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Readily Available Phosphine–Phosphoramidite Ligands for Highly Efficient Rh-Catalyzed Enantioselective Hydrogenations

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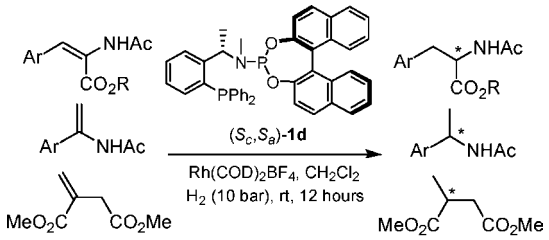
ABSTRACT



A new family of air- and moisture-stable phosphine–phosphoramidite ligands (PEAPhos) has been prepared from commercially available and inexpensive (*S*)-α-phenylethylamine through a two- or three-step transformation and successfully applied in the rhodium-catalyzed enantioselective hydrogenations of a variety of substrates, in which up to 99.9% ee was obtained for all of these kinds of substrates.

The catalytic asymmetric hydrogenation is one of the most powerful tools for obtaining a wide range of enantiomerically pure or enriched compounds.[1] Although great progress has been made by use of a variety of bidentate P-chelate ligands in past decades and monodentate phosphorus ligands more recently,[2] the need to develop new and unique phosphorus-containing ligands with properties superior to their predecessors remains. The minimum criteria for an optimum Rh−catalytic system include the following: (1) a broad substrate scope, (2) the ability to operate at low levels of catalyst for a range of substrates, (3) the ability to operate under a low H_2 pressure, (4) and a direct and simple ligand synthesis, with the starting material being inexpensive or readily available from single step synthesis. Moreover, it is most desirable to develop protocols for the whole process that do not necessitate the use of a glovebox, including the ligand synthesis. However, many bidentate P-chelate ligands reported so far suffered from either a lengthy synthesis or the use of an expensive chiral starting material, and some of them have poor thermal and air stability. These shortcomings have seriously prevented their practical application in asymmetric catalysis. Therefore, exploring the new catalytic system to overcome these drawbacks and fulfill the above criteria is an important, but still difficult task for chemists. In the present work, we report a new class of modular phosphine−phosphoramidite ligands, which can be easily

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(1) For recent reviews, see: (a) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; p 121. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-Interscience: New York, 2000; p 1.

(2) For reviews, see: (a) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029.

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prepared through a two- or three-step transformation from the commercially available and inexpensive chiral α-phenylethylamine (α-PEA). These phosphine−phosphoramidite ligands (abbreviated as PEAPhos, meaning *P*henyl*E*thyl-*A*mine derived *Phos*phine) are air-stable and can be exposed to the air for several months without any changes in their ^{1}H or ^{31}P NMR spectra and any loss in the catalytic activity and enantioselectivity. PEAPhos proved to be highly efficient for the rhodium-catalyzed enantioselective hydrogenation of a wide range of substrates, including α-dehydroamino acid esters, enamides, and dimethyl itaconate, in which up to 99.9% ee was obtained for all of these kinds of substrates, comparable to the most efficient ligands reported so far.

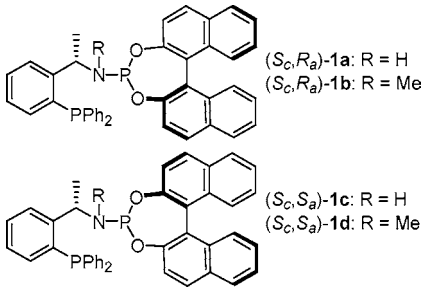
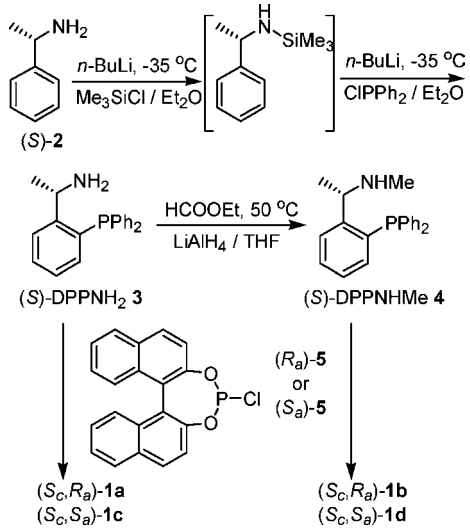


Figure 1. Readily available phosphine−phosphoramidite ligands, PEAPhos **1a**−**d**.

PEAPhos **1a**−**d** were conveniently prepared in a short synthetic procedure from the chiral α-phenylethylamine, which is outlined in Scheme 1. α-Phenylethylamine is one

Scheme 1. Synthesis of Key Intermediates (*S*)-DPPNH$_2$ **3** and (*S*)-DPPNHMe **4** and Targeted PEAPhos **1a**−**d**



of the most typical nonnatural-type chiral compounds, and both its enantiomers are readily available commercially at a low price. Although α-PEA has been extensively used as a chiral ligand precursor for many asymmetric reactions,[3] its *o*-diphenylphosphino-substituted derivative, (*S*)-1-[2-(diphenylphosphino)phenyl]ethylamine [(*S*)-DPPNH$_2$ **3**], has never been explored to construct chiral ligands, to the best of our knowledge, probably due to its difficult synthesis. Since (*S*)-DPPNH$_2$ **3** is a key intermediate to prepare the targeted phosphine−phosphoramidite ligands **1**, developing an efficient and direct method from α-phenylethylamine to manufacture (*S*)-DPPNH$_2$ **3** becomes a timely and important objective. One of the most direct ways to prepare (*S*)-DPPNH$_2$ **3** would be based on the direct ortho-lithiation of α-phenylethylamine, followed by diphenylphosphination. Although the *N*,*N*-dimethylamino group is commonly used as an ortho-directing group for metalation of aromatic rings,[4] direct use of primary amines for such a transformation was much less explored.[5] Polniaszek et al. have reported 1-(2-chlorophenyl)ethylamine or 1-(2,6-dichlorophenyl)ethylamine could be prepared from α-phenylethylamine via ortho-lithiation directed by the in situ-generated *N*-lithiosilylamine.[6] On the basis of Polniaszek's procedure, we successfully prepared (*S*)-DPPNH$_2$ **3** from α-phenylethylamine by a direct and experimentally convenient one-pot protocol.

The treatment of (*S*)-α-phenylethylamine with *n*-BuLi at −35 °C, followed by slow addition of neat Me$_3$SiCl generated the monosilylated product, *N*-(trimethylsilyl)-1-phenylethylamine.[7] The latter was dilithiated by further addition of 3 equiv of *n*-BuLi at −35 °C and then ortho-phosphinated with chlorodiphenylphosphine. Following work-up and crystallization, (*S*)-DPPNH$_2$ **3** was produced in 40% overall yields. By the treatment with HCOOC$_2$H$_5$ at 40−50 °C and then followed by the reduction with LiAlH$_4$ in THF, (*S*)-DPPNH$_2$ **3** was monomethylated to form (*S*)-DPPNHMe **4** in 52% yields. The resulting (*S*)-DPPNH$_2$ **3** and (*S*)-DPPNHMe **4** can be easily converted into the corresponding phosphine−phosphoramidite ligands in good yields by the reaction with (*R*)- or (*S*)-BINOL-derived chlorophosphite **5** in toluene at 0 °C in the presence of 3 equiv of Et$_3$N as a scavenger for HCl eliminated. These PEAPhos ligands **1** are air- and moisture-stable and can be used in open air, which make these ligands highly practical for general laboratory preparations as well as scale-up operations.

In the first set of experiments, we used the Rh-catalyzed asymmetric hydrogenation of a variety of methyl (*Z*)-acetamidocinnamates **6** to benchmark the potential of this class of new phosphine−phosphoramidite ligands in the asymmetric catalysis. Hydrogenation was conducted in CH$_2$-

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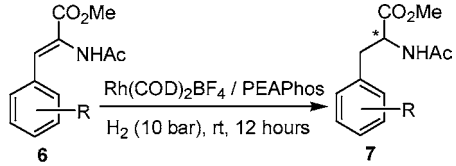
Cl_2 at room temperature under a H_2 pressure of 10 bar in the presence of 1.0 mol % of catalyst prepared in situ from $Rh(COD)_2BF_4$ and 1.1 equiv of PEAPhos **1**. The results are summarized in Table 1. (S_c,R_a)-PEAPhos **1a** and **1b** with a (R_a)-binaphthyl moiety proved to be inferior ligands and induced a very low ee (17.3% ee and 48.5% ee, respectively) in this transformation (entries 1 and 2). In sharp contrast, (S_c,S_a)-PEAPhos **1c** with a (S_a)-binaphthyl moiety exhibited a significantly high enantioselectivity in 98.1% ee (entry 3). This result indicated that the absolute configuration of PEAPhos strongly influenced the enantioselectivity of the reaction and the matched stereogenic elements are (S_c)-central and (S_a)-axial chirality. The increase of the steric hindrance at the nitrogen atom of the ligands proved to be favorable for the enantioselectivity of the reaction. By use of the *N*-methylated (S_c,S_a)-PEAPhos **1d**, the enantioselectivity was further increased to 99.1% ee (entry 4). Noticeably, all of the hydrogenation products obtained in the above procedures had a (*R*)-configuration no matter the chirality of the binathphtyl moiety in these PEAPhos ligands, meaning that the central chirality controls the absolute configuration of the product. This result is entirely opposite from those obtained by phosphoramidite-containing ligands in the Rh-catalyzed asymmetric hydrogenation, in which the axial chirality has the crucial role in determining the chirality of hydrogenation product.[8,9] Solvent screening indicated that the solvent had a great effect on the enantioselectivity and CH_2Cl_2 proved to be the best solvent in terms of enantioselectivity (entries 4−7).[4]

Table 1. Rh-Catalyzed Asymmetric Hydrogenation of α-Dehydroamino Acid Esters **6**[a]



a: R = H; **b**: R = 2-Cl;
c: R = 4-Cl; **d**: R = 2-OMe;
e: R = 4-OMe

entry	ligand	substrate	solvent	Rh (mol %)	ee %[b] (config)
1	(S_c,R_a)-**1a**	**6a**	CH_2Cl_2	1.0	17.3 (*R*)
2	(S_c,R_a)-**1b**	**6a**	CH_2Cl_2	1.0	48.5 (*R*)
3	(S_c,S_a)-**1c**	**6a**	CH_2Cl_2	1.0	98.1 (*R*)
4	(S_c,S_a)-**1d**	**6a**	CH_2Cl_2	1.0	99.1 (*R*)
5	(S_c,S_a)-**1d**	**6a**	PhMe	1.0	80.1 (*R*)
6	(S_c,S_a)-**1d**	**6a**	MeOH	1.0	93.5 (*R*)
7	(S_c,S_a)-**1d**	**6a**	EtOAc	1.0	92.3 (*R*)
8	(S_c,S_a)-**1d**	**6b**	CH_2Cl_2	1.0	99.6 (*R*)
9	(S_c,S_a)-**1d**	**6c**	CH_2Cl_2	1.0	99.0 (*R*)
10	(S_c,S_a)-**1d**	**6d**	CH_2Cl_2	1.0	>99.9 (*R*)
11	(S_c,S_a)-**1d**	**6e**	CH_2Cl_2	1.0	99.7 (*R*)
12	(S_c,S_a)-**1d**	**6a**	CH_2Cl_2	0.02	99.0 (*R*)
13	(S_c,S_a)-**1d**	**6a**	CH_2Cl_2	0.01	98.8 (*R*)

[a] Reactions were performed in 3 mL of solvent with 0.5 mmol of substrates and 1 mol % of catalyst prepared in situ from $Rh(COD)_2BF_4$ and 1.1 equiv of PEAPhos **1** at room temperature and a H_2 pressure of 10 bar for 12 h. Full conversions were achieved in all reactions. [b] Enantiomeric excesses were determined by GC, using a CP-Chiralsil-L-Val capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the GC retention times with GC data in the literature.

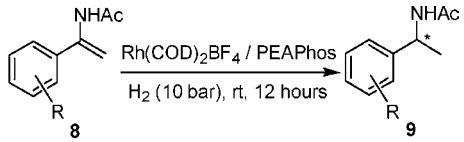
Hydrogenation of a series of substituted α-dehydroamino acid esters **6b**−**e** was then performed in CH_2Cl_2 by use of (S_c,S_a)-PEAPhos **1d**. The results revealed that there is no major effect on the substitution pattern of α-dehydroamino acid derivatives, and all of the substrates were hydrogenated in excellent enantioselectivity with full conversions (entries 8−11). Thus, all of the tested substrates were hydrogenated in over 99% ee and the best result was obtained in the hydrogenation of 2-methoxy-substituted substrate **6d**, affording the hydrogenation product in over 99.9% ee (entry 10). To demonstrate the efficiency of the catalyst Rh/(S_c,S_a)-PEAPhos **1d**, the hydrogenation of **6a** was also carried out with the reduced catalyst loadings as low as 0.01 mol % (S/C = 10 000), affording the corresponding amino acid derivative **7a** in full conversions without loss of enantioselectivity (entry 13).

For the hydrogenation of enamide substrates **8**, the Rh catalyst composed of PEAPhos was also particularly effective, and the results are summarized in Table 2. With the exception of (S_c,R_a)-**1b**, all of the PEAPhos ligands showed high enantioselectivity in the hydrogenation of *N*-(1-phenylethenyl)acetamide **8a**. It is very strange that (S_c,R_a)-**1a**, which proved to have unmatched chiral elements and displayed very low enantioselectivity in the hydrogenation of α-dehydroamino acid esters, unexpectedly gave a hydrogenation product in 95.9% ee (entry 1). Again, (S_c,S_a)-**1d** exhibited the highest enantioselectivity in up to 99.5% ee (entry 4). Under the optimized reaction conditions as used in the hydrogenation of α-dehydroamino acid esters, various enamide substrates could be hydrogenated with the catalysis of Rh/(S_c,S_a)-**1d** to afford the corresponding α-phenylethylamine derivatives with extremely high enantiomeric excess values. The substituted group in the phenyl ring of enamide substrates had little impact on the enantioselectivity of the reaction, and all of the substituted *N*-(1-phenylethenyl)-

(8) For review of asymmetric hydrogenation with monophosphoramidite ligands, see: (a) Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2101. For some recent examples of asymmetric hydrogenation with monophosphoramidite ligands, see: (b) Peng, H.-Y.; Lam, C.-K.; Mak, T. C. W.; Cai, Z.; Ma, W.-T.; Li, Y.-X.; Wong, H. N. C. *J. Am. Chem. Soc.* **2005**, *127*, 9603. (c) Liu, Y.; Ding, K. *J. Am. Chem. Soc.* **2005**, *127*, 10488. (d) Hoen, R.; Boogers, J. A. F.; Bernsmann, H.; Minnaard, A. J.; Meetsma, A.; Tiemersma-Wegman, T. D.; de Vries, J. G.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1896. (e) Panella, L.; Feringa, B. L.; de Vries, J. G.; Minnaard, A. J. *Org. Lett.* **2005**, *7*, 4177. (f) Bernsmann, H.; van den Berg, M.; Hoen, R.; Minnaard, A. J.; Mehler, G.; Reetz, M. T.; de Vries, J. G.; Feringa, B. L. *J. Org. Chem.* **2005**, *70*, 943. (g) Zeng, Q.-H.; Hu, X.-P.; Liang, X.-M.; Zheng, Z. *Chin. Chem. Lett.* **2005**, *16*, 1321. (h) Zeng, Q.-H.; Hu, X.-P.; Duan, Z.-C.; Liang, X.-M.; Zheng, Z. *J. Org. Chem.* **2006**, *71*, 393.

(9) For the bidentate phosphoramidite-containing ligands, see: (a) Franciò, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428. (b) Diéguez, M.; Ruiz, A.; Claver, C. *Chem. Commun.* **2001**, 2702. (c) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2004**, *6*, 3585. (d) Jia, X.; Li, X.; Lam, W. S.; Kok, S. H. L.; Xu, L.; Lu, G.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron*: *Asymmetry* **2004**, *15*, 2273. (e) Burk, S.; Franciò, G.; Leitner, W. *Chem. Commun.* **2005**, 3460. (f) Zeng, Q.-H.; Hu, X.-P.; Duan, Z.-C.; Liang, X.-M.; Zheng, Z. *Tetrahedron*: *Asymmetry* **2005**, *16*, 1233. (g) Hu, X.-P.; Zheng, Z. *Org. Lett.* **2005**, *7*, 419.

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of Enamides **8**[a]



a: R = H; **b**: R = 4-Me;
c: R = 4-CF_3; **d**: R = 4-Br;
e: R = 4-Cl; **f**: R = 4-OMe;
g: R = 3-OMe

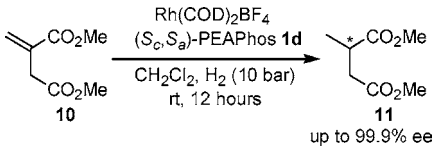
entry	ligand	substrate	ee % (config)[b]
1	(S_c,R_a)-**1a**	**8a**	95.9 (*R*)
2	(S_c,R_a)-**1b**	**8a**	73.9 (*R*)
3	(S_c,S_a)-**1c**	**8a**	98.6 (*R*)
4	(S_c,S_a)-**1d**	**8a**	99.5 (*R*)
5	(S_c,S_a)-**1d**	**8b**	99.1 (*R*)
6	(S_c,S_a)-**1d**	**8c**	99.0 (*R*)
7	(S_c,S_a)-**1d**	**8d**	98.8 (*R*)
8	(S_c,S_a)-**1d**	**8e**	98.5 (*R*)
9	(S_c,S_a)-**1d**	**8f**	99.8 (*R*)
10	(S_c,S_a)-**1d**	**8g**	99.9 (*R*)

[a] Reactions conditions: 3 mL of CH_2Cl_2, 0.5 mmol of substrates, 1 mol % of catalyst prepared in situ from $Rh(COD)_2BF_4$ and 1.1 equiv of PEAPhos **1**, room temperature, 10 bar of H_2 pressure, 12 h. Full conversions were achieved in all reactions. [b] Enantiomeric excesses were determined by GC, using a Chiral select 1000 capillary (0.25 mm × 30 m) column. The absolute configuration was determined by comparing the GC retention times with GC data in the literature.

acetamides were hydrogenated in 98.5−99.9% ee (entries 4−10).

Remarkable enantioselectivity and catalytic reactivity were also observed in the Rh-catalyzed asymmetric hydrogenation of dimethyl itaconate **10**. The most efficient catalyst was prepared in situ from $Rh(COD)_2BF_4$ and (S_c,S_a)-**1d**, which provided the hydrogenation product in up to 99.9% ee under the same conditions as the hydrogenation of α-dehydroamino acid esters (Scheme 2).

Scheme 2. Rh-Catalyzed Asymmetric Hydrogenation of Dimethyl Itaconate **10** with (S_c,S_a)-PEAPhos **1d**



In conclusion, we have developed a concise and practical method for the preparation of a new class of unsymmetrical hybrid phosphine−phosphoramidite ligand (PEAPhos) through a two- and three-step transformation from commercially available and inexpensive (*S*)-α-phenylethylamine. PEAPhos is highly efficient for the Rh-catalyzed enantioselective hydrogenation of a variety of substrates including α-dehydroamino acid esters, enamides, and dimethyl itaconate, in which up to 99.9% ee was obtained for all of these kinds of substrates. Most interestingly, the central chirality in the phenylethylamine backbone decided the absolute configuration of the hydrogenation product no matter the (*R*)- or (*S*)-configuration of binathphyl moiety, contrary to the results obtained by phosphoramidite-containing ligands reported so far. Furthermore, these PEAPhos ligands are air- and moisture-stable, and can be held in open air for several months. All of these features make these PEAPhos ligands highly practical for general laboratory preparations as well as academic and industrial applications.

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Supporting Information Available: Experimental details, characterization data, and analytic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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