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# Synthesis and Application of Planar-Chiral Phosphaferrocene-Oxazolines, a New Class of P,N-Ligands

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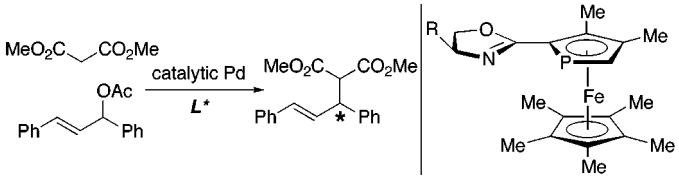
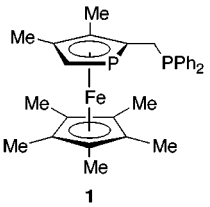
## ABSTRACT



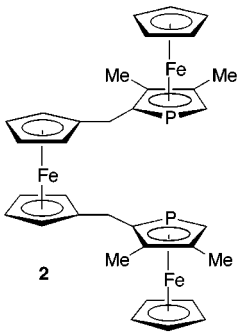

**The synthesis of several phosphaferrocene-oxazolines, members of a new family of planar-chiral ligands, is described. These bidentate P,N-ligands are applied to enantioselective palladium-catalyzed allylic alkylations, for which it is shown that the planar-chirality of the phosphaferrocene, not the chirality of the oxazoline, determines the stereochemical outcome of the reaction.**

In 1998, we described the use of bisphosphine ligand **1** in the rhodium(I)-catalyzed enantioselective hydrogenation of dehydroamino acids, the first effective application of a planar-chiral phosphorus heterocycle in asymmetric catalysis.[2] More recently, Ganter has reported a palladium-catalyzed enantioselective allylic alkylation with phosphaferrocene **2**,[3] and we have documented an asymmetric isomerization of allylic alcohols to aldehydes catalyzed by Rh/**1**.[4]

Phosphaferrocene ligands differ significantly from tertiary phosphines, which are the most widely employed ligands in asymmetric catalysis. For example, unlike the $sp^3$-hybridized phosphorus of a typical tertiary phosphine, the $sp^2$-hybridized phosphorus of a phosphaferrocene has a marked propensity to engage in metal-to-phosphorus $\pi$ back-bonding,[5] a stabilizing interaction that can organize a metal−phosphaferrocene complex. Furthermore, the phosphorus atom of phosphaferrocenes **1** and **2** is stereogenic, whereas the phosphorus atom of most chiral tertiary phosphines is not.




**1**




**2**

During the past decade, oxazolines have emerged as extraordinarily versatile chiral ligands in asymmetric catalysis.[6,7] In view of this exceptional utility, as well as the

(1) Correspondence concerning the X-ray crystal structure should be directed to M. M.-C. Lo.

(2) Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168−4169.

(3) Ganter, C.; Kaulen, C.; Englert, U. *Organometallics* **1999**, *18*, 5444−5446. See also: Ganter, C.; Glinsböckel, C.; Ganter, B. *Eur. J. Inorg. Chem.* **1998**, 1163−1168.

(4) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.*, accepted for publication.

(5) For leading references, see: Deschamps, B.; Ricard, L.; Mathey, F. *J. Organomet. Chem.* **1997**, *548*, 17−22.

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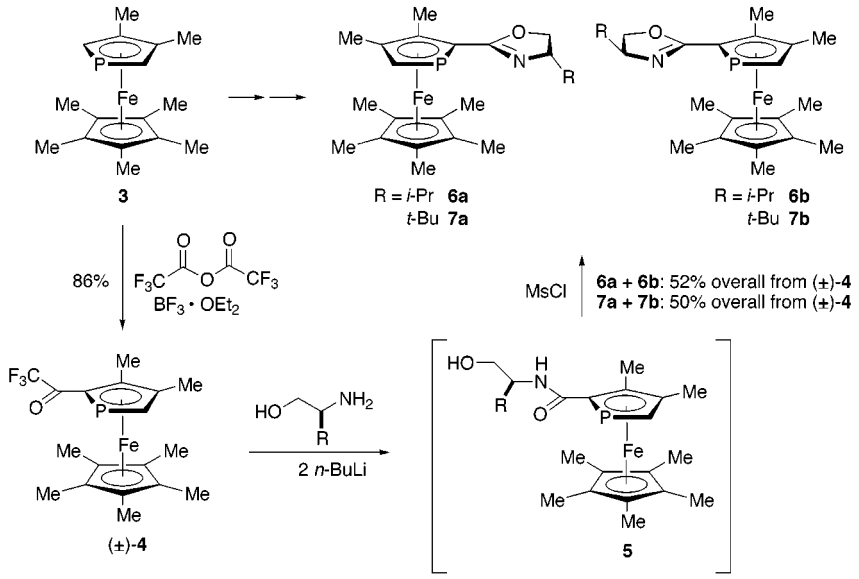
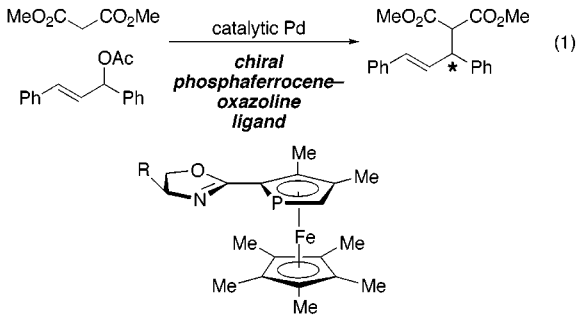



**Figure 1.** Synthesis of chiral phosphaferrocene-oxazolines.

increasing number of applications of P,N bidentate ligands,[8] we have recently initiated a program focused on the development of chiral phosphaferrocene-oxazolines. In this communication, we describe the synthesis and the application in asymmetric catalysis of the first members of this new class of ligands (eq 1).




Acylation of phosphaferrocene **3**[9] with trifluoroacetic anhydride furnishes trifluoromethyl ketone **4** (Figure 1), which we have converted to the target oxazoline in a straightforward process. Thus, reaction of the ketone with the dianion of an amino alcohol,[10] followed by activation of the hydroxyl group and cyclization, provides diastereomeric phosphaferrocene-oxazolines that are separable by column chromatography. Through this general pathway, we have synthesized new enantiopure bidentate ligands derived from valinol (**6a**, **6b**) and *tert*-leucinol (**7a**, **7b**). The X-ray crystal structure of phosphaferrocene-oxazoline **7b** is illustrated in Figure 2.

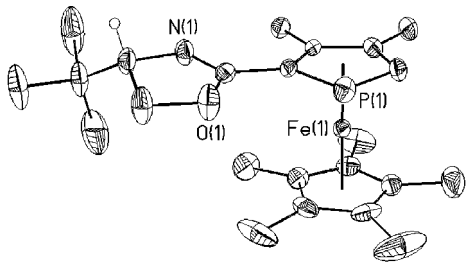



**Figure 2.** ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of phosphaferrocene-oxazoline **7b**.

With the target ligands in hand, we have turned our attention to investigating their potential in asymmetric catalysis; as a starting point, we chose to explore enantioselective palladium-catalyzed allylic alkylations.[8] With valinol-derived phosphaferrocene-oxazoline **6a**, we obtain moderate ee in the reaction of dimethyl malonate with 1,3-diphenylallyl

(6) (a) Brunner, H.; Obermann, U.; Wimmer, P. *J. Organomet. Chem.* **1986**, *316*, C1−C3. (b) Nishiyama, H.; Sakaguchi, H.; Nakamura, T.; Horihata, M.; Kondo, M.; Itoh, K. *Organometallics* **1989**, *8*, 846−848. Nishiyama, H. In *Advances in Catalytic Processes*; Doyle, M. P., Ed.; JAI Press: Greenwich, CT, 1997; Vol. 2, pp 153−188.

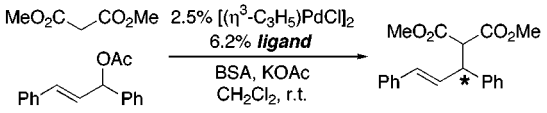
(7) (a) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005−6008. (b) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728. (c) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991**, *113*, 728−729. (d) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232−240. (e) For a review of applications of $C_2$-symmetric bis(oxazolines) in asymmetric catalysis, see: Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1−45.

(8) For example, see: Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: 1999; Chapter 24.

(9) Synthesized in two steps from commercially available compounds: (a) 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. (b) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 4534−4535.

(10) We are aware of only one report of the synthesis of an amide from the reaction of a trifluoromethyl ketone with $MNR_2$ or MNHR (M = metal): Hassinger, H. L.; Soll, R. M.; Gribble, G. W. *Tetrahedron Lett.* **1998**, *39*, 3095−3098.

**Table 1.** Enantioselective Allylic Alkylation with Chiral Phosphaferrocene-Oxazoline Ligands **6** and **7**[a]




| entry | ligand | time (h) | yield (%) | ee (%) |
|---|---|---|---|---|
| 1 | **6a** | 16 | 80 | 68 (*R*) |
| 2 | **6b** | 4.5 | 94 | 79 (*S*) |
| 3 | **7a** | 36 | 70 | 73 (*R*) |
| 4 | **7b** | 4.5 | 92 | 82 (*S*) |

[a] All data are the average of two runs. The yields that are reported are isolated yields.

acetate (68% ee; Table 1, entry 1). When we employ diastereomeric ligand **6b**, which differs only in the stereochemistry of the planar-chiral phosphaferrocene subunit, we observe enhanced and opposite enantioselectivity (79% ee; entry 2). The fact that the opposite enantiomer is favored establishes that *the planar-chirality of the phosphaferrocene, not the chirality of the oxazoline, is the dominant stereocontrol element.* The greater ee for ligand **6b**, relative to **6a**, indicates that for ligand **6b** the planar-chirality and the chirality of the oxazoline are working in concert to preferentially generate the *S* product. Even with an extremely bulky oxazoline substituent (*tert*-butyl; **7a** and **7b**), the planar-chirality of the phosphaferrocene subunit, not the chirality of the oxazoline, is clearly dominant (entries 3 and 4).

It is worthwhile to contrast ligands **6** and **7** with related ligands. Helmchen, Pfaltz, and Williams have established that the oxazoline chirality of bidentate P,N-ligand **8** (Figure 3) furnishes exceptional stereocontrol in palladium-catalyzed allylic alkylations (ee's as high as 99%).[11] Furthermore, Ahn and Park (M = FeCp)[12] and Helmchen (M = $Mn(CO)_3$)[13] have demonstrated that the chirality of the oxazoline subunit, not the planar-chirality, is the primary determinant of the stereochemical outcome of allylations catalyzed by Pd/**9**. In contrast, for our bidentate P,N-ligands, the chirality of the oxazoline plays only a minor role in the stereochemical

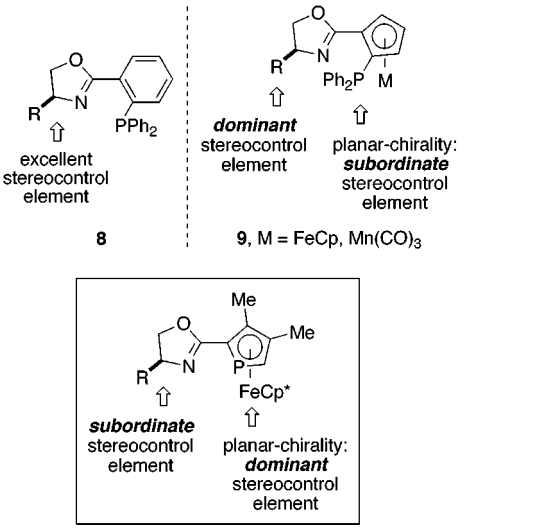



**Figure 3.** Stereocontrol by oxazoline chirality versus by planar-chirality.

course of the allylic alkylation, which is largely controlled by the planar-chiral phosphaferrocene subunit (Table 1).[14,15]

In conclusion, we have synthesized several planar-chiral phosphaferrocene-oxazolines, members of a new class of P,N-ligands. In a preliminary study, we have applied these ligands to enantioselective palladium-catalyzed allylic alkylations, and we have determined that the planar-chirality of the phosphaferrocene, not the chirality of the oxazoline, is the dominant stereocontrol element. In view of the steric tunability of planar-chiral heterocycles,[16] we are optimistic that phosphaferrocene-oxazolines will prove to be useful ligands in asymmetric catalysis.

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

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(12) (a) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Tetrahedron: Asymmetry* **1997**, *8*, 1179−1185. (b) Ahn, K. H.; Cho, C.-W.; Park, J.; Lee, S. *Bull. Korean Chem. Soc.* **1997**, *18*, 789−791.

(13) Kudis, S.; Helmchen, G. *Angew. Chem., Int. Ed.* **1998**, *37*, 3047−3050.

(14) For ligands **8** and **9**, the phenyl groups of the diphenylphosphino subunit are believed to play a critical role in stereoselection. For a discussion, see: Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336−345.

(15) For an early report of a ligand in which planar-chirality, rather than central chirality, is the dominant stereocontrol element, see: Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, M. *J. Am. Chem. Soc.* **1976**, *98*, 3718−3719.

(16) For example, see: Ruble, J. C.; Latham, H. A.; Fu, G. C. *J. Am. Chem. Soc.* **1997**, *119*, 1492−1493.