Piano-stool Ru(II)-benzene complexes bearing D/L-alanine derived chiral aroylthiourea ligands for asymmetric transfer hydrogenation of ketones in water

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Abstract. The new water soluble chiral Ru(II)-benzene complexes of the type $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L}]$ were obtained from the reactions between $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ and the chiral aroylthiourea ligands (L) derived from unprotected D/L-alanine and characterized. The solid-state structure of representative complexes was confirmed by single crystal X-ray diffraction technique. The Ru(II)-benzene complexes catalyzed the asymmetric transfer hydrogenation (ATH) of aromatic ketones to their enantiopure secondary alcohols. The reactions were carried out in the presence of formic acid–triethylamine mixture in water, and the product alcohols were obtained with excellent conversions (up to 99%) and enantiomeric excesses (up to 99%). The scope of the catalytic system was extended to various aromatic ketones. The catalytic activity of the present water-soluble Ru-benzene complexes toward enantioselective reduction of ketones was considerably higher than that of *p*-cymene analogues in water.

Keywords. Aroylthiourea; Ru-benzene; asymmetric transfer hydrogenation; aqueous medium.

1. Introduction

In organic synthesis, transfer hydrogenation is one of the most significant reduction reactions. The commonly used hydrogen donors for the reduction of ketones other than molecular hydrogen are 2-propanol/base, formic acid/triethylamine (azeotrope mixture) and formate salts. The use of formic acid/triethylamine is accompanied by the evolution of CO_2 gas, which makes the reaction irreversible and has attracted the attention of chemists.^{1–3} In presence of water-soluble formic acid and its salts, transfer hydrogenation is more feasible in water which is undoubtedly a green reaction medium.^{4–6} However, compared to the most extensively studied aqueous-phase hydrogenation reactions, transfer hydrogenation in water has been investigated infrequently.^{7,8}

ATH reactions in aqueous media with Ru(II) complexes were initially concerned with organic-water biphasic systems, with the effort being focused on the design of water-soluble catalysts.^{9,10} However, the catalysts displayed activities and/or enantioselectivities lower than expected. The Noyori-Ikariya

catalyst, derived *in situ* from $[\text{RuCl}_2(p\text{-cymene})]_2$ and sulfonamide ligands, enabled efficient ATH in neat water.¹¹ The reaction was considerably faster than in organic media and afforded excellent enantioselectivities. Thus, following the addition of 5 equivalents of HCOONa and acetophenone with a molar substrate to catalyst ratio (S/C) of 100, the ketone was fully converted into (*R*)-1-phenylethanol in 95% ee after 1 h reaction time; in comparison, the reaction run in the HCOOH-NEt_3 azeotrope afforded a conversion of less than 2% in 1 h, with full conversion requiring more than 10 h (97% ee).¹² Interestingly, β -aminoalcohol ligands were believed to be incompatible with formic acid as a reductant for ATH of ketones,³ the commercially available simple β -aminoalcohol ligands did catalyze the ATH of acetophenone by HCOONa or HCOOH-NEt_3 in water.¹³

Ruthenium complexes demonstrate a variety of useful characteristics, which include low redox potential, high electron transfer ability, high coordination ability to heteroatoms, Lewis acid acidity, unique reactivity of metallic species and intermediates such as oxo-

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metals, metallocycles, and metal carbene complexes.^{12,14,15} Ru-arene compounds are relatively inert towards substitution; arene moiety stabilizes and protects the metal center from rapid oxidation of Ru(II) to Ru(III).¹⁶ Half-sandwich Ru-arene complexes containing asymmetric ligands have been used as effective catalysts in various asymmetric organic transformations.¹⁷ Therefore, a large number of novel, useful reactions have begun to be developed using catalytic amounts of ruthenium complexes.

The demand for enantiopure compounds is rapidly growing due to their prominence in the progress of several new biologically active compounds, such as pharmaceuticals and agrochemicals.¹⁸ For pharmaceuticals or pesticides, usually, only one enantiomer is responsible for the preferred biological activity, whereas the other is inactive or even causes dangerous side effects. Use of enantiomerically pure agrochemicals diminishes their effect on the environment.¹⁹ Likewise, production of many flavors, fragrances, chiral polymers, advanced materials with nonlinear optical properties, ferroelectric liquid crystals, etc., depends on the availability of chiral building blocks.^{20–24} Particularly, enantiomerically pure secondary alcohols are valuable resources for the synthesis of numerous pharmaceuticals. The need for enantiopure drugs has been improved in recent years and, hence, chiral alcohols are in demand.²⁵ ATH of pro-chiral aromatic ketones is one of the impressive methods for the production of optically active secondary alcohols.

Here, we report the synthesis and characterization of new water-soluble Ru(II)-benzene complexes of the type $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L}]$ (**1–6**) where L = (*R*)/(*S*)-2-(3-benzoylthioureido)propanoic acid (L1/L2), (*R*)/(*S*)-2-(3-(thiophene-2-carbonyl)thioureido)propanoic acid (L3/L4) or (*R*)/(*S*)-2-(3-(furan-2-carbonyl)thioureido)propanoic acid (L5/L6). The catalytic performance of the complexes (**1–6**) was tested in ATH of aromatic, heterocyclic and bulky pro-chiral ketones to form corresponding enantiopure secondary alcohols in water medium.

2. Experimental

2.1 Materials and methods

The chiral aroylthiourea ligands and $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ were prepared by following available procedures.^{26,27} UV-Visible spectra were recorded on a Shimadzu 2600 spectrophotometer, operating in the range of 200–800 nm. FT-IR spectra in the range of 600–4000 cm^{-1} were recorded on a Nicolet iS5 FT-IR spectrophotometer as KBr pellets. CHNS

analyses were performed using a Perkin Elmer 2400 series II elemental analyzer. NMR spectra were recorded on a Bruker 500 MHz spectrometer. Melting points were determined on a Sigma melting point apparatus and are uncorrected. GC-MS analyses for catalytic experiments were performed using a Shimadzu GCMS-QP 2010 Ultra gas chromatograph mass spectrometer with a Restek-5 capillary column. Enantiomeric excesses (ee) were determined using a Shimadzu HPLC instrument with a Daicel Chiralcel OB-H column. Specific rotation values were measured on a Rudolph Autopol IV polarimeter.

2.2 Synthesis of the complexes (**1–6**)

$[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ (110 mg, 0.22 mmol) in toluene (10 mL) was added to the suspension of (*R*)/(*S*)-2-(3-benzoylthioureido)propanoic acid (111 mg, 0.44 mmol) or (*R*)/(*S*)-2-(3-(thiophene-2-carbonyl)thioureido)propanoic acid (113.6 mg, 0.44 mmol) or (*R*)/(*S*)-2-(3-(furan-2-carbonyl)thioureido)propanoic acid (106.5 mg, 0.44 mmol) in toluene (15 mL) and the resulting solution was stirred for 20 h at 27 °C. In the course of the reaction, an orange precipitate was formed; further, the addition of hexane gave an orange solid product. The product was collected by filtration, washed with hexane and dried *in vacuo*.

2.2a $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L1}](\mathbf{1})$: Yield: 89 mg, 88%. M.p.: 178 °C. $[\alpha]_D^{27}$: -72° . Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_3$ RuS: C, 40.64; H, 3.61; N, 5.58; S, 6.38. Found: C, 40.56; H, 3.54; N, 5.47; S, 6.29. ^1H NMR δ , ppm (500 MHz, DMSO- d_6): 1.49 (d, 3H, J = 10 Hz, CH_3), 4.81–4.87 (m, 1H, C*HMe), 5.96 (s, 6H, C_6H_6), 7.50–8.30 (m, 5H, aromatic protons), 11.29 (d, 1H, J = 10 Hz, C=S attached N-H), 11.49 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH) ppm. ^{13}C NMR δ , ppm (125 MHz, DMSO- d_6): 17.1 (CH_3), 53.0 (asymmetric carbon), 87.6 (C_6H_6), 128.4, 128.5, 132.0, 133.0 (aromatic carbons), 168.4 (C=O), 172.8 (C=S), 179.8 (COOH) ppm. FT-IR (KBr, cm^{-1}): 3343 (m, ν (amide N-H)), 3166 (s, ν (thiourea N-H)), 1684 (s, ν (C=O)), 1751 (s, ν (COOH)), 1182 (s, ν (C=S)). UV-Vis [CHCl_3 ; λ , nm (ϵ , $\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$): 442 (7836), 320 (40167), 253 (171032).

2.2b $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L2}](\mathbf{2})$: Yield: 91 mg, 90%. M.p.: 178 °C. $[\alpha]_D^{27}$: $+74^\circ$. Anal. Calcd. for $\text{C}_{17}\text{H}_{18}\text{Cl}_2\text{N}_2\text{O}_3$ RuS: C, 40.64; H, 3.61; N, 5.58; S, 6.38. Found: C, 40.54; H, 3.55; N, 5.49; S, 6.28. ^1H NMR δ , ppm (500 MHz, DMSO- d_6): 1.49 (d, 3H, J = 5 Hz, CH_3), 4.83–4.86 (m, 1H, C*HMe), 5.97 (s, 6H, C_6H_6), 7.51–7.94 (m, 5H, aromatic protons), 11.30 (d, 1H, J = 10 Hz, C=S attached N-H), 11.50 (s, 1H, C=O and C=S attached N-H), 13.23 (bs, 1H, COOH) ppm. ^{13}C NMR δ , ppm (125 MHz, DMSO- d_6): 17.1 (CH_3), 53.0 (asymmetric carbon), 87.6 (C_6H_6), 128.4, 128.5, 132.0, 133.0 (aromatic carbons), 168.4 (C=O), 172.8 (C=S), 179.8 (COOH) ppm. FT-IR (KBr, cm^{-1}): 3222 (m; ν (amide N-H)), 3181 (s; ν (thiourea N-H)), 1674 (s; ν (C=O)), 1747 (s; ν (COOH)), 1195 (s; ν (C=S)). UV-Vis [CHCl_3 ; λ ,

nm (ϵ , $\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$): 442 (10527), 320 (31589), 254 (116862).

2.2c $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L3}](\mathbf{3})$: Yield: 88 mg, 86%. M.p.: 182 °C. $[\alpha]_D^{27}$: +71°. Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3\text{RuS}_2$: C, 35.44; H, 3.17; N, 5.51; S, 12.61. Found: C, 35.36; H, 3.06; N, 5.43; S, 12.49. ^1H NMR δ , ppm (500 MHz, DMSO-d_6): 1.47 (d, 3H, J = 5 Hz, CH_3), 4.79–4.85 (m, 1H, C^*HMe), 5.97 (s, 6H, C_6H_6), 7.22–8.35 (m, 3H, aromatic protons), 11.15 (d, 1H, J = 5 Hz, C=S attached N-H), 11.56 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH) ppm. ^{13}C NMR δ , ppm (125 MHz, DMSO-d_6): 17.1 (CH_3), 53.0 (asymmetric carbon), 87.6 (C_6H_6), 128.6, 132.5, 135.2, 136.5 (aromatic carbons), 162.2 (C=O), 172.8 (C=S), 179.5 (COOH) ppm. FT-IR (KBr, cm^{-1}): 3348 (m; ν (amide N-H)), 3211 (s; ν (thiourea N-H)), 1697 (s; ν (C=O)), 1725 (s; ν (COOH)), 1191 (s; ν (C=S)). UV-Vis [CHCl_3 ; λ , nm (ϵ , $\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$): 442 (11483), 330 (70000), 296 (133161), 253 (177806).

2.2d $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L4}](\mathbf{4})$: Yield: 90 mg, 88%. M.p.: 183 °C. $[\alpha]_D^{27}$: -76°. Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3\text{RuS}_2$: C, 35.44; H, 3.17; N, 5.51; S, 12.61. Found: C, 35.38; H, 3.07; N, 5.45; S, 12.52. ^1H NMR δ , ppm (500 MHz, DMSO-d_6): 1.48 (d, 3H, J = 10 Hz, CH_3), 4.80–4.85 (m, 1H, C^*HMe), 5.97 (s, 6H, C_6H_6), 7.23–8.36 (m, 3H, aromatic protons), 11.15 (d, 1H, J = 5 Hz, C=S attached N-H), 11.57 (s, 1H, C=O and C=S attached N-H), 13.21 (bs, 1H, COOH) ppm. ^{13}C NMR δ , ppm (125 MHz, DMSO-d_6): 17.1 (CH_3), 53.0 (asymmetric carbon), 87.6 (C_6H_6), 128.6, 132.5, 135.2, 136.5 (aromatic carbons), 162.2 (C=O), 172.8 (C=S), 179.5 (COOH) ppm. FT-IR (KBr, cm^{-1}): 3347 (m; ν (amide N-H)), 3207 (s; ν (thiourea N-H)), 1697 (s; ν (C=O)), 1725 (s; ν (COOH)), 1195 (s; ν (C=S)). UV-Vis [CHCl_3 ; λ , nm (ϵ , $\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$): 446 (9196), 330 (65026), 294 (114225), 253 (154844).

2.2e $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L5}](\mathbf{5})$: Yield: 89 mg, 91%. M.p.: 163 °C. $[\alpha]_D^{27}$: -48°. Anal. Calcd. for $\text{C}_{19}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O}_4\text{RuS}$: C, 41.16; H, 5.45; N, 5.05; S, 5.78. Found: C, 41.05; H, 5.34; N, 4.97; S, 5.69. ^1H NMR δ , ppm (500 MHz, DMSO-d_6): 1.47 (d, 3H, J = 5 Hz, CH_3), 3.39 (bs, COOH, H_2O and COOCH_3 merged), 4.80–4.83 (m, 1H, C^*HMe), 5.97 (s, 6H, C_6H_6), 6.73–8.05 (m, 3H, aromatic protons), 11.04 (d, 1H, J = 5 Hz, C=S attached N-H), 11.23 (s, 1H, C=O and C=S attached N-H). ^{13}C NMR δ , ppm (125 MHz, DMSO-d_6): 17.1 (CH_3), 53.0 (asymmetric carbon), 87.6 (C_6H_6), 112.5, 118.5, 144.5, 148.3 (aromatic carbons), 157.7 (C=O), 172.7 (C=S), 179.4 (COOH) ppm. FT-IR (KBr, cm^{-1}): 3211 (m; ν (amide N-H)), 3116 (s; ν (thiourea N-H)), 1665 (s; ν (C=O)), 1701 (s; ν (COOH)), 1201 (s; ν (C=S)). UV-Vis [CHCl_3 ; λ , nm (ϵ , $\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$): 449 (7571), 323 (41360), 284 (114398), 253 (97812).

2.2f $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)\text{L6}](\mathbf{6})$: Yield: 86 mg, 88%. M.p.: 164 °C. $[\alpha]_D^{27}$: +45°. Anal. Calcd. for $\text{C}_{19}\text{H}_{30}\text{Cl}_2\text{N}_2\text{O}_4\text{RuS}$: C, 41.16; H, 5.45; N, 5.05; S, 5.78. Found: C, 41.07;

H, 5.35; N, 4.96; S, 5.67. ^1H NMR δ , ppm (500 MHz, DMSO-d_6): 1.47 (d, 3H, J = 5 Hz, CH_3), 4.79–4.84 (m, 1H, C^*HMe), 5.97 (s, 6H, C_6H_6), 6.73–8.05 (m, 3H, aromatic protons), 11.04 (d, 1H, J = 10 Hz, C=S attached N-H), 11.23 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH) ppm. ^{13}C NMR δ , ppm (125 MHz, DMSO-d_6): 17.1 (CH_3), 53.0 (asymmetric carbon), 87.6 (C_6H_6), 112.5, 118.5, 144.5, 148.3 (aromatic carbons), 157.8 (C=O), 172.8 (C=S), 179.4 (COOH) ppm. FT-IR (KBr, cm^{-1}): 3222 (m; ν (amide N-H)), 3157 (s; ν (thiourea N-H)), 1681 (s; ν (C=O)), 1740 (s; ν (COOH)), 1196 (s; ν (C=S)). UV-Vis [CHCl_3 ; λ , nm (ϵ , $\text{dm}^3\text{mol}^{-1}\text{cm}^{-1}$): 445 (5354), 324 (29193), 281 (88548), 251 (71193).

2.3 X-ray structure analysis

The details of data collection are given in Table S1 (Supplementary Information). The crystal was placed in a cold nitrogen stream maintained at 150 K. A BRUKER APEX2 X-ray (three-circle) diffractometer was employed for crystal screening, unit cell determination and data collection. The goniometer was controlled using the APEX2 software suite, v2008-6.0.²⁸ Integrated intensity information for each reflection was obtained by the reduction of the data frames with the program APEX2.²⁸ The absorption correction program SADABS²⁹ was employed to correct the data for absorption effects. A solution was obtained readily using XT/XS in APEX2.^{28,30,31} Hydrogen atoms were placed in idealized positions and were set riding on the respective parent atoms. All the non-hydrogen atoms were refined with anisotropic thermal parameters. The absence of additional symmetry and voids were confirmed using PLATON (ADDSYM).³² The structure was refined (weighted least-squares refinement on F^2) to convergence.^{30,31,33} Olex2 was employed for the final data presentation and structure plots.³³

2.4 Procedure for ATH of ketones in water

$\text{HCOOH-Et}_3\text{N}$ (molar ratio 1.0:5.1) mixture was added to the Ru(II)-benzene complex (0.005 mmol) in water (0.5 mL). Subsequently ketone (1 mmol) was introduced into the mixture and stirred at 60 °C for 15 h. Then, the reaction mixture was cooled to room temperature, quenched with ice and extracted with dichloromethane. The extracts were dried over Na_2SO_4 , filtered, then passed through a silica gel short column with *N*-hexane-ethyl acetate (1:1) eluent to remove the Ru catalyst.

3. Results and Discussion

3.1 Synthesis of the Ru(II)-benzene complexes

The air-stable, water-soluble half-sandwich Ru(II) complexes (**1–6**) were prepared in good yields from the reactions between $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ and unprotected

Scheme 1. Synthesis of the complexes (1–6).

D/L-alanine derived chiral aroylthiourea ligands (L1–L6) (Scheme 1). The new complexes were soluble in water, DMSO, DMF, CH₃CN, CHCl₃, CH₂Cl₂, CH₃OH and C₂H₅OH. The Ru(II)-benzene complexes were characterized by elemental analyses, and UV-Visible, FT-IR, ¹H NMR and ¹³C NMR spectral studies. The optical rotation values of the compounds were obtained from polarimetric analyses. The molecular structure of the Ru(II) complexes (1, 3 and 5) was confirmed by single crystal X-ray diffraction study.

3.2 Spectroscopic characterization of the complexes

The absorption bands observed in the UV-Visible spectra of the complexes in the regions 442–449 and 320–330 nm were assigned to the d–d and ligand to metal charge transfer transitions respectively. The FT-IR spectra of the ligands showed bands in the regions 3385–3254 cm^{−1} for amide N–H, 3157–3106 cm^{−1} for thiourea N–H, 1659–1679 cm^{−1} for C=O and 1258–1284 cm^{−1} for C=S. On complexation, the ν(C=S) of the ligands decreased to 1182–1201 cm^{−1} while the other frequencies were unaltered, which confirmed the monodentate sulfur only coordination mode of the aroylthiourea ligands.³⁴

In the ¹H NMR spectra of the complexes (1–6), the carbonyl and thiocarbonyl attached N–H, and thiocarbonyl attached N–H protons were observed around 11.04–11.30 ppm (doublet) and 11.23–11.57 ppm (singlet) respectively. The signals at 5.96–5.97 ppm specified the presence of benzene moiety in the complexes.^{35,36} All other chemical shift values of the complexes were comparable to those of the free

ligands. The ¹³C NMR chemical shift values did not change significantly upon coordination of the ligands to Ru(II). A new signal observed at 87.6 ppm confirmed the presence of benzene in all the complexes.

3.3 Crystal structure of the complexes

The single crystal X-ray structure of complexes 1, 3 and 5 are shown in Figures 1–3 respectively. Complex 1 crystallized in the chiral monoclinic crystal system with the space group *P*2₁, and complexes 3 and 5 crystallized in the chiral orthorhombic system with the space group *P*2₁2₁2₁. The absolute configuration of complexes 1, 3 and 5 was clearly determined directly from the X-ray data. The presence of a water molecule(s) in the lattice stabilized the structures. Elongated thermal ellipsoids and a Q peak (~2 e[−]/Å³) suggested a disorder of the COOH and COOCH₃ groups (both present) in 5. The disorder was successfully modeled with an occupancy ratio of 0.58:0.42. The occupancy of O1W also refined close to 0.58. For the final refinement, the occupancies were fixed. The values of bond lengths Ru(1)–S(1), Ru(1)–Cl(1) and Ru(1)–Cl(2), and bond angles S(1)–Ru(1)–Cl(1), S(1)–Ru(1)–Cl(2), Cl(2)–Ru(1)–Cl(1) and C(1)–S(1)–Ru(1) were comparable with those provided in the previous report.³⁶ The monodentate sulfur only coordination of the aroylthiourea ligands was explicitly seen in the complexes. In the complexes, Ru ion exhibited half-sandwich “3-legged piano-stool” coordination geometry.

3.4 Asymmetric transfer hydrogenation of ketones

Catalytic activity of the water soluble Ru(II)-benzene complexes (1–6) was studied for the asymmetric transfer hydrogenation of ketones to provide their respective chiral alcohols in water medium with the use of formic acid–triethylamine mixture at 60 °C. The complexes performed as effective catalysts to show up to 99% conversion and 99% ee after 15 h (Table 1).

ATH of acetophenone was carried out with enhanced efficiency using the Ru(II)-benzene complexes as catalysts. The efficacy of the present Ru-benzene catalytic system was compared with that of already reported catalysts based on [RuCl₂(η⁶-benzene)]₂, particularly with respect to ATH of acetophenone to 1-phenylethanol in water medium (Table 1, entries 1–6). The complexes derived from (1*R*, 2*R*)-diaminocyclohexane and [RuCl₂(η⁶-benzene)]₂ were used as catalysts with HCOONa in water, which offered 94% conversion and 54% ee.³⁷ The optical purity of 1-phenylethanol is very much less compared to that obtained from the

Table 1. Asymmetric transfer hydrogenation of ketones catalyzed by the Ru(II) complexes (**1–6**)^a.

$ \begin{array}{c} \text{O} \\ \parallel \\ \text{R}_1-\text{C}-\text{R}_2 \\ \xrightarrow[\text{H}_2\text{O, HCOOH-Et}_3\text{N}]{\text{Ru(II)-benzene Complex (1-6)}} \\ 60\text{ }^\circ\text{C} \\ \text{R}_1-\text{C}^*\text{(OH)}-\text{R}_2 \end{array} $						
Entry	Catalyst	Substrate	Product	Conversion ^b (%)	ee ^c (%) / Configuration ^d	TON ^e
1	1			99	74 / <i>S</i>	198
2	2			54	96 / <i>S</i>	108
3	3			99	64 / <i>R</i>	198
4	4			99	99 / <i>S</i>	198
5	5			99	99 / <i>S</i>	198
6	6			61	99 / <i>S</i>	122
7	1			71	99 / <i>R</i>	142
8	2			78	89 / <i>R</i>	156
9	3			84	87 / <i>R</i>	168
10	4			62	97 / <i>R</i>	124
11	5			81	92 / <i>R</i>	162
12	6			63	72 / <i>R</i>	126
13	1			88	65 / <i>R</i>	176
14	2			94	82 / <i>R</i>	188
15	3			90	94 / <i>R</i>	188
16	4			71	50 / <i>R</i>	142
17	5			92	74 / <i>R</i>	184
18	6			86	94 / <i>R</i>	172
19	1			98	86 / <i>R</i>	196
20	2			98	84 / <i>R</i>	196
21	3			97	88 / <i>S</i>	194
22	4			86	58 / <i>R</i>	172
23	5			97	97 / <i>S</i>	194
24	6			98	62 / <i>R</i>	196
25	1			78	45 / <i>S</i>	156
26	2			60	98 / <i>R</i>	120
27	3			70	90 / <i>R</i>	140
28	4			78	78 / <i>R</i>	156
29	5			85	80 / <i>R</i>	190
30	6			54	82 / <i>S</i>	108

^aReactions were carried out at 60 °C using 1 mmol of ketone, 0.005 mmol of Ru(II)-benzene complex in 0.5 mL of water and HCOOH:Et₃N (molar ratio 1.0:5.1) for 15 h. ^bThe conversion was determined by GC-MS. ^cee was calculated by chiral HPLC analysis. ^dAbsolute configuration was determined from the optical rotation values. ^eTON = moles of the product formed/moles of the catalyst used.

present catalytic system. [RuCl₂(η⁶-benzene)]₂ along with bulky roofed *cis*-diamine catalyzed the ATH of acetophenone to 1-phenylethanol in water with very good conversion (98%) and ee (93%) using HCOOH–NEt₃ mixture as a hydrogen donor,³⁸ which was comparable with the present results. Pseudo-dipeptide on combination with [RuCl₂(η⁶-benzene)]₂ assisted the transformation and offered 95% ee³⁹, similar to the present catalytic system. To the best of our knowledge, there is no report available on enantioselective reduction reaction catalyzed by Ru-benzene complexes containing aminoacid or aminoacid derived ligands.

The ability of Ru(II)-benzene complexes (**1–6**) to catalyze the ATH of acetophenone was compared with our previously reported Ru(II)-benzene catalysts. The present catalysts required 15 h to exhibit 99% conversion and 99% ee. Nevertheless, our previous Ru(II)-benzene catalysts bearing chiral phenylalanine derived aroylthiourea ligands needed only 8 h for 99% conversion and 99% ee.⁴⁰ With chiral amine based aroylthiourea ligands, Ru(II)-benzene catalysts took 14 h for the same performance.³⁶ Though the present Ru(II)-benzene catalysts wanted more time for excellent conversion and ee, it is to be noted that the reactions were

Figure 1. Thermal ellipsoidal plot (50% probability level) of **1**. Selected bond distances (Å) and angles (°): Ru(1)–S(1) 2.4062(9), Ru(1)–Cl(1) 2.4373(10), Ru(1)–Cl(2) 2.4300(10), S(1)–Ru(1)–Cl(1) 93.47(3), S(1)–Ru(1)–Cl(2) 89.91(2), Cl(2)–Ru(1)–Cl(1) 87.88(2) and C(1)–S(1)–Ru(1) 117.18(10).

Figure 2. Thermal ellipsoidal plot (50% probability level) of **3**. Selected bond distances (Å) and angles (°): Ru(1)–S(1) 2.4047(6), Ru(1)–Cl(1) 2.4162(6), Ru(1)–Cl(2) 2.4130(6), S(1)–Ru(1)–Cl(1) 89.12(2), S(1)–Ru(1)–Cl(2) 92.54(2), Cl(2)–Ru(1)–Cl(1) 87.36(2), C(1)–S(1)–Ru(1) 117.08(8).

carried out in water medium whereas in the previous cases the solvent was isopropanol. Further, the comparison was also made with Ru(II)-*p*-cymene complexes containing the same ligands. The *p*-cymene complexes required 20 h to exhibit 99% conversion and 99% ee whereas Ru(II)-benzene catalysts (**1–6**) demonstrated the same conversion and ee within 15 h. The enhanced reactivity of the Ru(II)-benzene complexes compared to the Ru(II)-*p*-cymene complexes was explained theoretically.³⁶

Figure 3. Thermal ellipsoidal plot (50% probability level) of **5**. Selected bond distances (Å) and angles (°): Ru(1)–S(1) 2.4082(12), Ru(1)–Cl(1) 2.4230(12), Ru(1)–Cl(2) 2.4131(12), S(1)–Ru(1)–Cl(1) 92.78(4), S(1)–Ru(1)–Cl(2) 89.35(4), Cl(2)–Ru(1)–Cl(1) 86.46(4), C(1)–S(1)–Ru(1) 116.49(14).

Using the optimized conditions, the scope of the system was extended to include more ketones. *R*-tomoxetine is a drug used for the treatment of attention deficit hyperactivity disorder, which is synthesized from 1-(*o*-tolyl)ethanol.⁴¹ Catalysts **1–6** were active for enantioselective reduction of 2-methyl acetophenone to yield (*R*)-1-(*o*-tolyl)ethanol with up to 84% conversion and 99% ee (Table 1, entries 7–12). Chiral Ru(II)-benzene complexes (**1–6**) were used as catalysts for the conversion of 4-fluoro acetophenone to (*R*)-1-(4-fluorophenyl)ethanol (up to 94% conversion and 94% ee) which possesses numerous biological applications (Table 1, entries 13–18).⁴² The enantioselective reduction of 2-acetylfuran to 1-(furan-2-yl)ethanol was attained in our method with up to 98% conversion and 97% ee (Table 1, entries 19–24). Chiral benzhydrol is broadly used for the synthesis of many pharmaceuticals.⁴³ Using the Ru(II)-benzene catalytic system, the transformation of 4-methoxy benzophenone to (4-methoxyphenyl)(phenyl)methanol was achieved with conversion up to 85% and ee up to 98% (Table 1, entries 25–30).

4. Conclusions

In this article, we have reported the synthesis and complete characterization of the half-sandwich Ru(II)-benzene complexes which were obtained from the reactions between $[\text{RuCl}_2(\eta^6\text{-C}_6\text{H}_6)]_2$ and chiral aroylthiourea ligands. The structure of the complexes was confirmed by single crystal X-ray diffraction study. In all the Ru(II)-benzene complexes, monodentate coordination of aroylthiourea ligand through sulfur atom and the

unprotected acid group were observed. All the Ru(II)-benzene complexes were found to be effective catalysts for the ATH of ketones to their corresponding chiral alcohols in water medium. The conversions and enantiomeric excesses were found to be good to excellent. The present catalytic system operates with an environmentally pleasant and simple procedure without inert condition, which will be very much helpful in industrial synthetic processes.

Supplementary Information (SI)

CCDC 1829315-1829317. The table of the X-ray crystallographic data, atomic coordinates in CIF format, ^1H and ^{13}C -NMR spectra of the complexes, GC-MS chromatogram and HPLC chromatograms are included. Supplementary Information is available at www.ias.ac.in/chemsci.

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