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New Chiral Mixed AMPP Ligands and their Use in Asymmetric Hydrogenation of Activated Ketones on Rhodium Catalysts

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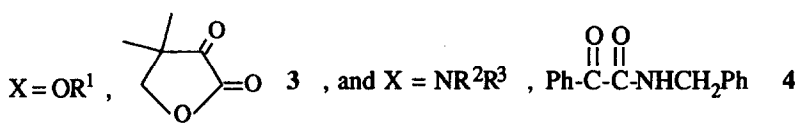
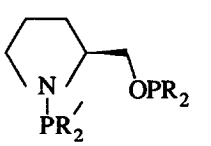
Summary - Chiral bidentate aminophosphinephosphinites (AMPP) ligands bearing different substituents at the aminophosphine and the phosphinite moieties are prepared in a one pot synthesis from aminoalcohols. Their use in asymmetric hydrogenation of activated ketones is described. Upon analysis of these results, it is suggested that the phosphinamido group governs both the activity and the enantioselectivity of this reaction.

The synthesis of alkylaminophosphinephosphinite ligands (alkyl-AMPP, **1**a,b and **2**a,b) and their application in asymmetric synthesis has recently shown their ability to hydrogenate ketones **3** and **4** (eq 1) under mild conditions with high activity and enantioselectivity on rhodium catalysts[1,2] :

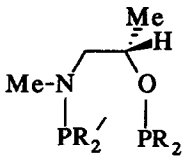


We now describe our preliminary results obtained with mixed AMPP ligands where the dialkyl substituents are different for the two phosphorus atoms (**1**c,d ; **2**c,d), and where the aminoalcohol used is either prolinol or isoalaninol.



R = R' = Cy : (S)-Cy-ProNOP **1 a**
R = R' = Cp : (S)-Cp-ProNOP **1 b**
R = Cp R'= Cy : (S)-Cy,Cp-ProNOP **1 c**
R = Cy R'= Cp : (S)-Cp,Cy-ProNOP **1d**

(Cy = cyclohexyl, Cp = cyclopentyl)



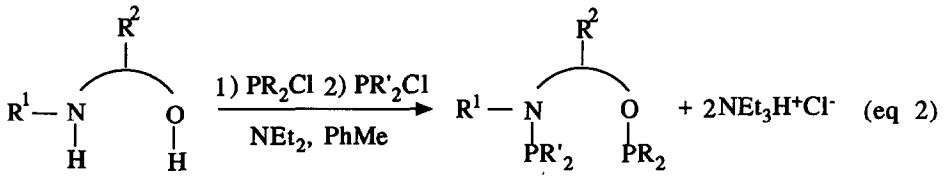
R = R' = Cy : (S)-Cy-isoAlaNOP **2 a**

R = R' = Cp : (S)-Cp-isoAlaNOP **2 b**

R = Cp, R' = Cy : (S)-Cy, Cp-isoAlaNOP **2 c**

R = Cy, R' = Cp : (S)-Cp, Cy-isoAlaNOP **2d**

The synthesis of such ligands is similar to that originally described in our previous paper[1], but uses a one pot reaction consisting in the reaction of 1 equivalent of the starting aminoalcohol, followed by the subsequent addition of 1 equivalent of the other chlorophosphine (eq 2).



(eq 2)

This method is of considerable interest since theoretically, it allows, directly from aminoalcohols, the one pot synthesis of new ligands, whose number is only limited by the availability of the dialkylchlorophosphines, as aminoalcohols could be easily synthesized in three steps from natural aminoacids[3].

Ligand synthesis

In a typical experiment, (S)-Cp,Cy-ProNOP **1c** is prepared as follows : 5mmol (1,023g) of PCp_2Cl and 5ml of triethylamine are added under N_2 in a solution of 5 mmol (0.505g) of (S)-prolinol dissolved in 40ml of anhydrous ether. The reaction mixture is stirred at room temperature for 16 hours. The resulting aminophosphinite intermediate is characterized by $^{31}P\{^1H\}$NMR spectroscopy (δ = 141,9ppm).

To the previous mixture, 4.8mmol (1,116g) of PCy_2Cl dissolved in 20ml of anhydrous ether are added dropwise under nitrogen at room temperature ; stirring is continued at the same temperature for 12 hours. After removal of the solvent, the crude product is filtered on basic and dry alumina to remove the chlorhydrate byproduct, and eluted with ether. After removal of the solvent, pure **1c** is obtained as a colorless oil (4.4 mmol, 92%) and characterized by $^{31}P\{^1H\}$NMR spectroscopy : (δ = 57.0 and 146.6ppm *vs*-H_3PO_4). This product can be used without further purification.

This simple synthesis contrasts with previous preparations of mixed diphosphine ligands described earlier by Achiwa, using a method which necessitates numerous steps (~10) from natural compounds, and is also limited only to phenyl and cyclohexyl group combinations[4,5].

Catalytic results

The results obtained during asymmetric hydrogenation of **3** with these new ligands are listed in table 1.

Table 1 : Asymmetric hydrogenation of **3** on $[Rh(COD)Cl]_2$-AMPP catalysts[a].

Entry	Ligand		$T_{1/2}$ (mn.)	Reaction time(h)	ee%(conf.)[b]
1	(S)-Cy-ProNOP	**1 a**	27	12	47(R)
2	(S)-Cp-ProNOP	**1 b**	19	1	76(R)
3	(S)-Cy,Cp-ProNOP	**1 c**	15	1.3	41(R)
4	(S)-Cp,Cy-ProNOP	**1 d**	10	1	81(R)
5	(S)-Cy-isoAlaNOP	**2 a**	13.5	1.3	80(S)
6	(S)-Cp-isoAlaNOP	**2 b**	8.5	0.5	89(S)
7	(S)-Cy,Cp-IsoAlaNOP	**2 c**	12	1.3	78(S)
8	(S)-Cp,Cy,-IsoAlaNOP	**2 d**	7	0.5	89(S)

[a] The catalysts are prepared *in situ* from $[Rh(COD)Cl]_2$ and 2 equivalents of ligand. All reactions were conducted with 12 mmol of substrate in 30 ml of anhydrous toluene under 1 atm of H_2 at 20°C with a substrate/catalyst ratio of 200. [b] Optical yields were calculated on the basis of the reported optical rotation for the optically pure products : (R)-pantolactone, $[\alpha]_D^{25}$ = -50.7°(c 2.05, H_2O)[6] ; they were confirmed by GLC analysis, on a CS-Fused silica capillary column (25m, 0.25mm), coated with heptakis (2,3,6-tri-O-methyl)-beta-cyclodextrine/polysiloxane.

From a comparaison between the results observed with **1a** and **1b** *versus* **1c** and **1d** on ketopantolactone **3**, it appears that the presence of the cyclopentyl group on the (P-N) moiety increases significantly both the activity and the enantioselectivity (**1d>1c**).

This observation confirms the hypothesis according to which the phosphinamido group would control the activity as well as the enantioselectivity in this reaction, as an alkyl-AMPP ligand gives similar results as those obtained on a mixed AMPP bearing only the same alkyl substituent on the P-N group and not on the phosphinite group.

These results are confirmed upon using another series of mixed AMPP ligands synthesized from isoalaninol **2**a-d : the best ee's and reaction rates are again obtained with the mixed ligand bearing a dicyclopentylaminophosphine group. In this case, ee's up to 89% are attained, in a configuration opposite to that obtained on ligands **1**a-d.

Although this effect is not so well established during asymmetric hydrogenation of N-benzylbenzoylformamide **4**, due to the fact that ee's are almost of the same order (~74 to 80%) a similar trend is also observed using **1a** to **1d** ligands for this reaction (table 2).

Table 2 Asymmetric hydrogenation of **4** on $[Rh(COD)Cl]_2$ - AMPP catalysts [a].

Entry	Ligand	$T_{1/2}$ (mn.)	Reaction time(h)	ee%(conf.)[b]
9	(S)-Cy-ProNOP **1 a**	19	1.5	74(S)
10	(S)-Cp-ProNOP **1 b**	5	0.2	79.5(S)
11	(S)-Cy,Cp-ProNOP **1 c**	15.5	2	74(S)
12	(S)-Cp,Cy-ProNOP **1 d**	9.5	1.3	77(S)

[a] Conditions: see table 1. [b] Determined on the basis of the optical rotations of the enantiomerically pure (S)-$PhCH(OH)CONHCH_2Ph$, $[\alpha]_D^{26}$ = +82 (c 1.09, $CHCl_3$)

The above results are in contrast with previous hypothesis by Achiwa, who has shown that with unsymmetrized ligands derived from DIOP, one phosphine group controls the enantioselectivity of asymmetric hydrogenation and the other accelerates its reaction rate[4].

Further studies are continuously under way to try to define the mechanistic implications of the effect of the dissymmetry of these new ligands according to our initial hypothesis on the mechanism of this asymmetric synthesis conducted with $(alkyl)_2$-AMPP bidentates.[2]

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