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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7947–7950

Me-AnilaPhos: a new chiral phosphine–phosphoramidite ligand for a highly efficient Rh-catalyzed asymmetric olefin hydrogenation

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Received 10 July 2006; revised 24 August 2006; accepted 31 August 2006
Available online 25 September 2006

Abstract—A cationic rhodium(I) complex with a novel chiral phosphine–phosphoramidite ligand based on 2-diphenylphosphino-*N*-methylaniline and *R*-BINOL moieties has been synthesized. The complex provided remarkably high activity and enantioselectivity in the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate (100% conversion after 10 min, 98% ee) and dimethyl itaconate (100% conversion after 26 min, 96% ee) under ambient conditions (1 bar hydrogen pressure, room temperature) using 1 mol % of the catalyst in dichloromethane as solvent. On the other hand, when hydrogenation was performed in methanol, both conversion and enantioselectivity were significantly diminished, due to the partial decomposition of the rhodium/phosphine–phosphoramidite complex.

Transition-metal asymmetric hydrogenation is a highly attractive strategy for the synthesis of optically active organic molecules with enormous academic and industrial interest, 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 phosphoramidites have been largely overlooked in asymmetric hydrogenation to date, and some monodentate phosphoramidites[2] (e.g., MonoPhos, SiPhos, DpenPhos, PipPhos, MorfPhos, and PegPhos) as well as diphosphoramidites[2a,3] have displayed high enantioselectivities. Most of these ligands are BINOL-based phosphoramidites, and possess chirality close to the phosphorus atom and also a rigid structure imposed by the binaphthyl group. Remarkable enantioselectivities have also been reported by the use of chiral phosphine–phosphoramidite ligands in transition-metal catalysis. Up to now, only two families of this type of chiral ligands have been applied in asymmetric hydrogenation: (a) 1,2-dihydroquinoline-based phosphine–phosphoramidites (QuinaPhos),[4] and (b) ferrocene-based phosphine–phosphoramidites.[5]

We have previously been engaged in preparing several new chiral phosphorus ligands[6] as well as non-chiral *P*,*N* (or *S*)-ligands[7] for transition-metal homogeneous catalysis. In our ongoing research on the development of new chiral ligands for asymmetric catalysis, we now introduce a new chiral phosphine–phosphoramidite ligand (Me-AnilaPhos, **2**)[8] based on 2-diphenylphosphino-*N*-methylaniline and *R*-BINOL moieties. The ligand, possessing two different phosphorus donor sites, is readily available from simple starting materials, and it was found to be a highly efficient ligand for the rhodium-catalyzed asymmetric hydrogenation of prochiral olefins.

The chiral phosphine–phosphoramidite ligand **2** (Me-AnilaPhos) was synthesized by hydrogen abstraction of 2-diphenylphosphino-*N*-methylaniline **1** (easily prepared from *N*-methylaniline)[9] using *n*-BuLi and subsequent reaction of the resulting lithium amide with 1 equiv of [(*R*)-(1,1′-binaphthalene-2,2′-diyl)]chlorophosphite (Scheme 1).[10] The phosphine and the phosphoramidite phosphorus atoms display two distinct doublets in the ^{31}P NMR spectrum of **2** at δ −14.9 and 141.8, respectively, with a P–P coupling constant of

Keywords: Chiral ligand; Phosphine; Phosphoramidite; BINOL; Asymmetric hydrogenation; Homogeneous catalysis.
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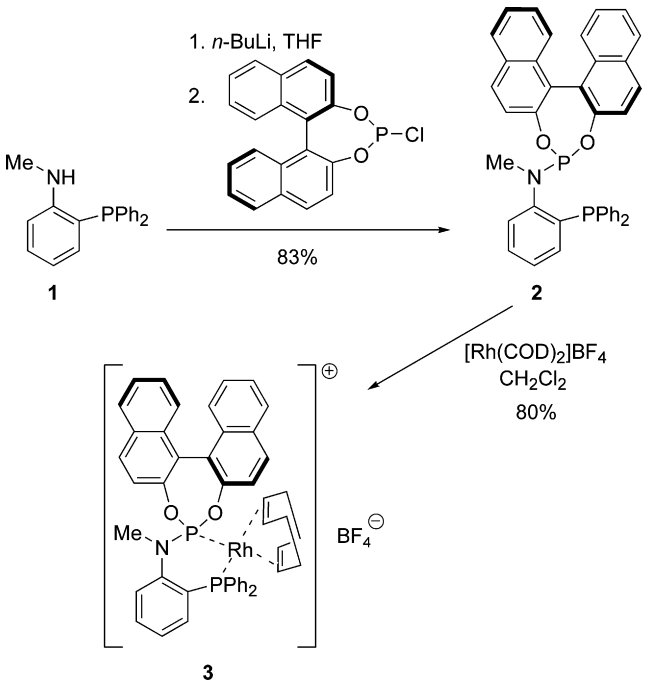
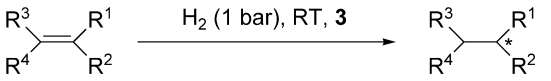
doi:10.1016/j.tetlet.2006.08.136



Scheme 1. Synthesis of the ligand Me-AnilaPhos **2** and the corresponding Rh-precatalyst **3**.

42.0 Hz. The treatment of $[Rh(COD)_2]BF_4$ in dichloromethane with 1 equiv of ligand **2** yielded the cationic rhodium complex **3**,[11] in which the rhodium is involved in a six-membered chelate ring according to the NMR data. The ^{31}P NMR spectrum of **3** showed a doublets of doublets at δ 24.2 for the phosphine phosphorus with a Rh–P coupling constant of 139.2 Hz and a P–P coupling constant of 53.4 Hz, and another doublets of doublets at δ 134.8 for the phosphoramidite phosphorus with a Rh–P coupling constant of 255.6 Hz and a P–P coupling constant of 53.4 Hz.

Complex **3** was tested in the asymmetric hydrogenation of the benchmark alkenes methyl (*Z*)-α-acetamidocinnamate (*Z*-AMe) and dimethyl itaconate ($ItMe_2$) (Scheme 2, Table 1).[12] Catalysis was performed under ambient conditions (1 bar hydrogen pressure, room temperature) with a substrate to a precatalyst molar ratio of 100:1. In non-protic solvents (CH_2Cl_2, THF), conversions were quantitative in only a few minutes, with enantioselectivities reaching 98% ee (entries 1, 2 and 4), indicating a remarkably high catalytic activity for the complex and also its potential for a high asymmetric induction. It is worth noting that the high enantioselectivity observed for complex **3** (Rh:ligand = 1:1) occurred without the addition of an excess of the ligand. A higher enantio-



Z-AMe: R^1 = COOMe, R^2 = NHAc, R^3 = H, R^4 = Ph
ItMe$_2$: R^1 = CH_2COOMe, R^2 = COOMe, R^3 = H, R^4 = H

Scheme 2. Asymmetric hydrogenation of prochiral olefins.

Table 1. Enantioselective hydrogenation of methyl (*Z*)-α-acetamidocinnamate (*Z*-AMe) and dimethyl itaconate ($ItMe_2$) catalyzed by the rhodium precatalyst **3**

Entry	Substrate	Solvent	Time (min)	Conv. (%)	ee (%) (Conf.)
1	*Z*-AMe	CH_2Cl_2	10	100	97.9 (*S*)
2	*Z*-AMe	THF	6	100	96.1 (*S*)
3	*Z*-AMe	MeOH	1380	85	19.5 (*S*)
4	$ItMe_2$	CH_2Cl_2	26	100	96.2 (*R*)
5	$ItMe_2$	MeOH	390	100	7.3 (*R*)

Reaction conditions: 0.5 mmol of prochiral olefin and 0.005 mmol of complex **3** in 7.5 mL of solvent at 25 °C, 1 bar H_2 pressure over the solution.

meric excess was obtained in CH_2Cl_2. In a recent paper reported jointly by four research groups (Minnaard, Reetz, de Vries, Feringa),[2m] twenty highly active monodentate phosphoramidite ligands were applied in the rhodium-catalyzed asymmetric hydrogenation under identical reaction conditions,[2m] although most were previously evaluated in hydrogenation under different conditions.[2] For the hydrogenation of *Z*-AMe and $ItMe_2$, only the following six ligands displayed similar or higher enantiomeric excesses to those observed for Me-AnilaPhos: PipPhos, the H_8-analogue of PipPhos, MorfPhos, the H_8-analogue of MorfPhos, the H_8-analogue of *N*-phenylpiperazinePhos and tetrahydroisoquinolinePhos. However, harsher conditions were required for a complete conversion (5 bar hydrogen pressure, 4 h, 2 mol % Rh) using these ligands compared to the conditions used with Me-AnilaPhos (1 bar hydrogen pressure, 10 or 26 min, 1 mol % Rh). In some cases, other chiral phosphine–phosphoramidite ligands provided similar or higher enantiomeric excesses to those observed with Me-AnilaPhos, but these ligands also required a hydrogen pressure of 10–30 bar and longer reaction times for the complete conversion of the substrate.[4,5]

Hydrogenation with complex **3** was also performed in methanol, and it was found that both conversion and enantioselectivity were significantly diminished (entries 3 and 5). This probably resulted from the partial decomposition of the rhodium/phosphine–phosphoramidite complex in the protic solvent. In order to confirm this, a sample of complex **3** dissolved in MeOH-d_4 was allowed to stand overnight in an NMR tube, under argon. The resulting ^{31}P NMR spectrum of **3** showed significant differences compared to the spectrum of the complex in CD_2Cl_2; in addition to the two sets of doublets of doublets assigned to the two phosphorus atoms in **3**, other peaks of a higher intensity were also observed. Although the decomposition products were not identified, it was obvious that this complex was not stable in protic solvents. Other phosphoramidites such as H_8-MonoPhos were also decomposed in MeOH,[2c] in contrast to MonoPhos which was stable over 48 h in MeOH at room temperature even in the presence of $[Rh(COD)_2]BF_4$.[2e] A lower activity and enantioselectivity during the Rh/phosphoramidite-catalyzed asymmetric olefin hydrogenation in MeOH compared to catalysis in non-protic solvents was also observed by other authors.[2a–c,e,5a] However, it was noted that the effect

of the solvent on both enantioselectivity and conversion was not always consistent.[2i]

In conclusion, we have developed a cationic rhodium complex with the new chiral phosphine–phosphoramidite ligand Me-Anilaphos. The precatalyst was utilized for the asymmetric hydrogenation of methyl (*Z*)-α-acetamidocinnamate and dimethyl itaconate under ambient conditions (1 bar hydrogen pressure, 25 °C), and led to excellent results (quantitative conversion in 10 or 26 min, ee of up to 98%), comparable with those observed for other highly efficient systems for asymmetric olefin hydrogenation. Taking into consideration (a) the ease and the relatively economic synthesis of the ligand, (b) the remarkably high catalytic activity and (c) the high enantioselectivity towards asymmetric hydrogenation, we consider Me-Anilaphos to be a very promising ligand for the asymmetric induction. The development of analogous chiral ligands for hydrogenation as well as other transition-metal-catalyzed asymmetric reactions is currently in progress.

Acknowledgement

This work was supported by the General Secretariat of Research and Technology of Greece and Deutsches Zentrum für Luft-und Raumfahrt e.V.

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8. We labelled this ligand *Me-AnilaPhos* as an *Me-Anil*ine-functionalized *Phos*phoramidite, in accordance with the acronyms previously given for analogous ligands, such as QuinaPhos.[4a]
9. Phosphine **1** was prepared according to a known procedure, in which *N*-methylaniline was converted into the lithium *N*-methyl-*N*-phenylcarbamate, *o*-lithiated with *t*-BuLi and treated with Ph_2PCl: van Oort, A. B.; Budzelaar, P. H. M.; Frijns, J. H. G.; Orpen, A. G. *J. Organomet. Chem.* **1990**, *396*, 33–47. We report here the NMR data for **1**, which has not been reported previously. ^1H NMR ($CDCl_3$): δ 7.68–7.34 (m, 11H, Ar), 6.79–6.63 (m, 3H, Ar), 5.10 (br s, 1H, NH), 2.83 (s, 3H, NCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 152.0–109.9 (Ar), 31.0 (NCH_3); $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ −22.2 (s).

10. Ligand **2** was prepared as follows: *n*-BuLi (1.70 M in methylcyclohexane, 0.96 mL, 1.63 mmol) was added dropwise to a solution of **1** (0.435 g, 1.49 mmol) in THF (3 mL) at −70 °C and the reaction mixture was stirred at this temperature for 4 h. Then the temperature was allowed to increase to −50 °C, and a solution of [(*R*)-(1,1′-binaphthalene-2,2′-diyl)]chlorophosphite (0.519 g, 1.48 mmol) in THF (5 mL) was added dropwise. The reaction mixture was warmed slowly to room temperature and stirred overnight. The volatiles were evaporated under reduced pressure, dichloromethane (10 mL) was added, and the mixture was filtered through Celite. The solvent was evaporated under reduced pressure and the remaining solid was washed with hexane (10 mL) and dried at 80 °C under vacuum, yielding **2** as a white solid (0.747 g, 83%), mp 119–127 °C. $[\alpha]_D^{25}$ −103.9 (*c* 1.0, CH_2Cl_2). ^1H NMR ($CDCl_3$): δ 7.94–7.88 (m, 4H, Ar), 7.59–7.20 (m, 21H, Ar), 6.97–6.94 (m, 1H, Ar), 2.53 (d, $^3J_{H,P} = 2.4$ Hz, 3H, NCH_3); $^{13}C\{^1H\}$ NMR ($CDCl_3$): δ 151.1–122.1 (Ar), 36.5 (NCH_3); $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 141.8 (d, $J_{P,P} = 42.0$ Hz, PN), −14.9 (d, $J_{P,P} = 42.0$ Hz, PPh_2). Anal. Calcd for $C_{39}H_{29}NO_2P_2$: C, 77.35; H, 4.83; N, 2.31%. Found: C, 76.94; H, 5.15; N, 2.38%.
11. Rhodium complex **3** was prepared as follows: A solution of ligand **2** (0.078 g, 0.13 mmol) in dichloromethane (5 mL) was added dropwise to a dark-red solution of $[Rh(COD)_2]BF_4$ (0.051 g, 0.13 mmol) in dichloromethane (3 mL) at −50 °C, and stirred at this temperature for 1 h. The reaction mixture was warmed to room temperature and stirred for an additional 2 h. The resulting orange solution was evaporated under reduced pressure, and the remaining solid was washed with ether (2 × 10 mL) and dried at 80 °C under vacuum, yielding **3** as an orange solid (0.094 g, 80%), mp (dec.) 230 °C. ^1H NMR (CD_2Cl_2): δ 8.24 (d, $^3J = 8.5$ Hz, 1H, Ar), 8.14 (d, $^3J = 9.2$ Hz, 1H, Ar), 8.08–8.00 (m, 2H, Ar), 7.81–7.24 (m, 22H, Ar), 5.76 (br m, 2H, COD–CH), 4.62 (br m, 1H, COD–CH), 3.97 (br m, 1H, COD–CH), 2.83–2.75 (m, 2H, COD–CH_2), 2.58 (m, 2H, COD–CH_2), 2.21 (d, $^3J_{H,P} = 5.5$ Hz, 3H, NCH_3), 2.07–1.96 (m, 4H, COD–CH_2); $^{13}C\{^1H\}$ NMR (CD_2Cl_2): δ 149.3–120.2 (Ar), 108.7–108.5 (m, CH–COD), 108.4–108.2 (m, CH–COD), 107.3–107.1 (m, CH–COD), 100.3–100.1 (m, COD–CH), 37.4 (NCH_3), 33.5, 28.1, 27.0 and 26.0 (COD–CH_2); $^{31}P\{^1H\}$ NMR (CD_2Cl_2): δ 134.8 (dd, $J_{Rh,P} = 255.6$ Hz, $J_{P,P} = 53.4$ Hz, PN), 24.2 (dd, $J_{Rh,P} = 139.2$ Hz, $J_{P,P} = 53.4$ Hz, PPh_2). Anal. Calcd for $C_{47}H_{41}NO_2BF_4P_2Rh$: C, 62.48; H, 4.57; N, 1.55%. Found: C, 61.91; H, 4.95; N, 1.97%.
12. *General experimental procedure for the asymmetric hydrogenation*: The prochiral olefin (0.5 mmol) and the rhodium precatalyst **3** (4.52 mg, 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 finished. The conversions were determined by GC/HPLC during analysis of the ee values; the integrals/areas of starting materials and products corresponded nearly exactly with the composition of the mixture. In some cases, conversions were also determined by ^1H NMR. Configurations were assigned by comparison with the retention time of a known enantiomer.