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Ru(II)-*p*-cymene complexes containing esters of chiral D/L-phenylalanine derived aroylthiourea ligands for enantioselective reduction of pro-chiral ketones†

Mani Mary Sheeba,[a] Manoharan Muthu Tamizh,[b] Sundaram Ganesh Babu,[a] Nattamai S. P. Bhuvanesh[c] and Ramasamy Karvembu*[a]

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A series of new chiral aroylthiourea ligands was derived from unprotected D/L-phenylalanine: (*R*)/(*S*)-2-(3-benzoylthioureido)-3-phenylpropanoic acid (**L1**/**L2**), (*R*)/(*S*)-2-(3-(thiophene-2-carbonyl)thioureido)-3-phenylpropanoic acid (**L3**/**L4**) and (*R*)/(*S*)-2-(3-(furan-2-carbonyl)thioureido)-3-phenylpropanoic acid (**L5**/**L6**). Chiral Ru(II) complexes (**1–6**) were obtained from the reactions between the chiral ligands (**L1–L6**) and $[RuCl_2(p\text{-cymene})_2]_2$ through *in situ* catalytic esterification of the ligand in the presence of methanol solvent. The ligands and complexes were characterized by analytical and spectral (^{1}H NMR, ^{13}C NMR, Mass, FT-IR, electronic) techniques. The molecular structure of the ligand **L1** showed the presence of an unprotected acid group and that of the representative complexes confirmed the conversion of acid to ester. The X-ray structure of two of the complexes (**3** and **6**) revealed the sulfur only monodentate coordination of the aroylthiourea ligands. All the chiral complexes turned out to be efficient catalysts for the enantioselective reduction of aromatic pro-chiral ketones in the presence of 2-propanol and NaOH to produce chiral alcohols in excellent conversions (up to 99%) and enantiomeric excesses (up to 99%) within 10–12 h.

1 Introduction

α-Amino acids are one of the readily obtainable and inexpensive natural chiral compounds, and are used as chiral auxiliaries or reagents for the synthesis of optically active molecules.[1] Although aroylthiourea ligands prepared from primary and secondary amines have been widely used to synthesize transition metal complexes for various applications,[2–7] amino acid derived aroylthiourea ligands which might provide more coordination possibilities, are not yet known. It was expected that the introduction of an amino acid moiety into the aroylthiourea ligand would make aroylthiourea complexes soluble in water. These factors induced us to synthesize chiral aroylthiourea ligands from D/L-phenylalanine.

The chemistry of amino acid complexes of transition metals has received considerable attention.[8–10] Amino acids/amino acid derived ligands and their complexes were used as catalysts in enantioselective reactions such as asymmetric transfer hydrogenation (ATH),[11–16] epoxidation,[17,18] deamination,[19] aldol reaction,[20] silylation of alcohols,[21] and allylic alkylation.[22] The number of Ru-*p*-cymene complexes with amino acids/amino acid derived ligands explored as catalysts for ATH is relatively less but they showed an outstanding activity.[11–16] The amino acids/amino acid derived ligands which employed with Ru-*p*-cymene for ATH of ketones are L-prolinamide,[23] *tert*-butyl-((*S*)-1-(((*S*)-2-hydroxypropyl)amino)-1-oxopropan-2-yl)carbamate, *tert*-butyl((*S*)-1-(((*R*)-2-hydroxy-1-phenylethyl)amino)-1-thioxopropan-2-yl)carbamate,[24] (*S*)-2-amino-3-methyl-*N*-phenylbutanamide, (*S*)-2-amino-*N*-(4-methoxyphenyl)-3-methyl butanamide,[14] *S*-phenylalanine,[25] (*R*)-*N*-hydroxypyrrolidine-2-carboxamide,[11] *tert*-butyl-((*S*)-1-(((*S*)-2-hydroxypropyl)amino)-1-oxopropan-2-yl)carbamate,[15] (2*S*)-*N*-(1-(1*H*-benzo[*d*]imidazol-2-yl)ethyl)pyrrolidine-2-carboxamide,[26] *tert*-butyl-*N*-((1*S*)-2-{[(1*R*)-2-hydroxy-1-phenylethyl]amino}-1-methyl-2-oxoethyl)carbamate[16] and *tert*-butyl-((*S*)-1-(((*S*)-2-hydroxy-2-phenylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate.[27]

Ru(II)-*p*-cymene complexes were reported as highly active catalysts or pre-catalysts for various organic transformations.[28] $[RuCl_2(p\text{-cymene})]_2$ itself acted as a catalyst in many organic transformations.[29,30] It was observed in the present work that

[a]Department of Chemistry, National Institute of Technology, Tiruchirappalli 620015, India. E-mail: kar@nitt.edu; Fax: +91 431 2500133; Tel: +91 431 2503631

[b]Department of Chemistry, Siddha Central Research Institute (SCRI), Arignar Anna Govt. Hospital Campus, Arumbakkam, Chennai-600106, India

[c]Department of Chemistry, Texas A & M University, College Station, TX 77842, USA

† Electronic supplementary information (ESI) available: A table of the X-ray crystallographic data, atomic coordinates in CIF format, ^{1}H NMR and ^{13}C NMR spectra of all the ligands and complexes, and GC-MS, GC and HPLC data are included. CCDC 1474599, 1458027–1458028. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra12428c

the amino acids were converted into corresponding esters in the presence of $[RuCl_2(p\text{-cymene})]_2$ and methanol prior to their coordination with Ru(II). The esters derived from amino acids are very important intermediates in organic synthesis and effective anticancer and antiviral drugs. The amino esters have been used as prodrugs to increase oral bioavailability in pharmaceuticals and helped to improve the physicochemical properties and reduce the toxicity.[31] Amino acid esters have wide applications in the area of peptide synthesis,[32] polymer synthesis,[33,34] asymmetric synthesis[35–38] and medicinal chemistry.[39,40]

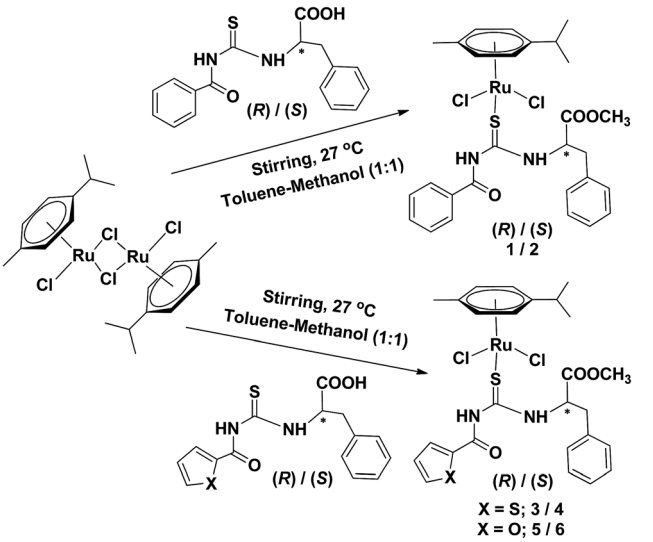
Chirality is significant for the designing of drug molecules. The pharmacological effect of organic compounds is very often caused by only one enantiomer while the other one can have a different effect or even have no effect. For that reason, direct methods of obtaining optically pure chiral compounds are highly in demand. Conventional organic reactions almost always lead to a racemic mixture, but asymmetric reactions can give a single enantiomeric product. The asymmetric reduction of pro-chiral ketones under mild catalytic hydrogen transfer conditions will offer a highly attractive route for the formation of enantiomerically pure secondary alcohols, an important building blocks, and synthetic intermediates in organic synthesis and pharmaceutical industry[41–43] and an important class of fine chemicals.[44]

We report here the synthesis and characterization of new chiral aroylthiourea ligands derived from D/L-phenylalanine such as (*R*)/(*S*)-2-(3-benzoylthioureido)-3-phenylpropanoic acid (**L1**/**L2**), (*R*)/(*S*)-2-(3-(thiophene-2-carbonyl)thioureido)-3-phenylpropanoic acid (**L3**/**L4**) and (*R*)/(*S*)-2-(3-(furan-2-carbonyl) thioureido)-3-phenylpropanoic acid (**L5**/**L6**), and their ester Ru-*p*-cymene complexes (**1–6**). These Ru-*p*-cymene complexes were successfully applied as catalysts for the enantioselective reduction of aromatic ketones to their corresponding enantiomerically enriched secondary alcohols. The *in situ* transformation of amino acid to amino ester in the presence of $[RuCl_2(p\text{-cymene})]_2$ as a catalyst was confirmed.

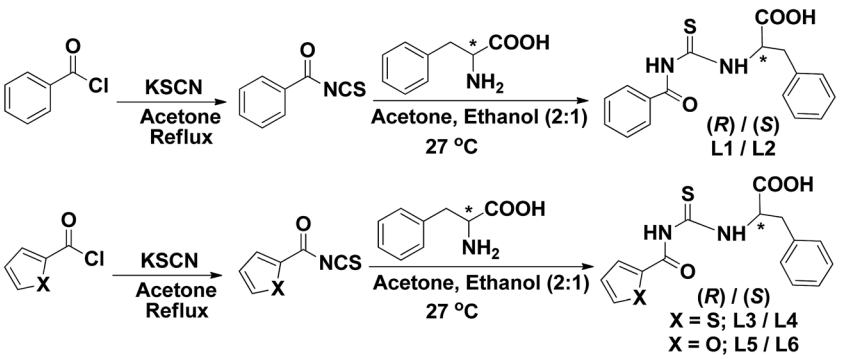
2 Results and discussion

2.1 Synthesis of the ligands and complexes

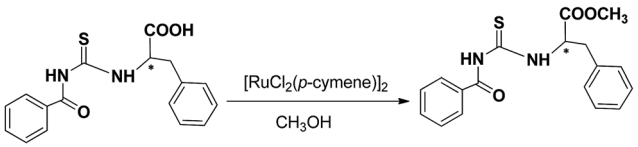
The chiral ligands (**L1–L6**) were synthesized from benzoyl chloride or thiophene-2-carbonyl chloride or furan-2-carbonyl chloride, potassium thiocyanate and D-phenylalanine or L-phenylalanine in acetone–ethanol mixture (Scheme 1). The chiral Ru(II) complexes (**1–6**) were obtained from the reactions between $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and the chiral ligands (L) in 1 : 1 mixture of toluene and methanol (Scheme 2). Methanol is essential for the solubility of the ligands. Due to the presence of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and methanol, the unprotected amino acid was converted into amino ester before coordination. This conversion clearly indicated that $[RuCl_2(p\text{-cymene})_2]_2$ acted not only as a Ru precursor but also as a catalyst for the *in situ* production of amino ester. To confirm this, amino acid (**L1**) was stirred at 27 °C in the presence of catalytic amount of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (Scheme 3). The formation of ester was attested by ^{1}H NMR analysis. This conversion is interesting because amino esters are very important for the design of many drug molecules and pro-drugs. However esterification of the ligands prevented the solubility of their Ru-*p*-cymene complexes in water. The ligands and Ru-*p*-cymene complexes were characterized by elemental analysis, and UV-Vis, FT-IR, ^{1}H NMR, ^{13}C NMR and HR-MS spectroscopic methods. The molecular structure of the ligand **L1** and complexes (**3** and **6**) was confirmed by single crystal X-ray crystallography. The optical rotation value of the



Scheme 2 Synthesis of complexes (**1–6**).



Scheme 1 Synthesis of ligands (L1–L6).



Scheme 3 Conversion of amino acid to amino ester.

compounds was obtained by polarimetric studies. All the ligands and complexes were air stable and soluble in toluene, benzene, CH_3OH, C_2H_5OH, $CHCl_3$, CH_2Cl_2, CH_3CN, DMF and DMSO.

2.2 Characterization of the ligands and complexes

In the ^{1}H NMR spectra of all the ligands (**L1–L6**), the signal due to carboxyl O–H proton was found as a broad singlet in the region 13.29–13.31 ppm. The thiocarbonyl attached N–H, and carbonyl and thiocarbonyl attached N–H protons were observed as doublet at 10.97–11.23 ppm and singlet at 11.27–11.59 ppm respectively. The resonances owing to the aromatic ring (phenyl, thiophene or furan) protons were appeared at 6.72–8.35 ppm in the spectra of all the ligands. A multiplet was observed at 5.09–5.16 ppm for the proton present in the chiral carbon. The CH_2 protons of the ligands were observed as two doublet of doublets at 3.16–3.35 ppm. In the ^{1}H NMR spectra of all the complexes (**1–6**), the signal due to carboxyl O–H proton was disappeared and a new signal observed at 2.59–3.91 ppm indicated the conversion of acid to ester. The new signals seemed in the region 1.26–1.34, 2.19–3.30 and 5.21–5.47 ppm indicated the presence of *p*-cymene moiety in the complexes.[5] All other chemical shift values of the complexes were almost similar to those of the corresponding free ligands. The ^{13}C NMR spectra of the ligands showed signals at 36.0 and 58.6 ppm for the CH_2 and asymmetric carbons respectively. The signals appearing at 112.6–147.8 ppm in the spectra of all the ligands were assigned to the aromatic (phenyl, thiophene or furan ring) carbons. The resonances due to C=O and C=S were observed around 158.3–168.8 and 171.2–175.5 ppm respectively. The carboxyl carbon signal was observed at 179.9–180.3 ppm.^{13}C NMR spectra of the complexes also confirmed the acid to ester conversion. The ester COO and CH_3 carbon signals were observed at 178.7–179.6 and 51.9–52.7 ppm respectively. All other chemical shift values did not undergo significant change upon coordination of the ligand to Ru. The new signals observed around 18.3, 22.2, 30.4, 82.6, 82.7, 84.2, 84.3, 100.0 and 103.4 ppm confirmed the presence of *p*-cymene in all the complexes.[5]

Further, the formation of the complexes was established from the d–d (441–448 nm) and charge transfer transitions (328–339 nm) observed in the UV-visible spectra of the complexes. The FT-IR spectra of the complexes were compared with that of the free ligands. The frequencies of the C=O and amide N–H stretching modes were almost unaltered upon coordination, but the C=S stretching frequency of the complexes decreased from the region 1240–1246 to 1183–1196 cm^{-1}, which strongly suggested that the ligands were bound to the Ru ion *via* the sulfur atom only.[3,5] The carboxylic acid C=O stretching frequency of the ligands observed in the region 1705–1718 cm^{-1} was increased to 1738–1741 cm^{-1} in the complexes, which confirmed the conversion of acid to ester prior to complexation.[45] Coordination mode of the ligands and functional group transformation were unambiguously confirmed by the single crystal X-ray diffraction study.

2.3 X-ray crystallographic study

The structure of the ligand **L1** and complexes **3** and **6** was elucidated by single crystal X-ray diffraction study and are shown in the Fig. 1–3. The ligand and complexes crystallized in the chiral orthorhombic crystal system with the space group $P2_12_12_1$. The molecular structure of ligand **L1** evidently displayed the presence of acid group in the free ligand. The thermal ellipsoidal plot of **3** and **6** confirmed the monodentate sulfur coordination of the thiourea ligand in the complexes and the formation of ester group in the coordinated ligand. In the complexes Ru ion displayed half-sandwich "3-legged pianostool" coordination geometry. The hydrogen bonding interactions N(1)–H(1)···O(3) and N(2)–H(2)···Cl(1) characteristic of this type of complexes were clearly seen[3,5] (Fig. 2 and 3).

2.4 Enantioselective reduction of ketones

The chiral Ru-*p*-cymene complexes (**1–6**) acted as effective catalysts for the asymmetric reduction of pro-chiral ketones to their corresponding secondary chiral alcohols. The reactions were carried out in the presence of NaOH and 2-propanol at 82 °C by using the optimized substrate : NaOH : catalyst ratio of 200 : 200 : 1. The conversions of up to 99% and enantiomeric excesses (ee) of up to 99% were achieved within 10 h for acetophenone and 12 h for other substituted ketones. The

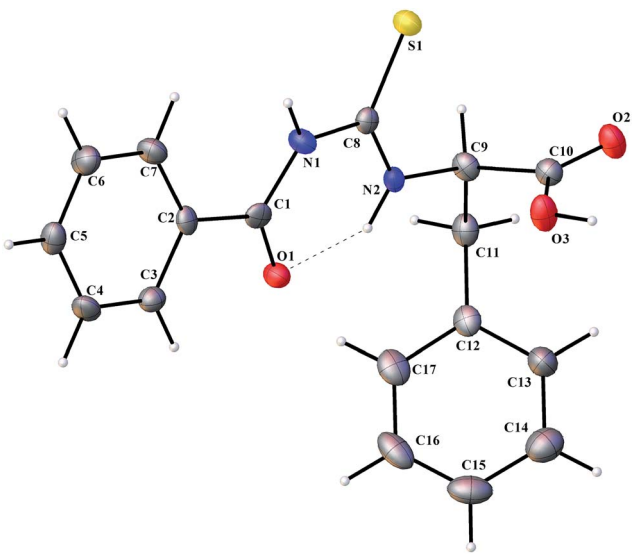


Fig. 1 Thermal ellipsoidal plot of L1 showing the atomic labeling scheme and thermal ellipsoids at the 50% probability level. Selected bond distances (Å) and angles (°): S(1)–C(8) 1.683(4), O(1)–C(1) 1.227(5), O(2)–C(10) 1.203(5), O(3)–H(3) 0.8400, O(3)–C(10) 1.325(5), N(1)–H(1) 0.8800, N(2)–H(2) 0.8800, C(8)–N(1)–H(1) 116.4, C(8)–N(2)–H(2) 119.0, N(2)–C(8)–S(1) 123.2(3), N(1)–C(8)–S(1) 119.4(3).

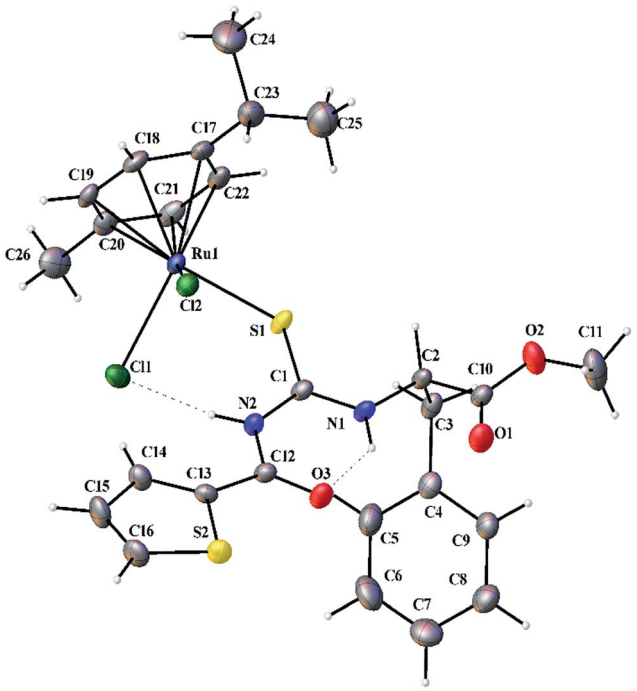


Fig. 2 Thermal ellipsoidal plot of **3** showing the atomic labeling scheme and thermal ellipsoids at the 50% probability level. Selected bond distances (Å) and angles (°): Ru(1)–S(1) 2.4157(9), Ru(1)–Cl(1) 2.4247(10), Ru(1)–Cl(2) 2.4239(10), S(1)–Ru(1)–Cl(1) 90.91(3), S(1)–Ru(1)–Cl(2) 91.36(4), Cl(2)–Ru(1)–Cl(1) 86.38(3), C(1)–S(1)–Ru(1) 116.00(11).

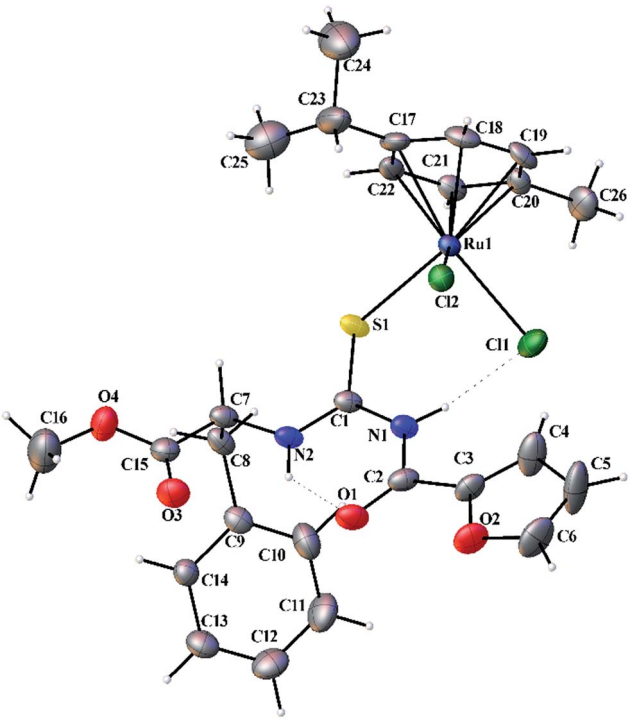


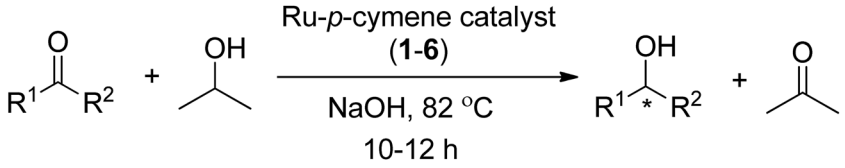
Fig. 3 Thermal ellipsoidal plot of **6** showing the atomic labeling scheme and thermal ellipsoids at the 50% probability level. Selected bond distances (Å) and angles (°): Ru(1)–S(1) 2.4221(11), Ru(1)–Cl(1) 2.4275(11), Ru(1)–Cl(2) 2.4280(10), S(1)–Ru(1)–Cl(1) 90.54(4), S(1)–Ru(1)–Cl(2) 91.40(4), Cl(2)–Ru(1)–Cl(1) 86.90(3), C(1)–S(1)–Ru(1) 115.60(13).

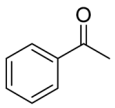
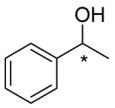
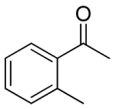
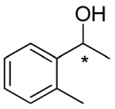
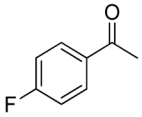
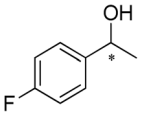
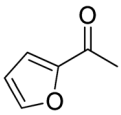
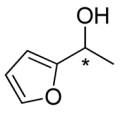
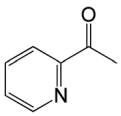
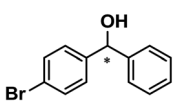
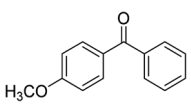
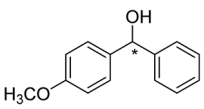
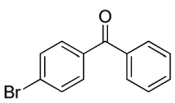
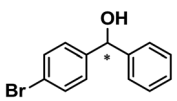
conversion and ee values were determined by GC and chiral HPLC analyses respectively and are given in Table 1.

The potency of the present catalytic system was compared with the previously existing catalysts based on amino acids with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$, mainly with respect to the enantioselective reduction of acetophenone (Scheme 4). Enantioselective reduction of ketones with (*S*)-pyrrolidine-2-carboxamide-Ru-*p*-cymene catalytic system showed reasonably good conversion (90%) and enantiomeric excess (79%) in 20 h.[23] But in the present catalytic system, catalyst **1** showed superior catalytic activity of 99% conversion and 98% ee within 10 h. $[RuCl_2(p\text{-cymene})]_2$ with *tert*-butyl-((*S*)-1-(((*R*)-2-hydroxy-1-phenylethyl)amino)-1-thioxopropan-2-yl)carbamate ligand provided only 35% conversion and 20% ee,[24] which was inferior to catalysts **1**–**6**. Nevertheless, $[RuCl_2(p\text{-cymene})]_2$ with *tert*-butyl-((*S*)-1-(((*R*)-2-hydroxy-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate ligand gave 83% conversion and 92% ee,[24] in which ee is comparable with that provided by **1** and **2**. (*S*)-2-Amino-3-methyl-*N*-phenylbutanamide/(*S*)-2-amino-*N*-(4-methoxyphenyl)-3-methylbutanamide with Ru-*p*-cymene offered the conversion of 77/98% and ee of 34/33%, and the highest ee reported in this system was only 47% [14] which was significantly lower than our present results. Ru(II)-*p*-cymene complexes containing (*S*)-phenylalanine were used as catalysts in ATH of ketones in isopropanol/KOH medium and the reported conversion was 74% and ee was only 28%.[25] But in the present case Ru-*p*-cymene with phenylalanine derived aroylthiourea exhibited an excellent conversion (99%) and ee (98%). (*R*)-*N*-Hydroxypyrrolidine-2-carboxamide/$[RuCl_2(p\text{-cymene})]_2$ catalytic system resulted 6% conversion and 41% ee after 17 h,[11] which is poor compared to the present results. Ru-*p*-cymene/*tert*-butyl-((*S*)-1-(((*S*)-2-hydroxypropyl)amino)-1-oxopropan-2-yl)carbamate system furnished 94% conversion and 96% ee[15] which are comparable with the performance of **1** and **2**. The ligand *tert*-butyl-((*S*)-1-(((*S*)-2-hydroxy-2-phenylethyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate on combination with $[RuCl_2(p\text{-cymene})]_2$ showed 86% conversion and 95% ee;[27] the ee is comparable with that exhibited by **1** and **2**. $[RuCl_2(p\text{-cymene})]_2$ bearing *tert*-butyl-((*S*)-1-(((*R*)-2-hydroxy-1-phenylethyl)amino)-1-oxopropan-2-yl)carbamate demonstrated a superior result (95% conversion and 93% ee) within 5 h.[16] (2*S*)-*N*-(1-(1*H*-Benzo[*d*]imidazol-2-yl)ethyl)pyrrolidine-2-carboxamide-Ru-*p*-cymene catalyst displayed an inferior result (65% ee).[26] The efficiency of the present catalysts was compared with our previous Ru-*p*-cymene catalysts containing aroylthiourea derived from (*R*)/(*S*)-1-phenylethylamine. The present catalysts which contain amino acid derived aroylthiourea were more active as it took only 10–12 h for the quantitative conversion of ketones to their respective chiral alcohols with 99% ee; but the same reactions previously required 24 h for completion.[5]

2-Methyl acetophenone was converted into 1-(*o*-tolyl)ethanol with up to 96% conversion and 99% ee (Table 1, entries 7–12). All the catalysts selectively yielded *R*-alcohols. Enantiopure

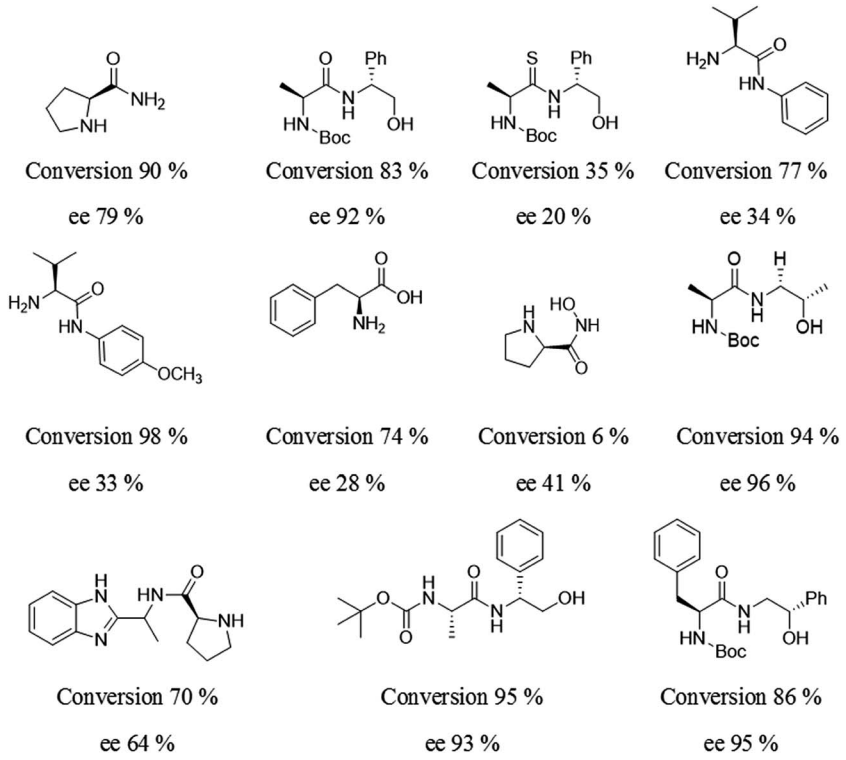
Table 1 Enantioselective reduction of ketones catalyzed by Ru-*p*-cymene complexes (**1–6**)[a]



Entry	Catalyst	Substrate	Product	Conversion[b] (%)	ee (%)[c]/configuration[d]	TON[e]
1	(**1**)			99	98/*R*	19 8
2	(**2**)			99	95/*R*	19 8
3	(**3**)			99	54/*S*	19 8
4	(**4**)			99	58/*R*	19 8
5	(**5**)			99	62/*S*	19 8
6	(**6**)			99	60/*S*	19 8
7	(**1**)			74	52/*R*	14 8
8	(**2**)			77	88/*R*	15 4
9	(**3**)			96	92/*R*	19 2
10	(**4**)			80	88/*R*	16 0
11	(**5**)			90	99/*R*	18 0
12	(**6**)			76	92/*R*	15 2
13	(**1**)			98	99/*R*	19 6
14	(**2**)			91	99/*R*	18 2
15	(**3**)			96	99/*R*	19 2
16	(**4**)			85	99/*R*	17 0
17	(**5**)			95	74/*R*	19 0
18	(**6**)			94	95/*R*	18 8
19	(**1**)			93	94/*R*	18 6
20	(**2**)			83	62/*R*	16 6
21	(**3**)			63	85/*R*	12 6
22	(**4**)			97	80/*R*	19 4
23	(**5**)			84	48/*R*	16 8
24	(**6**)			94	80/*R*	18 8
25	(**1**)			99	70/*R*	19 8
26	(**2**)			99	89/*R*	19 8
27	(**3**)			99	99/*R*	19 8
28	(**4**)			99	99/*R*	19 8
29	(**5**)			99	91/*R*	19 8
30	(**6**)			99	99/*R*	19 8
31	(**1**)			85	99/*S*	17 0
32	(**2**)			89	97/*S*	17 8
33	(**3**)			77	99/*S*	15 4
34	(**4**)			83	98/*S*	16 6
35	(**5**)			83	98/*S*	16 6
36	(**6**)			78	99/*S*	15 6
37	(**1**)			77	99/*R*	15 4
38	(**2**)			99	99/*R*	19 8
39	(**3**)			98	99/*R*	19 6
40	(**4**)			99	99/*R*	19 8
41	(**5**)			99	95/*S*	19 8
42	(**6**)			99	99/*R*	19 8

[a] Reactions were carried out at 82 °C using 1 mmol of ketone, 0.005 mmol of Ru(II) complex in 5 mL of 2-propanol and 1 mmol of NaOH for 10–12 h. [b] The conversion was determined by GC-MS or GC. [c] ee was determined by chiral HPLC. [d] Absolute configuration was determined from the optical rotation value. [e] TON = moles of the product formed/moles of the catalyst used.

fluoro-organic compounds are rare and have various biological applications in the fields of anti-cancer, anti-viral and anti-infection.[46–48] The half-sandwich Ru-*p*-cymene complexes (**1–6**) were used as catalysts for the conversion of pro-chiral 4-fluoro acetophenone to its corresponding chiral secondary alcohol with the conversions and ee up to 99% (Table 1, entries 13–18). Even though many ketones were enantioselectively reduced by ATH, reduction of heterocyclic ketones was rarely presented. The asymmetric reduction of 2-acetylfuran was achieved in our method which gave corresponding chiral alcohol with 93% conversion and 94% ee using catalyst **1** (Table 1, entries 19–24). The reduction of 2-acetylpyridine was performed, which



Scheme 4 Efficacy of reported amino acids/amino acid derived ligands with $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ towards asymmetric reduction of acetophenone.

provided corresponding chiral alcohol with 99% conversion and 99% ee using catalysts **3**, **4** and **6** (Table 1, entries 25–30). All the catalysts (**1–6**) were selectively offered the *R* alcohol. Chiral benzhydrol is widely used in the synthesis of various pharmaceuticals.[49] Using the present catalytic system, conversion of 4-methoxy benzophenone and 4-bromo benzophenone to corresponding chiral benzhydrol was accomplished (Table 1, entries 30–42 respectively). Based on our previous experience, arene might control the enantioselectivity and change of arene might lead to different enantioselectivity, which is under investigation.

3 Experimental section

3.1 General methods

The solvents were dried and stored over activated molecular sieves. $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ was prepared by following a literature procedure.[50] 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 4000–600 cm^{-1} region on a Nicolet iS5 FT-IR spectrophotometer. 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. Catalysis experiments were monitored using a Shimadzu GCMS-QP 2010 Ultra gas chromatograph mass spectrometer or Shimadzu GC 2010 gas chromatograph equipped with a Restek-5 capillary column. ee values 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.

3.2 Synthesis of ligands (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 (70 °C) under reflux for 45 minutes and then cooled to room temperature. A solution of D/L-phenylalanine (0.8259 g, 5 mmol) in acetone (40 mL) and ethanol (20 mL) was added, and the resulting mixture was stirred for 12 h 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 an ethanol–dichloromethane mixture (1 : 2).

3.2.1 (*R*)-2-(3-Benzoylthioureido)-3-phenylpropanoic acid (L1). Yield: 1.31 g, 80%. M.p.: 154 °C. $[\alpha]_D^{27}$: −44°. Anal. calcd for $C_{17}H_{15}N_2O_3S$: C, 62.37; H, 4.62; N, 8.56; S, 9.79. Found: C, 62.21; H, 4.47; N, 8.41; S, 9.62. ^1H NMR (DMSO-d_6, 500 MHz): δ 3.16–3.20 (dd, 2H, J = 5 Hz, CH_2), 5.14 (q, 1H, J = 5 Hz, asymmetric hydrogen), 7.20–7.92 (m, 10H, CH of phenyl rings), 11.22 (d, 1H, J = 10 Hz, C═S attached N–H), 11.52 (s, 1H, C═O and C═S attached N–H), 13.31 (bs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.0 (CH_2), 58.6 (asymmetric carbon), 126.9, 128.4,

128.4, 128.6, 129.2, 131.9, 133.1, 136.2 (aromatic CH), 168.4 (C=O), 171.3 (C=S), 180.3 (COOH). FT-IR (KBr, cm^{-1}): 3272 (m; ν(amide N–H)), 3196 (s; ν(thiourea N–H)), 1665 (s; ν(C=O)), 1709 (s; ν(COOH)), 1240 (s; ν(C=S)).

3.2.2 (*S*)-2-(3-Benzoylthioureido)-3-phenylpropanoic acid (L2). Yield: 1.28 g, 78%. M.p.: 154 °C. $[\alpha]_D^{27}$: +79°. Anal. calcd for $C_{17}H_{15}N_2O_3S$: C, 62.37; H, 4.62; N, 8.56; S, 9.79. Found: C, 62.13; H, 4.53; N, 8.40; S, 9.65. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.16–3.20 (dd, 2H, J = 5 Hz, CH_2), 5.14 (q, 1H, J = 5 Hz, asymmetric hydrogen), 7.23–7.92 (m, 10H, CH of phenyl rings), 11.22 (d, 1H, J = 5 Hz, C=S attached N–H), 11.51 (s, 1H, C=O and C=S attached N–H), 13.30 (bs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.1 (CH_2), 58.6 (asymmetric carbon), 126.9, 128.3, 128.3, 128.5, 129.1, 131.9, 133.0, 136.1 (aromatic CH), 168.3 (C=O), 171.3 (C=S), 180.2 (COOH). FT-IR (KBr, cm^{-1}): 3272 (m; ν(amide N–H)), 3196 (s; ν(thiourea N–H)), 1665 (s; ν(C=O)), 1709 (s; ν(COOH)), 1240 (s; ν(C=S)).

3.2.3 (*R*)-3-Phenyl-2-(3-(thiophene-2-carbonyl)thioureido) propanoic acid (L3). Yield: 1.43 g, 85%. M.p.: 160 °C. $[\alpha]_D^{27}$: −53°. Anal. calcd for $C_{15}H_{13}N_2O_3S_2$: C, 54.04; H, 3.93; N, 8.40; S, 19.23. Found: C, 53.93; H, 3.79; N, 8.28; S, 19.09. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.17 (dd, 2H, J = 5 Hz, CH_2), 5.12 (q, 1H, J = 5 Hz, asymmetric hydrogen), 7.19–7.31 (m, 5H, CH of phenyl ring and 1H, CH of thiophene ring), 8.02 (dd, 1H, J = 5 Hz, CH of thiophene ring), 8.33 (dd, 1H, J = 5 Hz, CH of thiophene ring), 11.07 (d, 1H, J = 5 Hz, C=S attached N–H), 11.58 (s, 1H, C=O and C=S attached N–H), 13.30 (bs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.0 (CH_2), 58.5 (asymmetric carbon), 126.8, 128.3, 128.6, 129.1, 132.6, 135.2, 136.1, 136.4 (aromatic CH), 162.1 (C=O), 171.2 (C=S), 179.9 (COOH). FT-IR (KBr, cm^{-1}): 3206 (m; ν(amide N–H)), 3168 (s; ν(thiourea N–H)), 1651 (s; ν(C=O)), 1706 (s; ν(COOH)), 1246 (s; ν(C=S)).

3.2.4 (*S*)-3-Phenyl-2-(3-(thiophene-2-carbonyl)thioureido) propanoic acid (L4). Yield: 1.42 g, 85%. M.p.: 161 °C. $[\alpha]_D^{27}$: +83°. Anal. calcd for $C_{15}H_{13}N_2O_3S_2$: C, 54.04; H, 3.93; N, 8.40; S, 19.23. Found: C, 53.94; H, 3.76; N, 8.29; S, 19.12. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.17 (dd, 2H, J = 5 Hz, CH_2), 5.12 (q, 1H, J = 5 Hz, asymmetric hydrogen), 7.19–7.32 (m, 5H, CH of phenyl ring and 1H, CH of thiophene ring), 8.03 (dd, 1H, J = 5 Hz, CH of thiophene ring), 8.34 (dd, 1H, J = 5 Hz, CH of thiophene ring), 11.08 (d, 1H, J = 10 Hz, C=S attached N–H), 11.59 (s, 1H, C=O and C=S attached N–H), 13.31 (bs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.0 (CH_2), 58.6 (asymmetric carbon), 126.8, 128.4, 128.7, 129.2, 132.6, 135.3, 136.2, 136.4 (aromatic CH), 162.2 (C=O), 171.3 (C=S), 179.9 (COOH). FT-IR (KBr, cm^{-1}): 3205 (m; ν(amide N–H)), 3168 (s; ν(thiourea N–H)), 1651 (s; ν(C=O)), 1705 (s; ν(COOH)), 1246 (s; ν(C=S)).

3.2.5 (*R*)-2-(3-(Furan-2-carbonyl)thioureido)-3-phenylpropanoic acid (L5). Yield: 1.27 g, 80%. M.p.: 175 °C. $[\alpha]_D^{27}$: −53°. Anal. calcd for $C_{15}H_{13}N_2O_4S$: C, 56.77; H, 4.13; N, 8.83; S, 10.10. Found: C, 56.66; H, 4.04; N, 8.71; S, 10.01. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.16 (q, 1H, J = 5 Hz, CH_2), 5.11 (q, 1H, J = 5 Hz, asymmetric hydrogen), 6.72 (q, 1H, J = 5 Hz, CH of furan ring), 7.18–7.31 (m, 5H, CH of phenyl ring), 7.80 (dd, 1H, J = 5 Hz, CH of furan ring), 8.04 (dd, 1H, J = 5 Hz, CH of furan ring), 10.98 (d, 1H, J = 5 Hz, C=S attached N–H), 11.27 (s, 1H, C=O and C=S attached N–H), 13.29 (bs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.0 (CH_2), 58.6 (asymmetric carbon), 112.6, 118.6, 126.8, 128.4, 129.2, 136.1, 144.4, 148.4 (CH), 157.8 (C=O), 171.3 (C=S), 179.9 (COOH). FT-IR (KBr, cm^{-1}): 3220 (m; ν(amide N–H)), 3162 (s; ν(thiourea N–H)), 1664 (s; ν(C=O)), 1718 (s; ν(COOH)), 1245 (s; ν(C=S)).

3.2.6 (*S*)-2-(3-(Furan-2-carbonyl)thioureido)-3-phenylpropanoic acid (L6). Yield: 1.25 g, 78%. M.p.: 174 °C. $[\alpha]_D^{27}$: +115°. Anal. calcd for $C_{15}H_{13}N_2O_4S$: C, 56.77; H, 4.13; N, 8.83; S, 10.10. Found: C, 56.62; H, 4.01; N, 8.70; S, 9.92. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.17 (q, 1H, J = 5 Hz, CH_2), 5.13 (q, 1H, J = 5 Hz, asymmetric hydrogen), 6.72 (q, 1H, J = 5 Hz, CH of furan ring), 7.19–7.31 (m, 5H, CH of phenyl ring), 7.81 (dd, 1H, J = 5 Hz, CH of furan ring), 8.04 (dd, 1H, J = 5 Hz, CH of furan ring), 10.99 (d, 1H, J = 10 Hz, C=S attached N–H), 11.27 (s, 1H, C=O and C=S attached N–H), 13.31 (bs, 1H, COOH). ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.0 (CH_2), 58.6 (asymmetric carbon), 112.6, 118.6, 126.9, 128.4, 129.2, 136.1, 144.4, 148.4 (CH), 157.8 (C=O), 171.3 (C=S), 179.9 (COOH). FT-IR (KBr, cm^{-1}): 3220 (m; ν(amide N–H)), 3162 (s; ν(thiourea N–H)), 1664 (s; ν(C=O)), 1717 (s; ν(COOH)), 1245 (s; ν(C=S)).

3.3 Synthesis of complexes (1–6)

$[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (122.5 mg, 0.2 mmol) and (*R*)/(*S*)-2-(3-benzoylthioureido)-3-phenylpropanoic acid (131 mg, 0.4 mmol) or (*R*)/(*S*)-2-(3-(thiophene-2-carbonyl)thioureido)-3-phenylpropanoic acid (133.3 mg, 0.4 mmol) or (*R*)/(*S*)-2-(3-(furan-2-carbonyl)thioureido)-3-phenylpropanoic acid (127 mg, 0.4 mmol) were dissolved in toluene–methanol mixture (1 : 1) and stirred for 6 h at 27 °C. The solution was concentrated to 2 mL under reduced pressure, and addition of hexane (10–15 mL) gave a clear orange solid. The product was collected by filtration, washed with hexane and dried *in vacuo*.

3.3.1 $[RuCl_2(\eta^6\text{-}p\text{-cymene})L1]$ (1). Yield: 109 mg, 85%. M.p.: 195 °C. $[\alpha]_D^{27}$: −84°. Anal. calcd for $C_{28}H_{31}Cl_2N_2O_3RuS$: C, 51.93; H, 4.82; N, 4.33; S, 4.95. Found: C, 51.79; H, 4.71; N, 4.26; S, 4.81. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, 6H, J = 10 Hz, $2CH_3$ of *p*-cymene), 2.26 (s, 3H, CH_3 of *p*-cymene), 3.00 (m, 1H, CH of *p*-cymene), 3.05 (s, 3H, $COOCH_3$), 3.32, 3.45 (dd, 2H, J = 5 Hz, CH_2), 5.26 (m, 1H, asymmetric hydrogen), 5.27–5.46 (m, 4H, aromatic protons of *p*-cymene), 7.23–8.21 (m, 10H, aromatic protons of the ligand), 11.22 (s, 1H, C=O and C=S attached N–H), 11.73 (d, 1H, J = 5 Hz, C=S attached N–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3 (CH_3 of *p*-cymene), 22.2 ($2CH_3$ of *p*-cymene), 30.5 (CH of *p*-cymene), 37.1 (CH_2), 52.4 (ester CH_3), 59.3 (asymmetric carbon), 82.5–84.3 (aromatic carbons of *p*-cymene), 99.9 and 103.5 (quaternary carbons of *p*-cymene), 127.2, 127.8, 128.5, 128.6, 128.7, 128.9, 129.2, 129.6, 131.1, 133.5, 135.8 (aromatic CH of the ligand), 168.5 (C=O), 171.3 (C=S), 179.4 ($COOCH_3$). FT-IR (KBr, cm^{-1}): 3220 (m; ν(amide N–H)), 3148 (s; ν(thiourea N–H)), 1674 (s; ν(C=O)), 1740 (s; ν($COOCH_3$)), 1183 (s; ν(C=S)). UV-vis ($CHCl_3$; λ, nm ε, $dm^3\ mol^{-1}\ cm^{-1}$): 441 (4584), 332 (19 201), 253 (88 187).

3.3.2 $[RuCl_2(\eta^6\text{-}p\text{-cymene})L2]$ (2). Yield: 105 mg, 83%. M.p.: 196 °C. $[\alpha]_D^{27}$: +116°. Anal. calcd for $C_{28}H_{31}Cl_2N_2O_3RuS$: C, 51.93; H, 4.82; N, 4.33; S, 4.95. Found: C, 51.80; H, 4.71; N, 4.23; S, 4.82. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (d, 6H, J = 5 Hz, $2CH_3$ of *p*-

cymene), 2.25 (s, 3H, CH_3 of *p*-cymene), 3.00 (m, 1H, CH of *p*-cymene), 3.22, 3.46 (dd, 2H, $J = 5$ Hz, CH_2), 3.63 (s, 3H, $COOCH_3$ of the ligand), 5.27 (m, 1H, asymmetric hydrogen), 5.27–5.46 (m, 4H, aromatic protons of *p*-cymene), 7.23–8.20 (m, 10H, aromatic protons of the ligand), 11.21 (s, 1H, C=O and C=S attached N–H), 11.72 (d, 1H, $J = 5$ Hz, C=S attached N–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3 (CH_3 of *p*-cymene), 22.2 ($2CH_3$ of *p*-cymene), 30.5 (CH of *p*-cymene), 37.2 (CH_2 of the ligand), 52.2 (ester CH_3 of the ligand), 59.1 (asymmetric carbon), 82.5–84.3 (aromatic carbons of *p*-cymene), 99.9 and 103.5 (quaternary carbons of *p*-cymene), 127.3, 127.8, 128.5, 128.6, 128.7, 128.9, 129.2, 129.6, 131.0, 133.5, 135.2 (aromatic CH of the ligand), 168.6 (C=O), 171.3 (C=S), 179.1 ($COOCH_3$). 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($COOCH_3$)), 1184 (s; ν(C=S)). UV-vis ($CHCl_3$; λ, nm ε, $dm^3\ mol^{-1}\ cm^{-1}$): 448 (5635), 328 (24 719), 253 (115 366).

3.3.3 [$RuCl_2(\eta^6$-*p*-cymene)L3] (3). Yield: 103 mg, 80%. M.p.: 182 °C. $[\alpha]_D^{27}$: −110°. Anal. calcd for $C_{26}H_{29}Cl_2N_2O_3RuS_2$: C, 47.78; H, 4.47; N, 4.29; S, 9.81. Found: C, 47.64; H, 4.35; N, 4.13; S, 9.74. HR-MS (*m*/*z*): found 583.06 ($M - 2Cl^-$); calcd value for $C_{26}H_{29}Cl_2N_2O_3RuS_2 = 647.60$. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (d, 6H, $J = 5$ Hz, $2CH_3$ of *p*-cymene), 2.27 (s, 3H, CH_3 of *p*-cymene), 2.59 (s, 3H, $COOCH_3$ of the ligand), 3.00 (m, 1H, CH of *p*-cymene), 3.30, 3.44 (dd, 2H, $J = 5$ Hz, CH_2), 5.24 (m, 1H, asymmetric hydrogen), 5.25–5.47 (m, 4H, aromatic protons of *p*-cymene), 7.10–8.45 (m, 8H, aromatic protons of the ligand), 11.00 (s, 1H, C=O and C=S attached N–H), 11.43 (d, 1H, $J = 5$ Hz, C=S attached N–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3 (CH_3 of *p*-cymene), 22.2 ($2CH_3$ of *p*-cymene), 30.4 (CH of *p*-cymene), 37.8 (CH_2 of the ligand), 52.7 (ester CH_3 of the ligand), 59.4 (asymmetric carbon), 82.6–84.3 (aromatic carbons of *p*-cymene), 100.0 and 103.4 (quaternary carbons of *p*-cymene), 127.5, 128.8, 129.2, 134.4, 134.7, 135.3, 135.9, (aromatic CH of the ligand), 162.9 (C=O), 169.6 (C=S), 179.9 ($COOCH_3$). FT-IR (KBr, cm^{-1}): 3211 (m; ν(amide N–H)), 3151 (s; ν(thiourea N–H)), 1660 (s; ν(C=O)), 1740 (s; ν($COOCH_3$)), 1187 (s; ν(C=S)). UV-vis ($CHCl_3$; λ, nm ε, $dm^3\ mol^{-1}\ cm^{-1}$): 444 (6288), 334 (30 756), 294 (69 381), 255 (95 360).

3.3.4 [$RuCl_2(\eta^6$-*p*-cymene)L4] (4). Yield: 100 mg, 78%. M.p.: 182 °C. $[\alpha]_D^{27}$: +176°. Anal. calcd for $C_{26}H_{29}Cl_2N_2O_3RuS_2$: C, 47.78; H, 4.47; N, 4.29; S, 9.81. Found: C, 47.74; H, 4.38; N, 4.19; S, 9.76. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, 6H, $J = 5$ Hz, $2CH_3$ of *p*-cymene), 2.27 (s, 3H, CH_3 of *p*-cymene), 2.98 (m, 1H, CH of *p*-cymene), 3.00 (s, 3H, $COOCH_3$ of the ligand), 3.30, 3.44 (dd, 2H, $J = 5$ Hz, CH_2 of the ligand), 5.24 (m, 1H, asymmetric hydrogen), 5.26–5.47 (m, 4H, aromatic protons of *p*-cymene), 7.10–8.45 (m, 8H, aromatic protons of the ligand), 10.99 (s, 1H, C=O and C=S attached N–H), 11.43 (d, 1H, $J = 10$ Hz, C=S attached N–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3 (CH_3 of *p*-cymene), 22.2–22.3 ($2CH_3$ of *p*-cymene), 30.5 (CH of *p*-cymene), 37.0 (CH_2), 52.5 (ester CH_3 of the ligand), 59.4 (asymmetric carbon), 82.4–84.4 (aromatic carbons of *p*-cymene), 100.6 and 103.5 (quaternary carbons of *p*-cymene), 128.6, 128.7, 129.2, 129.6, 131.3, 134.3, 135.1, 136.2, (aromatic CH of the ligand), 162.5 (C=O), 171.2 (C=S), 178.6 ($COOCH_3$). FT-IR (KBr, cm^{-1}): 3207 (m; ν(amide N–H)), 3149 (s; ν(thiourea N–H)), 1660 (s; ν(C=O)), 1740 (s; ν($COOCH_3$)), 1187 (s; ν(C=S)). UV-vis ($CHCl_3$; λ, nm ε, $dm^3\ mol^{-1}\ cm^{-1}$): 446 (6735), 339 (32 371), 294 (73 127), 255 (100 824).

3.3.5 [$RuCl_2(\eta^6$-*p*-cymene)L5] (5). Yield: 98 mg, 78%. M.p.: 191 °C. $[\alpha]_D^{27}$: −50°. Anal. calcd for $C_{26}H_{29}Cl_2N_2O_4RuS$: C, 48.98; H, 4.58; N, 4.39; S, 5.03. Found: C, 48.90; H, 4.43; N, 4.29; S, 4.97. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (d, 6H, $J = 10$ Hz, $2CH_3$ of *p*-cymene), 2.26 (s, 3H, CH_3 of *p*-cymene), 2.99 (m, 1H, CH of *p*-cymene), 3.29 (s, 3H, $COOCH_3$ of the ligand), 3.30, 3.43 (dd, 2H, $J = 5$ Hz, CH_2), 5.21 (m, 1H, asymmetric hydrogen), 5.27–5.47 (m, 4H, aromatic protons of *p*-cymene), 6.50–7.90 (m, 8H, aromatic protons of the ligand), 10.89 (s, 1H, C=O and C=S attached N–H), 11.29 (d, 1H, $J = 10$ Hz, C=S attached N–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.4 (CH_3 of *p*-cymene), 22.2–22.3 ($2CH_3$ of *p*-cymene), 30.5 (CH of *p*-cymene), 38.0 (CH_2 of the ligand), 52.4 (ester CH_3 of the ligand), 59.3 (asymmetric carbon), 82.4–84.3 (aromatic carbons of *p*-cymene), 100.0 and 103.6 (quaternary carbons of *p*-cymene), 112.9, 118.0, 121.2, 127.2, 128.7, 129.2, 129.6, 135.7, 146.4, 147.7 (aromatic CH of the ligand), 158.3 (C=O), 172.6 (C=S), 179.5 ($COOCH_3$). FT-IR (KBr, cm^{-1}): 3222 (m; ν(amide N–H)), 3151 (s; ν(thiourea N–H)), 1682 (s; ν(C=O)), 1738 (s; ν($COOCH_3$)), 1196 (s; ν(C=S)). UV-vis ($CHCl_3$; λ, nm ε, $dm^3\ mol^{-1}\ cm^{-1}$): 439 (6884), 325 (30 383), 286 (86 958), 249 (71 554).

3.3.6 [$RuCl_2(\eta^6$-*p*-cymene)L6] (6). Yield: 102 mg, 82%. M.p.: 192 °C. $[\alpha]_D^{27}$: +40°. Anal. calcd for $C_{26}H_{29}Cl_2N_2O_4RuS$: C, 48.98; H, 4.58; N, 4.39; S, 5.03. Found: C, 48.89; H, 4.46; N, 4.32; S, 4.95. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.26 (d, 6H, $J = 10$ Hz, $2CH_3$ of *p*-cymene), 2.19 (s, 3H, CH_3 of *p*-cymene), 2.94 (m, 1H, CH of *p*-cymene), 3.22, 3.36 (dd, 2H, $J = 5$ Hz, CH_2), 3.91 (s, 3H, $COOCH_3$ of the ligand), 5.15 (m, 1H, asymmetric hydrogen), 5.21–5.40 (m, 4H, aromatic protons of *p*-cymene), 7.43–7.83 (m, 8H, aromatic protons of the ligand), 10.83 (s, 1H, C=O and C=S attached N–H), 11.22 (d, 1H, $J = 5$ Hz, C=S attached N–H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.3 (CH_3 of *p*-cymene), 22.2 ($2CH_3$ of *p*-cymene), 30.5 (CH of *p*-cymene), 37.1 (CH_2 of the ligand), 52.7 (ester CH_3 of the ligand), 59.1 (asymmetric carbon), 82.4–84.3 (aromatic carbons of *p*-cymene), 100.0 and 103.7 (quaternary carbons of *p*-cymene), 112.7, 121.3, 127.4, 128.7, 129.2, 129.5, 135.0, 144.6, 147.7, (aromatic CH of the ligand), 158.1 (C=O), 171.4 (C=S), 179.0 ($COOCH_3$). FT-IR (KBr, cm^{-1}): 3226 (m; ν(amide N–H)), 3150 (s; ν(thiourea N–H)), 1682 (s; ν(C=O)), 1739 (s; ν($COOCH_3$)), 1196 (s; ν(C=S)). UV-vis ($CHCl_3$; λ, nm ε, $dm^3\ mol^{-1}\ cm^{-1}$): 444 (6506), 325 (30 005), 286 (86 958), 251 (72 342).

3.4 X-ray structure determinations

Details of data collection are given in Table S1 (ESI†). The crystal was placed in a cold nitrogen stream maintained at 150 K. A BRUKER APEX2 and APEX3 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.[51] Integrated intensity information for each reflection was obtained by reduction of the data frames with the program APEX2.[51] The absorption correction program SADABS[52] was employed to correct the data for absorption

effects. A solution was obtained readily using XT/XS in APEX2.[51,53,54] 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).[55] The structure was refined (weighted least-squares refinement on F^2) to convergence.[53,54,56] Olex2 was employed for the final data presentation and structure plots.[33]

3.5 Procedure for enantioselective reduction of ketones

The Ru complexes (**1–6**) of the type [$RuCl_2(\eta^6$-*p*-cymene)L] (0.005 mmol) and NaOH (1 mmol) were dissolved in 2-propanol (5 mL). The mixture was stirred at 82 °C for 10 minutes. Then ketone (1 mmol) was introduced into the mixture and continued the stirring at 82 °C. After 10 h, the reaction mixture was cooled to room temperature and then passed through a silica gel short column with *n*-hexane–ethyl acetate (1 : 1) eluent to remove the catalyst. The conversions were monitored by GC-MS and GC, and the enantiomeric excesses were calculated by using chiral HPLC.

3.6 Synthesis of (*R*)-methyl-2-(3-benzoylthioureido)-3-phenylpropanoate

To confirm [$RuCl_2(\eta^6$-*p*-cymene)]$_2$-catalyzed conversion of amino acid to amino ester, the unprotected D-phenylalanine derived thiourea ligand (**L1**) (0.5 mmol) and [$RuCl_2(\eta^6$-*p*-cymene)]$_2$ (0.005 mmol) were dissolved in methanol (10 mL) and the reaction was proceeded at 27 °C. After 12 h, the solvent was evaporated under reduced pressure and the reaction mixture was dissolved in ethyl acetate and passed through a silica gel column to obtain the pure ester. The ester product was confirmed by ^{1}H NMR.

3.6.1 (*R*)-Methyl-2-(3-benzoylthioureido)-3-phenylpropanoate. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.54 (s, 3H, $COOCH_3$), 3.29, 3.46 (dd, 2H, $J = 5$ Hz, CH_2), 5.37 (m, 1H, asymmetric hydrogen), 7.26–7.84 (m, 10H, CH of phenyl ring), 9.10 (s, 1H, C=O and C=S attached N–H), 11.59 (d, 1H, J = 10 Hz, C=S attached N–H).

4 Conclusions

The new chiral aroylthiourea ligands have been derived from D/L-phenylalanine and reacted with [$RuCl_2(\eta^6$-*p*-cymene)]$_2$. Ru-*p*-cymene precursor initially catalyzed the conversion of amino acids to corresponding amino esters, then formed new Ru complexes with the ester of aroylthiourea ligands (**1–6**). Spectroscopic studies exposed the monodentate sulfur coordination of the aroylthiourea ligand with Ru(II), which was further confirmed by the crystal structure of the ligand **L1** and two of the complexes (**3** and **6**). The chiral Ru-*p*-cymene complexes (**1–6**) catalyzed the enantioselective reduction of ketones to their analogous chiral secondary alcohols in the presence of 2-propanol (hydrogen donor) and NaOH (base) with good to excellent conversion and enantioselectivity. The performance of the present catalytic system is superior to most of the existing Ru-*p*-cymene/amino acid or amino acid derived ligand systems in terms of conversion and ee. Our current focus is on retaining acid group in the Ru-*p*-cymene complexes to promote the solubility of the complexes and subsequently catalysis in water.

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References

1 G. M. Coppola and H. F. Schuster, *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*, Wiley, New York, 1987.
2 N. Selvakumaran, L. Sandhiya, N. S. P. Bhuvanesh, K. Senthilkumar and R. Karvembu, *New J. Chem.*, 2016, **40**, 5401–5413.
3 M. Mary Sheeba, S. Preethi, A. Nijamudheen, M. Muthu Tamizh, A. Datta, L. J. Farrugia and R. Karvembu, *Catal. Sci. Technol.*, 2015, **5**, 4790–4799.
4 N. Selvakumaran, N. S. P. Bhuvanesh and R. Karvembu, *Dalton Trans.*, 2014, 16395–16410.
5 M. Mary Sheeba, M. Muthu Tamizh, L. J. Farrugia, A. Endo and R. Karvembu, *Organometallics*, 2014, **33**, 540–550.
6 N. Gunasekaran, P. Ramesh, M. N. G. Ponnuswamy and R. Karvembu, *Dalton Trans.*, 2011, 12519–12526.
7 K. R. Koch, *Coord. Chem. Rev.*, 2001, **216**, 473–488.
8 E. Farkas and I. Sovago, *Amino Acids, Pept., Proteins*, 2014, **39**, 21–67.
9 T. G. Appleton, *Coord. Chem. Rev.*, 1997, **166**, 313–359.
10 A. Iakovidis and N. Hadjiliadis, *Coord. Chem. Rev.*, 1994, **135–136**, 17–63.
11 K. Ahlford and H. Adolfsson, *Catal. Commun.*, 2011, **12**, 1118–1121.
12 F. Tinnis and H. Adolfsson, *Org. Biomol. Chem.*, 2010, **8**, 4536–4539.
13 J. Wettergren, A. B. Zaitsev and H. Adolfsson, *Adv. Synth. Catal.*, 2007, **349**, 2556–2562.
14 P. Pelagatti, M. Carcelli, F. Calbiani, C. Cassi, L. Elviri, C. Pelizzi, U. Rizzotti and D. Rogolino, *Organometallics*, 2005, **24**, 5836–5844.
15 P. Västilä, J. Wettergren and H. Adolfsson, *Chem. Commun.*, 2005, **2**, 4039–4041.
16 I. M. Pastor, P. Västilä and H. Adolfsson, *Chem.–Eur. J.*, 2003, **9**, 4031–4045.
17 D. Chatterjee, S. Basak, A. Mitra, A. Sengupta, J. Le Bras and J. Muzart, *Inorg. Chim. Acta*, 2006, **359**, 1325–1328.
18 D. Chatterjee, S. Basak, A. Riahi and J. Muzart, *J. Mol. Catal. A: Chem.*, 2006, **255**, 283–289.
19 J. R. Khusnutdinova, Y. Ben-David and D. Milstein, *Angew. Chem., Int. Ed.*, 2013, **52**, 6269–6272.
20 K. Sakthivel, W. Notz, T. Bui and C. F. Barbas, *J. Am. Chem. Soc.*, 2001, **123**, 5260–5267.

21 Y. Zhao, J. Rodrigo, A. H. Hoveyda and M. L. Snapper, *Nature*, 2006, **443**, 67–70.
22 B. M. Trost and K. Dogra, *J. Am. Chem. Soc.*, 2002, **124**, 7256–7257.
23 J. W. Faller and A. R. Lavoie, *Organometallics*, 2001, **20**, 5245–5247.
24 A. B. Zaitsev and H. Adolfsson, *Org. Lett.*, 2006, **8**, 5129–5132.
25 T. Ohta, S. Nakahara, Y. Shigemura, K. Hattori and I. Furukawa, *Appl. Organomet. Chem.*, 2001, **15**, 699–709.
26 X.-N. Li, H.-Y. Zhou, L. Feng, K. Duan and J.-X. Wang, *Appl. Organomet. Chem.*, 2012, **26**, 168–174.
27 A. Bøgevig, I. M. Pastor and H. Adolfsson, *Chem.–Eur. J.*, 2004, **10**, 294–302.
28 P. Kumar, R. K. Gupta and D. S. Pandey, *Chem. Soc. Rev.*, 2014, **43**, 707–733.
29 H. Cao, L.-H. Cai, C.-X. Wang, X.-H. Zhu, Z.-M. Li and X.-F. J. Hou, *J. Organomet. Chem.*, 2015, **775**, 60–66.
30 S. K. Manna, S. L. K. Manda and G. Panda, *Tetrahedron Lett.*, 2014, **55**, 5759–5763.
31 B. S. Vig, P. J. Lorenzi, S. Mittal, C. P. Landowski, H.-C. Shin, H. I. Mosberg, J. M. Hilfinger and G. L. Amidon, *Pharm. Res.*, 2003, **20**, 1381–1388.
32 G. C. Barrett, *Amino Acids, Peptides and Proteins*, RSC Publications, London, 1996, vol. 27, p. 1.
33 N. Atsushi, M. Toyoharu, K. Hiroto and E. Takeshi, *Macromolecules*, 2003, **36**, 9335–9339.
34 S. Fumio and E. Takeshi, *Macromol. Chem. Phys.*, 1999, **200**, 2651–2661.
35 J. Kim, J. Kim, S. Song, O. Jung and H. Suh, *J. Inclusion Phenom. Macrocyclic Chem.*, 2007, **58**, 187–192.
36 G. Pollini, N. Baricordi, S. Benetti, C. De Risi and V. Zanirato, *Tetrahedron Lett.*, 2005, **46**, 3699–3701.
37 C. Somlai, A. Peter, P. Forgo and B. Penke, *Synth. Commun.*, 2003, **33**, 1815–1820.
38 Z. Tomasz, A. Michał and J. Janusz, *Tetrahedron: Asymmetry*, 2002, **13**, 2053–2059.
39 V. K. Tandon, D. B. Yadav, R. V. Singh, A. K. Chaturvedi and P. K. Shukla, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5324–5328.
40 S. L. Manjinder, K. R. Yeeman, N. G. J. Michael and C. V. John, *J. Org. Chem.*, 2002, **67**, 1536–1547.
41 E. Pękala and D. Żelaszczyk, *Sci. Pharm.*, 2009, **77**, 9–17.
42 S. T. Marino, D. Stachurska-Buczek, D. A. Huggins, B. M. Krywult, C. S. Sheehan, T. Nguyen, N. Choi, J. G. Parsons, P. G. Griffiths, I. W. James, A. M. Bray, J. M. White and R. S. Boyce, *Molecules*, 2004, **9**, 405–426.
43 R. Noyori and T. Ohkuma, *Angew. Chem., Int. Ed.*, 2001, **40**, 40–73.
44 *Chirality in Industry: The Commercial Manufacture and Applications of Optically Active Compounds*, ed. A. N. Collins, G. N. Sheldrake and J. Crosby, John Wiley & Sons, Chichester, 1997.
45 A. Barth, *Prog. Biophys. Mol. Biol.*, 2000, **74**, 141–173.
46 X.-J. Zhang, T.-B. Lai and R. Y.-C. Kong, *Top. Curr. Chem.*, 2011, **308**, 365–404.
47 S. D. Taylor, C. C. Kotoris and G. Hum, *Tetrahedron*, 1999, **55**, 12431–12477.
48 T. J. Barbarich, C. D. Rithner, S. M. Miller, O. P. Anderson and S. H. Strauss, *J. Am. Chem. Soc.*, 1999, **121**, 4280–4281.
49 J. Wu, J.-X. Ji and A. S. C. Chan, *Proc. Natl. Acad. Sci. U. S. A.*, 2005, **102**, 3570–3575.
50 M. A. Bennet, T. N. Huang, T. W. Matheson and A. K. Smith, *Inorg. Synth.*, 1982, **21**, 74–78.
51 *APEX2 and APEX3 Program for Data Collection on Area Detectors*, BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373, USA.
52 G. M. Sheldrick, SADABS, *Program for Absorption Correction of Area Detector Frames*, BRUKER AXS Inc., 5465 East Cheryl Parkway, Madison, WI 53711-5373, USA.
53 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2015, **71**, 3–8.
54 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.
55 A. L. J. Spek, *Appl. Crystallogr.*, 2003, **36**, 7–13.
56 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.