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 investigated 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 monoaryl sulfonfylated 1,2 diamine or \(\beta\)-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 \(\beta\)-amino alcohol ligands for ATH reactions, as \(\beta\)-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 \(\beta\)-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 \(\beta\)-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 \(\beta\)-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$_2$O), rhodium chloride trihydrate (RhCl$_3$·3H$_2$O), and iridium chloride (IrCl$_3$·xH$_2$O) 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.

![Structure of chiral ligands](image)
Figure 2.1: Chiral ligands used in this study.

2.2.2 Synthesis of transition metal complexes

The transition metal 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-d$_6$ 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 Instruments, Italy.

2.2.2.1 Synthesis of Di-$\mu$-chloro-bis (η-benzene) chlororuthenium (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 $\delta$ 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 %).
2.2.2.2 Synthesis of Di-μ-chloro-dichlorobis (η⁵-pentamethylcyclopentadienyl)dirhodium(III) complex. [[Rh(Cp*)(Cl]₂ complex]

\[
2\text{RhCl}_3\cdot3\text{H}_2\text{O} + 2\text{C}_5\text{Me}_5\text{H} \rightarrow \text{[Rh(η⁵-C₅Me₅)Cl]₂} + 2\text{HCl}
\]

Rh(Cp*)(Cl₂)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 cm³). Air drying gives 0.8 g (75% yield) of [Rh(Cp*)Cl₂]. The complex was characterized by IR spectra (KBr) cm⁻¹: 2987, 2911 cm⁻¹ (C-H bending of CH₃ of Cp*), 1471, 1374 cm⁻¹ (C-C stretching of Cp*), 1027 cm⁻¹ (CH₃ 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 Rh₂C₂₀H₃₀C₁₄ 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*)Cl₂]₂](image-url)
2.2.2.3 Synthesis of Di-μ-chloro-dichlorobis (η⁵-pentamethylocyclopentadienyl di-iridium(III) complex. [[Ir(Cp*)Cl₂]₂ complex]

\[
2\text{IrCl}_3\cdot\text{XH}_2\text{O} + 2\text{C}_5\text{Me}_5\text{H} \rightarrow [\text{Ir(η}^5\text{-C}_5\text{Me}_5\text{Cl}_2]_2 + 2\text{HCl}
\]

The complex was prepared by a method described by P. M. Maitlis et al. Iridium trichloride trihydrate (1.0 g, 0.0026 mol) and pentamethylocyclopentadiene (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 cm³). Air drying gives 0.5 g (45% yield) of [Ir(Cp*)Cl₂]. Elemental analysis for \(\text{Ir}_2\text{C}_{20}\text{H}_{30}\text{C}_{14}\) 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\text{H NMR spectra which give singlet at 1.60 ppm of protons of pentamethylocyclopentadiene as shown in Figure 2.6 and by IR spectra (KBr pellets): 2987, 2913 cm}^{-1} \text{ (C-H bending of CH}_3\text{ of Cp*), 1449, 1377 cm}^{-1} \text{ (C-C stretching of Cp*) 1034 cm}^{-1}, \text{ (CH}_3\text{ twisting) (Figure 2.7).
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.

![Experimental set-up for Asymmetric transfer hydrogenation](image)

**Figure 2.8:** Experimental set-up for Asymmetric transfer hydrogenation

In a typical experiment, $[\text{Ru(benzene)Cl}_2]_2$ 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

<table>
<thead>
<tr>
<th>Injector (split) Temperature</th>
<th>250°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flame ionization detector</td>
<td>Temperature: 300°C</td>
</tr>
<tr>
<td></td>
<td>Hydrogen: 35.0ml/min</td>
</tr>
<tr>
<td></td>
<td>Zero Air: 320.0ml/min</td>
</tr>
<tr>
<td>Split ratio for Injector</td>
<td>150:1</td>
</tr>
<tr>
<td>Column Temperature</td>
<td>Rate (°C /min)</td>
</tr>
<tr>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>35</td>
</tr>
<tr>
<td>Column Pressure</td>
<td>10 Psi</td>
</tr>
</tbody>
</table>

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.](image)

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 \( \times \) 320 μm ID \( \times \) 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 \( \times \) 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.

\[
\text{%Conversion} = \left( \frac{\text{Initial moles of substrate} - \text{Final moles of substrate}}{\text{Initial moles of substrate}} \right) \times 100
\]
\[
\% \text{ ee} = \frac{(\text{No. of moles of S-isomer} - \text{No. of moles of R-isomer})}{(\text{No. of moles of S-isomer} + \text{No. of moles of R-isomer})} \times 100
\]

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

2.3. RESULTS AND DISCUSSION

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

**Reaction scheme:**

![Reaction scheme](image)

**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.\textsuperscript{5,10} Another possible reason is that the central metal atom might combine with hydroxide first forming catalytically inactive species.\textsuperscript{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 required 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 \textit{ee} was around 70\%. For highest catalyst concentration (0.0252 mmol) initially (at 15 minutes) the \textit{ee} was around 70 \% which decreased to 63 \% with time (180 minutes).
Our results are similar to the results obtained by Gavrilidis et al. 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\textsubscript{2}]\textsubscript{2}, 1.26 \times 10^{-5} \text{ mol}; (1R, 2S) ephedrine, 5.1 \times 10^{-5} \text{ mol}; KOH, 1.2 \times 10^{-4} \text{ mol}; IPA, 25 \text{ 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$_2$], 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.](image)

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

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
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of reaction for Ru(II)/amino alcohol catalyst in IPA-base system was observed by Noyori et al. and other groups also.\textsuperscript{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 $1.26 \times 10^{-5}$, $5.1 \times 10^{-5}$ and $2.5 \times 10^{-3}$ 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base: Ru</th>
<th>Conversion %</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0 : 1</td>
<td>No reaction</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2.5 : 1</td>
<td>71</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>5 : 1</td>
<td>91</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>10 : 1</td>
<td>91</td>
<td>68</td>
</tr>
</tbody>
</table>

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

Chowdhury and Backvall\textsuperscript{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.\textsuperscript{13,14} In the present work [Ru(benzene)Cl\textsubscript{2}]\textsubscript{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 $\beta$-amino alcohol ligand and
Cl\textsuperscript{−} from the \([\text{Ru(benzene)}\text{Cl}_2]\textsubscript{2}\) catalyst to give catalytic species 2 in the presence of base. (Figure 2.15)

\[
\begin{align*}
\text{[Ru(benzene)Cl}_2\textsubscript{2} &+ \text{Ph}NHR\text{OH} \xrightarrow{\text{base}} \text{RuCl}_2O\text{NHPh} - \text{HCl} \\
\end{align*}
\]

**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.

\[
\begin{align*}
\text{RuCl}_2O\text{NHPh} &- \text{HCl} \xrightarrow{\text{base}} \text{Ru}_\text{O}N\text{RPh} \\
\end{align*}
\]

**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.\textsuperscript{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 $1.26 \times 10^{-5}$, $2.5 \times 10^{-3}$ and $1.2 \times 10^{-4}\text{mol}$ 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).

![Figure 2.17: Effect of concentration of ligand on conversion (A) and ee (B)](image)

**Reaction conditions:** $[\text{Ru(benzene)Cl}_2]_2$, $1.26 \times 10^{-5}\text{mol}$; Acetophenone, $2.5 \times 10^{-3}\text{mol}$; KOH, $1.2 \times 10^{-4}\text{mol}$; 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. $\beta$-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 $[\text{Ru}(\rho\text{-cymene})\text{Cl}_2]_2$ 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](image)

**Reaction conditions:** [Ru(benzene)Cl₂]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 cm³

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)Cl₂]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 cm³

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.

![Graph showing the reaction profile for ATH of acetophenone along with % ee](image)

**Figure 2.20:** Typical reaction profile for ATH of acetophenone along with % ee. 

**Reaction conditions:** Catalyst, $1.26 \times 10^{-5}$ mol; (1R, 2S) ephedrine, $5.1 \times 10^{-5}$ mol; Acetophenone, $2.5 \times 10^{-3}$ mol; IPA, 25 cm$^3$; KOH, $1.2 \times 10^{-4}$ 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. 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.
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 concentration) 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amplitude</th>
<th>Conversion</th>
<th>ee</th>
<th>TOF (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20%</td>
<td>40%</td>
<td>68</td>
<td>201</td>
</tr>
<tr>
<td>2</td>
<td>40%</td>
<td>73%</td>
<td>68</td>
<td>367</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
<td>91%</td>
<td>69</td>
<td>457</td>
</tr>
<tr>
<td>4</td>
<td>70%</td>
<td>89%</td>
<td>69</td>
<td>445</td>
</tr>
<tr>
<td>5</td>
<td>80%</td>
<td>88%</td>
<td>66</td>
<td>437</td>
</tr>
</tbody>
</table>

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

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.

![Graph of moles of total product formed vs. time](image)

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

**Reaction conditions:** $[\text{Ru(benzene)}\text{Cl}_2]_2$, $1.26 \times 10^{-5}\text{mol}$; (1R, 2S) ephedrine, $5.1 \times 10^{-5}\text{mol}$; Acetophenone, $2.5 \times 10^{-3}\text{mol}$; KOH, $1.2 \times 10^{-4}\text{mol}$; IPA, 25 cm$^3$; Temperature, 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.\textsuperscript{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 \([\text{Ru(benzene)}\text{Cl}_2]_2/(1R, 2S)\) 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](image)

**Reaction conditions**: \([\text{Ru(benzene)}\text{Cl}_2]_2, 1.26 \times 10^{-5}\text{mol}; (1R, 2S)\) ephedrine, \(5.1 \times 10^{-5}\text{mol};\) Acetophenone, \(2.5 \times 10^{-3}\text{mol};\) IPA, 25 cm\(^3\); KOH, \(1.2 \times 10^{-4}\text{mol};\) 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: \([\text{Ru(benzene)}\text{Cl}_2]_2, \ 1.26 \times 10^{-5} \text{mol}\); (1R, 2S) ephedrine, \(5.1 \times 10^{-5} \text{mol}\); Acetophenone, \(2.5 \times 10^{-3} \text{mol}\); IPA, \(25 \text{ cm}^3\); KOH, \(1.2 \times 10^{-4} \text{mol}\); 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.
Figures 2.25: Effect of substrate concentration on conversion (A) and ee (B) of ATH of acetophenone under ultrasound

**Reaction conditions:** \([\text{Ru(benzene)}\text{Cl}_2], 1.26 \times 10^{-5}\) mol; \((1R, 2S)\) ephedrine, \(5.1 \times 10^{-5}\) mol; IPA, \(25\) cm³; KOH, \(1.2 \times 10^{-4}\) 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 \([\text{Ru(benzene)Cl}_2]_2/(1R,\ 2S)\ ephedrine\) 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:** \([\text{Ru(benzene)Cl}_2]_2, \ 1.26 \times 10^{-5}\text{mol}; (1R, 2S)\ ephedrine, 5.1 \times 10^{-5}\text{mol};\ Acetophenone, 2.5 \times 10^{-3}\text{mol}; KOH, 1.2 \times 10^{-4}\text{mol}; IPA, 25 \text{cm}^3;\ Temperature, 298\ K; \ Reaction\ time, 12\ minutes; pulse\ ratio 3:1\)

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: \([\text{Ru(benzene)Cl}_2], 1.26 \times 10^{-5}\) mol; \((1R, 2S)\) ephedrine, \(5.1 \times 10^{-5}\) mol; Acetophenone, \(2.5 \times 10^{-3}\) mol; KOH, \(1.2 \times 10^{-4}\) mol; IPA, 25 cm\(^3\); Temperature, 298 K; Reaction time, \(12\) minutes, silent-120 minutes; 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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst used</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>TOF (h⁻¹)</th>
<th>Silent reaction</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>TOF (h⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ru(benzene)Cl₂]₂</td>
<td>91</td>
<td>69</td>
<td>457</td>
<td>90</td>
<td>69</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>2ᵃ</td>
<td>[Rh(Cp*)Cl₂]₂</td>
<td>90</td>
<td>77</td>
<td>896</td>
<td>95</td>
<td>81</td>
<td>189</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>[Ir(Cp*)Cl₂]₂</td>
<td>41</td>
<td>78</td>
<td>204</td>
<td>87</td>
<td>83</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>[Ru(p-cymene)Cl₂]₂</td>
<td>36</td>
<td>91</td>
<td>136</td>
<td>81</td>
<td>91</td>
<td>27</td>
<td></td>
</tr>
</tbody>
</table>

**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 cm³; 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*)Cl₂]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*)Cl₂], 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 cm³; 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

<table>
<thead>
<tr>
<th>No.</th>
<th>Ligand</th>
<th>Time, min</th>
<th>Conv., %</th>
<th>ee, %</th>
<th>Time, min</th>
<th>Conv., %</th>
<th>ee, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(1S, 2R) ephedrine (Lig.1)</td>
<td>6</td>
<td>91</td>
<td>78</td>
<td>30</td>
<td>95</td>
<td>81</td>
</tr>
<tr>
<td>2</td>
<td>(2S)-1-(1S phenylethylamino) propane-2-ol (Lig.2)</td>
<td>6</td>
<td>40</td>
<td>83</td>
<td>30</td>
<td>60</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>(1S)-1-phenyl-2-(1S-phenyl ethylamino)ethanol (Lig.3)</td>
<td>12</td>
<td>49</td>
<td>81</td>
<td>120</td>
<td>84</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>1R,2S cis aminoindanol (Lig.4)</td>
<td>6</td>
<td>95</td>
<td>84</td>
<td>30</td>
<td>95</td>
<td>83</td>
</tr>
</tbody>
</table>

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. 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 \([\text{Ru(benzene)Cl}_2]_2/(1R, 2S)\text{ ephedrine}\) 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>
<thead>
<tr>
<th>Sr. no.</th>
<th>Ketone</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>TOF (h(^{-1}))</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
<th>TOF (h(^{-1}))</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetophenone</td>
<td>91</td>
<td>69</td>
<td>457</td>
<td>90</td>
<td>69</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>4-Bromoacetophenone</td>
<td>97</td>
<td>48</td>
<td>485</td>
<td>98(^#)</td>
<td>51</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>4-Chloroacetophenone</td>
<td>98</td>
<td>51</td>
<td>488</td>
<td>97(^#)</td>
<td>52</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>4-Methylacetophenone</td>
<td>70</td>
<td>62</td>
<td>349</td>
<td>77</td>
<td>65</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>4-Isobutylacetophenone</td>
<td>78</td>
<td>61</td>
<td>390</td>
<td>80</td>
<td>63</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>2,5-Dimethylacetophenone</td>
<td>26</td>
<td>8</td>
<td>131</td>
<td>37</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>4-Methoxyacetophenone</td>
<td>44</td>
<td>61</td>
<td>218</td>
<td>51</td>
<td>63</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>2-Acetyl-6-methoxy naphthalene*</td>
<td>60</td>
<td>56</td>
<td>300</td>
<td>61</td>
<td>57</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>4-Nitroacetophenone</td>
<td>59</td>
<td>39</td>
<td>292</td>
<td>46</td>
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<td>23</td>
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<tr>
<td>10</td>
<td>3-Acetyl pyridine</td>
<td>92</td>
<td>42</td>
<td>461</td>
<td>98(^#)</td>
<td>42</td>
<td>98</td>
</tr>
</tbody>
</table>

**Table 2.6: Screening of various ketones for asymmetric transfer hydrogenation**

**Reaction conditions:** \([\text{Ru(benzene)Cl}_2]_2, \ 1.26 \times 10^{-5}\text{mol}; (1R, 2S)\text{ ephedrine}, 5.1 \times 10^{-3} \text{mol}; \ 4\text{BrCH}_2\text{COCH}_3, 2.5 \times 10^{-3}\text{mol}; \ \text{IPA}, 25 \text{cm}^3; \ \text{KOH}, 1.2 \times 10^{-4}\text{mol}; \ \text{Temperature}, 298 \text{K}

**Reaction time:** Sonochanical 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 NaBH₄ 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). Reten: 16.1 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.
Figure 2.31: Influence of temperature on activity of the catalyst under ultrasound

Reactivity conditions: \([\text{Ru(benzene)}\text{Cl}_2]_2, 1.26 \times 10^{-5}\text{mol; } (1R, 2S)\text{ ephedrine, } 5.1 \times 10^{-5}\text{mol; } \text{Acetophenone, } 2.5 \times 10^{-3}\text{mol; } \text{IPA, } 25\text{ cm}^3; \text{KOH, } 1.2 \times 10^{-4}\text{mol; })\) 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\textsuperscript{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, \(\beta\)-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.\textsuperscript{32}
REFERENCES


SPECTRA
1. 1-Phenyl ethanol

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

[Graph of GC analysis with peaks labeled 105, 106, 107, 108, 109, and 110.

GC-MS Spectra (70 eV, EI)

[Graph of GC-MS spectra with peaks at m/z 79, 76, 31, 51, 107, 122, 137, 148, 151, 162.
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)**

Abundance

4. 1-p-Methylphenylethanol

GC Analysis: Standard racemic alcohol and reaction mixture

![GC-MS Spectra (70 eV, EI)](image)

![GC-MS Spectra (70 eV, EI)](image)
5. 1-p-Isobutylphenylethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture

GC-MS Spectra (70 eV, EI)

Scan 1210 (8.129 min): EP18.D

117 163 91 178
6. 1-(2,5-Dimethylphenyl)ethanol

HPLC Analysis: Standard racemic alcohol and reaction mixture

GC-MS Spectra (70 eV, EI)

Scan 1645 (9.658 min): 25DMAP.D
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)](image)

**GC-MS Spectra (70 eV, EI)**

![GC-MS Spectra](image)
10. 1-(pyridin-3-yl) ethanol

**GC Analysis: Standard racemic alcohol and reaction mixture**

**GC-MS Spectra (70 eV, EI)**

Scan 558 (5.031 min): DSK11T15.D