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 (DH₂) in the presence of a catalyst”, as depicted in 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 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. 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.

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 $\alpha$-$\beta$ 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 $\beta$-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. 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 \( \alpha, \beta \)-unsaturated aldehydes in aqueous biphasic media: A detailed literature on selective hydrogenation of carbonyl or olefinic group in \( \alpha, \beta \)-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\(_2\)/\((1R,2S)\)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)Cl₂]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/m³). 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:

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

Where \( R \) = rate of reaction, expressed in kmol/m³/s; \( A \) = concentration of nitrobenzene (kmol/m³); \( B \) = concentration of potassium formate (kmol/m³); \( C \) = concentration of catalyst (kg/m³); \( D \) = Concentration of water (kmol/m³) \( k \) = 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/m³). 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)Cl2/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 \textit{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/m3). 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.

\[ R = \frac{k[A][B][C][D]}{(1 + K_B[B]^2)(1 + K_C[C]^3)(1 + K_D[D]^3)} \]

Where, \( R \) = rate of reaction, kmol/(m³s); [A] = concentration of catalyst (kmol/m³); [B] = concentration of cinnamaldehyde (kmol/m³); [C] = concentration of sodium formate (kmol/m³); [D] = concentration of ligand (TPPTS) (kmol/m³); \( k \) = 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