0957-4166(94)00346-7

Catalytic Asymmetric Hydrogenation of Activated Keto Compounds by some Homogeneous and Silica-Supported di(μ-carboxylato)bis(aminophosphinephosphinite)dirhodium Complexes

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Abstract : New soluble and silica-supported rhodium complexes have been synthesized and tested as catalyst precursors for the enantioselective hydrogenation of α-ketoesters and an α-ketoamide. The homogeneous catalysts have been found to be efficient in terms of activity and asymmetric induction (up to 94% enantiomeric excess). On the other hand, the heterogenized systems exhibited lower performances and were gradually deactivated.

Catalytic asymmetric hydrogenation of α-ketoesters is a potentially important transformation for the production of optically active α-hydroxyesters, which are usefull building blocks for the industrial production of pharmaceuticals and agrochemicals. Numerous homogeneous rhodium and, to a lesser extent, ruthenium complexes chelated by chiral diphosphines have been developed for this purpose, and high enantiomeric excesses were generally achieved.[1] Nevertheless, although very high substrate/catalyst ratios could be used, the cost of the metal, especially that of rhodium, and many times that of the ligand, are often major drawbacks for final industrialization of the processes. This is the main reason why, in the last thirty years, increasing attention has been paid to homogeneous catalysts coordinately or covalently bound to organic and mineral supports,[2] but to our knowledge there have been very few reports focussed toward asymmetric hydrogenation of α-ketoesters.[3] In this field, we wish to present here our first results on the synthesis of new homogeneous and silica-supported di(μ-carboxylato)bis(aminophosphinephosphinite)dirhodium(I) complexes and their application in the enantioselective hydrogenation of activated keto compounds.

Scheme 1.
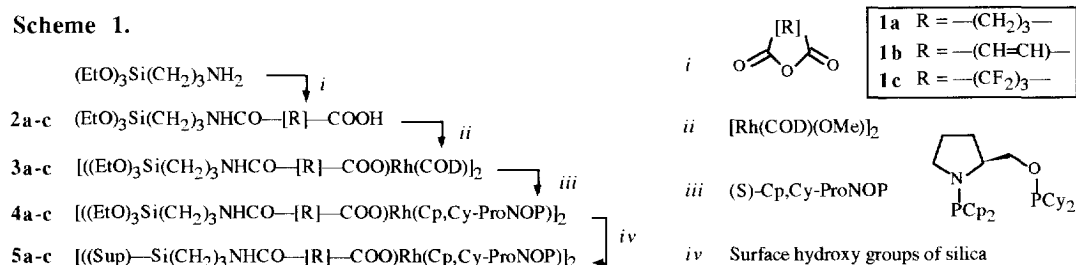
The title rhodium complexes were prepared in four steps as depicted in Scheme 1.[4] The ring-opening of cyclic anhydrides **1a-c** by 1-amino-3-(triethoxysilyl)propane gave the corresponding 3-(triethoxysilyl)amide carboxylic acids **2a-c**.[5,6] These afforded through reaction with [Rh(COD)(OMe)]₂ (COD = 1,5-cyclooctadiene)

the di(µ-carboxylato)bis(cyclooctadiene)dirhodium(I) complexes **3a-c** [7] which reacted by displacement of cyclooctadiene with the aminophosphinephosphinite (*S*)-Cp,Cy-ProNOP,[8] choosen as a model ligand for this study, to give the expected complexes **4a-c**. The immobilized complexes **5a-c** were obtained by reaction, in toluene, of the soluble complexes **4a-c** with silica.[2d,9]

First, the catalytic behavior of the complexes **4a-c** was evaluated in the homogeneous asymmetric hydrogenation of some activated keto compounds such as ketopantolactone **A**, *N*-benzylbenzoylformamide **B**, ethyl pyruvate **C** and methyl benzoylformate **D**. Representative results are summarized in Table 1.

A   **B**   **C**   **D**
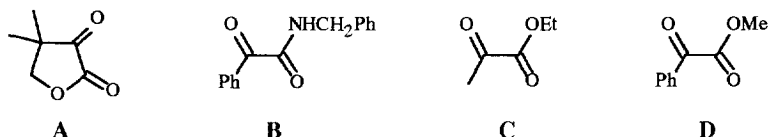
Table 1. Asymmetric Hydrogenation of Keto Compounds Catalyzed by the Homogeneous Complexes **4a-c** [a]

Run	Complex [R] =	Substrate	Subst/Rh (molar ratio)	Reaction time (h)[b]	Conv.[c] (%)	ee[d] (%, conf)
1	-(CH$_2$)$_3$-	**A**	60	2	77	84 (R)
2	"	**B**	170	8.75	92	74 (S)
3	"	**C**	225	1.25	99	65 (R)
4	"	**D**	364	0.75	99	10 (S)
5	-CH=CH-	**A**	43	3	100	85 (R)
6	"	**B**	36	1	100	74 (S)
7	"	**C**	98	3	100	70 (R)
8	"	**D**	165	0.75	100	14 (S)
9	-(CF$_2$)$_3$-	**A**	99	1	100	91 (R)
10[e]	"	**A**	79	1	99	94 (R)
11	"	**B**	95	0.5	100	89 (S)
12	"	**C**	245	1	97	84 (R)
13	"	**D**	162	0.75	100	7 (S)

(*a*) Hydrogenations were carried out at room temperature (unless otherwise stated) in dry degassed toluene solutions (20 mL) in a 100 mL flask under 1 atm of H$_2$ for **A** (0.39 mmol) and **B** (1 mmol), and in a 100 mL stainless steel autoclave under 50 atm of H$_2$ for **C** (1.82 mmol) and **D** (1.41 mmol). (*b*) Not optimized. (*c*) Determined by GC analysis (FS-CYCLODEX ß-I/P, 50m x 0.32 mm capillary column) for **A**, **C**, **D** and by ^{1}H and ^{13}C NMR for **B**. (*d*) Enantiomeric excesses were measured by GC analysis (FS-CYCLODEX ß-I/P) for the hydrogenation products of **A** and **C**, by polarimetry based on the specific rotation value [α]$_D^{26}$ = + 82.2 (*c* 1.09, CHCl$_3$) for (*S*)-(+)-*N*-benzylmandelamide, and by HPLC analysis (Chiralcel OD column, hexane:2-propanol = 90:10, 1 mL/min) for the hydrogenation product of **D**. (*e*) Reaction temperature = - 13°C.

All the substrates could be hydrogenated quantitatively. However, ethyl pyruvate and methyl benzoylformate required fairly high pressure (50 atm) for significant reaction rates at room temperature. Based on the calculated turnover frequencies (TOF, not reported in the table), we observed for each substrate the following activity order for the catalyst precursors **4a** < **4b** << **4c**; this effect is more pronounced for the hydrogenation of **A** (TOF at 50% conversion : 20, 50 and 1180 h^{-1}, respectively). The nature of the substituent

also greatly affected the enantiomeric excesses : complexes **4a** and **4b** led to almost similar results (a slow increase was observed for the hydrogenation of **C** and **D** with **4b**), whereas the introduction of the perfluorobutyro group (**4c**) resulted in a significant increase of the ee's, except for **D** which led in every case to poor optical yields. It is noteworthy that upon using such group (perfluorobutyro) instead of the classical chloro,[8] the enantiomeric excesses obtained for the hydrogenation of **A** and **B** with a similar diphosphine (*i.e.* (*S*)-Cp,Cy-ProNOP), could be increased significantly (91% *vs.* 81% and 89% *vs.* 77%, respectively).[10]

In a second time, the performances of the silica-immobilized complexes **5b-c** were evaluated in the hydrogenation of **A**. As it can be seen from Table 2 in which some illustrative examples are shown, the supported catalysts were less enantioselective and moreover less active than their soluble homologues **4b-c**. During the first batch, the optical yields were comparable to the homogeneous case, but upon recycling of the solid catalyst, the activity dropped significantly. We attribute this to the dimeric nature of the supported catalyst precursor for which only one unit might be immobilized on the silica, inducing leaching of both rhodium and ligand moieties. Alteration of the phosphinite residue of the ligand through reaction with free surface hydroxy groups of silica is also highly probable as evidenced by CP-MAS ^{31}P NMR and XPS analyses.[9]

Table 2. Asymmetric Hydrogenation of Ketopantolactone Catalyzed by Silica-Supported Complexes **5b-c** [a]

Run	Catalyst [R] =	Temp. (°C)	Cycle[b] (n°)	Reaction time (h)	Conv. (%)	ee (%, conf)	Leaching[c]
1	-(CH=CH)-	45	1	45	52	75 (R)	weak
	"	"	2	95	7	58 (R)	not observed
2	"	70	1	5	100	81 (R)	medium
	"	"	2	18	22	57 (R)	not observed
3	-(CF$_2$)$_3$-	20	1	4	100	91 (R)	high
	"	"	2	18	27	86 (R)	weak
	"	"	3	47	4	79 (R)	not observed .
4	"	40	1	1	100	90 (R)	high
	"	"	2	2.6	27	85 (R)	not observed
	"	"	3	18	5	65 (R)	not observed

(a) General considerations similar to those indicated for A in Table 1. Substrate/Rhodium = 100. *(b)* 1st, 2nd and 3rd runs of a same sample of catalyst. *(c)* Loss of phosphorus and rhodium as indicated by ^{31}P NMR analysis and colour of the final reaction solution.

In summary, this study shows that the asymmetric efficiency and the activity of homogeneous rhodium catalyst precursors can be rather improved by changing the nature of non chiral ligands. In particular, (μ-perfluorocarboxylato)rhodium(I) complexes exhibit very interesting properties which will be further discussed in future reports.[11] So far, the supported catalysts showed only poor efficiencies. Work is currently under progress to improve the definition of the linkage between support and complexes, by using new supporting processes and/or by using more suitable chiral mononuclear complexes.

References and Notes.

1.   For recent reviews, see : (a) H. Takaya, T. Ohta, R. Noyori, in *Catalytic Asymmetric Synthesis*; I. Ojima Ed., VCH Publishers Inc. : New York, 1993. (b) R. Noyori, in *Asymmetric Catalysis in Organic Synthesis*; J. Wiley & Sons Inc. : New York, 1994. (c) J. Seyden-Penne, *Synthèse et Catalyse Asymétriques*, InterEditions-CNRS Ed. : Paris, 1994; pp 194-199. (d) See also : K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Humobayashi, N. sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.*, **1994**, *59*, 3064.

2.   Leading reviews on supported organometallic catalysts : (a) F. R. Hartley, in *Supported Metal Complexes*; D. Reidel Publishing Co. : Dordrecht, 1985. (b) F. R. Hartley, in *The Chemistry of the Metal-Carbon Bond. The Use of Organometallic Compounds in Organic Synthesis*; F. R. Hartley Ed., J. Wiley & Sons Inc. : Chichester, 1987; vol. 4, pp 1163-1225. (c) J. Hetflejs, in *Studies in Surface Science and Catalysis*, **1986**, *27*, 497. (d) M. Capka, *Collect. Czech. Chem. Commun.*, **1990**, *55*, 2803.

3.   Achiwa has reported the asymmetric hydrogenation of ketopantolactone (A) up to 75% ee with polymer-supported Rh-BPPM catalysts : K. Achiwa, *Heterocycles*, **1978**, *9*, 1539.

4.   All the reactions were performed under a dry atmosphere of dinitrogen using classical Schlenk techniques. In a typical experiment, perfluoroglutaric anhydride **1c** (0.25 mL, 1.85 mmol) was dissolved in dry degassed THF (10 mL) and added dropwise under magnetic stirring to a THF solution (10 mL) of 1-amino-3-(triethoxysilyl)propane (409 mg, 1.85 mmol). After 30 min, a sample of the solution was analysed by NMR ($CDCl_3$) indicating the formation of **2c** in nearly quantitative yield; ^1H NMR δ : 0.62 (t, $^3J = 8$ Hz, 2H, $SiCH_2$), 1.17 (t, $^3J = 7$ Hz, 9H, CH_3), 1.66 (m, 2H, CH_2), 3.32 (m, 2H, CH_2NH), 3.78 (q, 6H, OCH_2), 7.35 (t, $^1J \sim 5$ Hz, 1H, NH); $^{13}C\{^1H\}$ NMR δ : 7.4 ($SiCH_2$), 17.9 (CH_3), 21.9 (CH_2), 42.2 (CH_2NH), 58.5 (OCH_2), 103-117 (CF_2), 158.4 and 160.2 (2 t, $^2J(CF) = 26$ and 28 Hz, NHCO and COOH). 2 mL of this solution were then introduced in a Schlenk tube containing [Rh(COD)(OMe)]$_2$ (45 mg, 0.093 mmol); the lemon yellow suspension turned rapidly to orange yellow. After 2 h of stirring, THF was evaporated under vacuum, and the resulting oily orange solid **3c** was successively washed with dichloromethane and pentane; MS-FAB$^+$: 1010.4, calculated isotopic mass for the monomer of **3c** : 1010.35. The crude complex **3c** was dissolved in toluene (10 mL) and a solution of (*S*)-Cp,Cy-ProNOP (83 mg, 0.178 mmol) in toluene (10 mL) was slowly added. The reddish solution was stirred for 1.5 h and toluene was removed at room temperature under vacuum to give **4c** as a red solid; $^{31}P\{^1H\}$ NMR, toluene δ : 111.2 (dd, J(Rh-PN) = 224.4 Hz, J(PO-PN) = 46.7 Hz), 179.2 (dd, J(Rh-PO) = 229.8 Hz); Anal. (calculated ratio) : P/Rh 1.99 (2), N/Rh 1.87 (2).

5.   U. Nagel, E. Kinzel, *J. Chem. Soc., Chem. Commun.*, **1986**, 1098.

6.   During the ring-opening of maleic anhydride **1b** by 1-amino-3-(triethoxysilyl)propane, small amounts (0-10%) of the corresponding cyclic maleimide were formed as a side-product. This product is assumed not to interfer in the subsequent reaction pathway.

7.   (a) R. Uson, L. A. Oro, J. A. Cabeza, *Inorg. Synth.*, **1985**, *23*, 126. (b) F. J. Lahoz, A. Martin, M. A. Esteruelas, E. Sola, J. Luis Serrano, L. A. Oro, *Organometallics*, **1991**, *10*, 1794. (c) J. C. Bayon, G. Net, J. Real, P. G. Rasmussen, *J. Organometal. Chem.*, **1990**, *385*, 409.

8.   (*S*)-Cp,Cy-ProNOP = (*S*)-*N*-(dicyclopentylphosphino)-2-(dicyclohexylphosphinoxymethyl)pyrrolidine. For the synthesis and some catalytic applications of this ligand, see : C. Hatat, N. Kokel, A. Mortreux, F. Petit, *Tetrahedron Lett.*, **1990**, *31*, 4139.

9.   In a typical experiment, a solution of **4b** (0.1 mmol) in toluene (20 mL) was added in a Schlenk tube containing 0.860 g of a Merck silica (Kieselgel-60) which was heated at 180°C at reduced pressure for 4h before use. The suspension was shaken (not stirred) at room temperature for 24 h. The resulting solid was filtered off, washed through several shakings in toluene for a few hours until the filtrates became colourless (7 x 5 mL) and dried under vacuum. **5b** is an orange powder. Anal. : Rh $0.8 \pm 0.1\%$; CP-MAS ^{31}P NMR : two broad signals unidentified at δ 58 and 63 ppm, and two equivalent signals at δ 103 (PN) and 155 (PO) ppm. So far, the linkage between rhodium complexes and the solid is not well defined.

10.   (a) E. A. Broger, Y. Crameri, to *F. Hoffmann-La Roche & Co.*, Eur. Pat. 218 970. (b) M. Cereghetti, J. Foricher, B. Heiser, R. Schmid, to *F. Hoffmann-La Roche & Co.*, Eur. Pat. 398 132.

11.   A. Roucoux, F. Agbossou, J.F. Carpentier, A. Mortreux, manuscript in preparation.