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Rhodium(I) Bis(aminophosphane) Complexes as Catalysts for Asymmetric Hydrogenation of Activated Ketones.

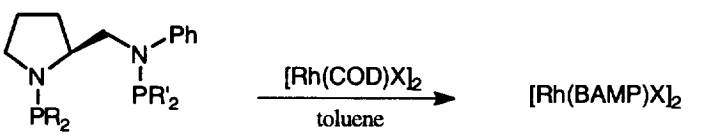
Alain Roucoux, Isabelle Suisse, Marc Devocelle, Jean-François Carpentier, Francine Agbossou* and André Mortreux*

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

Abstract: The synthesis of new homochiral bis(aminophosphanes) (BAMP) **1**—**5** and their application in rhodium based asymmetric hydrogenation of dihydro-4,4-dimethyl-2,3-furandione **12** and *N*-benzylbenzoylformamide **14** are presented. Under mild conditions, the hydrogenations led to high enantiomeric excesses (up to 87% and 75% ee respectively for both substrates).

Asymmetric hydrogenation of prochiral substituted ketones, mainly by use of chiral Rh(I) and Ru(II) catalysts, is one of the most active research area of asymmetric organometallic catalysis.[1] For such reactions, C_2 symmetric diphosphine ligands have played a predominant role. However, recent works have highlighted the contribution of non C_2 symmetric diphosphines and of unequivalently substituted diphosphines.[1a, 2]

In earlier reports, we described the easy synthesis of non C_2 symmetric chiral diphosphines (AMPP) derived from α-amino and α-amido alcohols and their successful application in asymmetric transformations.[2] During the course of our studies, we extended our research towards the synthesis and the properties of new bis(aminophosphanes) (BAMP). Such type of phosphines has been only little studied, essentially in association with rhodium(I) complexes for the hydrogenation of activated olefins.[3] Here we wish to report the preparation of new homochiral bis(aminophosphanes) and their use as ligand in rhodium-catalysed asymmetric hydrogenation of activated ketones.



(BAMP)

$R = C_6H_5$	$R' = C_6H_5$	(*S*)-Ph,Ph-ProNN'P **1**	X = Cl	**6**	
C_5H_9	C_5H_9	(*S*)-Cp,Cp-ProNN'P **2**	Cl	**7**	
C_6H_{11}	C_6H_{11}	(*S*)-Cy,Cy-ProNN'P **3**	Cl	**8**	
C_5H_9	C_6H_5	(*S*)-Cp,Ph-ProNN'P **4**	Cl	**9**	$X = CF_3CO_2$ **11**
C_6H_{11}	C_6H_5	(*S*)-Cy,Ph-ProNN'P **5**	Cl	**10**	

All the BAMP ligands were synthesised starting from commercial (*S*)-2-(anilinomethyl)pyrrolidine. The bis(aminophosphane) (*S*)-Ph,Ph-ProNN'P **1** was prepared following the general procedure described

earlier for AMPP using chlorodiphenylphosphine.[4,5] Unfortunately, this typical procedure could not be used for the synthesis of ligands bearing dialkylphosphino groups due to the non reactivity of the —NHPh residue towards the PR_2Cl - NEt_3 combination. Consequently, the diamino precursor was first reacted in diethyl ether with 2.2 eq. of BuLi at 0 °C and then with 2.2 eq. of chlorodicyclopentylphosphine to give after workup (*S*)-Cp,Cp-ProNN'P **2**[5] in 85% yield. (*S*)-Cy,Cy-ProNN'P **3**[5] was obtained in a similar way in 80% yield. Other BAMP ligands bearing two different phosphino groups were synthesised following a previously described two steps procedure.[2b] Accordingly, (*S*)-Cp,Ph-ProNN'P **4**[5] and (*S*)-Cy,Ph-ProNN'P **5**[5] were isolated in 72% and 70% yield, respectively.

The catalyst precursors $[Rh\{BAMP\}Cl]_2$ were prepared *in situ* through reaction of $[Rh(COD)Cl]_2$[6] with 2.2 eq. of ligands **1**—**5** giving the corresponding complexes **6**—**10** (Scheme).[7] A trifluoroacetato complex **11** was obtained through reaction of $[Rh(COD)(OCOCF_3)]_2$[8] with 2.2 eq. of ligand **4**.[2a,7] These *in situ* prepared precursors were applied in the asymmetric hydrogenation of two activated ketones, *i.e.* dihydro-4,4-dimethyl-2,3-furandione **12** and *N*-benzylbenzoylformamide **14** into pantolactone **13** and *N*-benzylmandelamide **15**, respectively. The results are summarized in Table 1 (entries 1—8) and Table 2 (entries 10—16). Two previously reported results are also presented (entries 9 and 17) for comparison.

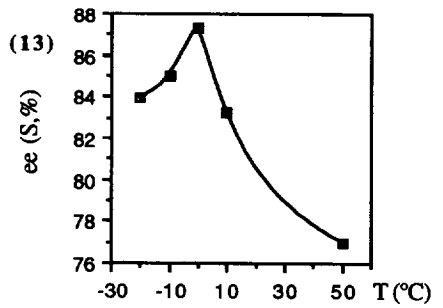
Table 1. Asymmetric Hydrogenation of dihydro-4,4-dimethyl-2,3-furandione **12**.[a]

Entry	Ligand	X (Complex)	$P(H_2)$ (atm), T (°C)	$t_{1/2}$ (min)[b]	time (h)[c]	ee (**13**) (%, conf)[d]
1	(*S*)-Ph,Ph-ProNN'P **1**	Cl **6**	50, 50	nd	18	33 (*R*)
2	(*S*)-Cp,Cp-ProNN'P **2**	Cl **7**	1, 20	5.5	0.2	70 (*S*)
3	(*S*)-Cy,Cy-ProNN'P **3**	Cl **8**	1, 20	nd	7	69 (*S*)
4	(*S*)-Cp,Ph-ProNN'P **4**	Cl **9**	1, 20	90	8	80 (*S*)
5	(*S*)-Cp,Ph-ProNN'P **4**	CF_3CO_2 **11**	1, 20	4.5	0.4	83 (*S*)
6	(*S*)-Cy,Ph-ProNN'P **5**	Cl **10**	1, 20	nd	48	62 (*S*)
7	(*S*)-Cp,Ph-ProNN'P **4**	Cl **9**	1, 50	19	2	78 (*S*)
8	(*S*)-Cp,Ph-ProNN'P **4**	Cl **9**	1, 70	13	4	64 (*S*)
9	(*S*)-Cp,Cp-5-oxo-ProNOP[e]	Cl	1, 20	17	1.2	96.0 (*R*)

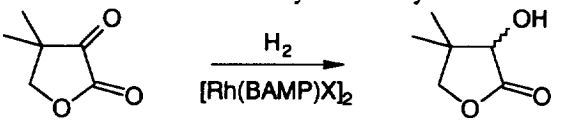
[a]Reactions were carried out by using 12 mmol of recrystallized substrate in 30 mL of dry degassed toluene under 1 or 50 atm of hydrogen. Substrate/Rh : 200/1. [b]Time for 50% conversion; nd: not determined. [c]The total conversions were determined by GC. Every reaction time was not necessarily optimized. [d]Determined by GC analysis (FS-Cyclodex β-I/P) of **13**. [e]taken from reference 2a.

Except for the ligand bearing two diphenylphosphino groups (entries 1 and 10), as already observed,[2a] activated ketones **12** and **14** were hydrogenated quantitatively in toluene under mild conditions (room temperature, 1 atm of hydrogen) to the corresponding alcohols. The highest ee's (80—83% ee) were obtained for the rigid substrate **12** with chloro- and trifluoroacetato-rhodium complexes of ligand **4** (entries 4 and 5). The hydrogenation of **12** has already been presented with such type of ligand but with the *N*-methyl analogue of **3** and a 52% ee was reported for the hydrogenation product **13**.[10] Interestingly, the enantioselectivity could be improved with complex **9** by lowering the temperature but, as depicted in the graph, the evolution of ee's with temperature was not monotone, since a maximum of 87 % ee was reached at 0 °C. Such a surprising behavior has never been observed with the related AMPP

rhodium complexes.[2] This could be due, in our opinion, to the existence in this temperature range of several catalytic species reacting simultaneously with their own enantioselectivity and activity.

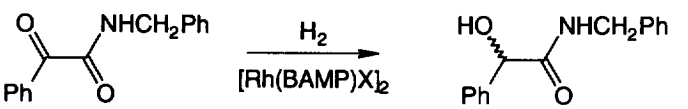


Effect of Reaction Temperature on the Enantioselective Hydrogenation of 12
(complex [9], S/Rh = 200, P = 50 atm)



12 **13**

Interestingly, for both substrates, we observed hydrogenated products of opposite configurations by replacing a phenyl group by a cycloalkyl group[2b] at the phosphorus atoms (entries 4 and 6 *vs.* entry 1 for **13** ; entries 13 and 16 *vs.* 10 for **15**). Fully alkylated ligands conducted also to opposite configurations when compared to phenyl substituted ligands (entries 2 and 3 *vs.* 1 for **13** ; entries 11 and 12 *vs.* 10 for **15**). Such a reversal of product configuration was also reported in going from tetra aryl to tetra cycloalkyl substituted C_2 symmetrical diphosphines.[11]



14 **15**

Table 2. Asymmetric Hydrogenation of *N*-benzylbenzoylformamide **14**.[a]

Entry	Ligand	Complex X =	P(H2) (atm), T (°C)	$t_{1/2}$ (min)[b]	time (h)[c]	ee (**15**) (%, conf)[d]
10	(*S*)-Ph,Ph-ProNN'P **1**	Cl **6**	50, 50	nd	18	17 (*S*)
11	(*S*)-Cp,Cp-ProNN'P **2**	Cl **7**	1, 20	< 10	2	72 (*R*)
12	(*S*)-Cy,Cy-ProNN'P **3**	Cl **8**	1, 20	< 10	7	42 (*R*)
13	(*S*)-Cp,Ph-ProNN'P **4**	Cl **9**	1, 20	77	6.5	75 (*R*)
14	(*S*)-Cp,Ph-ProNN'P **4**	Cl **9**	1, 50	10	1.7	72 (*R*)
15	(*S*)-Cp,Ph-ProNN'P **4**	CF_3CO_2 **11**	1, 20	nd	7	66 (*R*)
16	(*S*)-Cy,Ph-ProNN'P **5**	Cl **10**	1, 20	5	28	56 (*R*)
17	(*S*)-Cp,Cp-5-oxo-ProNOP[e]	Cl	1, 20	30	2.3	80 (*S*)

[a]Reactions were carried out by using 12 mmol of recrystallized substrate in 30 mL of dry degassed toluene under 1 or 50 atm of hydrogen. Substrate/Rh: 200/1. [b]Time for 50% conversion; nd: not determined. [c]The total conversions were determined by ^{1}H NMR. Every reaction time was not necessarily optimized. [d]Based on the specific rotation value $[\alpha]_D^{26}$ = + 82.2 (*c* 1.09, $CHCl_3$) for (*S*)-(+)-*N*-benzylmandelamide **15**.[9, 2a] [e]taken from reference 2a.

In agreement with our previous conclusions relative to rhodium-based asymmetric hydrogenations, the enantioselectivity seems to be mainly controlled by the pyrrolidinic aminophosphine residue.[2b] More, although less easily accessible, bis(aminophosphane) rhodium complexes exhibit similar activities and

enantioselectivities than their aminophosphine-phosphinite counterparts. In conclusion, BAMP ligands can also be considered as good candidates for the asymmetric hydrogenation of ketones, as they are for hydrogenation of prochiral dehydroamino acid derivatives.[3]

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5. Typical $^{31}P\{^{1}H\}$ NMR data of ligands (121 MHz, $C_6D_5CD_3$, ppm): **1** : 44.9 (s), 64.7 (s); **2** : 55.9 (s), 83.6 (s); **3** : 52.1 (s), 82.7 (s); **4** : 54.4 (s), 64.6 (s); **5** : 51.4 (s), 64.8 (s).

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7. All the complexes prepared *in situ* by reaction between $[Rh(COD)Cl]_2$ and BAMP were checked by ^{31}P NMR prior to catalysis, and presented typical spectra as two doublets of doublets, due to the non equivalence of the phosphorus atoms and coupling with ^{103}Rh. A similar behavior is also observed for the $[Rh(COD)(OCOCF_3)]_2$ complex. Typical $^{31}P\{^{1}H\}$ NMR data (121 MHz, $C_6D_5CD_3$, ppm): **6** : δ 87.3 (dd, J(Rh-PN) = 204.7 Hz, J(PN-PN') = 39.4 Hz), 106.8 (dd, J(Rh-PN) = 221.5 Hz, J(PN-PN') = 39.4 Hz); **9** : δ 89.7 (dd, J(Rh-PN) = 200.8 Hz, J(PN-PN') = 39.4 Hz), 106.7 (dd, J(Rh-PN) = 228.4 Hz, J(PN-PN') = 39.4 Hz); **10** : δ 93.8 (dd, J(Rh-PN) = 200.8 Hz, J(PN-PN') = 33.4 Hz), 109.6 (dd, J(Rh-PN) = 231.1 Hz, J(PN-PN') = 33.4 Hz).

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