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Chiral amino-urea derivatives of (1*R*,2*R*)-1,2-diaminocyclohexane as ligands in the ruthenium catalysed asymmetric reduction of aromatic ketones by hydride transfer

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Abstract—Several new chiral urea and thiourea ligands have been prepared by reaction of (1*R*,2*R*)-1,2-diaminocyclohexane with various organic isocyanates and isothiocyanates. These were used as ligands in the ruthenium catalysed enantioselective reduction of aromatic ketones by isopropanol. The reduction proceeded at room temperature using 2 mol% of ruthenium catalyst to give good yields of the (*R*)-alcohol with enantiomeric excesses of up to 83%. By contrast, the use of bis-urea ligands gave much lower enantioselectivities. Amino-thiourea ligands led to the (*S*)-alcohol with low enantiomeric excess.

1. Introduction

Hybrid materials, combining organic and inorganic components, have attracted the attention of chemists and material scientists due to interest in their applications.[1] In this context, we are currently studying poly(silsesquioxane)s[2–4] networks containing chiral organic sub-structures.[5–8] These chiral hybrid solids are prepared by sol-gel hydrolysis–condensation of optically active trialkoxysilylated organic molecules[6–8] and are of potential interest in the fields of molecular recognition and asymmetric catalysis.[9] We recently reported the use of chiral hybrids derived from (*R*)-binol or (1*R*,2*R*)-1,2-diaminocyclohexane as support for heterogeneous catalytic species. Chiral matrix effects leading to enhanced enantioselectivity have been observed.[6,7] As part of our studies of chiral hybrid catalytic materials for asymmetric synthesis, we are interested in the use of urea derivatives as a result of their capability of auto-association via hydrogen bonds.[8]

The asymmetric reduction of prochiral aromatic ketones in the presence of soluble transition metal catalysts was developed several years ago.[10–13] Nitrogen containing chiral ligands were shown to be useful for catalytic asymmetric reductions, giving high enantioselectivities.[11,14–19] Interestingly, chiral urea ligands derived mainly from 1,2-diamino-1,2-diphenylethane have been recently described by Lemaire et al.[20] Also, the catalytic activity of rhodium, ruthenium and iridium complexes containing mono(thio)urea or di(thio)urea ligands was studied in the enantioselective reduction of acetophenone by hydride transfer.[20–23]

We decided to explore the use of urea derivatives of the readily available chiral (1*R*,2*R*)-1,2-diaminocyclohexane, with the aim of incorporating them in chiral helical hybrid materials.[8] Herein, we report the synthesis of new urea ligands derived from (1*R*,2*R*)-1,2-diaminocyclohexane and their use in the ruthenium catalysed reduction of prochiral ketones by hydride transfer. We found that amino-urea derived ligands containing the rigid cyclohexane unit led to good conversions and enantioselectivities, much higher than those observed with 1,2-bis-ureido cyclohexane derivatives. The absolute configuration of the product could be changed by use of amino-thiourea ligands, but the latter led to both lower conversions and selectivities.

2. Results and discussion

2.1. Synthesis of mono-urea 2, bis-urea 3 and thio-urea 4 ligands

Mono-urea ligands **2** have been prepared by reaction of (1*R*,2*R*)-1,2-diaminocyclohexane hydrochloride with a variety of isocyanates RNCO, according to Eq. (1).

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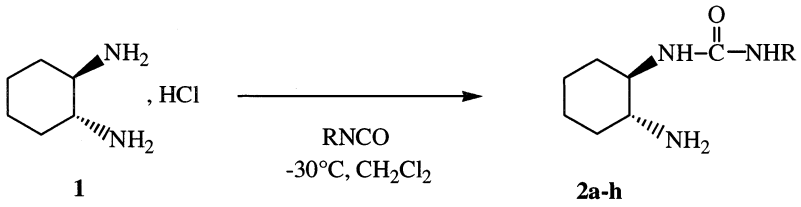


(1)

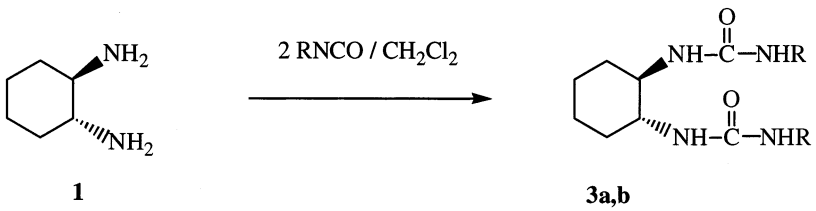
2a, R=*n*-Pr, 61%; **2b**, R=cyclohexyl, 65%; **2c**, R = *t*-Bu, 63%; **2d**, R=Ph, 58%; **2e**, R=*p*-MeO-Ph, 61%; **2f**, R=*p*-CF_3-Ph, 68%; **2g**, R=*o*-Me-Ph, 55%; **2h**, R=1-naphthyl, 72%

The formation of **2** was always accompanied by the formation of bis-urea derivatives. It was minimised by dropwise addition of the isocyanate at −30°C to an excess of the diamine hydrochloride **1** (1.4 equivalents) in CH_2Cl_2. Compounds **2a**–**2h** were isolated with yields ranging from 55 to 72%, and in all cases, the bis-urea formed as a side product (20–35%). Mono-ureas **2** were easily isolated by selective extraction, the bis-urea being insoluble in CH_2Cl_2. The ligands **2** were analysed by FTIR, ^1H and ^{13}C NMR and mass spectroscopy. The FTIR spectra of **2a**–**2h** exhibit the characteristic vibrations of the urea function (3360, 3310, 1640 and 1560 cm^{-1}).

Two bis-ureas **3a** and **3b** were also prepared by reaction of two equivalents of the isocyanate RNCO (with R = cyclohexyl or dodecyl) with one equivalent of the (1*R*,2*R*)-1,2-diaminocyclohexane, according to Eq. (2).

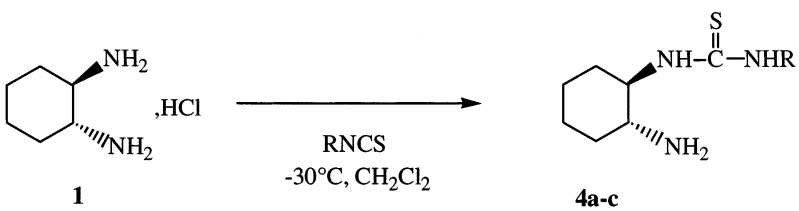
2.2. Catalytic reduction of acetophenone with chiral urea/ruthenium complexes

Complexes of ruthenium were formed by reacting one equivalent of $[RuCl_2(p\text{-cymene})]_2$ with two equivalents of ligand **2** in propan-2-ol (ligand to metal ratio: **2**/Ru = 1) upon stirring for 30 minutes at 80°C. Evidence for the formation of **2**–ruthenium complexes was obtained upon analysing the solution by UV spectroscopy; in all cases, the absorption bands characteristic of $[RuCl_2(p\text{-cymene})]_2$ at 341 and 436 nm shifted to 310–320 and 380–390 nm, respectively, in the presence of the amino-urea ligands **2**. The hydride transfer reductions of acetophenone were performed at 20°C according to Eq. (4), using 2 or 3 mol% of ruthenium, a ratio KOH/Ru = 5 and a 0.1 M concentration of acetophenone in propan-2-ol. The results are summarised in Table 1.



(2)

3a, R=cyclohexyl, 92%; **3b**, R=n-$C_{12}H_2$, 95%

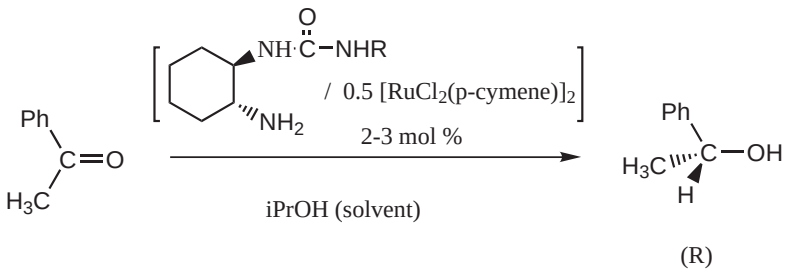


(3)

4a, R=*n*-Bu, 65%; **4b**, R=*t*-Bu, 59%; **4c**, R=cyclohexyl, 68%

Moreover, we prepared amino-thiourea ligands **4** according to the procedure described above for amino-ureas, using thioisocyanates instead of isocyanates. The compounds **4a**–**4c** were isolated in 59–68% yields (Eq. (3)). The reaction of phenylisothiocyanate with diaminocyclohexane did not give amino-thiourea. The formation of a guanidine derivative occurred, it results from the cyclisation of the mono-thiourea and elimination of H_2S, as already described in the case of diaminodiphenylethane.[24]

For most ligands, after a reaction of 24 hours, a conversion of between 60 and 90% was reached. Complexes with aryl-substituted urea ligands appeared less reactive (entries 5–10) than the alkyl-substituted urea ligands (entries 1, 2 and 3). A lower reactivity was also observed upon increasing the steric hindrance of the urea substituents (entries 4 and 8). The (*R*)-enantiomer of 1-phenylethanol was always the major product and good to excellent enantiomeric excess (e.e.) up to 83% (in the case of the cyclohexyl urea, entries 2 and 3) were



(4)

Table 1. Catalytic activity of mono-urea **2**/ruthenium complexes in the reduction of acetophenone by isopropanol (according to Eq. (4))

Entry	R[a]	Catalyst mol% (with **2**/Ru = 1)	*T* (°C)	Reaction time (h)	Conversion[b] (%)	E.e.[c] (%) (configuration)
1	*n*-Propyl	3	20	4	75	63 (*R*)
				23	83	59 (*R*)
2	Cyclohexyl	2	20	4	57	83 (*R*)
				22	85	81 (*R*)
3	Cyclohexyl	3	20	4	73	83 (*R*)
				24	90	82 (*R*)
4	*t*-Butyl	2	22	18	54	66 (*R*)
				36	70	57 (*R*)
				72	84	57 (*R*)
5	Phenyl	2	20	4	17	73 (*R*)
				28	45	57 (*R*)
6	Phenyl	3	20	4	27	74 (*R*)
				32	71	52 (*R*)
7	*p*-MeO-phenyl	2	20	3	35	72 (*R*)
				22	68	72 (*R*)
8	*o*-Tolyl	2	20	4	8	43 (*R*)
				29	23	38 (*R*)
9	*p*-CF_3-phenyl	2	20	4	35	38 (*R*)
				22	55	33 (*R*)
10	1-Naphtyl	2	20	4	26	68 (*R*)
				24	68	59 (*R*)
				30	73	59 (*R*)
11	Cyclohexyl	2[d]	20	4	80	82 (*R*)
				22	100	82 (*R*)
12	Cyclohexyl	2[e]	20	4	90	82 (*R*)

[a] R = alkyl or aryl substituent in amino-ureas **2a**–**h** (cf. Eq. (2)).
[b] The reaction was monitored by capillary gas chromatography.
[c] The e.e. was determined by HPLC on a Chiralcel OD column.
[d] With **2**/Ru = 2.
[e] With **2**/Ru = 8.

obtained. The e.e. as a function of reaction time was examined and did not significantly decrease with time when using alkyl substituted urea ligands, indicating that the active catalytic species was stable during the reduction reaction. With the exception of the urea ligand having a *p*-methoxyphenyl substituent (entry 7), for which no variation in e.e. was noted, a small decrease in the e.e. values was observed in the case of aryl substituted ureas (entries 5–10). The catalytic species seemed to be more stable with electron donating substituents such as alkyl or *p*-MeO-phenyl. The use of 3 mol% instead of 2 mol% of catalyst led to increased conversion but did not change the e.e. (entries 2 and 3, 5 and 6).

We also examined the influence of the ligand/ruthenium ratio (**2**/Ru) both on the yield and on the e.e. Using the cyclohexyl urea ligand **2b**, the reaction was performed with a **2**/Ru ratio = 2 or 8, in both cases, the reaction rate slightly increased (100% conversion after 22 hours), but the e.e.'s were identical to those obtained when **2**/Ru = 1 (entries 11 and 12).

The amino-urea ligand **2e** (R = *p*-MeO-phenyl) was tested in the ruthenium catalysed reduction of three other aromatic ketones: 1-acetonaphthone, 2-acetonaphthone and 2-methoxyacetophenone. The results are summarised in Table 2. The reactions were performed at 20°C with 2 mol% of catalyst and **2e**/Ru = 1. In these cases, the reactivities were lower owing to steric effects, but the enantioselectivities were similar to those obtained with acetophenone and did not decrease with time, indicating a good stability of the catalytic species with the *p*-MeO-phenyl substituted ligand.

Bis-urea and thio-urea chiral ligands have been shown to give higher selectivities than amino-ureas derivated

Table 2. Catalytic activity of the mono-urea **2e** (R = *p*-MeO-phenyl)/ruthenium complex in the reduction of aromatic ketones by isopropanol (according to Eq. (4))

Aromatic ketone	Reaction time[a] (h)	Conversion[b] (%)	E.e.[c] (%) (configuration)
1-Acetonaphthone	22	51	74 (*R*)
	40	72	74 (*R*)
	120	92	74 (*R*)
2-Acetonaphthone	4	15	75 (*R*)
	22	28	72 (*R*)
	72	78	71 (*R*)
2-MeO-acetophenone	4	18	78 (*R*)
	22	35	76 (*R*)
	72	85	76 (*R*)

[a] The reactions were performed at 20°C with 2 mol% of catalyst and **2e**/Ru = 1.
[b] The reactions were monitored by capillary gas chromatography.
[c] E.e. was measured by HPLC on a Chiralcel OD column.

ligands in the rhodium, iridium or ruthenium catalysed reduction of acetophenone.[20–23] We also studied the catalytic activity of chiral ruthenium complexes prepared with the bis-urea and the amino-thiourea ligands derived from the (1*R*,2*R*)-1,2-diaminocyclohexane. The reduction reactions of acetophenone were performed using two different bis-ureas (**3a** with R = cyclohexyl and **3b** with R = dodecyl) and three amino-thioureas (**4a** R = *n*-butyl, **4b** R = *t*-butyl, **4c** R = cyclohexyl) under the same reaction conditions (0.1 M concentration in acetophenone, 2 or 3 mol% of catalyst and **3**/Ru or **4**/Ru = 1). The results are given in Table 3.

Using bis-urea ligands, a much slower reaction occurred (entries 1 and 2). Furthermore, it led to low selectivities and the e.e. values obtained in this case decreased markedly with time. Very low e.e.'s were measured at high conversion. The ruthenium complexes formed with the bis-ureas appeared much less stable than those obtained with mono-ureas. In the case of amino-thiourea ruthenium complexes (entries 3, 4 and 5), both reactivities and selectivities were lower than those obtained with the mono-ureas (Table 1). Surprisingly the (*S*)-enantiomer of 1-phenylethanol was obtained as the major product (Table 3, entries 3, 4 and 5), in contrast to the amino-urea ruthenium complexes which predominantly gave the (*R*)-enantiomer (Table 1).

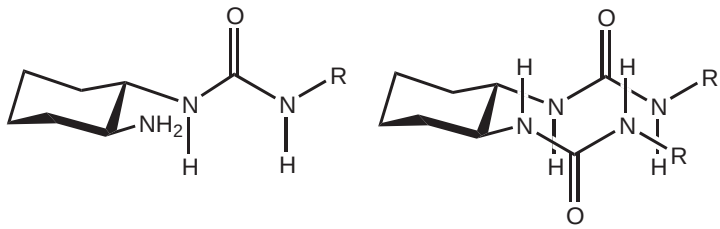
Lemaire et al. underlined the effect of the structure of the ligands in the metal catalysed hydride transfer reduction of aromatic ketones.[21] On the basis of theoretical and experimental studies,[25] it was concluded that the active complex in the catalytic asymmetric reduction of ketones is most likely a metal complex with one diamine and differed from the use of phenanthroline ligands for which it was proposed in that two ligands were coordinated to the metal centre.[11,26] Moreover, Noyori et al.[17,27] determined the structure of the complex formed upon reaction of $[RuCl_2(mesitylene)]_2$ with two equivalents of (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine. Only one amino-sulfonamide ligand and the arene cycle were found to be coordinated to ruthenium. This led us to assume that in our case, 1:1 complexes of **2** and ruthenium formed, consistent with the observed absence of effect of the **2**/Ru ratio on the conversion and selectivities.

Our observations with urea ligands derived from diaminocyclohexane are quite different from those reported using other ligands, the structures of which derived from 1,2-diamino-1,2-diphenylethane. In the latter, bis-ureas were found to give higher selectivities than amino-ureas,[21] when using ligand to metal ratios from 2 to 10[21,22] (lower selectivities were sometimes

Table 3. Catalytic activity of bis-urea **3a**–**b** and amino-thiourea **4a**–**c**/ruthenium complexes in the reduction of acetophenone by isopropanol (according to Eq. (4))

Entry	Ligand[a]	Catalyst mol% (with **2**/Ru = 1)	*T* (°C)	Reaction time (h)	Conversion[b] (%)	E.e.[c] (%) (configuration)
1	Bis-urea **3a** (R = cyclohexyl)	3	20	4	15	30 (*R*)
				23	30	20 (*R*)
				120	78	4 (*R*)
2	Bis-urea **3b** (R = *n*-dodecyl)	2	20	4	20	20 (*R*)
				22	69	6 (*R*)
3	Amino-thiourea **4a** (R = *n*-butyl)	2	20	4	29	32 (*S*)
				23	45	32 (*S*)
4	Amino-thiourea **4b** (R = *t*-butyl)	2	20	2	37	42 (*S*)
				22	72	36 (*S*)
5	Amino-thiourea **4c** (R = cyclohexyl)	2	20	4	20	22 (*S*)
				22	64	22 (*S*)

[a] Ligands derived from (1*R*,2*R*)-1,2-diaminocyclohexane (cf. Eqs. (3) and (4)).
[b] The reaction was monitored by capillary gas chromatography.
[c] The e.e. was determined by HPLC on a Chiralcel column.



2 3

Figure 1. Representation of amino-ureas **2** and bis-ureas **3**.

observed for L/M = 1). The highest enantioselectivities were obtained in the case of *N*-methylated bis-thiourea derivatives.[22] Concerning our ligands derived from the diaminocyclohexane structure, the highest selectivities were observed for the amino-ureas. The bis-urea ligands gave much lower selectivities and the ruthenium complexes exhibited poor stability under the reaction conditions, as shown by the observed decrease in e.e. values as a function of time. With amino-urea ligands, a stable catalytic species formed for **2**/Ru = 1 and gives e.e.'s of up to 83%. These observations may be related to the rigid structure of the urea ligands derived from diaminocyclohexane. Bis-urea derivatives **3** have been shown[28] to adopt a conformation in which the two ureido groups lay up and down in parallel plans, as shown in Fig. 1. These rigid structures easily auto-associate in solution by intermolecular hydrogen bonds.[29] Complexation of ruthenium may therefore be more difficult in this case than in the case of the more flexible diaminodiphenylethane structure.[21]

The amino-urea ligand **2** with one primary amine group does not have the same structural properties and may easily form a 1:1 complex with ruthenium. Complex formation may occur by coordination of the 1,2 nitrogen atoms of the diaminocyclohexane unit in a structure similar to the one described by Noyori et al. in the case of amino-sulfonamide derivatives.[17,27] Complex formation is probably more difficult with the more rigid bis-urea structure **3**. Also, amino-thiourea showed a different behaviour. With these ligands, enantioselectivities lower than those observed with amino-urea were found, moreover, the major configuration was the opposite one. The coordination mode of the amino-thiourea is probably different from that of amino-urea, since the absolute configuration of the alcohol product reversed by replacing amino-urea with amino-thiourea. Coordination of the sulfur atom to ruthenium may be responsible for the observed changes upon using the thio ligand.

3. Conclusion

We have synthesised and characterised several new chiral urea-containing ligands from (1*R*,2*R*)-1,2-diaminocyclohexane. Ligand structural effects are important to the observed enantioselectivity. The amino-urea ligands containing the cyclohexane substructure formed chiral complexes with ruthenium which catalyse the reduction of acetophenone by hydride transfer in good yields and higher e.e. than those obtained with other amino-urea ligands. Bis-urea or thiourea based ligands led to lower selectivities. We are currently investigating the heterogenisation of such catalytic species by immobilisation in hybrid silica matrices.

4. Experimental

All reactions were performed under a nitrogen atmosphere using Schlenk tube techniques. The solvents were distilled under nitrogen over P_2O_5 (CH_2Cl_2) or Mg turnings (propan-2-ol) before use. Isocyanates were purchased from Aldrich, $[RuCl_2(p\text{-cymene})]_2$ from Strem Chemicals and they were used as received without further purification. Commercial acetophenone was distilled before use and kept at −30°C under nitrogen. Homochiral (1*R*,2*R*)-diaminocyclohexane was obtained in enantiomerically pure form from the commercial racemic *cis*/*trans* mixture according to the method of Jacobsen.[30] ^1H and ^{13}C NMR spectra in solution were recorded on a Bruker AC-200 spectrometer and $CDCl_3$ or DMSO-d_6 were used as solvents. Chemical shifts (δ, ppm) are relative to tetramethylsilane. IR spectra were determined with a Perkin–Elmer 1000 FTIR spectrometer. Mass spectra were measured on a JEOL MS-DX 300 mass spectrometer. Elemental analyses were carried out by the Service Central de Microanalyse du CNRS in Vernaison (France). The UV spectra of solutions were recorded on a Hewlett Packard 8453 spectrophotometer. Optical rotations were measured on a Perkin–Elmer polarimeter 241. Enantiomeric excesses were determined by HPLC analysis using a chiral column (Chiralcel OD), UV detector at 254 nm, hexane/propan-2-ol: 90/10 as eluant, flow 0.5 mL min^{-1}.

4.1. General procedure for the synthesis of mono-urea ligands 2

(1*R*,2*R*)-1,2-Diaminocyclohexane hydrochloride (1.05 g, 7 mmol) in dry CH_2Cl_2 (100 mL) was placed in a

Schlenk tube under nitrogen at −30°C. A solution of the isocyanate (5 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise under nitrogen. After stirring for one night at −30°C, the solution was washed with an aqueous Na_2CO_3 solution to remove the excess diamine hydrochloride. The organic phase was dried over $MgSO_4$ and after filtration, the solvent was evaporated. The residue was dried under vacuum to afford a white powder. The mono-urea was obtained together with some bis-urea. The mono-urea was soluble in CH_2Cl_2 whereas the bis-urea precipitated and these two products were separated by extraction with CH_2Cl_2 to give the mono-ureas **2a**–**2h** as colourless solids.

4.1.1. (1*R*,2*R*)-1,2-Diaminocyclohexane propylurea 2a. Yield: 61% (607 mg); mp = 133°C; $[\alpha]_D = -1.7$ ($CHCl_3$, $c = 5$); ^{1}H NMR ($CDCl_3$, δ): 0.92 (3H, t), 1.19 (4H, m), 1.49 (2H, q), 1.8 (4H, m), 2.35 (1H, m), 3.15 (2H, m), 4.42 (1H, d), 5.18 (1H, d); ^{13}C NMR ($CDCl_3$, δ): 11.42, 23.42, 25.03, 33.19, 42.29, 56.36, 57.69, 159.08; ν_{max} (KBr, cm^{-1}): 3359, 3305, 2954, 2871, 1643, 1561; mass spectrum: m/z [FAB$^+$] (%): 200 (100, M$^+$), 183 (7), 141 (10), 115 (20), 98 (32); anal. calcd for $C_{10}H_{21}N_3O$: C, 60.30; H, 10.55; N, 21.1. Found: C, 59.88; H, 10.58; N, 21.0%.

4.1.2. (1*R*,2*R*)-1,2-Diaminocyclohexane cyclohexylurea 2b. Yield: 65% (776 mg); mp = 189°C; $[\alpha]_D = -2.4$ ($CHCl_3$, $c = 5$); ^{1}H NMR ($CDCl_3$, δ): 1.1–1.9 (18H, m), 2.36 (1H, m), 3.12 (1H, m), 3.5 (1H, m), 4.41 (1H, d), 5.05 (1H, d); ^{13}C NMR ($CDCl_3$, δ): 24.9, 25.03, 25.25, 25.65, 33.18, 33.91, 35.01, 49.01, 56.3, 57.43, 159.78; ν_{max} (KBr, cm^{-1}): 3362, 3310, 2955, 2867, 1642, 1561; mass spectrum: m/z [FAB$^+$] (%): 240 (100, M$^+$), 230 (12), 154 (68), 136 (52), 98 (52); anal. calcd for $C_{13}H_{25}N_3O$: C, 65.17; H, 10.46; N, 17.57. Found: C, 64.81; H, 10.39; N, 17.46%.

4.1.3. (1*R*,2*R*)-1,2-Diaminocyclohexane tertiobutylurea 2c. Yield: 63% (670 mg); mp = 149°C; $[\alpha]_D = -5.8$ ($CHCl_3$, $c = 5$); ^{1}H NMR ($CDCl_3$, δ): 1.19 (4H, m), 1.28 (9H, s), 1.85 (4H, m), 2.35 (1H, m), 3.30 (1H, m), 4.42 (1H, d), 5.18 (1H, d); ^{13}C NMR ($CDCl_3$, δ): 24.27, 25.20, 29.43, 31.44, 32.53, 49.79, 57.13, 66.63, 159.32; ν_{max} (KBr, cm^{-1}): 3349, 3311, 2947, 2861, 1642, 1562; mass spectrum: m/z [FAB$^+$] (%): 214 (72, M$^+$), 181 (4), 155 (5), 141 (8), 116 (35), 98 (38); anal. calcd for $C_{11}H_{23}N_3O$: C, 61.97; H, 10.79; N, 19.7. Found: C, 61.63; H, 10.55; N, 19.87%.

4.1.4. (1*R*,2*R*)-1,2-Diaminocyclohexane phenylurea 2d. Yield: 58% (675 mg); mp = 142°C; $[\alpha]_D = -19.5$ ($CHCl_3$, $c = 5$); ^{1}H NMR ($CDCl_3$, δ): 1.15 (4H, m), 1.85 (4H, m), 2.38 (1H, m), 3.3 (1H, m), 5.25 (1H, d), 7.05–7.35 (5H, m), 8.15 (1H, s); ^{13}C NMR ($CDCl_3$, δ): 24.73, 25.05, 32.85, 34.82, 55.65, 56.39, 119.62, 122.74, 129, 139.37, 156.81; ν_{max} (KBr, cm^{-1}): 3358, 3302, 2948, 2862, 1640, 1625, 1563; mass spectrum: m/z [FAB$^+$] (%): 234 (100, M$^+$), 217 (6), 176 (4), 154 (58), 136 (45), 107 (16), 98 (27); anal. calcd for $C_{13}H_{19}N_3O$: C, 66.9; H, 8.15; N, 18.00. Found: C, 66.46; H, 8.43; N, 17.33%.

4.1.5. (1*R*,2*R*)-1,2-Diaminocyclohexane *para*-methoxyphenylurea 2e. Yield: 61% (802 mg); mp = 171°C; $[\alpha]_D = -3.6$ ($CHCl_3$, $c = 5$); ^{1}H NMR ($CDCl_3$, δ): 1.21 (4H, m), 1.82 (4H, m), 2.38 (1H, m), 3.31 (1H, m), 3.78 (3H, s), 4.79 (1H, d), 6.85–7.25 (4H, m), 7.42 (1H, s); ^{13}C NMR ($CDCl_3$, δ): 24.91, 25.14, 32.97, 35.09, 35.51, 55.96, 57.16, 114.47, 123.32, 129.45, 139.62, 157.05; ν_{max} (KBr, cm^{-1}): 3359, 3306, 2951, 2865, 1640, 1623, 1562, 1157; mass spectrum: m/z [FAB$^+$] (%): 264 (79, M$^+$), 247 (4), 166 (8), 154 (100), 137 (78), 123 (25), 107 (25), 98 (18); anal. calcd for $C_{14}H_{21}N_3O_2$: C, 63.85; H, 7.98; N, 15.96. Found: C, 63.55; H, 7.89; N, 15.64%.

4.1.6. (1*R*,2*R*)-1,2-Diaminocyclohexane *ortho*-tolylurea 2f. Yield: 68% (935 mg); mp = 167°C; $[\alpha]_D = -4.7$ ($CHCl_3$, $c = 5$); ^{1}H NMR ($CDCl_3$, δ): 1.18 (4H, m), 1.86 (4H, m), 2.28 (3H, s), 3.33 (1H, m), 3.34 (1H, m), 5.5 (1H, d), 7.05–7.58 (4H, m), 7.54 (1H, s); ^{13}C NMR ($CDCl_3$, δ): 18.29, 24.77, 25.05, 32.88, 34.49, 55.68, 56.47, 123.63, 124.58, 126.73, 130.74, 136.82, 157.05; ν_{max} (KBr, cm^{-1}): 3360, 3307, 2951, 2866, 1643, 1625, 1563; mass spectrum: m/z [FAB$^+$] (%): 248 (12, M$^+$), 221 (12), 207 (18), 191 (8), 147 (46), 136 (20) 98 (13); anal. calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56; N, 16.99. Found: C, 67.75; H, 8.29; N, 16.79%.

4.1.7. (1*R*,2*R*)-1,2-Diaminocyclohexane *para*-(trifluoromethyl)phenylurea 2g. Yield: 55% (827 mg); mp = 155°C; $[\alpha]_D = -5.2$ ($CHCl_3$, $c = 5$); ^{1}H NMR ($CDCl_3$, δ): 1.15 (4H, m), 1.9 (4H, m), 2.59 (1H, m), 3.47 (1H, m), 6.24 (1H, m), 7.38–7.54 (4H, m), 8.8 (1H, s); ^{13}C NMR ($CDCl_3$, δ): 24.26, 24.87, 32.69, 34.37, 55.58, 56.30, 118.35, 122.85, 126.06, 142.66, 156.31; ν_{max} (KBr, cm^{-1}): 3362, 3308, 2949, 2865, 1641, 1624, 1562, 1256; mass spectrum: m/z [FAB$^+$] (%): 302 (15, M$^+$), 281 (6), 221 (6), 207 (12), 193 (5), 147 (24), 98 (16); anal. calcd for $C_{14}H_{18}N_3OF_3$: C, 55.81; H, 6.02; N, 13.95. Found: C, 55.78; H, 6.29, N, 13.42%.

4.1.8. (1*R*,2*R*)-1,2-Diaminocyclohexane 1-naphthylurea 2h. Yield: 72% (1.02 g); mp = 287°C; $[\alpha]_D = -2.9$ ($CHCl_3$, $c = 2$); ^{1}H NMR (DMSO-d_6, δ): 1.21 (4H, m), 1.85 (4H, m), 2.4 (1H, m), 3.3 (1H, m), 6.58 (1H, d), 7.4–8.08 (7H, m), 8.52 (1H, s); ^{13}C NMR (DMSO-d_6, δ): 24.83, 25.11, 32.85, 34.90, 55.70, 56.45, 119.50, 124.65, 125.73, 129.44, 130.61, 132.77, 138.88, 139.75, 157.25; ν_{max} (KBr, cm^{-1}): 3311, 3290, 2928, 2851, 1623, 1561, 1395, 1342; mass spectrum: m/z [FAB$^+$] (%): 284 (100, M$^+$), 283 (14), 267 (8), 207 (12), 176 (6), 169 (23), 154 (93), 136 (95), 113 (32), 98 (47); anal. calcd for $C_{17}H_{21}N_3O$: C, 72.08; H, 7.42; N, 14.80. Found: C, 72.08; H, 7.35; N, 14.56%.

4.2. General procedure for the synthesis of bis-urea ligands 3

The bis-ureas **3a** and **3b** were prepared according to the general procedure described by Kellogg et al.[29] starting from (1*R*,2*R*)-1,2-diaminocyclohexane (5 mmol) and isocyanate (11 mmol).

4.2.1. (1*R*,2*R*)-1,2-Diaminocyclohexane cyclohexylbis-urea 3a. Yield: 92% (1.68 g); mp = 286°C; $[\alpha]_D = +0.28$ ($CHCl_3$/EtOH 1/1 v/v, $c = 1$); ^1H NMR (DMSO-d_6, δ): 1.2–1.9 (28H, m), 3.15 (1H, m), 3.55 (2H, m), 4.46 (2H, d), 5.26 (2H, d); ^{13}C NMR (DMSO-d_6, δ): 25.05, 25.62, 33.22, 33.95, 35.17, 49.01, 56.85, 159.35; ν_{max} (KBr, cm^{-1}); 3320, 2919, 2887, 1633, 1585; mass spectrum: m/z [FAB$^+$] (%): 365 (25, M$^+$), 363 (5), 307 (18), 289 (12), 266 (18), 240 (22), 222 (10), 154 (100), 136 (75), 107 (25), 98 (40); anal. calcd for $C_{20}H_{36}N_4O_2$: C, 65.90; H, 9.95; N, 15.37. Found: C, 66.25; H, 10.22; N, 15.10%.

4.2.2. (1*R*,2*R*)-1,2-Diaminocyclohexane dodecylbis-urea 3b. Yield: 95%. This compound was obtained as described in Ref. 29, and exhibited identical analytical characteristics to those reported.

4.3. General procedure for the synthesis of amino-thiourea ligands 4

The amino-thioureas **4** were synthesised according to the same procedure as described for the synthesis of the mono-ureas **2** using the corresponding commercial isothiocyanates. The amino-thioureas, which formed together with some bis-thioureas, were isolated by recrystallisation from acetone.

4.3.1. (1*R*,2*R*)-1,2-Diaminocyclohexane *n*-butylthiourea 4a. Yield: 65% (745 mg); mp = 77°C; $[\alpha]_D = +5.3$ ($CHCl_3$, $c = 5$); ^1H NMR ($CHCl_3$, δ): 0.91 (3H, t), 1.22 (4H, m), 1.49 (4H, m), 1.8 (4H, m), 2.35 (1H, m), 2.56 (1H, m), 3.18 (2H, m), 4.12 (1H, d), 5.78 (1H, d); ^{13}C NMR ($CHCl_3$, δ): 13.80, 20.04, 20.17, 24.71, 24.88, 31.19, 32.21, 34.97, 56.03, 61.33, 182.15; ν_{max} (KBr, cm^{-1}): 3425, 3302, 2929, 1547, 1442; mass spectrum: m/z [FAB$^+$] (%): 230 (100, M$^+$), 228 (22), 157 (19), 133 (45), 97 (96), 57 (86); anal. calcd for $C_{11}H_{23}N_3S$: C, 57.60; H, 10.11; N, 18.32, S, 13.98. Found: C, 57.97; H, 10.22; N, 18.12; S, 13.69%.

4.3.2. (1*R*,2*R*)-1,2-Diaminocyclohexane tertiobutylth-iourea 4b. Yield: 59% (675 mg); mp = 98°C; $[\alpha]_D = +6.5$ ($CHCl_3$, $c = 5$); ^1H NMR ($CHCl_3$, δ): 1.22 (4H, m), 1.47 (9H, s), 1.8 (4H, m), 2.32 (1H, m), 2.54 (1H, m), 4.52 (1H, d), 5.81 (1H, d); ^{13}C NMR ($CHCl_3$, δ): 24.79, 24.83, 29.35, 32.26, 35.04, 53.08, 56.24, 62.04, 181.58; ν_{max} (KBr, cm^{-1}): 3425, 3301, 2928, 1547, 1452; mass spectrum: m/z [FAB$^+$] (%): 230 (100, M$^+$), 228 (18), 157 (18), 133 (40), 97 (98), 57 (82); anal. calcd for $C_{11}H_{23}N_3S$: C, 57.60; H, 10.11; N, 18.32; S, 13.98. Found: C, 57.94; H, 10.25; N, 18.15; S, 13.76%.

4.3.3. (1*R*,2*R*)-1,2-Diaminocyclohexane cyclohexylth-iourea 4c. Yield: 68% (867 mg); mp = 85°C; $[\alpha]_D = +7.5$ ($CHCl_3$, $c = 5$); ^1H NMR ($CHCl_3$, δ): 1.05–1.85 (18H, m), 2.37 (1H, m), 3.16 (1H, m), 3.61 (1H, m), 4.58 (1H, d), 5.72 (1H, d); ^{13}C NMR ($CDCl_3$, δ): 24.67, 24.82, 25.35, 25.48, 32.75, 34.62, 35.26, 53.12, 55.61, 57.18, 181.14; ν_{max} (KBr, cm^{-1}): 3425, 3263, 2928, 1547, 1447; mass spectrum: m/z [FAB$^+$] (%): 256 (35, M$^+$), 222 (8), 176 (6), 154 (100), 136 (75), 77 (38); anal. calcd for $C_{13}H_{25}N_3S$: C, 61.13; H, 9.87; N, 16.45; S, 12.55. Found: C, 61.15; H, 10.14; N, 16.26; S, 12.15%.

4.4. Typical procedure for ruthenium-catalysed reduction of aromatic ketones

A mixture of $[RuCl_2(p\text{-cymene})]_2$ (18.4 mg, 0.03 mmol) and the chiral urea ligand (0.06 mmol) was placed in freshly distilled propan-2-ol (10 mL) and this solution was stirred at 80°C for 30 min. After cooling to 20°C, additional propan-2-ol (20 mL) was added followed by the addition of solid KOH (16.8 mg) and the aromatic ketone (3 mmol). The orange solution became brown. The reaction was monitored by capillary gas chromatography and the e.e. was measured by HPLC on a Chiralcel OD column. The results are summarised in Table 1.

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