Tetrahedron: Asymmetry Vol. 4, No. 11, pp. 2279-2282, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

New Alkylarylamidophosphinephosphinites as Chiral Diphosphines for Asymmetric Hydrogenation of Activated Keto Compounds

Alain Roucoux, Francine Agbossou, André Mortreux*, and Francis Petit†

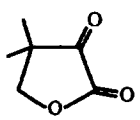
Laboratoire de Chimie Organique Appliquée de l'ENSC Lille, URA Centre National de la Recherche Scientifique 402, Université des Sciences et Technologies de Lille, BP 108, 59652 Villeneuve d'Ascq Cedex, France

(*Received in UK* 16 *July* 1993)

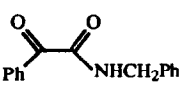
Abstract : Syntheses of new easily accessible chiral alkylarylamidophosphinephosphinite chelating ligands are described. Their rhodium complexes $[Rh(L_2^*)Cl]_2$ are highly effective precursors for the catalytic asymmetric hydrogenation of functionalized ketones. Ketopantoyllactone and N-benzylphenyl glyoxamide are converted to the corresponding alcohols up to 96 and 79.6 % ee respectively.

Considerable efforts have been devoted to the elaboration of functionalized ketones to optically active hydroxy compounds.[1] As such, increasing attention is being directed at asymmetric hydrogenation involving rhodium and ruthenium catalysts. Thus, rhodium and ruthenium complexes bearing chiral diphosphines are now readily available and offer a great variety of activities and selectivities for that reaction.[2]

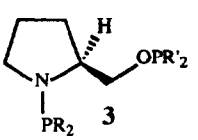
We have had an ongoing interest in the synthesis and application in asymmetric catalysis of easily accessible chiral diphosphine ligands.[3] Thus, we recently reported on the enantioselective hydrogenation of a ketoester (ketopantoyllactone)[4] (**1**) and a ketoamide (N-benzylphenylglyoxamide)[5] (**2**) in the presence of chiral diphosphine rhodium catalysts ($[Rh(COD)Cl]_2/L_2^*$) (COD : 1,5-cyclooctadiene).[6] We have described the easy synthesis of chiral bidentate aminophosphinephosphinite (AMPP) ligands bearing different substituents at the aminophosphine and phosphinite residus (general formula **3** and **4**), and we have shown that these mixed ligands were the most active and selective for the asymmetric hydrogenation of activated ketones **1** and **2**.[6]



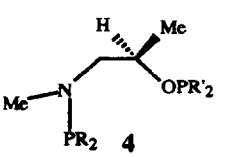
1



2



3



4

Also, we proposed that the reaction rate and the enantioselectivity of the asymmetric hydrogenation are both controlled by the phosphinamino moiety.[6a] Hence, we sought to study the synthesis and application of new closely related diphosphines with specific constraints and electronic properties in order to improve both activity

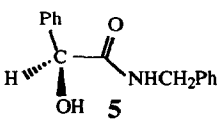
† Professor Francis Petit deceased in december 1992.

and selectivity for the hydrogenation. In this communication, we report the synthesis of new chelating diphosphine ligands derived from amidoalcohols and their use in enantioselective hydrogenation of ketones **1** and **2**.

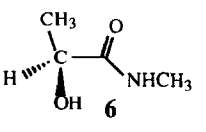
Amidoalcohols **5** and **6** were easily synthesized through standard procedures starting from (S)-(+)-mandelic acid and L-lactic acid, respectively. Then, under nitrogen, the reaction of these amidoalcohols with one equivalent of chlorodicyclopentylphosphine[7] (diethyl ether, room temperature) in presence of an excess of triethylamine and subsequently one equivalent of chlorodiphenylphosphine gave unsymmetrical diphosphines **7** and **8** as white powders in 76 and 94 % yield respectively after work up.

Commercial (S)-5-(hydroxymethyl)-2-pyrrolidinone (**9**) was similarly converted to the corresponding (S)-Cp,Ph-5-oxo-ProNOP (**10**) (scheme 1) in 85% yield by subsequent additions of chlorodicyclopentylphosphine and chlorodiphenylphosphine. Reaction of the precursor **9** with two equivalents of chlorodiphenylphosphine or chlorodicyclopentylphosphine gave the ligands (S)-Ph-5-oxo-ProNOP) (**11**) (80% yield) and (S)-Cp-5-oxo-ProNOP (**12**) (81% yield) (scheme 1). These synthesized ligands were characterized by NMR (^1H, ^{13}C and ^{31}P).[8]

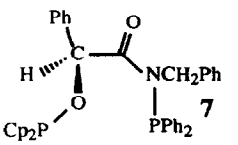
Next, optically active neutral rhodium catalysts of general formula $[Rh(L_2^*)Cl]_2$ were generated from the dimeric $[Rh(COD)Cl]_2$[9] and 2.2 equivalents of ligands **7**, **8**, **10**, **11** or **12** (PhMe, room temperature). These catalysts were prepared either in situ or isolated quantitatively as orange powders prior to catalysis. They were characterized analogously to the previously reported complexes.[6b]



5

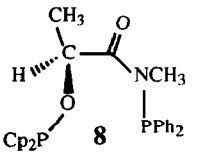


6

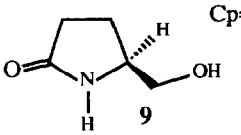


7

Cp=cyclopentyl



8

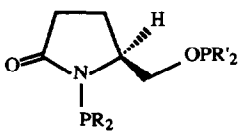


9

Asymmetric hydrogenations of **1** and **2** were carried out in toluene at a temperature ranging from room temperature to 50 °C, under hydrogen from 1 to 60 bar. The substrates were hydrogenated quantitatively in fair to high optical yields (47 - 96% ee) to the corresponding optically active alcohols (isolated in > 90% and > 95% yield, respectively). The results are summarized in table 1. The higher ee's were associated with the more basic and constraining ligand **12** (for **1** 96% ee, run 5 and for **2** 79.6% ee, run 11). As expected from our previous hypothesis[6a] related to the control of the N-PR_2 coordination site on the activity as well as the selectivity of the hydrogenation of **1**, a cyclopentyl substituted ligand (**12**) (run 5) gave similar results as compared to a ligand bearing only one cycloalkyl ligand on the P-N moiety (**10**) (run 3). Accordingly, in the presence of a less basic ligand (**11**), more drastic conditions were required to obtain reasonable reaction rates (runs 4 and 10). If we compare the asymmetric induction obtained under the same catalysis conditions with (S)-Cp-ProNOP (**3**, R=R'=Cp) based catalysts ($t_{1/2}$ = 19 mn, ee = 75.6% (R))[6b] and run 5 ($t_{1/2}$ = 17 mn, ee = 96% (R)) we observe a net increase in enantioselection. This is attributed to a higher constraint of the pyrrolidinone ring compared to the pyrrolidine ring. Nevertheless, for both ligands the activities are the same. Noteworthy is the inversion of configuration for the hydrogenated products if compared to the cyclic ligands (runs 1 and 2 vs 3 to

5 and runs 7 and 8 vs 9 to 11).

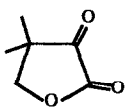
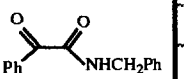
Temperature effect on the selectivity was also investigated. We could observe that the enantioselectivity increased slightly with the temperature in the hydrogenation of **1** (96% ee at 20 °C and 96.9% at 70 °C for ligand **12**). In contrast, for substrate **2**, an increase of temperature gave a decrease in ee for the hydrogenation of **2** (79.6% ee at 20 °C, 75.5% ee at 50 °C with ligand **12**). When the substrate to catalyst ratio was increased to 10000:1, there was no loss in enantioselectivity (run 6). In this case, the hydrogenation of **1** went to completion within 2 hours under 60 bar of H_2 and at room temperature (95% ee). To the best of our knowledge, the neutral rhodium complex of the new chiral ligand **12** is the most effective catalyst so far reported for the asymmetric hydrogenation of **1** (96% ee).



	R	R'
(S)-Cp,Ph-5-oxo-ProNOP (**10**)	Cp	Ph
(S)-Ph-5-oxo-ProNOP (**11**)	Ph	Ph
(S)-Cp-5-oxo-ProNOP (**12**)	Cp	Cp

Scheme 1.

Table 1 : Hydrogenation of actived ketones **1** and **2** in presence of rhodium-amidophosphiniphosphinite catalysts[a].

Substrate	Run	Ligand	P_{H_2} (bar)	T (°C)	Reaction time (h)[b]	ee (%)[c] (config.)
 **1**	1	**7**	50	50	20	90.4 (S)
	2	**8**	50	50	20	86.2 (S)
	3	**10**	1	20	26	90.7 (R)
	4	**11**	50	20	48	51.8 (R)
	5	**12**	1	20	1,2	96 (R)
	6[d]	**12**	60	20	2	95 (R)
 **2**	7	**7**	50	50	17	53.3 (R)
	8	**8**	50	50	24	70 (R)
	9	**10**	60	20	18	61 (S)
	10	**11**	50	50	19	47.4 (S)
	11	**12**	50	50	2,3	79.6 (S)

[a] Reactions were carried out by using 6.10^{-3} M of recristallized substrates in dry degassed toluene. Substrate:Rh : 200:1. For the reactions done under pressure a 100 ml stainlesss steel autoclave was used. [b] The total conversion was determined by GC for **1** and ^{1}H NMR for **2**. [c] Determined by GC analysis (FS-Cyclodex beta-I/P) for hydrogenation product of **1** and based on the specific rotation value $[\alpha]_D^{26} = +82.2$ (*c* 1.09, $CHCl_3$) for (S) - (+) - N - benzylmandelamide.[10] [d] Substrate:catalyst : 10000:1.

In summary, this study has shown the ready accessibility of new diphosphine ligands. Also, they are of considerable interest when used for high efficient asymmetric hydrogenation of ketones. The results presented confirm our previous hypothesis that activities and selectivities are both controlled by the phosphinamino moiety.[6a] New catalysts and asymmetric induction studies are under way and will be described in subsequent

reports.[11]

Acknowledgements. The authors gratefully acknowledge the "Ministère de la Recherche et de la Technologie" and the "Centre National de la Recherche Scientifique et Technique" for financial supports.

References and notes.

1. This literature is extensive. For representative reviews, see : (a) H. B. Kagan, and M. Sasaki, in "*The Chemistry of Organophosphorus Compounds*", F. R. Hartley Ed., John Wiley & Sons, **1990**,*Vol. 1*, 53 ; (b) J. C. ApSimon, and T. Lee Collier, *Tetrahedron*, **1986**, *42*, 5157 ; (c) H. B. Kagan in "*Comprehensive Organometallic Chemistry*", G. Wilkinson, Ed., Pergamon Press, Oxford, **1982**, *Vol 8*, chap. 53, p. 463 ; (d) U. Matteoli, P. Frediani, M. Bianchi, C. Botteghi, and S. Gladiali, *J. Mol. Catal*, **1981**, *12*, 265 ; (e) H. Brunner, *Synthesis*, **1988**, 645.

2. Some representative examples : (a) H. Takahashi, S. Sakuraba, H. Takeda, and K. Achiwa, *J. Am. Chem. Soc.*, **1990**, *112*, 5876 ; (b) T. Chiba, A. Miyashita, H. Nohira, H. Takaya, *Tetrahedron Lett.*, **1991**, *32*, 4745 ; (c) K. E. Koenig in "*Asymmetric Synthesis* ", J. D. Morrisson, Ed., Academic Press, New York, **1985**, *Vol 5*, p. 71 ; (d) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, and R. Noyori, *J. Am. Chem. Soc.*, **1990**, *110*, 629 ; (e) T. Okhuma, M. Kitamura, and R. Noyori, *Tetrahedron Lett.*, **1990**, *31*, 5509 ; (f) L. Shao, T. Seki, H. Kawano, and M. Saburi, *Tetrahedron Lett.*, **1991**, *32*, 7699 ; (g) M. Kitamura, T. Ohkuma, H. Takaya, and R. Noyori, *Tetrahedron Lett.*, **1988**, *29*, 1555 ; (h) R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, and H. Kumobayashi, *J. Am. Chem. Soc.*, **1989**, *111*, 9134 ; (i) K. Mashima, K.-h. Kusano, T. Ohta, R. Noyori, and H. Takaya, *J. Chem. Soc., Chem., Comm.*, **1989**, 1208 ; (j) M. Kitamura, T. Ohkuma, M. Tokunaga, and R. Noyori, *Tetrahedron : Asymmetry*, **1990**, *1*, 1 ; (k) K. Mashima, Y.-i. Matsumura, K.-h. Kusano, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, and H. Takaya, *J. Chem. Soc., Chem. Comm.*, **1991**, 609 ; (l) M. Kitamura, M. Tokunaga, T. Ohkuma, and R. Noyori, *Tetrahedron Lett.*, **1991**, *32*, 4163 ; (m) J.-P. Genet, C. Pinel, S. Mallard, S. Juge, S. Thorimbert, and J. A. Laffitte, *Tetrahedron : Asymmetry*, **1991**, *2*, 555 ; (n) L. Shao, K. Takeuchi, M. Ikemoto, T. Kawai, M. Ogasawara, H. Takeuchi, H. Kawano, and M. Saburi, *J. Organomet. Chem.*, **1992**, *435*, 133 ; (o) J.-P. Genet, C. Pinel, S. Mallard, S. Juge, N. Cailhol, and J. Laffitte, *Tetrahedron Lett.*, **1992**, *33*, 5343 ; (p) X. Zhang, T. Taketomi, T. Yoshizumi, H. Kumobayashi, S. Akutagawa, K. Mashima, and H. Takaya, *J. Am. Chem. Soc.*, **1993**, *115*, 3318.

3. (a) A. Mortreux, F. Petit, G. Buono, and G. Peiffer, *Bull. Soc. Chim. Fr.*, **1987**, *4*, 631 ; (b) C. Hatat, A. Karim, N. Kokel, A. Mortreux, and F. Petit, *Tetrahedron Lett.*, **1988**, *29*, 3675 ; (c) A. Karim, A. Mortreux, and F. Petit, *Tetrahedron Lett.*, **1986**, *27*, 345 ; (d) P. Denis, A. Jean, J.-F. Croisy, A. Mortreux, and F. Petit, *J. Am. Chem. Soc.*, **1990**, *112*, 1292 ; (e) S. Mutez, A. Mortreux, and F. Petit, *Tetrahedron Lett.*, **1988**, *29*, 1911.

4. I. Ojima, T. Kogure, and Y. Yoda, *Org. Synth.*, **1985**, *63*, 18.

5. K. Tani, E. Tanigawa, Y. Tatsuno, and S. Otsuka, *J. Organomet. Chem.*, **1985**, *279*, 87. Pantolactone is a key intermediate of pantothenic acid. D. Valentine, R. Sun, and K. Toth, *J. Org. Chem.*, **1980**, *45*, 3703.

6. (a) C. Hatat, N. Kokel, A. Mortreux, and F. Petit, *Tetrahedron Lett.*, **1990**, *31*, 4139 ; (b) C. Hatat, A. Karim, N. Kokel, A. Mortreux, and F. Petit, *New J. Chem.*, **1990**, *14*, 141.

7. The procedure used is a modification of a described one : W. Voskuil, and J. F. Arens, *Rec. Trav. Chim. Pays-Bas*, **1963**, *82*, 302.

8. Typical NMR data of the ligands are : $^{31}P\{^{1}H\}$ NMR at 32 MHz (ppm, C_7D_8) **7** : 50.8 (s, $NPPh_2$), 114.7 (s, $OPPh_2$) ; **8** : 63.7 (s, $NPPh_2$), 112.1 (s, $OPPh_2$) ; **10** : 59.4 (s, $NPPh_2$), 116.8 (s, $OPPh_2$) ; **11** : 36,2 (s, $NPPh_2$), 117.0 (s, $OPPh_2$) ; **12** : 59.3 (s, $NPPh_2$), 145.5 (s, $OPPh_2$).

9. (a) J. Chatt, and L. M. Venanzi, *J. Chem. Soc.*, **1957**, 4735 ; (b) G. Giordano, and R. H. Crabtree, *Inorg. Synth.*, **1979**, *19*, 218.

10. The specific rotation reported by Tani and al. for the optically pure (S)-(+)-N-benzylmandelamide is lower than that we obtained (see ref. 3b). K. Tani, K. Suwa, E. Tanigawa, T. Ise, T. Yamagata, Y. Tatsuno, and S. Otsuka, *J. Organomet. Chem.*, **1989**, *370*, 203.

11. A. Roucoux, F. Agbossou, A. Mortreux, and F. Petit, manuscript in preparation.