ORGANIC LETTERS

2002
Vol. 4, No. 21
3699−3702

Copper-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to Acyclic Enones in the Presence of Planar-Chiral Phosphaferrocene-Oxazoline Ligands

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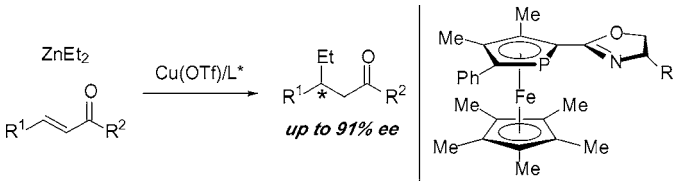
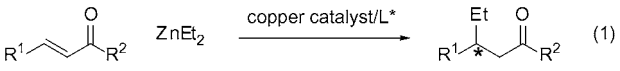
Received August 1, 2002

ABSTRACT



A new subclass of chiral phosphaferrocene-oxazoline ligands has been applied to the copper-catalyzed asymmetric conjugate addition of diethylzinc to acyclic enones, furnishing good enantioselectivity. The ligand design readily lends itself to modification, thereby facilitating optimization of ee. Although the dominant stereocontrol element in these 1,4-addition processes is the central chirality of the oxazoline subunit of the ligand, not the planar chirality of the phosphaferrocene, altering the phosphaferrocene subunit can provide useful enhancement of enantioselectivity.

Conjugate addition to α,β-unsaturated carbonyl compounds is a useful strategy for the construction of carbon−carbon bonds.[1] The development of chiral catalysts that can achieve this transformation enantioselectively has therefore been investigated extensively,[2] with copper-catalyzed additions of organozinc reagents to enones being a particular focus of interest.[2a]



(1)

Although early successes in this area were restricted almost entirely to cyclic enones (e.g., 2-cyclohexen-1-one), very recently a few catalysts have been reported that provide very good enantioselectivity for a number of acyclic enones.[3]

Two years ago, we initiated a program directed at the development of planar-chiral phosphaferrocene-oxazolines as ligands for enantioselective catalysis, and as part of that investigation we described the use of P,N-ligands **1** and **2** in asymmetric palladium-catalyzed allylic alkylations.[4,5] In this communication, we report the synthesis of a new

(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis;* Tetrahedron Organic Chemistry Series Volume 9; Pergamon: Tarrytown, NY, 1992.

(2) For an overview, see: (a) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; Chapter 31.1. Feringa, B. L.; Naasz, R.; Imbos, R.; Arnold, L. A. In *Modern Organocopper Chemistry*; Krause, N., Ed.; Wiley-VCH: New York, 2002, Chapter 7. (b) Yamaguchi, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: New York, 1999; Chapter 31.2. (c) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171−196.

(3) For recent progress and leading references, see: (a) Alexakis, A.; Benhaim, C.; Rosset, S.; Humam, M. *J. Am. Chem. Soc.* **2002**, *124*, 5262−5263. (b) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 779−780. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353. (d) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518−3521.

(4) Shintani, R.; Lo, M. M.-C.; Fu, G. C. *Org. Lett.* **2000**, *2*, 3695−3697.

10.1021/ol026651c CCC: $22.00
Published on Web 09/17/2002

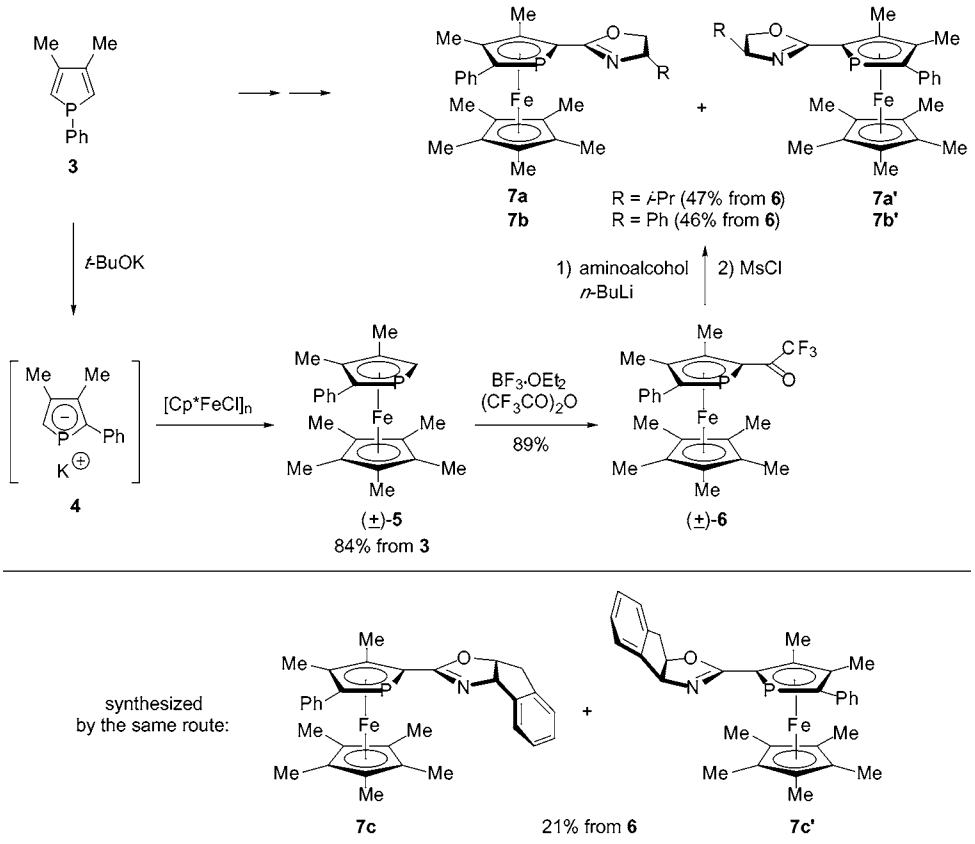
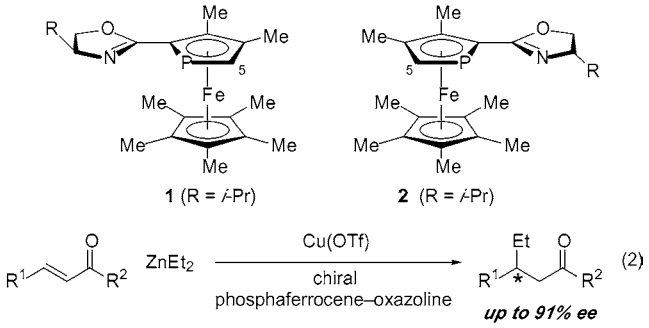
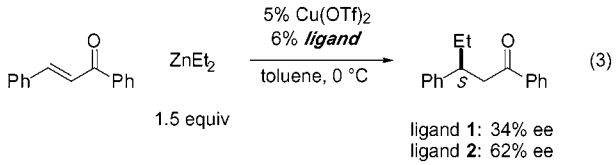


Figure 1. Synthesis of new phosphaferrocene-oxazoline ligands.

subclass of phosphaferrocene-oxazoline ligands and demonstrate their usefulness in copper-catalyzed enantioselective conjugate additions of diethylzinc to a range of acyclic enones (eq 2).



In an early study, we determined that $Cu(OTf)_2$/**1** catalyzes the 1,4-addition of $ZnEt_2$ to chalcone with 34% ee, whereas diastereomeric ligand **2** provides significantly higher enantioselection (62% ee; eq 3). The two ligands, which share the same absolute configuration in the oxazoline subunit, both furnish the *S* product preferentially; this establishes that the stereocenter of the oxazoline, not the planar chirality of the phosphaferrocene, is primarily responsible for defining the stereochemistry of the conjugate addition. Interestingly, this conclusion contrasts with palladium-catalyzed allylic alkylations in the presence of ligands **1** and **2**, for which the stereochemical course is clearly dominated by the planar chirality of the phosphaferrocene.[4]

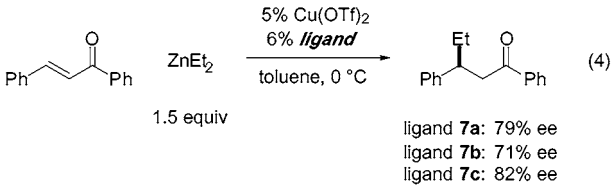


Due to their design and the routes to their synthesis, modifying the chiral environment of these phosphaferrocene-oxazoline ligands is straightforward, e.g., through changes in R, in the substituents on the phospholyl ring, and in the metal subunit (FeCp*). For palladium-catalyzed allylic alkylations, we only investigated the impact on enantioselection of changes in R.[4] For copper-catalyzed conjugate additions, we decided to explore variations both in R and in the phospholyl ring. With regard to the latter, we concluded

(5) For applications in asymmetric catalysis of chiral phosphaferrocenes that do not bear an oxazoline, see: (a) Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168−4169. (b) 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. (c) Tanaka, K.; Qiao, S.; Tobisu, M.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 9870−9871. Tanaka, K.; Fu, G. C. *J. Org. Chem.* **2001**, *66*, 8177−8186. (d) Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2001**, *20*, 3913−3917.

that substitution in the 5-position would be the most worthwhile modification to examine. Specifically, we chose a phenyl substituent, since Mathey has shown that phosphole **3**, available on a large scale through treatment of 2,3-dimethyl-1,3-butadiene with Cl_2PPh, reacts with *t*-BuOK to furnish phospholide **4** (Figure 1).[6] Complexation of **4** to $[Cp^*FeCl]_n$ provides phosphaferrocene **5**, from which the target phosphaferrocene-oxazoline ligands **7a**−**c** and **7a′**−**c′** can be generated via acylation and then oxazoline formation.[7]

We were pleased to discover that ligand **7a**, the 5-phenyl-substituted derivative of ligand **2**, affords improved enantiomeric excess in the copper-catalyzed conjugate addition of $ZnEt_2$ to chalcone (62% ee → 79% ee; eq 3 vs eq 4). Of course, the choice of oxazoline also influences the level of stereoselection: of the three members of this new subclass of phosphaferrocene-oxazoline ligands (**7a**−**c**), phenylglycinol-derived **7b** furnishes the lowest enantioselectivity (71% ee), whereas aminoindanol-derived **7c** provides the highest (82% ee).[8]

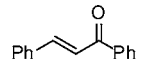
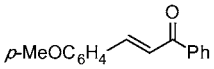
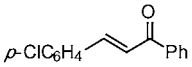
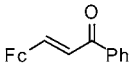
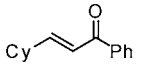
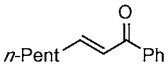
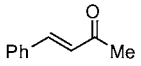


Additional optimization (e.g., Cu(OTf) instead of Cu(OTf)$_2$) led to further enhancement in the stereoselection of this process (87% ee; Table 1, entry 1). Importantly, the scope of enones for which these phosphaferrocene-oxazoline ligands are effective is fairly broad. Thus, we can achieve catalytic enantioselective conjugate additions with good ee's for both electron-rich and electron-poor chalcone derivatives (91 and 80% ees; entries 2 and 3). Interestingly, a β-ferrocene-substituted enone is also an excellent substrate for this catalyst system (90% ee; entry 4).

The utility of these phosphaferrocene-oxazoline ligands is not limited to 1,4-additions to chalcones and related compounds. For example, β-alkyl-substituted enones are also suitable reaction partners, although a relatively modest ee is obtained if the β-substituent is unbranched (84 and 61% ees; entries 5 and 6). Finally, alkyl ketones undergo conjugate addition with good enantioselection (81% ee; entry 7).[9,10]

To gain some insight into the nature of the species that are generated under our reaction conditions, we have examined the relationship between product ee and ligand ee.[11] As shown in Figure 2, in the presence of ligand **7b** we observe a clear, albeit small, negative nonlinear effect, suggesting the presence of heterochiral bis- (or higher) ligated complexes in the reaction mixture.

Table 1. Copper-Catalyzed Enantioselective Conjugate Addition of Diethylzinc to Acyclic Enones in the Presence of Phosphaferrocene-Oxazoline Ligands[a]

entry	enone	ligand	% ee	% yield
1		**7c**	87	82
2		**7c**	91	82
3		**7b**	80	89
4		**7b**	90	89
5		**7c'**	84	74
6		**7b**	61	79
7		**7b**	81	79

[a] All data are the average of two runs. Reaction conditions: enone (0.15 mmol, 1.0 equiv), $ZnEt_2$ (0.23 mmol, 1.5 equiv), $[Cu(OTf)]_2 \cdot C_6H_6$ (3.8 μmol, 2.5%), ligand (9.0 μmol, 6%), toluene (2.5 mL), 0 °C, 24 h.

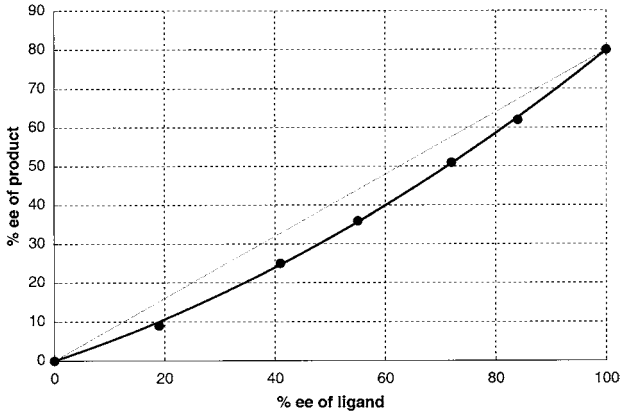


Figure 2. Negative nonlinear effect for the enantioselective conjugate addition of diethylzinc to 4-chlorochalcone catalyzed by Cu(OTf)/**7b**.

In conclusion, we have synthesized a new family of chiral phosphaferrocene-oxazoline ligands and have applied them to the copper-catalyzed asymmetric conjugate addition of diethylzinc to a range of acyclic enones with generally high

(6) Holand, S.; Jeanjean, M.; Mathey, F. *Angew. Chem., Int. Ed. Engl.* 1**997**, *36*, 98−100.

(7) The structures of **7a′**, **7b**, and **7c′** were determined by X-ray crystallography (see Supporting Information for the structure of **7a′**).

(8) Ligands **7a′**, **7b′**, and **7c′** furnish 26, 65, and 81% ees, respectively (major enantiomer: *S*).

(9) Under identical conditions, Cu(OTf)/**7c** catalyzes the conjugate addition of $ZnEt_2$ to 2-cyclohexen-1-one in 78% ee and 83% yield.

(10) Under identical conditions, Cu(OTf)/**7c** catalyzes the conjugate addition of $ZnMe_2$ to chalcone in 89% ee in a very slow process (<10% conversion after 18 h at 0 °C).

(11) For a review of nonlinear effects in asymmetric catalysis, see: Kagan, H. B.; Luukas, T. O. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 4.1.

enantioselectivity. The ligand design readily lends itself to modification, thereby facilitating optimization of ee. The dominant stereocontrol element in these 1,4-addition processes is the central chirality of the oxazoline subunit of the ligand, not the planar chirality of the phosphaferrocene; nevertheless, altering the phosphaferrocene portion of the ligand can provide useful enhancement of enantiomeric excess. In view of the ease with which the chiral environment can be tuned, including the availability of a broad spectrum of enantiopure β-amino alcohols, we anticipate that phosphaferrocene-oxazoline ligands may find application in an array of asymmetric metal-catalyzed processes.

Acknowledgment. We thank Ivory D. Hills for X-ray crystallographic work. Support has been provided by Bristol-Myers Squibb, Novartis, and Pharmacia. Funding for the MIT Department of Chemistry Instrumentation Facility has been furnished in part by NSF CHE-9808061 and NSF DBI-9729592.

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

OL026651C