STUDIES IN CATALYTIC TRANSFER HYDROGENATION REACTIONS

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BY
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UNDER THE GUIDANCE OF
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AND
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AT
CHEMICAL ENGINEERING AND PROCESS DEVELOPMENT DIVISION
NATIONAL CHEMICAL LABORATORY
PUNE-411 008
INDIA
FEBRUARY 2012

CERTIFICATE

This is to certify that the work incorporated in the thesis, **“Studies in Catalytic Transfer Hydrogenation Reactions”** submitted by **Ms. Savita Kiran Shingote,** for the Degree of **Doctor of Philosophy,** was carried out by the candidate under my supervision in the Chemical Engineering and Process Development Division, National Chemical Laboratory, Pune – 411 008, India. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

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February 2012
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Dr. A. A. Kelkar
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DECLARATION BY THE CANDIDATE

I hereby declare that the thesis entitled **“Studies in Catalytic Transfer Hydrogenation Reactions”** 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 February 2007 to October 2011 under the guidance of **Dr. R. M. Deshpande** and **Dr. A. A. Kelkar** and has not formed the basis for the award of any degree, diploma, associateship, fellowship, titles in this or any other University or other institution of Higher learning.

I further declare that the material obtained from other sources has been duly acknowledged in the thesis.

Savita Kiran Shingote
(Candidate)

February 2012
Pune

Dedicated to

My Beloved

Parents & Daughter

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List of Abbreviations

1,5 COD	1,5 Cyclooctadiene
Aq.	Aqueous
AP	Acetophenone
ATH	Asymmetric transfer hydrogenation
BET	Brunauer- Emmett-Teller
BINAP	2, 2’-bis (diphenylphosphino)- l, l’-binaphthyl
BINAS	Sulphonated 2, 2’-bis (diphenylphosphinomethyl) - l, l’-binaphthylene
BISBIS	Sulfonated (2, 2’-bis (diphenylphosphinomethyl)-1, 1’-biphenyl
Bpy	2, 2’ bipyridine
CALD	Cinnamaldehyde
Conc.	Concentration
CTH	Catalytic transfer hydrogenation
C-T	Concentration-time
CTAB	Cetyltrimethylammonium bromide
Cp*	Pentamethylcyclopentadiene
DDAPS	Dodecyl dimethyl ammoniopropanesulphonate
DPEN	1,2-Diphenyl-1,2-ethylenediamine
DMAc	N-N-Dimethyl acetamide
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)

HCALD	Hydrocinnamaldehyde
IPA	Isopropyl alcohol
ICP-AES	Inductive copuplled Plasma- atomic emission spectrophotometry
NMP	N-methyl 2-pyrolidone
NMR	Nuclear magnetic resonance
org.	Organic
OTPPTS	Triphenyl phosphine trisulfonate oxide
Ph	Phenyl
PPM	4-(diphenylphosphino)-2-(diphenylphosphinomethyl)- pyrrolidine
ppm	Parts per million
PTN	7-phospha-3-methyl-1,3,5-triazabicyclo[3.3.1]nonane
PTA	1, 3, 5-triaza-7-phosphaadamantane
rpm	Rotation per minute
RT	Room temperature
SAPC	Supported aqueous phase catalysts
SDS	Sodium dioctyl sulfosuccinate
SEM	Scanning electron microscopy
Skewphos	2,4-bis(diphenylphosphino)pentane
STAC	Stearyl trimethyl ammonium chloride
T	Temperature
TEM	Transmission electron microscopy
THF	Tetrahydrofuran
TOF	Turnover frequency
TPP	Triphenyl phosphine
TPPMS	Triphenyl phosphine monosulfonate monosodium
TPPTS	Triphenyl phosphine trisulfonate trisodium
TsDPEN	N-[-2-amino-1,2-diphenylethyl]-4-methylbenzenesulfonamide
XPS	X-ray photoelectron spectroscopy

Abstract of the thesis

Studies in Catalytic Transfer Hydrogenation Reactions

General introduction

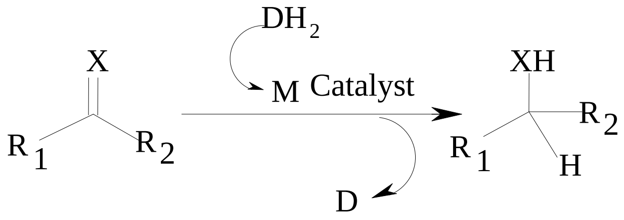
Catalysis has revolutionized the chemical industry by cutting down the need for stoichiometric reagents and reducing the side products or unwanted reactions.[1] Catalysts have found increasing demand in the synthesis of fine chemicals, pharmaceuticals and specialty chemicals, which were conventionally, manufactured using stoichiometric organic syntheses. Major drawbacks of the conventional processes were: utilization of corrosive and toxic reagents and formation of stoichiometric amounts of by products and waste products consisting of inorganic salts. Today, catalytic technologies account for the large-scale industries like the petroleum refinery to small-scale synthesis of drugs in the pharmaceutical industries. The share of catalytic processes in specialty and fine chemical industry has increased considerably in last few decades. With increasing environmental awareness and global competition, it is imperative to design alternate processes that are clean, atom efficient, and use non-toxic and non-hazardous raw materials. In this respect, homogeneous and heterogeneous catalysts have played a vital role towards the development of environmentally harmless and industrially profitable processes.

Some general features of homogeneous catalysts are the mild reaction conditions employed, high activity and high selectivity as the catalyst is dissolved in solution and all the molecules are available for reaction.[2] However, catalyst-product separation is the major problem of homogeneous catalysis. The mechanism of homogeneous catalysis is much better understood. Examples of homogeneous catalysis are carbonylation, hydrogenation, hydroformylation, oxidation, Heck-Suzuki coupling, telomerization, co-polymerization, metathesis etc. Heterogeneous catalysts on the other hand employ generally severe temperature and pressure conditions and mostly operate in continuous mode. Heterogeneous catalysts generally have a higher catalyst life, are stable to temperature and offer an easy catalyst-product separation.[3] Processes utilizing heterogeneous catalysts include hydrogenation, catalytic reforming, catalytic cracking,

hydro-desulfurization and other bulk chemical processes such as ammonia synthesis, sulfuric acid synthesis etc.

Among these industrially important reactions hydrogenation reaction is a subject of remarkable interest both from academic and industrial point of view. Catalytic hydrogenation is being used industrially for many products. However, safety related to the use of hydrogen is of utmost importance. For small scale operation the cost necessary for high pressure reactors is high. Also, for functionalized molecules selective hydrogenation of desired functional group is very important. This has led to the development of catalytic transfer hydrogenation (CTH), which offers certain advantages over alternative methodologies. CTH is highly selective method and reduces the risks and safety restrictions associated with the use of molecular hydrogen. In CTH cheaper and less hazardous hydrogen donors like formate salts, IPA etc. are used. Furthermore, CTH 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.

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 Scheme 1.



Scheme 1

In 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, depending on the nature of metal catalyst and hydrogen donor. Various hydrogen donors like formic acid and formates, phosphinic acid, phosphinates, phosphorous acid, phosphites, hydrazine, alcohols etc. are used in CTH.

The knowledge of this basic reaction goes back to the turn of the 20th century, when Knoevenagel[4] first used palladium black catalyst for the reduction of dimethyl terephthalate. It was observed that the Pd/C catalyst was active for reduction of various functional groups like ethylenic and acetylenic linkages, halides, aliphatic and aromatic nitro groups, Azo, azoxy, and azomethine groups. Various homogeneous catalysts have been developed for transfer hydrogenation reaction to expand scope and synthetic applications of the reaction. 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 CTH reactions can be categorized based 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. Recently asymmetric transfer hydrogenation (ATH) has emerged as a powerful, practical and versatile tool for the enantioselective reduction of various functional groups including carbonyl compounds.[5] The optically active products are common intermediates for pharmaceuticals, biologically active compounds and fine chemicals.

A major problem with homogeneous catalysts is the separation of products from catalyst. To overcome this, various strategies have been developed and aqueous biphasic catalysis using water soluble ligands is one of them. Aqueous biphasic catalysis has gained importance after successful application of propylene hydroformylation on commercial scale by Ruhr Chemie in 1970's, however; limited work is done on aqueous biphasic transfer hydrogenation reactions.[6]

Considering the above facts, the present study was focused on the catalytic transfer hydrogenation reactions of three class of substrates having different functional groups viz. carbonyl group of prochiral ketone, nitro group of nitroarens and olefinic group of α-β unsaturated carbonyl compounds. The hydrogenated products of these substrates viz. chiral alcohols, aniline and saturated carbonyl compounds respectively; are useful as intermediates in pharmaceutical, agricultural, dyes and perfume production. The objective of this work was to improve the catalytic systems with high activity and selectivity for the selected systems. It was also important to study the kinetic behavior and mechanistic features of these reactions to develop a deeper understanding. Therefore, following specific problems were chosen for the present work.

- Detailed investigations on asymmetric transfer hydrogenation of acetophenone using homogeneous ruthenium complexes with β-amino alcohol as a ligand.

- The use of ultrasound to improve the catalytic activity of asymmetric transfer hydrogenation reactions using β-amino alcohol as ligands.
- Kinetic studies of transfer hydrogenation of nitrobenzene using 5% Pd/C
- Investigations on 5% Pt/C catalyzed transfer hydrogenation of nitrobenzene: parametric studies.
- Investigations on kinetics of transfer hydrogenation of cinnamaldehyde in aqueous biphasic medium with the objective of developing a suitable rate equation.
- The use of co-solvent in transfer hydrogenation of α-β unsaturated carbonyl compounds using water-soluble rhodium-TPPTS catalyst in a biphasic medium.

The research work carried out for this thesis has been 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 homogeneous asymmetric, heterogeneous and biphasic transfer hydrogenation reaction is presented. Depending on the topics chosen for work, the literature search is divided in three parts.

i) Asymmetric transfer hydrogenation (ATH) of ketones: For developing a catalytic system for ATH reaction the choice of hydrogen donor, the transition metal source, and the chiral ligand has considered as major aspects. Extensive work has been carried out to understand the role of different catalysts, ligands, hydrogen donors on the activity and enantioselectivity towards desired product. The transition metals; ruthenium, iridium and rhodium catalysts have been reported for transfer hydrogenation of ketones.[7] The majority of the work has been carried out using ruthenium complex catalysts with IPA and formic acid- triethylamine as a hydrogen donor. The activity and enantioselectivity is strongly dependent on the type of ligand used. Various N-, P-, O- and S- containing ligands have been used for ATH reaction. Among them β-amino alcohols are mostly used in ATH reactions with IPA as a hydrogen donor. Several chiral β-amino alcohols are commercially available, mono-substitution at nitrogen exerts a positive effect on stereoselectivity. The detailed literature on ATH of ketones using β-amino alcohol ligands is also discussed in this section. Work is being carried out by number of researchers on the development of new ligands with the aim of improving catalytic activity and *ee*; however detail parametric study is scarcely done for existing catalytic systems.

The use of non conventional techniques like microwave and ultrasound has been discussed in brief. It is observed that the use of ultrasound in homogeneous ATH reactions is not explored so far. In this context, the brief introduction to sonochemistry is discussed in this section.

ii) Transfer hydrogenation using Pd/C and Pt/C catalysts: The literature on Pd/C and Pt/C catalyzed heterogeneous CTH has been discussed in detail in this section. The use of various hydrogen donors for reduction of various substrates has been discussed. From literature it can be seen that the information of kinetic study available of these reactions are scanty. A detailed kinetics of transfer hydrogenation of nitro compounds have not been investigated so far. It can also be seen from literature that Pt/C catalyst has been rarely used in CTH reactions and detailed parametric study has not done so far.

iii) Transfer hydrogenation of α,β-unsaturated aldehydes in aqueous biphasic media: A detailed literature on selective hydrogenation of carbonyl or olefinic group in α-β unsaturated carbonyl compounds is presented in this section. In general it is found that rhodium based catalysts selectively reduce olefinic group. Sodium formate has been mostly used as a hydrogen donor. Various water soluble ligands like TPPTS, TPPMS, and PTA have been used to prepare water soluble complexes. It can be viewed from literature that very few reports on the kinetics of the aqueous biphasic transfer hydrogenation reactions are discussed. The use of co-solvent in aqueous biphasic transfer hydrogenation is not explored till now.

Chapter 2: Asymmetric transfer hydrogenation of ketones using ruthenium-ephedrine complex catalyst and use of ultrasound to enhance the rate of reaction.

The first section of this chapter presents the experimental results on asymmetric transfer hydrogenation of acetophenone using $Ru(benzene)Cl_2]_2$/(1R,2S)ephedrine catalyst system, IPA as a hydrogen donor and KOH as a base. The effect of various reaction parameters: i) addition sequence of reactants ii) catalyst concentration iii) substrate concentration iv) base concentration v) ligand concentration and vi) temperature on the catalytic activity and enantioselectivity has been investigated.

The results indicate that presence of base is essential for catalytic activity. The ratio Ru: ligand: acetophenone: base of 1:2:100:5 was found to be optimum for higher catalytic activity and enantioselectivity. The reaction is equilibrium controlled and it is observed that maximum substrate concentration should be less than or equal to 0.1 M to achieve high conversion. With increase in reaction temperature, conversion of acetophenone increased with reasonable decrease in enantioselectivity.

The second section of this chapter presents the experimental results of ultrasound promoted transfer hydrogenation of acetophenone using Ru(benzene)$Cl_2]_2$/(1R,2S) ephedrine catalyst system, IPA as a hydrogen donor and KOH as a base. The sonochemical parameters like effect of amplitude and pulse mode on conversion and enantioselectivity have been investigated. The effects of concentrations of catalyst, base and substrate on conversion and *ee* under ultrasound have also been studied. The comparative study of silent and ultrasound promoted reaction has been carried out using various catalyst precursors, ketones and ligands.

The results showed that 60% amplitude and 3:1 pulse ratio gave high activity. Under ultrasound, the activity of the catalyst was found to increase 5-10 folds without loss of enantioselectivity for different precatalysts, β-amino alcohol ligands and ketones screened. This was the first time, where ultrasound was used to increase the rate of reaction in homogeneously catalyzed ATH reactions.

Chapter 3: Catalytic transfer hydrogenation (CTH) of Nitrobenzene using 5% Pd/C and 5% Pt/C catalyst

This chapter discusses the transfer hydrogenation of nitrobenzene using 5% Pd/C and 5% Pt/C catalysts. In the first section, the results obtained using 5% Pd/C catalyst were discussed. The effect of pretreatment of hydrogen donor, screening of solvents and hydrogen donor has been discussed. The kinetics of transfer hydrogenation of nitrobenzene was carried out using potassium formate as a hydrogen donor in solvent ethanol in a temperature range of 308-328 K. The effect of concentration of catalyst, nitrobenzene, potassium formate and water on the rate of reaction has been studied. It was found that the rate increases with increase in catalyst concentration, decreases with increase in nitrobenzene and water concentration. The rate was found to increase linearly with potassium formate concentration in the lower concentration range (<4 kmol/m^3). With further increase in potassium formate concentration the rate increased only marginally. The rate data were fitted to various empirical rate models. The following rate equation was found to predict the rates in good agreement with experimental values:

$$R = \frac{k.A.B.C.D}{\left(1+K_A A\right)^2 \left(1+K_B B\right)\left(1+K_D D\right)^2}$$

Where R = rate of reaction, expressed in kmol/m^3/s; A = concentration of nitrobenzene (kmol/m^3); B = concentration of potassium formate (kmol/m^3); C = concentration of catalyst (kg/m^3); D= Concentration of water (kmol/m^3) k = rate constant, K_A, K_B, K_C are equilibrium constants.

A comparison of the experimental rates with the rates predicted using this model indicates a good agreement between experimental and predicted rates. The average percent error between the experimental and predicted data was 0.97 %. The activation energy for this model was calculated to be 55.2 kJ/mol.

The second section of this chapter discusses the use of 5% Pt/C catalyst for transfer hydrogenation of nitrobenzene. As a first step screening of solvents and formate salts was carried out. Ammonium formate was found to be the best hydrogen donor, while methanol was found to be the best solvent for the reaction. The effect of parameters like water concentration, formate concentration and substrate concentration on initial rate of reaction of reaction was investigated and the results are discussed.

The results showed that the rate increased with increase in catalyst concentration and decreased with increase in nitrobenzene and water concentration. The rate was found to increase linearly with potassium formate concentration in the lower concentration range (<4 kmol/m^3). With further increase in potassium formate concentration the rate increased only marginally.

Over all results shows that optimum relative concentrations of the three components (nitrobenzene, water and formate salt) are necessary to achieve high activity for 5% Pd/C as well as for 5% Pt/C catalyst.

Chapter 4: Transfer hydrogenation of α-β unsaturated carbonyl compounds in aqueous biphasic medium using water soluble Rh/TPPTS catalyst.

This chapter presents the experimental results and discussion on the transfer hydrogenation of α-β unsaturated carbonyl compounds in aqueous biphasic medium using water-soluble Rh/TPPTS catalyst. Various catalyst precursors, substrates, hydrogen donors and organic solvents were screened. Highest activity was observed with $Rh(COD)Cl]_2$/TPPTS catalyst system with sodium formate hydrogen donor. Selectivity to olefinic reduction was 100% to give saturated aldehydes as product. Kinetics of aqueous biphasic transfer hydrogenation of *trans* cinnamaldehyde has been investigated in a temperature range of 313-333K using the water-soluble Rh-TPPTS catalyst in this chapter. The influences of agitation speed, aqueous phase hold up ratio, cinnamaldehyde concentration, catalyst concentration, ligand concentration and hydrogen donor concentration on the initial rate of reaction have been studied in detail.

The rate was found to be first order with respect to catalyst concentration. The rate showed a linear dependence on substrate concentration in the lower concentration range (< 1.3 kmol/m^3). With further increase in substrate concentration the rate increased marginally. The rate passed through a maximum and then leveled off at higher concentration of sodium formate. The rate was maximum at Rh:L ratio of 1:6. At higher Rh:L ratio the rate decreased slightly. The following empirical rate equation has been proposed and found to be in good agreement with the observed rate data within the limit of experimental error. The activation energy for this model was calculated to be 126 kJ/mol.

$$R = \frac{k[A][B][C][D]}{(1+K_B[B]^2)(1+K_C[C])^2(1+K_D[D]^2)}$$

Where, R = rate of reaction, kmol/(m^{3}s); [A]= concentration of catalyst (kmol/m^3); [B] = concentration of cinnamaldehyde (kmol/m^3); [C] = concentration of sodium formate (kmol/m^3); [D]= concentration of ligand (TPPTS) (kmol/m^3); k = rate constant; K_B, K_C, K_D are equilibrium constants.

The substrates like methyl cinnamate, ethyl cinnamate, citral and chalcone with low solubility in water gave poor activity for aqueous biphasic transfer hydrogenation. It was found that for such substrates the activity improved with the addition of co-solvents. Various co-solvents were screened for that purpose. The effect of concentration of co-solvent in water was also investigated. The effect of various parameters like concentrations of catalyst, substrate and sodium formate on the initial rate of reaction was investigated at 353 K using methyl cinnamate as model substrate in toluene-water-NMP biphasic medium.

30% NMP in aqueous phase resulted in high activity (TOF: 49 h^{-1}) for the reaction for transfer hydrogenation of methyl cinnamate. For other substrates also the rate of reaction increased significantly when NMP was used as co-solvent. This is the first report on the use of co-solvents in transfer hydrogenation of α-β unsaturated carbonyl compounds. The reaction rate was found to have first order dependence with catalyst and substrate concentrations. It was also observed that the rate passed through a maximum and then levels off at higher formate concentration.

References

1. R. J. Farranto and C.H. Bartholomew (Eds) *Fundamentals of Industrial Catalytic Processes*, Blackie Academic and Professional, London, **1997**.
2. B. Cornills and W. A. Herrmann (Eds.), *Applied homogeneous Catalysis with Organometallic Compounds*, VCH, Weinheim, **2003,** Vol-1, 2 and 3.
3. F.R. Hartley, Supported Metal Complexes, Reidel, Dordrechiet, **1985.**
4. E. Knoevenagei and B. Bergdolt, *Chem. Ber*. **1903,***36*, 2857.
5. (a)H. U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, *Adv. Synth. Catal.* **2003,** *345*, 103; (b) W. J. Tang and X. M. Zhang, *Chem. Rev*.**2003**, *103*, 3029;
6 F. Joó, *Aqueous organometallic catalysis, Vol. 23*, Springer Netherlands, **2001**.
7. P. G. Andersson, I. J. Munslow, C. Ebooks, *Modern reduction methods*, Wiley-VCH Weinheim, Germany, **2008**.

Chapter 1

Introduction and Literature Survey

1.1 INTRODUCTION

Catalysis is the key to both life and lifestyle. Nearly all biological reactions and most industrial syntheses require catalysts. It is an essential technology for chemical and materials manufacturing, for energy conversion systems (fuel cells), for combustion devices, and for pollution control systems. Numerous organic intermediate products, required for the production of plastics, synthetic fibers, dyes, pharmaceuticals, crop-protection agents, resins, and pigments can only be produced by catalytic processes. Most of the processes involved in crude-oil processing and petrochemistry, such as purification stages, refining and chemical transformations require catalysts. Environmental protection measures like automobile exhaust control, purification of off-gases from power stations and industrial plants would be inconceivable without catalysts.

Catalysts, in the definition developed by Berzelius and others in the last century, are materials which change the rate of attainment of chemical equilibrium without themselves being changed or consumed in the process.[1,2] While it was formerly assumed that the catalyst remained unchanged during the course of the reaction, it is now known that the catalyst is involved in chemical bonding with the reactants during the catalytic process. Thus catalysis is a cyclic process: the reactants are bound to one form of the catalyst, and the products are released from another, regenerating the initial state. In theory, an ideal catalyst would not be consumed, but this is not the case in practice. Owing to competing reactions, the catalyst undergoes chemical changes, and its activity becomes lower (catalyst deactivation). Thus catalysts must be regenerated or eventually replaced. Apart from accelerating reactions, catalysts have another important property: they can influence the selectivity of chemical reactions. This means that completely different products can be obtained from a given starting material by using different catalyst systems. Industrially, this targeted reaction control is often even more important than the catalytic activity.

There are different types of catalysts. They range from the proton, H^+, through Lewis acids, organometallic complexes, organic and inorganic polymers, all the way to enzymes. To simplify things, we divide catalysis into three categories depending on the physical nature of the catalyst employed[3]:

- Homogeneous catalysis: The reactants, products and catalyst are present in the same phase. Homogeneous catalysts are generally well-defined chemical compounds or coordination complexes, which, together with the reactants, are molecularly dispersed in the reaction medium. The main drawback of homogeneous catalysis is the expensive catalyst product separation, and the recycle/recovery of the catalyst. Examples of homogeneous catalysts include mineral acids and transition metal compounds (e. g., rhodium carbonyl complexes in oxo synthesis).
- Heterogeneous catalysis: Reactants/products and catalyst are present in separate phases; the catalyst is generally solid and the reactants are either liquid or gas. Heterogeneous catalysts generally employ relatively severe temperature and pressure conditions and mostly operate in a continuous mode. Heterogeneous catalysts generally have a higher catalyst life, are stable to temperature and offer an easy catalyst-product separation. Examples of heterogeneous catalysts are Pt/Rh nets for the oxidation of ammonia to nitrous gases (Ostwald process) and amorphous or crystalline aluminosilicates for cracking petroleum fractions.
- Biocatalysis or enzymatic catalysis: Enzyme catalysis is homogeneous in nature and provides regioselective and stereoselective transformations at ambient reaction conditions with almost no byproduct formation.[4] However, the biocatalysts are not stable at extremes of specific pH and temperatures. One of the examples of biocatalytic process used in industry is the lipases catalyzed resolution of racemic alcohol and amine to give enantiopure alcohol and amine.

Table 1.1 summarizes the advantages and drawbacks of homogeneous and heterogeneous catalysis.

Table 1.1 Homogeneous versus heterogeneous catalysis[5]

Properties	Homogeneous catalysis	Heterogeneous catalysis
Effectivity		
Active centers	all metal atoms	only surface atoms
Concentration	low	high
Selectivity	high	lower
Reaction conditions	mild (50–200 °C)	severe (often >250°C)
Diffusion problems	practically absent	present (mass-transfer-controlled reaction)
Applicability	limited	wide
Activity loss	irreversible reaction with products (cluster formation); poisoning	sintering of the metal crystallites; poisoning
Catalyst properties		
Structure/ stoichiometry	defined	undefined
Modification possibilities	high	low
Thermal stability	low	high
Catalyst separation	sometimes laborious (chemical decomposition, distillation, extraction)	fixed-bed: unnecessary suspension: filtration
Catalyst recycling	possible	unnecessary (fixed-bed) or easy (suspension)
Cost of catalyst losses	high	low

The homogeneous and heterogeneous catalysts have played a vital role in the development of environmentally benign and industrially lucrative processes. Hydroformylation, hydrogenation, carbonylation, C-C coupling, amination, oxidation and polymerization reactions are some of the industrially important reactions carried out with the help of catalysts.[6] Among these, hydrogenation reaction is a subject of remarkable interest both from an academic and from an industrial point of view. The hydrogenation reactions are used extensively in industrial processes for synthesis of methanol, liquid fuels, hydrogenated vegetable oils, fatty alcohols from corresponding carboxylic acids, alcohols from aldehydes, cyclohexanol from phenol and cyclohexane from benzene, hexamethylenediamine for the synthesis of nylon from adiponitrile. The prochiral olefins, carbonyl compounds and imines can be hydrogenated to give corresponding chiral products using asymmetric catalysts. Several viable methodologies have been established for this purpose. Following are the procedures for hydrogenation which are more familiar to chemists

A. Electron transfer from an electropositive metal (or via electrolysis) followed by proton quenching
B. Reduction by metal hydride
C. Addition of molecular hydrogen mediated by transition metal catalysis
D. Catalytic transfer hydrogenation (CTH).

The wider acceptance of electrolysis as a mean of hydrogenation has held back by its relatively slow natute (controlled by the need for large surface area of electrodes), the need for special solvent systems with supporting electrolytes and the need for the preliminary experiments which required to ascertain the correct voltage for ensuring that only required reduction takes place.

The major disadvantages for the methods in which the reducing agents such as sodium borohydride, lithium aluminium hydride, zinc, iron hydrogen sulfides etc are used (reduction by metal hydride) are as follows.

- These reagents produced stoichiometric amount of organic or inorganic wastes, which causes environmental hazards
- The reagents can not be recycled.
- The separation of reagents from the reaction mixture is difficult.
- Many of these processes involve tedious work up, which increases the manufacturing cost.
- Corrosion of the reactor takes place in case of iron acid reduction methods.

These problems can be overcome by catalytic hydrogenation route where the reduction of organic compounds takes place by addition of molecular hydrogen in the presence of a catalyst. The hydrogen is commercially available in molecular form. The reactions are usually performed in the atmosphere of gaseous hydrogen and in the presence of metal catalysts such as palladium, platinum, rhodium, ruthenium and iridium etc. The reduction of various substrates under catalytic hydrogenation is very popular. 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 which involves risks and safety restrictions associated with the use of pressure vessels.

Therefore, there was a necessity for the development of procedures which does not require molecular hydrogen gas as a reactant. It was found that some molecules, such as cyclohexadiene, isopropanol and ammonium formate etc, readily release hydrogen in situ in 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:

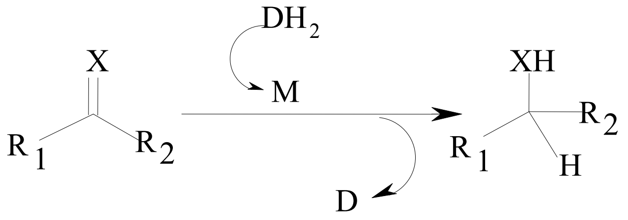
- The hydrogen source is easy to handle (no pressure vessels are necessary).
- Possible hazards associated with the handling of molecular hydrogen are minimized.
- The mild reaction conditions used can afford enhance selectivity.
- Variations in the choice of donors are also possible.
- Chemoselectivity of multifuctionalised compound is highest with transfer hydrogenation reaction.
- The accompanying co-products can easily be disposed off and some of them can be rehydrogenated back easily.
- Catalytic asymmetric transfer hydrogenation can be applied in the presence of chiral ligands.

Thus catalytic transfer hydrogenation process is safe, simple, and ecologically friendly. In the view of growing importance of safe and ecologically friendly processes, the aim of this thesis is to explore the catalysis, chemistry, kinetics and mechanism of the various transfer hydrogenation reactions. The focus of this chapter is to present a detailed survey of the relevant literature on transfer hydrogenation reaction.

1.2 TRANSFER HYDROGENATION REACTION

1.2.1 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 Scheme 1.1



X=O/CHR/NHR, M-catalyst, R_1/R_2=Phenyl/alkyl, DH_2-hydrogen donor, D-byproduct

Scheme 1.1: General transfer hydrogenation reaction

In 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, depending on the nature of metal catalyst and hydrogen donor.

1.2.1.1 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 (Scheme 1.1). In the large majority of cases the two hydrogens of the donor are nonequivalent 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[7], 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 its transfer, hydrogen may appear as a proton, atom, or hydride depending on reagents and conditions. e.g. on dissolving gaseous HCl in water, hydrogen is transferred as a proton to water; the reaction of lithium tetrahydroaluminate to 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 transferred. For example, formic acid may be regarded as providing a proton and a hydride or two hydrogen atoms. However, it is clear that the best hydrogen donor is the compound which contains the hydrogen bonded to the elements or groups with similar electronegativity. 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 H-transfer processes when compared with processes such as catalytic hydrogenation. Furthermore, upon losing two hydrogen atoms the hydrogen donor (DH_2) itself becomes a hydrogen acceptor that may be in competition with the substrate until equilibrium is reached. Example is where an alcohol (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.

1.2.2 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[8] first observed that dimethyl 1,4-dihydroterephthalate disproportionated 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, Linstead et al.[9], 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 presence of palladium black. The striking discovery of reduction of ethylenic and acetylenic 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 adding the use of formate salts as hydrogen donors. It was further shown that carbonyl groups are generally not susceptible to reduction with palladium black and cyclohexene as 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 alkoxides 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-Ponndorf-Verley (MPV) reduction).[10] The next milestone was the discovery that some transition metal complexes which were able to catalyze the H-transfer reduction of ketones homogeneously. The first reports illustrating this property, published in 1967[11], were preceded by preliminary work reporting the Ir-catalyzed reduction of cyclohexanones to alcohols with 2-propanol as a hydrogen donor, which had been almost completely overlooked.[12] 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[13], who demonstrated that Ru-triphenylphosphine 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 Ru-catalyzed asymmetric transfer hydrogenation (ATH) of ketones emerging a new area in asymmetric catalysis.[14] 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 IPA and the azeotropic 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.[15] Now transfer hydrogenation in water has afforded an effective and green alternative for fast and selective (and enantioselective) reduction.

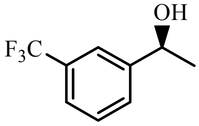
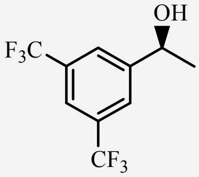
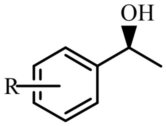
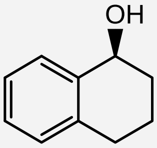
Thus transfer hydrogenation reactions can be carried out using hydrogen sources which are cheap, easily available, generating non hazardous waste in the reduction. Apart from these merits, the reduction is easy to conduct, requiring mild reaction conditions and often no inert gas protection. The aqueous transfer hydrogenation process provides a use of soluble form of formate and enables easy catalyst/product separation. The progress of transfer hydrogenation in asymmetric, aqueous (homogeneous or biphasic) and heterogeneous areas is still emerging and in terms of catalyst activity, productivity and enantioselectivity, there is still space to improve.

The major objective of this work was to study transfer hydrogenation reaction of different functional groups like C=O of ketone, -NO_2 of nitroarenes and C=C of α-β unsaturated carbonyl compound. The model substrates such as acetophenone, nitrobenzene and cinnamaldehyde were chosen for that purpose. A detailed literature search was hence conducted keeping these objectives in mind. An overview of the important details like choice of hydrogen donor, catalysts, solvent etc on (i) asymmetric transfer hydrogenation reaction, (ii) transfer hydrogenation of nitrobenzene using supported Pd/C and Pt/C as catalyst and (iii) aqueous biphasic transfer hydrogenation of α-β unsaturated carbonyl compounds is presented in the following sections.

1.3 ASYMMETRIC TRANSFER HYDROGENATION (ATH) OF KETONES

Chirality or handedness is one of the most important symbols of nature and living organisms. Life itself depends on chirality because biological systems recognize molecules with specific chirality. Among small chiral molecules, chiral alcohols occupy a central place in the synthesis of pharmaceuticals, flavour, aroma and agricultural chemicals and specialty materials. Chiral alcohols are accessed by the asymmetric reduction of prochiral ketones. Asymmetric transfer hydrogenation (ATH) has now emerged as a powerful tool for production of optically pure chiral alcohols because of its selectivity, efficiency, scope, simplicity, and economic viability.[16] Table 1.2 presents the industrial use of ATH in the production of optically active chiral alcohols.[17]

Table 1.2 Catalytic asymmetric transfer hydrogenation used in industry.

Catalyst system	Hydrogen Donor	Chiral Alcohol Obtained	Final Product	Ref. [17]
Ru(TsDPEN)(*p*-cymene)	IPA or HCO_2H / $N(C_2H_5)_3$		Herbicide (MA20565)	Okanas
Ru(TsDPEN)(*p*-cymene) Or Cp*Rh(TsDPEN)	IPA or HCO_2H / $N(C_2H_5)_3$		Antiemetics (NK-1)	Merk
Chiral catalyst	HCO_2H / $N(C_2H_5)_3$		Chiral amine	NIPL pharma
Cp*Rh(Amino Indanol)	IPA- i-PrONa		Chiral alcohol	Avecia[18]

The first ATH was reported by Doering et al.[19], 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. *ee* up to 5% was obtained for the method employed. In the 1970s, the Ohkubo and Sinou groups[20] 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[21], Genet's chiral diphosphine Ru(II) catalysts[22] 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) or β-amino alcohols were discovered to be highly efficient and enantioselective for the reduction of ketones with isopropyl alcohol (IPA) or $HCOOH/Et_3N$ azeotrope.[23] 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.[24] 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 consider: 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 stereoselectivity. Considering these three major aspects the literature on ATH of ketones is presented in the following sections.

1.3.1 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)[25]- 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. 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 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 byproduct-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.

2) Formic acid-triethylamine azeotrope (FA-TEA)[18,27] -When this azeotrope(5:3 mixture of formic acid and triethylamine respectively) is used as hydrogen donor, the reaction is irreversible and kinetically controlled; which gives CO_2 gas as the dehydrogenated product and 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,

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[28]-Recently it is found that the ATH of aromatic ketones is significantly accelerated when the reaction is carried out in neat water with sodium formate as hydrogen donor. A number of ATH reactions with various catalysts using formate in water have been reported. The reaction is not reversible. The bi-carbonate byproducts of corresponding formate salts are generated.

1.3.2 Catalysts Used in ATH

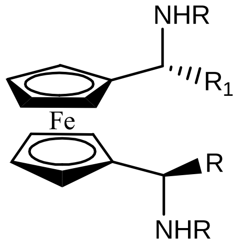
After the discovery of Noyori's Ru-TsDPEN catalyst complex, a variety of related metal catalysts have been developed and have since been applied to ATH of various ketones. Some lanthanides La, Sm and Gd in combination with chiral ligands such as binaphthol and the amino alcohol have shown high activities and enantioselectivities (over 99% *ee*) in the reduction of aryl alkyl ketones.[29,30] Iron based complexes such as Fe-porphyrin are also found to give good catalytic activity in the reduction of ketones.[31] Cu-complexes with chiral bisoxazolines in the presence of Hantzsch esters are able to reduce α-keto esters to α-hydroxy esters in over 99% *ee*.[32] 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 iridium and rhodium catalysts, respectively.[33] 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 $[RuCl_2(\eta^6\text{-arene})]_2$ and $[Cp^*MCl_2]_2$ (M=Rh, Ir). The η^6-arene fragment contributes significantly to the performance of these catalyst through $C(sp^2)H/\pi$ interaction 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 bidentate ligand and one site for halide or hydride. The complexes prepared by this type of precatalyst and protic ligands (like β-amino alcohol) act as bifunctional scaffolds for anchoring the substrate and transferring the hydride.

1.3.3 Chiral Ligands Used in ATH

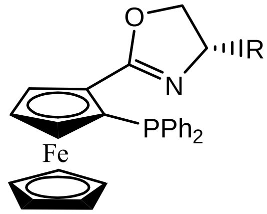
A number of ligands of diverse structure have been developed for the synthesis of Ru, Rh and Ir complexes in d^6 and d^8 electronic configurations, which have been used in hydrogen transfer reductions. The ligands differ in the number and type of the donor atom(s) and in symmetry properties. They can be neutral or anionic, depending on whether or not they possess a protonated donor centre –XH of appropriate acidity. These ligands contain various combinations of nitrogen, oxygen, phosphorus and sulfur as the donor atoms. They can be bidentate, tridentate or tetradentate. A brief summary of most notable ligands is given below.

1.3.3.1 Neutral chiral ligands

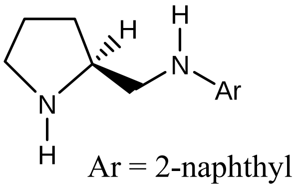
A selection of neutral chiral ligands recently reported in the Ru-catalyzed ATH of ketones is shown in Figure1.1 along with % *ee*, hydrogen donor used, reaction time and temperature.



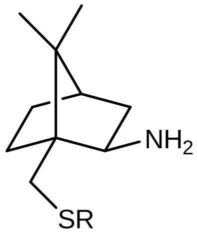
[1][34] 80%
(IPA-KOH,
1.5h, 22°C)



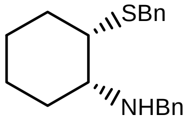
[2][35] 99%
(IPA-NaO^{i}Pr,
2h, RT)



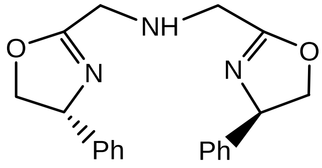
[3][36] 91%
(IPA-NaO^{i}Pr,
0.5h, RT)



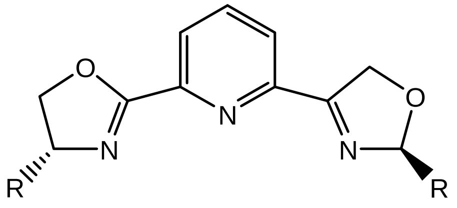
[4][37] 80%
(IPA-KO^{i}Pr,
0.5 h, 80°C)



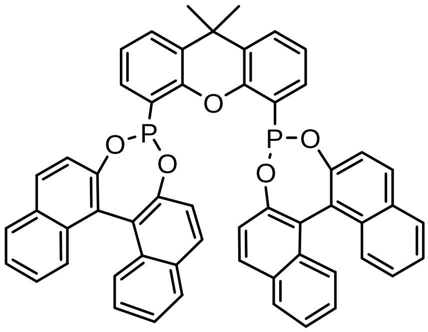
[5][38] 80%
(IPA- KO^{t}Bu, 1h, RT)



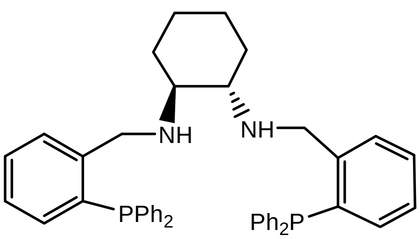
[6][39] 97%
(IPA-KO^{i}Pr, 10min, 82°C)



[7][40] 95%
(IPA-NaOH, 2min, 82°C)



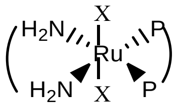
[8]41 97 %
(IPA-KO^{t}Bu, 28h, 40°C)



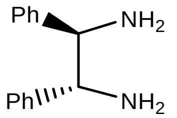
[9]42 97%
(IPA-KO^{i}Pr, 7h, 45°C)

Figure 1.1: Neutral chiral ligands for Ru catalyzed ATH of acetophenone, %*ee*

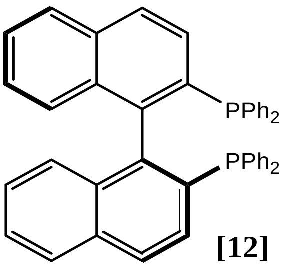
The stereoselectivity of these types of polydentate neutral chiral ligands ranges from good to excellent for ATH of acetophenone, but the catalytic activity varies widely. Among these only **[7]**-N, N, N tridentate ligand gives TOF up to 10000 h^{-1}. In contrast to asymmetric hydrogenation, bidentate P-donor ligands give poor activity in transfer hydrogenation of ketones. But some diphosphonite ligands like **[8]** which possess a large bite angle give exceptionally high stereoselectivity in ATH of ketones. The chiral tetradentate P_2N_2 ligand **[9]** which consists of two chelating (one P,P and one N,N) atoms in single ligand also give *ee* up to 97%. Similar type of Ru complex can be obtained by using a different pair of cooperative P,P and N,N-donor ligands (complex of type **[10])** as shown in Figure 1.2.



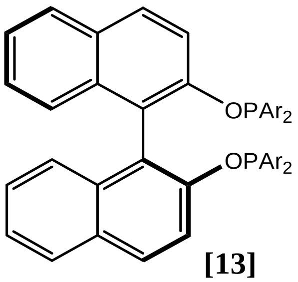
[10]



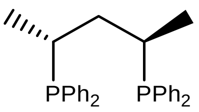
[11]



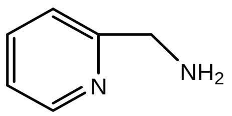
[12]



[13]



[14]



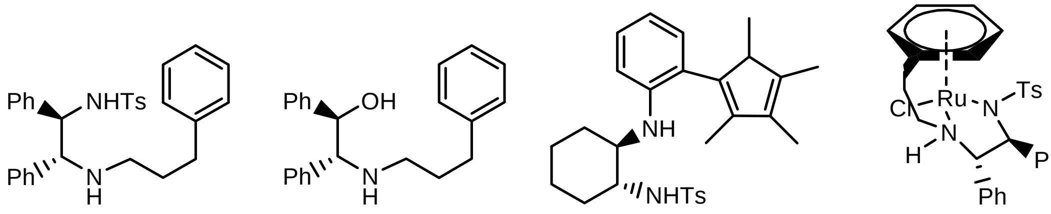
[15]

Figure 1.2: Co-operative ligands for Ru-catalyzed ATH of ketones

The Ru complex obtained using one chiral C_2-symmetric chelating diamine ligand such as DPEN **[11]** and one chiral C_2-symmetric diphosphine ligand such as BINAP **[12]**, shows impressive activity and stereoselectivity in the hydrogenation of ketones.[43] But it is less efficient in ATH.[44] However recently Morris[45] and Baratta[46] have succeeded in discovering matched pairs of cooperative P,P and N,N donor ligands, DPEN **[11]**-BINOP**[13]** and Skewphos **[14]**-aminomethyl pyridine**[15]** respectively, which provide catalysts of high activity (over 270000h^{-1}) and enantioselectivity over 85% *ee* in the reduction of acetophenone at 82°C using IPA/KOH as hydrogen donor.[46b]

1.3.3.2 Tethered ligands

As discussed in section 1.3.2, the η^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. have prepared a new range of ligands which they called as "tethered ligands" as shown in Figure 1.3. It allows a highly organized transition state by locking of the chiral elements by the three coordination sites of the ligand as shown in Figure 1.3 **[19].** The lifetime of the catalyst was improved significantly when tethered catalysts are used.[47-50]



[16][48] 96% (FA-TEA,3h, 28°C)

[17][49] 67% (IPA-KOH, 7h, 28°C)

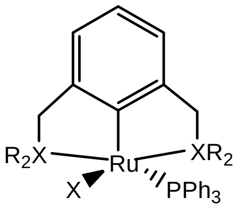
[18][50] 96% (FA-TEA, 2h, 28°C)

[19] Ru complex of tethered ligand

Figure 1.3: Chiral tethered catalyst for transfer hydrogenation of ketone, % *ee*.

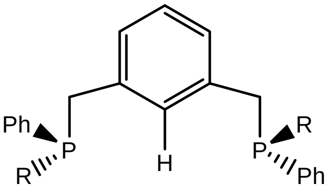
1.3.3.3 Pincer or cyclometalated ligands

The pincer or cyclometalated ligands are polydentate ligands which bind to metal via a carbon-metal σ bond, stabilized by one or two intramolecular dative heteroatom to metal bonds as shown in Figure 1.4 **[20]**. The achiral cyclometalated Ru-pincer complex of PCP type gave high catalytic activity, with TOF of 27000-33000 h^{-1} for cyclohexanone[51]; but after introduction of chiral P-centers to it as in ligand **[21]** did not result in high *ee* values.[52] Whereas the chelating chiral diphosphine and aminomethylpyridine ligand such as **[22]** internally cyclometalated to a pincer-like coordination with Ru or Os, to give very high stereoselectivity (95% *ee*).[53]



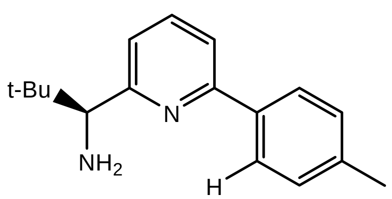
$XR_2 = PPh_2 / NMe_2 / PCy_2$

[20] Ru-Pincer complex



R= Me / iPr

[21][52] 18%
(IPA-KOH, 17h, 82°C)

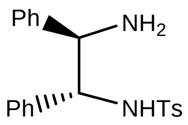


[22][53] 95%
(IPA-NaO^{i}Pr, 82°C)

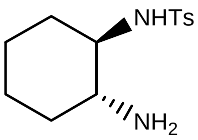
Figure 1.4: Cyclometalated Ru catalysts for ATH of ketones, % *ee*

1.3.3.4 Monotosylated diamine ligands

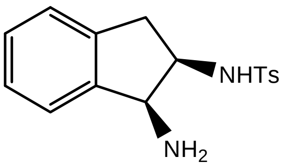
The most popular anionic ligand for ATH is the monotosyl diamine (TsDPEN) **[23]** reported by Noyori and coworkers in a series of papers initiated in 1995.[54] Since then the library of monosulfonyl diamines for ATH of carbonyl compounds has increased steadily. A selection of these ligands is shown in Figure 1.5 [**23-26**].



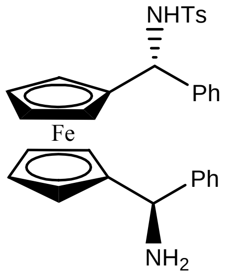
[23][54] 98%



[24][34a] 94%



[25][55] 83 %



[26][56] 83%

(IPA-KOH, 15h) or (FA-TEA, 22h)

(FA-TEA, 24h)

(FA-TEA, 20h)

(FA-TEA, 3days)

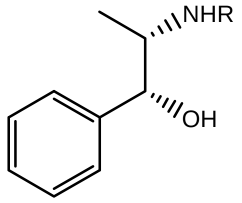
Temperature- RT (in all cases)

Figure 1.5: Diamine ligands for Ru catalyzed ATH of acetophenone, % *ee*

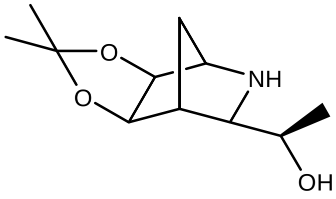
The activity of the catalysts obtained from these ligands is fair to good. Complexes of these ligands maintain their catalytic activity even in formic acid as hydrogen donor. By changing the hydrogen donor (IPA or FA-TEA); the selectivity of the reaction was only marginally affected, e.g for ligand **[23]**, 98% *ee* is obtained in both hydrogen donor systems. The stereochemistry of the products depends on the configuration of the carbon bound to the tosyl-amino group.[57] These ligands have also been used in the preparation of Rh(III) and Ir(III) cyclopentadienyl (Cp*) complexes that have resulted in the successful H-transfer reduction of carbonyl compounds.[58]

1.3.3.5 β-amino alcohol ligands

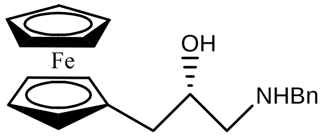
The second most abundant class of anionic ligands is that of β-amino alcohols, introduced by Noyori, almost supplementary to tosyl diamines. Noyori et al.[59] reported that a $\mathrm{RuCl_2(\eta^6C_6Me_6)]_2}$ catalyst along with some simple amino alcohol ligands such as ephedrine **[27]** showed high catalytic activity and *ee* (95% conversion and 91% *ee*) in the reduction of ketone. Andersson et al.[60] have developed 2-azanorboronyl based amino alcohol **[28]** which displayed good to excellent enantioselectivities (85-96% *ee*) in the Ru-catalyzed ATH reaction. Wills et al.[55] used (1R, 2S)-cis -1-aminoindan-2-ol **[30]** as a ligand in the Ru-catalyzed ATH, achieving good to excellent enantioselectivities.(see Figure 1.6)



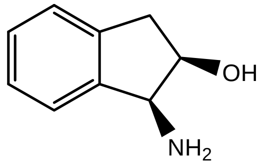
[27][59, 61] 91%
(IPA-KO^{i}Pr, 0.5h, 20°C)



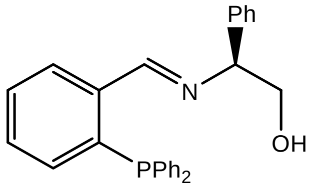
[28][62] 96%
(IPA-KOH, 2h, RT)



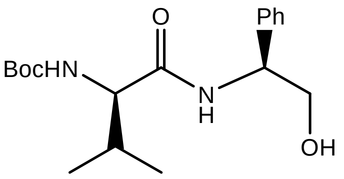
[29][63] 70%
(IPA-KOH, 2h, RT)



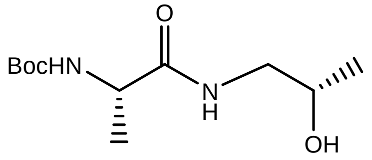
[30][55] 90%
(IPA-KOH, 1.5h, RT)



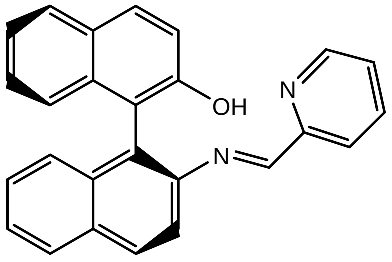
[31][64] 75%
(IPA-KO^{t}Bu, 15min, 80°C)



[32][65] 95%
(IPA-NaOH, 2h, RT)



[33][66] 95%
(IPA-NaOH, 9min, 60°C)



[34][67] 96%
(IPA- KO^{t}Bu, 15h, 28°C)

Figure 1.6: β-amino alcohol ligands for Ru catalyzed ATH of acetophenone, %*ee*

Besides these representative ligands, there are a number of chiral amino alcohol ligands that were reported to be efficient for Ru-catalyzed ATH of ketones. Table 1.3 presents the literature on ATH using chiral amino alcohol ligands in detail.

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

- In general, β-amino alcohols produce catalysts of higher activity than tosyl diamine derivatives when IPA is used as a hydrogen donor, for example ligand **[28]** achieves 96% *ee* with high catalytic activity (8500 h^{-1}).[62]
- The mono-substitution at nitrogen exerts a positive effect on stereoselectivity.
- Both syn and anti configured ligands give high enantioselectivity as compared to mono tosylated diamine ligands which require anti configuration for high optical purity of the products.[57]
- The extent of asymmetric induction is determined primarily by the configuration of the hydroxyl bearing carbon. 1-(S) Amino alcohols afford S-alcohol preferentially. However the amine-substituted asymmetric carbon also affects the extent of the enantioselection.
- Both arene and amino alcohol ligands influence the enantioselectivity but the tendency is not straightforward. High *ee* is obtained only when appropriate arene and chiral amino alcohol auxiliary are combined.
- It is also found that amino alcohols are weakly coordinating ligands hence the ligand to metal ratio has proven to be critical.

- The main limit of these ligands is that the activity of the catalysts prepared with these ligands is completely inhibited in FA-TEA hydrogen donor; probably because deprotonation of the hydroxyl group is completely suppressed in formic acid.[68]
- Easy preparation and ready availability of various β-amino alcohol ligands has led to intense exploration of [Ru^{II}(arene)(β-amino alcohol)] systems mainly for rationalizing the *ee*, designing more efficient ligands and for improving catalyst activity. But detail parametric study is scarcely reported.

Table 1.3: Literature survey on ATH using β- 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.** $RhCl_3.H_2O$ **G.** $RuCl_3.H_2O$ **Aq. NaF**= $HCOONa_{(aq)}$

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	PhCOMe	IPA, KOH	200:1:2:5	28	1	94	92	Activity is decreased with increase in the bulkiness of the arene auxiliary of cat., threo and erythro series of ligands are studied	59
2	**B**	(1R,2S) cis 1-amino-2indanol	PhCOMe	IPA, KOH	400:1:4:10	RT	1.6	70	91	Other ruthenium complexes like **A** and **E** give less *ee*.	69
3	**C**	(1S,2R) norephedrin	PhCOMe	IPA, KOH	200:1: 4: 4	RT	2	90	84	Patent describing procedure of ATH using β- Amino alcohol ligands	70
4	**A**	(1S,3R,4R)-2-azanorbornyl methanol	PhCOMe	IPA, KO^{i}Pr	400 :1 :8 : 10	83	5	92	95	Cat **B** also gives comparable yield and *ee*	71
5	**E**	(1S,2R) Ephedrine	β-keto ester	IPA, KO^{i}Pr	100 :1 :2 : 6	50	15	85	94	Ru complexes with various arenes are screened and *p*-cymene was found effective.	72
6	**E**	(1R,2S) Ephedrine	PhCOMe	IPA, KO^{t}Bu	400 : 1 :2.2 : 3.3	20	1	86	58	The enantioselectivity of the reaction is studied by molecular modeling using DFT calculations.	73
7	**B**	NH-Benzyl (1*R*,2*S*) norephedrine	PhCOMe	IPA, KO^{t}Bu	400:1:2.2:6	RT	2	91	95	Although ligand is tetradentate, active cat contain one ligand per metal which co-ordinates in didentate N,-O fashion.	74

Sr no	Cat	Ligand	Substrate	H - donor, base	Reaction conditions			Results		Remarks	Ref
					S: Ru: L: Base	T, °C	Time, h	yield %	*ee* %		
8	**B**	2 –aza Norbornyl derivec alcohols	PhCOMe	IPA, KO^{i}Pr	200:1: 4: 5	RT	2	95	95	To improve the selectivity and rate the structure of ligand is optimized.	75
9	**B**	NH-benzyl (1R,2S) norephedrine tethered to silica	PhCOMe	IPA, KO^{t}Bu	166:1:5:12	RT	2	95	88	3 recycles without loss in *ee* in batch slurry reactors in continuous flow reactor constant activity was obtained for period of 1 week	76
10	**B**	1(α amino benzyl)-2 naphthol	PhCOMe	IPA, KOH	200:0.5:1:4	RT	2	95	67	Patent describing the use of 1(α amino benzyl)-2 naphthol ligand for ATH of aryl alkyl ketone	77
11	**E**	Chiral ferrocenyl amino alcohol	PhCOMe	IPA, KOH	200:1:2 :5	RT	2	94	70	Stereogenic carbon is at β-position with respect to cyclopentadienyl ring	63
12	**B**	Cis-1 amino 2 –indanol	PhCOMe	IPA, KOH	400:1:4:10	RT	1.5	70	91	cis -1 amino 2-indanol gives high activity & *ee* than trans isomer.	55
13	**B**	Modified –aza norbornyl amino alcohol	PhCOMe	IPA, KOH	100 :1 :4 : 5	RT	2	97	96	Extremely active cat is formed by introducing the ketal functionality at rear end of ligand. Enhanced activity was explained by DFT calculations.	60
14	**B**	(1S,2R) cis amino 2- indanol	Tri fluro methyl AP	IPA, KOH	100 :1 :2 : 5	RT	2	98	91	Inclusion complex with DABCO developed to upgrade *ee*	78
15	**B**	Dendritic ligand of norephedrine	PhCOMe	IPA, KOH	100:1:2.5:5	25	2	70	93	Catalyst is active for 3 successive recycles. *ee* does not decrease after prolonged exposure of cat in reaction medium.	79

Sr no	Cat	Ligand	Substrate	H - donor, base	Reaction conditions			Results		Remarks	Ref
					S: Ru: L: Base	T, °C	Time, h	yield %	*ee* %		
16	**F**	L-norephedrine tethered to a tetramethylcyclopentadienyl gr.	PhCOMe	IPA, KO^{t}Bu	S: C: Base 100:5:2.5	RT	4	94	64	Catalyst does not remain stable under reaction conditions. *ee* decreases with time.	80
17	**F**	(1R,2S)-(N-3 cyclohexa-1,4-dienyl-propyl) norephedrine	PhCOMe	IPA, KOH	S: C: Base 200:1:5	28	1	98	54	Ruthenium dimer was prepared with this ligand which then forms a tethered complex.	81
18	**B**	2-azanorbornyl ,2-methanol	PhCOMe	IPA, KOH	500 :1 :2 : 5	RT	1	90	96	The origin of the *ee* was studied by DFT calculations	82
19	**C**	1R,2S amino indanol	PhCOMe	IPA, NaO^{i}Pr	200 :1 :2 : 8	30	1	95	97	Effect of ketone concentration, catalyst concentration & effect of temp studied in detail.	83
20	**B**	Ephedrine HCL	PhCOMe	Aq NaF	S: C: formate 40 :1 : 5	RT	2	99	75	First example of ATH in water with ephedrine hydrochloride salt as ligand.	84
21	**B**	Dipeptide ligands derived from amino acid	PhCOMe	IPA, NaOH	100 :0.5 :3 : 1	RT	2	81	80	Smaller R group on amino acid part of ligand gave better conversion. Presence of primary alcohol is also desirable.	85
22	**B**	Amino alcohols derived from di-ethyl tartarate	PhCOMe	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.	86
23	**B**	Amino alcohols derived from terpenes	PhCOMe	IPA, tBuOK	100:2:0.5:5	25	72	99	63	The highest *ee* is reported for terpene based amino alcohol containing a tertiary alcohol moiety.	87

Sr no	Cat	Ligand	Substrate	H - donor, base	Reaction conditions			Results		Remarks	Ref
					S: Ru: L: Base	T, °C	Time, h	yield %	*ee* %		
24	**B**	1S,2R cis amino 2-indanol	PhCOMe	IPA, tBuOK	400:1:4:10	33	1.5	99	92	Reaction conditions are optimized The kinetics of reaction reported.	88
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.	89
26	**E**	Amino alcohols from isosorbide	PhCOMe	IPA, tBuOK	100:1:1.5:1.5	70	21	96	60	Ligands are designed and synthesized from isosorbide, a by-product from the starch industry.	90
27	**B**	Amino alcohol from enantiopure phenylglycidol	PhCOMe ketones	IPA, KOH Or Aq NaF	50:1:2:4 S/C=50 2ml water	25 25	4 24	99 72	82 60	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.	91
28	**B**	Ephedrine	PhCOMe	Aq NaF	40:1:1.2:2	25	4	79	71	Secondary amine was used as additive to increase conversion.	92
29	**E**	Amino alcohol from isosorbide	PhCOMe ketones	IPA, tBuOK	100:1:2:2	70	21	94	70	Two series of epimeric β-amino alcohols are easily prepared from isosorbide and isomannide.	93
30	**E**	Amino alcohol from isosorbide	PhCOMe	IPA, tBuOK	40:1:2:2	25	2	99	70	In ligand synthesis original wedge-shaped structure is retained as it is.	94

1.3.4 Mechanism of ATH reaction

Noyori et al.[95] established the identity of the catalyst precursors and true active species involved in the transfer hydrogenation process promoted by [Ru(arene)(TsDPEN)] catalysts. The nature of the corresponding [Ru(arene)(β-amino alcohol)] intermediates was speculated to be analogous.[96] Repeated attempts were made by Carpetier et al.[24b] to isolate intermediates from the $RuCl_2$(*p*-cymene)$]_2$ and ephedrine system using synthetic methodologies similar to that reported by Noyori for TsDPEN led to mixture of products. However with other ligand (1S,2R)-(4-biphenylmethyl) nor-ephedrine the three speculated intermediates were prepared and the mechanism pathway was formally established using amino alcohol as a ligand which is shown in Figure 1.7 [24b]

The metal-ligand bifuctional mechanism is considered to be valid here. When a chelating ligand having NHR and OH groups are mixed with[$RuCl_2$(benzene)$]_2$ and base in 2-propanol, a very active catalyst system will produce. The active form of the catalyst will be **3** RuHOCH(R)CH(R)N(R) (η6-arene) and it is generated from the precursor chloride complexe **2** RuCl-HOCH(R)CH(R)N(R) (η6-arene) by reaction with a base (KOH) as shown in Figure 1.7.

After formation of the catalyst **3** the vacant d orbital of Ru will interact with 2-propanol and will abstract a proton leaving acetone to the reaction mixture. The hydride complex **4** has Ru(II) d^6, 18 electron, octahedral geometry where the arene ligand is a six-electron donor and occupies three coordination sites. The incoming substrate is oriented in such a way that it will form a hydrogen bond with the NH hydrogen on the amine ligand that is axial with respect to the five-member Ru–N–C–C–O-ring as shown in species **5**. The other two points of recognition for chiral induction are proposed to be the hydride (δ^-) to substrate sp^2-carbon (δ^+) contact and a substrate aromatic ring to η^6-ring attractive interaction. Due to such interaction in the chiral ethanolamine based Ru catalysts, the hydroxyl bearing carbon configuration is the primary determinant of the asymmetric sense in the reaction of acetophenone.

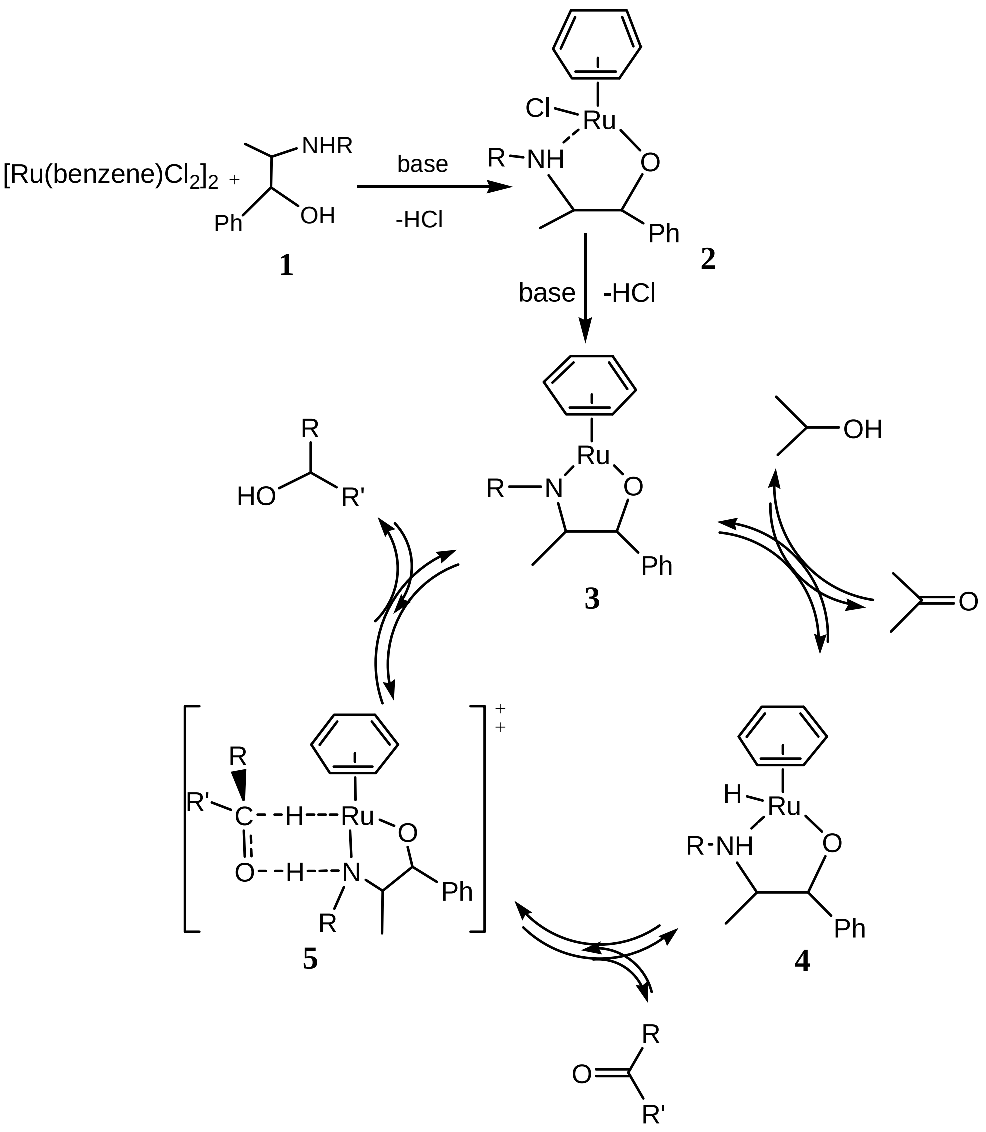


Figure 1.7: Mechanism of asymmetric transfer hydrogenation reaction of ketone

1.3.5 ATH under non conventional techniques

To enhance the activity and enantioselectivity of ATH reactions various approaches are being taken into consideration to look for alternative reaction conditions and reaction media. In this respect, ATH under non-traditional conditions like microwave and ultrasound has gained importance. Among them, the use of microwave (MW) assisted catalytic reaction has been successfully applied as alternate energy sources for ATH reaction. Moberg et al.[97] have reported the use of MW for ATH of acetophenone using $[RuCl_2(p\text{-cymene})]_2$ as a catalyst precursor and TsDPEN or ephedrine as ligands.

An increase in the activity of the catalyst was observed; however enantioselectivity was lower than that observed under conventional conditions. This may be because there is an increase in reaction temperature (above 100°C) under MW condition. In comparison, the reactions using ultrasound can be carried out under constant temperature condition and are hence found more advantageous than MW.

So far, ultrasound has been applied in organic synthesis, catalysis, extraction, emulsification, material processing, food processing, and waste water treatment.[98] It has been extensively applied in the preparation of supported noble metal catalysts.[99] The supported Pd or Pt catalysts prepared with sonochemical treatment have been used for asymmetric hydrogenation of ketones such as acetophenone, diketones and β-ketoesters. Torok et al.[100] have investigated the asymmetric hydrogenation of a prochiral C=O group using cinchonidine modified Pt/Al_2O_3 catalyst system and found that sonochemical pretreatment during preparation of the catalyst was most advantageous in giving very high *ee* values. Observed improvement was explained on the basis of the synergistic effect of the transformation and surface cleaning of metal particles and enhanced adsorption of cinchona (chiral modifier) initiated by ultrasound. In most of the cases ultrasound has been used to modify the nature of active catalytic sites leading to significant increase in activity and in some cases enantioselectivity. However, there are no reports on the effect of ultrasound promotion in homogeneously catalyzed ATH reactions. So it was proposed to study the ATH reaction under ultrasound. For this purpose a brief introduction of ultrasound or sonochemistry is necessary and is presented in the next section.

1.3.5.1 Application of ultrasound to chemical reactions:

1.3.5.1.1 Introduction to Sonochemistry

The European Society of Sonochemistry has defined sonochemistry as the application of ultrasound to chemical reactions and processes.[101] Hence Sonochemistry is chemistry assisted/enhanced by ultrasound. Ultrasound is defined as sound of a frequency beyond the range that the human ear can respond. The normal range of hearing is between 10 Hz and about 18 kHz and ultrasound is generally considered to lie between 20 kHz to beyond 100 MHz. Sonochemistry generally uses frequencies between 20 and

40 kHz because this is the range employed in common laboratory equipment. High frequency ultrasound from around 5 MHz and above does not produce cavitation and is used in medical imaging. Figure 1.8 shows the frequency ranges of sound and the applied frequencies in the field of sonochemistry.

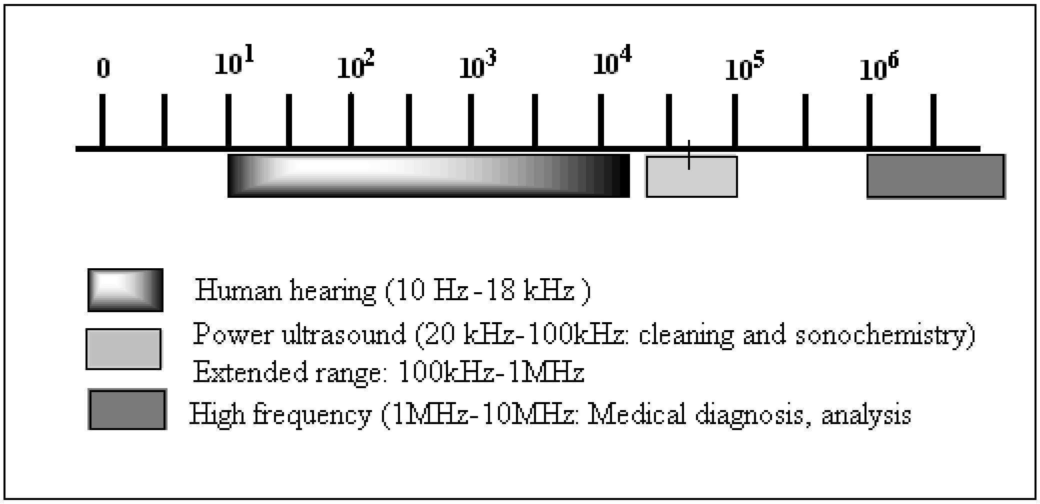


Figure 1.8: Frequency ranges of sound and its application[98b]

1.3.5.1.2 The Role of Ultrasound in Chemistry

The role of ultrasound in chemistry has been well documented in the literature. The possible benefits from the use of ultrasound in the chemical reaction are as follows.[102]

- A reaction may be accelerated or less forcing condition may be required if sonication is applied (energy saving).
- Induction periods are often significantly reduced.
- Sonochemical reactions often make use of cruder reagents than conventional techniques.
- Reactions are often initiated by ultrasound without the need for additives (can reduce waste).
- The number of steps that are normally required in a synthetic route can sometimes be reduced.
- In some situations a reaction can be directed to an alternative pathway.

These chemical effects of ultrasound arise from the physical processes that create, enlarge and implode gaseous and vaporous cavities in a liquid.[103] This phenomenon called as 'cavitation' is described below.

1.3.5.1.3 Cavitation Process

Like all sound waves, ultrasound waves consist of cycles of compression and expansion. Compression cycle exerts a positive pressure on the liquid, pushing the molecules together; expansion cycle exerts a negative pressure, pulling the molecule away from one another.

During the expansion cycle a sound wave of sufficient intensity can generate cavities. A liquid is held together by attractive forces, which determine the tensile strength of a liquid. In order for a cavity to form, a large negative pressure associated with the expansion cycle of the sound wave is needed to overcome the liquid's tensile strength. The amount of negative pressure needed depends on the type and purity of the liquid. However, the tensile strength of liquids is reduced by gas trapped in the crevices of small solid particles. When a gas-filled crevice is exposed to a negative-pressure cycle from a sound wave, the reduced pressure makes the gas in the crevice expand until a small bubble is released into solution. Most liquids are sufficiently contaminated by small particles to initiate cavitation. A bubble in a liquid is inherently unstable. If the bubble is large, it will float away and burst at a surface; if it is small, it will redissolve into the liquid. A bubble irradiated with ultrasound, however, continually absorbs energy from alternating compression and expansion cycles of the sound wave. These cause the bubbles to grow and contract, attaining a dynamic balance between the vapor inside the bubble and the liquid outside. In some cases the ultrasonic waves will sustain a bubble that simply oscillates in size. Cavity growth depends on the intensity of sound. The growing cavity can eventually reach a critical size where it will most efficiently absorb energy from the ultrasound. Once a cavity has experienced a very rapid growth caused by either low or high-intensity ultrasound, it can no longer absorb energy as efficiently from the sound waves. Without this energy input the cavity can no longer sustain itself. The liquid rushes in and the cavity implodes. Figure1.9 presents sound propagation in a liquid showing cavitation bubble formation and collapse.

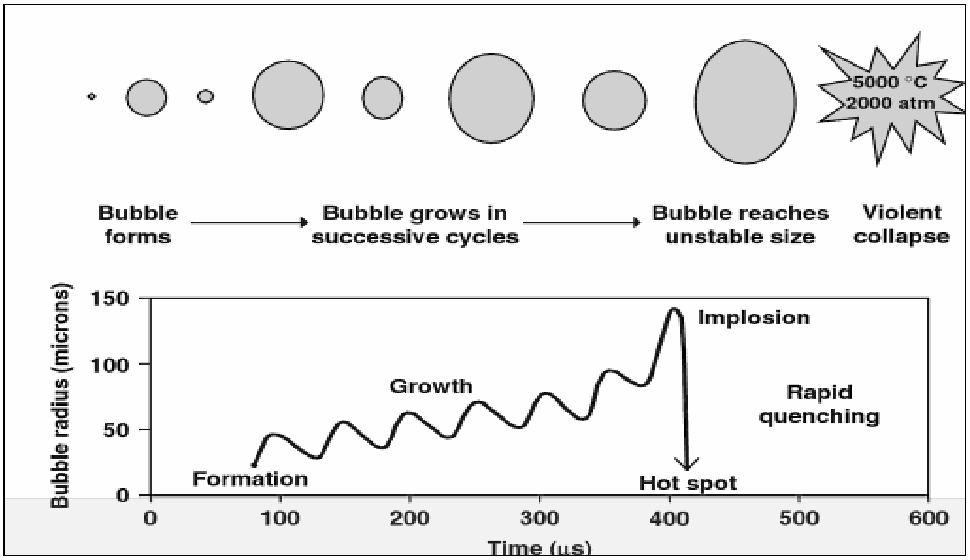


Figure1.9: Sound propagation in a liquid showing cavitation bubble formation and collapse[104]

The implosion of cavities establishes an unusual environment for chemical reactions. The gases and vapors inside the cavity are compressed, generating intense heat that raises the temperature of the liquid immediately surrounding the cavity and creates a local hot spot. The energy released during the implosion creates high local pressures up to 1000-2000 atmosphere and high transitory temperatures up to 5000°C.[105] This energy releasing phenomena of the bubble formation and collapse is termed as acoustic cavitation.[106] Even though the temperature of this region is extraordinarily high, the region itself is so small that the heat dissipates quickly. Thus, sonochemistry depends on the nature or physicochemical properties of the solvent, solute or gas in the bubble which have dramatic effect on the cavitational collapse.

1.3.5.1.4 Parameters Influencing Cavitation

1.3.5.1.4.1 Effect of solvent

Cavities are readily formed when using solvents with high vapour pressure, low viscosity and low surface tension. The intermolecular forces in the liquid must be overcome in order to form the bubbles. Thus, solvents with high densities, surface tensions and viscosities generally have higher threshold for cavitation but higher amplitudes are required when cavitation begins.[106a]

1.3.5.1.4.2 Effect of ambient gas

The heat capacity ratio Cp/Cv or polytropic ratio of the gas in the bubble affects the amount of heat released and, hence the final temperature produced in an adiabatic compression. Higher temperatures and pressures are generated with monoatomic gases with higher polytropic ratio. Also a gas with low thermal conductivity reduces heat dissipation from cavitation site and hence should favor higher collapse temperature compared with high thermal conductivity gas.[103b, 107]

1.3.5.1.4.3 Effect of temperature

Unlike most of the reaction systems, the rate of reaction in ultrasound increases with lowering of the reaction temperature. As the liquid temperature decreases, the amount of gas dissolved increases and the vapor pressure of the liquid decreases. At low vapor pressure, fewer vapors have an opportunity to diffuse into the bubble making the implosion more violent and thus increase the intensity of cavitation.[108]

1.3.5.1.4.4 Effect of acoustic intensity

An increase in ultrasound intensity implies an increase in the acoustic amplitude. The collapse time, the temperature and the pressure of collapse are all dependent on the acoustic amplitude. The cavitation bubble collapse will be more violent at higher acoustic amplitudes. So an increase in intensity will result in greater sonochemical effects in the collapsing bubble.[107]

1.3.5.1.4.5 Frequency of ultrasonic irradiation

Frequency has a significant effect on the cavitation process because it alters the critical size of the cavitational bubble.[109] At high frequencies, the cavitational effect is reduced because either (i) the rarefaction cycle of the sound wave produces a negative pressure which is insufficient in its duration and/or intensity to initiate cavitation or (ii) the compression cycle occurs faster than the time for the microbubble to collapse. Lower frequency ultrasound produces more violent cavitation, leading to higher localized temperature and pressure.

1.3.5.1.5 Laboratory equipments

The first requirement for sonochemistry is a source of ultrasound. Whatever type of commercial instrument is used the energy will be generated via an ultrasonic transducer. It is a device by which mechanical or electrical energy can be converted to sound energy. There are three main types of ultrasonic transducers used in sonochemistry: liquid-driven (effectively liquid whistles), magnetostrictive (based on the reduction in size of certain metals, e.g. nickel, when placed in a magnetic field) and piezoelectric. Most of the current equipments used for sonochemistry utilize transducers constructed of piezoelectric ceramics. These are brittle and so it is normal practice to clamp them between metal blocks for protection. The overall structure is known as a piezoelectric 'sandwich'. Usually two ceramic elements are combined so that their overall mechanical motion is additive. Piezoelectric transducers are very efficient and, depending on their dimensions, can be made to operate over the whole ultrasonic range. The two most common sources of ultrasound for laboratory sonochemistry are the ultrasonic cleaning bath and the ultrasonic horn or probe system.[110]

1. The ultrasonic cleaning bath: It usually consists of a tank fitted with a transducer at the bottom. The reaction flask can be immersed in to the tank filled with some liquid mostly water. The intensity within the bath is fixed, low, location dependent and inconsistent due to fluctuation in the level of bath and temperature of the liquid.
2. Ultrasonic horn or probe system: In the ultrasonic horn/probe system, the piezoelectric ceramic transducer is attached to a tapered titanium rod, which serves to amplify the sound. The horn vibrates at a fixed acoustic frequency but the intensity is variable. This apparatus allows acoustic energy to be introduced directly into the system rather than rely on its transfer through the water of a tank. With an ultrasonic probe system, processing is fast and highly reproducible. The energy at the probe tip is high, focused and adjustable

After investigating the homogeneous catalysis for transfer hydrogenation for asymmetric synthesis, the second objective of thesis was to study the heterogeneous catalysis for transfer hydrogenation reactions. The following section describes the use of heterogeneous and homogeneous (biphasic) catalysis for transfer hydrogenation reaction.

1.4 HETEROGENEOUS CATALYTIC TRANSFER (CTH) USING Pd/C CATALYST.

As discussed in historical overview of transfer hydrogenation reaction (section 1.2.2), the first transfer hydrogenation reaction discovered by Knoevenagel et al.[8] was carried out with palladium black as the catalyst. Since then the most of the catalysts developed for transfer hydrogenation were based on palladium metal. Among various supported palladium catalysts, Pd/C catalyst has been used as the most effective heterogeneous catalyst for transfer hydrogenation reactions. It has been the most widely used hydrogenation catalyst both in research laboratories in academia and chemical industry. Over the period, various hydrogen donors such as cyclohexene,[111] phosphinic acid,[112] formic acid,[113,114] ammonium formate,[115-117] sodium formate, potassium formate,[118] and methyl cyclohexene[119] have been developed for CTH with Pd/C catalyst. A large variety of substrates with different functional groups have been reduced with Pd/C catalyst with different hydrogen donors. The literature of CTH using Pd/C catalyst based on hydrogenation of specific functional groups with special emphasis on nitro group hydrogenation is described below.

Until the first report on the use of sodium formate for Pd/C catalyzed transfer hydrogenation by Sasson et al.[120], the reports on CTH of various substrates were concentrated on hydrogen donors such as hydrocarbons (cyclohexene, d-limonene, tetralene, d-phellandrene etc) [121,122] and amines (indoline, N-benzylaninline etc).[123] Use of salts such as sodium phosphonate,[124-126] triethyl and tributylammonium salts of formic acid are also reported to be effective hydrogen donors for CTH of various substrates.[127,128] The literature on CTH using these hydrogen donors is well documented in the literature reviews.[129] In 1984 Sasson et al.[120] first time reported the use of sodium formate as efficient hydrogen donor for CTH of alkenes and nitro compounds using 10% Pd/C catalyst. Since then the research was concentrated on CTH of various substrates using formate salts as hydrogen donors. The details of these reactions are summarized below.

<u>Olefins</u>- Pd/C-catalyzed transfer hydrogenation of olefins such as styrene, cyclohexene, cyclohexene, allylbenzene, 4-allylanisol, acetylenes etc with sodium formate as hydrogen donor was first reported by Sasson et al. as stated above.[120] The reaction proceeds mainly

by a direct hydrogen transfer mechanism rather than via initial decomposition of the formate into molecular hydrogen and carbon dioxide. The CTH of C=C double bond of γ-keto-α-β unsaturated carboxylic acids has also been reported by Cavinato et al.[130] with sodium formate as a hydrogen donor. The CTH of olefinic bond of in cyclic α-β unsaturated ketones has been reported with ammonium formate as hydrogen donor.[131,132] After that, a series of steroidal olefins with the double bonds of different type of substitution pattern and steric hindrance were reduced by ammonium formate in refluxing methanol.[133] Recently, hetero-aromatic furan ring has also been reduced to corresponding tetrahydrofuran moiety in THF and methanol mixture with 10% Pd/C.[134] The kinetics of the CTH of linolenic acid over 5% Pd/C catalyst in aqueous ammonium formate has been discussed in detail in order to facilitate process design attempts.[135] With 1,4 cyclohexadiene as a hydrogen donor the olefinic bond of cinnamic acid was reported to reduce completely with in 5-10 min at 100°C in microwave.[136]

Azo, Azide compounds- Several azides have been reduced to the corresponding primary amines through catalytic transfer reduction with Pd/C and ammonium formate.[137] The use of recyclable polymer-supported formate for reduction of azo compound to corresponding amine in high yield (88-98%) has reported by Gowda et al.[138] using Pd/C catalyst.

Ketones and Aldehydes-Early observations of Braude et al.[139] have showed that hydrogen transfer from cyclohexene in presence of Pd/C was completely inhibited by the presence of carbonyl compounds. But further investigations showed that CTH of carbonyl compounds was possible with Pd/C catalyst by adding Lewis acid promoter such as ferric chloride.[140] The C=O of carbonyl compound was reduced directly to hydrocarbon (CH_2). No intermediate alcohol could be isolated. Further, Ram and Spicer[141] found that ketones could be hydrogenated to alcohols with 91% yield with ammonium formate as a hydrogen donor and 10% Pd/C as a catalyst. Aldehydes were reduced with only 16% yield with this approach. However, Sasson et al.[142] were successful to reduce aldehyde selectively to the corresponding alcohols using potassium formate as the hydrogen donor and 5% Pd/C as a catalyst. This was attributed to the presence of the basic potassium bicarbonate, which is generated in situ by the reaction of potassium formate and water in presence of Pd/C. Ketones however did not react under these conditions.

Hydrogenolysis-These reactions include the cleavage of C-O, C-N, C-S, and C-halogen bonds. The rapid dehalogenation of mono-or polychlorinated aromatic compounds was achieved using ammonium formate under ambient conditions of temperature and pressure.[143] The catalytic activity of Pd/C has been found to improve significantly by pretreatment with ammonium formate for 10 to 30 minutes.[144] The detailed mechanistic study on Pd/C-catalyzed transfer hydrogenolysis of aryl halides by formate salts was carried out by Sasson et al.[145] and Spatola et al.[146] Sodium formate was also found to be effective for the rapid dehalogenation of aromatic chlorocarbons in water at room temperature.[147] Hydrodechlorination of aryl chlorides has also been performed in a solution of 2-propanol/methanol containing NaOH in the presence of a supported palladium catalyst (Pd/C, Pd/TiO_2, or Pd/Al_2O_3) at 30–40°C.[148]

Nitroarenes- The CTH of nitroarenes to corresponding amines with Pd/C catalysts has been reported with various hydrogen donors like cyclohexene[121,149], hydrazine[150] phosphinic and phosphorous acids and their salts[151,152] and triethylammonium formate.[153] The use of ammonium formate for Pd/C catalyzed CTH of nitro-compounds in high yields was reported for the first time by Ram et al.[154] The α-nitro esters were found to reduce rapidly to corresponding α-amino esters, however, α-nitro acids on reduction decarboxylated to corresponding alkylamines.[116] Oximes could be easily produced in good yields by reduction of α-β unsaturated nitroalkenes using ammonium formate in the presence of 5% Pd/C catalyst at room temperature in methanol and THF solvent system.[155] Recently Mahajani et al.[156] have thrown light on various process development aspects for CTH of o-nitro anisole to o-anisidine using Pd/C catalyst and ammonium formate as hydrogen donor. Instead of ammonium formate, sodium formate was also used by Sasson et al. effectively to reduce 4-nitrotoluene to toluidine.[157]

Gowda and co-workers[158] showed that the use of formic acid alone with a catalytic amount of Pd/C instead of ammonium formate was an interesting alternative for reduction of nitro compounds as it generates only carbon dioxide as a by-product. But, the reported reaction conditions were not practical due to its highly exothermic nature (30 -50% wt of Pd/C and almost 12 equivalents of formic acid were used). However, Prasad et al.[113] have recently shown that if catalytic amount of base is added to formic acid only 3.6 equivalents of acid is sufficient to reduce nitro compound. If the substrate that needed to be reduced was basic enough to form salts with formic acid, no additional base was found necessary.

1.4.1 Kinetics of CTH reaction using Pd/C catalyst

Kinetics provides the framework for describing the rate at which a chemical reaction occurs and enables us to relate the rate to a reaction mechanism that describes how the molecules react via intermediates to the eventual product. It also allows us to relate the rate to macroscopic process parameters such as concentrations, pressures, and temperatures. Hence, kinetics provides us with the tools to link the microscopic world of reacting molecules to the macroscopic world of industrial reaction engineering. Obviously, kinetics is a key discipline for catalysis.

Compared to the large volume of literature on CTH using Pd/C catalyst, only few studies have reported the kinetics of reaction. Table 1.4 presents the details of kinetic investigations on CTH various substrates systems with Pd/C catalyst. Majority of kinetic investigations have been reported for CTH of alkenes and hydrogenolysis reaction and there is only one report on CTH of nitro-arene reaction. The kinetics has been done at single temperature only and rate equations have not been derived in most of the cases. The catalytic cycle in every case has been proposed to proceed through the adsorption of the hydrogen donors, followed by a hydride abstraction from absorbed formate and water. Hydrogens transfer from this hydride and water to the substrate yields the products and regenerates the catalyst, after the desorption steps. The brief description of the kinetic study is given below.

The initial studies were carried out on Pd/C catalyzed CTH reaction used indoline as a hydrogen donor.[159] The olefin hydrogenation of cycloheptene as substrate at 90°C was carried out. The rates were found to vary first order with respect to catalyst concentration and first order tendering to zero with donor concentration. The rate passed through a maximum with varying cycloheptene concentration. The activation energy calculated was 11.2 kcal /mol.

Further studies on Pd/C catalyzed transfer hydrogenation was done with aqueous sodium formate as a hydrogen donor. 4-allyl anisole was used as substrate, benzene as solvent and reactions were carried out at 33°C.[160] Authors have estimated that at low substrate concentration) the reaction followed first-order kinetics. Best results were obtained at a molar ratio of water: formate of 2. Above this ratio the rates dropped. Authors assumed that the water forms a thin film of sodium formate solution on the surface of the catalyst and served as medium of contact. Two different mechanisms have been suggested to operate in the system as follows,

(i) A two-stage mechanism in which sodium formate is initially decomposed according to following equation and then the liberated molecular hydrogen is used to reduce unsaturated substrate

$$HCOONa + H_2O \longrightarrow H_2 + NaHCO_3$$

(ii) A mechanism that involves direct hydrogen transfer from the formate to the substrate adsorbed on the surface of the catalyst.

The major reduction was found to proceed by direct hydrogen transfer from the donor to the acceptor however contribution of mechanism (i) was not excluded.

Cavinato et al.[161] further studied the selective hydrogenation of C=C bond of γ-keto-α-β unsaturated carboxylic acids using sodium formate as a hydrogen donor and 10 % Pd/C catalyst at 90°C. The reaction rate was found to increase with the increasing concentrations of formate and substrate. The rate passes through a maximum with increase in water concentration.

Recently Mahajani et al.[162] have studied the kinetics of CTH of soybean oil (reduction of olefinic bond of linolenic acid) using 5% Pd/C catalyst and ammonium formate as hydrogen donor at 90°C. The rate model in terms of iodine value (IV) has been derived as $k_{IV} = k^*_{IV}(D_H)(\omega)$. The energy of activation was found to be 43.1 kJ/mol.

The kinetic study of CTH of 4-nitrotoluene has been reported with aqueous potassium formate as hydrogen donor at 70°C.[157] A three phase system (liquid/liquid/solid) was chosen for this study. The rate was found to be independent of the substrate concentration in the range 0.5-5M and above this concentration a drop in rate was observed. A very sharp optimum initial rate was obtained when the water/formate molar ratio was 2.7. This ratio corresponds to an 11M solution of potassium formate in water. Following mechanism has been suggested to operate.

1. $C + S \rightleftharpoons CS$
2. $CS + F \rightleftharpoons SCF$
3. $SCHF + W \rightleftharpoons CFSW$
4. $CFSW \longrightarrow (SH_2)CB$
5. $(SH_2)CB \longrightarrow C + B + SH_2$

Where C is the active site of catalyst; S is hydrogen acceptor (substrate); F is formate anion; W is water molecule; and B is bicarbonate anion.

Similar types of trends have been reported for kinetics of hydrogenolysis of chlorobenzene using aqueous potassium formate as a hydrogen donor at 50°C by the same group.[163] With sodium formate as a hydrogen donor, kinetics of hydrodechlorination of 2-chlorotoluene at 20°C has been reported by Rajgopal et al.[164] The role of water as hydrogen donor has been completely ruled out and the rate expression derived was, $R = k' [HCOONa] / [Pd/C]$. For hydrogenolysis of benzyl acetate with ammonium formate as a hydrogen donor, the rate equation derived was $R = k' [HCOONH_4] [Pd/C]$.[165]

In general, the trends observed for kinetics of transfer hydrogenation using Pd/C catalyst for different substrates can be summarized as follows:

1. First order in catalyst concentration.
2. The initial rate increases linearly with donor concentration. However, at higher concentration the rate is either independent of the donor concentration or decreases with donor concentration
3. Rate depends largely on type of substrates used. The rate either passes through maxima or is initially linear and then decreases or in some cases is independent on substrate concentration,
4. Water, at low concentration has a beneficial effect on the reaction rate.

Table 1.4: Kinetics of transfer hydrogenation of using Pd/C catalyst

Here, R = Rate of reaction A = concentration of substrate B = concentration of hydrogen donor; C = Concentration of the catalyst; D = Concentration of water; EA= activation energy; k = Rate Constant

Sr. no	Substrate	Type of reduction	Conditions			Remarks	Ref.
			Hydrogen Donor	Solvent	T, °C		
1	Cycloheptene	olefin reduction	Indoline	Toluene	65-140	$R \propto C$, Rate is linear upto 0.3 M concentration. of B then become independent at high concentration of B, rate passes through maxima with respect to A, EA= 11.2 kcal/mol	159
2	4-Allylanisole	olefin reduction	HCOONa	Benzene	33	Follows first order kinetics at lower substrate conc., rate decreases at D: B ratio greater than 2. Mechanism discussed where direct hydrogen transfer from donor to substrate is suggested, No rate equation is derived.	160
3	Nitrotoluene	Nitro reduction	HCOOK	Toluene	70	$R \propto C$, independent with A at low concentration, at high conc. rate decreases, D:B = 2.7, EA= 10.6 kcal/mol	157
4	Chlorobenzene	Hydrogenolysis	HCOOK	Ethanol	50	Rate max at D:B=3, suggested that scission of formyl C-H bond or water O-H bond is not RDS	163
5	2-Chlorotoluene	Hydrogenolysis	HCOONa	Ethanol	20	$R \propto C$, B independent with A, No role of water as H-donor, $R = k'$ [HCOONa]/[Pd]	164
6	Benzyl acetate	Hydrogenolysis	$HCOONH_4$	Ethanol	20	$R \propto C$,B and independent with A, No role of water as H-donor, R = k' [$HCOONH_4$] /[Pd/C].	165
7	γ-keto-α-β unsaturated carboxylic acid	olefin reduction	HCOONa	Dioxane	90	Parametric study, Yield increases with increase in B and A, yield max at D:B=2.8, rate equation not derived.	161
8	soybean oil	olefin reduction	$HCOONH_4$	Water	90	At high concentration of A and B, rate decreases, $k_{IV} = k^{*}_{IV}(D_H)(\omega)$ EA=43.1 kJ/mol	162

1.4.2 Heterogeneous Transfer hydrogenation using Pt catalysts.

Under transfer hydrogenation conditions hydrogenolysis is also possible with palladium catalyst as discussed in last section. The selective hydrogenation of nitro compounds in presence of other functional groups particularly in presence of halogens is not possible by palladium catalysts as dehalogenation reaction is also observed there. In this context platinum metal is useful as dehalogenation is not observed and selective hydrogenation is possible. Gowda et al.[166] have showed it first time that selective transfer hydrogenation of aromatic nitro compounds in presence of halogen is possible with the use of 5% Pt/C catalyst and ammonium formate and formic acid as hydrogen donor.

However unlike Pd metal, the literature on use of Pt metal for CTH reactions is relatively scarce. There are few reports describing the use of platinum metal for CTH of Schiff bases, propylene, acetophenone and nitro-compounds. But detail optimization of reaction parameters has not been reported so far.

Platinized titanium (IV) oxide suspended in 2-propanol has been used for CTH of Schiff bases to corresponding amines (95% yield) when photoirradiated at >300 nm. Dehydrogenatiom of 2-propanol occurred as side reaction.[167] Platinum catalysts supported on γ -Al_2O_3 and on various zeolites were reported to be active in CTH of propylene (90% conversion) using n-butane as the hydrogen source.[168] Recently, Alonso et al.[169] have reported that platinum nanoparticles supported on titania (Pt/TiO_2) and on activated carbon (Pt/C) can catalyze the CTH of acetophenone to 2-phenyl ethanol in IPA as hydrogen donor. These catalysts were easily reused and retained their catalytic activity over five consecutive cycles without any apparent loss of catalytic activity.

1.5 TRANSFER HYDROGENATION IN BIPHASIC MEDIA

As discussed in section 1.1, homogeneous catalysis has its own advantages. The selectivity of the desired reaction can be fine-tuned by designing special ligands in homogeneous catalysis. However the major drawback of homogeneous catalytic processes is that the catalyst recovery is very complex and there is an inevitable loss of the catalyst during separation. To overcome the problem of catalyst-product separation in homogeneously catalyzed processes, different methodologies have been investigated to heterogenise the homogeneous catalysts. These catalysts could then combine the advantages of homogeneous catalyst i.e. high activity and selectivity with those of heterogeneous catalysts i.e. long lifetime and ease of separation. These methodologies have been broadly categorized as biphasic catalysis and solid supported catalysis of which biphasic catalysis is described below.

1.5.1 Biphasic Catalysis

In biphasic catalysis, the catalyst resides in one of the two liquid phases while the substrate and products reside in the other phase. During reactions, the two layers are vigorously stirred, thus allowing suitable interaction of catalyst and substrate. Once the reaction is completed, the stirring is stopped and the two phases separate into two layers, one containing the product and the other containing the catalyst. Separation of the two phases is then carried out by simple decantation and, in principle; the catalyst solution is available for immediate reuse. Clearly, these biphasic reactions offer a potential answer to the problems associated with homogeneous catalysis. The biphasic catalysis is advantageous than conventional homogeneous catalysis in the following respect.

- It provides an easier way of separation of product and catalyst. This has direct impact on the recycle/recovery of the catalysts and the economy of the process.
- Contamination of product with the catalyst is minimized and helps in preventing deactivation of the catalyst.
- For substrate-inhibited kinetics, higher activity is achievable in such systems as the concentration of reactants in the catalyst phase can be controlled by taking advantage of solubility limitations.

Various possible biphasic systems employed are presented below in brief. A detailed account of aqueous biphasic catalysis with particular emphasis on transfer hydrogenation is presented later.

1.5.1.1 Organic-organic biphasic catalysis

The system is based on the immiscibility of liquids that have different polarities. This organic-organic biphasic procedure was first introduced to industry by Shell in its SHOP process for production of higher olefins by oligomerisation of ethene. Ni-containing catalyst is dissolved in 1, 4 butane diol and the other phase is composed of compressed ethene. The products separate as a second liquid phase above the 1,4 butanediol and can therefore be removed without any difficulty.[170]

1.5.1.2 Biphasic catalysis in ionic liquid

This approach employs ionic salts, which have a low melting point. They form biphasic systems with numerous organic solvents. The ionic liquids in this context are liquids at ambient temperature. The cations utilized in ionic liquids are often tetra-alkyl ammonium, tetra-alkyl phosphonium, N-alkyl-pyridinium, N-alkylated imidazolium or N-alkylated pyrolidinium cations. The anions commonly used includes $[N(CF_3SO_2)_2]^-$, $[CF_3SO_3]^-$, $[PF_6]^-$, $[BF_4]^-$, $[NO_3]^-$. The system has mainly been used by academia in several organometallic-catalyzed reactions, but not found an application in industry yet, mainly because of their very high cost.[171]

1.5.1.3 Fluorous- Organic biphasic catalysis

In this system, the catalyst containing phase is of fluorohydrocarbons and second phase is of organic solvent with limited solubility in fluorous phase. Organometallic complexes can be solublised in fluorous phase by the attachment of fluorocarbon moieties to ligands such as phosphines, phosphites and porphyrin. The fluoro-hydrocarbons are miscible with organic phase at reaction temperatures but immiscible at lower temperature. This property facilitates easy catalyst and product separation. The concept has been tested for hydroformylation and oligomerisation reactions. The major drawback of this system is the residual fluorocarbons produced cause environmental damage and high cost of fluorinated phosphines.[172]

1.5.1.4 Aqueous Biphasic Catalysis

Kuntz at Rhone-Poulenc first realized the fundamental concept of aqueous biphasic catalysis.[173] The general principle of aqueous biphasic catalysis is the use of a water soluble catalyst, which is insoluble in the organic phase containing reactants and products. The catalyst brings about the particular catalytic reaction in the aqueous phase and is then removed from the product-phase by simple phase separation or decantation. The selection of water is straightforward and offers many benefits. Aqueous biphasic catalysis particularly gained importance because of the many advantages of water as the solvent. Water is cheap, non-toxic, easily purified and readily obtained; also, wide ranges of organic solvents are immiscible with water.[174]

Aqueous biphasic catalysis requires a water-soluble catalyst to be used. The solubility of the catalysts in water is determined by their overall hydrophilic nature which may arise either as a consequence of the charge of the complex ion as a whole, or may be the good solubility of the ligands.[175] Some of the neutral ligands are water soluble because of their ability to form hydrogen bonds with the surrounding water molecules. These ligands usually contains several N or O atoms, such as the 1, 3, 5-triaza-7-phosphaadamantane (PTA), tris(hydroxymethyl) phosphines, ($P(CH_2OH)_3$) or several phosphines containing long polyether chains (e.g. polyethyleneglycol-PEG-type). But the most frequently used ligands in aqueous biphasic catalysis are derived from water insoluble tertiary phosphines by attaching ionic or polar groups onto them. The hydrophilic entities generally reported are sulfonate, sulfate, phosphonate, carboxylate, phenolate, quaternary ammonium and phosphonium, hydroxylic, polyether, or polyamide (peptide) substituents or any combination of them. Sulfonated phosphines are the most important ligands in aqueous organometallic catalysis since they dissolve well throughout the pH-range and are insoluble in common non-polar organic solvents. These ligands can be prepared with straightforward methods. The sulfonate group is deprotonated in a wide pH-range so its coordination to the metal need not be considered, and they are sufficiently stable under most catalytic conditions. For these reasons the most important ligands used in aqueous catalysis in both academia and industry are the sulfonated monodentate phosphines e.g. TPPMS, TPPTS, and sulfonated bidentate tertiary phosphines such as BINAPS, BISBIS and BINAS. Figure 1.10 shows some of the important water-soluble ligands used in aqueous biphasic hydrogenation reaction.

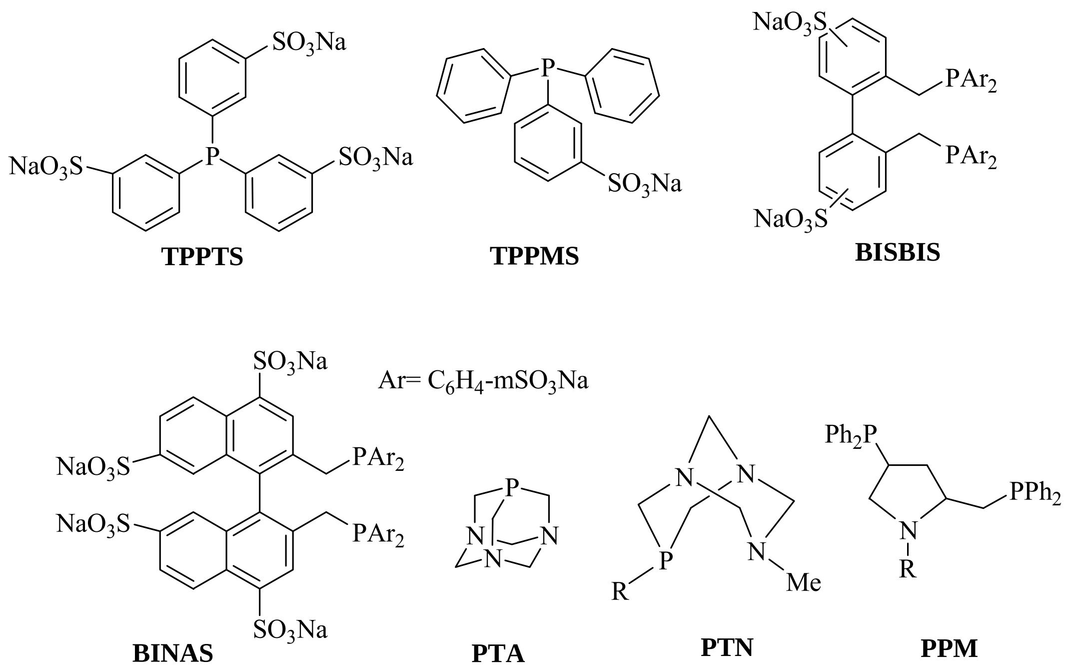


Figure 1.10: Structures of some water soluble ligands

These ligands have industrial application for the reactions like hydroformylation, hydrogenation, hydrodimerisation, and telomerisation etc. Table 1.5 shows some of the commercial processes which use the aqueous biphasic catalysts.[176]

Table 1.5: Industrial aqueous biphasic catalysts and commercial processes

Reaction product	Catalyst	Capacity tons/yr.	Process[176]
n-Butyraldehyde	Rh-TPPTS	800,000	Ruhrchemie/Rhone-Poulenc (now Hoechst Celanese)
n-Octanol, nonanediol	Ru-TPPMS	5,000	Kuraray Co.Ltd
Substituted biphenyls	Pd-TPPTS	<1,000	Clariant AG
Vitamin precursors	Rh-TPPTS	Exact capacity not known	Rhodia (former Rhone – Poulenc)

1.5.1.5 Approaches to Improve Reaction Rates in Aqueous Biphasic Medium

One of the major limitations of the aqueous biphasic catalysis is the lower activity for reactions due to poor solubility of some substrates in the aqueous catalyst phase. (e.g. hydroformylation of higher olefins). Different attempts have been made to increase the solubility of substrates in water (catalyst phase). These involve addition of various components such as co-solvents, surfactants, phase transfer agents and promoter ligands to the reaction mixture.

- Addition of co-solvents to the catalyst (aqueous) phase improves the solubility of substrate in the aqueous phase within a wide range of operating conditions.[177] The ideal co-solvent should have following properties.
  - Sufficient solubility in water
  - Inertness towards reactants and products.
  - Negligible solubility in organic phase.
  - Should not enhance solubility of water in the organic phase
- Amphiphilic ligands can act as a surfactant (surface-active agent) and can aggregate in aqueous nonpolar media forming micelles, which increase liquid-liquid interfacial area and thereby reaction rates. Typical micelle forming surfactants are SDS, CTAB, STAC and DDAPS. The considerable improvements in activities in the presence of surfactants for different reactions such as hydroformylation, hydrogenation including transfer hydrogenation have been reported in literature.[178] The major drawback of the use of surfactant is the separation of product from the micellar system.
- It is also possible to achieve better activity in biphasic transfer hydrogenation reaction using phase transfer catalysis. For example the ruthenium complex $RuCl_2(PPh_3)_3$, was used to catalyze transfer hydrogenation of aromatic aldehydes with aqueous sodium formate as a hydrogen donor and catalytic amounts of quaternary ammonium salts under phase transfer conditions.[179] The important advantage of phase transfer catalyst is the easy separation of the catalyst from the product.

Since the major objective of this work was to study the transfer hydrogenation reaction of α-β unsaturated carbonyl compounds in aqueous biphasic media, a detailed literature search was conducted keeping these objectives in mind. Initially the literature on aqueous biphasic medium is presented and thereafter a detailed literature analysis on the kinetic studies on this reaction is presented.

1.5.2 Literature on Transfer Hydrogenation in Aqueous Biphasic Medium

The use of water soluble sulfonated phosphines in hydrogenation was first reported in 1973 with a publication by Joo and Beck[180] and initiated a development in the field of aqueous biphasic hydrogenation with achiral and chiral catalysts.[181] Since then, various transition metal complexes of Rh, Ru, Ir, Pd and Os have been reported for biphasic catalytic hydrogenation.[182] A number of attempts to design biphasic catalysts for transfer hydrogenation have also been made because of the good water solubility of the hydrogen donors like formate salts and 2-propanol, which are frequently used. The transition metal complexes of ruthenium and rhodium have been successfully applied for transfer hydrogenation of various substrates in biphasic media. Different water soluble ligands like TPPMS, TPPTS, PTA and PTN have been reported for that purpose. The details of transfer hydrogenation reaction in aqueous biphasic media are presented below.

Bar et al.[183] were the first to demonstrate the application of aqueous formate salts as hydrogen donor for transfer hydrogenation of saturated and unsaturated ketones in organic phase using $[RuCl_2(PPh_3)_3]$ and $[RhCl(PPh_3)_3]$ catalyst. Since in this case both the catalyst and the substrate reside in the organic phase, a phase transfer agent was necessary to transport $HCOO^-$ from the aqueous into the organic phase. Quaternary ammonium salts $[R_4N]^+$ were applied for this purpose. An important feature of the reaction is the strong substrate inhibition which does not allow the reduction of substrate e.g. benzaldehyde in solutions with higher than 0.8 M concentration. The precise nature of this substrate inhibition is not clear. It may be due to formation of catalytically inactive intermediates either via η^1-O or η^6-C_6H_5CHO coordination of the substrate aldehydes.

As $[RuCl_2(PPh_3)_3]$ and $[RhCl(PPh_3)_3]$ complexes were found effective for transfer hydrogenation in aqueous systems with phase transfer agents, the use of water soluble analogues of these catalysts for CTH was also demonstrated by many authors. In a series of investigations with Ru/TPPMS and Rh/TPPMS catalysts, linear olefins have been hydrogenated with HCOOH/HCOONa as hydrogen donor.[184]

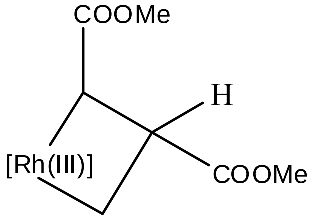
Various aldehydes have also been hydrogenated using sodium formate as a hydrogen donor and water soluble [$RuCl_2(TPPMS)_2]_2$ catalyst with excess of TPPMS.[185,186] The organic phase reported for this study was chlorobenzene. Unsaturated aldehydes, such as cinnamaldehyde and citral have been hydrogenated to the corresponding unsaturated alcohols with high selectivity. No *cis-trans* isomerization was observed around the C=C double bond. It is important to note, that in this arrangement of an aqueous/organic biphasic reaction the substrate inhibition discussed above was hardly observable. Although the aldehydes are sufficiently soluble in water to allow a fast reaction, still most of the substrate is found in the organic phase at all times. Therefore the concentration of the aldehydes in the catalyst containing aqueous phase is not high enough to cause significant inhibition of catalysis.[186] However, the reaction rate is dependent on the solubility of reactants in water. This fact was confirmed by Joo et al.[187] with findings that the rate of transfer hydrogenation of aldehydes decreases substantially with decreasing solubility of aldehydes in the catalyst containing aqueous phase.

The α-β unsaturated carboxylic acids such as itaconic, mesaconic, citraconic, tiglic, α-acetamidoacrylic and α-acetamidocinnamic acids have been hydrogenated to saturated carboxylic acids using water-soluble Rh(I) complexes containing TPPTS ligand.[188] HCOOM ($M= Na^+, K^+, NH4^+$) was used as hydrogen donor. The reactions were run at 50°C for 15-67 h, during which 48-100 % conversions were achieved. Use of the chiral tetrasulfonated cyclobutanediop, led to an enantiomeric excess of up to 43% for α-acetamidocinnamic acid reduction, which is close to the value obtained in biphasic hydrogenations catalyzed by the same rhodium complex.[189]

Although the complex [$RhCl(PPh_3)_3$] was an active catalyst for reduction of ketones with aqueous HCOONa as hydrogen donor with phase transfer agent, the water soluble [$RhClP_3$] complexes (P = TPPMS or TPPTS) did not promote the hydrogenation of C=O function in ketones using HCOONa in biphasic systems.[185, 190] It is not easy to rationalize this difference in the activity provided by [$RhCl(PPh_3)_3$] dissolved in the organic phase and by [$RhCl(TPPMS)_3$] in the aqueous phase. One reason may be that when a solution of [$RhCl(PPh_3)_3$] + PPh_3 in a water-immiscible organic solvent is stirred with an aqueous solution of a mild base (sodium formate in this case), formation of [$RhH(PPh_3)_4$] can be assisted by extraction of chloride into the aqueous phase which can help to shift the equilibrium to the right. Thus in aqueous biphasic catalysis, a minor change in system (dissolving the catalyst in the aqueous or, contrary, in the organic phase) may lead to major changes in the rate and/or the selectivity of the reaction under identical conditions.

Thus, the [RhCl(TPPMS)$_3$] catalyst was found to be inactive for transfer hydrogenation of ketones with aqueous sodium formate. But Ajjou and Pinet[190] have shown that these ketones along with aldehydes can be hydrogenated efficiently using 2-propanol as the hydrogen donor under basic conditions. The catalyst is generated in situ from [Rh(COD)Cl]$_2$ and TPPTS. The various aliphatic and aromatic aldehydes and ketones have been selectively reduced to the corresponding alcohols. The catalytic system can be recycled and reused with only negligible loss of catalytic activity.

The kinetics of transfer hydrogenation of olefinic bond in dimethyl itaconate has been reported with aqueous sodium formate and [Rh(COD)Cl]$_2$ /TPPTS catalyst system.[191,192] Based on isotope labeling $D_2O/HCOO^-$ and $H_2O/DCOO^-$ experiments, a possible rhodacyclobutane intermediate was suggested for the mechanism involved.[193] (structure below). In this respect the reaction pathway differs substantially from those of hydrogenation with H_2.



Like TPPMS analogues Ru(II) and Rh(I) complexes of PTA (1,3,5 triaza 7-phosphaadmantane) behaved very similar. The catalyst [RuCl$_2$(PTA)$_4$] led to exclusive formation of unsaturated alcohols while catalyst [RhCl(PTA)$_3$] selectively produced saturated aldehydes in the reduction of unsaturated aldehydes with aqueous sodium formate as hydrogen donor.[194-196] The complex Cp*RuCl(PTA)$_2$ was reported to be a highly active catalyst for the selective hydrogenation of benzylidene acetone to the saturated ketone with aqueous sodium formate (conversion 97%, selectivity 99%, temperature 90°C, time 6 h). However cinnamaldehyde was found to be over-reduced (both carbonyl and olefinic groups were hydrogenated) to saturated alcohol, 3-phenyl-1-propanol.[197]

A new class of neutral and cationic Rh(I) complexes bearing the water-soluble aminophosphine cage ligand PTN (PTN = 7-phospha-3-methyl-1,3,5-triazabicyclo[3.3.1] nonane) was reported to be an effective catalyst for selective transfer hydrogenation of olefinic bond in benzylidene acetone and C=O in acetophenone using sodium formate as hydrogen source in water at a 1% catalyst loading.[198]

The aqua complex of ruthenium $[(C_6Me_6)Ru^{II}(bpy)(H_2O)]^{2+}$ was also reported by Oga et al.[199] for pH dependent transfer hydrogenation of ketones with sodium formate as a hydrogen donor, giving 98% yield within 4 hrs. The active catalyst $[(C_6Me_6)Ru^{II}(bpy)H]^+$ is formed at pH 4.

The triphasic environment can be obtained attaching the metal complexes to an insoluble polymeric support so that they become easily separable from the products at the end of the reaction and can be reused. Liu et al.[200] reported the preparation of swellable polymer (CCPAA absorbent) supported ruthenium (II) complexes, and their catalytic applications in the transfer hydrogenation of aldehydes.

The detailed literature on aqueous biphasic transfer hydrogenation using different catalysts and ligands for hydrogenation of C=O or C=C bonds in various ketones, aldehydes and of α-β carbonyl compounds is presented in Table 1.6.

Table 1.6: Literature on transfer hydrogenation in aqueous biphasic medium

Sr. no.	**Catalyst**	**Substrate**	**H-donor**	**System**	**Conditions**		**Results**		**Remarks**	**Ref.**
					Temp (°C)	**Time (h)**	**Conv (%)**	**Sel [#] (%)**		
1	$RhCl(PPh_3)_3$, $RuCl_2(PPh_3)_4$, $Ir(CO)Br(PPh_3)_2$	1-octene	HCOOH HCOOLi	Homogeneous DMF (trace amt. of water used)	100 or 60	3	100	C=C	Addition of alkali formate to formic acid increase the rate	201
2	$RuCl_2(TPPMs)_2$	Unsaturated aldehydes	HCOONa	Biphasic (water, Neat)	80	5	98	C=O	Benzylidene-acetophenone is unreactive.	185
3	$RuCl_2(TPPMs)_2$	Benzaldehyde	HCOONa	Biphasic Water-chlorobenzene	80	2	99	C=O	Kinetic study done but rate equation is not derived	186
4	$[Rh(COD)Cl]_2$ /TPPTS	Carboxylic acids	HCO_2NH_4	Homogeneous (sub is water soluble)	50	17	100	C=C	(S,S)-cyclobutane diop used as a ligand to get 43 % *ee*	188
5	$RuCl_2(PTA)_4$ (PTA)= 1,3,5 triaza 7-phosphaadmantane	Aldehydes	HCOONa	Biphasic Water-chlorobenzene	80	3	95	C=O	For olefin hydrogenation $RhCl(PTA)_2$ catalyst used.	194
6	$RuCl_2(PTA)_4$	Benzaldehyde	HCOONa	Biphasic Water-chlorobenzene	80	4	100	C=O 100	Kinetics studied. Reaction is greatly retarded with excess use of ligand.	195

Sr. no.	Catalyst	Substrate	H-donor	System	Conditions		Results		Remarks	Ref.
					Temp (°C)	Time (h)	Conv (%)	Sel $^{\#}$ (%)		
7	$Rh(PTAH)(PTA)_2$ Cl]Cl	CALD Allyl benzene	HCOONa	Biphasic Water-chlorobenzene	75	3.3	100	C=C 94	Complex preparation and characterization described in detail	196
8	$RuCl_2(TPPTS)_2$	D-Glucose D-mannose	HCOONa FA/TEA	Homogeneous (substrate is water soluble)	100	3	90	C=O 93	FA/TEA system gives good results than aq. Formate	202
9	$[Rh(COD)Cl]_2$ /TPPTS	Dimethyl itaconate	HCOONa	Biphasic Water-cyclohexane	40	4	100	C=C	Kinetic study in a batch reactor, rate equation derived , EA=71kj/mol	191
10	$[Cp^{*}Ir^{III}(H_2O)_3]^{2+}$	Water soluble carbonyl compounds	HCOONa	Homogeneous (substrate is water soluble)	25	1	100	C=O	Active catalyst is formed at pH 3.2	203
11	$[Rh(COD)Cl]_2$ /TPPTS	Dimethyl itaconate	HCOONa	Biphasic Water-cyclohexane	30-60	4	100	C=C	Kinetic & mechanistic study, rhodacyclobutane is suggested as a possible intermediate.	193
12	$[(C_6Me_6)Ru^{II}(bpy)(H_2O)]^{2+}$	ketones	HCOONa	Biphasic (water, Neat)	70	3-13	99	C=O	Active catalyst $[(C_6Me_6)Ru^{II}(bpy)H]^{+}$ formed at pH 4 hence pH sensitive reaction	199

Sr. no.	Catalyst	Substrate	H-donor	System	Conditions		Results		Remarks	Ref.
					Temp (°C)	Time (h)	Conv (%)	Sel $^{\#}$ (%)		
13	$[Cp^{*}Ir^{III}(bpy)(H_2O)]^{2+}$	Carbonyl compounds	HCOOH	Biphasic (water, Neat)	70	1	99	C=C	Active catalyst is formed in a pH range of 2-3	204
14	$[Cp^{*}RuCl(PTA)_2]$	Benzylidine acetone CALD	HCOONa	Homogeneous (methanol+ water) Biphasic (water, Neat)	90 80	6 5	97 99	C=C 97 C=C and C=O 86	Higher activity is obtained with Cp* complex than that with Cp complex as catalyst	197
15	$[Rh(COD)Cl]_2$ / TPPTS	Benzaldehyde, AP	IPA Or HCOONa	Biphasic (water, Neat)	80	2	98	C=C	Reactions are done under basic condition, with sodium formate yields are low	190
16	$[(C_6Me_6)Ru(5\text{-}NO_2\text{-phen})(OH_2)]^{2+}$ $[(C_6Me_6)Ru(5\text{-}NH_2\text{-phen})(OH_2)]^{2+}$	AP	HCOONa	Biphasic (water, Neat)	50	60	82	82	pH 3.8 was maintained using a buffer of HCO_2H/HCO_2Na ,inert atmosphere is used	205
17	$[(Cp^{*}IrCl_2)_2]$, Ts(en)	ketones, α-β unsaturated ketones	HCOONa	Biphasic Water, neat	80	3	97	C=O	Initial TOF reported was up to 1.3 x 10^5 h^{-1}	206
18	$DpRu(PTA)_2Cl$ Dp=1,2 dihydropentanelyl	Chalcone Benzylidine acetone	HCOONa Or HCOOH	Homogeneous H_2O-Methanol	80 80	13 24	93 83	C=C C=C	active catalyst is formed at pH 3	207

Sr. no.	Catalyst	Substrate	H-donor	System	Conditions		Results		Remarks	Ref.
					Temp (°C)	Time (h)	Conv (%)	Sel [#] (%)		
19	Ru-bound to swellable polymer matrix	Aldehydes	HCOONa	Triphasic PTC-Aliquat® 336.	80	4	100	C=O	Phase transfer agent is used. Kinetics studied Rate equation derived. Ea=20.8kcal/mol	200
20	$[(Cp^*MCl)_2(bpym)]^{2+}$ M-Rh, Ir	AP	HCOONa	water	50	8	98	C=O	Active catalyst is formed at pH 4, buffer solution is used to maintain the pH.	208
21	$[Cp^*Ir^{III}(DHBP)(H_2O)]^{2+}$ DHBP=4, 4' dihydroxy 2,2' bipyridine	ketones, α-β unsaturated ketones	HCOONa	Water-neat	40 40	24 0.5	72 99	C=O (at pH 2.6) C=C (at pH 7.3)	The change in activity at diff. pH is due to electronic effect based on acid-base equilibrium of phenolic -OH group of ligand	209
22	$[RuCl_2(benzene)]_2$	Citral	HCOONa Or $HCOOH-NaHCO_3$	Biphasic Neat-H_2O–PEG	80	3	100	C=C And C=O 86	Decomposition of Ru-complex was observed during the recycle study	210

Selectivity is 100 % unless otherwise stated.

1.5.3 Kinetics and Mechanism of the Transfer Hydrogenation Reaction in Biphasic Medium

There are very few reports on kinetic study of transfer hydrogenation reaction in aqueous biphasic media. Major work has been done using the substrates like benzaldehyde and dimethyl itaconate. The ruthenium and rhodium complexes of TPPMS, TPPTS and PTA have been used to study kinetics of the reaction. Most of data obtained was only at single temperatures; moreover rate equations were not derived in most of the studies. The literature on kinetics of transfer hydrogenation reactions is presented below.

Joo and co-workers[185b] have studied the kinetics of transfer hydrogenation of benzaldehyde using $RuCl_2(TPPMS)_2$ catalyst at 80°C in water-chlorobenzene biphasic medium. The rate was first order with respect to catalyst concentration. The rate of reaction was found to increase with formate concentration upto 0.25 M and thereafter it levels off and decreases above 5M concentration. The authors have also reported a pronounced maximum of reaction rate as a function of aldehyde concentration. The rate showed steady increase with increase in TPPMS concentration up to solubility limit of the TPPMS.

The kinetic study of biphasic transfer hydrogenation of benzaldehyde has also been reported by Darensbourg et al.[195] using $RuCl_2(PTA)_4$ as catalyst. The rate of reaction was found to be first order in catalyst and substrate concentration and independent of formate concentration at higher concentration. The rate of reaction was found to decrease with increase in ligand concentration.

The kinetics of transfer hydrogenation of cinnamaldehyde to hydro-cinnamaldehyde using $[Rh(PTAH)(PTA)_2Cl]Cl$ as catalyst has reported by Darensbourg et al.[196] Sodium formate was used as a hydrogen donor in water-chlorobenzene biphasic medium at 75°C. The rate of reaction showed first order dependence with respect to catalyst concentration. The rate increased with increase in aldehydes concentration and was independent of aldehyde concentration above 3M. They have shown that the reaction was strongly inhibited by even one equivalent excess of ligand.

Bellefon et al.[191,193] have investigated the kinetics of transfer hydrogenation of dimethyl itaconate using aqueous sodium formate and Rh/TPPTS catalyst system. The authors have found that the reaction rate varied with a first order dependence with respect to catalyst concentration and decreased with increase in ligand concentration. The linear increase of initial rate was observed until the aqueous formate concentration reaches 1 kmol/m^3, after which the rate decreased with increasing formate concentration. According to them the formate concentration had a strong influence on the partition coefficient of substrates and products. The effect of substrate concentration at different formate concentration was studied and found that the initial rate showed an apparent zero order with respect to substrate at formate concentration of 1 kmol/m^3. The rate was found to be linearly dependent in the range of low substrate concentrations, and with further increase, rate increased only marginally. This particular trend was obtained for 2.5 kmol/m^3 concentration of formate. The rate order was close to one when formate concentration was 5 kmol/m^3. A semi empirical rate model was developed as shown below

$$r_{org} = \frac{kC_{aq}^{Rh}}{\left(1+\alpha P_{DMI}\right)} \frac{C_{org}^{DMI}}{\left(\frac{K}{P_{DMI}} C_{org}^{DMI} + C_{aq}^{HCOO^-} C_{aq}^{P}\right)} \left(kmol.m_{org}^{-3} s^{-1}\right)$$

In summary, the majority of the work has been carried out with the aim of development of catalytic systems for selective transfer hydrogenation under biphasic conditions and not much work has been carried out on kinetic study. All the work reported on kinetics is restricted to one temperature only.

Mechanism

The transfer hydrogenation of C=C bonds in unsaturated carboxylic compounds can be achieved by either molecular hydrogenation or transfer hydrogenation. For a wide range of substrates and catalysts, there are striking similarities in reactivity (and or stereoselectivity when chiral rhodium phosphine complexes are used as catalysts) for both techniques.[211] The major reaction paths and the key intermediates involved during the hydrogen addition step are mostly similar in both the processes.[212] Figure 1.11 presents a mechanistic scenario for the transfer hydrogenation of α-β unsaturated carbonyl compounds using formate as a hydrogen donor based on the findings of Lange et al.[213]

The first step of the mechanism is dissociation of one phosphine ligand to give a Rh complex **I** containing two phosphine equivalent as shown in Figure 1.11. In the second step the activation of formate occurs (species **II)**. Decarboxylation of coordinated formate occurs to yield a rhodium hydride intermediate such as **III**. CO_2 evolved in reaction is trapped as bicarbonate in aqueous medium. Following this an insertion of the olefinic bond into the Rh-H bond to form the chelated σ-alkyl intermediate **IV** takes place. Irreversible liberation of the product from rhodium center through protolytic cleavage of the metal alkyl bond in **IV** finally leads to the hydrogenated product.

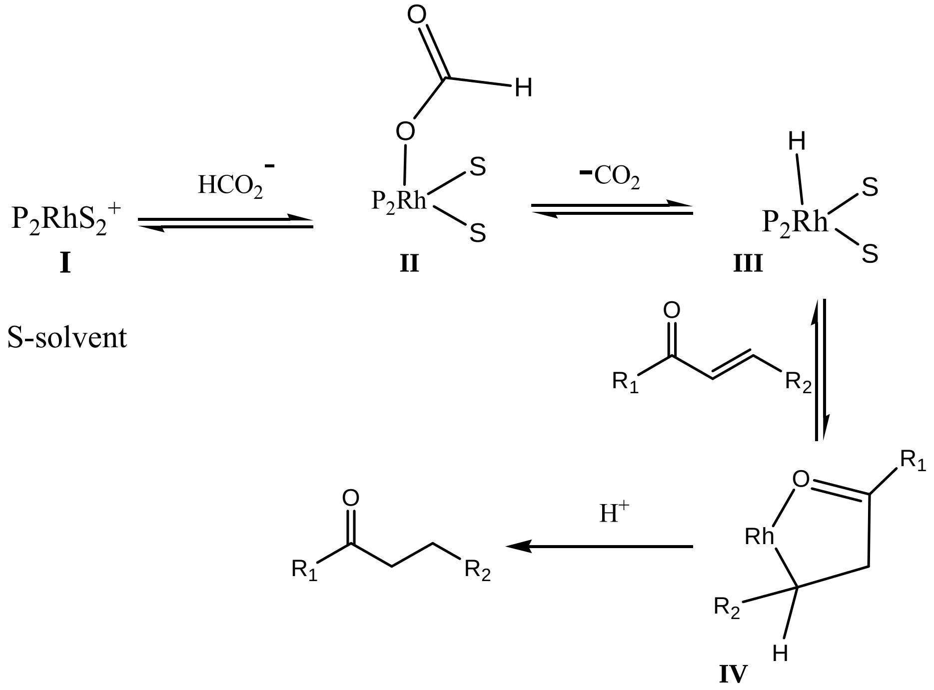


Figure1.11: Mechanism of transfer hydrogenation of unsaturated carbonyl compounds using formate as hydrogen donor.[213]

1.6. SCOPE AND OBJECTIVE OF THE THESIS

Transfer hydrogenation is attractive especially for small scale production of various chemicals as it requires no special equipments and avoids the handling of potentially hazardous gaseous hydrogen. Extensive work has been carried out on this reaction including homogeneous, heterogeneous, biphasic and asymmetric catalysis. Considering the literature facts discussed above, the present study was focused on asymmetric transfer hydrogenation and transfer hydrogenation reactions catalyzed by heterogeneous and biphasic catalytic systems. Accordingly, acetophenone, nitrobenzene and α,β-unsaturated carbonyl compounds were chosen as model substrates for these studies. The main objective of this study was to investigate transfer hydrogenation reactions in detail including kinetic studies. With these objectives in mind, the following specific problems were chosen for the present work:

- Asymmetric transfer hydrogenation reaction using homogeneous Ru(II)/(1R,2S)ephedrine complex catalyst: Optimization of the reaction conditions in order to get high activity and enantioselectivity.
- Asymmetric transfer hydrogenation reaction using homogeneous Ru(II)/(1R,2S)ephedrine complex catalyst under ultrasound promotion.
- Investigation of kinetics of transfer hydrogenation reaction of nitrobenzene using a heterogeneous 5% Pd/C catalyst, with the objective of developing a suitable rate equation for the reaction
- Investigations on 5% Pt/C catalyzed transfer hydrogenation of nitrobenzene: parametric studies.
- Transfer hydrogenation of *trans* cinnamaldehyde using water soluble rhodium-TPPTS complex in biphasic media: Activity, selectivity and kinetic study.
- The use of co-solvent in transfer hydrogenation of α,β-unsaturated carbonyl compounds in a biphasic media.

REFERENCES

1 J.Berzzelius, *J Ann. Chim. Phys.***1836**, *61*, 146.

2 Z.Ostwald, *Phys.chem* **1894**, 15, 705

3 (a) G. W. Parshall, *Homogeneous Catalysis*, Wiley-Interscience, New York, **1980**. (b) C. Masters, *Homogeneous Transition-Metal Catalysis*, Chap-man and Hall, London, **1981**

4 (a)A. S. Bommarius, B. R. Riebel, *Biocatalysis: fundamentals and applications*, Vch Verlagsgesellschaft Mbh, **2004**.(b)J. Wetley, H. O. Halvorson, H. L. Roman, E. Bell *Enzymic Catalysis,* Harper and Row Publishers Inc. New York, **1969**.

5 Hagen J, Industrial Catalysis, A Practical Approach, Wiley–VCH, Weinheim, **2006**

6 (a) A.G. BASF, *Hydrocarbon Process* **1977**, *11*, 135 (b) R. Jira, *Ethylene and Its Industrial Derivatives*, S. A. Miller, (Ed.) Ernest Benn Ltd. **1969**, 650 (c) J. *J.* Falbe, *Organomet. Chem.* **1975**, 94**,** 213 (d) J. F.Roth, *Platinum Met. Rev* **1975**, *19***,** 12 (e) F. E. Paulik, J. F. Roth, *Chem. Commun.* **1968**, 1578(f) T. Dekleva, D. Forster, *Adv. Catal.* **1986**, *34*, 81 (g) G. W. Adamson, J. J. Daly, D. *J.* Forster, *Organomet. Chem.* **1974**, *71***,** C17(h) C. S. Garland, M. F.Giles, J. G. Sunley, *Eur. Pat.* 643034**, 1995. (**i) K. Zeigler, *Brit. Pat.* 799392**, 1958**. (j)G. C. Bond (Eds.) *Heterogeneous Catalysis: Principles and Application*, second edition Oxford Clarendon Press **1987**.

7 L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press: Ithaca, NY, **1939**, 64.

8 E. Knoevenagei and B. Bergdolt, *Chem. Ber.***1903,** *36*, 2857.

9 E. A. Braude, R. P. Linstead, L. M. Jackman, P. W. D. Mitchell, and K. R. H. Wooldridge. *Nature (London),* **1952,***169*, 100.

10 (a) H.Meerwein, R. Schmidt, *Liebigs Ann. Chem.* **1925**, *444*, 221. (b) A. Verley, *Bull. Soc. Chim. Fr.* **1925**, *37*, 537.(c) W. Ponndorf, *Angew. Chem.* **1926**, *39*, 138. (c) A. L. Wilds, *Org. React.* **1944**, *2*, 178.

11 (a) J.Grimshaw T. H.B Henbest, *Chem. Commun.* **1967**, 544.(b)M. McPartli and R. Mason, *Chem. Commun.,* **1967**, 545.

12 Y. M. Y. Haddad, H. B. Henbest, J. Husbands, and T. R. B. Mitchell, Proc. *Chem. Soc.*, **1964**, 361.

13 (a) Y. Sasson and J. Blum, *Tetrahedron Lett.,* **1971**, *12*, 2167;(b) J. Blum, Y. Sasson and S. Iflah, *Tetrahedron Lett*., **1972**, *13*, 1015; (c) Y. Sasson and J. Blum, *J. Org. Chem.,* **1975**, *40*, 1887.

14 (a) K. Ohkubo, K. Hirata, K. Yoshinaga and M. Okada, *Chem. Lett.,* **1976**, 183; (b) G. Descotes and D. Sinou, *Tetrahedron Lett.,***1976**, *17*, 4083.

15 X. F. Wu, J. L. Xiao, *Chem. Comm.* **2007**, 2449.

16 (a) H. U. Blaser, C. Malan, B. Pugin, F. Spindler, H. Steiner and M. Studer, *Adv. Synth. Catal.***2003**, *345*, 103. (b) W. J. Tang and X. M. Zhang, *Chem. Rev.* **2003**, *103*, 3029.(c) A. J. Blacker,in *The Handbook of Homogeneous Hydrogenation*; J. G de Vries, C. J. Elsevier, Wiley- VCH Germany, **2007**, 1215.

17 T. Ikariya, A. J. Blacker, *Accounts of Chemical Research* **2007,** *40*, 1300.

18 H. U. Blaser, B. Pugin, F. Spindler, *Journal of Molecular Catalysis A: Chemical* **2005**, *231*, 1.

19 W. V. E. Doering, R. W. Young, *J. Am. Chem. Soc.* **1950**, *72*, 631.

20 (a) G. Descotes, D. Sinou, *Tetrahedron Lett.* **1976**, *17*, 4083 (b) K. Ohkubo, K. Hirata, K. Yoshinaga, M. Okada, *Chem. Lett.* **1976**, 183.

21 D. Müller, G. Umbricht, B. Weber, A. Pfaltz, *Helv. Chim. Acta*, **1991**, *74*, 232

22 J.-P. Genêt, V. Ratovelomanana-Vidal, C. Pinel, *Synlett*, **1993**, 478.

23 A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.***1996**, *118*, 2521

24 (a)J. S. M. Samec, J. E. Backvall, P. G. Andersson, P. Brandt, *Chemical Society Reviews* **2006**, *35*, 237. (b)K. Everaere, A. Mortreux, J. F. Carpentier, *Adv. Synth. Catal*. **2003**, *345*, 67.

25 T. Ohkuma, M. Kitamura, R. Noyori, in *Catalytic Asymmetric Synthesis*, 2nd edn.,(Ed.: I.Ojima), Wiley-VCH, New York, **2000**, 1.(b) M. J. Palmer, M. Wills, *Tetrahedron Asymmetry* **1999**, *10*, 2045.

26 H.Adkins, R.M.Elofson, A.G.Rossow, C.C.Robinson, *J.Am.Chem.Soc*.**1947**, *71*, 3622.

27 (a)K. Murata, T. Ikariya, R. Noyori, *Journal of Organic Chemistry* **1999**, *64*, 2186. (b)A. Kawamoto, M. Wills, *Tetrahedron Asymmetry* **2000**, *11*, 3257.(c) D. S. Matharu, D. J. Morris, G. J. Clarkson, M. Wills, *Chemical Communications* **2006**, 3232.(d) A. Fujii, S. Hashiguchi, N. Uematsu, T. Ikariya, R. Noyori, *J. Am. Chem. Soc.* **1996**, *118*, 2521.

28 Review: (a) X. F. Wu, J. L. Xiao, *Chem. Comm.* **2007**, 2449. (b) X. F. Wu, J. K. Liu, D. Di Tommaso, J. A. Iggo, C. R. A. Catlow, J. Bacsa, J. L. Xiao, *Chemistry-a European Journal* **2008**, *14*, 7699. (c) C. Wang, X. F. Wu, J. L. Xiao, *Chemistry-an Asian Journal* **2008**, *3*, 1750.(d) X. F. Wu, C. Wang, J. L. Xiao, *Platinum Metals Review* **2010**, *54*, 3.

29 (a) D. A. Evans, J. *J.* Wu, *Am. Chem. Soc.* **2003**, *125*, 10162. (b) W.B Yang, J.M. Fang, *J. Org. Chem.* **1998**, *63*, 1356. (c) D. A. Evans, S. G. Nelson, M. R. Gagne, A. R. Muci, *J. Am. Chem. Soc.* **1993**, *115*, 9800. (d) A.Lebrun, J.L. Namy, H. G. Kagan, *Tetrahedron Lett.* **1991**,*32*, 2355. (e) D. A.Evans, S. G. Nelson, M. R.Gagne, A. R. Muci, *J. Am. Chem. Soc*. **1993**, *115*, 9800. (f) S Fukuzawa, K .Mutoh, T. Tsuchimoto, T. Hiyama, *J. Org.Chem.* **1996**, *61*, 5400. (g) T.Hanamoto, Y. Sugimoto, A. Sugino, J. Inanaga, *Synlett* **1994**, 377. (h) S. Fukuzawa, T. Tsuchimoto, T. Kanai, *Chem. Lett.* **1993**, 1981.

30 (a) W. Baratta, M. Ballico, G. Chelucci, K. Siega, P. Rigo, *Angewandte Chemie – International Edition* **2008**, *47*, 4362.(b) W. Baratta, M. Ballico, A. Del Zotto, K.Siega, Magnolia, S.; Rigo, P. *Chemistry - A European Journal* **2008**, *14*, 2557.

31 (a) J.S. Chen, L.L. Chen, Y. Xing, G. Chen, W.Y. Shen, Z.R. Dong, Y.Y. Li and J.X. Gao, *Acta Chim. Sin.* (Huaxue Xuebao) **2004**, *62*, 1745. (b) S. Enthaler, G. Erre, M. K. Tse, K. Junge and M. Beller,*Tetrahedron Lett.* **2006**, *47*, 8095.(c) S. Enthaler, B. Spilker, G. Erre, K. Junge, M. K. Tse and M. Beller, *Tetrahedron* **2008**, *64*, 3867.(d) C. Sui-Seng, F. Freutel, A. J. Lough and R. H. Morris, *Angew. Chem., Int. Ed.* **2008**, *47*, 940. (e) N. Meyer, A. J. Lough and R. H. Morris, *Chem.*

Eur. J. **2009**, *15,*5605. (f) A. A. Mikhailine, A. J. Lough and R. H. Morris, *J. Am. Chem. Soc.***2009**, *131*, 1394.

32 J.W.Yang and B.List , *Organic Letter* **2006**, *8*, 5653

33 P. G. Andersson, I. J. Munslow, C. Ebooks, *Modern reduction methods*, Wiley-VCH Weinheim, Germany, **2008**.

34 K. Pauntener, L. Schwink, P. Knochel, *Tetrahedron Lett.* **1996**, *37*, 8165. (b) S. Fukuzawa, T. Suzuki, *European Journal of Organic Chemistry* **2006**, 1012.

35 (a)Y. Nishibayashi, I. Takei, S. Uemura, M. Hidai, *Organometallics* **1999**, *18*, 2291. (b) Y. Arikawa, M. Ueoka, K. Matoba, Y. Nishibayashi, M. Hidai, S. Uemura, *Journal of Organometallic Chemistry* **1999**, *572*, 163.

36 M. Aitali, S. Allaoud, A. Karim, C. Meliet, A. Mortreux, *Tet.Asy.* **2000**, *11*, 1367.

37 A. Gayet, C. Bolea, P. G. Andersson, *Org. & Biomol.Chem.* **2004**, *2*, 1887.

38 I. Schiffers, T. Rantanen, F. Schmidt, W. Bergmans, L. Zani, C. Bolm, *Journal of Organic Chemistry* **2006**, *71*, 2320.

39 Y. Jiang, Q. Jiang, X. Zhang, *J. Am. Chem. Soc.* **1998**, *120*, 3817.

40 D. Cuervo, M. P. Gamasa, J. Gimeno, *Chem. - A European Journal* **2004**, *10*, 425.

41 M. T. Reetz, X. Li, *Journal of the American Chemical Society* **2006**, *128*, 1044.

42 J. X. Gao, T. Ikariya, R. Noyori, *Organometallics* **1996**, *15*, 1087.

43 Review: R. Noyori. and T. Ohkuma, *Angew. Chem., Int. Ed.* **2001**, *40*, 40.

44 V Rautenstrauch,. X. Hoang-Cong, R. Churlaud, K. Abdur-Rashid, R. H. Morris, *Chemistry - A European Journal* **2003**, *9*, 4954-4967.

45 R. Guo, C. Elpelt, X.Chen, D. Song, R. H. Morris, *Chem. Comm.* **2005**, 3050.

46 (a) W. Baratta, P. Da Ros, A. Del Zotto, A. Sethi, E. Zangrando, and P. Rigo, *Angewandte Chemie International Ed.* **2004,** *43,* 3584. (b) W. Baratla, E. Herdtweck, K. Siega, M. Toniutti, and P. Rigo,*Organomctllics* **2005**, 24, 1660. (c) W. Baratta, M. Ballico, G.Esposito, P. Rigo, *Chemistry - A European Journal* **2008**, *14*, 5588.

47 (a) F. K. Cheung, A. M. Hayes, J. Hannedouche,A. S.Y.Yim and M.Wills, *Journal of Organic Chemistry* **2005**, *70*, 3188. (b) F. K. Cheung, A. M. Hayes, D. J. Morris, M. Wills, *Organic and Biomolecular Chemistry* **2007**, *5*, 1093.

48 A. M. Hayes, D. J. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2005**, *127*, 7318.

49 J. Hannedouche, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2004**, *126*, 986.

50 D. S. Matharu, D. J. Morris, G. J. Clarkson, M. Wills, *Chem. Comm.* **2006**, 3232.

51 (a) P. Dani, T. Karlen, R. A. Gossage, S. Gladiali, C. van Koten, *Angew. Chem., Int. Ed.* **2000**, *39*, 743. (b) M. Gagliardo, P. A. Chase, S. Brouwer, G. P. M. van Klink, G. van Koten, *Organometallics* **2007**, *26*, 2219.(c) D. Amoroso, A. Jabri, G. P. A. Yap, D. G. Gusev, E. N. dos Santos, D. E. Fogg, *Organometallics* **2004**, *23*, 4047.

52 S. Medici, M. Gagliardo, S. B. Williams, P. A. Chase, S. Gladiali, M. Lutz, A. L. Spek, G. P. M. van Klink, G. van Koten, *Helvetica Chimica Acta* **2005**, *88*, 694.

53 (a)W. Baratta, M. Bosco, G. Chelucci, A. Del Zotto, K. Siega, M. Toniutti, E. Zangrando, P. Rigo, *Organometallics* **2006**, *25*, 4611.(b) W. Baratta, F. Benedetti,

A. Del Zotto, L. Fanfoni, F. Felluga, S. Magnolia, E. Putignano, P. Rigo *Organometallics* **2010**, *29*, 3563.

54 S. Hashiguchi, A. Fujii, J. Takeliara. T. Ikanya. and R. Noyori, *Journal of the American Chemical Society* **1995,** *117*, 7562. .(b) A. Hayes, G. Clarkson, M. Wills, *Tetrahedron Asymmetry* **2004**, *15*, 2079.

55 M. J. Palmer, J. A. Kenny, T. Walsgrove, A. M. Kawamoto, M. Wills, *Journal of the Chemical Society Perkin Transactions 1* **2002**, 416.

56 L. Schwink, T. Ireland, K. Puntener, P. Knochel, *Tet. Asy.* **1998**, *9*, 1143.

57 A. Hayes, G. Clarkson, M. Wills, *Tetrahedron Asymmetry* **2004**, *15*, 2079.

58 K. Murata, T. Ikariya, R. Noyori, *Journal of Organic Chemistry* **1999**, *64*, 2186.

59 J. Takehara, S. Hashiguchi, A. Fujii, S. I. Inoue, T. Ikariya, R. Noyori, *Chemical Communications* **1996**, 233.

60. S. J. M. Nordin, P. Roth, T. Tarnai, D. A. Alonso, P. Brandt, P. G. Andersson, *Chemistry - A European Journal* **2001**, *7*, 1431.

61 (a)K. Everacre, A. Mortreux, J. F. Carpentier, *Advanced Synthesis and Catalysis* **2003**, *345*, 67.(b) C. G. Frost, P. Mendonca, *Tetrahedron-Asymmetry* **2000**, *11*, 1845.

62 S. J. M. Nordin, P. Roth, T. Tarnai, D. A. Alonso, P. Brandt, P. G. Andersson, *Chemistry - A European Journal* **2001***,* *7*, 1431.

63 A. Patti, S. Pedotti, *Tetrahedron Asymmetry* **2003**, *14*, 597.

64 H. L. Kwong, W. S. Lee, T. S. Lai, W. T. Wong, *Inorganic Chemistry Communications* **1999**, *2*, 66.

65 I. M. Pastor, P. VÃ¤stilÃ¤, H. Adolfsson, *Chemical Communications* **2002**, 2046.

66 (a) A. Bogevig, I. M. Pastor, H. Adolfsson, *Chemistry-a European Journal* **2004**, *10*, 294. (b) J. Wettergren, A. Bogevig, M. Portier, H. Adolfsson, *Advanced Synthesis and Catalysis* **2006**, *348*, 1277.

67 H. Brunner, F. Henning, M. Weber, *Tetrahedron-Asymmetry* **2002**, *13*, 37.

68 (a)S. Gladiali, E. Alberico, *Chemical Society Reviews* **2006**, *35*, 226.(b) H. U. Blaser, E. Schmidt, *Asymmetric catalysis on industrial scale*, Wiley Online Library, **2004**,265.

69 M. Palmer, T. Walsgrove, M. Wills, *Journal of Organic Chemistry* **1997**, *62*, 5226.

70 A. J. Blacker *PCT Int. Appl.* WO 9842643, **1998.**

71 D. A. Alonso, D. Guijarro, P. Pinho, O. Temme, P. G. Andersson, *Journal of Organic Chemistry* **1998**, *63*, 2749.

72 K. Everaere, J. F. Carpentier, A. Mortreux, M. Bulliard, *Tetrahedron Asymmetry* **1998**, *9*, 2971.

73 D. G. I. Petra, J. N. H. Reek, J. W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. Van Leeuwen, *Chemistry – A European Journal* **2000**, *6*, 2818.

74 D. G. I. Petra, P. C. J. Kamer, P. W. N. M. Van Leeuwen, K. Goubitz, A. M. Van Loon, J. G. De Vries, H. E. Schoemaker, *Eur.J. Inorg. Chem.* **1999**, 2335.

75 D. A. Alonso, S. J. M. Nordin, P. Roth, T. Tarnai, P. G. Andersson, M. Thommen, U. Pittelkow, *Journal of Organic Chemistry* **2000**, *65*, 3116.

76 A. J. Sandee, D. G. I. Petra, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. Van Leeuwen, *Chemistry - A European Journal* **2001**, *7*, 1202.

77 F. Le Guyader,F. Manfre,F. Bienewald, *PCT Int. Appl.* WO/2002/040493, **2002.**

78 K. B. Hansen, J. R. Chilenski, R. Desmond, P. N. Devine, E. J. J. Grabowski, R. Heid, M. Kubryk, D. J. Mathre, R. Varsolona, *Tet. Asy.* **2003**, *14*, 3581.

79 P. N. Liu, Y. C. Chen, X. Q. Li, Y. Q. Tu, J. G. Deng, *Tetrahedron Asymmetry* **2003**, *14*, 2481.

80 D. J. Cross, I. Houson, A. M. Kawamoto, M. Wills, *Tet. Lett.* **2004**, *45*, 843.

81 J. Hannedouche, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.* **2004**, *126*, 986.

82 P. Brandt, P. Roth, P. G. Andersson, *J. Org. Chem.* **2004**, *69*, 4885.

83 X. Sun, G. Manos, J. Blacker, J. Martin, A. Gavriilidis, *Organic Process Research and Development* **2004**, *8*, 909.

84 J. Mao, B. Wan, F. Wu, S. Lu, *Tetrahedron Letters* **2005**, *46*, 7341.

85 A. S. Y. Yim, M. Wills, *Tetrahedron* **2005**, *61*, 7994.

86 K. Aboulaala, C. Goux-Henry, D. Sinou, M. Safi, M. Soufiaoui, *Journal of Molecular Catalysis A: Chemical* **2005**, *237*, 259.

87 C. C. Watts, P. Thoniyot, F. Cappuccio, J. Verhagen, B. Gallagher, B. Singaram, *Tetrahedron Asymmetry* **2006**, *17*, 1301.

88 R. V. Wisman, J. G. De Vries, B. J. Deelman, H. J. Heeres, *Organic Process Research and Development* **2006**, *10*, 423.

89 X. F. Wu, X. H. Li, M. McConville, O. Saidi, J. L. Xiao, *Journal of Molecular Catalysis a-Chemical* **2006**, *247*, 153.

90 S. Guillarme, T. X. Mai Nguyen, C. Saluzzo, *Tet. Asy.* **2008**, *19*,1449.

91 E. Alza, A. Bastero, S. Jansat, M. A. PericÃ s, *Tetrahedron Asymmetry* **2008**, *19*, 374.

92 Z. Xu, J. C. Mao, Y. W. Zhang, J. Guo, J. L. Zhu, *Catal. Commun.* **2008**, *9*, 618.

93 T. T. Le, S. Guillarme, C. Saluzzo, *Tetrahedron*, **2010,** *66*, 8893.

94 K. D. Huynh, H. Ibrahim, M. Toffano, V. T. Giang, *Tetrahedron-Asymmetry*, **2010,** *21*, 1542.

95 K.-J. Haack, S.Hashiguchi, A. Fujii, T. Ikariya, R. Noyori, Angew. *Chem. Int. Ed.* **1997**, *36*, 285

96 M. Yamakawa, H. Ito, R. Noyori, *J. Am. Chem. Soc*. **2000**, *122*, 1466.

97 S. Lutsenko, C. Moberg, *Tetrahedron Asymmetry* **2001,** *12*, 2529.

98 (a) A. Shoh, Industrial Applications of Ultrasound, in *Ultrasound: Its Chemical, Physical, and Biological Effects* (Ed.: K. S. Suslick), VCH Publishers, Inc., New York, **1988**, 97.(b) T. J. Mason, J. P. Lorimer, Ultrasonics, in *Sonochemistry: Theory, Applications and Uses of Ultrasound in Chemistry*, Ellis Horwood Publishers, Chichester, **1988**, 1.

99 K. Okitsu, Y. Mizukoshi, H. Bandow, Y. Maeda, T. Yamamoto, Y. Nagata, *Ultrasonics Sonochem*. **1996,** *3*, S249.

100 (a) B. Torok, K. Balazsik, M. Torok, K. Felfoldi, M. Bartok, *Catal. Lett.* **2002,** *81 (1–2)*, 55. (b) B. Torok, K. Balazsik, K. Felfoldi, M. Bartok, *Ultrasonics Sonochem.* **2001,** *8,* 191. (c) B. Torok, K. Balazsik, M. Torok, G. Szollosi, M. Bartok, *Ultrasonics Sonochem*. **2000,** *7,* 151.(d) B. Torok, G. Szollosi, K. Balazsik, K. Felfoldi, I. Kun, M. Bartok, *Ultrasonics Sonochem.* **1999,** *6*, 97. (e)

K. Balazsik, B. Torok, K. Felfoldi, M. Bartok, *Ultrasonics Sonochem*. **1999,** *5*, 149.(f) B. Torok, K. Felfoldi, G. Szakonyi, K. Balazsik, M. Bartok, *Catal. Lett.* **1998**, *52,* 81.

101 European Society of Sonochemistry, Sonochemistry - Introduction, http://www.fbchemie.uni-rostock.de/ess/intro.htm.

102 T. J. Mason, J. P. Lorimer, *Applied sonochemistry: the uses of power ultrasound in chemistry and processing*; Vch Verlagsgesellschaft Mbh, **2002.**

103. (a)Ultrasonics, Kirk-Othmer Encyclopedia of Chemical Technology, 3'rd Ed., Wiley NewYork, **1983**, *23*, 462 (b)Y. G. Adewuyi, *Ind. Eng. Chem. Res*. **2001**, *40*, 4681.

104 K. S. Suslick, *Scientific American* **1989**, *260*, 80.

105 (a)E. B. Flint, K. S. Suslick, *Science*, **1991**, *253*, 1397.(b) K.Suslick, *Science,* **1990**, *247,* 1439. (c) K.Makino, M. M.Mossoba, P. J. Reisz, *Phys. Chem.***1983**, *87,* 1369. (d) N. Serpone, P. Colarusso, *Research on Chemical Intermediates* **1994,** *20*, 635.

106 (a) F. R.Young, *Cavitatio*n, McGraw-Hill, New York, **1989**.(b) C.Von Sonntag, G. Mark, A. Tauber, Schuchmann, *Adv. Sonochem*. **1999**, 5.(c) J. Lorimer, T. Mason, *Chem. Soc. Rev.* **1987**, *16*, 239.

107 P. K. Chendke, H. S. Fogler, *Chem. Eng. J.* **1974**, *8*, 165.

108 C. M. Sehgal, S. Y. Wang, *J. Am. Chem. Soc.* **1981**, *103*, 6606.

109 Entezari, M. H.; Kruus, P. *Ultrason. Sonochem.* **1996**, *3*, 19.

110 T. J. Mason, *Practical Sonochemistry*, Ellis Horwood Publishers, Chichester, **1991.**

111 (a) I. D. Entwistle, R. A. W. Johnstone, T. J. Povall, *Journal of the Chemical Society, Perkin Transactions 1* **1975**, 1300

112 I. D.Entwistle, A. E.Jackson, R. A. W. Johnstone, R. P. Telford, *Journal of the Chemical Society, Perkin Transactions 1* **1977**, 443.

113 K. Prasad, X. Jiang, J. S. Slade, J. Clemens, O. Repic, T. J. Blacklock, *Adv. Synth. Catal.* **2005**, *347*, 1769.

114 D. C. Gowda, S. Gowda, *Indian Journal of Chemistry - Section B Organic and* Medicinal Chemistry **2000**, 39, 709.

115 (a) S. Ram, R.E. EhrenKaufer, *Tetrahedron Letters* **1984**, 25, 3415. (b) S.Ram, R.E. Ehrenkaufer, *Synthesis* **1986**, 133

116 A.G. M. Barrett, C.D. Spilling, *Tetrahedron Letters* **1988**, *29*, 5733

117 H. Berthold, T. Schotten, H. Honig, *Synthesis-Stuttgart* **2002**, 1607.

118. (a)M. K. Anwer, D. B. Sherman, J. G. Roney, A. F. Spatola, *Journal of Organic Chemistry* **1989**, *54*, 1284. H.(b) Wiener, Y. Sasson, J. Blum, *Journal of Molecular Catalysis* **1986**, *35*, 277. (c)A. Arcadi, G. Cerichelli, M. Chiarini, R. Vico, D. Zorzan, *European Journal of Organic Chemistry* **2004**, 3404.

119 N. Chapman, B. Conwey, F.O'Grady, M.D. Wall, *Synlett* **2006**,*7*, 1043.

120 A. Zoran, Y. Sasson, J. Blum, *Journal of Molecular Catalysis* **1984**, *26*, 321.

121 E. A. Braude, R. P. Linstead, P. W. D. Mitchell, K. R. H. Wooldridge, *J . Chem. Soc***.1954**, 3595.

122 T.-L. Ho, G. A. Olah, *Synthesis* **1977,** 169.

123 (a) G. A. Olah, G. K. S. Prakash, *Synthesis* **1978,** 397**.** (b) G. Brieger, T. J. Nestrick, T. H. Fu, *J. Org. Chem.* **1979,** ***44*,** 1876.

124 I. D. Entwistle, A. E. Jackson, R. A. W. Johnstone, R. P. Telford, *Journal of the Chemical Society, Perkin Transactions 1* **1977**, 443.

125 (a) R. Sala, G. Doria, C. Passarotti, *Tetrahedron Lett.* **1984,** *25*, 4565**.** (b) R. A. W. Johnstone, A. H. Wilby, *Tetrahedron* **1981,** *37*, 3667.

126 I. D. Entwistle, T. Gilkerson, R. A. W. Johnstone, R. P. Telford, *Tetrahedron* **1978,** *34*, 213.

127 N. A. Cortese, R. F. J. Heck, *Org. Chem***. 1978,** *43,* 3985.

128 M. J. Andrews, C. N. Pillai, *Indian J. Chem***. 1978,** 465.

129 (a)G. Brieger, T. J. Nestrick, *Chemical Reviews* **1974**, *74*, 567.(b) R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, *Chemical Reviews* **1985**, *85*, 129.

130 G. Cavinato, L. Toniolo, *Journal of Molecular Catalysis A: Chemical* **1996**, *106*,25.

131 H. S. P.; Rao, K. S. Reddy, *Tetrahedron Letters* **1994**, *35*, 171.

132 B. C. Ranu, A. Sarkar, *Tetrahedron Letters* **1994**, *35*, 8649.

133 Z. Paryzek, H. Koenig, B. Tabaczka, *Synthesis* **2003**, 2023.

134 S. K. Nandy, J. Liu, A. A. Padmapriya, *Tetrahedron Letters* **2008**, *49*, 2469.

135 M. A. Tike, V. V. Mahajani, *Chemical Engineering Journal* **2006**, *123*, 31.

136 J. F. Quinn, D. A. Razzano, K. C. Golden, B. T. Gregg, *Tetrahedron Letters* **2008**, *49*, 6137.

137 T. Gartiser, C. Selve, J. J. Delpuech, *Tetrahedron Lett.***1983,** ***24*,** 1609**.**

138 K. Abiraj, G. R. Srinivasa, D. C. Gowda, *Synthetic Communications* **2005**, *35*, 223.

139 E. A Braude, R. P. Linstead, K. R. H. Wooldridge, *J. Chem. Soc.* **1954,** 3586.

140 (a) I. D. Entwistle, R. A. W. Johnstone, T. J. Povall, *Journal of the Chemical Society, Perkin Transactions 1* **1975**, 1300.(b) G. Brieger, T. H. Fu, *Journal of the Chemical Society, Chemical Communications* **1976,** 757a. (c) G. Brieger, T. J. Nestrick, T. H. Fu, *Journal of Organic Chemistry* **1979**, *44*, 1876.

141 S. Ram, L. D. Spicer, *Synthetic Communications* **1992**, *22*, 2683.

142 M. Baidossi, A. V. Joshi, S. Mukhopadhyay, Y. Sasson, *Synthetic Communications* **2004**, *34*, 643.

143 M. K. Anwer, A. F. Spatola, *Tetrahedron Letters* **1985**, *26*, 1379.

144 M. K. Anwer, D. B. Sherman, J. G. Roney, A. F. Spatola, *Journal of Organic Chemistry* **1989**, *54*, 1284.

145 H.Wiener, J. Blum, Y. Sasson, *Journal of Organic Chemistry* **1991**, *56*, 4481.

146 S. Rajagopal, A. F. Spatola, *Journal of Organic Chemistry* **1995**, *60*, 1347.

147 A. Arcadi, G. Cerichelli, M. Chiarini, R.Vico, D. Zorzan, *European Journal of Organic Chemistry* **2004**, 3404.

148 Y. Ukisu, *Applied Catalysis A: General* **2008**, *349*, 229.

149 I. D. Entwistle, R. A. W. Johnstone, T. J. Povall, *J. Chem. Soc. Perkin Trans. 1* **1976**,1300.

150 (a) A Furst, R. C. Berlo, S. Hooton. *Chem. Rev***. 1965,** ***65*,** 51.

151 I. D. Entwistle, A. E. Jackson, R. A. W. Johnstone, R. P. Telford, *Journal of the Chemical Society, Perkin Transactions 1* **1977**, 443.

152 I. D. Entwistle, T. Gilkerson, R. A. W. Johnstone, R. P. Telford, *Tetrahedron* **1978,** *34*, 213.

153 N. A Cortese, R. F. Heck, *J. Org. Chem.* **1977,** *42***,** 3491**.**

154 (a) S. Ram, R.E. EhrenKaufer, *Tetrahedron Letters* **1984**, *25*, 3415. (b) S.Ram, R.E. Ehrenkaufer, *Synthesis* **1986**, 133

155 G. W. Kabalka R. D. Pace, P.P. Wadgaonkar, *Synthetic Commun.* **1990**, *20*, 2453.

156 P. Haldar, V. V. Mahajani, *Chemical Engineering Journal* **2004**, *104*, 27.

157 H. Wiener, J. Blum, Y. Sasson, *Journal of Organic Chemistry* **1991**, *56*, 4481.

158 D. C. Gowda, S. Gowda, *Indian Journal of Chemistry - Section B Organic and* Medicinal Chemistry **2000**, 39, 709.

159 T. Nishiguchi, H. Imai, Y. Hirose, K. Fukuzumi, *J. Catal.* **1976**, *41*, 249.

160 A. Zoran, Y. Sasson, J. Blum, *Journal of Molecular Catalysis* **1984**, *26*, 321.

161 G. Cavinato, L. Toniolo, *J. Mol. Catal. A: Chemical* **1996**, *106*, 25.

162 M. A. Tike, V. V. Mahajani, *Chemical Engineering Journal* **2006**, *123*, 31.

163 H. Wiener, J. Blum, Y. Sasson, *Journal of Organic Chemistry* **1991**, *56*, 6145.

164 S. Rajagopal, A. F. Spatola, *Journal of Organic Chemistry* **1995**, *60*, 1347.

165 S. Rajagopal, A. F. Spatola, *Applied Catalysis A: General* **1997**, *152*, 69.

166 D. Channe Gowda, B. Mahesh, *Synth. Commun.* **2000,** *30*, 3639.

167 B. Ohtani, Y. Goto, S. Nishimoto, I. Tomoyuki, *J. Chem. Soc. Faraday Trans.* **1996,** *92*, 4291.

168 R.J. Pellet, *J. Catal*. **1998,** *177*, 40.

169 (a)F. Alonso, P. Riente, F. Rodriguez-Reinoso, J. Ruiz-Martinez, A. Sepulveda-Escribano, M. Yus, *J. Catal.* **2008**, *260*, 113.(b) F. Alonso, P. Riente, F. Rodriguez-Reinoso, J. Ruiz-Martinez, A. Sepulveda- Escribano, M. Yus, *ChemCatChem* **2009**, *1*, 75.

170 R. S. G. Bauer, P. W.Keim, W.van Zwet, H. Chung. *U.S.Patent 3,644,563* **1972**.

171 (a) T. Welton, *Chem. Rev.* **1999**, *99*, 2071. (b) P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **2000,** *39,* 3773. (c) T.Welton, *Coord. Chem. Rev.* **2004**, *248,* 2459. (d) K. R. Seddon, A. Stark, M. J. Torres, *Pure Appl. Chem.***2000**, *72*, 2275.

172 (a) I. T Horvath, J. Rabai, *Science* **1994**, *266*, 72.(b) D. P.Curran, S. Hadida *J. Am. Chem.Soc.*, **1996**, *118*, 2531. (c) S. G. Dimgno, S. G.Dussault *J. Am. Chem. Soc.,* **1996**, *118*, 5312.

173 E.G. Kuntz ,*Chemtech*, **1987**, 570.

174 B. Cornils, W. A. Herrmann (Eds.) *Aqueous Phase Organometallic Catalysis: Concept and Application,* Viley-VCH, Weinheim (Germany) **1998.**

175 F. Joo. *Aqueous Orgonometattic Cotolysis;* Kluv/er Academic Publishers: Dordrecht, **2001**.

176 U. M. Lindström, Organic reactions in water: principles, strategies and applications; Wiley-Blackwell, **2007**.

177 (a) F. Monteil, R. V. Kastrup, A. A. Ostwald, *Catal. Lett.,* **1985**, *2*, 85. (b)Purwanto, H. Delmas, *Catal. Today* **1995**, *24*, 134. (c) R.M. Deshpande, Purwanto, H. Delmas, R. V. Chaudhari, *Ind. Eng. Chem. Res.,* **1996**, *35*, 3927. (d) Y. Zhang, Z. Mao, J. Chen, *Catal. Today,* **2002**, *74*, 23. (e) R. M. Deshpande, Purwanto, H. Delmas, R.V.Chaudhari, *J. Mol. Catal A: Chemical,* **1997**, *126*,133. (f) F. Monteil, R. Dueau, P. Kalck *J.Organomet. Chem.,* **1994**, *480*, 177.

178 (a)F. Wang, H. Liu, L. F. Cun, J. Zhu, J. G. Deng, Y. Z. Jiang, *Journal of Organic Chemistry* **2005**, *70*, 9424. (d) H.Chen, Y. Li, J. Chen, P. Cheng, Y. He, X. Li, *J. Mol. Catal. A: Chemical,* **1999**, *149*, 1

179 (a) R. Bar, Y. Sasson, J. Blum, *J. Mol. Catal.,* **1984**, *26,* 324. (b) R. Bar, L.K. Bar, Y. Sasson, J. Blum, *J. Mol. Catal.,* **1985,** *33*,161.

180 F. Joo, M.T. Beck ,*Magyar Kemiai Folyoirat* **1973**, *79*,189.

181 F. Joo , A. Katho, in Aqueous-Phase Organometallic Catalysis; Concepts and Applications, (Eds.: B. Cornils,W. A. Herrmann), Wiley-VCH, Weinheim, **1998**, pp.340

182 F. Lopez-Linares, M. G. Gonzales, D. E. Paez, *J. Mol. Catal. A Chem*. **1999**, *145*, 61

183 (a)R. Bar, Y. Sasson, *Tetrahedron Lett.* **1981**, *22,* 1709(b) R. Bar, Y. Sasson, *J. Mol. Catal.* **1984**, *26,* 327(b) R. Bar, L. K. Bar, Y. Sasson, J. Blum, *J. Mol. Catal.* **1985**, *33,* 161

184 (a) G. A. Chukhajian, N. A. Balyushina, V. P. Kukolev, *Armianskii Khim. Zh.* **1982**,35,445.(b) V. P. Kukolev, N. A. Balyushina, G.A.Chukhajian, V. A. Matossian, *Armianskii khim Khim. Zh.* **1984**, *37*, 115 (c) V. P. Kukolev, N. A. Balyushina, G. A. Chukhajian, *Armianskii Khim. Zh.***1982**,35,688 (d) G. A. Chukhajian, V. P. Kukolev, L. N. Melkonyan, V. A. Matossian, N. A. Balyushina.,*Armianskii Khim. Zh.* **1983**, *36*, 412

185 F. Joo, A. Benyei, *Journal of Organometallic Chemistry* **1989**, *363*, C19.

186 A. Benyei, F. Joo, *Journal of Molecular Catalysis* **1990**, *58*, 151.

187 F. Joo, J. Kovacs, A.C. Benyei, L. Nadasdi, G. Laurenczy, *Chemistry-a European* Journal **2001,** 7, 193.

188 D. Sinou, M. Safi, C. Claver, A. Masdeu, *J. Mol. Catal.* **1991**, *68*, L9

189 Y. Amrani, L. Lecomte, D. Sinou, J. Bakos, I. Tóth, B. Heil, *Organometallics* **1989**, *8,* 542.

190 A. N. Ajjou, J. L. Pinet, *J. Mol.Catal.A Chem.* **2004**, *214*, 203

191 C. de Bellefon, N. Tanchoux, S. Caravieilhes, D. Schweich, *Catalysis Today* **1999**,*48*, 211.

192 C. de Bellefon, N. Tanchoux, S. Caravieilhes, *Journal of Organometallic Chemistry* **1998**, *567*, 143.

193 N. Tanchoux, C. de Bellefon, *Eur. J. Inorganic Chemistry* **2000**, *7*,1495.

194 D. J. Darensbourg, F. Joó, M. Kannisto, Á. Kathó, J. H. Reibenspies, O*rganometallics* **1992**, *11*, 1990

195 D. J. Darensbourg, F. Joó, M. Kannisto, Á. Kathó, J. H. Reibenspies, D. J. Daigle, *Inorg.Chem.* **1994**, *33*, 200

196 D. J. Darensbourg, N. W. Stafford, F. Joó, J. H. Reibenspies, *J. Organometal. Chem.* **1995**, *488*, 99

197 S. Bolano, L. Gonsalvi, F. Zanobini, F. Vizza, V. Bertolasi, A. Romerosa, M. Peruzzini, *J. Mol. Catal. A: Chem.* **2004**, *224,* 61.

198 A.D. Phillips, S. Bolano, S.S. Bosquain, J.-C. Daran, R. Malacea, M. Peruzzini, R. Poli, L. Gonsalvi, Organometallics **2006,** *25*, 2189.

199 S. Oga, T. Abura, Y. Watanabe, Organometallics **2002**, *21*, 2964.

200 Z.S. Liu, G.L. Rempel , *J. Mol.Catal.A Chem.* **2007,** *278*, 228.

201 M. E. Volpin, V. P. Kukolev, Chernysh.Vo, Kolomnik.Is, *Tetrahedron Letters* **1971**, *46*, 4435.

202 S. Kolaric, V. Sunjic, *Journal of Molecular Catalysis a-Chemical* **1996**, *110*, 189.

203 S. Ogo, N. Makihara, Y. Watanabe, *Organometallics* **1999**, *18*, 5470

204 T. Abura, S. Ogo, Y. Watanabe, S. Fukuzumi, *J.Am.Chem.Soc.* **2003**, *125*, 4149.

205 J. Canivet, L. Karmazin-Brelot, G. Suss-Fink, *J.Organomet.Chem.* **2005**, *690*, 3202.

206 X. F. Wu, J. K. Liu, X. H. Li, A. Zanotti-Gerosa, F. Hancock, D. Vinci, J. W. Ruan, J. L. Xiao, *Angewandte Chemie-International Edition* **2006**, *45*, 6718.

207 C. A. Mebi, R. P. Nair, B. J. Frost, *Organometallics* **2007**, *26*, 429.

208 P. Govindaswamy, J. Canivet, B. Therrien, G. Suss-Fink, P. Stepnicka, J. Ludvik, *Journal of Organometallic Chemistry* **2007**, *692*, 3664.

209 Y. Himeda, N. Onozawa-Komatsuzaki, S. Miyazawa, H. Sugihara, T. Hirose, K. Kasuga, *Chemistry - A European Journal* **2008**, *14*, 11076.

210 H. Y. Cheng, R. X. Liu, J. M. Hao, Q. A. Wang, Y. C. Yu, S. X. Cai, F. Y. Zhao, *Applied Organometallic Chemistry* **2010**, *24*, 763.

211 (a)H. Brunner, W. Leitner, *Angew. Chem.-Int. Edit. Eng.* **1988**, *27*, 1180 (b)H. Brunner, E. Graf, W. Leitner, K. Wutz, *Synthesis-Stuttgart* **1989**, 743. (c)H. Brunner, W. Leitner, *Journal of Organometallic Chemistry* **1990**, *387*, 209.

212 (a)T. Nishiguchi, K. Tachi, K. Fukuzumi, *Journal of Organic Chemistry* **1975**, *40*,240. (b)W. Leitner, J. M. Brown, H. Brunner, *J. Am. Chem. Soc.* **1993**, *115*, 152.

213 S. Lange, W. Leitner, *Journal of the Chemical Society-Dalton Trans.* **2002**, 752.

Chapter 2

Asymmetric Transfer Hydrogenation of Ketones Using Ruthenium -Ephedrine Complex Catalyst and Use of Ultrasound to Enhance the Rate of Reaction.

2.1 INTRODUCTION

Chiral alcohols are the important building blocks in the pharmaceutical and fine chemical industry. There is a constant need to discover and develop new methods capable of supplying such building blocks containing an increasingly diverse range of structural features. The enantioselective synthesis of chiral secondary alcohols by catalytic reduction of the corresponding ketones is becoming an important transformation in organic synthesis.[1] Many efforts have been devoted to the development of new chiral catalysts and rapid progress has been made in this area. Among these, asymmetric transfer hydrogenation (ATH) of ketones is a highly efficient method for the synthesis of chiral alcohols.

The ATH of various aromatic ketones has been invstigated using ruthenium, rhodium and iridium complex catalysts. A number of chiral ligands containing various combinations of nitrogen, oxygen, phosphorous and sulfur atoms have been developed for the synthesis of the complexes. The detailed literature review on ATH of ketones is presented in Chapter 1 (section 1.3). After very little progress in the development of catalysts for ATH reaction, one of the most significant breakthroughs was reported by Noyori et al. in 1995.[2] The use of chlororuthenium(II)arene precursors with chiral monoarylsulfonylated 1,2 diamine or β-amino alcohol ligand system developed by Noyori-group enabled the highly effective reduction of a variety of aryl alkyl and related ketones.[3] After this discovery, a lot of work has been done using β-amino alcohol ligands for ATH reactions, as β-amino alcohol ligands are quite simple to synthesize as compare to chiral diamine ligands.[3] 2-Propanol (IPA) with base has been used as hydrogen donor system for most of the ATH reactions where β-amino alcohol ligands are used. IPA is a safe, inexpensive and easy to handle hydrogen donor which can simultaneously be employed as a solvent for the reaction.

As large variety of β-amino alcohol ligands can be easily prepared from various abundant sources, significant work has been done on synthesis of these ligands and their application for ATH reactions. The work has been restricted to designing a catalyst system to give better results in terms of catalytic activity and enantioselectivity. The optimization of reaction conditions was done in very few cases.[4,5] Among the various simple β-amino alcohol ligands studied, ephedrine [(1R, 2S) or (1S, 2R)] is one of the good ligand which gives high conversion and moderate enantioselectivity for ATH of ketones. But a detailed work of optimization of this reaction has not been carried out so far.

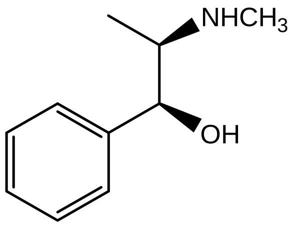
In this work the ATH reaction of acetophenone has been studied using ruthenium (II) arene/ (1R, 2S) ephedrine as a catalyst system and IPA as a hydrogen donor. The effect of various reaction conditions on activity and enantioselectivity has been investigated in detail. The use of ultrasound to enhance the rate of reaction also has been investigated in this study. The effect of different sonochemical parameters on activity and enantioselectivity in ATH of acetophenone has been studied. The results obtained with and without sonochemical promotion have been compared and discussed.

2.2 EXPERIMENTAL SECTION

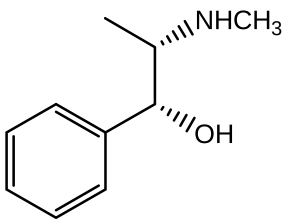
2.2.1 Materials

Ruthenium chloride trihydrate ($RuCl_3.3H_2O$), rhodium chloride trihydrate ($RhCl_3.3H_2O$), and iridium chloride ($IrCl_3.xH_2O$) were obtained from Arora-Matthey India. All the ketones, (1R, 2S) cis aminoindanol and 1,4-cyclohexadiene were procured from Sigma Aldrich USA. Ethanol, 2-Propanol, KOH etc were procured from the commercial sources (Loba Chemicals, India) and used as received. 2-Acetyl-6-methoxy naphthalene, (1R, 2S) ephedrine, (1S, 2R) ephedrine were obtained as a free samples from a private company. The purity of these compounds (>98%) was confirmed by GC and GC-MS analysis. The ligands (2S)-1-(1S-phenylethylamino) propan-2-ol and (1S)-1-phenyl-2-(1S-phenylethyl-amino) ethanol were prepared by literature procedure.[6]

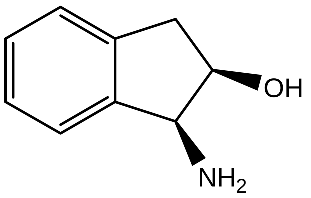
Figure 2.1 shows the structure of chiral ligands which are used in this study.



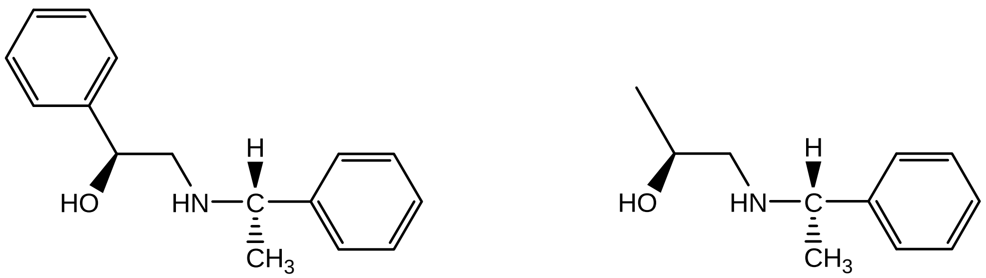
(1R, 2S) Ephedrine



(1S, 2R) Ephedrine



(1R, 2S) cis-amino indanol



(*S*)-1-phenyl-2-((*S*)-1-phenylethylamino)ethanol (*S*)-1-((*S*)-1-phenylethylamino)propan-2-ol

Figure 2.1: Chiral ligands used in this study.

2.2.2 Synthesis of transition metal complexes

The transition metals complexes were prepared as per the literature procedure and analyzed using FTIR, ^{1}H-NMR and elemental analysis. ^{1}H NMR spectra of complexes were obtained on a Bruker AC-200 spectrometer in $CDCl_3$ or DMSO-d6 at room temperature. FT-IR spectra were recorded on a Bio-Rad FTS 175C machine in transmission mode using KBr pellets. The elemental analyses were done on a CHNS-O EA 1108, elemental analyzer of Carlo-Erba Insrtuments, Italy.

2.2.2.1 Synthesis of Di-μ-chloro-bis (η-benzene) chlororutheniun (II) complex. $[RuCl_2(benzene)]_2$ complex

The complex was prepared by using the method described by Bennet and coworkers.[7] Hydrated ruthenium trichloride (1g, 3.82 mmol) in ethanol (50 ml) was heated under reflux with 1, 4- cyclohexadiene (5 ml, 5.31 mmol) for 4 h under nitrogen atmosphere. After cooling the reaction mixture, the brown precipitate was filtered off, washed with methanol, and dried in vacuum. Practical yield of complex was 0.91g (95%). The IR shifts for this complex are at 3074, 3037 cm^{-1}(aromatic C-H stretching) 1432 cm^{-1}(C-C stretching of benzene), and 1148, 844 cm^{-1}(C-H bending) as shown in Figure 2.2. The ^{1}H NMR spectrum (in DMSO-d6) of complex as shown in Figure 2.3 shows the singlet at δ 5.97 which is characteristic of coordinated arene protons. The elemental analysis of $[RuCl_2(benzene)]_2$ was in agreement with theoretical values. (Found: C=28.9 %; H=2.6 %; Cl=28.8 %. Calculated: C=28.4 %; H=2.4 %; Cl=28.3 %).

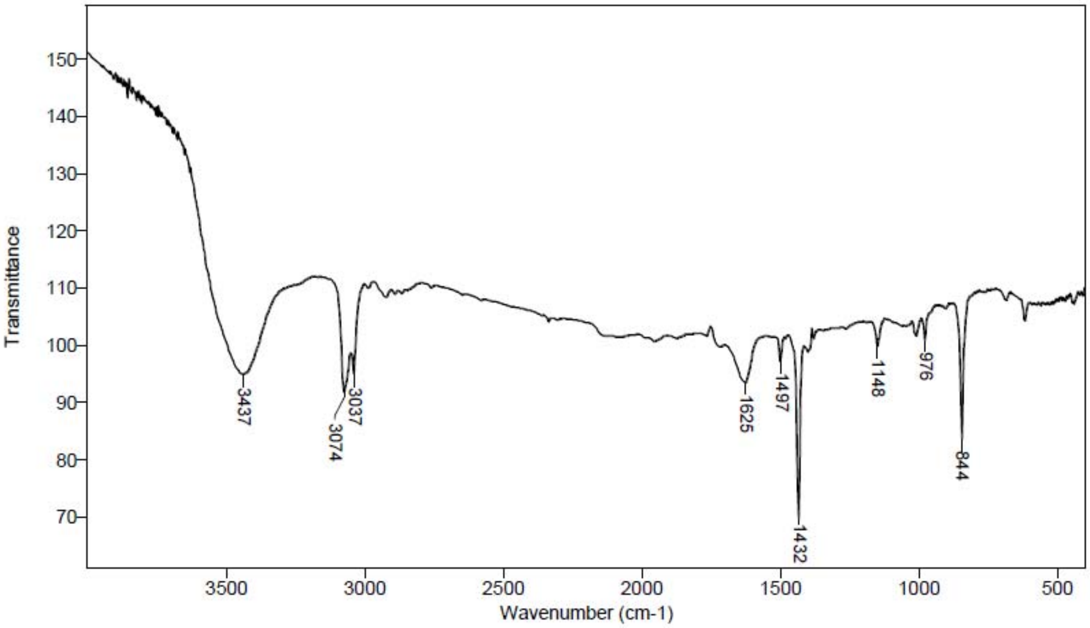


Figure 2.2: FTIR spectrum of [$RuCl_2$(benzene)]

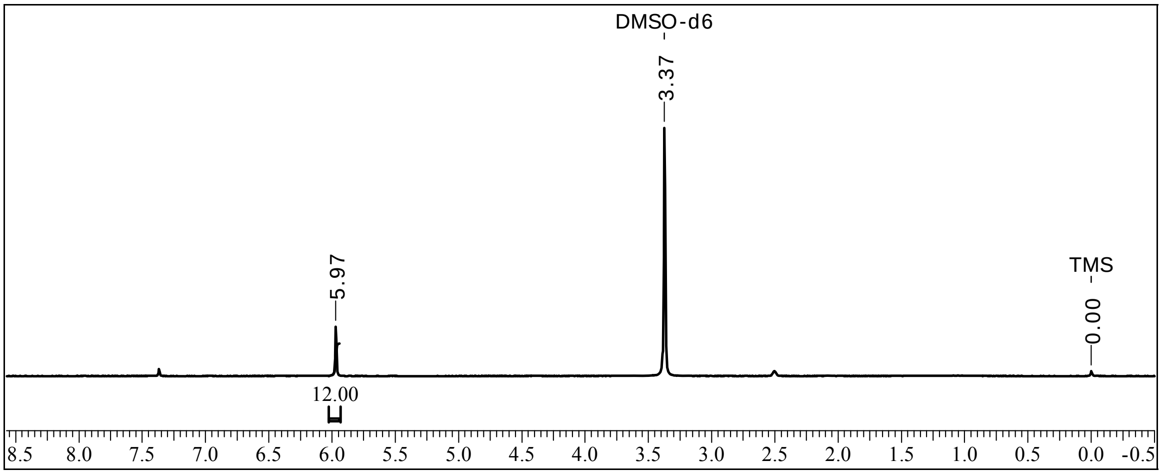


Figure 2.3: ^{1}H NMR spectrum of [$RuCl_2$(benzene)]$_2$

2.2.2.2 Synthesis of Di-μ-chloro-dichlorobis (η^5-pentamethylcyclopentadienyl)di-rhodium(III) complex. [[Rh(Cp*)Cl $_2$]$_2$ complex]

$$2RhCI_3.3H_2O + 2C_5Me_5H \longrightarrow [Rh(\eta^5\text{-}C_5Me_5)Cl_2]_2 + 2HCl$$

Rh(Cp*)Cl $_2$]$_2$ complex was prepared by a method described by P. M. Maitlis et al.[8] 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, the apparatus was purged with nitrogen for 5 min, 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 that were combined with the first crop and washed with diethyl ether (3 x 5 cm^3). Air drying gives 0.8 g (75% yield) of $[Rh(Cp^*)Cl_2]_2$. The complex was characterized by IR spectra (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 2.4) and also by using ^1H NMR which shows sharp singlet at 1.62 ppm of protons of pentamethylcyclopentadiene as shown in Figure 2.5. The Elemental analysis calculated for $Rh_2C_{20}H_{30}C_{14}$ was in agreement with theoretical values. (Calculated: C-38.9 %, H-4.9 %, Cl-22.9 %. Found: C-38.8 %, H-4.8 %, Cl-22.3 %).

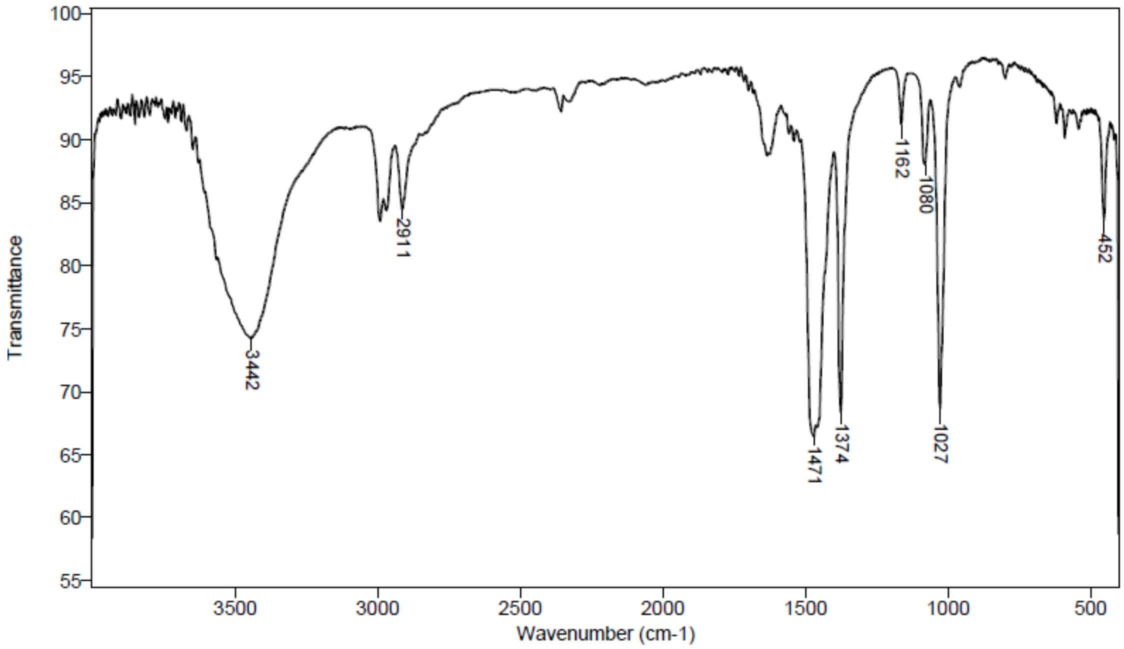


Figure 2.4: FTIR spectrum of $[Rh(Cp^*)Cl_2]_2$

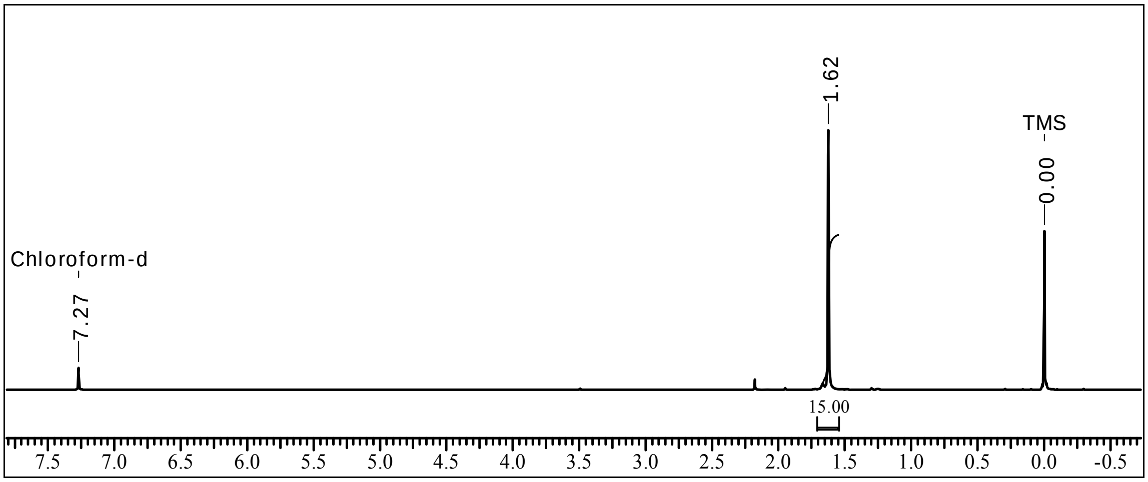


Figure 2.5 ^{1}H NMR spectrum of $[Rh(Cp^*)Cl_2]_2$

2.2.2.3 Synthesis of Di-µ-chloro-dichlorobis (η^5-pentamethylcyclopentadienyl di-iridium(III) complex. [$[Ir(Cp^*)Cl_2]_2$ complex]

$$2IrCl_3.XH_2O + 2C_5Me_5H \longrightarrow [Ir(\eta^5\text{-}C_5Me_5)Cl_2]_2 + 2HCl$$

The complex was prepared by a method described by P. M. Maitlis et al.[8] 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. A nitrogen bubbler was attached to the top of the condenser, the apparatus was purged with nitrogen for 5 min, and the mixture was then 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 orange filtrate was reduced in volume to 5 mL using a rotary evaporator to give more orange crystals that were combined with the first crop and washed with diethyl ether (3 x 5 cm^3). Air drying gives 0.5 g (45% yield) of $[Ir(Cp^*)Cl_2]_2$. Elemental analysis for $Ir_2C_{20}H_{30}C_{14}$ was in agreement with theoretical values. (Calculated: C-30.2 %, H-3.8 %, Cl-17.8 %. Found: C-30.5 %, H-3.7 %, and Cl-16.5 %). The complex was characterized by ^{1}H NMR spectra which give singlet at 1.60 ppm of protons of pentamethyl-cyclopentadiene as shown in Figure 2.6 and by IR spectra (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) (Figure 2.7).

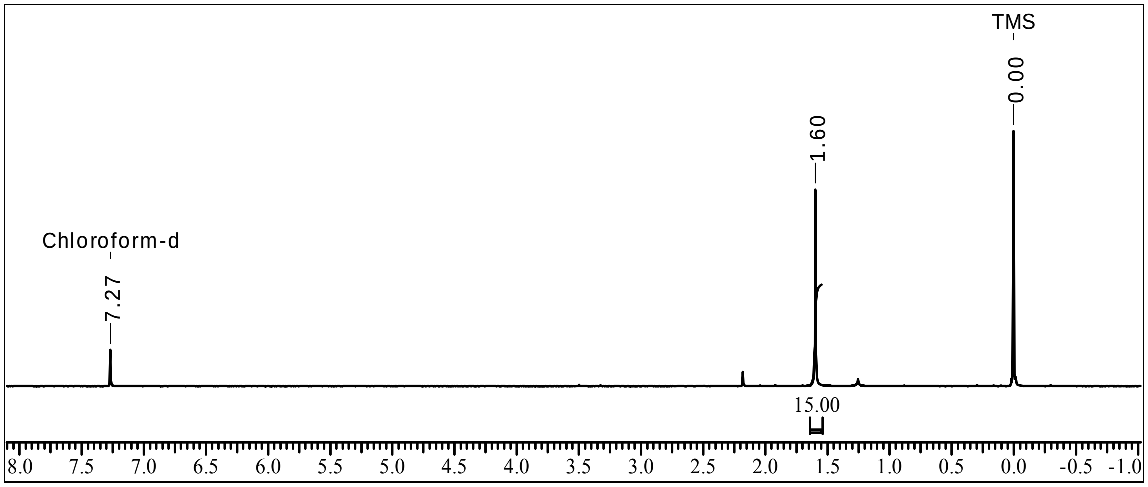


Figure 2.6 ^{1}H NMR spectrum of $[Ir(Cp^*)Cl_2]_2$

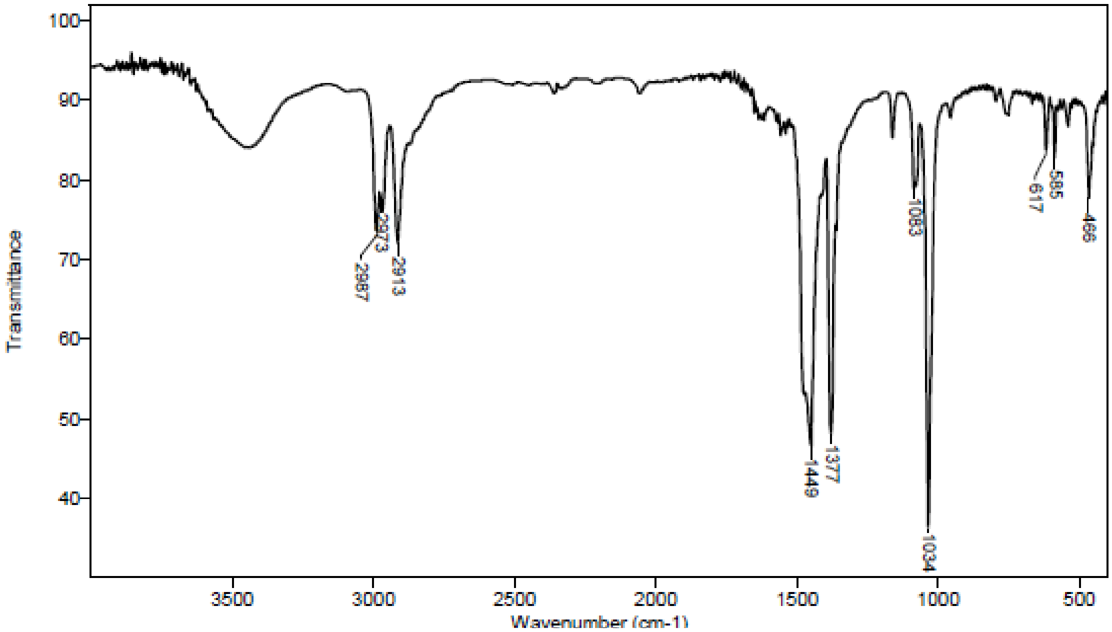


Figure 2.7: FTIR spectrum of $[Ir(Cp^*)Cl_2]_2$

2.2.2.4 Preparation of KOH solution in IPA

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

2.2.3 Experimental setup and procedure for ATH reaction

The schematic representation of experimental setup is presented in Figure 2.8. The reactions were carried out in a jacketed glass reactor flushed with argon prior to the addition of reactants.

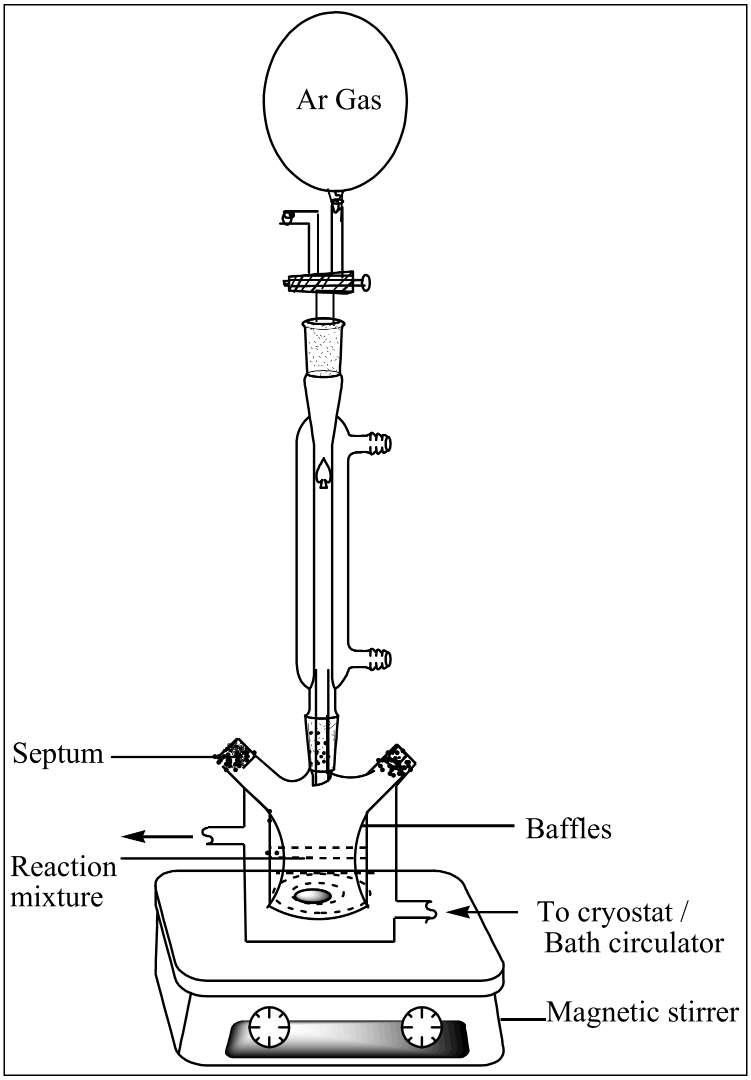


Figure 2.8: Experimental set-up for Asymmetric transfer hydrogenation

In a typical experiment, [Ru(benzene)Cl_2]$_2$ 6.3 mg (0.013 mmol) and (1R,2S)ephedrine 8.5 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 298 K 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 2 h. The reaction samples were withdrawn at regular time intervals and quenched by the addition of acetic acid. From the quantitative analysis on GC, the conversion, enantioselectivities and turnover frequency (TOF) were calculated.

2.2.4 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 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 conditions for the analysis of products of ATH of acetophenone reaction are given in Table 2.1.

Table 2.1: Conditions for GC analysis

Injector (split) Temperature	250ºC		
Flame ionization detector	Temperature: 300ºC		
	Hydrogen: 35.0ml/min		
	Zero Air: 320.0ml/min		
Split ratio for Injector	150:1		
Column Temperature	Rate (ºC /min)	T (ºC)	Hold time (min)
		60	0
	5	90	5
	5	100	10
	35	200	1
Column Pressure	10 Psi		

Figure 2.9 represents a typical GC chart obtained for ATH reaction of acetophenone under the analysis condition given in Table 2.1. The distinct separation of both the enantiomers was obtained. (R-phenyl alcohol and S-phenyl alcohol peaks appear at 15.9 and 17.0 minutes retention time respectively). The position of R-isomer and S-isomer of

1-phenyl ethanol was confirmed using authentic enantiopure (R) and (S) 1-phenyl ethanol.

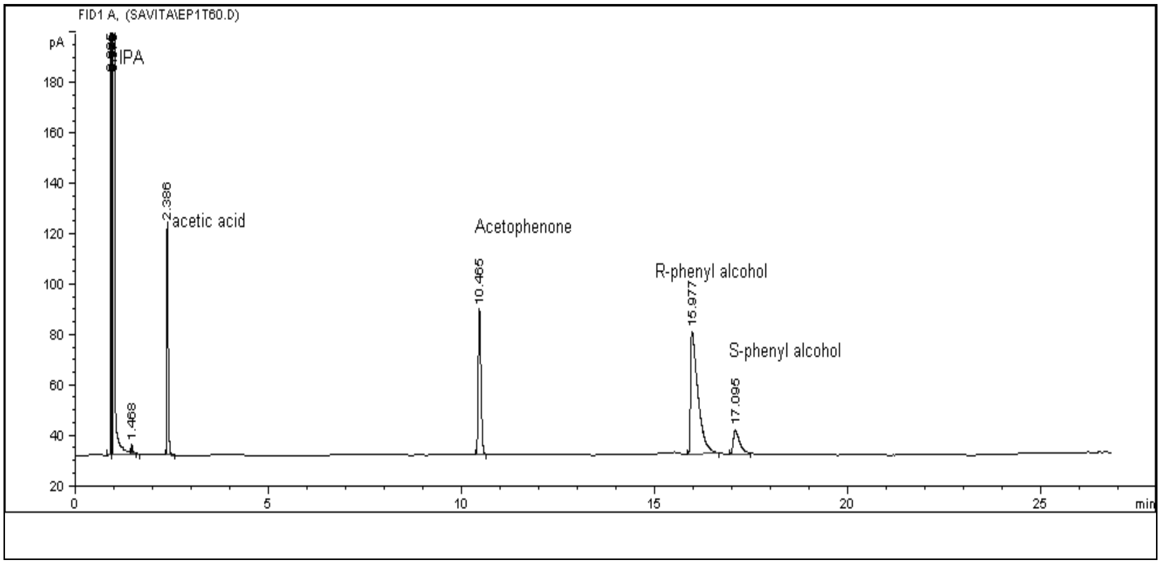


Figure 2.9: A typical GC chart showing the solvent IPA, reactant acetophenone, and products R and S alcohol.

Some chiral alcohols obtained from reactions of other ketones are not separated on HP-chiral column. For such compounds the analysis were done on HPLC. For calculation of conversions the sample analysis were done on Agilent 6850 GC using HP-1 column (30m × 320 μm ID × 0.25 μm film thicknesses) and FID detector. To determine enantiomeric excesses the reaction mixture was analyzed on HPLC (Perkin Elmer series 200) using Diacel Chiracel OD-H column (25 x 1 cm). The detector used was a UV-DAD and the monitoring wavelength used in typical analysis was 220 nm or 254 nm. The analysis was done with injection volume of 5 μl, using n-hexane-isopropyl alcohol as the mobile phase.

Complete mass balance of the liquid phase components was obtained from the quantitative GC analysis. The percent conversion, percent enantioselectivity and turnover frequency (TOF h^{-1}) were calculated using the formulae given below.

$$\%\text{Conversion} = \frac{(\text{Initial moles of substrate - Final moles of substrate})}{\text{Initial moles of substrate}} \text{ x } 100$$

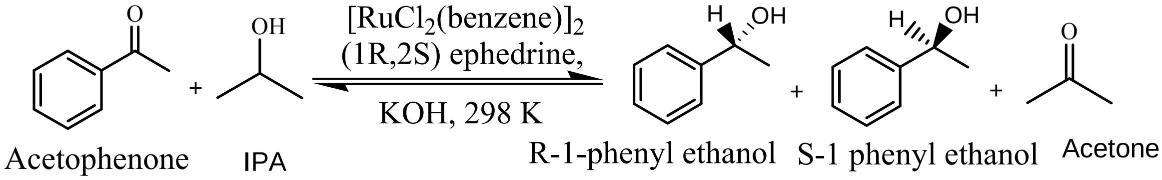
$$\% \text{ ee} = \frac{(\text{No. of moles of S-isomer - No. of moles of R-isomer})}{(\text{No. of moles of S-isomer + No. of moles of R-isomer})} \times 100$$

$$\text{TOF}(\text{h}^{-1}) = \frac{\text{No. of moles of product formed}}{\text{No. of moles of catalyst x time in hours}}$$

2.3. RESULTS AND DISCUSSION

The preliminary experiments on the transfer hydrogenation of acetophenone were carried out at 298 K using $[\text{Ru(benzene)Cl}_2]_2$/(1R, 2S) ephedrine catalyst system and KOH as a base as schematically shown below. For the $[\text{Ru(benzene)Cl}_2]_2$/(1R, 2S) ephedrine catalyst system, R-1-phenyl alcohol was obtained as major isomer as reported in literature.[9]

Reaction scheme:



Scheme 2.1: Asymmetric transfer hydrogenation of acetophenone

The effects of various reaction parameters on conversion of acetophenone and enantioselectivity to R-1-phenyl ethanol were studied. The reaction conditions were optimized. These optimized reaction conditions were then used to study the effect of ultrasound on transfer hydrogenation reactions.

2.3.1 Influence of addition sequence of reactants

The influence of addition sequence of reactants was investigated first. For this purpose two sets of experiments were performed. The catalyst was prepared in-situ by adding precatalyst to ligand solution in both cases. In first sequence, acetophenone in IPA was added to catalyst solution and this mixture was stirred for 10 min. Following this, KOH solution was added. The procedure for the second sequence consisted of mixing catalyst and KOH in IPA and, after 10 minutes of stirring, adding acetophenone. The conversion and enantioselectivity obtained from each addition sequence were then compared.

It was observed that in the second case the reaction mixture became dark and no conversion of acetophenone to alcohol was seen, indicating the deactivation of the catalyst. When KOH solution was added after addition of acetophenone (sequence 1), 92 % conversion of acetophenone was obtained with 69 % *ee*.

As per mechanism given in Chapter 1 section 1.3.4, the formation of the intermediate species **2** and **3** occurs as a first step in presence of KOH. However, when KOH and catalyst interact in absence of ketone, there is probability of formation of dimeric species which are reported inactive for transfer hydrogenation reaction.[5,10] Another possible reason is that the central metal atom might combine with hydroxide first forming catalytically inactive species.[5] Combination of both of this phenomenon can lead to loss in catalytic activity observed on pretreatment of KOH.

Since the conversion of acetophenone was greatly influenced by the addition sequence, all the experiments were carried out by mixing precatalyst solution and acetophenone prior to the addition of KOH solution.

2.3.2 Effect of catalyst concentration

The effect of concentration of catalyst on conversion and enantioselectivity was further investigated. The catalyst concentration was varied from 0.063 mmol to 0.252 mmol. The results obtained are presented in Figure 2.10 in terms of conversion and enantioselectivity.

As expected the conversion of acetophenone increased with increase in catalyst concentration. For catalyst concentration of 0.0252 mmol, 91% conversion was obtained within 30 minutes, while it requird almost 120 minutes for the same conversion when catalyst concentration was 0.0126 mmol. For lower catalyst concentrations (0.0063 mmol) the reaction was very slow and only 75% conversion was obtained in 180 minutes. For catalyst concentrations of 0.0063 and 0.0126 mmol, the *ee* was around 70%. For highest catalyst concentration (0.0252 mmol) initially (at 15 minutes) the *ee* was around 70 % which decreased to 63 % with time (180 minutes).

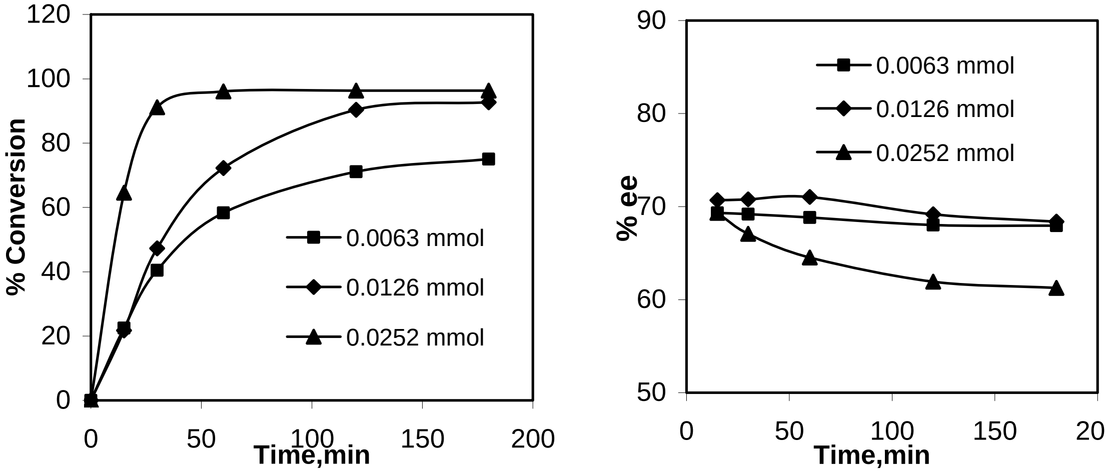


Figure 2.10: Effect of catalyst concentration on conversion and enantioselectivity
***Reaction conditions**: (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3; Temperature:* 298 K

Our results are similar to the results obtained by Gavriilidis et al.[5] They have shown that *ee* decreases slightly at higher catalyst concentration for ATH of acetophenone using cis amino indanol/ pentamethylcyclopentadienyl-rhodium complex.

At higher concentration of catalyst (0.0252 mmol), high conversion was obtained but enantioselectivity was less. Hence 0.0126 mmol catalyst concentration was fixed for further reaction. At this catalyst concentration 91% conversion was obtained within 120 minutes and 68% *ee*.

2.3.3 Effect of substrate concentration

The effect of substrate concentration on conversion and enantioselectivity of ATH of acetophenone was investigated at constant catalyst, ligand and base concentrations of 1.26 x 10^{-5} mol, 5.1 x 10^{-5} mol and 1.2 x 10^{-4} mol respectively. Figure 2.11 represents the effect of different molar concentrations (M) of acetophenone on conversion of the reaction.

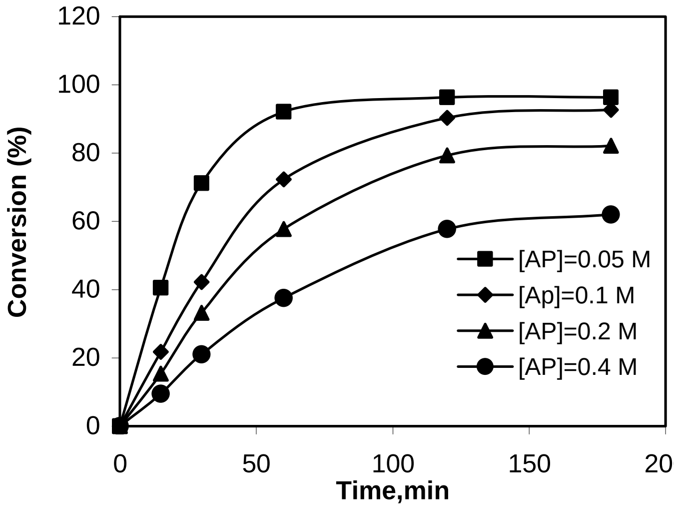


Figure 2.11: Effect of substrate concentration on conversion

Reaction conditions: *[Ru(benzene)Cl$_2$]$_2$,1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperature,* 298 K

Results indicate that at low substrate concentration (0.05 M), much higher conversion (91%) was obtained within 60 minutes. While for 0.1 M substrate concentration, 91 % conversion was obtained within 120 minutes. Higher initial substrate concentrations (0.2 and 0.4 M) required longer reaction times and gave lower conversions. (82 % and 62 % conversion within 180 minutes respectively). With increase in concentration of substrate although conversion reduces, the productivity of the alcohols in fact increases. This has been discussed in detail in later part of this section.

Figure 2.12 represents enantiomeric excesses obtained at different molar concentration of acetophenone as a function of conversion. The results indicate that higher *ee* (70 %) was obtained at 0.05 M and 0.1 M concentrations of acetophenone at 91% conversion. With increase in concentration of acetophenone as well as contact time, *ee* was found to decrease. Thus 65% *ee* was obtained with 0.2M and 0.4 M concentrations of acetophenone at 82 and 62% conversions respectively (at 180 minutes).

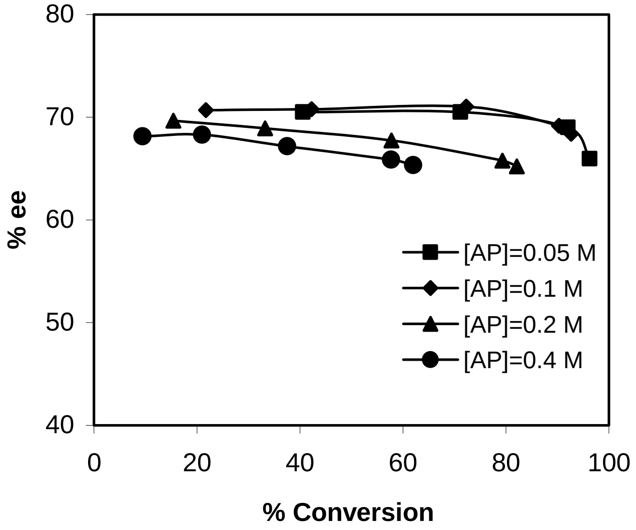


Figure 2.12: Effect of substrate concentration on *ee* with respect to conversion

***Reaction conditions**: [Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperature,* 298 K

Observed results on decrease in conversion and *ee* can be rationalized as follows: The ATH reaction with IPA as a hydrogen donor is reversible. During the process acetophenone is converted to chiral alcohol (R and S-1 phenylethanol) and IPA is converted to acetone. The products are in equilibrium with starting materials as represented in Figure 2.13.

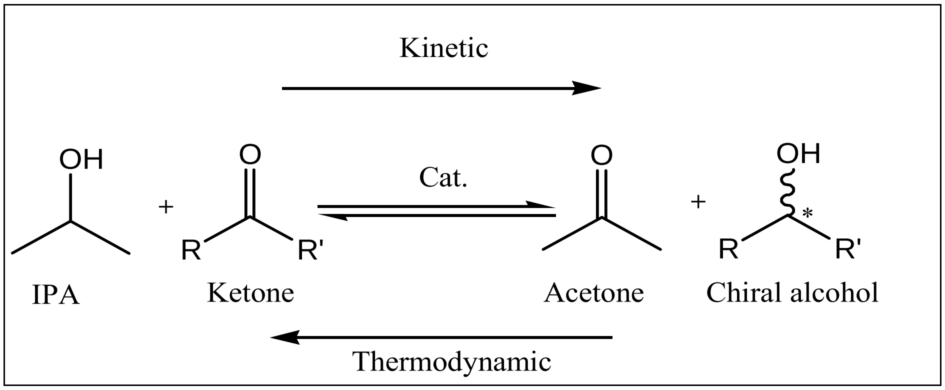


Figure 2.13: Equilibria between the kinetic and thermodynamic products (R is aryl).

To enhance formation of the product, IPA is used in large excess (as a solvent). As the reaction proceeds, the products acetone and chiral alcohols (one enantiomer is in excess depending on metal/ligand system) are formed in reaction mixture. Initially reaction is controlled kinetically and the conversion is high. As the concentration of the products increase the rate of reverse reaction also increases. One of the enantiomer which is formed in high concentration is preferentially converted back to ketone thereby reducing the *ee*. Hence to obtain high conversion and *ee*, it is necessary to work under dilute conditions and avoid longer contact time.

To explain this observation better, the actual concentration of R-1-phenyl ethanol (major enantiomer) at different conversions for different initial concentration were calculated. The plot of concentration (moles) of the R-1-phenyl ethanol versus conversion is presented in Figure 2.14.

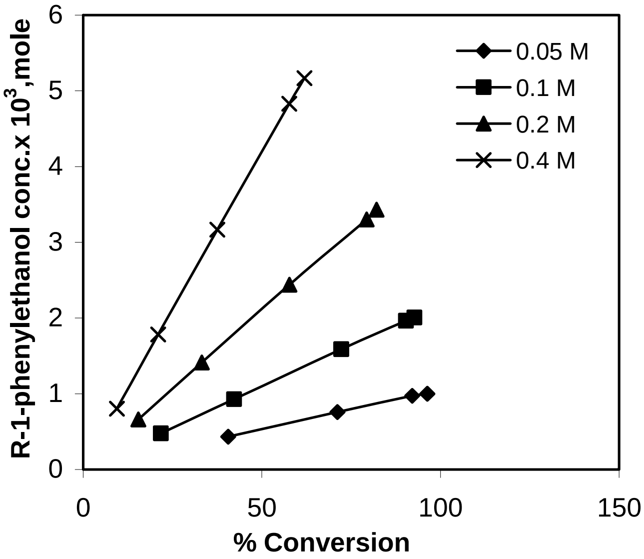


Figure 2.14: Effect of substrate concentration on R-1-phenylethanol concentration with respect conversion.

***Reaction conditions**: [Ru(benzene)Cl$_2$]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperature,* 298 K

The results clearly show that concentration of R-1-phenylethanol increases significantly with increase in initial concentration of acetophenone. At higher concentration of R-1-phenylethanol reverse reaction takes place thereby reducing its concentration in reaction mixture resulting lower *ee*. Thus decrease in *ee* was observed at high acetophenone concentration. Similar type of observation of deterioration of *ee* due to reversible nature of reaction for Ru(II)/amino alcohol catalyst in IPA-base system was observed by Noyori et al. and other groups also.[11]

In order to minimize unfavorable reaction condition, substrate concentration was kept as low as 0.1M for further reactions.

2.3.4 Effect of concentration of base

The effect of concentrations of base (KOH) (expressed as base to Ru ratio) was studied at constant catalyst, ligand and substrate concentration of 1.26 x 10^{-5}, 5.1 x 10^{-5} and 2.5 x 10^{-3}mole respectively at 298 K. The results are presented in Table 2.2. It was observed that the reaction was not initiated in the absence of a base (entry 1). Conversion increases with increase in base concentration. Highest conversion 91% was obtained at Ru: base ratio of 5 (entry 3). Further increase in Ru: base ratio did not affect the conversion (entry 4). The enantioselectivity was not affected by change in base concentration and was in the range of 68 to 69%.

Table 2.2: Effect of base concentration on conversion and enantioselectivity

Entry	Base: Ru	Conversion %	*ee* %
1	0 : 1	No reaction	-
2	2.5 : 1	71	68
3	5 : 1	91	69
4	10 : 1	91	68

***Reaction conditions**: [Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; IPA, 25 cm^3,Temperature,* 298 K*; Time, 120 min.*

Chowdhury and 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 [Ru(benzene)Cl_2]$_2$ is used as catalyst precursor. As per the reported mechanism (described in detail in Chapter 1, section 1.3.4), first step in metal-ligand complex formation is removal of proton from β-amino alcohol ligand and

Cl^- from the $[Ru(benzene)Cl_2]_2$ catalyst to give catalytic species **2** in the presence of base.(Figure 2.15)

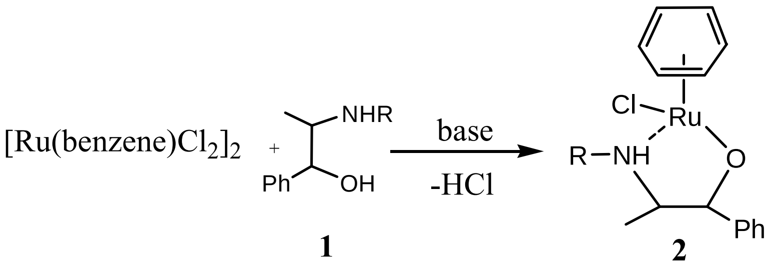


Figure 2.15: Formation of catalytic species **2** in presence of base

Further the base is required for elimination of HCl from complex **2** to give catalytically active species **3** as shown in Figure 2.16.

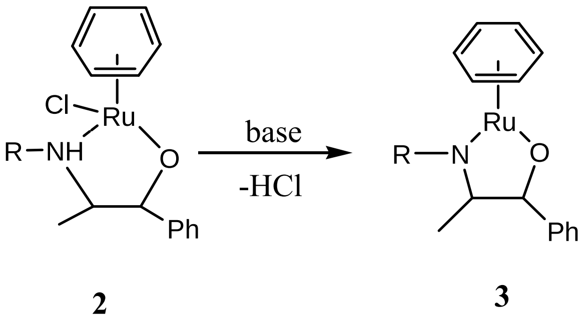


Figure 2.16: Formation of catalytically active species **3** in presence of base

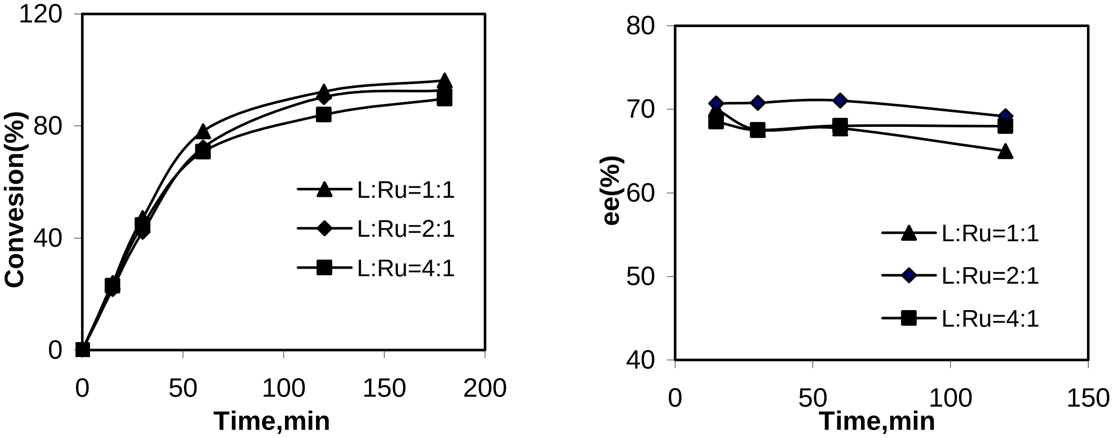
Thus in the initial stage base is necessary to generate a catalytically active species. IPA and acetophenone then interact with this catalytically active species to give (R) or (S)-1-phenylethanol as a product. In these steps base is not involved hence *ee* of product is not affected by change in base concentration.

Adolfsoon et al.[15] also have studied the effect of base concentration in ATH of acetophenone using amino acid derived rhodium complexes. They have shown that the conversion increases with increase in base concentration up to 5:1 base to Rh ratio and with further increase ratio up to 20, the conversion did not increase further. They also found that enantioselectivity was not affected by change in base concentration.

As base to ruthenium ratio 5 gave best results, the same ratio was used further work.

2.3.5 Effect of concentration of ligand

The effect of concentration of ligand on conversion and enantioselectivity on ATH reaction of acetophenone was further investigated. The concentrations of catalyst, substrate and base were kept constant at 1.26 x 10^{-5}, 2.5 x 10^{-3} and 1.2 x 10^{-4}mol respectively. The concentration of ligand was varied by changing ligand to ruthenium ratio in the range of 1 to 4. The results (Figure 2.17 (A) and (B)) indicate that the conversion of reaction was not affected by change in ligand to ruthenium ratio in the studied concentration range (90 to 89 % conversions). The enantioselectivity was lower (64%) at ligand to ruthenium 1 and increased to 69% with increase ligand to ruthenium ratio of 2 and 4 as presented in Figure 2.17 (B).



(A) **(B)**

Figure 2.17: Effect of concentration of ligand on conversion (A) and *ee* (B)
***Reaction conditions**: [Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperature,* 298 K.

The chiral shielding around the metal centre 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 hence their ratio with metal have proven to be critical.[16] Palmer et al.[17] fixed ligand to metal ratio 4, since for a 1:1 ratio decrease in *ee* was observed from 91 to 68% in [Ru(ρ-cymene)Cl_2]$_2$ catalyzed ATH of acetophenone with (1R,2S) cis 1-amino 2-indanol ligand. The result in this study agrees with the experimental and theoretical predictions done by Van Leeuwen and group[18] where they showed that ligand-to-metal ratio of two is sufficient to maintain the enantioselectivity for Ru(II)-amino alcohol catalyzed ATH of acetophenone.

Since a higher enantiomeric excess was obtained using ligand to metal ratio 2, the same was used for further experiments.

2.3.6 Effect of temperature

The effect of temperature on catalytic activity and enantioselectivity for ATH of acetophenone using Ru(II)/(1R,2S)ephedrine catalyst system was investigated further. The experiments were conducted at different temperatures ranging from 278 K to 318 K. The results in terms of conversion (Figures 2.18) and enantioselectivity (Figure 2.19) are presented below.

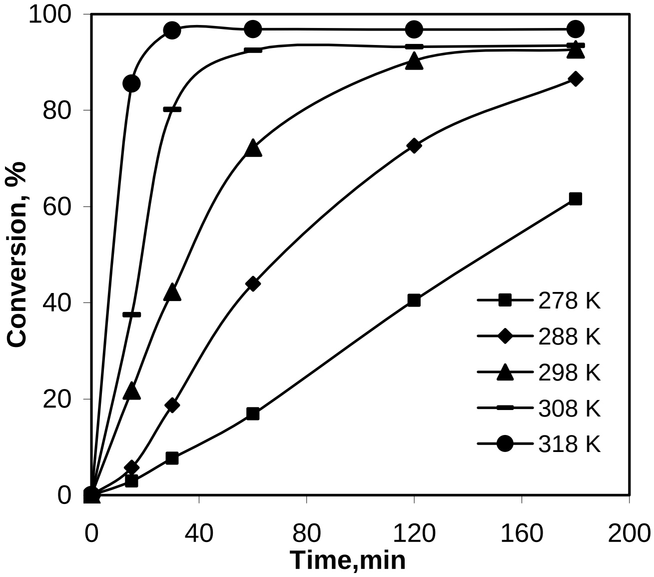


Figure 2.18: Effect of temperature on conversion of ATH of acetophenone

***Reaction conditions**: [Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3*

The results show that with increasing reaction temperature, the conversion increased as per expectation. Thus, 96 % conversion was obtained within 30 minutes at 318 K whereas only 65 % conversion was achieved in 180 minutes at 278 K temperature.

However enantioselectivity decreased significantly with increase in temperature from 72 % (at 278 K) to 62% (at 318 K). The results are presented in Figure 2.19.

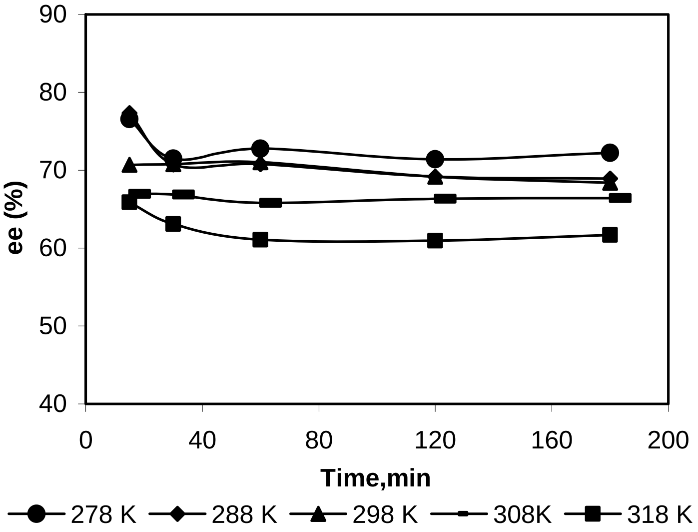


Figure 2.19: Effect of temperature on enantioselectivity of ATH of acetophenone
Reaction conditions: *[Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3*

Wills et al.[19] have observed a change in *ee* from 95% to 14% for the reduction of chloroacetophenone by Ru/phosphinamide complex for the temperature range of 313 to 383 K. Zassinovich et al.[20] also have observed a change of *ee* from 25% to 2 % for the range of 338 to 356 K for the reduction of acetophenone by Rh/ 3-*sec*-butyl-1, 10-phenanthroline complex catalyst. It is well known that increase of the temperature leads to a decrease of the energy difference between the diastereoisomeric transition states. Hence at higher temperature decrease in *ee* is observed.[21]

2.3.7 C-T profile of ATH reaction of acetophenone

A concentration-time (C-T) profile along with *ee* of ATH reaction of acetophenone with products R-phenyl ethanol and S-phenyl ethanol is presented in Figure 2.20. As discussed in previous sections, the experiment was performed using the optimized parameters as follows: Ru: ligand: base: substrate ratio 1:2:5:100 at 298 K. An aliquot of the reaction mixture was removed at regular time intervals, quenched and analyzed on GC using chiral column. 91% conversion of acetophenone was obtained with 68% *ee* of R-phenyl alcohol at 120 minutes reaction time. The formation of total 1-phenyl ethanol(R and S-alcohol) in the reaction was found to be stoichiometric with the consumption of acetophenone. It can be seen that the initial reaction rate is fast. The initial enantioselectivity of 71% dropped with time to 68 % at the end of 120 minutes.

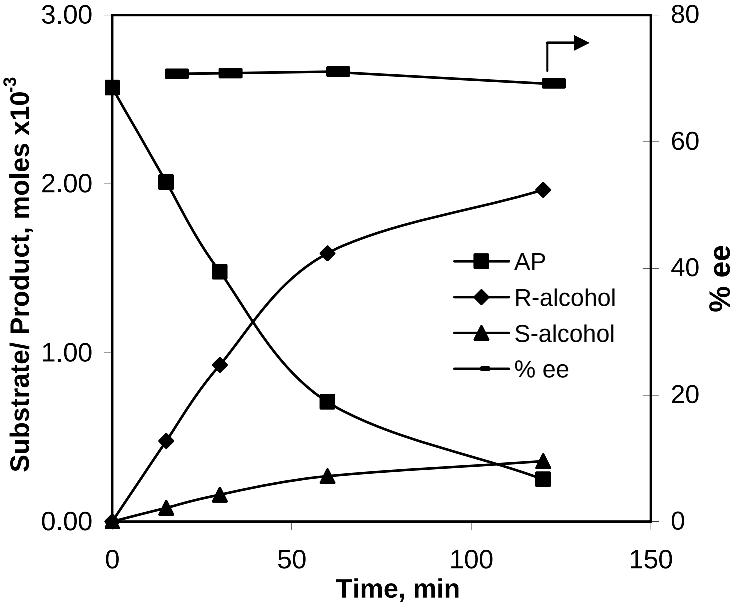


Figure 2.20: Typical reaction profile for ATH of acetophenone along with % *ee* ***Reaction conditions****: Catalyst, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; IPA, 25 cm^{3}; KOH, 1.2 x 10^{-4}mol; Temperature,* 298 K*; Reaction time, 3h.*

2.4 EFFECT OF ULTRASOUND ON ATH

The use of ultrasound (US) for acceleration of reaction rate is gaining importance as seen from literature available in last couple of decades. There are few reports on the use of US for ATH reactions of ketones using heterogeneous catalysts. [22] However in all cases US has been used during catalyst preparation. To the best of our knowledge there are no reports on use of US in homogeneously catalyzed ATH reaction. With this background it was decided to investigate the ATH reaction of acetophenone using Ru(II)/ephedrine complex catalyst system. The results obtained with and without sonochemical promotion are discussed and compared in the following sections. [The reactions carried out under ultrasound are denoted as “)))))”, while the reactions carried out without US are denoted as “silent reaction”].

2.4.1 Experimental setup for ultrasound promoted ATH reaction

As discussed in chapter 1 (section 1.3.5.1.5), the immersion probes usually show better performance in homogeneous systems, in contrast with baths.[23] Hence immersion probe system was used to study the effect of ultrasound on ATH of acetophenone. All the experiments were carried out using the sonochemical probe purchased from Sonics, USA (Sonics Vibra Cell Model VCX 750). It consists of a programmable microprocessor. Real time display provides digital display of amount of energy (Joules) and amount of power (watts) delivered to the probe. The probe tip can be set to any desired amplitude by using variable power output control. It also has independent on/off pulser mode. Elapsed time indicator monitors both the elapsed time and the duration of processing. Figure 2.21 shows a schematic diagram of an Immersion Horn which is used to generate ultrasound.

The sonochemical reaction vessel consists of a borosilicate reaction chamber (jacketed glass reactor) with three necks. This glass chamber slides on to the outside diameter portion of the tubular teflon adapter placed on the horn (through central neck). The adapter can be moved in or out of the vessel so that probe can be immersed at different depths to ensure optimum transfer of energy into the reaction medium. Septa are placed in two necks to facilitate removal of the reaction samples using syringe.

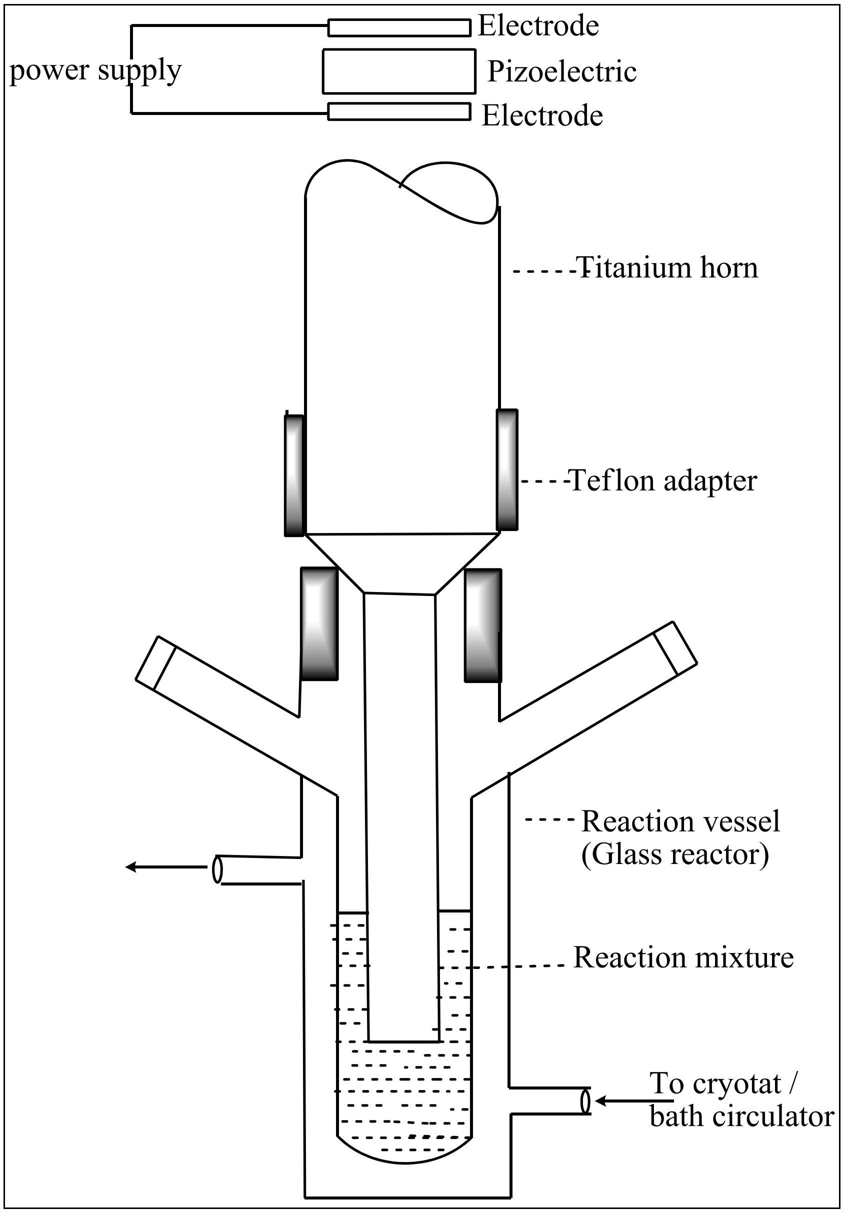


Figure 2.21: Schematic diagram of an Immersion Horn

2.4.2 Experimental procedure for ultrasound promoted ATH reaction

In a typical experiment, $[Ru(benzene)Cl_2]_2$ 6.3 mg (0.013 mmol) and (1R, 2S) ephedrine 8.5 mg (0.051 mmol) were added to 25 ml 2-propanol (IPA) in a glass reactor. To this solution, acetophenone 0.3025g (2.5 mmol, 0.1 M cocentration) and stock solution of KOH, 7 mg (0.12 mmol) were added. The glass reactor was attached to the sonochemical probe using a Teflon adapter to hold the flask in place such that the tip of the horn was immersed in the reaction mixture up to a depth of 2.5cm and glass part did not touch the sonochemical probe. The glass reactor temperature was kept at 298 K using a water circulation bath. The reaction was carried out using 60% amplitude and energy supplied under these conditions was 62 Watts. Reaction was carried out in a pulse mode keeping sonochemical probe on for 3 seconds followed by 1 second on silent. The reaction was continued for 12 minutes or till the reaction got completed (in few cases reaction was over in less than 12 minutes). Intermediate samples were withdrawn (quenched by the addition of acetic acid) to monitor the progress of the reaction.

2.4.3 RESULTS AND DISCUSSION

A few preliminary experiments were carried out on ATH of acetophenone using Ru(II) arene/ (1R,2S)ephedrine complex catalyst in IPA/KOH system as hydrogen donor under ultrasound to fix sonochemical parameters like amplitude, pulse mode and external parameters like temperature and substrate concentration.

2.4.3.1 Effect of sonochemical and reaction parameters

2.4.3.1.1 Effect of amplitude on activity and enantioselectivity

The effect of wave amplitude is directly related to energy. To optimize the energy parameter for this reaction, the experiments were carried out at different ultrasonic wave amplitudes. The results are presented in Table 2.3.

These results show that the conversion is affected by a change in the amplitude of the sonochemical probe. It was observed that with increase in amplitude the conversion increases from 40% at 20% amplitude to 91% at 60% amplitude. With further increase in amplitude conversion reduced marginally to 88% at 80% amplitude. The enantiomeric excess (68-69%) was reduced marginally to 66 % at higher (80%) amplitude.

Table 2.3: Effect of amplitude of sonication on ATH of acetophenone

Entry	**Amplitude %**	**Conversion (%)**	***ee* (%)**	**TOF (h^{-1})**
1	20	40	68	201
2	40	73	68	367
3	60	91	69	457
4	70	89	69	445
5	80	88	66	437

***Reaction conditions**: [Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperature,* 298 K*; Reaction time, 12 minutes, pulse ratio 3:1*

Similarly many authors have found that as the power delivered to the reaction mixture increases, the rate of reaction increases to a maximum and then decreases with a continued increase in power.[24] A possible explanation for the observed decrease is given as follows: The chemical effects of ultrasound are caused by cavitation bubbles which are generated during the rarefaction period of sound waves (as described in Chapter 1 section 1.3.5.1.3 in detail). The amplitude of the wave is directly related to energy supplied to the system and to cavitation process. With increase in amplitude; energy supplied increases hence cavitation also increases resulting in an increase in conversion. But beyond the optimum amplitude dense cloud of cavitation bubbles are formed near the tip of probe which blocks the energy transmitted from the probe to the reaction mixture.[25] This could result in a marginal drop of activity observed. Thus for this system optimal power level (amplitude) was found to be 60% and hence used for further work.

2.4.3.1.2 Effect of pulse mode on activity and enantioselectivity

The pulse mode simply consists of timer attached to amplifier which switches the power to the probe on and off repeatedly. The off time allows the system to cool between the pulses of sonication. The effect of pulse mode on ATH of acetophenone was studied by putting this mode either “on” and “off”. For this; one reaction was carried out without pulse mode (that is under continuous sonication) and other keeping pulse mode on. When the reaction was carried out in a continuous mode, 90% conversion and 66% *ee* was obtained in 12 minutes reaction time. For the other experiment, the pulse ratio was kept as 3:1. This means, the sonochemical probe was "on" for 3 seconds followed by "off" for 1 second. Using this procedure, 91% conversion and 69% *ee* was obtained in 12 minutes reaction time.

The graph of moles of total product formed (R + S phenyl ethanol) vs. time and ee vs. time is plotted and presented in Figure 2.22.

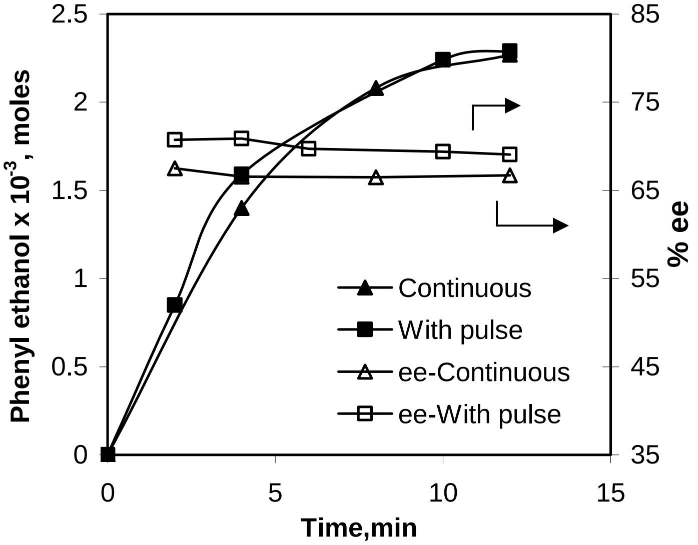


Figure 2.22: Effect of pulsed mode on ultrasound promoted ATH of acetophenone.

Reaction conditions: *[Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperatur,* 298 K*; Reaction time, 12 minutes; amplitude 60%*

The Figure showed that the moles of total phenyl ethanol formed in both the reactions were comparable, but enantioselectivity increased from 66 to 69% for the reaction with pulse mode. Pulse mode provides mixing of reaction mixture by repeatedly allowing the sample to settle back under the probe after each burst. It enables safe treatment of temperature sensitive samples at high intensity. This also offers considerable energy savings, particularly for processes carried out on a large scale.

Similar type of study was done by Mason et al.[26] for dehydrogenation of tetrahydronaphthalene where they have shown that pulsed ultrasound is more effective than continuous sonication. As in this case, enantioselectivity was better using pulse mode; all the experiments with sonochemical promotion were carried out using pulse mode.

2.4.3.1.3 Effect of temperature on activity and enantioselectivity

The effect of temperature on ultrasound promoted ATH of acetophenone using $[Ru(benzene)Cl_2]_2$ /(1R, 2S) ephedrine complex catalyst was investigated in the temperature range of 278-318 K. Figure 2.23 presents the conversion and *ee* values obtained at 12 minutes. From the results presented it can be seen that conversion increases with increase in temperature while *ee* decreases from 70 to 62%.

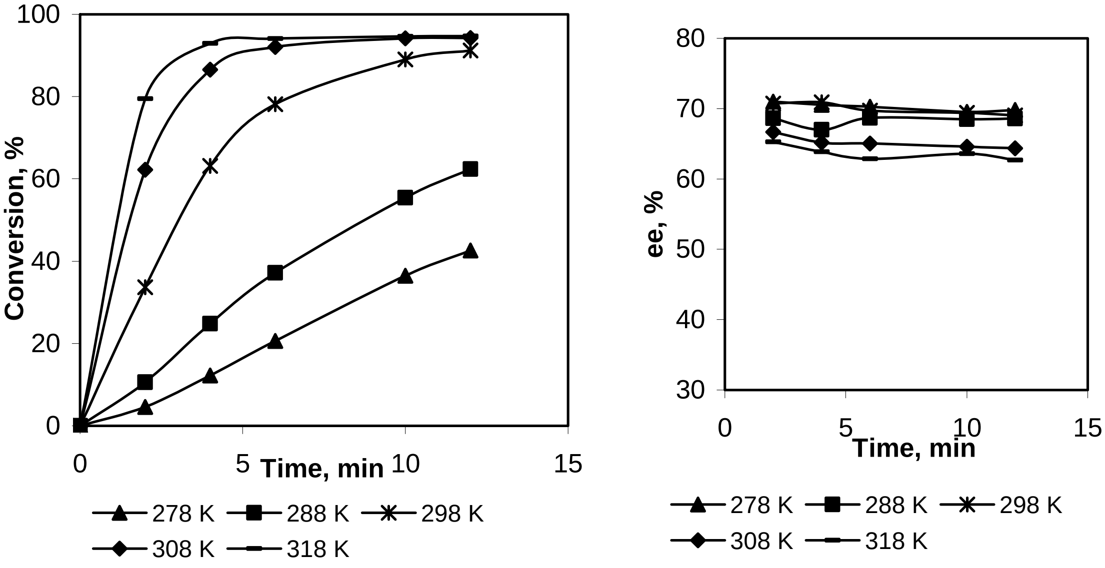


Figure 2.23: Effect of temperature on ultrasound promoted ATH of acetophenone
Reaction conditions-: *$[Ru(benzene)Cl_2]_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; IPA, 25 cm^3; KOH, 1.2 x 10^{-4}mol; Pulse ratio 3:1; amplitude 60% Reaction time, 12 minutes*

Figure 2.24 presents TOF (h^{-1}), conversion and *ee* obtained at 4 minutes reaction time which also shows the observed trend. Further reactions were performed at 298 K, since at 298 K high *ee* was obtained.

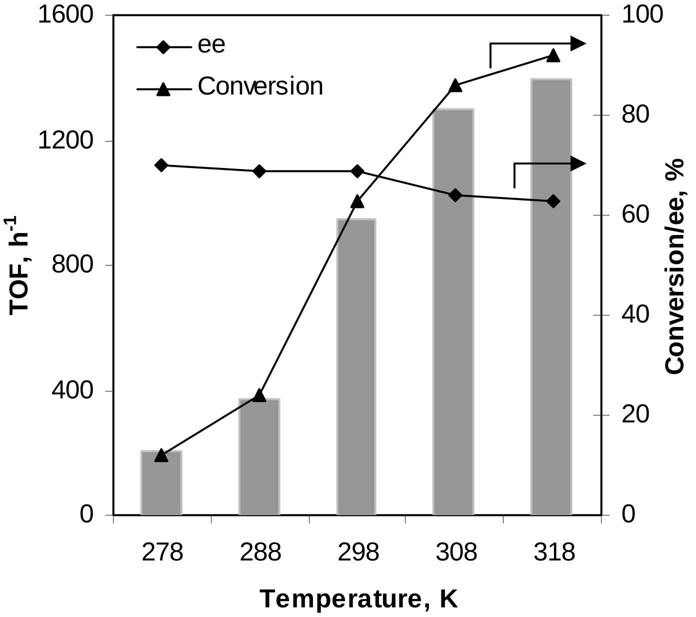


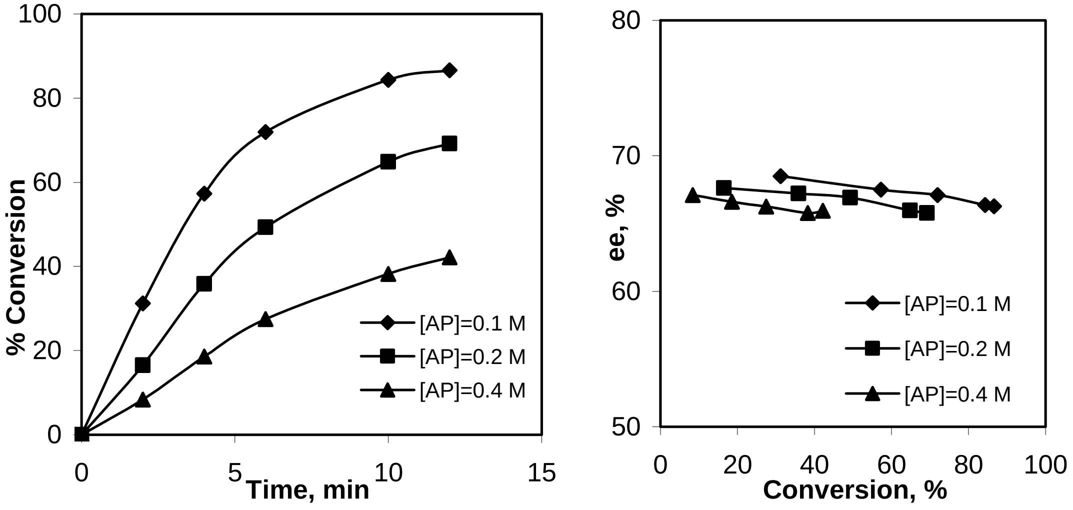
Figure 2.24: Effect of temperature on conversion, *ee* and activity of catalyst

***Reaction conditions-**: [Ru(benzene)Cl$_2$]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; IPA, 25 cm^3; KOH, 1.2 x 10^{-4}mol; Pulse ratio 3:1; amplitude 60% Reaction time, 4 minutes*

2.4.3.1.4 Effect of substrate concentration on ATH of acetophenone under ultrasound

The effect of substrate concentration on ATH of acetophenone under ultrasound was conducted at 0.1, 0.2 and 0.4 M concentration of acetophenone keeping catalyst concentration constant at 298 K. The results of this study are presented in Figures 2.25 (A), (B) and 2.26.

Results indicate that at low substrate concentration (0.1 M), higher conversion (91%) was obtained within 12 minutes. Higher initial substrate concentrations (0.2 and 0.4 M) required longer reaction times and gave lower conversions. (74 % and 46 % conversion respectively in 12 minutes). As discussed in effect of substrate concentration for silent reaction (section 2.3.3), here also it was observed that with increase in concentration of substrate, although conversion reduces, the productivity of the alcohol increases.



(A) **(B)**

Figures 2.25: Effect of substrate concentration on conversion (A) and *ee* (B) of ATH of acetophenone under ultrasound

Reaction conditions-: *[Ru(benzene)Cl$_2$]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; IPA, 25 cm^3; KOH, 1.2 x 10^{-4}mol; temperature* 298 K*; Pulse ratio, 3:1; amplitude 60% ; Reaction time, 12 minutes*

Figure 2.25(B) represents enantiomeric excesses obtained at different molar concentration of acetophenone as a function of conversion. The results indicate that higher *ee* (69 %) was obtained at 0.1 M concentrations of acetophenone at 91% conversion. With increase in concentration of acetophenone as well as contact time, *ee* was found to be decreased. Thus 66 % *ee* was obtained with 0.2M and 0.4 M concentrations of acetophenone at 69 and 42 % conversions respectively (at 12minutes).

The plot of concentration (moles) of the major product R-1-phenyl ethanol versus conversion is presented in Figure 2.26. The results clearly show that concentration of R-1-phenylethanol increases significantly with increase in initial concentration of acetophenone. At higher concentration of R-1-phenylethanol reverse reaction takes place (as discussed in section 2.3.3 for silent reaction) thereby reducing its concentration in reaction mixture resulting in lower *ee*.

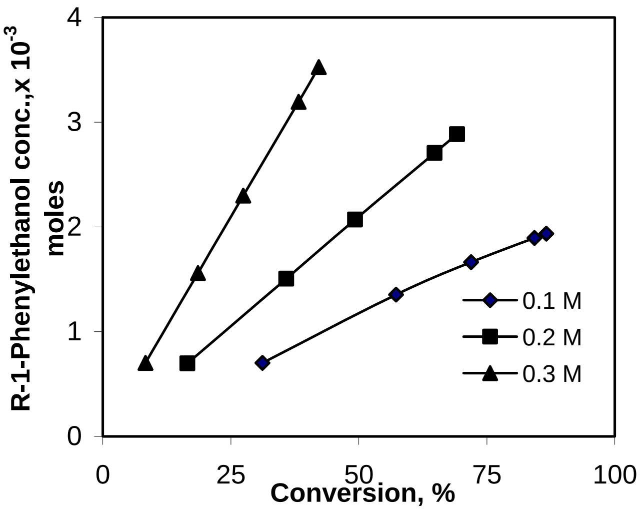


Figure 2.26: The plot of concentration of the major product R-1-phenyl ethanol versus conversion for different substrate concentration under ultrasound.

From comparison of the results obtained under ultrasound presented here with those obtained under silent condition (as discussed in section 2.3.3), it can be seen that under ultrasound only activity of the catalyst is increased without affecting the *ee* pattern. (Figure 2.27)

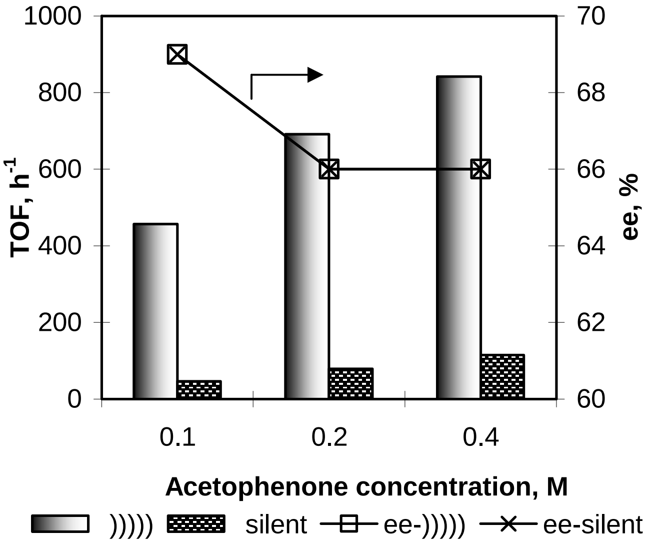


Figure 2.27: Effect of substrate concentration of ATH on conversion, enantioselectivity and activity of catalyst-comparative study under ultrasound and silent reaction.

Reaction conditions: *For silent reaction: as per figure 2.20; time, 120 min;)))),12 min.*

2.4.3.2 C-T profile for ATH of acetophenone under ultrasound

After finalizing the amplitude and mode of operation (pulse mode), ATH of acetophenone was carried out using $[Ru(benzene)Cl_2]_2$/(1R, 2S) ephedrine complex catalyst and KOH as a base under ultrasound at 298 K; using pulse ratio 3:1 and 60% amplitude. 91% conversion of acetophenone was obtained with 68% *ee* of R-phenyl alcohol at 12 minutes reaction time. A concentration-time (C-T) profile along with %*ee* of ATH of acetophenone under ultrasound with products R-1-phenyl ethanol and S-1-phenyl ethanol is presented in Figure 2.28. The formation of total 1-phenyl ethanol in the reaction was proportionate with the consumption of acetophenone with respect to stoichiometry. The initial enantioselectivity 71 % dropped with time to 68 % at the end of 12 min.

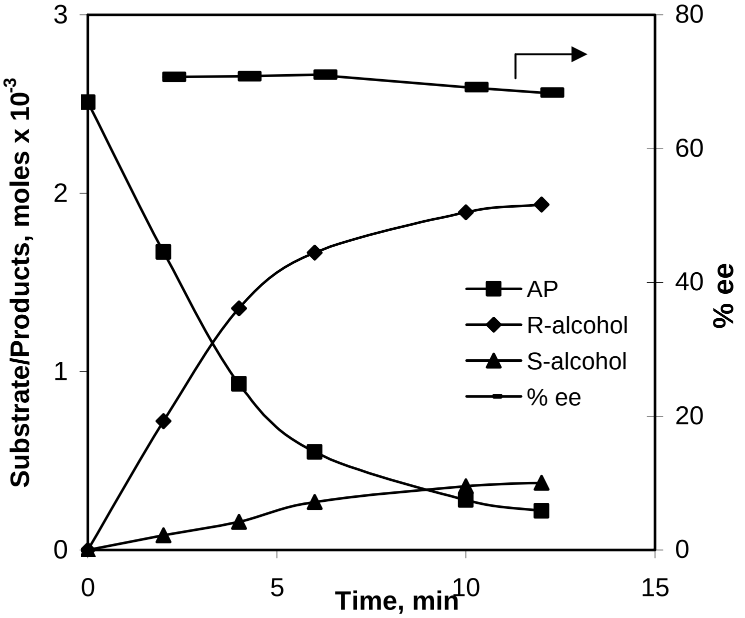


Figure 2.28: Typical CT profile of ultrasound promoted ATH of acetophenone.

Reaction conditions: *$[Ru(benzene)Cl_2]_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperature,* 298 K*; Reaction time, 12 minutes; pulse ratio 3:1*

The performance of the catalyst is compared with the reaction under silent condition as shown in Figure 2.29 which clearly shows that there is enhancement in catalytic activity without affecting the enantioselectivity when reaction is performed under ultrasound.

Thus, the reaction which required about 2 h at 298 K for silent reaction was completed in just 12 minutes under ultrasound, without affecting the enantioselectivity.

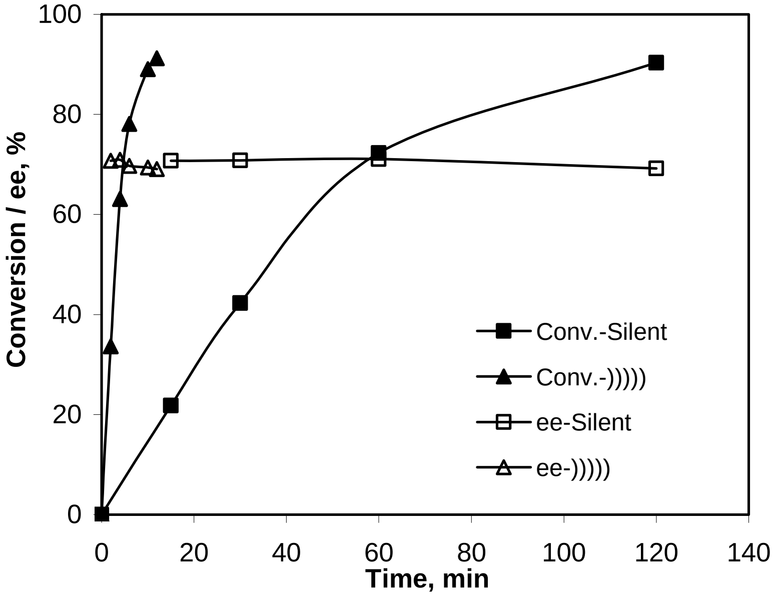


Figure 2.29: Comparison of % conversion and % *ee* of ATH of acetophenone with ultrasound and without ultrasound

***Reaction conditions**: [Ru(benzene)Cl_2]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3;Temperature,* 298 K*; Reaction time,))))12 minutes, silent-120minutes; pulse ratio 3:1 for))))*

2.4.3.3 Effect of catalyst precursors on ATH of acetophenone under ultrasound

The rate and enantioselectivity of the ATH reactions are strongly affected by the central metal atoms in precatalyst. To study the effect of precatalyst, the reactions under ultrasound were performed using different precatalysts. For the comparison, same reactions were done under "silent" condition. The results are presented in Table 2.4. The overall comparison showed that the activity of catalyst under ultrasound in terms of TOF was higher as compared to silent reaction. There was almost 5-10 fold increase in activity of catalysts under ultrasound. For both ultrasound promoted and silent reaction, the Rh complex with (1R, 2S) ephedrine was found to be a better catalyst as compared to the Ru and Ir complex. (Table 2.4, entry 2). The results agree with the literature reports for the silent reaction.[27]

Table 2.4: Effect of catalyst precursors on ATH of acetophenone under ultrasound

Entry	Catalyst used	)))))			Silent reaction		
		Conv. (%)	***ee* (%)**	**TOF (h^{-1})**	**Conv. (%)**	***ee* (%)**	**TOF (h^{-1})**
1	$[Ru(benzene)Cl_2]_2$	91	69	457	90	69	46
2[a]	$[Rh(Cp^*)Cl_2]_2$	90	77	896	95	81	189
3	$[Ir(Cp^*)Cl_2]_2$	41	78	204	87	83	43
4	$[Ru(p\text{-cymene})Cl_2]_2$	36	91	136	81	91	27

***Reaction conditions**-: Catalyst, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; IPA, 25 cm^3; KOH, 1.2 x 10^{-4}mol; Temperature,* 298 K*; Reaction time:))))) : 12 minutes, Silent reaction : 120 minutes*

a: Reaction time:))))) : 6 minutes, Silent Reaction: 30 minutes

2.4.3.4 Effect of different β-amino alcohol ligands on catalytic activity under ultrasound

In order to check generality of sonochemical promotion, transfer hydrogenation of acetophenone was investigated using $[Rh(Cp^*)Cl_2]_2$ as a catalyst with few β-amino-alcohol ligands. The results are presented in Figure 2.30 (activity expressed in terms of TOF at 6 and 30 minutes reaction time for ultrasound and silent reaction respectively) and Table 2.5 (conversion at different reaction time).

Figure 2.30 shows that the activities of the catalyst increases without affecting *ee* for the amino alcohol ligands studied under ultrasound. However the extent of increase in activity was significantly lower for ligand 2 and ligand 3. The Reactions with these ligands were continued for longer reaction times (refer Table 2.5). For silent reaction conversion increases significantly with increase in reaction time to 120 minutes, while conversion did not increase with increase in reaction time to 12 minutes under ultrasound. With these ligands the rhodium complex is probably less stable under ultrasound.

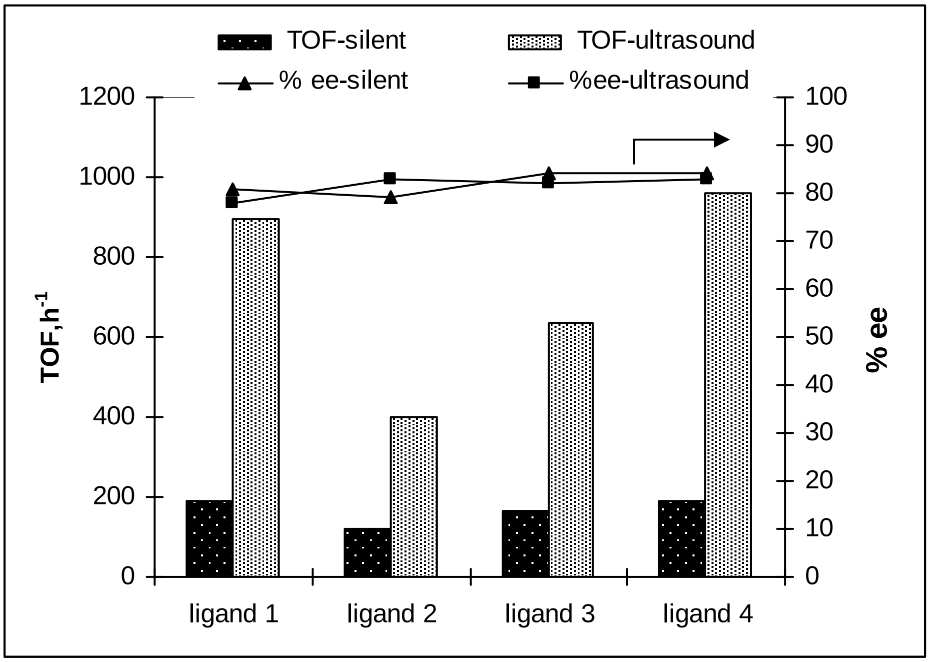


Figure 2.30: Comparison of activity of ATH of acetophenone using different β-amino alcohol ligands under ultrasound and silent condition#

***Reaction conditions**: [Rh(Cp*)Cl$_2$]$_2$, 1.26 x 10^{-5}mol; ligand, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; KOH, 1.2 x 10^{-4}mol; IPA, 25 cm^3; Temperature,* 298 K*; Reaction time:))))) 6 minutes, pulse ratio 3:1, for silent reaction 30 min*

 # Refer Figure 2.1 for structure of ligands.

Table 2.5: Effect of ultrasound on catalyst activity with different β-amino alcohol ligands

No.	**Ligand**	**)))))**			**Silent**		
		Time, min	**Conv., %**	***ee* %**	**Time, min**	**Conv., %**	***ee* %**
1	(1S, 2R) ephedrine **(Lig.1)**	6	91	78	30	95	81
2	(2S)-1-(1S phenylethylamino) propane-2-ol **(Lig.2)**	6 12	40 49	83 81	30 120	60 84	79 77
3	(1S)-1-phenyl-2-(1S-phenyl ethylamino)ethanol **(Lig.3)**	6 12	64 69	82 80	30 120	81 94	84 76
4	1R,2S cis aminoindanol**(Lig.4)**	6	95	84	30	95	83

***Reaction conditions**: Details same as above (Figure 2.30)*

2.4.3.5 Screening of various ketones for ATH reaction under ultrasound

For a given catalytic system, rate and selectivity are sensitive to the steric crowding of the substrates as well as to the electronic properties of the phenyl ring substituents.[28] In order to elucidate the effect of ultrasound on the catalytic activity and enantioselectivity for ATH of various substrates, the reactions were performed under ultrasound using $[Ru(benzene)Cl_2]_2$/(1R, 2S) ephedrine as catalyst system and KOH as base. For comparison of activities to that of silent reactions, pot reactions were also performed using the identical conditions. The reaction products were confirmed using GC-MS analysis. Only ketone hydrogenated products were observed in all the reactions. The results of the reactions are summarized in Table 2.6.

Table 2.6: Screening of various ketones for asymmetric transfer hydrogenation

Sr. no.	**Ketone**	**)))))**			**Silent reactions**		
		Conv. (%)	***ee* (%)**	**TOF (h^{-1})**	**Conv. (%)**	***ee* (%)**	**TOF (h^{-1})**
1	Acetophenone	91	69	457	90	69	46
2	4-Bromoacetophenone	97	48	485	98[#]	51	98
3	4-Chloroacetophenone	98	51	488	97[#]	52	96
4	4-Methylacetophenone	70	62	349	77	65	38
5	4-Isobutylacetophenone	78	61	390	80	63	40
6	2,5-Dimethylacetophenone	26	8	131	37	8	19
7	4-Methoxyacetophenone	44	61	218	51	63	25
8	2-Acetyl-6-methoxy naphthalene[*]	60	56	300	61	57	31
9	4-Nitroacetophenone	59	39	292	46	41	23
10	3-Acetyl pyridine	92	42	461	98[#]	42	98

Reaction conditions: *$[Ru(benzene)Cl_2]_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; ketone, 2.5 x 10^{-3}mol; IPA , 25 cm^3; KOH, 1.2 x 10^{-4}mol; Temperature,* 298 K
Reaction time: Sonochemical reaction: 12 minutes; Silent reactions: 2 h
*# : Reaction time : 60 minutes; * : Acetonitrile (2 ml) was added to dissolve substrate.*

The results show that the activity of the catalyst increases significantly for almost all the ketones investigated under ultrasound, without significantly affecting the enantioselectivity.

2.4.3.5.1 Conditions for GC and HPLC analysis of enantiomeric separation of chiral alcohols.

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 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.

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).Reten16.1 min (R), 17.1 min (S) alcohol.
2. 1-p-Bromophenylethanol-HPLC, λ-220 nm, solvent Hexane: IPA 98:2, Flow-1ml, 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-0.5 ml, Injection volume- 5µl. 16.2 min(R), 17.5 min (S) 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- 5µl. 12.3 min (R), 13.9 min (S) alcohol.
6. 1-(2, 5-Dimethylphenyl)ethanol – HPLC, λ-220 nm, solvent Hexane: IPA 98:2, Flow-1ml, Injection volume- 5µl. 7.3 min(R), 8.3 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 (R), 24.6 min (S) alcohol.
8. 1-(6-Methoxynaphthalen-2-yl) ethanol- HPLC, λ-254 nm, solvent Hexane: IPA 90:10, Flow-0.5ml, Injection volume- 5µl. 15.8 min(R), 20.5 min (S) 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.

2.4.3.6 Influence of temperature on activity and enantioselectivity under ultrasound and silent reaction

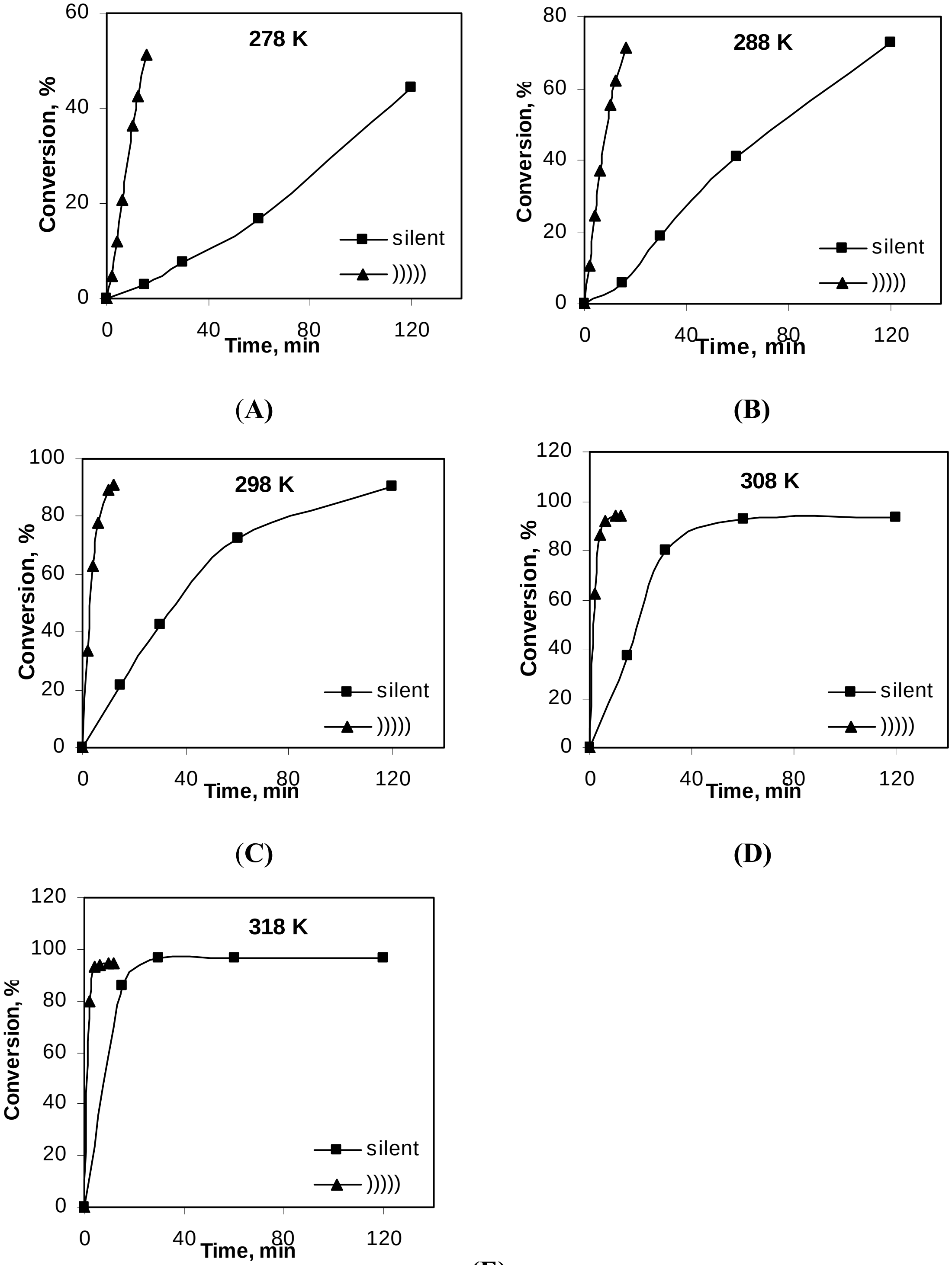
Effect of temperature on activity and enantioselectivity for silent and sonochemical reaction at different temperatures of 278, 288, 298, 308 and 318 K are presented in Figure 2.31 A, B, C, D and E respectively.

As discussed in earlier sections 2.3.6 and 2.4.3.1.3 activity of the catalyst increases with increase in temperature for both silent and sonochemical reaction. However a closer look at the results indicates that the sonochemical promotion is highest at 278 K. The extent of sonochemical promotion was found to decrease with increase in reaction temperature.

With increase in reaction temperature, the vapor pressure of the reaction mixture will increase. This leads to an easier cavitation but to a less violent collapse of bubbles. Hence cavitation becomes less effective. Also at high temperature a large number of microbubbles are generated at the same time in reaction medium. This can act as a barrier to the sound transmission.[29] Hence there is reduction of effective ultrasonic energy which enters the reaction liquid medium. Thus, with increase in temperature the sonochemical effect is less pronounced.

Arenda et al.[30] in series of publication have shown a similar type of trend for N-alkylated imidazole synthesis and for Claisen Schmidt condensation reaction using alkaline doped carbons catalyst under ultrasound.

As far as the enantiomeric excess of the product considered, it decreased with increase in temperature for both the conditions.



(A) (B)

(C) (D)

(E)

Figure 2.31: Influence of temperature on activity of the catalyst under ultrasound

Reaction conditions: *[Ru(benzene)Cl$_2$]$_2$, 1.26 x 10^{-5}mol; (1R, 2S) ephedrine, 5.1 x 10^{-5} mol; Acetophenone, 2.5 x 10^{-3}mol; IPA, 25 cm^3; KOH, 1.2 x 10^{-4}mol;)))))Pulse ratio 3:1; amplitude 60%*

Thus, fast and efficient Ru(II)/Ephedrine catalysed asymmetric transfer hydrogenation of ketones was achieved using the ultrasound promotion. The activity of the catalyst increased 5-10 folds under ultrasound without significantly affecting the enantioselectivity. The high temperatures and pressure developed locally by cavitation may lead to higher activity observed. Also, as mentioned by Cravotto and Cintas[31], it is likely that transition metal complexes undergo ligand-metal bond cleavage producing co-ordinatively unsaturated complexes. Combination of above two factors may have resulted in the high activity of the catalyst for ATH reaction.

2.5 CONCLUSIONS

The asymmetric transfer hydrogenation reaction of acetophenone using IPA as hydrogen donor and ruthenium (II)/(1R, 2S) ephedrine complex catalyst has been investigated in detail. The reaction has also been studied under ultrasound promotion. Highlights of the results are presented below:

- Best results (91% conversion and 68% *ee*) were obtained at ruthenium: ligand: base: substrate ratio of 1:2:5:100 respectively.
- Sonochemical promotion lead to increase in activity by 5-10 folds retaining the enantioselectivity.
- The effect of rate enhancement was more pronounced at lower temperature (278 to 298 K)
- The effect of rate enhancement by sonochemical promotion was found to be generic and increase in activity was observed for different transition metal catalysts, β-amino alcohol ligands and substrates investigated.
- This is the first report on the sonochemical promotion in asymmetric transfer hydrogenation of ketones using soluble metal complex catalyst. The advantage with sonochemical promotion is that the overall temperature of the solution is not changed. In the present work, the glass reactor temperature has been maintained constant, at 298 K using water circulation bath. Hence enantioselectivity of the reaction has not been affected unlike microwave irradiation.[32]

REFERENCES

1 Q-H Fan, Y-M Li, A. S. C Chan, *Chem. Rev.* **2002**, *102*, 3385.

2 S. Hashiguchi, A. Fujii, J. Takeliara. T. Ikanya. and R. Noyori, *Journal of the American Chemical Society* **1995,** *117*, 7562

3 (a)R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97.(b)C. Saluzzo, M. Lemaire, *Adv. Synth. Catal.* **2002**, *10*, 344. (c) A. Zanotti-Gerosa, W. Hems, M. Groarke, F. Hancock, *Platinum Metals Rev.***2005**,*49*, 158.

4 R. V. Wisman, J. G. De Vries, B. J. Deelman, H. J. Heeres, *Organic Process Research and Development* **2006**, *10*, 423.

5 X. Sun, G. Manos, J. Blacker, J. Martin, A. Gavriilidis, *Organic Process Research and Development* **2004**, *8*, 909.

6 S. H. Deshpande, A. A. Kelkar, R. G. Gonnade, S. K. Shingote, R. V. Chaudhari, *Catalysis Letters* **2010**, *138*, 231

7 M. A. Bennet, and A. J. Smith, *J. Chem. Soc. Dalton. Trans.* **1974**, 233.

8 C. White, A. Yates, and P. M. Maitlis, *Inorganic Synthesis* **1992**, *29*, 228

9 J. Takehara, S. Hashiguchi, A. Fujii, S. I. Inoue, T. Ikariya, R. Noyori, *Chemical Communications* **1996**, 233. P. Brandt, P. Roth, P. G. Andersson, *Journal of Organic Chemistry* **2004**, *69*, 4885.

10 S. Gladiali, L. Pinna, G. Delogu, S.Martine, G.Zassinovich, G.Mestroni, *Tet. Asy.* **1990**, *1*, 635.

11 H. U. Blaser, *Asymmetric catalysis on industrial scale: challenges, approaches and solutions*, Wiley-VCH, **2004**.

12 R. L. Chowdhury, J. E. Backvall, *J. Chem. Soc. Chem. Commun.* **1991**,*16*, 1063

13 R. Jianga, X. Sun, W. He, H.Chena and Y. Kuangb, *Appl. Organometal.Chem.* **2009**, *23*,179.

14 W. Baratta , K. Siega, P. Rigo, *Chem. Eur. J.* **2007**, *13*, 7479.

15 K. Ahlford, J. Ekstrom, A. B. Zaitsev, P. Ryberg, L. Eriksson, H. Adolfsson, *Chemistry-a European Journal* **2009**, *15*, 11197.

16 R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97.

17 M. Palmer, T. Walsgrove, M. Wills, *Journal of Organic Chemistry* **1997**, *62*, 5226.

18 D. G. I. Petra, P. C. J. Kamer, P. W. N. M. Van Leeuwen, K. Goubitz, A. M. Van Loon, J. G. De Vries, H. E. Schoemaker, *European Journal of Inorganic Chemistry* **1999**, 2335.(b) D. G. I. Petra, J. N. H. Reek, J. W. Handgraaf, E. J. Meijer, P. Dierkes, P. C. J. Kamer, J. Brussee, H. E. Schoemaker, P. W. N. M. Van Leeuwen, *Chemistry - A European Journal* **2000**, *6*, 2818.

19 M. Wills, M. Gamble, M. Palmer, A. Smith, J. Studley, J. Kenny, *J. Mol. Catal. A: Chem.* **1999**, *146*, 139

20 G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev.* **1992**, 1051.

21 P.Gamez, F.Fache and M.Lemaire, *Tetrahedron Asymmetry* **1995,** *6*, 705.

22 (a) B. Torok, K. Balazsik, M. Torok, K. Felfoldi, M. Bartok, *Catal. Lett.* **2002,** *81 (1–2)*, 55. (b) B. Torok, K. Balazsik, K. Felfoldi, M. Bartok, *Ultrasonics Sonochem.* **2001,** *8,* 191. (c) B. Torok, K. Balazsik, M. Torok, G. Szollosi, M. Bartok, *Ultrasonics Sonochem*. **2000,** *7,* 151.(d) B. Torok, G. Szollosi, K. Balazsik, K. Felfoldi, I. Kun, M. Bartok, *Ultrasonics Sonochem.* **1999,** *6*, 97. (e) K. Balazsik, B.

Torok, K. Felfoldi, M. Bartok, *Ultrasonics Sonochem*. **1999,** *5*, 149.(f) B. Torok, K. Felfoldi, G. Szakonyi, K. Balazsik, M. Bartok, *Catal. Lett.* **1998**, *52*, 81.

23 (a) T. J. Mason, J. P. Lorimer, *Applied sonochemistry*, Wiley Online Library, **2002**. (b) P. Boudjouk in: K.S. Suslick (Ed), *Ultrasounds, its Chemical, Physical, and Biological Effects,* VCH, **1988**, p.165. (c) K.S. Suslick in G.Ert, H. Knozinger, J. Weitkamp (Eds.), *Handbook of Heterogeneous Catalysis*, *Vol.3*,Wiley-VCH, New York, **1997**, 1350.(d) J.L. Luche, *Synthetic Organic Sonochemistry*, Plenum Press, New York, **1998.**

24 M. Gutierrez, A. Henglein, *The Journal of Physical Chemistry* **1990**, *94*, 3625. a) J. C. De Souza-Barboza, C. Paltrier, J. L. Luche, *Journal of Organic Chemistry* **1988**, *53*, 1212. (b) M. A. Margulis, *Russ. J .Phys. Chem.* **1974**, 48, 1378.

25 (a)F. Contamine, F. Faid, A. M. Wilhelm, J. Berlan, H. Delmas, *Chemical Engineering Science* **1994**, *49*, 5865. (b) L.H.Thompson, L.K.Doraiswamy, *Industrial & Engineering Chemistry Research* **1999**, *38*, 1215.(c) J.-L. Luche, *Synthetic Organic Sonochemistry*, Plenum Press, New York, **1998**.

26 T. J. Mason, J. P. Lorimer, L. Paniwnyk, P. W. Wright, and A. R. Harris, *J. Catal.* **1994**, *147*, 1.

27 K. Murata, T. Ikariya, R. Noyori, *J. Org. Chem.* **1999**, *64*, 2186.

28 S. Gladiali, E. Alberico, *Chem. Soc. Rev.* **2006**, *35*, 226.

29 T. J. Mason, *Practical Sonochemistry*, Ellis Horwood, New York, **1991**

30 (a) C. J. Duran-Valle, I. M. Fonseca, V. Calvino-Casilda, M. Picallo, A. J. Lopez-Peinado, R. M. Martin-Aranda, *Catalysis Today* **2005**, *107-08*, 500. b) V. Calvino-Casilda, R. M. Martin-Aranda, A. J. Lopez-Peinado, M. Bejbiova, J. Cejka, *Applied Catalysis a-General* **2008**, *338*, 130.((c) S. Ferrera-Escudero, E. Perozo-Rondon, V. Calvino-Casilda, B. Casal, R. M. Martin-Aranda, A. J. Lopez-Peinado, C. J. Duran-Valle, *Applied Catalysis a-General* **2010**, *378*, 26.

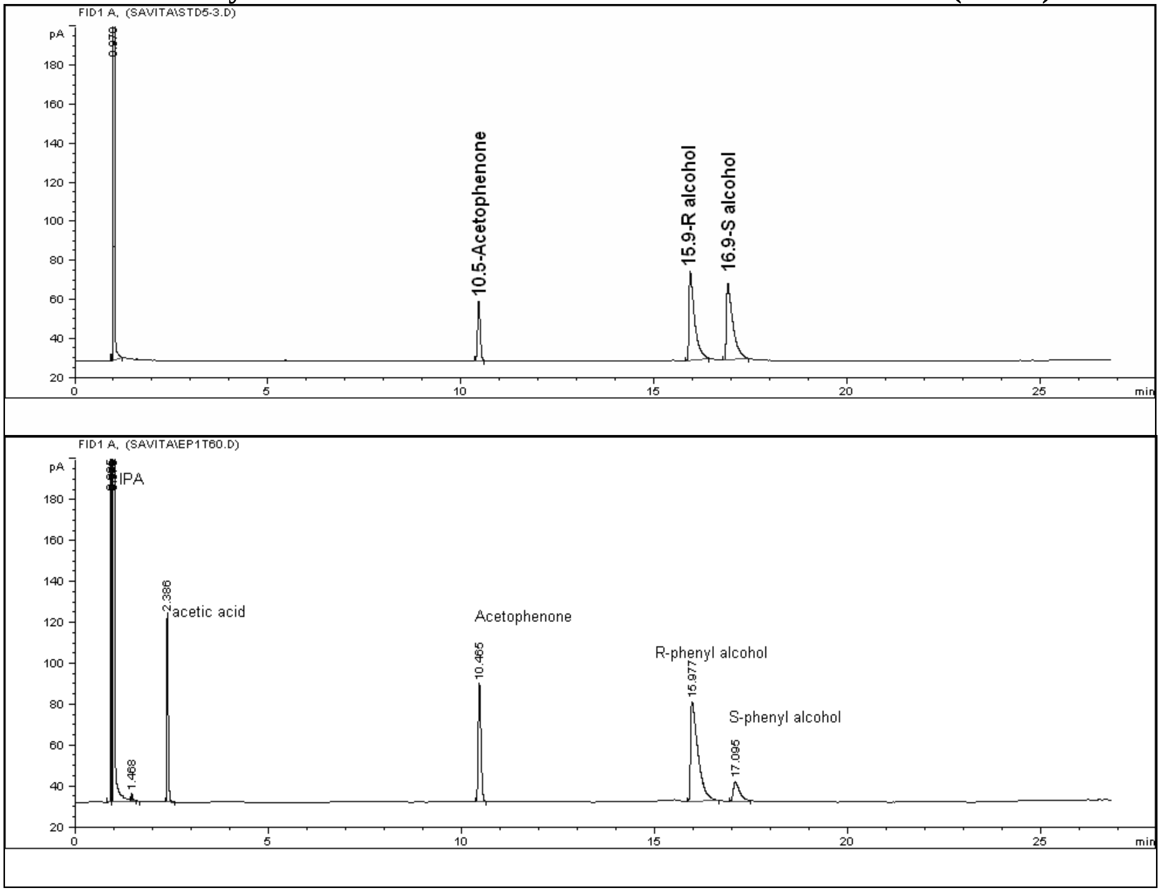
31 G. Cravotto, P. Cintas, *Chem. Soc. Rev.* **2006,** *35,* 180

32 S. Lutsenko, C. Moberg, *Tetrahedron Asymmetry* **2001,** *12*, 2529.

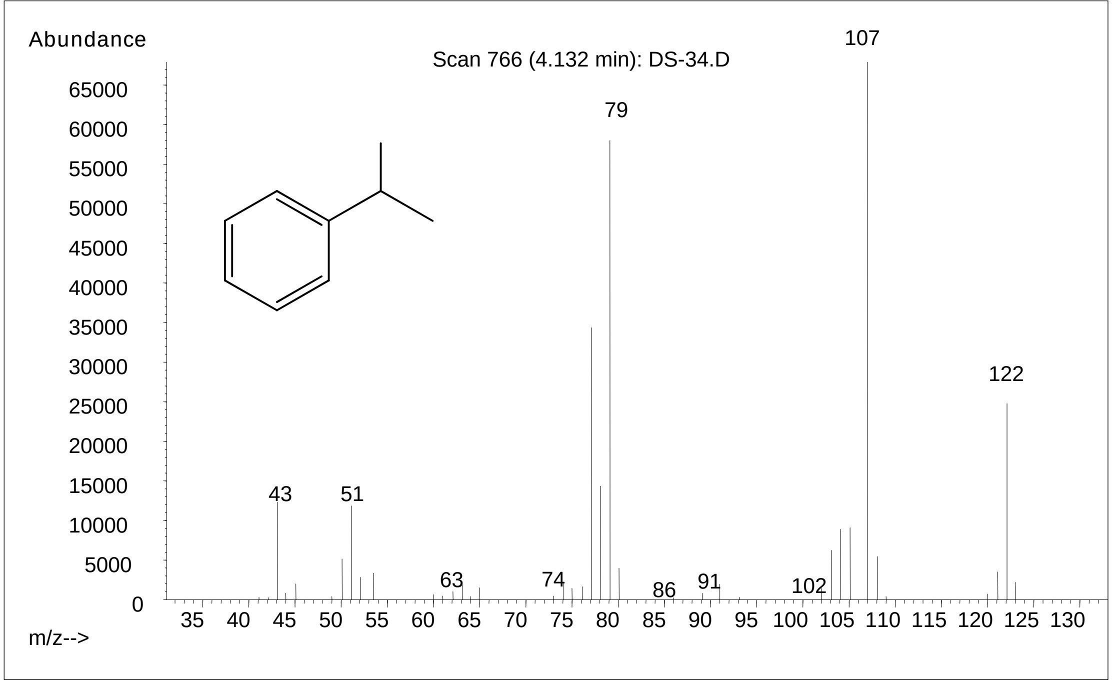
SPECTRA

1. 1-Phenyl ethanol

GC Analysis: Standard racemic alcohol and reaction mixture (chiral)

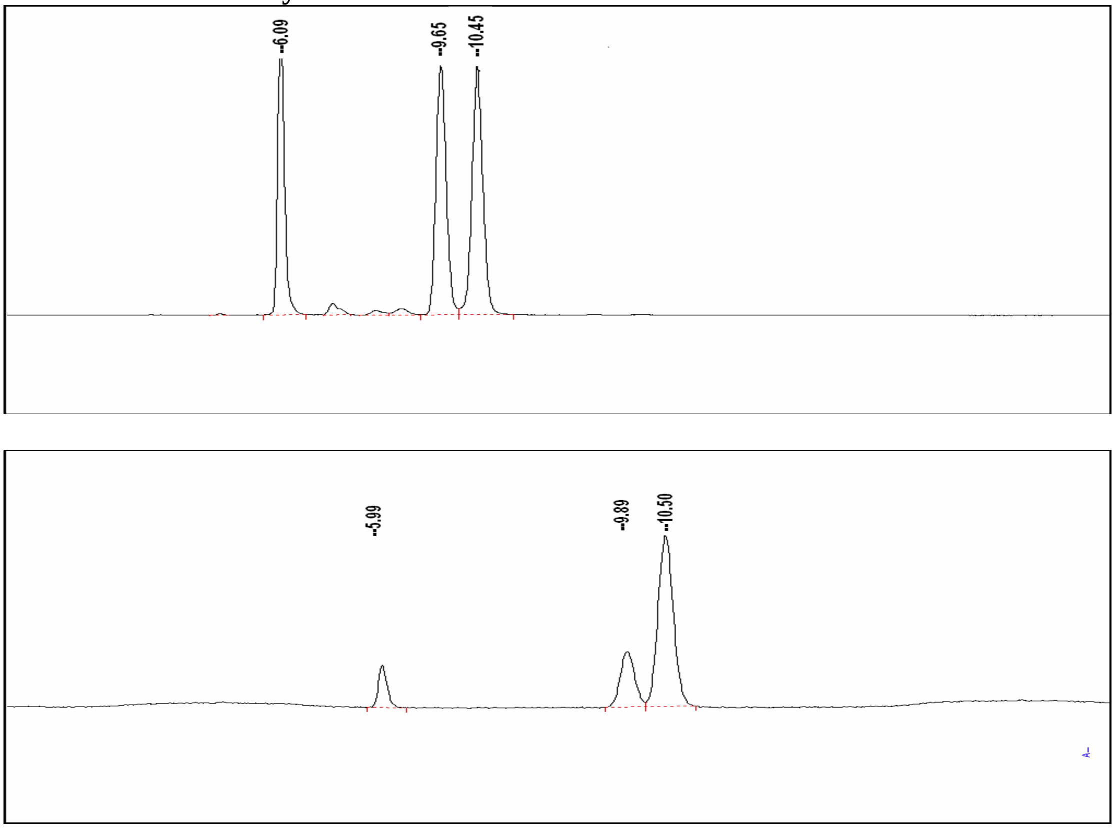


GC-MS Spectra (70 eV, EI)

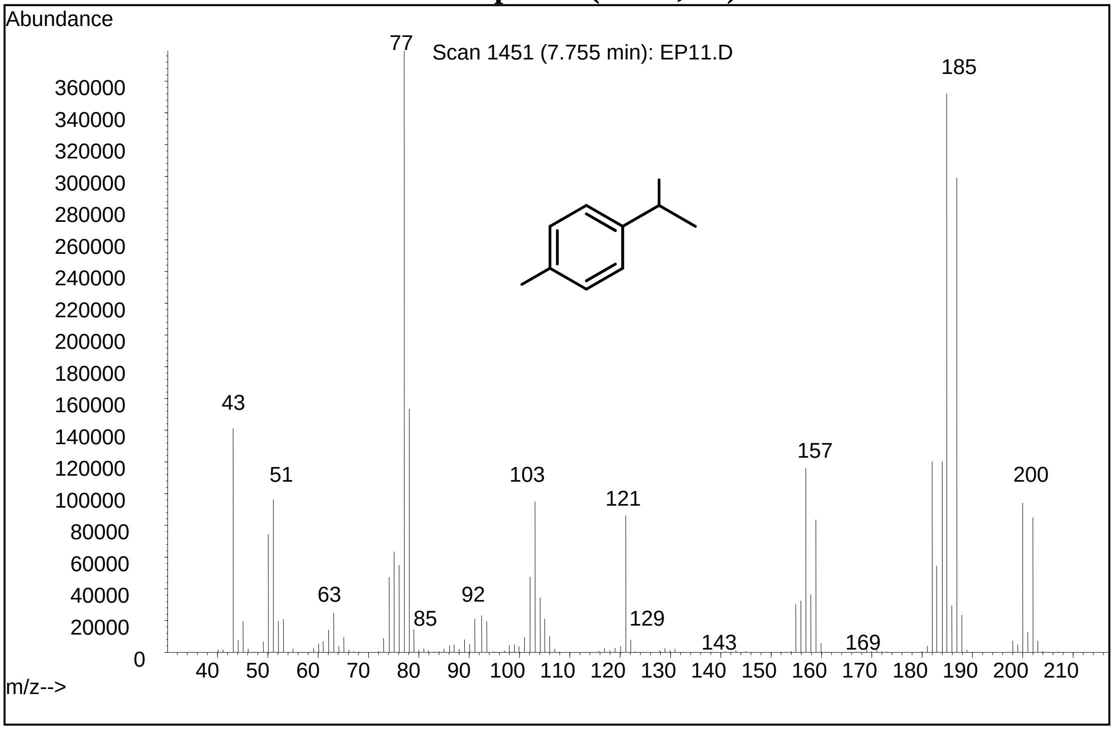


2. 1-p-Bromophenylethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture

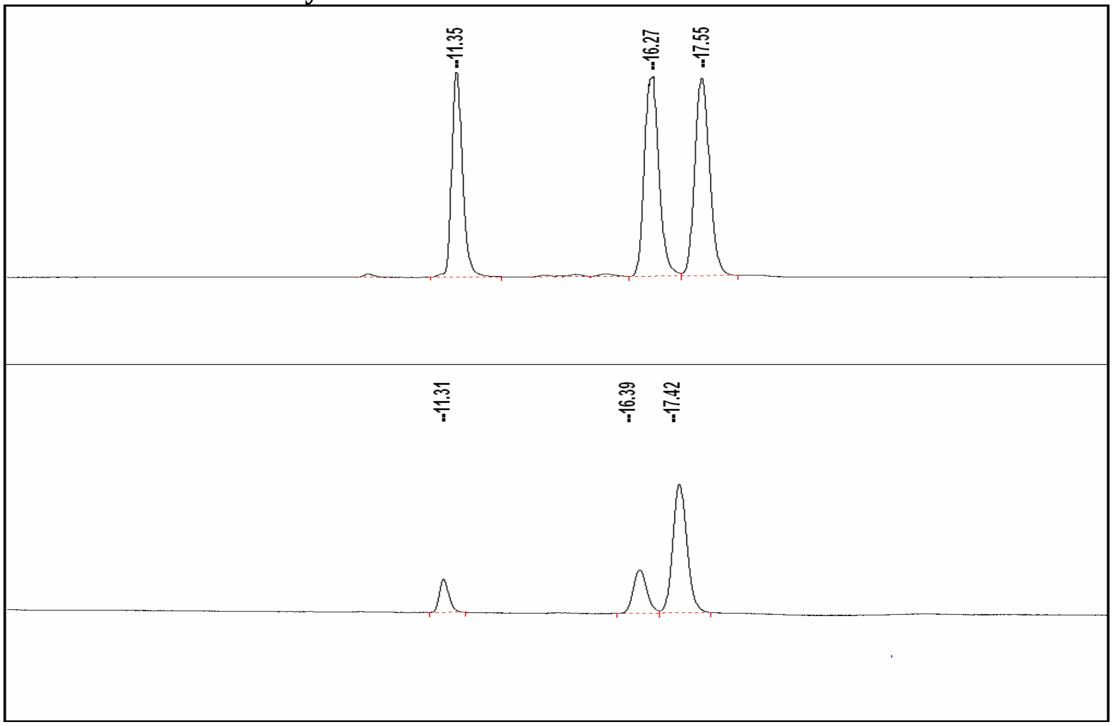


GC-MS Spectra (70 eV, EI)

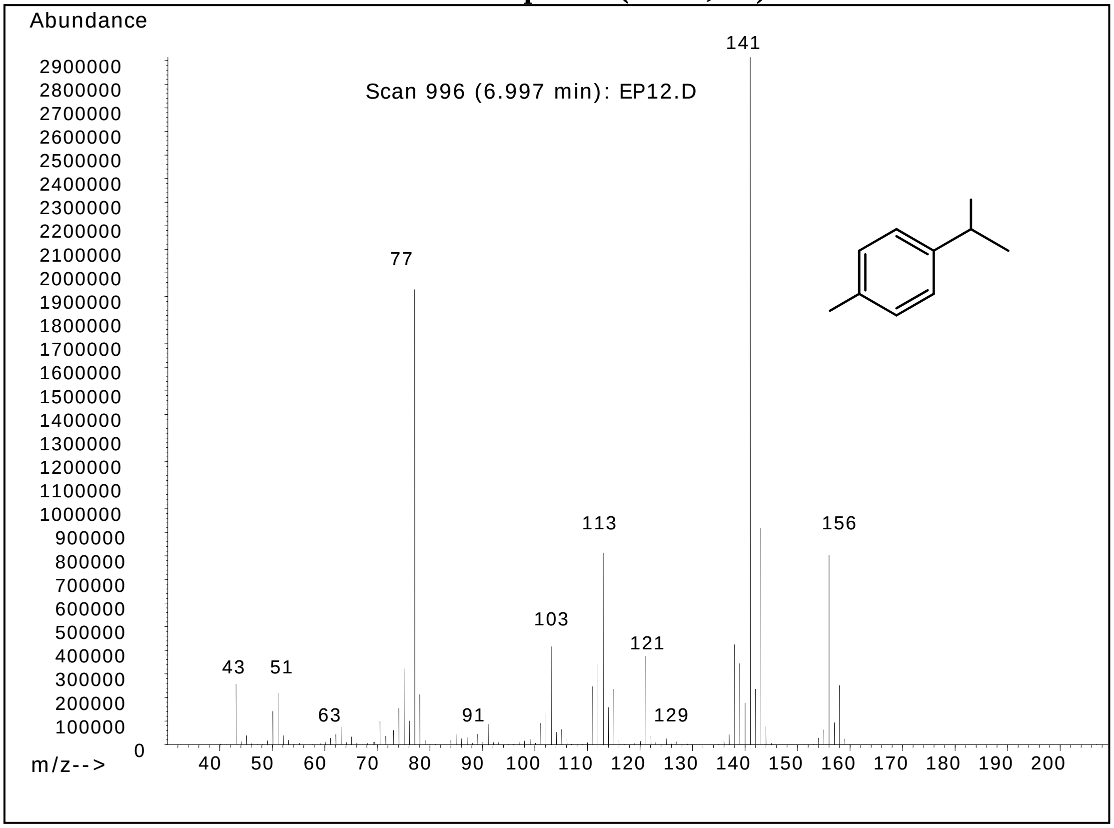


3. 1-p-Chlorophenylethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture

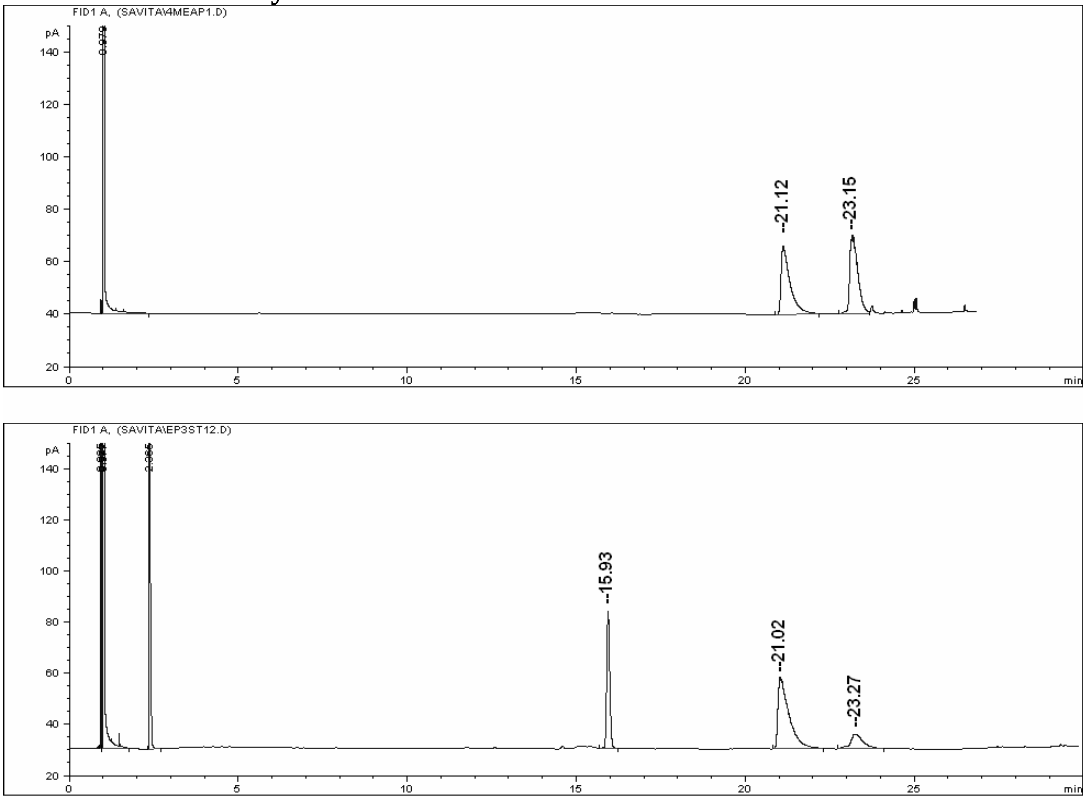


GC-MS Spectra (70 eV, EI)

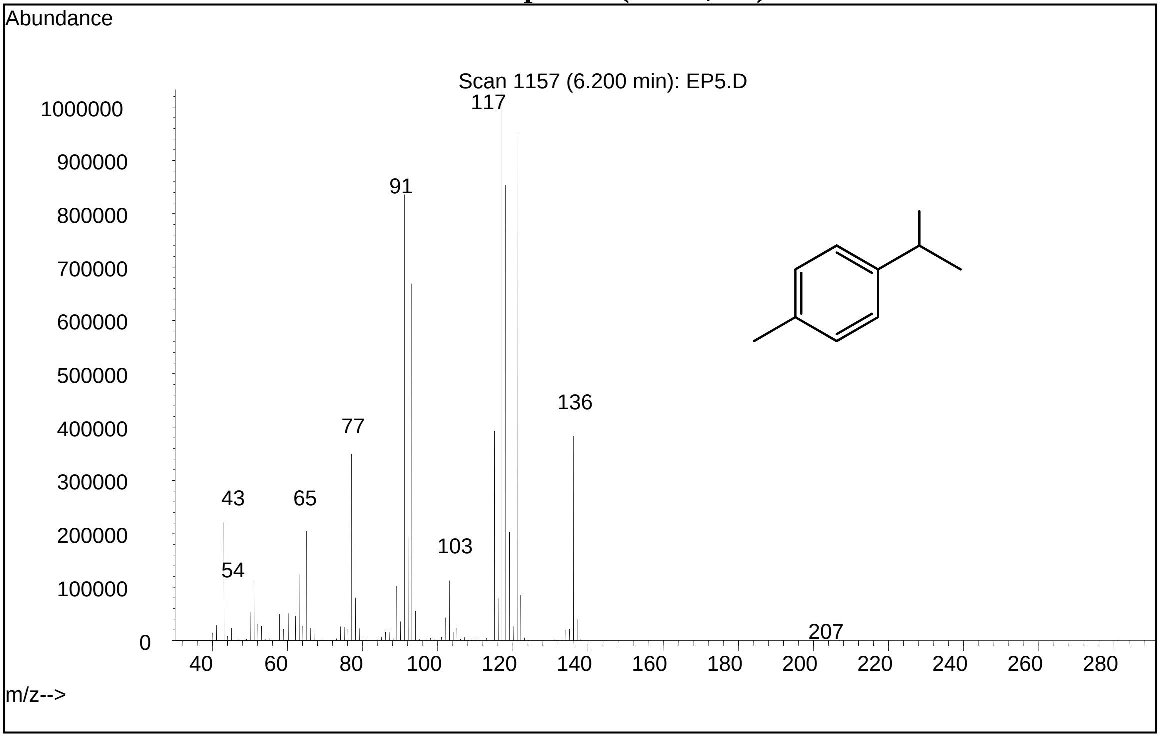


4. 1-p-Methylphenylethanol

GC Analysis: Standard racemic alcohol and reaction mixture

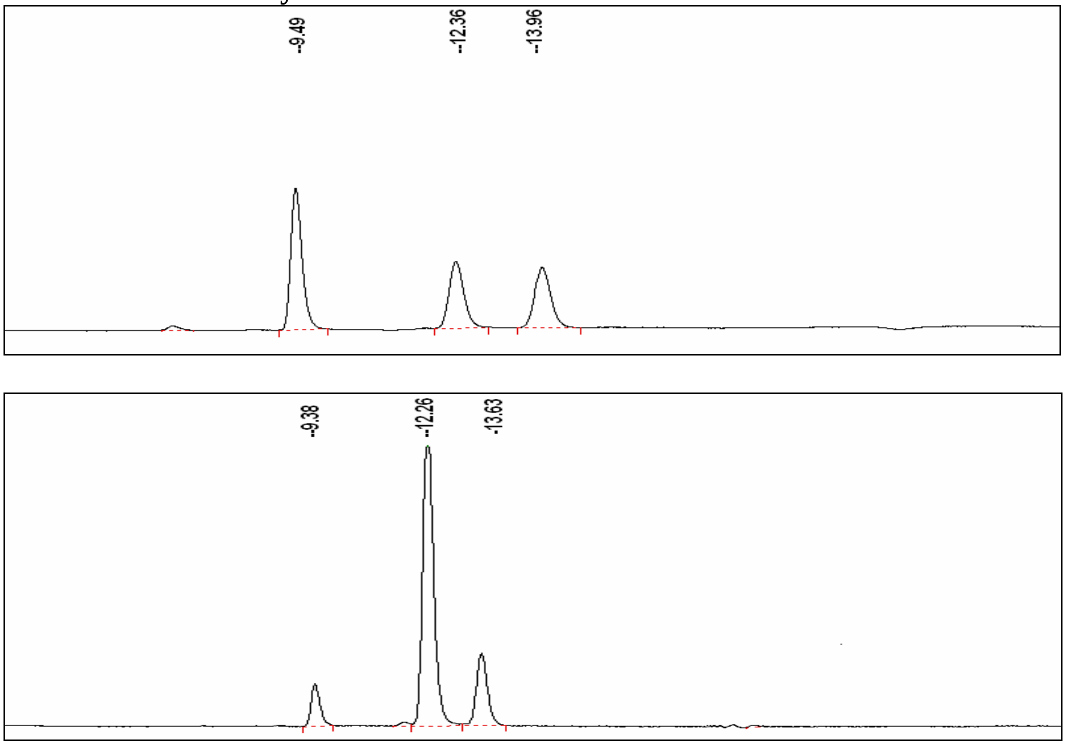


GC-MS Spectra (70 eV, EI)

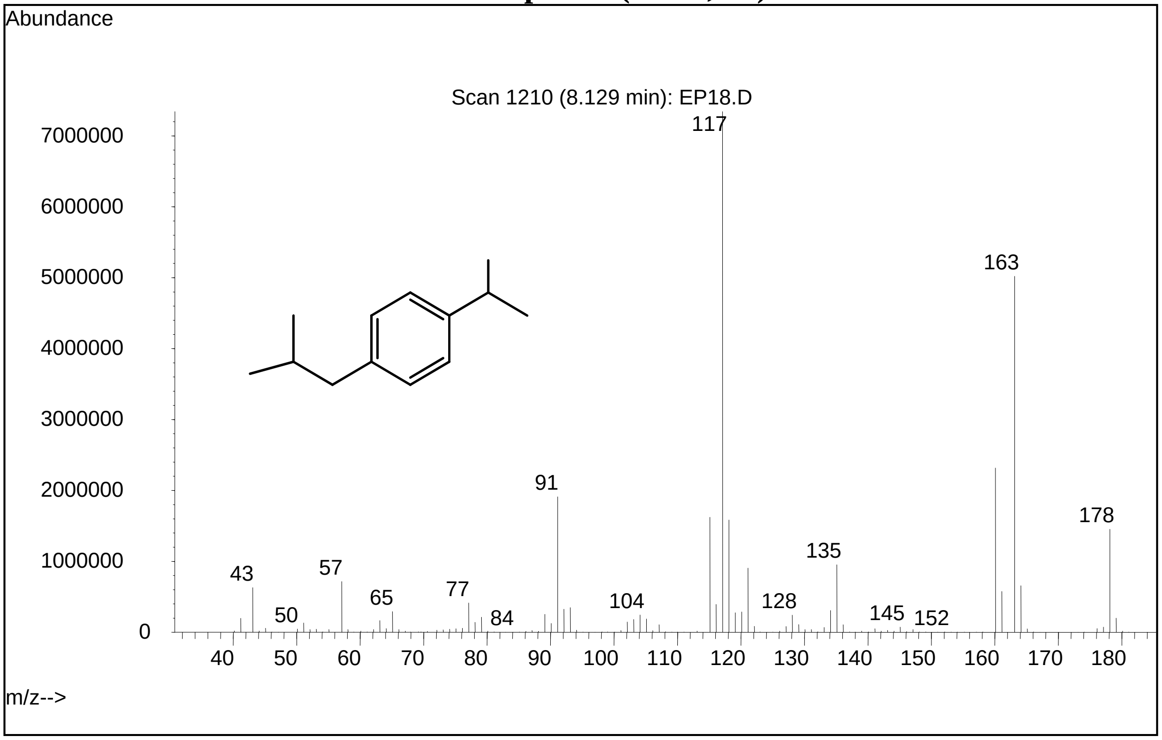


5. 1-p-Isobutylphenylethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture

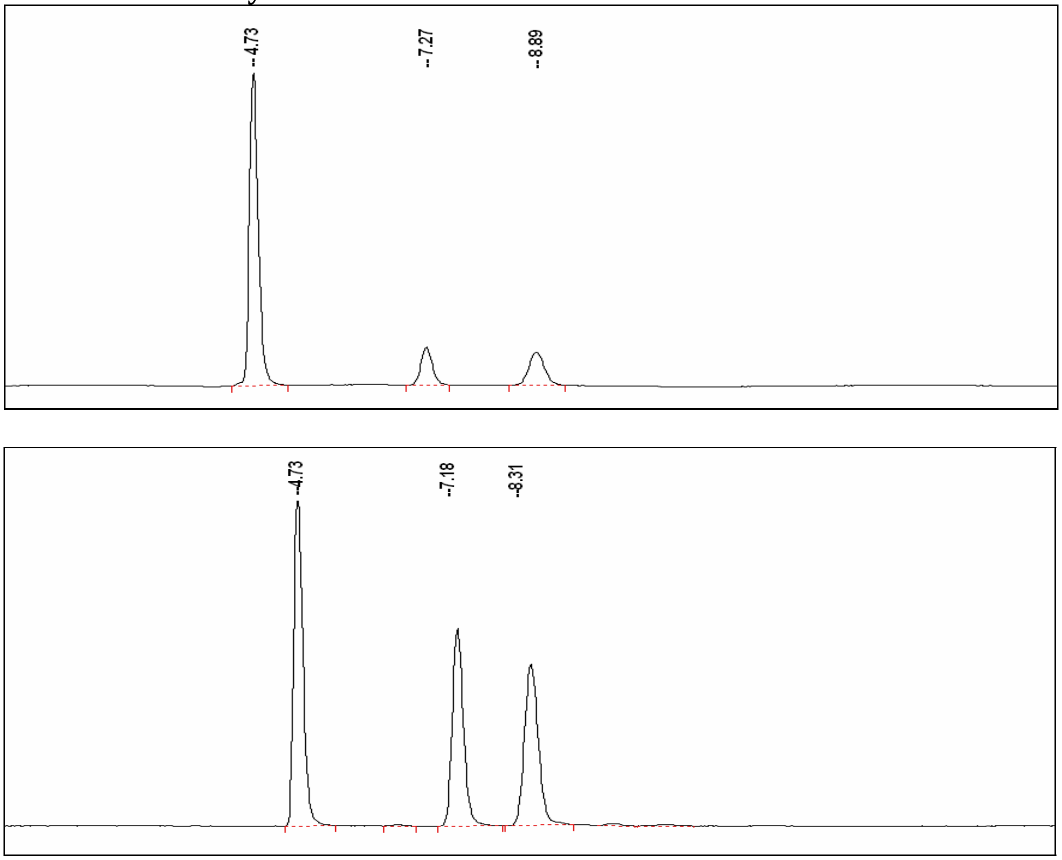


GC-MS Spectra (70 eV, EI)

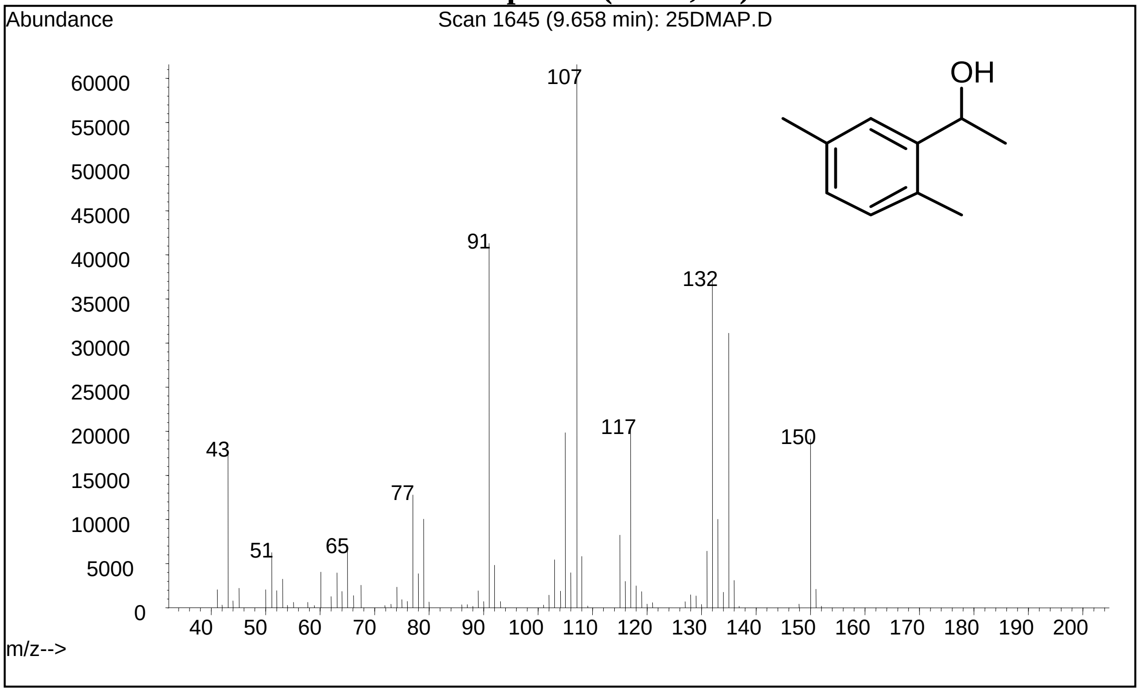


6. 1-(2,5-Dimethylphenyl)ethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture

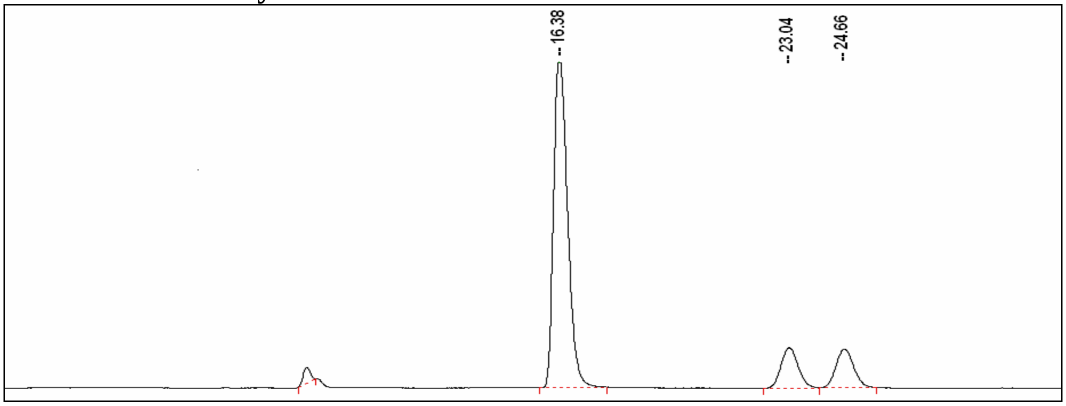


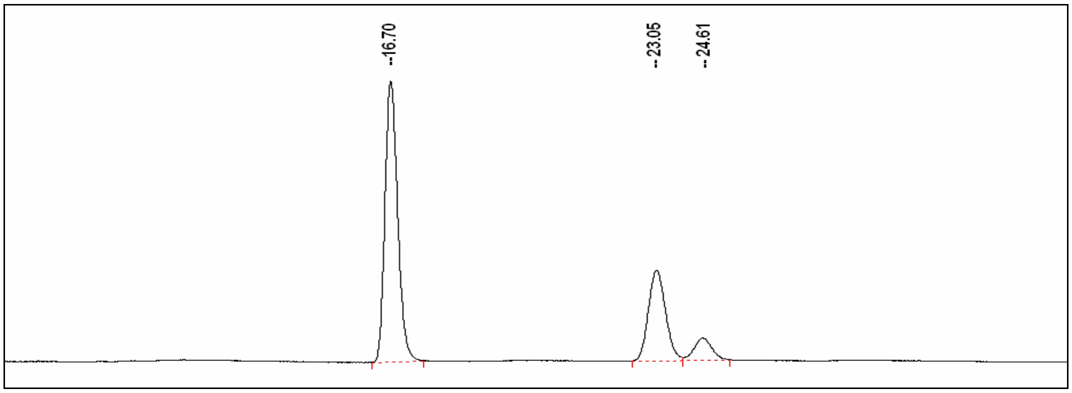
GC-MS Spectra (70 eV, EI)



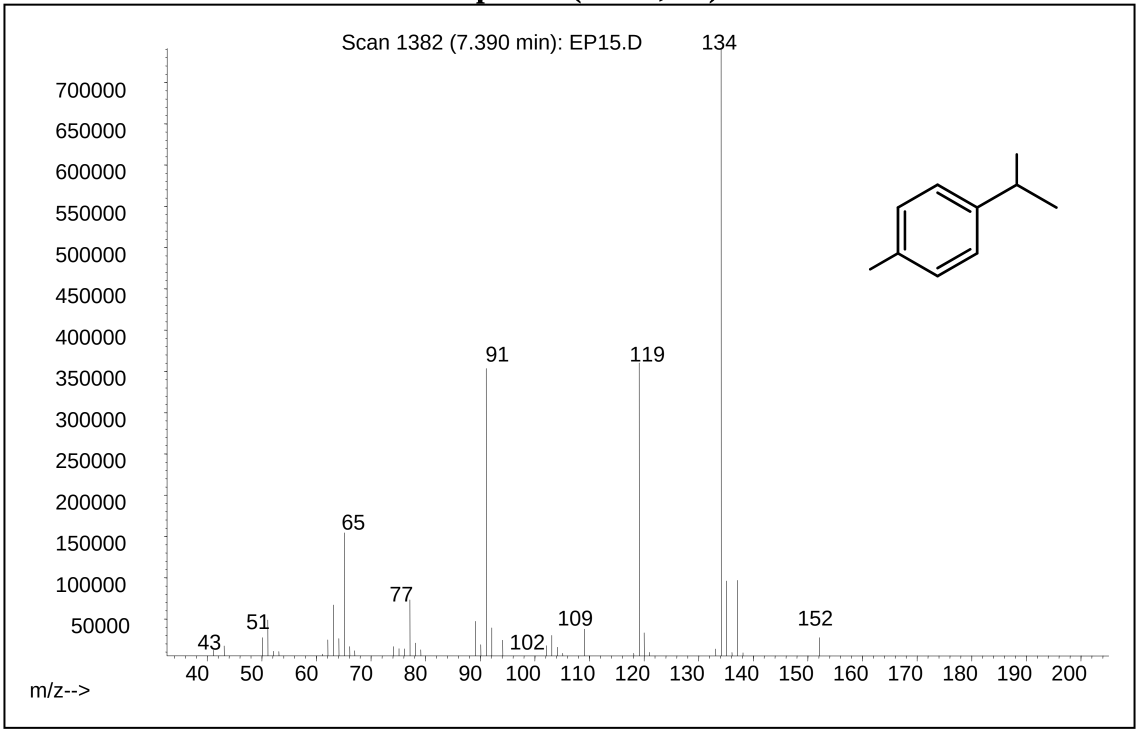
7. 1-p-Methoxyphenylethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture



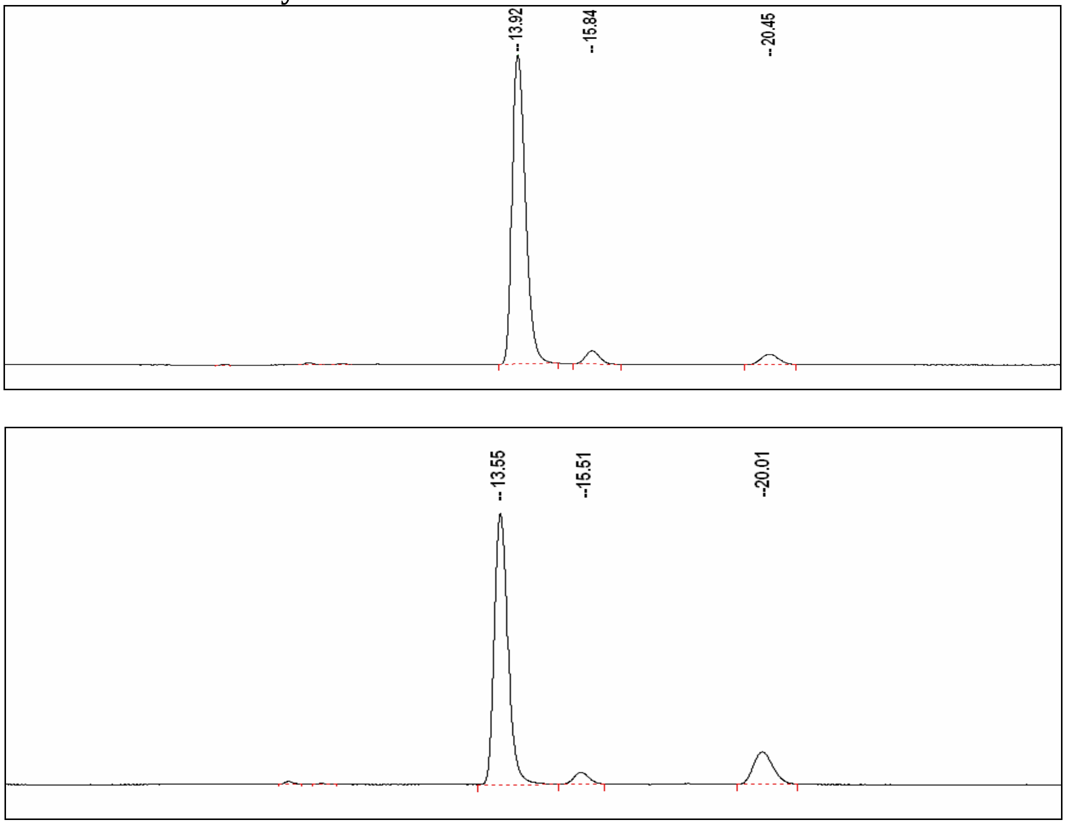


GC-MS Spectra (70 eV, EI)

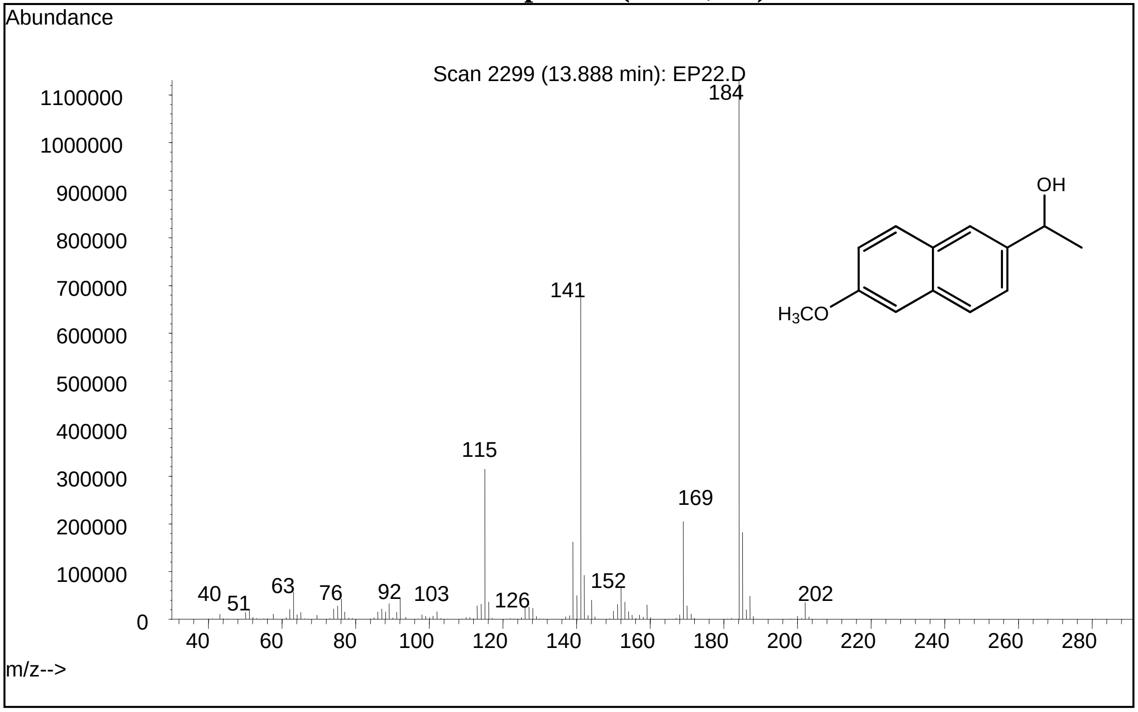


8. 1-(6-Methoxynaphthalen-2-yl) ethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture

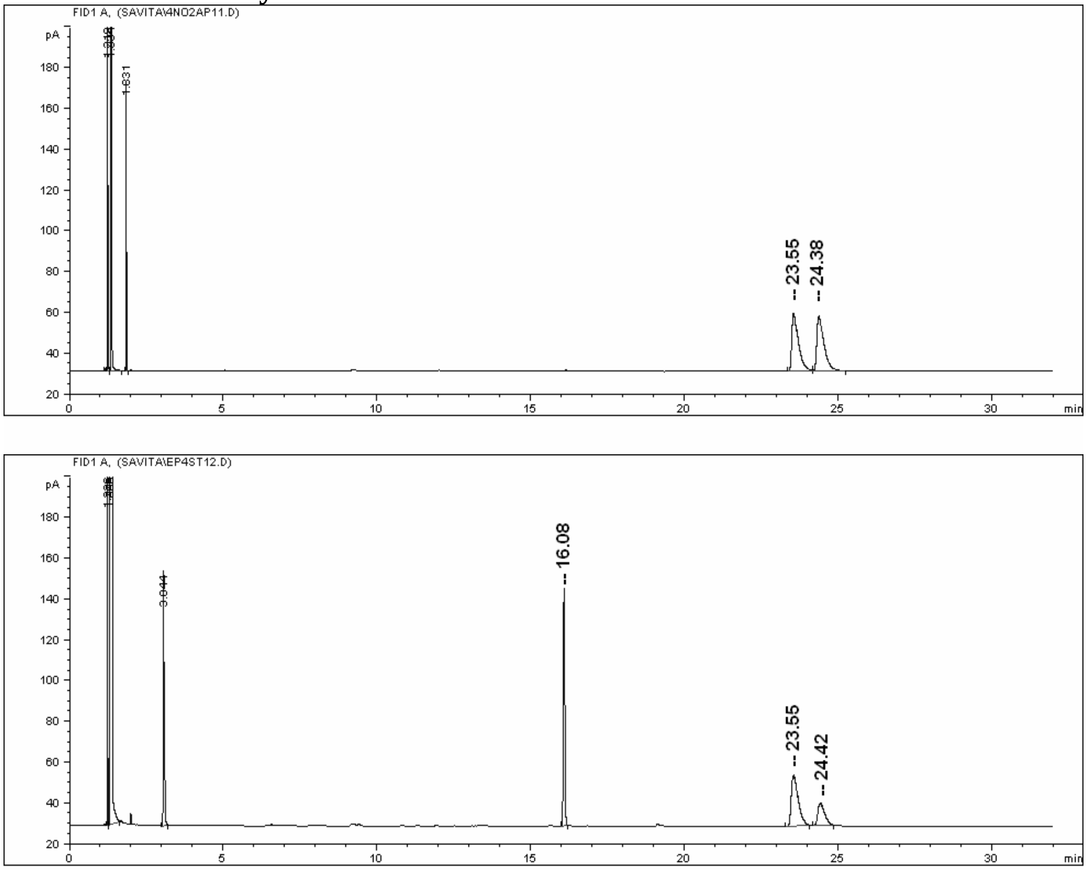


GC-MS Spectra (70 eV, EI)

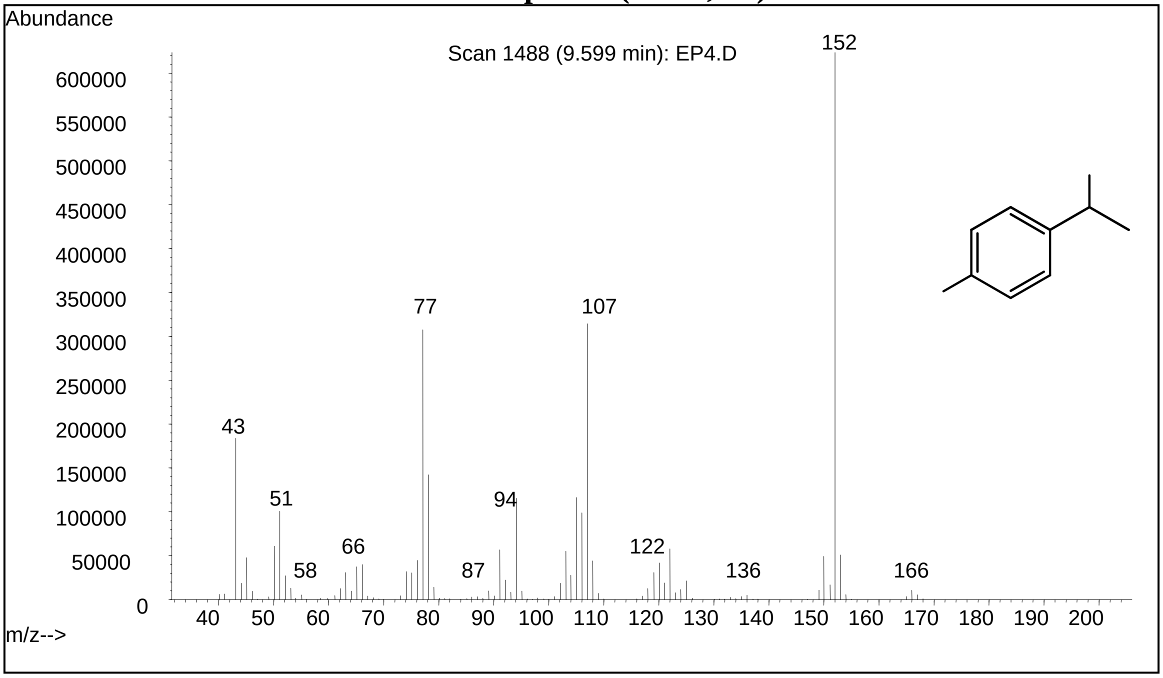


9. 1-p-Nitrophenylethanol

GC Analysis: Standard racemic alcohol and reaction mixture

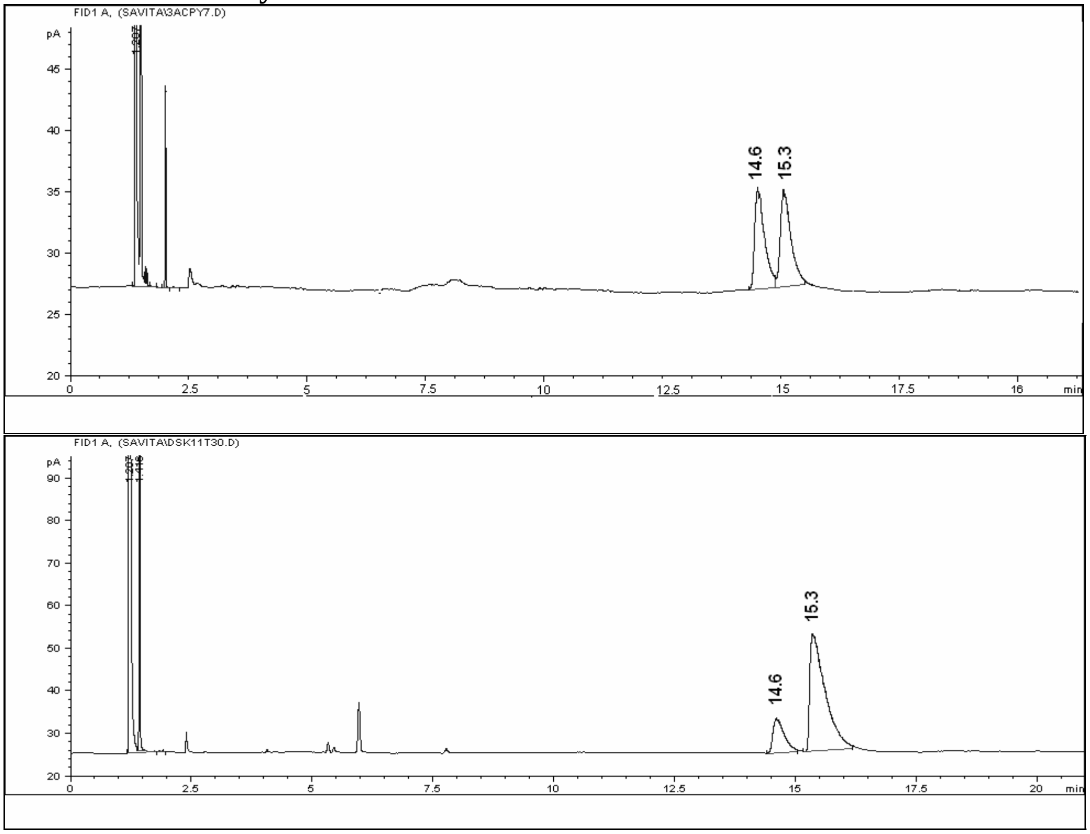


GC-MS Spectra (70 eV, EI)

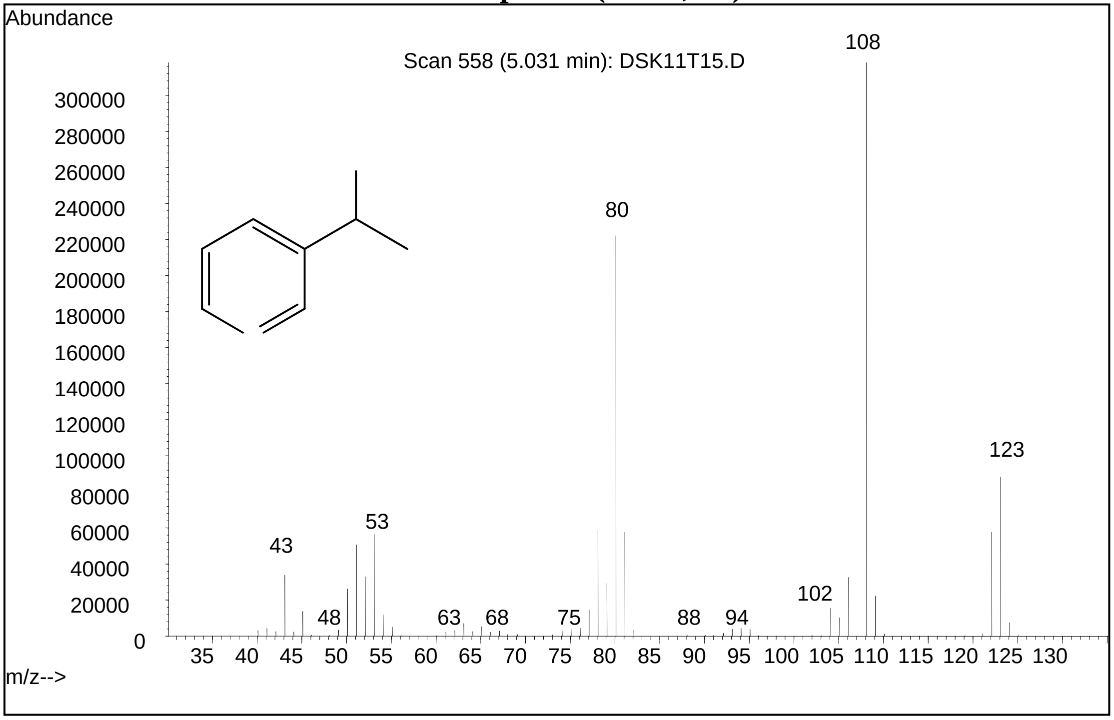


10. 1-(pyridin-3-yl) ethanol

GC Analysis: Standard racemic alcohol and reaction mixture



GC-MS Spectra (70 eV, EI)



Chapter 3

Catalytic Transfer Hydrogenation
of Nitrobenzene Using
5% Pd/C and 5% Pt/C Catalysts.

This Chapter is divided into two parts viz. study of catalytic transfer hydrogenation of nitrobenzene using 5% Pd/C catalyst (**3.1)** and study of catalytic transfer hydrogenation of nitrobenzene using 5% Pt/C catalyst **(3.2).**

3.1 CATALYTIC TRANSFER HYDROGENATION (CTH) OF NITROBENZENE USING 5% Pd/C CATALYST

3.1.1 INTRODUCTION

Catalytic transfer hydrogenation (CTH) is carried out at near ambient conditions and can be advantageously applied for the synthesis of high value chemicals. CTH of nitroarenes to corresponding amino-arenes has been investigated using both homogeneous and heterogeneous catalysts.[1] Aromatic amines are important starting materials and intermediates for the manufacture of a variety of chemicals such as dyestuffs, pharmaceutical products, agricultural chemicals, surfactants and polymers.[2]

Heterogeneous CTH using Pd/C catalyst has been investigated in detail since 1977 because of its high activity and ease of catalyst separation.[3] Various hydrogen donors have been used for the CTH of nitro compounds as described in Chapter 1 section 1.4 in detail.

It is observed that ammonium formate and potassium formate are the most widely used hydrogen donors for Pd/C catalyzed CTH of nitro compounds.[4] Gowda et al. have showed that formic acid can be used as hydrogen donor when used in 12 equivalents with 30-50 % Pd/C catalyst.[5] However, Blacklock et al. have showed that 3.6 equivalents of formic acid is sufficient when used along with catalytic amount of organic amine.[6]

The kinetic study of this reaction has been investigated using potassium formate (Sasoon et al.[7]) and ammonium formate (Mahajani et al.[8]) as hydrogen donors. Sasoon et al. proposed that all the three components-substrate, formate and water are adsorbed in a competitive manner onto a single active site of Pd/C catalyst. Maximum rate is obtained when the relative concentrations of the three components are such that active sites are accessible to all the three components.

From the work carried out so far it can be seen that there are few reports on the kinetics of CTH of nitroarenes using Pd/C catalyst and all the work has been carried out at a single temperature only. Thus the aim of the present work was to investigate CTH of nitrobenzene to aniline using 5% Pd/C catalyst and formate salts as hydrogen transfer agent. The detailed investigations were carried out in the temperature range of 308-328 K. The effect of pretreatment of catalyst by hydrogen donor has also been investigated. The effect of catalyst, substrate hydrogen donor and water concentration on the concentration-time profiles was studied. A detailed analysis of the rate data was done and an empirical rate model was proposed to fit the data.

3.1.2 EXPERIMENTAL SECTION

3.1.2.1 Materials

5 %Pd/C was purchased from Narmada Chemicals Pvt. Ltd. Solvents like ethanol; methanol etc, formic acid and formate salts were procured from the commercial sources (Loba Chemicals India) and are used as received. The reactions were carried out in a 50 ml jacketed 3-necked stirred glass reactor fitted with condenser and kept at desired temperature by circulating water through thermostat. The reaction mixture was stirred with the help a magnetic stirrer.

3.1.2.2 Characterization of the catalyst

The commercially available catalyst used in this study (5 %Pd/C) was characterized to determine surface area, morphology and oxidation state of Pd metal. Specific surface area of the catalyst was determined with an Omnisorb CX-100 Coulter Instrument. X-ray photoelectron spectroscopy (XPS) measurements were recorded using a VG Microtech ESCA 3000 instrument at 10^{-10} torr pressure, using un-monochromatized Mg-K_α (photon energy –1253.6 eV) as the radiation. For scanning electron microscopy (SEM), the catalyst was suspended in IPA, cast on gold plated discs, followed by drying under vacuum and were imaged on a Philips XL 30 Instrument.

3.1.2.2.1 Surface Area Measurements

The surface area of Pd/C catalyst was measured using the BET method by N_2-physisorption-desorption technique. The surface area of the catalyst was 597.38 m^2/g.

3.1.2.2.2 X-Ray Photoelectron Spectroscopy

Surface analysis by XPS spectra was carried out in terms of the binding energy values of elements present (carbon and palladium) in the catalyst, and the support after the necessary C(1s) correction. The XPS data in Figure 3.1 shows a full-scale binding energy data for the catalyst. The binding energy values were then compared with literature to assign the oxidation states of Pd as given in Table 3.1.

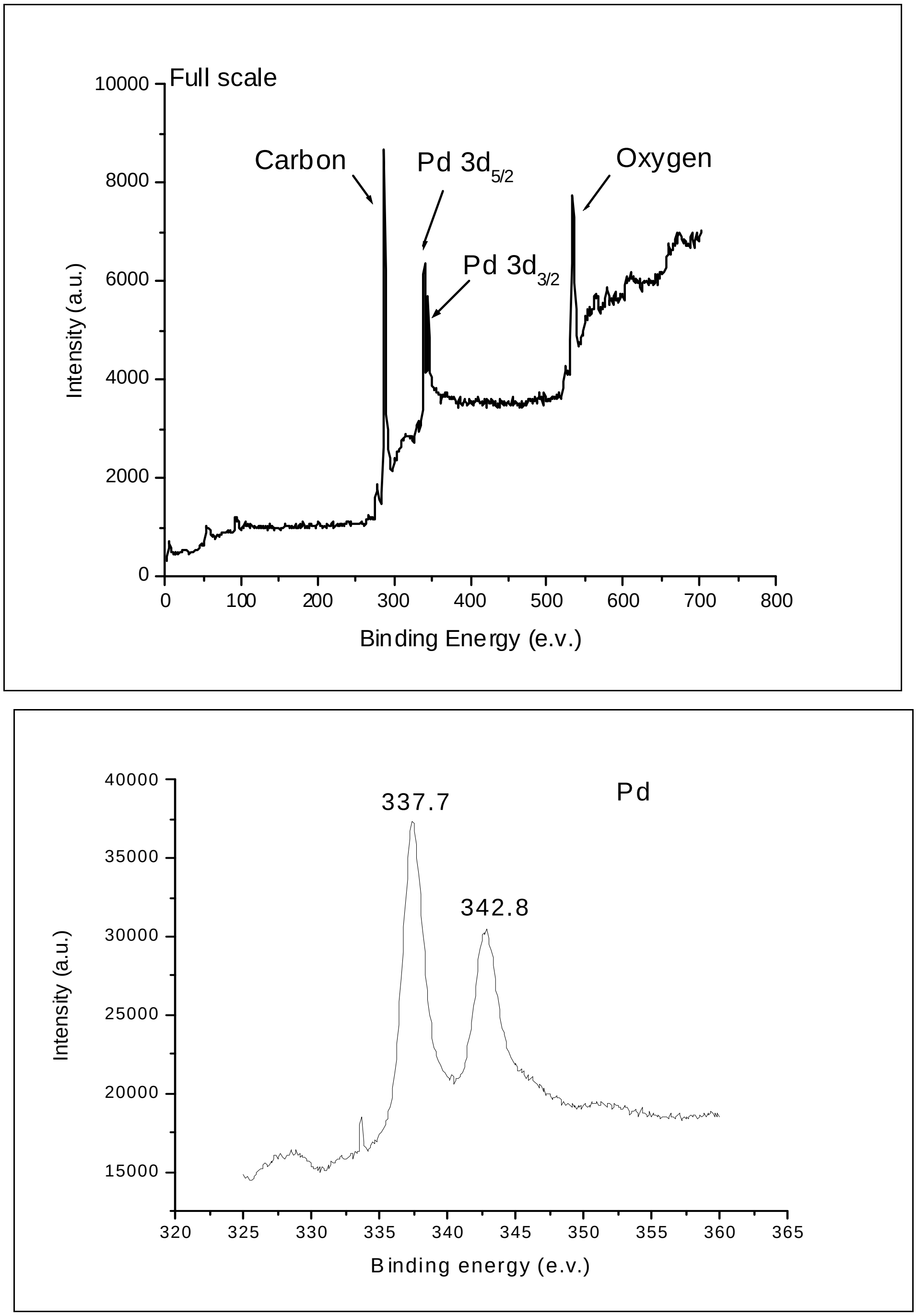


Figure 3.1: XPS data for 5% Pd/C

The binding energies of palladium were 337.6eV and 342.8 eV, which were assigned to its $3d_{5/2}$ and $3d_{3/2}$ states respectively, showing Pd present in Pd(II) oxidation state. (These peaks are due to hydrated palladium oxide which is formed due to storage of the catalyst in air.[9]) No peaks in the vicinity of 335 eV was observed showing the absence of Pd(0) state in the catalyst. (This catalyst was found to reduce to Pd(0) state under pretreatment conditions prior to catalytic reaction. This has been discussed in further sections).

Table 3.1: XPS data for the catalyst 5 % Pd/C

Elements	Pd(4p)	C(1S)	Pd($3d_{5/2}$)	Pd($3d_{3/2}$)	O(1S)	Pd(3p)
eV	55	285.41	337.66	342.78	532.18	563.52

3.1.2.2.3 Scanning Electron Microscopy

Scanning electron microscopy provides us the sight of the morphological pattern of the catalyst on a sub-micron level. Figure 3.2 shows agglomeration of Pd particles (bright dots) up to 300nm in size.

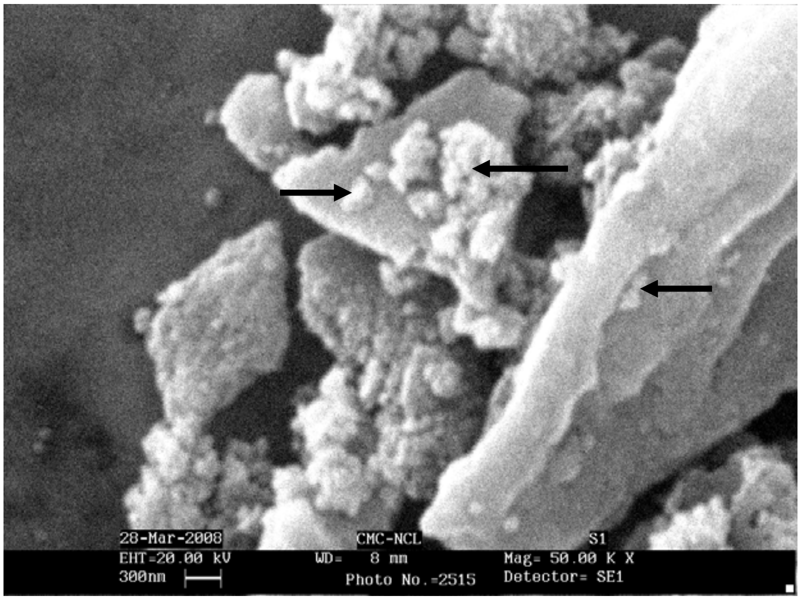


Figure 3.2: SEM micrograph for 5% Pd/C

3.1.2.3 Experimental setup and procedure for CTH reaction of nitrobenzene using 5% Pd/C catalyst

The reactions were carried out in three-necked glass reactor of 50 ml capacity. The setup used for conducting the experiments is shown in Figure 3.3. In a typical experiment, 75 mmol (6.3 gm) of formate salt, water (4.05 gm) and 0.1 gm 5% Pd/C were taken in glass reactor. The glass reactor temperature was kept constant at desired temperature using water circulation bath. The mixture was stirred for 10 minutes. The reaction was started by adding 25 mmol (3.08 gm) of nitrobenzene in 25 ml ethanol to this mixture. The reaction was continued for desired period (generally 3 hours). Samples were withdrawn at regular intervals of time to monitor the progress of reaction. The samples were filtered to remove solid catalyst and analyzed by GC for conversion of nitrobenzene and the reduction product (aniline) formed.

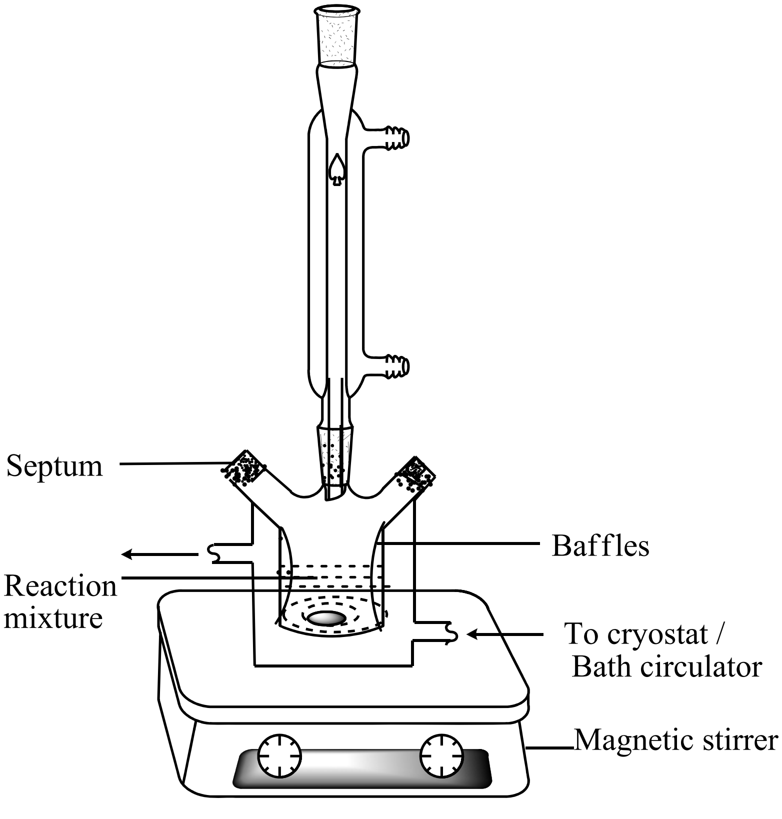


Figure 3.3: Experimental set-up for CTH of Nitrobenzene

3.1.2.4 GC analysis

The analysis of the contents of the reaction mixture was done using Agilent 6850 series II gas chromatograph, on HP-I capillary column (30m length, 320µm diameter, and 0.25µm stationary phase film thickness, methyl siloxane as stationary phase) using helium gas as the mobile phase and Flame Ionization Detector. The GC was equipped with an auto sampler. The quantitative analysis was done using a calibration curve prepared using synthetic standards in the range of concentrations studied. Mass balance was obtained from the quantitative GC analysis. The standard GC conditions used for the analysis of products of different reactions are given in Table 3.2.

Table 3.2: Conditions for GC analysis

Injector (split) Temperature	250ºC		
Flame ionization detector Temperature	300ºC		
	Hydrogen 35 ml/min		
	Zero Air 320 ml/min		
Inlet flow–total (He)	96.4 ml/min		
Split ratio for Injector	50:1		
Column Temperature	Rate (ºC /min)	T (ºC)	Hold time (min)
		80	1
	20	120	2
	30	220	0
Column Pressure	Constant Pressure 10 Psi		

A typical GC chart (Figure 3.4) shows the reactant (nitrobenzene) and (product) aniline under the analysis condition given in Table 3.2.

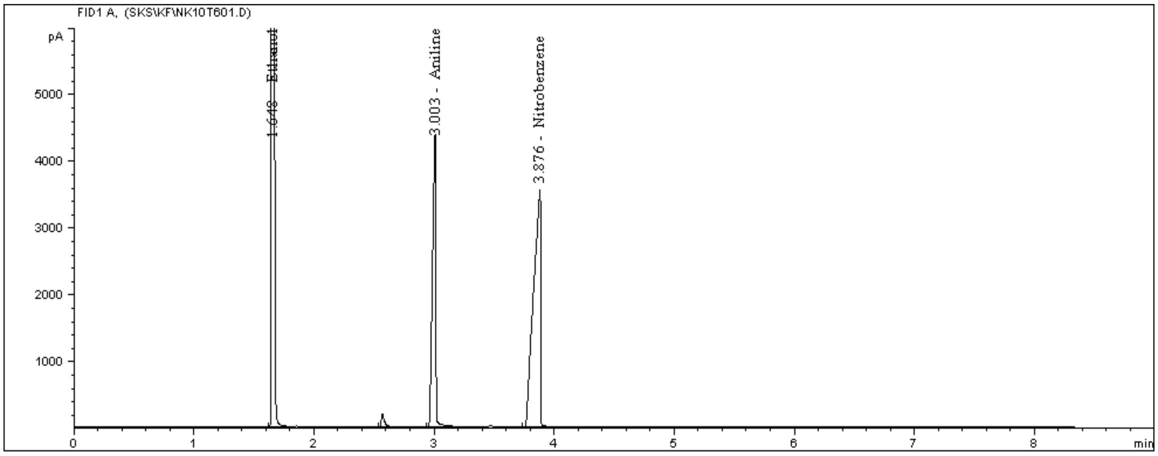


Figure 3.4: A typical GC chart showing reactant nitrobenzene and product aniline

Complete mass balance of the liquid phase components was obtained from the quantitative GC analysis. From the quantitative analysis conversion of nitrobenzene and selectivity were calculated by using following formulae (Equation 3.1 to 3.3)

$$\%\text{Conversion} = \frac{(\text{Initial moles of substrate - Final moles of substrate})}{\text{Initial moles of substrate}} \text{ x } 100 \qquad 3.1$$

$$\%\text{ Selectivity} = \frac{\text{No. of moles of product formed}}{\text{No. of moles of substrate converted}} \text{ x } 100 \qquad 3.2$$

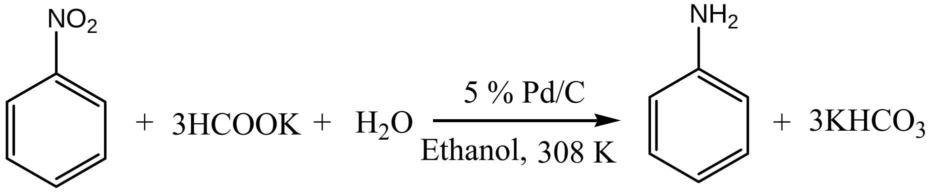
3.1.3 RESULTS AND DISCUSSION

3.1.3.1 Preliminary experiments

A few preliminary experiments were carried out on CTH of nitrobenzene (as shown in Scheme 3.1) using 5% Pd/C as a catalyst to ensure material balance of aniline formed and nitrobenzene consumed and to select the suitable solvent and hydrogen donor for the kinetic study.

The GC analysis of intermediate samples of the reaction showed the presence of substrate, nitrobenzene and product, aniline, no intermediate azoxybenzene or azobenzene derivatives were detected.

Reaction scheme



Scheme 3.1: CTH of nitrobenzene using Pd/C catalyst

3.1.3.1.1 Screening of hydrogen donors

Formic acid and various formate salts were screened as hydrogen donors for transfer hydrogenation of nitrobenzene in ethanol solvent. From the literature it was observed that for dehalogenation reaction the catalytic activity of 10% Pd/C is improved when it was pretreated with ammonium formate for 10 to 30 minutes.[10] Hence for this study the catalyst was pretreated with aqueous solution of hydrogen donor for 10 minutes and then the reaction was carried out by adding other reagents as per the experimental procedure. The results are presented in Figure 3.5.

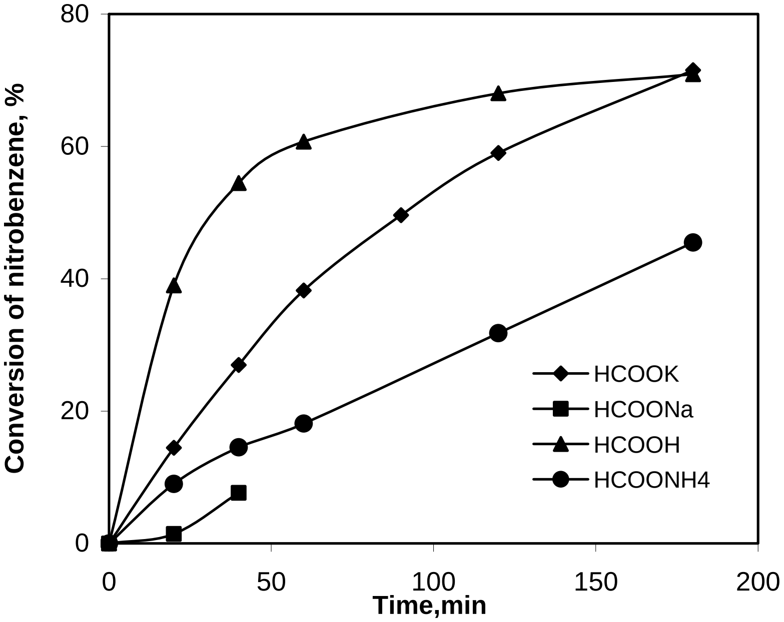


Figure 3.5: Screening of hydrogen donors for CTH of nitrobenzene

Reaction conditions*-Nitrobenzene, 0.86 kmol/m^3 ; Hydrogen donor, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; ethanol, 25ml; temperature, 308 K, Pretreatment: 10 minutes*

The results show that formic acid and potassium formate give higher activity (71% conversion within 180 minutes) compared to the other formates. With sodium formate, activity of the catalyst was very poor and the solution became thick slurry due to precipitation of sodium bicarbonate in the course of reaction. It was difficult to stir the reaction mixture afterwards which resulted in very low reaction rates. Sodium bicarbonate can also precipitate on the catalyst surface resulting in reduced access to reactants lowering the activity.

With aqueous formic acid as hydrogen donor, about 70% conversion was obtained within 180 minutes. This is in contrast to the reports of Gowada et al[5], where almost 12 equivalent of formic acid was found necessary for good catalytic activity. The observed result could be attributed to the pretreatment of the catalyst with formic acid before addition of substrate, which was absent in the earlier studies.

A systematic investigation on the effect of the time of formic acid pretreatment was carried out and the results are presented in Figure 3.6.

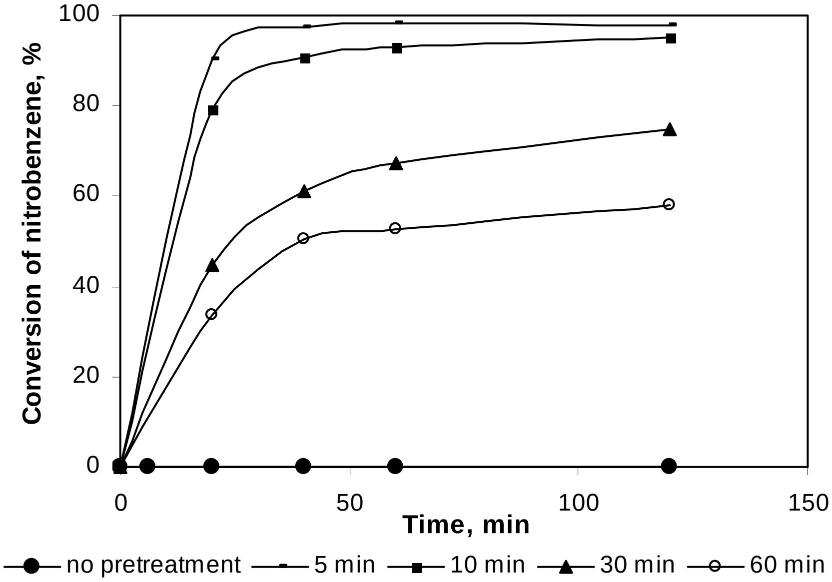


Figure 3.6: Effect of pretreatment time by formic acid on conversion of nitrobenzene ***Reaction conditions***-*Nitrobenzene, 0.86 kmol/m*^{3} *; HCOOH, 2.58 kmol/m*^{3}*;* H_2O*, 7.66 kmol/m*^{3}*; 5% Pd/C, 3.45 kg/m*^{3}*; ethanol, 25ml; temperature, 308K*

For the experiment carried out without any pretreatment, no activity was observed, indicating that pretreatment is necessary for catalytic activity. It can be seen that if catalyst is pretreated using 3 equivalent of formic acid, for five minutes, 100 % conversion of nitrobenzene was obtained within 50 minutes at 308 K. With increase in the pretreatment time, a drop in conversion of nitrobenzene was observed. The observed results can be explained on the basis of deactivation of catalyst by formation of surface carbonyl species (by abstraction of CO from formic acid) on catalyst surface as suggested by Ruthven et al.[11] Thus it was found out that small variation in pretreatment time led to major variation in activity of the catalyst.

Formic acid as a hydrogen donor was not suitable for kinetic studies as the data would be subject to the pretreatment effects. To finalize the hydrogen donor, potassium formate was selected and initial experiments were conducted to understand the pretreatment effect for potassium formate.

With potassium formate as a hydrogen donor good activity was observed with pretreatment of the catalyst for 10 minutes. No change in catalytic activity was observed even after pretreatment of the catalyst for a period of 1h indicating that extended pretreatment had no beneficial effect on activity. Hence further work was carried out using potassium formate as hydrogen donor.

3.1.3.1.2 Effect of catalyst pretreatment on CTH reaction

To find out the effect of catalyst pretreatment using potassium formate as a hydrogen donor a set of three experiments was carried out: In one of the experiments the catalyst was pretreated with aqueous potassium formate solution for a period of 10 minutes at 308 K temperature (as described in previous section) and then reaction was carried out by adding other reagents. In another experiment the catalyst was pretreated with nitrobenzene in ethanol for 10 minutes and the reaction was carried out by adding other reagents. In the last experiment reaction was carried out without giving any pretreatment.

The results are presented in Figure 3.7. Results indicate that unlike pretreatment study with formic acid, all three reactions proceeded to give almost 80% conversions in 240 minutes. However, no induction period was observed when catalyst was pretreated with potassium formate, while in other 2 cases induction of about 20 minutes was observed. For all the reactions, the product profile was similar at the end of reaction, indicating that the overall performance of the catalyst was not affected by pretreatment.

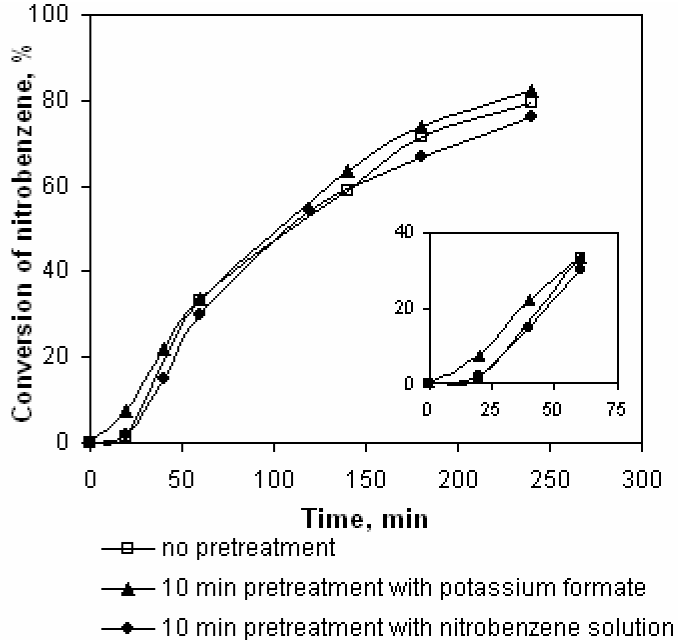


Figure 3.7: Effect of catalyst pretreatment on the conversion of nitrobenzene

Reaction conditions-*Nitrobenzene, 0.86 kmol/m*^{3} *; HCOOK, 2.58 kmol/m*^{3}*;* H_2O*, 7.66 kmol/m*^{3}*; 5% Pd/C, 3.45 kg/m*^{3}*; ethanol, 25ml; temperature, 308 K*

The observed effect of catalyst pretreatment with potassium formate can be explained on the basis of reduction of Pd(II) to active Pd(0) species.

The XPS data of catalyst after pretreatment of potassium formate is presented in Figure 3.8 which showed the peaks at 335.2 eV and 340.4 eV showing the presence of Pd(0) state in the catalyst. Thus active Pd(0) species is formed with pretreatment of the catalyst with potassium formate.

For reaction carried out with catalyst pretreatment with potassium formate, the product formation was observed in the initial stages of the reaction (See Inset, Figure 3.7) and will give more reliable data for initial rate determination. Hence all further experiments were carried out with catalyst pretreatment.

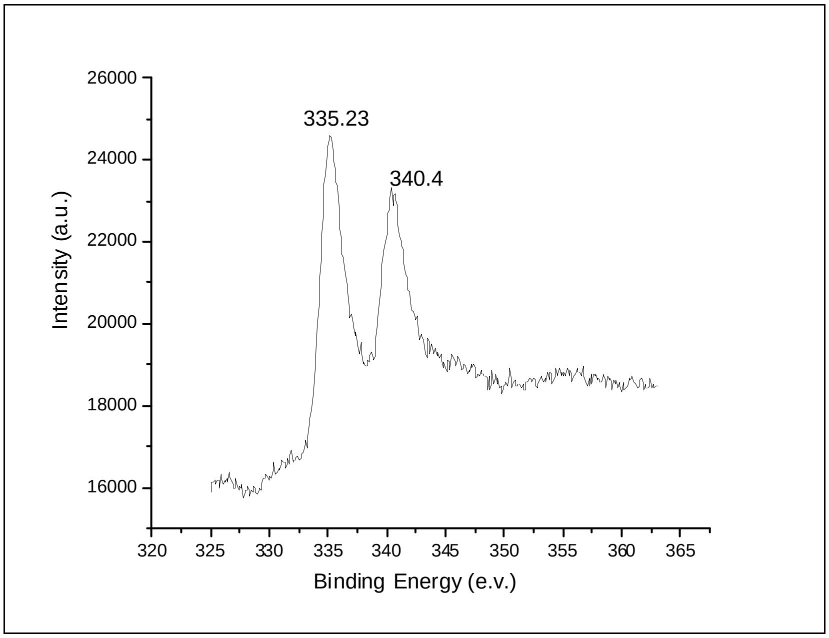


Figure 3.8: XPS data for 5% Pd/C after pretreatment by potassium formate

3.1.3.1.3 Screening of solvents

Few solvents were screened for transfer hydrogenation of nitrobenzene using potassium formate as a hydrogen donor and the results are presented in Table 3.3.

Table 3.3 Solvent screening studies on CTH of nitrobenzene.

Entry	Solvent	Conversion %
1	Methanol	33
2	Ethanol	81
3	IPA	57
4	n-Butanol	45
5	n-Pentanol	41
6	Ethyl acetate	32
7	Toluene	21

***Reaction conditions**: Nitrobenzene, 0.86 kmol/m^3 ; HCOOK, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; Solvent,25ml; temperature, 308 K , Time-4h*

The transfer hydrogenation proceeded in all solvents which suggests that these solvents are not adsorbed on the catalyst strongly enough to act as poisons and inhibit reactions. Low conversion was obtained with toluene and ethyl acetate as solvents, may be due to the biphasic nature of the reaction system. Methanol also resulted in a poor performance (only 33 % conversion in 4h). Ethanol was found to be the most effective solvent for the reaction. Sasoon et al.[7] also have reported higher activity with ethanol as a solvent and explained the observed results on the basis of better stabilization of transition states involved during the reaction.

Thus, in the present work high conversion is obtained using ethanol as a solvent and hence further experiments were carried out using ethanol as a solvent. The reduction of nitrobenzene in ethanol, in the absence of potassium formate did not proceed. This confirms that ethanol is not acting as a hydrogen donor under reaction conditions.

3.1.3.1.4 Effect of reaction temperature

The effect of temperature on transfer hydrogenation of nitrobenzene was investigated in a temperature range of 308-328 K under the following reaction conditions: nitrobenzene, 0.86 kmol/m^3; HCOOK, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 0.1 gm; ethanol, 25ml. The rate increases with the temperature as shown in Figure 3.9.

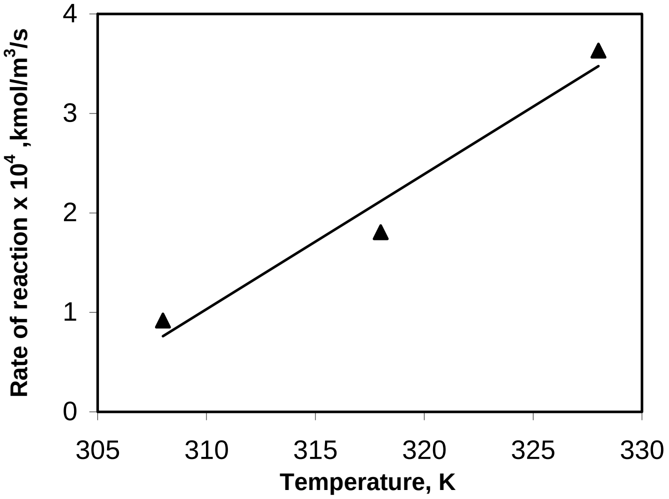


Figure 3.9: Effect of temperature on rate of CTH of nitrobenzene

Reaction conditions-*Nitrobenzene, 0.86 kmol/m^3 ; HCOOH, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; ethanol, 25ml.*

3.1.3.2 Kinetic studies of transfer hydrogenation of nitrobenzene using 5% Pd/C

The main aim of the present study was to investigate the kinetics of transfer hydrogenation of nitrobenzene using potassium formate as a hydrogen donor in presence of 5% Pd/C catalyst. The effect of concentrations of catalyst, substrate, potassium formate and water on the initial rate of transfer hydrogenation of nitrobenzene has been studied in detail. A suitable rate equation has also been proposed after rigorous model discrimination. The activation energy has been calculated.

The preliminary experiments were conducted to check the material balance and reproducibility of the experiments. The amount of substrate consumed and the product formed were compared for this purpose. A typical concentration-time profile is presented in Figure 3.10.

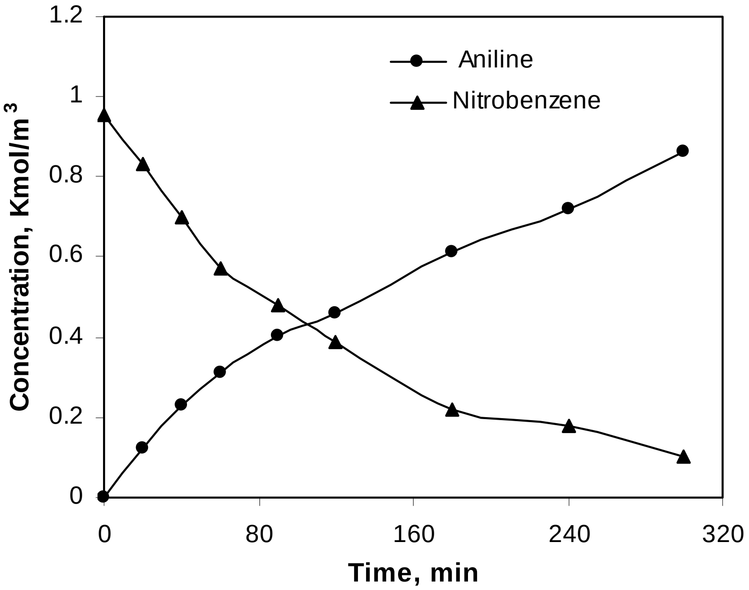


Figure 3.10: Concentration-time profile for the standard reaction.

Reaction conditions*-Nitrobenzene, 0.86 kmol/m^3 ; HCOOK, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; ethanol, 25ml; temperature, 308 K.*

A good mass balance between the amount of nitrobenzene consumed and the product aniline was obtained. No other byproducts were detected. It was also observed that the profile is unchanged even at higher temperature and material balance was >95%.

The kinetic experiments were carried out at three different temperatures for short duration such that the nitrobenzene conversion was less than 20-25% to ensure differential conditions. The experiments were found to be reproducible within error of ±4-6%. In each reaction, the initial, intermediate and final samples were analyzed for nitrobenzene consumed and aniline produced in order to check the material balance. Following this procedure, the effect of catalyst, nitrobenzene, potassium formate and water concentrations on the rate of reaction was studied in the range of reaction conditions shown in Table 3.4. The initial rates were calculated from the observed data on the formation of aniline as a function of time. The rate of reaction was calculated from the slope of the product formed vs. time plot as given in equation:

$$R=\frac{\text{Slope of product formation vs. time plot}}{\text{Total volume of liquid}}$$

Table 3.4: Range of conditions studied for the kinetics of CTH of nitrobenzene

Concentration of 5% Pd/C, kg/m^3	1.72-5.18
Concentration of nitrobenzene, kmol/m^3	0.21-1.72
Concentration of potassium formate, kmol/m^3	1.29-5.19
Concentration of water, kmol/m^3	5.95-10.75
Temperature (K)	308-328
Solvent	Ethanol
Reaction volume (cm^3)	29

The results showing the influence of different reaction parameters on the rate of the reaction and the kinetic modeling are discussed below.

3.1.3.2.1 Effect of catalyst concentration

The effect of the catalyst concentrations on the rate of reaction was studied at nitrobenzene concentration of 0.86 kmol/ m^3, potassium formate concentration of 2.58 kmol/m^3, and H_2O concentration of 7.66 kmol/m^3 in a temperature range of 308 K to 328 K in ethanol. The results are presented in Figure 3.11.

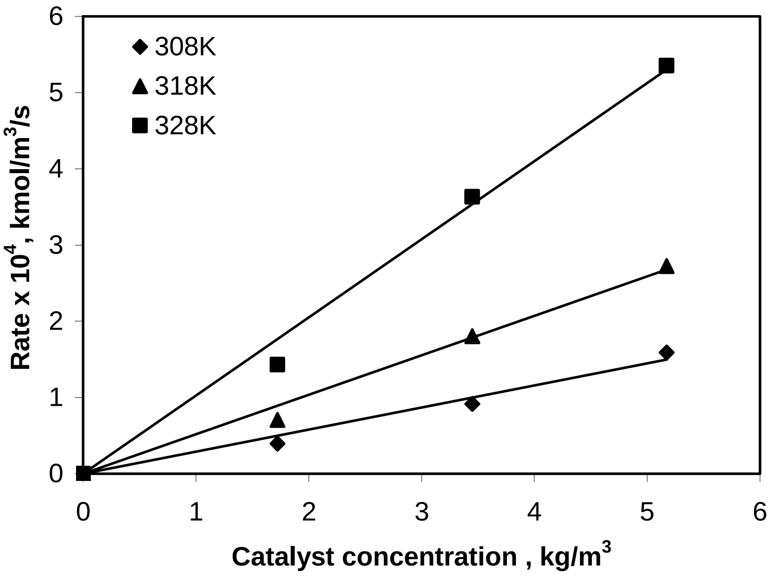


Figure 3.11: Effect of catalyst concentration on the rate of CTH of nitrobenzene

Reaction conditions: *Nitrobenzene, 0.86 kmol/m^3; HCOOK, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; ethanol, 25ml.*

The rate was found to have a first order dependence on the catalyst concentration. This is expected since the increase in catalyst concentration will lead to increase in number of active sites for hydrogenation. This is in agreement with the earlier reports on 10% Pd/C catalyzed transfer hydrogenation of 4-nitrotolune using potassium formate as hydrogen donor.[7]

3.1.3.2.2 Effect of nitrobenzene concentration on the rate of reaction

The effect of nitrobenzene concentration on the rate of transfer hydrogenation was investigated at constant potassium formate, H_2O and catalyst concentrations of 2.58, 7.66 kmol/m^3 and 3.45 kg/m^3, respectively; in a temperature range of 308 K to 328 K. The results are presented in Figure 3.12.

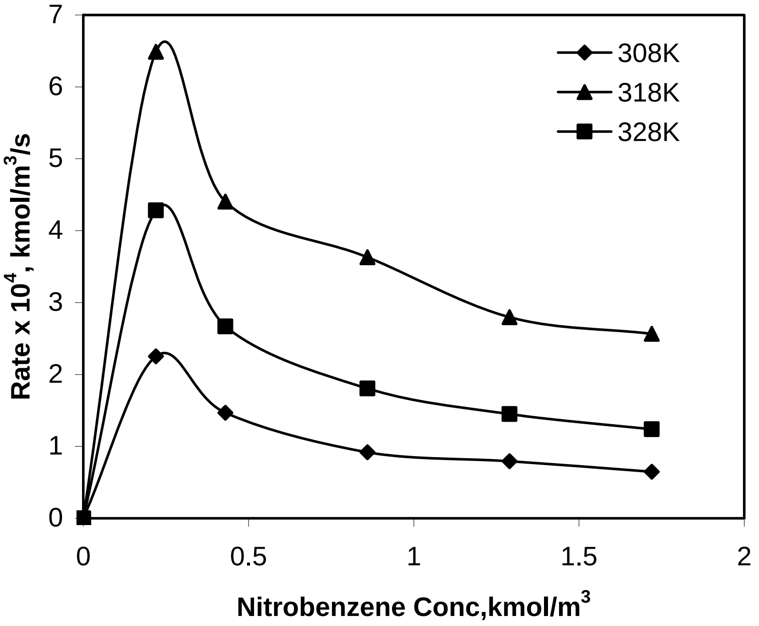


Figure 3.12: Effect of nitrobenzene concentration on the rate of CTH reaction

Reaction conditions: *HCOOK, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3 ; ethanol, 25ml.*

The rate was found to decrease with increase in nitrobenzene concentration showing typical substrate inhibition kinetics. The decrease in rate with increase in nitrobenzene concentration suggests that at higher concentration of nitrobenzene the active sites are saturated preferentially with nitrobenzene and are less available for activation of other reactants like water and formate. Earlier reports on nitrotoluene reduction with 10% Pd/C by Sasson and co-workers[7] showed zero order dependence on nitrotoluene up to 5M concentration and then decreased at higher substrate concentration (up to 8M) using aqueous potassium formate as hydrogen donor in toluene solvent.

3.1.3.2.3 Effect of potassium formate concentration on the rate of reaction

The effect of potassium formate concentration on the rate of transfer hydrogenation of nitrobenzene to aniline was investigated at constant nitrobenzene, H_2O and catalyst concentrations of 0.86, 7.66 kmol/m^3 and 3.45 kg/m^3 respectively in a temperature range of 308 to 328 K. The results are presented in Figure 3.13.

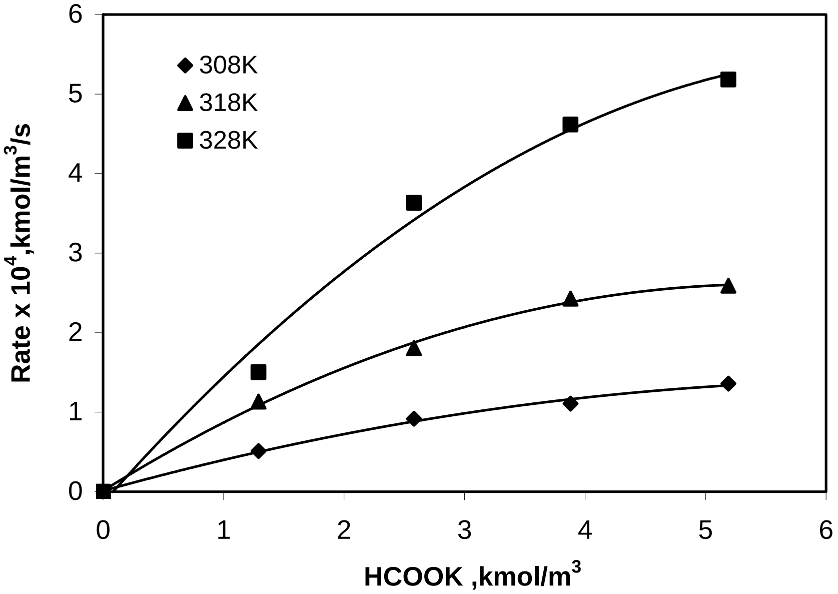


Figure 3.13: Effect of formate concentration on the rate of CTH of nitrobenzene

Reaction conditions: *Nitrobenzene, 0.86 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; ethanol, 25ml.*

The rate was found to increase linearly with potassium formate concentration in the lower concentration range (<4 kmol/m^3). With further increase in potassium formate concentration, a partial order dependence was observed. This may be because at higher concentration of the potassium formate, the active sites of catalyst are covered preferentially with formate giving less access to other reactants (nitrobenzene and water). The first order dependence on hydrogen donor concentration (sodium formate) was shown by Cavinato et al.[12] in case of C=C bond reduction and Rajgopal et al.[13] for the hydrodechlorination reaction. But the concentration ranges used were significantly lower (below 1M solution). The formate concentration range used in the present study is higher (minimum concentration of potassium formate used in this study is 9.4 M) than that used in the earlier studies. This can result in partial order dependence at higher concentrations. It can also be seen that in the lower range of concentrations the rate has a first order dependence.

3.1.3.2.4 Effect of water concentration on the rate of reaction

The effect of water concentration on the rate of reaction was studied at constant nitrobenzene and potassium formate and catalyst concentrations of 0.86, 2.58 kmol/m^3 and 3.45 kg/m^3 respectively in a temperature range of 308 to 328 K. The results are presented in Figure 3.14.

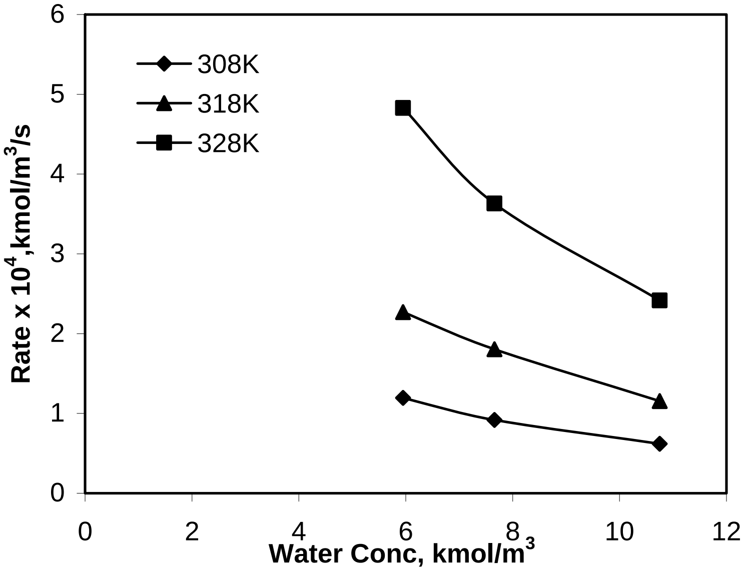


Figure 3.14: Effect of water concentration on the rate of CTH of nitrobenzene

Reaction conditions: *Nitrobenzene, 0.8620 kmol/m^3; HCOOK, 2.5813 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; ethanol, 25ml.*

As reported earlier, the presence of water is necessary for the hydrogen transfer process to take place, as it serves as a medium for contact of the solid hydrogen donor with the metal and the substrate by forming a thin film of formate solution on the surface of the catalyst.[14] The results show that the rate of reaction decreased with increase in concentration of water. At lower concentration of water (below 6 kmol/m^3) the reaction mixture became very thick and it became difficult to stir the reaction mixture. The potassium bicarbonate formed during reaction and precipitated out of the reaction mixture resulting in a viscous mixture. Hence results below water concentrations of 6 kmol/m^3 are not presented in this work.

The results show that water is an actual reactant in the hydrogen transfer reaction and it has to compete with other two substrates for an adsorption site on the catalyst surface. If the relative concentration of water is increased, access to other two substrates is decreased resulting in lower rate of reaction.

Thus from the results presented it is found that the rate of reaction is sensitive to the concentrations of nitrobenzene, potassium formate and water. The optimum relative concentrations of the three components are necessary to achieve high activity. In order to ascertain this a set of experiments was carried out at constant nitrobenzene concentration and simultaneously varying the concentrations of water and potassium formate, keeping ratio of water:formate constant (2.96 used for standard reaction). The results are presented in Figure 3.15. From the results it can be clearly seen that the rate of reaction is independent of concentrations of potassium formate and water, provided the molar ratio of water:formate was kept constant. Thus the maximum rate is obtained only when the optimum relative concentration of the donors-water and potassium formate are used during the reaction.

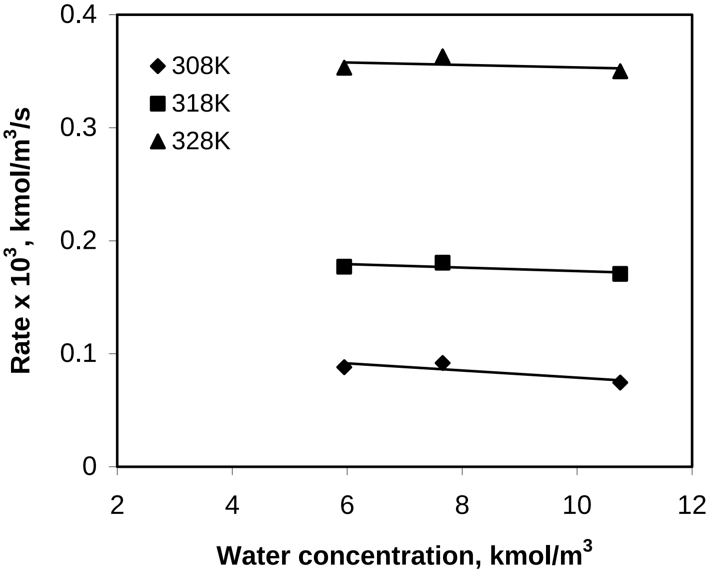


Figure 3.15: Effect of water concentration keeping formate to water ratio constant on the rate of CTH of nitrobenzene

Reaction conditions*-Nitrobenzene, 0.86 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; solvent, ethanol, 25ml; water: formate =2.96*

3.1.3.3 Rate Model

The kinetic data was used to develop a rate equation for the transfer hydrogenation of nitrobenzene using potassium formate as hydrogen donor. Based on the observed trends, a variety of empirical models were examined, and the best model was selected based on the criterion of the least average error between predicted and experimental rates (Φ_{min}) which is defined as:

$$\Phi_{\mathrm{min}} = \sum_{\mathrm{i=1}}^{\mathrm{n}} (\mathrm{R}_{\mathrm{exp}} - \mathrm{R}_{\mathrm{pre}})^2$$

Where R_{exp} is the observed rate of reaction and R_{pre} is the rate predicted by the respective models.

3.1.3.3.1 Estimation of kinetic parameters and model discrimination

The rate parameters k, K_A, K_B, and K_D were evaluated at 303,318 and 328K by fitting the experimental rate data with Equations. (I)–(V) using non-linear regression analysis and an optimization routine based on the Marquardt's method.[15] The values of the rate parameters at different temperatures are presented in Table 3.5. The values of Φ_{min} suggest the extent of fit of the kinetic models used (least value of the Φ_{min} shows the best fit):

$$R = \frac{k.A.B.C.D}{\left(1+K_A A\right)^2\left(1+K_B B\right)\left(1+K_D D\right)^2} \qquad \text{(I)}$$

$$R = \frac{k.A.B.C.D}{\left(1+K_A A\right)^2\left(1+K_B B\right)\left(1+K_D D\right)} \qquad \text{(II)}$$

$$R = \frac{k.A.B.C.D}{\left(1+K_A A\right)^3\left(1+K_B B\right)^3\left(1+K_D D\right)^3} \qquad \text{(III)}$$

$$R = \frac{k.A.B.C.D}{\left(1+K_A A\right)\left(1+K_B B\right)^2\left(1+K_D D\right)} \qquad \text{(IV)}$$

$$R = \frac{k.A.B.C.D}{\left(1+K_A A\right)\left(1+K_B B\right)^2\left(1+K_D D\right)^2} \qquad \text{(V)}$$

Where R = rate of reaction, expressed in $kmol/m^3/s$;
A = concentration of nitrobenzene ($kmol/m^3$);
B = concentration of potassium formate ($kmol/m^3$);
C = concentration of catalyst (kg/m^3);
D= Concentration of water ($kmol/m^3$)
k = rate constant, K_A, K_B, K_C are equilibrium constants.

Table 3.5: Values of kinetic parameters at different temperatures

Rate Model	T (K)	k	K_A	K_B	K_D	ϕ_{min}
I	308	1.82×10^{-1}	10.14	2.59×10^{-1}	3.36	9.27×10^{-10}
	318	4.93×10^{-1}	10.03	2.18×10^{-1}	4.22	2.57×10^{-9}
	328	6.72×10^{-1}	5.65	1.28×10^{-1}	6.33	1.45×10^{-8}
II	308	2.69×10^{-2}	10.2	2.55×10^{-1}	13.5	2.57×10^{-9}
	318	1.84	10.1	2.15×10^{-1}	5.38×10^{2}	8.67×10^{-9}
	328	-5.62×10^{-1}	5.67	1.26×10^{-1}	-2.67×10^{2}	4.23×10^{-8}
III	308	-3.61×10^{-1}	-17.2	1.40	1.19×10^{-1}	1.34×10^{-7}
	318	4.64×10^{-3}	2.57	4.93×10^{-2}	2.82×10^{-1}	7.80×10^{-9}
	328	8.05×10^{-3}	1.90	3.46×10^{-2}	3.69×10^{-1}	2.90×10^{-8}
IV	308	3.23×10^{-2}	5.64×10^{2}	1.20×10^{-1}	2.75	2.22×10^{-8}
	318	4.94×10^{-2}	5.70×10^{2}	1.07×10^{-1}	2.27	7.76×10^{-8}
	328	2.35	7.37×10^{2}	6.49×10^{-2}	56.3	1.41×10^{-7}
V	308	4.59×10^{-1}	2.52×10^{3}	1.25×10^{-1}	9.46×10^{-1}	2.02×10^{-8}
	318	1.39	4.47×10^{3}	1.12×10^{-1}	9.18×10^{-1}	7.02×10^{-8}
	328	2.62	2.05×10^{3}	6.63×10^{-2}	1.58	1.13×10^{-7}

The discrimination of rate models was done based on the thermodynamic criteria, activation energy and the Φ_{min} values. The rate models IV and V were rejected based on the thermodynamic criteria of inconsistency of temperature dependence of equilibrium constant and range of activation energy values. Model III and II had rate parameters which were negative and hence were rejected. The model I thus turned out to be superior among all the models considered.

Thus, the following rate equation was found to predict the rates in good agreement with experimental values:

$$R = \frac{k.A.B.C.D}{\left(1 + K_A A\right)^2 \left(1 + K_B B\right)\left(1 + K_D D\right)^2}$$

A comparison of the experimental rates with the rates predicted by model I is presented in Figure 3.16, which shows a reasonably good fit. The average percent error between the experimental and predicted data was 0.97 %

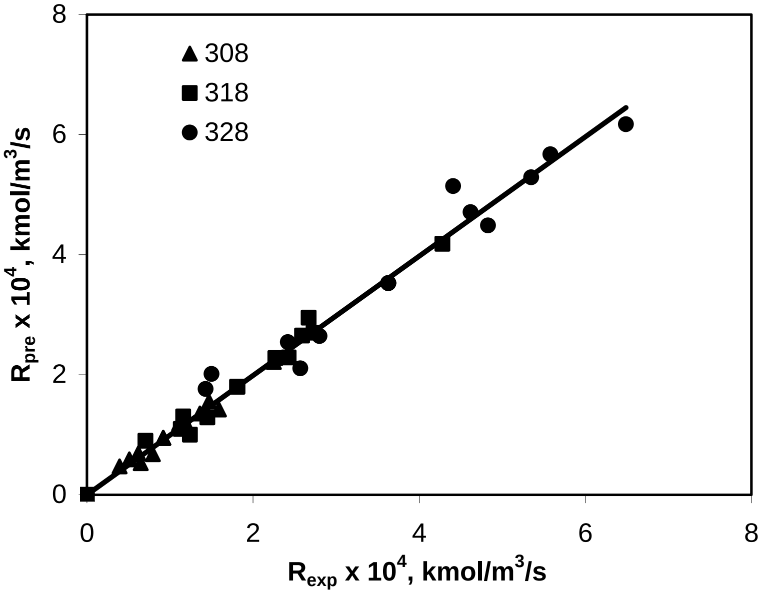


Figure 3.16: Comparison of experimental rates and rates predicted using model I.

The Arrhenius plot showing the effect of temperature on the rate parameters is presented in Figure 3.17 from which the activation energy was evaluated as 55.2 kJ/mol.

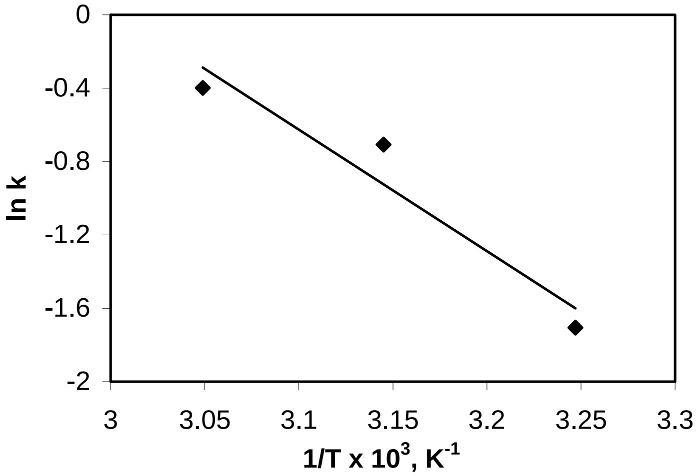


Figure 3.17: Plot of ln k vs. 1/T

Figures 3.18 to 3.21 show the comparison of experimental and predicted rates for the varying concentration of catalyst, nitrobenzene, potassium formate and water at temperatures of 308-328 K respectively. The constants K_{A}, K_{B} and K_{D} found to be mild function of temperature as seen in Figure 3.22.

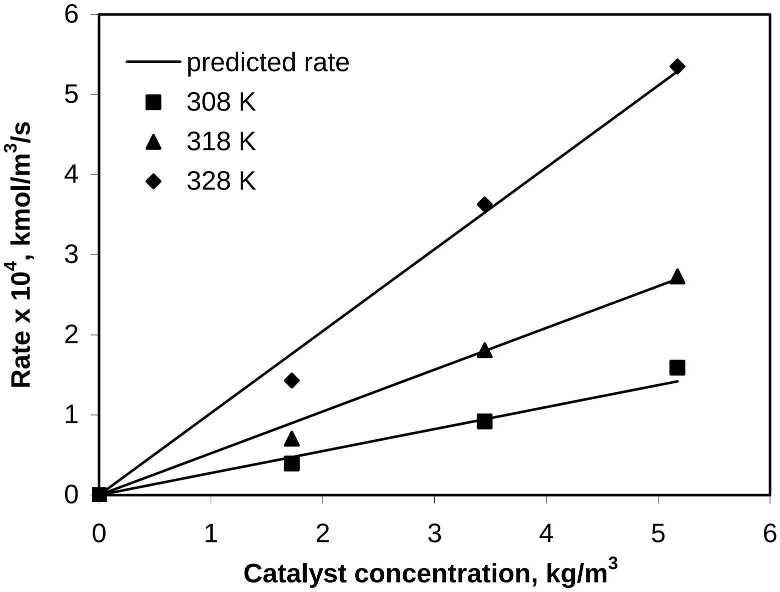


Figure 3.18: Effect of catalyst concentration on reaction rates

Reaction conditions: *Nitrobenzene, 0.86 kmol/m^3 ; HCOOK, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; ethanol, 25ml.*

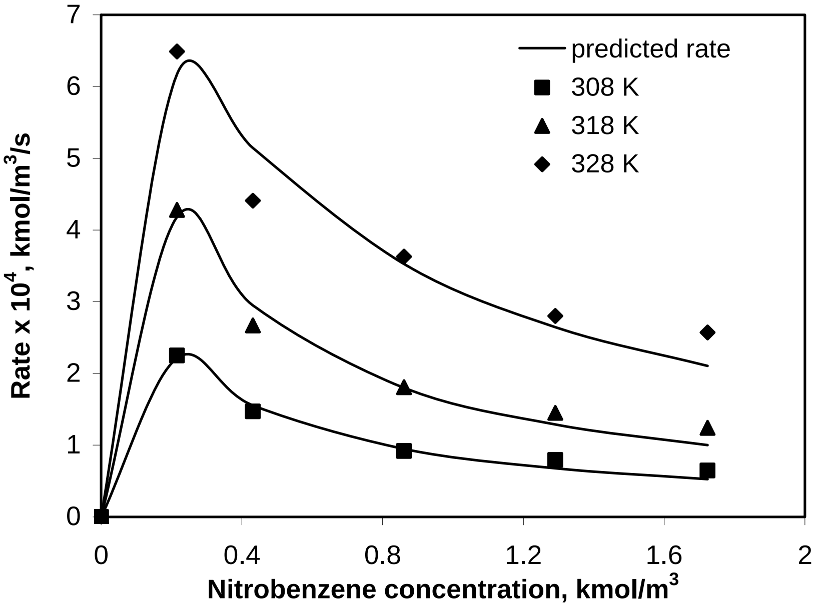


Figure 3.19: Comparison of experimental and predicted rates for effect of nitrobenzene concentration at various temperatures

Reaction conditions-*Nitrobenzene, 0.86 kmol/m^3 ; HCOOK, 2.58 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; solvent, ethanol, 25ml.*

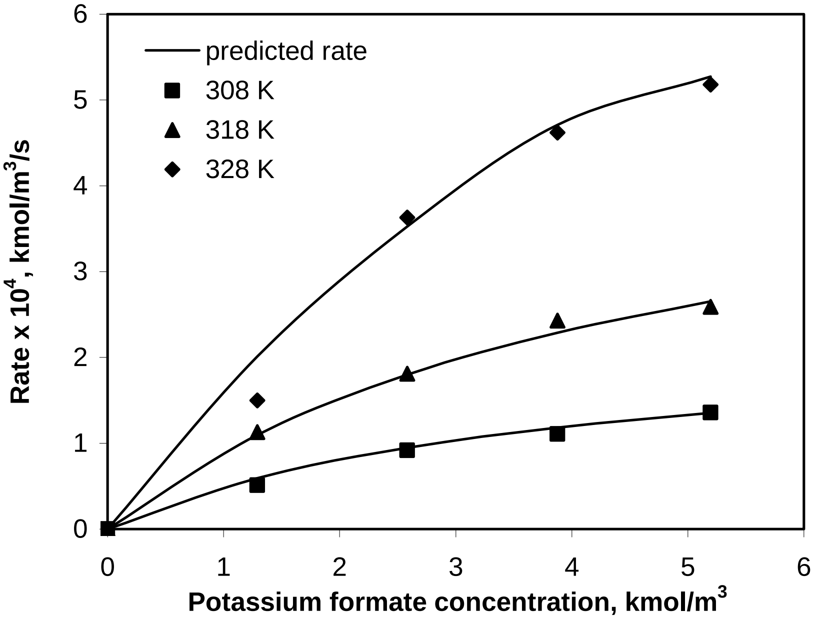


Figure 3.20: Comparison of rates for effect of potassium formate concentration

Reaction conditions: *Nitrobenzene, 0.86 kmol/m^3; H_2O, 7.66 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; solvent, ethanol, 25ml.*

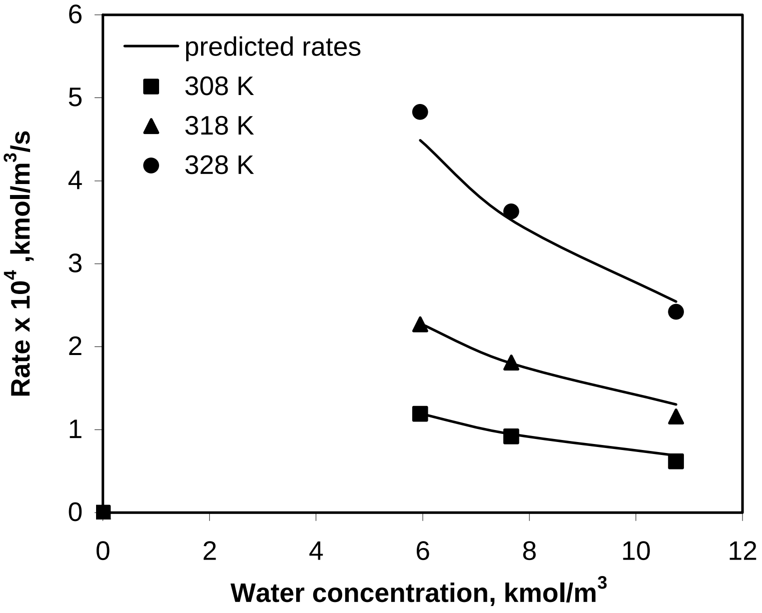


Figure 3.21: Comparison of rates for effect of water concentration

Reaction conditions: *Nitrobenzene, 0.86 kmol/m^3; HCOOK, 2.58 kmol/m^3; 5% Pd/C, 3.45 kg/m^3; solvent, ethanol, 25ml.*

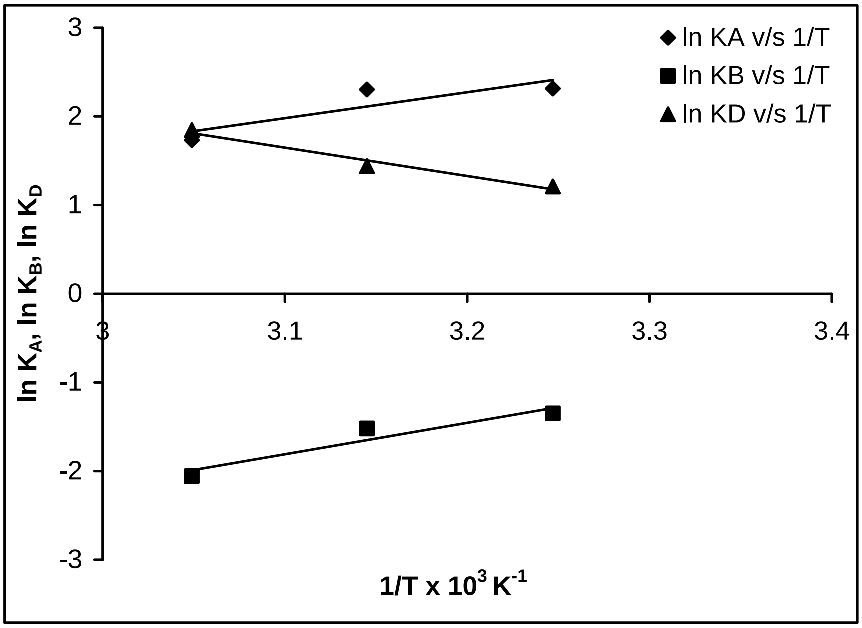


Figure 3.22: Temperature dependence of equilibrium constants K_A, K_B and K_D obtained using Model I.

3.1.3.4 Mechanism

All the three substrates: potassium formate, water and nitrobenzene, are adsorbed in a competitive manner onto the active site on the catalyst surface as suggested by Sasoon et al.[7] In the present work the induction period of almost 20 minute was found when reaction was done without pretreatment of the catalyst by aqueous potassium formate. Here the activation of catalyst is achieved by pretreatment with potassium formate solution (prior to addition of nitrobenzene). Thus it is likely that adsorption of formate anion is the first step of the reaction which is also suggested by Rajagopal and coworkers.[16]

This adsorption leads to dissociative chemisorption resulting in the formation of Pd-hydride species and CO_2. Simultaneously there is adsorption of substrate (S) and water on catalyst surface as shown below.

$$\mathrm{Pd + HCOOK \rightleftharpoons Pd(HCOO)^{-}_{ad} \longrightarrow PdH + Pd(CO_2) + Pd(K)^{+}}$$

$$\mathrm{Pd + H_2O \rightleftharpoons Pd(H_2O)_{ad}}$$

$$\mathrm{Pd + S \rightleftharpoons Pd(S)_{ad}}$$

The substrate is then adsorbed on the hydride species. This species then picks up proton from water giving OH^- anion

$$\mathrm{PdH + PdS \longrightarrow PdSH + Pd}$$

$$\mathrm{PdSH + Pd(H_2O) \longrightarrow Pd(HSH) + [Pd(OH)]^{-}}$$

The hydroxide anion then reacts with CO_2 to form bicarbonate.

$$\mathrm{[Pd(OH)]^{-} + Pd(CO_2) \longrightarrow [Pd(HCO_3)]^{-}}$$

Then there is desorption of the products

$$\mathrm{Pd(HSH) \longrightarrow Pd + SH_2}$$

$$\mathrm{[Pd(HCO_3)]^{-} + Pd(K)^{+} \longrightarrow Pd + KHCO_3}$$

3.1.4 CONCLUSIONS

The systematic study of CTH of nitrobenzene was performed using 5 % Pd/C and potassium formate as hydrogen donor in ethanol-water solvent. Pretreatment of the catalyst with substrate and hydrogen transfer agent influenced the catalytic activity significantly. Activity of catalyst decreased significantly with increase in pretreatment time with formic acid as a hydrogen transfer agent. Detailed investigations were carried out using potassium formate as a hydrogen transfer agent. The effect of different parameters viz., concentrations of nitrobenzene, catalyst and donors (formate salt and water) on the initial rate of the reaction was investigated in the temperature range of 308–328K. It was found that the rate increases with increase in catalyst concentration, decreases with increase in nitrobenzene and water concentration. The rate was found to increase linearly with potassium formate concentration in the lower concentration range (<4 kmol/m^3). With further increase in potassium formate concentration the rate increased only marginally. The rate data were fitted to various empirical rate models. The following rate equation was found to predict the rates in good agreement with experimental values:

$$R = \frac{k.A.B.C.D}{\left(1+K_A A\right)^2\left(1+K_B B\right)\left(1+K_D D\right)^2}$$

The activation energy was evaluated as 55.2 kJ/mol.

3.2 CATALYTIC TRANSFER HYDROGENATION (CTH) OF NITROBENZENE USING 5% Pt/C CATALYST

3.2.1 INTRODUCTION

As discussed in Chapter 1 (section 1.4.5), platinum catalysts have been rarely applied in CTH reactions. There are still fewer reports on the CTH of nitroarenes using 5% Pt/C catalyst and ammonium formate as hydrogen donor.[17] However, the systematic studies on the effect of the reaction conditions such as temperature, H-donor concentration, effect of water concentration, etc are not reported. In this work the transfer hydrogenation of nitrobenzene has been studied using 5% Pt/C as catalyst and formate salts as hydrogen donors. The effect of different process parameters like the effect of catalyst, substrate, hydrogen donor and water concentration on the rate of reaction has been studied in detail.

3.2.2 EXPERIMENTAL SECTION

3.2.2.1 Materials

5% Pt/C was purchased from Narmada Chemicals Pvt. Ltd. Solvents like ethanol; methanol etc and formic acid, formate salts were procured from the commercial sources (Loba chemicals India) and used as received. The reactions were carried out in a 50 ml jacketed 3-necked stirred glass reactor fitted with condenser and kept at a desired temperature by circulating water through thermostat. The reaction mixture was stirred with the help of magnetic stirrer.

3.2.2.2 Characterization of the catalyst

The commercially available catalyst used in this study (5% Pt/C) was characterized to determine surface area, morphology and oxidation state of Pt metal. The instrumental details are given in section 3.1.2.2

3.2.2.2.1 Surface Area Measurements

The surface area of 5% Pt/C catalyst was measured using the BET method by N_2-physisorption-desorption technique. The surface area of the catalyst was 761.88 m^2/g.

3.2.2.2.2 X-Ray Photoelectron Spectroscopy

Surface analysis by XPS spectra was carried out in terms of the binding energy values of elements present (carbon and platinum) in the catalyst, and the support after the necessary C(1s) correction. The XPS data in Figure 3.23 shows a full-scale binding energy data for the catalyst. The binding energy values were then compared with literature to assign the oxidation states of Pt as given in Table 3.6.

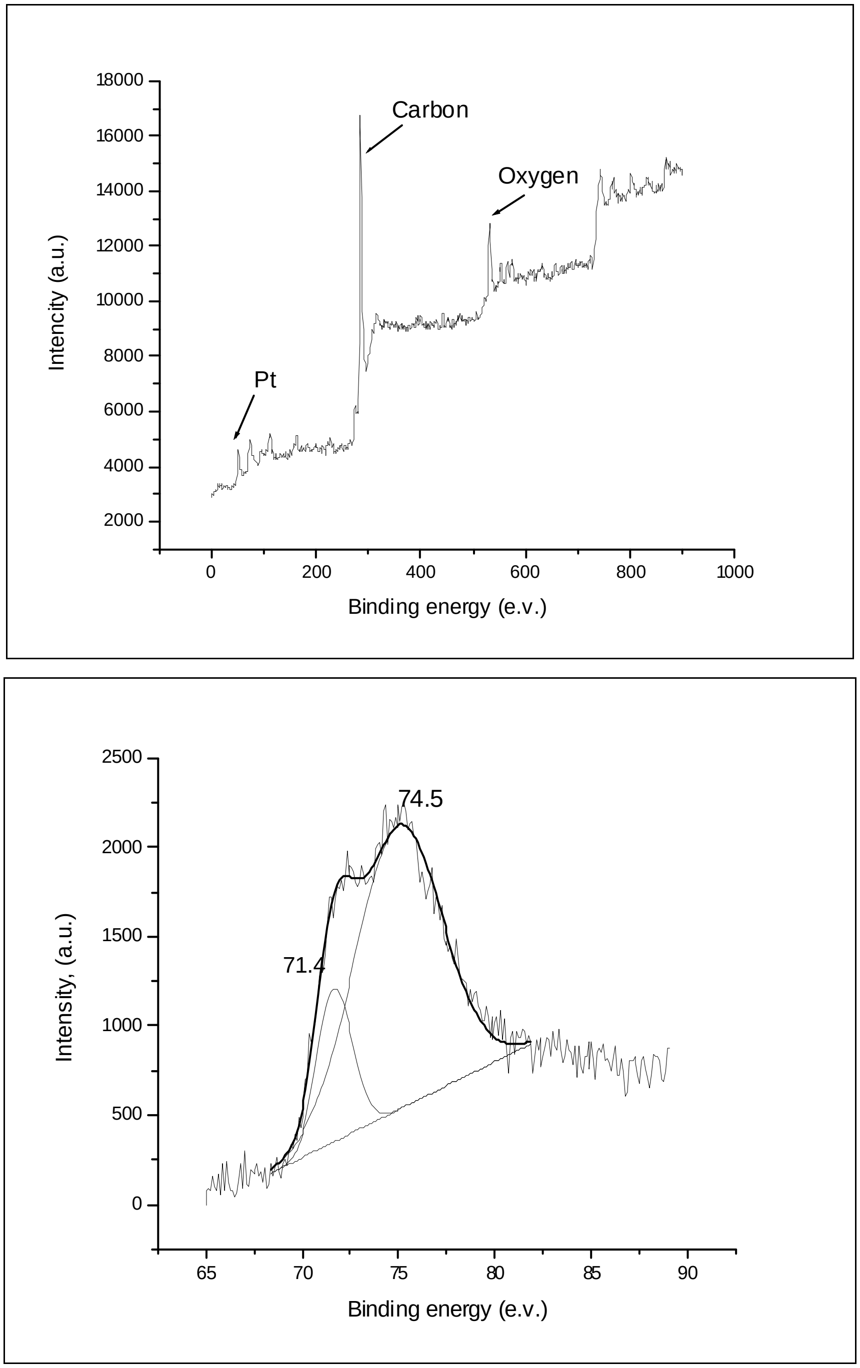


Figure 3.23 : XPS data for 5% Pt/C

The binding energies of platinum were 71.4 eV and 74.5 eV respectively, which were assigned for its $4f_{7/2}$ and $4f_{5/2}$ states and indicate that the Pt is present in its metallic, Pt(0) state.

Table 3.6: XPS data for Catalyst 5 % Pt/C

Elements	C(1S)	$Pt4f_{7/2}$	$Pt4f_{5/2}$	O(1S)
eV	285.6	71.4	74.5	532.18

3.2.2.2.3 Scanning Electron Microscopy

Scanning electron microscopy provides us the sight of the morphological pattern of the synthesized materials in a sub-micron level. Figure 3.24 shows agglomerated small Pt particles (bright dots) approximately below 2 μm in size.

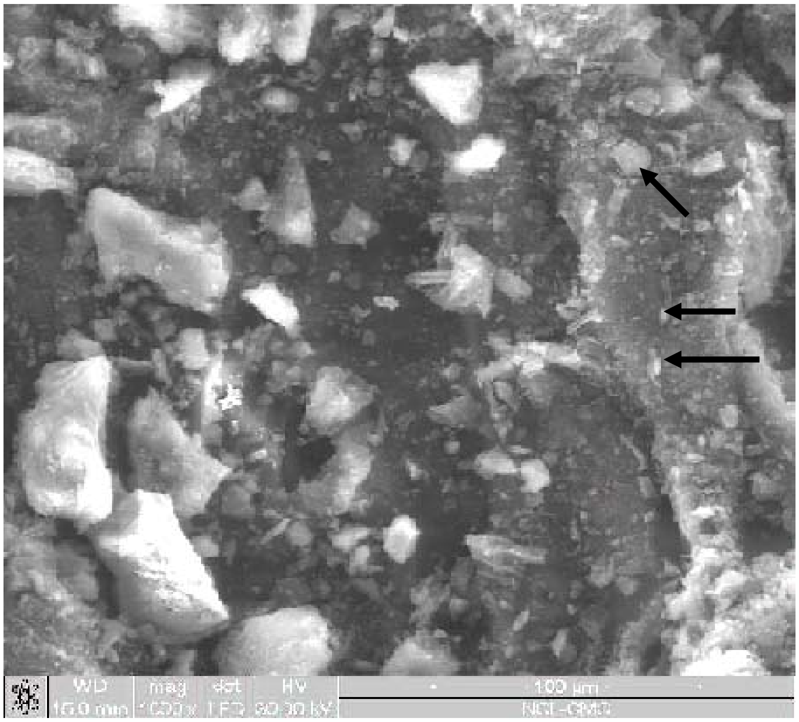


Figure 3.24: SEM micrograph for 5% Pt/C

3.2.2.3 Experimental setup and procedure for CTH reaction using 5% Pt/C

The reactions were carried out in a three-necked glass reactor of 50 ml capacity. The setup used for conducting the experiments is shown in Figure 3.3 in section 3.1.2.3. In a typical experiment, 2.76 gm (44 mmol) of formate salt, water (1.2 gm, 67 mmol) and 1.55 gm (12.6 mmol) of nitrobenzene in 25ml methanol were taken in 50 ml jacketed three necked glass reactor. The glass reactor temperature was kept constant at desired temperature using water circulation bath. The reaction was started by adding 0.2 gm 5%

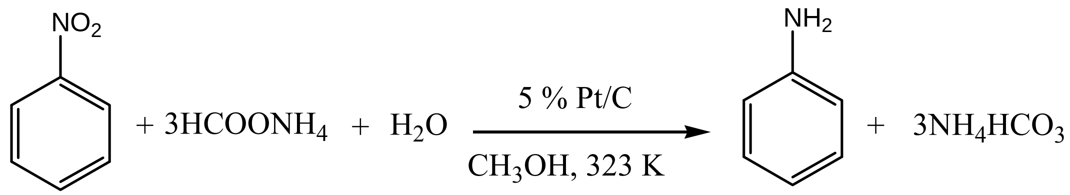
Pt/C to this mixture. The reaction was continued for desired time (generally 3 hours). Samples were withdrawn at regular intervals of time to monitor the progress of reaction. The samples were filtered to remove the solid catalyst. The analysis of the contents of the reaction mixture was done using an Agilent 6850A gas chromatograph, with HP-1 capillary column. The standard conditions for GC analysis are given in Section 3.1.2.4 and Table 3.1.

3.2.3 RESULTS AND DISCUSSION

3.2.3.1 Preliminary experiments

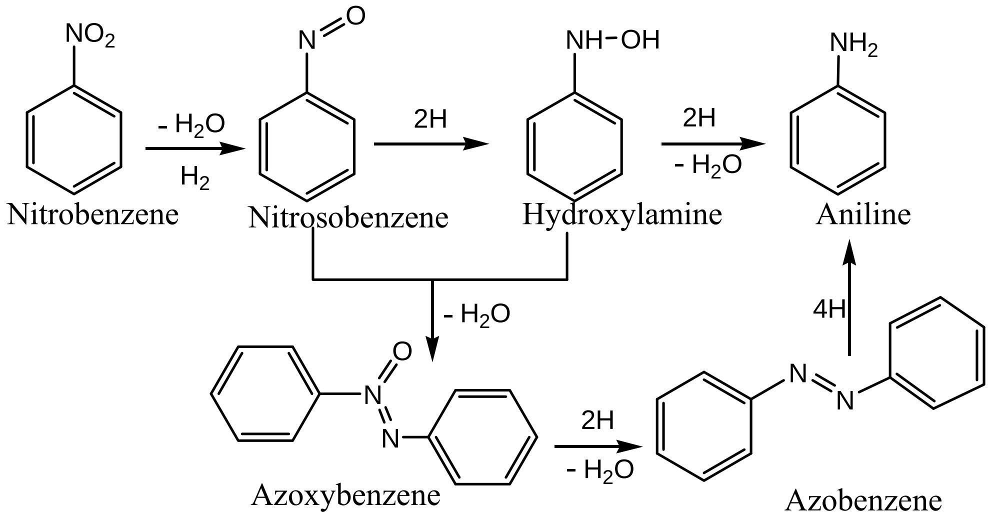
A few preliminary reactions were carried out on transfer hydrogenation of nitrobenzene using 5% Pt/C as a catalyst to access the material balance of the reaction and to select the suitable solvent and hydrogen donor for further study.

Reaction scheme



Scheme 3.2: CTH of nitrobenzene using 5% Pt/C

Preliminary experiments were carried out using ammonium formate as hydrogen donor and methanol a solvent. Intermediate reaction samples were analyzed on GC. It was observed that selectivity to aniline was very high (~ 100%) at higher conversion of nitrobenzene. However at lower conversions, selectivity to aniline was low (up to ~85%). Formation of intermediate products azoxybenzene and azobenzene was observed (confirmed by GC-MS analysis) in these reactions, leading to lower selectivity. At higher conversions these intermediates react further giving high selectivity to aniline. The reaction sequence is presented in Scheme 3.3.[18,19]



Scheme 3.3: Intermediates formed during CTH of nitrobenzene over Pt/C catalyst.

3.2.3.1.1 Screening of solvents

Various solvents were screened for transfer hydrogenation of nitrobenzene using ammonium formate as a hydrogen donor at 323K and the results are presented in Table 3.7.

Table 3.7: Screening of Solvent for CTH of nitrobenzene using 5 % Pt/C

Entry	Solvent	Time (min)	Conversion %	% Selectivity to aniline at 30% conversion*
1	Methanol	180	98	95
2	Ethanol	90	99	45
3	IPA	90	99	67
4	n-Butanol	120	98	72
5	n-Hexanol	120	97	82
6	DMAc	180	97	67
7	Acetonitrile	90	99	83

Reaction conditions*-Nitrobenzene, 0.51 kmol/*m^3 *; HCOONH*$_4$*, 1.75 kmol/*m^3*; 5% Pt/C, , 8 kg/*m^3*; Solvent,25ml; Temperature, 323K*

** 100 % selectivity was obtained for all experiments with conversion of nitrobenzene above 90 %*

It was observed that for all the solvents screened complete selectivity to aniline was observed at high conversion (97-99%). However, at lower conversion like 30% the selectivity was low in most of the solvents screened. GC-MS analysis carried out for all the reactions showed the formation of azoxybenzene and azobenzene as intermediates products. Thus as the reaction progressed the intermediate products observed were converted in to aniline as a product with very high selectivity (See scheme 3.3). With methanol as a solvent high selectivity of 95% was observed at 30% conversion also, indicating fast conversion of intermediate product to aniline. GC-MS analysis for this reaction did not show intermediate product after 20 minutes of reaction time. Hence methanol was chosen as a solvent for this study.

3.2.3.1.2 Screening of hydrogen donors

The effect of type of hydrogen donor on CTH of nitrobenzene was studied. Experiments were conducted at the reaction temperature 323K with 1.75 kmol/m^3 donor concentration in aqueous methanol. The results are presented in Figure 3.25.

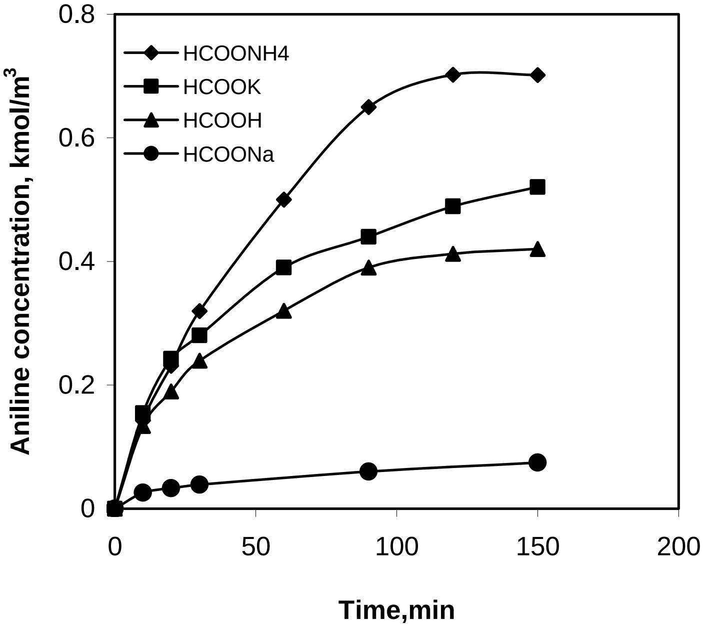


Figure 3.25: Screening of formate salts for transfer hydrogenation of nitrobenzene

Reaction conditions-*Nitrobenzene, 0.51 kmol/m*^{3}*; H-donor, 1.75 kmol/m*^{3}*; 5% Pt/C, , 8 kg/m*^{3}*; Water, 2.7 kmol/m*^{3}*; Methanol, 25ml; Temperature, 323K*

It was observed that ammonium formate exhibited better activity under the conditions employed during the catalytic transfer hydrogenation. In case of sodium and potassium formate as a donor the reaction proceeded slowly as compared to ammonium formate. This might be due to formation of alkali salts in the reaction mixture ($NaHCO_3$ and $KHCO_3$), which can affect the adsorption of reactants on catalyst surface. Ammonium formate will result in the formation of ammonia which can escape in gas phase.[8] As rate of aniline formation was higher in ammonium formate, further work was done using ammonium formate as a hydrogen donor.

The reactions involved in CTH of nitrobenzene using ammonium formate as a hydrogen donor are presented below:[8]

$$R\text{-}NO_2 + H_2O + 3HCO_2NH_4 \rightleftharpoons R\text{-}NH_2 + 3NH_4HCO_3 \tag{1}$$

$$NH_4HCO_3 \longrightarrow NH_4OH + CO_2\uparrow \tag{2}$$

$$NH_4OH \longrightarrow NH_3\uparrow + H_2O \tag{3}$$

Thus when ammonium formate is used as a H-donor, NH_3 and CO_2 are liberated under given operating conditions.

3.2.3.1.3 Effect of water concentration

The effect of concentration of added water in the solvent was studied for CTH of nitrobenzene using ammonium formate as hydrogen donor. The results are represented in Figure 3.26. It was observed that rate of formation of aniline depends on the concentration of water present in the system. The experimental results indicate that reaction with 5% aqueous solvent gave maximum reaction rate. Above 5% aqueous concentration the reaction rate decreased. It was also observed that when water is not added to reaction mixture, the selectivity of initial sample (at 10-20% conversion of nitrobenzene) was 85 %, which was increased to 98 % with the addition of 5 % water to methanol. In Pd/C catalyzed transfer hydrogenation of nitrobenzene as discussed in section 3.1.3.2.4, it was also found that the rate of reaction decreases with increase in concentration of water.

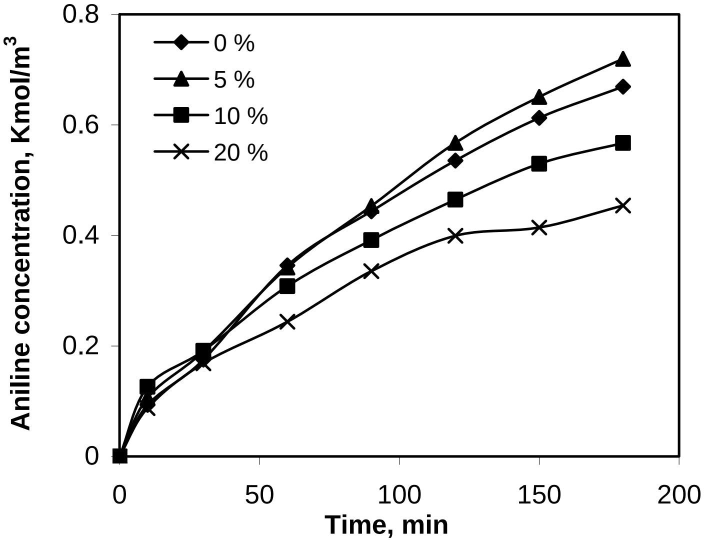


Figure 3.26: Effect of water concentration on CTH of nitrobenzene using 5% Pt/C
Reaction conditions-*Nitrobenzene, 0.51 kmol/m*^{3} *; HCOONH*$_4$*, 1.75 kmol/m*^{3}*; 5% Pt/C, 8 kg/m*^{3}*; Methanol, 25ml; Temperature, 323K*

3.2.3.2 Parametric study of CTH of nitrobenzene using 5% Pt/C catalyst

A typical concentration-time (C-T) profile for CTH of nitrobenzene using 5 % Pt/C catalyst and ammonium formate as a hydrogen donor is presented in Figure 3.27. A good mass balance between the amount of nitrobenzene consumed and the product aniline formed was observed. It was observed that complete conversion of nitrobenzene was achieved in 180 minutes at temperature of 323 K.

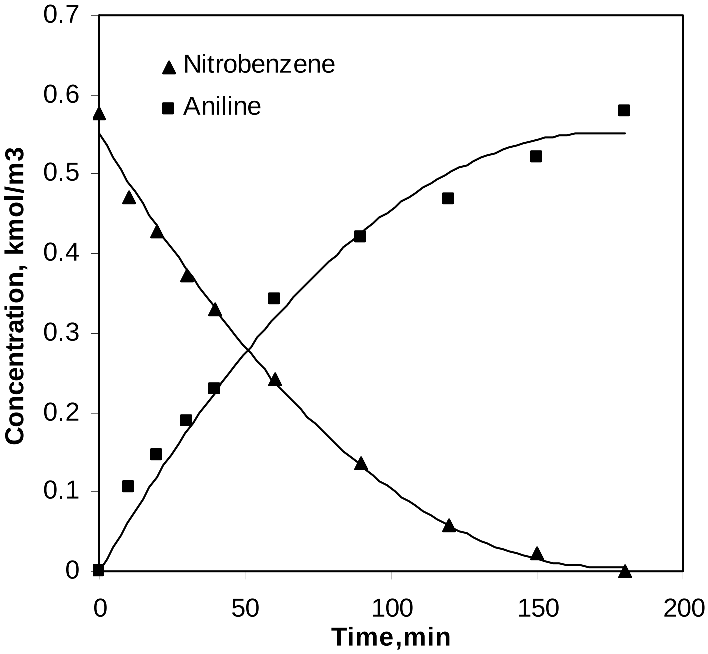


Figure 3.27: Typical C-T profile for CTH of nitrobenzene using 5 % Pt/C
Reaction conditions-*Nitrobenzene, 0.51 kmol/m^3 ; $HCOONH_4$, 1.75 kmol/m^3; H_2O, 2.69 kmol/m^3;5% Pt/C, 8 kg/m^3; methanol, 25ml; Temperature, 323K*

In order to study the kinetics of CTH of nitrobenzene the experiments were carried out in the range of conditions as shown in Table 3.8. The initial rates of transfer hydrogenation were calculated from the plots of product formation as a function of time as shown by formula:

$$R=\frac{\text{Slope of product formation vs. time plot}}{\text{Total volume of liquid}}$$

Table 3.8: Range of conditions used for parametric study

Concentration of 5% Pt/C, kg/m^3	4-12
Concentration of nitrobenzene, kmol/m^3	0.25-1.0
Concentration of ammonium formate, kmol/m^3	0.875-3.5
Temperature (K)	323
Solvent	Methanol
Reaction volume (cm^3)	25

The results showing the influence of different reaction parameters on the rate of the reaction are discussed below.

3.2.3.2.1 Effect of catalyst concentration on the rate of reaction

The effect of the catalyst concentrations on the rate of reaction was studied at nitrobenzene concentration of 0.51 kmol/m^3, ammonium formate concentration of 1.75 kmol/m^3, and H_2O concentration of 2.69 kmol/m^3 at 323 K. The results are presented in Figure 3.28.

The rate was found to have a first order dependence on the catalyst concentration. This is expected, as increase in catalyst concentration will lead to increase in number of active sites for hydrogenation, and hence the rate.

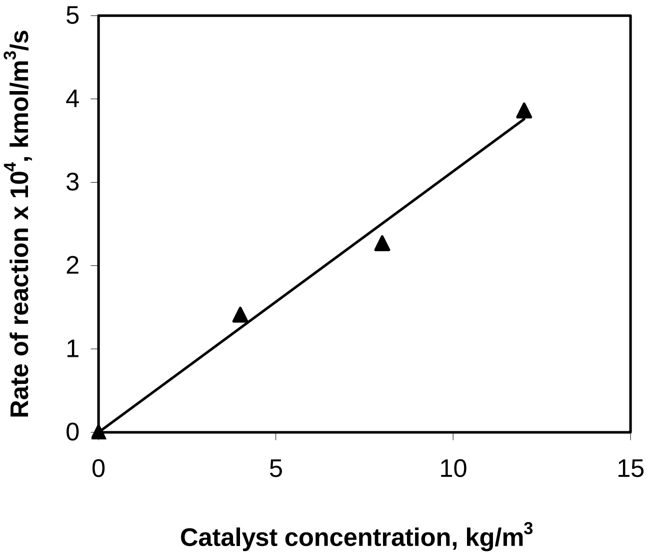


Figure 3.28: Effect of catalyst concentration on the observed initial rate

Reaction conditions*-Nitrobenzene, 0.51 kmol/m^3 ; $HCOONH_4$, 1.75 kmol/m^3; H_2O, 2.69 kmol/m^3; methanol,25ml; Temperature, 323 K*

3.2.3.2.2 Effect of nitrobenzene concentration on the rate of reaction

The effect of nitrobenzene concentration on the rate of transfer hydrogenation was investigated at constant ammonium formate, H_2O and catalyst concentrations of 1.75, 2.69 kmol/m^3 and 8 kg/m^3, respectively; at 323 K. The results are presented in Figure 3.29.

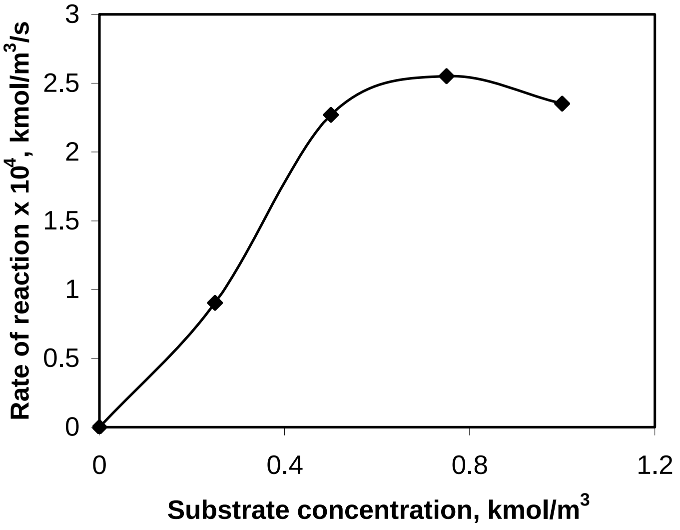


Figure 3.29: Effect of substrate concentration on the observed initial rate
Reaction conditions- *$HCOONH_4$, 1.75 kmol/m^3; H_2O, 2.69 kmol/m^3;5% Pt/C, 8 kg/m^3; methanol, 25ml; Temperature, 323 K*

The rate was found to increase with increase in nitrobenzene concentration up to the nitrobenzene concentration of 0.75 kmol/m^3. Above this concentration rate decreases slightly. The rate decrease at higher concentration suggests that with higher concentration of nitrobenzene the active sites become saturated with nitrobenzene and are less available for activation of other reactants like water and formate.

3.2.3.2.3 Effect of ammonium formate concentration on the rate of reaction

The effect of ammonium formate concentration on the rate of transfer hydrogenation was investigated at constant nitrobenzene, H_2O and catalyst concentrations of 0.51, 2.69 kmol/m^3 and 8 kg/m^3 respectively at a temperature of 323 K. The results are presented in Figure 3.30. The rate was found to increase with ammonium formate concentration in the lower concentration range (<1.75 kmol/m^3). With further increase in ammonium formate concentration the rate increased only marginally. This may be due to saturation of active sites of catalyst by ammonium formate which may lead to reduced access to other reactants like water and substrate.

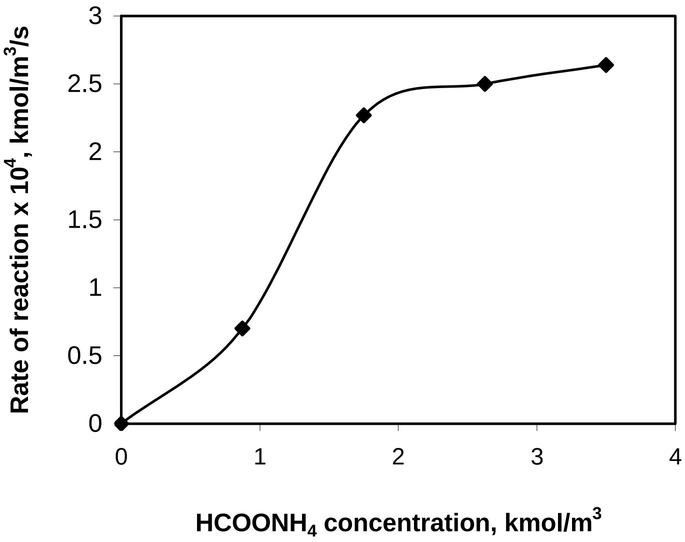


Figure 3.30: Effect of ammonium formate concentration on the observed initial rate
Reaction conditions-*Nitrobenzene, 0.51 kmol/m*^{3}*; H*$_2$*O, 2.69 kmol/m*^{3}*;5% Pt/C, 8 kg/m*^{3}*; methanol,25ml; Temperature, 323 K*

3.2.3.2.4 Effect of temperature

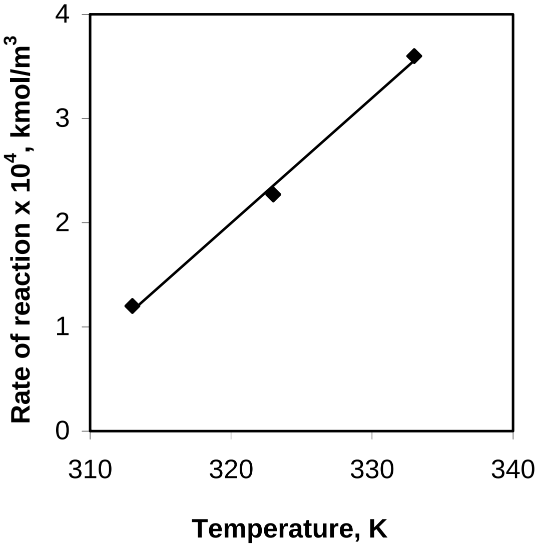


Figure 3.31: Effect of temperature on CTH of nitrobenzene using 5% Pt/C catalyst
Reaction conditions-*Nitrobenzene, 0.51 kmol/m*^{3} *; HCOONH*$_4$*, 1.75 kmol/m*^{3}*; 5% Pt/C, 8 kg/m*^{3}*; Water, 2.7 kmol/m*^{3}*; Methanol,25ml.*

The effect of temperature on the initial rate of reaction was investigated in a temperature range of 313-333 K. Rate of reaction increases linearly with increase in temperature as shown in Figure 3.31.

3.2.4 CONCLUSIONS

The detailed study on CTH of nitrobenzene was carried out using 5% Pt/C catalyst and ammonium formate as a hydrogen donor in methanol-water solvent system. The effect of different parameters viz., concentrations of nitrobenzene, catalyst and donor (formate salt) on the initial rate of the reaction was investigated at a temperature of 323K. It was found that the rate increases with increase in catalyst concentration and decreases with increase water concentration. The linear increase in rate with increase in nitrobenzene concentration was observed up to 0.75 kmol/m^3 concentration of nitrobenzene. Above this concentration rate decreases slightly. The rate was found to increase with ammonium formate concentration in the lower concentration range (<1.75 kmol/m^3). With further increase in potassium formate concentration the rate increased only marginally. The results of these effects indicates that like the Pd/C catalyst, all the three substrates (nitrobenzene, water and formate) are adsorbed in a competitive manner onto a active site on the catalyst surface. Therefore excess of any reactant would be unfavorable for rest of the species to adsorb on the catalyst surface; resulting in lower rates of reaction.

From the results presented for CTH reaction of nitrobenzene, using 5% Pd/C and 5% Pt/C catalysts, following observations can be concluded.

- Depending on solvent used, higher activity was obtained with potassium formate for palladium catalyzed reaction (ethanol solvent) and with ammonium formate for platinum catalyzed (methanol solvent) CTH reaction.
- Optimum relative concentrations of the three components (nitrobenzene, water and formate salt) are necessary to achieve high activity for 5% Pd/C as well as for 5% Pt/C catalyst.
- Substrate (nitrobenzene) inhibition was observed for 5% Pd/C catalyzed reaction. For 5% Pt/C catalyzed reaction the substrate inhibition was less severe.

REFERENCES

1 R. A. W. Johnstone, A. H. Wilby, I. D. Entwistle, *Chemical Reviews* **1985**, *85*, 129.

2 B. Basu, S. Das and P. Das, *Molecular Diversity* **2005**, *9*, 259.

3 I. D. Entwistle, A. E. Jackson, R. A. W. Johnstone, R. P. Telford, *Journal of the Chemical Society, Perkin Transactions 1* **1977**, 443.

4 S. Ram, R. E. Ehrenkaufer, *Synthesis-Stuttgart* **1988**, 91.

5 D. C. Gowda, and S. Gowda, Indian Journal of Chemistry - Section B Organic and Medicinal Chemistry **2000**, 39, 709.

6 K.Prasad, X.L. Jiang, J.S. Slade, J. Clemens, O.Repic and T.J. Blacklock, *Advanced Synthesis & Catalysis* **2005,** *347*,1769.

7 H. Wiener, J. Blum, Y. Sasson, *Journal of Organic Chemistry* **1991**, *56*, 4481.

8 P. Haldar, V. V. Mahajani, *Chemical Engineering Journal* **2004**, *104*, 27.

9 S. Hub, L. Hilaire and R. Touroude, *Applied Catalysis* **1988,** *36,* 307.

10 (a)M. K. Anwer, D. B. Sherman, J. G. Roney, A. F. Spatola, *Journal of Organic Chemistry* **1989**, *54*, 1284. (b)S. Rajagopal, A. F. Spatola, *Journal of Organic Chemistry* **1995**, *60*, 1347.

11 D. M. Ruthven, R. S. Upadhye, *Journal of Catalysis* **1971**, *21*, 39.

12 G. Cavinato, L. Toniolo, Journal of Molecular Catalysis A: Chemical **1996**, 106, 25.

13 S. Rajagopal, A. F. Spatola, *Journal of Organic Chemistry* **1995**, *60*, 1347.

14 A. Zoran, Y. Sasson, J. Blum, *Journal of Molecular Catalysis* **1984**, *26*, 321.

15 D.W.J. Marquardt, *Soc.Ind.Appl.Math*.**1963**, *11*,431

16 S. Rajagopal, A. F. Spatola, *Applied Catalysis A: General* **1997**, *152*, 69.

17 D. Channe Gowda, B. Mahesh, *Synth. Commun.* **2000,** *30*, 3639.

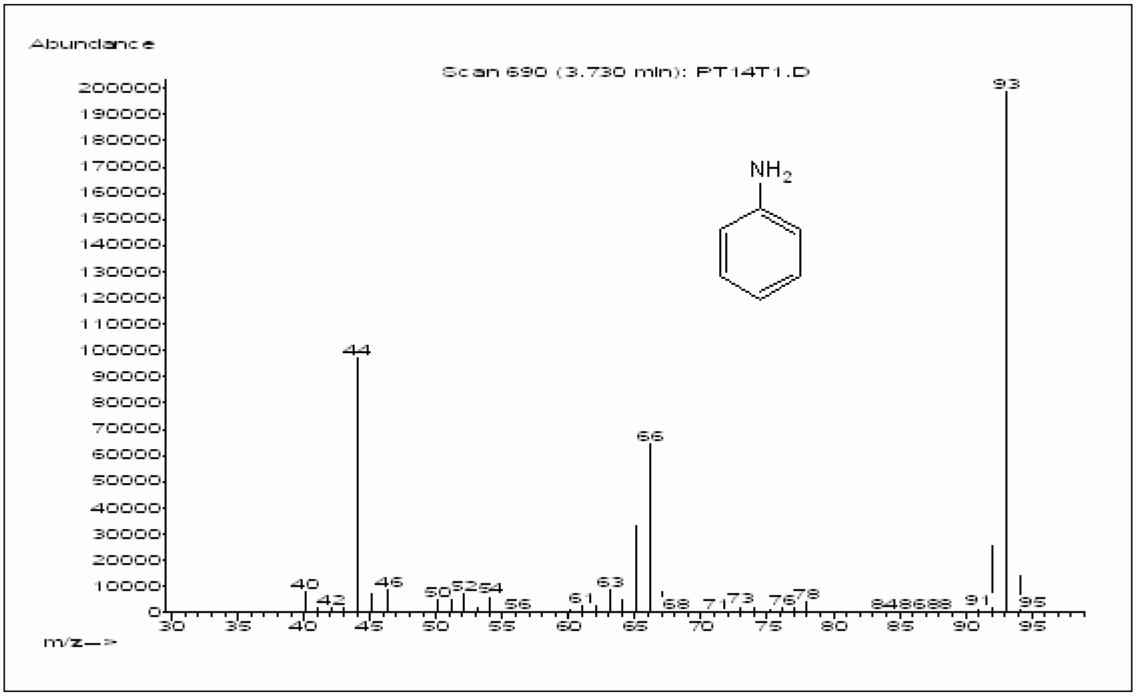
18 J. March, *Adv. Org. Chem.* **1992**,1217

19 V. Holler, D. Wegricht, I. Yuranov, L. Minsker, A. Renken, *Chemical Engineering Technology 2000*, *23*, 251.

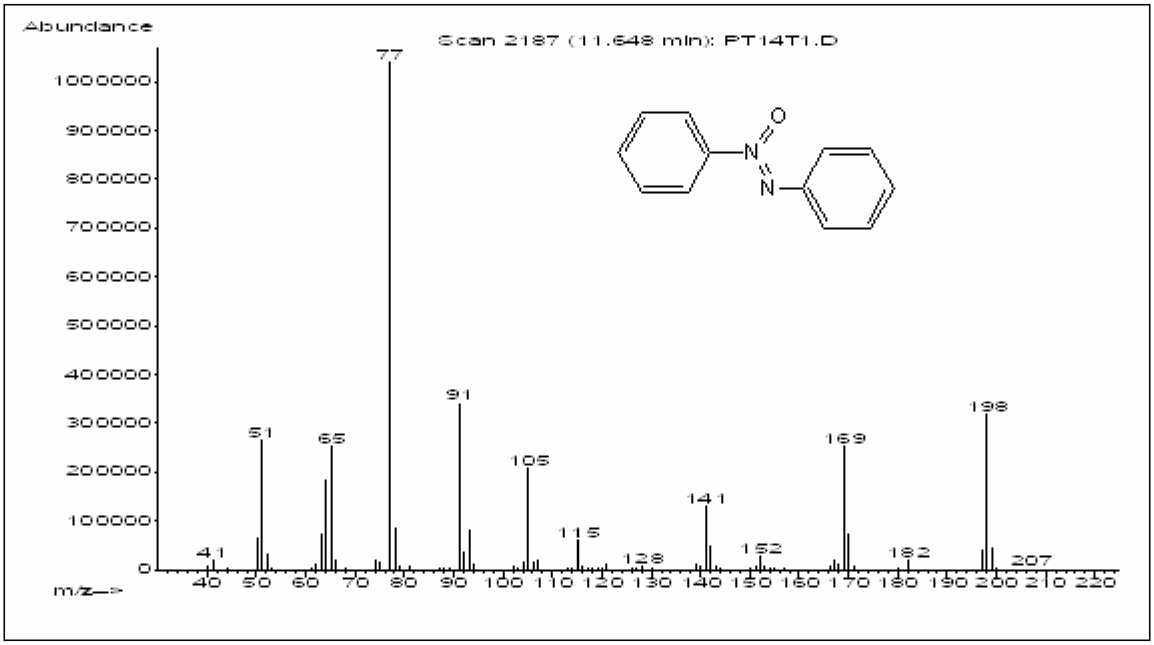
SPECTRA

GC-MS Spectra (70 eV, EI)

1. Aniline



2. Azoxybenzene



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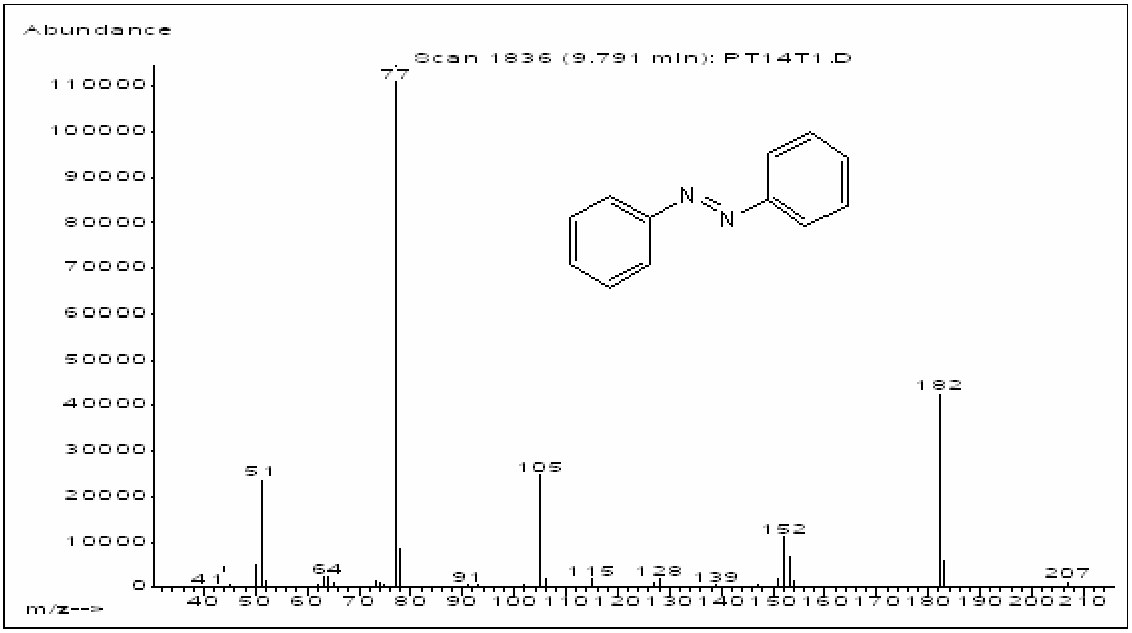


Chapter 4

Transfer Hydrogenation of α-β Unsaturated Carbonyl Compounds in Aqueous Biphasic Medium Using Water Soluble Rh/TPPTS Catalyst.

4.1 INTRODUCTION

Homogeneous catalysts offer a number of important advantages over their heterogeneous counterparts, like (i) high activity, as the catalysts are usually a dissolved metal complex and hence all catalytic sites are accessible, (ii) possibility to tune the chemoselectivity, regioselectivity, and/or enantioselectivity of the catalyst by proper choice of ligands. However, inspite of the obvious advantages many homogeneous catalytic systems cannot be commercialized because of difficulties associated with catalyst-product separation and catalyst recovery/recycle, especially for expensive noble metal catalysts. In most of the reactions, the products are non-volatile and thermally unstable and hence their separation from catalysts poses a serious challenge. To overcome these difficulties several new strategies are being developed to heterogenize the homogeneous catalysts. These catalysts could then combine the advantages of homogeneous catalyst i.e. high activity and selectivity, with those of heterogeneous catalyst i.e. longer lifetime and ease of separation. Different methodologies for the heterogenization of the catalyst have been proposed. These include immobilization of homogeneous catalysts on solid supports or heterogenization as a soluble catalyst in a different phase. The latter is generally termed as biphasic catalysis. Various biphasic catalytic systems are described in Chapter 1, section 1.5.1.

Biphasic catalysis has been one of the most significant developments in past few decades.[1] The emergence of aqueous biphasic catalysis has extended the scope of homogeneous catalysis by simplifying the catalyst recovery from the product mixture and its subsequent recycle. In aqueous biphasic catalysis, the water soluble catalyst is used. The catalyst is insoluble in the organic phase containing reactants and products, and brings about the particular transformation in the aqueous phase. It is then separated from the desired product (organic phase) at the end of reaction by simple phase separation and decantation. The research on water-soluble catalysis gained momentum only after the work of Kuntz et al.[2] on the synthesis of triphenylphosphine trisulfonate (TPPTS) ligand. The concept has been proven on a commercial scale for the hydroformylation of propene to butyraldehyde by Ruhrchemie-Rhône-Poulenc using Rh/TPPTS catalyst.[3] Other applications of biphasic catalysis have been listed in Table 1.5 in Chapter 1.

The development of polar and water-soluble ligands and their incorporation into organometallic complexes is integral to aqueous phase catalysis. Water-soluble ligands containing phosphorous and nitrogen as donor atoms are some of the most commonly utilized ligands. TPPTS and TPPMS are some of the most well known ligands for the aqueous-biphasic hydrogenation as well as for transfer hydrogenation.

The literature on aqueous biphasic catalysis for transfer hydrogenation of α-β unsaturated carbonyl compounds has already been discussed in detail in Chapter 1, section 1.5. Numerous ruthenium and rhodium based catalysts have been used for hydrogenation of α-β-unsaturated carbonyl compounds under biphasic conditions. Using sodium formate as hydrogen donor, the water soluble Ru complexes like $RuCl_2(TPPMS)_2$[4,5], $[(\eta^6\text{-}C_6Me_6)Ru(bpy)(H_2O)]SO_4$[6], $RuCl_2(PTA)_4$[7], $[Cp^*Ir^{III}(H_2O)_3]^{2+}$ [8] are used to selectively reduce the carbonyl group of unsaturated aldehydes or ketones to give unsaturated alcohols. The Rh complex catalysts such as $[Rh(COD)Cl]_2$/TPPTS[9-11] , $[Rh(PTAH)(PTA)_2Cl]Cl$[12] and $[Rh(cod)\{PTN(Ph)\}](BAr^F{}_4)$[13] have been used to selectively reduce the C=C bond of various α-β unsaturated carbonyl compounds giving saturated aldehydes or ketones using HCOOM ($M= Na^+,K^+,NH_4^+$) as hydrogen donor under biphasic conditions.

As evident from the literature, the majority of the work has been done for development of catalytic systems for selective transfer hydrogenation under biphasic conditions and very little work has been done on kinetic study. The studies on kinetics are restricted to a single temperature only. It was observed that the catalyst activity was strongly dependent on the solubility of substrates in aqueous phase. The transfer hydrogenation activity decreased substantially with decrease in solubility of aldehydes in aqueous phase.[14] To circumvent these problems, generally, the reaction can be conducted in the presence surface active agents[15,16] or co-solvent.[17,18] The catalyst may also be supported on silica (SAPC) to obtain an efficient reaction.[19] For industrial application, the use of co- solvent is generally preferred over the SAPC or surface active agents modified systems. However the use of co-solvent in biphasic transfer hydrogenation is not yet explored.

In this chapter the aqueous biphasic transfer hydrogenation of α-β unsaturated carbonyl compounds has been investigated in detail using Rh-TPPTS catalyst complex.

The effect of co-solvents, their composition in aqueous phase and some reaction parameters have been studied using methyl cinnamate as a model substrate. The detailed kinetic study on transfer hydrogenation of trans cinnamaldehyde using water soluble $[Rh(COD)Cl]_2$/TPPTS catalyst and sodium formate as a hydrogen donor, in a temperature range of 313-333 K has been presented in this chapter.

4.2 EXPERIMENTAL SECTION

4.2.1 Materials

Rhodium trichloride ($RhCl_3$. $3H_2O$), obtained from Arora-Matthey was used as received. Cinnamaldehyde, chalcone, benzylidiene acetone, methyl cinnamate, ethyl cinnamate, cinnamic acid, citral, and crotonaldehyde were obtained from Sigma-Aldrich, USA and used as received. $(Rh(Cp^*Cl)_2)_2$ was procured from Strem chemicals. Sodium formate, formic acid, ammonium fomate and potassium formate were procured from Loba Chemie, India. The solvents, toluene, cyclohexane, NMP, DMAc, bromobenzene, chlorobenzene, ethanol, acetonitrile, DMF etc. were freshly distilled, dried and degassed prior to use. Oleum of 65% (w/w of SO_3 in H_2SO_4) strength was prepared by dissolving the SO_3 gas (produced from the reaction of H_2SO_4 with P_2O_5) in concentrated H_2SO_4 in required proportion. Distilled degassed water was used in all operations.

4.2.2 Synthesis of TPPTS and transition metal complexes

The transition metal complexes and TPPTS ligand were prepared as per known literature procedure described in the following sections. The ligand and complexes formed were characterized thoroughly. ^{31}P NMR and ^{1}H NMR spectra were obtained on a Bruker AC-200 or MSL-300 spectrometer in $CDCl_3$ at room temperature. The peak positions are reported with positive shifts in ppm downfield of external H_3PO_4 (^{31}P). FT-IR spectra were recorded on a Bio-Rad Spectrophotometer 175C

4.2.2.1 Synthesis of TPPTS

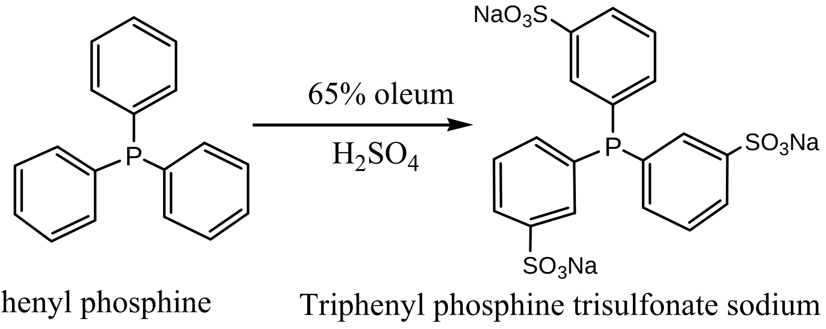
Sulfonated phosphines are useful ligands for preparing water-soluble catalysts, for biphasic catalysis. Triphenyl phosphine trisulfonate (TPPTS) forms complexes with most of the transition metals, just like triphenyl phosphine (TPP)[20] and hence can be widely used for a variety of reactions. Moreover, it has a higher solubility in water (1.1 kg/l) as compared to other phosphines.[21] For the synthesis of TPPTS a procedure standardized by Bhanage et al. was used.[22]

Sulfonation reactor set up

For synthesis of triphenyl phosphine trisulfonate (TPPTS), a double-jacketed 1 L glass reactor equipped with a high-speed half-moon stirrer was used. This reactor was designed so that operation under argon atmosphere was possible. The temperature was controlled by circulation of water at a constant temperature using a cryostat. A similar reactor of larger volume was used for neutralization of the crude reaction mixture. The procedure used was similar to that reported in the literature.[22]

Procedure

Reaction Scheme



Scheme 4.1: Synthesis of TPPTS ligand

Reaction charge for the synthesis of TPPTS

SO_3/TPP =12 (molar ratio)

$SO_3/(SO_3 + H_2SO_4 + TPP) = 34\%$ (w/w)

$H_2SO_4/(SO_3 + H_2SO_4 + TPP) = 56\%$ (w/w)

200 g of 98% pure sulfuric acid was introduced into the sulfonation reactor. The acid was cooled under constant stirring to 12-15ºC by means of a cryostat. 50 g of triphenyl phosphine (TPP) (190.75 mmol) was introduced slowly at 15ºC over a period of 30-45 min. This gave a homogeneous yellow colored solution of TPP in sulfuric acid.

280 g (141 ml, d=1.98 at 35ºC) of 65% oleum (SO_3 content: 2.275 mol) was transferred into the addition funnel from the oleum receiver. This oleum was then introduced in the sulfonation reactor containing TPP solution in sulfuric acid, over a period of 40-45 minutes maintaining a maximum temperature of 15ºC with rapid stirring. The temperature of the reaction mixture was then raised to 22ºC and was maintained for 76 hours using a cryostat. This step of keeping the reaction mixture at 22ºC is critical for optimum yield of TPPTS. Thereafter, the temperature of the reactor was lowered to ~ 10ºC and 50 g of distilled water was introduced while maintaining the temperature at 10ºC. This addition is necessary to quench the excess SO_3 present after the sulfonation reaction is complete. The addition of water is highly exothermic, and hence temperature was maintained at < 10ºC while adding water. This gave a solution of sulfonated triphenyl phosphine in sulphuric acid. This reaction mixture was further diluted to approximately 800 ml under cooling (10ºC). This diluted solution was then transferred into a neutralization reactor under argon atmosphere. The reactor was similar to the reaction vessel but of a larger capacity (~3 liters). The solution was neutralized using 50% (w/w) degassed sodium hydroxide solution maintaining 10ºC temperature. The reaction mixture obtained was in a slurry form. The neutralized mixture was then filtered and the filtrate was evaporated under reduced pressure at 50-60ºC till the volume reduced to about 250 ml from the initial two liters. 1.5 liters of methanol was added to the above solution and the mixture was refluxed under argon atmosphere for 2 hours. TPPTS dissolved in methanol completely, which was filtered hot, with the solid residue comprising only sodium sulphate. The filtrate was evaporated under reduced pressure. The solid TPPTS obtained was recrystallized from ethanol, weighed and stored under argon atmosphere. The yield was found to be 80-85%.

^{31}P NMR analysis shows singlet at δ= -5.15 (TPPTS) and δ= 35.22 (OTPPTS) which is consistent with that reported in the literature[23], showing approximately 95% TPPTS and 5% OTPPTS formation as shown in Figure 4.1. No further purification of TPPTS was undertaken for use as a ligand for the preparation of water-soluble catalyst precursors.

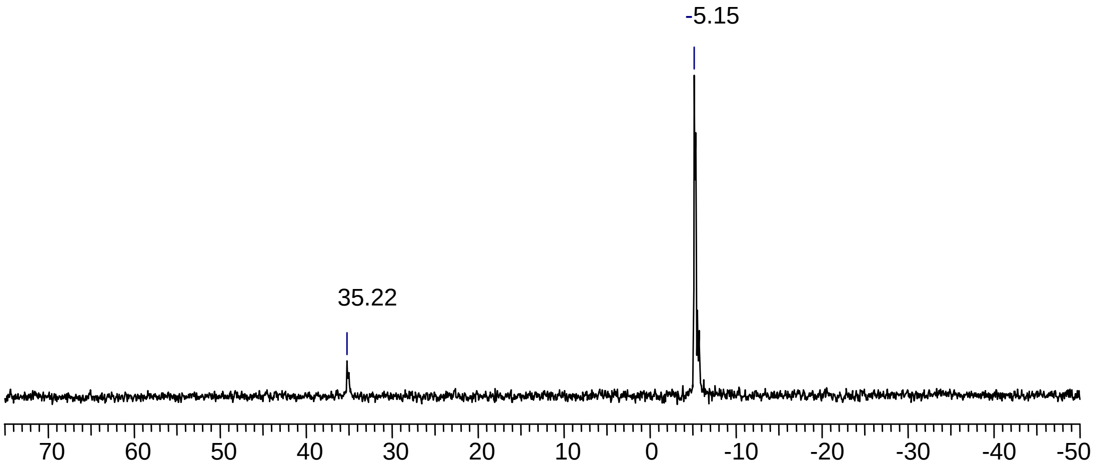


Figure 4.1: ^{31}P NMR spectrum of TPPTS

4.2.2.2 Synthesis of [Rh(Cp*Cl)$_2$]$_2$

[Rh(Cp*Cl)$_2$]$_2$ complex was prepared by standard procedure[24], given in Chapter 2 section 2.2.2.2.

4.2.2.3 Synthesis of [Rh(COD)Cl]$_2$

[Rh(COD)Cl]$_2$ was prepared according to a procedure reported by Chatt and Venanzi.[25] Rhodium trichloride trihydrate (1 g, 4.77 mmoles) in ethanol (30 ml) was boiled under reflux with a solution of 1, 5 cyclo-octadiene (COD) (2 ml) for 3 hours. The solution was cooled and the orange solid filtered, washed with ethanol and dried. (Yield, 0.7 g, 60%). Characteristic IR shifts for this complex at 2874 cm^{-1}(C-H stretching), 1468 cm^{-1}(C=C stretching) and 960cm^{-1} (C-H bending) are shown in Figure 4.2. The elemental analysis of [Rh(COD)Cl]$_2$ calculated was in agreement with theoretical values. (Found: C=39.1%; H=4.85%; Cl=14.3%. Calculated: C=39.05%; H=5.0%; Cl=14.4%).

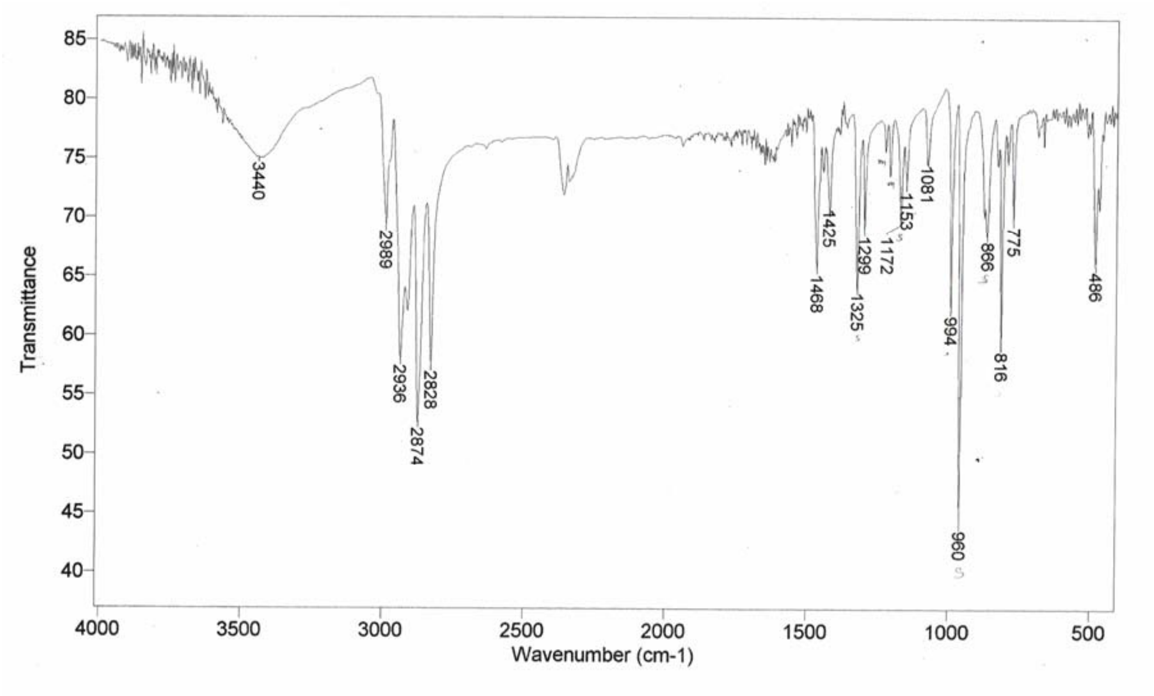


Figure 4.2: FTIR spectrum of $[Rh(COD)Cl]_2$

4.2.3 Experimental set up for transfer hydrogenation

A high pressure autoclave manufactured by Parr (USA) of capacity 50 ml was used for the reactions. Although CTH does not require a pressure apparatus, it was preferred to use a reactor to maintain effective stirring and inert atmosphere. The reactor was provided with arrangements for sampling of liquid and gaseous contents. It was also provided with automatic temperature control and variable agitation speed. A schematic diagram of the experimental set up is shown in Figure 4.3.

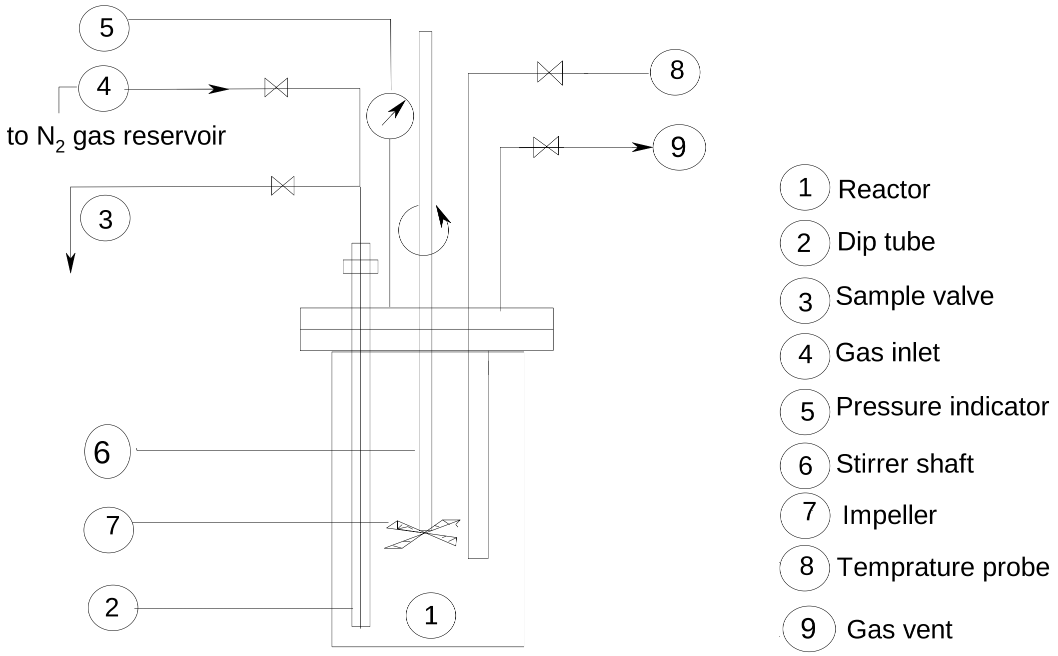


Figure 4.3: A schematic of the reactor setup used for the reaction

4.2.4 Experimental procedure

In a typical experiment, $[Rh(COD)Cl]_2$ (0.01 mmol) and TPPTS (0.12 mmol) were dissolved in degassed water (18 ml) under nitrogen atmosphere in a 50 ml stainless steel autoclave at room temperature. To this yellow colored solution, sodium formate (51 mmol) was added and allowed to dissolve completely under nitrogen atmosphere. Then a solution of the substrate (10 mmol) in degassed toluene (12 ml) was added to the autoclave. (N.B.: In the experiments when co-solvent was used, it was added before the addition of organic phase).The autoclave was flushed several times with 50 psig of N_2 and then heated to required temperature under low stirring (200 rpm). The reaction was initiated by increasing the stirring speed to 1200 rpm. The reaction was then continued under nitrogen atmosphere (~50 psi pressure). After the completion of reaction, the reactor was cooled and a final sample was taken for analysis. In each kinetic run, intermediate samples were withdrawn at specific time intervals and analyzed for reactants and products in order to check the progress of the reaction and material balance. The reproducibility of the experiments was found to be in a range of 5-7%. Following this procedure, the effect of the catalyst, aldehyde and formate concentrations and temperature on the rate of transfer hydrogenation was studied.

4.2.5 Analytical methods

The analysis of the contents of the reaction mixture was done using Agilent 6850 series II gas chromatograph, on HP-I capillary column of 30 m length, 320µm diameter, and 0.25µm stationary phase film thickness (methyl siloxane as stationary phase, helium gas as the mobile phase) and a Flame Ionization Detector. The GC was equipped with an auto sampler. The quantitative analysis was done using a calibration curve prepared using synthetic standards in the range of concentration studied. Mass balance was obtained from the quantitative GC analysis. Conditions for GC analysis are given in Table 4.1. The reaction products were identified using GC-MS, (Agilent GC 6890N with 5973 mass selective detector).

Table 4.1: Conditions for GC analysis

Injector (split) Temperature	250ºC		
Flame ionization detector Temp	300ºC		
Inlet flow–total (He)	96.4 ml/min		
Split ratio for Injector	50:1		
Column Temperature	Rate (ºC /min)	T (ºC)	Hold time (min)
		80	1
	20	120	4
	20	220	1
	30	300	0
Column Pressure	Constant Pressure 10 Psi		

A typical GC chart (Figure 4.4) shows the reactant (cinnamaldehyde) and product (hydrocinnamaldehyde) under the analysis condition given in Table 4.1

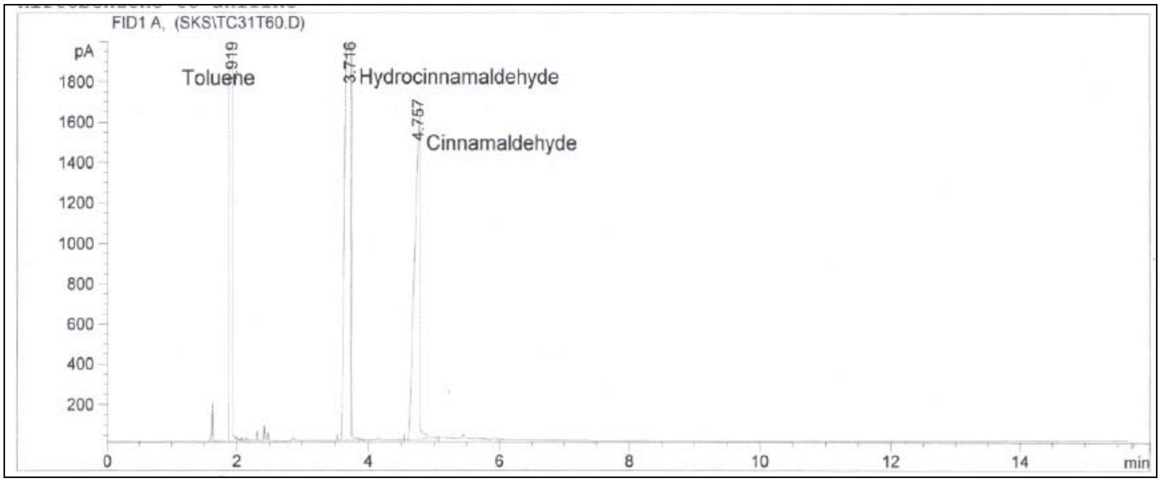


Figure 4.4: A typical GC chart showing the reactant CALD and product HCALD.

The percent conversion and percent selectivity were calculated using the formulae given in Chapter 3, section 3.1.2.4 equations 3.1 to 3.2. The turn over frequency (TOF h^{-1}) was calculated using the formula given below:

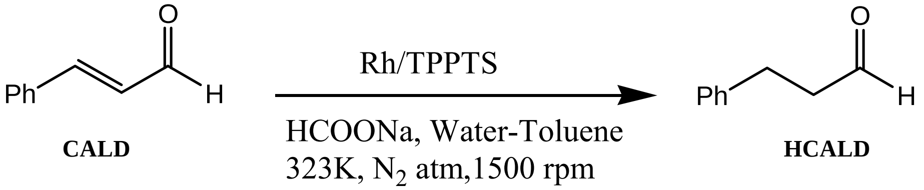
$$\mathrm{TOF}(h^{-1}) = \frac{\text{No. of moles of product formed}}{\text{No. of moles of catalyst x time in hours}}$$

4.3 RESULTS AND DISCUSSION

4.3.1 Preliminary experiments

Preliminary experiments were carried out on the transfer hydrogenation of CALD under aqueous biphasic conditions to find suitable precatalyst, hydrogen donor and organic solvent for the reaction system to ensure good material balance of the reaction. As reported earlier with Rh metal complexes, the selective reduction of olefinic bond of α,β-unsaturated carbonyl compounds was observed to give saturated aldehyde as the major product as presented in Scheme 4.2.[9-13]

Reaction scheme:



Scheme 4.2: Transfer hydrogenation of CALD using Rh/TPPTS catalyst system.

4.3.1.1 Screening of catalyst precursors for transfer hydrogenation of CALD

A few catalyst precursors were screened for aqueous biphasic transfer hydrogenation of CALD. The results are presented in Table 4.2. It was observed that Rh(I) complex ($[Rh(COD)Cl]_2$) was more active than Rh(III) complexes ($RhCl_3.3H_2O$ and $[Rh(Cp^*Cl)_2]_2$). Brunner et al. have also observed in enantioselective transfer hydrogenation of itaconic acid that when the rhodium precursor is in a higher oxidation state ($RhCl_3.3H_2O$ and $Rh_2(OAc)_4$), the reaction is slower.[26] This may be because Rh(III) complexes require to be reduced to Rh(I) for generating active catalyst.[27] Lowest activity observed for $[Rh(Cp^*Cl)_2]_2$ complex (only 32% conversion in 360 minutes) is probably due to difficulty in removal of Cp* ligand from $[Rh(Cp^*Cl)_2]_2$ precatalyst.

As the $[Rh(COD)Cl]_2$ precatalyst was found more active, it was used for further study.

Table 4.2 Screening of precatalysts for transfer hydrogenation of CALD

Entry	**Catalyst precursor**	**Temp (K)**	**Time (min)**	**Conversion (CALD) (%)**	**Selectivity (HCALD)(%)**	**TOF[a] (h^{-1})**
1	$[Rh(COD)Cl]_2$	323	80	99	100	196
2	$RhCl_3.3H_2O$	323	290	99	100	116
3	$[Rh(Cp^*Cl)_2]_2$	323	360	32	100	13

Reaction condition: *CALD, 0.85 kmol/*$m^3_{(org)}$*; catalyst, 1.1 x* 10^{-3} *kmol/*$m^3_{(aq)}$*; TPPTS, 1.4 x* 10^{-2} *kmol/*$m^3_{(aq)}$*; HCOONa, 1.36 x* 10^{-2} *kmol/*$m^3_{(aq)}$*; toluene,12 ml; water, 18 ml; rpm, 1200;* N_2 *gas, 50 psi;* a-*TOF calculated at the end of reaction*

4.3.1.2 Screening of solvents

Different organic solvents were screened for the aqueous biphasic transfer hydrogenation of CALD. The aqueous phase holdup of 0.6 was used for all reactions. The results on solvent screening are presented in Table 4.3. The results indicate the moderate effect of solvent polarity on conversion of CALD. For halogenated solvents with high dielectric constant catalytic activity was slightly lower (Table 4.3, entries 4, 5) while for non halogenated solvents the catalytic activity was higher in terms of TOF (h^{-1})

(Table 4.3, entries 1, 2, 3). Among non halogenated solvents, toluene was selected as the organic phase solvent for further work.

Table 4.3: Screening of organic solvent on transfer hydrogenation of CALD

Entry	Solvent	Dielectric constant[28]	Conversion (CALD) (%)	Selectivity (HCALD) (%)	TOF[a] (h^{-1})
1	Cyclohexane	2.02	100	100	196
2	p-Xylene	2.27	100	100	196
3	Toluene	2.38	100	100	196
4	Bromobenzene	5.45	95	100	188
5	Chlorobenzene	5.69	93	100	182

Reaction condition: *CALD, 0.85 kmol/*$m^3_{(org)}$*;* [Rh(COD)Cl]$_2$*, 1.1 x* 10^{-3} *kmol/*$m^3_{(aq)}$*; TPPTS, 1.4 x* 10^{-2} *kmol/*$m^3_{(aq)}$*; HCOONa, 2.86 kmol/*$m^3_{(aq)}$*; organic solvent,12 ml; water, 18 ml; T, 323 K ; rpm, 1200; Time; 80min,* N_2 *gas, 50 psi.*

a-TOF calculated at the end of reaction

4.3.1.3 Screening of hydrogen donors

Hydrogen donors like formic acid, potassium formate, ammonium formate and sodium formate were evaluated in biphasic transfer hydrogenation of CALD and the results are presented in Figure 4.5.

Like many other transfer hydrogenation reactions, this reaction also did not proceed with only formic acid as a hydrogen donor.[29] Reaction with ammonium formate was very slow giving 29 % conversion within 180 min. The low activity associated with the ammonium salt probably results from an equilibrium with the liberated NH_3 (as discussed earlier in Chapter 3, section 3.2.3.1.2), which can then compete with formate for coordination to Rh as proposed by Xiao et al.[30] Sodium and potassium formate gave comparable activity (98 % and 96 % conversion at 80 minutes respectively). With sodium formate, a marginally higher conversion was obtained compared to potassium formate. All further work was carried out using sodium formate was as hydrogen donor.

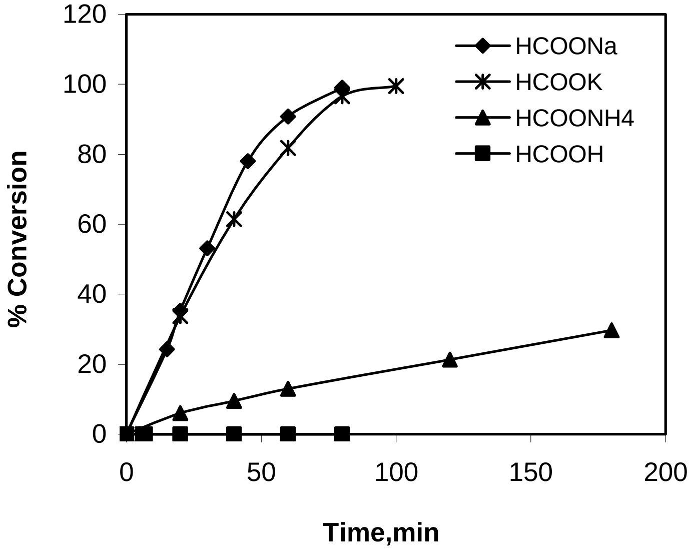


Figure 4.5: Screening of hydrogen donors on transfer hydrogenation of CALD

Reaction conditions: *CALD, 0.85 kmol/*$m^3_{(org)}$*; [Rh(COD)Cl]*$_2$*, 1.1 x* 10^{-3} *kmol/*$m^3_{(aq)}$*; TPPTS, 1.4 x* 10^{-2} *kmol/*$m^3_{(aq)}$*; HCOONa, 2.86 kmol/*$m^3_{(aq)}$*; organic solvent,12 ml; water, 18 ml; T, 323 K; rpm, 1200;* N_2 *gas, 50 psi.*

4.3.1.4 Effect of ligand to rhodium ratio

The effect of ligand to rhodium ratio on activity of transfer hydrogenation of CALD was studied using [Rh(COD)Cl]$_2$ precatalyst in presence of additional TPPTS ligand. The results are presented in Figure 4.6 in terms of average TOF(h^{-1}).

The results indicate that activity was very low for ligand to rhodium ratio 1 and 2. With increase in ligand to rhodium ratio (3 and 6), the activity increased significantly. However with further increase in ratio to 9 or 12 the average activity decreased.

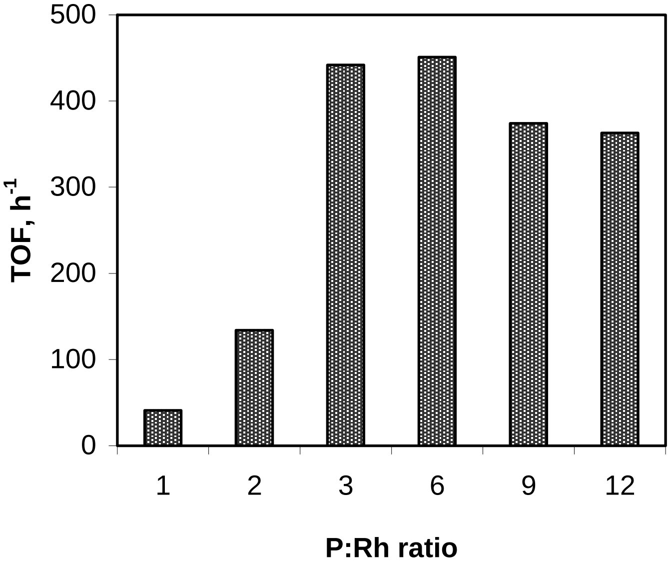


Figure 4.6: Effect of ligand to rhodium ratio on transfer hydrogenation of CALD
Reaction conditions: *CALD, 0.85 kmol/m^3$_{(org)}$; [Rh(COD)Cl]$_2$, 1.1 x 10^{-3} kmol/m^3$_{(aq)}$; HCOONa, 2.86 kmol/m^3$_{(aq)}$; organic solvent,12 ml; water, 18 ml; T, 333 K; Time, 40min rpm, 1200; N$_2$ gas, 50 psi.*

The addition of TPPTS ligand to precursor [Rh(COD)Cl]$_2$ resulted in catalyst formation represented as [P$_3$RhS]$^+$ (where P-TPPTS and S-solvent). The lower activity for ratio 1 and 2 may be because of insufficient ligand concentration for formation of [P$_3$RhS]$^+$ catalyst. Also according to mechanism discussed by Bellefon et al.[10], the first step of mechanism is a de-coordination of one phosphine ligand from [P$_3$RhS]$^+$ catalyst to give a Rh complex containing two phosphine equivalent as shown in Scheme 4.3. (Detail mechanism is discussed in Chapter 1, section 1.5.3).

$$[P_3RhS\,]^+ \underset{+\,P}{\overset{-P}{\rightleftharpoons}} [P_2RhS_2]^+$$

P- TPPTS, S-solvent, Cl is not shown for simplicity

Scheme 4.3: De-coordination of phosphine ligand from the catalyst

At higher concentration of ligand, there is possibility of reverse reaction converting species $[P_2RhS_2]^+$ back to $[P_3RhS]^+$ species, resulting in lower activity of the catalyst (for ligand to rhodium ratio 9 and 12).

As the highest activity was obtained for P:Rh ratio 6, the same ratio is used for further reaction.

4.3.1.5 Effect of substrate to formate ratio

The reaction involves the substrate dissolved in the bulk aqueous phase which along with catalysts contains the hydrogen donor. Hence the substrate to formate ratio also affects the activity. The effect of substrate (CALD) to hydrogen donor (HCOONa) ratio on activity was studied and the results are represented in Figure 4.7.

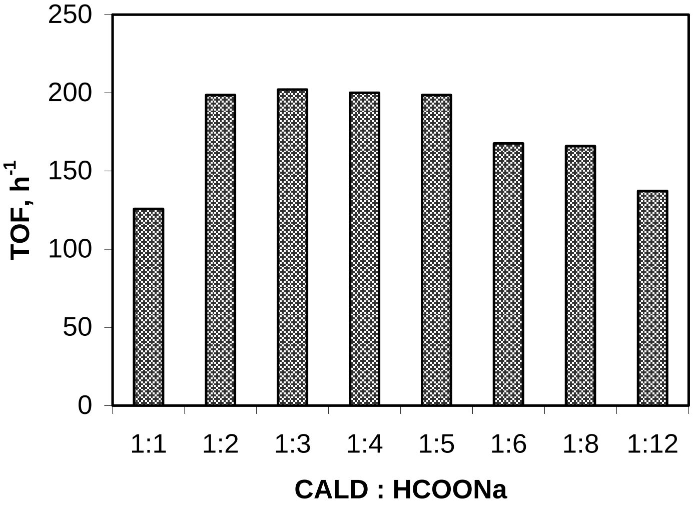


Figure 4.7: Effect of substrate to formate ratio on transfer hydrogenation of CALD

Reaction conditions: *CALD, 0.85 kmol/m$^3_{(org)}$; $[Rh(COD)Cl]_2$, 1.1 x 10^{-3} kmol/m$^3_{(aq)}$; TPPTS, 1.4 x 10^{-2} kmol/m$^3_{(aq)}$; Toluene,12 ml; water, 18 ml; T= 323 K; rpm, 1200; N_2 gas, 50 psi*

The TOFs (h^{-1}) were calculated at 50% conversion of CALD. It was observed that at CALD/HCOONa ratio of 1:1, activity was less (TOF=126h^{-1}). Highest activity was observed for the CALD: HCOONa ratios in the range of 1:2 to 1:5 (TOF= 196h^{-1}). With further increase in the ratio, the activity decreased.

Due to increase in concentration of sodium formate in aqueous phase, ionic strength of aqueous phase increased resulting in lower solubility of substrate in aqueous phase. Hence the activity was found to decrease at high CALD: HCOONa ratio. Similar behavior was observed for aqueous biphasic hydroformylation of 1-octene where increase in concentration of Na_2HPO_4 in aqueous phase resulted in lower rate. The solubility of 1-octene in aqueous phase was decreased because of high ionic strength of aqueous medium.[31]

To ensure that formate concentration is relatively constant for the duration of the hydrogenation, 1:5 ratio of CALD: HCOONa was used for further study.

4.3.1.6 Catalyst recycles study

The activity of the $[Rh(COD)Cl]_2$/TPPTS catalyst on recycle was also investigated at 333K temperature. A recycle experiment was performed by separating the aqueous catalyst phase from the organic phase at the end of reaction, followed by addition of fresh organic phase along with CALD. However for this reaction no conversion of CALD was observed. Hence the recycle experiments were carried out by adding fresh organic phase of CALD along with fresh sodium formate (as per initial charge) to the used aqueous phase. The results are presented in Table 4.4. For virgin run 100% conversion was obtained within 30 minutes, so all the recycle-experiments were carried out for 30 minutes reaction time. It was found that the aqueous catalytic phase was recycled for three times with loss in activity with number of recycle.

Table 4.4: Catalyst recycle study

Recycle No.	**TOF (h^{-1})**	**Rh leaching (%)**
Virgin run	526	0.02 %
1	400	0.025 %
2	339	0.1 %
3	94	1 %

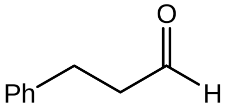
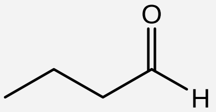
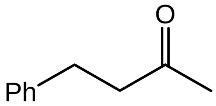
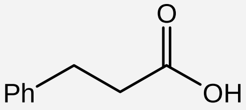
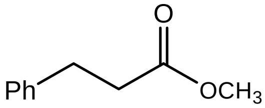
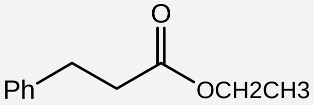
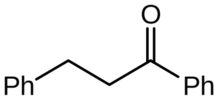
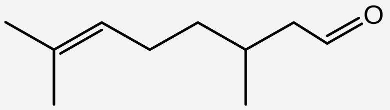
Reaction conditions: *CALD, 0.85 kmol/*$m^3_{(org)}$*;* $[Rh(COD)Cl]_2$*, 1.12 x* 10^{-3} *kmol/*$m^3_{(aq)}$*; TPPTS, 1.36 x* 10^{-2} *kmol/*$m^3_{(aq)}$*; HCOONa, 2.85 kmol/*$m^3_{(aq)}$*; toluene,1.2 x* 10^{-5} m^3*; water, 1.8 x* 10^{-5} m^3*; total volume, 3.0 x* 10^{-5} m^3*; T, 333K; agitation, 1200 rpm;* N_2 *gas,50 psi*

One of the reasons for drop in activity may be because of leaching of Rh in organic phase; however the ICP analysis shows that the Rh leaching was below 1%. It was observed that after each recycle the aqueous layer became cloudy and a white powdery residue settled at the bottom, probably consisting of sodium bicarbonate byproduct. Darensbourge et al. have observed sodium bicarbonate formation in aqueous biphasic transfer hydrogenation of benzaldehyde using $RuCl_2(PTA)_4$ complex.[32] This may result in a decrease in the solubility of cinnamaldehyde in aqueous phase with each recycle leading to lower activity.

4.3.1.7 Screening of substrates

The activity of $[Rh(COD)Cl]_2$ /TPPTS catalyst for transfer hydrogenation of various α-β unsaturated carbonyl compounds was studied in toluene-water biphasic medium using sodium formate as hydrogen donor. The results are presented in Table 4.5. The aqueous phase consists of catalyst and hydrogen donor whereas organic phase consist of substrate or product in toluene solvent. Saturated carbonyl compounds were the only products of hydrogenation, and neither alcohols nor hydrocarbons were detected in the reaction mixtures. For all the substrates except CALD and crotonaldehyde, at 323K, only negligible products were formed within 2h; hence temperature was increased to 353K for all such reactions. It was observed that α-β unsaturated compounds having comparatively higher solubility in water showed higher activity (Table 4.5, entries 1 to 3). For benzyliden acetone, though solubility in water is high, the activity at 323K was very low hence the reaction was carried out at 353K. The ketone was found to require higher temperature for reaction as compared to the aldehyde (Table 4.5, entry 1 & 3). Although the cinnamic acid has lower solubility in water, it showed higher activity as compared to methyl cinnamate which has almost similar solubility (compare entry 4 and 5). This is because in presence of sodium formate, cinnamic acid is converted into its sodium salt and dissolves in aqueous (catalyst) phase and reacts. The product was separated by acidifying the aqueous phase with HCl and the isolated yield was calculated. (Table 4.5, entry 4). The compounds like methyl cinnamate, chalcone (1,3-diphenyl-2-propene-1-one) showed poor activity even at 353 K. (Table 4.5, entries 5 to 8). The poor activity observed with these compounds is probably due to their lower solubility in aqueous phase. The products of all these reaction were confirmed by GC-MS and ^{1}H NMR spectroscopy. No aldehyde or ketone hydrogenation products (alcohol or hydrocarbon) were observed.

Table 4.5: Transfer hydrogenation of α-β unsaturated carbonyl compounds using $[Rh(COD)Cl]_2$/TPPTS catalyst system

NO.	**Substrate**	**Aq.Sol. (gm/lit) 25°C^{33}**	**Product**	**Temp K**	**Time (h)**	**Yield %**	**TOF (h^{-1})**
1	CALD	1.34		323	1.3	100	196
2	Croto-naldehyde	181[34]		323	1	95	240
3	Benzyliden acetone	1.398		353	1.8	100	135
4	Cinnamic acid	0.511		353	0.5	81[a]	396
5	Methyl cinnamate	0.405		353	5	20	11
6	Ethyl cinnamate	0.178		353	5	7	3.6
7	Chalcone	0.093[35]		353	5	20	10
8	Citral[b]	0.299		353	5	8	3.8

***Reaction conditions**: Substrate, 0.85 kmol/$m^3_{(org)}$; $[Rh(COD)Cl]_2$, 1.12 x 10^{-3} kmol/$m^3_{(aq)}$; TPPTS, 1.36 x 10^{-2} kmol/$m^3_{(aq)}$; HCOONa, 2.85 kmol/$m^3_{(aq)}$; toluene, 1.2 x 10^{-5} m^3;water, 1.8 x 10^{-5} m^3; total volume, 3.0 x 10^{-5} m^3; agitation speed, 1200 rpm; N_2 gas,50 psi.*

a: no organic solvent was used, the product was obtained by acidifying the aqueous layer and isolated yield was calculated. .b: mixture of geranial and neral 2/1

4.4 KINETICS OF TRANSFER HYDROGENATION OF *TRANS* CINNAMALDEHYDE USING $[Rh(COD)Cl]_2$ /TPPTS CATALYST SYSTEM

There are very few reports on the kinetics of transfer hydrogenation of α, β-unsaturated carbonyl compounds. Knowledge of the kinetics is important in understanding the mechanistic features of such complex catalytic reactions. Considering the industrial importance of this reaction in synthesis of perfumery chemicals, the study would also provide useful data for the purpose of reactor designing. The main aim of the present study was to investigate the transfer hydrogenation of trans-cinnamaldehyde using $[Rh(COD)Cl]_2$ /TPPTS catalyst in a water-toluene biphasic medium using sodium formate as hydrogen donor. The effect of concentration of different parameters such as catalyst, substrate, TPPTS, and hydrogen donor (sodium formate) on the initial rate of transfer hydrogenation has been studied. A suitable rate equation has been proposed after rigorous model discrimination. The different kinetic parameters and the activation energy have also been evaluated.

Prior to conducting the experiments to observe kinetic data, preliminary experiments were carried out to check the material balance and reproducibility of experiments. For this purpose, a few experiments were carried out in which the amount of substrate consumed and the product formed were compared. A typical concentration time profile for a reaction is shown in Figure 4.8, which clearly shows a very good mass balance between the amount of reactant (CALD) consumed and the product (HCALD) formed. These results represent concentrations in the organic phase. It was observed that the concentrations of CALD and HCALD in the aqueous phase were negligible throughout the course of the reaction. This indicates a complete extraction of the products in the organic phase after reaction. It was observed that the product profile is unchanged even at higher temperature.

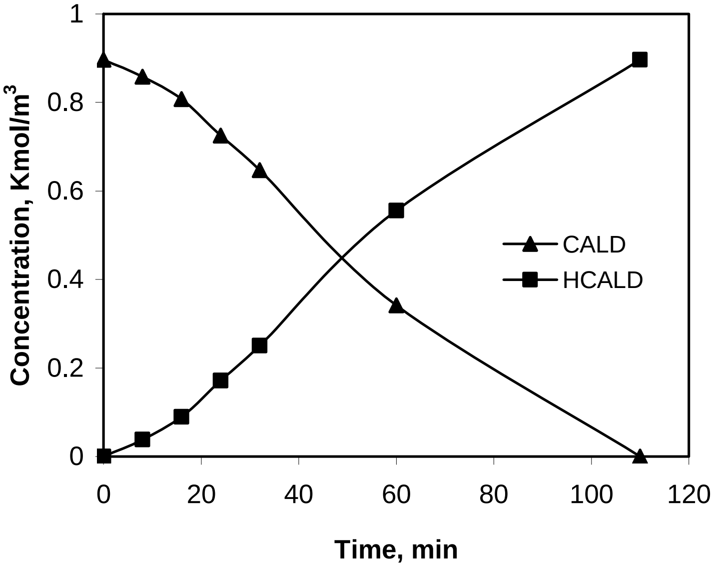


Figure 4.8: A typical concentration –time profile for transfer hydrogenation of CALD ***Reaction conditions:*** *CALD, 0.85 kmol/m$^3_{(org)}$; [Rh(COD)Cl]$_2$, 5.6 x 10^{-4}kmol/m$^3_{(aq)}$; TPPTS, 6.9 x 10^{-3} kmol/m$^3_{(aq)}$; HCOONa, 2.86 kmol/m$^3_{(aq)}$; Phase holdup (water-toluene), 0.6; total volume, 3.0 x 10^{-5} m^3 ; T, 323; agitation speed, 1200 rpm; N$_2$ gas, 50 psi.*

4.4.1 Solubility Data

The solubility of *trans* cinnamaldehyde in aqueous phase containing 2.86 M sodium formate was determined experimentally. The experimental data for liquid-liquid equilibrium for cinnamaldehyde in toluene- water (aqueous 2.86 M solution of sodium formate) mixture at different temperatures is presented in Table 4.6. It was observed that temperature has only a marginal effect on the solubility of cinnamaldehyde in the aqueous phase.

Table 4.6: Liquid-Liquid equilibrium data for CALD-Water-Toluene System

T, K	**CALD in organic phase, Kmol/m^3**	**CALD in aqueous phase x 10^3 Kmol/m^3**
313	0.85	3.93
323	0.85	4.28
333	0.85	4.80

4.4.2 Mass transfer effects in liquid-liquid systems

The transfer hydrogenation reaction in a biphasic aqueous –organic (toluene) medium is a typical case of a liquid-liquid reaction and hence for investigation of intrinsic kinetics of these reactions, it is important to ensure that the rate data obtained are in the kinetic regime. A careful consideration to the significance of mass transfer must be given for kinetic analysis of a complex biphasic reaction involving liquid-liquid system. For a liquid-liquid reaction system, the overall rate would depend on the liquid-liquid mass transfer and the intrinsic kinetics of the reaction in the aqueous phase.

A few experiments were carried out to investigate the effect of agitation speed and aqueous catalyst phase holdup on the rate of reaction. These experiments were important to understand the role of mass transfer and to ensure the kinetic regime.

4.4.2.1 Effect of Agitation Speed

The following reaction conditions were used for carrying out experiments on the effect of the agitation speed: $CALD_{(org)}$ = 0.85 $kmol/m^3$, two phases = toluene and water, (aqueous-phase holdup) $\varepsilon = 0.6$, $[Rh(COD)Cl]_{2(aq)}$=1.13 x 10^{-3} $kmol/m^3$, $TPPTS_{(aq)}$ = 1.36 x10^{-2} $kmol/m^3$, $HCOONa_{(aq)}$,= 2.86 $kmol/m^3$, total volume = 3.0 x 10^{-5} m^3 and T = 333 K.

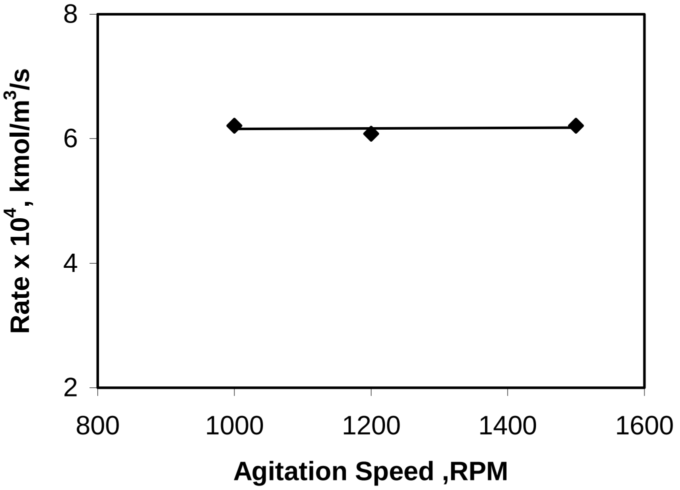
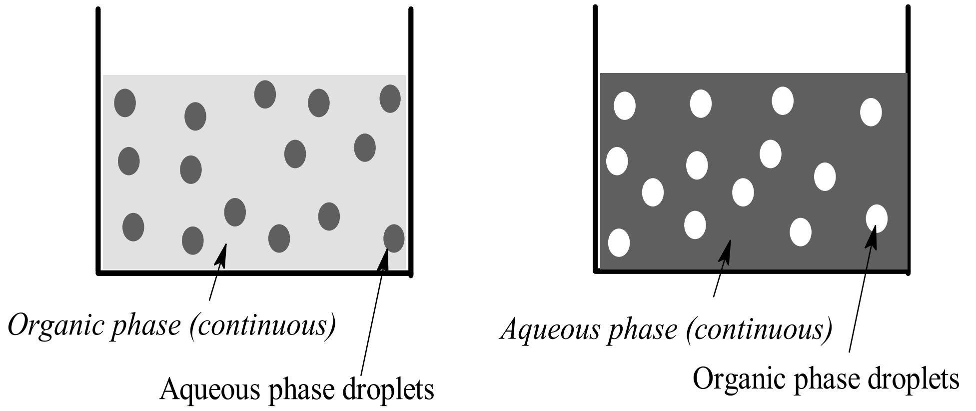


Figure 4.9: Effect of agitation speed on initial rate of transfer hydrogenation of CALD. ***Reaction conditions:*** *CALD, 0.85* $kmol/m^3_{(org)}$; $[Rh(COD)Cl]_2$, *1.1 x* 10^{-3} $kmol/m^3_{(aq)}$; *TPPTS, 1.4 x* 10^{-2} $kmol/m^3_{(aq)}$; *HCOONa, 2.86* $kmol/m^3_{(aq)}$; *Toluene,1.2 x* $10^{-5}m^3$; *water, 1.8 x* $10^{-5}m^3$; *T= 333 K;* N_2, *50 psi.*

Figure 4.9 shows that the rate is independent of the agitation speed beyond 1000 rpm. This observation indicates that the mass transfer effects are not important above 1000 rpm. Therefore, all the reactions for kinetic study were carried out at an agitation speed of 1200 rpm to ensure that the reaction occurred in the kinetic regime.

4.4.2.2 Effect of phase holdup

Figure 4.11 shows the effect of aqueous catalyst phase holdup (ε) on the initial rate of transfer hydrogenation of CALD at a agitation speed of 1200 rpm. It was observed that the phase inversion takes place at an aqueous-phase holdup of about 0.5. For aqueous phase holdup < 0.5, the aqueous phase is the dispersed phase, as shown schematically in Figure 4.10a. In this case, the liquid-liquid interfacial area is determined by aqueous-phase holdup (ε). For aqueous-phase holdup > 0.5, the organic phase is the dispersed phase, as shown schematically in Figure 4.10b. In this case, the liquid-liquid interfacial area will be determined by the organic-phase holdup (1 - ε).



(a) Aqueous Phase dispersed

($0<\varepsilon < 0.5$)

(b) Organic phase dispersed

($0.5<\varepsilon < 1.0$)

Figure 4.10: Schematic presentation of two different physical situations prevailing in the reactor depending upon the phase hold up

At an agitation speed of 1200 rpm (20 Hz), a plot of initial rate versus aqueous (catalyst) phase holdup (Figure 4.11) shows that the rate first increases with the increase in aqueous-phase holdup. The maximum rate was observed for aqueous phase holdup of 0.7

with respect to toluene layer. In the kinetic regime, the rate per unit volume of the aqueous phase is expected to remain constant with linear dependence on aqueous-phase holdup. However, in the case where the reaction occurs essentially at the liquid-liquid interface, it would depend on the liquid-liquid interfacial area, which is governed by both agitation speed and holdup of the dispersed phase. The results at an aqueous-phase holdup < 0.7 indicate a kinetic regime. For higher aqueous phase hold up the decreasing rate indicates mass transfer limitation. Detailed investigations are necessary to understand this effect, however for the kinetic modeling the data below aqueous phase hold up of 0.7 were used, wherein kinetic regime prevails. Hence all the kinetic studies were conducted at $\varepsilon = 0.6$.

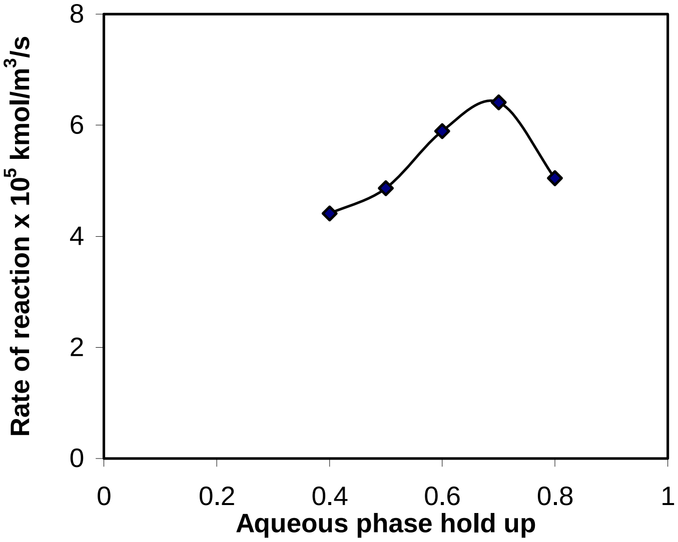


Figure 4.11: Effect of aqueous phase holdup on initial rate of transfer hydrogenation of CALD.

Reaction conditions: *CALD, 0.85* $kmol/m^3_{(org)}$; *[Rh(COD)Cl]*$_2$, *5.68 x* 10^{-4} $kmol/m^3_{(aq)}$; *TPPTS, 6.89 x* 10^{-3} $kmol/m^3_{(aq)}$; *(Rh:L = 1:6); HCOONa, 2.86* $kmol/m^3_{(aq)}$; *total volume (toluene and water), 3.0 x* 10^{-5} m^3; *T, 323 K; rpm, 1200;* N_2, *50 psi.*

4.4.3 Initial rate data

In order to study the kinetics of the transfer hydrogenation of *trans* cinnamaldehyde, several experiments were carried out in the range of conditions presented in Table 4.7. The initial rates of transfer hydrogenation were calculated from the plots of product formation as a function of time. Under the conditions chosen for kinetic study, no side reactions were found to occur and hence, these data would be representative of the overall transfer hydrogenation of α-β unsaturated aldehydes to the corresponding saturated aldehydes. The initial rates of transfer hydrogenation were calculated from the saturated aldehyde product formed as a function of time. The rate of transfer hydrogenation was calculated as follows:

$$R = \frac{\text{Slope of product formation vs. time plot}}{\text{Total volume of liquid (organic + aqueous)}}$$

Table 4.7: Range of conditions used for kinetic studies

Parameter/units	Quantity
Concentration of $[Rh(COD)Cl]_2$ $(kmol/m^3)_{(aq.)}$	2.82×10^{-4} – 1.12×10^{-3}
Concentration of *trans* cinnamaldehyde $(kmol/m^3)_{(org.)}$	0.43-1.70
Concentration of TPPTS ligand $(kmol/m^3)_{(aq.)}$	3.42×10^{-3} – 1.36×10^{-2}
Concentration of sodium formate $(kmol/m^3)_{(aq.)}$	1.44-4.29
Temperature (K)	313 – 333
Solvents	Toluene: Water
Aqueous phase hold up(ε)	0.6
Agitation speed (RPM)	1200
Reaction volume (m^3)	3.0×10^{-5}

4.4.3.1 Effect of catalyst concentration on the rate of the reaction

The effect of catalyst concentration on the rate of transfer hydrogenation of *trans* cinnamaldehyde was studied in the temperature range of 313-333 K, cinnamaldehyde concentration of 0.85 $kmol/m^3$, and sodium formate concentration 2.86 $kmol/m^3_{(aq.)}$ and keeping Rh:L ratio of 1:6. The results are presented in Figure 4.12. The rate was found to be linearly dependent on the catalyst concentration, indicating first order kinetics. Increase in catalyst concentration will increase concentration of active catalyst species in the reaction, which leads to rate enhancement.

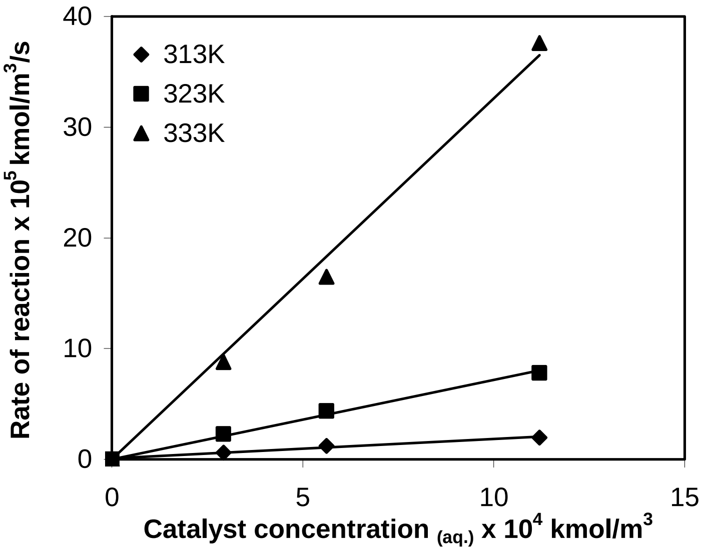


Figure 4.12: Effect of catalyst concentration on the rate of biphasic transfer hydrogenation of CALD.

Reaction conditions: *CALD, 0.85 kmol/m$^3_{(org)}$; TPPTS, 6.9 x 10^{-3} kmol/m$^3_{(aq)}$; (Rh:L=1:6) HCOONa, 2.86 kmol/m$^3_{(aq)}$; Phase holdup (water and toluene), 0.6; total volume, 3.0 x 10^{-5} m^3 ; agitation speed, 1200 rpm; N_2, 50 psi.*

4.4.3.2 Effect of substrate concentration on the rate of the reaction

The effect of CALD concentration on the rate of transfer hydrogenation reaction was studied at constant catalyst, TPPTS and sodium formate concentrations of 5.6 x 10^{-4}, 6.9 x 10^{-3} and 2.86 kmol/m^3, respectively, in a temperature range of 313-333 K. The results are presented in Figure 4.13. The rate showed a linear dependence on substrate concentration in the lower concentration range (< 1.3 kmol/m^3). With further increase in substrate concentration the rate increases marginally.

In this biphasic system CALD (substrate) is partitioned between two immiscible phases and highest concentration in the aqueous phase can be reached by using neat CALD phase. An experiment which was carried out using neat CALD shows that total conversion obtained within 50 minutes with 100 % selectivity to HCALD. This observation indicates that highest concentration does not inhibit the process totally. Similar type of observation was also found by Darensbourg et al.[7] in transfer hydrogenation of CALD using [Rh(PTAH)(PTA)$_2$Cl]Cl as catalyst and Bellefon et al.[10,11] in transfer hydrogenation of dimethyl itaconate with Rh/TPPTS complex.

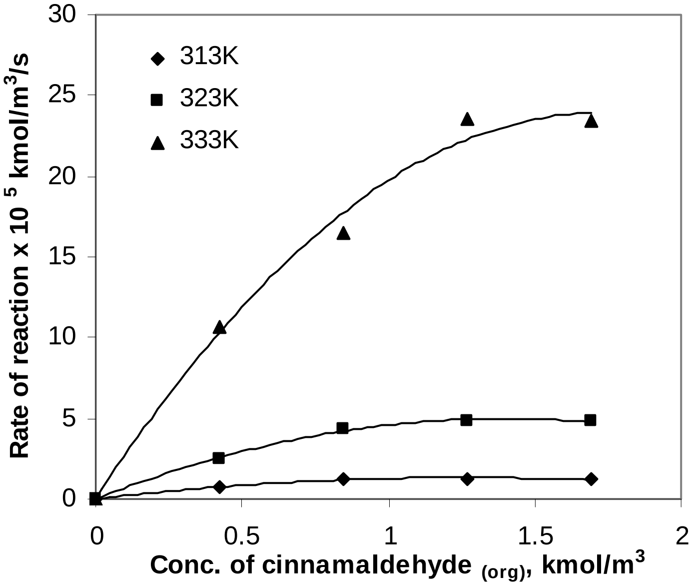


Figure 4.13: Effect of substrate concentration on the rate of biphasic transfer hydrogenation of CALD.

Reaction conditions: *[Rh(COD)Cl]$_2$, 5.6 x 10^{-4}kmol/m^3$_{(aq)}$; TPPTS, 6.9 x 10^{-3} kmol/m^3$_{(aq)}$; HCOONa, 2.86 kmol/m^3$_{(aq)}$; Phase holdup (water and toluene), 0.6; total volume, 3.0 x 10^{-5} m^3 ; agitation speed, 1200 rpm; N$_2$, 50 psi.*

4.4.3.3 Effect of formate concentration on the rate of the reaction

The influence of sodium formate concentration was also studied at constant catalyst, TPPTS and substrate concentrations of 5.6 x 10^{-4}, 6.9 x 10^{-3} and 0.85 kmol/m^3, respectively, in a temperature range of 313-333 K. From Figure 4.14, it can be seen that the rate passes through maximum around formate concentration of 1.43 kmol/m^3 and levels off after a concentration of 2.86 kmol/m^3. Such behavior has also been observed by Bellefon[10,11]in transfer hydrogenation of dimethyl itaconate using Rh-TPPTS complex catalyst and Joo et al.[5] in the transfer hydrogenation of aldehydes using water soluble Ru-TPPMS complex in a biphasic medium.

The trend observed in the present work can be explained on basis of lower solubility of substrate in aqueous phase with high ionic strength as discussed in previous section 4.3.1.5.

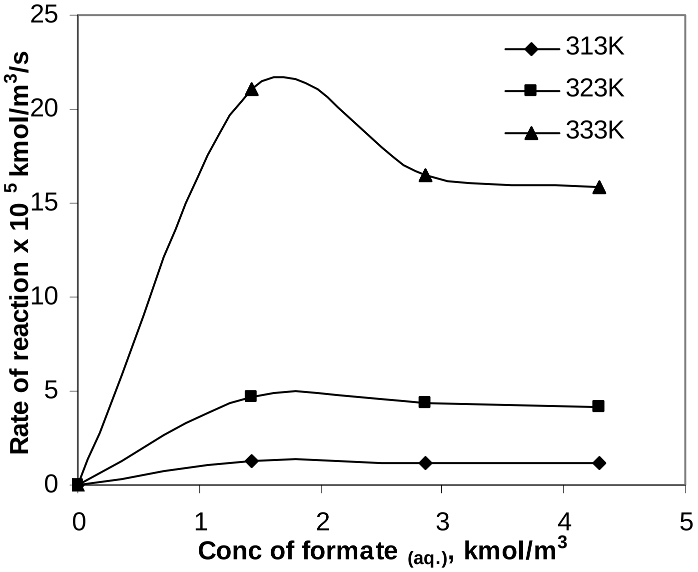


Figure 4.14: Effect of Sodium formate concentration on the rate of biphasic transfer hydrogenation of CALD.

Reaction conditions*: CALD, 0.85 kmol/m*$^3_{(org)}$*; [Rh(COD)Cl]*$_2$*, 5.6 x 10*$^{-4}$*kmol/m*$^3_{(aq)}$*; TPPTS, 6.9 x 10*$^{-3}$ *kmol/m*$^3_{(aq)}$*; Phase holdup (water and toluene), 0.6; total volume, 3.0 x 10*$^{-5}$ *m*^{3} *; agitation speed, 1200 rpm; N*$_2$*, 50 psi.*

4.4.3.4 Effect of TPPTS concentration on the rate of the reaction

The effect of TPPTS ligand concentration on the rate of transfer hydrogenation reaction was studied at constant catalyst, CALD and sodium formate concentrations of 5.6 x 10^{-4}, 0.85 and 2.86 kmol/m^3, respectively, in a temperature range of 313-333 K. The results are presented in Figure 4.15. The ligand concentration was varied from Rh:L= 1:3 to 1:12. The plot of rate vs. ligand concentration shows maximum at Rh:L ratio 1:6. With further increase in ligand concentration, the rate decreased marginally. This may be due to inhibition of dissociation of phosphine from catalyst $[P_3RhS]^+$ to get catalytically active species $[P_2RhS_2]^+$ at high concentration of ligand (as discussed in section 4.3.1.4) Bellefon et al.[10] showed similar trend for Rh/TPPTS catalyst system in transfer hydrogenation of dimethyl itaconate while for Rh/PTA catalyst system as shown by

Darensbourg et al.[7] the reaction was strongly inhibited by even one equivalent excess concentration of ligand (PTA) as inactive catalytic species $[Rh(PTAH)_3(PTA)Cl]Cl_3$ is formed due to excess of ligand.

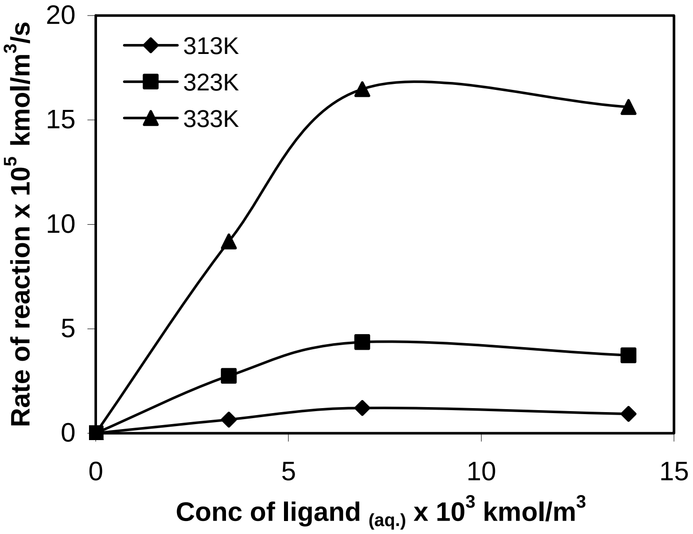


Figure 4.15: Effect of ligand concentration on the rate of biphasic transfer hydrogenation of CALD.

Reaction conditions: *CALD, 0.85* $kmol/m^3_{(org)}$*;* $[Rh(COD)Cl]_2$*, 5.6 x* $10^{-4} kmol/m^3_{(aq)}$*; HCOONa, 2.86* $kmol/m^3_{(aq)}$*; Phase holdup (water and toluene), 0.6; total volume, 3.0 x* $10^{-5}\ m^3$ *; agitation speed, 1200 rpm;* N_2*, 50 psi.*

4.4.3.5 Kinetic modeling

The kinetic data was used to develop a rate equation for the transfer hydrogenation of trans cinnamaldehyde using $[Rh(COD)Cl]_2$ /TPPTS catalyst and sodium formate as hydrogen donor in a biphasic medium. Based on the observed trends, a variety of empirical models were examined, and the best model was selected based on the criterion of the least average error between predicted and experimental rates ($\Phi_{\min}$) which is defined as:

$$\Phi_{\min} = \sum_{i=1}^{n} (R_{EXP} - R_{PRE})^2$$

Where R_{EXP} is the observed rate of the reaction and R_{PRE} is the rate predicted by the respective models.

4.4.3.5.1 Estimation of kinetic parameters and model discrimination

The rate parameters *k*, K_B, K_C, and K_D were evaluated at 313, 323, and 333K by fitting the experimental rate data with Eqs. (I)–(V) using non-linear regression analysis and an optimization routine based on the Marquardt's method.[36] The values of the rate parameters at different temperatures for various models are presented in Table 4.8.

$$R = \frac{k[A][B][C][D]}{(1+K_B[B]^2)(1+K_C[C])^2(1+K_D[D]^2)} \qquad \text{(I)}$$

$$R = \frac{k[A][B][C][D]}{(1+K_B[B]^2)(1+K_C[C]^2)(1+K_D[D]^2)} \qquad \text{(II)}$$

$$R = \frac{k[A][B][C][D]}{(1+K_B[B]^2)(1+K_C[C])(1+K_D[D]^2)} \qquad \text{(III)}$$

$$R = \frac{k[A][B][C][D]}{(1+K_B[B])(1+K_C[C]^2)(1+K_D[D]^2)} \qquad \text{(IV)}$$

$$R = \frac{k[A][B][C][D]}{(1+K_B[B])^2(1+K_C[C])^2(1+K_D[D])} \qquad \text{(V)}$$

Where R = rate of reaction, expressed in kmol/(m^3 /s); [A]= concentration of catalyst (kmol/m^3); [B] = concentration of cinnamaldehyde (kmol/m^3); [C] = concentration of sodium formate (kmol/m^3); [D]= concentration of ligand (TPPTS) (kmol/m^3); k = rate constant; K_B, K_C, K_D are equilibrium constants.

Table 4.8: Values of kinetic parameters at different temperatures

Rate Model	T (K)	k	K_B	K_C	K_D	ϕ_{min}
I	313	19.57	0.56	0.57	1.40×10^4	0.018×10^{-9}
	323	72.52	0.46	0.60	1.34×10^4	0.084×10^{-9}
	333	361.85	0.26	0.78	1.16×10^4	2.650×10^{-9}
II	313	9.31	0.57	0.28	1.41×10^4	0.022×10^{-9}
	323	33.19	0.46	0.29	1.35×10^4	0.124×10^{-9}
	333	143.74	0.26	0.38	1.16×10^4	3.030×10^{-9}
III	313	-23.78	0.54	-3.40	1.38×10^4	0.014×10^{-9}
	323	-83.51	0.44	-3.43	1.32×10^4	0.483×10^{-9}
	333	-193.27	0.25	-2.35	1.15×10^4	2.460×10^{-9}
IV	313	22.11	2.75	0.29	1.38×10^4	0.024×10^{-9}
	323	64.07	1.85	0.30	1.32×10^4	0.168×10^{-9}
	333	212.96	0.88	0.39	1.15×10^4	3.230×10^{-9}
V	313	95.09	0.56	0.62	5.75×10^3	0.032×10^{-9}
	323	347.57	0.46	0.64	6.06×10^3	0.218×10^{-9}
	333	1206.52	0.27	0.84	4.03×10^3	5.880×10^{-9}

The discrimination of rate models was done based on the thermodynamic criteria, activation energy and the Φ_{min} values. The rate model V was rejected based on the thermodynamic criteria of inconsistency of temperature dependence of equilibrium constant. Model III had negative rate parameters and hence was rejected. In the remaining three models I, II and V, the models II and V were discriminated based on the higher Φ_{min} values than model I. The model I thus turned out to be superior among all the models considered. Thus, the following rate equation was found to predict the rates in good agreement with experimental values:

$$R = \frac{k[A][B][C][D]}{(1+K_B[B]^2)(1+K_C[C])^2(1+K_D[D]^2)}$$

The Arrhenius plot showing the effect of temperature on the rate parameters is shown in Figure 4.16 from which the activation energy was evaluated as 126 kJ/mol, which is typical of a chemically controlled transfer hydrogenation reaction.[37]

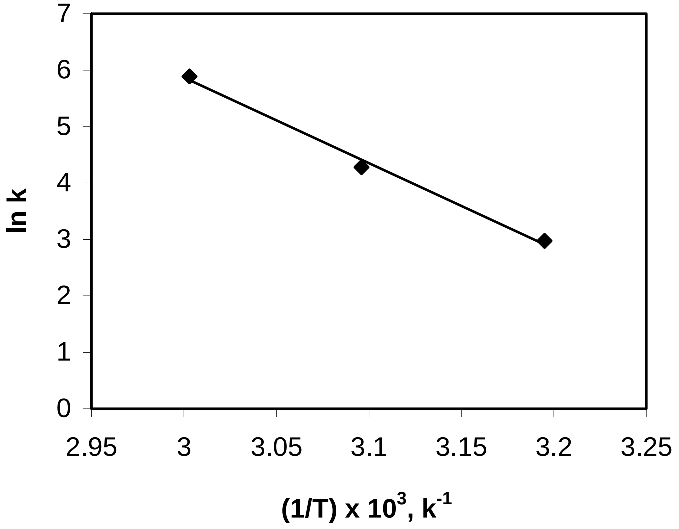


Figure 4.16: Temperature dependence of rate constant (*k*) (Arrhenius plot)

A comparison of the experimental rates with the predicted rates using model (I) is shown in Figure 4.17, which indicates a good agreement between experiments and predictions. The average percent error between the experimental and predicted data was 0.98 %.

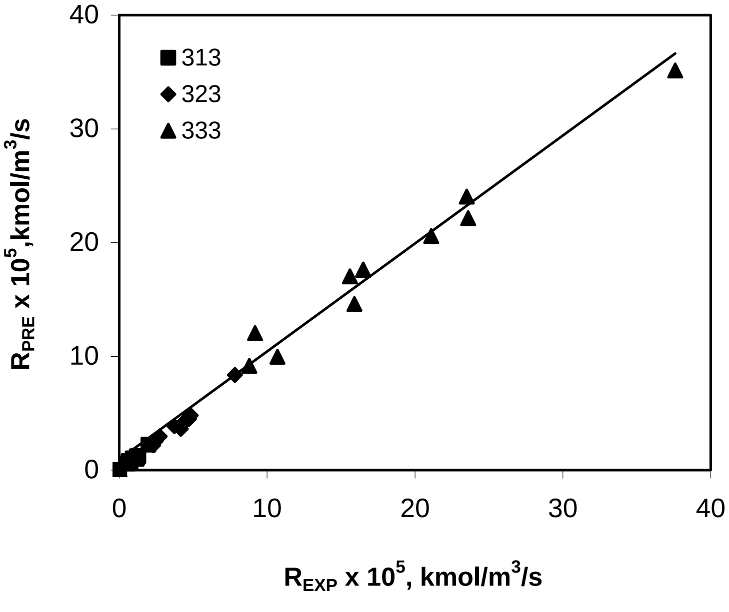


Figure 4.17: Comparison of experimental rates and predicted rates using model (I).

The validity of the proposed model I was crosschecked by plotting the experimental and observed rates at varying concentrations of the variables for all temperature (Figure 4.17).

The model was found to predict the trends in good agreement with experimental observations.

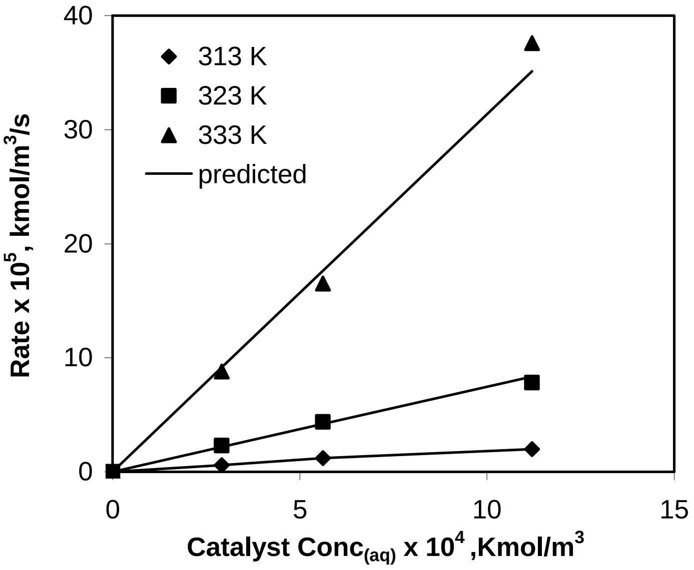


Figure 4.18: Comparison of experimental and predicted rates for effect of catalyst concentration at various temperatures

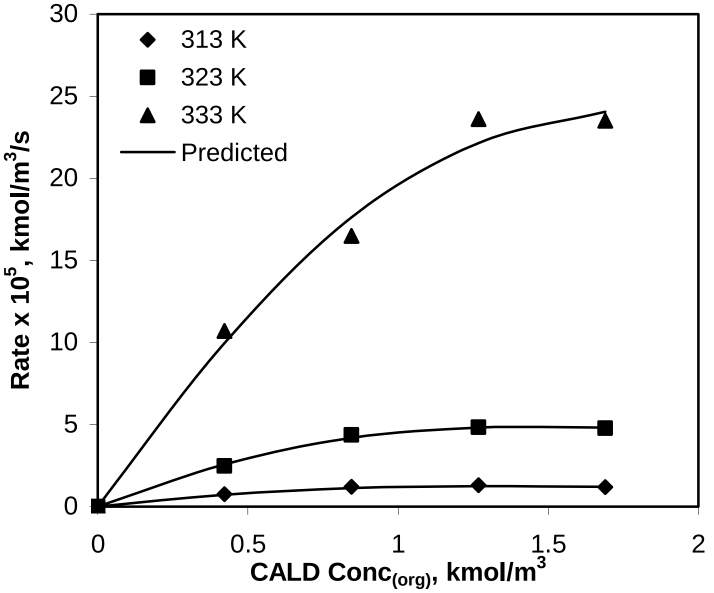


Figure 4.19: Comparison of experimental and predicted rates for effect of substrate concentration at various temperatures

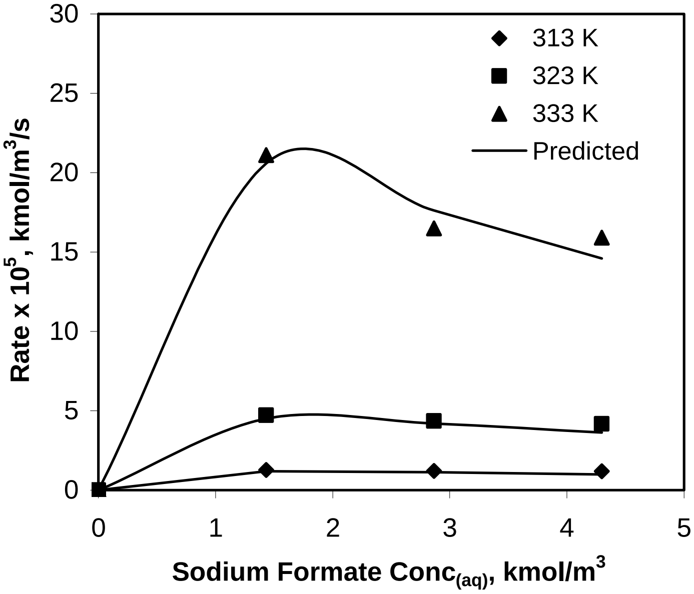


Figure 4.20: Comparison of experimental and predicted rates for effect of sodium formate concentration at various temperatures

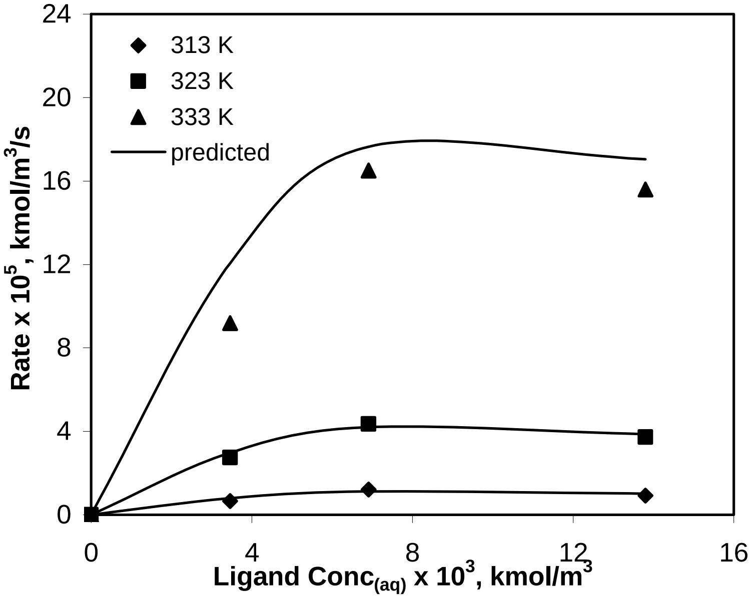


Figure 4.21: Comparison of experimental and predicted rates for effect of ligand concentration at various temperatures

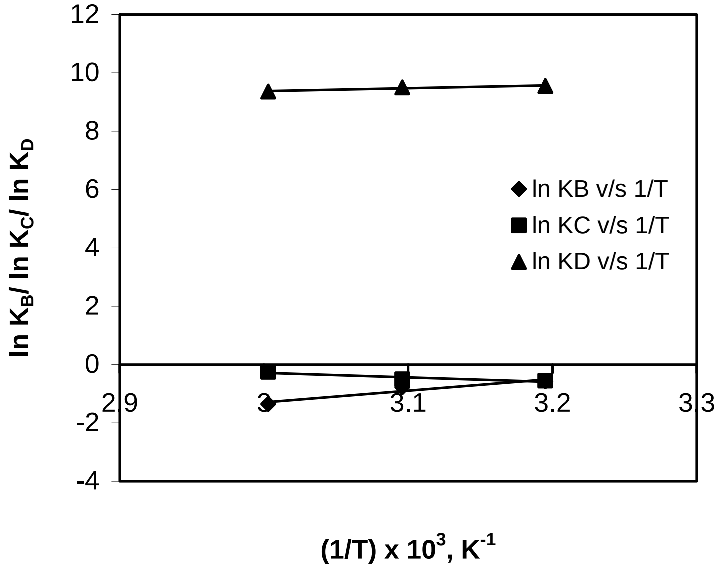


Figure 4.22: Plot of ln K_B, ln K_C, ln K_D v/s 1/T

4.5 EFFECT OF CO-SOLVENT ON BIPHASIC TRANSFER HYDROGENATION REACTION OF α-β UNSATURATED CARBONYL COMPOUNDS

While screening various α-β unsaturated carbonyl compounds as substrates in aqueous biphasic transfer hydrogenation; it was found that some of the substrates having lower solubility in water were less active. (Table 4.5 entries 5-8). Several approaches have been proposed to enhance the reaction rates in biphasic medium as discussed in chapter 1, section 1.5.1.5. It has been reported that the addition of co-solvent to the biphasic system improves the solubility of higher olefins in the aqueous phase retaining the biphasic nature of the system for hydroformylation reaction.[38] There are no reports on the use of co-solvents in biphasic transfer hydrogenation reaction. Hence the effect of the co-solvents in enhancing the rates for our system was investigated.

4.5.1 Screening of co-solvents

In the present work transfer hydrogenation of methyl cinnamate as a model substrate has been investigated in the presence of several co-solvents such as ethanol, ethylene glycol, DMF, DMAc and NMP. Amount of co-solvent used was 30% of aqueous catalyst phase. The results are presented in Figure 4.23.

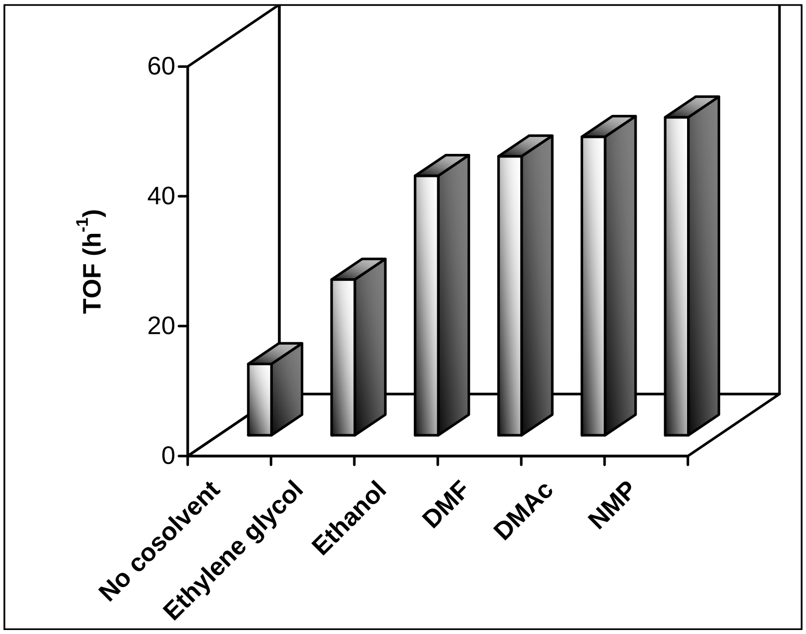


Figure 4.23: Effect of co-solvents on biphasic transfer hydrogenation of methyl cinnamate

***Reaction conditions**: Substrate, 0.85 kmol/m$^3{}_{(org)}$; [Rh(COD)Cl]$_2$, 1.12 x10^{-3} kmol/m$^3{}_{(aq)}$; TPPTS, 1.36 x10^{-2} kmol/m$^3{}_{(aq)}$; HCOONa, 2.85 kmol/m$^3{}_{(aq)}$; toluene, 1.2 x10^{-5} m^3; water, 1.3 x10^{-5} m^3; co-solvent, 0.5 x10^{-5} m^3; T, 353K; time, 5h; agitation speed, 1200 rpm, total volume, 3.0 x 10^{-5} m^3 ; N$_2$, 50 psi..*

From the results it can be seen that the activity increased significantly (almost 4-5 fold rate enhancement) with the use of co-solvents and best result (TOF:49 h^{-1}) was obtained using NMP as the co-solvent. The co-solvents can be arranged in decreasing order of activity as follows: NMP>DMAc>DMF>Ethanol>ethylene glycol. No side product like decarboxylation product was observed. Usually the presence of co-solvents increases the solubility of substrate in catalyst containing aqueous phase resulting in higher activity and yield of product. Since the best results (TOF: 49h^{-1}) were obtained using NMP as a co-solvent, further work was carried out using NMP as a co-solvent.

4.5.2 Effect of NMP concentration (co-solvent) on activity

The effect of NMP concentration (as a co-solvent) in the aqueous medium on the activity was studied at 353 K for the transfer hydrogenation of methyl cinnamate using

$[Rh(COD)Cl]_2$/TPPTS catalyst in the water-toluene biphasic medium. The reactions were carried out by varying the NMP composition in the aqueous phase from 0-50% (v/v). The results are presented in Figure 4.24.

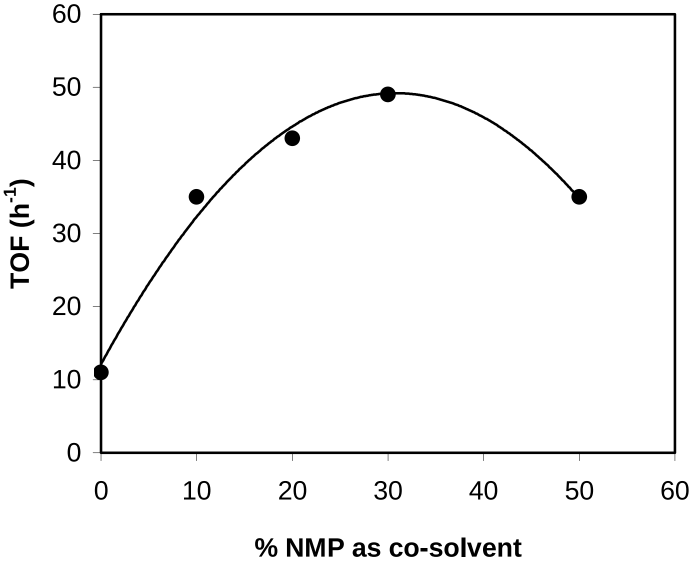


Figure 4.24: Effect of % NMP co-solvent on biphasic transfer hydrogenation of methyl cinnamate

***Reaction conditions**: Methyl cinnamate, 0.85 kmol/$m^3_{(org)}$; $[Rh(COD)Cl]_2$, 1.12 x10^{-3} kmol/$m^3_{(aq)}$; TPPTS, 1.36 x10^{-2} kmol/$m^3_{(aq)}$; HCOONa, 2.85 kmol/$m^3_{(aq)}$; solvent, toluene(1.2 x10^{-5} m^3); total volume(water-NMP-Toluene), 3.0 x 10^{-5} m^3; T, 353K; time, 5h; agitation speed, 1200 rpm; N_2gas, 50psi.*

The TOF increased with increase in NMP concentration up to 30% NMP concentration and then decreased with further increase in NMP concentration in aqueous phase. The highest TOF (49 h^{-1}) was observed at water-NMP composition of 70:30. At higher NMP concentration, sodium formate precipitates from aqueous medium, resulting in lower activity. The optimum ratio of water-NMP of 70:30 was then chosen for further studies.

4.5.3 Screening of various substrates using NMP as co-solvent

The substrates which showed very low activity in a biphasic medium (See Table 4.5, entries 5 to 8) were screened for transfer hydrogenation reaction in the presence of

30% NMP as a co-solvent. The results are presented in Table 4.9. From the results it can be clearly seen that the use of NMP as a co-solvent increases activity for all the substrates. Transfer hydrogenation of methyl cinnamate and chalcone with NMP as a co-solvent gave 97 and 96% conversions respectively in 5 h, compared to 20% for both in absence of any co-solvent.

Table 4.9: Screening of various substrates using NMP as co-solvent

Entry	**substrate**	**Without co-solvent**			**With co-solvent NMP**		
		Conv. %	**Time h**	**TOF (h^{-1})**	**Conv. %**	**Time h**	**TOF (h^{-1})**
1	Methyl cinnamate	20	5	11	97	5	49
2	Ethyl cinnamate	7	5	3.6	70	5	35
3	Chalcone	20	5	10	96	5	48
4	Citral	8	5	3.8	40	5	20

***Reaction conditions**: Substrate, 0.85 kmol/m$^3_{(org)}$; [Rh(COD)Cl]$_2$, 1.12 x10^{-3} kmol/m$^3_{(aq)}$; TPPTS, 1.36 x10^{-2} kmol/m$^3_{(aq)}$; HCOONa, 2.85 kmol/m$^3_{(aq)}$; toluene,1.2 x10^{-5} m^3; water,1.3 x10^{-5} m^3; NMP, 0.5 x10^{-5} m^3; total volume, 3.0 x 10^{-5} m^3;T, 353K; agitation speed, 1200 rpm; N$_2$gas, 50psi.*

4.5.4 Parametric study for transfer hydrogenation of methyl cinnamate using NMP as a co-solvent

For effect of various reaction conditions on transfer hydrogenation of methyl cinnamate was investigated in a biphasic medium using NMP as a co-solvent as it gave very good activity. A typical concentration-time profile for the transfer hydrogenation of methyl cinnamate using sodium formate as a hydrogen donor and NMP as co-solvent in water-toluene biphasic media is represented in Figure 4.25, which clearly shows a good mass balance between the amount of reactant consumed and the product formed. It was observed that almost complete conversion of methyl cinnamate was achieved in 5h at 353K temperature. The samples of aqueous phase injected did not show any peak for methyl cinnamate or product, indicating complete extraction of reactant and product in organic phase.

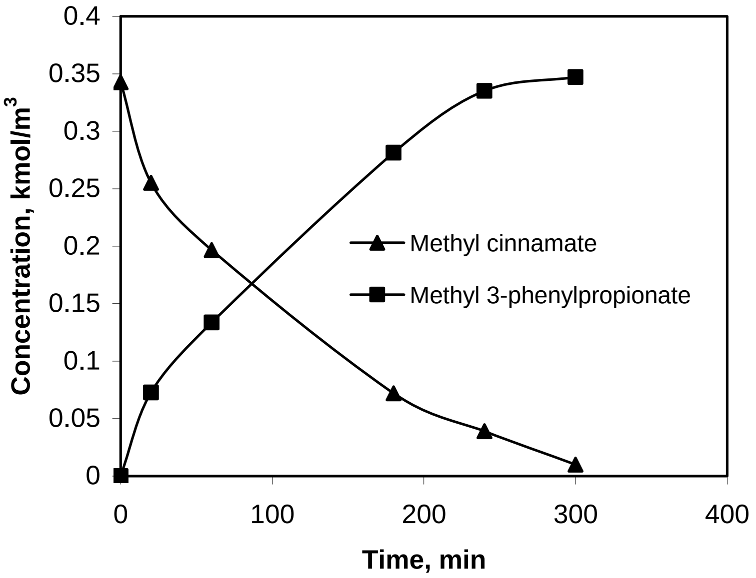


Figure 4.25: Typical concentration-time profile for the transfer hydrogenation of methyl cinnamate

***Reaction conditions**: Methyl cinnamate, 0.85 kmol/$m^3_{(org)}$; $[Rh(COD)Cl]_2$, 1.12 x10^{-3} kmol/$m^3_{(aq)}$; TPPTS, 1.36 x10^{-2} kmol/$m^3_{(aq)}$; HCOONa, 2.85 kmol/$m^3_{(aq)}$; toluene, 1.2 x10^{-5} m^3; water, 1.3 x10^{-5} m^3;NMP, 0.5 x10^{-5} m^3; total volume, 3.0 x 10^{-5} m^3;T, 353K; agitation speed, 1200 rpm; N_2gas, 50psi.*

The effect of various reaction conditions on the initial rate of reaction was investigated at 353 K temperature. For this study, several experiments were carried out in the range of conditions shown in Table 4.10. Preliminary studies showed that the rate of reaction was independent of agitation speed above 1000 rpm. Hence the reactions were carried out at 1200 rpm to ensure kinetic regime. The initial rates of reactions were calculated from the slope of product formed versus time plot.

Table 4.10: Range of conditions for parametric study

Concentration of $[Rh(COD)Cl]_2$, $kmol/m^3_{(aq)}$	5.60×10^{-4} - 1.68×10^{-3}
Concentration of methyl cinnamate, $kmol/m^3_{(org)}$	0.43-1.69
Concentration of sodium formate, $kmol/m^3_{(aq)}$	1.43-4.28
Temperature (K)	353
Solvent	Toluene:Water:NMP
Total volume (m^3)	3.0×10^{-5}
Agitation speed (rpm)	1200

4.5.4.1 Effect of catalyst concentration on initial rate of reaction

Effect of catalyst concentration on initial rate of reaction was investigated in a concentration range of $5.60 \times 10^{-4} – 1.68 \times 10^{-3}$ $kmol/m^3$ and keeping P:Rh ratio of 6 constant. The results are depicted in Figure 4.26.

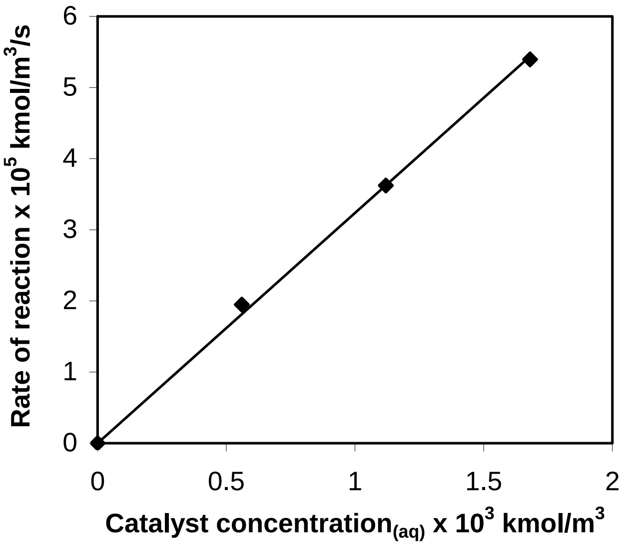


Figure 4.26: Influence of catalyst concentration on the observed initial rate

Reaction conditions*: Methyl cinnamate, 0.85 $kmol/m^3_{(org)}$;* Rh: TPPTS , 1:6; *HCOONa, 2.85 $kmol/m^3_{(aq)}$; toluene, 1.2×10^{-5} m^3; water, 1.3×10^{-5} m^3; NMP, 0.5×10^{-5} m^3; total volume, 3.0×10^{-5} m^3; T, 353K; agitation speed, 1200 rpm; N_2gas, 50 psi.*

The rate was found to increase linearly with increase in catalyst concentration. This trend is expected since the concentration of active Rhodium species increases with increase in the catalyst precursor concentration, linearly.

4.5.4.2 Effect of methyl cinnamate concentration on the initial rate of reaction

The effect of methyl cinnamate concentration on the rate of transfer hydrogenation reaction was studied at constant catalyst, TPPTS and sodium formate concentrations of 1.12 x10^{-3}, 1.36 x10^{-2} and 2.85 kmol/$m^3_{(aq)}$, respectively, at 353 K. (Figure 4.27). The rate of reaction showed first order dependence with methyl cinnamate concentration in the range studied.

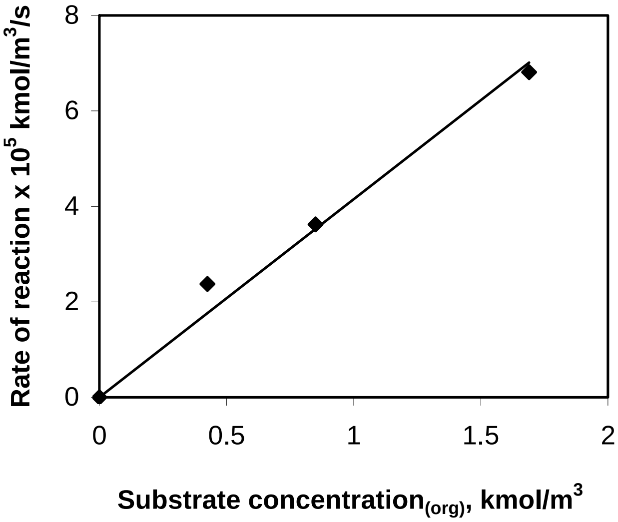


Figure 4.27: Influence of substrate concentration on observed initial rate

***Reaction conditions**: [Rh(COD)Cl]$_2$, 1.12 x10^{-3} kmol/$m^3_{(aq)}$; TPPTS, 1.36 x10^{-2} kmol/$m^3_{(aq)}$; HCOONa, 2.85 kmol/$m^3_{(aq)}$; toluene, 1.2 x10^{-5} m^3; water, 1.3 x10^{-5} m^3; NMP, 0.5 x10^{-5} m^3; total volume, 3.0 x 10^{-5} m^3;T, 353K, agitation speed, 1200 rpm; N_2, 50 psi.*

4.5.4.3 Effect of sodium formate concentration on the initial rate of reaction

The influence of sodium formate concentration was also studied at constant catalyst, TPPTS and substrate concentrations of 1.12 x 10^{-3}, 1.36 x 10^{-2} and 0.85 kmol/m^3, respectively. From Figure 4.28, it can be seen that the rate passes through maximum around formate concentration of 1.43 kmol/m^3 and levels off after a concentration of 2.86 kmol/m^3. This is because the reaction involves aldehyde which is dissolved in aqueous phase and at high concentration of formate salt. With increase in concentration of formate salt in medium, ionic strength of aqueous phase increased which could lead to lower aldehyde solubility in aqueous phase resulting in lower rate.

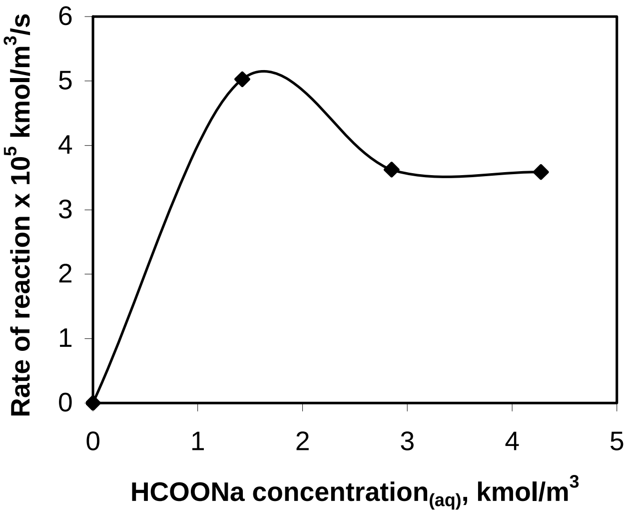


Figure 4.28: Influence of sodium formate concentration on observed initial rate
Reaction conditions: *Methyl cinnamate, 0.85 kmol/m*^{3}$_{(org)}$*; [Rh(COD)Cl]*$_2$*, 1.12 x10*$^{-3}$ *kmol/m*^{3}$_{(aq)}$*; TPPTS, 1.36 x10*$^{-2}$ *kmol/m*^{3}$_{(aq)}$*; toluene, 1.2 x10*$^{-5}$ *m*^{3}*; water, 1.3 x10*$^{-5}$ *m*^{3}*; NMP, 0.5 x10*$^{-5}$ *m*^{3}*; total volume, 3.0 x 10*$^{-5}$ *m*^{3}*;T, 353K; agitation speed, 1200 rpm; N*$_2$ *gas, 50 psi.*

4.5.4.4 Effect of temperature on the initial rate of reaction

The effect of temperature on the transfer hydrogenation of cinnamaldehyde has been investigated in a temperature range of 343-363 K under following conditions: Methyl cinnamate: 0.85 kmol/m^3$_{(org)}$, [Rh(COD)Cl]$_2$: 1.12 x10^{-3} kmol/m^3$_{(aq)}$, TPPTS: 1.36 x10^{-2} kmol/m^3$_{(aq)}$. As expected, the rate increases with the temperature without affecting selectivity (100 %).

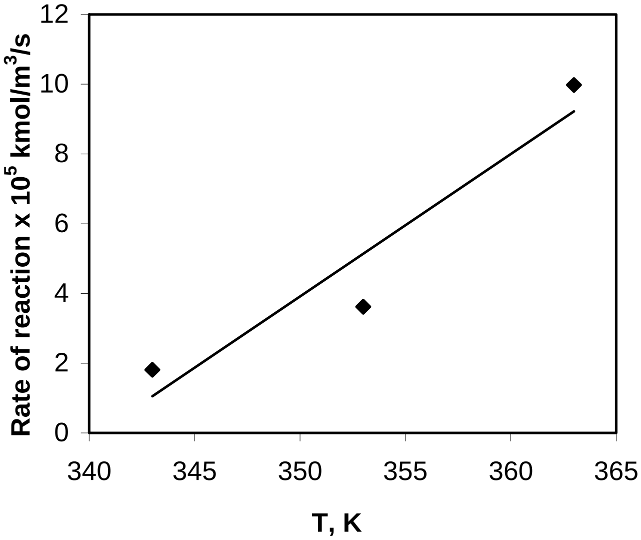


Figure 4.29: Effect of temperature on the initial rate of reaction

Reaction conditions*: Methyl cinnamate, 0.85 kmol/m$^3_{(org)}$; [Rh(COD)Cl]$_2$, 1.12 x10^{-3} kmol/m$^3_{(aq)}$; TPPTS, 1.36 x10^{-2} kmol/m$^3_{(aq)}$;HCOONa, 2.85 kmol/m$^3_{(aq)}$; toluene, 1.2 x10^{-5} m^3; water, 1.3 x10^{-5} m^3; NMP, 0.5 x10^{-5} m^3; total volume, 3.0 x 10^{-5} m^3; agitation speed, 1200 rpm, N$_2$gas,50 psi.*

4.6 CONCLUSIONS

The transfer hydrogenation of various α-β unsaturated carbonyl compounds was investigated using [Rh(COD)Cl]$_2$/TPPTS catalyst in aqueous biphasic medium using sodium formate as hydrogen donor. The olefinic bond was selectively reduced to give saturated carbonyl compounds. The hydrogenated products were isolated and identified by GC-MS and ^{1}H NMR. The role of solvents, various hydrogen donors, phosphine to Rh ratio and substrate to hydrogen donor ratio on the activity of the catalyst has been investigated. Various substrates have been screened and it was observed that the substrates which have comparatively high solubility in aqueous phase react faster than others. Benzyliden acetone required higher temperature (353K) to react than those of aldehydes like cinnamaldehyde (323K) indicating aldehydes react faster than ketone.

The detailed kinetics of transfer hydrogenation of cinnamaldehyde has been investigated using Rh(COD)Cl]$_2$/TPPTS catalyst and sodium formate as hydrogen donor in two phase system (water-toluene). The effect of different parameters viz. effect of agitation speed, aqueous phase hold-up ratio, concentrations of catalyst, substrate, ligand and hydrogen donor on the rate of reaction has been investigated in the temperature range of 313-333 K. The initial rate was found to be first order with respect to catalyst concentration and first order tending to zero order with respect to CALD concentration. The rate passed through a maximum with variation of sodium formate concentration and was also found to be maximum at Rh: ligand ratio of 1:6. Various empirical rate equations were considered to fit the rate data and the best fitting model has been selected. The following rate equation was found to predict the rates in good agreement with experimental values with ±5 % error.

$$R = \frac{k[A][B][C][D]}{(1+K_B[B]^2)(1+K_C[C])^2(1+K_D[D]^2)}$$

The activation energy was evaluated as 126 kJ/mol.

While screening of the various substrates it was observed that the substrates which have low solubility in water react very slowly. So the transfer hydrogenation of such α-β unsaturated carbonyl compounds has been investigated using co-solvents in a aqueous biphasic system. Effect of various co-solvents has been investigated using methyl cinnamate as a model substrate. NMP was found to be the best co-solvent and the water: NMP ratio of 70:30 was found to be optimum for the reaction (TOF: 49 h^{-1}). This is the first report on the use of co-solvents in transfer hydrogenation of α-β unsaturated carbonyl compounds. The effect of various parameters like concentration of catalyst, substrate and sodium formate on the initial rate of reaction has been investigated at 353 K. The rate was found to have first order dependence on catalyst and substrate concentrations and the rate increased with increase in formate concentration and then levels off at high concentration.

REFERENCES

1 B. Cornils, W.A. Hermann (Eds) *Aqueous-Phase Organometallic Catalysis: Concepts and Application,* Wiley VCH , **1998**.

2 (a) E. Kuntz, *FR 2,314,910*, **1975**, *US 4,248,802* (1981); (b) E. Kuntz,*CHEMTECH,* **1970**, 570

3 (a) B. Cornils, J. Falbe, *Proc. 4th Int. Symp. on Homogeneous Catalysis,* Leningrad, Sept. **1984**, p. 487; (b) H. Bach, W Gick, E. Wiebus, B. Cornils, Abstr. *1st IUPAC Symp. Org. Chemistry,* Jerusalem **1986**, 295; (c) E. Wiebus, B. Cornils, *Chem. Ing. Tech.,* **1994**, *66*, 916; (d) B, Cornils, E. Wiebus, *CHEMTECH,* **1995**, *25*, 33

4 F. Joo, A. Benyei, *J. Organomet. Chem*. **1989,** *363*, C19.

5 A. Benyei, F. Joo, *J. Mol.Catal.* **1990,** *58*,151.

6 S. Ogo, T. Abura, Y. Watanabe, *Organometallics* **2002,** *21*, 2964.

7 D.J. Darensbourg, F. Joo, M. Kannisto, A. Katho, J.H. Reibenspies, D.J. Daigle, *Inorganic Chemistry* **1994**,*33,* 200.

8 S. Ogo, N. Makihara, Y. Watanabe, Organometallics 18 (1999) 5470-5474.

9 D. Sinou, M. Safi, C. Claver, A. Masdeu, *J. Mol. Catal.* **1991,** *68*, L9.

10 C. de Bellefon, N. Tanchoux, S. Caravieilhes, D. Schweich, *Catal. Today* **1999,** *48* 211.

11 N. Tanchoux, C. de Bellefon, *Eur. J. Inorg. Chem.* **2000,** 1495.

12 D.J.Darensbourg, , N.W. Stafford, F. Joo, J.H. Reibenspies, *Journal of Organometallic Chemistry* **1995,** *488*, 99.

13 A.D. Phillips, S. Bolano, S.S. Bosquain, J.-C. Daran, R. Malacea, M. Peruzzini, R. Poli, L. Gonsalvi, *Organometallics* **2006,** *25*, 2189.

14 F. Joo, J. Kovacs, A.C. Benyei, L. Nadasdi, G. Laurenczy, *Chemistry-a European Journal* **2001,** *7*, 193.

15 H. Ding, B.E. Hanson, J. Bakos, *Angew. Chem., Int. Ed. Engl*. **1995,** *34,* 1645.

16 F. Robert, G. Oehme, I. Grassert, D. Sinou, *J. Mol. Catal. A: Chem.* **2000,** *156,*127.

17 Y. Dror, J. Manassen, *J. Mol. Catal*. **1977,** *2*, 219.

18 R. Grzybek, *React. Kinet. Catal. Lett.* **1996,** *58,* 315.

19 E. Fache, C. Mercier, N. Pagnier, B. Despeyroux, P. Panster, *J. Mol.Catal.* **1993,** *79*, 117.

20 (a) W. A. Herrmann, J. Kellner, H. Riepl, *J. Organomet. Chem*. **1990**, *389*, 103 (b) W. A. Herrmann, J. A. Kulpe, J. Kellner, H. Riepl, H. Bahrmann, W. Konkol, *Angew. Chem. Int. Ed. Engl.*, **1990**, *32*, 391

21 E. G. Kuntz, *CHEMTECH*, **1987**, *17*, 570

22 B. M. Bhanage, S. S. Divekar, R. M.Deshpande, and R.V. Chaudhari *Organic Process Research and Development* **2000**, *4*, 342.

23 T. Bartik, B. Bartik, B. E. Hanson, T. Glass, W. Bebout, *Inorg. Chem.* **1992**, *31*, 2667.

24 C. White, A. Yates, and P. M. Maitlis, *Inorganic Synthesis* **1992**, *29*, 228

25 J. Chatt, L. M. Venanzi, *J. Chem. Soc. A*, **1957**, 4735.

26 H. Brunner ,E. Graf, W.Leitner, K Wutz, *Synth. Communications* **1989,** 743.

27 F.A. Cotton, G. Wilkinson, *Advanced inorganic Chemistry,* J. Wiley & Sons. New York, **1980**, p. 935.

28 D.R. Lide, *CRC Handbook of Chemistry and Physics*, *2003-2004: A Ready reference Book of Chemical and Physical Data*, CRC press, **2003**.

29 (a)H. Wiener, J. Blum, Y. Sasson, *Journal of Organic Chemistry* **1991,** *56,* 4481. (b) S. Rajagopal, A.F. Spatola, *Journal of Organic Chemistry* **1995,** *60,* 1347.

30 X.F. Wu, J.K. Liu, D. Di Tommaso, J.A. Iggo, C.R.A. Catlow, J. Bacsa, J.L. Xiao, *Chemistry-a European Journal* **2008,** *14*, 7699.

31 H. Ding, B.E.Hanson and T. E. Glass, *Inorganic Chimica Acta,* **1995**, *229,* 329.

32 D. J. Darensbourg, F. Joó, M. Kannisto, Á. Kathó, J. H. Reibenspies, D. J. Daigle, *Inorg.Chem.* **1994**, *33*, 200

33 S.H. Yalkowsky, Y. He, *Handbook of aqueous solubility data*, CRC, **2003**.

34 K.C. Tin, N.B. Wong, R.X. Li, Y.Z. Li, J.Y. Hu, X.J. Li, *J. Mol.Cat.A: Chem.* **1999,***137*, 121.

35 D.S. Wishart, D. Tzur, C. Knox, R. Eisner, A.C. Guo, N. Young, D. Cheng, K. Jewell, D. Arndt, S. Sawhney, C. Fung, L. Nikolai, M. Lewis, M.A. Coutouly, I. Forsythe, P. Tang, S. Shrivastava, K. Jeroncic, P. Stothard, G. Amegbey, D. Block, D.D. Hau, J. Wagner, J. Miniaci, M. Clements, M. Gebremedhin, N. Guo, Y. Zhang, G.E. Duggan, G.D. MacInnis, A.M. Weljie, R. Dowlatabadi, F. Bamforth, D. Clive, R. Greiner, L. Li, T. Marrie, B.D. Sykes, H. J. Vogel, L. Querengesser, *Nucleic Acids Research* **2007,** *35,* D521.

36 D.W. Marquardt, *J. Soc. Ind. Appl. Math.* **1963,** *11,* 431.

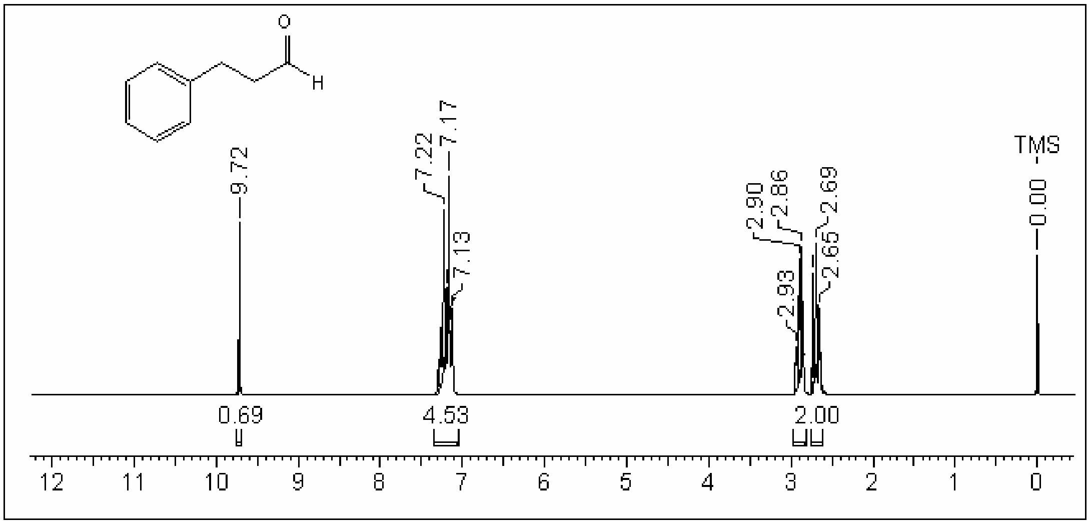
37 (a)Y. Sasson, J. Blum, *J. Org. Chem.* **1975,** *40,* 1887. (b) Z.S.Liu, G.L. Rempel, *J. Mol. Catal. A: Chemical* **2007,** *278,* 228. (c) S.Caravieilhes, C. De Bellefon, N. Tanchoux, *Catal. Today* **2001,** *66*, 145.

38 (a)R. V. Chaudhari, B. M. Bhanage, R. M. Deshpande, H. Delmas, *Nature* **1995**, *373*,501. (b)F. Monteil, R.V. Kastrup, A.A. Ostwald *Catal. Lett.* **1985**, *2*, 85.(c) Purwanto, H. Delmas *Catal. Today* **1995**, *24*, 134. (d) R. M. Deshpande, Purwanto, H. Delmas, R. V. Chaudhari, *Ind. Eng. & Chem. Res.* **1996**, *35*, 3927. (e) H. Zang *Catal. Today* **2002**, *74*, 23. (f) R. M. Deshpande, Purwanto, H. Delmas, R.V. Chaudhari, *J. Mol. Catal. A: Chemical* **1997,** *126,* 133. (g) F. Monteil, R. Dueau, P. Kalck *J. Organomet. Chem.***1994**, *480*, 177.(h) I. Hablot, J. Jenck, G. Casamatta, H. Delmas, *Chem. Eng. Sci.* **1992**, *47*, 1267.(i) P. Kalck, P. Escaffre, Serein-Spriau, A. Thorez, B. Besson, Y. Colleuille, R. Perron, *New J. Chem.* **1988**, *12*, 687.

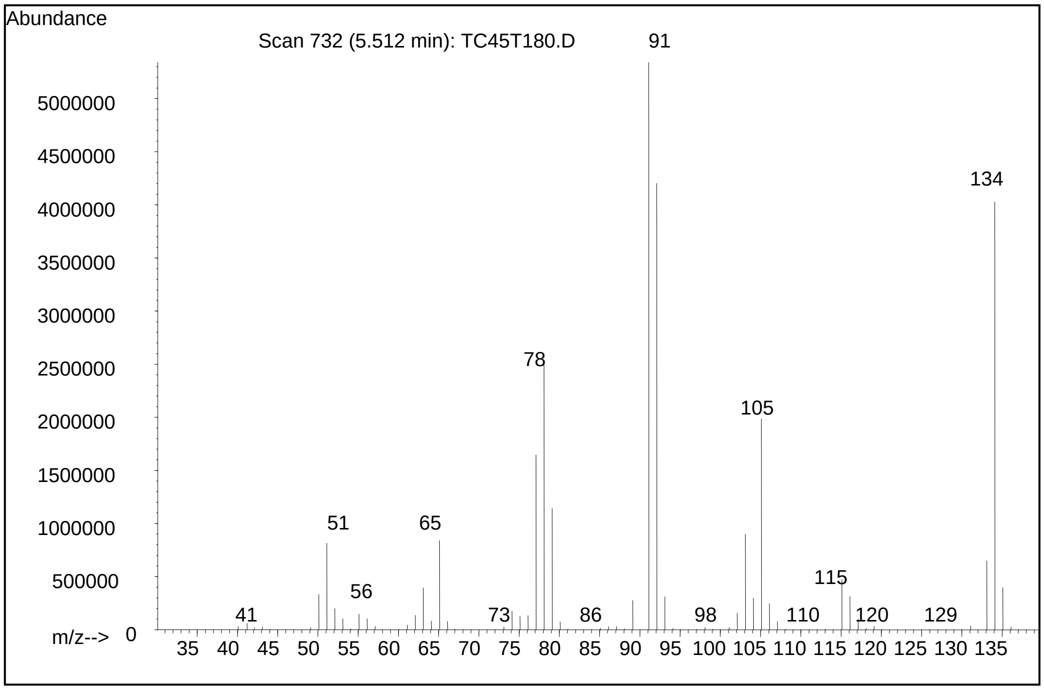
SPECTRA

1. Hydrocinnamaldehyde

^{1}H NMR in $CDCl_3$ ($CDCl_3$, 200 MHz)

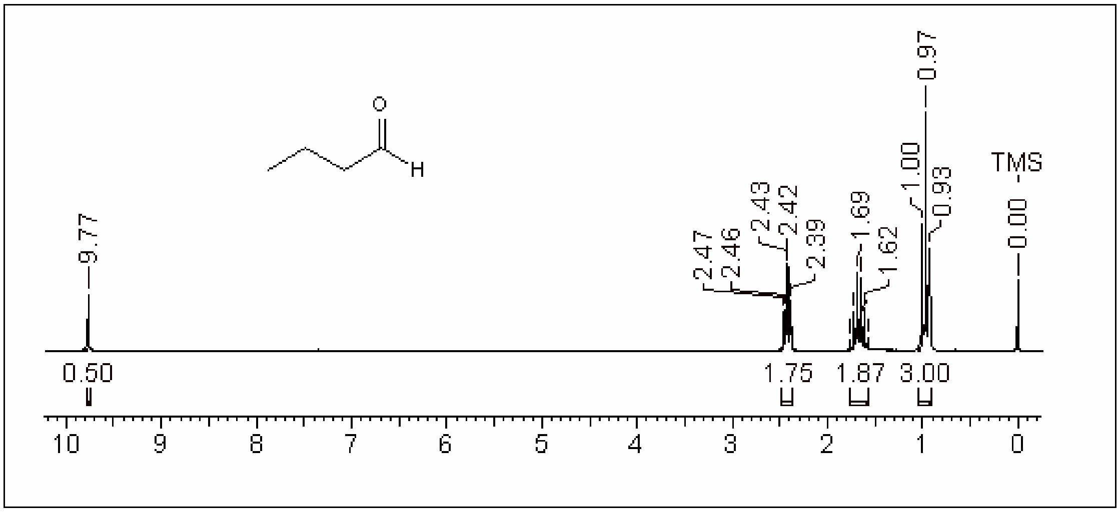


GC-MS Spectra (70 eV, EI)

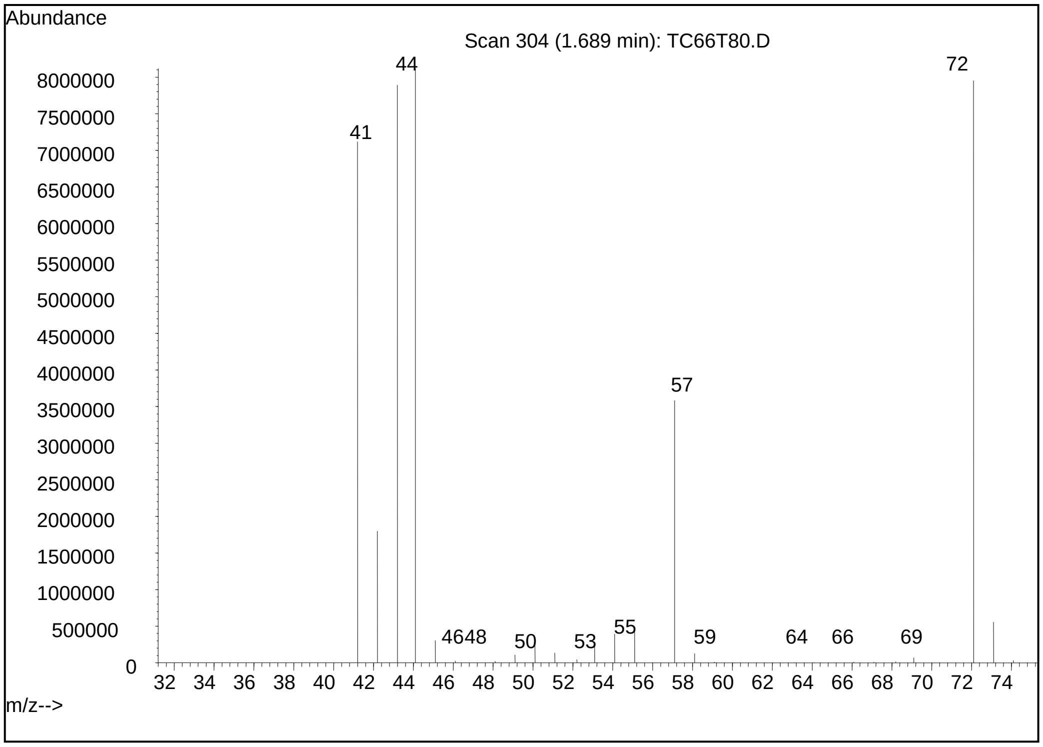


2. Butyraldehyde

^{1}H NMR (CDCl$_3$, 200 MHz)

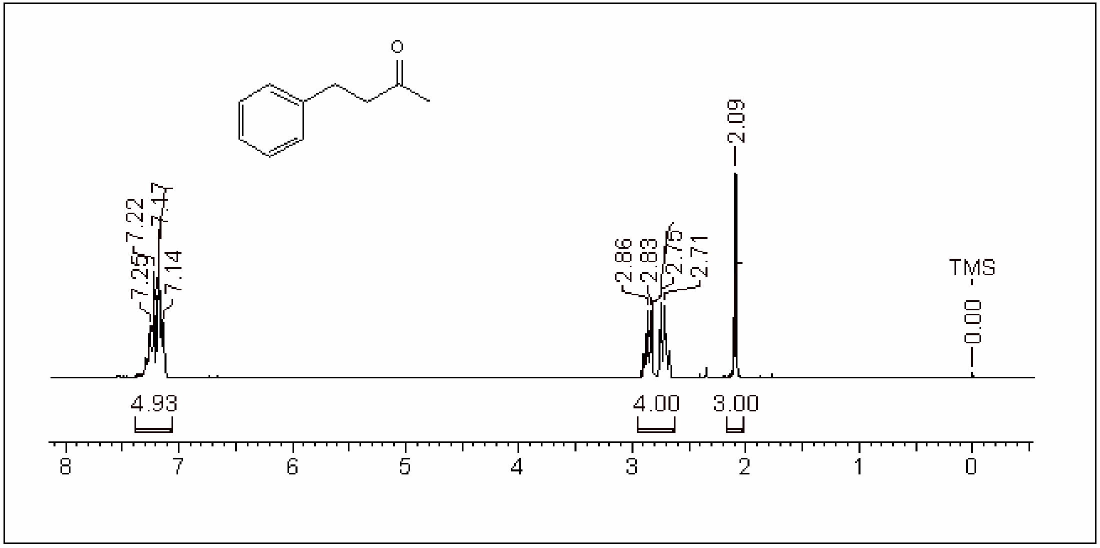


GC-MS Spectrum (70 eV, EI)

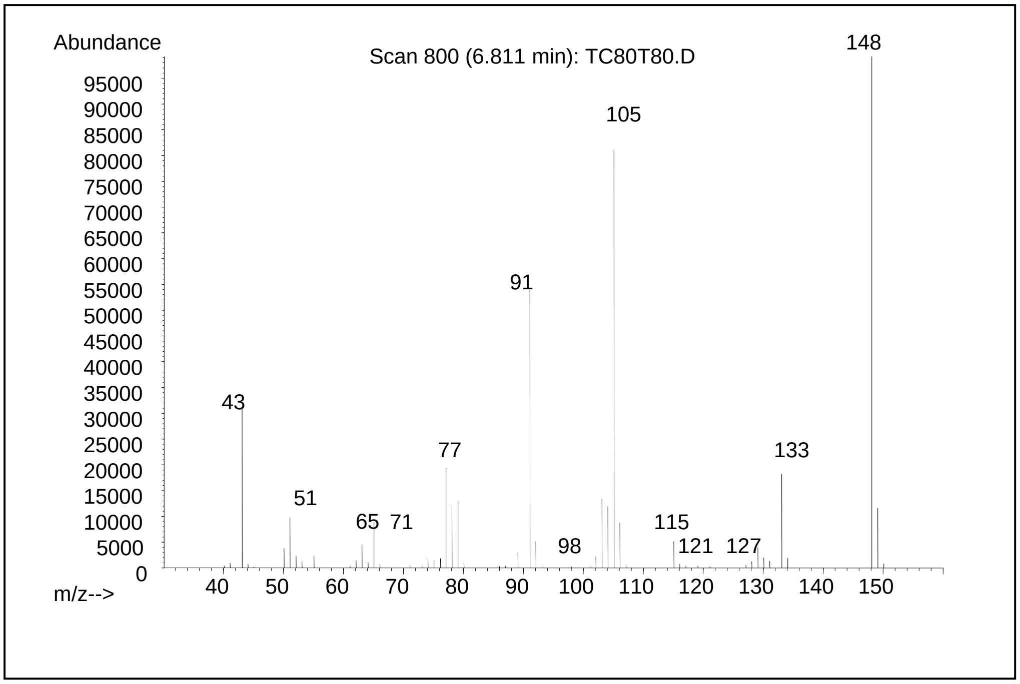


3. 3-phenylpropanal

^{1}H NMR Spectrum ($CDCl_3$, 200 MHz)

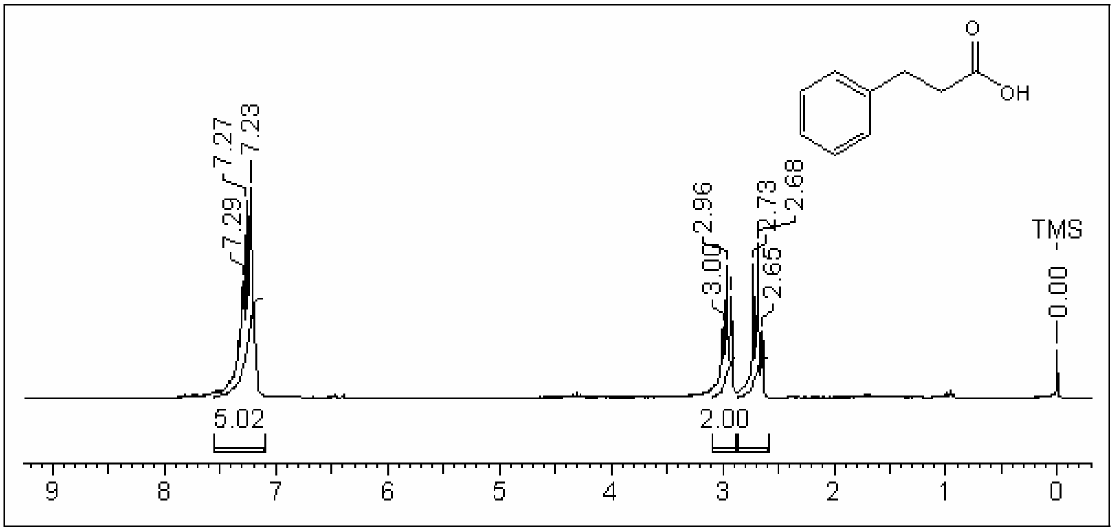


GC-MS Spectrum (70 eV, EI)

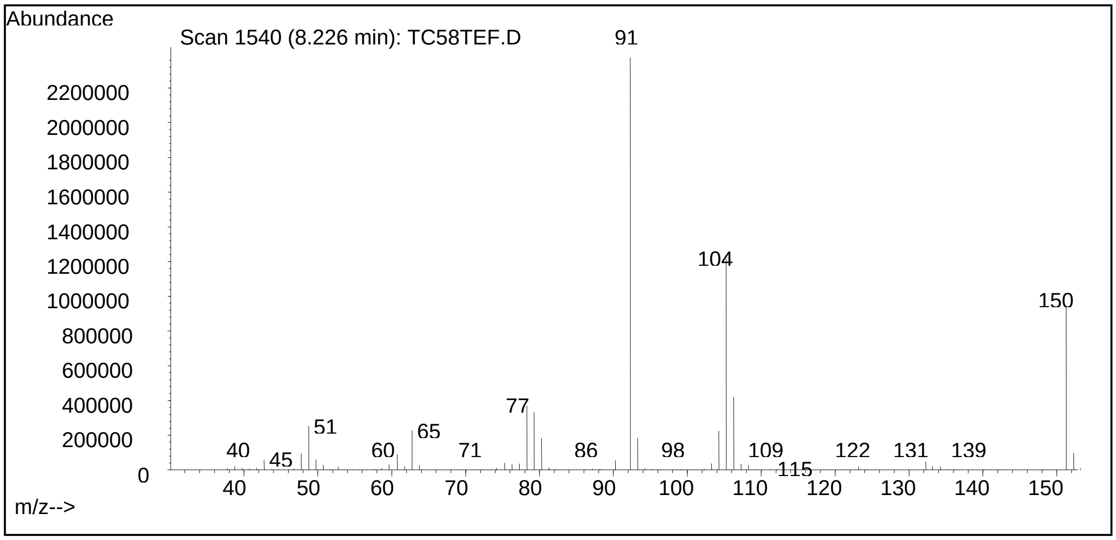


4. 3-phenylpropanoic acid

^{1}H NMR Spectrum (CDCl3, 200 MHz)

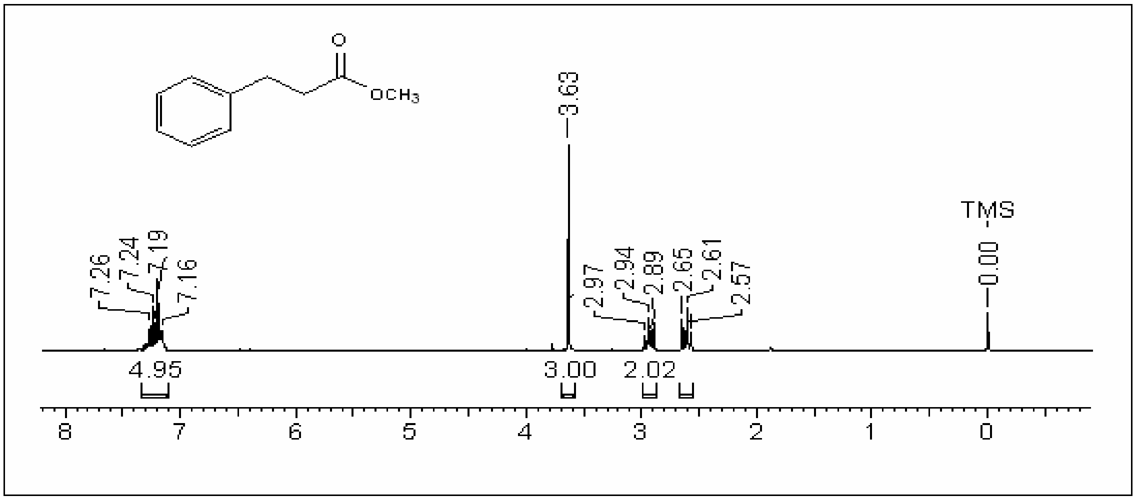


GC-MS Spectrum (70 eV, EI)

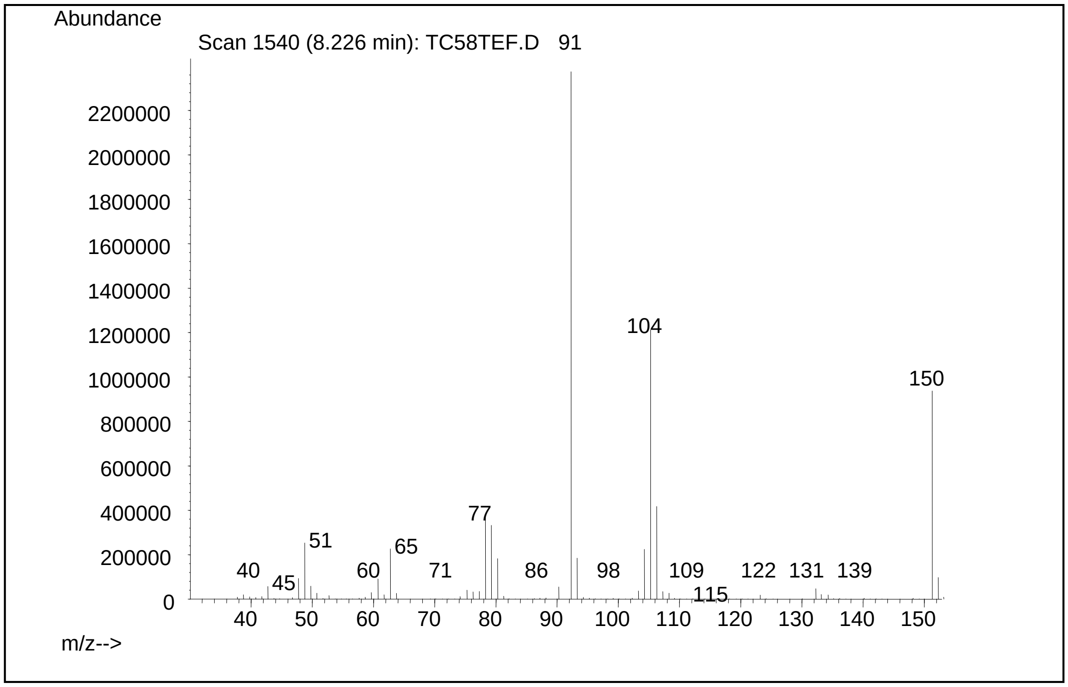


5. Methyl 3-phenylpropanoate

^{1}H NMR Spectrum of (CDCl$_3$, 200 MHz)

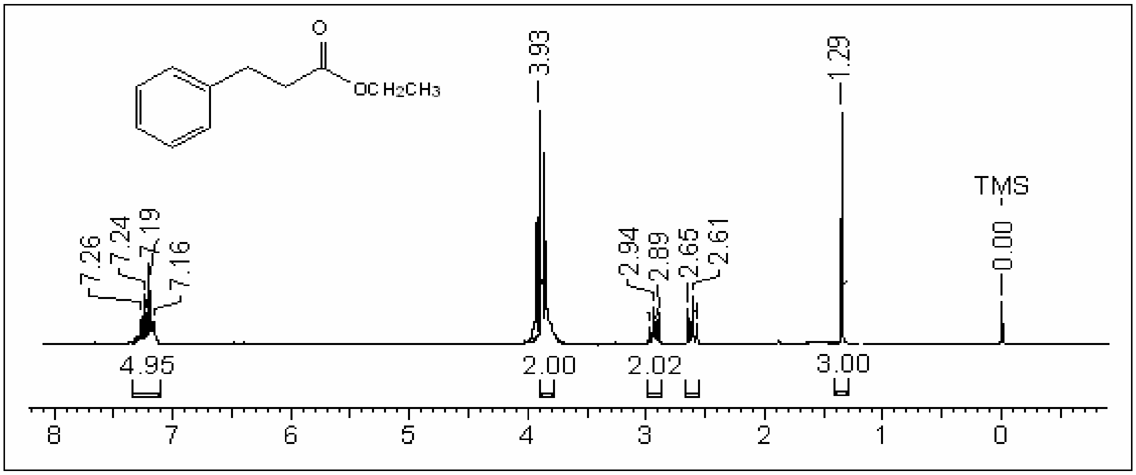


GC-MS Spectrum (70 eV, EI)

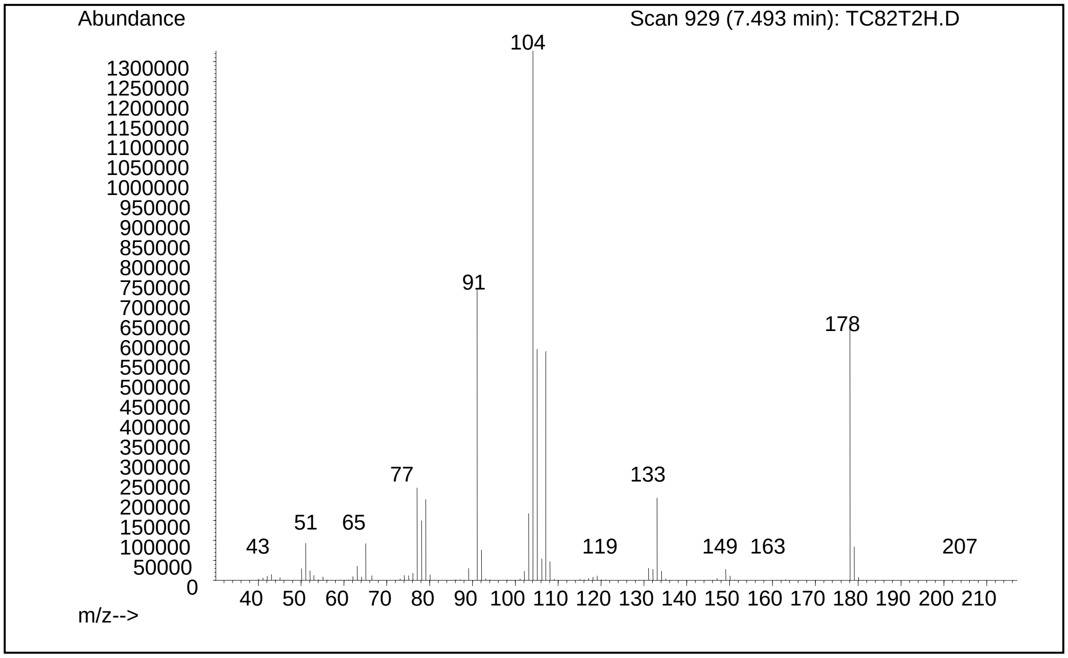


6. Ethyl 3-phenylpropanoate

^{1}H NMR Spectrum (CDCl$_3$, 200 MHz)

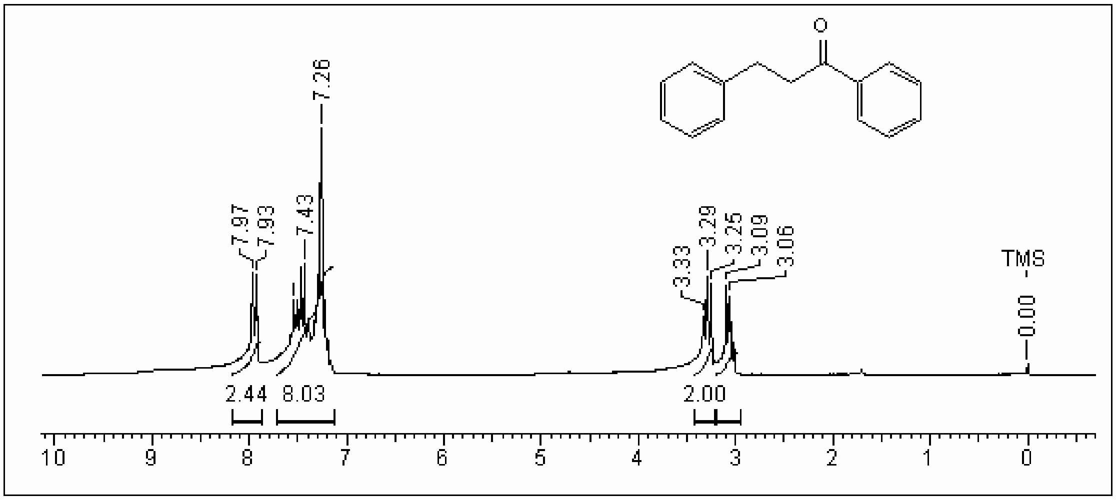


GC-MS Spectrum (70 eV, EI)

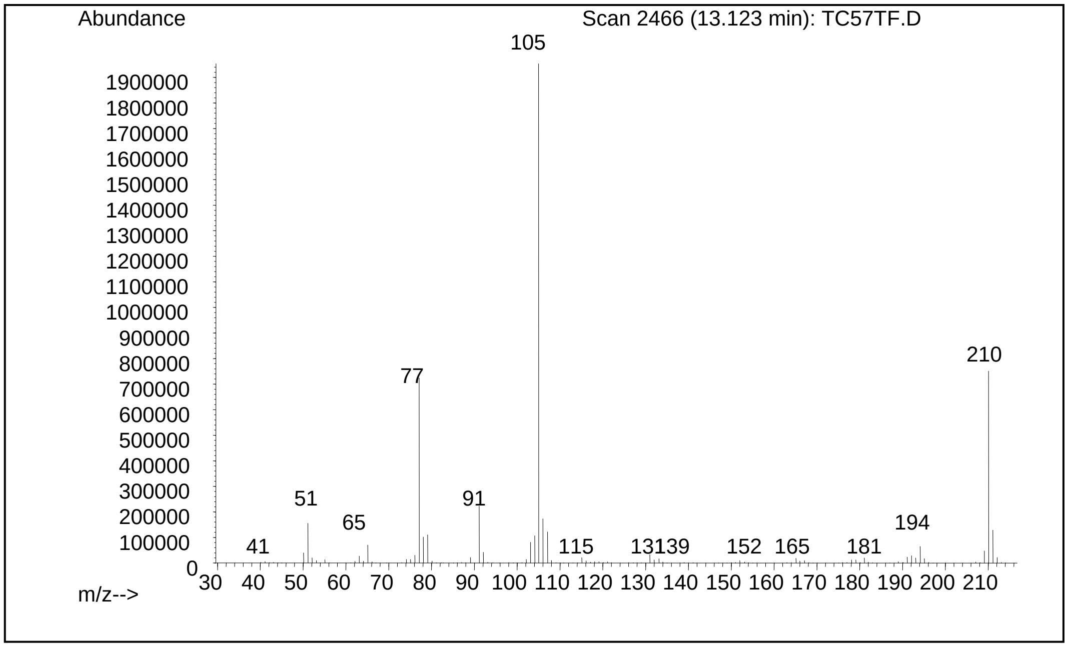


7. 1,3-diphenylpropan-1-one

^{1}H NMR Spectrum (CDCl$_3$, 200 MHz)

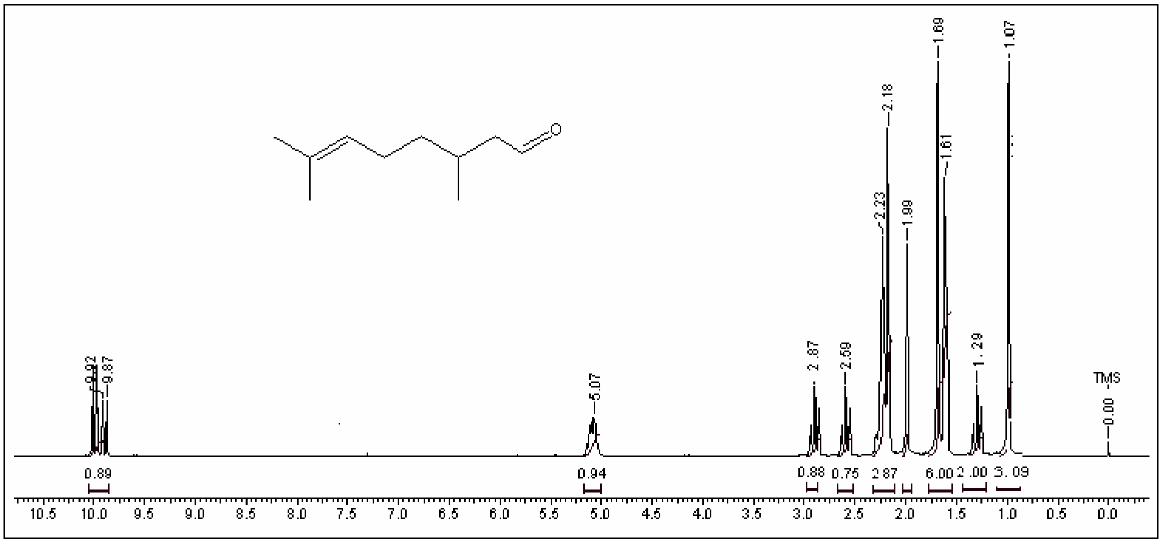


GC-MS Spectrum (70 eV, EI)

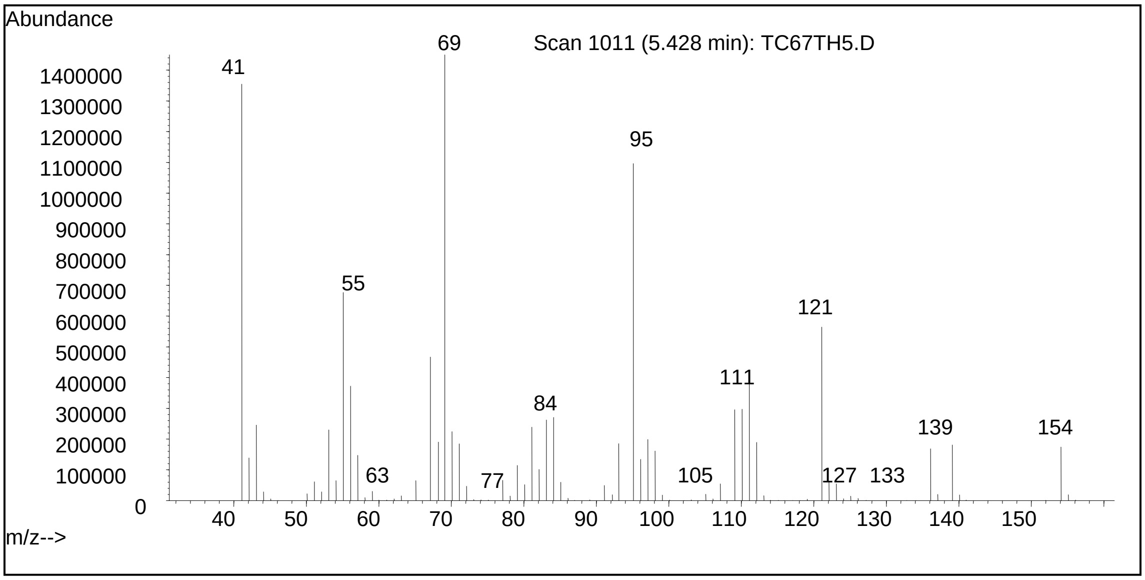


8. 3,7-dimethyloct-6-enal

^{1}H NMR Spectrum (CDCl$_3$, 200 MHz)



GC-MS Spectrum (70 eV, EI)



Publications/Symposia

- Ultrasound promoted asymmetric transfer hydrogenation of ketones using Ru(II)arene/amino alcohol catalyst system
  Savita K. Shingote, A. A. Kelkar, Y. L. Borole, P. D. Joshi, R.V. Chaudhari
  Ultrasonics Sonochemistry 15 (2008) 289–293
- Catalytic asymmetric transfer hydrogenation of ketones using [Ru(p-cymene) $Cl_2]_2$ 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
- Transfer hydrogenation of α,β- unsaturated carbonyl compounds in aqueous biphasic medium: Effect of co-solvents
  Savita K. Shingote, Ashutosh A. Kelkar and Raj M. Deshpande
  To be communicated
- Aqueous biphasic Transfer Hydrogenation of Cinnamaldehyde: A Kinetic Study
  Savita K. Shingote, Ashutosh A. Kelkar and Raj M. Deshpande
  To be communicated to
- The Kinetic study of transfer hydrogenation of nitrobenzene using 5% Pd/C catalyst
  Savita K. Shingote, Ashutosh A. Kelkar1 and Raj M. Deshpande
  To be communicated
- Catalytic transfer hydrogenation of nitrobenzene using Pd/C catalyst.
  S. K. Shingote, A. A. kelkar, R. M. Deshpande
  Poster Presentation -19th National Symposium on Catalysis (CATSYMP-19) at NCL, Pune, India January 18-21, 2009.
- Catalytic transfer hydrogenation of cinnamaldehyde
  S. K. Shingote, A. A. kelkar, R. M. Deshpande
  Poster Presentation-Advances in Chemical Engineering and Process Technology (ACEPT'09) June 4-6, 2009