Asymmetric Hydrogenation of α, β, and γ-Aminoketones Catalyzed by Cationic Rhodium(I){AMPP} Complexes

Marc Devocelle, Francine Agbossou*, André Mortreux

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

FAX 33 3 21 43 65 85; e-mail agbossou@pop.univ-lille1.fr

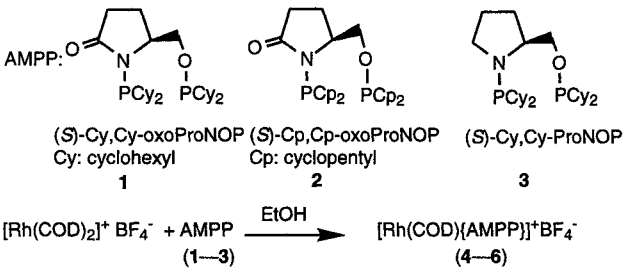
Received 11 July 1997

Abstract: The chiral cationic rhodium aminophosphine-phosphinite complexes **4—6** were applied successfully in the asymmetric hydrogenation of α- (**7—9**), β- (**10**, **11**) and γ- (**12**) aminoketone hydrochloride derivatives leading to the corresponding aminoalcohols in up to 97, 93, and 92 % enantiomeric excesses for the three types of substrates respectively.

Various biologically relevant compounds are synthesized from optically active alcohols bearing a neighbouring functional group. Consequently, the enantioselective hydrogenation of functionalized ketones to secondary alcohols has attracted much interest.[1] Among such hydrogenation products, chiral aminoalcohols are potent agents with important pharmacological activities. The preparation of optically active aminoalcohols has been reported using asymmetric hydrogenation of prochiral aminoketones catalyzed by chiral ruthenium[2] and rhodium[3] bisphosphine complexes.

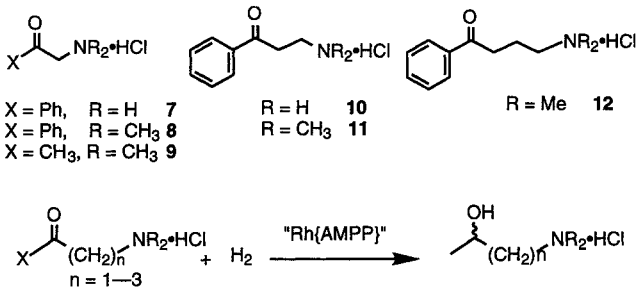
We have reported recently the hydrogenation of prochiral functionalized ketones catalyzed by rhodium aminophosphine-phosphinite complexes.[4] We have shown also the efficiency of peralkylated diphosphines during the hydrogenation of 2-aminoacetophenone hydrochloride.[5] In further investigations, we sought to study related cationic "rhodium(I){AMPP}" catalysts and extend their use in the reduction of other aminoketones as well. Here, we report the asymmetric hydrogenation of α-, β- and γ-aminoketone hydrochloride derivatives catalyzed by rhodium(I) complexes bearing peralkylated diphosphines.

The three AMPP ligands used in this study i.e. (*S*)-Cy,Cy-oxoProNOP **1**, (*S*)-Cp,Cp-oxoProNOP **2**, and (*S*)-Cy,Cy-ProNOP **3** were prepared according to previously reported procedures (Scheme 1).[4] The corresponding optically active cationic rhodium precatalysts [Rh(I){AMPP}(COD)]BF_4 **4—6** were synthesized prior to catalysis by reaction of $[Rh(COD)_2]BF_4$[6] with 1.1 equivalents of the appropriate diphosphine in ethanol at room temperature (Scheme 1). They were applied in asymmetric hydrogenation of α- , β- , and γ- aminoketones (**7—12**) (Scheme 2).[7] The catalytic results are summarized in Tables 1 (runs 1—11) and 2 (runs 12—19). For comparison, Table 1 contains also, in runs 1—3, data obtained earlier with neutral precatalysts applied in the hydrogenation of substrate **7**. All asymmetric hydrogenations proceeded smoothly in methanol either at room temperature or at 50 °C under an initial hydrogen pressure of 50 bar and in the presence of 0.5 mol % of rhodium precatalysts. The chiral aminoalcohols were produced in high yields.



Scheme 1

As can be seen from both Tables 1 and 2, the cationic rhodium complexes **4** and **5**, bearing the AMPP ligands **1** and **2**, respectively, give higher enantioselectivities (83—97% ee) than complex **6** (62—77% ee). A similar behaviour was already observed with neutral Rh(I){AMPP} catalysts during the hydrogenation of other functionalized ketones.[4] We proposed earlier[5] that when the hydrogenations were carried out in methanol in the presence of neutral precatalysts, the resulting active species might be cationic. Consequently, any effect provided by an anionic ligand (i.e. $OCOCF_3$) was expected to be lost here. In fact, when comparing runs 1 and 2, conducted with the neutral chloro- and trifluoroacetato-Rh catalysts, respectively, with run 4, based on the cationic precatalyst **4**, we measured the same enantioselectivity (93% ee) in agreement with the proposed hypothesis. Moreover, when comparing the half reaction times, we can see that the precatalysts are producing the corresponding active species in the following qualitative rate order "Rh^+" ≈ "$Rh(OCOCF_3)$" > "RhCl". Also, the fact that both cationic and trifluoroacetato precursors are giving quite close half reaction times is attributed to the equal ease of formation of the active species from the two complexes, when compared to the neutral chloro rhodium precursor. Nevertheless, in the case of the *m*-chloro substituted substrate **7**, the hydrogenation rate increased further by a factor of three when using the cationic precursor **4** rather than the corresponding trifluoroacetato complex (half reaction time of 10 min and 30 min respectively). Thus, the use of cationic precursors can be relevant for an industrial purpose. The difference in enantioselectivity induced by both ligands **1** and **2** for substrate **7** (runs 3 and 4) is not observed for substrates **8** and **9** (run 6 *vs* 5 and run 9 *vs* 7).



Scheme 2

The presence of cyclohexyl groups on the phosphorous atoms (**1**) induced a slightly higher enantioselectivity than cyclopentyl moieties (**2**) for the hydrogenation of the β-aminoketone **11** (Table 2, run 16 *vs* 13). However, the enantioselectivities, even if lower than those obtained for the hydrogenation of α-aminoketones remained good. The catalytic activity is strongly affected by the β-substitution. For example, at 20 °C and under 50 bar of H_2 full conversion was not reached in 45 h of reaction (run 13). Thus, the reaction is more conveniently performed at a higher temperature without an important decrease of enantioselectivity (run 14). Also, for the β-(*N*,*N*-dialkylamino)alkyl aryl ketone **11**, a β-elimination process takes place under the reaction conditions. This undesired competing reaction[9] is favoured by a temperature increase

Table 1. Asymmetric Hydrogenation of the α-Aminoketone Hydrochloride Derivatives **7—9** [a]

run	subst.	complex	AMPP	temp. (° C)	$t_{1/2}$ (h)	time[b] (h)	ee (%)[c] (config.)
1	**7**	*d, e*	**1**	20	2	7	93 (*S*)
2	**7**	*d,f*	**1**	20	1	5	93 (*S*)
3	**7**	*d, g*	**2**	20	1.5	5	83 (*S*)
4	**7**	**4**	**1**	20	1	5	**93** (*S*)
5	**8**	**4**	**1**	20	1	5	**96** (*S*)
6	**8**	**5**	**2**	20	nd[h]	17	96 (*S*)
7	**9**	**4**	**1**	20	1.5	5	**97** (*S*)
8	**9**	**4**	**1**	50	nd[h]	6	91 (*S*)
9	**9**	**5**	**2**	20	1.5	16	97 (*S*)
10	**9**	**6**	**3**	20	22	112	72 (*S*)
11	**9**	**6**	**3**	50	nd[h]	20	65 (*S*)

[a]The reactions were carried out by using 1-1.5 mmol of recrystallized substrate, 0.1 M in dry degassed methanol under 50 atm of hydrogen. Substrate/Rh : 200/1. [b]The conversions were determined by ^{1}H NMR and were complete for all the runs reported. Reaction times were not optimized. [c]Determined by HPLC analysis (chiralcel OD (Daicel)) of the free aminoalcohol obtained from **7** and of the resulting *N*-benzoyl aminoalcohol for **8**, determined on the basis of the specific rotation value $[\alpha]_D$ = - 44.5 (*c* 1, MeOH) for (*R*)-(-)-1-dimethylamino-2-propanol hydrochloride[8] for **9**. [d]Taken from ref. 5. [e]Precatalyst [Rh{(*S*)Cy,Cy-oxoProNOP}Cl]$_2$. [f]Precatalyst [Rh{(*S*)Cy,Cy-oxoProNOP}(OCOCF$_3$)]$_2$. [g]Precatalyst [Rh{(*S*)Cp,Cp-oxoProNOP}(OCOCF$_3$)]$_2$. [h]Not determined

(run 14) or , as expected, by the presence of a base such as triethylamine (run 15). The intermediate vinylketone is formed and is further hydrogenated and propiophenone is observed at the end of the reaction. The presence of triethylamine had no relevant effect on the enantioselectivity of the catalysts (runs 15 *vs.* 14). The catalysts derived from **4** is also active in the hydrogenation of the γ-aminoketone **12** (run 19). Interestingly, the enantioselectivity remains as high as for substrate **11**. In fact, a 92% ee was obtained at 80 °C (run 19).

From the results presented in Tables 1 and 2, it appears that cationic rhodium (I) amidophosphine-phosphinite complexes **4** and **5** exert efficient asymmetric induction in the hydrogenation of aminoketone hydrochloride derivatives, whereas the aminophosphine-phosphinite complex **6** is less effective in terms of activity as well as of enantioselectivity. From the two (*S*)-5-(hydroxymethyl)-2-pyrrolidinone derived ligands **1** and **2**, the dicyclohexylphosphino-substituted one has been the most successfull in order to achieve the highest chiral multiplication. The use of the enantioselective aminoketone hydrogenation in the asymmetric synthesis of an optically pure drug will be reported in the near future.[10]

Acknowledgements. The authors gratefully thank Prof. Dr. Bertrand Castro and Dr. Jean-Robert Dormoy from Elf Sanofi (Gentilly, France) for helpful discussions and both Elf Sanofi and the "Centre National de la Recherche Scientifique" for financial support.

References and Notes

(1) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994; Chapter 2, p 56. (b) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH Publishers, Inc.: New York, 1993; Chapter 1.

(2) Kitamura, M.; Okuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629.

(3) (a) Hayashi, T.; Katsumura, A.; Konishi, M.; Kumada, M. *Tetrahedron Lett.* **1979**, 425. (b) Hayashi, T; Mise, T.; Kumada, M. *ibid.* **1976**, 4351. (c) Toros, S.; Kollar, L.; Heil, B.; Marko, L. *J. Organomet. Chem.* **1982**, *232*, C17. (c) Takahashi, H.; Sakuraba, S.; Takeda, H.; Achiwa, K. *J. Am. Chem. Soc.* **1990**, *112*, 5876. (d) Takeda, H.; Hosokawa, S.; Aburatani, M.; Achiwa, K. *Synlett* **1991**, 193. (e) Takeda, H.; Tachinami, T.; Aburatani, M.; Takahashi, H.; Motimoto, T.; Achiwa, K. *Tetrahedron Lett.* **1989**, *30*, 363. (f) Sakuraba, S.; Nakajima, N.; Achiwa, K. *Tetrahedron : Asymmetry* **1993**, *4*, 1457. (g) Sakuraba, S.; Achiwa, K. *Synlett* **1991**, 689. (h) Sakuraba, S.; Nakajima, N.; Achiwa, K. *Synlett* **1992**, 829.

(4) (a) Agbossou, F.; Carpentier, J.-F.; Hatat, C.; Kokel, N.; Mortreux, A.; Betz, P.; Goddard, R.; Krüger, C. *Organometallics* **1995**, *14*, 2480. (b) Roucoux, A.; Suisse, I.; Devocelle, M.; Carpentier, J.-F.; Agbossou, F.; Mortreux, A. *Tetrahedron: Asymmetry* **1996**, *7*, 379. (c) Roucoux A., Thieffry L., Carpentier J.-F., Devocelle M., Meliet C., Agbossou F., Mortreux A. *Organometallics* **1996**, *15*, 2440.

(5) Roucoux, A.; Devocelle, M.; Carpentier, J.F.; Agbossou, F.; Mortreux, A. *Synlett* **1995**, 358.

(6) Complex [Rh(COD)$_2$]BF$_4$ is commercially available.

Table 2. Asymmetric Hydrogenation of β- and γ-Aminoketone Hydrochloride Derivatives **10—12** [a]

run	substr.	complex	AMPP	temp. (° C)	time[b] (h)	conv.[c] (%)	selectivity[d] (%)	ee (%)[e] (config.)
12	**10**	**4**	**1**	50	21.5	94	100	85 (*R*)
13	**11**	**4**	**1**	20	45	95	95	**93** (*R*)
14	**11**	**4**	**1**	50	22	100	88	89 (*R*)
15	**11**	**4**[f]	**1**	50	18	96	19	87 (*R*)
16	**11**	**5**	**2**	20	26	87	96	85 (*R*)
17	**11**	**6**	**3**	20	44	59	64	77 (*R*)
18	**11**	**6**	**3**	50	16	77	nd[g]	62 (*R*)
19	**12**	**4**	**1**	80	40	96	100	92 (*R*)

[a]Conditions see Table 1, except substrate : 1-2.5 mmol. [b]Reaction times were not optimized. [c]Determined by ^{1}H NMR. [d]% hydrogenation/% β-elimination, determined by ^{1}H NMR. [e]Determined by ^{1}H and ^{19}F NMR of the Mosher derivative of the resulting *N*-benzoyl aminoalcohol for **10**; determined by HPLC analysis (chiralcel OD (Daicel)) of its free amine for **11**, and determined by ^{1}H and ^{19}F NMR of the Mosher derivative of the resulting aminoalcohol for **12**. [f]Addition of triethylamine, NEt$_3$ / Rh : 5 / 1. [g]Not determined

(7) Substrates **7**, **9** and **11** were commercially available. The synthesis of **8** was adapted from Chapman, N. B.; Clarke, K.; Harvey, D. J. *J. Chem. Soc. (C)* **1971**, 1202. The syntheses of **10** and **12** were adapted from ref 3h.

(8) Sullivan, H. R.; Beck, J. R.; Pohland, A. *J. Org. Chem.* **1963**, *28*, 2381.

(9) Heating a 0.1M solution of **11** in methanol under 50 atm of hydrogen at 50 °C during 22 h leads to 71 % of β-elimination.

(10) Devocelle, M.; Agbossou, F.; Mortreux, A. manuscript in preparation.