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Phosphinoferrocenylaminophosphines as Novel and Practical Ligands for Asymmetric Catalysis

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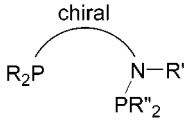
ABSTRACT



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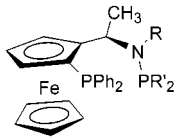

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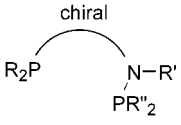
A new series of ligands with a novel phosphine–aminophosphine ligation design as depicted in structure 1 has been prepared on a ferrocenylethyl backbone. These *BoPhoz* ligands of structure 2 have afforded exceedingly high activity and enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of dehydro-α-amino acid derivatives, itaconic acids, and α-ketoesters. These air-stable ligands are readily prepared from cost-effective and non-pyrophoric intermediates.

Asymmetric catalysis is usually performed using a metal catalyst complexed to one or more chiral ligands. These ligands have between one and four donor atoms, with bidentate systems being the most prevalent. Most bidentate ligands for asymmetric hydrogenation have two phosphine donor atoms, although there are several systems with both a phosphorus and a nitrogen donor.[1] Of the bis-phosphine ligands, the large majority are C_2-symmetrical ligands with carbon-linked phosphines (including triaryl, trialkyl, and alkylaryl species), although there are other arrangements such as carbohydrate-based bis-phosphinites,[2] bis-aminophosphines,[3] and mixed aminophosphine−phosphite ligands.[4] To our knowledge, there are no reports of mixed phosphine−aminophosphine species as ligands for asymmetric catalysis.

We wish to report the preparation of the first examples of this class of compounds, the structural characteristics of which can be simply represented as a phosphine and an aminophosphine linked by a chiral backbone as exemplified by structure **1**.



1

The *BoPhoz* ligands[5] presented in this paper possess structure **2** wherein the phosphine−aminophosphine substructure has been superimposed on a chiral ferrocenylethyl

(1) For recent reviews, see: (a) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 1−110. (b) Brown, J. M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfalz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. I, pp 121−182.

(2) (a) Selke, R. *J. Organomet. Chem.* **1989**, *370*, 249−256. (b) Casulnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc*, **1994**, *116*, 9869−9882. (c) RajanBabu, T. V.; Casalnuovo, A. L. *Pure Appl. Chem*. **1994**, *66*, 1535−1542. (d) RajanBabu, T. V.; Ayers, T. A.; Halliday, G. A.; You, K. K.; Calabrese, J. C. *J. Org. Chem.* **1997**, *62*, 6012−6028.

(3) (a) Fiorini; M.; Giongo, G. M. *J. Mol. Cat*. **1979**, *5*, 303−310. (b) Pracejus, G.; Pracejus, H. *Tetrahedron Lett*. **1977**, 3497−3500.

(4) (a) Cesarotti, E.; Chiesa, A.; Ciani, G.; Sironi, A. *J. Organomet. Chem*. **1983**, *251*, 79. (b) Kreuzfeld, H.-J.; Schmidt, U.; Döbler, C.; Krause, H. W. *Tetrahedron*: *Asymmetry* **1996**, *7*, 1011. (c) Mi, A.; Lou, R.; Jiang, Y.; Deng, J.; Qin, Y.; Fu, F.; Li, Z.; Hu, W.; Chan, A. S. C. *Synlett* **1998**, 847. (d) Krause, H. W.; Schmidt, U.; Taudien, S.; Costisella, B.; Michalik, M. *J. Mol. Catal*. **1995**, *104*, 147.

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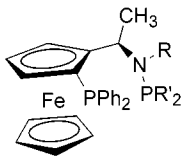
backbone. Transition-metal complexes of these ligands afford excellent results in asymmetric hydrogenation reactions.



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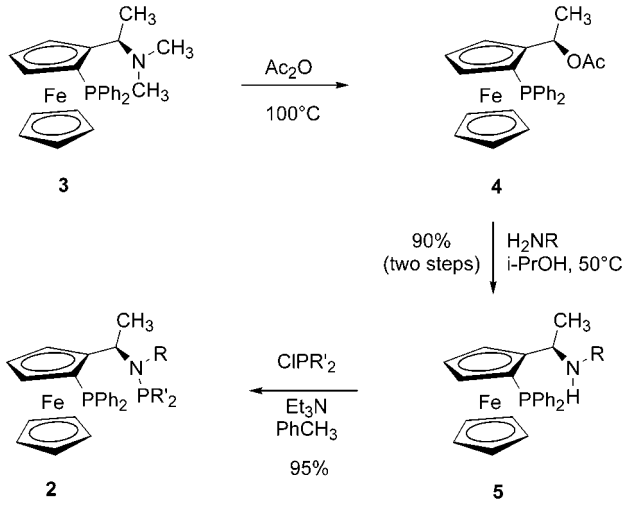
a: R = H, R' = Ph
b: R = CH_3, R' = Ph
c: R = Et, R' = Ph
d: R = n-Pr, R' = Ph
e: R = CH_3, R' = cyc-C_6H_{11}

The design of effective nonsymmetrical chiral ligands such as phosphine-aminophosphines is challenging, as these species lack the stereochemical redundancy implicit in their C_2-symmetrical cousins. For this reason, the ferrocenylethyl scaffold, which has a rich history of affording effective nonsymmetrical ligands[6] such as the BPPFA[7] and the Josiphos[8] systems, was chosen to provide a large three-dimensional steric shield to help enforce the ligand stereoselectivity. In addition, the simple preparation of single enantiomer *N*,*N*-dimethyl-1-ferrocenylethylamine,[9] its ready one-step conversion to phosphine **3**,[7] and the transformation of the dimethylamino substituent of these α-ferrocenylethyl systems into a variety of other functionalities with retention of configuration[10] allows the necessary functional group transformations required for our systems. Thus, our ligand synthesis involved the transformation of the dimethylamino species of monophosphine **3** into a variety of secondary amines that could then be converted to the desired aminophosphines. This strategy was accomplished as shown in Scheme 1 through the intermediacy of acetate **4**, prepared by reaction of **3** with acetic anhydride.[7] Reaction of **4** with a variety of primary amines led to the secondary amines **5**. Coupling of the amino substituent with the desired chlorophosphine afforded ligands **2**.[11] Thus, a series of simple transformations involving no pyrophoric or even air-sensitive intermediates led to the desired ligands in expedient fashion. Indeed, the facile nature of the reactions (innocuous and inexpensive reagents, no low temperature or pyrophoric chemistry, and high yields) results in eminently practical ligands that are readily scaled up (>100 g of ligand **2b** was prepared within a few months of its discovery), an elusive goal that has generally hampered the wider use of asymmetric catalysis in industrial settings. In addition, simple modification of either the amine or the chlorophosphine allows ready optimization of the electronic and steric properties of the ligands.

Scheme 1. Synthesis of *BoPhoz* Ligands **2**



Unlike many phosphines, the *BoPhoz* ligands display outstanding air stability: Ligand **2b** held at ambient temperature open to the air for more than 1 year retained complete activity and enantioselectivity for asymmetric hydrogenation reactions, even at very low (10000:1 substrate/catalyst) loadings. This stability serves to enhance the practical appeal of these species, as it allows the use of nondegassed solvents and reaction mixtures for asymmetric hydrogenation screening reactions using **2b** complexed to rhodium as the catalyst.

These ligands were first examined in asymmetric hydrogenation reactions of a variety of dehydro-α-amino acid derivatives. The reactions were performed, often in a screening protocol in high-throughput fashion, by in situ preparation of the ligand−metal complex from the desired ligand and bis(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate followed by substrate introduction and hydrogenation. The results of reactions using the rhodium complex of **2** with a variety of dehydro-α-amino acid substrates at low hydrogen pressure (10 psig) are shown in Table 1. Entries 1−7 indicate that the *N*-methyl ligand **2b** provides excellent enantioselectivity regardless of the distal, amino, or carboxyl substitutents. Thus, a wide range of highly enantiopure α-amino acids with a variety of desired protection strategies (Boc, Cbz, acetamide, ester, acid) can be readily obtained through the use of this ligand. The high enantioselectivities with the highly desirable Boc and Cbz groups are particularly noteworthy, as the performance of some ligands suffers in these cases.[12] The viability of the parent carboxylic acid substrates with ligand **2b** was unexpected, as cleavage of the nitrogen−phosphorus bond might have been anticipated.

(5) Due to the rather lengthy systematic names for these compounds (e.g., the chemical name for **2b** is *R*-*N*-methyl-*N*-diphenylphosphino-1-[*S*-2-(diphenylphosphino)ferrocenyl]ethylamine), we have given the core structure the trivial name "BoPhoz". BoPhoz is a trademark of Eastman Chemical Co.

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(7) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138−1151.

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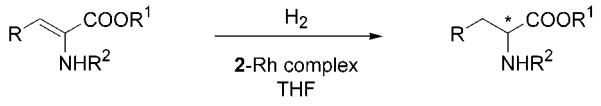
(10) Gokel, G. W.; Marquarding, D.; Ugi, I. K. *J. Org. Chem*. **1972**, *37*, 3052−3058.

(11) The same sequence using the opposite enantiomer of **3** afforded the enantiomeric ligands to **2**.

(12) (a) Kreuzfeld, H.-J.; Döbler, C.; Krause, H. W.; Facklam, C. *Tetrahedron*: *Asymmetry* **1993**, *4*, 2047−2051. (b) Ojima, I.; Yoda, N.; Yatabe, M.; Tanaka, T.; Kogure, T. *Tetrahedron* **1984**, *40*, 1255−1268. (c) Achiwa, K. *Chem. Lett.* **1977**, 777−778.

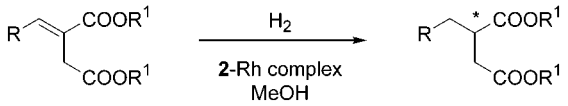
Table 1. Asymmetric Hydrogenation of Dehydro-α-amino Acid Derivatives[a]



entry	ligand	R	R^1	R^2	ee[b] (%)
1	**2b**	Ph	Me	Boc	99.5 (*S*)
2	**2b**	Ph	H	Ac	99.4 (*S*)
3	**2b**	Ph	Me	Ac	99.1 (*S*)
4	**2b**	H	Me	Ac	98.5 (*S*)
5	**2b**	H	Me	Cbz	98.0 (*S*)
6	**2b**	H	H	Ac	96.1 (*S*)
7	**2b**	cyc-C_3H_5	CH_2Ph	Boc	98.2 (*S*)
8	**2a**	Ph	Me	Ac	97.2 (*S*)
9	**2c**	Ph	Me	Ac	94.3 (*S*)
10	**2d**	Ph	Me	Ac	93.3 (*S*)

[a] All reactions were performed at room temperature for 1 h with 1 mol % catalyst under 10 psig hydrogen. All reactions afforded >95% conversion to a single product. [b] Enantiomeric excess determined by chiral GC (±0.2%).

Table 2. Asymmetric Hydrogenation of Itaconic Acid Derivatives[a]



entry	ligand	R	R^1	ee (%)
1	**2b**	H	H	97.4[b] (*R*)
2	**2a**	H	H	94.0[b] (*R*)
3	**2a**	Ph	H	99[c] (*R*)
4	**2b**	Ph	H	89[c] (*R*)
5	**2b**	H	Me	94.0[b] (*R*)
6	**2a**	H	Me	91.6[b] (*R*)
7	**2a**	Ph	Me	80[c] (*R*)

[a] All reactions were performed at room temperature for 6 h with 1 mol % catalyst under 300 psig hydrogen. All reactions afforded >95% conversion to a single product. [b] Enantiomeric excess determined by chiral GC (±0.2%). [c] Enantiomeric excess determined by chiral HPLC (±1%).

These reactions were also investigated at high pressure (300 psig) with very little loss of enantioselectivity (1−2% ee lower as compared with 10 psig), indicating the robustness of rhodium catalysts of ligands **2** with regards to pressure.

Entries 8−10 (Table 1) show the effect of alternative nitrogen substituents in ligand **2** on the enantioselectivity of the asymmetric hydrogenation of methyl 2-acetamidocinnamate. Although the rhodium complexes of these ligands all afford over 90% ee for this reaction, they are clearly inferior to the 99.1% ee obtained with *N*-methyl analogue **2b** (entry 3).

The rhodium complex of this preferred ligand **2b** is particularly effective for the hydrogenation of dehydro-α-amino acid derivatives at low catalyst loadings (substrate/catalyst ratio of up to 10000:1). In addition to maintaining high enantioselectivities, these reactions are very rapid, with initial rates in excess of 30 000 catalyst turnovers per hour for the reaction of rhodium-**2b** with methyl 2-acetamidocinnamate.[13] This extremely high turnover rate is of great practical importance as it results in very short reaction times even at low catalyst loadings. This rapid rate is likely due at least in part to the seven-membered rhodium-*BoPhoz* chelate, as it is known that seven-membered chelates tend to undergo internal reorganization more rapidly than their five-membered analogues and thus afford faster reactions.[13a,14] Fortunately, the *BoPhoz* ligands have a sufficient balance between flexibility and rigidity to allow the observed rapid reaction rates without sacrificing enantioselectivity. These results were observed in methanol as solvent, again demonstrating the surprising stability of the *BoPhoz* ligands toward solvolysis of the N−P bond, particularly when the ligand is complexed to rhodium.

Preliminary results indicate that the rhodium complexes of the *BoPhoz* ligands afford high enantioselectivities for the asymmetric catalytic hydrogenation of itaconic acid derivatives and α-ketoesters. As with the dehydro-α-amino acid hydrogenations, these reactions were performed using a high-throughput screening protocol, although they were generally run at higher hydrogen pressure (300 psig).

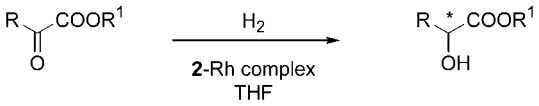
Rhodium complexes of *BoPhoz* ligands **2a** and **2b** afford highly enantioselective hydrogenations of a variety of itaconic acid derivatives. As indicated in Table 2, the parent diacid substrates are reduced with higher enantioselectivities than the corresponding dimethyl esters (entries 1−4 as compared to 5−7, respectively). The rhodium complex of ligand **2b** (the best ligand for amino acid preparation) is particularly effective for the hydrogenation of itaconic acid (97.4% ee) and dimethyl itaconate (94.0% ee). However, the rhodium complex of **2a** appears more generally applicable, affording consistently high enantioselectivities for a variety of substituted itaconates, and is particularly well-suited for *β*-substituted itaconic acids as shown by the preparation of 2-benzylsuccinic acid in 99% ee (entry 3).

The *BoPhoz* ligands also exhibit high enantioselectivity for the rhodium-catalyzed asymmetric hydrogenation of α-ketoesters (Table 3). As with the itaconates, these reactions are best performed at high hydrogen pressure (300 psig). Comparisons of entries 4−6 indicate that ligand **2e** is the preferred *BoPhoz* ligand for this transformation, as it is decidedly superior to ligand **2a** (the best ligand for many itaconate hydrogenations) and slightly better than ligand **2b** (the best ligand for dehydroamino acid hydrogenations). Indeed, as shown in Table 3, a variety of α-ketoester substrates are hydrogenated with high enantioselectivity with the rhodium complex of **2e**, with the best result being 97% ee for the preparation of 3,3-dimethyl-2-hydroxy-*γ*-butyrolactone (entry 2).

(13) For some comparative examples using other ligands see (a) Oliver, J. D.; Riley, D. P. *Organometallics* **1983**, *2*, 1032−1038. (b) Landis, C. R.; Halpern, J. *J. Am. Chem. Soc.* **1987**, *109*, 1746−1754. (c) Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1977**, *99*, 6262. (d) Döbler, C.; Kreuzfeld, H.-J.; Krause, H. W.; Michalik, M. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1833−1842. (e) Selke, R.; Pracejus, H. *J. Mol. Catal.* **1986**, *37*, 213−225.

(14) Landis, D. R.; Halpern, J. *J. Organomet. Chem.* **1983**, *250*, 485−490.

Table 3. Asymmetric Hydrogenation of α-Ketoesters[a]



entry	ligand	R	R^1	ee[b] (%)
1	**2e**	$PhCH_2CH_2$	Et	92.4 (*R*)
2	**2e**	$-C(CH_3)_2CH_2-$		97.2 (*R*)
3	**2e**	Me	Et	90.8 (*R*)
4	**2e**	Me	Me	88.1 (*R*)
5	**2a**	Me	Me	46.0 (*R*)
6	**2b**	Me	Me	86.8 (*R*)

[a] All reactions were performed at room temperature for 6 h with 1 mol % catalyst under 300 psig hydrogen. All reactions afforded >95% conversion to a single product. [b] Enantiomeric excess determined by chiral GC (±0.2%).

Thus, we have prepared the first examples of phosphine−aminophosphine ligands for asymmetric catalysis. These ligands, based on a ferrocenylethyl backbone, are readily prepared and air-stable. The rhodium complexes of these ligands afford excellent enantioselectivities for the asymmetric hydrogenation reactions of dehydro-α-amino acids, itaconic acids, and α-ketoesters. We are continuing our examination of these ligands in other asymmetric reactions as well as the preparation of other ligands with the phosphine-aminophosphine structure.

Acknowledgment. We thank Dr. Michael D. Meadows for carbon and phosphorus NMR analysis, Dr. Paula S. Cahill and Dr. Thomas R. Floyd for chiral HPLC analysis, and Mr. James L. Little for high-resolution mass spectral analysis.

Supporting Information Available: Experimental procedures for the preparation of **5b** and **2b**, asymmetric hydrogenation procedures, and enantiomeric excess and absolute configuration determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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