A New Class of Planar−Chiral Ligands: Synthesis of a C_2-Symmetric Bisazaferrocene and Its Application in the Enantioselective Cu(I)-Catalyzed Cyclopropanation of Olefins

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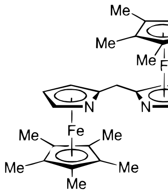
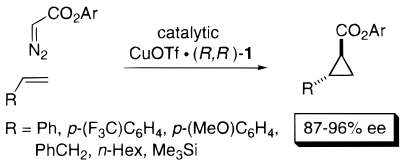
Prior to 1996, there had been no reports of applications of planar−chiral heterocycles in asymmetric catalysis. Several years ago, we initiated a program directed at the development of this family of compounds as enantioselective nucleophilic catalysts[1] and as chiral ligands for transition metals.[2] Our early work in the area of ligand design focused on complexes with C_1-symmetry,[2] but we have recently expanded the scope of our investigation to include C_2-symmetric systems. In this paper, we describe the synthesis and resolution of a new bidentate, C_2-symmetric planar−chiral bisazaferrocene (**1**), and we establish its effectiveness as a chiral ligand in the Cu(I)-catalyzed enantioselective cyclopropanation of olefins (eq 1).[3,4]

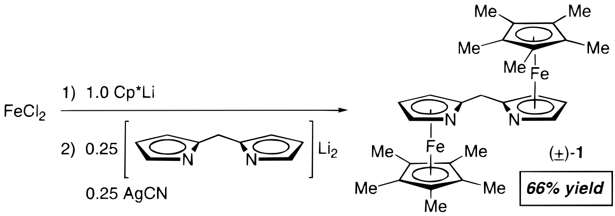


(+)-(*R*,*R*)-**1**



(1)

The synthesis of bisazaferrocene **1** is quite straightforward; treatment of $FeCl_2$ first with Cp*Li and then with the dilithio salt of di(2-pyrrolyl)methane[5] in the presence of AgCN provides (±)-**1** in 66% yield (eq 2; separated from the meso diastereomer by flash chromatography).[6] The enantiomeric ligands can be separated readily by chiral HPLC (Daicel Chiraldex OD).[7] We have determined the absolute configuration of (*S,S*)-**1** by X-ray crystallography (vide infra).



(2)

Bisazaferrocene **1** bears a resemblance to semicorrins and to bisoxazolines, insofar as they are all bidentate ligands in which the ligating sites are sp^2-hybridized nitrogen atoms. Pfaltz, Masamune, and Evans have established that copper complexes of C_2-symmetric semicorrins and bisoxazolines function as highly efficient catalysts for the enantioselective cyclopropanation of olefins by diazoacetates.[8−11] In view of these reports, we decided that an investigation of copper-catalyzed cyclopropanation would provide a suitable testing ground for determining the effectiveness of our ligand design.

Treatment of styrene with ethyl diazoacetate in the presence of 1% CuOTf•(*R*,*R*)-**1** furnishes the desired cyclopropane with modest diastereo- and enantioselectivity (Table 1, entry 1).[12] When chiral semicorrins or bisoxazolines are employed as ligands in copper-catalyzed cyclopropanation, increasing the steric demand of the diazo ester can lead to a significant improvement in stereoselectivity.[4,8−10] We have observed parallel behavior with bisazaferrocene ligand **1** (Table 1, entries 1−5). Thus, in the presence of 1% CuOTf•(*R*,*R*)-**1**, styrene reacts with the BHT ester of diazoacetic acid to produce *trans*-cyclopropane with excellent diastereo- and enantioselectivity (Table 1, entry 5).[13]

The use of the more hindered diazo ester provides the added bonus of an increased yield of cyclopropane, due to decreased formation of maleates and fumarates from copper-catalyzed coupling of the diazo ester.[14] The data in entries 3 and 4 indicate that the stereochemistry of a chiral diazo ester has little impact on the selectivity established by ligand **1**.[15]

With the BHT ester of diazoacetic acid as the carbene source, we investigated the [CuOTf•(*R*,*R*)-**1**]-catalyzed asymmetric cyclopropanation of an array of monosubstituted olefins (Table 2).[16,17] For styrene derivatives, we have determined that the

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[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.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.*, **1998**, *120*, 7479−7483.

[2] (a) Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445. (b) Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168−4169.

[3] (a) Nozaki, H.; Moriuti, S.; Takaya, H.; Noyori, A. *Tetrahedron Lett.* **1966**, 5239−5244. (b) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839−1844.

[4] For reviews, see: (a) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911−935. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1998. (c) Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137−149. (d) Calter, M. A. *Curr. Org. Chem.* **1997**, *1*, 37−70.

[5] Di(2-pyrrolyl)methane can be synthesized in one step from pyrrole and formaldehyde: Wang, Q. M.; Bruce, D. W. *Synlett* **1995**, 1267−1268.

[6] In the absence of AgCN, (±)-**1** is generated with poor diastereoselectivity and in low yield.

[7] Solvent system: 0.1/5/95 Et_2NH/*i*-PrOH/hexanes; retention time of (+)-**1**: 6.6−7.8 min; retention time of (−)-**1**: 9.0−10.8 min.

[8] (a) Fritschi, H.; Leutenegger, U.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1005−1006. (b) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta* **1991**, *74*, 232−240. (c) Pfaltz, A. *Adv. Catal. Proc.* **1995**, *1*, 61−94.

[9] Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005−6008.

[10] Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726−728.

[11] Bisazaferrocene **1** also bears a resemblance to chiral bipyridine and to chiral pyrazole-derived ligands. (a) For applications of bipyridines in catalytic asymmetric cyclopropanation, see: Ito, K.; Tabuchi, S.; Katsuki, T. *Synlett* **1992**, 575−576. Chelucci, G.; Cabras, M. A.; Saba, A. *J. Mol. Catal. A: Chem.* **1995**, *95*, L7-L10. Kwong, H.-L.; Lee, W.-S.; Ng, H.-F.; Chiu, W.-H.; Wong, W.-T. *J. Chem. Soc., Dalton Trans.* **1998**, 1043−1046. For a review of applications of bipyridines in asymmetric catalysis, see: Chelucci, G. *Gazz. Chim. Ital.* **1992**, *122*, 89−98. (b) For applications of pyrazole-derived ligands in catalytic asymmetric cyclopropanation, see: Brunner, H.; Singh, U. P.; Boeck, T.; Altmann, S.; Scheck, T.; Wrackmeyer, B. *J. Organomet. Chem.* **1993**, *443*, C16−C18. Christenson, D. L.; Tokar, C. J.; Tolman, W. B. *Organometallics* **1995**, *14*, 2148−2150.

[12] CuOTf (Salomon, R. G.; Kochi, J. K. *J. Am. Chem. Soc.* **1973**, *95*, 3300−3310) was the most effective of the copper complexes that were surveyed.

[13] For the first report of use of the BHT ester of diazoacetic acid to control trans:cis selectivity in metal-catalyzed cyclopropanations, see: Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906−1912.

[14] Other workers have minimized this deleterious coupling reaction by employing a large excess of olefin in their cyclopropanations; under these conditions, the diazo ester is the limiting reagent. In our procedure, on the other hand, we use the olefin as the limiting reagent.

[15] For similar observations by others, see ref 4.

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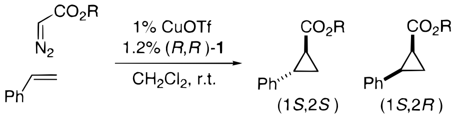
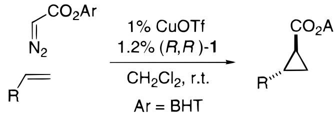
Table 1. Catalytic Enantioselective Cyclopropanation of Styrene: Stereoselectivity as a Function of Diazo Ester[a]



entry	OR	trans:cis	% ee		isolated yield, trans (%)
			trans	cis	
1	OEt	76:24	73	44	39
2	O-*t*-Bu	86:14	87	82	63
3	(+)-menthyl	88:12	87	81	67
4	(−)-menthyl	85:15	89	84	66
5	O-BHT	96:4	94		79

[a] All data represent the average of two runs.

Table 2. Catalytic Enantioselective Cyclopropanation of Monosubstituted Olefins[a]



entry	R	trans:cis	% ee, trans	yield (%)[b]
1	Ph	96:4	94	79
2	*p*-$(F_3C)C_6H_4$	94:6	96	81
3	*p*-$(MeO)C_6H_4$	94:6	87	90
4	$PhCH_2$	94:6	91	78
5	*n*-Hex	93:7	90	80
6[c]	Et_3Si	99:1	95	64

[a] All data represent the average of two runs. [b] For entries 1, 4, 5, and 6, the yield refers to the isolated yield of the trans diastereomer. For entries 2 and 3, the yield refers to the isolated yield of a mixture of cis and trans isomers. [c] 2% CuOTf/2.4% (*R*,*R*)-**1** was used.

enantioselectivity is moderately sensitive to electronic effects. Thus, electron-poor *p*-trifluoromethylstyrene (entry 2) undergoes addition with greater enantiomeric excess than does either styrene (entry 1) or electron-rich *p*-methoxystyrene (entry 3).

Importantly, CuOTf·(*R*,*R*)-**1** is an efficient catalyst not only for the asymmetric cyclopropanation of aryl-substituted olefins but also for alkyl- and silyl-substituted olefins. Thus, allylbenzene and 1-octene react with the diazoester to produce the *trans*-cyclopropane in high enantiomeric excess (entries 4 and 5). Furthermore, vinyltrimethylsilane undergoes addition with excellent diastereo- and enantioselectivity (entry 6).[18]

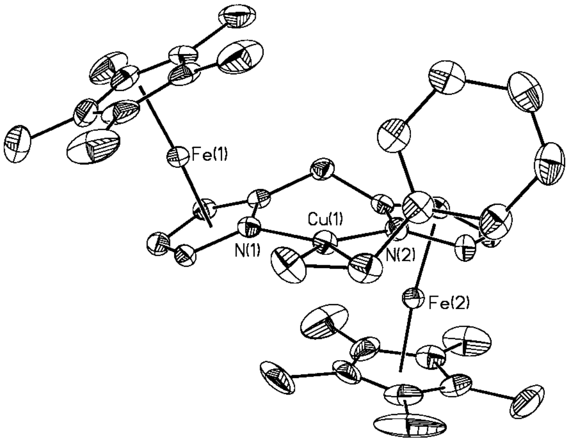


Figure 1. ORTEP illustration, with thermal ellipsoids drawn at the 35% probability level, of [Cu((*S*,*S*)-**1**)(styrene)]OTf (the triflate is noncoordinating and is not included).

Finally, we have obtained an X-ray crystal structure of [Cu((*S*,*S*)-**1**)(styrene)]OTf (Figure 1).[19,20] Ligand **1** binds to copper to provide an adduct with approximate C_2-symmetry. Complexation of the olefin leads to a square-planar geometry, and the phenyl substituent occupies one of the two quadrants left open by the bisazaferrocene. While this crystal structure nicely reveals the effective chiral environment generated by ligand **1**, it is interesting to note from a mechanistic point of view that the olefin face that is bound to copper in this structure is not the face that undergoes cyclopropanation.

In summary, we have developed a straightforward synthesis and resolution of bisazaferrocene **1**, a member of a new class of bidentate, C_2-symmetric ligands based on planar−chiral heterocycles. Furthermore, we have established that ligand **1** can effectively mediate the enantioselective Cu(I)-catalyzed cyclopropanation of an array of olefins. In future work, we intend to tune the stereoselection of this new family of ligands by changing the metal (Fe), the ligand on the metal (Cp*), and the linker (CH_2) between the heterocycles.

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Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystal structure data (20 pages). See any current masthead page for ordering information and Web access instructions.

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(16) Sample experimental (Table 2, entry 1): A solution of CuOTf·0.5 C_6H_6 (1.4 mg, 0.0056 mmol) and (*R*,*R*)-**1** (3.6 mg, 0.0067 mmol) in 1.0 mL of CH_2Cl_2 was transferred to a vessel containing styrene (59.6 mg, 0.570 mmol). The resulting solution was stirred for five min, and then the BHT ester of diazoacetic acid (68.5 mg, 0.240 mmol, 0.42 equiv) was added. TLC analysis after 10 h showed that the diazo ester had been completely consumed. Additional diazo ester (0.40 equiv) was then added, and the resulting mixture was stirred for 10 h. The final batch of diazo ester (0.40 equiv) was then added, and the reaction mixture was stirred for 16 h, at which time TLC analysis showed no residual styrene or diazo ester. The reaction mixture was filtered through a plug of silica gel, and an aliquot was analyzed by GC, which revealed a 96:4 trans:cis mixture. The product was purified by chromatography, which afforded the *trans*-cyclopropane as a colorless liquid (154 mg, 74%; chiral GC ⟹ 95% ee).

(17) The absolute stereochemistry of the product cyclopropanes is the "expected" one, based on the structural and steric analogy between bisazaferrocene **1** and semicorrins/bisoxazolines.

(18) We have begun to explore reactions of more highly substituted olefins. For example, in preliminary experiments we have found that CuOTf·(*R*,*R*)-**1** catalyzes the cyclopropanation of *trans*-β-methylstyrene with good diastereo- and enantioselectivity (94% de; 87% ee (trans)).

(19) We have also obtained an X-ray crystal structure of [Cu((*S*,*S*)-**1**)(allylbenzene)]OTf.

(20) For a previous study of a [Cu(chiral diimine)(olefin)]$^+$ complex, see: Quan, R. W.; Li, Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8156−8157.