The First Application of a Planar-Chiral Phosphorus Heterocycle in Asymmetric Catalysis: Enantioselective Hydrogenation of Dehydroamino Acids

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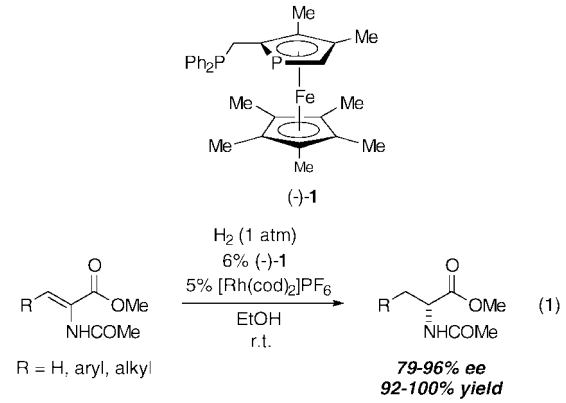
We recently initiated a program directed at the development of planar-chiral heterocycles as enantioselective nucleophilic catalysts[1] and as chiral ligands for transition metals.[2] These studies provided the first reports of applications of planar-chiral heterocycles in asymmetric catalysis. While our earliest work focused on π-bound nitrogen heterocycles, more recently we have expanded the scope of our investigation to include phosphorus heterocycles.[3] In this paper, we describe the synthesis and resolution of a new, planar-chiral bisphosphine (**1**), and we establish its utility in enantioselective catalysis, specifically, in the Rh(I)-catalyzed asymmetric hydrogenation of dehydroamino acids (eq 1).



Achiral phosphaferrocene **2**, first prepared by Mathey,[4,5] serves as the starting point for our synthesis of planar-chiral bisphosphine **1** (Figure 1).[6] Vilsmeier−Haack formylation of **2** through treatment with *N*-methylformanilide and $POCl_3$ provides racemic phosphaferrocene **3** in 70% yield.[7] Reduction with $LiAlH_4$ then furnishes alcohol **4** (98%),[7] which can be resolved by chiral HPLC (Chiralcel OD). We have determined the absolute configuration of enantiopure (+)-**4** through X-ray crystallography. Subjection of **4** to a one-pot chlorination and displacement sequence then affords bisphosphine **1** (50% for two steps). It is important to note that Ganter has recently described the resolution of the Cp analogue of **3**,[8] as well as the synthesis and coordination chemistry of the racemic Cp analogue of **1**.[9]

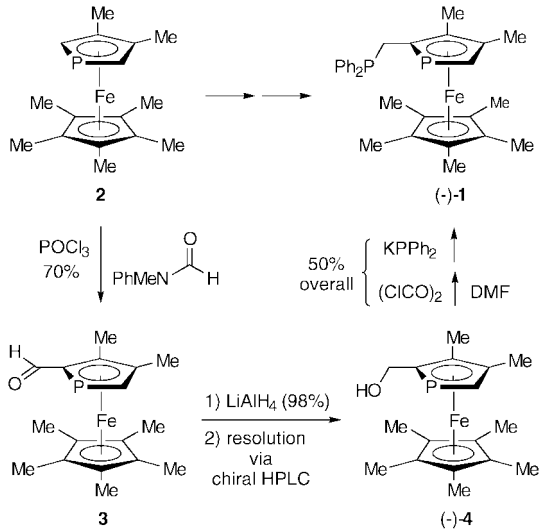
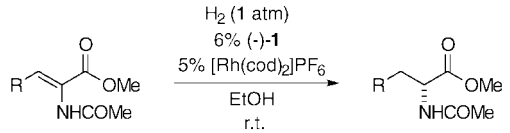


Figure 1. Synthesis of enantiopure planar-chiral bisphosphine **1**.

Table 1. Catalytic Asymmetric Hydrogenation in the Presence of Bisphosphine 1



entry	R	% ee	yield
1	H	87	99
2	Ph	87	95
3	4-$OMeC_6H_4$	87	96
4	4-ClC_6H_4	85	95
5	4-$NO_2C_6H_4$	79	100
6	Me	88	96
7	Et	96	92
8	*i*-Pr	90	96

The asymmetric hydrogenation of dehydroamino acids is frequently used as a proving ground for new chiral bisphosphines,[10,11] in part because of the significance of the product α-amino acids. We have established that, in the presence

(1) (a) Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230−7231. (b) Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493. (c) Ruble, J. C.; Tweddell, J.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 2794−2795. (d) Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154−3155. (e) Garrett, C. E.; Fu, G. C. Submitted for publication.

(2) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445.

(3) (a) Nucleophilic catalysis (achiral): Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 4534−4535. (b) Synthesis of an enantiopure diphosphaferrocene: Qiao, S.; Hoic, D. A.; Fu, G. C. *Organometallics* **1998**, *17*, 773−774.

(4) Synthesized in two steps from commercially available compounds: Roman, E.; Leiva, A. M.; Casasempere, M. A.; Charrier, C.; Mathey, F.; Garland, M. T.; le Marouille, J.-Y. *J. Organomet. Chem.* **1986**, *309*, 323−332. See also ref 3a.

(5) For a review of phospholide and phosphaferrocene chemistry, see: Mathey, F. *Coord. Chem. Rev.* **1994**, *137*, 1−52.

(6) All yields in Figure 1 are the average of ≥2 runs.

(7) For precedent with the Cp analogue of phosphaferrocene **2**, see: de Lauzon, G.; Deschamps, B.; Fischer, J.; Mathey, F.; Mitschler, A. *J. Am. Chem. Soc.* **1980**, *102*, 994−1000.

(8) Through chromatographic separation of diastereomeric aminal derivatives: Ganter, C.; Brassat, L.; Ganter, B. *Tetrahedron: Asymmetry* **1997**, *8*, 2607−2611.

(9) Ganter, C.; Brassat, L.; Ganter, B. *Chem. Ber./Recueil* **1997**, *130*, 1771−1776. Ganter prepared the racemic Cp analogue of **1** by a route that is somewhat different from that outlined in Figure 1. See also: Ganter, C.; Brassat, L.; Glinsböckel, C.; Ganter, B. *Organometallics* **1997**, *16*, 2862−2867. Deschamps, B.; Ricard, L.; Mathey, F. *J. Organomet. Chem.* **1997**, *548*, 17−22.

(10) For recent examples, see: (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635−1636. (b) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570−9571. (c) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *119*, 6207−6208.

(11) For reviews, see: (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994; Chapter 2. (b) Knowles, W. S. *Acc. Chem. Res.* **1983**, *16*, 106−12. (c) Pfaltz, A.; Brown, J. M. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: New York, 1996; Part D, Section 2.5.1.2. Most of the effective bisphosphines that have been reported to date have C_2 symmetry.

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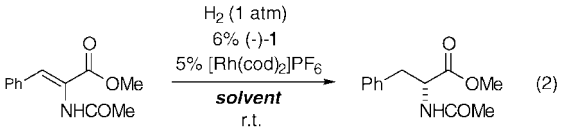
of planar-chiral phosphaferrocene **1**, the $[Rh(cod)_2]PF_6$-catalyzed hydrogenation of methyl α-acetamidocinnamate proceeds with modest ee in CH_2Cl_2, but with very good ee in THF or EtOH (eq 2).[12]



(2)

solvent	% ee
CH_2Cl_2	38
THF	86
EtOH	87

As illustrated in Table 1, a wide array of dehydroamino acids are reduced with good to excellent enantioselectivity under the following conditions: 5% $[Rh(cod)_2]PF_6$, 6% **1**, 1 atm of H_2, EtOH, room temperature.[13] An investigation of a range of cinnamate derivatives reveals an electronic effect on selectivity for this class of compounds—more electron-rich systems furnish higher ee (Table 1, entries 2−5). β-Alkyl-substituted esters are also reduced stereoselectively (Table 1, entries 6−8), with methyl α-acetamidobut-2-enoate providing the highest enantiomeric excess (96% ee; Table 1, entry 7).

Unfortunately, we have not yet been able to obtain a crystal structure of a rhodium complex of ligand **1**. However, a ^{31}P NMR study of the reaction of $[Rh(cod)_2]PF_6$ with 1 equiv of ligand **1** ($^{31}P\{^1H\}$ NMR of **1**: δ −61.4 (d, J = 27 Hz) for phosphole, −11.6 (d, J = 27 Hz) for tertiary phosphine) establishes that both phosphines bind to rhodium ($^{31}P\{^1H\}$ NMR of reaction mixture: δ 22.6 (dd, J = 28, 172 Hz) for phosphole, 61.8 (dd, J = 28, 141 Hz) for tertiary phosphine).

In summary, we have developed a straightforward synthesis and resolution of a new, planar-chiral bisphosphine (**1**), and we have described its use in the rhodium-catalyzed enantioselective hydrogenation of dehydroamino acids. To the best of our knowledge, this is the first example of the application of a planar-chiral phosphorus heterocycle in asymmetric catalysis. In future work, we intend to explore the utility of this and related chiral ligands in other transition metal-catalyzed processes.

Acknowledgment. We thank Michael Man-Chu Lo for solving the crystal structure of (+)-**4** and Jack Liang for helpful discussions. Support has been provided by the Alfred P. Sloan Foundation, the American Cancer Society, the Camille and Henry Dreyfus Foundation, Eli Lilly, Firmenich, Glaxo Wellcome, the National Science Foundation (Young Investigator Award, with funding from Merck, Pharmacia & Upjohn, Bristol-Myers Squibb, DuPont, Bayer, Rohm & Haas, and Novartis), Pfizer, Procter & Gamble, and the Research Corporation.

Supporting Information Available: Experimental procedures, compound characterization data, and X-ray structural data (16 pages).

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(12) The use of counterions other than PF_6 (e.g., SbF_6, OTf, and BF_4) results in lower enantioselectivities.

(13) General procedure for asymmetric hydrogenation: A 100 mL Schlenk tube was charged with substrate (0.22 mmol), (−)-**1** (6.7 mg, 0.013 mmol), $Rh(cod)_2PF_6$ (5.1 mg, 0.011 mmol), and anhydrous EtOH (6.0 mL). After three vacuum/H_2-refill cycles, the valve to the Schlenk tube was closed. The reaction mixture was then stirred for 12 h at rt, at which time TLC indicated that all of the starting material had been consumed. The reaction mixture was concentrated and then passed through a short column (50:50 EtOAc/hexane). The ee was determined by chiral GC.