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Thioureas: new ligands for the metal catalyzed asymmetric reduction of carbonyl compounds

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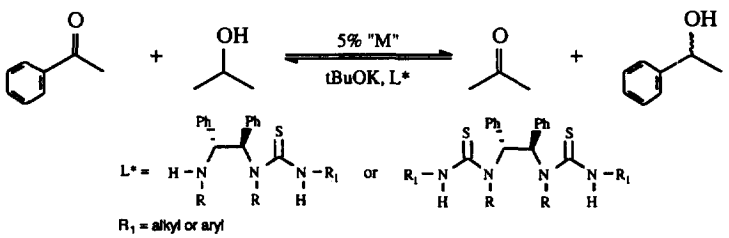
Abstract: The catalytic enantioselective hydride transfer reduction of prochiral ketones using differently substituted mono and dithioureas with several catalyst precursors is reported. The best results are obtained with a ruthenium complex and a C_2 symmetric ligand. © 1997 Elsevier Science Ltd

Asymmetric catalysis is certainly one of the most attractive methods to produce optically active compounds. Only small amounts of chiral inductors are required to convert large quantities of prochiral reactants into the desired chiral products. However, it suffers generally from the high price of the ligands (due to their difficult access) which often cannot easily, or not at all, be recycled and which moreover need precautions to prevent their degradation (easy oxidation of phosphorus for example).

We have recently developed chiral thioureas. They have the advantage, among others, of being easily accessible (starting from the corresponding diamine: *vide infra*) and easy to use: they do not need to be handled or stored under an inert atmosphere. They were found to be good ligands for the hydride transfer reduction of prochiral ketones with isopropanol,[1] giving access to optically active secondary alcohols with competitive or better results than the already existing systems.[2–5]

We want to report here on the structure–activity relationship of this type of ligand. We have first studied the reduction of acetophenone with mono and dithioureas substituted with alkyl or aryl groups (Scheme 1, Tables 2 and 3). Several catalyst precursors have been tested. Finally, we have used our best ligand in the reduction of some prochiral ketones (Table 4) in order to evaluate the efficiency of our catalytic system.



Scheme 1. Enantioselective reduction of acetophenone with thiourea ligands.

Ligand synthesis

The interest of our catalytic system, as already mentioned, is the easy accessibility of our ligands. They are simply synthesized by reaction of chiral diamines with one or two equivalents of isothiocyanates. The reaction takes place overnight, at room temperature, in dry dichloromethane without any other special precautions (no inert atmosphere). We kept the same chiral backbone

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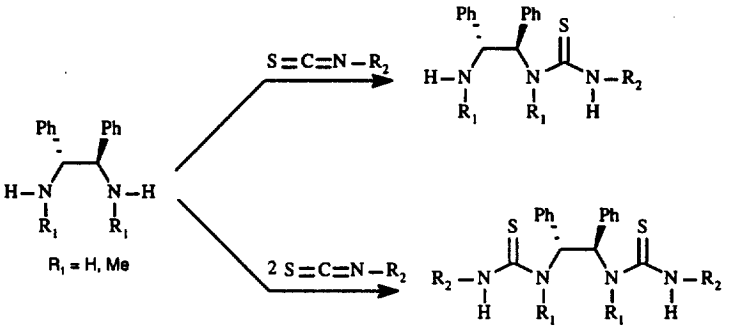
throughout the study and chose 1,2-diphenyl-1,2-ethylenediamine and N,N′-dimethyl-1,2-diphenyl-1,2-ethylenediamine as chiral starting materials (Scheme 2, Table 1).



Scheme 2. Synthesis of chiral thioureas.

The dithioureas were always obtained with good yields (>80%) after purification. We either took advantage of their insolubility to precipitate them in pentane (when R_2=aryl) or did just a filtration through a small column of silica (when R_2=alkyl) to eliminate the excess of isothiocyanate. Whatever the method, it is of noticeable simplicity.

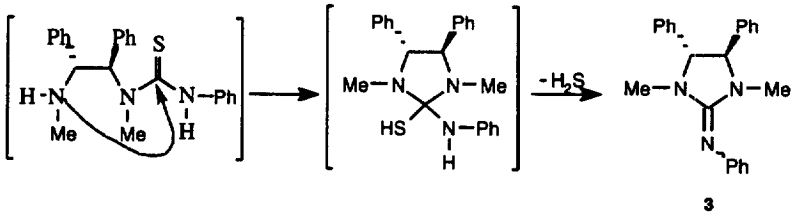
Obtaining the monothioureas was more problematic. They were always formed together with the corresponding dithioureas which explains the yields, reduced to about 50% (purification by TLC). In the case of N,N′-dimethyl-1,2-diphenyl-1,2-ethylenediamine with phenylisothiocyanate (R_1=Me, R_2=Ph), we did not isolate the expected monothiourea but guanidine **3** after cyclisation and H_2S elimination (quantitative yield — Scheme 3; use of this method to synthesize chiral guanidines is under evaluation in our laboratory). Even if this was not observed with the other monosubstituted ligands, this transformation is likely to happen during the reduction of acetophenone in the presence of tBuOK under refluxing isopropanol and thus the corresponding guanidine may have some effect in the active catalytic cycle. Anyway, this kind of ligand proved to be effective for the metal catalyzed hydride transfer reduction (Entry 3, Table 2).

Ligand structure and metallic precursor

Many precursors exist for each metal (Rh, Ir, Ru) but we limited our study to $[RuCl_2C_6H_6]_2$, $[Rh(cod)Cl]_2$ and $[Ir(cod)Cl]_2$. Even if it would have been necessary to test other catalysts for full optimization of the results, the figures (conversion and enantiomeric excess) give a general tendancy of the behaviour with a given kind of metallic precursor: $[RuCl_2arene]_2$, $[Rh(diene)Cl]_2$ and $[Ir(diene)Cl]_2$. In each case, we varied the ligand to metal ratio (from 1 to 2, 3 and 4) and the tables report the best results obtained concerning the selectivity (by increasing the corresponding ratio,

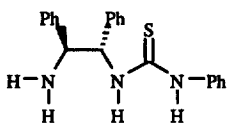
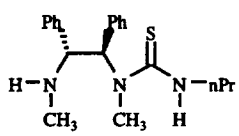
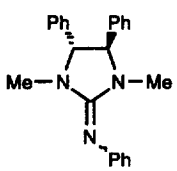
Table 1. Yield of the synthesized ligands (the reaction conditions have not been optimized)

diamine (R_1)	isothiocyanate (R_2)	isolated yield%	
		mono	di
H	Ph	52	80
Me	nPr	50	88
Me	1-Napht	-	83
Me	Ph	-	85



Scheme 3. Guanidine obtained by reaction of (R,R)-(−)-N,N′-dimethyl-1,2-diphenyl-1,2-ethylenediamine with 1 equivalent of phenyl isothiocyanate.

Table 2. Evaluation of monothioureas and guanidine: influence of the ligand structure and the catalyst precursor on the enantioselectivity of the reduction of acetophenone

Entry	Ligand	Metal	Time (days)	Conversion (%)	ee % (a)
1	 1	Ru Rh Ir(RT)	1 1 7	99 99 95	57 (R) 21 (R) 54 (R)
2	 2	Ru (b) Rh Ir	1 2 1	94 96 98	57 (S) 47 (S) 49 (S)
3	 3	Ru (b)(RT) Rh (b)(RT) Ir (b)(RT)	1 3 4	97 90 80	37 (S) 18 (S) 62 (S)

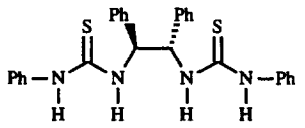
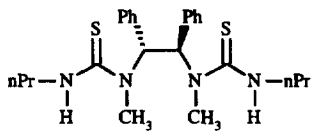
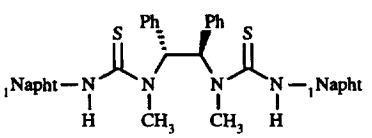
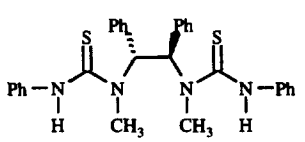
conditions : (S) = 6.10^{-2} (initial concentration) ; (Metal)/(S) = 5% ; (L*)/(Metal) = 3 ; T = 82°C ; (a) : absolute configuration ; (b) : (L*)/(Metal) = 2 ; Ru = $[RuCl_2C_6H_6]_2$, Rh = $[Rh(cod)Cl]_2$, Ir = $[Ir(cod)Cl]_2$.

the enantiomeric excess is not improved). Table 2 reports the results with monosubstituted ligands (monothioureas and guanidine) and Table 3 with disubstituted ones (exclusively dithioureas).

Monothioureas and guanidine

The three ligands (**1**, **2**, **3**, Table 2) are efficient for the asymmetric hydride transfer reduction of acetophenone, the best selectivities being close or higher than 60% and the activities acceptable. With **1** and **2** (Entries 1 and 2, Table 2), completion was usually reached within one day except when the reaction took place at room temperature (with Ir). Even if weaker activity was observed, the tests being carried out at room temperature, guanidine **3** required a lower ligand to metal ratio (Entry 3, Table 2). Ruthenium nevertheless enabled the reaction to proceed once again within 24 h. This metal seems thus to lead to the most active systems and also to the most selective ones for the monothioureas. Iridium appears to be nonetheless the most versatile metal since it gave nearly the same e.e.s as ruthenium

Table 3. Evaluation of dithioureas: influence of the ligand structure and the catalyst precursor on the enantioselectivity of the reduction of acetophenone

Entry	Ligand	Metal	Time (days)	Conversion (%)	ee % (a)
1	 **4**	Ru (b) Rh Ir	3d 4d 8d	15 75 85	24 (R) (c) (c)
2	 **5**	Ru (b) Rh Ir (b)	1d 2d 1d	93 97 99	56 (S) 37 (S) 25 (S)
3	 **6**	Ru (b) Rh Ir	1d 3d 4d	90 98 98	86 (S) 65 (S) 50 (S)
4	 **7**	Ru (b) Rh Ir Co	1d 2d 2d 2d	94 97 94 9	89 (S) 63 (S) 36 (S) 63 (S)

conditions : (S) = 6.10^{-2} (initial concentration) ; (Metal)/(S) = 5% ; (L*)/(Metal) = 3 ; T = 82°C ; (a) : absolute configuration ; (b) : (L*)/(Metal) = 2 ; (c) : e.e. < 10% ; Ru = $[RuCl_2C_6H_6]_2$, Rh = $[Rh(cod)Cl]_2$, Ir = $[Ir(cod)Cl]_2$, Co = $CoCl_2$.

with **1** and **2** and by far the best one with **3** (62% e.e., Entries 1, 2 and 3, Table 2). In contrast, rhodium exhibited lower selectivities with the added disadvantage of being less active than ruthenium.

At this point, if the precursors had to be compared, iridium would rank first, then ruthenium and rhodium far behind. As far as the ligands are concerned, guanidine **3** led to the highest selectivity.

Dithioureas

We found that the combined use of isopropanol and $CoCl_2$ did not lead to an active system, the conversion not exceeding 10% after two days even if significant e.e. was observed (Entry 4, Table 3). It seems to be a characteristic feature of cobalt in these conditions as such observations had already been made in the laboratory with 1–4 diamine ligands (unpublished results). We thus gave up this catalyst for the other tests.

The behaviour of rhodium and iridium contrasts with what had been observed with monothioureas and guanidine **3**: with equivalent activities, rhodium led always to the better selectivities, up to 65% e.e. (Entries 2, 3 and 4, Table 3). In terms of efficiency, it is similar to the 62% e.e. obtained with iridium and **3** in Table 2. Anyway, both precursors required the use of three equivalents of ligand per metal atom for optimal behaviour (see conditions of Table 3). This is not the case with ruthenium for which the ratio can be reduced to two and which has moreover the advantage of being cheaper.

Table 4. Efficiency of the catalytic system (ligand **7**, $[RuCl_2C_6H_6]_2$) with several ketones (RCOR')

Entry	R	R'	Time (hours)	Conversion (%)	ee % (a)
1	Ph	CH_3	9h	98	89 (S)
2	Ph	C_2H_5	17h	96	91 (S)
3	Ph	iPr	17h	92	94 (S)
4	Ph	tBu	48h	93	85 (R)
5	2 CF_3-Ph	CH_3	17h	96	77 (S)
6	4 CF_3-Ph	CH_3	48h	93	62 (S)

conditions : (S) = 6.10^{-2} (initial concentration) ; (Metal)/(S) = 5% ; (L*)/(Metal) = 2 ; Metal = Ru = $[RuCl_2C_6H_6]_2$; T = 82°C ; (a) : absolute configuration.

Finally, this metal led to all of the best results observed with our thioureas, both in terms of activity and selectivity: the reaction always took place within 24 h with e.e.s reaching 89% (Entry 4, Table 3).

It is noticeable that the (S,S) dithioureas always led to the R alcohol, and the (R,R) to the S alcohol, and this whatever the metal and the substituents. Concerning the latter, it is important to point out that the presence of the methyl group on the nitrogen atom of the starting diamine is really determinant for the selectivity: the e.e. passed from 24% (with a low activity, Entry 1, Table 3) to 89% (Entry 4, Table 3) just by replacing the hydrogen atom with a methyl group. The activity was also remarkably improved by this structural variation (3 days for 15% conversion versus 1 day and 95% conversion). We had already observed similar effects when using the corresponding diamines.[3]

The nature of the nitrogen substituent of the isothiocyanate appears to be another critical factor. Going from propyl to phenyl increased the selectivity from 56% to 89% e.e. (Entries 2 and 4, Table 3) and naphthyl and phenyl led to approximately the same results. If steric effects can explain part of this result, π–π interaction between the ligand and acetophenone, which would impose to the substrate a way of approaching the metallic center cannot be excluded.

Ruthenium appears thus to be the most suitable metal for thioureas, the best ligand bearing a methyl group on the nitrogen atom of the diamine and a phenyl group on the isothiocyanate. Even if monothioureas and guanidine led to acceptable selectivities (close to 60% e.e.) they do not compete with dithioureas.

Substrate

Several ketones have been reduced to test the efficiency of our catalytic system, composed of **7** (10 mol%) and $[RuCl_2C_6H_6]_2$ (2.5 mol%). The results are collected in Table 4.

Activity and selectivity seem to be related to steric hindrance in the vicinity of the carbonyl group. As the bulkiness of the alkyl group was raised from methyl to ethyl to isopropyl (Entries 1, 2 and 3, Table 4), and so as the steric differentiation between phenyl and alkyl groups decreased, the selectivity increased. The result of entry 5 goes in the same way.

With the *tert*-butyl analogue, the selectivity was reversed (Entry 4, Table 4). In this case, the (R,R) dithiourea led to the R alcohol. This phenomenon had already been observed.[1,3] The bulkier *tert*-butyl group forces the substrate to approach by its *Si* face instead of the *Re* face for the other ketones.

Electronic factors are also to be taken into account to explain the selectivities: CF_3 in position 4 led to an important decrease of e.e. (Entries 1 and 6, Table 4) though the steric environment of the carbonyl has not really changed.

The selectivities here prove that we succeeded in developing an efficient catalytic system: the results are better than the ones observed with ureas[5] (we moreover reduced drastically the necessary amount of ligand) or C_2 symmetric diamines.[3] Thioureas are on the whole not as selective as monosulfonamides,[3] but can compete for selected substrates (94% e.e.with isopropylphenylketone is one of the best results so far recorded in hydride transfer reduction).

Conclusion

This work shows that chiral thioureas are good ligands for the asymmetric hydride transfer reduction of prochiral ketones as e.e.s up to 94% have been measured (reduction of isopropylphenylketone). Even if sulfur containing compounds are usually considered as poisons for both homogeneous and heterogeneous catalysis, we have shown that it was not true for this kind of ligands which can compete with the more classical ones. We observed that ruthenium (ruthenium source=$[RuCl_2C_6H_6]_2$) was the metal of choice and that the dithioureas (C_2 symmetric molecules) led to the best selectivities. We also stressed the necessity of a good choice of the diamine and isothiocyanate. A phenyl group on the latter (likely for π stacking) and the methyl group on the N,N′-dimethyl-1,2-diphenyl-1,2-ethylenediamine are indeed crucial for the catalytic behaviour (activity and selectivity). So, we developed an efficient, easy to use catalyst. The next challenge is its recovery and thus the development of an heterogeneous version. This is currently under investigation.

Experimental

All the solvents and commercial products were used as received, without any further purification.

^1H and ^{13}C Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AM-200 Fourier transform spectrometer and obtained generally in chloroform-*d*. Chemical shifts are reported in parts per million (ppm) with TMS as internal reference, and coupling constants are reported in Hertz (Hz). Infrared spectra were recorded on a Perkin–Elmer 1720-X spectrometer. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. The enantiomeric excesses were measured by capillary gas chromatography using a chiral column (cydex B SGE column, 25 m × 0.25 mm Ø).

(S,S)-(−)-1,2-diphenyl-1,2-ethylenediamine is commercial.

(R,R)-(−)-N,N′-dimethyl-1,2-diphenyl-1,2-ethylenediamine has been synthesized according to the procedure already described by Mangeney *et al.*[6]

General synthesis of dithioureas

To a solution of the diamine (2 mmol) in 10 ml of dichloromethane was added the isothiocyanate (4 mmol). 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 μm) and washed with pentane. Finally, it was dried *in vacuo* (P=0.1 mmHg).

General synthesis of monothioureas

To a solution of the diamine (2 mmol) in 10 ml of dichloromethane was added the isothiocyanate (2 mmol). The solution was stirred overnight at room temperature. The solvent was then removed and the ligand purified over a pre-coated PLC plate (Silica gel 60 F-254, Merck Art.5717) as the mono is always obtained together with the dithiourea and the diamine which has not reacted.

(S,S)-(−)-1,2-Diphenyl-1,2-ethyleneamine-phenylthiourea 1

This has been synthesized according to the general procedure given for monothioureas. The solvent used for purification was a mixture of dichloromethane/methanol (98/2). Isolated yield: 52%. Mp=87°C. $[\alpha]_D$=−75 (0.47-$CHCl_3$). IR (KBr) ν 3268, 3027, 2924, 1596, 1520, 1495, 1450, 1384, 1312, 1240, 750, 697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.74 (NH_2), 4.42 (1 H, d, J=3.1 Hz), 5.55 (1 H, broad), 7.2–7.6 (15 H, m), 7.8 (NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 59.6 (CH), 64.4 (CH), 125–142 (Carom), 180.9 (CS). HRMS Calcd for $C_{21}H_{19}N_3$ (H_2S elimination): 313.1579. Found: 313.1591.

(R,R)-(−)-N,N′-Dimethyl-1,2-diphenyl-1,2-ethyleneamine-propylthiourea 2

This has been synthesized according to the general procedure given for monothioureas. The solvent used for purification was a mixture of Et_2O/Et_3N (80/20). Isolated yield: 50%. Mp=82°C. $[\alpha]_D=-215.4$ (0.48-$CHCl_3$). IR (KBr) ν 3247, 3030, 2961, 1641, 1530, 1480, 1455, 1387, 1343, 1228, 1067, 762, 735, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.9 (3 H, t, J=7.4 Hz), 1.6 (2 H, qt, $J_1=J_2=7.4$ Hz), 2.1 (3 H, s), 2.82 (3 H, s), 3.6 (2 H, m), 4.2 (1 H), 7–7.3 (11 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.5 (CH_3), 22.6 (CH_2), 34 (CH_3), 34.7 (CH_3), 48.1 (CH_2), 64.7 (CH), 74.2 (CH), 127–141 (Carom), 184.1 (CS). HRMS Calcd for $C_{20}H_{28}N_3S$ (MH^+): 342.2004. Found: 342.1993.

(R,R)-(−)-2-Phenyl-1,3-dimethyl-4,5-diphenylcyclopentaguanidine 3

This has been obtained following the general procedure given for monothioureas. Quantitative yield. Mp=190°C. $[\alpha]_D=-447$ (0.49-$CHCl_3$). IR (KBr) ν 3434, 3025, 2921, 1652, 1591, 1490, 1455, 1435, 1380, 1356, 1204, 1012, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.53 (6 H, s), 4.02 (2 H, s), 6.8–7.3 (15 H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.3 (CH_3), 73.4 (CH), 120–148 (Carom), 156.4 (CN). HRMS Calcd for $C_{23}H_{23}N_3$: 341.1892. Found: 341.1873.

(S,S)-(−)-1,2-Diphenyl-1,2-ethylenyl-diphenyldithiourea 4

This has been synthesized according to the general procedure given for dithioureas. Isolated yield: 80%. Mp=198°C. $[\alpha]_D=-44.3$ (0.52-$CHCl_3$). IR (KBr) ν 3244, 3028, 2982, 1595, 1540, 1496, 1452, 1388, 1347, 1315, 1244, 1072, 719, 697 cm^{-1}. ^1H NMR (200 MHz, DMSOd) δ 6 (2 H, broad s), 7–7.4 (20 H, m), 8.4 (2 NH), 9.8 (2 NH). ^{13}C NMR (50 MHz, DMSOd) δ 62.1 (CH), 123–139 (Carom), 180.3 (CS). Anal. Calcd for $C_{28}H_{26}N_4S_2$: C, 69.68; H, 5.43; N, 11.61; S, 13.28. Found: C, 69.60; H, 5.47; N, 11.55; S, 13.38.

(R,R)-(−)-N,N′-Dimethyl-1,2-diphenyl-1,2-ethylenyl-dipropyldithiourea 5

This has been synthesized according to the general procedure given for dithioureas. Nevertheless, as the ligand did not precipitate in pentane, it was purified by column chromatography with cyclohexane–ethyl acetate (80/20). Yield: 88%. Mp=149°C. $[\alpha]_D=-553.7$ (0.49-$CHCl_3$). IR (KBr) ν 3432, 3339, 2960, 1524, 1488, 1451, 1436, 1394, 1372, 1343, 1310, 1225, 1062, 712, 695 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (6 H, t, J=7.4 Hz), 1.56 (4 H, qt, $J1=J_2=7.4$ Hz), 2.86 (6 H, s), 3.58 (4 H, m), 5.42 (2 H, broad s), 7.1–7.2 (6 H, m), 7.4–7.5 (4 H, m), 7.75 (2 NH). ^{13}C NMR (50 MHz, DMSOd) δ 11.1 (CH_3), 22 (CH_2), 32.7 (CH_3), 47.3 (CH_2), 59.9 (CH), 127–138 (Carom), 181.6 (CS). HRMS Calcd for $C_{24}H_{35}N_4S_2$ (MH^+): 443.2303. Found: 443.2320.

(R,R)-(−)-N,N′-Dimethyl-1,2-diphenyl-1,2-ethylenyl-dinaphtyldithiourea 6

This has been synthesized according to the general procedure given for dithioureas. Yield: 83%. Mp=167°C. $[\alpha]_D=-277$ (0.52-$CHCl_3$). IR (KBr) ν 3381, 3271, 3058, 2923, 1597, 1498, 1453, 1396, 1375, 1327,1252, 1074, 773, 700 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 3.22 (6 H, s), 7.2–7.6 (20 H, m), 7.8–7.9 (6 H, m), 8 (2 NH). ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.4 (CH_3), 61.5 (CH), 122–137 (Carom), 183.9 (CS). HRMS Calcd for $C_{38}H_{35}N_4S_2$ (MH^+): 611.2303. Found: 611.2297.

(R,R)-(−)-N,N′-Dimethyl-1,2-diphenyl-1,2-ethylenyl-diphenyldithiourea 7

Synthesis and characterization have already been given.[1]

Typical procedure for the reduction of ketones

The appropriate amount of ligand was added to the catalyst precursor ('M': 6×10^{-3} mmol) in 2 ml of a solution of potassium terbutoxyde in 2-propanol (0.012 mol/l) and stirred for 1 h 30 min under an inert atmosphere ((tBuOK)/(M)=4). After addition of the ketone (0.12 mmol) the mixture was kept overnight at room temperature. The solution was then heated (82°C) in order for the reaction to proceed. All the reduction products were identified by GC by comparison with the commercial optically pure products ((R)-1-phenyl-1-ethanol, (R)-1-phenyl-1-propanol, (R)-2-methyl-

1-phenyl-1-propanol: Aldrich) or with literature data ((R)-4-trifluoromethyl-phenethyl alcohol,[7] (R)-2-trifluoromethyl-phenethyl alcohol[8]). The absolute configuration of (R)-2,2-dimethyl-1-phenyl-1-propanol was determined by polarimetry ($[\alpha]^{23}_D$=+30.6 (4-acetone)).[9]

References

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