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Synthesis, resolution and crystallographic characterization of a new C_2-symmetric planar-chiral bipyridine ligand: application to the catalytic enantioselective cyclopropanation of olefins

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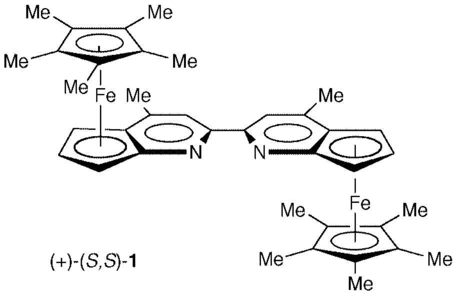
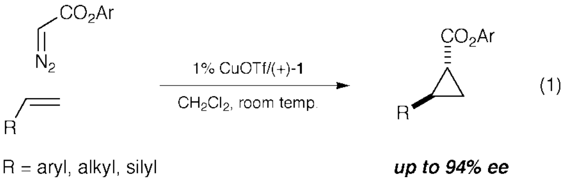
The synthesis of a new C_2-symmetric planar-chiral bipyridine ligand is described, as well as its application to the enantioselective Cu^I-catalyzed cyclopropanation of olefins.

As Togni and Venanzi have recently documented, the use of transition metal catalysts that employ nitrogen-donor ligands is expanding rapidly.[1] With respect to neutral, bidentate, nitrogen donors, 2,2′-bipyridine is one of the most widely used.[2,3] As a consequence, the development of an effective chiral derivative of bipyridine is a challenge of considerable importance.[4,5] We have recently been exploring the application of planar-chiral heterocycles in asymmetric catalysis, both as enantioselective nucleophilic catalysts[6] and as chiral ligands for transition metals.[7] Here we describe our first investigation in the area of chiral bipyridine chemistry, specifically, the synthesis, resolution and crystallographic characterization of C_2-symmetric planar-chiral ferrocene derivative **1**. To benchmark this new ligand, we have chosen to follow the lead of others by examining its utility in the Cu^I-catalyzed cyclopropanation of olefins [eqn. (1)].[8–10]



(+)-(*S*,*S*)-**1**



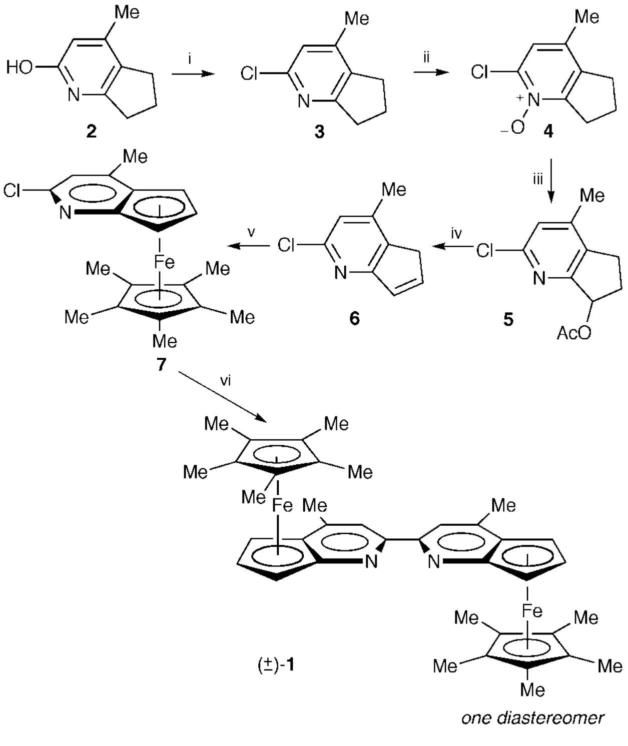
(1)

Our synthesis of ligand **1** begins with previously reported pyridine derivative **2**,[11] which is available in one step from commercially available materials (Scheme 1). Chlorination with $POCl_3$ affords compound **3** in 74% yield, and a standard sequence of oxidation, acetoxylation and elimination then furnishes pyrindine **6**.[6a] The five-membered ring of **6** is complexed to iron through reaction of its lithium salt with $(Cp^*FeCl)_n$ (59%),[6a] and the resulting ferrocene derivative is then reductively coupled with $NiBr_2(PPh_3)_2/Zn/Et_4NI$,[12] thereby providing racemic **1** as a single diastereomer in 58% yield. This route is amenable to the synthesis of multi-gram quantities of this new C_2-symmetric, planar-chiral bipyridine ligand.

The enantiomers of ligand **1** can be separated by chiral HPLC (Regis Whelk-O column). We have established the absolute configuration of (+)-**1** through X-ray crystallography.

In order to validate our ligand design, we chose to investigate the application of bipyridine **1** to the Cu^I-catalyzed cyclopropanation of olefins, a reaction that has previously been used to benchmark new chiral bipyridine designs.[8] We were pleased to observe that with the 2,6-di-*tert*-butyl-4-methylphenyl ester of diazoacetic acid as the carbene source, we can cyclopropanate an array of olefins with high stereoselectivity (Table 1). For example, treatment of styrene with 1% CuOTf, 1.2% (+)-**1**, and 2 equiv. of diazo ester in CH_2Cl_2 at room temperature furnishes the *trans*-cyclopropane in very good diastereomeric and enantiomeric excess (94% de, 87% ee; Table 1, entry 1). The stereoselection remains unchanged even at a very low catalyst loading (0.25%), although the yield drops somewhat (60%). It is worth noting that, in contrast to many previously reported Cu^I-catalyzed cyclopropanations wherein the diazo ester is the limiting reagent, our conditions employ the olefin as the limiting reagent. Among the copper sources and the solvents that we have examined, CuOTf and CH_2Cl_2 appear to be optimal.

In the presence of CuOTf/**1**, we can effect the catalytic enantioselective cyclopropanation of an array of olefins (Table



Scheme 1 *Reagents and conditions*: i, $POCl_3$, 74%; ii, H_2O_2, AcOH, 88%; iii, Ac_2O, 58%; iv, H_2SO_4, 79%; v, BuLi, then $(Cp^*FeCl)_n$, 58%; vi, 30% $NiBr_2(PPh_3)_2$, Zn, Et_4NI, 58%.

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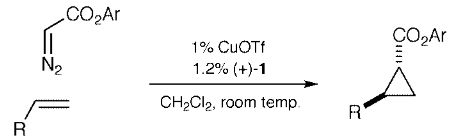
Table 1 Scope of the $\mathrm{Cu^I}$/**1**-catalyzed enantioselective cyclopropanation of olefins[a]



Entry	R	*trans*:*cis*	Ee (%) (*trans*)	Yield (%)
1	Ph	97:3	87	78
2	*p*-(MeO)C_6H_4	95:5	75	71
3	*p*-(F_3C)C_6H_4	94:6	94	83
4	*n*-Hexyl	94:6	78	78
5	Et_3Si	96:4	80	60

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

1). For styrene derivatives, we have made the interesting observation that whereas the electronic nature of the aromatic ring has only a modest effect on *trans*:*cis* diastereoselectivity, it exerts a very significant impact on enantioselectivity (entries 1–3). Thus, reaction of electron-rich 4-methoxystyrene proceeds with relatively moderate ee (75%, entry 2), whereas reaction of electron-poor 4-trifluoromethylstyrene occurs with quite high ee (94%, entry 3). Alkyl-substituted olefins (entry 4) and vinylsilanes (entry 5) undergo cyclopropanation with excellent diastereoselectivity and good enantioselectivity.

An examination of the X-ray crystal structure of [Cu((−)-**1**)(styrene)]PF_6† clearly shows that bidentate complexation of ligand **1** to copper furnishes a well-defined C_2-symmetric binding pocket [Fig. 1(*a*)]. The styrene is bound to copper in an orientation that is predictable on the basis of minimizing steric interactions with ligand **1** [Fig. 1(*b*)].

In summary, we have described the synthesis, resolution and crystallographic characterization of a new class of C_2-symmetric planar-chiral bipyridine ligands, and we have demonstrated the effectiveness of our ligand design through a study of $\mathrm{Cu^I}$-catalyzed cyclopropanations of olefins. The chiral environment afforded by this family of bidentate ligands should be readily tunable, both through a change in the metal fragment (*e.g.* FeCp* → FeC_5Ph_5[6b]) and through the incorporation of substituents in the 7 and 7′ positions. The large number of processes known to be catalyzed by bipyridine–metal complexes provides a wealth of opportunities for applications of these ligands in asymmetric catalysis.

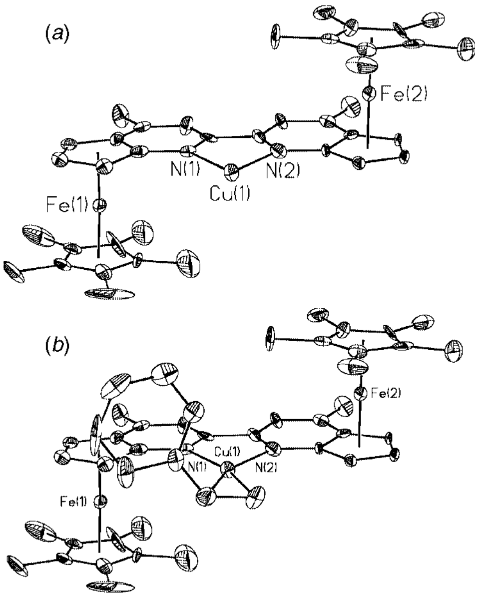


Fig. 1 X-Ray crystal structure of [Cu((−)-**1**)(styrene)]PF_6 (the non-coordinating PF_6 counter ion has been omitted for clarity): (*a*) without styrene; (*b*) with styrene.

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Notes and references

† *Crystal data* for [Cu((*R*,*R*)-**1**)(PhCH=CH_2)]PF_6 (green): $C_{46}H_{52}CuF_6Fe_2N_2P$, M = 953.11, orthorhombic, space group $P2_12_12_1$, μ = 1.315 mm^{-1}, a = 7.8830(16), b = 20.670 (4), c = 25.167(5) Å, V = 4100.8(14) $Å^3$, Z = 4, T = 183(2) K, 16506 reflections collected, 5878 independent reflections (R_{int} = 0.1378), 518 variables, R = 0.0465, R_w = 0.0549 [$I > 2\sigma(I)$], Flack parameter = −0.02(2). CCDC 182/1534.

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