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Rhodium-catalyzed reduction of α-amino acid precursors using chiral 4-(diphenylphosphanyl)-1-(dialkylamino)butane ligands

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Abstract

The enantioselectivity of the hydrogenation of some unsaturated amino acids using rhodium complexes in association with chiral 4-(diphenylphosphanyl)-1-(dialkylamino)butane ligands is higher (ee values of up to 60%) in water as the solvent in the presence of SDS than in methanol. © 2000 Elsevier Science S.A. All rights reserved.

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1. Introduction

Since the pionneering work of Knowles [1] and Horner [2] on homogeneous asymmetric hydrogenation with rhodium complexes bearing chiral tertiary phosphanes, this methodology is becoming one of the most attractive approaches to optically active compounds. Most of the ligands giving very high enantioselectivities (> 95% ee) in the reduction of α-aminoacid precursors are diphosphanes with chirality at the phosphorus or on the carbon backbone, diphosphinites, bis(aminophosphines), or aminophosphine-phosphinites [3–10]. However while P,N-based ligands have been successfully employed in asymmetric allylic alkylation [11–15] or in Grignard cross-coupling reactions [16–19] giving very high enantioselectivities, the use of such ligands in asymmetric hydrogenation is limited, the highest enantioselectivity obtained being 71% in the reduction of α-acetamidocinnamic acid [20–25].

We recently reported the synthesis of new chiral 4-(diphenylphosphanyl)-1-(dialkylamino)butane ligands **3** derived from tartaric acid (Scheme 1). In association with palladium, they gave enantioselectivities of up to 68% in asymmetric allylic alkylation [26]. In this paper we describe the evaluation of these ligands in the reduction of some unsaturated amino acid precursors.

2. Results and discussion

We first investigated the reduction of (*Z*)-2-acetamidocinnamic acid (**1a**) in methanol in the presence of a rhodium complex prepared from $[Rh(COD)_2]PF_6$ and the aminophosphane (**3**) (Scheme 1). It is to be noticed that the ^{31}P-NMR spectrum of the compound obtained by mixing $[Rh(COD)_2]PF_6$ and ligand **3a** exhibited a doublet at δ 24.2 ppm with a coupling constant $J_{Rh-P} =$ 148 Hz.

The highest enantioselectivity (57% ee) was obtained using **3e** as the chiral ligand (Table 1, entry 9). Concerning the use of 4-(diphenylphosphanyl)-1-(phenylamino)butane, higher enantioselectivities were obtained with ligand **3b** and **3c**, where the nitrogen bears two different substituents, compared to ligand **3a** which has two identical phenyl groups on the nitrogen (Table 1, entries 1, 2, and 5). However, ligand **3d** gave a very low enantioselectivity (Table 1, entry 8). The same trends were observed in the reduction of methyl (*Z*)-acetamidocinnamate (**1b**) with enantioselectivity of up to 37% using ligand **3c** (Table 1, entry 15).

The higher efficiency of the ligands **3b** and **3c**, bearing different substituents at the nitrogen atom, could be

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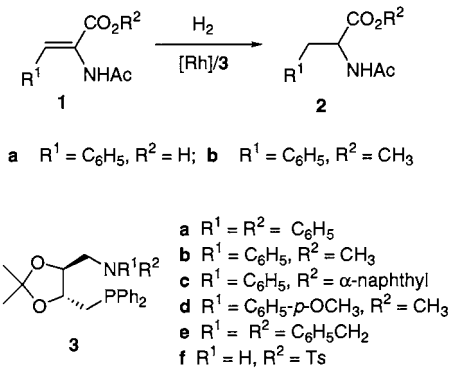


Scheme 1.

due to the formation of a stereogenic center at nitrogen by coordination to the rhodium. Perhaps the diastereomeric species giving the highest enantioselectivity is also the more active in the reduction. However, since a low enantioselectivity was obtained using ligand **3d**, the basicity of the nitrogen seems also crucial for the obtention of good enantioselectivity.

We noticed that the complexes are not very stable in methanol and that metallic rhodium precipitates rapidly, probably due to the very weak complexation of the nitrogen to the rhodium. The very slow rate of the reduction compared to the hydrogenation of the same substrates using Diop as the ligand (ca. 50 times slower) is also noteworthy.

We performed some reductions in water in the presence or absence of SDS (sodium dodecylsulfonate) as the surfactant, using ligands **3b**, **3c**, **3d**, and **3e**. In the reduction of (*Z*)-acetamidocinnamic acid (**1a**) in water in the presence of SDS, using **3b** or **3c** as the chiral ligands, higher enantioselectivities than in methanol were obtained: 39 and 47% ee, respectively (Table 1, entries 4 and 7). In the reduction of methyl (*Z*)-acetamidocinnamate (**1b**), ligands **3b**, **3c**, and **3e** gave enantioselectivities of up to 46, 60 and 49%, respectively (Table 1, entries 14, 17, and 23), higher again than the values obtained in methanol. Only ligand **3d** gave low enantioselectivity in water in the presence of SDS (11%), as in methanol (Table 1, entry 20). It is to be noticed that reduction in water alone is very slow, since the catalyst and the substrates are not very soluble in water, and the enantioselectivities obtained quite low.

The presence of SDS as the surfactant drastically increases the enantioselectivity of the reduction. Although such enhancements were already noticed for diphosphanes [27–36], this is the first example of such enhancement using 4-(dialkylamino)-1-(diphenylphosphanyl)butane as chiral ligands in association with

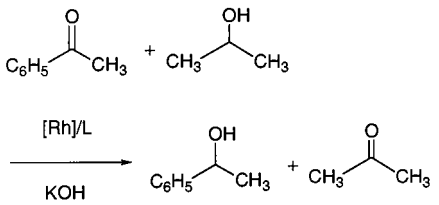
Table 1
Reduction of different unsaturated aminoacid precursors with the catalytic system [Rh(COD)(**1**)]PF_6[a]

Entry	Substrate	Ligand	Solvent	T.T.% [b]	ee% [c] (Config.)
1	**1a**	**3a**	CH_3OH	100	4 (*R*)
2	**1a**	**3b**	CH_3OH	100	29 (*R*)
3	**1a**	**3b**	H_2O	48	4 (*R*)
4	**1a**	**3b**	H_2O+SDS	100	39 (*R*)
5	**1a**	**3c**	CH_3OH	100	38 (*R*)
6	**1a**	**3c**	H_2O	50	10 (*R*)
7	**1a**	**3c**	H_2O+SDS	100	47 (*R*)
8	**1a**	**3d**	CH_3OH	100	4 (*R*)
9	**1a**	**3e**	CH_3OH	100	57 (*R*)
10	**1a**	**3f**	CH_3OH	100	24 (*R*)
11	**1b**	**3a**	CH_3OH	100	5 (*R*)
12	**1b**	**3b**	CH_3OH	100	30 (*S*)
13	**1b**	**3b**	H_2O	8	13 (*R*)
14	**1b**	**3b**	H_2O+SDS	98	46 (*R*)
15	**1b**	**3c**	CH_3OH	100	37 (*R*)
16	**1b**	**3c**	H_2O	7	16 (*R*)
17	**1b**	**3c**	H_2O+SDS	100	60 (*R*)
18	**1b**	**3d**	CH_3OH	100	4 (*R*)
19	**1b**	**3d**	H_2O	10	9 (*R*)
20	**1b**	**3d**	H_2O+SDS	99	11(*R*)
21	**1b**	**3e**	CH_3OH	100	11 (*R*)
22	**1b**	**3e**	H_2O	10	15 (*R*)
23	**1b**	**3e**	H_2O+SDS	97	49 (*R*)
24	**1b**	**3f**	CH_3OH	100	20 (*R*)

[a] Reaction conditions: 25°C; 0.1 MPa H_2; 7.5 ml solvent; [substrate] = 67 mmol l^{-1} (0.5 mmol per experiment); [substrate]:[catalyst] = 100; [amphiphile]:[catalyst] = 20.

[b] Determined by NMR.

[c] Determined by glc with a 10 m capillary column coated with XE-60-L-valine-*tert*-butylamide, after esterification in the case of the acid.



Scheme 2.

rhodium in a micellar system. We notice also in this latter case the formation of metallic rhodium as in methanol. However, in methanol as the solvent, reduction occurs probably via the homogeneous system and also via metallic rhodium, giving lower enantioselectivities and also unreproducible results. In the presence of SDS, it was previously assumed that the reaction occurs only in the micelle [30,31,34]; in this case, the reduction is only due to the soluble organometallic complex which is in the micelle, and so the enantioselectivity will be higher.

We also tested some of these ligands for the asymmetric reduction of acetophenone via transfer hydrogenation [36] with isopropanol as the hydride source (Scheme 2). The catalysts prepared from $[Rh(COD)Cl]_2$ and ligands **3b** or **3e** are very active (94 and 99% conversion, respectively, after 24 h at 50°C); however, the enantioselectivities are very low: 16 and 5% ee, respectively. The catalyst prepared by mixing $RuCl_2(PPh_3)_3$ and one equivalent of ligand **3d** is also very active using a ratio [substrate]/[catalyst] of 10^3 (100% conversion after 1 h at 80°C), but the enantioselectivity is again very low (4%).

In conclusion, we have shown that 4-(dialkylamino)-1-(diphenylphosphanyl)butanes, easily obtained from tartaric acid, are effective ligands in the reduction of unsaturated aminoacid precursors. The problem of the decrease in enantioselectivity, due probably to the formation of metallic rhodium, can be circumvented by performing the reduction in water in the presence of a surfactant. The use of these ligands in hydrogen transfer reactions gave very active catalysts, exhibiting however very low enantioselectivities. Work is currently directed towards the modification of the nitrogen substituents in order to obtain more understanding of the influence of the substituents at the nitriogen on both the activity and the enantioselectivity of the catalyst, and so to increase the enantioselectivity of the reduction.

3. Experimental

The syntheses of ligands **3a**–**d** have been previously described [26]. Sodium dodecyl sulfate (SDS) is from a commercial source and was used as obtained.

3.1. Hydrogenation

Hydrogenation was performed under normal pressure and at 25°C. The solvent, the substrate, the surfactant, the rhodium complex $[Rh(COD)_2]PF_6$ and the phosphane (**3**) were placed in a deaerated hydrogenation flask and stirred for 15 min in an argon atmosphere. Then argon was replaced by hydrogen and the reaction was followed by a volumetric measurement at 25°C. When the reaction was complete, the mixture was extracted with chloroform in the case of the methyl ester, the conversion was determined by NMR and the enantioselectivity by glc. In the case of the acid, the solvent was evaporated and the residue dissolved in ethanol was esterified with diazomethane; then the enantioselectivity was measured by glc. The enantiomeric excess (% ee $\pm$ 0.5%) was determined by glc on the methyl ester of phenylalanine with a 10 m capillary column coated with XE-60-L-valine-*tert*-butylamide.

3.2. Transfer hydrogenation

Transfer hydrogenation was performed by mixing the rhodium (5%) or the ruthenium complex (0.1%), the ligand (ligand/metal = 1), KOH (25%), *i*-PrOH, and acetophenone under a nitrogen atmosphere at the desired temperature. Conversion and e.e. were determined by glc with a capillary column Cydex-B (25 m).

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