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Ureas and thioureas as Rh-ligands for the enantioselective hydride transfer reduction of acetophenone

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Abstract

Different chiral amines, ureas and thioureas have been synthesized and tested as ligands in the enantioselective hydride transfer reduction of acetophenone catalyzed by rhodium I. Structural effects have been noticed on both activity and selectivity.

Keywords: Asymmetric catalysis; Rhodium; Nitrogen ligands

1. Introduction

It is now well-established that nitrogen-containing compounds are useful ligands in asymmetric catalysis. High enantioselectivities are reached with these products in various reactions such as cyclopropanation [1], Pd-catalyzed alkylation [2], dihydroxylation [3], epoxidation [4], etc. They also turned out to be ligands of choice for hydride transfer reduction of ketones. Different families of nitrogen compounds have been successfully used in this reaction such as amines [5], sulfonylamines [6], aminoalcohols [7] diaminoferrocenyl derivatives [8] and recently in our laboratory diureas [9] and dithioureas [10]. With the aim of approaching the 'ideal' ligand, we studied the effect of its structure on both activity and selectivity in the rhodium catalyzed enantioselective hydride transfer reduction of acetophenone. We describe here our results with C_2-symmetric diamines, mono- and di-ureas and thioureas (Fig. 1).

2. Synthesis of the ligands

2.1. Diamine ligands

Compound **1** was synthesized according to Normant et al. [11]. Compounds **2** and **3** (Fig. 2) were obtained by addition of (1*S*, 2*S*)-(−)-diphenylethanediamine on the corresponding acid chloride (respectively, acetyl chloride for product **2** and propionyl chloride for product **3**). The yields are quantitative and the diamide thus obtained is used without further purification.

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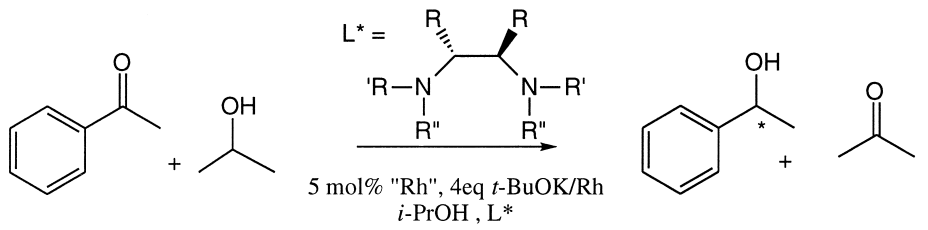


Fig. 1. Test reaction.

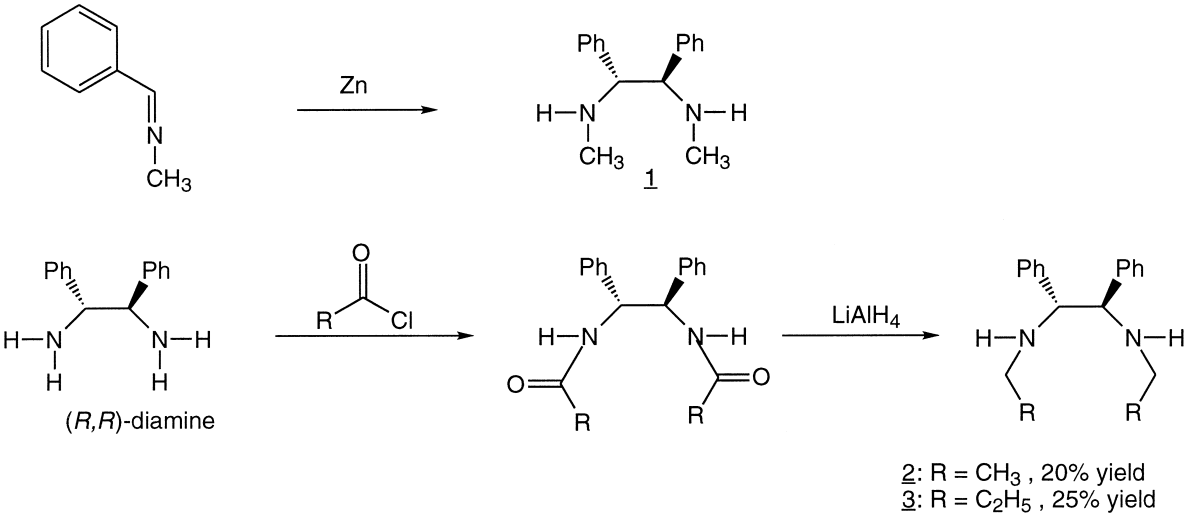


Fig. 2. Synthesis of dialkyldiamines.

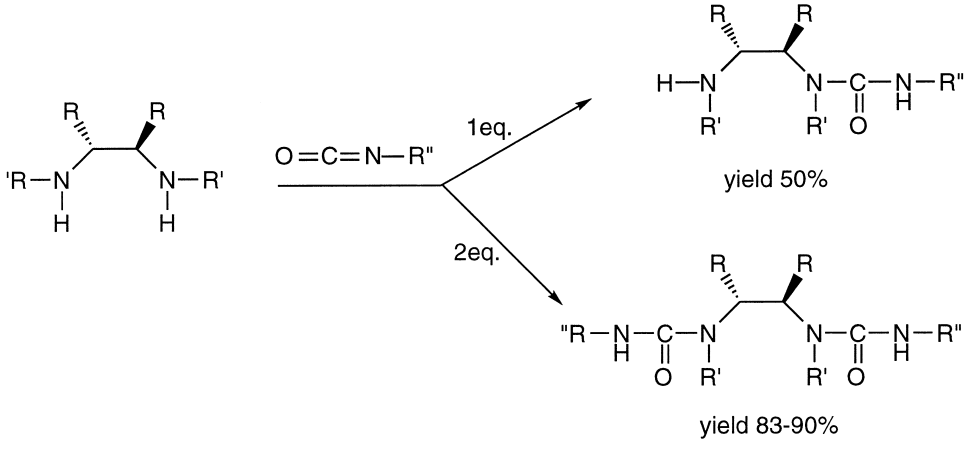


Fig. 3. Synthesis of urea ligands.

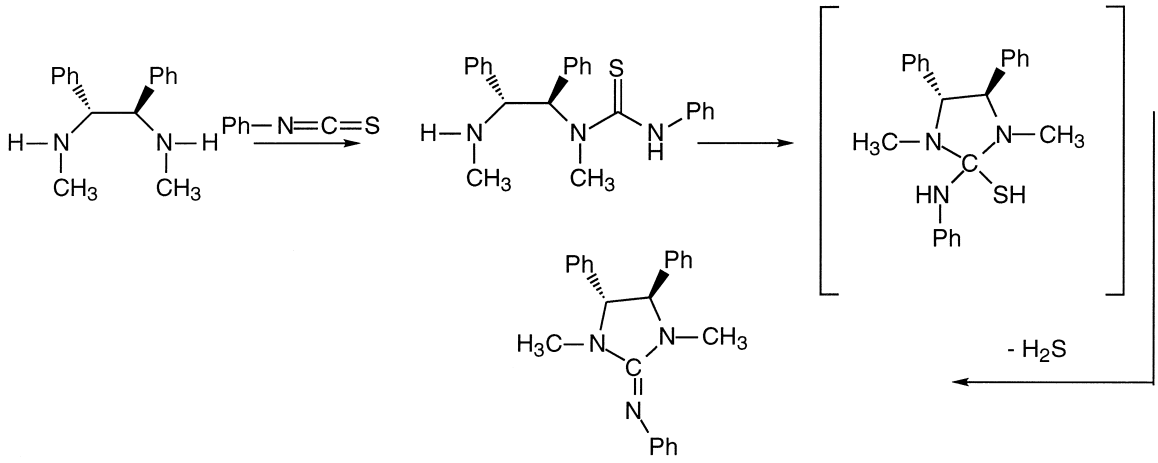


Fig. 4. Formation of the guanidine.

Reduction with $LiAlH_4$ led to the desired dialkyldiamine with low yield due to the difficult separation of the diamine from excess of aluminium salt.

2.2. Urea ligands

Ureas were synthesized by reacting diamine with one equivalent of isocyanate for monoureas and two equivalents for diureas (Fig. 3).

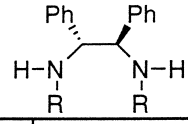
The moderate yields obtained with the monoureas were due to the concomitant formation of the corresponding diureas and to purification problems.

2.3. Thiourea ligands

Monothioureas were obtained according to the same procedure as described for ureas using isothiocyanates. Moderate yields (around 50%) were obtained for the same reasons as for monoureas. The synthesis with high yield of dithioureas has been already reported in a previous article [13].

It was impossible to synthesize monothiourea with *N,N*-dimethyldiphenylethanediamine and phenyl isothiocyanate as starting material. Instead of the desired product, we obtained the corresponding guanidine by cyclisation of the

Table 1
Influence of the alkyl chain length on both activity and selectivity of the reaction. Reaction conditions: after 40 h reaction, room temperature; catalyst precursor = $[Rh(cod)Cl]_2$; [*t*-BuOK]/[Rh] = 4; [Rh]/[acetophenone] = 5 mol%



Entry	R	Conversion(%)	e.e. (%)
1	CH_3	98	46
2	C_2H_5	94	46
3	C_3H_7	98	45

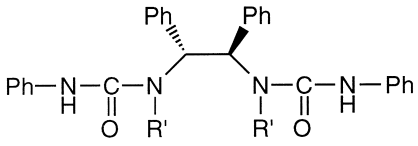


Fig. 5. Diurea ligand.

supposed monothiourea intermediate and intramolecular H_2S elimination (Fig. 4).

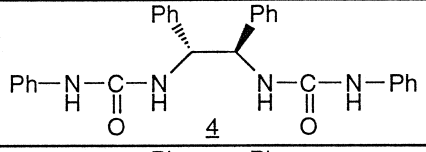
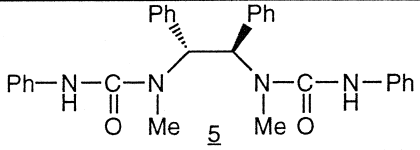
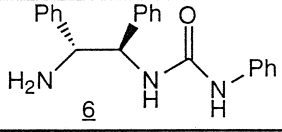
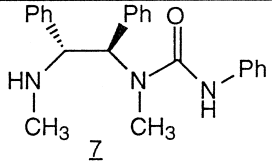
3. Results and discussion

During our study, we have to face the problem of the number of ligand equivalents per metal atom. Typically, we have increased the ratio ligand/metal atoms until the enantioselectivity reached its highest level and remained constant. In all the cases we observed that the activity decreased in the same time. The excess of ligand should hinder the substrate approach and slowed down the reaction. In most cases, only the best results in terms of enantioselectivity are reported here.

3.1. Diamine ligands

In the diamine series, we have extensively studied the influence of the diamine structure (the substituents between and/or on the two nitrogen atoms) [12]. The nitrogen needed to be substituted by two different groups to give high enantioselectivity, because it thus became a

Table 2
Activity and selectivity of monourea and diurea ligands: influence of the C_2-symmetry. Conditions: [*t*-BuOK]/[Rh] = 4; [Rh]/[acetophenone] = 5 mol%; *i*-PrOH, 70°C

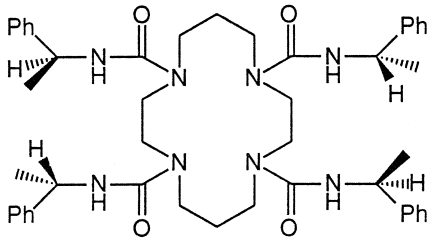
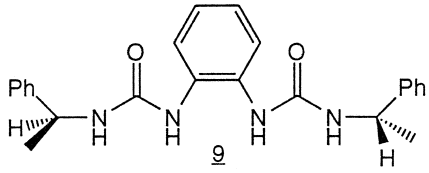
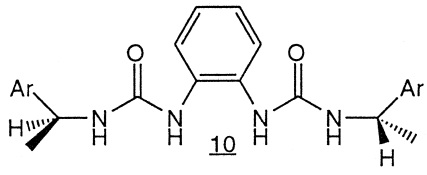
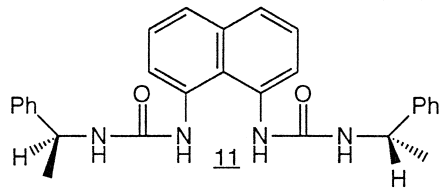
Entry	Ligand	L*/Rh ratio	Conversion (%)	e.e. % (configuration)	Time
1	 4	6	89	14(*S*)	3 days
2	 5	10	97	43(*S*)	7 days
3	 6	2 6	99 19	5 (*S*) 21(*S*)	5 h 4 days
4	 7	2 7	98 32	30(*S*) 38(*S*)	24 h 3 days

stereogenic center when bound to the rhodium. The best results were obtained with *N,N*-dimethyldiphenylethanediamine. We here examined the influence of the alkyl chain length on the nitrogen atoms (Table 1).

No effect of the alkyl chain length could be noticed. The diamine with R = isopropyl has already been tested and led to lower activity and selectivity in similar conditions [2]. Therefore, we turned our attention to an other family of nitrogen ligands: the ureas. Preliminary results have shown that 43% e.e. (97% conversion, 7 days, R′ = Me) [9] were reached with ureas in the hydride transfer reduction of acetophenone (Fig. 5). Nevertheless, with these ligands a high ligand/metal ratio was required (L∗/M = 10).

We studied the influence of the urea substituent R′. Considering the results obtained with

Table 3
Activity and selectivity of diurea ligands obtained with chiral isocyanates. Conditions: [*t*-BuOK]/[Rh] = 4; [Rh]/[acetophenone] = 5 mol%; *i*-PrOH, 70°C

Entry	Ligand	L*/Rh ratio	Conversion (%)	e.e. % (configuration)	Time (day)
1	 8	0.5	90	0	2
		1	84		2
		2.5	90		2
		5	85		2
2	 9	1	100	< 5%	1
		2	97	21(*R*)	1
		5	84	34(*R*)	2
		10	71	33(*R*)	2
3	 10 Ar = naphtalene	1	96	< 5%	2
		2	92	< 5%	2
		5	80	12(*R*)	2
		10	98	21(*R*)	2
4	 11	1	97	< 5%	1
		2	89		1
		5	97		1
		10	97		1

unsymmetrical sulfonamide [6] we also examined the potential of monosubstituted aminoureas derived from C_2-diamines.

3.2. Urea ligands

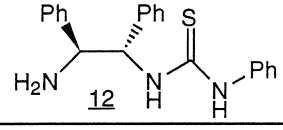
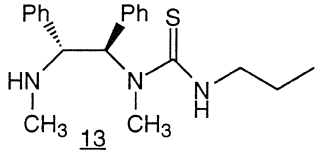
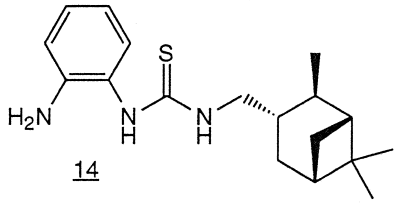
With ligand **4**, the catalytic system exhibited lower activity and selectivity than ligand **5** which has an alkyl substituent on the nitrogens of the diamine precursor. The optimal ligand/metal ratio is lower with aminourea ligands (Table 2, entries 3 and 4) than with diureas (Table 2, entry 2), but the e.e. is lower also. Contrary to results obtained with ruthenium [6], disymmetric ligands give low e.e. In the course of the reaction, ligand **7** turned into the corresponding guanidine (Fig. 4) and observed results were similar to those obtained with the pure guanidine [13].

The chirality could be introduced during the synthesis of the ligand by the diamine but also by the isocyanate. Therefore we have also synthesized and tested various diurea ligands starting from achiral diamines and commercially available chiral isocyanates (Table 3).

Whatever the ligand, one equivalent per rhodium was insufficient to stabilize the system and racemic phenylethanol was obtained. There is always undissolved ligand in the reaction mixture due to the low solubility of the ureas in 2-propanol.

Ligand **8** (Table 3, entry 4) led to no e.e. even with a ratio ligand/metal of 5, probably because it was too bulky: so it could not complex the metal properly. Thus, heterogeneous rhodium metal particles precipitated in the reaction medium. Moreover, recent studies in our laboratory have shown that only one diamine ligand can be bound to the rhodium [14]. The excess of ligand was here used to displace the

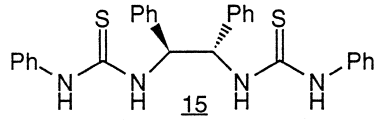
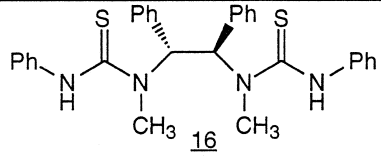
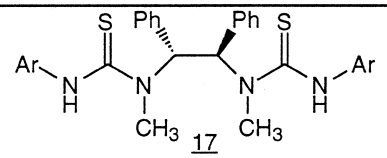
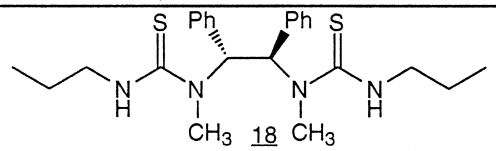
Table 4
Activity and selectivity of various monothiourea ligands in the reduction of acetophenone. Conditions: [*t*-BuOK]/[Rh] = 4; [Rh]/[acetophenone] = 5 mol%; *i*-PrOH, 70°C; a: room temperature

Entry	Ligand	L*/Rh ratio	Conversion (%)	e.e. % (configuration)	Time (day)
1[a]	 12	1	94	24(*R*)	4
		2	97	23(*R*)	4
		3	90	23(*R*)	10
2	 13	1	92	9(*S*)	4
		2	92	21(*S*)	4
		3	96	47(*S*)	2
		4	98	47(*S*)	2
3	 14	1	96	< 5%	4
		2	90		4
		5	31		4
		10	2		4

equilibrium towards the formation of the more stable complex and avoided the formation of metallic particles. Therefore, if ureas and diamines bound the metal with the same pattern, a four-point coordinating ligand could not be suitable. The best results were obtained with ligand **9** (Table 3, entry 2) which gave 34% e.e..

Substitution of the phenyl group by a naphtyl one (Table 3, ligand **10**, entry 3) decreased the enantioselectivity but the activity was the same. These two facts indicated that the steric hindrance of the substituent on the nitrogen atoms interfered. Replacing the *o*-dianiline moiety by a α,α′-naphtalenediamine one (Table 3, entry 4), led to e.e. < 5% whatever the ratio ligands/Rh. The number of atoms between the two nitrogen atoms is thus important and can lead to modifications in the chelating pattern. Different sites of complexation can be identified in the various ligands: the two nitrogen atoms of the diamine moiety, the two oxygen atoms of the carbonyl group and the two other nitrogen atoms from the isocyanate part. All the results described here with ureas, mono- or di-, indicated that this kind of ligands are effective for the enantioselective hydride transfer reduction of acetophenone using rhodium as the catalyst. Nevertheless, no more than 43% e.e. were obtained with this substrate. The coordination pattern of rhodium could be incriminated even if at this stage of our study, we have only few information concerning this feature. Therefore,

Table 5
Activity and selectivity of various dithiourea ligands in the reduction of acetophenone. Conditions: [*t*-BuOK]/[Rh] = 4; [Rh]/[acetophenone] = 5 mol%; *i*-PrOH, 70°C

Entry	Ligand	L*/Rh ratio	Conversion (%)	e.e. % (configuration)	Time (day)
1	 15	1	95	0	2
		2	71	0	4
		3	75	0	4
2	 16	1	98	15(S)	1
		2	90	44(S)	1
		3	97	63(S)	2
3	 17 Ar = naphthalene	2	92	60(S)	1
		3	98	65(S)	3
4	 18	2	98	32(S)	2
		3	97	37(S)	2

we investigated an other class of ligands, with a similar structure and potentially better chelating properties: the thioureas.

3.3. Thiourea ligand

Results obtained with monothioureas are reported in Table 4.

In the monothiourea series, with ligand **12**, the system was moderately active at room temperature and the enantioselectivity limited to 24%. By heating the reaction mixture, the activity was increased and the selectivity remained the same until the ratio ligand/metal was 3. With compound **13**, 47% e.e. were measured with a ratio ligand/Rh of 3. This selectivity is comparable to the one obtained with the best ureas but with higher activity [9] (2 days compared to 7, Table 2, entry 2). Moreover, only 3 equivalents of ligands are required instead of 10 with diureas. It is a general statement with thioureas: only 3 ligands/Rh are necessary to have good activity and selectivity whereas ureas need generally more ligand per mol of metal. Compound **14** (Table 4, entry 3) led to no enantioselectivity, whatever the excess of ligand per rhodium, probably because the chiral center is too far from the catalytic center.

Dithioureas were also tested and results are depicted in Table 5.

Ligand **15** (Table 5, entry 1) gives no enantioselectivity. Conversely, ligand **16** leads to 63% e.e. with 3 ligands per rhodium atom (97% conversion, 2 days) (Table 5, entry 2). Methylated precursors led to better ligands than non-methylated ones. Introduction of a methyl group on the nitrogen atoms increased the basicity of the nitrogen atoms. Thus, the nitrogen atoms of the diamine part of the ligand have better chelating properties than the nitrogen atoms of the thioisocyanate part. In this case, we assumed that the former atoms chelated the metal. With unsubstituted nitrogen atoms the chelating pattern could be different. Replacing the phenyl group by naphtyl causes no modification on both activity and selectivity contrary to that observed in the diurea series. Changing phenyl by propyl decreases the selectivity. The approach of the substrate may be easier with the propyl group and thus there is less facial selectivity than with the phenyl. Π stacking effects could also be important. In the case of thiourea ligands, it is difficult to conclude on the importance of the C_2-axis (compare ligands **12** and **15** in one side and ligands **13** and **18** in the other side).

4. Conclusion

In this study, only one rhodium (I) precursor was tested, the aim of the article being to evaluate new types of ligands. We show that chiral diamines, the corresponding guanidine, mono- and di-ureas and thioureas can be suitable ligands in asymmetric catalysis. Few or no example of asymmetric catalysis was previously described with such type of ligands. Taking into account the increasing interest of nitrogen containing ligands in asymmetric catalysis, ureas and thioureas could be suitable for many other catalytic systems and reactions. In the more specific case of the rhodium catalyzed enantioselective reduction of acetophenone by hydride transfer, dithioureas turned out to be the ligand of choice, even if the enantioselectivity generally measured with rhodium is lower than that obtained with ruthenium [10,14]. Moreover, the number of ligands that can be synthesized by our method is almost infinite as both chiral diamines and chiral isothiocyanates are commercially available. C_2-axis symmetrical or dissymmetrical ligands could be easily obtained and the spacer between the two nitrogens could be optimized in size and in nature (sp^2 or sp^3 carbone). This result opens a large field of investigations.

Further studies are in progress to evaluate the scope of applications of these new families of ligands with different metals, substrates and in other reactions.

5. Experimental

NMR spectra were recorded on a Bruker AC 200 (^{1}H 200 MHz, ^{13}C 50 MHz). IR spectra were recorded on a Perkin-Elmer 1720-X spectrometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter.

5.1. Typical procedure for the reduction of acetophenone

The appropriate amount of ligand was added to the catalyst precursor $[Rh(COD)Cl]_2$ ($3 \cdot 10^{-3}$ mmol) in 2 ml of a solution of potassium terbutoxyde in 2-propanol (0.012 mol l^{-1}) and stirred for 1 h 30 under inert atmosphere (tBuOK/Rh = 4). After addition of acetophenone (0.12 mmol) the mixture was kept overnight at room temperature. The solution was then heated (70°C) unless otherwise stated in order for the reaction to proceed. The reaction was monitored and the e.e. was measured by GC using a capillary column CYDEX-B from SGE.

5.2. Typical procedure for the synthesis of alkyldiamine ligands

Under argon, (1*S*, 2*S*)-(−)-diphenylethylenediamine (1.18 mmol) and 3 equivalents of Et_3N (3.54 mmol) were dissolved in 10 ml of dichloromethane. The corresponding acid chloride (2.95 mmol of acetylchloride for product **2** and propionylchloride for product **3**) were added slowly at 0°C. The mixture was stirred overnight at room temperature. After hydrolysis and extraction with dichloromethane (50 ml) the product was dried over $MgSO_4$. The crude product (0.27 mmol) was engaged in the second step without further purification and dissolved in 4 ml anhydrous THF. $LiAlH_4$ (6 eq) was then added by small portion at 0°C. After complete addition, the reaction mixture was maintained at THF reflux for 12 h. After careful hydrolysis with brine, the product was extracted with Et_2O. Purification by chromatography over SiO_2 (Et_2O saturated with NH_3).

5.2.1. Product **2**

Yield: 20%; $[\alpha]_D = -28.7$ ($c = 6$, $CHCl_3$); oil; ^{1}H NMR ($CDCl_3$): δ (ppm) 1.06(t, 6H, $J = 7.1$ Hz), 1.99 (s, NH), 2.47 (m, 4H), 3.66 (s, 2H), 7.01–7.22 (m, 10H); ^{13}C NMR ($CDCl_3$): δ (ppm) 15.4, 41.9, 69.2, 126.7, 127.8, 141.6; I.R. (cm^{-1}): 3313, 3062, 3026, 2960, 1492, 1455, 1164, 1124, 756, 698.

5.2.2. Product **3**

Yield: 25%; $[\alpha]_D = -7.1$ ($c = 3.1$, $CHCl_3$); oil; ^{1}H NMR ($CDCl_3$): δ (ppm) 0.87 (t, 6H, $J = 6.9$ Hz), 1.48 (m, 4H), 2.04 (s, NH), 2.36 (m, 4H), 3.62 (s, 2H), 7.01–7.18 (m, 10H); ^{13}C NMR ($CDCl_3$): δ (ppm) 11.9, 23.4, 49.8, 69.5, 126.8, 127.9, 141.9; I.R. (cm^{-1}): 3313, 3062, 3027, 2959, 2930, 2873, 1492, 1453, 1115, 909, 734, 699.

5.3. Typical procedure for the synthesis of (thio)urea ligands

To a solution of 2 mmol of diamine in 10 ml of dichloromethane was added 2 mmol in the case of mono(thio)urea or 4 mmol in the case of di(thio)urea of iso(thio)cyanate. The solution was stirred overnight at room temperature. The ligand was precipitated in pentane, filtered through a millipore filter (vv type, pore size 0.10 mm), washed with pentane and dried under vacuum.

In the case of monoureas, the ligands were purified by preparative TLC (CH_2Cl_2/MeOH: 95/5).

5.3.1. Product **6**

Yield: 47%; $[\alpha]_D = -15.5$ (c = 1.8, $CHCl_3$); m.p.: 88°C; ^{1}H NMR ($CDCl_3$): δ (ppm) 2.55(m, NH_2), 4.16 (d, 1H, $J = 5.4$ Hz), 5.05(t, 1H, $J = 7$ Hz), 6.97–7.5(m, 15H), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$): δ (ppm) 60.4, 70.3, 126.6–127.6, 128.4–129.6, 139.1, 140.7, 156.2; I.R. (cm^{-1}): 3316, 3060, 3028, 1653, 1598, 1553, 1497, 1452, 1312, 1235, 752, 698; Mass: calculated for $C_{21}H_{21}N_3O$ = 331.1762875, found = 331.1780000.

*5.3.2. Product **7***

Yield: 50%; $[\alpha]_D = -34.1$ ($c = 2$, $CHCl_3$); m.p.: 102°C; ^{1}H NMR ($CDCl_3$): δ (ppm) 1.90 (m, NH), 2.33 (s, 3H), 2.82 (s, 3H), 4.24 (d, 1H, $J = 9$ Hz), 5.58 (d, 1H, $J = 9$ Hz), 7.0–7.18 (m, 15H), 7.95 (m, NH); ^{13}C NMR ($CDCl_3$): δ (ppm) 34.5, 34.6, 64.7, 119.7, 122.6, 122.7, 127.5, 127.6, 128.2, 128.3, 128.6, 128.8, 128.9, 129.0, 137.3, 139.7, 140.3, 150.4; I.R. (cm^{-1}): 3448, 3352, 3062, 3031, 2938, 2862, 1701, 1654, 1602, 1533, 1500, 1455, 1391, 1360, 1311, 1242, 1078, 1014, 754, 703; Mass: calculated for $C_{23}H_{25}N_3O = 359.2075877$, found = 359.2097000.

*5.3.3. Product **8***

Yield: 90%; $[\alpha]_D = +16.2$ ($c = 0.52$, $CHCl_3$); m.p.: 113°C; ^{1}H NMR ($CDCl_3$): δ (ppm) 1.46 (d, 3H, $J = 7$ Hz), 1.74 (m, 4H), 3.13–3.36 (m, 16H), 4.97(m, CH, 4H), 5.55 (NH), 7.17–7.3(m, 20H); ^{13}C NMR ($CDCl_3$): δ (ppm) 22.8, 28.3, 46.2, 48.4, 126–144, 157.8; I.R. (cm^{-1}): 3334, 3061, 3028, 1629, 1532, 1450, 1375, 1314, 1247, 763, 700. Elemental anal. for $C_{46}H_{60}N_8O_4$: Found: C, 69.7; H, 7.6; N, 13.9; O, 8.8. Calc. C, 70.0; H, 7.7; N, 14.2; O, 8.1.

*5.3.4. Product **9***

Yield: 90%; $[\alpha]_D = -5.3$ (c = 0.5, *N,N*-dimethylacetamide); m.p.: 208°C; ^{1}H NMR (CF_3-COOD): δ (ppm) 1.6 (d, 3H, $J = 6.9$ Hz), 5.01 (q, 1H, $J = 6.9$ Hz), 7.22–7.51 (m, 14H); ^{13}C NMR (CF_3COOD): δ (ppm) 22.7, 54.2, 127–144, 160.3; I.R. (cm^{-1}): 3314, 3060, 3030, 1634, 1571, 1494, 1450, 1374, 1305, 1246, 745, 698; Elemental anal. for $C_{24}H_{26}N_4O_2$ Found: C, 71.1; H, 6.5; N, 14.0; O, 8.4. Calc. C, 71.6; H, 6.5; N, 13.9; O, 8.0.

*5.3.5. Product **10***

Yield: 83%; $[\alpha]_D = +51.2$ ($c = 0.5$, *N,N*-dimethylacetamide); m.p.: > 264°C; ^{1}H NMR (D_6-DMSO): δ (ppm) 1.54(d, 3H, $J = 6.8$ Hz), 5.65 (q, 1H, $J = 6.8$ Hz), 6.95 (m, 2H), 7.17 (d, 2H, $J = 7.8$ Hz), 7.47–7.63 (m, 8H), 7.85 (d, 2H, $J = 8$ Hz), 7.95 (m, 2H), 8.18 (m, 2H); ^{13}C NMR (D_6-DMSO): δ (ppm) 22.72, 44.8, 122–141, 155; I.R. (cm^{-1}): 3309, 3060, 3030, 1632, 1568, 1449, 1372, 1312, 1238, 776, Elemental anal. $C_{32}H_{30}N_4O_2$: Found: C, 76.4; H, 6.0; N, 11.2; O, 6.4. Calc. C, 76.5; H, 6.0; N, 11.1; O, 6.4.

*5.3.6. Product **11***

Yield: 85%; $[\alpha]_D = -18.9$ (c = 0.12, CF_3COOH); m.p.: > 264°C; ^{1}H NMR (D_6-DMSO): δ (ppm) 1.6 (d, 3H), 4.9 (m, 1H), 7.36–7.57 (m, 14H), 8.0 (m, 2H); ^{13}C NMR (D_6-DMSO): δ (ppm) 22.3, 54.8, 127–143, 161.1; I.R. (cm^{-1}): 3305, 3055, 3027, 1638, 1565, 1494, 1447, 1373, 1341, 1287, 1246, 781, 753, 699. Elemental anal. $C_{28}H_{28}N_4O_2$: Found: C, 74.3; H, 6.1; N, 12.6; O, 7.0. Calc. C, 74.3; H, 6.2; N, 12.4; O, 7.1

Products **12**, **13** and **15** to **18** have been described in Ref. [14].

Product **14**: yield: 50%; $[\alpha]_D = -24.4$ ($c = 0.46$, MeOH); m.p.: 135°C; ^{1}H NMR ($CDCl_3$): δ (ppm) 0.59 (d, $J = 9.8$ Hz, 1H), 0.92–0.97 (m, 6H), 1.14 (s, 3H), 1.38 (m, 1H), 1.59–1.72 (m, 2H), 1.82–2.04 (m, 3H), 2.22 (m, 1H), 3.43 (m, 1H), 3.63 (m, 1H), 4.04 (s, NH_2), 5.95 (s, NH), 6.74 (m, 2H), 7.11 (m, 2H), 8 (s, NH); ^{13}C NMR ($CDCl_3$): δ (ppm) 21.6–22.8, 31.8, 33.4, 35.4, 38.6, 40.4, 41.2, 47.6, 53.4; 116–144, 181; I.R. (cm^{-1}): 3403, 3286, 1617, 1542, 1495, 1453, 1303, 1239, 783. Elemental anal. $C_{18}H_{27}N_3S$: Found: C, 68.1; H, 8.5; N, 13.3; S, 10.1. Calc. C, 68.1; H, 8.6; N, 13.2; S, 10.1.

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