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Cationic complexes with chiral diamine or dithiourea ligands as catalysts for molecular asymmetric hydrogenation

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Abstract

The asymmetric reduction of phenylglyoxylate methyl ester with molecular hydrogen and catalytic amounts of cationic chiral diamine and dithiourea complexes of rhodium and iridium is reported. The catalytic activity of the complexes is rather different if the C_2-symmetric ligand is a diamine or a dithiourea, even if enantioselectivity is always observed, with ee values up to 72%. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

The synthesis of chiral alcohols with neighbouring functional groups is of obvious interest in the biochemical area.[1] One of the best methods to obtain these alcohols is the asymmetric reduction of the corresponding ketones with molecular hydrogen because it is a cheap readily available reducing agent and no by-products are formed. Numerous chiral diphosphine ligands have been combined with ruthenium or rhodium precursors to catalyze the hydrogenation of functionalized ketones. For the asymmetric hydrogenation of α-keto carboxylic acid derivatives, ruthenium systems led to very efficient catalysts, such as the ones formed with BICHEP,[1] BINAP,[2] BIPHEP[3] and DUPHOS[3] for example, which achieved the reduction of the methyl phenylglyoxylate to the corresponding alcohol with enantioselectivities of 99%, 89%, 86% and 80%, respectively. These results are excellent but chiral diphosphines are rather unstable and often costly, which justifies the need to find more accessible chiral ligands. Much effort has already been concentrated on enantioselective synthesis to find new chiral inducers and the use of nitrogen containing ligands has increased, particularly in asymmetric catalysis.[4–6] Concerning the catalytic transfer hydrogenation of carbonyl compounds, we proved that good enantioselectivities can be achieved by means of chiral diamines,[7] mono- and di-thioureas[8,9] with ruthenium, rhodium and iridium precursors. When H_2 is used as reducing agent for the hydrogenation of α-ketoesters and ketones,

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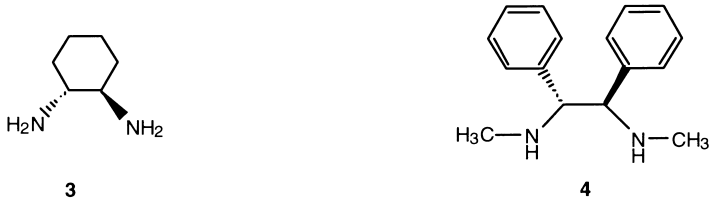
catalytic amounts of chiral diamine and neutral cobalt, rhodium and iridium complex precursors[10,11] gave moderate enantioselectivities, the best being 50% for the hydrogenation of methyl phenylglyoxylate with a rhodium (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethylenediamine catalyst. As the cobalt precursors led to poorly active species, our current studies are mainly focused on rhodium and iridium systems. We now report the preparation of new cationic rhodium and iridium complexes containing C_2-symmetric diamine or dithiourea ligands and their catalytic activities for the asymmetric reduction of phenylglyoxylate methyl ester by means of molecular hydrogen.

2. Results and discussion

2.1. Tests with chiral diamines

Enantiomerically pure C_2-symmetric diamines (Scheme 1), (1*R*,2*R*)-cyclohexanediamine **3** or (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethylenediamine **4**, were complexed in THF to different rhodium and iridium neutral and cationic precursors in a molar ratio of two ligands per metal. The resulting solutions were used for the hydrogenation of phenylglyoxylate methyl ester **1** under 50 bar of dihydrogen at 50°C and the reactions were stirred for 15 hours. The cooled and degassed reaction mixtures were then analyzed by chiral gas chromatography (see Experimental). The hydrogenations led exclusively to the corresponding alcohol **2** with the (*R*) configuration, with the various yields and selectivities reported in Table 1.



3 **4**

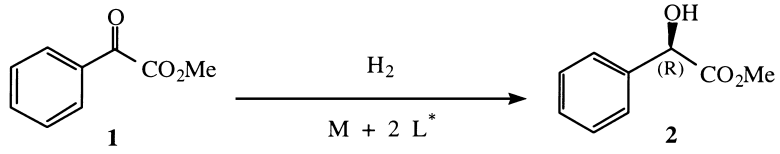
Scheme 1. Chiral diamines used as ligands for asymmetric hydrogenation of **1**

For the rhodium systems (entries 1 to 4), the catalytic behaviours are not modified when cationic precursors are employed instead of neutral ones if the chiral ligand remains unchanged. The neutral and cationic species formed with chiral diamine **3** show low catalytic activity (entries 1 and 3) while the complexes obtained with ligand **4** are moderately active and enantioselective (entries 2 and 4).

When iridium is employed, a catalytic activity enhancement occurs (entries 5 to 6). Similar conversions are obtained with neutral or cationic precursors, but the latter significantly increase the enantioselectivity. This is clearly observed for chiral diamine **4** which leads to our best result when the cationic species is used: 72% ee of (*R*)-alcohol. Complete conversion is reached in 6 hours with the same enantioselectivity (entry 9).

Even if both diamines are C_2-symmetric, the observed asymmetric inductions of diamines **3** (31% ee) and **4** (72% ee) are quite different when combined to the same metallic precursor, $[Ir(COD)_2]BF_4$. Better enantiomeric excesses were also achieved by means of ligand **4** instead of **3** in our preceding work.[11] This is due to both the chiral carbon structure and the nature of the amine (primary vs secondary). In both ligands, amine groups are spaced by a two stereogenic carbon bridge, but of significantly different nature: while in diamine **3** this bridge is strained, as being part of a cyclohexyl ring, in diamine **4** it carries two bulky phenyl groups. Moreover, the secondary amines of ligand **4** may lead to a new stereogenic centre when bound to the metal.[12,13]

Table 1
Hydrogenation of **1** with Rh or Ir catalysts and chiral diamines **3** or **4**



50 bars H_2; 50 °C; 15 hrs; THF; [ketone] = 0.5 M; 5% M *vs* ketone; M = Rh, Ir; L^* = **3** or **4**

Entry	Metal precursor	L^*	% Yield	% ee (R)
1	$[Rh(COD)Cl]_2$	**3**	10	10
2	$[Rh(COD)Cl]_2$	**4**	47	22
3	$[Rh(NBD)_2]BF_4$	**3**	4	11
4	$[Rh(NBD)_2]BF_4$	**4**	48	37
5	$[Ir(COD)Cl]_2$	**3**	96	17
6	$[Ir(COD)Cl]_2$	**4**	83	27
7	$[Ir(COD)_2]BF_4$	**3**	99	31
8	$[Ir(COD)_2]BF_4$	**4**	100	72
9	$[Ir(COD)_2]BF_4$	**4**[a]	100	72

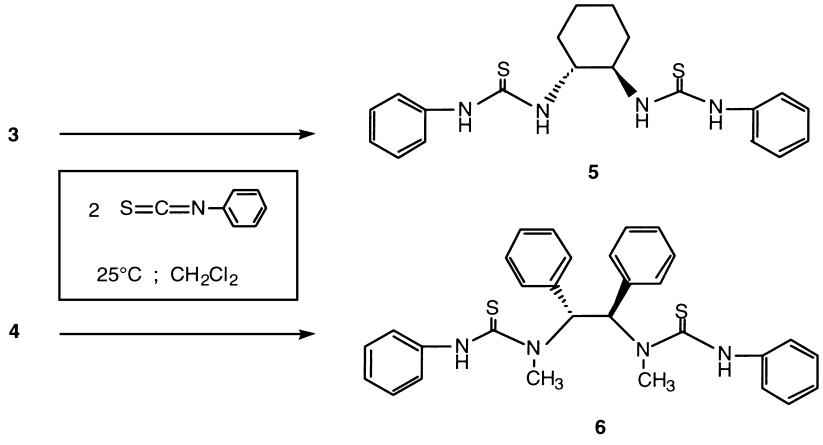
[a] in 6 hours

In the previous study the same conditions were employed except that hydrogenations were carried out in methanol.[11] Our present best catalytic system ($[Ir(COD)]BF_4$+ligand **4**) was then used in methanol and similar activity was observed but the enantioselectivity decreased to 57% (vs 72% ee in THF). Solvent molecules may contribute to the stabilization of the active species, and the better results obtained in less polar THF may also be due to its coordinating ability.

2.2. Tests with chiral dithioureas

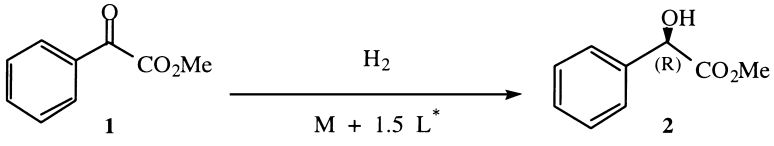
Enantiomerically pure ligands **5** and **6** (Scheme 2) are easily synthesized from the corresponding chiral diamines **3** and **4** and stoichiometric amounts of phenylisothiocyanate in dichloromethane at room temperature (see Experimental).

Chiral dithioureas were then combined with different rhodium or iridium neutral and cationic precursors in various solvents. The catalytic tests for the hydrogenation of phenylglyoxylate methyl ester **1** were carried out following the same procedure as for the chiral diamine ligands (see Experimental). When neutral rhodium and iridium complexes were used, conversions did not exceed 7%. More encouraging results were obtained with cationic metallic precursors and they are reported in Table 2.



Scheme 2. Chiral dithioureas used as ligands for asymmetric hydrogenation of **1**

Table 2
Hydrogenation of **1** with Rh or Ir catalysts and chiral dithioureas **5** or **6**



50 bars H_2; 50 °C; 15 hrs; THF; [ketone] = 0.5 M; 5% M *vs* ketone; M = Rh, I r; L^* = **5** or **6**

Entry	Metal precursor	L^*	Solvent	% Yield	% ee (R)
1	$[Rh(NBD)_2]BF_4$	**5**	THF	19	47
2	$[Rh(NBD)_2]BF_4$	**6**	THF	28	54
3	$[Rh(NBD)_2]BF_4$	**6**	Dioxane	31	58
4	$[Rh(NBD)_2]BF_4$	**6**	MeOH	30	19
5	$[Rh(NBD)_2]BF_4$	**6**	CH_2Cl_2	3	17
6	$[Ir(COD)_2]BF_4$	**5**	THF	1	-
7	$[Ir(COD)_2]BF_4$	**6**	THF	16	6

A preliminary study on cationic rhodium systems showed that the best molar ratio of ligand per metal (*n*) is 1.5 for both dithioureas **5** (entry 1) and **6** (entry 4). Even if only one molecule of ligand is not enough to form efficient catalysts, an excess of ligand (*n*=2) considerably decreases the activities and does not enhance the asymmetric inductions. These results suggest that various active species are in equilibria during the catalytic cycle. Attempts to crystallize ex situ complexes are ongoing, but to date, no suitable X-ray crystals have been obtained.

Activity and enantioselectivity slightly increase when dithiourea **6** is used instead of **5** (entries 2 vs 1 and 7 vs 6). The isothiocyanate moieties being the same for both dithioureas, this should only be due to the nature of the diamine part of the ligands. In fact, the same tendency had already been observed for

the corresponding diamines **4** and **3** (see Table 1, entries 3 and 4). This suggests that the coordination of the dithioureas **5** and **6** to the metal atom occurs mainly by means of the nitrogen atoms closer to the stereogenic centres. Sulfur atoms may also contribute to form the metallic complexes. This prompted a dramatic activity loss of the iridium catalysts when dithioureas are used instead of diamines.

As for diamines, the nature of the solvent is very important. Better conversions and enantioselectivities are obtained in ethers, dioxane leading to the highest, but still moderate, ee value of 58% (entry 3). As for diamines, methanol does not affect the activity of the catalytic species but its enantioselection and only 19% ee is obtained (entry 4 vs entry 2). When the hydrogenation was carried out in dichloromethane, the activity dropped to a conversion of 3%, even if enantioselectivity decreased less dramatically. The negative effect of the CH_2Cl_2 may be due to the leaching under the reaction conditions of Cl^- which coordinates the rhodium atom too strongly, blocking the catalytic activity of the complex by forming neutral species, which proved to be less active and selective.

3. Conclusion

Asymmetric molecular hydrogenation of phenylglyoxylate methyl ester was succesfully achieved in the presence of different cationic rhodium and iridium species containing C_2-symmetric diamines or dithioureas. The results reported here concern (*R*,*R*)-C_2-symmetric ligands leading, after hydrogenation of the α-ketoester, to the (*R*)-alcohol in various excesses. Some tests done with the corresponding (*S*,*S*)-diamine and dithiourea ligands led, as expected, to equivalent enantiomeric excesses of the (*S*)-alcohol. This study shows that the catalytic activity of the complexes is clearly enhanced when they are obtained from cationic precursors instead of neutral ones. Different ligand preferences are observed: rhodium for dithioureas and iridium for diamines. The latter combinations led to the better enantioselectivities, with values up to 72%, even if chiral dithioureas led to moderate asymmetry (ee=58%). These results are still lower than those now currently obtained with phosphorous containing ligands. Considering the enormous amount of work devoted over the last 20 years to phosphines as compared to amine and thiourea ligands, our results are rather encouraging. Finally, it is important to note the influence of the solvent on both activity and enantioselectivity of the catalytic systems; the more appropriate solvent should be of low polarity and easily coordinated to (or removed from) the rhodium centre, stabilizing complexes when needed. Further studies are in hand to determine and characterize the different active species. Extension of this work to ruthenium precursors may lead to better performing catalysts since ruthenium complexes are known to be very active in hydrogenation reactions. We also continue our research tuning new chiral monothiourea ligands which are promising since they are easily synthesized. C_2-symmetric aromatic thioureas can also be polymerized to form reusable catalysts with rhodium or ruthenium.

4. Experimental

4.1. General

Anhydrous solvents from Aldrich (THF, 99.9%, CH_2Cl_2, 99.8% and dioxane, 99.8%) were used as received from their Sure/Seal™ bottles (under nitrogen). MeOH and pentane were purchased from Normapur and degassed by prolonged argon bubbling before use. Phenylglyoxalate methyl ester **1** and (1*R*,2*R*)-cyclohexanediamine **3** were obtained from Aldrich. (1*R*,2*R*)-(+)-*N*,*N*′-dimethyl-1,2-diphenyl-1,2-ethylenediamine **4** was synthesized according to recently published procedures[14,15] and the corres-

ponding dithiourea **6** was prepared and characterized as already described.[9] 2,5-Norbornadiene, $AgBF_4$ and $[Rh(NBD)Cl]_2$ were purchased from Aldrich and $[Rh(COD)Cl]_2$, $[Ir(COD)Cl]_2$ and $[Ir(COD)_2]BF_4$ from Strem Chemicals were used. Gas chromatography analyses were carried out with a JW DB-1701 (non-chiral) or a Lipodex A (chiral) 25 m column on Shimadzu GC-14A chromatographs using a flame-ionization detector and Shimadzu C-R6A integrators. Melting points were determined with a Perkin–Elmer DSC-7 apparatus. NMR spectra were recorded on a Bruker AC200 Fourier transform spectrometer and δ values are given in ppm (200.13 MHz for ^1H and 50.32 MHz for ^{13}C). Microanalyses were performed by the CNRS's Service Central d'Analyses (Solaize).

4.2. Synthesis of $[Rh(NBD)_2]BF_4$

This synthesis was carried out under an argon atmosphere using Schlenk techniques. $AgBF_4$ (0.931 g, 4.78 mmol) was added to an orange solution of $[Rh(NBD)Cl]_2$ (1.016 g, 2.39 mmol) and 2,5-norbornadiene (0.515 mL, 4.78 mmol) in CH_2Cl_2 (40 mL). The resulting suspension was stirred at room temperature for 2 hours and decanted for 30 minutes, leading to a red solution and a fine grey precipitate of AgCl. The solution and the powder's washings (2×5 mL of CH_2Cl_2) were filtered through Celite over a glass-fritted (no. 4) Schlenk to yield a dark red solution. This solution was concentrated near to dryness in vacuo and addition of cold THF (40 mL) afforded orange crystals. These were filtered, washed with cooled THF (5 mL) and dryed in vacuo. Isolated yield: 51%.^1H NMR ($CDCl_3$): δ=5.66 (m, 4H); 4.29 (m, 2H); 1.62 (m, 2H). ^{13}C NMR & DEPT ($CDCl_3$): δ=94.35 (CH vinyl); 69.85 (CH_2); 55.70 (CH).

4.3. Synthesis of chiral dithiourea **5**

Phenylisothiocyanate (5 mL, 41.8 mmol) was added to a solution of (1*R*,2*R*)-cyclohexanediamine **3** (2.214 g, 19.4 mmol) in CH_2Cl_2 (20 mL) in a Schlenk flask under argon. The pale yellow solution formed was stirred at room temperature under an inert atmosphere overnight. The reaction mixture was then poured into 400 mL of pentane and the corresponding dithiourea **5** was precipitated. After filtration, the cream coloured powder was washed (2×20 mL of pentane) and dried in vacuo. Isolated yield: 87%. Melting point: 150°C. $[\alpha]_D$=43 (0.44, $CHCl_3$). ^1H NMR (DMSO-d_6): δ=9.60 (broad s, 2H, NH), 7.74 (broad s, 2H, NH), 7.42–7.05 (m, 10H, C_6H_5), 4.32 (broad s, 2H), 2.15 (broad s, 2H), 1.69 (broad s, 2H), 1.27 (broad s, 4H). ^{13}C NMR (DMSO-d_6): δ=179.72 (C=S), 139.03, 128.58, 123.96, 122.86 (C_6H_5), 56.68 (CH), 31.51 (CH_2), 24.27 (CH_2). HRMS calcd for $C_{20}H_{24}N_4S_2 \cdot H^+$=385.1520; found=385.1528. Anal. calcd (%) for $C_{20}H_{24}N_4S_2$: C, 62.46%; H, 6.29%; N, 14.57%; S, 16.68%. Found: C, 62.72%; H, 6.10%; N, 14.63%; S, 16.94%.

4.4. Catalytic hydrogenations

In a typical 4 mL test, the metal precursor (25 mmol L^{-1} of Rh or Ir) and the appropriate amount of chiral ligand (25 to 50 mmol L^{-1}) are dissolved in anhydrous THF under an argon atmosphere. The solution is stirred at room temperature for at least one hour and phenylglyoxalate methyl ester **1** (0.5 mol L^{-1}) is added just before transferring the reaction mixture into a glass-coated stainless steel autoclave, which is immediately sealed and purged over various argon cycles. The autoclave is then purged with two dihydrogen cycles, pressurized with 50 bars of H_2 and stirred (1250 cycl/min) at 50°C for 15 hours. The reactor is then cooled and gently degassed. The resulting solutions are filtered through Celite before being analyzed by gas chromatography. All of the ee values were determined with a 25 m chiral Lipodex A column, the retention times of (*R*-**2**) and (*S*-**2**) being 14.52 and 15.22 min, respectively.

Acknowledgements

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