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FULL PAPER

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Water soluble Ru (II)–*p*-cymene complexes of chiral aroylthiourea ligands derived from unprotected D/L-alanine as proficient catalysts for asymmetric transfer hydrogenation of ketones

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The newfangled chiral aroylthiourea ligands (L1-L6) were produced from unprotected D/L-alanine and their water soluble Ru (II) organometallic catalysts (**1**–**6**) were designed from their reaction with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$. The analytical and spectral methods were used to confirm the structure of the ligands and complexes. The solid state structure of L1, **5** and **6** was confirmed by single crystal XRD. The organometallic compounds (**1**–**6**) catalyzed the asymmetric transfer hydrogenation of aromatic, heteroaromatic and bulky ketones to yield respective enantiopure secondary alcohols with admirable conversions (up to 99%) and attractive enantiomeric excesses (ee up to 98%), in presence of formic acid and triethylamine in water medium under non-inert atmospheric conditions.

KEYWORDS
aqueous medium, aroylthiourea asymmetric hydrogenation, ruthenium

1 | INTRODUCTION

Water is an eco-friendly solvent in catalysis and also, diverse interactions are possible among water, catalyst and substrate, which make the catalytic system homogeneous and effective. The development of water soluble chiral catalysts is a crucial area of green chemistry. Amino acids or altered amino acids are applied as chiral catalysts in water medium in the Diels-Alder,[1] Michael,[2] asymmetric transfer hydrogenation (of ketones[3,4] and imines[4]) and direct asymmetric aldol reactions.[5]

The isolation of pure chiral compounds is of significance as each enantiomer can have different properties in biological systems (asymmetric protein targets, metabolic enzymes, transporters, etc.).[6] Chiral alcohols are one of the utmost essential key chiral building blocks for various single enantiomer pharmaceuticals.[7,8] Asymmetric reduction of pro-chiral ketones is a powerful method for the production of chiral alcohols. Asymmetric transfer hydrogenation (ATH) of ketones by organometallic homogeneous catalysis in water is of abundant attention in green chemistry. Recently, many have described the ATH of ketones in water solvent under non-inert conditions, which are useful for industrial applications.[4,9–29] Chiral Ru (II)-*p*-cymene complexes are found to be promising catalysts for ATH of ketones. But there are only a few reports on Ru-*p*-cymene complex-catalyzed ATH of ketones to resultant

chiral alcohols in an aqueous medium. The chiral ligands used in these systems are, (*R*)-N-(4-fluorophenyl)-pyrrolidine-2-carboxamide,[13] N-((1*S*,2*S*)-2-amino-1,2-bis(2-aminophenyl)ethyl)-4-methylbenzene sulfonamide,[4] sodium-2,2′-((1*R*,2*R*)-1-amino-2-(4-methylphenylsulfonamido)ethane-1,2-diyl)dibenzenesulfonate,[12] N-(*p*-toluenesulfonyl)-1,2-diphenyl-ethylenediamine,[11] N-((1*S*,2*S*)-2-aminocyclohexyl)-4-methyl benzenesulfonamide[30] and (−)-ephedrine hydrochloride.[21]

In metal-catalyzed reactions, the unprotected amino acids are infrequently used as chiral-influence.[31] The aroylthiourea ligands derived from D/L-alanine have been utilized in the unprotected form in this work due to the expectation that the carboxylic acid group might promote the solubility of the complexes in water.[32] The chiral half-sandwich Ru (II)-arene complexes catalyze various asymmetric transformations.[33] Steric factors of the arene complexes help to get high stereoselectivity in organic synthesis.[33] Simple amino acids are complexed with Ru-*p*-cymene dimer, where the ligands exhibit bidentate (O, N) coordination mode.[34] The aroylthiourea ligands obtained from amino acids may provide more opportunity for tuning the electronic property of the metal. Our earlier attempt to prepare water soluble Ru-*p*-cymene complexes using D/L-phenylalanine-aroylthiourea ligands did not succeed as amino acid was converted in to its ester during the complexation.[35] Fortunately, amino acid in D/L-alanine derivative of aroylthiourea is unchanged when it is reacted with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$. In this article, the preparation and characterization of new chiral water soluble Ru (II)-*p*-cymene complexes (**1**–**6**) bearing enantiopure D/L-alanine-aroylthiourea ligands (L1-L6) are described. The organometallic compounds (**1**–**6**) are utilized as active catalysts for the ATH of aromatic ketones to result enantiopure alcohols in aqueous medium employing formic acid and triethylamine as a hydrogen source and base respectively.

2 | EXPERIMENTAL

2.1 | Materials and instrumentation

$[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ was synthesized by using a literature procedure.[36] UV–visible spectra were recorded using a Shimadzu 2600 spectrophotometer, operating in the range of 200–800 nm. FT-IR spectra were recorded in the range of 600–4000 cm^{-1} on a Nicolet iS5 FT-IR spectrophotometer as KBr pellets. CHNS analyses were performed using a Perkin Elmer 2400 series II elemental analyzer. ^1H and ^{13}C NMR spectra were recorded on a Bruker 500 MHz and 125 MHz spectrometer, respectively. Melting points were determined in open capillary tubes on a Sigma melting point apparatus and are uncorrected. GC–MS measurements for catalytic experiments were performed using a Shimadzu GCMS-QP 2010 Ultra gas chromatograph mass spectrometer with a Restek-5 capillary column. For GC measurements, Shimadzu GC 2010 was used with the same 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 L1-L6

A solution of benzoyl chloride (0.6 ml, 5 mmol)/thiophene-2-carbonyl chloride (0.5 ml, 5 mmol) /furan-2-carbonyl chloride (0.5 ml, 5 mmol) in acetone (30 ml) was added to a suspension of potassium thiocyanate (0.4859 g, 5 mmol) in acetone (30 ml). The reaction mixture was heated under reflux for 45 min and then cooled to room temperature. A solution of D/L-alanine (0.4454 g, 5 mmol) in acetone (40 ml) and ethanol (20 ml) was added, and the resulting mixture was stirred for 15 hr at 27 °C. Hydrochloric acid (0.1 N, 300 ml) was then added, and the resulting solid was filtered off. The solid product was washed with water and purified by recrystallization from ethanol/dichloromethane mixture (1/2).

2.2.1 | (*R*)-2-(3-benzoylthioureido) propanoic acid (L1)

Yield: 74%, 0.93 g. M.p.: 134 °C. $[\alpha]_D^{27}$: +11°. Anal. calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10; S, 12.71. Found: C, 52.11; H, 4.57; N, 10.98; S, 12.58. ^1H NMR δ, ppm (500 MHz, DMSO-d_6): 1.48 (d, 3H, J = 10 Hz, CH_3), 4.79 (m, 1H, C*HMe), 7.50–7.94 (m, 5H, CH of phenyl rings), 11.30 (d, 1H, J = 5 Hz, C=S attached N-H), 11.44 (s, 1H, C=O and C=S attached N-H), 13.52 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.2 (CH_3), 53.3 (asymmetric C), 128.3, 128.4, 132.1, 132.9 (aromatic), 168.2 (C=O), 172.8 (C=S), 179.5 (COOH). FT-IR (KBr, cm^{-1}): 3385 (m, ν (amide N-H)), 3153 (s, ν (thiourea N-H)), 1729 (s, ν (COOH)), 1679 (s, ν(C=O)), 1258 (s, ν(C=S)).

2.2.2 | (*S*)-2-(3-benzoylthioureido) propanoic acid (L2)

Yield: 72%, 0.91 g. M.p.: 135 °C. $[\alpha]_D^{27}$: − 13°. Anal. calcd for $C_{11}H_{12}N_2O_3S$: C, 52.37; H, 4.79; N, 11.10; S, 12.71. Found: C, 52.13; H, 4.59; N, 11.01; S, 12.54. ^1H NMR δ, ppm (500 MHz, DMSO-d_6): 1.49 (d, 3H, J = 5 Hz, CH_3),

4.85 (m, 1H, C*HMe), 7.48–7.95 (m, 5H, CH of phenyl rings), 11.29 (d, 1H, J = 5 Hz, C=S attached N-H), 11.49 (s, 1H, C=O and C=S attached N-H), 13.15 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3), 53.0 (asymmetric C), 128.3, 128.5, 132.0, 133.0 (aromatic), 168.4 (C=O), 172.8 (C=S), 179.8 (COOH). FT-IR (KBr, cm^{-1}): 3384 (m, ν (amide N-H)), 3157 (s, ν (thiourea N-H)), 1728 (s, ν (COOH)), 1679 (s, ν(C=O)), 1258 (s, ν(C=S)).

2.2.3 | (*R*)-2-(3-(thiophene-2-carbonyl) thioureido) propanoic acid (L3)

Yield: 78%, 1.06 g. M.p.: 144 °C. $[\alpha]_D^{27}$: +62°. Anal. calcd for $C_9H_{10}N_2O_3S_2$: C, 41.85; H, 3.90; N, 10.84; S, 24.83. Found: C, 41.73; H, 3.77; N, 10.78; S, 24.78. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.40 (d, 3H, J = 5 Hz, CH_3), 4.75 (m, 1H, C*HMe), 7.16–8.28 (m, 3H, CH of thiophene ring), 11.49 (d, 1H, J = 5 Hz, C=S attached N-H), 11.08 (s, 1H, C=O and C=S attached N-H), 13.08 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.6 (CH_3), 53.5 (asymmetric C), 129.2, 133.0, 135.7, 137.0 (aromatic), 162.7 (C=O), 173.3 (C=S), 180.0 (COOH). FT-IR (KBr, cm^{-1}): 3261 (m, ν (amide N-H)), 3110 (s, ν (thiourea N-H)), 1717 (s, ν (COOH)), 1659 (s, ν(C=O)), 1271 (s, ν(C=S)).

2.2.4 | (*S*)-2-(3-(thiophene-2-carbonyl) thioureido) propanoic acid (L4)

Yield: 75%, 1.01 g. M.p.: 143 °C. $[\alpha]_D^{27}$: − 58°. Anal. calcd for $C_9H_{10}N_2O_3S_2$: C, 41.85; H, 3.90; N, 10.84; S, 24.83. Found: C, 41.72; H, 3.78; N, 10.69; S, 24.76. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.40 (d, 3H, J = 5 Hz, CH_3), 4.75 (m, 1H, C*HMe), 7.16–8.29 (m, 3H, CH of thiophene ring), 11.08 (d, 1H, J = 5 Hz, C=S attached N-H), 11.49 (s, 1H, C=O and C=S attached N-H), 13.11 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.6 (CH_3), 53.5 (asymmetric C), 129.1, 133.0, 135.7, 137.0 (aromatic), 162.7 (C=O), 173.3 (C=S), 180.0 (COOH). FT-IR (KBr, cm^{-1}): 3254 (m, ν (amide N-H)), 3106 (s, ν (thiourea N-H)), 1718 (s, ν (COOH)), 1659 (s, ν(C=O)), 1274 (s, ν(C=S)).

2.2.5 | (*R*)-2-(3-(furan-2-carbonyl) thioureido) propanoic acid (L5)

Yield: 76%, 0.98 g. M.p.: 114 °C. $[\alpha]_D^{27}$: +16°. Anal. calcd for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.56; S, 13.24. Found: C, 44.54; H, 4.07; N, 11.48; S, 13.18. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.47 (d, 3H, J = 5 Hz, CH_3), 4.82 (m, 1H, C*HMe), 6.73–8.05 (m, 3H, CH of furan ring), 11.05 (d, 1H, J = 10 Hz, C=S attached N-H), 11.23 (s, 1H, C=O and C=S attached N-H), 13.17 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3), 53.0 (asymmetric C), 112.5, 118.4, 144.5, 148.3 (aromatic), 157.7 (C=O), 172.7 (C=S), 179.4 (COOH). FT-IR (KBr, cm^{-1}): 3263 (m, ν (amide N-H)), 3153 (s, ν (thiourea N-H)), 1727 (s, ν (COOH)), 1674 (s, ν(C=O)), 1283 (s, ν(C=S)).

2.2.6 | (*S*)-2-(3-(furan-2-carbonyl) thioureido) propanoic acid (L6)

Yield: 75%, 0.96 g. M.p.: 115 °C. $[\alpha]_D^{27}$: − 18°. Anal. calcd for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.56; S, 13.24. Found: C, 44.52; H, 4.05; N, 11.49; S, 13.15. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.47 (d, 3H, J = 5 Hz, CH_3), 4.82 (m, 1H, C*HMe), 6.73–8.05 (m, 3H, CH of furan ring), 11.05 (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). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3), 53.0 (asymmetric C), 112.5, 118.5, 144.5, 148.3 (aromatic), 157.8 (C=O), 172.8 (C=S), 179.5 (COOH). FT-IR (KBr, cm^{-1}): 3264 (m, ν (amide N-H)), 3154 (s, ν (thiourea N-H)), 1729 (s, ν (COOH)), 1675 (s, ν(C=O)), 1284 (s, ν(C=S)).

2.3 | Synthesis of Ru (II)-*p*-cymene complexes 1–6

$[RuCl_2(\eta^6$-*p*-cymene)$]_2$ (122.5 mg, 0.2 mmol) and (*R*)/(*S*)-2-(3-benzoylthioureido) propanoic acid (101 mg, 0.4 mmol) or (*R*)/(*S*)-2-(3-(thiophene-2-carbonyl) thioureido) propanoic acid (103 mg, 0.4 mmol) or (*R*)/(*S*)-2-(3-(furan-2-carbonyl)thioureido) propanoic acid (96.9 mg, 0.4 mmol) were dissolved in toluene (20 mL) and stirred for 4 hr at 27 °C. During the reaction, an orange precipitate was formed, further, the addition of hexane gave an orange color solid product. The product was collected by filtration, washed with hexane and dried in *vacuo*.

2.3.1 | [$RuCl_2(\eta^6$-*p*-cymene)L1] (1)

Yield: 74%, 165 mg. M.p.: 167 °C. $[\alpha]_D^{27}$: − 74°. Anal. calcd for $C_{21}H_{26}Cl_2N_2O_3RuS$: C, 45.16; H, 4.69; N, 5.02; S, 5.74. Found: C, 45.02; H, 4.55; N, 4.89; S, 5.65. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.19 (d, 6H, J = 7.0 Hz, $2CH_3$ of *p*-cymene), 1.49 (d, 3H, J = 7.2 Hz, CH_3 of the ligand), 2.08 (s, 3H, CH_3 of *p*-cymene), 2.83 (m, 1H, CH of *p*-cymene), 4.85 (m, 1H, C*HMe), 5.76–5.81 (m, 4H,

aromatic protons of *p*-cymene), 7.50–7.94 (m, 5H, aromatic protons of the ligand), 11.29 (d, J = 7.0 Hz, 1H, C=S attached N-H), 11.49 (s, 1H, C=O and C=S attached N-H), 13.22 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3 of the ligand), 17.8 (CH_3 of *p*-cymene), 21.4 ($2CH_3$ of *p*-cymene), 29.9 (CH of *p*-cymene), 53.0 (asymmetric carbon), 85.4–86.3 (aromatic carbons of *p*-cymene), 100.0 and 106.3 (quaternary carbons of *p*-cymene), 128.3, 128.5, 132.0, 133.0 (CH), 168.4 (C=O), 172.8 (C=S), 179.8 (COOH). FT-IR (KBr, cm^{-1}): 3217 (m, ν (amide N-H)), 3150 (s, ν (thiourea N-H)), 1672 (s, ν(C=O)), 1741 (s, ν (COOH)), 1193 (s, ν(C=S)). UV–vis [$CHCl_3$; λ, nm (ε, dm^3 mol^{-1} cm^{-1})]: 444 (6600), 330 (30600), 254 (138100).

2.3.2 | [$RuCl_2(\eta^6$-*p*-cymene)L2] (2)

Yield: 77%, 172 mg. M.p.: 166 °C. $[\alpha]_D^{27}$: +78°. Anal. calcd for $C_{21}H_{26}Cl_2N_2O_3RuS$: C, 45.16; H, 4.69; N, 5.02; S, 5.74. Found: C, 45.05; H, 4.55; N, 4.90; S, 5.62. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.19 (d, 6H, J = 7.0 Hz, $2CH_3$ of *p*-cymene), 1.49 (d, 3H, J = 7.2 Hz, CH_3 of the ligand), 2.08 (s, 3H, CH_3 of *p*-cymene), 2.83 (m, 1H, CH of *p*-cymene), 4.84 (m, 1H, C*HMe), 5.76–5.81 (m, 4H, aromatic protons of *p*-cymene), 7.50–7.94 (m, 5H, aromatic protons of the ligand), 11.29 (d, J = 7.0 Hz, 1H, C=S attached N-H), 11.49 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3 of the ligand), 17.8 (CH_3 of *p*-cymene), 21.4 ($2CH_3$ of *p*-cymene), 29.9 (CH of *p*-cymene), 53.0 (asymmetric carbon), 85.4–86.3 (aromatic carbons of *p*-cymene), 100.0 and 106.3 (quaternary carbons of *p*-cymene), 128.3, 128.5, 132.0, 133.0 (CH), 168.4 (C=O), 172.8 (C=S), 179.8 (COOH). FT-IR (KBr, cm^{-1}): 3211 (m, ν (amide N-H)), 3143 (s, ν (thiourea N-H)), 1672 (s, ν(C=O)), 1729 (s, ν (COOH)), 1194 (s, ν(C=S)). UV–vis [$CHCl_3$; λ, nm (ε, $dm^3mol^{-1}cm^{-1}$)]: 443 (8200), 329 (38500), 254 (173000).

2.3.3 | [$RuCl_2(\eta^6$-*p*-cymene)L3] (3)

Yield: 74%, 166 mg. M.p.: 164 °C. $[\alpha]_D^{27}$: − 80°. Anal. calcd for $C_{19}H_{24}Cl_2N_2O_3RuS_2$: C, 40.42; H, 4.29; N, 4.96; S, 11.36. Found: C, 40.35; H, 4.19; N, 4.89; S, 11.26. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.18 (d, 6H, J = 7.0 Hz, $2CH_3$ of *p*-cymene), 1.48 (d, 3H, J = 7.2 Hz, CH_3 of the ligand), 2.09 (s, 3H, CH_3 of *p*-cymene), 2.84 (m, 1H, CH of *p*-cymene), 4.83 (m, 1H, C*HMe), 5.77–5.83 (m, 4H, aromatic protons of *p*-cymene), 7.23–8.36 (m, 3H, aromatic protons of the ligand), 11.15 (d, J = 7.0 Hz, 1H, C=S attached N-H), 11.56 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3 of the ligand), 17.8 (CH_3 of *p*-cymene), 21.4 ($2CH_3$ of *p*-cymene), 29.9 (CH of *p*-cymene), 53.0 (asymmetric carbon), 85.4–86.3 (aromatic carbons of *p*-cymene), 100.0 and 106.3 (quaternary carbons of *p*-cymene), 128.6, 132.5, 135.2, 136.5 (CH), 162.2 (C=O), 172.8 (C=S), 179.5 (COOH). FT-IR (KBr, cm^{-1}): 3202 (m, ν (amide N-H)), 3132 (s, ν (thiourea N-H)), 1659 (s, ν(C=O)), 1745 (s, ν (COOH)), 1194 (s, ν(C=S)). UV–vis [$CHCl_3$; λ, nm (ε, dm^3mol^{-1} cm^{-1})]: 449 (6700), 335 (35000), 294 (76500), 255 (102900).

2.3.4 | [$RuCl_2(\eta^6$-*p*-cymene)L4] (4)

Yield: 81%, 183 mg. M.p.: 165 °C. $[\alpha]_D^{27}$: +76°. Anal. calcd for $C_{19}H_{24}Cl_2N_2O_3RuS_2$: C, 40.42; H, 4.29; N, 4.96; S, 11.36. Found: C, 40.33; H, 4.15; N, 4.87; S, 11.25. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.18 (d, 6H, J = 7.0 Hz, $2CH_3$ of *p*-cymene), 1.48 (d, 3H, J = 7.2 Hz, CH_3 of the ligand), 2.09 (s, 3H, CH_3 of *p*-cymene), 2.84 (m, 1H, CH of *p*-cymene), 4.83 (m, 1H, C*HMe), 5.77–5.83 (m, 4H, aromatic protons of *p*-cymene), 7.23–8.36 (m, 3H, aromatic protons of the ligand), 11.15 (d, J = 7.0 Hz, 1H, C=S attached N-H), 11.56 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3 of the ligand), 17.8 (CH_3 of *p*-cymene), 21.4 ($2CH_3$ of *p*-cymene), 29.9 (CH of *p*-cymene), 53.0 (asymmetric carbon), 85.4–86.3 (aromatic carbons of *p*-cymene), 100.0 and 106.3 (quaternary carbons of *p*-cymene), 128.6, 132.5, 135.2, 136.5 (CH), 162.2 (C=O), 172.8 (C=S), 179.5 (COOH). FT-IR (KBr, cm^{-1}): 3217 (m, ν (amide N-H)), 3153 (s, ν (thiourea N-H)), 1673 (s, ν(C=O)), 1741 (s, ν (COOH)), 1184 (s, ν(C=S)). UV–vis [$CHCl_3$; λ, nm (ε, dm^3mol^{-1} cm^{-1})]: 448 (5900), 336 (32560), 293 (72825), 255 (102530).

2.3.5 | [$RuCl_2(\eta^6$-*p*-cymene)L5] (5)

Yield: 77%, 177 mg. M.p.: 158 °C. $[\alpha]_D^{27}$: +60°. Anal. calcd for $C_{19}H_{30}Cl_2N_2O_4RuS$: C, 41.16; H, 5.45; N, 5.05; S, 5.78. Found: C, 41.05; H, 5.36; N, 4.93; S, 5.65. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.19 (d, 6H, J = 7.0 Hz, $2CH_3$ of *p*-cymene), 1.48 (d, 3H, J = 7.2 Hz, CH_3 of the ligand), 2.09 (s, 3H, CH_3 of *p*-cymene), 2.84 (m, 1H, CH of *p*-cymene), 4.82 (m, 1H, C*HMe), 5.77–5.83 (m, 4H, aromatic protons of *p*-cymene), 7.23–8.06 (m, 3H, aromatic protons of the ligand), 11.05 (d, J = 7.0 Hz, 1H, C=S attached N-H), 11.23 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3 of the

ligand), 17.8 (CH_3 of *p*-cymene), 21.4 ($2CH_3$ of *p*-cymene), 29.9 (CH of *p*-cymene), 53.0 (asymmetric carbon), 85.4–86.3 (aromatic carbons of *p*-cymene), 100.0 and 106.3 (quaternary carbons of *p*-cymene), 112.5, 118.4, 144.5, 148.3 (CH), 157.8 (C=O), 172.7 (C=S), 179.4 (COOH). FT-IR (KBr, cm^{-1}): 3223 (m, ν (amide N-H)), 3182 (s, ν (thiourea N-H)), 1682 (s, ν(C=O)), 1743 (s, ν (COOH)), 1200 (s, ν(C=S)). UV–vis [$CHCl_3$; λ, nm (ε, dm^3mol^{-1} cm^{-1})]: 443 (6000), 333 (22700), 282 (72000).

2.3.6 | [$RuCl_2(\eta^6$-*p*-cymene)L6] (6)

Yield: 83%, 180 mg. M.p.: 157 °C. $[\alpha]_D^{27}$: − 54°. Anal. calcd for $C_{19}H_{30}Cl_2N_2O_4RuS$: C, 41.16; H, 5.45; N, 5.05; S, 5.78. Found: C, 41.03; H, 5.37; N, 4.91; S, 5.67. ^{1}H NMR δ, ppm (500 MHz, DMSO-d_6): 1.19 (d, 6H, *J* = 7.0 Hz, $2CH_3$ of *p*-cymene), 1.48 (d, 3H, *J* = 7.2 Hz, CH_3 of the ligand), 2.09 (s, 3H, CH_3 of *p*-cymene), 2.84 (m, 1H, CH of *p*-cymene), 4.82 (m, 1H, C*HMe), 5.77–5.83 (m, 4H, aromatic protons of *p*-cymene), 7.23–8.06 (m, 3H, aromatic protons of the ligand), 11.05 (d, *J* = 7.0 Hz, 1H, C=S attached N-H), 11.23 (s, 1H, C=O and C=S attached N-H), 13.20 (bs, 1H, COOH). ^{13}C NMR δ, ppm (125 MHz, DMSO-d_6): 17.1 (CH_3 of the ligand), 17.8 (CH_3 of *p*-cymene), 21.4 ($2CH_3$ of *p*-cymene), 29.9 (CH of *p*-cymene), 53.0 (asymmetric carbon), 85.4–86.3 (aromatic carbons of *p*-cymene), 100.0 and 106.3 (quaternary carbons of *p*-cymene), 112.5, 118.4, 144.5, 148.3 (CH), 157.8 (C=O), 172.7 (C=S), 179.4 (COOH). FT-IR (KBr, cm^{-1}): 3221 (m, ν (amide N-H)), 3182 (s, ν (thiourea N-H)), 1682 (s, ν(C=O)), 1743 (s, ν (COOH)), 1200 (s, ν(C=S)). UV–vis [$CHCl_3$; λ, nm (ε, dm^3mol^{-1} cm^{-1})]: 443 (5100), 333 (21400), 283 (69500).

2.4 | Procedure for asymmetric reduction of ketones in water

To the [$RuCl_2$(*p*-cymene)(L1-L6)] complex (**1**–**6**) (0.005 mmol) in water (0.5 ml), HCOOH-NEt_3 (molar ratio 1.0:5.1) mixture was added. Then ketone (1 mmol) was introduced into the mixture and the solution was stirred at 60 °C. After 20 hr, the reaction mixture was cooled to room temperature, quenched with ice and then extracted with dichloromethane. The extracts were dried over Na_2SO_4, filtered, and passed through a silica gel short column with *n*-hexane-ethyl acetate (1:1) eluent to remove the Ru catalyst. The conversions were monitored by GC–MS and GC analyses, and the enantiomeric excesses were determined by using chiral HPLC.

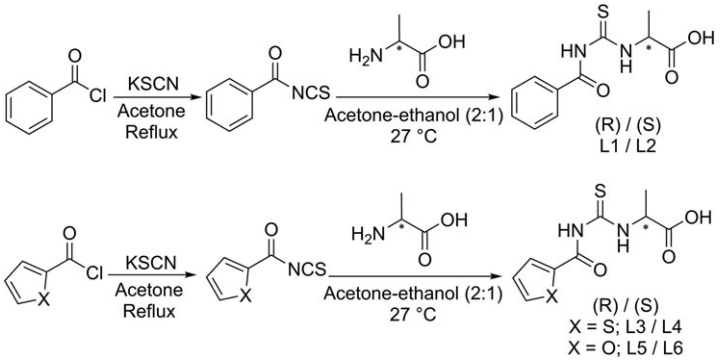
3 | RESULTS AND DISCUSSION

3.1 | Formation of the ligands and complexes

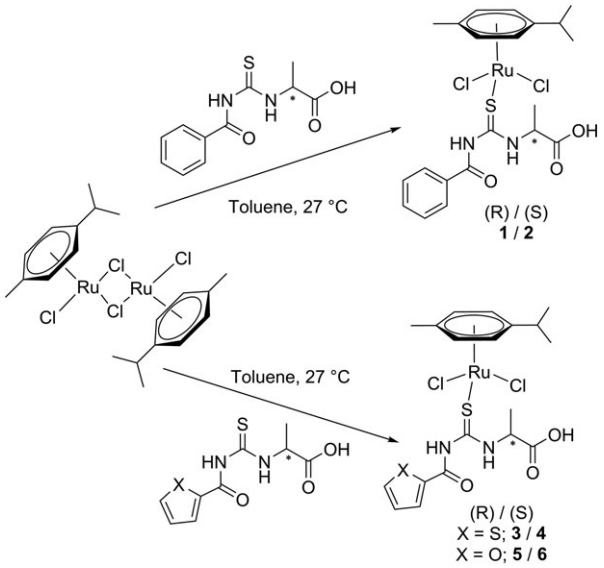
The unprotected D/L-alanine based aroylthiourea derivatives (L1-L6) were prepared (Scheme 1) and used for the synthesis of chiral water soluble [$RuCl_2$(*p*-cymene)(L1-L6)] complexes (**1**–**6**) on reaction with [$RuCl_2(\eta^6$-*p*-cymene)]$_2$ in toluene (Scheme 2). The ligands and their Ru-*p*-cymene complexes were characterized by using various spectroscopic (^{1}H NMR, ^{13}C NMR, FT-IR and UV–Vis) techniques and elemental analysis. The solid state structure of L1, **5** and **6** was proven by single crystal X-ray diffraction analysis. The optical rotation value of the compounds was determined from the polarimetric study. All the synthesized compounds are stable in air and soluble in aqueous and organic solvents.

3.2 | Structure of the ligands and complexes

In the ^{1}H NMR spectra of L1-L6 (Figure S1–S6), a broad singlet was observed in the chemical shift value of 13.08–13.52 ppm, which corresponds to the carboxyl O-H proton present in all the ligands. The C=S connected N-H, and C=O and C=S connected N-H protons were identified as doublet and singlet respectively in the region 11.08–11.49 ppm. The resonances due to the aromatic protons appeared at 6.73–8.29 ppm in the spectra of the aroylthiourea derivatives. The proton attached to the



SCHEME 1 Synthesis of the ligands (L1-L6)



SCHEME 2 Synthesis of the complexes (**1**–**6**)

chiral carbon was observed as a multiplet at 4.75–4.85 ppm. The CH_3 protons were detected as a singlet at 1.40–1.49 ppm. The broad signal witnessed at 13.2 ppm due to carboxyl O-H proton in the ^{1}H NMR spectra of the complexes (**1**–**6**) indicated the presence of D/L-alanine in the unprotected form (Figure S7-S12). The existence of *p*-cymene in the complexes was confirmed from the new signals appeared at 1.18–1.19, 2.08–2.09, 2.83–2.84 and 5.76–5.83 ppm (Figure S13–S18).[35,37] The chemical shift values of CH_3, C*H and aromatic protons of the complexes were virtually comparable to those of the corresponding ligands. The ^{13}C NMR spectra of L1-L6 contained signals around 17.1–17.6 and 53.0–53.5 ppm (Figure S13–S18), which were attributed to CH_3 and asymmetric carbons respectively. The aromatic ring carbons showed signals at 112.5–148.3 ppm. The C=O and C=S resonances were noticed at 157.7–168.4 and 171.2–175.5 ppm correspondingly. The signal pertaining to carboxylic acid was seen at 179.4–180.0 ppm. There was no substantial alteration in the ^{13}C NMR spectra consequent to coordination of the ligands with Ru (Figures S19–S24). The *p*-cymene moiety showed new signals at 17.8, 21.4, 29.9, 85.4, 86.3, 100.0 and 106.3 ppm in the spectra of the complexes.[35,37] In general, the observed chemical shift values were consistent with the literature values.[35,37]

Further, the complex formation and coordination mode of the aroylthiourea ligands were recognized from the FT-IR spectra. The C=O and amide N-H stretching frequencies were nearly unaffected upon complexation, while the stretching frequency of the C=S decreased from 1258–1283 to 1184–1200 cm^{-1}, which proposed monodentate coordination of the ligands to Ru ion *via* the sulfur atom.[35,37,38] The carboxylic acid C=O stretching frequency observed in the region 1729–1745 cm^{-1} in the spectra of the complexes confirmed the presence of the acid group.[39] UV–visible spectra of **1**–**6** displayed d-d and charge transfer transition bands in the regions 443–449 and 329–336 nm, respectively; which attested formation of the complexes. The bands due to n-π* and π-π* transitions were observed in the regions 283–294 and 251–257 nm, respectively.

The structure of L1, **5** and **6** was ascertained by XRD studies and is shown in Figures 1–3. The experimental parameters and crystal data are given in Table S1. The structure of the complexes exposed monodentate sulfur coordination mode of the aroylthiourea ligands and the uncoordinated COOH group. The "3-legged piano-stool" coordination geometry was present around Ru ion. The hydrogen bonding interactions O(3)-H(3)...S(1)#1 and N(2)-H(2)...O(1) (L1), and O(4)-H(4)...Cl(1), N(1)-H(1)...Cl(2) and N(2)-H(2)...O(1) (**5** and **6**), characteristic of aroylthiourea and its Ru-*p*-cymene complex, respectively, were perceived.[35,37] Bond lengths and angles were comparable with the literature values.[35,37]

3.3 | Asymmetric hydrogenation of pro-chiral ketones in water

The chiral water soluble [$RuCl_2$(*p*-cymene)(L1-L6)] complexes (**1**–**6**) were applied for the enantioselective hydrogenation of aromatic ketones to produce their respective alcohols in enantiopure form. The reactions were performed with formic acid-triethylamine mixture in water. The effect of variables such as pH, temperature, solvent, reaction time and catalyst amount was studied.

The ATH reaction was often accomplished in isopropanol or the azeotropic mixture of HCOOH and

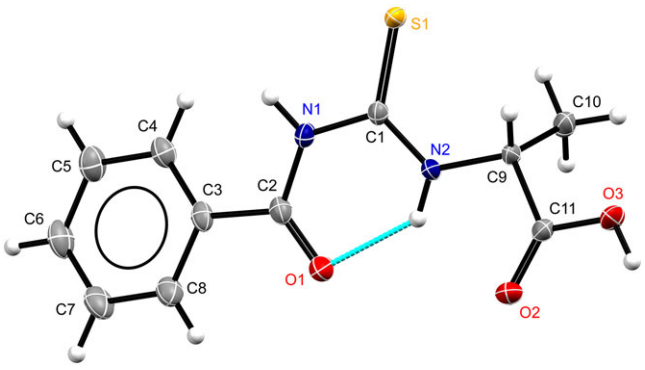


FIGURE 1 Thermal ellipsoidal plot of L1 showing the atomic labeling scheme and thermal ellipsoids at the 50% probability level. Selected bond distances (Å) and angles (°): S(1)-C(1) 1.6774(18), O(1)-C(2) 1.221(2), O(2)-C(11) 1.206(2), O(3)-H(3) 0.8400, O(3)-C(11) 1.322(2), N(1)-H(1) 0.8800, N(2)-H(2) 0.8800, C(1)-N(1)-H(1) 116.4, C(1)-N(2)-H(2) 118.6, N(1)-C(1)-S(1) 119.44(13), N(2)-C(1)-S(1) 123.59(13), N(2)-C(1)-N(1) 116.96(15), O(1)-C(2)-N(1) 121.97(16)

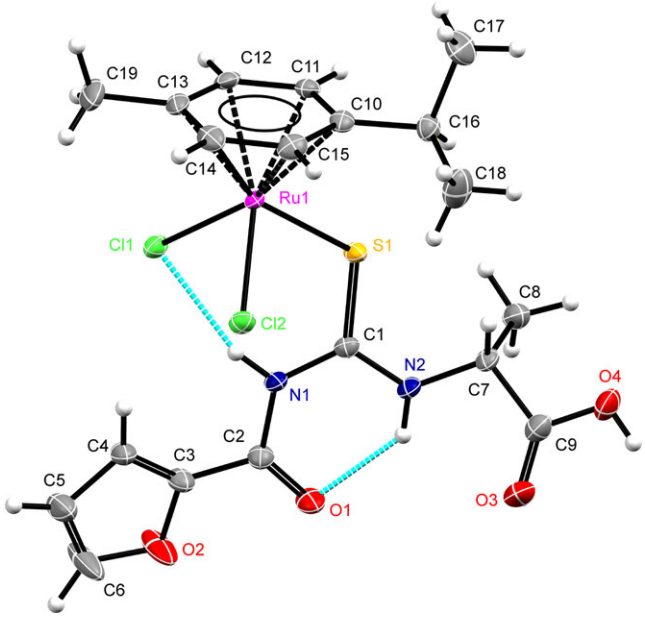


FIGURE 2 Thermal ellipsoidal plot of **5** showing the atomic labeling scheme and thermal ellipsoids at the 50% probability level. Selected bond distances (Å) and angles (°): Ru(1)-S(1) 2.3971(19), Ru(1)-Cl(1) 2.439(2), Ru(1)-Cl(2) 2.429(2), S(1)-Ru(1)-Cl(1) 91.87(7), S(1)-Ru(1)-Cl(2) 89.83(7), Cl(2)-Ru(1)-Cl(1) 86.64(6), C(1)-S(1)-Ru(1) 116.25(13)

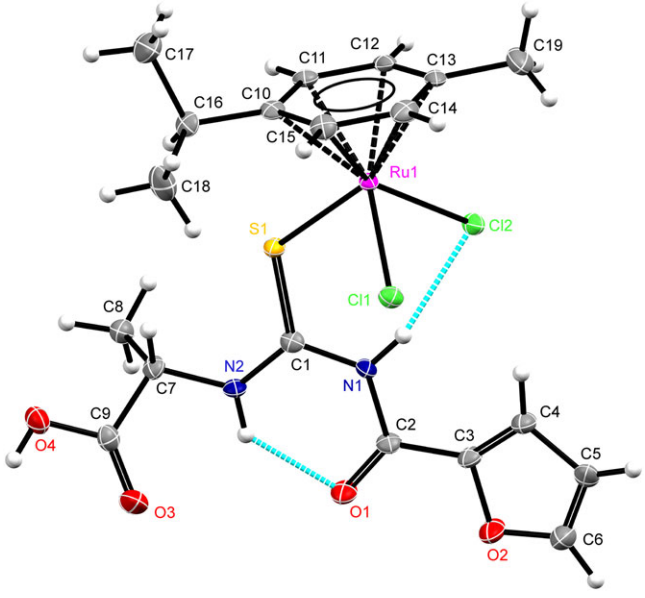


FIGURE 3 Thermal ellipsoidal plot of **6** showing the atomic labeling scheme and thermal ellipsoids at the 50% probability level. Selected bond distances (Å) and angles (°): Ru(1)-S(1) 2.3979(13), Ru(1)-Cl(1) 2.4276(13), Ru(1)-Cl(2) 2.4390(12), S(1)-Ru(1)-Cl(1) 89.81(5), S(1)-Ru(1)-Cl(2) 91.93(5), Cl(1)-Ru(1)-Cl(2) 86.63(4), C(1)-S(1)-Ru(1) 116.18(18)

NEt_3 in water. When HCOOH-NEt_3 mixture was used as a reductant, ATH was found to be pH dependent and hence the ratio of the amount of HCOOH and NEt_3 was crucial.[40–45] Very few reports explained the effect of pH on the ATH.[46,47] For example, Noyori–Ikariya catalyst exhibited pH-dependent activity towards the ATH of ketones in the presence of HCOOH-NEt_3 mixture in water.[48] This stimulated us to study the effect of pH on the ATH of ketones by varying the molar ratio of HCOOH and NEt_3, which gave interesting results (Figure 4.). At pH = 8, maximum conversion (99%) was obtained and hence the corresponding molar ratio of HCOOH and NEt_3 (1.0:5.1) was utilized in further experiments. The influence of temperature on the reaction was investigated (Figure 5.). The results revealed that lower (30, 40 and 50 °C) temperatures were not favorable whereas excellent conversion (99%) and ee (92%) were observed at 60 °C. Further increase of temperature to 80 °C slightly decreased the conversion (95%) and ee (88%). So the optimum temperature was 60 °C. To choose the appropriate solvent/hydrogen donor, ATH of acetophenone was carried out in 2-propanol, water and without solvent (neat) (Table 1.). When 2-propanol was used as solvent/hydrogen donor in the presence NaOH, the conversion and ee were 83 and 94% respectively after 20 hr. Interestingly, the use of H_2O as a solvent and HCOOH-NEt_3 mixture as a hydrogen donor/base lead to 99% conversion and 92% ee after the same duration. In the presence of HCOOH-NEt_3 mixture under the neat condition (without H_2O), only 81% of acetophenone was converted into (*S*)-1-phenylethanol (77% ee) even after 24 hr. It was obvious from the results that HCOOH-NEt_3/H_2O combination was the best choice for the present catalytic system. The ATH of acetophenone in water was monitored at different time intervals. The maximum

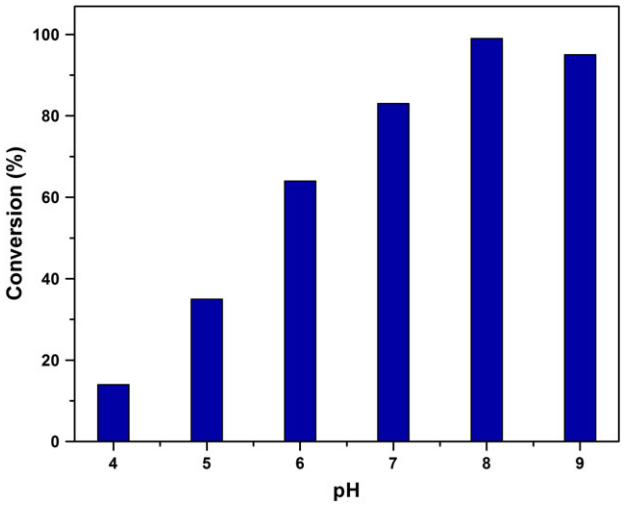


FIGURE 4 Effect of pH on conversion for the asymmetric hydrogenation of acetophenone (1 mmol) using **1** as catalyst (0.005 mmol) and HCOOH-NEt_3 (by varying the molar ratio from 1.0:13.0 to 1.0:4.7) as hydrogen donor in water (0.5 ml) at 60 °C for 20 hr

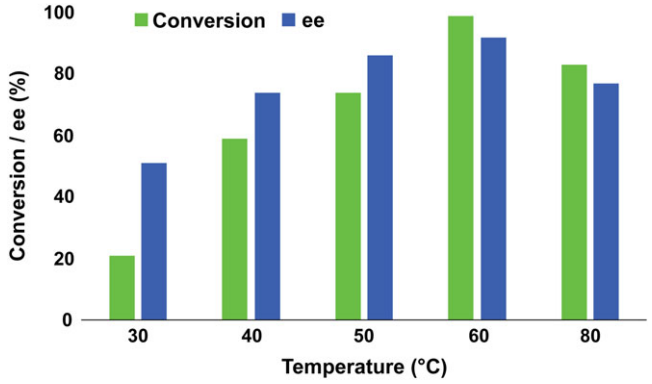


FIGURE 5 Effect of temperature on conversion and ee for the hydrogenation of acetophenone (1 mmol) in water (0.5 ml) using catalyst **1** (0.005 mmol) and HCOOH-NEt_3 (molar ratio 1.0:5.1) after 20 hr

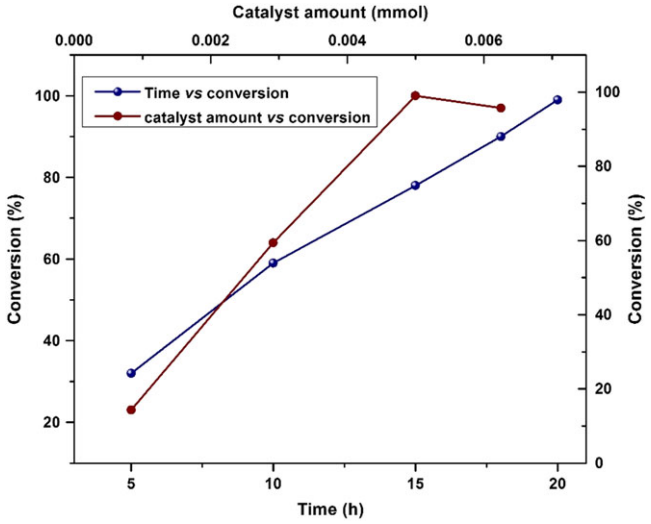


FIGURE 6 Effect of time and catalyst amount on conversion for hydrogenation of acetophenone (1 mmol) in water (0.5 ml) using catalyst **1** (0.005 mmol) and HCOOH-NEt_3 (molar ratio 1.0:5.1) at 60 °C

conversion and ee were achieved after 20 hr (Figure 6.). The catalyst loading was optimized by using different amount (0.001, 0.003, 0.005 and 0.007 mmol) of catalyst **1** towards ATH of acetophenone (Figure 6.). When 0.005 mmol of catalyst **1** was used, quantitative conversion and excellent ee (99%) were reached.

Asymmetric reduction of various aromatic ketones to their respective enantiopure alcohols was demonstrated using chiral Ru (II)-*p*-cymene catalysts (**1**–**6**) in water in the presence of HCOOH-NEt_3 at 60 °C. Excellent conversion and optical purity were attained within 20 hr for acetophenone, 24 hr for 4-methoxy benzophenone and 22 hr for other substituted ketones (Table 2.). The effectiveness of the current asymmetric catalytic system was compared with that of the recognized Ru-*p*-cymene catalysts, specifically with attention to the ATH of acetophenone in water (Scheme 3). Asymmetric reduction of acetophenone with Ru-η^6-*p*-cymene dimer and (*R*)-N-(4-fluorophenyl)pyrrolidine-2-carboxamide proceeded for 18 hr to show 98% conversion and 67% ee.[14] Though the conversion was comparable with the present system, ee was significantly lower. The combination of $[RuCl_2(p\text{-cymene})]_2$ and N-((1*S*,2*S*)-2-amino-1,2-bis(2-aminophenyl) ethyl)-4-methylbenzene sulfonamide offered 33% conversion and 95% ee within 1 hr[5]; ee was comparable with that produced by **1**, **3**, **4**, **5** and **6**, but the conversion was very much lower. Ru-*p*-cymene dimer with sodium 2,2′-((1*R*,2*R*)-1-amino-2-(4-methylphenylsulfonamido) ethane-1,2-diyl) dibenzene sulfonate provided 99% conversion and 95% ee after 24 hr,[12] which was comparable with the present catalysts (**1**–**6**). Ru-*p*-cymene-TsDPEN (TsDPEN = N-(*p*-toluenesulfonyl)-1,2-diphenyl-ethylenediamine) demonstrated superior results (conversion 99% and ee 94%) within 12 hr.[11] Ru (II)-*p*-cymene complex containing N-((1*S*,2*S*)-2-aminocyclohexyl)-4-methylbenzenesulfonamide or (−)-ephedrine hydrochloride catalyzed asymmetric reduction of acetophenone efficiently in water medium, which was comparable with our catalytic system.[21,30] It is clear from the comparison that the Ru-*p*-cymene organometallic compounds reported in this paper are among the few effective catalysts for ATH of ketones in water.

The synthesis of optically pure enantiomer of substituted aromatic alcohols is very important as they can be used as chiral building blocks for many pharmaceuticals such as L-chlorprenaline, *R*-tomoxetine, *S*-fluoxetine, *R*-salbutamol, *S*-duloxetine and *R*-

TABLE 1 Optimization of hydrogen donor

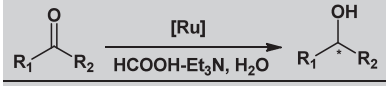
Entry	Catalyst 1 (mg)	Solvent	H-Donor	Conversion (%)	ee (%)
1[a]	3.5	2-propanol	2-propanol/NaOH	83	94
2[b]	3.5	H_2O	HCOOH/NEt_3	99	92
3[c]	3.5	Neat	HCOOH/NEt_3	81	77

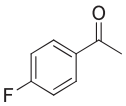
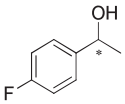
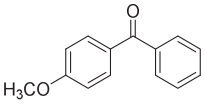
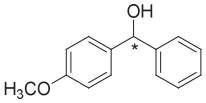
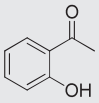
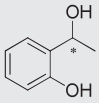
[a]0.005 mmol of **1** in 5 ml of 2-propanol, 1 mmol of NaOH and 1 mmol of acetophenone at 80 °C, for 20 hr.

[b]0.005 mmol of **1** in 0.5 ml of water, HCOOH:NEt_3 (molar ratio 1.0:5.1) and 1 mmol of acetophenone at 60 °C for 20 hr.

[c]0.005 mmol of **1**, HCOOH:NEt_3 (molar ratio 1.0:5.1) and 1 mmol of acetophenone at 60 °C for 24 hr.

TABLE 2 Enantioselective reduction of ketones catalyzed by Ru (II) complexes (**1–6**)[a]



Entry	Catalyst	Substrate	Product	Conversion[b] (%)	ee[c] (%) /Configuration[d]	TON[e]
1	**1**			99	92/*S*	198
2	**2**			99	76/*S*	198
3	**3**			99	98/*S*	198
4	**4**			82	93/*S*	164
5	**5**			81	91/*S*	162
6	**6**			83	94/*S*	166
7	**1**			63	86/*R*	126
8	**2**			73	97/*R*	146
9	**3**			61	98/*R*	122
10	**4**			98	97/*R*	196
11	**5**			95	91/*R*	190
12	**6**			97	97/*R*	194
13	**1**			91	70/*S*	181
14	**2**			94	63/*S*	188
15	**3**			98	90/*R*	196
16	**4**			79	94/*R*	158
17	**5**			91	94/*R*	182
18	**6**			98	90/*R*	196
19	**1**			97	73/*R*	194
20	**2**			94	84/*S*	188
21	**3**			74	78/*S*	148
22	**4**			99	91/*S*	198
23	**5**			99	76/*S*	198
24	**6**			97	66/*S*	194
25	**1**			64	68/*R*	128
26	**2**			57	66/*R*	114
27	**3**			69	96/*S*	138
28	**4**			54	75/*R*	108
29	**5**			75	90/*R*	150
30	**6**			62	84/*S*	124
31	**1**			98	99/*R*	196
32	**2**			99	99/*S*	198
33	**3**			99	99/*R*	198
34	**4**			99	99/*S*	198
35	**5**			97	99/*R*	194
36	**6**			99	99/*R*	198

[a]Reactions were carried out at 60 °C using 1 mmol of ketone, 0.005 mmol of Ru (II)-*p*-cymene complex in 0.5 ml of water and HCOOH:NEt_3 (molar ratio 1.0:5.1) for 20–24 hr.

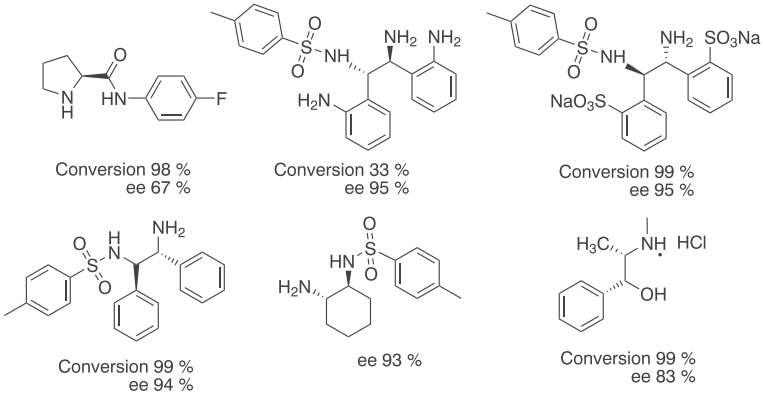
[b]The conversion was determined by GC–MS.

[c]ee was determined by chiral HPLC.

[d]Absolute configuration was determined from the optical rotation values.

[e]TON = moles of the product formed/moles of the catalyst used.

denopamine.[49–56] 2-Methyl acetophenone was transformed into (*R*)-1-(2-methylphenyl) ethanol with 98% conversion and 98% ee (Table 2, entries 7–12). The catalysts (**1–6**) were used for the conversion (up to 98%) of 4-fluoro acetophenone to 4-fluorophenylethanal (up to 94% ee) (Table 2, entries 13–18). The enantioselective reduction of heterocyclic ketone, 1-(2-furanyl)-ethanone, was successful in our method which offered 1-(furan-2-yl) ethanol with 99% conversion and 91% ee using catalyst **4** (Table 2, entries 19–24). Using the present catalytic system, chiral benzhydrol was derived from a bulky ketone, 4-methoxy benzophenone (Table 2, entries 25–30). 2-Hydroxy acetophenone was converted in to 2-(1-hydroxyethyl) phenol in 99% conversion and 99% ee



SCHEME 3 Conversion and ee obtained from reported chiral ligands with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ in water

(Table 2, entries 31–36). ATH of aliphatic and cyclic ketones was not successful with the present reaction conditions.

3.4 | Plausible mechanism

The homogeneous ATH of pro-chiral ketones to the respective chiral secondary alcohols might follow the concerted mechanism proposed by Noyori *et al*.,[57] and explained by Wu *et al*.[23] Presently, the catalysis proceeds under basic condition and the possible mechanism is presented in Figure 7.[34,58,59] The similar concerted mechanism was proposed for our previous system and confirmed by experimental and theoretical studies.[37,38] The Ru-hydride species which formed after the exposure of the catalyst with HCOOH-NEt_3 interacted with the ketone substrate through the Ru-H and N-H units to form a cyclic six-membered transition state that delivered enantiopure secondary alcohols. The rate of the hydrogenation reaction increases at pH values greater than 4, which could be due to the improved concentration of $HCOO^-$. At pH > 4, HCOOH (pKa = 3.7) stays predominately as $HCOO^-$, which is desirable to form the ruthenium formato complex. The configuration of product alcohols did not depend on that of the complexes in most of the cases. This may be due to the fact that only diastereomers (resulting from chiral centered Ru) with equal configuration might be active.[37]

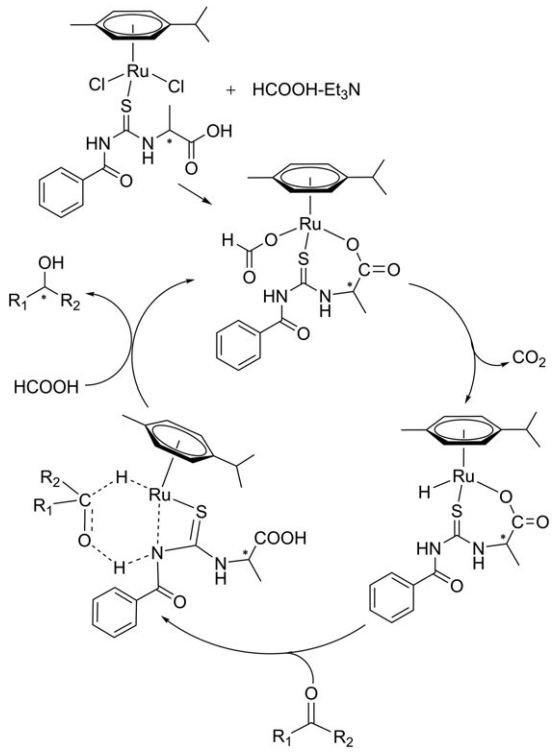


FIGURE 7 Proposed catalytic cycle for asymmetric hydrogenation of ketones under acidic and basic conditions

4 | CONCLUSIONS

The chiral water soluble $[RuCl_2(p\text{-cymene})(L1\text{-}L6)]$ complexes (**1**–**6**) obtained from the reaction between Ru (II)-η^6-*p*-cymene dimer and the chiral D/L-alanine-aroylthiourea derivatives (L1-L6) were characterized. In all the complexes, aroylthiourea exhibited monodentate sulfur coordination with Ru ion. All the complexes (**1**–**6**) demonstrated high catalytic activity towards the asymmetric reduction of aromatic ketones to the respective chiral secondary alcohols in water. The water medium and non-inert atmospheric condition made the present system of enantioselective reduction of aromatic ketones eco-friendly and simple. To add, the efficiency of the catalytic system is comparable to superior systems. The encouraging results of ATH may prompt the scientists to use these catalysts for other asymmetric reactions in water medium.

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