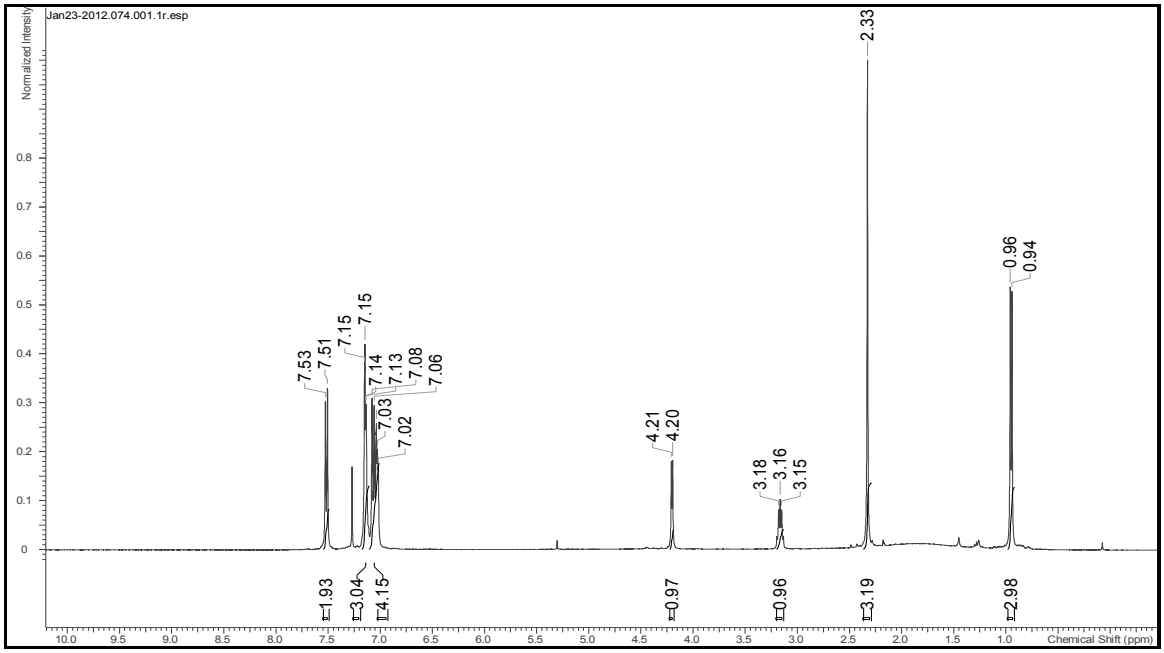
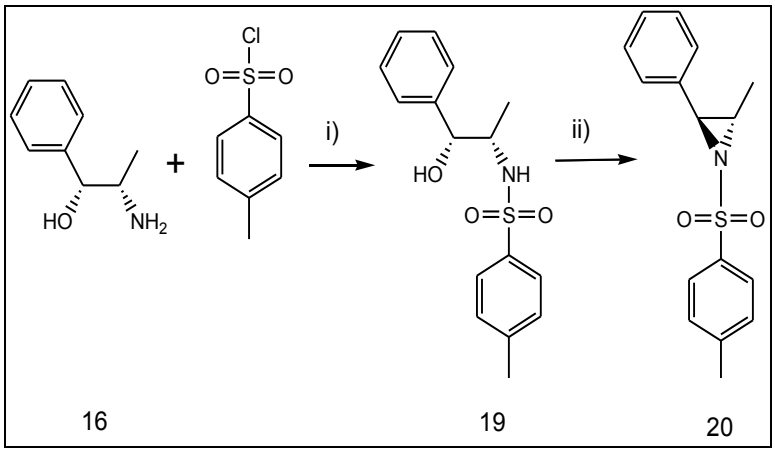


Fig. 2.8: ^{1}H NMR spectrum of compound 18 (ligand 6)

2.4.3 Synthesis of ligand 7 (compound 22) and ligand 11 (Compound 22a)

Synthesis of ligand 7 (compound **22)** has been carried out as per the literature procedure[47, 48], till 3 steps. The schematic diagram is shown in Fig.2.8.



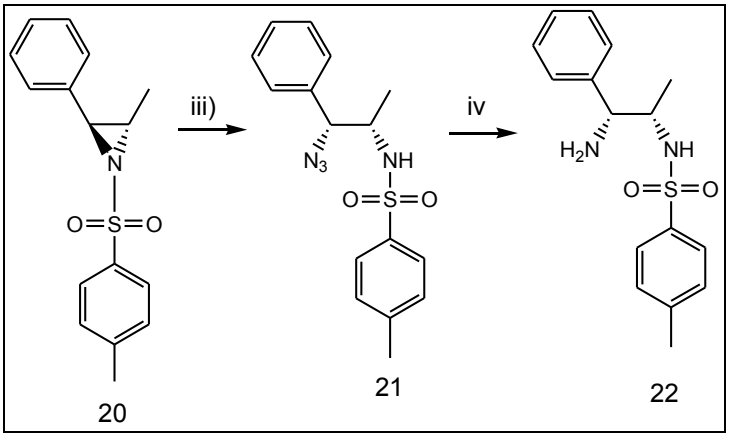


Fig. 2.9: Synthetic methodology for compound 22 (ligand 7 and ligand 11)

Reaction conditions: i) Triethyl amine in t-Butyl methyl ether ii) DEAD, Triphenyl phosphine in THF, iii) Sodium azide in Acetonitrile: water, iv) Triphenyl phosphine in THF and water

In first step norephedrine (compound **16**) was tosylated using *p*-Toluene sulfonyl chloride; to get compound **19**. The purification was done using crystallization in toluene, whereas in literature column chromatogephy was used to obtain pure compound. In second step Mitsunobu reaction was carried out with tosylated norephedrine derivative (compound **19**). The resultant N-tosylated aziridine compound **20** showed coupling constants in ^{1}H NMR which are characteristic for the vicinal protons in a strained 3 membered ring. It was observed that intramolecular cyclisation occurs with inversion of configuration at the hydroxyl carbon. This observation was found to be consistent with literature.[47, 48] In the third step ring opening of tosylated aziridine (compound **20**) was carried out using sodium azide in mixture of water and acetonitrile in 20:80 volume ratio to obtain compound **21** as the product.[47] The ring opening of this tosylated aziridine occurs with complete inversion at the phenyl carbon resulting in overall retention of the configuration (w.r.t starting norephedrine configuration). Reduction of **21** with triphenyl phosphine and water gave compound **22** (ligand **7**). Thus starting compound **16** and final compound **22** (ligand **7**) will have the same configuration at the chiral carbon. The observation was found to be consistent as in synthesis of compound **18.**

2.4.3.1Preparation of compound 19:

Step1:**N-[(1S,2R)-2-hydroxy-1-methyl-2-phenyl-ethyl]-4-methyl-benzene sulfonamide**

In a 3 necked 250 ml round bottom flask norephedrine (15.0 g, 100 mmol) was taken and tert-butyl methyl ether (50 ml) and triethyl amine (10 ml) were added to it. *p*-toluene sulfonyl chloride (19 g, 100 mmol) dissolved in tert-butyl methyl ether (50 ml) was added drop wise to the solution containing norephedrine at 0^{o}C. The solution was stirred at room temperature for 6 h. After 6 hours the solution was washed with 2 N HCl (50 ml). The tert-butyl methyl ether layer was concentrated to get the crude sulfonamide derivative, which was crystallized from toluene to get the pure product yield (22 g), yield 72%.

Compound **19.**

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.84 (d, *J*=6.8 Hz, 3 H) 2.33 (s, 3 H) 3.47 (dq, *J*=6.7, 3.4 Hz, 1 H) 4.72 (d, *J*=3.01 Hz, 1 H) 7.13 - 7.24 (m, 7 H) 7.69 (d, *J*=7.7 Hz, 2 H)^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 14.6 ,21.5 ,55.1 ,75.8 , 126.1 , 127.1 , 127.6 , 128.3 , 129.8 ,137.8 , 140.4 ,143.5140.4, 143.; FT IR (KBr,cm^{-1}): 3500, 3278, 1494, 1326, 1159, 1088 ;HR-MS calculated Mass: 305.1086, measured Mass: 305.1083 diff (0.9ppm);[α] $^{25}_{D}$= -16.8 (1.0, CHCl3);

2.4.3.1.1. Preparation of compound 19a

N-[(1R,2S)-2-hydroxy-1-methyl-2-phenyl-ethyl]-4-methyl-benzene sulfonamide

The enaniomer **19a** was synthesized using the same procedure described in earlier for compound 19 and starting from 1S, 2R norephedrine.

Compound **19a**

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 0.84 (d, *J*=6.8 Hz, 3 H) 2.33 (s, 3 H) 3.47 (dq, *J*=6.8, 3.4 Hz, 1 H) 4.72 (d, *J*=3 Hz, 1 H) 7.13 - 7.24 (m, 7 H) 7.69 (d, *J*=7.7 Hz, 2 H)^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 14.5 , 21.6 , 55.1 , 75.8, 126.1 , 127.0 , 127.6 , 128.3 , 129.8 ,137.9 , 140.3 , 143.5;FT-IR (KBr, cm^{-1}): 3480, 3306, 14941327, 1200, 1157, 1093;HR-MS calculated Mass: 305.1086, measured Mass: 305.1081 diff 2.0 ppm[α] $^{25}_{D}$= +16.8 (1.0, CHCl3);

2.4.4 Preparation of compound 20

Step 2: (2S, 3S)-2-methyl-3-phenyl-1-(p-tolylsulfonyl) aziridine,

In a 100 ml 3 necked flask 6.1 g (20 mmol) of compound **19** was taken and THF (50 ml) was added to it. Triphenyl phosphine (5.26 g, 20 mmol) dissolved in THF (20 ml) was added to the solution. The reaction mixture was cooled to 0^{o}C, DIAD (4.1 g, 20 mmol) was added slowly to the reaction mixture, maintaining the temperature at 0 to 5^{0}C. The reaction mixture was further stirred for 6 h and then concentrated to remove THF. Cyclohexane (50 ml) was added to the solids and contents were heated at 50^{0}C for 1h. The resulting suspension was filtered off, and the cyclohexane layer was concentrated to get the crude tosylated aziridine. Crude product was purified by column chromatography to get pure sample (cyclohexane: ethyl acetate; 9:1), (5g, yield, 86%).

Compound 20

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.82 (d, *J*) 8.3 Hz, 2H), 7.25 (m,5H), 7.15 (m, 2H), 3.79 (d, *J*) 4.4 Hz, 1H), 2.91 (m, 1H), 2.39 (s,3H), 1.84 (d, *J*) 6.1 Hz, 3H);^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm, 143.9, 137.9, 135.5, 129.5, 128.5, 128.0, 127.2, 126.3, 49.2, 49.1, 21.5, 14.1.FT IR (neat,cm^{-1}) 1321, 1159 cm^{-1} ;HR-MS calculated mass: 287.0980, measured mass: 287.0979 difference 0.4 ppm; [α] $^{25}_{D}$=60.6(1.0, $CHCl_3$);

2.4.4.1 Preparation of Compound 20a,

Step 2: (2R, 3R)-2-methyl-3-phenyl-1-(p-tolylsulfonyl) aziridine,

The enaniomer **20a** was synthesized using the same procedure used for compound 20 and starting from 1S, 2R norephedrine

Compound 20a

^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm, 7.82 (d, *J*) 8.3 Hz, 2H), 7.25 (m,5H), 7.15 (m, 2H), 3.79 (d, *J*) 4.4 Hz, 1H), 2.91 (m, 1H), 2.39 (s,3H), 1.84 (d, *J*) 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) 143.9, 137.9, 135.5, 129.5, 128.5, 128.0, 127.2, 126.3, 49.2, 49.1, 21.5, 4.1.FT IR (neat) 1321, 1159 cm^{-1}HR-MS calculated mass: 287.0980, measured mass: 287.0986 difference 2.08 ppm;[α] $^{25}_{D}$= -62.9(1.0, CHCl3);

2.4.5 Preparation of Compound 21

Step 3: N-[(1S 2R)-2-azido-1-methyl-2-phenyl-ethyl]-4-methyl-benzene sulfonamide,

In a 100 ml, round bottom flask, tosylated aziridine compound **20** (2.87 g, 10 mmol) was dissolved in acetonitrile (40 ml) and sodium azide (1.95 g, 30 mmol) in water (10 ml) was added to it. The contents were stirred at 50 ^{0}C for 8h. After the reaction, acetonitrile was removed under reduced pressure and contents were concentrated to ~10ml. The aqueous layer containing the solid was filtered off and washed with water (10 ml x 2). The product isolated was pure enough to be used for the next step (3.0 g , 90 % yield).

Compound **21**

^{1}H NMR (CDCl3, 400 MHz) δ ppm, 7.75 (d, *J* = 7.9 Hz, 2H), 7.20(m, 7H), 4.62 (m, 2H), 3.57(m, 1H), 2.43 (s, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ ppm ,143.6, 137.8,136.3, 129.7, 128.7, 128.3, 126.9, 126.8, 69.6, 54.0, 21.5, 15.2,; FT IR (KBr cm $^{-1}$)3251, 2099, 1378, 1299, 1166; HR-MS calculated Mass: 330.1150, measured Mass: 330.1152 difference 0.6 ppm;[α] $^{25}_{D}$= -105.8 (1.0, $CHCl_3$)

2.4.5.1 Preparation of compound 21a

Step 3 **N-[(1R, 2S)-2-azido-1-methyl-2-phenyl-ethyl]-4-methyl-benzenesulfonamide,**

The enaniomer **21a** was synthesized using the procedure described in the synthesis of compound 21 starting from 1S, 2R norephedrine.

^{1}H NMR (CDCl3, 400 MHz) δ ppm ,7.78 (d, *J* = 7.9 Hz, 2H), 7.21 (m, 7H), 4.68 (m, 2H), 3.57(m, 1H), 2.43 (s, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); C NMR (CDCl3, 101 MHz) δ ppm ,143.6, 137.8,136.2, 129.8, 128.8, 128.3, 126.9, 126.8, 69.7, 54.0, 21.5, 15.2; FT IR (KBr) cm $^{-1}$3251, 2099, 1378, 1299, 1166;HR-MS calculated Mass: 330.1150, measured Mass: 330.1149difference 0.3 ppm;[α] $^{25}_{D}$= +107.8 (1.0, $CHCl_3$);

2.4.6 Preparation of compound 22 (ligand 7)

Step4:**N-[(1S, 2R)-2-amino-1-methyl-2-phenyl-ethyl]-4-methyl-Benzenesulfonamide**

(1.65 g, 5 mmol) of the compound **21** was dissolved in THF (40 ml) and triphenyl phosphine (1.31 g 5 mmol) was added to it and the resultant mixture was stirred at 50^{0}C for nearly 6 h. After 6 h water (5ml) was added to the reaction mixture and the heating was continued for further 8 h.The reaction mixture was concentrated to (~5ml). The aqueous layer was extracted with DCM (10 ml) and concentrated to get

sticky mass. Toluene (10 ml) and the 4 N HCl (1 ml) in dioxane were slowly added to get white precipitate of hydrochloride salt of the resultant amine. The resultant solution was filtered off to get white powder of hydrochloride. Traces of toluene were removed by drying under vacuum. Water (5 ml) was added to dissolve the hydrochloride and 1N NaOH was slowly added till the pH reached 7. The solution was extracted with ethyl acetate (10 ml x 2) and concentrated to get sticky mass. (1.0 g, yield = 67%).

Compound 22

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.77 (d, *J*=6.78 Hz, 3 H) 2.38 (s, 3 H) ,3.35 (s, 3 H) 3.47 - 3.65 (m, 1 H) 4.17 (d, *J*=5.27 Hz, 1 H) 7.31 - 7.46 (m, 7 H) 7.61 (d, *J*=7.73 Hz, 2 H) 7.77 (d, *J*=7.78 Hz, 1 H) 8.64 (br. s., 3 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 21.9 , 26.2 , 56.84 ,63.05 , 131.8 , 133.4 , 133.6 , 133.8 , 134.9 , 139.6 143.2,148.0,143.3;FT IR (KBr cm $^{-1}$)3288, 3230, 1598, 1328, 1151 ;HR-MS calculated mass: 330.1149, measured mass: 304.1245,difference 1.3 ppm;
[α] $^{25}_{D}$= +13.4 (0.5, CHCl3);

2.4.6.1 Preparation of compound 22a (ligand 11) Step 4:
N-[(1R, 2S)-2-amino-1-methyl-2-phenyl-ethyl]-4-methyl-benzenesulfonamide

The **ligand 11** was synthesized using the procedure described in the synthesis of compound 22 and starting from 1S, 2R norephedrine.

Compound 22a

^{1}H NMR (δ=0.805-0.822 (3H d, J= 6.4,) 2.34 (3H, s) 3.51-3.55 (1H, m) 3.93-4.05 (1H, d ,6.4Hz),7.74-7.76, (2H d, 8.0), 7.18-7.30(7H, m); ^{13}C (δ= 16.0, 21.6, 54.4 59.0, 126.7, 126.9, 127.1, 127.7 128.5, 129.8, 137.8, 141.4, 143.3;FT IR (KBr cm $^{-1}$)3288, 3230, 1598, 1328, 1151;HR-MS calculated mass: 304.1245, measured mass: 304.1248, difference 1.1 ppm;[α] $^{25}_{D}$= -13.4 (0.5, CHCl3);

2.4.7 Synthesis of compounds 28 and 29 (ligands 8 and 9)

The sulfonamide and amine geometry in ligands 6 and 7 was cis but the position of amine and sulfonamide group was different. The aim of the thesis was also to synthesize the compounds where the amine and sulfonamide geometry would be trans. To prepare the trans isomers synthetic methodology as shown in Fig.2.10 was followed.

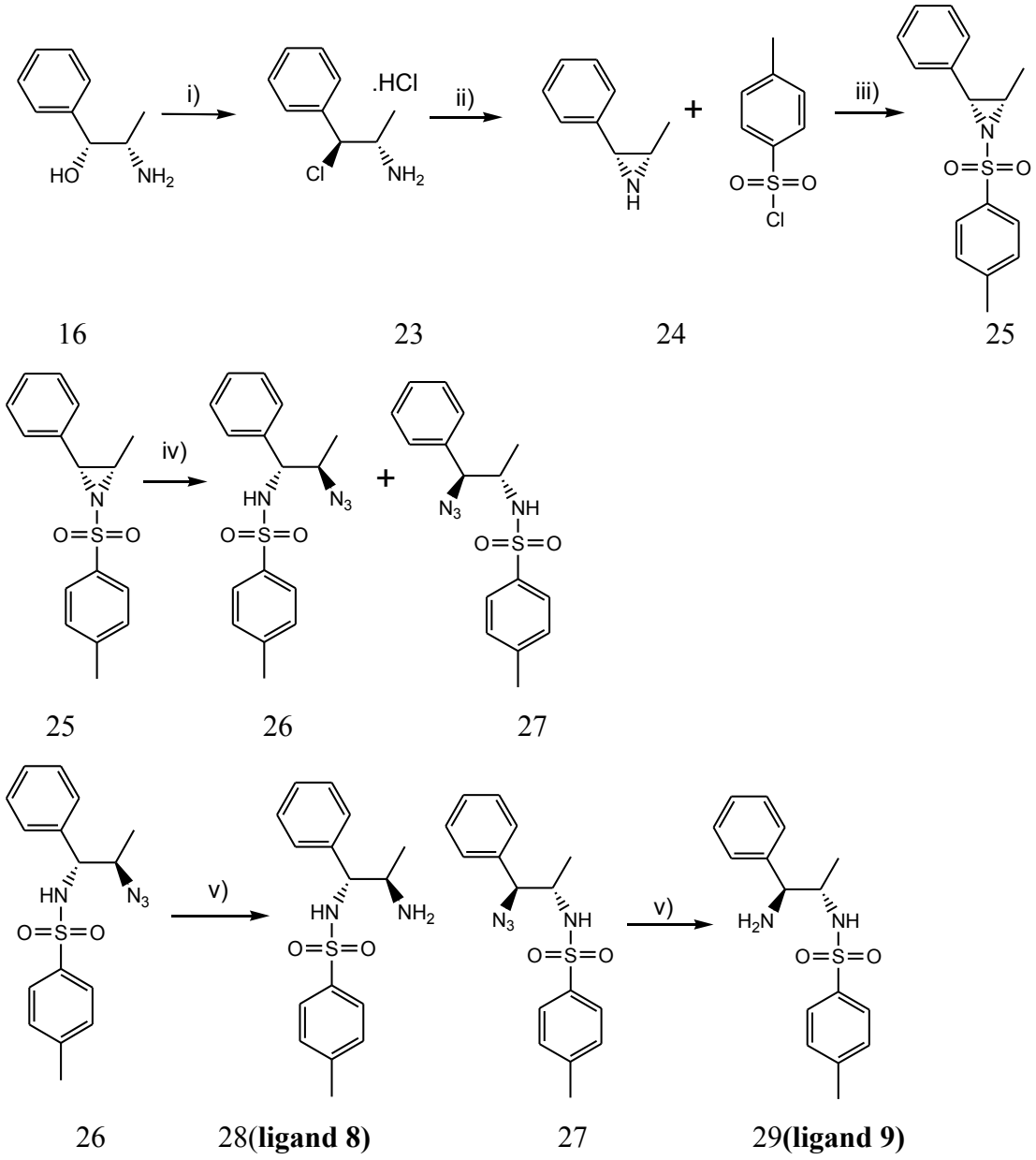


Fig. 2.10: synthetic methodology for ligands 8 and 9

Reaction conditions: i) $SOCl_2$, ii) 4N NaOH, in Methanol, iii) Pyridine in t-butyl methyl ether iv) DABCO and TMS azide, v) Triphenyl phosphine in THF and H_2O

The starting material used was 1R,2S norephedrine, and chlorination was carried out using thionyl chloride as per the procedure described in literature. The chloro norephedrine, compound 23 was formed with the inversion of configuration at the carbon bearing hydroxyl group.[49] The proton NMR spectrum (see Fig 2.11.) in D_2O showed the coupling constant of 12 Hz, confirming the trans geometry of the chloro and amine group in chlorinated compound **23.**

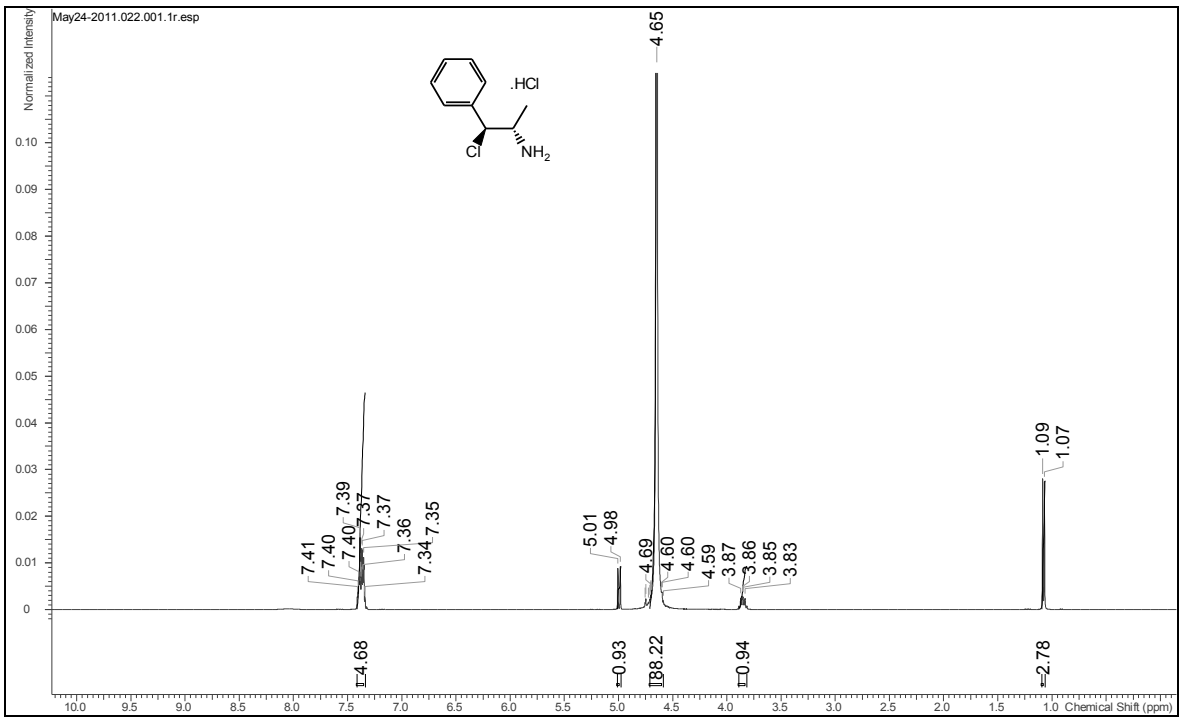


Fig. 2.11: ^{1}H NMR of compound 23

The chloroephedrine hydrochloride compound **23** was treated with sodium hydroxide, resulting in compound 24. This transformation again takes place with the inversion of configuration at benzylic carbon to form Aziridine[46, 50] (**compound 24**). The aziridine was converted to tosylated form using *p*-toluene sulfonyl chloride and pyridine at 0^0c (**compound 25**). The ring opening of activated aziridine (**compound 25**) was carried out using various nitrogen nucleophiles like sodium azide, TMS azide as mentioned in the literature procedure[47, 48] and using various Lewis acids like $AlCl_3$ and $CeCl_3$. TLC analysis carried out indicated completion of the reaction and a mixture of two products in a 60:40 ratio. Products obtained were proposed to be regioisomers based on LC-MS and NMR analysis. We wanted to synthesize both the isomers as ligands for ATH of ketones. For this purpose suitable reaction conditions

for ring opening of sulfonated aziridine (compound 25) were standardized using DABCO in 2 equivalence and TMS azide as a nucleophile and azide source. The two compounds (compound 26 and compound 27) which were formed during this reaction were found to be very difficult to separate by column chromatography or crystallization methods. The purification method by Flash chromatography was developed for separation of these two compounds. Once the compounds were purified, the detailed structural analysis was carried out. The proton NMR spectrum showed that the ring opening of the sulfonated aziridine (**compound 25**) took place form phenyl as well as methyl side. It was observed that, the ring opening of aziridine and activated aziridine in ephedrine type compounds is governed by the stereochemistry of the phenyl and methyl groups,[45-48] Ring opening of the sulfonated aziridine having trans geometry proceeds only by the attack of the nucleophile on carbon attached to phenyl ring.[47, 48] Phenyl and methyl groups in sulfonated aziridine (compound **20**) are trans with respect to each other. This resulted in single regio and stereo isomer (**compounds 18 and 21).**

However in the reaction of sulfonated aziridine (**compound 25)**, the compound is having geometry of phenyl and methyl to be cis w.r.t each other. This probably results in attack of nucleophile from both the sides. Thus the ring opening of activated unsymmetrical aziridine generates regioisomers and is dependent on the geometry of both the groups attached to the carbon.[44-46] The SN^1 type attack on phenyl bearing carbon or methyl bearing carbon was not proposed. As stereoisomer, with retention of the configuration for carbon bearing phenyl as well as methyl group was not observed by NMR analysis. The analysis of NMR spectrum for compound 26 clearly showed that benzylic proton had an additional coupling constant and is coupled to NH the proton of the sulfonamide group (8Hz)(NMR spectrum attached Fig 2.12. This indicated the ring opening of sulfonated aziridine (compound **25**), is proceeding from methyl side also. In compound**27** azide is attached to the carbon having phenyl group (formed due to ring opening of the sulfonated aziridine**25** from phenyl side) and sulfonamide group is attached to carbon having methyl group showed coupling constant of 5.8Hz (Fig. 2.13). To confirm the trans geometry of amine and sulfonamide in compound 27) X ray single crystal structure of the azide (27) was done. ORTEP diagram for the confirmation of azide intermediate compound 27 is presented in (Fig.2.15). Thus it was clearly found that the azide and sulfonamide

geometry in compound 27 is trans. Details of Single crystal analysis are reported in Appendix.

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.26 (d, *J*=6.53 Hz, 3 H) ,2.34 (s, 3 H) 3.72 (dd, *J*=6.53, 5.27 Hz, 1 H) 4.25 (dd, *J*=7.28, 5.27 Hz, 1 H) 5.23 (d, *J*=7.03 Hz, 1 H) 7.03 - 7.12 (m, 4 H) 7.15 - 7.22 (m, 3 H) 7.50 (d, *J*=7.86 Hz, 2 H)

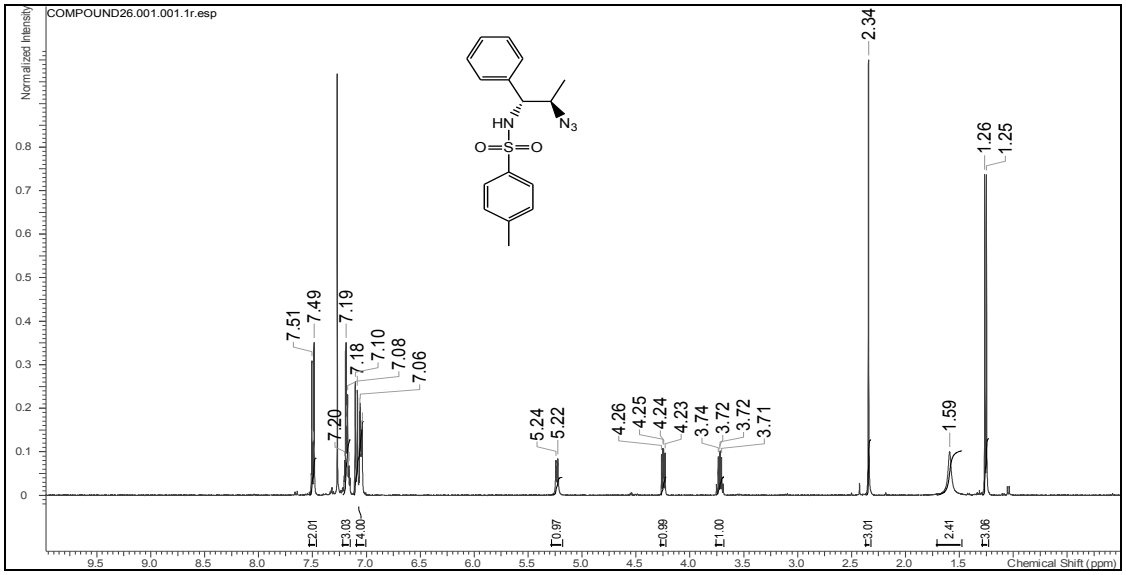


Fig. 2.12:^{1}H NMR of compound 26

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.64 (d, *J*=8.0 Hz, 2H), 7.33 - 7.13 (m, 7H), 4.87 (d, *J*=7.8 Hz, 1H), 4.49 (d, *J*=5.8 Hz, 1H), 3.56 - 3.45 (m, 1H), 2.38 (s, 3H), 0.97 (d, *J*=6.8 Hz, 3H

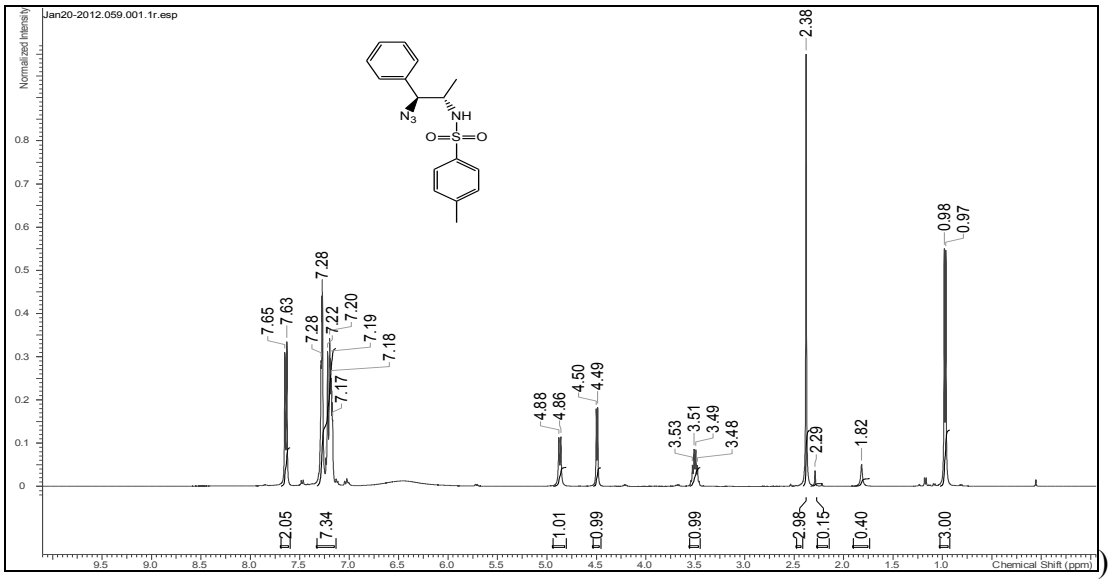


Fig. 2.13: 1H NMR of compound 27

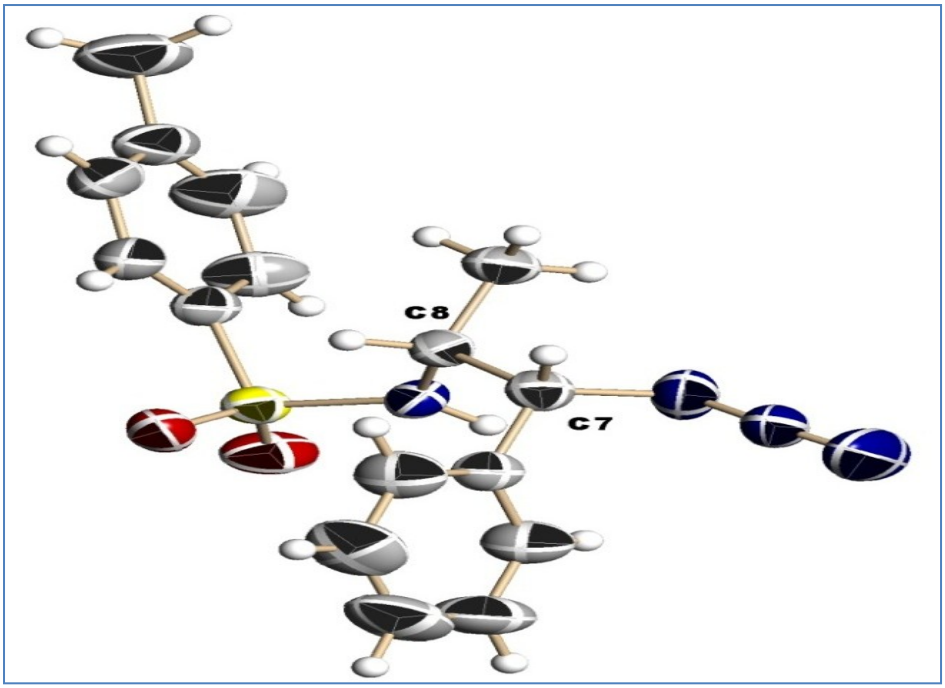


Fig. 2.14: ORTEP Diagram of compound 27a

The reduction of azide compounds (**26** and **27**) was carried out by triphenyl phosphine/water method (Staudinger reaction).The purification procedure was found to be complex. As acid base work up was giving either protonation of the amine or deprotonation of the sulfonamide group. However with acid base work up ligand 8, (**compound 28**) was isolated as a white solid. In the case of ligand 9 (compound **29**) however, purification procedure gave gummy mass which on standing for two days became off white sticky solid.

For ligand 9 hydrochloride salt was prepared using 4N HCl in Dioxane so as to obtain free flowing solid.

2.4.7.1 Preparation of compound 23 (1S, 2S)-1-chloro-1-phenyl-propan-2-amine.

In a 3 necked round bottom flask 1R, 2S norephedrine hydrochloride (30.0 g, 200 mmol) was taken and thionyl chloride (70.9 g 596 mmol) was added drop wise. After the addition was complete the reaction mixture was stirred for 3h. Vacuum was applied to remove the excess thionyl chloride, and then acetone (50 ml) was slowly added to the slurry. The resultant solution was filtered and washed with acetone and recrystalised from methanol to obtain white solid of compound **23** (22 g, yield 67%).

^{1}H NMR D_2O (δ=1.12 (3H d, J= 6.4,) 2.25(3H, s,) 3.86 (1H, m) 5.03-5.058(1H, d 9.2Hz), 7.40-7.44, (5H, m) ^{13}C δ=16.1, 52.4, 64.1, 126.1, 127.5, 128.3, 137.3,FT-IR

(KBr, cm^{-1}) = 3420, 3058, 2996, 2924, 2958, 716, 692;[α] $^{25}_{D}$= 10.4 ,(0.1, water);HR-MS calculated Mass: 169.0658, measured Mass: 169.0656, Difference -1.61 ppm

2.4.7.1.1 Preparation of Compound 23a

(1R, 2R)-1-chloro-1-phenyl-propan-2-amine

The enaniomer **23a** was synthesized using the same procedure and starting from 1S, 2R norephedrine.

Compound 23a

^{1}H NMR D_2O (δ=1. (3H d, J= 6.4,) 2.25(3H, s,) 3.860-3.907 (1H, m) 5.035-5.058(1H, d 9.2Hz), 7.401-7.441, (5H, m) ^{13}C δ=16.1, 52.4, 64.1, 126.1, 127.5, 128.3, 137.3,FT-IR (KBr, cm^{-1}) = 3425, 3059, 2996, 2924, 2958, 716, 690 HR-MS calculated Mass: 169.0659, measured Mass: 169.0656, Difference 2.4,ppm;[α] $^{25}_{D}$= -10.4 ,(0.1, water);

2.4.7.2 Preparation of compound 24

(2R, 3R)-2-methyl-3-phenyl-aziridin-2-amine

The compound **23** (10.0 g, 50 mmol) was dissolved in methanol (40 ml). NaOH (4 N, 50 ml) was slowly added under stirring to the methanol solution. The mixture was further stirred for 4h, and then was concentrated to 20 ml. The aqueous layer was cooled to 10^{0}C to get the crystals of aziridine. The solution was filtered and washed 2-3 times with water (10 ml). Light yellow crystals (low melting solid) of aziridine compound **24** (5g, 76 % yield) were obtained after recrystallization from hexane.

Compound24

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm, 7.30 - 7.16 (m, 5H), 3.19 (d, *J*=6.5 Hz, 1H), 2.39 - 2.32 (m, 1H), 0.87 - 0.84 (m, 3H);^{13}C NMR (101MHz, CHLOROFORM-d) δ ppm, 137.7, 127.9, 127.8, 126.7,37.2,32.2,13.68;FT-IR (KBr, cm^{-1}):3226, 1612, 1485, 1062, 849HR-MS calculated Mass: 133.0891, measured Mass: 133.0895 Difference -2.2 ppm;[α] $^{25}_{D}$= -75.2 ,(0.4, $CHCl_3$);

2.4.7.2.1 Preparation of compound 24a

(2S, 3S)-2-methyl-3-phenyl-aziridin-2-amine

The enaniomer **24a** was synthesized using the same procedure starting from 1S, 2R norephedrine.

Compound 24a

^{1}H NMR $CDCl_3$ (δ ppm.0.84-0.86 (3H, d, J= 6.4,) 2.31-2.37 (1H, m) 3.17-3.18(1H, d 6.4Hz), 7.13-7.28, (5H, m) ^{13}C δ,ppm 14.2, 37.2, 40.5, 125.1, 126.2, 127.2, 137.1, FT-IR ((KBr, cm^{-1})3236, 1602, 1495, 1072, 849;HR-MS calculated Mass: 133.0891, measured Mass: 133.0894 ,Difference -2.25 ppm;[α] $^{25}_{D}$= +73.0 ,(0.4, $CHCl_3$);

2.4.7.3 Preparation of compound 25
(2S, 3R)-2-methyl-3-phenyl-aziridine; methylsulfonylbenzene

(5.3g, 40 mmol) of compound **9** was dissolved in TBME (30 ml), and pyridine (5ml) was slowly added to it at 0^0C. *p*-toluene sulfonyl chloride (7.1 g) was dissolved in TBME (30 ml) and the resultant solution was added slowly to the TBME containing compound **9**. The reaction mixture was stirred for 4 h and then of 1 N HCl (20 ml) and 30 ml water was added to the reaction mixture. Contents were shaken vigorously and the layers were separated. Aq. layer was discarded and TBME layer was washed again with 30 ml of water. The TBME layer was concentrated to get the compound **25** which was crystalized from hexane to get off white crystals, (7.5 g, 65 % yield).

Compound 25

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm, 7.89 (d, *J*=7.9 Hz, 2H), 7.35 - 7.19 (m, 7H), 3.93 (d, *J*=7.3 Hz, 1H), 3.19 (qd, *J*=5.8, 7.2 Hz, 1H), 2.45 (s, 3H), 1.02 (d, *J*=5.8 Hz, 3H), ^{13}C δppm,18.2, 21.6, 53.7, 69.6, 126.7, 127. 7, 127.9, 128.8, 129.4 129.7, 135.6, 137.5, 143.4; FT-IR ((KBr, cm^{-1}) 2984, 1596, 1320, 1161,; HR-MS calculated Mass: 287.0980, measured Mass: 287.0979, Difference 0.4 ppm;[α] $^{25}_{D}$= -100.1 ,(1.0, $CHCl_3$);

2.4.7.3.1 Preparation of compound 25a
(2S, 3R)-2-methyl-3-phenyl-aziridinemethylsulfonylbenzene

The enaniomer **25a** was synthesized using the same procedure and starting from 1S, 2R norephedrine

Compound 25a

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm, 7.85 (d, *J*=7.8 Hz, 2H), 7.30 - 7.19 (m, 7H), 3.92 (d, *J*=7.2 Hz, 1H), 3.21 (qd, *J*=5.8, 7.2 Hz, 1H), 2.42 (s, 3H), 1.02 (d, *J*=5.8 Hz, 3H);^{13}C NMR (101MHz, CHLOROFORM-d) δ = 141.7, 135.8, 134.0, 128.0, 127.1, 127.0, 126.0, 125.4, 125.3, , 67.8, 52.0, 19.9, 16.6; FT-IR ((KBr, cm^{-1})

2984, 1596, 1320, 1161;HR-MS calculated Mass: 287.0980, measured Mass: 287.0986, Difference 1.95 ppm;[α] $^{25}_{D}$= +99.2 ,(1.0, $CHCl_3$);

2.4.7.4 Preparation of compound 26 and compound 27

(N-[(1R,2R)-2-azido-1-phenyl-propyl]-4-methyl-benzenesulfonamide)(N-[(1S, 2S)-2-azido-1-methyl-2-phenyl-ethyl]-4-methyl-benzenesulfonamide)

Compound **10** (5.74g, 20 mmol) was dissolved in acetonitrile (40 ml) and DABCO (2.24 g, 20 mmol) was added to it.TMS azide (2.5ml) was slowly added to the reaction mixture. The reaction mixture was heated at 50^0C for 4 h. After 4 h the reaction mixture was cooled to room temperature and concentrated to remove acetonitrile. Distilled water (25 ml) was added to the sticky mass and stirred vigorously. The off white solid precipitated out was filtered through sintred funnel and washed 2-3 times with water. The NMR showed approximately 60:40 ratios of regioisomers, compounds **26** and **27**(combined yield = 6.0g, yield 90%)**.**

Purification of the regioisomers was done by Flash chromatography, to get individually pure azide isomers, compound **26** (2.0g, theoretical yield 80 %), compound **27** (2.5 g, theoretical yield 72%).

Compound 26

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.26 (d, *J*=6.53 Hz, 3 H) 2.34 (s, 3 H) 3.72 (dd, *J*=6.53, 5.27 Hz, 1 H) 4.25 (dd, *J*=7.28, 5.27 Hz, 1 H) 5.23 (d, *J*=7.03 Hz, 1 H) 7.03 - 7.12 (m, 4 H) 7.15 - 7.22 (m, 3 H) 7.50 (d, *J*=7.86 Hz, 2 H);^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 16.8 , 21.5 , 61.8 , 62.1 ,127.1 , 128.0 , 128.5 , 129.3 137.3 137.8 , 143.2 ;FT-IR ((KBr, cm^{-1}) 3255, 2893, 2112,1445, 1159;HR-MS calculated Mass: 330.1150, Measured Mass: 330.1149, Difference 0.4 ppm;[α] $^{25}_{D}$= -66.3 ,(0.5, $CHCl_3$);

Compound 27

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm 7.64 (d, *J*=8.0 Hz, 2H), 7.33 - 7.13 (m, 7H), 4.87 (d, *J*=7.8 Hz, 1H), 4.49 (d, *J*=5.8 Hz, 1H), 3.56 - 3.45 (m, 1H), 2.38 (s, 3H), 2.29 (s, 1H), 0.97 (d, *J*=6.8 Hz, 3H), ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 18.2 , 21.6 , 53.6 , 69.5 , 127.0 , 127.7 , 128.7 ,128.8 , 129.7 , 135.5 , 137.5 , 143.4;FT-IR, KBr, cm^{-1}) 3236, 1602, 1495, 1072, 849; HR-MS330.1150, Measured Mass: 330.1152, Difference 0.61 ppm;[α] $^{25}_{D}$= +91.3 (1.0, $CHCl_3$);

2.4.7.4.1 Preparation of compound 26a and compound 27a

(N-[(1S,2S)-2-azido-1-phenyl-propyl]-4-methyl-benzenesulfonamide)and (N-[(1R,2R)-2-azido-1-methyl-2-phenyl-ethyl]-4-methyl-benzenesulfonamide)

The enaniomer **26a** and **27a** was prepared using the procedure starting from 1S, 2R norephedrine

Compound 26a

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.26 (d, *J*=6.5 Hz, 3 H) 2.34 (s, 3 H) 3.72 (dd, *J*=6.5, 5.27 Hz, 1 H) 4.25 (dd, *J*=7.3, 5.27 Hz, 1 H) 5.23 (d, *J*=7.0 Hz, 1 H) 7.03 - 7.12 (m, 4 H) 7.15 - 7.22 (m, 3 H) 7.50 (d, *J*=7.86 Hz, 2 H) ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 16.8 , 21.5 , 61.8 , 62.1 ,127.1 , 128.0 128.5,129.3 , 137.3 , 137.8 , 143.2 ; FT-IR ((KBr, cm^{-1}) 3255, 2893, 2112,1445, 1159;HR-MS calculated Mass: 330.1150, Measured Mass: 330.1143, Difference 2.3 ppm;[α] $^{25}_{D}$= +64.3 ,(0.5, $CHCl_3$);

Compound 27a

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm, 0.96 (d, *J*=6.78 Hz, 3 H) 2.34 (s, 3 H) 3.47 (m, 1 H) 4.41 - 4.50 (m, 2 H) 7.11 - 7.27 (m, 8 H) 7.57 (d, *J*=7.90 Hz, 2 H) ^{13}C NMR (101 MHz, CHLOROFORM-*d*) δ ppm 18.2 , 21.6 , 53.6 , 69.5 , 127.0 , 127.7 , 128.7 ,128.8 , 129.7 , 135.5 , 137.5 , 143.4 ;FT-IR ((KBr, cm^{-1}) 3269,2987, 2119,1599,1328, 1161;HR-MS calculated Mass: 330.1150, Measured Mass: 330.1153, Difference 0.9 ppm;[α] $^{25}_{D}$= -90.3 ,(1.0, $CHCl_3$);

2.4.7.5 Preparation of compound 28 (ligand 8)

N-[(1R, 2R)-2-amino-1-phenyl-propyl]-4-methyl benzene sulfonamide

(1.65 g, 5 mmol) of compound **26** was dissolved in THF (40 ml) and triphenyl phosphine (1.31g, 5mmol) was added to the solution and the resultant mixture was stirred at 50^{0}C for nearly 6 h. After 6 h water (5ml) was added to the reaction mixture and the heating was continued for further 8h.The reaction mixture was concentrated to (~5ml) remove THF. The aqueous layer was extracted with DCM (10 ml) and concentrated to get sticky mass. Toluene (10ml) and 4 N HCl (1 ml) in dioxane were slowly added to get white precipitate of hydrochloride. The resultant solution was filtered off to get white powder of hydrochloride. Traces of toluene were removed by drying the precipitate under vacuum. Water 5ml was added to dissolve the

hydrochloride and 1N NaOH was slowly added till the pH reached 7.0. The solution was extracted with ethyl acetate (10 ml x 2) and concentrated to get off white solid of compound **28** (0.8 g, yield=53%).

Compound 28 (ligand 8)

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm,0.92 (3H d, J= 6.4,) 2.41(3H, s) 3.24 (1H,m) 3.77(1H, d, 7.2Hz),7.67, (2H d,8.4), 7.17(7H, m); ^{13}C (δ= 18.8, 21.5, 55.3, 60.4, 127, 127.7, 128.3, 128.5, 128. 7, 129.7, 129.1, 137.8, 141.8, 143.4FT-IR ((KBr, cm^{-1}) 3288, 3230, 1517, 1328, 1151;HR-MS calculated Mass: 304.1245, measured Mass: 304.1248 difference 1.0 ppm;[α] $^{25}_{D}$= -90.7 ,(1.0, $CHCl_3$);

2.4.7.5.1 Preparation of compound 28a

N-[(1S, 2S)-2-amino-1-phenyl-propyl]-4-methyl benzene sulfonamide

The enaniomer 2**8a** and was synthesized using the same procedure and starting from 1S, 2R norephedrine.

Compound 28a

^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm,0.92 (3H d, J= 6.4,) 2.41(3H, s) 3.24 (1H,m) 3.77(1H, d, 7.2Hz),7.67, (2H d,8.4), 7.17(7H, m); ^{13}C δ ppm, 18.8, 21.5, 55.3, 60.4, 127, 127.7, 128.3, 128.5, 128. 7, 129.7, 129.1, 137.8, 141.8, 143.4, (KBr, cm^{-1}) 3385, 3279, 1597, 1328, 1162; HR-MS calculated Mass: 304.1245, measured Mass: 304.1248 difference 1.0 ppm;FT-IR;[α] $^{25}_{D}$= +92.1 ,(0.5, $CHCl_3$);

2.4.7.6 Preparation of compound 29 (ligand 9)

N-[(1S2S)-2-amino-1-methyl-2-phenyl-ethyl]-4-methyl-benzenesulfonamide

(1.65 g, 5 mmol) of the compound **27** was dissolved in THF (40 ml) and triphenyl phosphine (1.31 g, 5 mmol) was added to the solution and the resultant mixture was stirred at 50^{0}C for nearly 6 h. After 6 h water (5 ml) was added to the reaction mixture and the heating was continued for further 8 h.The reaction mixture was concentrated to (~5ml) remove the THF. The aqueous layer was extracted with DCM (10 ml) and concentrated to get sticky mass. Toluene (10ml) and the 4 N HCl (1 ml) in dioxane were slowly added to get white precipitate of hydrochloride. The resultant solution was filtered off to get white powder of hydrochloride. Traces of toluene were removed by drying the powder under vacuum. Water (5 ml) was added to dissolve the hydrochloride and 1N NaOH was slowly added till the pH reached 7.0. The solution

was extracted with ethyl acetate (10 ml x 2) and concentrated to get off white sticky mass (0.8 g, yield=53%).

Compound 29

^{1}H NMR (400MHz, CHLOROFORM-d) δ = 7.51 (d, *J*=7.8 Hz, 2H), 7.27 (s, 1H), 7.16 - 7.03 (m, 7H), 4.06 (d, *J*=6.0 Hz, 1H), 3.18 - 2.90 (m, 3H), 2.33 (s, 3H), 0.98 (d, *J*=6.3 Hz, 3H); ^{13}C (δ= 20.8, 21.5, 51.6, 63.5, 126.9, 127.0, 127.3, 127.7, 128.3, 129.2, 137.7, 139.6, 142.8)FT-IR ((KBr, cm^{-1}) 3268, 3240, 1507, 1323, 1152; HR-MS calculated Mass: 304.1245, measured Mass: 304.1249, Difference 1.3 ppm

Compound 29 isolated as hydrochloride , ^{1}H NMR (400MHz, CHLOROFORM-d)+DMSO-d6) δ = 8.64 (br. s., 3H), 7.95 (d, *J*=7.8 Hz, 1H), 7.75 - 7.64 (m, *J*=8.3 Hz, 2H), 7.42 (t, *J*=3.6 Hz, 2H), 7.28 - 7.20 (m, 4H), 7.17 - 7.12 (m, *J*=8.3 Hz, 2H), 4.31 (d, *J*=7.0 Hz, 1H), 3.76 - 3.66 (m, 1H), 2.29 (s, 3H), 0.68 (d, *J*=6.8 Hz, 3H) ^{13}C NMR (101MHz, CHLOROFORM-d) δ ppm,143.1, 138.2, 134.3, 129.6, 129.1, 128.9, 128.5, 127.0 , 60.01, 52.8, 21. 8, 17.4 ;[α] $^{25}_{D}$= -87.7 ,(0.5, CH_3OH);

2.4.7.6.1Preparation of compound 29a (ligand 13)

N-[(1R2R)-2-amino-1-methyl-2-phenyl-ethyl]-4-methyl-benzenesulfonamide

The enaniomer **29a** and was synthesized using the same procedure and starting from 1S, 2R norephedrine

Compound 29a

^{1}H NMR (400MHz, CHLOROFORM-d) δ ppm, 7.51 (d, *J*=7.8 Hz, 2H), 7.27 (s, 1H), 7.16 - 7.03 (m, 7H), 4.06 (d, *J*=6.0 Hz, 1H), 3.18 (m, 1H), 2.90 (s, 2H)2.33 (s, 3H), 0.98 (d, *J*=6.3 Hz, 3H);^{13}C δ= 20.8, 21.5, 51.6, 63.5, 126.9, 127.0, 127.3, 127.7, 128.3, 129.2, 137.7, 139.6, 142.8;FT-IR ((KBr, cm^{-1}) 3288, 3230, 1517, 1328, 1151,; HR-MS calculated Mass: 304.1245, measured Mass: 304.1248 difference 1.0 ppm

[α] $^{25}_{D}$= +87.0 ,(0.5, CH_3OH);

2.5 Conclusions:

Overall five amino alcohol and eight, unsymmetrical monotosylated diamines ligands were prepared starting from cheap and easily available S-(-)-methyl lactate and racemic methyl mandalate and Norephedrine. The amino alcohols have different electronic and steric properties than those used in ATH of ketones. For example the amino alcohols used in ATH of ketones have chirality residing on vicinal carbon atoms, and/or have some rigidity in the structures; The amino alcohol ligands synthesized in the present work do not have chirality on the vicinal carbon atoms. Monosulfonated diamine ligands were synthesized with systemic variation in the regio and stereo positions of amine and sulfonamide groups.

- Simple procedures like amide formation from amine nucleophiles and reduction of amides with Lewis acid in combination with sodium borohydride was used.for amino alcohol synthesis
- For Ligands based from mandelic acid, method of fractional crystallization of diastereoisomers was developed using toluene as a solvent, which enabled the use of racemic mandelic acid to prepare chiral amino alcohols on gm(s) scale.
- Mitsunobu reactions were used to produce amino sulfonamide ligands (**6 and 7))**, in a single diastereoisomer form [42, 44-46].
- Retention of configuration of norephedrine was observed with BOc protected sulfonamide under Mitsunobu reaction conditions, **(ligand 6)** this is due to participation neighboring amine group leading to trans aziridine as intermediate.[42, 44-46], Retention of configuration in(**ligand 7**) is observed, (w.r.t norephedrine) due to formation trans sulfonated Aziridine [47, 48].
- Ring opening of trans aziridine proceeds with complete regio and stereo control, to give single diastereoisomer.
- Ring opening of cis aziridine proceed with complete stereo control (i.e. No SN1, mechanism was observed), however, regioselectivity was not observed (**ligands 8 and 9**).

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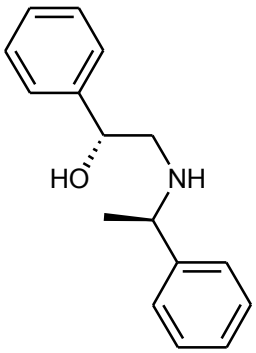
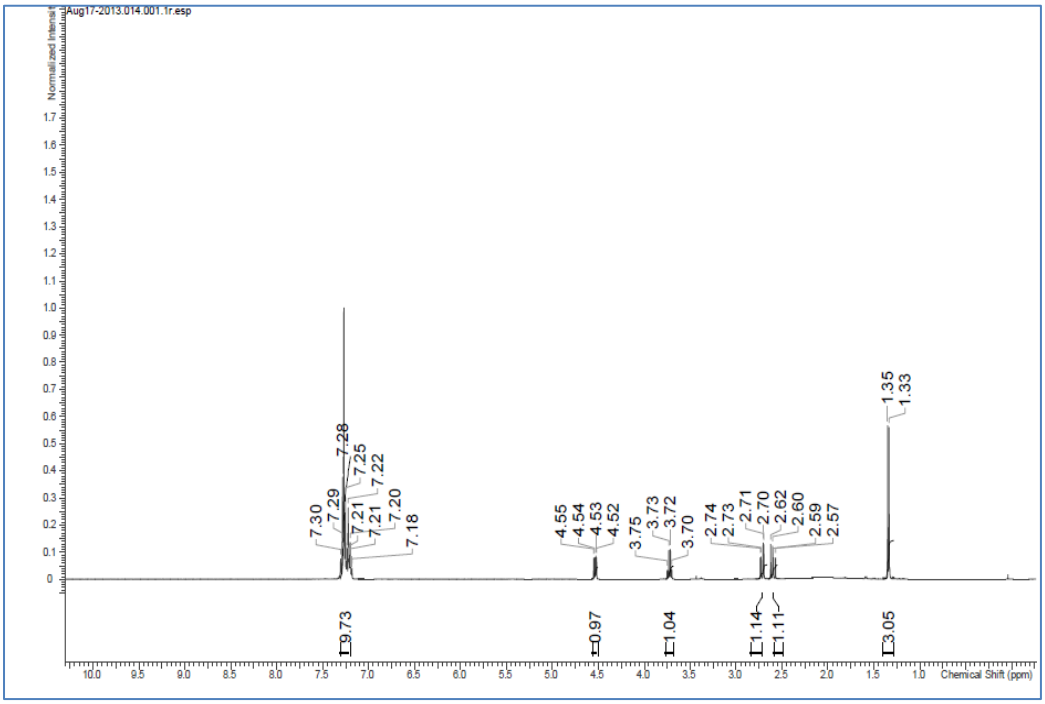
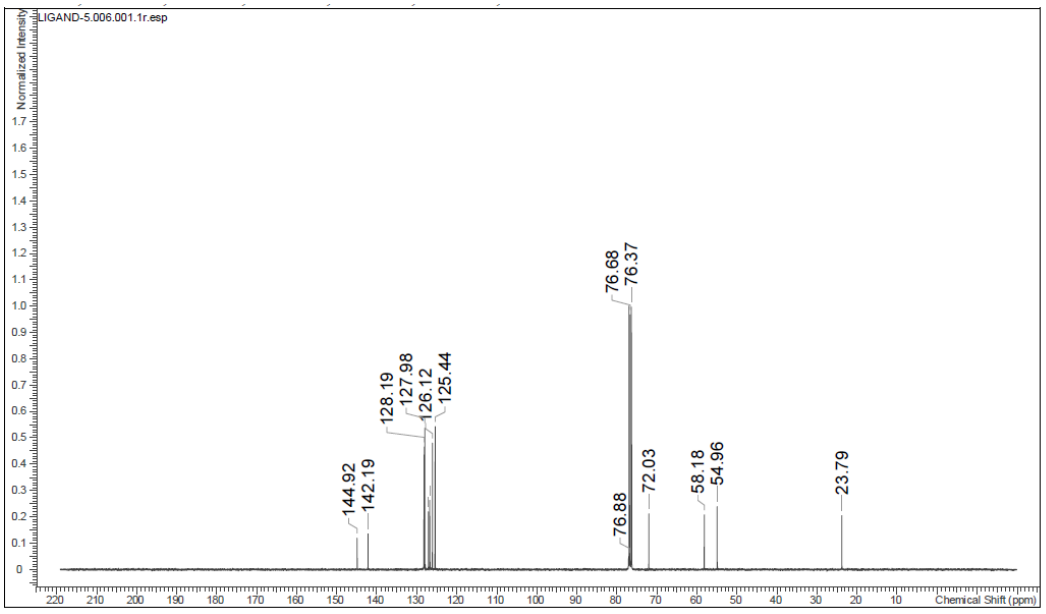
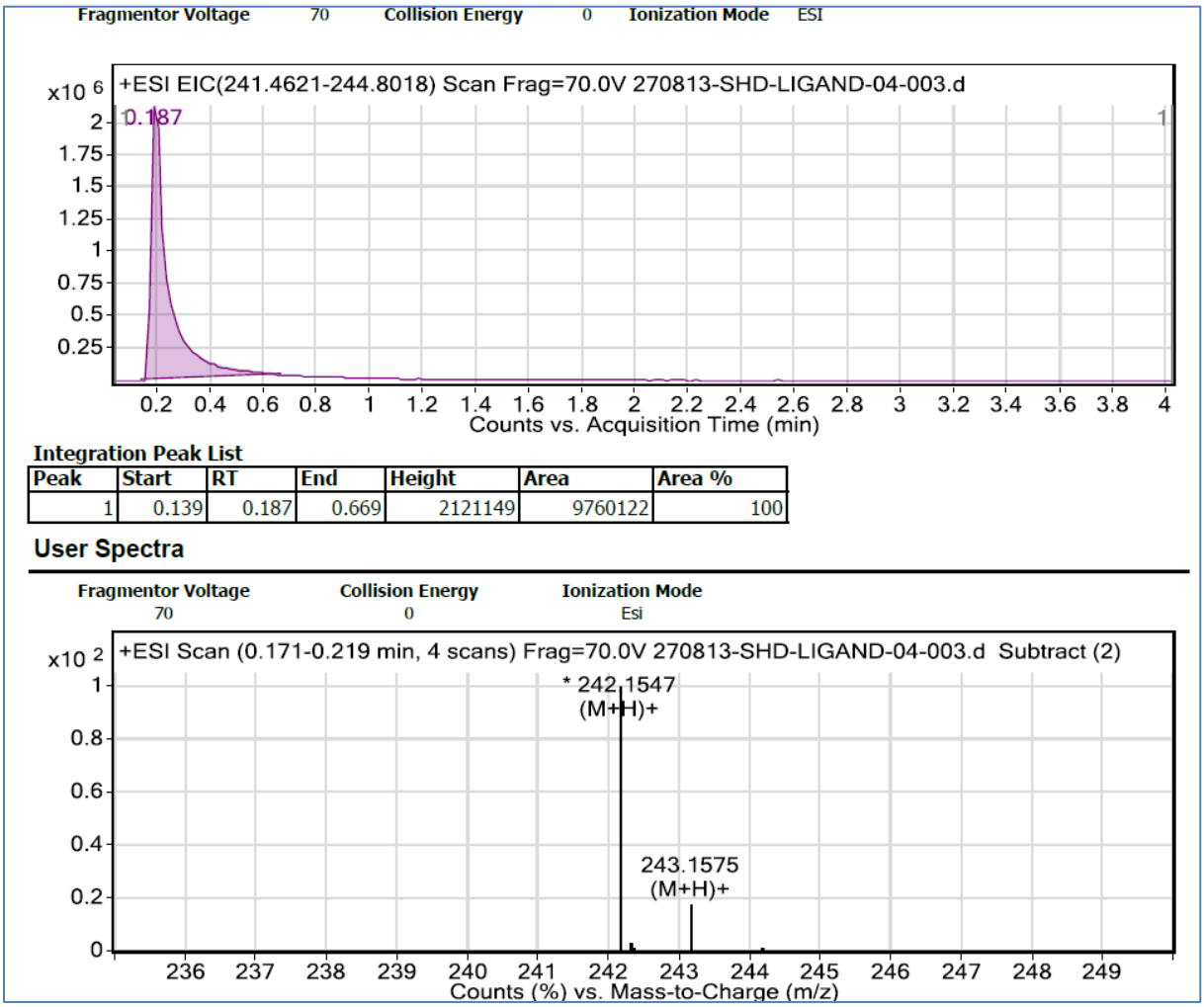
1. **^{1}H and ^{13}C NMR spectra of Compound 15,(ligand 5)**







HR-MS of compound 5

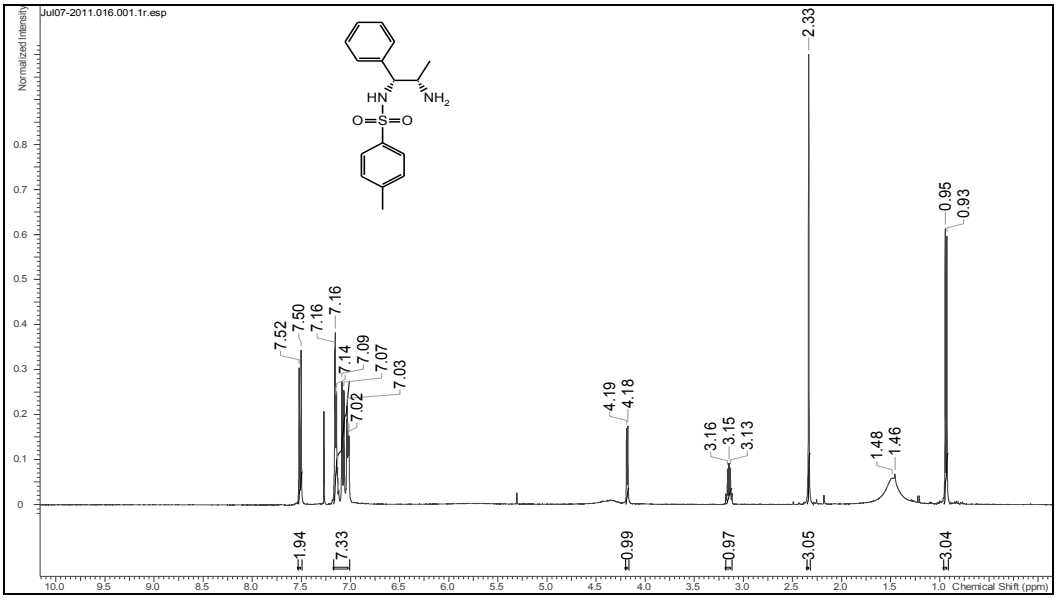


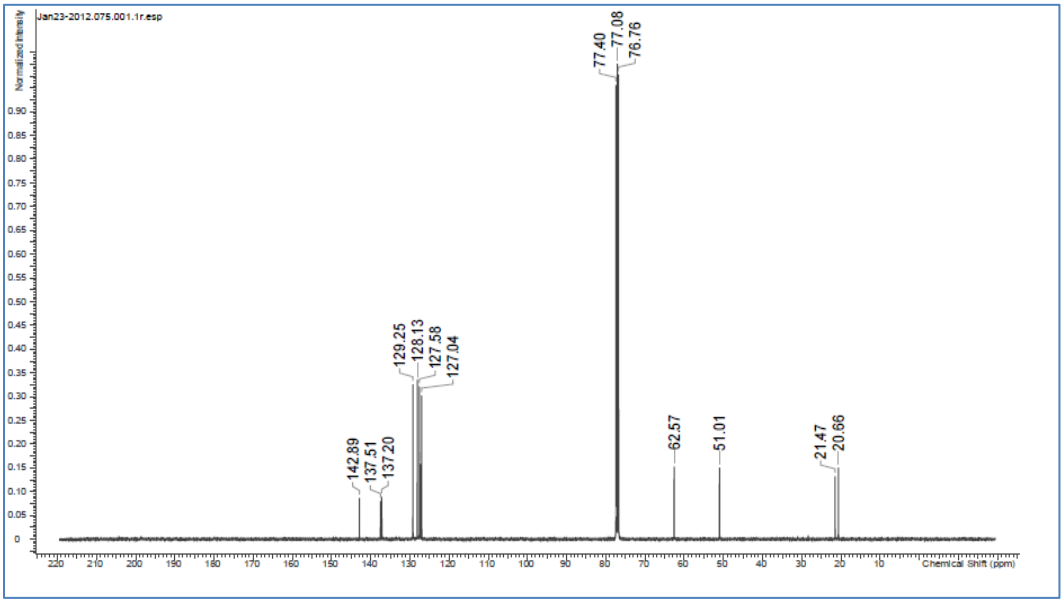
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	0.139	0.187	0.669	2121149	9760122	100

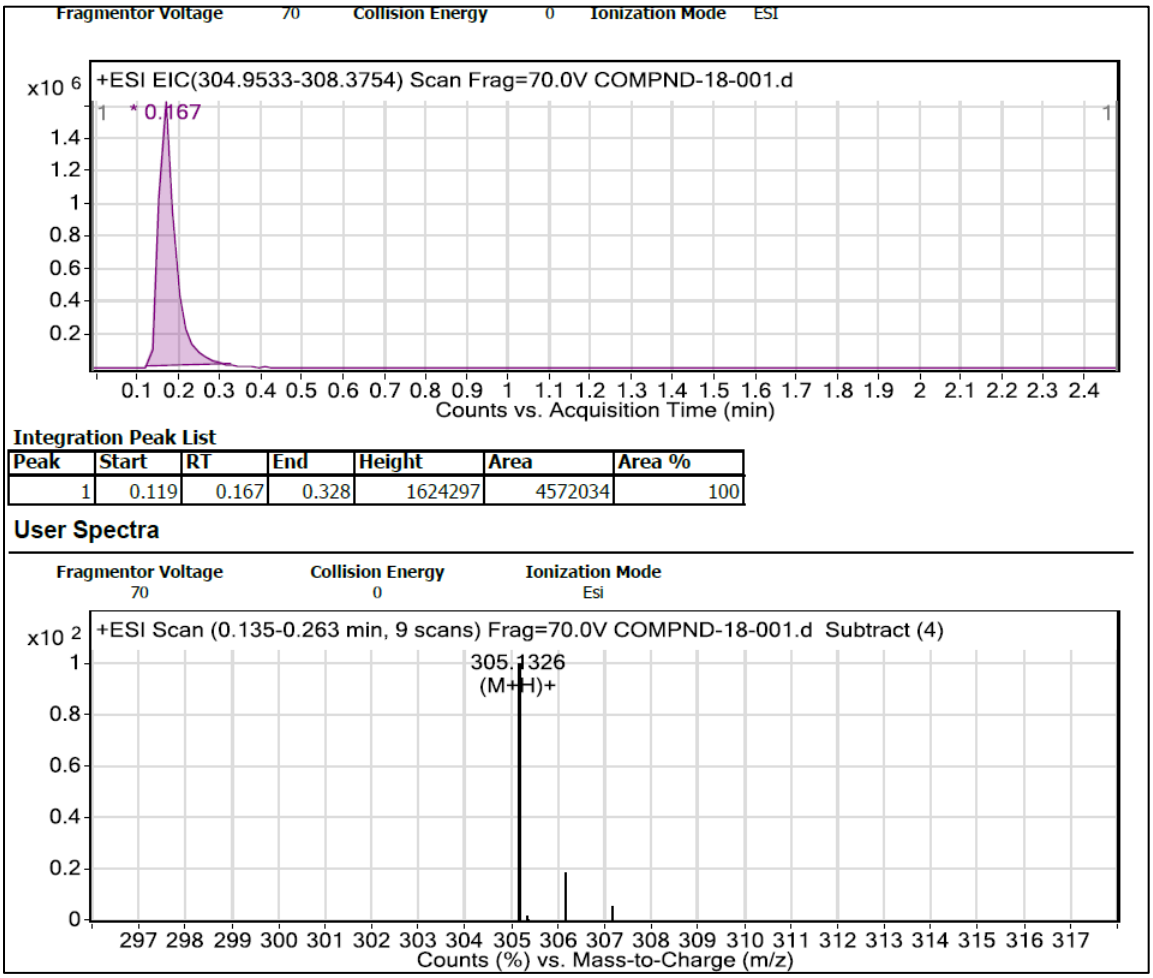
User Spectra

2. ^{1}H and ^{13}C NMR spectra of Compound 18





HR-MS of compound 18 (Ligand 1)

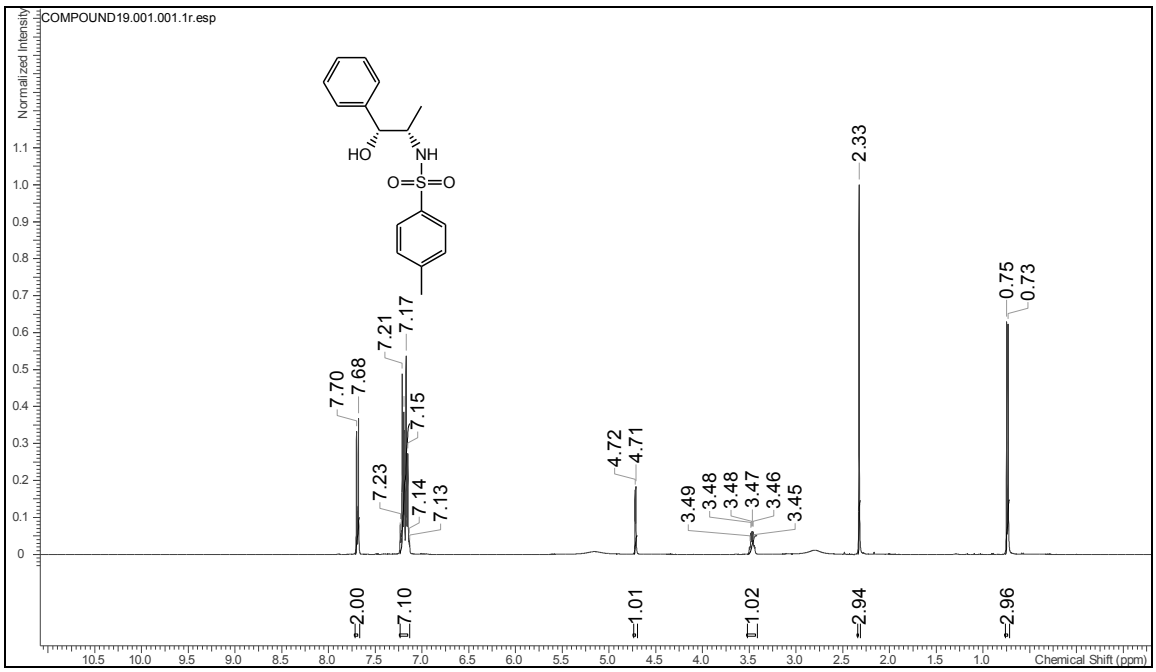


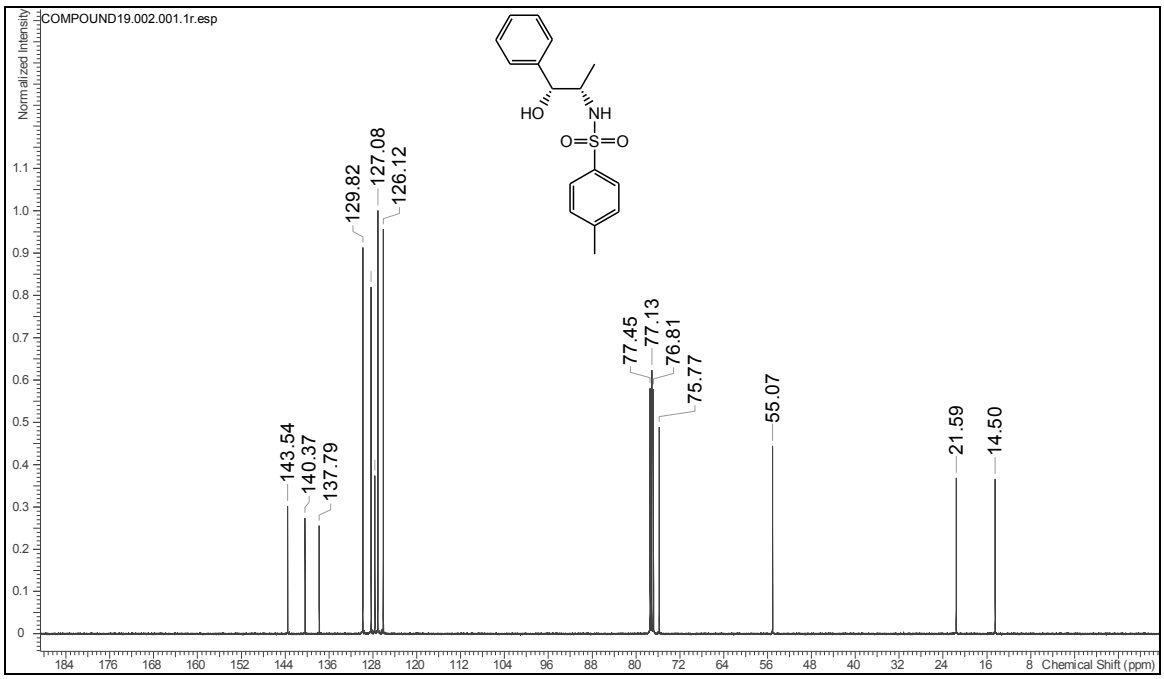
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	0.119	0.167	0.328	1624297	4572034	100

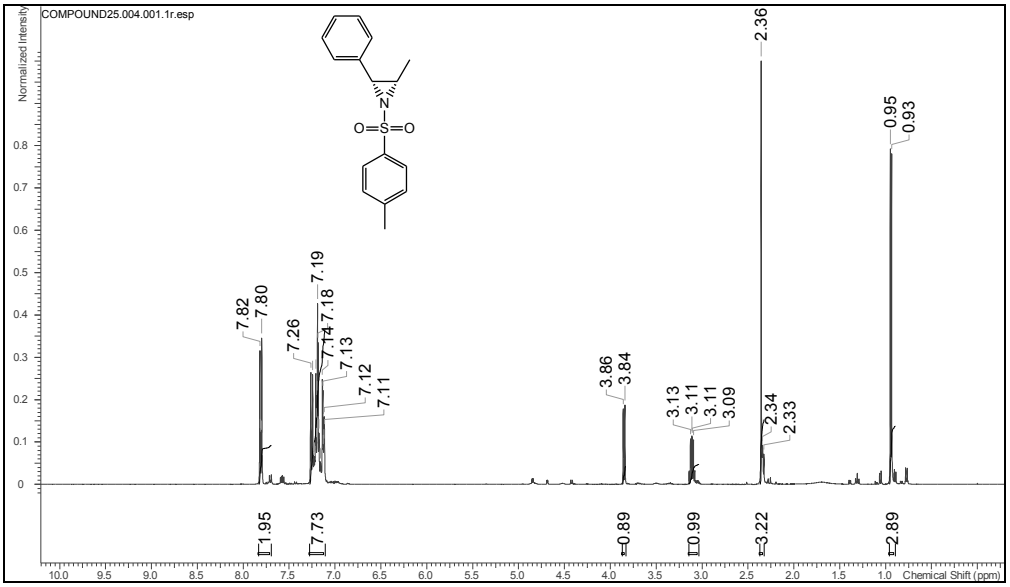
User Spectra

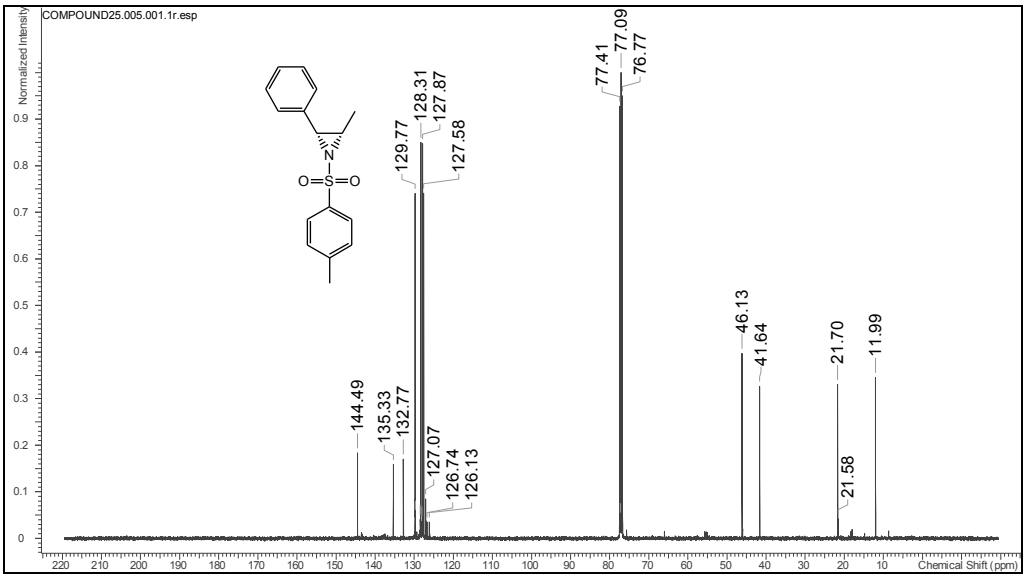
2 ^{1}H and ^{13}C NMR spectra of Compound 19



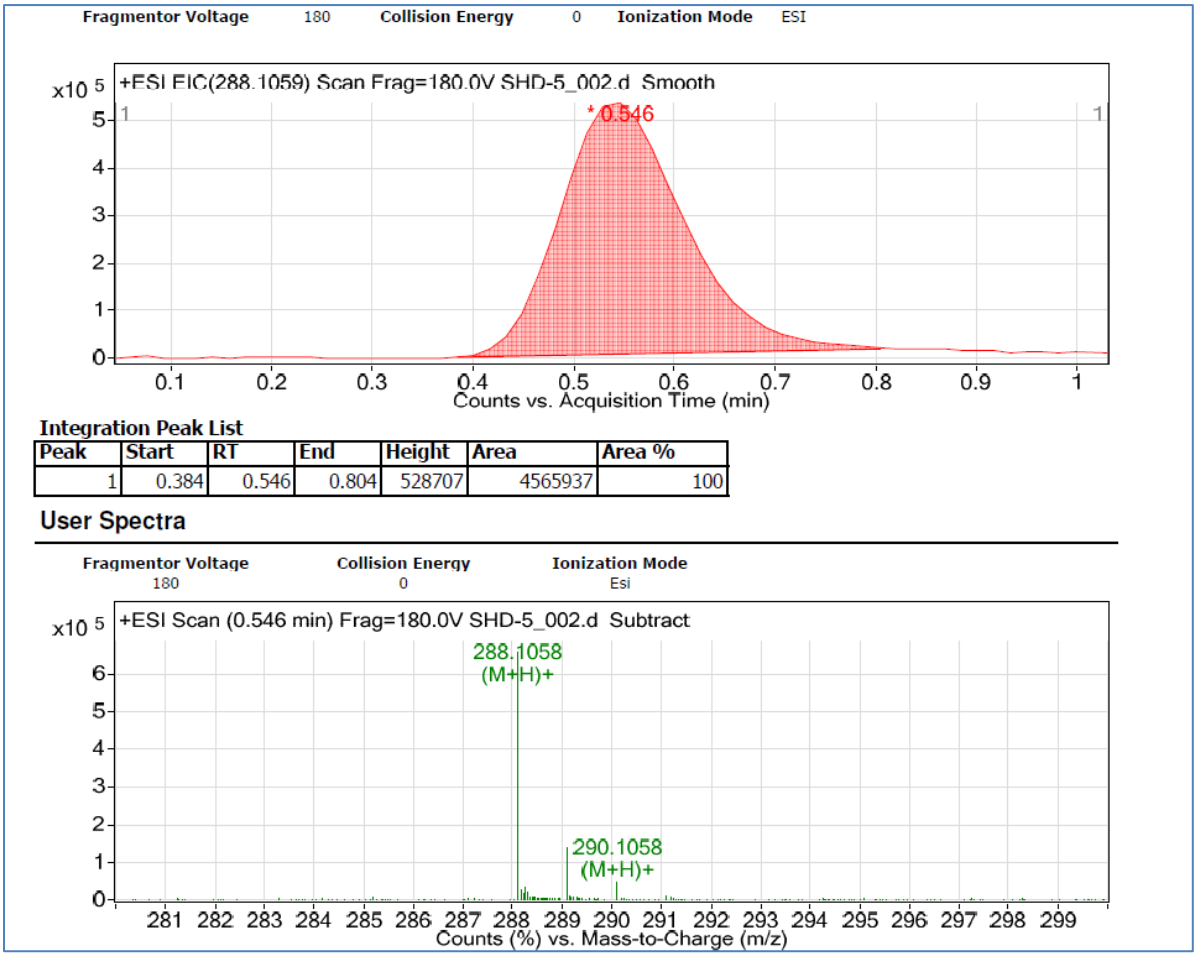


1. ^{1}Hand ^{13}C NMR spectra of Compound 20





HR-MS of compound 20

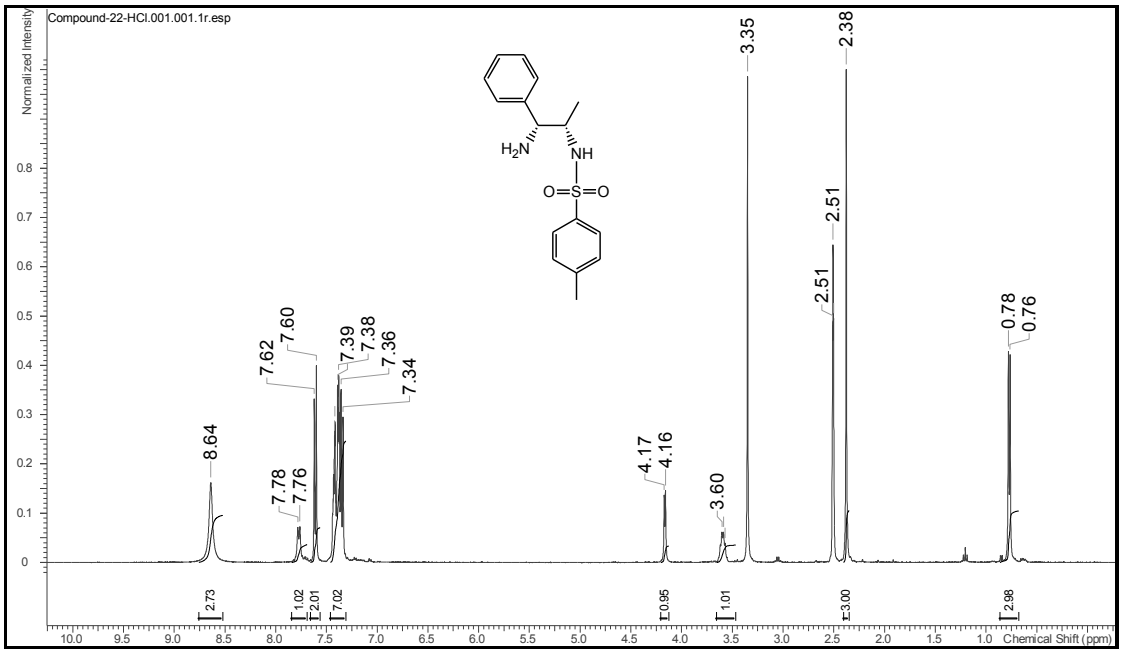


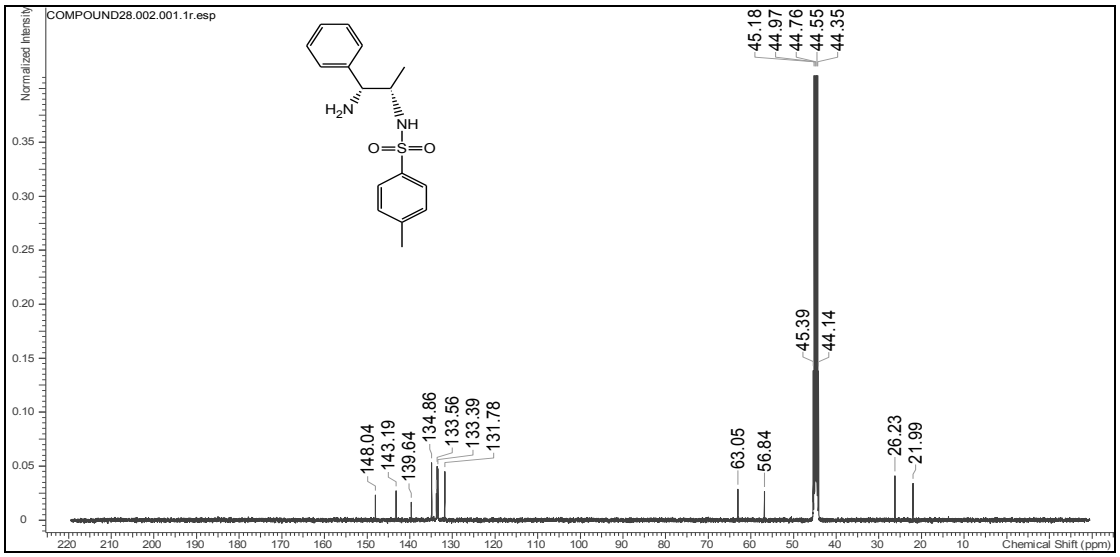
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	0.384	0.546	0.804	528707	4565937	100

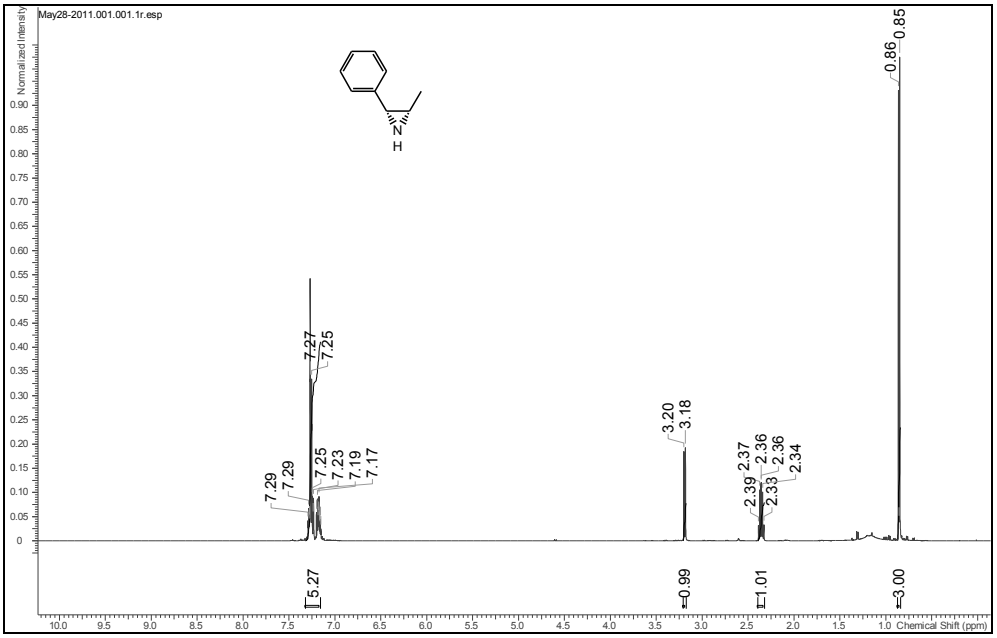
User Spectra

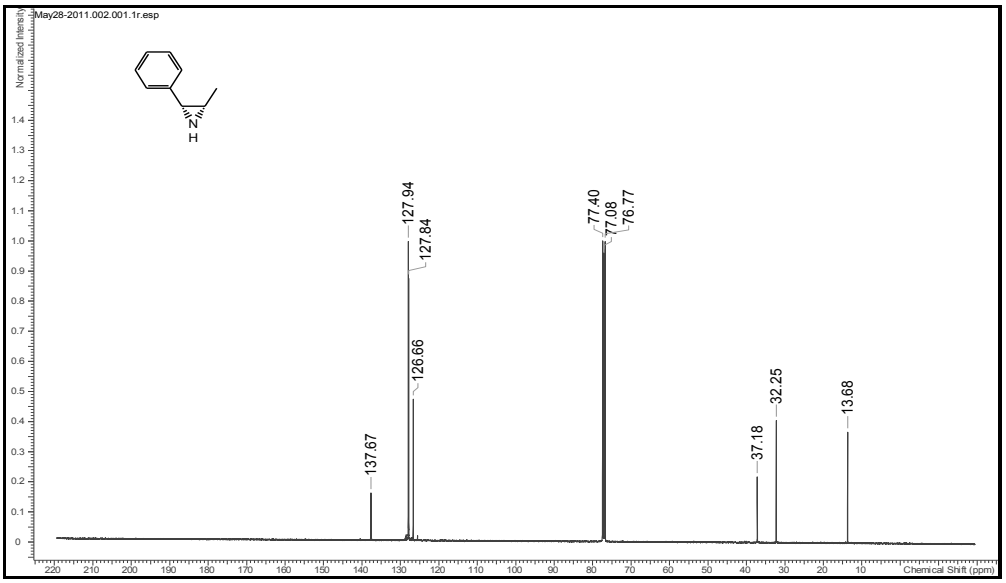
4..^{1}H and ^{13}CNMR of compound 22



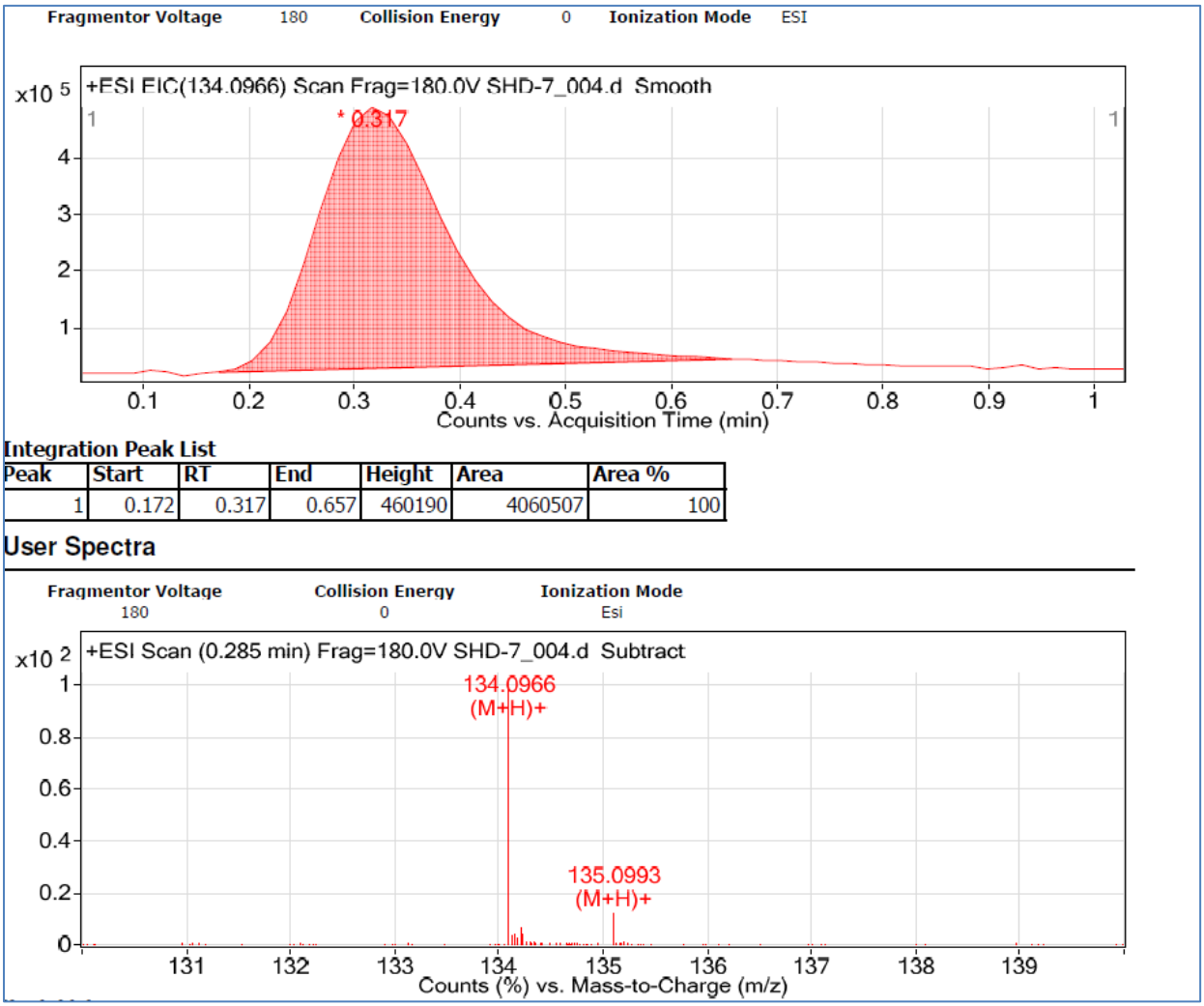


5..^{1}H and ^{13}CNMR of compound 22





HR-MS of compound 24

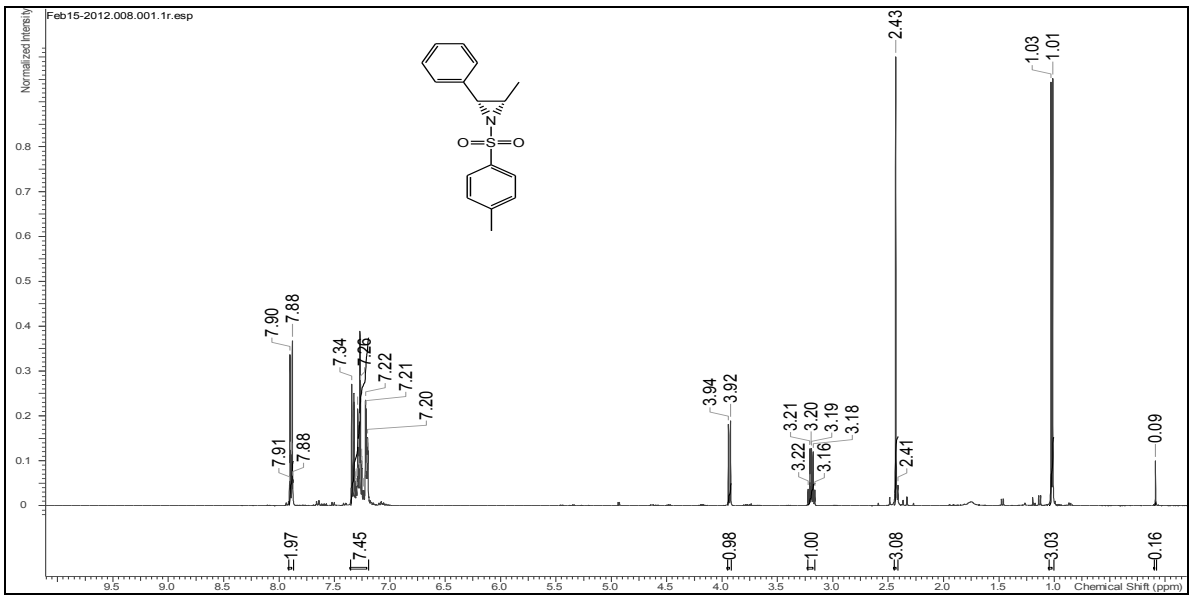


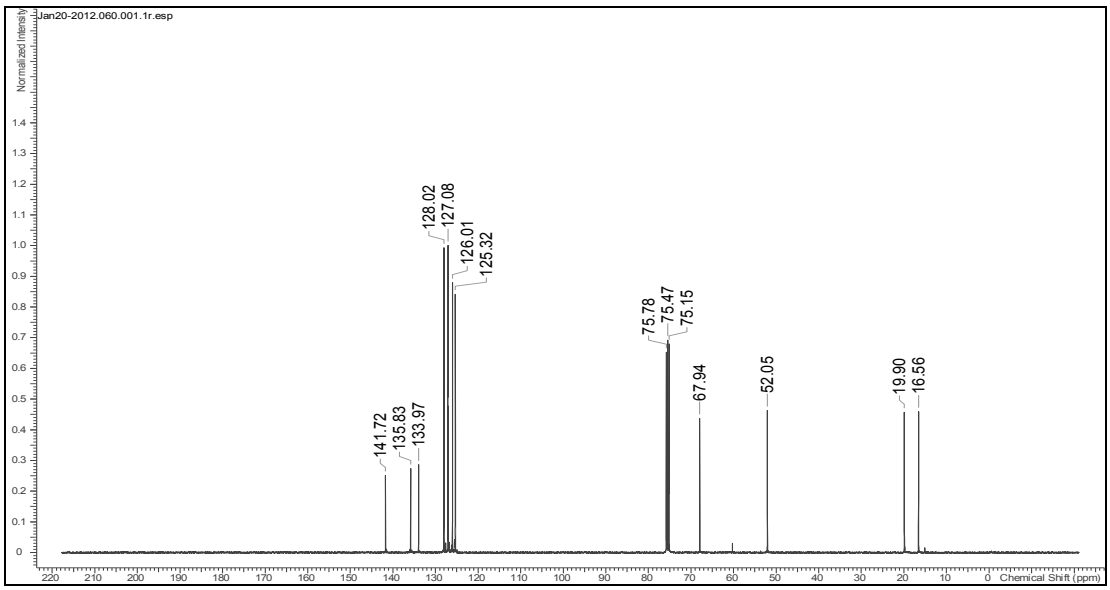
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	0.172	0.317	0.657	460190	4060507	100

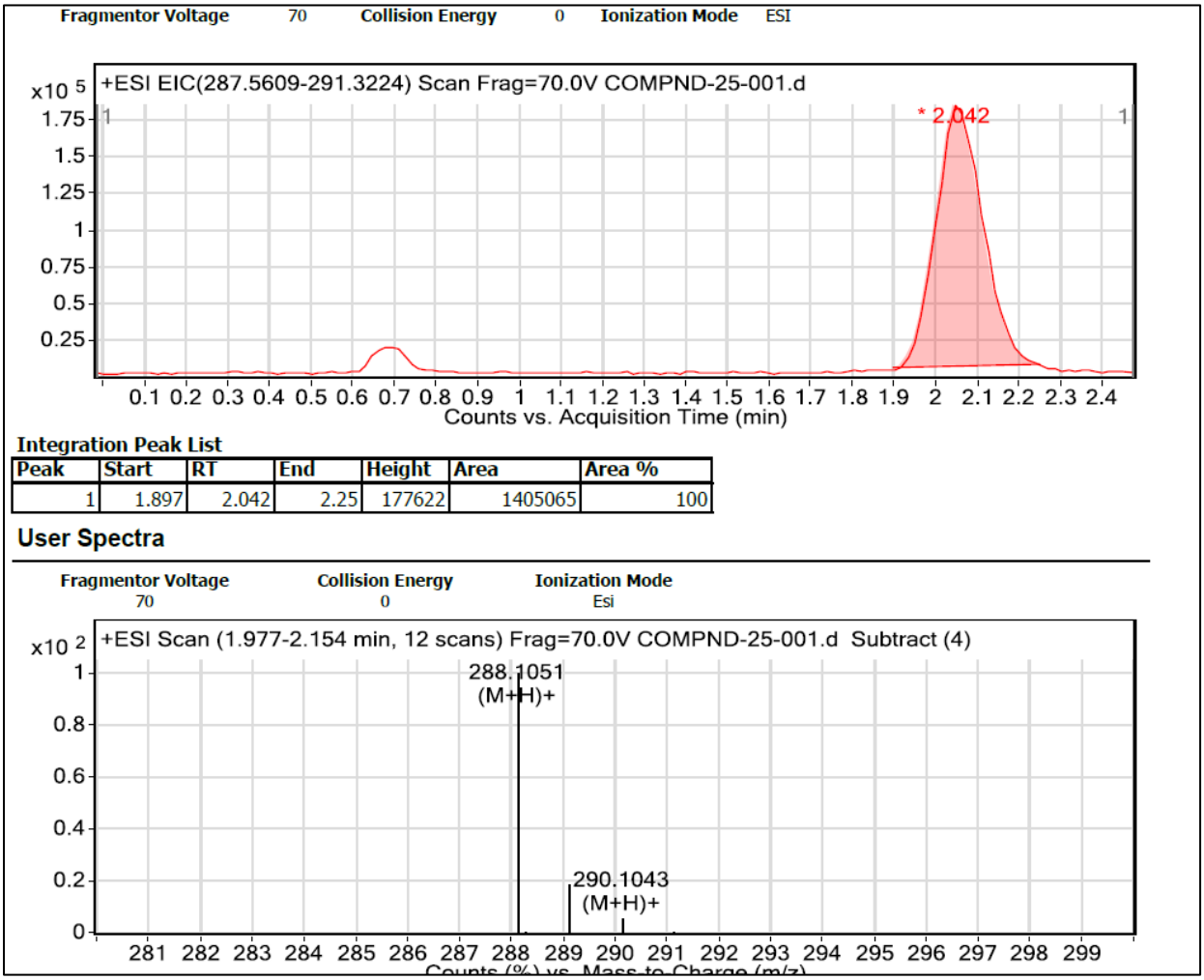
User Spectra

6. ^{1}H and ^{13}C NMR spectra of Compound 25





HR-MS of compound 25

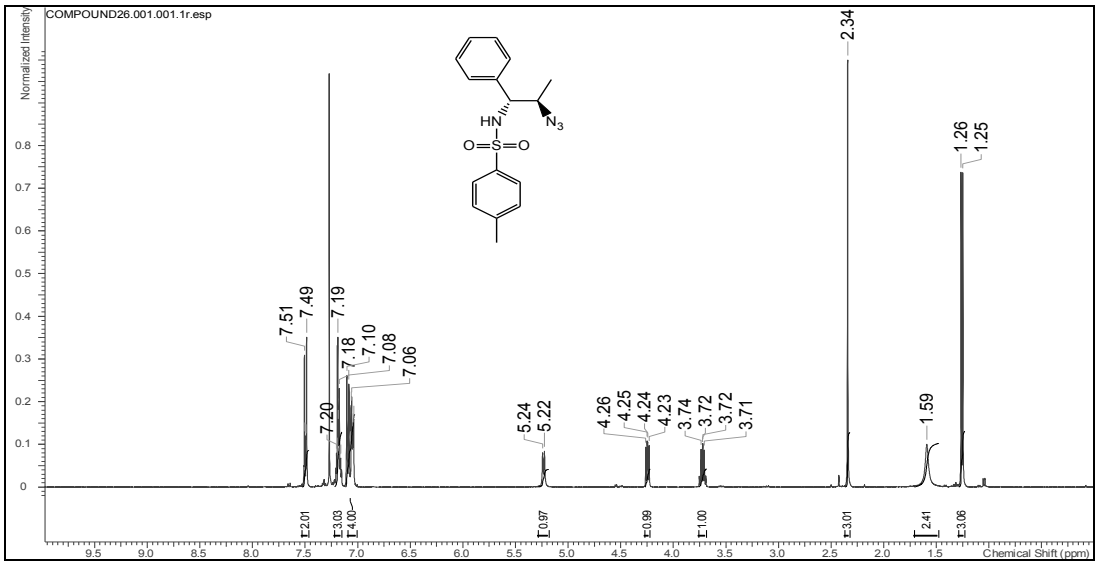


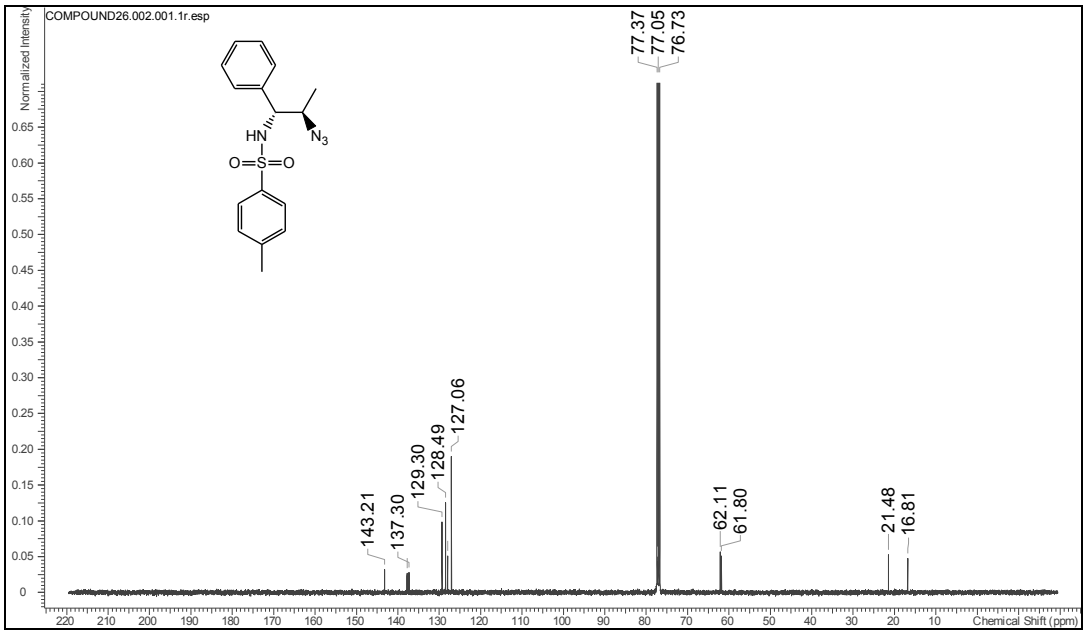
Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	1.897	2.042	2.25	177622	1405065	100

User Spectra

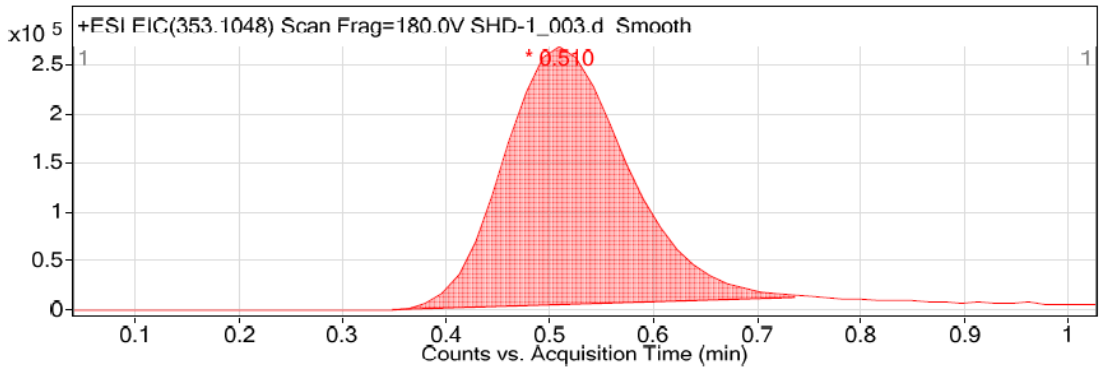
7. ^{1}H and ^{13}C NMR spectra of Compound 26





HR-MS of compound 26

Fragmentor Voltage 180 **Collision Energy** 0 **Ionization Mode** ESI

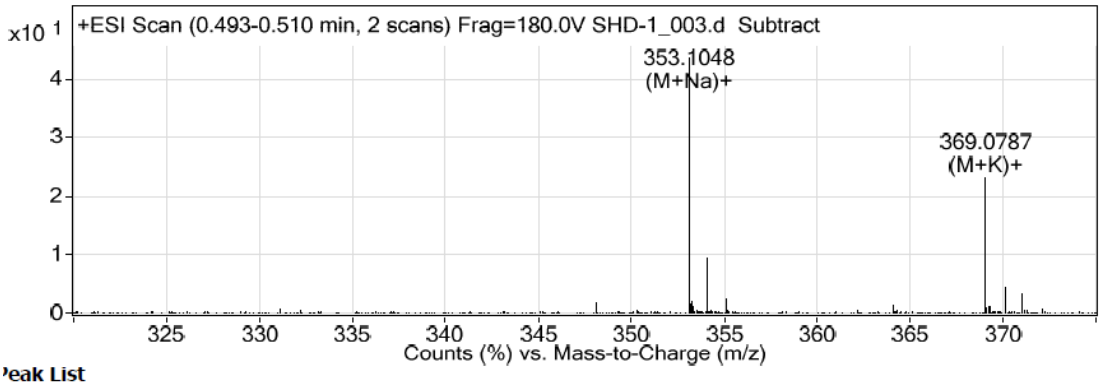


ntegration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	0.348	0.51	0.736	262565	2195042	100

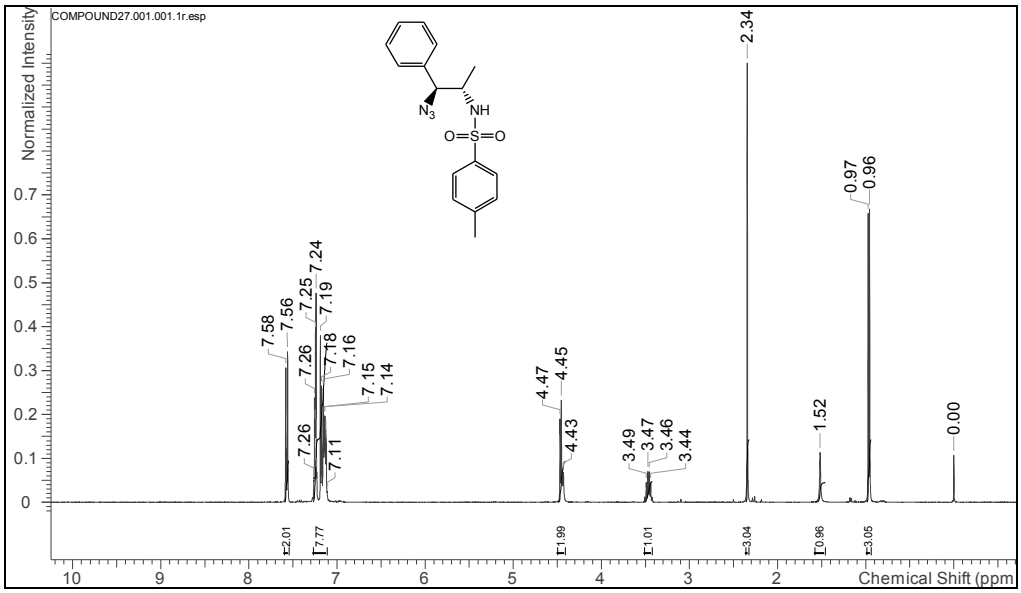
Jser Spectra

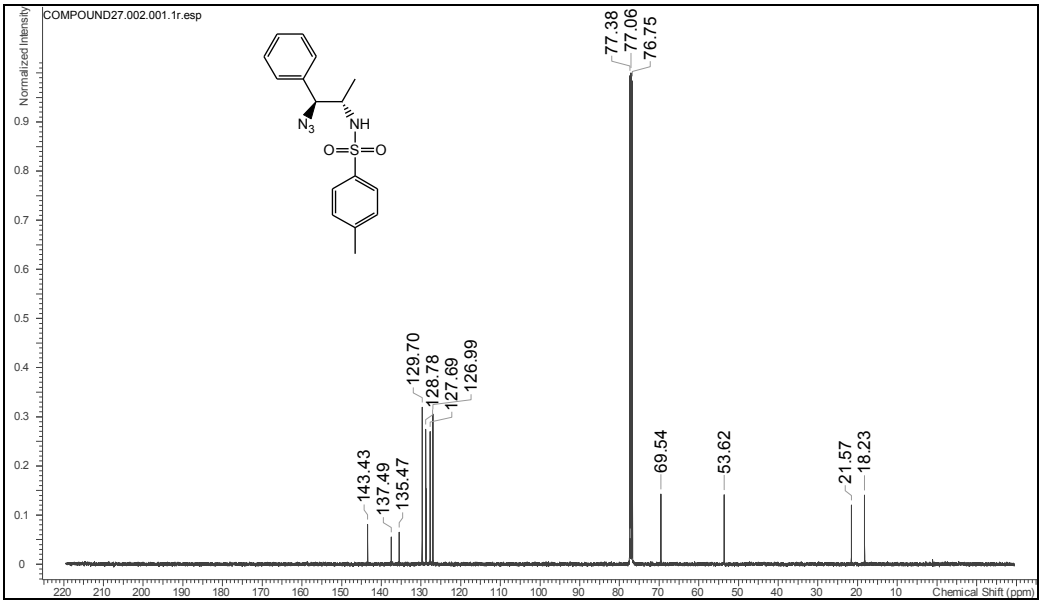
Fragmentor Voltage 180 **Collision Energy** 0 **Ionization Mode** Esi



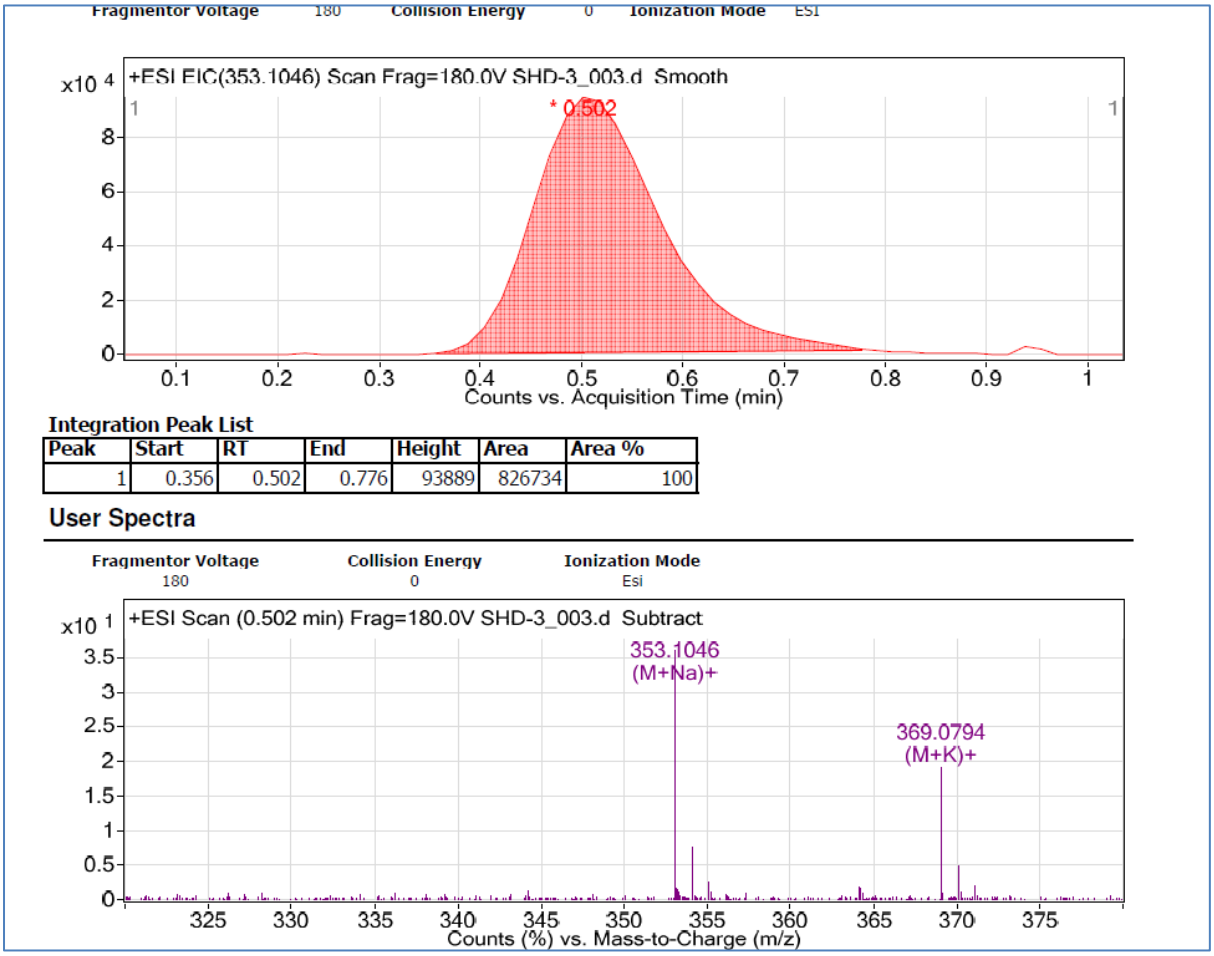
Peak List

8. ^{1}H and ^{13}C NMR spectra of Compound 27





HR-MS of compound 27



Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
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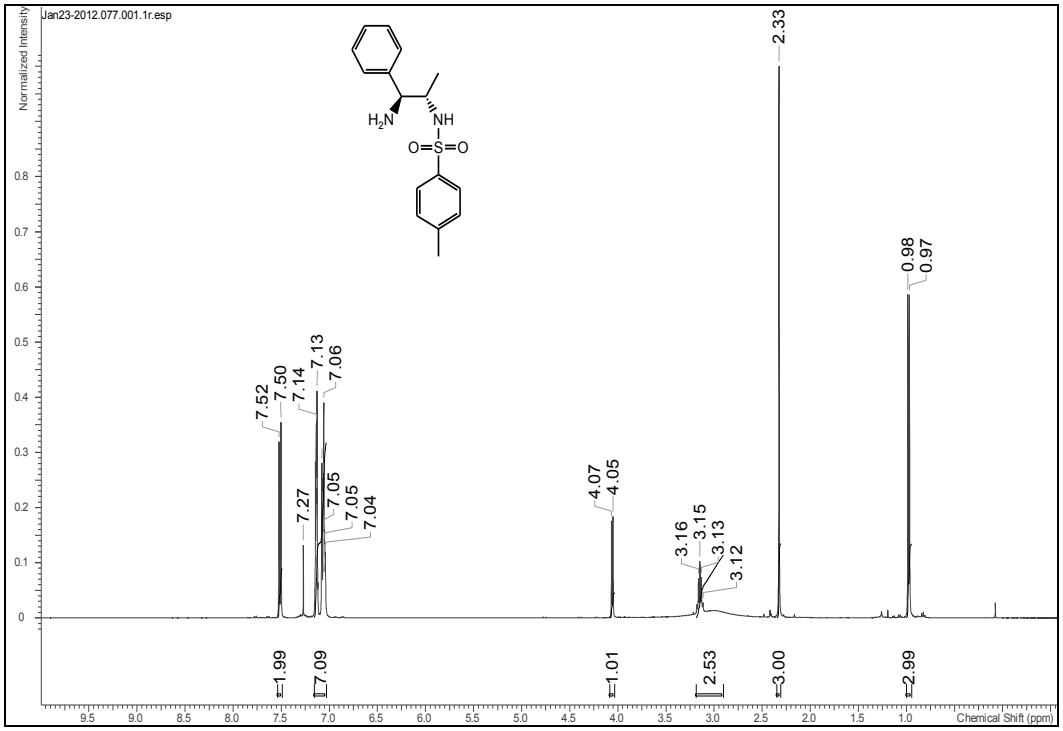
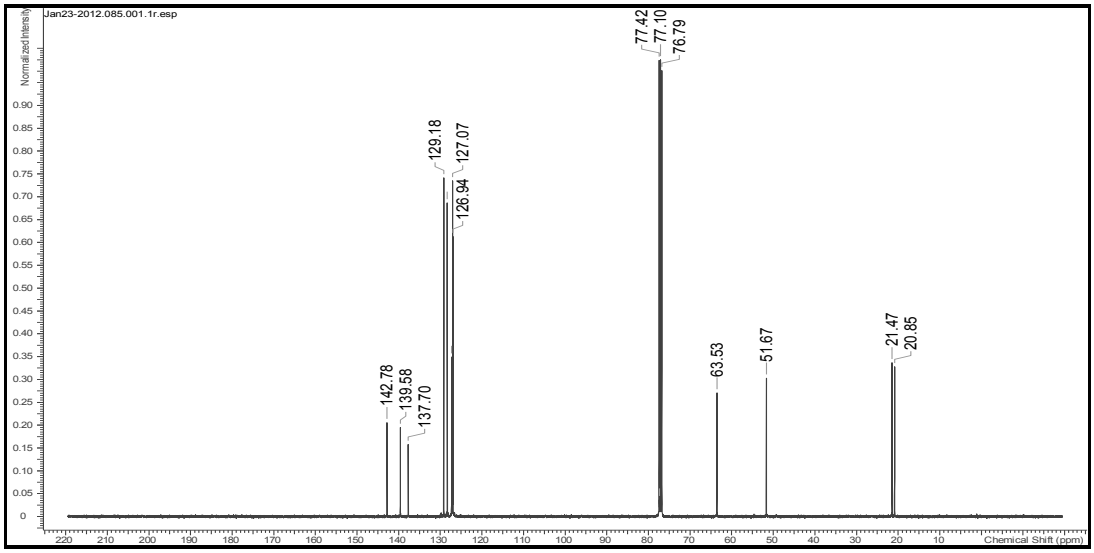
User Spectra

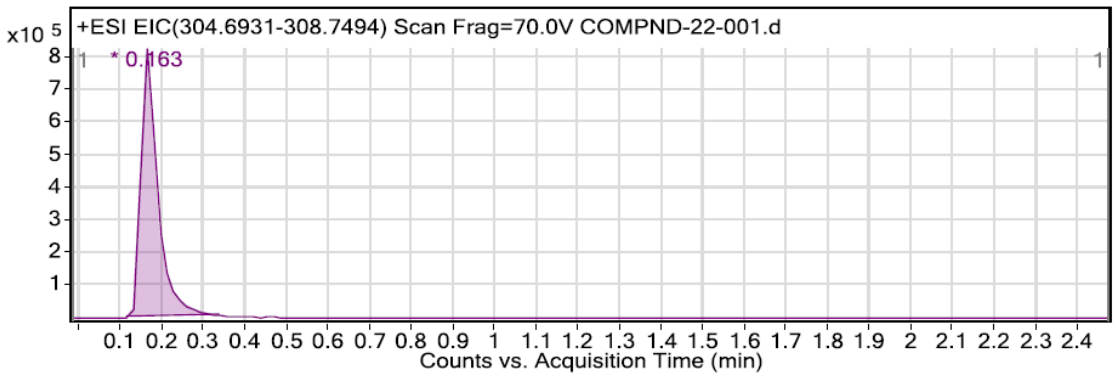
9. ^{1}H and ^{13}C NMR spectra of Compound 29





10. HR-MS of compound 29

Fragmentor Voltage 70 **Collision Energy** 0 **Ionization Mode** ESI

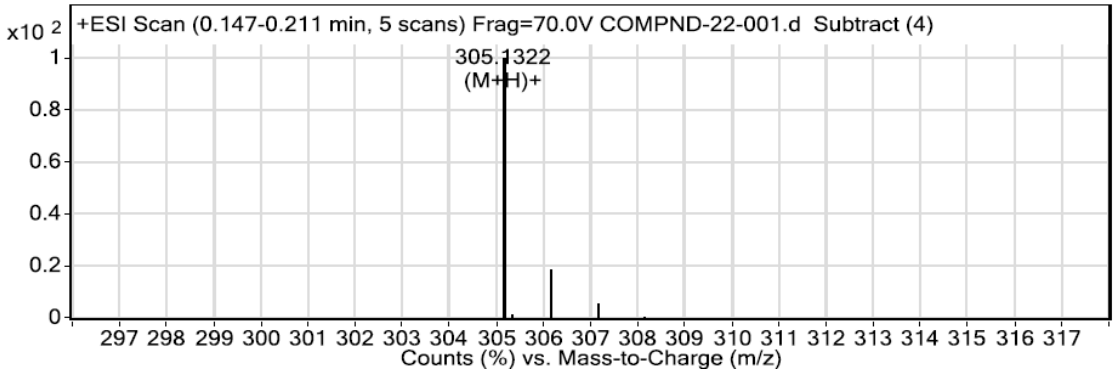


Integration Peak List

Peak	Start	RT	End	Height	Area	Area %
1	0.115	0.163	0.34	822969	2323251	100

User Spectra

Fragmentor Voltage 70 **Collision Energy** 0 **Ionization Mode** Esi



Appendix:

1. Crystal structure data for ligand 4

Crystal structure of ligand 4 is presented below. The data has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 645066

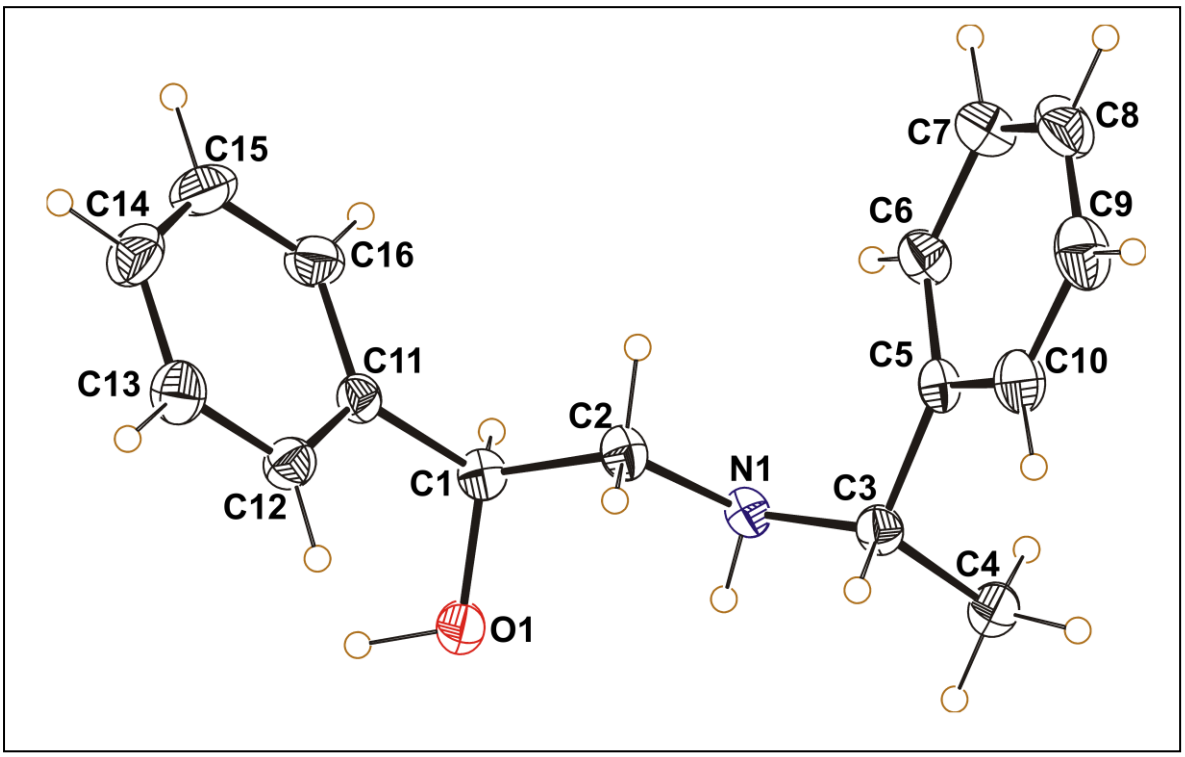


Table 1.Crystal data and structure refinement for ligand 4.

Identification code	4
Empirical formula	$C_{16}H_{19}NO$
Formula weight	241.32
Temperature	297(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $P2_12_12_1$
Unit cell dimensions	a = 8.586(3) Å, α = 90º. b = 8.644(3) Å, β = 90º. c = 18.181(5) Å, γ = 90º.
Volume	1349.3(7) $Å^3$
Z, Calculated density	4, 1.188 Mg/m^3
Absorption coefficient	0.074 mm^{-1}
F(000)	520
Crystal size	0.63 x 0.22 x 0.16 mm
Theta range for data collection	2.24 to 26.00º.
Limiting indices	-5<=h<=10, -10<=k<=10, -22<=l<=22

Reflections collected / unique	7384 / 2655 [R(int) = 0.0242]
Completeness to theta = 26.00	99.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9886 and 0.9555
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2655 / 0 / 239
Goodness-of-fit on F^2	1.079
Final R indices [I>2sigma(I)]	R1 = 0.0343, wR2 = 0.0788
R indices (all data)	R1 = 0.0373, wR2 = 0.0814
Absolute structure parameter	0.6(16)
Largest diff. peak and hole	0.150 and -0.152 e. $Å^{-3}$

Table 2. Bond lengths [Å] and angles [º] for ligand 4

O(1)-C(1)	1.4215(18)
O(1)-H(1A)	0.98(2)
N(1)-C(2)	1.4660(18)
N(1)-C(3)	1.4704(19)
N(1)-H(2)	0.877(16)
C(1)-C(2)	1.512(2)
C(1)-C(11)	1.514(2)
C(1)-H(1)	0.949(15)
C(2)-H(2A)	0.977(18)
C(2)-H(2B)	0.989(16)
C(3)-C(5)	1.518(2)
C(3)-C(4)	1.525(2)
C(3)-H(3)	0.979(16)
C(4)-H(4A)	0.957(19)
C(4)-H(4C)	0.99(2)
C(4)-H(4B)	0.98(2)
C(5)-C(10)	1.382(2)
C(5)-C(6)	1.389(2)
C(6)-C(7)	1.383(2)
C(6)-H(6)	0.917(17)
C(7)-C(8)	1.372(3)
C(7)-H(7)	1.01(2)
C(8)-C(9)	1.375(3)
C(8)-H(8)	0.954(19)
C(9)-C(10)	1.386(3)
C(9)-H(9)	0.94(2)
C(10)-H(10)	0.932(18)
C(11)-C(16)	1.383(2)
C(11)-C(12)	1.388(2)
C(12)-C(13)	1.379(2)
C(12)-H(12)	0.941(17)

C(13)-C(14)	1.382(3)
C(13)-H(13)	0.95(2)
C(14)-C(15)	1.374(3)
C(14)-H(14)	0.965(18)
C(15)-C(16)	1.382(2)
C(15)-H(15)	0.949(19)
C(16)-H(16)	0.949(18)

C(1)-O(1)-H(1A)	108.5(13)
C(2)-N(1)-C(3)	113.47(11)
C(2)-N(1)-H(2)	108.6(10)
C(3)-N(1)-H(2)	107.0(10)
O(1)-C(1)-C(2)	107.08(13)
O(1)-C(1)-C(11)	113.28(12)
C(2)-C(1)-C(11)	110.42(12)
O(1)-C(1)-H(1)	110.0(9)
C(2)-C(1)-H(1)	108.0(9)
C(11)-C(1)-H(1)	108.0(9)
N(1)-C(2)-C(1)	111.59(12)
N(1)-C(2)-H(2A)	110.9(10)
C(1)-C(2)-H(2A)	107.9(10)
N(1)-C(2)-H(2B)	109.5(9)
C(1)-C(2)-H(2B)	107.7(9)
H(2A)-C(2)-H(2B)	109.2(13)
N(1)-C(3)-C(5)	112.50(12)
N(1)-C(3)-C(4)	108.54(12)
C(5)-C(3)-C(4)	110.36(12)
N(1)-C(3)-H(3)	109.3(9)
C(5)-C(3)-H(3)	108.0(9)
C(4)-C(3)-H(3)	108.1(9)
C(3)-C(4)-H(4A)	110.0(11)
C(3)-C(4)-H(4C)	111.3(12)
H(4A)-C(4)-H(4C)	109.4(16)
C(3)-C(4)-H(4B)	108.7(11)

H(4A)-C(4)-H(4B)	109.1(15)
H(4C)-C(4)-H(4B)	108.2(17)
C(10)-C(5)-C(6)	118.08(15)
C(10)-C(5)-C(3)	119.46(14)
C(6)-C(5)-C(3)	122.34(13)
C(7)-C(6)-C(5)	120.78(16)
C(7)-C(6)-H(6)	120.8(10)
C(5)-C(6)-H(6)	118.4(10)
C(8)-C(7)-C(6)	120.33(19)
C(8)-C(7)-H(7)	121.4(12)
C(6)-C(7)-H(7)	118.3(12)
C(7)-C(8)-C(9)	119.69(18)
C(7)-C(8)-H(8)	119.7(12)
C(9)-C(8)-H(8)	120.6(12)
C(8)-C(9)-C(10)	120.03(18)
C(8)-C(9)-H(9)	120.1(12)
C(10)-C(9)-H(9)	119.8(12)
C(5)-C(10)-C(9)	121.07(18)
C(5)-C(10)-H(10)	119.7(11)
C(9)-C(10)-H(10)	119.2(11)
C(16)-C(11)-C(12)	118.47(14)
C(16)-C(11)-C(1)	120.49(14)
C(12)-C(11)-C(1)	121.04(13)
C(13)-C(12)-C(11)	120.59(15)
C(13)-C(12)-H(12)	121.3(11)
C(11)-C(12)-H(12)	118.1(11)
C(12)-C(13)-C(14)	120.39(16)
C(12)-C(13)-H(13)	120.7(12)
C(14)-C(13)-H(13)	118.9(12)
C(15)-C(14)-C(13)	119.41(16)
C(15)-C(14)-H(14)	118.9(11)
C(13)-C(14)-H(14)	121.7(11)
C(14)-C(15)-C(16)	120.26(17)
C(14)-C(15)-H(15)	120.4(12)

C(16)-C(15)-H(15)	119.3(12)
C(15)-C(16)-C(11)	120.88(16)
C(15)-C(16)-H(16)	119.9(11)
C(11)-C(16)-H(16)	119.3(11)

Symmetry transformations used to generate equivalent atoms:

2 . X-ray Crystal Structure Analysis of compound 27a

Crystal Data: Data for compound 27a was collected on SMART APEX-II CCD using Mo-K_α radiation (λ = 0.7107 Å). Crystal to detector distance 5.00 cm, 512 x 512 pixels / frame, Oscillation / frame -0.5º, maximum detector swing angle = –30.0º, beam center = (260.2, 252.5), in plane spot width = 1.24, SAINT integration with different exposure time per frame and SADABS correction applied. All the structures were solved by direct methods using SHELXTL. All the data were corrected for Lorentzian, polarization and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2. Hydrogen atoms were included in the refinement as per the riding model. The refinements were carried out using SHELXL-97.

Liagnd 27a: Single crystals of the compound 27a grown by slow evaporation-. Pale yellow plate like crystal of approximate size 0.34 x 0.32 x 0.16 mm^3, was used for data collection at T = 296K. Multirun data acquisition. Total scans = 3, total frames = 1439, exposure / frame = 8.0 sec / frame, θ range = 2.84 to 24.99º, completeness to θ of 24.99º is 99.40 %. C_{16} H_{18} N_4 O_2 S, M = 330.40. Crystals belong to Monoclinic, space group $P2_1$, *a* = 8.2251(1) Å ,*b* = 10.3695(1) Å , *c* = 9.9358(1) Å , *V* = 845.09(2) $Å^3$, *Z* = 2 , D_c = 1.298 g/cc,μ (Mo–Kα) = 0.206 mm^{-1}, 6855 reflections measured, 2791unique , R1 = 0.0291, wR2 = 0.0791. Largest diff. peak and hole 0.210 and -0.265 e.$Å^{-3}$ .The conformation of the molecule was established by single crystal X-ray analysis shows C7 and C8 both to have R configuration.

Table 1. Crystal data and structure refinement for compound 27a

Empirical formula	C16 H18 N4 O2 S
Formula weight	330.4
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 8.2251 (1) Å α= 90°. b = 10.3695 (1) Å β= 94.2510(7)°. c = 9.9358 (1) Å γ = 90°.
Volume	845.095(16) $Å^3$
Z	2
Density (calculated)	1.298 g/cc
Absorption coefficient	0.206 mm^{-1}
F(000)	348
Crystal size	0.34 x 0.32 x 0.16 mm^3
Theta range for data collection	2.84 to 24.99°.
Index ranges	-9<=h<=9, -11<=k<=12, -11<=l<=11
Reflections collected	6855
Independent reflections	2791 [R(int) = 0.0197]
Completeness to theta = 24.99°	99.40%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9682 and 0.9323
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2791 / 1 / 210
Goodness-of-fit on F2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0291, wR2 = 0.0791
R indices (all data)	R1 = 0.0297, wR2 = 0.0800

Absolute structure parameter	0.04(6)
Largest diff. peak and hole	0.210 and -0.265 e.Å^{-3}

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (Å^{2}x 103) for 27a 2_0m. U(eq) is defined as one third of the trace of the orthogonalizedUij tensor.

	x	y	z	U(eq)
S(1)	10635(1)	2529(1)	131(1)	44(1)
O(1)	10194(2)	3747(1)	-450(1)	58(1)
O(2)	11974(2)	1832(2)	-340(2)	67(1)
N(1)	9067(2)	1588(1)	-91(1)	43(1)
N(2)	5966(3)	262(2)	-689(2)	69(1)
N(3)	4845(3)	-98(2)	-1471(2)	78(1)
N(4)	3858(4)	-547(4)	-2171(3)	121(1)
C(1)	6935(3)	1634(3)	-3031(2)	66(1)
C(2)	6967(3)	2174(3)	-4287(3)	83(1)
C(3)	6273(4)	3373(4)	-4537(3)	92(1)
C(4)	5599(4)	4028(3)	-3527(3)	85(1)
C(5)	5573(3)	3486(2)	-2269(2)	66(1)
C(6)	6224(2)	2278(2)	-2011(2)	45(1)
C(7)	6092(2)	1694(2)	-641(2)	47(1)
C(8)	7506(2)	1998(2)	390(2)	43(1)
C(9)	7214(3)	1401(2)	1762(2)	61(1)
C(10)	10963(2)	2760(2)	1890(2)	48(1)
C(11)	10278(3)	3802(2)	2494(2)	58(1)
C(12)	10400(3)	3884(3)	3896(2)	73(1)
C(13)	11181(3)	2958(3)	4690(2)	75(1)
C(14)	11882(4)	1949(4)	4055(3)	90(1)
C(15)	11775(3)	1827(3)	2659(2)	72(1)
C(16)	11252(4)	3038(5)	6212(3)	117(1)

Table 3. Bond lengths [Å] and angles [°] for compound 27a

1)-O(1)	1.4245(15)
S(1)-O(2)	1.4250(15)
S(1)-N(1)	1.6195(15)
S(1)-C(10)	1.7644(18)
N(1)-C(8)	1.466(2)
N(1)-H(1N)	0.86
N(2)-N(3)	1.219(3)
N(2)-C(7)	1.489(3)
N(3)-N(4)	1.129(3)
C(1)-C(2)	1.370(3)
C(1)-C(6)	1.380(3)
C(1)-H(1)	0.93
C(2)-C(3)	1.383(5)
C(2)-H(2)	0.93
C(3)-C(4)	1.363(5)
C(3)-H(3)	0.93
C(4)-C(5)	1.373(4)
C(4)-H(4)	0.93
C(5)-C(6)	1.378(3)
C(5)-H(5)	0.93
C(6)-C(7)	1.501(3)
C(7)-C(8)	1.525(2)
C(7)-H(7)	0.98
C(8)-C(9)	1.532(3)
C(8)-H(8)	0.98
C(9)-H(9A)	0.96
C(9)-H(9B)	0.96
C(9)-H(9C)	0.96
C(10)-C(15)	1.375(3)
C(10)-C(11)	1.377(3)
C(11)-C(12)	1.392(3)

C(11)-H(11)	0.93
C(12)-C(13)	1.372(4)
C(12)-H(12)	0.93
C(13)-C(14)	1.370(4)
C(13)-C(16)	1.512(3)
C(14)-C(15)	1.389(4)
C(14)-H(14)	0.93
C(15)-H(15)	0.93
C(16)-H(16A)	0.96
C(16)-H(16B)	0.96
C(16)-H(16C)	0.96
O(1)-S(1)-O(2)	119.77(10)
O(1)-S(1)-N(1)	107.64(8)
O(2)-S(1)-N(1)	106.03(9)
O(1)-S(1)-C(10)	107.26(9)
O(2)-S(1)-C(10)	109.20(9)
N(1)-S(1)-C(10)	106.19(8)
C(8)-N(1)-S(1)	119.22(12)
C(8)-N(1)-H(1N)	120.4
S(1)-N(1)-H(1N)	120.4
N(3)-N(2)-C(7)	112.0(2)
N(4)-N(3)-N(2)	173.5(3)
C(2)-C(1)-C(6)	120.6(2)
C(2)-C(1)-H(1)	119.7
C(6)-C(1)-H(1)	119.7
C(1)-C(2)-C(3)	119.7(3)
C(1)-C(2)-H(2)	120.1
C(3)-C(2)-H(2)	120.1

Chapter 3: Application of the amino alcohols and 1, 2 monotosylated diamines to ATH of ketones

3.1 Introduction

Chiral alcohols occupy central place in the synthesis of pharmaceuticals, flavors, aroma, agricultural chemicals and specialty chemicals. The increasing demand for optically active secondary alcohols, has led to the development of a variety of powerful catalytic procedures in the recent past. Asymmetric transfer hydrogenation has emerged as powerful, highly efficient and practical method for the synthesis of chiral alcohols. This has been primarily due to the discovery by Noyori et al.[1-3]of highly active catalysts derived from Ru(II) complexes of β-amino alcohols such as (1R,2S)-1,2-diphenyl-2-(N-methylamino)-ethan-1-ol and monotosylated 1,2-diamine such as TsDPEN. Noyori's catalyst system based on Ru (II) arene complex and simple β-amino alcohols such as 1,2-phenyl ethanol amine gave ligand acceleration effect in ATH of ketones. High catalytic activity as well as high enantioselectivity was achieved (95% yield and 91% ee in 1 h, using $[RuCl_2(C_6Me_6)]_2$ as a catalyst precursor).[3] This key development led to intense exploration of Ru (II) arene(amino alcohol) catalyst systems, over TsDPEN ligands with the aim of designing new ligands and broadening the scope of asymmetric transfer hydrogenation reaction. A variety of β-amino alcohols were synthesized and used as ligands in the transition metal catalyzed asymmetric transfer hydrogenation of ketones. Nearly 80 amino alcohol ligands were synthesized in the period of 1995 to 2013. Most of these are derived from easily available ephedrine or norephedrine building blocks. From steric and electronic perspective most of these chiral ligands used are having chiral vicinal carbon centers. From the literature, it is found that when amino alcohols are used as chiral auxiliaries, the best results are obtained using 2-propanol as the hydride source.

Monotosylated diamines constitute another important class of ligands used for ATH of ketones. In the initial study 2-propanol and FA:TEA (5:2 azeotropic mixture were used as hydrogen donors. Ketone conversion and enantioselectivity were good, however, reaction times were very high (24 to 48 h). Another major development in the ATH of ketones was the use of sodium formate as hydrogen donor in water as a solvent by Xiao et al,[4-6] Use of water as a solvent is important because of the substantial environmental and economical gains. Xiao observed that the activity was very good with water as a solvent and complete conversion of acetophenone was observed in 2 h with 96 % enantioselectivity using Ru(II)-

TsDPEN catalyst. Xiao has carried out detailed work on the ATH of ketones in water using Rh, Ru and Ir catalysts and various ketones were screened. This has led to the use of water as a solvent in ATH reaction. Stability of catalyst was found to be very high with water as a solvent; however, one drawback of the reactions in water is non-homogeneous nature of the reaction mixture. Because of this reason reactions cannot monitor by intermittent sampling. Xiao has investigated the role of co-solvents g DMF as a co-solvent. However, most of the work has been carried out using TsDPEN and TsCYDN ligands and there are very recent reports on the use of unsymmetrical monotosylated diamines as ligands.

In this chapter work carried out on the ATH of ketones using amino alcohol ligands has been presented using Ru and Rh catalysts and 2-propanol as hydrogen donor in the first part. In the second part detailed work on the ATH of ketones using Rh complex with monotosylated diamine ligands prepared during this work with sodium formate as hydrogen donor with water and methanol as solvents is presented. Effect of reaction conditions on the acetophenone conversion and enantioselectivity has been investigated.

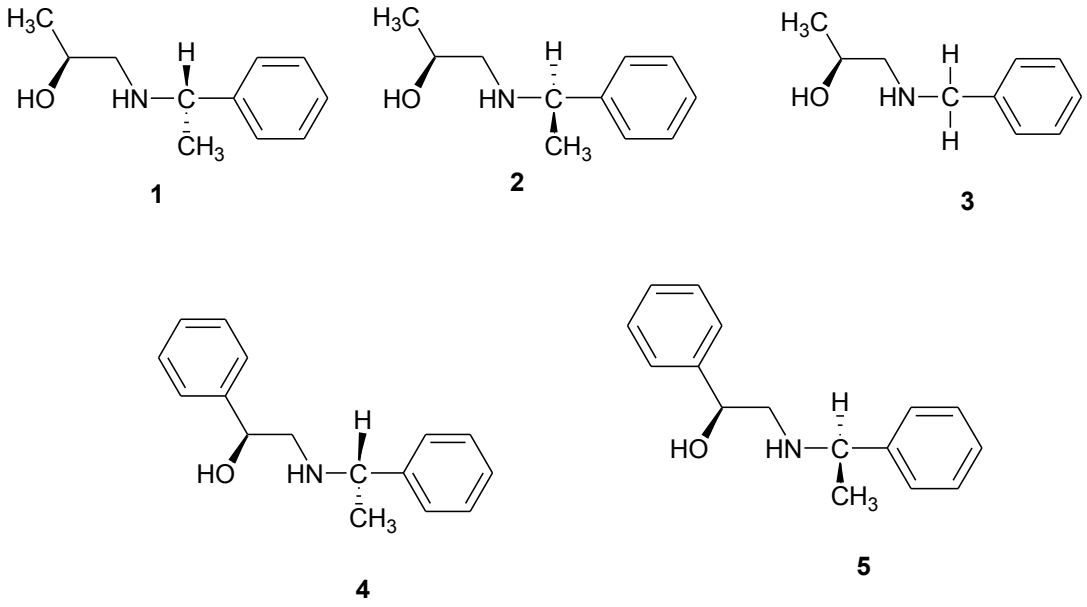


Fig. 3.1: Various Amino alcohols used in the ATH of ketones

3.1.1 Experimental Section

3.1.2 Materials

Rhodium chloride trihydrate ($RhCl_3.3H_2O$) and iridium chloride ($IrCl_3.xH_2O$) were obtained from Arora-Matthey India. All the ketones, [Ru(*p*-cymene)Cl_2]$_2$, TsCYDN, TsDPEN were procured from Sigma Aldrich India. Ethanol, 2-Propanol, KOH etc. were procured from Loba Chemicals, India and used as received. 2-Acetyl-6-methoxy naphthalene, (1R, 2S)-norephedrine, (1S, 2R) norephedrine were obtained as free samples from a private company. The purity of these compounds (>98%) was confirmed by GC and GC-MS analysis. Sodium formate, potassium formate, formic acid, and ammonium formate were procured from Thomas Baker, India.

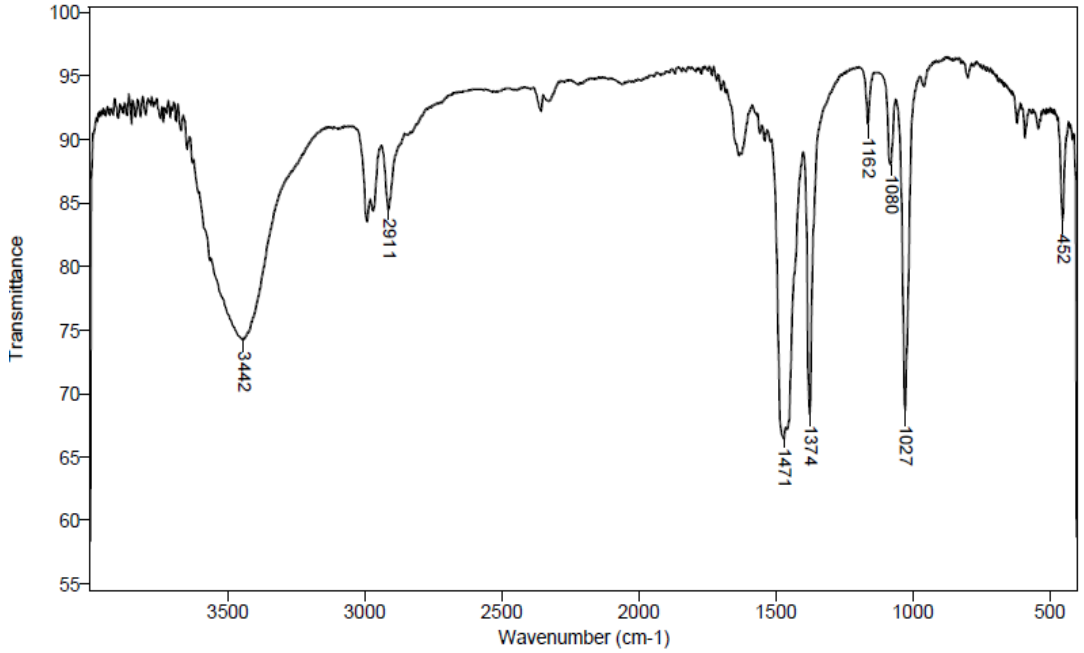
3.1.3 Synthesis of transition metal complexes

The transition metal complexes were prepared as per the literature procedures and analyzed using FTIR, and ^{1}H-NMR spectroscopy. ^{1}H NMR spectra of complexes were obtained on a Bruker AV-200 or AV-400 spectrometer in $CDCl_3$ or DMSO-d_6 at room temperature. FT-IR spectra were recorded on a Bio-Rad FTS 175C machine in transmission mode by preparing KBr pellets.

3.1.4 Synthesis of Di-μ-chloro-dichlorobis(η5-pentamethylcyclopentadienyl) rhodium(III) complex. [Rh(Cp*)Cl_2]$_2$

$2RhCI_3.3H_2O + 2C_5Me_5H \longrightarrow$ [Rh(Cp*)Cl_2]$_2$+ 2HClRh(Cp*)Cl_2]$_2$ complex was prepared by a method described by P. M. Maitlis et al.[7] Rhodium trichloride trihydrate (1.0 g, 0.0042 mol) and pentamethylcyclopentadiene (0.6 g, 0.0044 mol) in dry methanol (30 mL) were placed in a 50 mL round-bottomed flask fitted with a reflux condenser. A nitrogen bubbler was attached to the top of the condenser and the mixture was refluxed gently under nitrogen for 48 h with stirring. The reaction mixture was allowed to cool to room temperature and the dark red precipitate was filtered off in air through a Gooch crucible. The red filtrate was reduced in volume to 5 mL using a rotary evaporator to give more red crystals. These were combined with the first crop and washed with diethyl ether (3 x 5 ml). Air drying gives 0.8 g (75% yield) of [Rh(Cp*)Cl_2]$_2$. The complex was characterized by IR spectroscopy (KBr) cm^{-1}: 2987, 2911 cm^{-1}(C-H bending of CH_3 of Cp*),1471, 1374 cm^{-1} (C-C stretching of Cp*), 1027cm^{-1} (CH_3 twisting) (Figure 3.2) and also by using ^{1}H NMR

spectroscopy which showed sharp singlet at .62 ppm for protons of pentamethylcyclopentadiene as shown in Figure 3.2.



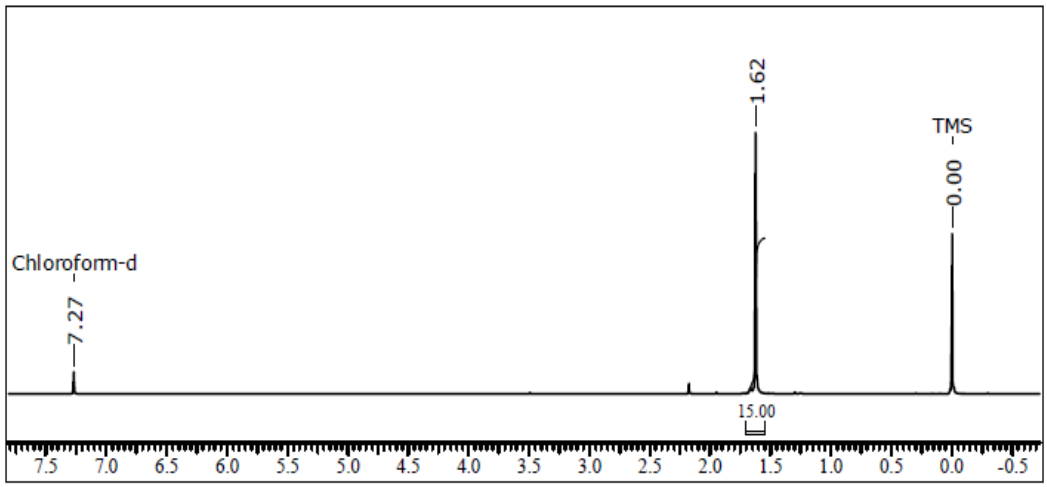


Fig.3.2: FT-IR and ^{1}H NMR spectrum of [Rh (Cp*)Cl_2]$_2$

3.1.4.1 Synthesis of di-μ-chloro-dichlorobis (η$_5$-pentamethylcyclopentadienyl diiridium(III) complex. [[Ir(Cp*)Cl_2]$_2$complex]

$2IrCl_3.XH_2O + 2C_5Me_5H \longrightarrow [Ir\ (C_5Me_5)Cl_2]_2 + 2HCl$

The complex was prepared by a method described by P. M. Maitlis et al.[7] Iridium trichloride trihydrate (1.0 g, 0.0026 mol) and pentamethylcyclopentadiene (0.5 g, 0.0036 mol) in dry methanol (30 mL) were placed in a 50 mL round-bottomed flask fitted with a reflux condenser. The procedure which was used for preparation of

$[Rh(Cp^*)Cl_2]_2$ complex was repeated. The complex was characterized by ^1H NMR analysis, which showed singlet at 1.60 ppm for protons of pentamethylcyclopentadiene and by IR analysis (KBr pellets): 2987, 2913 cm^{-1}(C-H bending of CH_3 of Cp*), 1449, 1377 cm^{-1} (C-C stretching of Cp*) 1034 cm^{-1}, (CH_3 twisting).

3.1.4.2 Preparation of KOH solution in IPA

1.56 g KOH was dissolved in 250 ml IPA. The solution was filtered and titrated against 0.1 N HCl using phenolphthalein indicators to calculate the normality. The normality was found to be 0.086 N.

3.2 Experimental procedure for ATH of acetophenone

3.2.1 ATH of acetophenone with 2-propanol as a hydrogen donor

In a typical experiment, (Fig. 3.3) $[Rh(Cp^*)Cl_2]_2$ complex, 6.18 mg (0.01 mmol) and ligand 4, 12.0 mg (0.051 mmol) were added to 25 ml 2-propanol (degassed with argon) in a glass reactor. To this solution, acetophenone 0.3 g (2.5 mmol, 0.1 M concentration) was added and argon bladder was attached to the reactor to maintain inert conditions. The glass reactor temperature was kept constant at 25^0C using water circulation bath. Reaction was initiated by adding stock solution of KOH (0.086 N) 6.99 mg (0.12 mmol). The reaction mixture was stirred for 3 h. The reaction samples were withdrawn at regular time intervals and quenched by the addition of acetic acid.. The conversion, enantioselectivities and turnover frequency (TOF) were calculated. from the quantitative analysis on GC, and HPLC.

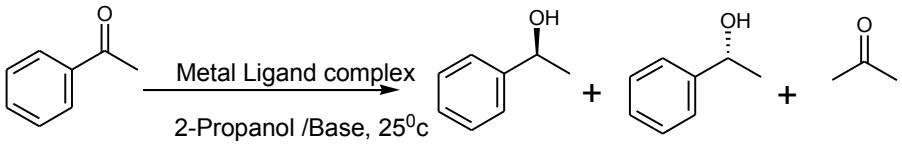


Fig. 3.3: ATH of Acetophenone using transition metal complex and amino alcohol ligands

3.2.2 Analytical methods

The reaction products were identified by GC-MS (Agilent GC 6890N with 5973 mass selective detector) analysis. For calculation of conversions the sample analysis

was carried out on Agilent 6850 GC using HP-1 column (30m× 320 μm ID × 0.25 μm film thicknesses) and FID detector. Enantioselectivity was estimated on Agilent 6850 series GC using HP-chiral column (20 % β-cyclodextrine, 30m × 250 μm ID × 0.25 μm, film thicknesses) supplied by Agilent Technologies (for acetophenone, 4-methyl acetophenone and 4-nitro acetophenone reactions). The standard GC and HPLC conditions for the analysis of products of ATH of acetophenone reaction are given in Appendix.

Alternatively, conversions of acetophenone and enantiomeric excesses of phenethanol were measured on HPLC (Waters, Acquity UPLC). Daicel Chiracel IB column (25 x 0.46 cm, 5u i.d) was used for this purpose. The detector used was a UV-DAD and the monitoring wavelength used in the analysis was 216 nm. Quantification of acetophenone and phenethanol was done using external standard method.

Some chiral alcohols obtained from reactions of other ketones could not be separated on HP chiral column. For such compounds the analysis was done on HPLC for measuring ee.

3.3 Results and discussion

Preliminary experiments on ATH of acetophenone were carried out with $[Rh(Cp^*)Cl_2]_2$ complex and ephedrine as catalyst system, KOH as a base and 2-propanol as hydrogen donor as well as solvent. Formation of products was confirmed by GC-MS analysis. Comparison of the retention times with that of authentic phenethanol samples (R and S) was made, by HPLC as well GC analysis. The R-phenethanol was obtained as the major product, and a standard experimental procedure was established.

ATH of acetophenone was investigated using Ru, Rh and Ir metal complexes as catalyst precursors with amino alcohols prepared as ligands (Chapter 2, 2.2). For comparison 1R, 2S-ephedrine (Ep) reported in the literature[3] was also used as a ligand. The results are presented in Table 3.1. The results showed that the catalysts prepared with amino alcohol ligands (Table 3.1, Sr. No. 2-6) were active and selective for asymmetric transfer hydrogenation of acetophenone. From results it was seen that Ligand-metal complex combination is important for high activity and enantioselectivity. For example $[Ru\ (Benz)Cl_2]_2$showed high activities for all the amino alcohol ligands synthesized, (85% to 92%) but with relatively lower ee (50 to

70%). Whereas [Ru(*p*-cymene)Cl_2]$_2$ showed very good conversion (80% to 90%) and ee for ligands **3**, **4** and **5 (**75**%** to 87**%)**. [RhCp*Cl_2]$_2$ showed good conversions (96%) and very good ee (83%) for ligands 4 and 5. Comparison of the results obtained using ligands prepared from (S)-(-)-lactic acid with various catalyst precursors (Table 1, Sr. No. 2-4) clearly showed that high enantioselectivity was obtained using ligand **3**, for [Ru(*p*-cymene)Cl_2]$_2$ catalyst (87%, compare Table 3.1, entry 4). Enantioselectivity decreased marginally for ligand-**1** (with [S, S] structure), while conversion as well as enantioselectivity decreased for ligand-**2**, having [S, R] structure for all the catalyst precursors investigated. Ligands **1** and **4** have same configuration except that the methyl group in the ligand **1** is replaced by phenyl group in the ligand-**4**. Results obtained for both the ligands are comparable (conv.90% and 91% ee 78% and 76% respectively) for [Ru (*p*-cymene)Cl_2]$_2$ (Table 1, compare Sr. No. 2 and 5). For [RhCp*Cl_2]$_2$ conversion as well as enantioselectivity was higher for ligand 4 (96% conversion 83% ee). [IrCp*Cl_2)]$_2$ in general showed moderate conversions (20% to 50%) for all ligands. For ephedrine and ligand 5, where the configuration for -OH bearing C is R, the product with R configuration was obtained. For all other ligands the configuration for -OH bearing C is S, the product configuration for these ligands with all metal precursors is S. This clearly indicates that the configuration of carbon attached to –OH group is impaired to the chiral alcohol product. The conversion of acetophenone and chiral induction obtained using various metal precursors and ligand-**3** which is having only one chiral center at hydroxyl carbon compares well with ephedrine[3, 8] as a ligand (Table 3.1, compare Sr. No. 1 and 4). This clearly indicates that the chiral center at the –OH group is more important in deciding the chiral selectivity and other chiral center attached to –N may have minimal role in deciding the chiral selectivity. Though in literature different view by carpentier et al. is suggested, that carbon attached to NH also plays important role in enantiosectivity. Similar observations have already been reported by several authors[3, 9-11]. Thus [RhCp*Cl_2]$_2$ and [Ru (*p*-cymene)Cl_2]$_2$ catalysts showed high conversion and good enantioselectivity with ligand 4 in 3 h. Also the structure of ligand 4 has been investigated by single crystal X-ray crystallography. Conversion vs time data was collected for both the catalysts and the results are presented in Fig. 3.4. From the results it was observed that conversion of acetophenone was very high in the initial 60 minutes for both the catalysts. . For Ru catalyst ee values were consistent (77-

79%) throughout the course of the reaction. However, the conversion was higher with Rh catalyst, and also ee was 96 % ~ 30 minutes, initially and decreased over the reaction time and reached 85% at the end of the reaction. Our results are similar to the results obtained by Gavriilidis et al.[12] as, ATH using 2-propanol is equilibrium controlled reaction. At high conversion the concentration of R-phenethyl alcohol is high and it functions as a hydrogen donor and reacts with Rh catalyst to give acetophenone and 2-propanol and reducing overall ee because of high activity of Rh catalyst. It was found that with Rh catalyst very high conversions were obtained, hence effect of various reaction conditions on activity and enantioselectivity was investigated in detail using Rh-ligand 4 catalyst system.

Table3.1: ATH of acetophenone using amino alcohol ligands and catalysts

Sr. No.	Ligand	$(Ru(Benz)Cl_2)_2$		$(Ru(p\text{-cymene})Cl_2)_2$		$(RhCp^*Cl_2)_2$		$(IrCp^*Cl_2)_2$	
		Conv. [%]	ee[a] [%]	Conv. [%]	ee[a] [%]	Conv. [%]	ee[a] [%]	Conv. [%]	ee[a] [%]
1	Ep	90	69*	81*	92*	95	66*	41	78*
2	**1**	87	54	90	78	83	77	30	30
3	**2**	85	40	59	54	42	-	20	-
4	**3**	93	68	84	87	96	67	52	77
5	**4**	91	50	91	76	96	83	51	61
6	**5**	92	50*	90	76*	96	81*	51	64*

Reaction conditions-*:* Catalyst: 0.0013 mmol; Ligand 0.0052 mmol; Acetophenone: 2.5 mmol; IPA: 25 cm^3; KOH: 0.013 mmol; Temperature: 25^0C; Reaction time: 3h *R-configuration

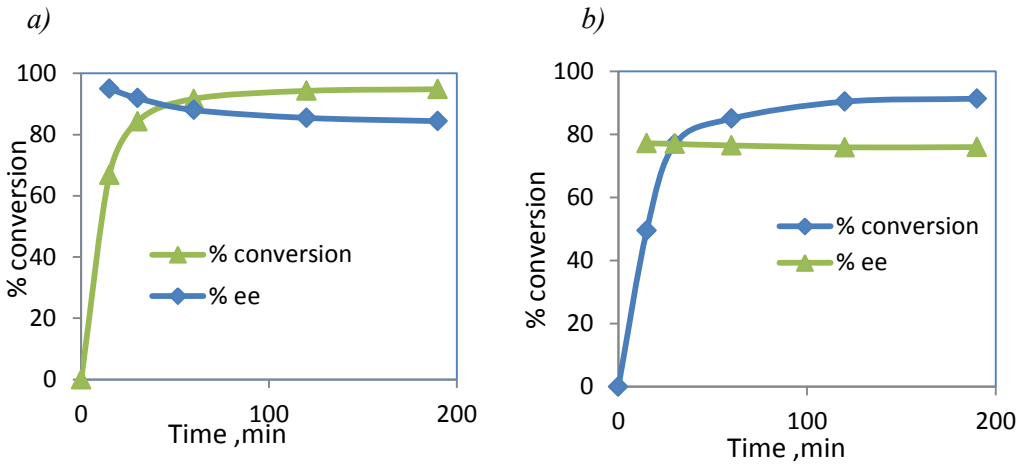


Figure 3.4- Reaction profile for ATH of acetophenone with a) [RhCp*Cl_2]$_2$and Ligand 4 b) [Ru (p-cymene)Cl_2]$_2$/ligand-4

Reaction conditions-: Catalyst,0.0013 mmol; Ligand ,0.0052 mmol; Acetophenone, 2.5 mmol; IPA, 25 cm^3; KOH, 0.013mmol; Temperature, 25^0C; Reaction time, 3h; *R-configuration

3.4 Effect of reaction conditions on activity and enantioselectivity using $[Rh(Cp^*)Cl_2]_2$/ligand 4 catalyst system

The effects of various reaction parameters on conversion of acetophenone and enantioselectivity were studied. There are very few reports in the literature on optimization of various reaction parameters using $[(RhCp^*Cl_2)_2]$[12], and cis Amino indanol. However as steric and electronic factors greatly affect the conversion and ee, we decided to study the effect of various reaction parameters using [Rh $(Cp^*)Cl_2]_2$ and ligand 4 as catalyst system.

3.4.1 Preliminary experiments

From the conversion vs time profile at acetophenone for Rh-Ligand 4 complex,(Fig.3.4) it was observed that the activity of the catalyst was very high and hence the reaction was carried out at a S/C ratio for 200 and the results are presented in Fig 3.5. The reaction was carried out in 2-propanol using a 0.1 M acetophenone solution (*S*/*C:* 200), with $[RhCp^*Cl_2]_2$ catalyst and ligand 4 (Rh: ligand 4, 1:2), and KOH (5 equiv to Rh atom) as a base at 25^{o}C. It was observed that the reaction was very fast and conversion of 66, 85 and 92 % were observed in 10, 15 and 30 minute respectively. The initial enantioselectivity obtained was 96% (in 10 minute), and afterwards it decreased with time up to 92 % after 30min. Other researchers have used different catalysts for the same reaction. Hashiguchi et al.[3] obtained (*S*)-1-phenylethanol with 97% ee and 95% yield using a 0.1 M solution of acetophenone in 2-propanol containing the in situ prepared Ru catalyst (*S*/*C* : 200) and KOH (5 equiv to Ru atom) at room temperature in 15 h.Palmer et al.[13] obtained (*S*)-1-phenylethanol in 70%isolated yield and 91% ee in 1.5 h with 1 mol % of (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol in conjunction with 0.25 mol % of $[RuCl_2(p\text{-cymene})]_2$ and 2.5 mol% of KOH in 2-propanol at room temperature.

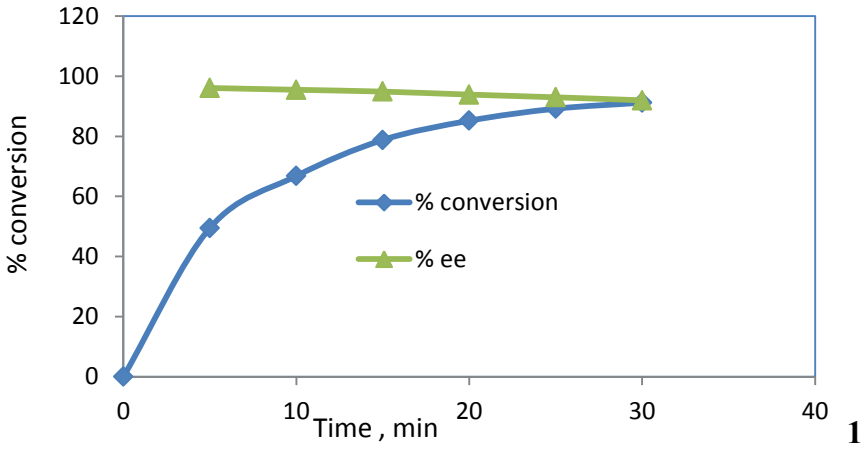


Fig 3.5: Reaction profile, for base case experiment, and % ee for Phenethanol

Reaction conditions*:* catalyst,[Rh (Cp*)Cl_2]$_2$, 0.005mmol;Ligand 4, 0.01mmol;acetophenone,2 mmol; IPA,25 cm^3;Temperature, 25^{0}C, KOH: 0.025mmol

3.5 Effect of inert atmosphere on conversion and ee

The ATH is usually carried out under N_2 or Ar atmosphere. In order to check whether inert atmosphere is necessary, two experiments were carried out using [Rh(Cp*)Cl_2]$_2$/ligand 4 catalyst (Fig 3.6). The reaction was carried out in 2-propanol using a 0.1 M acetophenone solution (*S*/*C:* 200), with [RhCp*Cl_2]$_2$ catalyst and ligand 4 (Rh: ligand 4, 1:2), and KOH (5 equiv to Rh atom) as a base at 25^{o}C. From the results it can be clearly seen that activity was low and only 60 % conversion was observed in 30 minutes compared to 93 % with Ar atmosphere. Enantioselectivity was marginally lower without Ar atmosphere. Thus inert atmosphere was found to be essential and further work was carried out using Ar atmosphere for all the reactions.

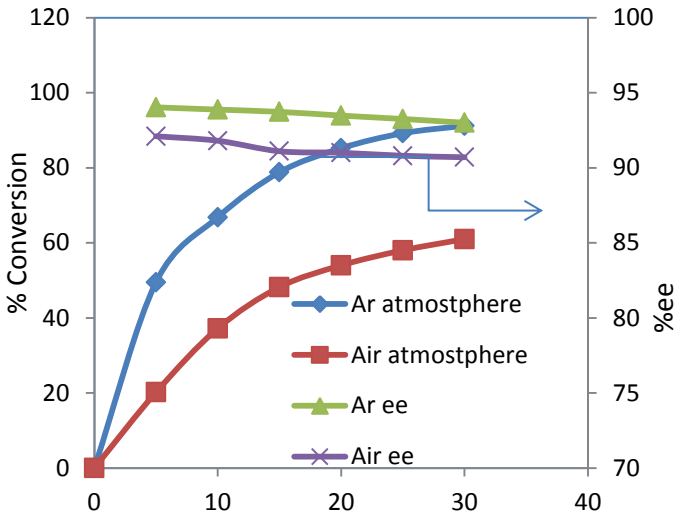


Fig 3.6: Effect of Ar and air atmosphere on conversion and ee for Phenethanol

Reaction conditions: $[Rh(Cp^*)Cl_2]_2$,0.005mmol;Ligand 4, 0.01mmol; Acetophenone, 2mmol; IPA, 25 cm^3; Temperature, 25^0C. KOH, 0.025mmol

3.5.1 Effect of KOH concentration

The effect of concentrations of base (KOH) (expressed as KOH: Rh molar ratio) was studied at constant catalyst, ligand and substrate concentration of 0.005 mmol, 1 mmol and 2mmol respectively at 25^0C. The results are presented in Table 3.2. It was observed that the reaction was not initiated in the absence of a base (entry 1). Conversion increased with increase in base concentration. Highest conversion 93% was obtained at an KOH: Rh ratio of 5:1 (entry 3). Further increase in the KOH:Rh ratio to 10:1 did not show any change in conversion. The enantioselectivity was not affected by a change in KOH concentration and was 91-92%. Backvall[12] have reported that the base is necessary for catalytic activity and the reaction is accelerated with increase in base concentration in ruthenium catalyzed ATH reactions in IPA. Since then most of ATH protocols developed have shown similar behavior.[13,14] In the present work $[Rh(Cp^*)Cl_2]_2$ was used as catalyst precursor. As per the reported mechanism (see Chapter 1, section 1.5), first step in metal-ligand complex formation is removal of proton from β-amino alcohol ligand and Cl^- from the $[Rh(Cp^*)Cl_2]_2$ catalyst to give catalytic species **2** in the presence of base (Figure 1.16).Thus KOH:Rh molar ratio of 5:1 (0.025 mmol)was used for further investigations.

Table 3.2: Effect of base concentration on conversion and enantioselectivity

Entry	KOH:Rh ratio	Conversion %	*ee* %
1	0:1	No reaction	
2	1:1	73	91
3	2:1	91	92
4	5:1	93	92
5	10:1	93	92

Reaction conditions*:* [Rh (Cp*)Cl_2]$_2$,0.005mmol; Ligand 4,1mmol; Acetophenone, 2mmol; IPA, 25 cm3;Temperature, 25^0C; Time, 30 min.

3.5.2 Effect of ligand concentration

The effect of concentration of ligand on conversion and enantioselectivity for ATH of acetophenone was investigated, keeping the concentrations of catalyst, substrate and base constant at 0.005 mmol, 2mmol and 0.025mmol respectively. The concentration of ligand was varied by changing ligand:Rh ratio in the range of 1 to 4. The results (Table 3.3 and Fig. 3.7 a and b) indicate that the conversion of the reaction as well as ee was low at a ligand:Rh ratio of 1:1 (76 % and 86 % respectively). Conversion and ee increased with increase in the ligand:Rh ratio to 2:1 (Table 3.3, Sr. No. 2) and further increase in ration had no effect on the reaction.

The chiral shielding around the metal center is highly dependent on the ligand structure and the number of ligand donor atoms that coordinate to the metal. β-amino alcohols are weakly coordinating ligands and hence ligand:Rh ratio higher than 1:1 is used in literature also to get higher conversion and enantioselectivity.[13],[14] ,their ratio with metal have proven to be critical. Palmer et al.[13] fixed ligand to metal ratio of 4, since for a 1:1 ratio decrease in *ee* was observed from 91 to 68% in [Ru(*p*-cymene)Cl_2]$_2$ catalyzed ATH of acetophenone with (1R,2S) cis 1-amino 2-indanol ligand. The result in this study agree with the experimental and theoretical predictions done by Van Leeuwen and group[15, 16] have carried out theoretical studies as well as ATH of ketones using Ru- catalyst system. They also have shown that ligand:Ru ratio of two is sufficient to maintain high enantioselectivity for Ru(II)-amino alcohol catalyzed ATH of acetophenone.

Since higher enantiomeric excess was obtained using ligand: Rh ratio 2, the same was used for further experiments.

Table 3.3: Effect of Rh: Ligand ratio on ATH of Acetophenone using [Rh (Cp*)Cl_2]$_2$, Ligand 4

Sr. No.	Cat/Ligand Ratio	Conversion (%)	ee (%)
1	1:1	76	86
2	1:2	91	91
3	1:4	91	92

Reaction conditions: *:* [Rh (Cp*)Cl_2]$_2$, 0.005mmol; Acetophenone, 2mmol; IPA, 25 cm3;Temperature, 25^{0}C; Time, 30 min; KOH, 0.025mmol

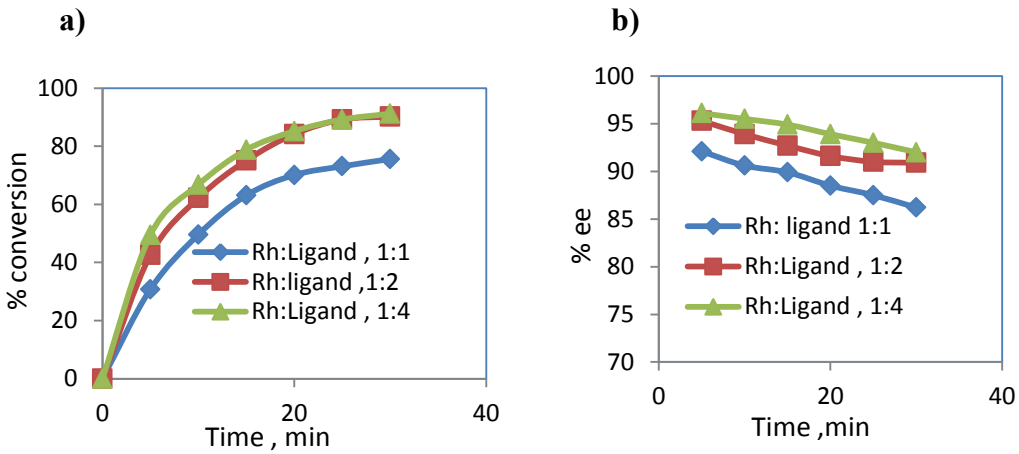


Fig 3.7:Effect of Ligand to Rh ratio on a) conversion b) ee for Phenethanol

Reaction conditions: [Rh (Cp*) Cl_2]$_2$, 0.005mmol; Acetophenone, 2mmol; IPA, 25 cm3;Temperature, 25^{0}C; Time, 30 min.*;* KOH, 0.025mmol

3.5.3 Effect of catalyst concentartion

The effect of catalyst concentration on conversion and enantioselectivity was investigated in a catalyst concentration range of 0.0025 mmol to 0.01mmol keeping other conditions constant. The results obtained are presented in Fig. 3.8. As expected the conversion of acetophenone increased with increase in catalyst concentration with marginal variation in enantioselectivity. For catalyst concentration of 0.01 mmol, 93% conversion was obtained within 25 minutes, for lower catalyst concentrations (0.0025 mmol) the reaction was slower and 81%

conversion was obtained in 25 minutes. For catalyst concentrations of 0.0025 and 0.01mmol, the *ee* was around 90%. With Rh catalyzed reactions ee was found to decrease with increase in reaction time and hence reaction with 0.01 mmol catalyst (highest loading) was continued for 180 minutes and it was found that ee decreased to 85 %.Our results are similar to the results obtained by Gavriilidis et al.[12] They have shown that *ee* decreases slightly (from 86% to 82%) at higher catalyst concentration for ATH acetophenone using cis amino indanol/$[Rh(Cp^*)Cl_2]_2$ catalyst. At higher concentration of catalyst (0.01mmol), high conversion was obtained but enantioselectivity was less. Hence 0.005 mmol catalyst concentration was fixed for further reaction (91 % conversion with 92% ee in 30 min).

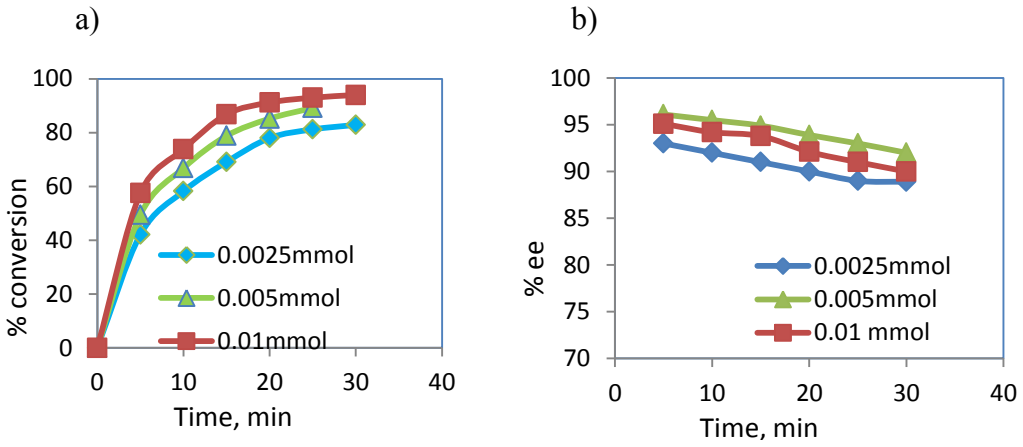


Fig 3.8: Effect of catalyst concentration on a) conversion b) ee for Phenethanol

Reaction conditions*:* [Rh $(Cp^*)Cl_2]_2$, 0.005mmol; Ligand 4, 0.01mmol;IPA,25 cm^3;Acetophenone, 2mmol; Temperature 25^0C; KOH, 0.025 mmol

3.5.4 Effect of substrate concentration

The effect of substrate concentration on conversion and enantioselectivity for ATH of acetophenone was investigated at constant catalyst, ligand and base concentrations of 0.5 x 10^{-5} mol, 1.05 x 10^{-5} mol and 1.2 x 10^{-4} mol respectively. Substrate concentration was varied from 0.05 M to 0.2M (1mmol, 2mmol land 4 mmol respectively).Figure 3.9 represents the effect of different molar concentrations (M) of acetophenone on conversion of the reaction. Results indicate that at low substrate concentration (0.05 M), conversion (86%) was obtained within 15 minutes, with increase in concentration of substrate conversion decreased significantly; however, enantioselectivity was marginally significantly affected by a

change substrate concentration. Although the conversion reduced, with increase in acetophenone concentration, the productivity of the alcohols was in fact higher.

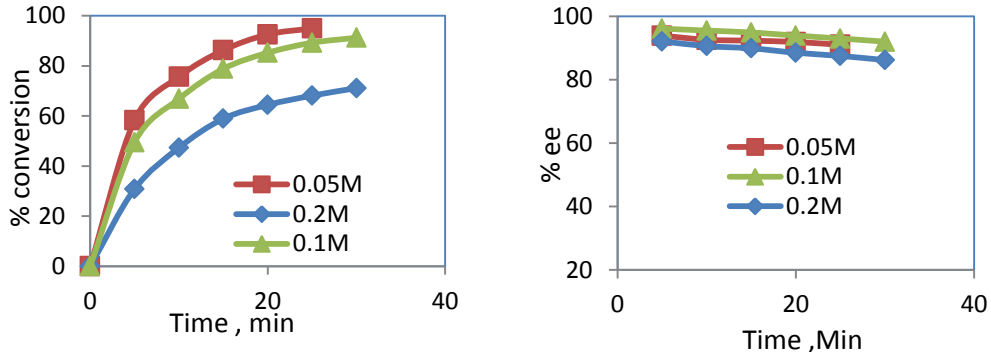


Fig 3.9: Effect of Substrate concentration on a) conversion b) ee for

Reaction conditions :[Rh (Cp*)Cl_2]$_2$, 0.005mmol; Ligand 4, 0.01mmol;IPA,25 cm^3;Acetophenone, 2mmol; Temperature 25^{0}C; KOH, 0.025 mmol

3.5.5 Effect of Temperature.

Effect of temperature on ATH of acetophenone was investigated in a temperature range of 15^{o}C to 35^{o}C. The results are presented in Fig. 3.10 in terms of conversion (Figure a) and ee (Figure). Conversion of acetophenone increased with increase in temperature and complete conversion was observed in 30 minutes at 25^{o}C and 35^{o}C. Enantioselectivity decreased significantly with increase in temperature and thus ee decreased from 94 % at 15^{o}C to 86% at 35^{o}C. Similar results for Rh catalyst are obtained by other researchers[12]. Increase in temperature leads to a decrease of the energy difference between the diastereoisomer transition states resulting in lower ee at higher temperature[17].

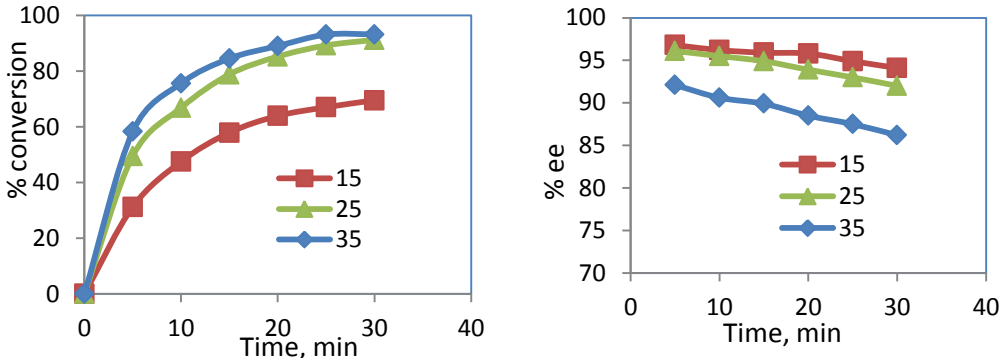


Fig 3.10: Effect of Temperature on a) conversion, b) ee for Phenethanol Reaction

conditions: [Rh (Cp*)Cl_2]$_2$, 0.005mmol; Ligand 4, 0.01mmol;IPA,25 cm^3;Acetophenone, 2mmol; Temperature ^{0}C.; KOH 0.025 mmol,

From the optimization of reaction conditions it was observed that [Rh (Cp*)Cl_2]$_2$ with ligand 4 was having good activity, however, ee decreased throughout the course of the reaction. In few cases reaction was conducted for higher reaction time like 180 minutes and ee was found to deteriorate further. Main reason for the observed results may be higher activity of the catalyst leading to conversion of product back to acetophenone and 2-propanol by reverse reaction and subsequently leading to lower ee at the end of the reaction. The erosion in ee, in very short time was the major problem of the Rh-ligand 4 catalyst system. Thus ATH using 2-propanol with Rh-ligand 4 catalyst system was found to be highly equilibrium controlled.Therefor screening of other ketones using Rh-ligand 4 catalyst system was difficult.

The Ru-Ligand 4 catalyst system showed consistency in the ee(without erosion)as shown in Fig. Thus it was decided to, screen various ketones, with [Ru(*p*-cymene)Cl_2]$_2$ and Ligand 4 catalyst system, as per the condition standarised.in section 3.2.1

3.5.6 Screening of various ketones using [Ru(*p*-Cymene)Cl_2]$_2$/ ligand-4 catalyst system

Activity of [Ru (*p*-Cymene)Cl_2]$_2$/ ligand-**4** catalyst was good and enantioselectivity was consistent throughout the course of the reaction (Fig.3.4) and hence various ketones were screened using this catalyst system (Table 3.4). Best results were obtained for ATH of acetophenone as a reactant (91% conversion and 76% ee). With electron withdrawing substituents in the para position activity increased significantly, while enantioselectivity decreased significantly (Table 3.2, compare Sr. No. 1 with Sr. nos. 2- 4, conversion 92-95% in 1 h compared to 91% in 2h; ee: 52-66 compared to 76%). With electron donating methyl group in Para position conversion as well as chiral selectivity decreased marginally (Table 3.4, compare Sr. nos. 1 and 5). With bulkier isobutyl group in para position, the reaction was sluggish (38% conversion in 3 h) with 74% ee. With substituent in the ortho position, conversion as well as chiral electivity decreased significantly (Table 3.4, Sr. no. 9 and 10). Thus, reaction did not proceed using 2-acetyl pyridine, while 99% conversion in 1 h reaction time with 64% enantioselectivity was achieved using 3-acetylpyridine as a reactant. 4-Methoxy acetophenone is known to be a challenging

substrate probably because of its low redox potential, giving lower conversions and enantioselectivity.[1, 3, 18] In the present study, transfer hydrogenation of 4-methoxyacetophenone gave 54% conversion with 65% ee in 2 h reaction time.

Table 3.4 ATH of Various ketones using amino alcohol ligand 4 and Ru (p-Cymene)$Cl_2]_2$ complex

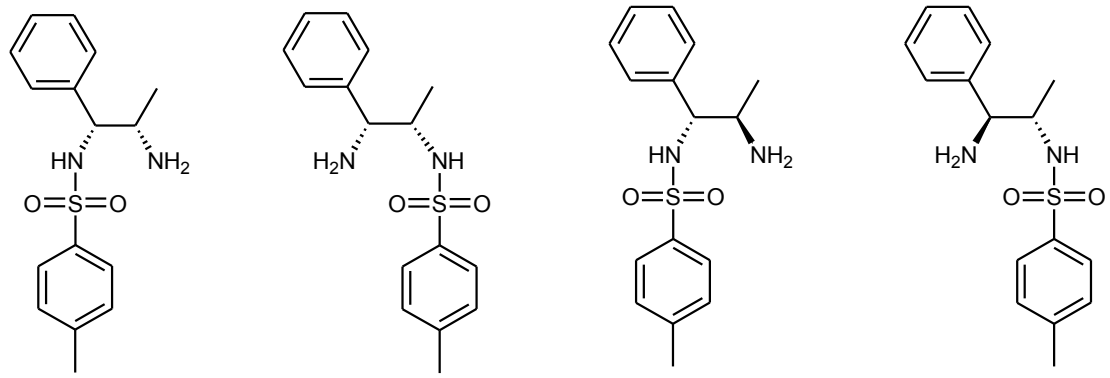
Entry	Ketone	Reaction time (h)	Conv %	ee %	Config
1	Acetophenone	2	91	76	R
2	4-Bromoacetophenone	1	99	52	S
3	4-Nitroacetophenone	1	92	56	S
4	4-Chloroacetophenone	1	95	57	S
5	4-Methylacetophenone	2	82	67	R
6	4-Isobutylacetophenone	2	38	74	R
7	4-Methoxyacetophenone	2	54	65	R
8	2 Acetyl 6-methoxy naphthalene	2	74	62	
9	2,5 Dimethylacetophenone	2	23	35	R
10	2- Acetyl pyridine	2	-	-	
11	3 -Acetyl pyridine	1	99	64	S

Reaction conditions: **Reaction conditions**-*:* Catalyst: 0.0013 mmol; Ligand 0.0052 mmol; Acetophenone: 2.5 mmol; IPA: 25 cm^3; KOH: 0.013mmol; Temperature: 25^0C; Reaction time: 3h

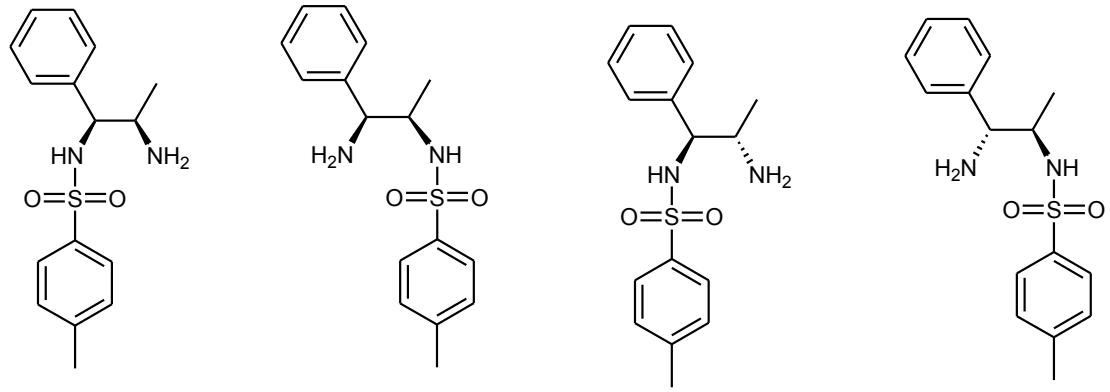
3.6ATH of Ketones with monotosylated Diamine ligands

The TsDPEN[1] and TsCYDN[19] ligands, although introduced earlier than amino alcohol, were used in 2-propanol[1, 19] as well as in FA:TEA[2] systems initially. Though the conversions and enantioselectivities were excellent, the reaction times were long (12h -24h), It was also found in the literature section 1.4, that the selectivity of –these ligands varies with metal complexes[19], and the choice of hydrogen donor[6]. Wills explored the unsymmetrical diamines ligands in 2002 with amino indanol[20] based tosylated diamines,. However much inferior results compared to TsDPEN were observed. These aminosulfonamide ligands which showed highest activity were having syn geometry of amino and sulfonamide groups. In 2004 the cis derivative of TsDPEN[21] was synthesized and used in ATH by Wills. The moderate activity of this cis isomer was suggested due to the importance of anti-substitution of amino and sulfonamide groups in TsDPEN ligands. Xiao et.al[4] presented significant breakthrough in 2004, when Ru-TsDPEN complexes were reported for ATH of ketones in water and sodium formate. The reaction was complete in 2h. at 40^0C and variety of ketones were reduced in excellent conversions and enanatioseclctivity[4]. This embarked the new era, of ATH in water using sodium formate. Since then these C2 symmetrical ligands has dominated the ATH of ketones as well as imines. $[Rh(Cp^*)Cl_2]_2$ complex of both TsCYDN[5] and TsDPEN [6], showed further enhancement of the activity in water and sodium formate in water.whcih was better than to the Ru–TsDPEN analogues.[4, 6]. The mechanism of the reaction was investigated in detail by Xiao etal.[22] The kinetic study and DFT calculation to support the mechanism were reported[22, 23]. Since then many derivatives of TsCYDN and TsDPEN are used in ATH of ketones. In all these reports modifications were made by keeping the C2 symmetric backbone intact and adding or changing the substitution either at phenyl positions[24] or by changing the sulfonyl ring of the ligand. Efforts were also made to immobilize[25], tethering[26], and adding a polymers[27] support. Ming xua- developed real versatile, but slightly difficult strategy to generate unsymmetrical vicinal diamine ligands and 6 new ligands were used in ATH[28]. Few strucrally diverse unsymmetrical diamines based on limonene[29, 30] were also explored in the literature for ATH of ketones, which showed good conversion and ee in ATH of ketones. From literature it was also observed that with TsDPEN ligands, metal complex combination gives significantly different activities. Ru-TsDPEN showed 99% conversion in 2h, with 94% ee. For

Rh -TsDPEN the conversion of 99% was reached within 0.5h the ee obtained, was 97% ee.DFT calculations for TsDPEN ligand showed that there is difference in transitions state energies of 2kcal/mole in Ru,and Rh TsDPEN[31, 32]. From literature it was clear that there are very few reports for use of structurally diverse monosulfonated diamines in ATH for ketones. These reports mainly described the use of anti-orientation of sulfonamide ligands. However unsymmetrical vicinal diamines give rise to number of probabilities to the regio and stereo positions of amino and sulfonamide group .This will generate number of new ligands which can be explored in ATH of ketones and imines.This clearly shows that there is scope and need to develop new unsymmetrical vicinal diamine ligands and understand the reasons for different reactivity in ATH of ketones.In literature the use of structurally diverse monosulfonated diamines with only ruthenium complexes is described. Other transition metal complexes like Rhodium and Iridium are not explored in ATH of structurally diverse monosulfonated diamines. In this section, the ATH of acetophenone using sodium formate in water using [Ru(*p*-cymene)Cl_2]$_2$, [Ir(-Cp*)Cl_2]$_2$.and 1,2 monotosylated diamines was studied[Rh(Cp*)Cl_2]$_2$.Various ketones were screened for expanding the scope. Effect of co-solvents was added and its appropriate composition with water was made. The effect of these co-solvents on conversion and ee was investigated and use of methanol as solvent for ATH of ketones using sodium formate was developed. Precatalyst preparation as per literature as well as modified procedure was done. X-Ray crystal structure of the pre catalyst was established. Using this modified procedure in methanol study of various reaction parameters was done. Finally comparison was made with the ligand 9 with and benchmark ligands TsDPEN and TsCYDN for [Rh(Cp*)Cl_2]$_2$.



6 7 8 9



10 11 12 13

Fig.3.11: various monotosylated diamines used in ATH of ketones

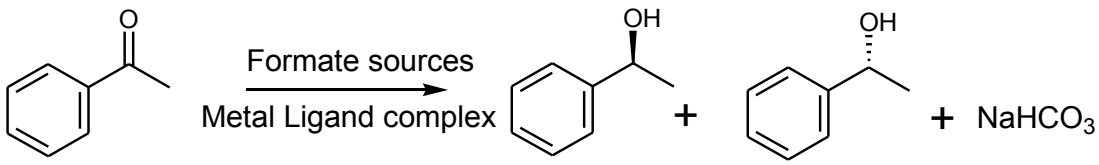


Fig. 3.12: ATH of acetophenone using sodium formate as a hydrogen donor in water

3.6.1 Experimental setup and procedure for ATH reaction

All the reactions (Fig.3.12) were carried out in a jacketed glass reactor. In a typical experiment, $[Rh\ (Cp^*)Cl_2]_2$, (0.005 mmol) and ligand 9 (0.01 mmol) was added to 2 ml water in a jacketed reactor. The contents were heated at 40^0C for one hour to form catalyst from the precursors. Then jacketed reactor was kept at 25^oC using water circulation bath. Acetophenone (0.12 g, 1 mmol) and sodium formate 0.34 g, 5 mmol) were added to the reactor and reaction was initiated by stirring the reaction mixture with the help of magnetic needle. Reaction was continued for 3 h and reaction sample was extracted with t-butyl methyl ether for analysis.

3.6.2 Results and Discussion:

ATH of acetophenone was investigated using Ru, Rh and Ir metal complexes as catalyst precursors with eight monosulfonated diamine ligands prepared as described in the chapter (2, section) 2.4---.The results are presented in Table 3.5. The results showed that the catalysts prepared with monosulfonated diamine ligands (Table 3.5, Sr. No. 1-8) were active and selective for asymmetric transfer hydrogenation of acetophenone. From results it was seen that ligand-metal complex combination was important for high activity and enantioselectivity. Rh showed Excellent conversions (>97%) and very good enantioselectivity (>90%) with ligands 8 and 9 (Table 3.5 entry 3,4,7,8) and very low conversion with other ligands. While Ru (10 to 36%) and Ir (10 to 22 %) catalysts showed lower activity with all the ligands. Enantioselectivity for all metal complexes and all ligands was good to excellent and was in a range of 68 to 92%.

Relative stereochemistry of the amine and sulfonamide group is critical in deciding the activity of the catalyst system. For example Ligand 6 and 7 which are having syn geometry of the amine and sulfonamide groups are less reactive irrespective of the metal complexes used. Thus ruthenium, rhodium and iridium complexes used in

study showed < 30 % conversion with moderate to good ee. (67-90 %.). Similar observation is noted by other research groups for compounds having syn or cis geometry.[21] However indane based cis sulfonamide ligands showed very good conversions and ee(96%, and 83% ee).[20]Ligands having anti or trans geometry (ligands 8 and 9) showed very good conversions and ee for the catalysts investigated (Table 3.5, Sr. No. 3 and 4).(>90% and 80%, respectively).

The structure activity relationship showed that the along with stereochemistry of the amine and sulfonamide groups, their regio position is also important. In ligand 8 sulfonamide groups is attached to the carbon having phenyl group and amino group is attached to the carbon having methyl group. In ligand 9 the amino group is attached to the carbon having the phenyl group and sulfonamide group is attached to the carbon having the methyl group. The results showed that ligand 9 and its enantiomer (entry 4 and 8) were most active for all the catalysts and best results were observed with Rh catalyst (>99% conversion With 92 % ee in1.25h). The activity was marginally higher than ligand 3 and its enantiomer for all the catalysts. In this case also best results were observed with Rh catalyst (97 % conversion with 92 % ee in 3 h) (Entry 3 and 7). The difference in activity between ligand 8 and 9 was probably because of the different positions of the amine and sulfonamide group. The enantioselectivity using both the ligands 8 and 9 was same, indicating that methyl and phenyl group attached to the carbon having sulfonamide group do not influence enantioselectivity.

It was found that the configuration of the resultant alcohol was having the same configuration as that of the carbon bearing sulfonamide group. Thus for all the entries it was observed that irrespective of the activity shown by ligand, configuration is driven by the carbon bearing sulfonamide group. For ligands 6 and 8 where sulfonamide group is attached to carbon having R configuration; the resultant alcohol configuration was also R. For ligands 7 and 9 where carbon bearing sulfonamide group is having S configuration; the resultant alcohol was having S configuration. These observations were found to be consistent with the literature observed reports[21, 28-30].

The use of specific metal complex also plays an important role in having good activity and enantioselectivity. Comparison of the results obtained using $[Rh(Cp^*)Cl_2]_2$ with benchmark ligands like TsDPEN, and TsCYDN, indicated that the conversion obtained with ligand 9 was comparable with both the ligands,

however enantioselectivity was lower (97 % for TsDPEN[6], 94 % for TsCYDN[5] vs 92 % for ligand 9)than that with TsDPEN.

Thus, various monotosylated diamines synthesized were screened for ATH of ketones using sodium formate as hydrogen source and water as solvent. The monotosylated diamines synthesized were having systematic variation in the stereo and regio position of amine and sulfonamide groups. The change in position of amine and sulfonamide groups with respect to each other had significant impact on conversion. This is the first example of successful ATH of ketone using $[Rh(Cp^*)Cl_2]_2$ and monosulfonated unsymmetrical diamines as ligands. Also this is the first systematic study on the screening of monosulfonated unsymmetrical diamine ligands with different metal complexes in the ATH of ketones. Best results (99 % conversion in 1.25 h with 92 % ee) were obtained using Rh-ligand 9 catalyst system and hence further work was carried out using the same.

Table 3.5: ATH of acetophenone using monosulfonated unsymmetrical diamines and transition metal complexes

Entry	**Ligand**	**(Ru(*p*-cymene)$Cl_2)_2$**			**$Rh(Cp^*)Cl_2]_2$**			**$[Ir(Cp)^*Cl_2)_2$**		
		Conv. [%]	**ee %**	**Config**	**conv. %**	**ee %**	**Config.**	**Conv. [%]**	**ee %**	**Config.**
1	6	12	68	R	23	78	R	10	86	R
2	7	<10	70	S	18	82	R	<10	75	S
3	8	22	90	R	**97**	**92**	**R**	22	82	R
4	9	36	85	S	**99***	**92**	**S**	22	90	S
5	10	10	70	S	21	80	R	10	85	S
6	11	<10	72	R	15	83	S	<10	77	R
7	12	21	91	S	**97**	**92**	**S**	20	80	S
8	13	32	83	R	**99***	**92**	**R**	20	88	R

Reaction conditions: $Rh(Cp^*)Cl_2]_2$, 0.005mmol; Ligand,0.01mmol; sodium formate 5 mmol; acetophenone, 1mmol; water 2cm^3 ; Temperature: 25^{0}C; Time 2 h, * 1.25 h

3.7 Screening of ketones using Rh-ligand 9 complex

ATH of various ketones was carried out using Rh-ligand catalyst system with sodium formate as a hydrogen donor in water and the results are presented in Table 3.7. With acetophenone; 95 % conversion was observed with 91 % ee in 1 h. With the presence of electron withdrawing groups in para position (*p*-chloro acetophenone and *p*-bromo acetophenone), the conversions as well as enantioselectivity were lower compared to acetophenone, (table 3.6, Entry 2 and 3). With electron donating groups in para position (methyl and isobutyl acetophenone), conversions were significantly lower, 90 % and 87 % in 2 h and 6 h respectively. The enantioselectivity however was higher for methyl acetophenone (97 %) compared to acetophenone (91 %) (Table 3.6 entry 5). For isobutyl acetophenone though the enantioselectivity also was lower to 89%. The difference in the conversions for different ketones is well explained in the literature and noted by other research groups. 4- Methoxy acetophenone is known to be a challenging substrate for ATH reaction, because of probably its low redox potential. In this particular system 4-Methoxy acetophenone was also reduced with very good conversion (82 % in 2h) and excellent enantioselectivity (97%). Although to reach more than 90 % conversion it took nearly 12 h (table 3.6entries 6).

Cyclic ketones like indanone and tetralone were reduced at much faster rate but lower than acetophenone and with significantly lower enantioselectivity (98 % conversion in 1.5 h with 84 % ee for indanone) and (95 % conversion if 2 h with 88 % ee for tetralone) (entry 8 and 9). For 6-methoxy-2- acetyl naphthalene (entry 10), however only 5 % conversion was observed with 98 % ee even after prolonged reaction time of 12 h. The ATH in water using sodium formate was found to be faster than with neat FA: TEA, or 2-propanol system[1, 2, 4] (for amino sulfonamide ligands). This was attributed to the fact that reaction in water with sodium formate as a hydrogen donor takes place at the interface of water and ketone. Catalyst and ketone have low solubility in water and form a separate layer on the water used as a solvent. Thus the concentration of catalyst in ketone layer (organic i.e. substrate layer) is much higher. Sodium formate is soluble in water phase and can interact with catalyst and ketone at the interface. Hence, the reactions sodium formate in water is faster. But 6-Methoxy 2- acetyl naphthalene being low density white solid and being insoluble in water floats on water and catalyst cannot form small separate phase with organic layer (i.e. substrate layer). Thus solubility in water and being

low density solid probably results in poor results in the ATH of 2-acetyl 6-Methoxy acetyl naphthalene in water.

Table 3.6: ATH of various ketones using $[Rh(Cp^*)Cl_2]_2$and ligand 9

Entry	Ketone	Reaction time (h)	Conversion %	%ee
1	Acetophenone	1	95	91
2	4-Bromo Acetophenone	1.5	99	88
3	4-Chloro Acetophenone	1.5	99	88
4	2,4 Dichloro acetophenone	2	95	86
5	4-methyl acetophenone	2	90	97
6	4-isobutyl acetophenone	6	87	89
7	4-Methoxy acetophenone	3(12)	82(95)	97
8	1 Indanone	1.5	98	84
9	1-tetralone	2	95	88
10	6-methoxy2-Acetylnaphthalene	12	5	98

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol;Ligand,0.01mmol; ketone.,mmol sodium formate 5 mmol; water, $2cm^3$; Temperature: 25^0C

Also, for all these reactions in water, the system was not homogeneous in nature and reactants and products were found to be present as small globules just above the water layer. Thus it was not possible to do intermediate sampling and check conversions and enantioselectivity at intermediate stages. Also, for 2-acetyl 6-Methoxy acetyl naphthalene the conversion was very low. With the use of co-solvents it will be possible to have formate, ketone and catalyst in the same phase thus effect of the cosolvent can be investigated. Thus in order to make the system homogeneous and improve the conversion for ATH of 2-acetyl 6-Methoxy acetyl naphthalene few co-solvents were tried and the results are presented in the following section. Xiao[23] have investigated the use of methanol, ethanol, and DMF as the co-solvents with water in ATH of acetophenone. They have carried out detailed kinetic investigations using water: DMF (1:1 volume ratio) as solvent system. Use of co-solvents was found to make system homogeneous and enhance

acetophenone conversion; however, enantioselectivity was not affected with the use of co-solvent. Based on literature reports screening of co-solvents was carried out using 1:1 volume mixture of co-solvent: water as presented below.

3.8 Effect of co-solvents on ATH of ketones with sodium formate as a hydrogen donor in water

3.8.1 Screening of co-solvents

The water miscible solvents like, methanol, ethanol, acetonitrile, DMF, NMP, dioxane and THF were screened for ATH of acetophenone using 1:1 volume ratio as per the literature reports[23]. The results obtained with various co-solvents are presented in Table 3.7.

Table 3. 7: Screening of co-solvents

Entry No.	Solvent	Time, h	conversion %	% ee	Config.
1	Water	1	95	91	S
2	Methanol	1	92	96	S
3	Ethanol	2	75	95	S
4	DMF	1	92	96	S
5	NMP	2	67	93	S
6	Dioxane	2	61	94	S
7	THF	2	63	93	S
8	DMSO	2	62	94	S
9	Acetonitrile	2	87	95	S

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol; Acetophenone,1mmol; sodium formate 5 mmol; Temperature: 25^0C;water –co solvent $1cm^3$-$1cm^3$;

Best results (95 % conversion with 91 % ee in1 h) were obtained with only water as solvent. However from the results we observed few interesting things. The conversions for methanol and DMF as co-solvents were comparable to that with only water as a solvent (>90%, in 1h. entry 2 and 4). However, the conversions with all other co-solvents were lower and were in a range of 61-87 % in 2 h. The enantioselectivities however for all the co-solvents used were on higher side (93 to

96 %) compared to neat water (91 %) (compare entry 1, vs. entry 2-9). The effect of the co-solvent on ee was small but measurable (91% vs 96%). This is in contrast to the observation made by Xiao et al. where, no change in the ee was observed with DMF as a co-solvent[23] for ATH of acetophenone with Ru-TsDPEN complex (water and DMF in equal volumes). A comparable conversion with improved ee was observed with methanol and DMF as co-solvents (in 1:1 ratio).A detailed investigation on the effect of co-solvents was carried out with methanol and DMF by systematically varying the co-solvent proportion and the results are presented below.

3.8.2 Effect of methanol composition in water:methanol solvent

Systematic variation in methanol composition with respect to water was carried out. For this purpose methanol composition was varied from 0 to 100%, with respect to water, in ratio of 0, 25, 50, 75 and 100% w.r.t water (Table 3.8). The results are presented in Table, 3.9 and Fig.3.13 (a: Acetophenone conversion vs time, b: ee vs time and c: final TOF for all the compositions).

Table 3.8: Variation of methanol composition in water: methanol solvent

Sr. No	**Methanol**		**Water**	
	Volume in ml	Volume in %	Volume in ml	Volume in %
1	0	0	2	100
2	0.5	25	1.5	75
3	1.0	50	1.0	50
4	1.5	75	0.5	25
5	1.75	87.5	0.25	12.5
6	2.0	100	0	0

From the results it was seen that, (Table 3.9, entry 6, 7) the conversions and ee were nearly similar for 75 % and100 % composition of methanol. Therefore in graph of conversion vs. time and ee vs time these reactions are omitted for better clarity.(Fig. 3.13) It was observed that, the use of co-solvents significantly changes the conversions as well as ee. With 25 % methanol in water highest conversion was observed in very short time (98 %, in 30 min Table 3.9 entry 3). The ee observed

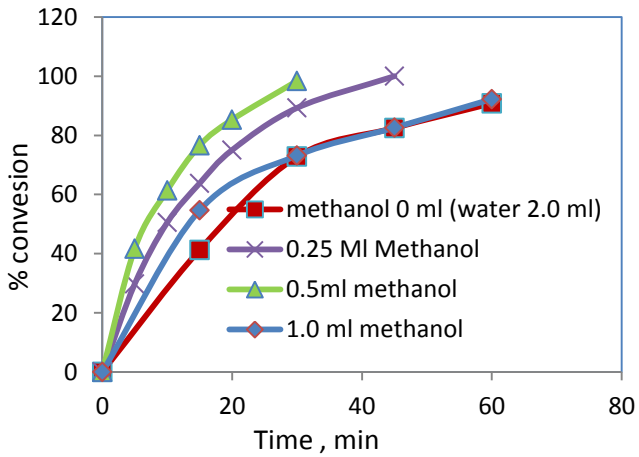
for this experiment was similar to that observed with pure water (91% Table 3.9, entry 1 and 3). It was observed that initial addition of solvent up to 25% composition increased the activity significantly (compare entry 1 with 2 and 3). Further increase in methanol composition led to significant drop in activity (Table 3.9, entry 4, 5, 6). From the graph of final TOF(Fig. 3.13 c) (final sample of the reactions) vs methanol volume, it can be seen that TOF increases with increase in methanol till 0.5 ml and with further increase in methanol final TOF decreases and is lowest (60 h^{-1}) for the reaction with methanol as a solvent. It was observed that ee increased consistently with increase in the methanol composition compared to that in neat water (96 % in 75 % Methanol vs. 91 % in neat water, entry 1 and 5). In order to confirm the observed increase in ee values with increase in methanol concentration (used as a co-solvent), similar study was carried out with DMF as a co-solvent and discussed below.

Table 3.9: effect of co solvent composition on conversion and ee

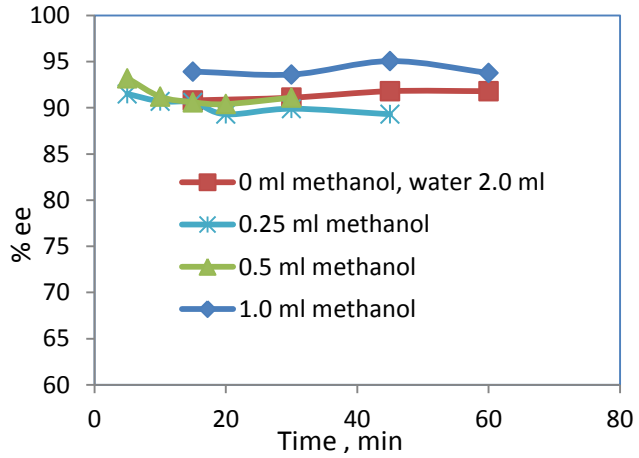
Entry	**Methanol composition (% w.r.t. water)**	**Time, minutes**	**Conversion,%**	**ee,%**
1	0 (only water)	60	95	91
2	12.5	45	99	90
3	25	30	98	91
4	50	90	97	94
5	75 % Methanol	60	92	96
6	100 (no water)	120	97	96

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol;Ligand,0.01mmol; acetophenone 1mmol; sodium formate 5 mmol; water, methanol 0- 2cm^3; Temperature: 25^{0}C

a) **Conversion**



b)



c)

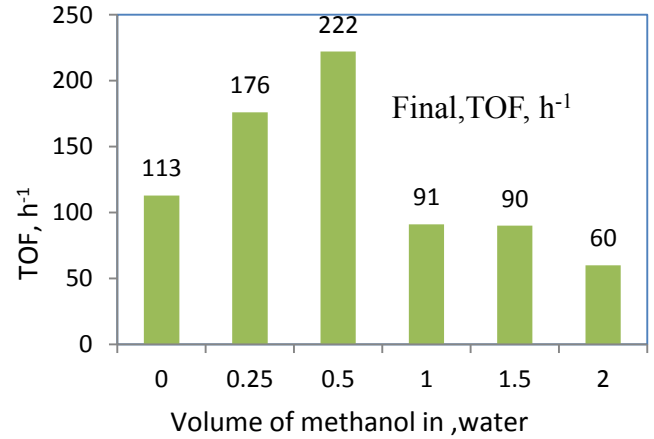


Fig 3.13: effect of varying volume of methanol on a) conversion b) ee c) Final TOF, h^{-1}

Reaction conditions: Rh $(Cp^*)Cl_2]_2$, 0.005mmol; Ligand,0.01mmol; acetophenone 1 mmol; sodium formate 5 mmol; water- methanol 0- $2cm^3$; Temperature: 25^0C

3.8.3 Effect of DMF composition in water:DMF solvent

Effect of DMF composition on acetophenone conversion and enantioselectivity was investigated by varying DMF concentration as described in section 3.8.2 for methanol as a co-solvent. The results are presented in the Table, 3.10 and Fig. 3.14 (a: Acetophenone conversion vs time, b: ee vs time and c: final TOF for all the compositions).All the data are presented in Table 3.14, while few data are not presented in Fig. 3.14 (a and b) for clarity. From results it was observed that the conversion as well as enantioselectivity was significantly affected with the use of DMF as co-solvent. Activity increased with increase in DMF concentration till 25 % and with further increase in DMF concentration activity decreased significantly as can be seen from time required for the reaction (Table 3.10) and TOF values from Fig. 3.14c. The significant change in the ee was observed with the use of DMF as co-solvent (93 to 96 %) compared to that observed in water (91 %). Observed results on increase in ee values are consistent with earlier results with methanol, as well as other solvents investigated. Xiao et al.[23] found that equal volume of DMF and water did not show any change in the ee. Based on this result it was suggested that co-solvent is not playing any role in rate determining step. However, in this publication ee value with pure water as a solvent were not reported. Observed results with all co-solvents indicate that ee value is lower in pure water as a solvent (~91 %) and increases with increase in co-solvent concentration (93 to 96 %) with 50 % co-solvent concentration (Tables 3.8, 3.10 and 3.11). Since conversion as well as ee was higher with DMF as a co-solvent (25 % in water), further work was carried out using this solvent system.

Table 3.10 effect of co solvent composition on ATH of acetophenone

Entry	DMF composition (%, w.r.t. water)	Time ,min	Conversion, %	ee, %
1	0 (only water)	60	95	91
2	12.5	45	97	93
3	25	30	96	95
4	50	60	91	96
5	75	120	75	96
6	100 (no water)	120	50	96

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol; acetophenone 1 mmol; sodium formate,5mmol; water, DMF 0- 2cm^3; Temperature: 25^{0}C

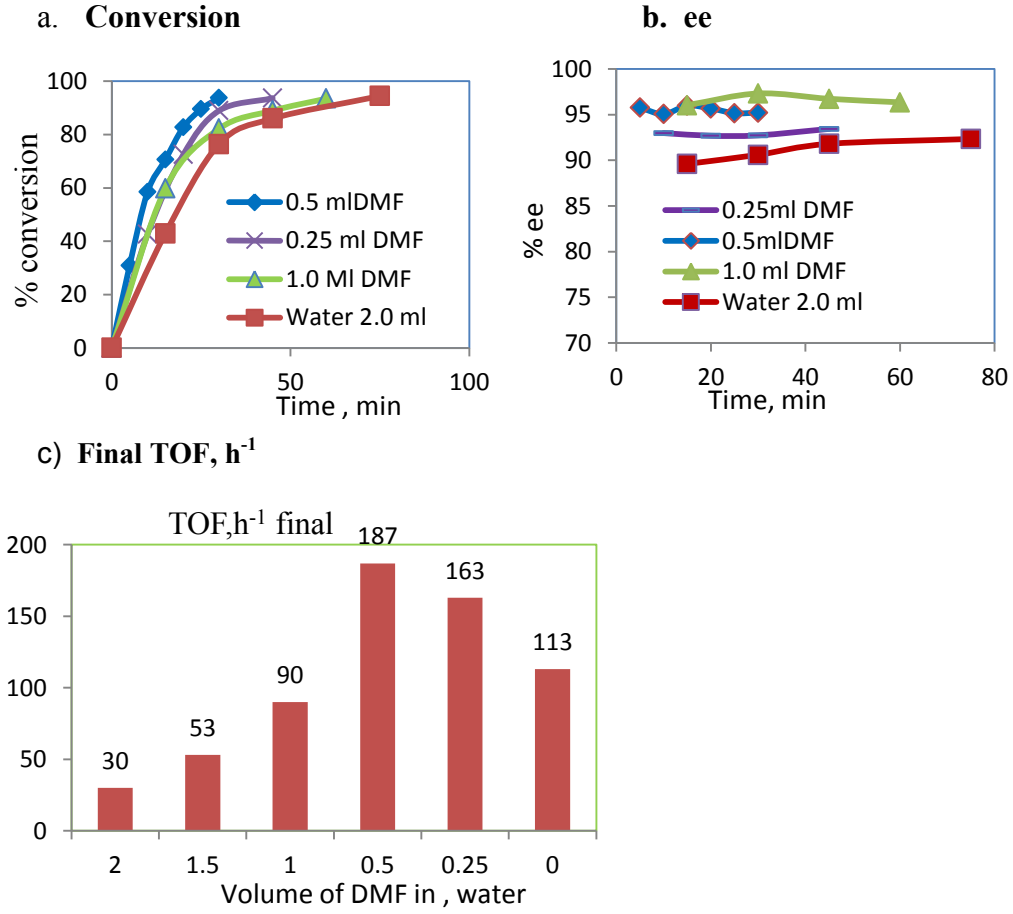


Fig.3.14: effect of varying volume DMF on a) conversion b) ee c) Final TOF, h^{-1}
Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol; acetophenone 1mmol; sodium formate,5 mmol;Temperature:25^{0}C; water-DMF 0- 2cm^3;

3.8.4 Effect of co-solvent at higher substrate to catalyst ratio :

ATH of acetophenone was carried out with high acetophenone concentration (1.5 M), however at this concentration solution was turbid and hence intermediate sampling was not possible. Hence in order to carry out optimization work with higher substrate: catalyst ratio (homogeneous reaction mixture), it was thought to increase reaction charge 10 times from 2 ml to 20 ml (5 mL DMF and 15 ml water), In this case sodium formate and acetophenone quantities were also increased 10 times (10 mmol and 50 mmol respectively), while catalyst and ligand quantities were not changed. Thus acetophenone: catalyst ratio of 1000, keeping formate substrate ratio constant at 5. With this charge it was possible to vary substrate: catalyst ratio between 100 to 1000 and keeping solution homogeneous. However conversion did not increase beyond 50% in 3h.The reason could be due to higher volume of DMF and lower catalyst quantity, where probable coordination with high ratio of DMF is happening. So, further attempts to optimize reaction conditions using DMF-water solvent were dropped.

3.8.5 Screening of various Ketone using DMF as a co-solvent

ATH of ketones was carried out with sodium formate and water-DMF solvent and the results are presented in Table 3.11.

Results showed excellent conversion for all the ketone screened. Acetophenone as already studied, was reduced within 30 minutes with 98% conversion and 95 % ee. ketones having electron withdrawing groups in para position like p-chloro acetophenone and p-bromo acetophenone, showed, comparable activity (99 % conversion in 30 min), while ee reduced marginally from 95 % to 91 % (Table 3.11, entry 2 and 3). Ketones having electron donating groups in para position like 4-methoxy and 4-methyl acetophenone required slightly higher reaction time (95 % in 0.75 h, and 93 %, in 2 h, respectively) (entry 5 and 6), while ee was slightly higher (97 %). Cyclic ketones like Indanone and tetralone were also reduced with excellent conversion within short time of 0.5h (98% and 95% respectively). The highlight of the screening was once again the increased enantioselectivity for all the ketones in comparison with the water and sodium formate without co-solvent. The increase in ee was although small (2-3% over water) it was clearly measurable. The significant change was observed for indanone.In water 84 % ee was observed for Indanone,

whereas in water-DMF, the ee increased to 92 %. For tetralone the ee in water was 88 %, which increased to 92 %, in water-DMF.

Table 3.11: ATH of various ketones using $[Rh(Cp^*)Cl_2]_2$and ligand 9

Entry	ketone	Reaction Time,h.	Conversion %	%ee	Config.
1	Acetophenone	0.5	98	95	S
2	4-Bromo acetophenone	0.5	99	91	S
3	4-Chloro acetophenone	0.5	99	91	S
5	4-methyl Acetophenone	0.75	95	97	S
6	4-Methoxy acetophenone	2	93	97	S
7	1 Indanone	0.5	98	92	S
8	1-tetralone	0.5	95	92	S

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol;Acetophenone 1 mmol; sodium formate, 5 mmol; water –DMF,1.5 -0.5cm^3 ; Temperature: 25^0C;

3.9 Conclusions

Based on the results obtained for methanol and DMF as co-solvent with water, following conclusion were drawn

- The Rh-ligand 9 complex was highly efficient and active catalyst system for ATH of acetophenone using water and sodium formate
- The role of co-solvent was important in enhancing the activity as well as ee. Thus Methanol and DMF (25 % (v/v) in water) were found to be best co-solvents.
- Enantioselectivity increased marginally from 91 % to 95 % with increase in DMF concentration used as a co-solvent.
- Use of 25% DMF in water as co-solvent further showed enhancement in the activity as well as ee

This is the first successful example for $[Rh(Cp^*)Cl_2]_2$ and unsymmetrical vicinal diamine (ligand 9) in ATH for various ketones with sodium formate as hydrogen donor and water as a solvent,

3.10 ATH of acetophenone in methanol.

From the co-solvent study presented in the earlier section, neat methanol showed very good conversions (90% in 90 mins, with 96% ee). The reaction system containing methanol, sodium formate and acetophenone was found to be homogeneous (although, the precipitation of by product sodium methyl carbonate was observed). It was decided to investigate ATH of acetophenone with methanol as a solvent. It is well known in the literature that alcohols (including, 2-propanol) act as hydrogen donor, when used with transition metal complexes. Recently Adolfsons[33] have carried out ATH of acetophenone with β-amino alcohol catalyst and ethanol as hydrogen donor. However, Noyori[34] and Blackmond[35] showed that alcohol can be used as solvent in ATH of imine with FA:TEA as a hydrogen donor. Thus it is necessary to understand the role of methanol (solvent or hydrogen donor) before starting the detailed work on ATH of ketones. Few diagnostic experiments were carried out to make sure that methanol is acting as a solvent. It is necessary to discuss the mechanism for ATH of ketones with Ru-tosylated diamine ligand catalyst and sodium formate as a hydrogen donor.

3.11 Mechanism for ATH of ketones

The mechanism proposed by Noyori and Ikaria, and Xiao et al. [10, 22, 36-38] for ATH of ketones with Ru-tosylated diamine catalyst with sodium formate as a hydrogen donor in water is as shown in Fig. 3.15.

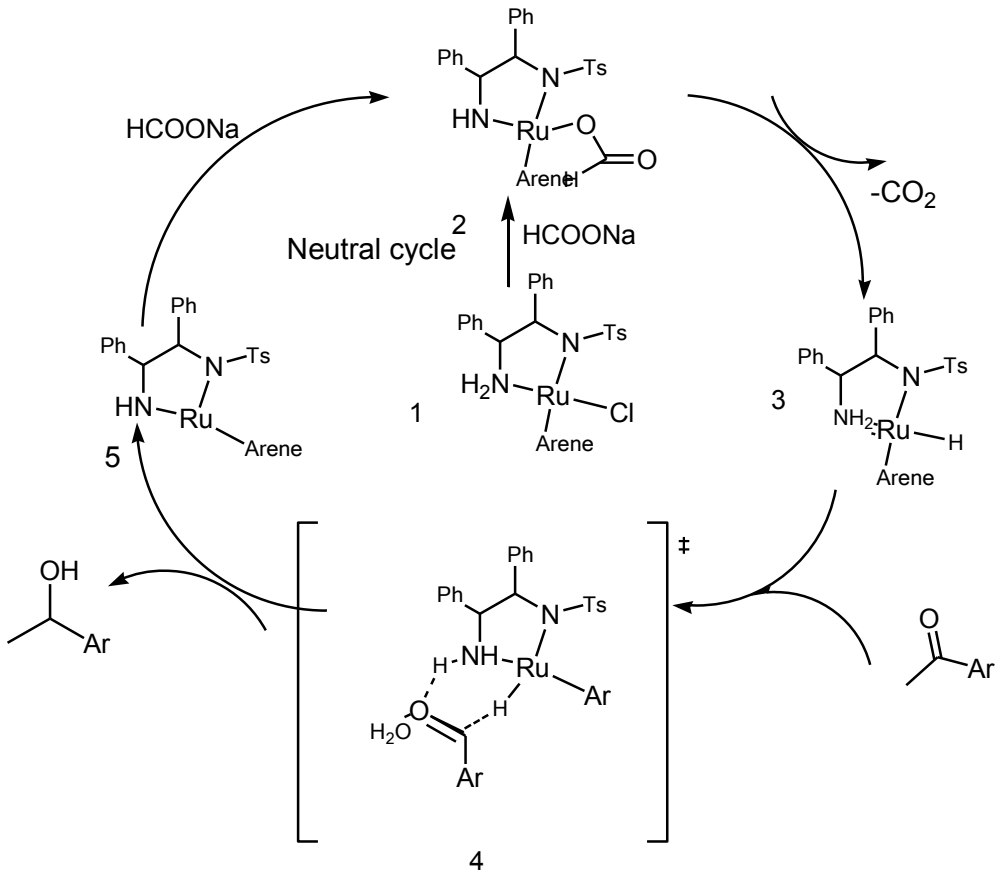


Fig. 3.15: Mechanism for ATH of ketones with sodium formate as a hydrogen donor in water[6, 22, 23, 31]

Precatalyst **1**[19, 36],reacts with sodium formate to generate the active hydride complex (18 electron complex) **3** via carbon dioxide elimination as proposed by Xiao et al.[22] The intermediate **3** interacts with ketone to form a six membered transition state **4.** Simultaneous transfer of hydride and hydrogen of NH to the ketone leads to the formation of enantiopure alcohol as the product and the 16 electron complex **5** is formed. Noyori has isolated species 5, which is a 16 electron complex and the true active catalytic species. As per the mechanisms reported for ATH of ketones with sodium formate[4, 22] of 2-propanol[36, 37] catalytic intermediate '5' can generate hydride species from either sodium formate or alcohol present in the reaction mixture.

In order to understand the role of methanol (solvent or hydrogen donor) few experiments on ATH of acetophenone were carried out using $[Rh\ (Cp^*)Cl_2]_2$ as a catalyst precursor, with the benchmark ligands like TsDPEN, TsCYDN and ligand 9. In the first experiment ATH of acetophenone was carried out using methanol as a solvent as well as hydrogen donor. The second experiment was carried out using methanol *d*-4 as a solvent and sodium formate (five equivalent w.r.t. acetophenone)

as a hydrogen donor. Here Threee different experiments were carried out using Rh catalyst and TsDPEN TsCYDN and ligand 9 as the ligands. The results are presented in Table.1.12 With methanol as hydrogen donor trace amount of product was observed after 3h reaction, indicating that methanol was not working as a hydrogen donor efficiently. For other experiments >95 % conversion of acetophenone was observed in 3h reaction time with (96%-97%ee). However, in this experiment deuterium incorporation in the phenethanol formed was not detected, confirming that methanol is not acting as hydrogen donor. This clearly showed that sodium formate generates hydride complex faster than methanol and methanol behaves purely as a solvent. Similar experiments by Noyori has reported similar results, for ATH of imine[34] using Ru-TsDPEN and FA:TEA as hydrogen donor and 2-propanol as a solvent.

Based on these results, ATH of acetophenone was investigated in detail with methanol as a solvent as the results are presented in the following section.

Table 3.12 ATH of ketone in Deutarated Methanol and sodium formate

Hydrogen donor	Methanol			Sodium formate in		
				Methanol d-4		
	Time	conv	ee	Time	Conv%.	ee%
Ligand 9	3h	<1		3h	95*	96
TsDPEN	3h	<1		2h	97*	97
TsCYDN	3h	<1		2h	97*	96

3.11.1 ATH of ketone using monosulfonated by diamines in methanol and Sodium Formate

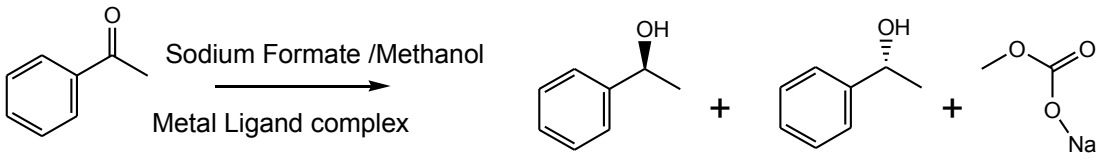


Fig. 3.16: ATH of ketones using Sodium formate in methanol

3.11.2 Experimental

3.11.2.1 Preparation precatalyst/Catalyst:

The procedure described by Xiao et al[4, 6, 22] was used. In a typical experiment $[Rh(Cp^*)Cl_2]_2$ (0.005 mmol, 3.09 mg) and ligand (1mmol, 3.05 mg) were mixed in

water/Methanol. The contents were heated at 40^0C for 1 h. To the same solution ketone 1 mmol and sodium formate 5 mmol were added and reaction was started.

3.12 Results and Discussion:

ATH of acetophenone was investigated using [Rh (Cp*)Cl_2]$_2$ as catalyst precursor with Ligands 6-9 and their enantiomers 10-13 with methanol as a solvent and sodium formate as a hydrogen donor, at 25^{o}C. The results are presented in Table 3.13. It was found that for ligand 9 very good conversion and ee was obtained (97%, 96% respectively in 2 h). The activity with ligand 8 was lower compared to ligand 9, and 98 % of acetophenone was obtained in 4 h. The enantioselectivity obtained however was similar for both the ligands (96% and 95% respectively) (entry 3, 4, 7, 8). Ligands 6 and 7 were found to be less active and 10 and 18 % conversion of acetophenone respectively was observed in 2 h with 85 % ee for both the ligands and their enantiomers (Entry 1, 2, 5 and 6). When we compare the results with those obtained with water (Section, Table 3.6), in general the ee values obtained in methanol were higher for all the ligands. Activity was lower in methanol for ligands 6, 8 and 9 and their enantiomers, while that for ligand 7 and its enantiomer was comparable. It was interesting to find out the inactivity of sulfonated dimaine complex. The activity for ATH of acetophenone with ligands 6 and ligand 7 with Rh catalyst was low, however reaction mixture became turbid after 2-3 h, indicating that sodium methyl carbonate is formed. The formation of sodium methyl carbonate is a result of 18 e^- electron hydride complex as discussed earlier in the mechanism section. It was not possible to get similar observations in water because sodium hydrogen carbonate generated is water soluble. Thus the Rh-hydride complexes formed with ligands 6 and 7 have trans or anti-geometry and probably they are not active for ATH of acetophenone, Similar results were obtained for ruthenium catalysts by Minghua-xu.[28] Xiao et al[26,31,32,40] also have predicted that rate determining step is not the one with metal hydride formation but transfer of hydride to kenotic substrate via 6 membered transition states. [6, 22, 23, 31]Best results were obtained with Rh-ligand 9 and hence further work was carried out with this catalyst system.

Table3.13: ATH of acetophenone using Rh- ligand 9

Entry	Ligand	Time (h)	Conversion, %	ee %
1	6	2	10	85
2	7	2	18	85
3	8	4	98	95
4	9	2	97	96
5	10	2	10	85
6	11	2	18	85
7	12	4	98	95
8	13	2	97	96

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol; acetophenone 1 mmol ; sodium formate 5 mmol; Temperature: 25^0C; Methanol , $2cm^3$

3.13 Screening of ketones with Rh-ligand 9 catalyst system

Various ketones were screened using $[Rh(Cp^*)Cl_2]_2$/ligand-**9** catalyst system and the results are presented in Table 3.14.All the ketones were reduced with excellent conversion and enantioselectivity. Acetophenone was reduced with 97 % conversion and 96 % ee in 2 h. With electron withdrawing substituents similar conversion and ee were observed (Entry 2-4). With 4-methyl acetophenone marginally lower activity was observed with 97 % ee in 2 h. However, with 4-isobutylacetophenone significantly lower activity was observed with 97 % ee (97% in 6h,entry 6).

Table 3.14: ATH of various ketones using ligand 9 and $[Rh(Cp^*)Cl_2]_2$ catalyst

Entry	Ketone	Reaction time (h)	Conversion %	ee %
1	Acetophenone	2	97	96
2	4-Bromoacetophenone	2	99	96
3	4-chloroacetophenone	2	99	96
4	2,4 Dichloroacetophnenone	2	95	92
5	4-Methyl acetophenone	2	94	97
6	4-Isobutyl acetophenone	6	97	97
7	4-Methoxy acetophenone	8	74	97
8	1-Indanone	2	98	97
9	1-Tetralone	2(3)	92(98)	98
10	2-Acetyl pyridine	12	88	86
11	3-Acetyl pyridine	14	98	98
12	p-Bromopropiophenone	2	88	92
13	2-Acetyl 6 Methoxy naphthalene	2	55	98

Reaction conditions $Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol; ketone 1 mmol; sodium formate 5 mmol; Temperature: 25^0C; Methanol 2cm^3

Cyclic ketone like Indanone was reduced within 2 h with 98% and 97% ee;(entry 7).

Tetralone was reduced within 3 h with more than 98 % ee. (Entry 9, 2 h conversion 92%). For ketones with substituent in the ortho position, conversion as well as chiral selectivity decreased marginally (Table 3.15, Sr. no. 9 and 10). Thus, reaction proceeded with 88% conversion and 86% ee after 12 h for 2-acetyl pyridine. For 3-Acetyl pyridine, 98% conversion in 14 h reaction time was achieved with 98 % ee. 4-methoxyacetophenone is known to be a challenging substrate probably because of its low redox potential, giving lower conversions and enantioselectivity. In the present study, transfer hydrogenation of 4-methoxyacetophenone gave 74% conversion with 97% ee in 8 h reaction time in methanol as solvent. Comparison of the results obtained with Rh-ligand 9 catalyst system with water and methanol as solvents, showed that activity was higher with water as a solvent, but the enantioselectivity in methanol was consistently higher by ~5 %. This is the first example of a $[Rh(Cp^*)Cl_2]_2$ and unsymmetrical vicinal diamine catalyst system used in ATH of ketones with very high conversions and enantioselectivity . ATH of variety of ketones proceeds smoothly with high enantioselectivity. This has provided excellent opportunity to study the effect of various parameters affecting conversion and ee, and overcome the drawback of water and water/solvent systems, which were described earlier in this chapter.

3.14 Optimsation of reaction conditions using $[Rh(Cp^*)Cl_2]_2$ and ligand 9 catalyst system

Based on these results acetophenone was selected as model substrate, and Effect of reaction conditions including catalyst preparation, screening of formates on the acetophenone conversion and enantioselectivity was investigated using $[Rh(Cp^*)Cl_2]_2$ and ligand 9 in methanol using sodium formate as hydrogen donor. The results are discussed below.

3.14.1 Effect of catalyst preparation on conversion and ee:

For ATH of acetophenone the metal ligand catalyst was prepared by four different methods as follows.

1.In the first procedure $[Rh\ (Cp^*)Cl_2]_2$ and ligand 9 were taken in required quantities in 1 ml methanol and heated at 40^oC for 1 hour[4-6] as per the literature procedure. The solution was cooled and used for the reaction.

2.Rh-ligand complex was prepared by the reaction of $[Rh(Cp^*)Cl_2]_2$ and ligand 9. The complex was isolated and structure was confirmed by single crystal X-ray crystallography and is shown in Fig.3.17. The detailed information about crystal structure is present in the appendix.

3.Ligand 9 is semi solid and hence it was also isolated as a hydrochloride salt. Hence, in the third procedure the, metal ligand complex was prepared by stirring metal complex and ligand hydrochloride in the presence of triethyl amine for 5 min and the solution was used for the reaction.

4.In the fourth procedure the metal ligand complex was prepared by stirring the metal complex and ligand 9 for 5 minutes in methanol. (Without triethylamine). And the solution was used for the reaction.

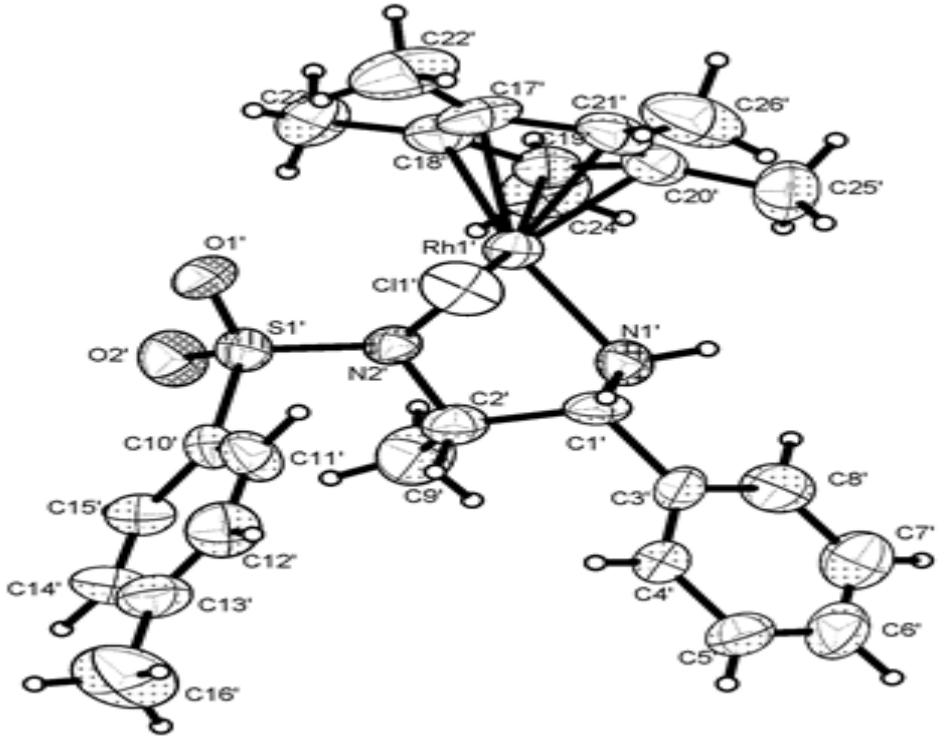


Fig.3.17: ORTPEP Diagram of Precatalyst Rh –Cp* with Ligand 9

The conversion time diagram (Fig.3.18a) showed that, the reaction with precatalyst prepared as per the literature procedure was marginally faster and conversions are reached with initial period of 30 mins. The initial TOF, h^{-1}(30 min) with the precatalyst was slightly higher at 119, h^{-1}. (Fig.3.18c). for all catalysts prepared with other procedures initial TOF,$h^{-1}$was slightly lower 100. No difference in enantioselectivity was observed and for all the procedures and 96 % to 97 % ee was obtained. The TOF, h^{-1} measured at the end was same for all the procedures. (58h^{-1},Fig 3.18c). Thus for all other studies, the simple procedure of premixing of ligand and metal complex was used. This is much simplified procedure, compared to the literature reported procedures.[5, 6, 22, 23]

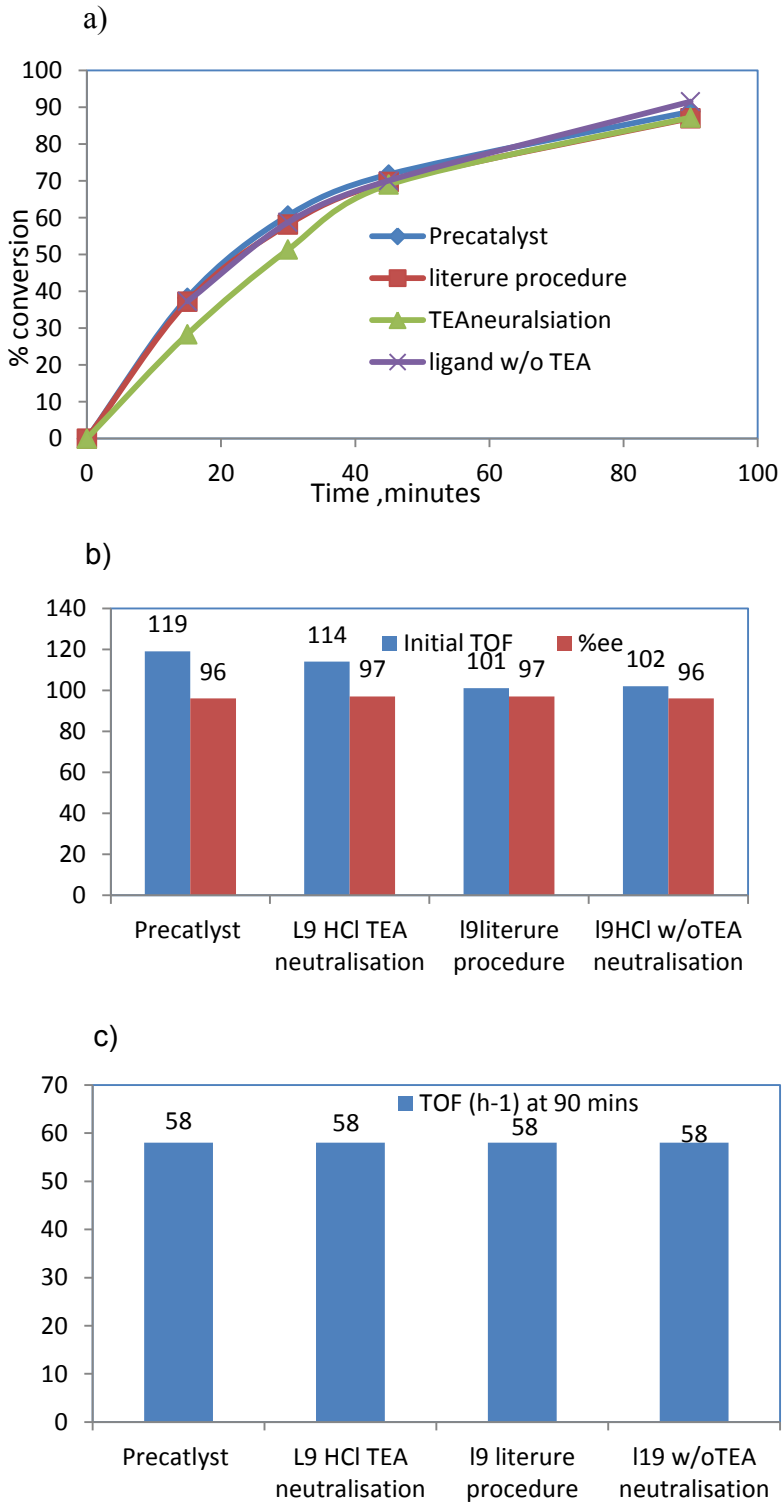


Fig. 3.18: effect of catalysts preparation procedure in a) Conversion b) initial TOF,h^{-1} and ee c) final TOF, h^{-1}

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol; Ligand,0.01mmol; acetophenone, 1mmol; sodium formate, 5 mmol; Methanol 1.88 cm^3; Temperature: 25^0C; Total volume 2cm^3

3.14.2 Scteening of formate precursors:

Various formate salts and formic acid were used as hydrogen donors for ATH of acetophenone. In these experiments formate concentration was kept constant at 5 mmol. (2.5 M) and the results are presented Fig. 3.19

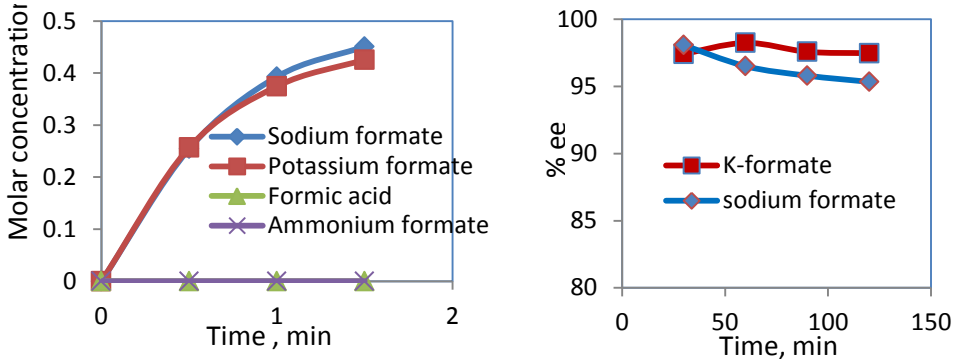


Fig. 3.19: Effect of type of Formate on ATH of Acetophenone a) conversion b) ee

Reaction conditions*:* $Rh(Cp^*)Cl_2]_2$,0.005mmol;Ligand, 0.01mmol; acetophenone 1mmol;Formate,5 mmol; Methanol, 1.88 cm^3; Temperature, 25^0C; Total volume 2cm^3

From the results it was clearly seen that, ammonium formate and formic acid were not active for the reaction. Sodium formate and potassium formate gave similar conversions of acetophenone after 90 mins (nearly 90 %). Potassium formate showed marginally better enantioselectivity compared to sodium formate (98%, and 96% respectively). However considering the marginal difference in enantioselectivity and difference in molecular weight (i.e. potassium formate is having higher molecular weight compared to sodium formate) Sodium formate was chosen as the formate source for further studies.

3.14.3 Effect of sodium formate concentration:

Once the choice of formate type was finalized, further experiments were done in order to find out the optimum concentration of the sodium formate. Thus sodium formate concentration was varied from 1 mmol to 5 mmol. The effect of sodium formate concentration in mmol, on acetophenone conversion and ee was studied (Fig.3.20).

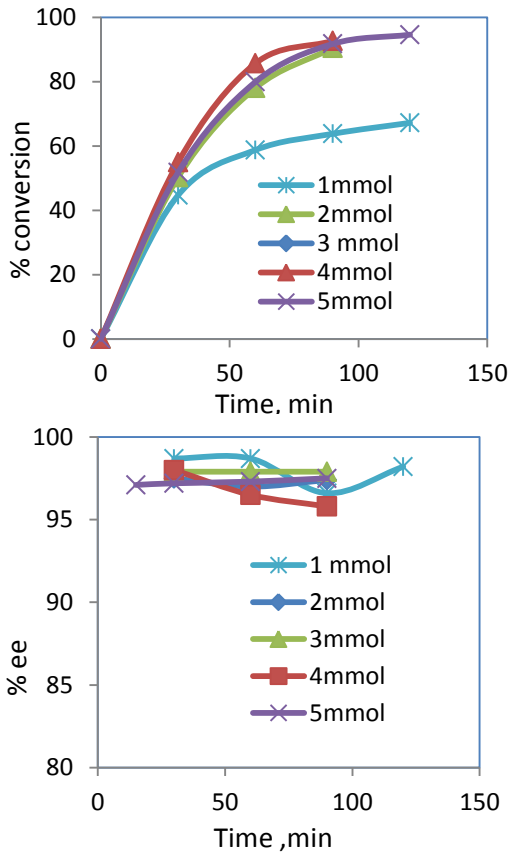


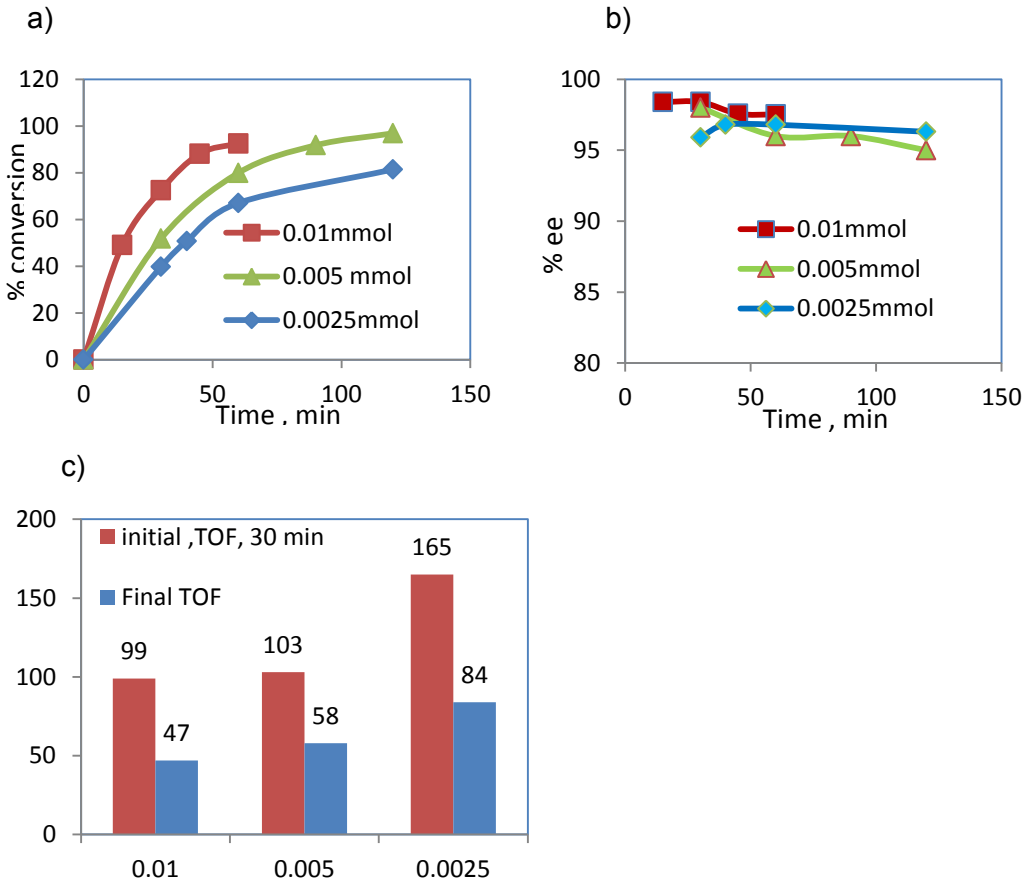
Fig 3.20 Effect of Sodium Formate Concentration on a) conversion b) ee

Reaction conditions: $Rh(Cp^*)Cl_2]_2$,0.005mmol;Ligand 9,0.01mmol; Methanol 1.88 cm^3; Temperature: 25^0C; Total volume 2cm^3

From the results it was seen that, acetophenone conversion was ~90 %(in 90 mins) with sodium formate concentration, range 2 mmol-5mmol. No variation in conversion was observed. Thus acetophenone conversion of 90 % with 96 % ee was observed in 90 min for all the sodium formate concentrations above 1mmol. With decrease in sodium formate concentration to 1mmol, 60 % conversion was observed in 60 mins. But conversion further did not increase, probably, because formate source got exhausted. Sodium formate: acetophenone ratio above 2 is optimum for the ATH reaction. This was found to be consistent with the literature reports where Xiao et a[6, 23] have shown that sodium formate ratio or equivalent[6, 23] between 3 to 10 shows no effect on conversion and ee using Rh-TsDPEN and Ru-TsDPEN complexes[26,32].Thus sodium formate to acetophenone ratio of 2 was optimum, however, for investigating higher substrate concentrations, sodium formate: acetophenone ration of 5 was used for further experiments.

3.14.4 Effect of catalyst Concentration:

The effect of catalyst concentration on ATH of acetophenone was studied by varying the catalyst concentration between 0.0025 mmol, 0.005 mmol and 0.01mmol keeping all other reaction conditions constant The results are presented in Fig 3.21.



Reaction conditions: Acetophenone, 1mmol; Sodium formate,5mmol; Methanol 1.88 cm^3; Temperature, 25^0C ; Total volume $2cm^3$

Fig.3.21: Effect of catalyst Concentration on a) conversion b) ee c) initial and Final TOF,h^{-1}

As expected activity increased with increase in catalyst concentration and enantioselectivity was not affected. Thus >95 % conversion with ~97 % ee was obtained in 50 min with catalyst concentration of 0.01 mol (with lower initial TOF,99 h^{-1}). In case of 0.005 mmol catalyst concentration, the initial (30 min) and final TOF, h^{-1} were 103 and 58, and the conversion were 97 % after 2 h.at lower catalyst concentration 0.0025 mmol, conversion reached only to 81% in 2h. Based

on these results, catalyst concentration of 0.005 mmol was selected for further work.

3.14.5 Effect of substrate concentration:

The Effect of substrate concentration was studied in the range of 0.25 M, 0.5 M, 1.0 M, and 1.5 M (0.5 mmol, 1.0 mmol, 2 mmol, and 3 mmol respectively), keeping all other reaction conditions constant. With this substrate to catalyst ratio was varied between S/C 50, to S/C 300. The results are shown in Fig. 3.23. At highest substrate concentration also sodium formate was present in excess and hence activity will not drop because of low sodium formate concentration. The results are presented in Fig.3.22.

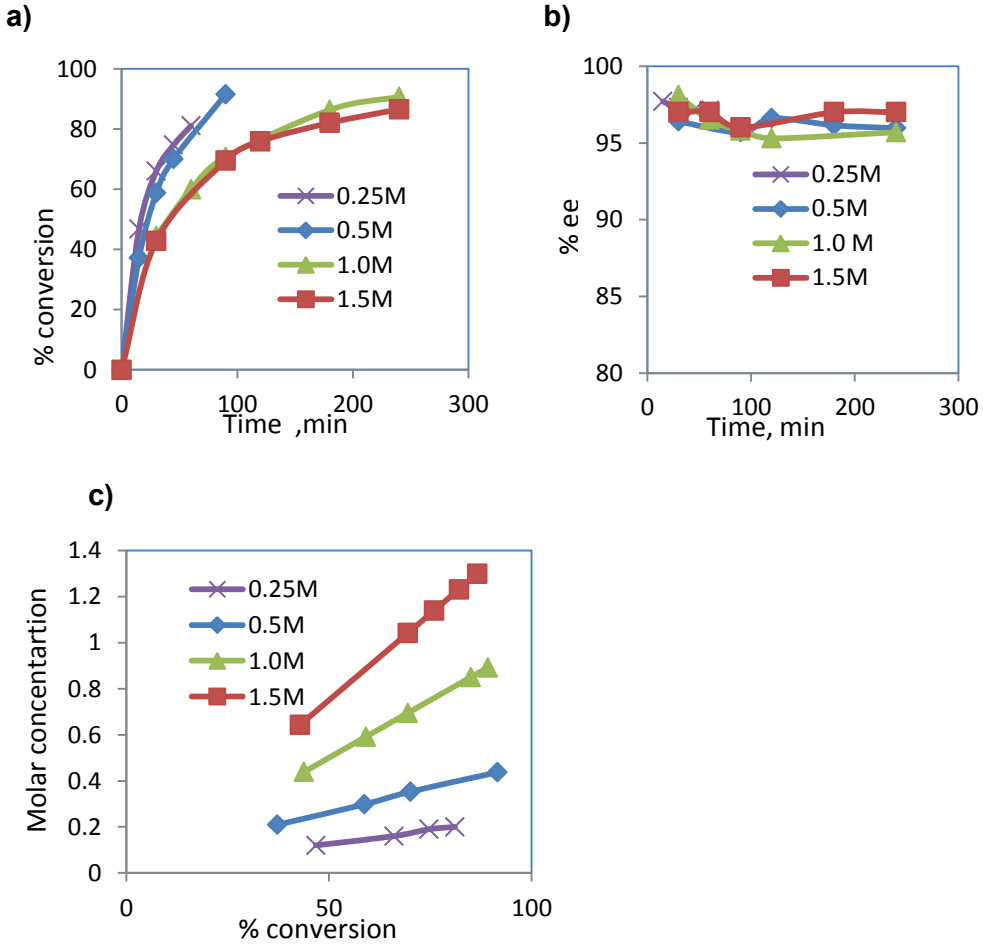


Fig 3.22: Effect of Substrate concentration on in a) % conversion b) ee c) molar concentration of Phenethanol vs% conversion

Reaction conditions: [Rh (Cp*)Cl_2]$_2$, 0.005mmol; Ligand 9, 0.01mmol; sodium formate, 5mmol; Methanol, 1.64- 1.94 cm^3; Total volume ,2cm^3; Temperature, 25^{0}C

The conversion time diagram does not show any conclusion as % convserions for 0.25M and 0.5M were found to showing equal conversions at 60 mins (80 %) Similarly for 1.0M and 1.5M concentartion % conversions were found to be equal. after 2h (75%).However,when graph of Molar concentartion vs percentage conversion was plotted From the Fig 3.22 c,it was clearly seen that the convrsions incraeses with incrase in substrate concentarion. It was found that actually higher amount of product formed at higher substrate concentration (at of 1.5M concntration 1.3 M indiacted by the graph.Fig. 3.22c. The enantioselctivity was practically constant for all the substrate concentartions.

3.14.6 Effect of temperature:

Effect of temperature on conversion and ee was studied in the temperatures range from 25^0 C to 40^0C keeping other reaction conditions constant. The results are presented in Fig. 3.23

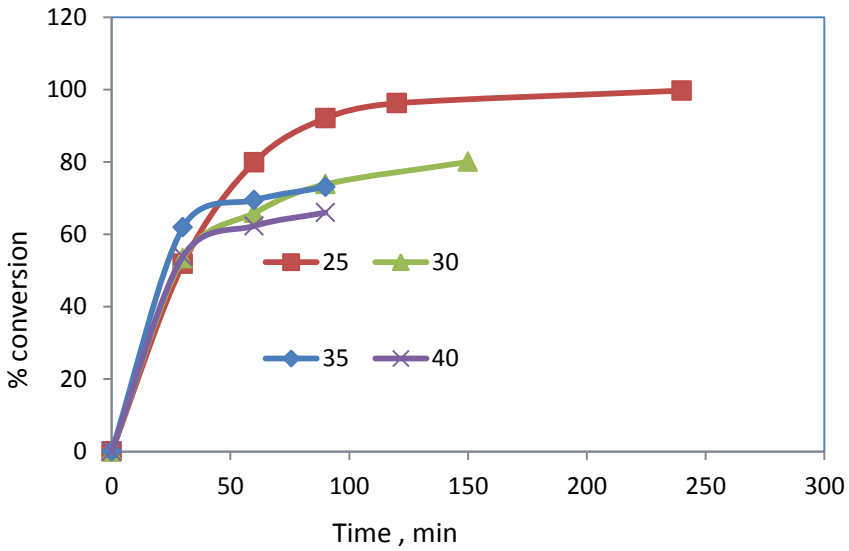


Fig. 3.23: Effect of temperature on conversion

Reaction conditions: $[Rh(Cp^*)Cl_2]_2$, 0.005mmol; ligand9, 0.01 mmol; acetophenone,1mmol; sodium formate,5mmol;Methanol 1.88 cm3; Temperature, ^{0}C

Normally, with increase in temperatures, the conversions increase, however we observed different trend. The results showed that at 25^0C the reaction proceeded smoothly and in 2 h nearly 97 % conversion was observed with 96 % ee. With increase in temperature to 35^0C, in the initial stages conversion was fast. Thus 60 % conversion was observed in 30 min and increased to 63 % after 60 min reaction

time. At 40^0C reaction was sluggish as can be seen from the profile, even after 2 hours only 60 % conversion was obtained.

Possible reasons for the observed trend include catalyst decomposition, substrate inhibition, product inhibition, by potentially chelating alcohols or sodium methyl carbonate generated from sodium formate. In the preliminary experiments, precatalyst was prepared at 40^oC and then reaction was carried out to obtain high conversion and hence catalyst decomposition at 40^oC can be ruled out. The substrate and product inhibition was also ruled as the substrate concentration was kept constant in all these experiments. The other factor to look for was that carbon dioxide forms reversible complexes with metal complex-monosulfonated diamine ligands which is assisted by alcohols.[39] However under the ATH conditions of sodium formate in methanol carbon dioxide formed in the system, reacts and precipitates as sodium methyl carbonate and comes out of methanol solution as solid. To confirm whether sodium mehyl carbonate acts as inhibitor, 2 equivalence of it was added and the reaction was done at 40^0C. However no significant change in the CT profile was observed. Schoemacker et.al.[40] also observed similar behavior with ATH of ketones using polymer supported Rh-TsDPEN catalyst, where consistency in CT profile above 40^0c was not obtained. Canivet et al.[41]observed sudden decrease in conversion for ATH of acetophenone using Ru-TsCYDN catalyst at 70^0c in water and sodium formate. However satisfactory explanation could not be found for inconsistent results at higher temperatures. Thus 25^0C was found to be optimum temperature for this reaction.

3.14.7 Comparison with the benchmark Ligands:

ATH of ketones with sodium formate as a hydrogen donor is investigated in detail using TsCYDN and TsDPEN ligands with various metal complex catalysts. The behavior of these ligands is different for different catalysts. Thus Ru-TsDPEN[4], is more efficient catalyst system compared to Ru-TsCYDN.[6, 41] However Rh - TsCYDN[5] are more efficient catalyst systems than Rh-TsDPEN[6]. It will be interesting to compare the activity obtained using Rh-ligand 9 with best ligands known in the literature. The ligand 9, which is unsymmetrical vicinal diamine showed less ee in water and sodium formate, (91%) although excellent conversion were observed. With methanol as a solvent and sodium formate as hydrogen donor this drawback was overcame and excellent enantioselectivities (96%) were observed for Ligand 9.

Thus ATH of acetophenone was carried out using Rh-TsDPEN, Rh-TsCYDN and Rh-ligand 9 catalysts using procedure described in this chapter and the results are presented in Fig 3.24. From results it was found that, Rh–TsDPEN catalyst gave best results (96 % conversion with 96 % in 75 min) followed by Rh-TsCYDN catalyst (98% conversion with 96 % ee in 90 minutes). The Rh-ligand 9 catalyst showed 89 % conversion with 96 % ee in 90 minutes. When we compare initial (15 min reaction time) Rh-TsDPEN gave TOF, h^{-1} of 213, followed by Rh-TsCYDN (170) followed by Rh-ligand 9 (167). Thus Rh-TsDPEN complex was most active for ATH of acetophenone with sodium formate as hydrogen donor and methanol as a solvent. Rh-TsCYDN and Rh-ligand closely followed. The enantioselectivity was highest again for TsDPEN, and similar for ligand 9 and TsCYDN. Though TsDPEN gave best results, the difference in activities was not very high. In conclusion we can say that the activity obtained with ligand 9 was very good and compared very well with best ligands known in the literature.

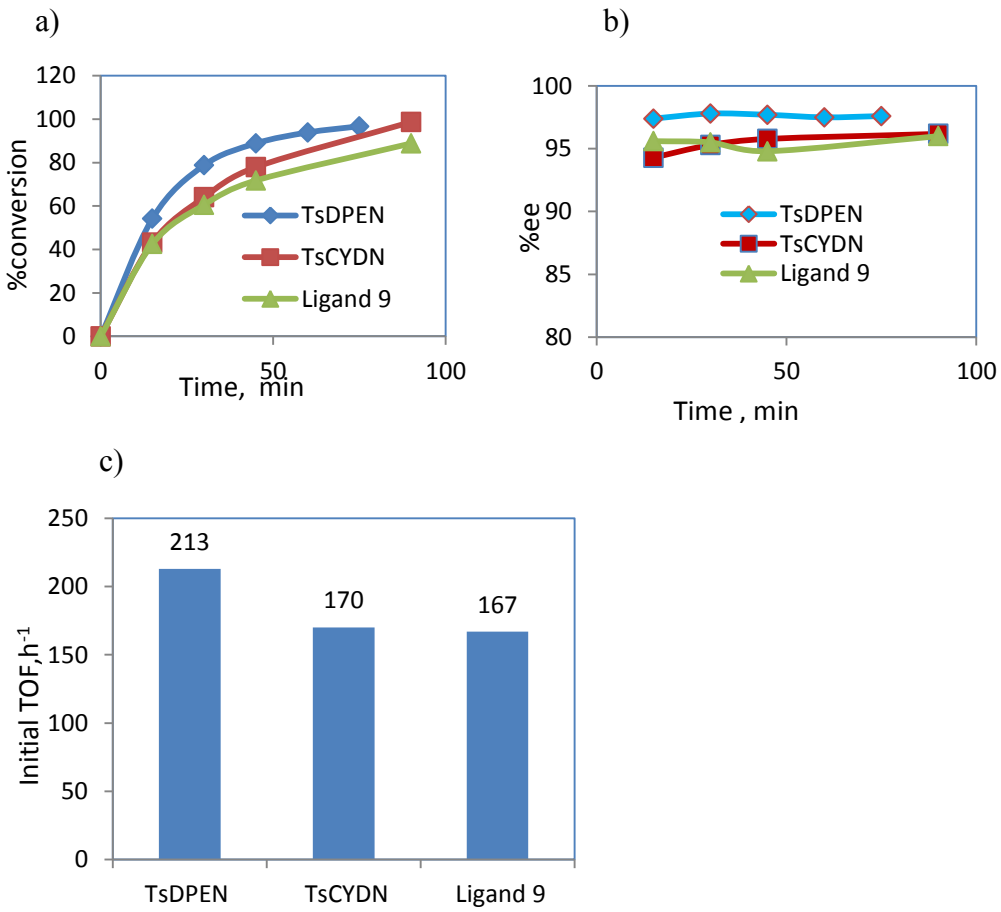


Fig. 3.24: Comparative data, for Ligand 9 with benchmark ligand TsCYDN, TsDPEN a) conversion, b) ee c) Initial TOF, h^{-1} (15 mins),

Reaction conditions: $[Rh(Cp^*)Cl_2]_2$, 0.005mmol; ligand 0.01mmol;sodium formate 5mmol acetophenone,1mmol;Temperature, 25^0C; Methanol 1.88 cm^3;

3.15 Conclusions:

Amino alcohol ligands synthesized, showed very good activity and moderate enantioselcvities for ATH of various ketones using various transition metal complexes. The **[**Ru(*p*-cymene)Cl_2]$_2$–ligand 4 catalyst system showed very good conversions and enantioselectivity. Various unsymmetrical diamine ligands synthesized with transition metal complexes were used in ATH of ketones using sodium formate as hydrogen donor in water as a solvent. Ligands having trans geometry of amine and sulfonamide groups were active in ATH of ketones and best results were obtained with [Rh(Cp*)Cl_2]$_2$-Ligand 9 catalyst system. Highlights of the work are as follows:

Amino alcohol ligands:

- [Rh(Cp*)Cl_2]$_2$ complex with ligand 4 and 2-propanol as hydrogen donor, gave 2 fold in increase in activity over corresponding **[**Ru(*p*-cymene)Cl_2]$_2$–ligand 4 catalyst system with higher activity and enantioselectivity (91%, conversion and 92% ee, in 30 mins). However, ee decreased during the course of the reaction. This was more pronounced at high catalyst and substrate concentrations.
- Ligand 3 has only one chiral center (chiral carbon bearing –OH group) and no rigid backbone. Still activity and enantioselectivity obtained for Ru and Rh catalysts were comparable to those observed with ephedrine. This clearly showed that chiral carbon center bearing –OH group is important in governing enantioselectivity of the reaction.

1,2 Monotosylated diamine ligands:

- [Rh(Cp*)Cl_2]$_2$ with ligand 9 gave best results in ATH of ketones with sodium formate as hydrogen donor, in water or methanol as solvents.
- From the screening of the ligands; it was found that the regio positions of amino and sulfonamide groups as well as their orientation (syn or anti-substitution) is important in deciding activity as well as enantioselectivity. Thus, e.g. for ligand with amine group attached to the carbon bearing phenyl group (ligand 9), showed highest activity in ATH with Rh catalyst. This finding was different than that reported by Ming

Xiao[28]. However, literature report deals with Ru (*p*-cymene)$Cl_2)_2$ catalyst.

- In ATH of ketones the product configuration is governed by chiral carbon bearing sulfonamide group[21] and is similar to literature reports.
- The activity of Rh-ligand 9 was excellent with sodium formate as hydrogen donor in water (95 % conversion in 60 min). Enanatioseclctivity obtained was slightly lower than TsDPEN[6] and TsCYDN ligands (91%).
- The use of co-solvents like DMF and methanol clearly enhanced the activity for ATH (>95% conversion in 30 mins) compared to that with water as a solvent (>95 % conversion in 1 h). Further, with DMF as a co-solvent ee increased significantly compared to that in water (96 % in DMF compared to 91% in water).
- Reaction proceeded smoothly with methanol as a solvent (95 % conversion with 96 % ee in 2 h). The enentiolselctivyty observed was higher than water. This was observed for all the ketones tested.
- Effect of various reaction parameters in methanol showed that, Reaction can be carried out at 1.5 M concentration scale without affecting the enantioselectivity.
- Activity with ligand 9 was found to be comparable to that with benchmark ligands like TsDPEN, TsCYDN with $[Rh(Cp^*)Cl_2]_2$.

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Appendix

1.HPLC Analytical methods for alcohols using Chiral HPLC.

The enantiomeric excess of all the chiral alcohols were determined on HPLC or GC using chiral columns. For this, racemic alcohols were obtained by reductions of all the ketone with $NaBH_4$ using standard procedure. The methods were developed (based on literature reports) on GC/HPLC using these alcohols such that two distinct peaks of both the isomers are obtained with 50% (equal) areas. The conditions for GC/HPLC to get chiral separation along with retention times of isomers of particular alcohol are given below.

Conditions for Acetophenone, R and S phenethanol: HPLC, λ-216 nm, solvent Hexane: IPA 92:8, Flow-0.8ml, Injection volume- 5µl., acetophenone 5.7 min 6.4 min (R), 7.0 min (S) alcohol,

1. 1-Phenyl ethanol -GC, Temperature program- 60°C-0 min, with ramp 5°C, 90°C for 5 min, with ramp 5°C, 100°C for 10 min, with ramp 35°C, 200°C for 1 min, He (15psi).Retention time: 16.1 min (R), 17.1 min (S) alcohol.

2. 1-p-Bromophenylethanol-HPLC, λ-220 nm, solvent Hexane: IPA 98:2, Flow-0.8ml, Injection volume- 5µl. 9.8 min (R), 10.4 min (S) alcohol.

3. 1-p-Chlorophenylethanol-HPLC, λ-220 nm, solvent Hexane: IPA 98:2, Flow-0.8 ml, Injection volume- 5µl. 16.2 min (isomer 1), 17.5 min (isomer 2) alcohol.

4. 1-p-methylphenylethanol- GC -Temp. program 60°C-0 min, with ramp 5°C, 90°C for 5 min, with ramp 5°C,100°C for 13 min, with ramp 35°C, 200°C for 1 min, He (15psi).21.1 min (R), 23.1 min (S) alcohol.

5. 1-p-Isobutylphenylethanol-HPLC λ-220 nm, solvent Hexane: IPA 98:2, Flow-0.5 ml, Injection volume- 5µ. 12.3 min (isomer 1), 13.9 min (S) alcohol.

6. Indanone - HPLC, λ-220 nm, solvent Hexane: IPA 95:5, Flow-1ml, Injection volume- 5µl. 10.0 min (isomer 1), 11.1 min (S) alcohol.

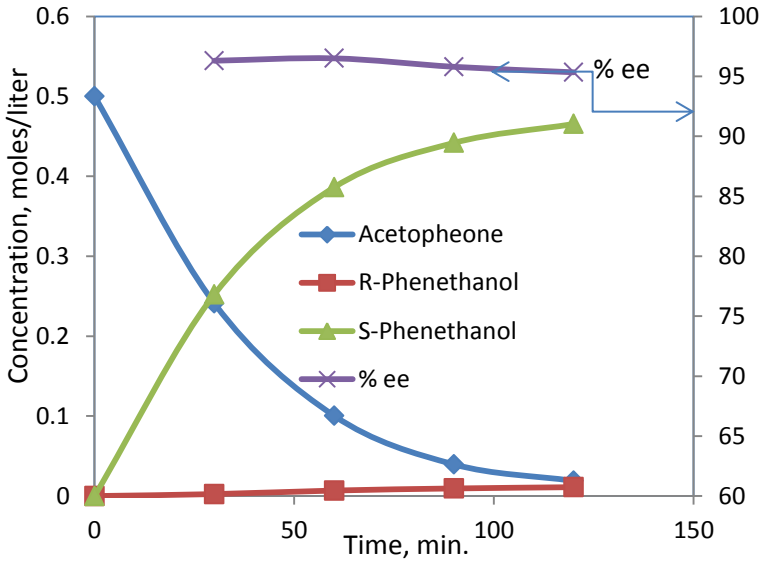
7. 1-p-Methoxyphenylethanol-HPLC, λ-220 nm, solvent Hexane: IPA 98:2, Flow-0.5ml, Injection volume- 5µl. 23.0 min (isomer 1), 24.6 min (S) alcohol.

8. 1-(6-Methoxynaphthalen-2-yl) ethanol- HPLC, λ-254 nm, solvent Hexane: IPA90:10, Flow-0.5ml, Injection volume- 5µl. 15.8 min (isomer 1), 20.5 min (isomer 2) alcohol.

9. 1-p-Nitrophenylethanol-GC, Temperature program-60°C-1min, with ramp 10°C, 170°C for 20 min, He (15psi).23.5 min (R), 24.3 min (S) alcohol.

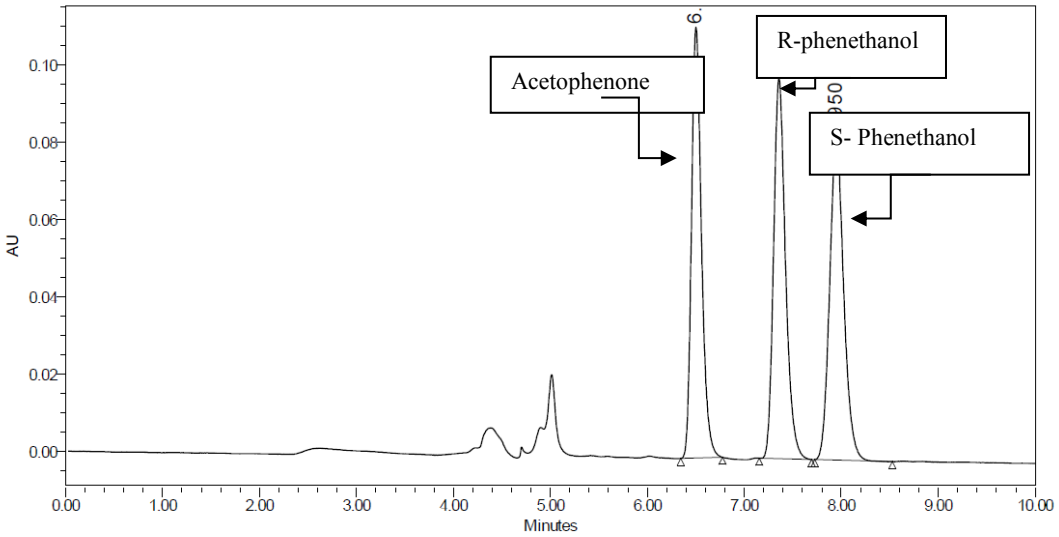
10. 1-(pyridin-3-yl) ethanol- GC, Temperature program-120°C for 20 min. He (15psi).14.6 min (R), 15.3 min (S) alcohol.

2. **Typical Concentration–Time profile for Acetophenone in methanol, Sodium formate using Rh-Ligand 9 complex**.

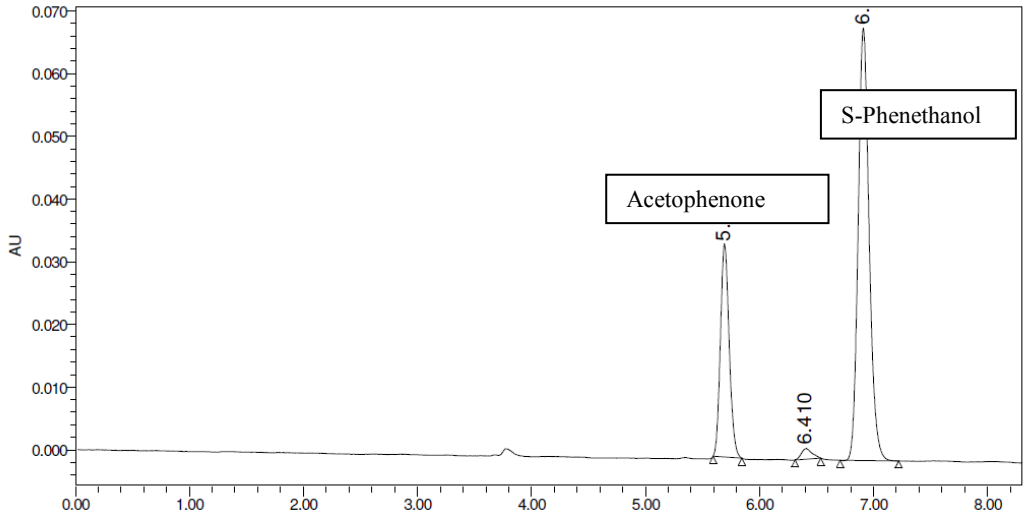


Reaction conditions: [Rh (Cp*)Cl_2]$_2$, 0.005mmol; Ligand 9, 0.01mmol; sodium formate, 5mmol; Methanol, 1.88 cm^3; Total volume ,2cm^3; Temperature, 25^{0}C

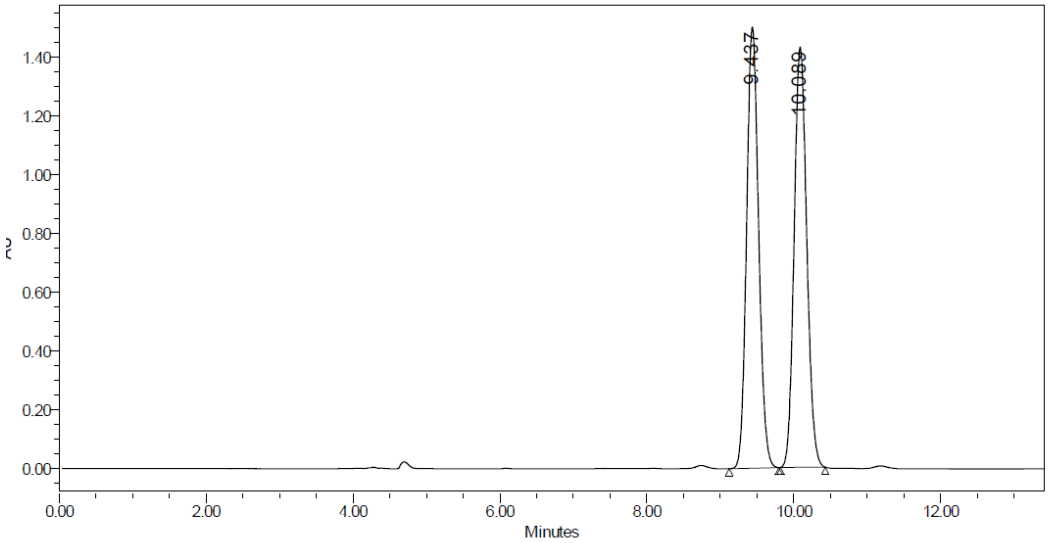
1. **Typical Chromatograms from acetophenone, and racemic phenethanol**



2. Topical chromatogram from reaction mixture for acetophenone, R and S-Phenethanol



3. **Typical Chromatogram for Racemic Indanone**



4. **Typical Chromatogram from reaction Mixture for Indanone**

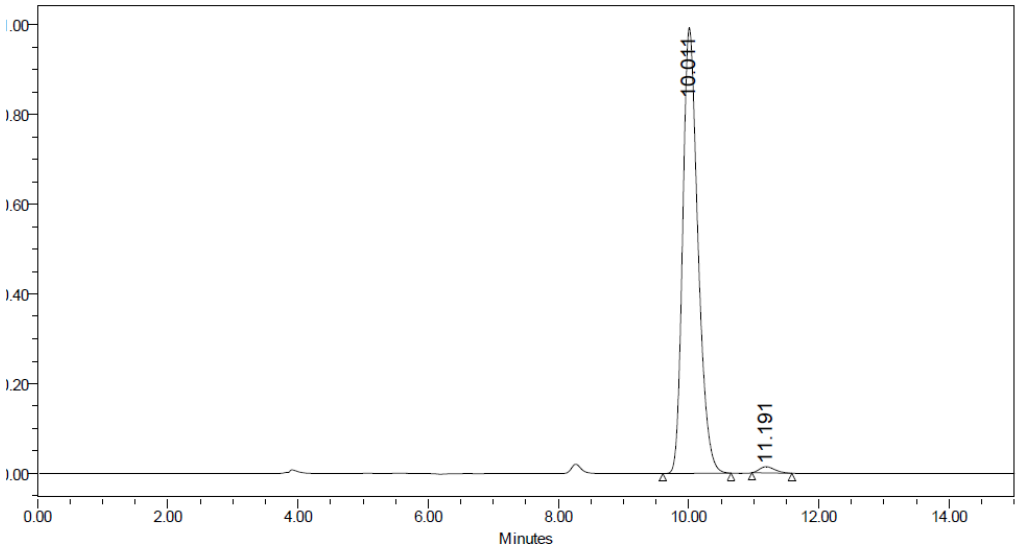


Table 1. Crystal data and structure refinement for Rh-complex.

Empirical formula	C26 H36 Cl N2 O3 Rh S	
Formula weight	594.99	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 8.5592(2) Å	α= 90°.
	b = 22.4141(7) Å	β= 101.293(2)°.
	c = 15.3272(5) Å	γ = 90°.
Volume	2883.54(15) $Å^3$	
Z	4	
Density (calculated)	1.371 g/cc	
Crystal size	0.29 x 0.15 x 0.03 mm^3	
Theta range for data collection	1.63 to 25.00°.	
Reflections collected	22595	
Independent reflections	9734 [R(int) = 0.0838]	
Completeness to theta = 25.00°	100.0 %	
Refinement method	Full-matrix least-squares on F^2	
Goodness-of-fit on F^2	1.015	
Final R indices [I>2sigma(I)]	R1 = 0.0609, wR2 = 0.1032	
R indices (all data)	R1 = 0.1028, wR2 = 0.1211	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3)
for kel_RoCom_0m. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Rh(1)	9221(1)	1287(1)	-261(1)	48(1)
Cl(1)	6753(3)	979(1)	157(2)	70(1)
S(1)	9858(3)	2027(1)	1632(2)	46(1)
O(1)	11244(7)	2357(3)	2053(4)	62(2)
O(2)	9824(7)	1415(3)	1906(4)	61(2)
N(1)	7774(11)	1966(4)	-979(6)	61(2)
N(2)	9549(8)	2049(3)	591(4)	43(2)
C(1)	8629(15)	2529(5)	-838(6)	66(3)
C(2)	9176(14)	2648(5)	181(7)	56(3)
C(3)	7699(19)	3046(6)	-1306(8)	100(5)
C(4)	6270(20)	3202(8)	-1126(11)	146(8)
C(5)	5370(30)	3698(11)	-1497(17)	212(14)
C(6)	6040(30)	3992(13)	-2100(19)	220(20)
C(7)	7510(30)	3905(9)	-2300(13)	191(12)
C(8)	8320(20)	3402(7)	-1902(9)	137(7)
C(9)	10473(19)	3084(7)	342(10)	97(5)
C(10)	8220(10)	2397(4)	1978(5)	41(2)
C(11)	6669(12)	2247(5)	1601(7)	59(3)
C(12)	5436(16)	2535(5)	1880(8)	71(3)
C(13)	5731(12)	2989(5)	2479(7)	60(3)
C(14)	7271(13)	3121(5)	2861(7)	61(3)
C(15)	8484(13)	2838(4)	2592(7)	54(3)
C(16)	4328(17)	3318(7)	2746(12)	109(5)
C(17)	9527(13)	515(6)	-1028(9)	74(4)
C(18)	10360(12)	1001(6)	-1295(7)	65(3)
C(19)	11537(12)	1209(5)	-578(8)	68(3)
C(20)	11514(14)	833(6)	194(8)	69(3)
C(21)	10287(18)	398(6)	-61(10)	76(4)
C(22)	8265(16)	177(8)	-1608(12)	126(7)
C(23)	10121(15)	1281(9)	-2207(8)	112(5)
C(24)	12713(14)	1686(6)	-594(12)	110(5)

C(25)	12610(14)	843(7)	1049(8)	101(5)
C(26)	9840(30)	-69(8)	490(17)	131(7)

Rh(1')	4465(1)	6510(1)	4629(1)	34(1)
Cl(1')	3915(3)	6654(1)	3035(2)	57(1)
S(1')	7712(3)	5840(1)	4248(2)	42(1)
O(1')	7900(6)	6449(3)	3976(4)	49(2)
O(2')	9100(7)	5601(3)	4854(4)	59(2)
N(1')	3022(8)	5743(3)	4404(5)	40(2)
N(2')	6109(8)	5789(3)	4618(4)	32(2)
C(1')	3858(10)	5254(4)	4945(7)	36(2)
C(2')	5505(10)	5179(4)	4716(7)	43(2)
C(3')	2856(10)	4686(4)	4879(7)	46(2)
C(4')	2572(10)	4355(4)	4095(7)	48(2)
C(5')	1600(11)	3849(4)	4013(10)	71(3)
C(6')	917(13)	3695(5)	4713(10)	80(4)
C(7')	1193(14)	4003(6)	5492(10)	87(4)
C(8')	2166(12)	4510(5)	5565(8)	66(3)
C(9')	6553(14)	4768(5)	5362(9)	71(4)
C(10')	7495(10)	5384(4)	3284(6)	43(2)
C(11')	6404(11)	5524(5)	2534(7)	51(3)
C(12')	6267(13)	5182(5)	1785(7)	61(3)
C(13')	7187(14)	4694(5)	1728(7)	61(3)
C(14')	8294(14)	4563(5)	2478(8)	65(3)
C(15')	8444(13)	4881(4)	3244(8)	57(3)
C(16')	7017(19)	4321(7)	910(8)	102(4)
C(17')	4913(14)	7435(5)	4863(8)	57(3)
C(18')	5962(11)	7108(4)	5538(6)	48(3)
C(19')	5008(11)	6745(4)	6002(6)	47(2)
C(20')	3366(11)	6876(5)	5643(7)	58(3)
C(21')	3295(12)	7290(4)	4958(7)	50(3)
C(22')	5349(18)	7901(5)	4277(9)	87(4)
C(23')	7711(11)	7140(5)	5730(8)	63(3)
C(24')	5671(14)	6358(5)	6769(6)	66(3)
C(25')	1987(12)	6603(6)	5974(8)	74(4)
C(26')	1834(15)	7560(6)	4381(9)	94(4)

O(3)	6989(16)	310(7)	2177(9)	93(4)
O(4)	230(11)	460(4)	3175(6)	109(3)
O(5)	2430(30)	2425(9)	7232(16)	113(9)

Chapter 4: Application of the 1, 2 monotosylated diamines to ATH of ketones and imines using FA: TEA as hydrogen source

4.1 Introduction.

Asymmetric transfer hydrogenation of ketones and imines has attracted increasing attention in the last decade, due to its great potential for applications in the fine chemical, pharmaceutical, agrochemical industries and in new materials,[1] Most important analysts developed for ATH reaction include Ru (II) complexes containing monotosylated 1,2-diamines used by Hashiguchi et al.[2-4] (TsDPEN) and Xiao, and co-workers[5] (TsCYDN). Catalytic transfer hydrogenation of ketones to alcohols with 2-propanol sometimes offers an attractive alternative to the reaction with molecular hydrogen because of the favorable properties of the organic hydrogen source.[6] However, when the method is applied to the asymmetric version, it encounters inherent chemical problems. Even if the reduction proceeds with excellent enantioselectivity, the occurrence of the reverse process originating from the structural similarity of the hydrogen donor and product, both being secondary alcohols, frequently deteriorates the enantiomeric purity of the chiral product. Use of formic acid in place of 2-propanol presents an possibility to solve these problems. It was discovered by Noyori et al.[3] that Ru(II) complexes modified with an arene ligand and a chiral *N*-tosylated 1,2-diamine ligand serve as an efficient catalyst for the ATH of ketones and imines using a 5:2 formic acid-triethylamine (FA:TEA) azeotrpic mixture under mild conditions. It was found that the reaction using FA:TEA,(section 1.4.1.2,and 1.4.1.3), azeotrope proceeded with complete kinetic control, without unfavorable thermodynamic equilibrium. But reaction time was too long and varied between 12 to 24 h, depending on the conditions (like substrate/catalyst ratio, temperature)[5, 7, 8] used in the literature. In 2004 , Xiao et al.[9] showed accelerating effect of water and sodium formate for ATH of ketones. Ru–TsDPEN complex showed 98% conversion in 2 h. The ee however, was lower compared to FA: TEA azeotrope (98%, and 94% respectively). This was followed by the use of Rh complex of TsCYDN[10] ; which gave almost complete conversion of ketones with 95 % ee in 15 min to 2 h with sodium formate as a hydrogen donor and water as a solvent. Rh-TsDPEN and Ir-TsDPEN (>90% conversion and > 90% ee), also proved highly active catalyst in water and sodium formate.[11] The higher rate with water as a solvent was attributed to the fact that as the reaction happens at the interface of aqueous and organic layer, where the concentration of reacting species such as, catalyst, substrate is highest. Since then (as mentioned in the introduction chapter) focus of the work

was mainly on the application of modified ligands to the use of sodium formate in water using various modified structure of the TsDPEN or TsCYDN ligands. Xiao et al. showed that ATH of ketones using Ru-TsDPEN, in equivolume mixture of FA:TEA and water serves as hydrogen donor and solvent.[5] As discussed in literature[3, 5, 9] ,(section 1.4.1.2,and 1.4.1.3), there is difference in the activity of Ru-TsDPEN complex in FA:TEA azeotrope as well as in water (by at least 10 fold) and difference in enantioselectivity by 4%. To understand and get more clarity on these abnormities Xiao et al[5]. carried out ATH of ketones at various ratios of FA:TEA along with water[5] and suggested that the difference in activities for Ru-TsDPEN complex in FA:TEA could be due to the pH of the reaction mixture. Watanabe and coworkers reported[12-14] that IrCp*, IrCp*methyl pyridine and Ir bipyidyl cp* complexes catalyze the transfer hydrogenation of carbonyl compounds at different pH. Thus indicating that electron donating ability of these complexes is dependent on pH and is different for pyridyl and bipyrydyl complexes. The similar concept in ATH using FA:TEA in water (different ratios of FA:TEA in equal volume of water) was shown by Xiao et al. for Ru–TsDPEN complex[5]. Thus Ru–TsDPEN complex, showed difference in the conversion as well as ee, below pH 4 and above pH 4. However it was observed that between pH 5 to pH 8 there was leveling effect on conversion and there was no change in ee[5]. The use of Rh-TsDPEN was found to be less effective in the pH range of 3-5, but in the neutral pH range the activity of Rh-TsDPEN was higher than Ru-TsDPEN. Similar trend was observed for Ru –TsCYDN[15] and Rh –TsCYDN. Thus few examples can be found on the use of FA: TEA as hydrogen source in literature. All these results are presented in Tables 1.2 and 1.3 in the literature chapter and it can be seen that with change in FA:TEA ratio and added volume of water the conversion as well as ee changes drastically. But as mentioned in the literature; complete understanding of exact factors affecting conversion and ee are still not known. For example, in equivolume ratio of (FA:TEA azeotrope) and water, Ru-TsDPEN showed complete conversion and good ee (97%), but the increase in activity was much more for Rh-TsDPEN. Thus Rh-TsDPEN at neutral pH showed 96% ee, whereas at higher ratios of FA: TEA (0.2:1) showed less ee (86%)[16].

From this it was clear that role of pH in ATH of ketone is important and almost all work in ATH is done by using TsDPEN ligand. There are no reports on ATH with FA:TEA in water as hydrogen donor using Rh-unsymmetrical vicinal dimaine ligand catalyst system.

In this chapter detailed investigations have been carried out on the ATH of acetophenone using Rh-ligand 9 complex catalyst and FA: TEA in water as hydrogen donor. Effect of pH on ATH of acetophenone has been investigated using Rh, Ru and Ir catalysts. Optimization of reaction conditions has been carried out using Rh-ligand 9. Also, to expand the scope of ligands developed, ATH of imines has been carried out using Ru-ligand 9 complex catalyst.

4.1.1 Experimental:

4.1.2 Materials

FA: TEA azeotrope, formic acid and triethylamine were purchased from Sigma Aldrich India. All the transition metal complexes were prepared as per the literature procedure and as presented in Chapter 3. (Sections 3.1.3 and 3.1.4) Methanol, ethanol, DMSO, DMF, and Acetonitrile, were purchased from local company as reagent grade materials.

4.1.3 Experimental procedure:

The FA: TEA Mixture in desired proportion along with equal volume of water was stirred in jacketed reactor using water circulation bath till desired temperature was attained**.** $[RhCp^*Cl_2)]_2$, 3.09 mg (0.005 mmol), ligand 9, 3.04 mg (0.01mmol), and acetophenone 1mmol, were added to the rector and the reaction was started. Reaction samples were withdrawn at regular intervals and analyzed using HPLC for conversion and enantioselectivity. Calibration curve was constructed using standard, Phenethanol and acetophenone. The response factors were calculated and used in the calculation of conversion and acetophenone and phenethanol by external standard method.

4.1.4 Analytical methods

The reaction products were identified using GC-MS, (Agilent GC 6890N with 5973 mass selective detector). Analysis of the reaction crude was carried out on Waters Acquity HPLC, H class using Chiracel IB Column, (25 x 4.6 mm id , 5 μ,Particle size) supplied by Daicel industries. The detector used was a UV-DAD and the monitoring wavelength used in typical analysis was 216 nm for acetophenone.

The standard HPLC conditions used for the analysis of reaction are given in Appendix of chapter 3.

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4.2 Preliminary experiments with FA: TEA in water as hydrogen donor

Based on the results presented in third chapter, ligand 9 was found to be the best for ATH of ketones in water and methanol using sodium formate as a hydrogen donor**.** Thus ligand 9 with transition metal complexes of Ru, Rh, and Ir were used as catalysts for ATH of acetophenone using FA: TEA azeotropic mixture. Main aim of the work in this chapter was to investigate ATH of ketones under different pH using FA:TEA in water. Preliminary experiments were carried out using FA: TEA mixture in a ratio of 5:2 and 0.2:1 as hydrogen and solvent and FA: TEA in same ratios with equal volume of water[5, 11] as hydrogen donor and solvent. The results are presented in Table 4.1.

From initial results it was found that, with Ru- Ligand 9 complex with FA:TEA 5:2 as hydrogen donor, showed only 25 % conversion after 16 h. Lowering the FA:TEA ratio (0.2:1) the conversion increased significantly to 65% in same time 16 h. (entry 2). The enantioselectivity in both the cases was constant at 94%. With the use of FA:TEA azeotrope (5:2) in equal volume of water, conversion increased from 25 % (in neat azeotrope) to 35 % conversion was observed. However, reaction did not proceed with FA:TEA (0.2:1) in equal volume of water. Similar trends were observed by Xiao et al. for ATH of acetophenone using Ru-TsDPEN catalyst[10, 11, 16].

Rh-Ligand 9 complex showed < 10 % conversion with FA:TEA azeotropic mixture (5:2). With lower FA:TEA ration (0.2:1), conversion increased from 10 to 15 %., however, the increase in conversion was lower compared to Ru (Table 4.1, entry 1). With the use of FA:TEA water system activity increased significantly for FA:TEA (5:2) with equal water and in this case the extent on increase was slightly higher than that observed for Ru catalyst (Table 1, Sr. No. 3 and 4). The enantioselectivity with Rh catalyst was lower (84-86 %) compared to that with Ru catalyst (93 - 94 %). The results obtained with Rh catalyst are consistent with literature reports.[11] Iridium-Ligand 9 complex showed very less activity and no trend was observed with change in FA: TEA compositions.

At very low ratio of FA:TEA (0.2:1) in equivolume water; reaction did not proceed with all the catalysts. This is probably because the, pH of the mixture is on higher side (>10). Preliminary experiments clearly showed that pH has significant influence on the rate of reaction for all the catalysts. There are no reports on the effect of pH using unsymmetrical tosylated diamine ligand and hence detailed work on the effect of pH

on activity and enantioselectivity was carried out using Ru, Rh and Ir catalysts and results are presented in the next section.

Table 4.1: ATH of Acetophenone using ligand 9 and transition metal complexes

Sr. No.	Hydrogen donor	$[RuCl_2(p\text{-cymene})]_2$			$[Rh(Cp^*)Cl_2]_2$			$Ir(Cp^*)Cl_2]_2$		
		Time, h	Conv. %	ee, %	Time, h.	Conv. %	ee, %	Time, h.	Conv%	ee %
1	FA:TEA (5:2)	16	25	94	12	<10	84	12	<10	-
2	FA:TEA (0.2 :1)	16	65	94	12	15	84	12	<10	-
3	FA:TEA (5:2)*,	16	35	93	12	25	86	12	<10	-
4	FA:TEA (0.2 :1)*	16	-	-	16	-	-	16	-	

Reaction conditions: FA:TEA: 2 ml;metal complex, 0.005 mmol;ligand 9: 0.01 mmol; acetophenone, 1mmol;temperature, 25^0C (* Water /FA:TEA 1ml each)

From the results presented in Table 1, addition of water had a contrasting effect on activity. With FA:TEA ratio of 5:2 (equivolume mixture with water), acetophenone conversion increased for Ru and Rh catalysts increased. While with FA:TEA 0.2:1 (equivolume mixture with water) acetophenone conversion was not observed. This clearly indicated that FA: TEA ratio along with presence of water (pH of the solution) is important for getting higher conversion and ee. Xiao et al[5].have shown that, the activity for ATH acetophenone increases significantly above pH 4, as free formic acid concentration increases[5] (Pka of formic acid 3.6). Initial results clearly showed that entire pH range should be evaluated with varying ratios of FA: TEA mixture. It was observed that pH modulation in broad range showed the contrasting behaviors of Ru and Rh catalyst with same ligand. Thus different trends for ATH of alpha substituted ketone by Ru-TsDPEN and Rh- TsDPEN is noted by Hamada[17] and Cross[18] in neat FA:TEA.

In order to understand the role of pH and ratio of formic acid on ligand 9 and transition metal complexes (Ru, Rh, and Ir) systematic variation in the FA: TEA ratio was done.

Table 4.2: Variation in FA: TEA ratio

Sr. No	FA, moles	TEA , moles	FA:TEA ratio	pH(50% water)
1	0.07426	0.05172	1.4	4.5
2	0.06630	0.05387	1.2	5.5
3	0.06100	0.05531	1.1	6.5
4	0.05835	0.05675	1.0	7.5
5	0.05304	0.05603	0.9	8.5
6	0.04509	0.05962	0.8	10
7	0.02652	0.06465	0.4	11

4.2.1 Variation in FA: TEA ratio

In order to investigate ATH of acetophenone at different initial solution pH, a systematic variation in FA:TEA ratio was carried out and equivolume solutions were prepared in water. Initial pH of all the solutions was measured and the details are presented in Table 4.2. During this exercise it was made sure that the amount of formic acid present in the solution was sufficient (at least five times in excess than acetophenone to be used as reactant) for the reaction and activity was not limited by formic acid in the solution. ATH of acetophenone was carried out using Ru, Rh and Ir catalysts and the results are presented for each catalyst separately and then compared.

4.2.1.1 Effect of FA: TEA ratio on ATH of acetophenone using Ru-Ligand 9 catalyst

ATH of acetophenone was carried out using Ru-ligand 9 catalyst and the results are presented in Fig.4.2. At initial FA: TEA ratio of 1.4:1 (initial pH value of 4.5) activity of Ru catalyst was low and 93% conversion with 93 % ee was observed in 18 h. C-T profile showed that rate was linear till 40 % conversion, acetophenone conversion increased significantly after this point, till it reached 80 %, however, enanatioselcvity did not change during the course of reaction. Comparing the results with Ru-TsDPEN, from literature[5], lower activity and ee was observed for ligand 9 in the present work.

Change in the initial FA: TEA Ratio from 1.4: 1. to 1.2:1 (initial pH 5.5), resulted in significant increase in activity for Ru-ligand 9 complex. Thus 88% conversion and 91% ee was observed in 8 h. Thus change in 1 pH unit, the activity for Ru catalyst increased by ~2 fold, however ee dropped down slightly by 2%.

Further change in initial FA:TEA ratio from 1.2:1 to 1.1:1 (initial pH 6.5) again led to significant increase in activity (86 % conversion and 86 % ee in 4 h). Activity increased 2 fold with change in initial pH, however, major shift was ee dropped during the course from 95 % initially to 86 % at the end of the reaction. This is in contrast to the literature reports for Ru-TsDPEN[5] complex where no change in ee was observed for experiments in a pH range of 5-8.

Further experiments at initial FA:TEA ratio of 1:1 (initial pH 7.5) again showed increased conversion (93 % conversion in 3 h, Fig. 4.1 c). Howver, here ee decreased significantly and was ~75 % from the start of the reaction. At initial FA:TEA ratio of 0.9:1 (initial pH 8.5) activity was very poor and only 10 % acetophenone conversion with 70 % ee was observed after 3 h reaction time. Thus observed results suggest that optimim pH range for Ru-ligand 9 complex is between 4.5 to7.5. This variation in the activity of Ru-Ligand 9 compex, can be attributed to the different elctronic and steric properties of ligand 9.

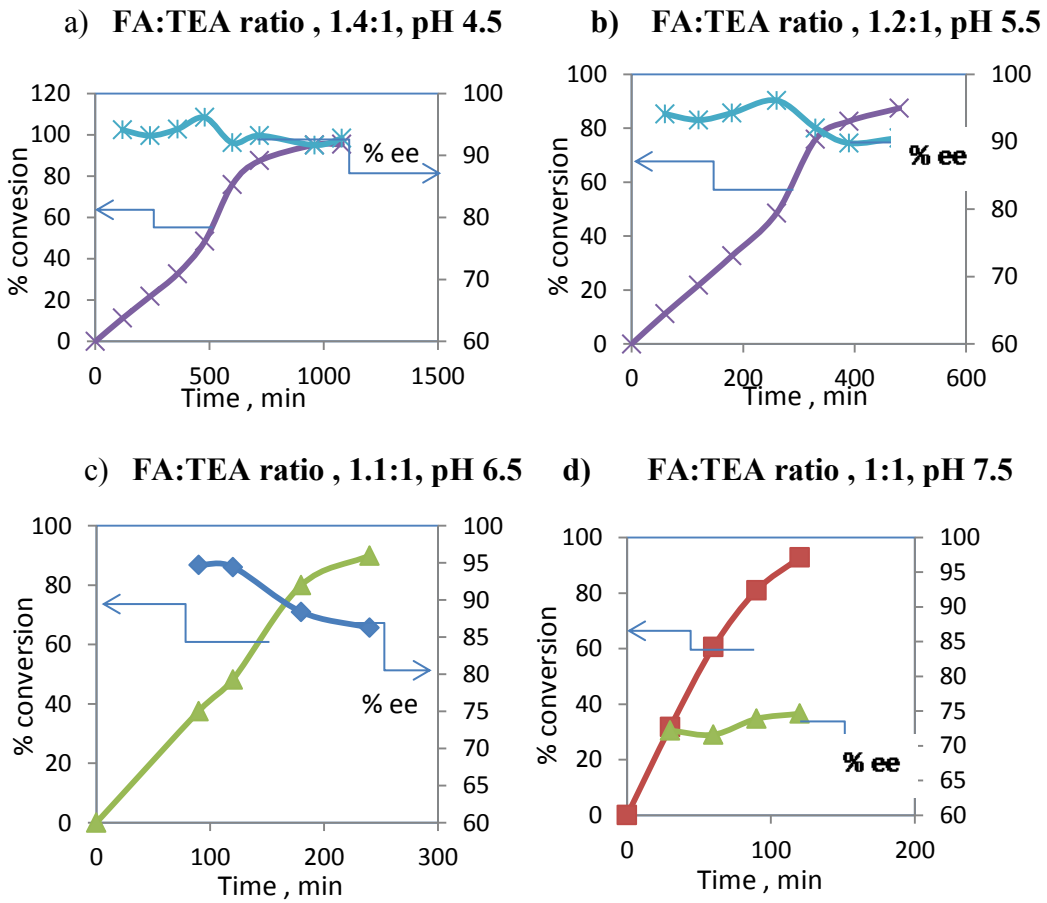


Fig.4.1: Effect of FA: TEA ratio and initial pH on conversion and ee for a) Ru – ligand 9 complex

Reaction Conditions:FA:TEA 1ml; water, 1 ml; Metal Complex: 0.005 mmol, ligand 9, 0.01 mmol; acetophenone,1mmol; temperature: 25^0C,

4.2.1.2 Effect of FA: TEA ratio on ATH of acetophenone using Rh-Ligand 9 catalyst

Effect of initial FA: TEA ratio in equivolume water as hydrogen donor on ATH of acetophenone was investigated using Rh-ligand catalyst and the results are presented in Fig 4.2. At initial FA: TEA ratio of 1.4:1 (initial pH 4.5), activity was very sluggish and 92% conversion with 88 % ee was observed in 28 h. It was observed that till 17 h, conversion was, linear and ee was 79 %, after 17 ee increased from 79% to 86%. Thereafter ee of stabilized till the end of the reaction. (88%).similar trends were observed by Xiao et al[11] for Rh-TsDPEN catalyst.

At initial FA:TEA ratio of 1.2:1 (initial pH 5.5), activity increased significantly for Rh catalyst and 98% conversion of acetophenone was observed in 8 hours, with ee

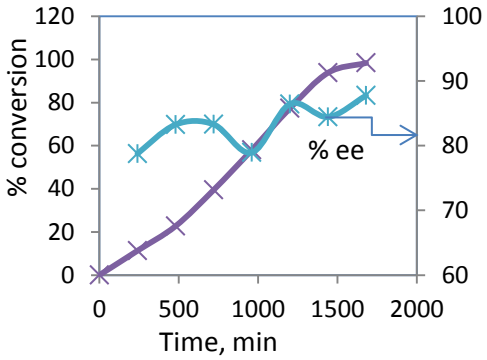
remaining constant at 87 %. Thus 3 fold increase in activity was observed compared to that at a ratio of 1.4:1.

Significant increase in activity was observed with initial FA: TEA ratio of 1.1:1 (initial pH 6.5) and the results are presented in Fig 4.2c. Thus 95% conversion of acetophenone was observed in just 2.5h, with ee increasing marginally to 90%. It was observed that activity increased was by ~3 fold (Fig 4.2c) compared to that at a ratio of 1.2:1 (compare Fig. 4.2 b and c).

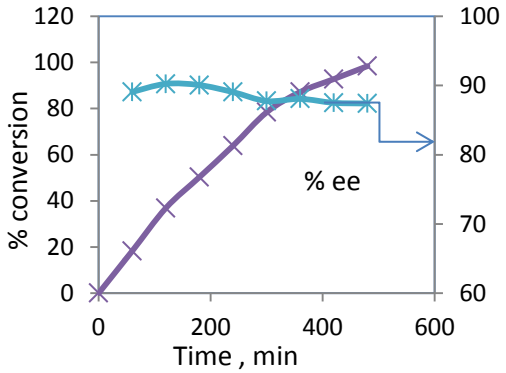
Further increase in initial FA:TEA ratio to 1:1 (initial pH 7.5) the activity for Rh catalyst increased and 99 % conversion of acetophenone was observed in 90 minutes with significant increase in ee value to 96 %. (2 fold incraese over that observed at FA:TEA ratio of 1.1:1)(compare Fig 4.2 c and d)

In conctrast to the results with Ru catalyst, activity of Rh catalyst increased further with initial FA:TEA ratio of 0.9:1 (initial pH 8.5) and 95 % conversion of acetophenone was obtained in 25 min with ee 94 % (Fig. 4.3 a). With further change in initial FA:TEA ratio to 0.8:1 (initial pH), sudden drop in conversion was observed (61% in 90 min and and 92% after 12 h. The ee also reduced from 94% to 90%). Trend continued and at initial FA:TEA ratio of 0.4:1, only 41 % conversion was observed with 85 % ee. Xiao et al also observed similar results for Rh–TsDpEN acatalyst using sodium formate and sodium hydroxide hydrogen donor at higher pH ranges [11]

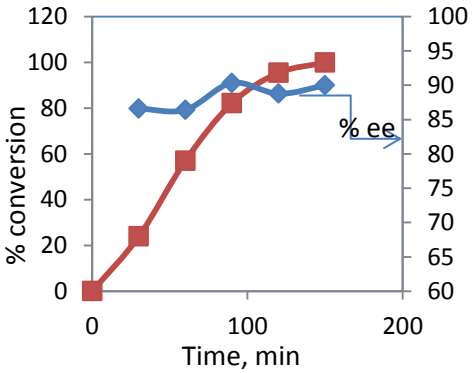
a) FA: TEA ratio, 1.4:1, pH 4.5



b) FA: TEA ratio, 1.2:1, pH 5.5



c) FA:TEA ratio , 1.1:1, pH 6.5



d) FA:TEA ratio , 1:1, pH 7.5

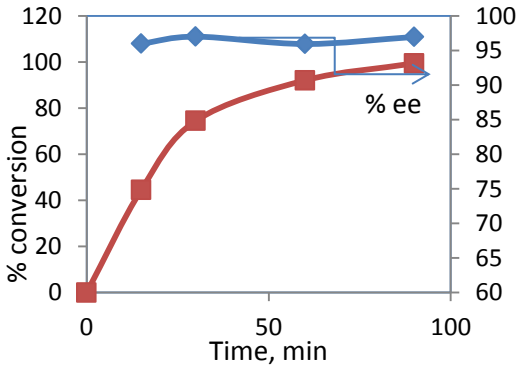


Fig.4.2: Effect of FA: TEA ratio on conversion and ee for Rh-Ligand 9 complex

Reaction Conditions :FA :TEA ratio (1.2:1),1ml; water 1, ml; Initial pH,5.5; Metal Complex,0.005 mmol; ligand 9 ,0.01 mmol;Acetophenone 1mmol; Temperature 25^0C

a) b)

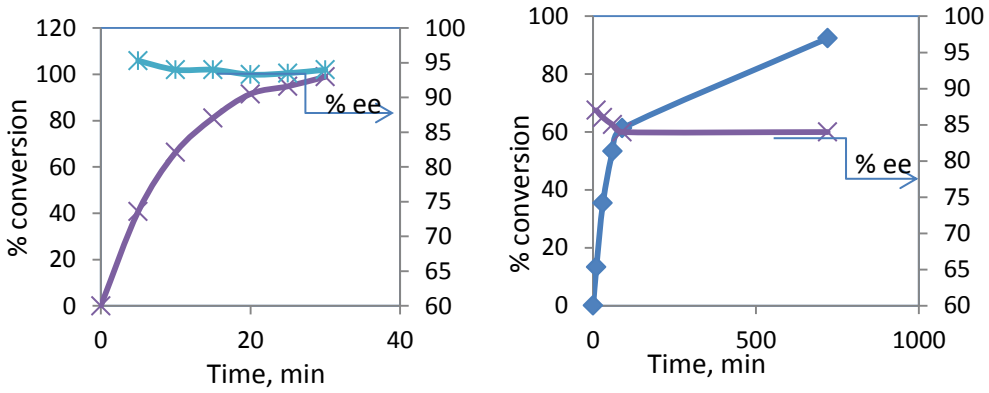


Fig.4.3: Effect of FA: TEA ratio on conversion and ee for Rh-Ligand 9 complex

Reaction Conditions :FA :TEA mixture,1ml;water, 1 ml; Temperature 25^0C
Metal Complex, 0.005 mmol; and ligand 9 ,0.01 mmol;Acetophenone ,1mmol

4.2.1.3 Effect of FA: TEA ratio on ATH of acetophenone using Ir-Ligand 9 catalyst.

The Ir-ligand 9 catalyst was also investigated by systematically varying initial FA:TEA ratio. However, Ir catalyst was found to be ineffective and < 15% conversion was reached within 4h for all the reactions. The best result was obtained at initial FA:TEA ratio of 0.9:1, where 98% conversion was obtained in 12h, with 91% ee. Since results with Ir were poor, they are not compared further in the work.

4.3 Results and Discussion based on Mechanisam of ATH of ketones

The results obtained clearly indcate that ATH of Acetophenone is significantly enhanced by the pH modulation for Ru and Rh catalysts with ligand 9. The dependence of activity expressed as (TOF,h^{-1}) and ee on initial FA:TEA ratio (initial pH of solution) observed for Ruthenium and Rhodium catalysts is shown in Fig 4.4 . Thus TOF, h^{-1} for Ru-Ligand 9 complex at initial ratio of 1.4:1 (pH 4.5) was only 5.2 and increased to 30 at initial ratio of 1.1:1(pH 7.5). Thus the increase in conversion was 5 fold with a change in pH by 3 units. Xia o et al. observed 20 fold incraese in conversion for Ru-TsDPEN with change in pH unit by 1[5]. This variation in the activity of Ru-Ligand 9 compex, can be attributed to the different elctronic and steric properties of ligand.9.

.The results obtained for Rh-ligand 9 complex,(95,% conv in 25 min)are found to be much more cocmparable to that observed for Rh-TsDPEN catalyst reported by Xiao

et al[11] (99% conv, in 30 min) showing that ligand 9 and TsDPEN are having similar activity for Rhodium complex in ATH of acetophenone.

For Ru-ligand 9, ee decreased significantly with change in pH from 4.5 to 7. 5 (94 % to 74%). However Xiao et al. observed that for Ru-TsDPEN catalyst the ee was constnat in the pH range of 5 -8.[5](97%).Thus results showed that Ru -liagnd 9 complex is having limited optimum pH range(4.5 to 6.5) compared to compared Ru-TsDPEN and lower actvity comared to Ru TsDPEN analougues, as observed in water and soium formate in earlier chapter (section,3.5) and literature[9, 11].

Rh-ligand 9 complex showed dramatic incraese in the acivity and significant improvement in ee. Thus at initial pH of 4.5 the.ee observed was 87 % and at pH 7.5 it increased to 96%, Further increase in to pH 8.5 drop in ee was observed for Rh-Ligand 9 complex to 94%. Comparing with literature report , Rh-TsDPEN showed[11] 97% ee at pH 9-11, and 86 % in FA:TEA ratio of 0.2:1 (in the absence of water).[16]. Thus different reports on ee were observed at higher pH(9.5) ,and at lower FA :TEA raio of 0.2:1. To summarise, it was obsrved that, Rh-ligand and Ru-ligand 9 showed optimum activity in different pH range.Typical Concentraion time profie ,for Ru-Ligand 9 compex and Rh-ligand 9 complex for ATH of acetophenone is shown in Fig. 4.5.

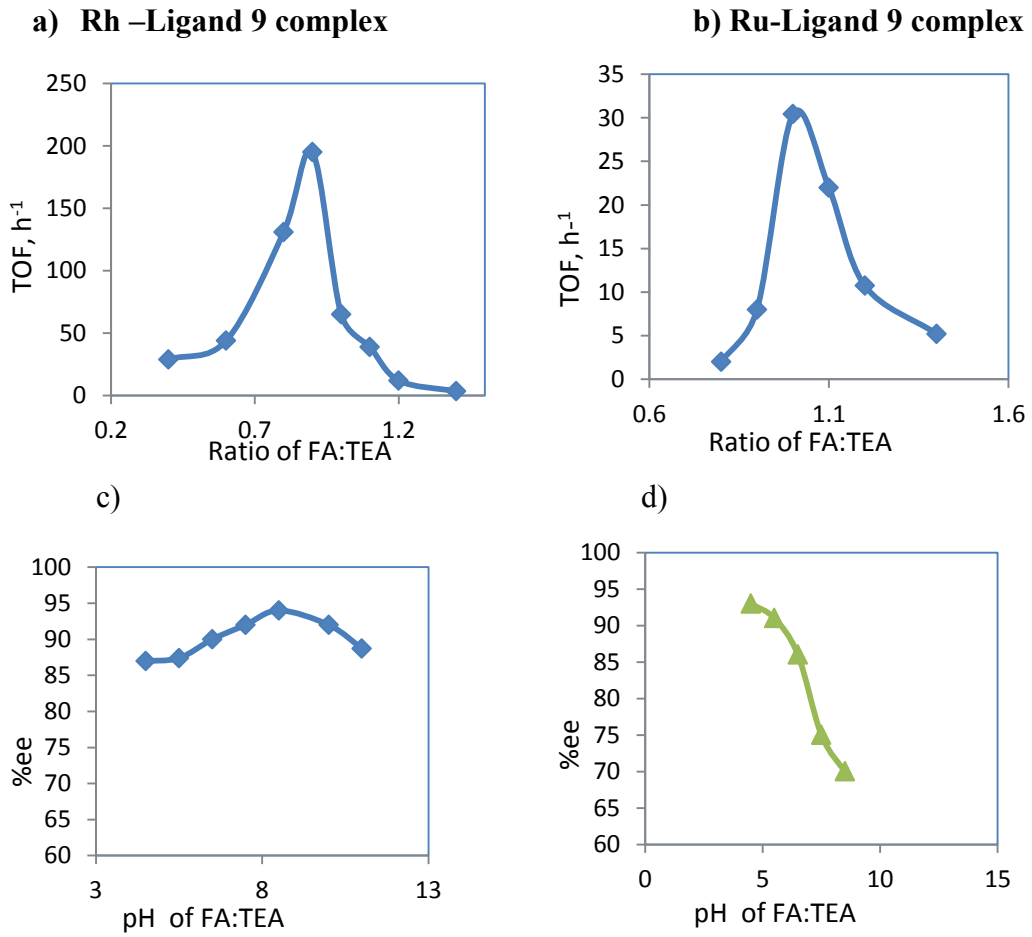


Fig 4.4: Effect of FA: TEA ratio on TOF h^{-1} and ee on Ru-ligand 9 complex (4.4 a and 4.4 c) and Rh-Ligand 9 complex (Fig. 4.4 b and d)

a)

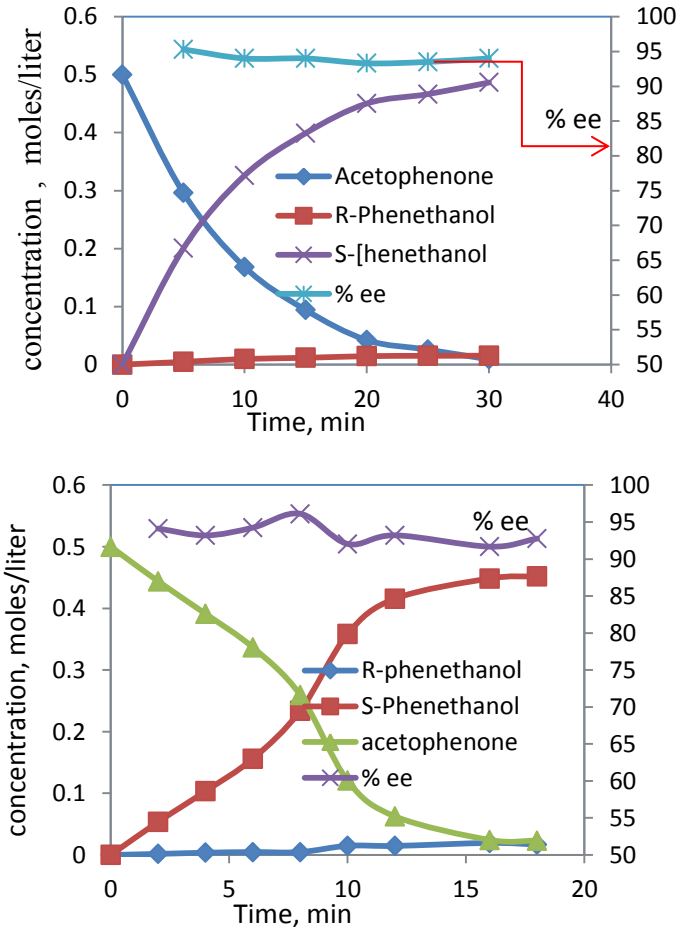


Fig.4.5: CT profile for (AP, R and S Phenethanol, % ee) a) Rh-Ligand 9 complex b) Ru-ligand 9 complex

The TOF,h^{-1} and ee dependent for Ru-Ligand 9 complex, and Rh-Ligand 9complex

From the results Rh-ligand 9 catalyst was found to be highly active in ATH of ketones with optimum initial FA:TEA ratio between 1.1 to 0.9:1 (initial pH 6.5 -8.5). However the optimim pH window is narrow like Rh-TsDPEN complex.[11] The results obtained, are discussed based on the mechanisam propsed by Xiao et al[5, 11].

4.4 Mechanisam for ATH of Ketones

The possible explanation for the results obtained with pH variation based on mechanisam is suggested. The mechanisam proposed by Xiao et al[5] is shown in Fig. 4.6 for acidic pH and in Fig. 4.7 for neutral and basic pH.

The mechanisam proposed by Xiao et al. shows that under acidic conditions protonation of sulfonamide group (of the Ru-TsDPEN) **1** leads to the intermediate (Fig. 4.6) **1a**, which on reaction with sodium formate, gives intermediate **2a**. The

formato complex **2a** undergoes decarboxylation to give 18 electron metal hydride complex **3a** . The **3a** forms a six memabred transition state with ketone and NH function of amino group. However, protonation of amide function makes transition state less stable and thus yilding low conversion and enentisleoctivity[5, 11].

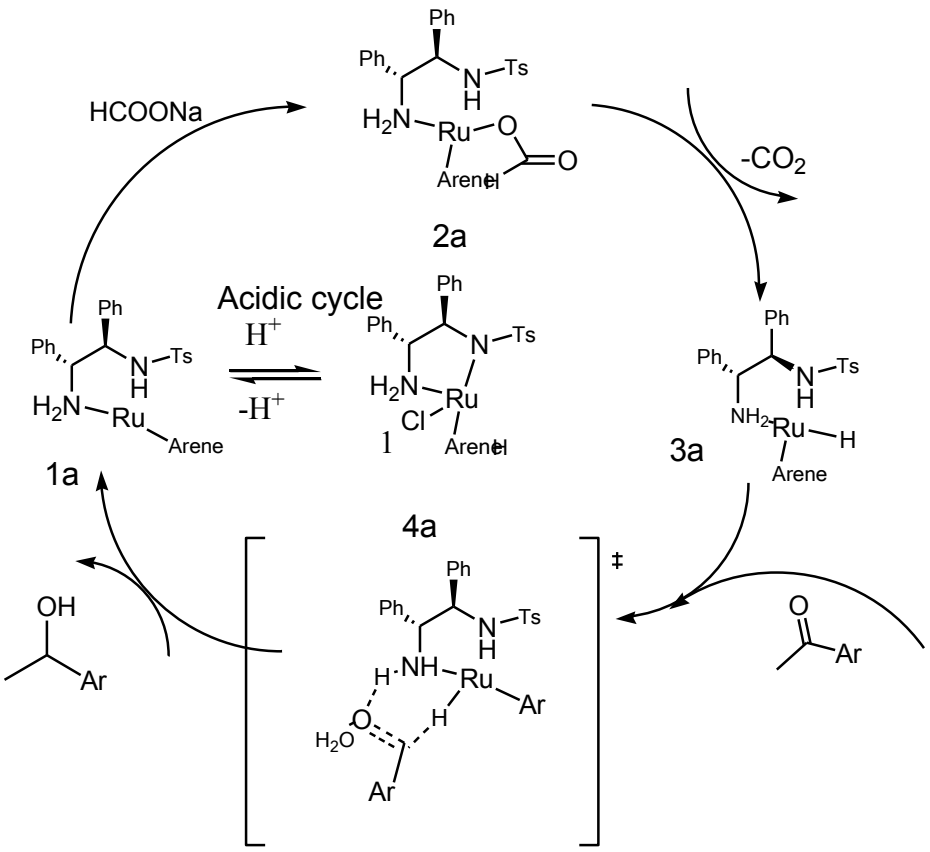


Fig. 4.6: Mechanism for ATH of ketone in acidic cycle

Under neutral conditions (Fig. 4.7) formato complex **2** is generated from precatalyst **1 by reaction** with soidum formate. The formato complex **2** undergoes decarboxylation to give 18 e metal hydride complex **3**. The intermediate **3** forms a six memabred transition state with ketone and NH function[5, 11]. Water plays an important role, as shown in Fig. 4.7 with help of hydrogen bonding and is shown to reduce the transition stae energy by 3.9 kCal/ mole for Rh-TsPEN and by 2.1 Kcal /mol Ru-TsDPEN[11, 19]. This explains the higher acivity of Rh-TsDPEN complex over Ru–TsDPEN in ATH of ketones with water. Same mechanis, may be applicable for Rh-ligand 9 and Ru-ligand 9 catalysts also.

As shown in the mechanisam (Fig. 4.7)at higher pH, the aqua complex **6** is repalced by hydroxy complex,7 which serves as a resrvoir for aqua complex. The carbon

dioxide formed during the reaction reduces solution pH and hence intermediate **7** is converted to **6**. In case of Rh-TsDPEN,[11] it is proposed that the hydroxy complex does not take part in catalystic cycle and hence ee remains uchanged. But in the case of Rh-ligand 9, and Ru-ligand 9 which are having different steric and electronic properties than TsDPEN and may behave differently, resulting in different activity and ee pattern. Thus significant decraese in the ee was observed in a pH range of 6.5 -7.5 for Ru-ligand 9 catalyst suggesting that dual mechanisam might be operating as mentioned by Xaio, neutral, acidc and basic medium and may be dependent on metal complex as well as steric and elcetronic properties of ligand used.After detailed screening Rh-ligand 9 was found to be the best catalyst with very high activity and high ee and hence was taken up for further investigations.

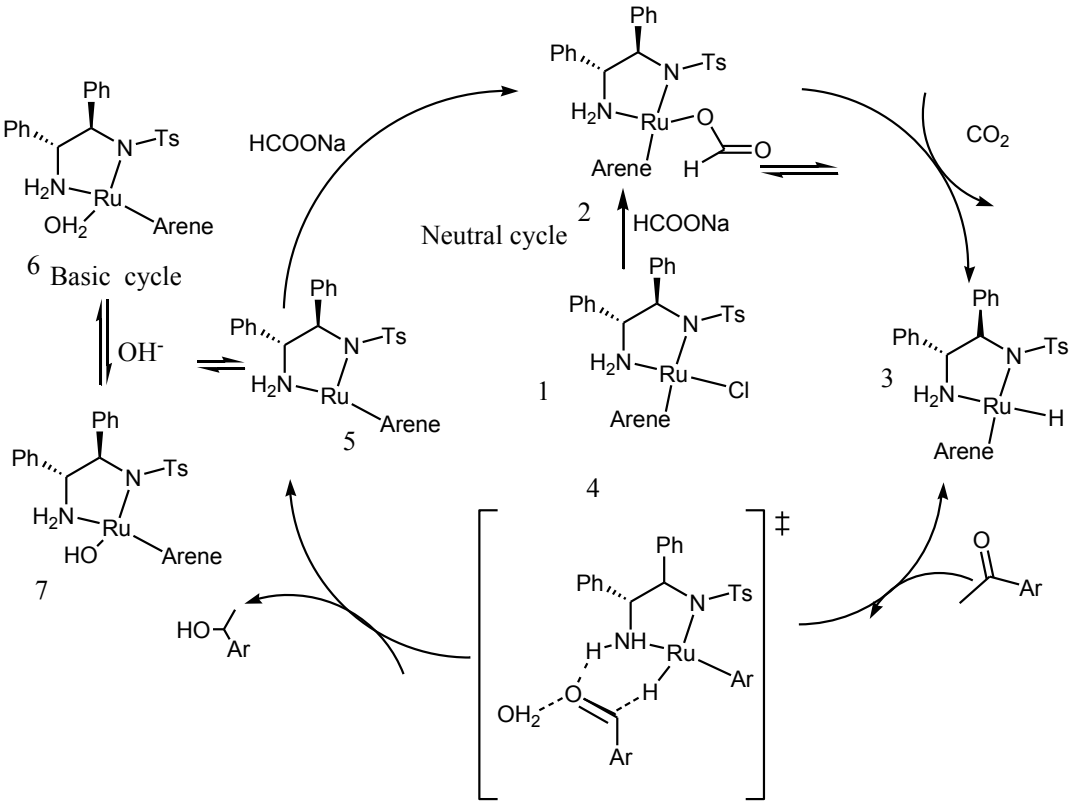


Fig.4.7 The mechanism for ATH of ketones in neutral and basic medium

4.5 Screening of various ketones using Rh-ligand 9 complex

Various ketones were screened using Rh-ligand 9 complext at initial FA:TEA ratio of 0.9:1 (initial pH 8.5), where best results were obtained. The ketones having different steric and elctronic properties were selcted. The results are presnted in Table 4.3. Acetophenone conversion of 98 % was observed in 30 min with 94 % ee. The ketones having elctron withdrwaing groups in para position, like p-chloro acetophenone and *p*-Bromo acetopheone,the consversions were slighly faster comapred to acetophenone (99% conversion in 20 mins) with little drop in ee for both the compounds (Table 4.2, Sr. No.2,3.). For ketones having electron donating alkyl or alkoxy groups in para position, like isobutyl acetophenone or methoxy acetophenone, the activity was low (90 % in 2 h and 82 % in 2 h respectively) with good enantioselectivity (96%). Cyclic Ketones like indanone and tetarlone showed good conversions (98 % in 30 min and 60 min respectively) and enatisoelcvity (92% and 94% respectively). Benzil also showed good activity and 82 % conversion was obtained in 2 h with 93 % ee. In summary Rh-ligand 9 catalyst was found to be efficient and tolerated to different substituents and gave good to high conversions (>90%) with good ee (>85%) for various substituted ketones.

Table 4.3ATH of ketones using ligand 9 and Rh –Ligand 9 complex

Sr.no.	Catalyst	Rhodium –ligand 9 complex		
	Substrate	Time ,mins	Conversion , %	%ee
1	Acetophenone	30	98	94
2	P-chloro acetophenone	20	99	92
3	P-bromo acetophenone	20	99	91
4	1-Indanone	30	98	92
5	1-tetralone	60	98	94
6	4-Methoxy acetophenone	120(300)	82(95)	96
7	Isobutyl acetophenone	120	90	96
8	Benzil	120	82	93

Reaction Conditions :FA :TEA mixture(0.9:1),1ml; water 1 ml;Temperature 25^0c Metal Complex 0.005 mmol, and ligand 9 ,0.01 mmol,Acetophenone (1mmol

4.6 Effect of reaction conditions on acetophenone conversion and enantioselectivity using Rh-ligand 9 catalyst

Preliminary Experiments were done using the conditions standardized in the earlier (section 4.2.1.2). The reaction mixtures were found to be homogeneous under standard conditions and the samples were removed at regular intervals. It was confirmed that C-T profile obtained using intermediate sampling from a reaction and that obtained by extraction method from reactions carried out at different reaction times were similar. However when water ratio was increased to more than 1.0 with respect to FA: TEA mixture, and when substrate concenatrion was 2.0 M, the reaction mixture was less homogeneous. For such cases experiments were carried out at different reaction times to generate CT profile. Conversions and ee were estimated by extracting the whole reaction mixture with t-butyl methyl ether. Complete mass balance of the liquid phase components was obtained from the quantitative HPLC analysis. The percent conversion, percent enantioselectivity, turn over Number (TON) and turnover frequency (TOF, h^{-1}) were calculated.

Effect of various reaction conditions like i) formic acid concentration ii) catalyst concentration iii) substrate concentration, iv) temperature, on the conversion and ee was investigated. The total volume of the reaction mixture was kept constant at 2 cm^3.

4.6.1 Effect of formic acid to substrate ratio

In these experiments formic acid ratio w.r.t substrate was varied from 1.3 to 7.8 by varying the volume of FA:TEA mixture (keeping the FA:TEA ratio constant). In these experiments volume of water changed from 0.38 ml to 1.63 ml. The results are presented in Fig.4.8.

Thus for base case experiment (FA: acetophenone: 5:1), conversion reached 60.8 % in 10 mins and 98 % within 25 mins, whereas ee were found to be 94%. Variation in formic acid ratio had significant impact on the conversion and ee. At a FA: acetophenone ratio of 2.6 convsiosn dropped to 46 % in 10 min and 97 % in 45 minutes. Enantioselectivity was constant through the reaction at 94%. At formic acid to substrate ratio of 1.3:1, the conversion was comparable to FA: acetophenone ratio of 2.6 in the beginning. However, afterwards the reaction became sluggish, probably because the formic acid ratio (w.r.t.substrate) started to go down very rapidly. The initial increase in the conversion can be attributed to the increased volume of water in reaction mixture, which makes dissociation of formic acid faster and thus more formic

acid ions are available for reduction. For the decrease in ee the although exact reason could not be find out, Ru-TsDPEN complex showed similar decrease in ee, with FA:TEA:water and water sodium formate system (97%, vs 94% respectively).[5, 9] With increase in formic acid ratio to 7.8, the initial conversion at the end of 10 mins was 46 %. In 20 min, conversions were 72 % (slower than formic acid substrate ratio of 5.2) and 96% ee was obtained. The results are presented in fig 4.8.

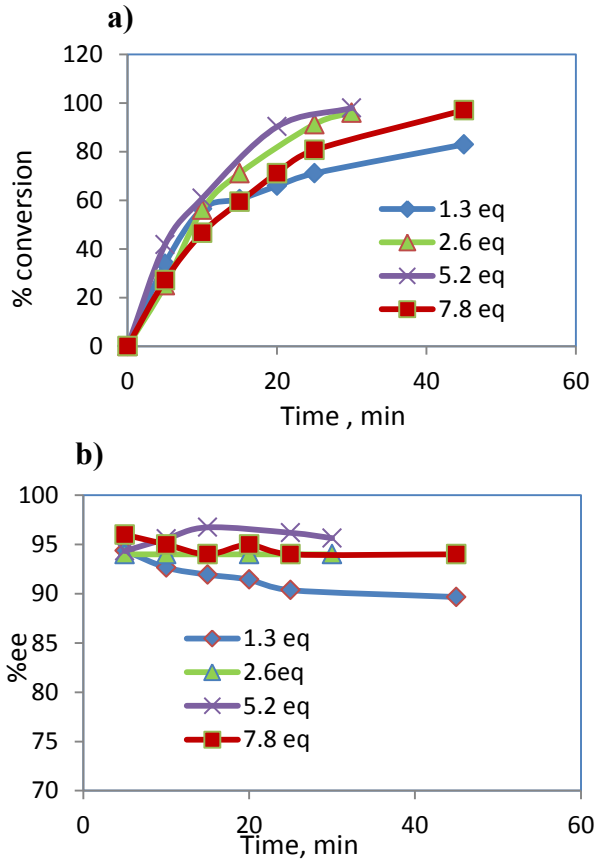


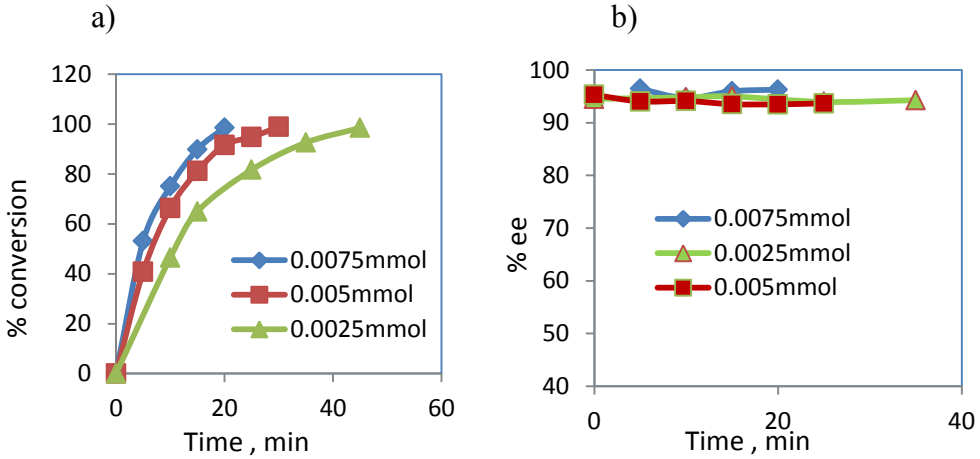
Fig 4. 8: Effect of Formic Acid, ratio on a) conversion b) ee

Reaction conditions: FA: TEA ratio (0.9:1),1ml; Initial pH: 8.5 $[Rh(Cp^*)Cl_2]_2$ 0.005 mmol; and ligand 9,0.01 mmol; Acetophenone,1 mmol; Temperature: 25^0C

4.6.2 Effect of Catalyst concentration

Effect of catalyst concentration was investigated in a catalyst concentration range of 0.0025 mmol to 0.0075 mmol by keeping other reaction conditions constant. The results are presented in Fig 4.9. As expected increase in catalyst concentration increased the conversion. Thus at Rh concentration of 0.0025 mmol 46 % conversion was observed within 10 min which increased to 75 % at a catalyst concentration of 0.0075 mmol. Enantioselectivity was not affected by a change in catalyst

concentration and was in a range of 94 to 96%. The plot of catalyst concentration verses initial TOF, h^{-1}(10 min) showed (Fig. 4.10) that at a catalyst concentration of 0.0025 mmol, highest TOF, h^{-1} where achieved (initial TOF: 441, and final TOF: 291), but complete conversion took relatively more time compared to catalyst concentration of 0.005mmol (45 mins vs 25 min respectively). To have optimum balance between catalyst concentration, reaction time and TOF, h^{-1} catalyst concentration of 0.005 mmol was used for further experiments.



Reaction Conditions: FA: TEA ratio (0.9:1), 1.0 ml; Water, 0.88 ml; Temperature 25^0C; Initial pH, 8.5;$[Rh(Cp^*)Cl_2]_2$,0.005 mmol; ligand 9, 0.01 mmol, acetophenone. 1mmol

Fig 4.9: Effect of catalyst concentration on a) conversion b) ee

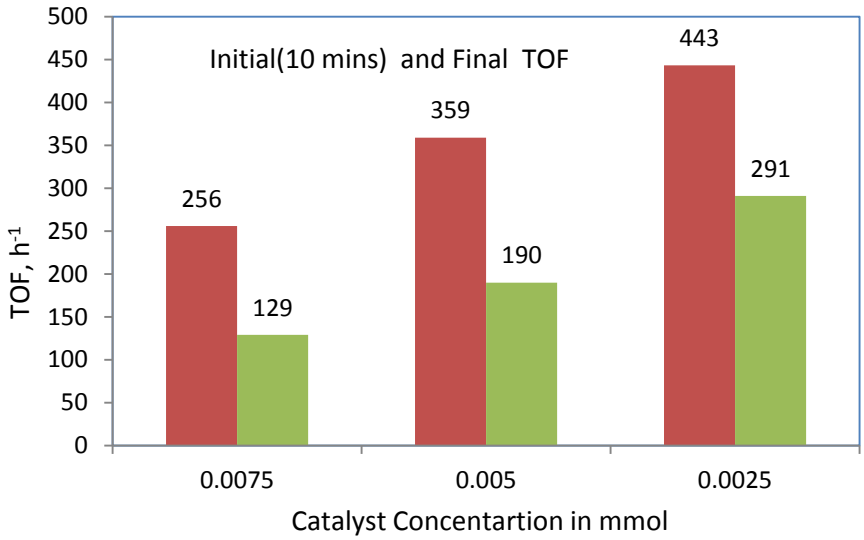


Fig 4.10: Effect of catalyst concentration c) Initial and Final TOF, h^{-1}

Reaction Conditions: FA: TEA ratio (0.9:1), 1.0 ml; Water, 0.88 ml; Temperature 25^0C; Initial pH, 8.5;$[Rh(Cp^*)Cl_2]_2$,0.005 mmol; ligand 9, 0.01 mmol, acetophenone. 1mmol

4.6.3 Effect of substrate concentration:

The effect of substrate concenatrion was studied by varying substrate concentration in the range of, 0.5 M, 1.0 M and 2.0M (1mmol, 2 mmol and 4mmol). The FA: TEA mixture volume was kept constant at 1ml. The volume of water was varied from 0.64 ml 0.88 ml (to keep total volume 2 ml constant) depending on the substrate concenatrion (acetophenone quantity was varied, as 0.12 g (1mmol), 0.24 g (2mmol) and 0.36 g (3mmol) respectively). The results are shown in Fig 4.11. From the C-T profile, it was observed that at a substrate concentration 0.5 M, 98% conversion was reached in 30 mins. It was observed that conversion decreased with increase in substrate concentration. Thus at acetophenone concenatrion of 1.0 M 88 % conversion was observed in30 min and reached 97% within 1h. With further increase in substrate concenatrion to 2.0M, the conversion dropped to 65%.and complete conversion was obtained within 2.25 h. The effect of substrate concentration can be better understood form the Fig. of molar concentration of Phenethanol formed as a product vs. % conversion (Fig. 4.11c). It was observed that phenethanol formed increased with increase in substrate concentration and ee was not affected by a change in substrate concentration (Fig. 4.11b). Activity expressed as turn over number (TON) and turn over frequency (TOF) calculated at 10 min (initial) and at the end of the reaction (final) is presented in Fig. 4.11d. From the figure we can see that TON as well initial TOF increased with increase in substrate concentration. However, final TOF increased with substrate concentration, but decreased at higher concentration of 2 M. At this concentration FA: substrate ratio becomes less than 1 as the reaction progresses resulting in lower TOF. Hence we were not able to investigate substrate concentration beyond 2 M.

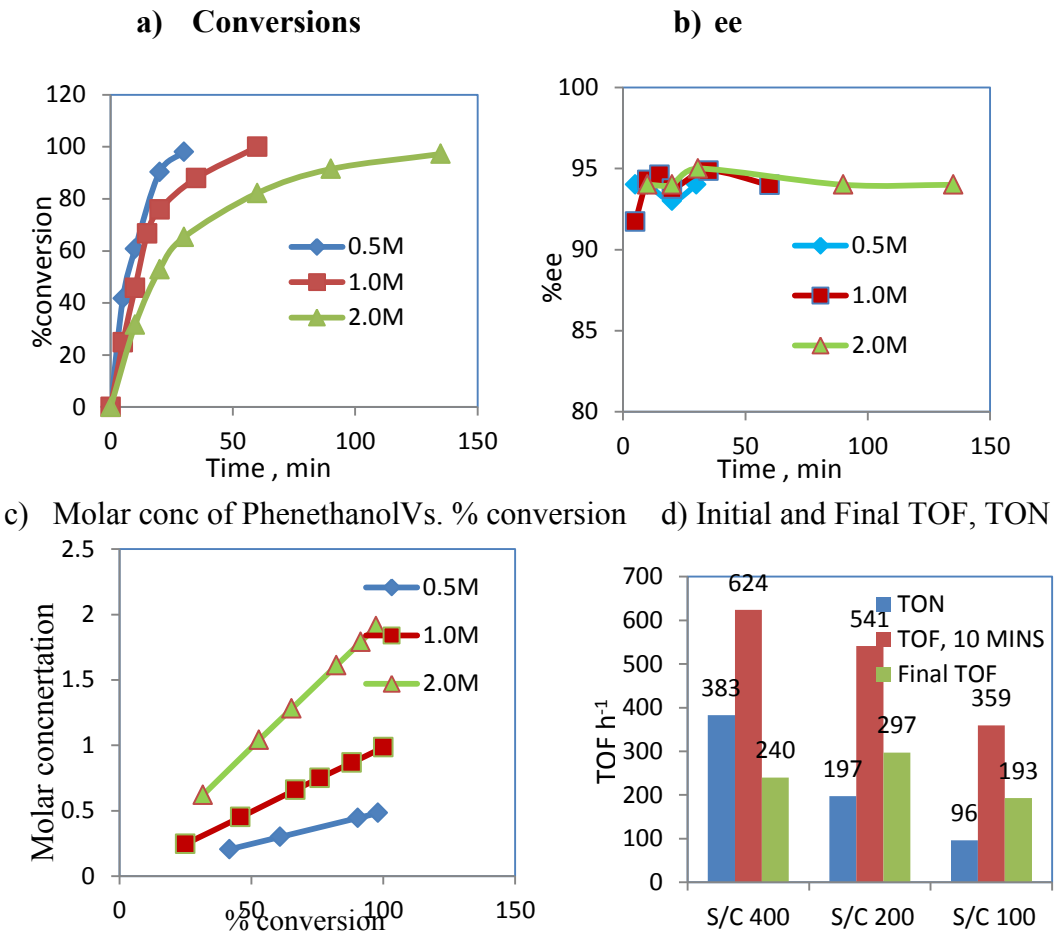


Fig 4.11: Effect of Substrate concentration on a) conversion b) ee c) molar concentration of product formed Vs conversion and d) Initial and Final TOF

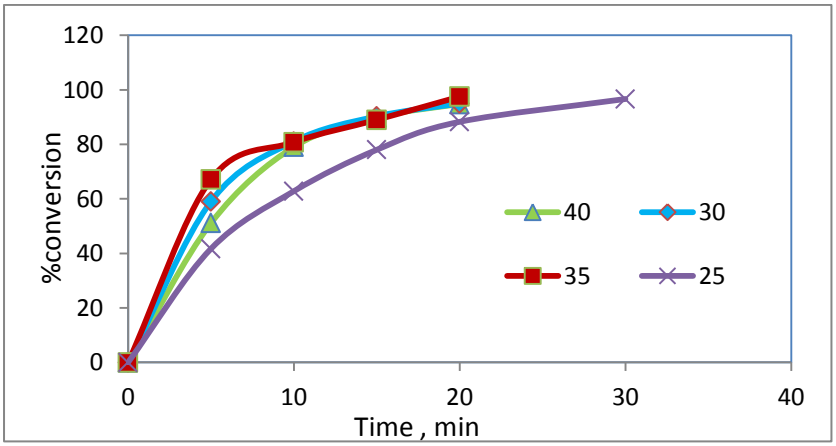
Reaction Conditions: FA: TEA ratio (0.9:1), 1ml, Water 0.52-0.88ml, Temperature 25^0C Initial pH, 8.5;$[Rh(Cp^*)Cl_2]_2$ 0.005 mmol; ligand 9, 0.01 mmol; Acetophenone. (1mmol-4mmol)

4.6.4 Effect of temperature:

Effect of temperature on conversion and ee was studied in the temperatures range of 25^0 C to 40^0C and the results are presented in Figure 4.12 .Normally, with increase in temperature, the conversion increases, however we observed different trend. With increase in temperature, conversion of acetophenone was found to be inconsistent. The results showed that at 25^0C , reaction was consistent and 97 % conversion of acetophenone was obtained within 30 min. With increase in the temperature to 35^0c, conversion increased very fast up to nearly 67 % in 5 min as against 42 % in 5 minutes at 25^0C minutes, but afterwards reached only to 89 % in 15 minutes and subsequently to 97% in 20 minutes. At 30^0C , the initial conversions were slightly

higher conversions were obtained than at 25^0C(59% , instead of 42%), and after 20 minutes the conversions at all the temperature except at 25^0c merged together and the reaction showed conversion around 97.5% . The careful observation of C-T diagram showed that, even though initial conversions at 30 and 35 were high, conversion at 40^oC showed drop in initial conversion (at 51% in 5 mins). This behavior was found to be similar to the one obtained, when ATH was carried with Rh-ligand 9 catalyst in Methanol as a solvent (Chapter3, section3.12.5). Enantioselectivity was not affected by a change in reaction temperature.

a)



b)

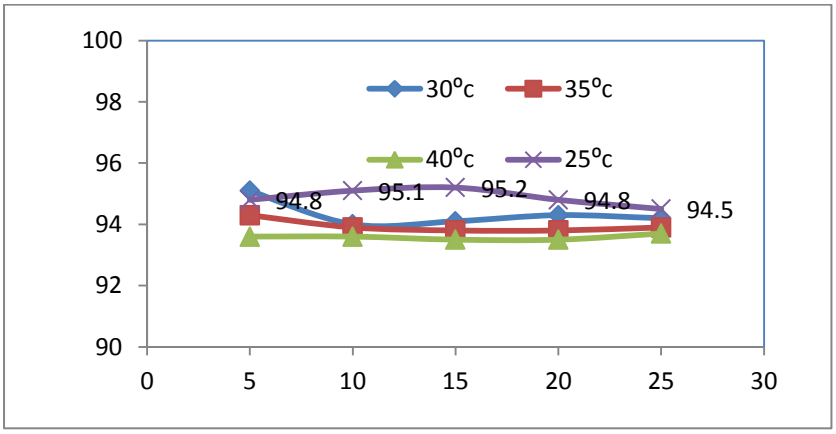


Fig 4.12: Effect of Temperature on a) conversion b) ee

Reaction Conditions: FA: TEA ratio (0.9:1), 1ml; Water, 0.88ml; Temperature ^{0}c Initial pH, 8.5:$[Rh(Cp^*)Cl_2]_2$ 0.005 mmol; ligand 9, 0.01 mmol; Acetophenone. 1mmol

Ikaria[20] has reported that carbon dioxide released during the reaction can form reversible complexes with Ru–monosulfonated diamine ligands and this is more accelerated by alcoholic solvent. Thus CO2 coordination with the Rh catalyst can be

one of the reason for inconsistent activity at high temperatures. Dimroth[21] also observed inconsistent activity at temperature higher that 40^{o}C for ATH of acetophenone with polymer supported Rh-TsDPEN catalyst. The use of Nitrogen and Ar as sweep gas could not improve the results and overall inconsistency was observed at high temperature with the sodium formate systems. Thus satisfactory explanation could not be found for inconsistent results obtained at higher temperatures. Since high conversion was obtained at 25 ^{o}C further work was carried out at this temperature.

4.7 Conclusion.

From the results it was observed that the acetophenone conversion increased with increase in FA: acetophenone ratio, catalyst concentration and substrate concentration, while ee was not affected. Temperature effect was different and consistent results were observed at 25^{o}C. Solvent composition (FA: TEA quantity and water quantity) probably has a significant role in deciding activity as well as enantioselectivity. Water helps in ionization of formic acid and a change in concentration of FA:TEA or acetophenone concentration leads to change in water, since total reaction volume is kept constant at 2 ml. In the present study we were not able to go beyond acetophenone concentration of 2 M (because of limiting FA concentration). Also water quantity change can affect overall activity as discussed above. In order to overcome this; optimization study was carried out by increasing total volume to 20 ml. This can give some flexibility in adjusting water quantity when other parameters are varied. The details are presented below.

4.8 Optimization at higher substrate and lower catalyst concentrations

Effect of reaction conditions on acetophenone conversion and enantioselectivity was investigated with Rh-ligand 9 catalyst by increasing total volume to 20 ml. Acetophenone, FA:TEA and water quantities were increased and catalyst quantity was not increased. Thus we can go to very high substrate: catalyst, which was not possible in the earlier experiments. Table 4.3 presents details of charge taken at different acetophenone concentrations by keeping total volume constant at 20 ml. With this charge optimization experiments were carried out and the results are presented below.

Table 4.4 Experimental designs at higher substrate to catalyst ratio

	Ligand 9 in mg	Rh cat.	acetophenone in g	FA:TEA (0.9:1) in ml	water in ml	Total volume	S/C ratio
wt. in mg	**3.4**	**3.09**	**0.48**	**10**	**9.52**	**20**	
molar concentration	**0.0005**	**0.0005**	**0.2**				**400**
wt. in mg	**3.4**	**3.09**	**0.6**	**10**	**9.4**	**20**	
molar concentration	**0.0005**	**0.0005**	**0.25**				**500**
wt in mg	**3.4**	**3.09**	**0.72**	**10**	**9.28**	**20**	
molar concentration	**0.0005**	**0.0005**	**0.3**				**600**
wt in mg	**3.4**	**3.09**	**0.96**	**10**	**9.04**	**20**	
molar concentration	**0.0005**	**0.0005**	**0.4**				**800**
wt in mg	**3.4**	**3.09**	**1.2**	**10**	**8.8**	**20**	
molar concentration	**0.0005**	**0.0005**	**0.5**				**1000**
wt in mg	**3.4**	**3.09**	**1.44**	**10**	**8.56**	**20**	
molar concentration	**0.0005**	**0.0005**	**0.5**				**1200**

4.8.1 Effect of substrate concentration:

Effect of substrate concentration was studied in a range of 0.2 M to 0.6 M (2 mmol to 12 mmol). Formic acid concenatrion was kept constant at 2.65 M, (ratio of formic acid w.r.t substrate was varied from 10 to 40 equivalence), total volume of the reaction was kept constant at 20 ml, the catalyst concentration was kept constant at 0.0005 mmol (5 X 10^{-5} M). The results are presented in Fig.4.13 to 4.16. Conversion in terms of molar concenatrion and enantioselevity was compared at 2h for clarity. It was found that the conversion increased with increase in substrate concenatrion in the range of 0.2 M to 0.5M. However, at 0.6 M concentration the conversion decreased,

marginally indicating substrate inhibition at high substrate concentration (S/C ratio of 1200, Fig.4.13 and 4.16). The eneatioseltivity was not affected by a change and substrate concentration and ~ 94% (Fig. 4.14).

TON and TOF, h^{-1} (30 min) showed that the increase in substrate concenatrion TOF, h^{-1} and TON increase consistently over the substrate to catalyst ratio of 1000. This indicated that though, the conversions were on lower side, the product formation in actual moles is on higher side as shown in the Fig 4.15a.The TON numbers increased steadily up to all the catalyst ratios up to S/C 1200.(1038 for S/C ratio of 1200, Fig. 4.15b) However TOF, h^{-1} decreased at substrate concentration of 0.6M. (545 for 0.5 M vs 469 at 0.6 M, Fig. 4.16). Thus we were able to get TON of 1038 for ATH of acetophenone using Rh-ligand catalyst system. Acetophenone concentration of 0.5 M (S/C ratio of 1000) was used for further experiments.

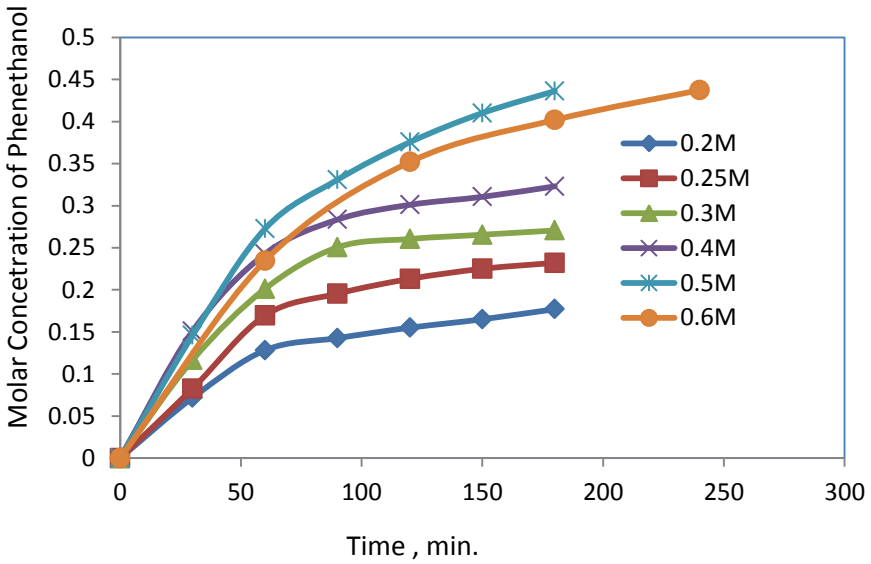


Fig 4.13: Molar concentration of Phenethanol vs Time

Reaction conditions: FA: TEA ratio (0.9:1), 10ml; Water, 8.8-9.52 ml; Temperature 25^0C; Initial pH, 8.5; $[Rh(Cp^*)Cl_2]_2$, 0.005 mmol; and ligand 9, 0.01 mmol; Acetophenone.(2-12mmol)

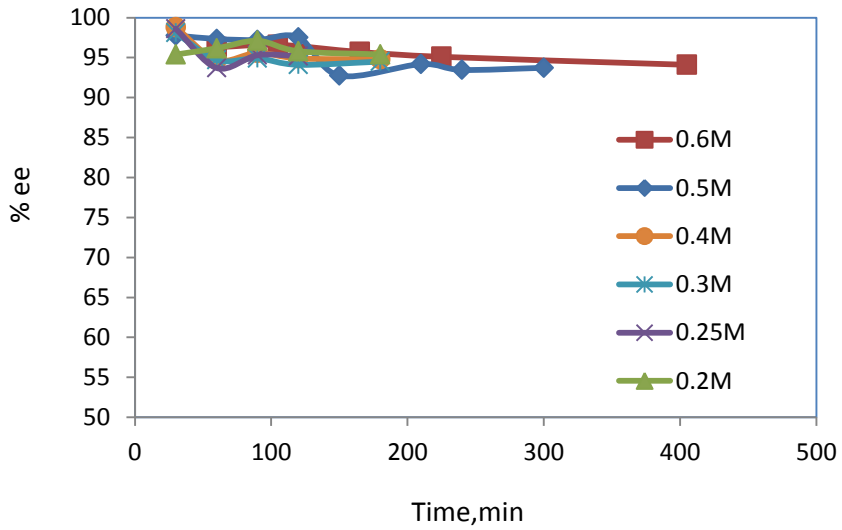


Fig 4.14: effect of substrate concentration on ee

Reaction conditions: FA: TEA ratio (0.9:1), 10ml; Water, 8.8-9.52 ml; Temperature 25^0C, Initial pH ,8.5;$[Rh(Cp^*)Cl_2]_2$ 0.005 mmol; and ligand 9 ,0.01 mmol; Acetophenone.(2-12mmol)

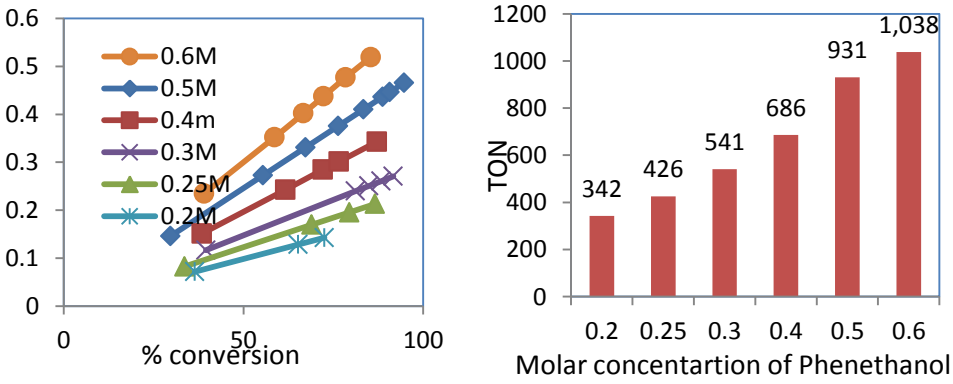


Fig 4.15: Effect of Substrate concentration on a) product formation b) TON

Reaction conditions: FA: TEA ratio (0.9:1), 10ml, Water 8.8-9.52 ml, Temperature 25^0C; Initial pH ,8.5;$[Rh(Cp^*)Cl_2]_2$,0.005 mmol; and ligand 9 ,0.01 mmol; Acetophenone.(2-12mmol)

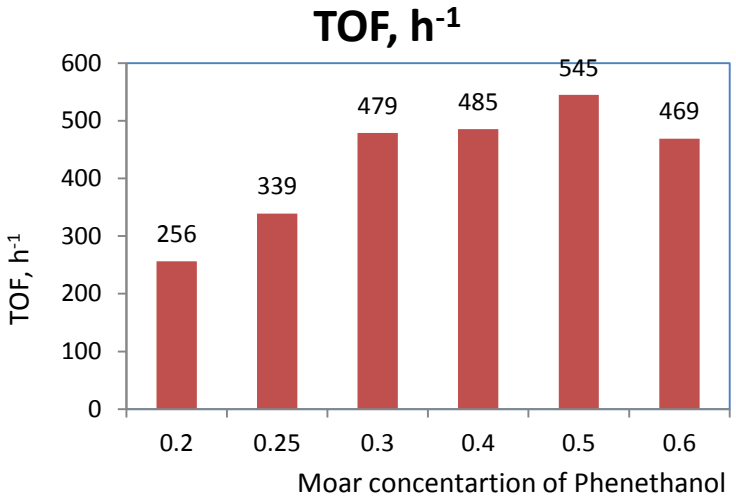


Fig 4.16: Effect of Substrate concentration on a) product formation b) TON

Reaction conditions: FA*:* TEA ratio (0.9:1), 10ml; Water 8.8-9.52 ml; Temperature 25^0C; Initial pH, 8.5;$Rh(Cp^*)Cl_2]_2$ 0.005 mmol; and ligand 9 ,0.01 mmol; Acetophenone (2-12mmol)

4.8.2 Effect of catalyst concentration:

The catalyst concentration was varied between (0.0025 mmol, 0.005 mmol and 0.01 mmol) keeping other reaction conditions constant (Fig. 4.17). As expected and observed in the earlier section, increase in catalyst concenatrion resulted in increased conversion of Acetophenone. While, enantioselectivity however remained consistent at 94%.Thus with catalyst concentration of 0.0025 mmol, 68 % conversion of acetophenone was observed after 6 h, while 88 % conversion was obtained in 75 min at a catalyst concentration of 0.01 mmol.

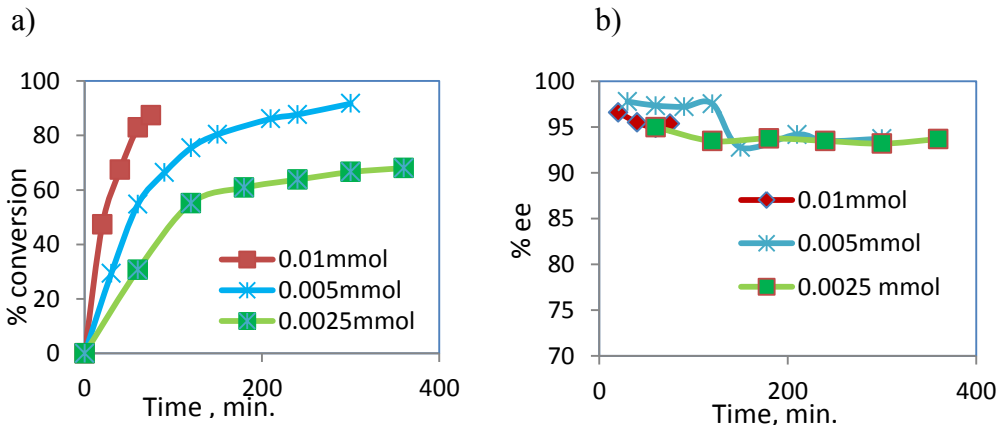


Fig 4.17: Effect catalyst concentration on a) conversion b) ee

Reaction conditions: FA: TEA ratio (0.9:1),10ml; Water, 8.8 ml; Temperature 25^0C Initial pH ,8.5l; Acetophenone.(10mmol)

4.8.3 Effect of formic acid: acetophenone ratio

In these experiments formic acid ratio w.r.t substrate was varied from 2.5 to 7.5 by varying the volume of FA: TEA mixture but keeping the FA:TEA ratio constant. In these experiments volume of water and % composition of water was changed significantly. The volume of water changed from 4.7 mL to 14.1 mL in order to keep total volume constant at 20 ml. All other reaction conditions were kept constant. The results are presented in Fig.4.18. With formic acid ratio of 5 with respect to acetophenone (standard experiment), 76 % Conversion was observed in 120 mins and 91 % within 300 min, with 94 % ee. Variation in formic acid ratio was found to have significant impact on the conversions and ee. At formic acid to acetophenone ratio of 2.5 (water quantity was high 14.1 ml), the conversion was fast in the start and was comparable to that with formic acid: acetophenone ratio of 7.5 at 70% in the 120 minutes. However, afterwards the reaction became sluggish, with only 5% more conversion in next 2 h. The initial increase in the conversion can be attributed to the increased volume of water in reaction mixture, which increases concentration of formate ions in the solution[22, 23] available for reduction. With progress of the reaction the concentration of formate ions decreases rapidly resulting in sluggish reaction observed. At formic acid to substrate ratio of 7.5 water quantity is very low 4.5 ml. Thus conversion was slightly less compared to the base experiment at 66 % conversion in 120 mins. Further reaction was observed to be slow showing 81% conversion in 4 h. Thus observed results are because of low water concentration, which leads to lower concentration of formate ions and in turn lower conversion the reaction. Enantioselectivity was not affected by a change in FA: acetophenone ratio.

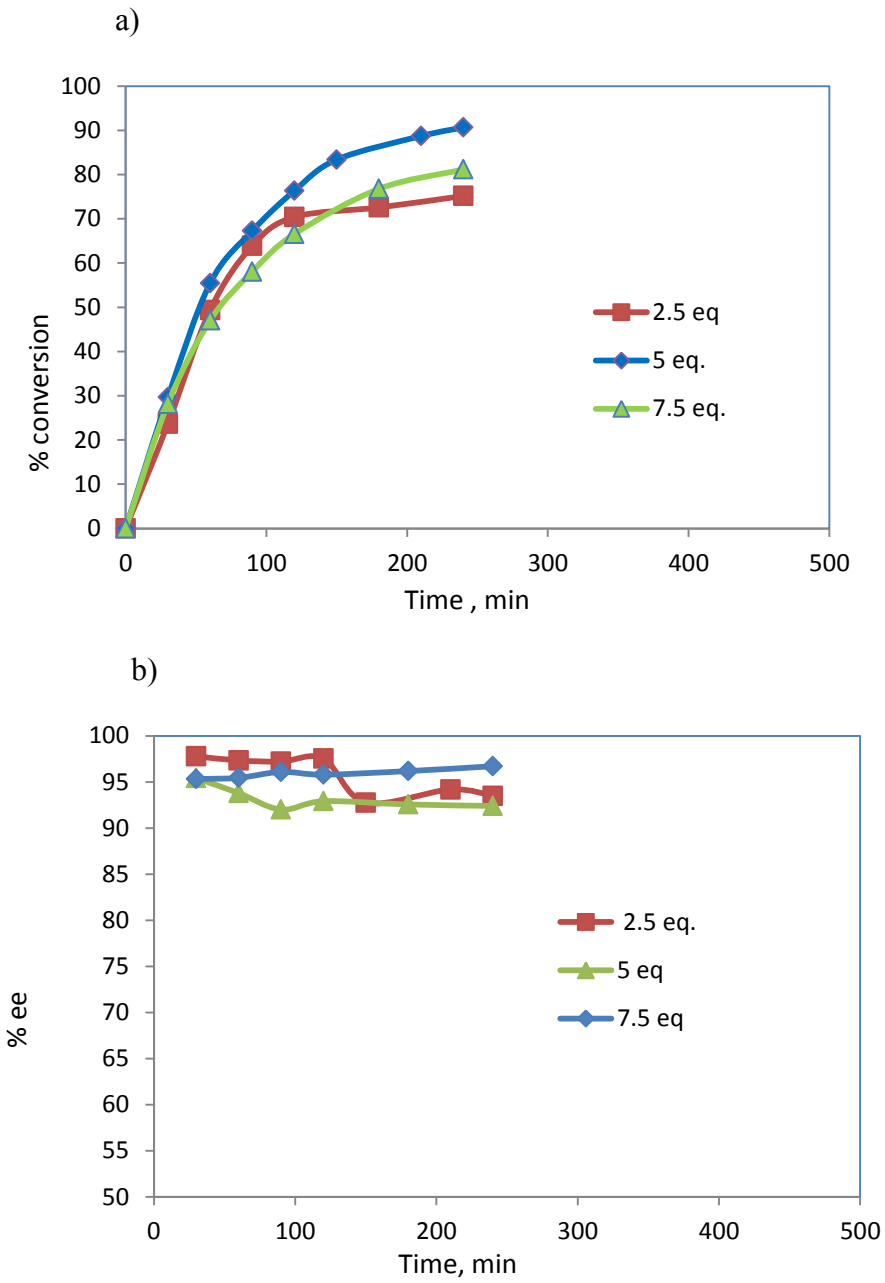


Fig 4.18: Effect Formic acid concentration on a) conversion b) ee

Reaction conditions: FA: TEA ratio (0.9:1); Temperature 25^0C; Initial pH, 8.5 $[Rh(Cp^*)Cl_2]_2$ 0.005 mmol, and ligand 9, 0.01 mmol, Acetophenone. 10mmol

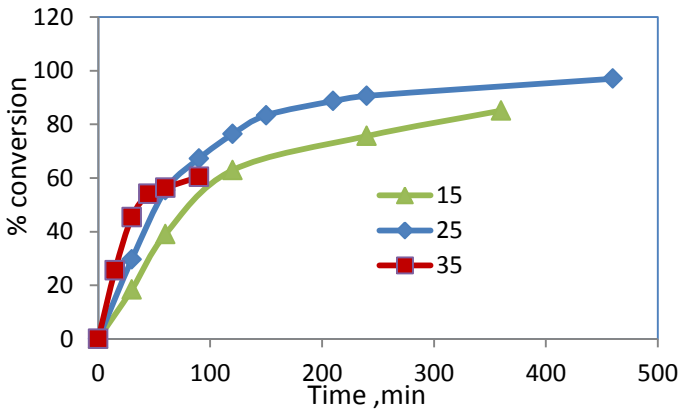
4.8.4 Effect of Temperature:

Effect of temperature on conversion and ee was studied in a temperatures range of 25^0 C to 35^0C by keeping other reaction conditions constant. The results are presented in Fig. 4.19. As observed in the earlier study at 2 ml level activity was good at and 25^oC

and ~90% conversion was observed in 4 h. However, at 35°C activity was high initially till 46% conversion took place in just 30 minutes. Afterwards reaching only to 60 % in 90 minutes and subsequently to 70 % in 240 minutes. This trend was found to be similar to the one obtained, in the earlier section with 2 ml reaction charge; where inconsistent but complete conversions were obtained. In the present case the trend was more evident and reaction almost stopped.

In the present case catalyst concentration is low and formic acid and acetophenone are 10 times higher. Thus as reaction progresses higher quantity of carbon dioxide is produced. As observed by Dimroth et al[20] and Ikaria[21] formation of carbon dioxide complex of Ru –hydride because of higher formic acid concentration and lower catalyst concentration could lead to significantly lower conversion.[20, 21].

a)



b)

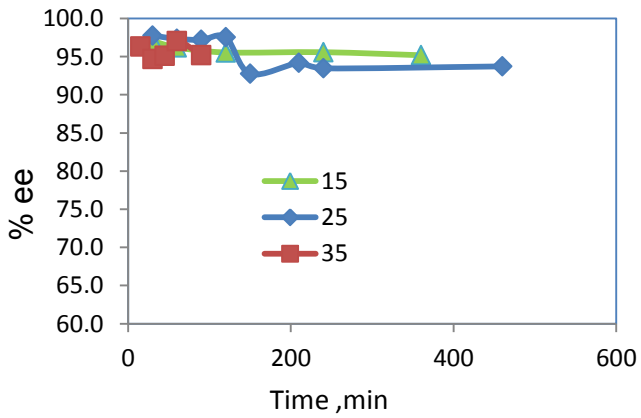


Fig 4.19: Effect of Temperature on a) conversion b) ee

Reaction conditions: FA: TEA ratio (0.9:1),10ml, Water 8.8 ml, Temperature ^{0}C Initial pH ,8.5;$[Rh(Cp^*)Cl_2]_2$ 0.005 mmol, and ligand 9 ,0.01 mmol, Acetophenone.(10 mmol)

4.9 Screening of ketones under optimized conditions:

ATH of ketones was carried out under the optimized conditions and the results are pesnted in Table 4.5. ATH of acetophenone gave 91 % conversion in 4 h with 94 % ee (Table 1, entry 1). For ketones with electron withdrawing groups in para position (*p*-chloro acetophenone and *p*-Bromo acetopheone), the activity was comparable (98% and 90% conversion in 5 h respectively Entry 2 and 3), however there was little drop in ee for both the compounds (92% and 91% respectively). Compounds having electron donating alkyl or alkoxy groups in para position, like isobutyl acetophenone or Methoxy acetophenone, the reductiosn were found to be on lower side (50% and 22% conversion in 5 h respectively). Similar trends were obtained for Rh-TsDPEN catalyst by Xiao –et al where 4-methoxy acetophenoen showed only 17% conversion at higher S/C ratio of 1000 in water and sodium formate.[11] Cyclic Ketones like indanone and tetarlone also showed less conversions (76% in 8h, entry 6) probably at this ratio, the indanone was not having complete solubilty(as obsrrved from reaction mixture). Howeve at S/C 500 very good convseriosn were obtained (97% in 2 h entry 7).Tetralolone showed 82 % conversion within 4 h (entry 8).

Table 4.5 ATH of ketones at S/C ratio 1000

Entry	Substrate	Time ,h	Conversion %	ee %
1	Acetophenone	4	91	94
2	P-chloro acetophenone	5	98	92
3	P-bromo acetophenone	5	90	91
4	4-Methoxy acetophenone	5	50	96
5	Isobutyl acetophenone	5	22	96
6	1-Indanone	8	76	92
7	1-indanone(S/C 500)	2	97	92
8	Tetralone	4	82	92

Reaction conditions: FA: TEA ratio (0.9:1), 10ml; Water, 9.4 ml; Temperature 25^0C Initial pH, 8.5; $[Rh(Cp^*)Cl_2]_2$ 0.005 mmol; ligand 9, 0.01 mmol; ketone 10mmol

4.10 Comparison with the benchmark ligands like TsDPEN and TsCYDN

Rh-ligand 9 complex was found to be highly active catalyst for ATH of ketones. TsDPEN and TsCYDN ligands are most investigated with Rh catalyst in the literature. After carrying out detailed investigations with Rh-ligand 9 catalyst, a comparison was carried out with these benchmark ligands using Rh catalyst and the results are presented below.

ATH of acetophenone was carried out by using FA: TEA mixture in equal volume of water at the reaction conditions used in the section 4.2.13 .

The experiments were carried out at S/C ratio of 100, with catalyst concentration of 0.005 mmol, ligand 0.01 mmol and acetophenone 1 mmol in 2ml of reaction mixture. The results are presented in Fig.4.20.

From the result it was found that all three complexes found to have comparable activity for ATH of ketones. The Reaction profile for all the three ligands is shown in Fig. 4.20. For all the ligands conversions within 25 min. were more than 95%, however for TsDPEN the ee were found to be better (97%) as compared to ligand 9 (94%) and TsCYDN (95%). However the difference in activity and ee was found to be very marginal under these conditions.

a) Conversion **b) ee**

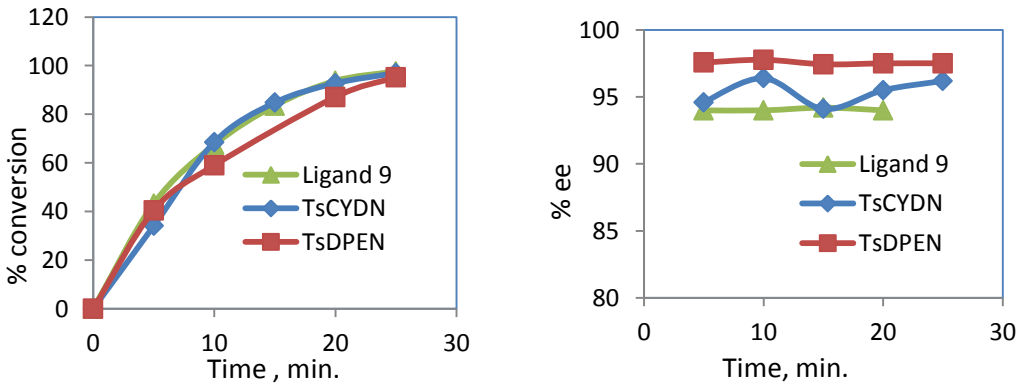


Fig 4.20: comparative data for ATH of acetophenone using ligand, 9 TsDPEN and TsCYDN with Rhodium

Reaction conditions: Catalyst: 0.5 x 10^{-5}mol; Ligand 1.05 x 10^{-5} mol Acetophenone: 1 x 10^{-3} mol; Water 0.88ml; FA: TEA mixture 1ml ,Temperature: 25^{0}C;

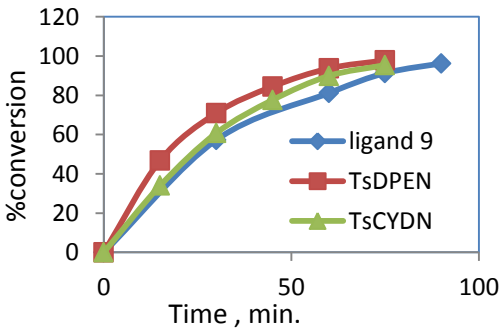
4.10.1 Comparison at higher S/C ratios

The comparison was made at higher Substrate to catalyst ratio of S/C 500 based on literature report and with FA:TEA mixture in equal volume of water as hydrogen

donor. The reaction was carried out using S/C ratio of 500 in 10 ml, with catalyst concentration of 0.005 mmol, and acetophenone concenatrion of 5 mmol. The formic acid ratio was kept constant using FA:TEA mixture 5 ml and 4.4 ml of water. The results are presented in Fig.4.21. From the results Rh-TsDPEN and Rh –TsCYDN showed equal conversions 96% and95 % in 75 minutes . However the conversion time diagram showed that, in 30 minutes 71% conversion were obtained for TsDPEN, afterwards the reaction becomes slower reaching conversions of 96% in 75 minutes. For Rh-TsCYDN, however initial conversion at 30 mins was 61%, and in 75 minutes 95% conversion was observed. The Rh ligand 9 catalyst showed slightly lower activity (in 30 minutes 55% conversion) was observed, and there after reaction followed similar path like TsDPEN, in 90 minutes reaching 95% conversion. This is clearly reflected in TOF, h^{-1} as shown in Fig 4.22 , where TOF at 30 mins for TsDPEN were highest at 698 compared to TsCYDN and ligand 9 (597 and 572 respectively). However it was found that the TOF at 75 mins were similar for TsDPEN and TsCYDN (at 384 and 376 respectively). TOF was slightly low for ligand 9 (321).

Th ee observed for Rh-TsDPEN were highest at 96%, followed by TsCYDN and ligand 9 at (95% and 94% respectively).

a) Conversion



b) ee

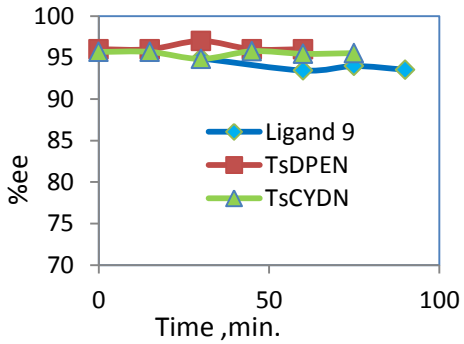


Fig 4.21: comparative data for ATH of acetophenone using TsDPEN, TsCYDN, and ligand 9 at S/C ratio of 500

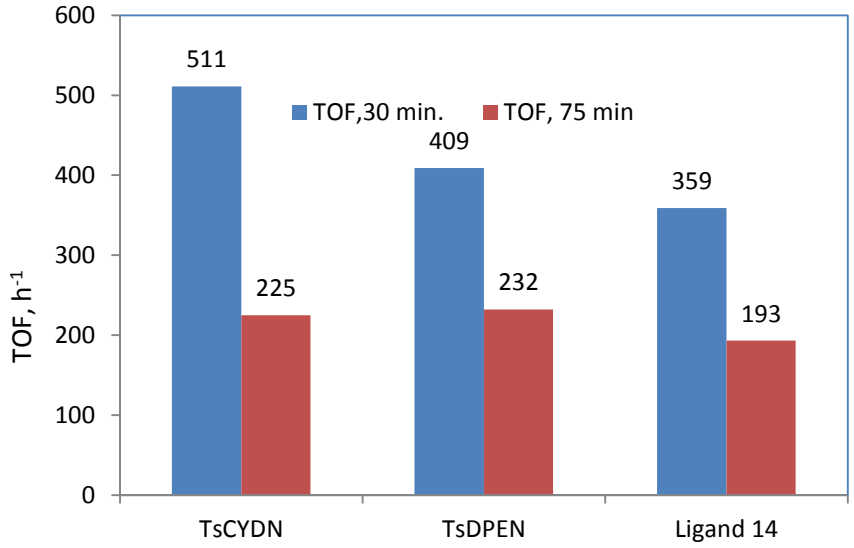


Fig 4.22: comparative data for ATH of acetophenone using TsDPEN, TsCYDN, and ligand 9 and (TOF, h^{-1})

Reaction conditions: FA: TEA ratio (0.9:1),5ml; Water, 4.4 ml; Temperature 25^0c Initial pH ,8.5$[Rh(Cp^*)Cl_2]_2$ 0.005 mmol, and ligand 9 ,0.01 mmol, Acetophenone (5mmol)

Thus in conclusion unsymmetrical tosylated diamine ligand 9 prepared in the present work was found to be comparable to the benchmark ligands. Activity was found to be marginally lower than TsDPEN ligand; however enantioselectivity was comparable to both the ligands.

4.11 ATH of Imines using 1, 2 Monotosylated Diamines

In 1996, Noyori applied[4] the Ru (II)-catalyzed asymmetric transfer hydrogenation protocol to the reduction of various imines in very efficient way. A preformed chiral Ru(II) complex, such as Ru-TsDPEN Catalysed the transfer hydrogenation of various cyclic and acylic imines with a FA:TEA mixture. Particularly effective substrates were dimethoxy dihydroisoquinoline derivatives which yielded tetrahydroisoquinolines with high conversions and ee[4].

The ATH process was conducted equally well in various aprotic solvents including DMF, DMSO and CH_2Cl_2. This catalytic method was found particularly useful for the enantioselective reduction of other 3,4-dihydroisoquinoline derivatives to corresponding amines with excellent ee. Shortly afterwards Baker et al.[24] reported the ATH of dimethoxy dihydroisoquinoline derivatives using chiral Rh Cp* complexes of TsDPEN and FA-TEA as the hydrogen donor. The reaction was fast and 95 % conversion was obtained in 10 min with 90 % ee, however, at a substrate: cat ratio of 1000 reaction proceeded slowly with a slight loss in enantioselectivity. The catalyst exhibited excellent enantioselectivity for ATH of a number of cyclic imines and cyclic sulfonimides. The research group of Blackmond[25] reported the detailed kinetic studies on the asymmetric transfer hydrogenation of imines with formic acid using Rh-TsDPEN catalysts. They discussed the role of bases like Et_3N in controlled release of formic acid into the catalytic cycle and showed that the rate behavior strongly depended on the reaction conditions, including the type of solvent and the method of addition of the hydrogen transfer agent. It was found that the reaction using controlled addition of formic acid gave high yields even at high substrate/catalyst ratio (S/C).Wills and co-workers used Ru(II) complexes of N'-alkylated TsDPEN derivatives, where Ru- benzene complexes of N-Alkylated TsDPEN ligands[26] gave a product with 85 % ee and 100 % conversion after a reaction time of 6h. . The N'-alkylated complexes in some cases gave reduction products of equal or improved ee, relative to the non-alkylated complexes in the reduction of certain cyclic imines.

Deng and coworkers reported the first asymmetric transfer hydrogenation of cyclic imines and iminiums in water by using sodium formic acid as the hydrogen source and CTAB as an additive catalyzed by a water-soluble and recyclable Ru- modified TsDPEN ligand complex[27].

The mechanism of the reduction of ketones was proposed by Noyori et al. [28-30]and supported by means of a theoretical study. In this case, both hydrogen atoms are transferred simultaneously and the transition state has the form of a six-membered cycle. For imines, this mechanism does not plausibly explain some of the observed phenomena, in particular the need for the imine to be either protonated or at least activated by a Lewis acid to undergo the reduction, and also the formation of the opposite configuration of the amine product. Theoretical study concerning the ATH of imines was recently carried out by Vaclavik et al., focusing on this CH interaction. The reaction coordinates for several different interactions were calculated and their stabilization effects were enumerated, supporting the hypothesis on the stabilizing effect of this interaction10.

Thus methods for the asymmetric transfer hydrogenation (ATH) of imines are still being intensively studied and developed. Of foremost interest is the use of Noyori's [Ru Cl (η6-arene)(N-TsDPEN)] complex in the presence of a hydrogen donor (i-, formic acid). These complexes have been extensively modified. The mechanism of the reaction needs to be explored to a great extent. From the literature reports it was observed that there are very few reports on ATH of imines.This se is restricted to the application of TsDPEN as ligand or the modification either in N-alkylation form, modifying the sulfonyl substitution, without really disturbing the C2 symmetric backbone. Even the other popular and successful ligand likeC2 symmetric TsCYDN ligands is not explored and tested in ATH of imines.There is only one report on ATH of imine by using unsymmetrical diamine as ligand. This report is also restricted to the use of Ru complexes as catalyst. The other transition metal complexes like Rh and Ir are totally unexplored (with unsymmetrical diamine) in the use of ATH of imines.

In this section ATH of imines has been investigated using transition metal complex and tosylated diamine ligand catalyst system.1, 2 Monotosylated diamine ligands synthesized in chapter 2 were used in combination with the transition metal complexes(Ru, Rh, Ir). Effect of reaction parameters, such substrate to catalyst ratio, temperature, catalyst concentration, on conversion and enantioselectivity was investigated using 1-ethyl -6, 7-dimethoxy-3, 4-dihydroisoquinoline as substrate and the results are presented. Based on the results best catalyst system was selected and various imines were screened finally the results of Ru-TsDPEN and Ru -Ligand 9 were compared.

4.11.1 Experimental section

4.11.1.1Materials:

Rhodium chloride trihydrate ($RhCl_3.3H2O$) and iridium chloride ($IrCl_3.xH2O$) were obtained from Arora-Matthey India., [Ru (p-cymene) Cl_2]2, TsDPEN, TsCYDN were procured from Sigma Aldrich India. Ethanol, 2-Propanol, KOH etc. were procured from the commercial sources (Loba Chemicals, India) and used as received.3, 4 dimethoxy Phenethylamine, acetyl chloride, propinoyl acid chloride, isopropyl acid chloride were procured from sigma Aldrich.. These materials were used as such.

4.11.1.2 Synthesis of imine derivatives

All imines were synthesized as per the modified literature procedure[31] presented in the Fig. 4.23. Total six cyclic imine derivatives were prepared. All imines were characterized by ^1H NMR, ^{13}C NMR analysis.

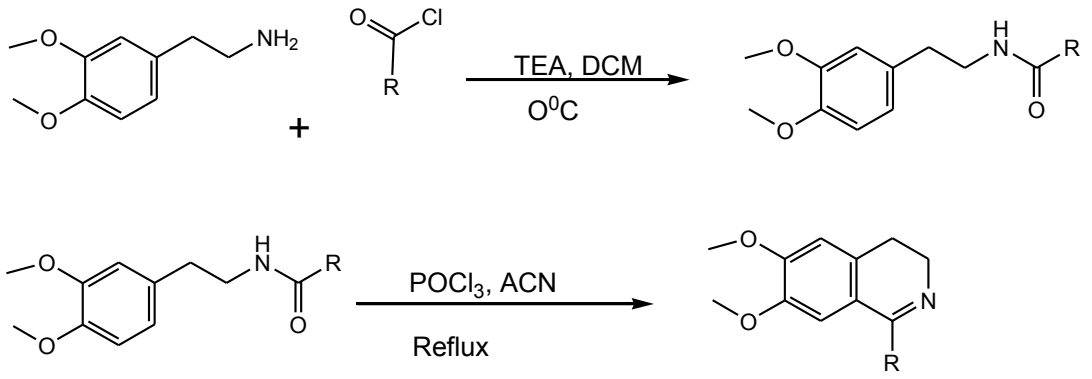


Fig. 4.23: Synthesis isoquinoline By Bischler–Napieralski procedure.

R= Methyl, ethyl, isopropyl, N-propyl, cyclohexyl, benzyl, and phenyl

4.11.2 Step 1: Synthesis of amide derivatives (general procedure)

Dichloromethane (50 ml) containing 20 mmol of 3, 4 –dimethoxyphenylethylamine, triethylamine (1.028 Equivalents) was added. This was followed by drop wise addition of alkyl/benzoyl chloride (1.045 Equivalents) at 0 °C. The reaction mixture was stirred at room temperature for 3 h reaction time.

The reaction mixture was washed with distilled water and separated into organic phase and aqueous phase. The aqueous phase was extracted twice with DCM, and the

organic phase thus separated was dried over sodium sulphate, filtered and concentrated under reduced pressure to obtain amide derivatives.

4.11.3 Synthesis of 1-alkyl/aryl -6, 7-dimethoxy-3, 4-dihydroisoquinoline

A solution of $POCl_3$ (2.7 mL, 28 mmol) in CH_3CN (5 mL) was added drop wise to a solution of the corresponding amide derivative (28 mmol) in CH_3CN (30 mL) under argon. The reaction mixture was heated under reflux for 2 h and concentrated to dryness. The crude material was dissolved in CH_2Cl_2 (30 mL) and washed with a saturated solution of $NaHCO_3$ (25 mL), NaOH (5%, 2x25 mL) and water. The organic layer was dried with $MgSO_4$ and concentrated under vacuum to obtain corresponding alkyl/aryl isoquinoline derivative. Using this procedure 7 dihydroisoquinoline derivatives were prepared.as show in the Fg4.24.

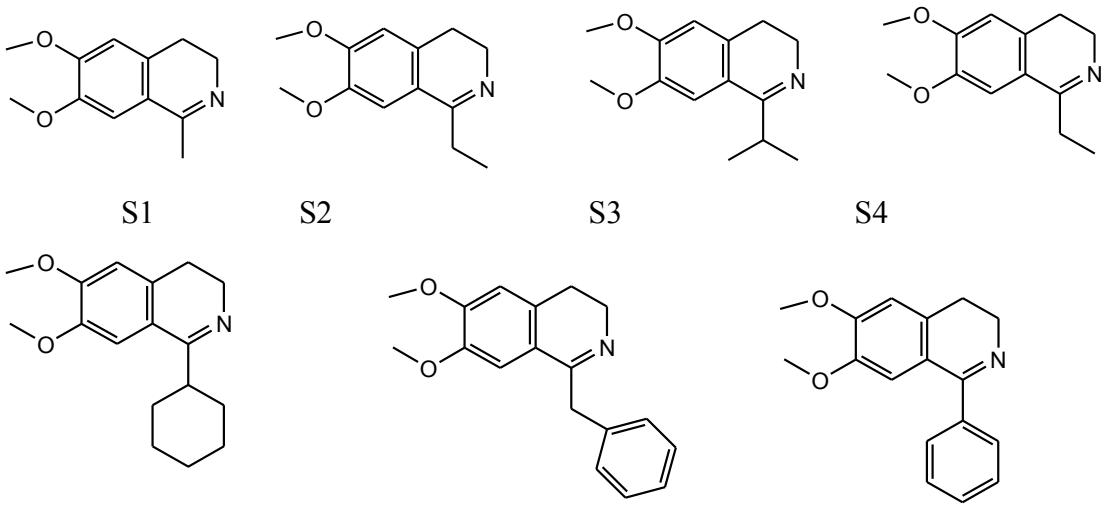


Fig 4.24 Various Imines synthesized using Bischler–Napieralski procedure

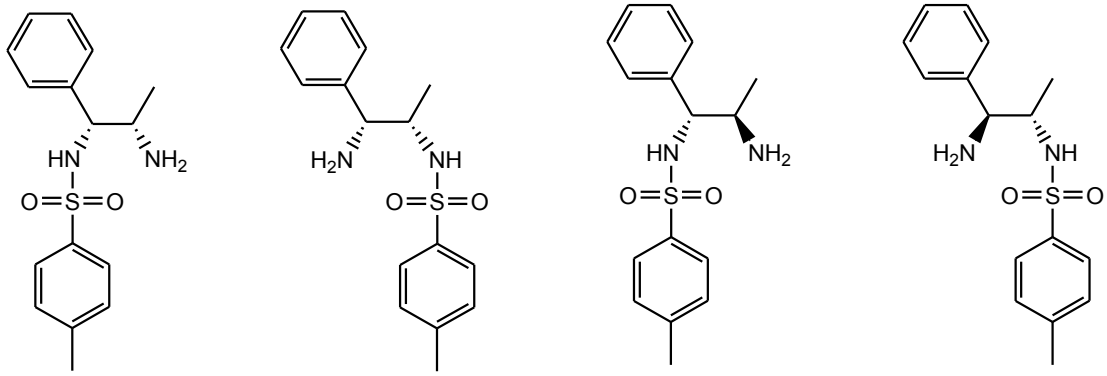
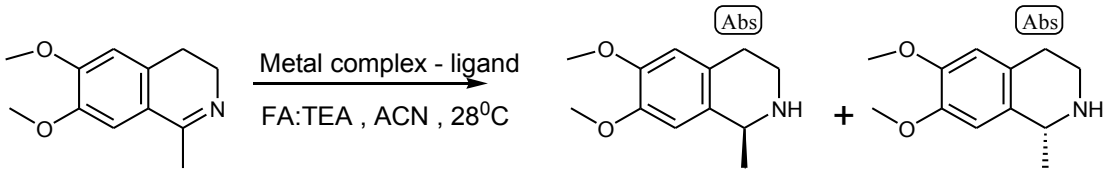


Fig.:4. 25 various monotosylated Diamines used in ATH of imines

4.11.3.1 **Experimental procedure**

Precatalyst solution was prepared by taking transition metal complex, ligand and triethylamine in 1 ml of reaction solvent. In atypical procedure ,$[RhCp^*Cl_2)]_2$, 3.09 mg (0.005 mmol), ligand 9, 3.04 mg (0.01mmol), and Imine 2 mmol, were added to the rector and the reaction was started. The reaction was carried out for desired time. Work-up of the reaction mixture was carried out by adding 0.5M Na_2CO_3 solution to the reaction mixture and then extracting with DCM. DCM layer was dried with sodium sulphate and concentrated to give amine product.

The reactions were conducted at a substrate/catalyst (S/C) molar ratio of 200:1 using a FA:TEA, 5:2 azeotrope as the hydrogen donor. Formation of amine product was confirmed by GC-MS analysis. Imine S1 was selected as the benchmark substrate and all the ligands synthesized 6 to 9 were screened using transition metal complexes of Ru, Rh, and Iridium with a FA:TEA (5:2) azeotropic mixture and acetonitrile as a solvent at 28 °C



S1

Fig.4.26: ATH of Imine using FA: TEA and Transition metal complexes

4.12 Results and Discussion:

ATH of imine, (substrate S1) was carried out using various diamine ligands synthesized and shown in Fig.4.25.The Ru, Rh, and Ir metal complexes were used as catalyst precursors and FA: TEA azeotropic mixture was used as hydrogen donor. The results are presented in Table 4.6. From the results it was observed that, each metal complex-ligand combination, showed different activity and ee, which is discussed separately in the following sections.

4.12.1 Ru complex with ligands .

Excellent activity was obtained for Ru -ligand 9 complex, in ATH of imines. Thus 99%, conversion and 93% enantioselectivity was observed in 1h. The results showed higher conversions when compared to the literature reports for ATH of S1 by Ru-TsDPEN[3], which took nearly 3 h for 99 % conversion and 95% ee. However when reaction using Ru-TsDPEN was carried out under identical conditions in our

laboratory, results obtained for Ru-Ligand 9 complex and Ru-TsDPEN were similar. This showed that Ru- Ligand 9 complex and Ru TsDPEN has comparable activity for ATH of imines using FA: TEA mixture.

For ligand 8, also very good conversion (94%, in 3h) was obtained with good enantioselectivity (80%). However, compared to ligand 9, there is significant drop in enentiolselctivyty. However as it was observed in case of ATH of ketones described in chapter 3.10 , the change in regio position of amine and sulfonamide group did not alter the ee. With Rh-ligand 8 complex and Rh-ligand 9 complex. This difference in behavior of ketones and imines can be due to higher activity of imines compared to ketones as mentioned by Noyori .[3]

Ligand 6 (entry 1) showed very little conversion (32% in 6h), the enantioselectivity observed was also very less (<10%). For ligand 7, similar results were found as far the activity was concerned (29% in 6h),> however enantioselectivity observed was more compared to ligand 6(47%, compared to 10%).As observed already in section ligand 6 and 7 have cis geometry of amine and sulfonamide groups, have lower activity in ATH of ketones. The low activity of cis TsDPEN ligand is well observed in literature by wills et al.[8], for ATH of ketones. In ATH of imines, there were no literature reports describing the importance of anti-substitution of amine and sulfonamide groups. The other difference in both the structures of the in ligand 6 and ligand 7 was the position of amine and sulfonamide group, which is probably the reason for difference in ee. However, tendency for increase in ee is not straight forward.

4.12.2 Rhodium complex with ligands:

The ATH of imines was carried out with $[Rh(Cp^*)Cl_2]_2$ and the ligands 6-9, it was found that , for ligand 6 it took 2hours for 63% conversion and the ee observed was poor (28%). For ligand 7 though conversion reached nearly 99% in 4.5 h. only 8 % ee was observed. For ligand 8 and 9, where geometry of amine and sulfonamide ligand is Trans, excellent and very fast conversions were obtained (97% in 15 min, and 99%in 10 min). However the ee recorded were average at about (50% and 61%). The conversion shown by ligand are similar to those obtained by Rh-TsDPEN complex[24], but enantioselectivities were lower by 30%. Comparing the ligand 8 and 9, again it was found that activities and ee for ligand 9 were slightly better than ligand 8, where amine group is attached to the carbon bearing phenyl group. This observation was

found to be same for Ru and Rhodium complexes of the ligands under investigation for ATH of imines.

Rhodium-TsDPEN under FA:TEA conditions are nearly inactive for ATH of ketones but showed better activity than corresponding Ru-TsDPEN in ATH of alpha substituted ketones. This contrasting behavior of Ru –TsDPEN and Rh –TsDPEN is well explained in the literature.[17, 18] But Blacker[24] showed that ATH of Imine using Rhodium complex and FA: TEA mixture ATH of imine was completed within 10 mins and very good enantioselectivity results. For Rh-ligand 9 complex nearly six fold increase in activity over Ru-Ligand 9 complex is obtained.

4.12.3 Iridium complex with ligands:

Compared to Ru and Rh, Iridium complex $[Ir (Cp^*) Cl2]_2$ are less active and less explored in ATH of ketones and imines. The screening monosulfonated diamine ligands were done and results are presented in Table 4.6.

For ligands, 6 to 9, the similar trend was observed with Ru, and Rh complexes were similar. i.e. with ligand 6 and ligand 7 very little conversions were observed (30% in 6h, 10% in 3h) respectively. Complete conversion was obtained with ligand 8however the time taken was higher (4h, >99 %,) for ligand 9 conversion was fast (99%, in 1h), and were to the similar obtained with Ru complex. However the trend in eneatioseltivity was much different than reported either for Ruthenium or rhodium complex. Iridium complexes of Ligand 6 and ligand 8, where sulfonamide group is attached to the carbon bearing phenyl group showed better enantioselectivity for Iridium complexes than that of Ligand 7 and 9.(contrast to the Ru and Rh complex with ligand 6-9).

Table 4.6. ATH of imines using Transition metal complexes.-and unsymmetrical vicinal monosulfonated diamine with FA-TEA

Ligand Number	$[RuCl_2(p\text{-cymene})]_2$			$[Rh(Cp^*)Cl_2]_2$			$[Ir(Cp^*)Cl_2]_2$		
	Time, h	Conv %	Ee %	Time, h	Conv %	Ee %	Time, h.	Conv %	ee %
6	6	32	<10	2	63	28	6	30	56
7	6	29	47	4.5	>99	8	3	<10	21
8	3	94	80	0.25	97	50	4	>99	57
9	**1**	**99**	**93**	**0.17**	**99**	**61**	**1**	**>99**	**21**

Reaction conditions: Metal complex,0.0025 mmol; Lig 9: 0.0050 mmol; TEA, 0.012mmol, 1.212mg, 2µ lit; Substrate, 1 mmol, 205mg; FA-TEA 5:2 -0.5ml; MeCN, 4.5 ml; Temp. 28°C

Thus unsymmetrical monotosylated vicinal diamine synthesized in chapter 2 proved to be active ligands in ATH of Imine using transition Metal complexes, as well. In particular Ru-ligand9complex, showed excellent activity and enantioselectivity for ATH of S1. The results found to be comparable with the benchmark ligand Ru - TsDPEN complex[4]. The Rh-ligand 9 complex also showed very high activity comparable with literature values, but enantioselectivity found (61%)compared[24] to the reported value of (92%) was less.

In order to expand the scope of ATH of imines, various imine substrates, which were synthesized, were screened for ATH, using Ru-ligand 9 complex.

4.13 Screening of various Substrates, cyclic imines for ATH using Ru - Ligand 9 complex

Various imines were screened for ATH reaction and the results are presented in Table 4.7. From the results it was found that, steric bulk on the carbon of imine has greater influence on activity as well as enantioselectivity. For imine S1, S2, and S3, conversions reached 99% within 1 hour. However, there was drop in enantioselectivity from 93% for methyl to 89 % for n-propyl. For linear alky groups like methyl, ethyl and n-propyl the difference was found to be marginal. With the alkyl groups like isopropyl and cyclohexyl, the conversions were slow (90% in 6h for S4, and 96% in 3.5 h for S5). The enantioselectivities in these cases was 89 %. For benzyl derivative as the steric bulk dropped, reaction was completed within 1h (99%),

with little lower enantioselectivity (91 %). In case of substrate with phenyl group (S7) reaction was not observed at all. As mentioned by Baker et al[24] it could interfere with catalyst binding. Another reason could be the imine double bond being in conjugation with the phenyl ring.

Table 4.7. ATH of imines using Ru-ligand 9 catalyst with FA-TEA

Sr. No.	Imines	Substrate Number	Time (h)	Conv (%)	ee (%)	Config.
1	**6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline**	**S1**	**1**	**99**	**93**	**R**
2	**1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline**	**S2**	**1**	**99**	**87**	**R**
3	**6,7-dimethoxy-1-propyl-3,4-dihydroisoquinoline**	**S3**	**1**	**99**	**89**	**R**
4	**1-isopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline**	**S4**	**6**	**90**	**89**	**R**
5	**1-cyclohexyl-6,7-dimethoxy-3,4 dihydroisoquinoline**	**S5**	**3.5**	**96**	**89**	**R**
6	**1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline**	**S6**	**1**	**99**	**91**	**R**
7	**6,7-dimethoxy-1-phenyl-3,4-dihydroisoquinoline**	**S7**		**No reaction**		

Reaction conditions: $[Ru(p\text{-cymene})Cl_2]_2$,0.0025 mmol;1.53mg; Lig 9,0.0050 mmol; 1.53 mg; TEA: 0.012 mmol, 1.212 mg, 2 µ lit; Substrate, 1 mmol; FA-TEA 5:2 -0.5 ml; MeCN: 5 ml; Temp. 28°C

It may be noted that the Ru-Ligand 9 complex exhibited excellent enaoselectivity, for all cyclic imines screened. Enantioselectivity of the reaction decreased with increase

in the steric bulk of the alkyl R group on the imino carbon as observed with the substrates S1 to S4. Thus this catalytic method is particularly useful for the enantioselective reduction of cyclic imines to amines with an ee value ranging from 87 % to 92 %.

4.14 **Optimisation of reaction parameters**

Based on the results obtained in earlier section for ATH of imines, the ligand 9 and [Ru(*p*-cymene)Cl_2]$_2$ complex was selected for optimization studies. The substrate selected was 1-Ethyl l-6, 7-dimethoxy-3, 4-dihydroisoquinoline. The methyl derivative was deliberately ignored as very recently, parametric study using methyl derivative was reported in the literature.[32] Effect of various reaction conditions like solvent, temperature, catalyst/ligand ratio, substrate:catalyst ratio, FA:substrate ratio on ATH of 1-ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline was investigated using Ru--Ligand 9 catalyst. The results are presented below.

4.14.1 Solvent Screening for ATH of 1-Ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline

Various polar protic and aprotic solvents were screened for ATH of 1-Ethyl l-6, 7-dimethoxy-3, 4-dihydroisoquinoline. The results are presented in Table 4.8. It was observed that complete conversion of imine (S2) took place in 1 h with methanol, DMF, DMSO and acetonitrile as solvents, with enantioselectivity ranging from 84 % to 87%. In chloroform, acetone and DCM moderate conversion (70 to 80% in 1 h) was observed with ee in a range of 83 to 85 %. Blackmond[25] also observed in their work on ATH of imines that with methanol conversion was highest with Rh-TsDPEN catalyst. This could be due the difference in dissociation of formic acid ions in different solvents based on their dielectric constant. Acetonitrile gave high enantioselectivity of 87% and hence was selected for further study.

Table 4.8: Solvent Screening for ATH of 1-Ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline

Sr. No.	Solvent	Time(h)	Conv (%)	Ee (%)
1	Methanol	1	98	84
2	Acetonitrile	1	98	87
3	DMF	1	98	85
4	DMSO	1	98	85
4	Chloroform	1	80	83
5	Acetone	1	70	84
6	DCM	1	79	85

Reaction conditions: [Ru (*p*-cymene) $Cl_2]_2$ (0.0025 mmol, 1.53 mg); Lig 9 (0.005 mmol, 1.55 mg); TEA (0.012 mmol, 1.212 mg, 2µ lit), Substrate (1 mmol, 219mg); FA-TEA 5:2 (0.5 ml); MeCN (4.5 ml); Temp. 28°C.

4.14.2 Effect of Ru/Ligand ratio

Effect of Ru: Ligand 9 ratio was investigated in a range of 1:1 to 1:2 by keeping all other conditions, constant. The results are presented in Table 4.9. From the results it can be clearly seen that conversion as well as enantioselectivity was not significantly affected in the range of conditions investigated. Thus conversion in a range of 94 to 96 % was observed with ee in a range of 86 to 87%. Monosulfonated diamine ligands, unlike amino alcohol ligands are strongly coordinating ligands and their stable crystalline complexes with 1:1 ratio of transition metals have been isolated and characterized in literature[24, 33-41] as well as described in the earlier section 3.12.1 of the chapter 3. Thus for further experiments catalyst: ligand ratio was kept constant at 1:1.

Table 4.9: Effect of Ru/Ligand ratio on ATH of 1-ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline

Sr. No.	Cat/Ligand Ratio	Conversion (%)	Enantiomeric Excess (%)
1	1:1	94	86
2	1:1.5	96	87
3	1:2	96	87

Reaction conditions: [Ru (*p*-cymene)Cl_2]$_2$ (0.0025 mmol, 1.53 mg); TEA (0.012 mmol, 1.212 mg, 2µ lit); Substrate, (1 mmol, 219mg); FA-TEA 5:2 (0.5 ml); MeCN (4.5 ml), Temp. 28°C.

4.14.3 Effect of Substrate/Catalyst ratio:

The effect of S/C ratio was investigated in a range of 100 to 300 by changing the imine concentration (0.005 mmol, 1.0 mmol and 1.5 mmol) and keeping other conditions constant. In these experiments formic acid: substrate ratio of was kept constant to make sure that formic acid concentration should not be limiting factor for activity at higher substrate concentration .The results are presented in Table 4.10 and Fig. 4.27 (conv vs time and ee vs time), Fig 4.28 (amine formed, mmol vs conversion) and Fig. 4.29 (TON and TOF at 30 min). From the results it can be seen that with increase in substrate concentration conversion decreased. For example at S/C ratio of 100 within 20 mins 74 % conversion was reached, while at S/C ratio of 200, 61 % conversion was achieved. Further increase in substrate ratio to 300, conversions dropped down to 49 % in 20 mins. At higher S/C ratio of 300 conversions could reach only 87% after 120 mins.

The enantioselectivity was not affected by a change in S/C ratio and remained constant at 86%. From the graph of product formed vs time, the product formed is higher at a higher substrate: catalyst ratio, though conversion is low. Thus at S/C 300 ratio even though conversion is 87% actual moles of product formed is (0.26) which is much higher than at S/C 100 and s/C 200(which is 0.093 and 0.196 respectively).

At S/C ratio of 300 TOF estimated at 30 min was slightly lower than that observed at S/C ratio of 200 indicating that activity is not dependent on substrate concentration. The detailed analysis of TOF,$h^{-1}$and TON showed that at higher ratios of S/C 300 the TOF, h^{-1}observed was slightly lower than at S/C200 ,(301 vs 292 respectively). This probably indicates the substrate inhibition at higher concentration.

Table 4.10: Effect of substrate: catalyst ratio on ATH of 1-ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline

Sr. No.	S/C Ratio	Time in h	Conversion (%)	Enantiomeric Excess (%)
1	100	0.75	96	87
2	200	1	96	86
3	300	2	87	86

Reaction conditions: [Ru (*p*-cymene)Cl_2]$_2$ (0.0025 mmol, 1.53 mg), Lig 9 (0.0050mmol, 1.75 mg), TEA (0.012 mmol, 1.212 mg, 2µ lit), FA-TEA 5:2 (0.5 ml), MeCN (4.5 ml), Temp. 28°C.

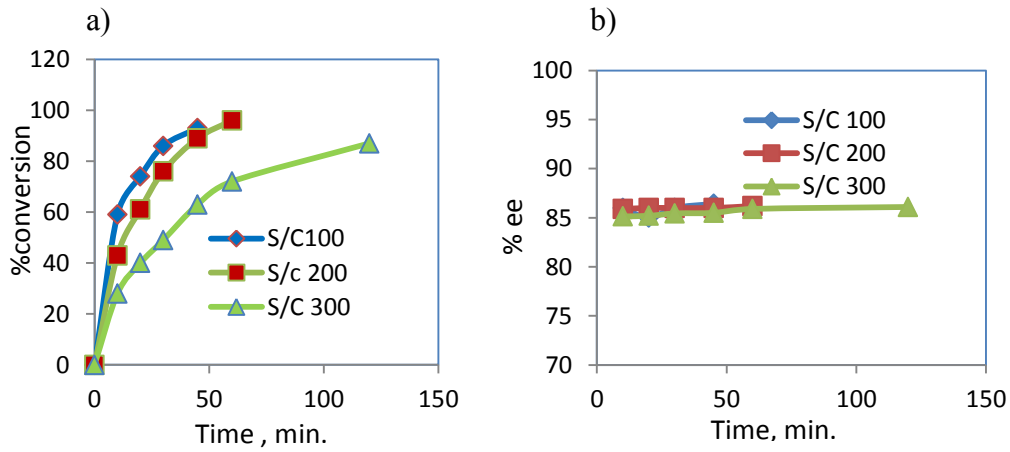


Fig.4.27 effect of substrate concentration on ATH of Imine a) conversion b) ee

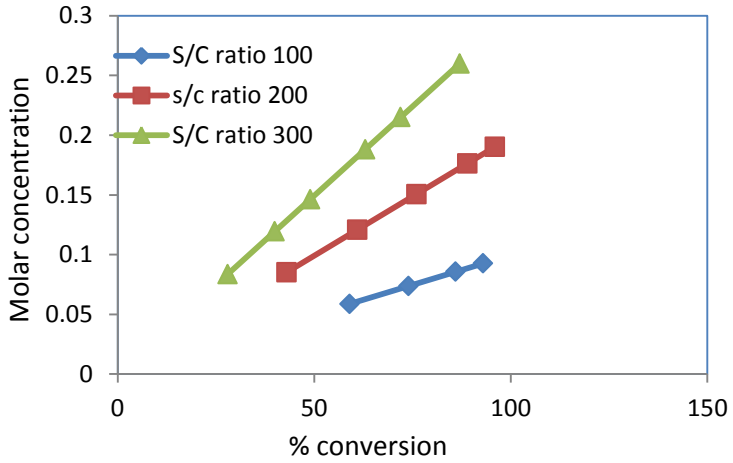


Fig.4.28 Graph of Molar concentration of Product Vs product conversion in%

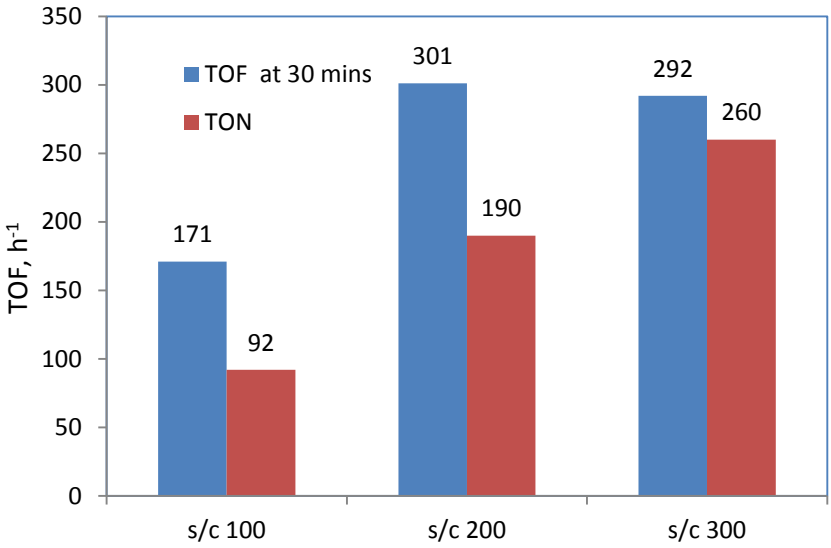


Fig.4.29 Graph of substrate concentration vs TOF,h^{-1} and TON

Reaction conditions: [Ru (*p*-cymene) Cl2]$_2$ (0.0025 mmol, 1.53 mg); Ligand 9 (0.0050mmol, 1.75 mg); TEA (0.012 mmol, 1.212 mg, 2µ lit); FA-TEA 5:2 (0.5 ml), MeCN (4.5 ml), Temp. 28°C.

4.14.4 Effect of temperature

Effect of temperature on ATH on 1-ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline was investigated in a temperature range of 18-38^{o}C. Substrate concentration was kept constant at 1 mmol, and catalyst concentration was kept at 0.0025mmol. The results are presented in Table 4.8 and in Fig.4.30. As expected conversion of S2 increased with increase in temperature. Thus at 38^{0}C 95 % conversion was observed within 30 min while at 18^{0}C however only 53% conversion was obtained at 30 mins. However ee was found to decrease considerably from 89 % at 18^{o}C to 84 % at 38^{o}C.

Anomalies observed in temperature effect for ATH of ketones with Rh-ligand 9 complex catalyst (Chapter 3, section 3.12.5 and 4.8.4) were not observed in case of imine. The probable reason could be loss of carbon dioxide in the acidic FA:TEA system used as hydrogen donor and absence of any assisting media like alcohol or water for carbon dioxide insertion in Ru-hydride complex[20]. Another reason also could be the use of different transition metal complex (Rh-ligand 9 complex) in case of ketones.

Table 4.11: Effect of temperature on ATH of 1-ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline

Sr. No.	Temperature	Time in h	Conversion (%)	Enantiomeric Excess (%)
1	18	2	90	89
2	28	1	96	86
3	38	0.5	95	84

Reaction conditions: [Ru (*p*-cymene)Cl_2]$_2$ (0.0025 mmol, 1.53 mg), TEA (0.012 mmol, 1.212 mg, 2µ lit), Substrate (1 mmol, 219mg), FA-TEA 5:2 (0.5 ml), MeCN (4.5 ml), Temp. 28°C.

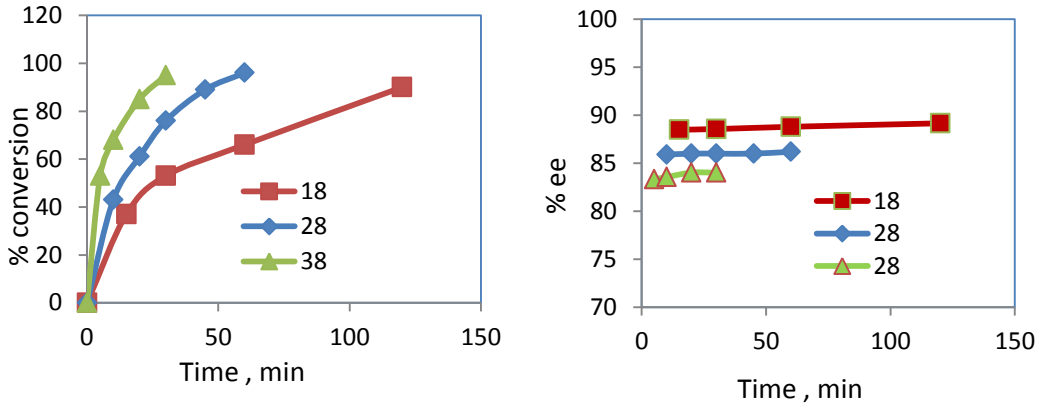


Fig.4.30: Effect of temperature on ATH of 1-ethyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline

Reaction conditions: [Ru (*p*-cymene) Cl_2]$_2$ (0.0025 mmol, 1.53 mg), TEA (0.012 mmol, 1.212 mg, 2µ lit), Substrate (1 mmol, 219mg), FA-TEA 5:2 (0.5 ml), MeCN (4.5 ml), Temp. °C

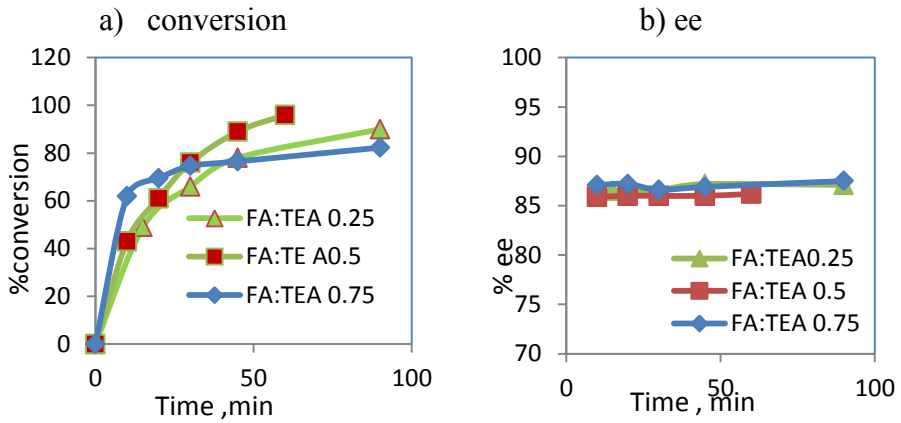


Fig.4.31 Effect of volume of FA: TEA mixture on a) conversion b) ee

Reaction conditions: [Ru (*p*-cymene) Cl_2]$_2$ (0.0025 mmol, 1.53 mg), TEA (0.012 mmol, 1.212 mg, 2µ lit), Substrate (1 mmol, 219mg), FA-TEA 5:2 (0.5 ml), MeCN (4.5 ml), Temp. °C

4.14.5 Effect of volume of FA: TEA mixture

Effect of formic acid concentration was studied by changing the volume of FA:TEA mixture used as hydrogen donor in the reaction. All other conditions like catalyst concentration, substrate concentration, Temperature were kept constant (Fig. 4.31). From the results it was found that at 0.5 ml of FA: TEA mixture, 43% conversion was obtained within10 min, and 61% conversion was obtained in 20 min. With decrease in volume of FA:TEA, to 0.25, initial conversion was 62 % in 10 minutes, however in next 10 minutes, only 9 % increase in conversion was found. This could be due to formic acid source getting exhausted. After 20 mins reaction became sluggish and only 82.5% conversion was obtained in 90 mins. The reason for higher conversions at lower volume of FA:TEA is observed by. Pechác̆ek et al[40].This could be due to lower volume of FA:TEA and can be based on solvation and dissociation[22, 23] ,as lower concentration formic acid resulting in more dissociation. At higher volume of 0.75 ml of FA: TEA however, 20 minutes conversions were lower at 61 %.the conversions increased consistently and 90% conversion was achieved in 90 minutes.

J. Pechác̆ek et al. suggested that under strongly acidic conditions the chiral diamine ligand becomes protonated and subsequently decoordinates from the Ru atom, which would lead to a loss of catalytic activity[5] . The other hypothesis states that in a large excess of the hydrogenation mixture, the protonated triethylamine is in a large excess over the protonated substrate. The triethylammonium cation is believed to be able to

create a hydrogen bond with the sulfonyl group of the ligand, by means of which it stericaly hinders the active site of the catalytic complex and prevents the substrate from reaching the active site. The reaction would then be limited by the amount of free active sites. A theoretical calculation of such structure was performed and the stabilization caused by this bond was calculated. Thus it was observed that FA: TEA ratio of 5:2 in 0.5 ml quantity is optimum.

4.15 Conclusions:

ATH of acetophenone was investigated in detail using Rh, Ru and Ir-ligand 9 complex catalysts and FA:TEA, mixture with equal volume of water. ATH of ketones is a pH dependent process and optimum conditions were developed by varying FA:TEA ratio in water, which helps to ionize formic acid. Rh-ligand 9 catalyst was found to be excellent for ATH of acetophenone. Important points of the work are as follows:

- Ruthenium and Rhodium complexes of ligand 9 showed good activity and enantioselectivity in ATH of acetophenone, which was strongly dependent on pH in the range of 4 to 10.
- Ru-Ligand 9 complex showed very good conversion and enentiolselctivyty (93 % conv, and 93% ee, maximum TOF, h^{-1}, 30) in the pH range of 4.5 to 6.5
- The activity for Ru-Ligand 9 complex was constant till pH 7.5, however drastic erosion in enantiosectivity was observed above pH 6.5, (93% to 75%).
- Rh-ligand 9 complex showed very good activity and enantiosectivity in ATH of acetophenone in the pH range of 6.5 to 8.5. The Trend was similar for Rh-TsDPEN, as reported by Xiao et al.[11] and at pH of 8.5, 95 % conversion of acetophenone with 94 % ee was obtained within 25 min with a TOF, h^{-1} of 197. Beyond pH 8.5 activity and enantioselectivity decreased for Rh catalyst.
- Iridium complex showed very low activity. Highest activity was obtained at pH 8.5 (98% conversion with 91% ee in 12 h)
- Optimization was carried out using Rh-ligand 9 catalyst with 20 ml reaction volume. With this reaction could be easily carried out with a S/C ratio of 1000 to 1200 (substrate concentration 0.2 M to 0.6 M) and TOF, h^{-1} of 545 and TON up to 1038 was achieved.
- Optimum results were obtained at a temperature of 25^{o}C. With increase in temperature activity decreased and at 40^{o}C poor activity was observed. Carbon

dioxide formed during the reaction inhibits the reaction probably by complexation with the catalyst.

- As per the mechanism reported in the literature[19]difference in diastereotopic transition states involving hydrogen bonding of water molecule with metal complex, Rh-TsDPEN is having more difference in energy (3.9 kcal/mol) compared to Ru TsDPEN complex(2.1 kcal /mol), hence Rh-TsDPEN in water is more active catalyst than Ru-TsDPEN. The result for Rh-Ligand 9 complex was found to be consistent with this observation.
- This is the first example on ATH of ketones with Rh-unsymmetrical vicinal diamine complex catalyst using FA: TEA in water as hydrogen donor.

ATH of imines was investigated using transition metal complexes of Ru, Rh, and Ir and unsymmetrical vicinal dimaines synthesized with azeotropic mixture of FA:TEA as hydrogen donor. This is first example on ATH of imines using unsymmetrical diamines and transition metal complex (Ru, Rh and Ir) catalysts. Important observations are as follows:

- Ru-ligand 9 complex showed excellent conversions and enantioselectivity (99 % and 93 % ee) within 1 h, and various cyclic imines were screened and shown to have excellent conversions (90 to 99 %) and enantioselectivity (87 % to 93 %).
- Activity was comparable with Ru-TsDPEN reported in literature, however, enantioselectivity was marginally, low (93% for ligand 9 vs 95 % for TsDPEN).
- The Rhodium-Ligand 9 showed excellent conversions (99% in 10 mins), however enenatiselctivity obtained was, lower (61%).
- Activity of Ru-ligand 9(99% in 1h and 93%ee) catalyst was comparable to the benchmark catalyst Ru-TsDPEN (99% in 1h and 95%ee)

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Appendix.

1. **GC method used for conversion of imines.**

Injector (split) Temperature	250ºC
Flame ionization detector	Temperature: 250ºC
	Hydrogen: 35.0ml/min
	Zero Air: 320.0ml/min
Split ratio for Injector	50:1
Column Temperature	160^0C isothermal
Column	HP-5 (5% Phenyl Methyl Siloxane)
Column Pressure	12 Psi

The enantiomeric excess of all the chiral amines were determined on HPLC chiral columns. For this, racemic amines were obtained by reductions of all the imines with NaBH4 using standard procedure. The methods were developed on HPLC using these alcohols such that two distinct peaks of both the isomers are obtained with 50% (equal) areas. The conditions for HPLC to get chiral separation along with retention times of isomers of particular amine are given below.

2. Analysis conditions for HPLC for estimation of Enantiomeric excess

1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

(Chiracel, OD-H, hexane: isopropanol: diethylamine = 90: 10: 0.1, 1.0 mL/min, 254 nm, t_R (S) 10.86 min, t_R (R) = 14.00 min)

1-ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

(Chiralcel, OD-H, hexane: isopropanol: diethylamine = 90: 10: 0.1, 1.0 mL/min, 270 nm, t_R (S) 8.83 min, t_R (R) = 11 min)

1-propyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

(Chiralcel, OD-H, hexane: isopropanol: diethylamine = 90: 10: 0.1, 1.0 mL/min, 254 nm, t_R (S) 9.85min, t_R (R) = 11.85 min)

1-isopropyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

(Chiralcel, OD-H, hexane: isopropanol: diethylamine = 90: 10: 0.1, 1.0 mL/min, 280 nm, t_R (S) 6.54 min, t_R (R) = 7.36 min)

1-cyclohexyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

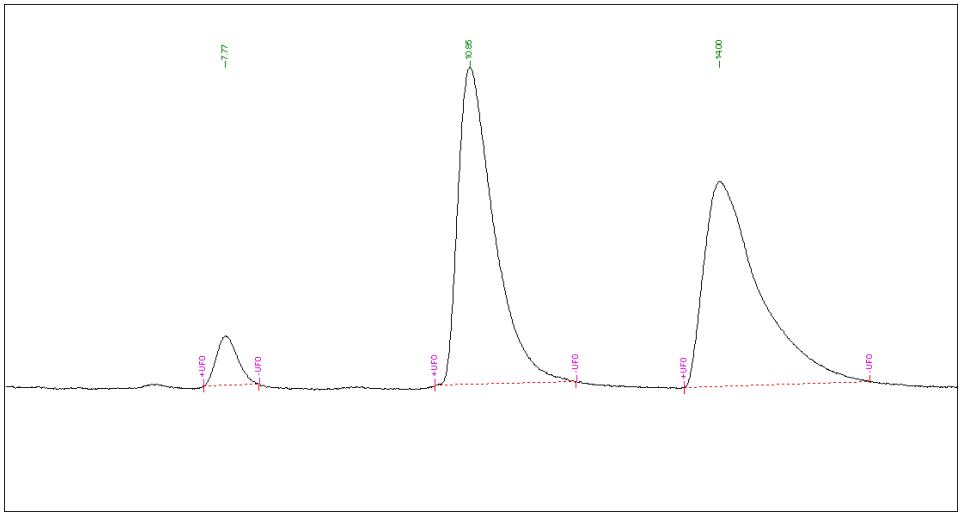
(Chiralcel, OD-H, hexane: isopropanol: diethylamine = 90: 10: 0.1, 0.5 mL/min, 274 nm, t_R (S) 7.05min, t_R (R) = 8.41 min)

1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

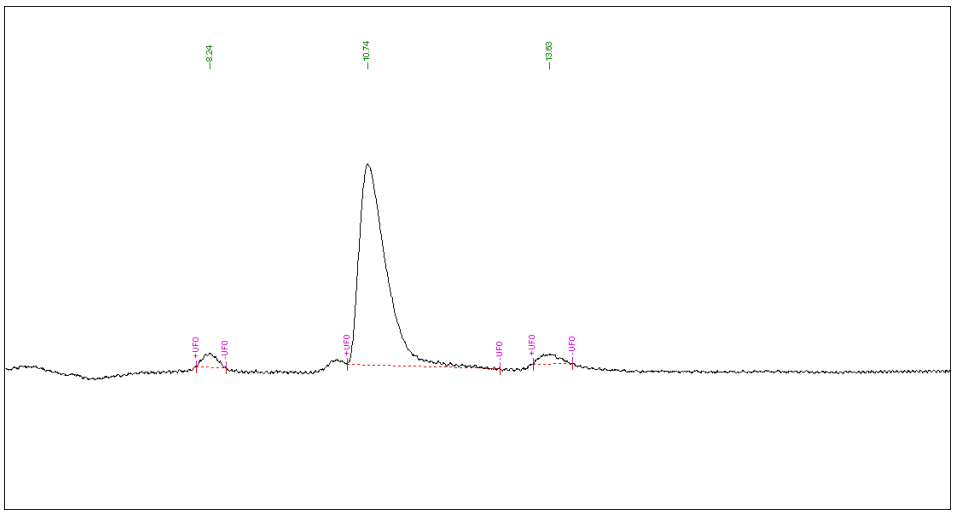
(Chiralcel, OD-H, hexane: isopropanol: diethylamine = 90: 10: 0.1, 0.5 mL/min, 290 nm, t_R (S) 13 min, t_R (R) = 19 min)

1-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline

(Chiralcel, OD-H, hexane: isopropanol: diethylamine = 80: 20: 0.1, 0.5 mL/min, 290 nm, t_R (S) 17.48 min, t_R (R) = 20.85 min)



HPLC chromatogram of Racemic 1-Methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydroisoquinoline



HPLC chromatogram of ATH of 1-Methyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline (1a)

Publication and Symposia.

1. Catalytic asymmetric transfer hydrogenation of ketones using $[RuCl_{2(}$p-cymene $)_2]_2$with chiral amino alcohol ligands
   S. H. Deshpande, A. A. Kelkar, R. G. Gonnade, S. K. Shingote, R. V. Chaudhari, Catal Lett (2010) 138:231–238

2. Catalyst for ATH of ketones and imines
   A.A.Kelkar, S.H.Deshpande, S.K. shingote, Vaishali Shende
   Provisional Indian Patent Appl. No. 3240/DEL/2013, Date: 11/01/2013

3. Rhodium and unsymmetrical monotosylated diamine, excellent catalyst for ATH of ketones in aqueous and organic media
   S.H.Deshpande, Vaishali Shende, S.K.Shingote, A.A.Kelkar
   To be communicated to Advanced Synthesis and Catalysis

4. Effect of pH variation on ATH of ketones using Rh-and unsymmetrical monotosylated diamine
   S.H.Deshpande, Vaishali Shende, S.K.Shingote, A.A.Kelkar
   To be communicated

5. Effect of Co-solvent on ATH of ketones using Rh-and unsymmetrical monotosylated diamine (Manuscript)
   S.H.Deshpande, Vaishali Shende, S.K.Shingote, A.A.Kelkar
   To be communicated

6. Asymmetric transfer hydrogenation of Imine using $[RuCl_{2(}$p- cymene $)]$ and unsymmetrical monostosylated diamine (Manuscript)
   Vaishali Shende, S.H.Deshpande, S.K.Shingote, A.A.Kelkar
   To be communicated

7. Effect of pH variation in ATH of ketones

   S.H.Deshpande, Vaishali Shende, S.K.Shingote A.A.Kelkar, Oral presentation in 21st National symposium on Catalysis, IICT Hyderabad, Feb. 2013