

A new easily accessible chiral phosphite–phosphoramidite ligand based on 2-anilinoethanol and *R*-BINOL moieties for Rh-catalyzed asymmetric olefin hydrogenation

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Abstract—A novel chiral phosphite–phosphoramidite ligand based on 2-anilinoethanol and *R*-BINOL moieties has been synthesized in one-pot. The ligand was evaluated in the rhodium-catalyzed enantioselective hydrogenation of α - and β -dehydroamino acid derivatives and dimethyl itaconate in three different solvents at 25 °C, at 1 or 50 bar of hydrogen pressure. The solvent and the pressure effect are discussed.

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Asymmetric hydrogenation with transition-metal complexes bearing chiral ligands is a highly attractive strategy for the synthesis of optically active organic molecules, and thus the development of new chiral ligands which provide high activity and enantioselectivity remains a challenge of high importance.¹ Among several classes of trivalent phosphorus ligands, chiral mono- or diphosphites^{2,3} as well as mono- or diphosphoramidites^{3g–j,4} have been largely overlooked in asymmetric hydrogenation to date. Most of these ligands are based on the BINOL moiety, and possess chirality close to the phosphorus atom and also a rigid structure imposed by the binaphthyl group. Remarkable enantioselectivities have also been reported using chiral ligands possessing two different phosphorus donor sites, such as phosphine–phosphoramidite ligands (e.g., QuinaPhos,⁵ Me-AnilaPhos,⁶ IndolPhos,⁷ ferrocene-based derivatives,⁸ and other ligands⁹).

In recent years, the combination of the functional moieties of phosphites and phosphoramidites in a new class

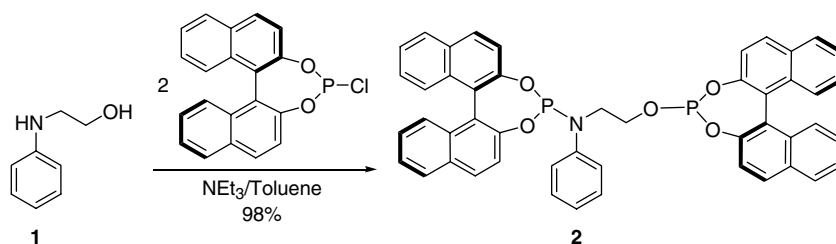
of bidentate ligands has received attention.^{3i,j,10,11} Chiral phosphite–phosphoramidite ligands have been evaluated in the Pt- and Rh-catalyzed hydroformylation,^{10,11a} Cu-catalyzed 1,4-addition reactions,^{3j,11b,f} Pd-catalyzed allylic alkylation,^{11c–e} and Rh-catalyzed hydrogenation.^{3i,j} As the phosphoramidite moiety is as good a π -acceptor group as the phosphite moiety,¹² this new family of chiral ligands offers the opportunity of electronic differentiation while maintaining a similar spatial disposition around the metal centre.^{11e}

We recently prepared the new chiral phosphine–phosphoramidite ligand Me-AnilaPhos, which displayed remarkably high activity and enantioselectivity in rhodium-catalyzed asymmetric olefin hydrogenation under ambient conditions.⁶ In our ongoing research on the development of new chiral bidentate ligands with two different phosphorus donor sites for asymmetric catalysis, we now introduce the new chiral phosphite–phosphoramidite ligand **2** based on the very cheap 2-anilinoethanol and *R*-BINOL moieties. Ligand **2** was evaluated in the rhodium-catalyzed enantioselective hydrogenation of a variety of prochiral olefins.

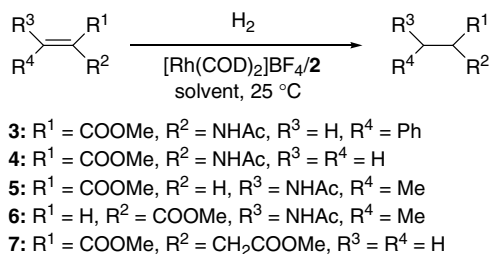
The chiral phosphite–phosphoramidite ligand **2** was synthesized easily in one-pot route by the treatment of 2-anilinoethanol (**1**) with 2 equiv of [(*R*)-(1,1'-binaphthalene-2,2'-diyl)]chlorophosphite in toluene/triethylamine

Keywords: Chiral ligand; Phosphite; Phosphoramidite; BINOL; Asymmetric hydrogenation; Homogeneous catalysis.

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Scheme 1. Synthesis of the phosphite–phosphoramidite ligand **2**.



Scheme 2. Asymmetric hydrogenation of α - and β -dehydroamino acid methyl esters and dimethyl itaconate.

(Scheme 1). The phosphite and the phosphoramidite phosphorus atoms displayed two distinct singlets in the ^{31}P NMR spectrum of **2** at δ 141.35 and 137.58.

Ligand **2** was tested in the rhodium-catalyzed asymmetric hydrogenation of α -dehydroamino acid derivatives (methyl (*Z*)- α -acetamidocinnamate (**3**) and methyl α -acetamidoacrylate (**4**)), β -dehydroamino acid derivatives (methyl (*Z*)- β -acetamidocrotonate (**5**) and (*E*)- β -acetamidocrotonate (**6**)) and dimethyl itaconate (**7**) (Scheme 2). In the standard procedure, ligand **2** was treated *in situ* with 1 equiv of $[\text{Rh}(\text{COD})_2]\text{BF}_4$ (without excess ligand), leading to the respective precatalyst, and catalysis was performed at room temperature with a substrate to rhodium molar ratio of 100:1. Three different solvents were chosen for the reaction: methanol, tetrahydrofuran and dichloromethane.

Hydrogenation was first performed under isobaric conditions (1 bar hydrogen pressure) (Table 1). In general, the rate of the reaction, the enantioselectivities and the configuration of the products were strongly dependent on the solvent and the substrate. The best results were observed for the α -dehydroamino acid derivatives **3** and **4**, in which conversions were quantitative in 1–4 h, yielding the products with the *S* configuration (entries 1–5). The highest enantioselectivities were obtained in methanol, 39% and 61% ee for the substrates **3** and **4**, respectively (entries 1 and 4), while the ee was only 4% for the hydrogenation of **3** in tetrahydrofuran (entry 2). Although dichloromethane was the solvent of choice for hydrogenation using ligands possessing the phosphoramidite moiety,⁶ poor enantioselectivities in dichloromethane and a remarkable improvement in methanol have been reported elsewhere.^{9c} The rates of hydrogenation of the β -dehydroamino acid derivative **5** (*Z*-isomer), and the obtained enantioselectivities (entries 6 and 7) were lower compared to the α -dehydroamino acid deriv-

Table 1. Asymmetric hydrogenation of α - and β -dehydroamino acid methyl esters and dimethyl itaconate catalyzed by $[\text{Rh}(\text{COD})_2]\text{BF}_4/\mathbf{2}$, using 1 bar H_2 pressure

Entry	Substrate	Solvent	Time (h)	Conversion (%)	ee (%) (Conf.)
1	3	MeOH	3	100	39 (<i>S</i>)
2	3	THF	1	100	4 (<i>S</i>)
3	3	CH_2Cl_2	4	100	18 (<i>S</i>)
4	4	MeOH	0.75	100	61 (<i>S</i>)
5	4	THF	1.5	100	53 (<i>S</i>)
6	5	MeOH	2	17	27 (<i>S</i>)
7	5	THF	20	55	15 (<i>R</i>)
8	7	MeOH	0.75	100	4 (<i>R</i>)
9	7	CH_2Cl_2	4	43	59 (<i>R</i>)

Reaction conditions: 0.5 mmol of prochiral olefin, 0.005 mmol of ligand **2** and 0.005 mmol of $[\text{Rh}(\text{COD})_2]\text{BF}_4$ in 7.5 mL of solvent at 25 °C, 1 bar H_2 pressure over the solution.

atives **3** and **4**, while the hydrogenations of the *E*-isomer **6** proceeded with yields less than 5% after 2–4 h, in all the solvents tested (methanol, tetrahydrofuran, dichloromethane). It is also worth noting the opposite chirality of the product depending on the solvent (entry 6 vs entry 7). The reverse enantioselectivity during hydrogenation as a result of the solvent effect has previously been explained by an entirely different mechanism or by a significant influence of the key enantiodifferentiating step due to modified transition states.^{9c} A strong effect of the solvent was also observed for the hydrogenation of dimethyl itaconate (**7**), in which the replacement of methanol by dichloromethane decreased the conversion, but dramatically increased the enantioselectivity (entries 8 and 9).

Catalysis was next performed under 50 bar hydrogen pressure for 20 h, yielding quantitatively the corresponding products with ee's of up to 63% (Table 2). In most of the hydrogenations of α -dehydroamino acid derivatives **3** and **4**, the ee's at 50 bar (Table 2, entries 1–4) were slightly lower compared to the ee's at 1 bar hydrogen pressure (Table 1, entries 1–4), with retention of the *S* configuration. The decreased optical yield on increasing the pressure during the rhodium-catalyzed hydrogenation is in accord with the results obtained using bidentate phosphines, and this phenomenon has mechanistically been investigated by Ojima et al.¹³ However, for reasons unclear, the obtained enantioselectivity for the hydrogenation of **4** was increased to 62% ee at 90 bar (Table 2, entry 5). At 50 bar, the solvent effect was found to play a crucial role in the enantioselectivity, as in the case of 1 bar hydrogen pressure. For instance,

Table 2. Asymmetric hydrogenation of α - and β -dehydroamino acid methyl esters and dimethyl itaconate catalyzed by $[\text{Rh}(\text{COD})_2]\text{BF}_4/\mathbf{2}$, using 50 bar H_2 pressure

Entry	Substrate	Solvent	Conversion (%)	ee (%) (Conf.)
1	3	MeOH	100	39 (S)
2	3	THF	100	2 (S)
3	3	CH_2Cl_2	100	13 (S)
4	4	MeOH	100	52 (S)
5 ^a	4	MeOH	100	62 (S)
6	4	THF	100	54 (S)
7	4	CH_2Cl_2	100	43 (S)
8	5	MeOH	100	33 (S)
9	5	THF	100	38 (S)
10	6	MeOH	100	53 (S)
11	6	THF	98	16 (S)
12	6	CH_2Cl_2	100	8 (S)
13	7	MeOH	100	29 (R)
14	7	THF	100	63 (R)
15	7	CH_2Cl_2	100	42 (R)

Reaction conditions: 0.5 mmol of prochiral olefin, 0.005 mmol of ligand **2** and 0.005 mmol of $[\text{Rh}(\text{COD})_2]\text{BF}_4$ in 7.5 mL of solvent at 25 °C, 50 bar H_2 pressure over the solution, 20 h.

^a 90 bar H_2 pressure.

for the hydrogenation of olefin **3** in tetrahydrofuran at 50 bar, the obtained ee was negligible (Table 2, entry 2), in agreement with the very low ee obtained at 1 bar hydrogen pressure (Table 1, entry 2). For olefins **5–7**, no realistic conclusion could be postulated concerning the pressure effect on the ee's, as the conversions of these substrates at 1 bar of hydrogen were not quantitative, in contrast to 100% conversions at 50 bar after 20 h. However, it is worth noting a reverse chirality in some cases (Table 1, entry 7 vs Table 2, entry 9). This phenomenon has previously been explained by a different mechanism at low pressure compared to elevated pressure for hydrogenation using diphosphine ligands.¹³

In summary, we have developed a new chiral phosphite–phosphoramidite ligand in only one-step using cheap and very easily accessible reagents. The ligand was utilized for the rhodium-catalyzed asymmetric hydrogenation of α - and β -dehydroamino acid methyl esters and dimethyl itaconate, and in most cases provided good activity, and enantioselectivities of up to 63% ee. It was found that the rate of the reaction, the enantioselectivities and the configuration in the products were strongly dependent on the solvent, the pressure and the substrate. In most hydrogenations of dehydroamino acid methyl esters, methanol as solvent led to better enantioselectivities compared to tetrahydrofuran or dichloromethane. Although the hydrogenation results are not excellent, the ease and economic synthesis of the ligand enables us to consider this phosphite–phosphoramidite as a useful ligand for asymmetric induction in other metal-catalyzed reactions.

Synthesis of ligand **2**

A solution of 2-anilinoethanol (0.0741 g, 0.54 mmol) and triethylamine (0.55 mL, 3.95 mmol) in toluene (3 mL) was added dropwise to a solution of [(R)-(1,1'-

binaphthalene-2,2'-diyl)]chlorophosphite (0.3783 g, 1.08 mmol) in toluene (25 mL) at 0 °C. The reaction mixture was stirred at this temperature for 3 h, and then the temperature was increased to room temperature and the mixture was stirred overnight. The mixture was then filtered, and the solvent was evaporated under reduced pressure. The remaining solid was dried at 70 °C under vacuum, yielding **2** (0.4038 g, 98%), mp 106–112 °C. $[\alpha]_{\text{D}}^{25} -435$ (c 0.5, CH_2Cl_2). ^1H NMR (300.13 MHz, CDCl_3): δ 8.07–7.85 (m, 8H, Ar), 7.63–7.15 (m, 18H, Ar), 6.77 (t, $J = 7.3$ Hz, 1H, Ar), 6.63 (d, $J = 8.6$ Hz, 2H, Ar), 4.16–4.08 (m, 1H, OCH_2), 3.98–3.88 (m, 1H, OCH_2), 3.31–3.28 (m, 2H, CH_2N); $^{13}\text{C}\{^1\text{H}\}$ NMR (75.47 MHz, CDCl_3): δ 148.43–113.13 (Ar), 63.57 (s, CH_2O), 44.42 (s, CH_2N); $^{31}\text{P}\{^1\text{H}\}$ NMR (121.50 MHz, CDCl_3): δ 141.35 (s, 1P), 137.58 (s, 1P). Anal. Calcd for $\text{C}_{48}\text{H}_{33}\text{NO}_5\text{P}_2$: C, 75.29; H, 4.34, N, 1.83. Found: C, 74.91; H, 4.59; N, 2.06.

General experimental procedure for the asymmetric hydrogenation

The prochiral olefin (0.5 mmol), ligand **2** (0.005 mmol) and $[\text{Rh}(\text{COD})_2]\text{BF}_4$ (0.005 mmol) were transferred into the hydrogenation device (a standard device for hydrogenation under 1 bar hydrogen pressure). Under a hydrogen atmosphere, the solvent (7.5 mL) was added and the hydrogenation was followed by measurement of the gas-consumption under isothermic (25 °C) and isobaric (1 bar) conditions with an automatically registering gas measuring device. When no further gas-consumption occurred, the reaction was complete. The conversions were determined by GC/HPLC during analysis of the ee values; the integrals/areas of the starting materials and products corresponded nearly exactly with the composition of the mixture. Configurations were assigned by comparison with the retention time of known enantiomers/diastereomers. Hydrogenation under 50 bar hydrogen pressure was performed in a stainless steel autoclave at 25 °C for 20 h, using the amounts of substrates, ligand and rhodium precursor mentioned above.

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