Catal Lett (2010) 138:231–238
DOI 10.1007/s10562-010-0408-y

Catalytic Asymmetric Transfer Hydrogenation of Ketones Using $[Ru(p\text{-cymene})Cl_2]_2$ with Chiral Amino Alcohol Ligands

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Received: 12 March 2010 / Accepted: 1 July 2010 / Published online: 20 July 2010

Abstract Catalytic asymmetric transfer hydrogenation of aromatic alkyl ketones has been investigated using [Ru(*p*-cymene)$Cl_2]_2$ and new derivatives of *β*-amino alcohols synthesized from (S)-(−)-lactic acid and mandelic acid as ligands. Chiral secondary alcohols were obtained with good to excellent conversion (60–90%) and moderate to good enantioselectivities (40–86%).

Keywords Asymmetric transfer hydrogenation · Ru catalyst · Ketones · Amino alcohol ligand

1 Introduction

Catalytic asymmetric transfer hydrogenation of ketones is one of the important transformations in organic chemistry and a large number of catalytic methods are available to achieve this goal [1–8]. Among these, transfer hydrogenation of prochiral ketones using 2-propanol as a reductant has emerged as a highly efficient technique [9, 10]. The advantages of asymmetric transfer hydrogenation using 2-propanol as a reductant are well documented in the literature [5, 9, 10]. Owing to simplicity of operation and importance of the subject, the reaction has been extensively investigated using various ligands and hydrogen sources in recent years [11–15]. One of the most significant breakthroughs in transfer hydrogenation was reported by Noyori et al. with the use of chlororuthenium (II) arene precursors with chiral monoarylsulfonylated-1,2-diamines [16–18] or *β*-amino alcohols [19] as ligands. The structurally well defined [Ru^{II}(arene) (TsDPEN)] (TsDPEN = (1R,2R)-*N*-(*p*-tolylsulfonyl)-1,2-diphenylethylene-diamine) system enables highly effective reduction of a variety of ketones with greater than 90% ee [16–18]. Noyori's catalyst system based on Ru(II) arene complex and simple *β*-amino alcohols such as ephedrine gives highest catalytic activity as well as high enantioselectivity (95% yield and 91% ee in 1 h, using $[RuCl_2(C_6Me_6)]_2$ as a catalyst precursor) [19]. This key development has led to intense exploration of Ru(II)arene(amino alcohol) systems with the aim of designing new ligands and broadening the scope of asymmetric transfer hydrogenation reaction. A variety of *β*-amino alcohols were synthesized and used as ligands in the Ru(II) catalyzed asymmetric transfer hydrogenation of ketones. From the literature, it is found that when amino alcohols are used as chiral auxiliaries, the best results are obtained using 2-propanol as the hydride source. Several research groups have reported on the incompatibility of amino alcohols with formic acid/triethylamine as the hydride source [6, 7, 20].

Andersson et al. [21–25] have successfully developed 2-Azanorboronyl based amino alcohols as ligands and used in the Ru(II) catalyzed asymmetric transfer hydrogenation of aryl alkyl ketones like acetophenone. Asymmetric

Electronic supplementary material The online version of this article (doi:10.1007/s10562-010-0408-y) contains supplementary material, which is available to authorized users.

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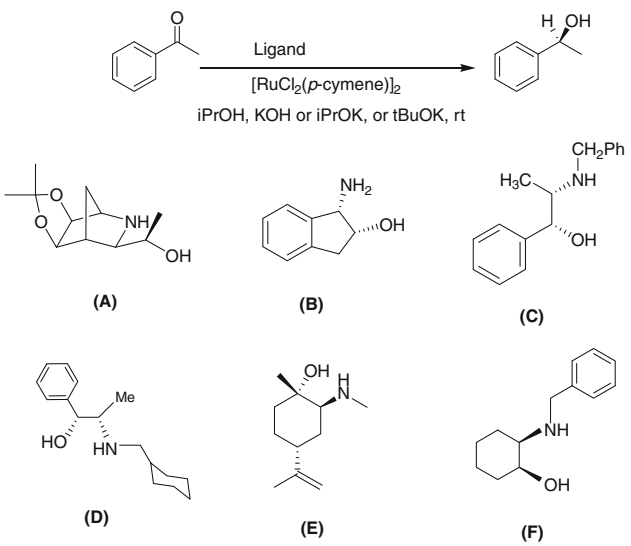
transfer hydrogenation using Azanorboronyl alcohol as a ligand (Scheme 1, **A**) was fast and 97% conversion of acetophenone with 96% ee was achieved in 0.25 h. A wide variety of ketones were reduced with high enantioselectivity (85–99%) using this catalyst system. Wills et al. [26–29] have investigated transfer hydrogenation of various ketones using (1R,2S)-cis-1-aminoindan-2-ol as a ligand (Scheme 1, **B**) with high asymmetric induction (70–98%). Van Leeuwen et al. [30, 31] have investigated various substituted amino ethanol and norephedrine based ligands and tetradentate ligands for transfer hydrogenation of ketones. Best results (88% conversion of acetophenone with 95% ee) were obtained using (1R,2S)-*N*-benzyl-norephedrine as a ligand (Scheme 1, **C**). They also found that bidentate coordination is desirable even for tetradentate ligand and catalytic activity decreased significantly with tetradentate ligands. Frost et al. [32] have prepared a series of amino alcohols (based on established amino alcohol backbone) and found that ligand **D** (Scheme 1) gave best results for transfer hydrogenation of acetophenone (91% conversion and 95% ee at 10 °C). Watts et al. [33] have prepared a series of terpene based amino alcohols and used for transfer hydrogenation of various ketones using $[RuCl_2(p\text{-cymene})_2]_2$ as a catalyst. Good to excellent yield with moderate enantioselectivity (up to 71%) was obtained using limonene derived amino alcohol (1S,2S,4R)-1-methyl-4-(1-methylethenyl)-2-(methylamino)cyclohexane (Scheme 1, **E**). Recently, Schiffers et al. [34] have used 2-aminocyclohexanol derivatives for transfer hydrogenation of acetophenone using $[RuCl_2(p\text{-cymene})_2]_2$ as a catalyst. Enantiomers of 2-aminocyclohexanol derivatives were separated by resolution using (R)- and (S)-mandelic acid. Best results (>95% conversion and up to 96% ee at 10 °C) were obtained using **F** (Scheme 1) as a ligand.



Scheme 1 Transfer hydrogenation of acetophenone using amino alcohol ligands

From the literature, it can be clearly seen that amino alcohol structure and substituents significantly affect conversion as well as selectivity, though the exact reasons for the observed effects (steric and electronic) are still not understood completely [9, 30, 31, 35]. From the literature, it was observed that most of the amino alcohol derivatives investigated have chiral centers on adjacent carbon atoms and are mostly derived from ephedrine or norephedrine. We decided to synthesize chiral amino alcohol ligands starting from cheap and easily available raw materials like (S)-(−)-lactic acid, racemic mandelic acid, benzyl amine and (R)- and (S)- α-methyl benzyl amine. In these amino alcohols the chiral centers will not be on the adjacent carbon atoms. One chiral center will be on the carbon attached to –OH group, while other chiral center will be on the carbon attached to –N of the amino alcohol. There are no reports on the transfer hydrogenation of ketones using such amino alcohols as ligands. In this paper, synthesis of new derivatives of amino alcohol ligands and their applications in Ru(II)(arene) catalyzed transfer hydrogenation of ketones have been reported.

2 Experimental

All the experiments were carried out under inert atmosphere of argon using oven-dried glassware. All the ketones used except 2-Acetyl-6-methoxy naphthalene were procured from Aldrich Chemicals, USA. 2-Acetyl-6-methoxy naphthalene was obtained as a free sample from private company and purity of the compound (>98%) was confirmed by GC and GC–MS analysis. $[Ru(p\text{-cymene})Cl_2]_2$ was purchased from Aldrich chemicals, USA, while $[RhCp^* Cl_2]_2$ and $[IrCp^* Cl_2]_2$ were purchased from Strem Chemicals, USA. 2-Propanol (HPLC grade) was procured from Merck, India. $[Ru(benzene)Cl_2]_2$ was prepared using the literature procedure [36]. The ^1H NMR spectra were recorded on a 200 MHz Bruker spectrometer. ^{13}C NMR spectra were recorded on a 400 MHz Bruker spectrometer. FTIR spectra were recorded on Shimadzu spectrometer (Model IR prestige 21) and reported in cm^{-1}. HPLC analysis was carried out using Perkin Elmer HPLC instrument with quaternary gradient pump, diode array detector and auto sampler. GC analysis was carried out using Agilent GC (Agilent Technologies, USA, Model 6850) using HP-Chiral column and HP-1 column purchased from Agilent Technologies. LC–MS analysis was carried out by Thermo Fisher Scientific LC–MS (MSQ plus Model).

2.1 Synthesis and Characterization of Amino Alcohol Ligands

(S) Methyl lactate and methyl mandalate were prepared using standard literature procedures.

Three ligands were prepared starting from S (−) methyl lactate and α-(S)-methyl benzyl amine, α-(R) methyl benzyl amine or benzyl amine as reactants. Typical procedure used for the synthesis of 2-Propanol-1-[(1-phenyl ethyl) amino] [S, S] using S (−) methyl lactate and α-(S)-methyl benzyl amine as reactants is presented below. Characterization details of ligands prepared are also presented below:

*2.1.1 Preparation 2-Propanol-1-[(1-phenyl ethyl) amino] [S,S] (Ligand-**1**)*

Step 1: S (−) methyl lactate 11.6 g (0.1 mol) and α-(S)-methyl benzyl amine 12.1 g (0.1 mol) were taken in a 100 mL round bottom flask and refluxed for 12 h. The contents were cooled to room temperature and 50 mL ice-cold solution of 1 N HCl was added to the flask. The contents were shaken vigorously and aqueous layer was discarded to remove unreacted amine. Toluene (50 mL) was added to the remaining organic layer in the flask. The contents were heated at 70 °C for about 10 min to get clear solution. The solution was dried over sodium sulphate and concentrated under reduced pressure using rotary evaporator to get amide derivative. Yield of the compound was 16 g (83%). Formation of the desired amide derivative was confirmed by NMR, LC–MS analysis. *Step 2*: $NaBH_4$ (3.33 g, 90 mmol) was taken in 250 mL round bottom flask containing 100 mL THF (dried over KOH). Amide derivative (4.2 g, 21.8 mmol) was dissolved in 50 mL THF (dried over KOH) in a separate flask and was added slowly to $NaBH_4$ solution. The resulting solution was cooled to 0–5 °C using ice water bath. BF_3·etherate 10 mL (11.4 g, 80 mmol) was taken in dropping funnel and was added carefully to the above solution over a period of 20 min, making sure that excessive pressure does not develop. The solution was stirred for 1 h and allowed to warm to room temperature. The solution was refluxed for 3 h and after cooling to room temperature 10 mL of 2 N HCl was added carefully, followed by 30 mL distilled water, to destroy excess $NaBH_4$ present. The resulting solution was concentrated to ∼40 mL and extracted with n-hexane (2 × 30 mL). 5 N NaOH solution was added to aqueous layer to adjust the pH to 11–12 and extracted with ethyl acetate (3 × 30 mL), dried over sodium sulphate and concentrated to get yellowish liquid as product (2.5 g, yield: 64%).

^{1}H NMR :δ = 1.06–1.09, 3H (d, J = 6.2 Hz), δ = 1.35–1.38, 3H (d, J = 6.6 Hz), δ = 2.28–2.38, 1H (dd, J = 9.0 Hz, 12.0 Hz), δ = 2.44–2.52, 1H (dd, J = 3.4 Hz, 11.9 Hz), δ = 2.91, 2H (br, singlet), δ = 3.58–3.78, 2H (multiplet), δ = 7.19–7.31, 5H (multiplet)

^{13}C NMR :(δ in ppm) 145.6, 128.6, 127.1, 126.5, 66.4, 58.7, 54.4, 24.4, 20.6

FT-IR: (neat) 3383, 3309, 2966, 2877, 1454, 1118, 744, 698

LC–MS: MH^+: 180

*2.1.2 Preparation of 2-Propanol-1-[(1-phenyl ethyl) amino] [S,R] (Ligand-**2**)*

The ligand was prepared using S (−) methyl lactate and α-(R) methyl benzyl amine as reactants and same procedure. Product obtained was yellowish solid (2.5 g, yield: 64%).

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

^{13}C NMR: (δ in ppm) 143.7, 127.5, 126.5, 125.5, 64.7, 56.7, 53.3, 23.2, 19.4

FT-IR: (KBr) 3390, 2924, 1450, 1118, 1064, 763, 702

LC–MS: MH^+: 180

*2.1.3 Preparation of 2-Propanol-1-(phenyl methyl) amino)] (S) (Ligand-**3**)*

The ligand was prepared using S (−) methyl lactate and benzyl amine as reactants and same procedure. Product was obtained as a yellowish liquid (2.7 g, yield: 75%).

^{1}H NMR: δ = 1.08–1.12, 3H (d, J = 6.3 Hz), δ = 2.39–2.49, 1H (dd, J = 9.2 Hz, 12.0 Hz), δ = 2.59–2.66, 1H (dd, J = 3.2 Hz, 12.0 Hz), δ = 3.60, 2H (br, singlet), δ = 3.75–3.88, 3H (multiplet), δ = 7.22–7.31, 5H (multiplet)

^{13}C NMR: (δ in ppm) 138.9, 127.4, 127.1, 126.1, 64.6, 55.3, 52.6, 19.3

FT-IR: (KBr)3309, 3029, 2970, 1455, 1110, 1030, 744, 700

LC–MS: MH^+: 166

Two ligands were prepared starting from methyl mandalate and α-(S) methyl benzyl amine or α-(R) methyl benzyl amine as reactants. Typical procedure used for the synthesis of α-[(1-phenylethyl)amino)methyl]-benzene ethanol] [SS] using methyl mandalate and α-(S) methyl benzyl amine as reactants is presented below.

*2.1.4 Preparation of α-[(1-phenylethyl)amino)methyl]-benzene ethanol] [SS] (Ligand-**4**)*

Step 1: Methyl Mandalate16.7 g (0.1 mol) and α-(S) methyl benzyl amine12.1 g (0.1 mol) were taken in a 250 mL round bottom flask and heated at 130 °C for 3 h.

The solution was cooled to room temperature and 100 mL of ice-cold solution of 1 N HCl was added with stirring. Sticky solid separated on stirring for 15 min. Sticky solid (mixture of racemic amide derivatives) was filtered and dissolved in 30 mL warm toluene to obtain clear solution. The clear solution obtained was cooled to 0 °C and kept standing for 12 h to obtain white crystalline solid. White crystalline solid was filtered and washed with toluene. White solid obtained was pure isomer of amide derivative (6.5 g, yield 25.5%). Purity of the epimer was confirmed by HPLC analysis using Silica column and using 5% IPA in n-Hexane, as mobile phase. Compound was characterized by GC–MS and ^{1}H NMR analysis. *Step 2*: $NaBH_4$ (3.33 g, 90 mmol) was taken in a 250 mL round bottom flask containing 100 mL THF (dried over KOH). Amide derivative (5.2 g, 20.4 mmol) was dissolved in 50 mL THF (dried over KOH) in a separate flask and was added slowly to $NaBH_4$ solution. The resulting solution was cooled to 0–5 °C using ice water bath. BF_3.etherate 10 mL (11.4 g, 80 mmol) was taken in dropping funnel and was added carefully to the above solution over a period of 20 min, making sure that excessive pressure does not develop. The solution was stirred for 1 h and allowed to warm to room temperature. The solution was refluxed for 3 h and after cooling to room temperature, 10 mL of 2 N HCl was added carefully followed by 30 mL distilled water, to destroy excess $NaBH_4$ present. The resulting solution was concentrated to ~40 mL and extracted with n-hexane (2 × 30 mL). 5 N NaOH solution was added to aqueous layer to adjust the pH to 11–12 and the solution was cooled to room temperature to get white crystalline product, which was recrystallized using methanol to get 3.5 g of the pure product (yield: 71.2%). Compound was characterized by LC–MS, ^{1}H NMR as well as single crystal X-ray analysis (Fig. 1, also see supplementary material for details).

Thus pure (S,S) amide derivative crystallized out preferentially from toluene solution on cooling (Step 1), while other isomer (S,R) was soluble in toluene solution. The separation of the desired diasteriomer of amide derivative by preferential crystallization of one of the isomer from the toluene solution (Step 1) is very interesting. This has allowed us to develop an easy procedure for the synthesis of (R,R) and (S,S) isomers starting from cheap racemic methyl mandalate as reactant.

^{1}H NMR: δ = 1.41–1.44, 3H (d, J = 6.6 Hz), δ = 2.37, 2H (br, singlet), δ = 2.62–2.72, 1H (dd, J = 8.6 Hz, 12.2 Hz), δ = 2.77–2.85, 1H (J = 3.9 Hz, 12.6 Hz), δ = 3.76–3.86, 1H (q, J = 6.8 Hz), δ = 4.59–4.65, 1H (dd, J = 3.8 Hz, 8.4 Hz), δ = 7.30–7.35, 10H (multiplet)

^{13}C NMR: (δ in ppm) 145.3, 142.5, 128.6, 128.4, 127.5, 127.1, 126.5, 125.8, 72.4, 58.5, 55.3, 24.1

FT-IR: (KBr) 3290, 2920, 1454, 1064, 703

LC–MS: MH^+: 242

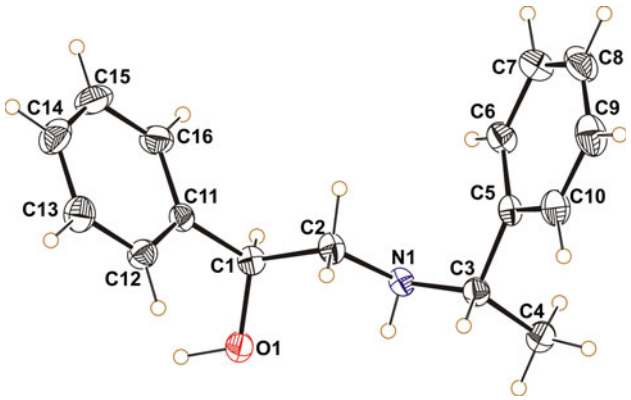


Fig. 1 ORTEP of α-[(1-phenylethyl)amino)methyl]-benzene ethanol] [SS] (Ligand-4) drawn at 30% displacement ellipsoids probability level; H atoms are shown as small spheres of arbitrary radii

2.1.5 *Preparation of α-[(1-phenylethyl)amino)methyl]-benzene ethanol] [RR] (Ligand-**5**)*

The ligand was prepared by reaction of Methyl Mandalate and α-(R) methyl benzyl amine using the procedure described. White crystalline product obtained was recrystallized using methanol to get 3.5 g of the pure product (yield: 71.2%).

1H NMR: δ = 1.42–1.45, 3H (d, J = 6.6 Hz), δ = 2.21, 2H (br, singlet), δ = 2.62–2.68, 1H (dd, J = 8.5 Hz, 12.2 Hz), δ = 2.72–2.83, 1H (dd, J = 3.8 Hz, 12.2 Hz), δ = 3.77–3.86, 1H (q, J = 6.8 Hz), δ = 4.59–4.65, 1H (dd, J = 3.8 Hz, 8.4 Hz), δ = 7.30–7.37, 10H (multiplet)

^{13}C NMR: (δ in ppm) 145.3, 142.5, 128.6, 128.4, 127.5, 127.1, 126.5, 125.8, 72.4, 58.5, 55.3, 24.1

FT-IR: (KBr) 3290, 2920, 1454, 1064, 703

LC–MS: MH^+: 242

2.2 Experimental Procedure

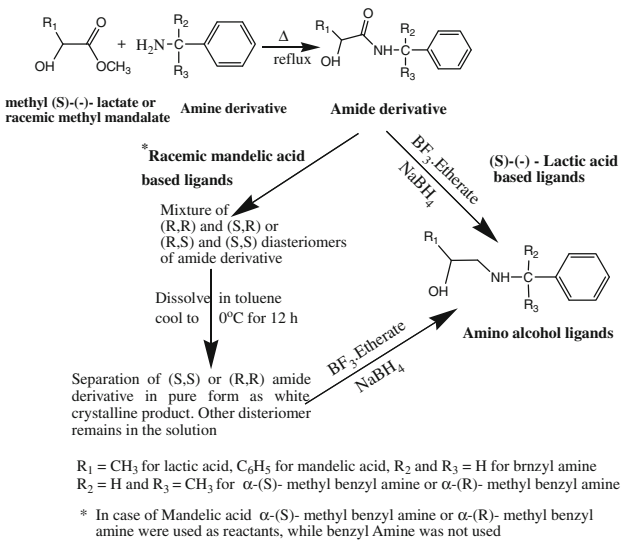
All the reactions were carried out in a jacketed glass reactor flushed with argon prior to the addition of reactants. In a typical experiment, $[Ru(p\text{-cymene})Cl_2]_2$ 7.7 mg (0.013 mmol) and ligand-**4** 13.4 mg (0.055 mmol) was added to 25 mL 2-propanol in a glass reactor. Acetophenone 0.3 g (2.5 mmol) and stock solution of KOH (0.086 N) 6.99 mg (0.12 mmol) were added to the glass reactor and Argon bladder was attached to the reactor to maintain inert conditions. The glass reactor temperature was kept constant at 25 °C using water circulation bath. Reaction was initiated by stirring the reaction mixture with the help of magnetic needle. Reaction was continued for 2 h and reaction sample was withdrawn and quenched by the addition of acetic acid. Analysis of the reaction crude

was carried out by chiral GC analysis (for acetophenone reactions) using HP-Chiral column supplied by Agilent Technologies, USA. For all other reactions enantiomeric excess was obtained by HPLC analysis using Chiracel OD-H column supplied by Daicel Company. Formation of alcohol products was confirmed by GC–MS analysis.

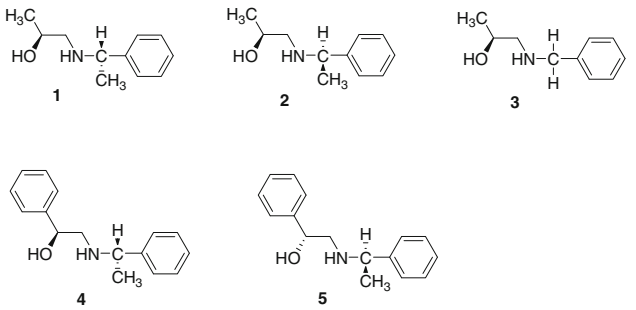
3 Results and Discussion

For our study we have prepared amino alcohols starting from cheap and easily available starting materials such as (S)-(−)-lactic acid and racemic mandelic acid. First, methyl esters of the (S)-(−)-lactic acid and mandelic acid were prepared by known literature methods. Condensation of methyl esters of these acids with amines such as benzyl amine, (R)- or (S)-α-methyl benzyl amine leads to the formation of respective amide derivatives, which on reduction with $NaBH_4$ and BF_3.etherate are converted to the required amino alcohol derivatives. For amino alcohols prepared from (S)-(−)-lactic acid, since chiral (S)-(−)-lactic acid was used as a starting material, required chiral amino alcohols were obtained directly by reduction of amide derivatives. However, for amino alcohols prepared from mandelic acid, racemic methyl mandalate was used as a starting material. The condensation of methyl mandalate with (R)- or (S)- α-methyl benzyl amine yields a mixture of diasteriomers. The mixture of diasteriomers obtained was dissolved in toluene and cooled to 0 °C for 12 h. On cooling the solution white solid crystallized out. The white solid obtained was filtered and washed with toluene. The white solid obtained was pure single isomer of amide derivative (depending on the amine used). With this simple technique, we were able to separate pure isomer (R,R or S,S) from the mixture of diasteriomers, while other diasteriomer (R,S or S,R) remained in the solution. Reduction of the purified amide isomer gives required amino alcohol derivative (Scheme 2). Using this strategy, 3 amino alcohols were prepared starting from (S)-(−)-lactic acid and 2 amino alcohols were prepared staring from racemic mandelic acid (Scheme 3) and used for the asymmetric transfer hydrogenation reaction.

Amino alcohols derived from (S)-(−)-lactic acid and mandelic acid have not been investigated in detail for asymmetric transfer hydrogenation of ketones. Most of the amino alcohols developed are based on ephedrine or norephedrine backbone. According to the proposed mechanism for Ru catalyzed transfer hydrogenation using amino alcohol as a ligand, precatalyst (18 electron Ru complex) is formed by the interaction of Ru(arene) catalyst precursor and amino alcohol ligand (Scheme 4) [24]. Thus both the chiral centers of amino alcohol ligand (for ephedrine based ligands) will be present in the five member Ru complex



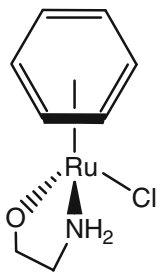
Scheme 2 Synthetic methodology used for the preparation of amino alcohol ligands starting from S-(+)-methyl lactate and racemic mandelic acid as starting materials



Scheme 3 Various amino alcohol ligands synthesized

formed as a precatalyst (Scheme 4). Amino alcohol prepared from (S)-(−)-lactic acid and benzyl amine in the present work (Scheme 3, ligand **3**) has only one chiral center on the C atom attached to –OH group, while there is no chiral center on the C atom attached to –N. For other amino alcohols prepared by condensation of (S)-(−)-lactic acid or racemic mandelic acid with (R)- or (S)-α-methyl benzyl amine (Scheme 3, ligand nos. **1**, **2**, **4** and **5**), second chiral C atom is attached to –N of the amino alcohol and is outside the coordination sphere of Ru. It will be interesting to see the effect of only one chiral center in the amino

Scheme 4 Proposed 18-electron catalyst precursor formed by reaction of Ru(arene) complex and amino alcohol ligand [17, 30]



alcohol ligand and also the effect of additional chiral center outside the coordination sphere on the conversion and chiral selectivity.

As a first step transfer hydrogenation of acetophenone was investigated using Ru, Rh and Ir metal complexes as catalyst precursors with 1R,2S-ephedrine (Ep) and amino alcohols prepared as ligands and the results are presented in Table 1. The results clearly show that the catalysts prepared with amino alcohol ligands (Table 1, Sr. No. 2–6) are active and selective for asymmetric transfer hydrogenation of acetophenone. From the results it can be seen that the configuration of the product was "R" using Ep and ligand **4** (marked with * in the Table 1, Sr. No. 1 and 6) for all the catalyst precursors, while for all other ligands (Table 1, Sr. No. 2–5) the product configuration was "S" for all the catalyst precursors screened. It may be noted that for 1R,2S-ephedrine (Ep) and ligand **4** the configuration of "C" attached to –OH group is "R", while for all other ligands screened the configuration of "C"attached to –OH group is "S". This clearly indicates that the configuration of carbon attached to –OH group is imparted to the chiral alcohol product. The conversion of acetophenone and chiral induction obtained using ligand-**3** compares very well with ephedrine as a ligand (Table 1, compare Sr. No. 1 and 4). As explained earlier configuration of product with Ep as a ligand is "R", while that with ligand **3** is "S". Ligand-**3** has only one chiral center present on the C attached to –OH group. This clearly indicates that the chiral center at the –OH group is more important in deciding the chiral selectivity and other chiral center attached to –N may have minimal role in deciding the chiral selectivity. Similar observations have already been reported by several authors [9, 19, 32, 35]. Comparison of the results obtained using ligands prepared from (S)-(−)-lactic acid for various catalyst precursors (Table 1, Sr. No. 2–4) clearly show that high enantioselectivity was obtained using ligand-**3**, except for $[RhCp^* Cl_2]_2$ catalyst (Compare Table 1, Entry 4 with 1 for Rh catalyst). Enantioselectivity decreased marginally for ligand-**1** (with [S,S] structure), while conversion as well as enantioselectivity decreased for ligand-**2**, having [S,R] structure for all the catalyst precursors investigated. This indicates negative influence of the [S,R] isomer on the catalytic activity and selectivity. Ligands **1** and **4** have same configuration except that the methyl group in the ligand **1** is replaced by phenyl group in the ligand-**4**. Results obtained for both the ligands are comparable for Ru catalyst precursors (Table 1, compare Sr. No. 2 and 5), while for $(RhCp^* Cl_2)_2$ and $(IrCp^* Cl_2)_2$ conversion as well as enantioselectivity was higher for ligand **4**, having phenyl group. Observed results for $[Ru(benzene)Cl_2]_2$ and $[Ru(p\text{-cymene})Cl_2]_2$ complexes as catalysts indicate that methyl group present on the chiral C attached to –OH is sufficient for chiral discrimination. Carpentier et al. also have obtained similar results for transfer hydrogenation of tert-butylacetoacetate using Ru(II) catalyst and ephedrine based ligands [35]. For ligands **4** and **5** prepared from racemic mandelic acid, high conversion (>90%) and moderate to good enantioselectivity was obtained using Ru and Rh catalysts, while low conversion and moderate enantioselectivity was obtained using Ir complex catalyst. Ligands **4** and **5** are enantiomers and (S)-(−)-1-phenyl ethanol was obtained in excess using ligand **4**, while (R)-(+)1-phenyl ethanol was obtained in excess using ligand **5**. Good results were obtained using $Ru(p\text{-cymene})Cl_2]_2$/ligand-**4** combination and also, structure of the ligand-**4** was confirmed by single crystal X-ray

Table 1 Asymmetric reduction of acetophenone using amino alcohol ligands and various catalysts

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

Reaction conditions: Catalyst: 1.3×10^{-5} mol; Ligand: 5.5×10^{-5} mol

Acetophenone: 2.5×10^{-3} mol; KOH: 1.2×10^{-4} mol; IPA: 25 cm^3

Temperature: 25 °C; Reaction time: 2 h

Benz = Benzene; Cp* = C_5Me_5, Ep = (1R, 2S)-ephedrine

[a] S configuration (confirmed by chiral GC analysis using authentic standard)

[b] R configuration (confirmed by chiral GC analysis using authentic standard)

Table 2 Asymmetric reduction of substrates using amino alcohol ligand **4** and $[Ru(p\text{-cymene})Cl_2]_2$ catalyst

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

Reaction conditions: $[Ru(p\text{-cymene})Cl_2]_2$: 1.3×10^{-5} mol; Ligand **4**: 5.5×10^{-5} mol ketone, 2.5×10^{-3} mol; KOH: 1.2×10^{-4} mol; IPA: 25 cm^3; Temperature: 25 °C

[a] Acetonitrile (2 mL) was added to dissolve 2-Acetyl-6-methoxy naphthalene

analysis (See Fig. 1). Further work on the screening of various ketones was carried out using ligand **4** and Ru $(p\text{-cymene})Cl_2]_2$ as a catalyst precursor.

Various ketones were screened using $[Ru(p\text{-cymene})Cl_2]_2$/ligand-**4** catalyst system and the results are presented in Table 2. Best results were obtained for transfer hydrogenation of acetophenone as a reactant (91% conversion and 76% ee). With electron withdrawing substituents in the para position activity increased significantly, while enantioselectivity decreased significantly (Table 2, compare Sr. No. 1 with Sr. No. 2–4, conversion 92–95% in 1 h compared to 91% in 2 h; ee: 52–66 compared to 76%). While with electron donating methyl group in Para position conversion as well as chiral selectivity decreased marginally (Table 2, Sr. No. 1 and 5). With bulkier isobutyl group in para position, the reaction was sluggish (38% conversion in 3 h) with 74% ee. With substituent in the ortho position, conversion as well as chiral selectivity decreased significantly (Table 2, Sr. No. 9 and 10). Thus, reaction did not proceed using 2-acetyl pyridine, while 99% conversion in 1 h reaction time with 64% enantioselectivity was achieved using 3-acetylpyridine as a reactant. 4-Methoxyacetophenone is known to be a challenging substrate probably because of its low redox potential, giving lower conversions and enantioselectivity [17, 23, 34]. In the present study, transfer hydrogenation of 4-methoxyacetophenone gave 54% conversion with 65% ee in 2 h reaction time.

4 Conclusions

The reduction of ketones under catalytic transfer hydrogenation conditions with 2-propanol as a hydrogen source is a mild and highly attractive route for the formation of secondary alcohols. We have shown that (S)-(−)-lactic acid and mandelic acid based β-amino alcohols can be used as ligands for catalytic asymmetric transfer hydrogenation of various ketones. The transfer hydrogenation proceeds smoothly with conversion ranging between 60 and 98% and enantioselectivity between 40 and 86%. Good enantioselectivity has been obtained using ligand having only one chiral center on the C attached to –OH group (ligand-**3**), indicating that the chiral center attached to –OH moiety is important in deciding chiral selectivity. Ligands have been prepared using simple procedure and starting from cheaper raw materials such as (S)-(−)-lactic acid and racemic mandelic acid. For ligands prepared using racemic mandelic acid, chiral resolution of racemic amide derivative was carried out by simple crystallization method using toluene as a solvent. Further work on the detailed investigation on asymmetric transfer hydrogenation is in progress in our laboratory.

Acknowledgement Authors thank CSIR for financial assistance (project CMM0005).

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