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Chiral Thiourea as Ligand for the Asymmetric Reduction of Prochiral Ketones

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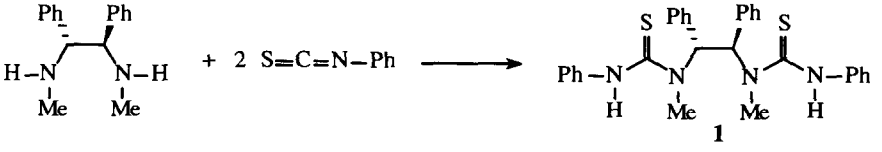
Abstract: The catalytic enantioselective reduction of prochiral ketones using a chiral thiourea as ligand is reported. Several metallic precursors were tested. e.e.'s up to 94% are obtained with a ruthenium complex. © 1997 Elsevier Science Ltd.

Although phosphines are still the most used in asymmetric catalysis, nitrogenous ligands present several advantages (accessibility, easy recovery ...). For these reasons, imines[1], amines[2], (sulfon)amides[2], diureas[3, 4] and others have been used and demonstrated to be efficient and selective ligands for both homogeneous and heterogeneous catalysis and particularly for the hydride transfer reduction of ketones. This last reaction is interesting in order to obtain optically active secondary alcohols. It is easy to perform and does not require the use of molecular hydrogen since the solvent (often isopropanol) can serve as the hydride donor. The systems developed so far lead to high enantiomeric excesses with a good catalytic activity and it is worth stressing that phosphines[5] have been supplanted by nitrogenous ligands[1, 2]. As the chemistry of nitrogenous organic compounds offers wider potentialities (syntheses, structures ...) than that of phosphorous ones, the search and evaluation of new kinds of ligands is still a topical issue.

We have recently shown that the urea function can be used[3, 4] with up to 80% e.e. in the reduction of propiophenone. The activity is nevertheless low (seven days are required to reach 97% conversion) and a 10/1 ratio ligand/metal is required. In order to overcome these limitations, we disclose here the use of the thiourea **1**. To our knowledge, no results have been obtained with sulphurous ligands of this kind[6]. Several metallic precursors were used to reduce aryl alkyl ketones.

1 was easily synthesised by reacting (1R,2R)-(+)-N,N'-dimethyl-1,2-diphenyl-1,2-ethanediamine with two equivalents of phenyl isothiocyanate (Scheme 1)[7] and tested in the reduction of acetophenone with some of the most common catalyst precursors (Scheme 2, Table 1).



1

Scheme 1 : synthesis of chiral thiourea **1**

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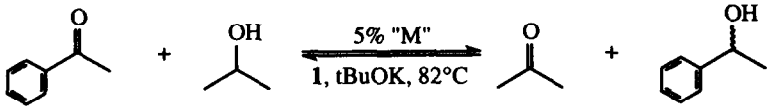


Scheme 2 : enantioselective reduction of acetophenone

Table 1. Influence of the Catalyst Precursor on the Enantioselectivity of the Reduction of Acetophenone

Entry	Precursor	(1)/(M)	Time (hours,days)	Conversion (%)	ee % (configuration)[a]
1	$CoCl_2$	1	2d	8	22 (S)
		2	2d	6	65 (S)
		3	2d	9	63 (S)
2	$(Ir(cod)Cl)_2$	1	1d	98	6 (R)
		2	2d	97	13 (S)
		3	2d	94	36 (S)
3	$(Rh(cod)Cl)_2$	1	1d	98	15 (S)
		2	1d	90	44 (S)
		3	2d	97	63 (S)
4	$(Rh(hex)Cl)_2$	1	2d	94	17 (S)
		2	2d	96	64 (S)
		3	2d	98	66 (S)
5	$(RuCl_2C_6H_6)_2$	1	3d	83	64 (S)
		2	3h	85	87 (S)
			9h	98	87 (S)
		3	2d	53	87 (S)

conditions[8] : (M)/(S) = 5%; (S) = 6 10^{-2} M (initial concentation); T = 82°C
[a] Enantiomeric excesses were determined by GC (estimated error : 1%) on a chiral Cydex B SGE column (25 m x 0.25mm Ø)

Due to its low price, cobalt catalysis is potentially interesting but it proved to proceed poorly in our conditions. The metal complexation is instantaneous (the color changes as soon as the compounds are mixed and the blue particles of $CoCl_2$ disappear) but the system is not active. The reaction proceeds much too slowly even if the selectivity is not negligible (Table 1, entry 1).

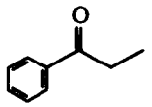
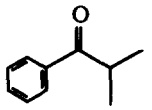
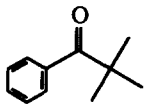
With $(Ir(cod)Cl)_2$ (Table 1, entry 2), the activity is acceptable but the e.e. remains low. It is noteworthy that the selectivity is inversed when going from 1 to 2 equivalents of ligand per metal atom. The increase of the ligand ratio must modify the nature of the most active catalytic species.

The rhodium catalysts, with an activity similar to that of $(Ir(cod)Cl)_2$, lead to higher e.e.'s (up to 66%). The nature of the diolefin (cyclooctadiene or hexadiene) does not seem to have any critical importance. $(Rh(cod)Cl)_2$ and $(Rh(hex)Cl)_2$ exhibit indeed similar behavior (Table 1, entries 3 and 4).

Finally, $(RuCl_2C_6H_6)_2$ provides by far the most active and selective system. The reduction is achieved in less than one day (98% conversion after 9h) and with 87% e.e. with two equivalents of ligand per metal atom. With 3 equivalents, the system appears to be less active (Table 1, entry 5).

So, we next evaluated the efficiency of the catalytic system composed with $(RuCl_2C_6H_6)_2$ ((Ru) = 5 mol%) and **1** (10 mol%) in the reduction of other ketones : RCOR' (Table 2).

Table 2. Activity and Selectivity of (**1**, $(RuCl_2C_6H_6)_2$) with Various Ketones (RCOR')

Entry	RCOR'	Time (hours)	Conversion (%)	ee % (confign)[a]
1		3h	35	91 (S)
		17h	96	91 (S)
2		3h	30	94 (S)
		17h	92	94 (S)
3		24h	67	85 (R)
		48h	93	85 (R)

conditions[8] : (S) = 6 10^{-2} M (initial concentration); (Ru)/(S) = 5%; (**1**)/(Ru) = 2; T = 82°C
[a] Enantiomeric excesses were determined by GC (estimated error : 1%) on a chiral Cydex B SGE column (25 m x 0.25mm Ø)

Activity seems clearly to be related to steric hindrance in the vicinity of the carbonyl group. The time for completion increases when going from Me to tBu (Table 1, entry 5 and Table 2, entries 1, 2, 3).

Selectivity also varies with steric requirement. The resulting alcohols present the (S) configuration (using the (R,R) thiourea) except for the *tert*-butyl group. It is a phenomenon already observed[5] : the bulkier *tert*-butyl group forces the substrate to approach by its *Si* face instead of the *Re* face for the other ketones.

This preliminary result indicates that thioureas are more efficient and selective than their oxygen counterparts[5] (with the same skeleton of C atoms for acetophenone reduction : 2 days and 63% *vs* 7 days and 43% e.e. with $(Rh(cod)Cl)_2$). The selectivities are close to or higher than 90% e.e. with $(RuCl_2C_6H_6)_2$. The replacement of O by S also enabled to reduce drastically the ligand/metal ratio (from ten to two). Moreover, these ligands are likely to be polymerized and used in heterogeneous phase[3]. Due to the easy synthesis of this kind of ligands, it could represent a possible solution in asymmetric catalysis.

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7. Thiourea synthesis : To a solution of 1.02 g (2 mmol) of (1R,2R)-(+)-N,N'-dimethyl-1,2-diphenyl-1,2-ethanediamine in 10 ml of dichloromethane was added 0.54 g (4 mmol) of phenyl isothiocyanate. 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). Isolated yield : 85%. Mp = 147°C. $[\alpha]_D$ = -532 (0.5-$CHCl_3$). IR (KBr) ν 3388, 3266, 3028, 1595, 1514, 1449, 1385, 1331, 1232, 1079, 761, 697 cm^{-1}; ^1H NMR (200 MHz, DMSOd) δ 3.13 (6 H, s), 7.17-7.39 (18 H, m), 7.62 (4 H, d, J = 7 Hz), 7.99 and 9.29 (2 NH); ^{13}C NMR (50 MHz, DMSOd) δ 35.1 (CH_3), 61.6 (CH), 126-142 (Carom), 183.5 (CS). *Anal.* Calcd for $C_{30}H_{30}N_4S_2$: C, 70.55; H, 5.92; N, 10.97; S, 12.55. Found : C, 70.6; H, 5.9; N, 11; S, 12.5.
8. Typical procedure for the reduction of ketones : The appropriate amount of **1** 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 M) and stirred for 1h30 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). The absolute configuration of (R)-2,2-dimethyl-1-phenyl-1-propanol was determined by polarimetry ($[\alpha]^{23}_D$ = +30.6 (4-acetone))[9].
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