

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

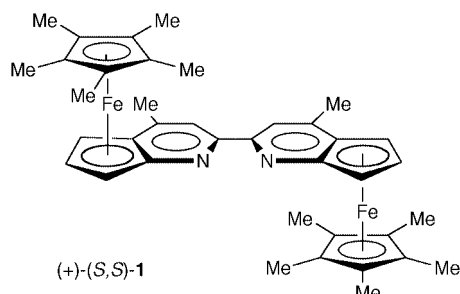
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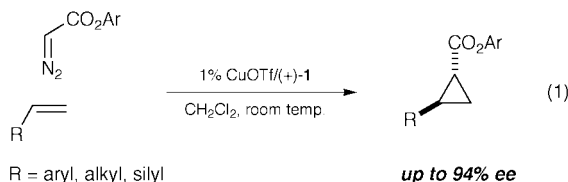
Received (in Corvallis, OR, USA) 29th November 1999, Accepted 26th January 2000

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 catalysts⁶ 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}

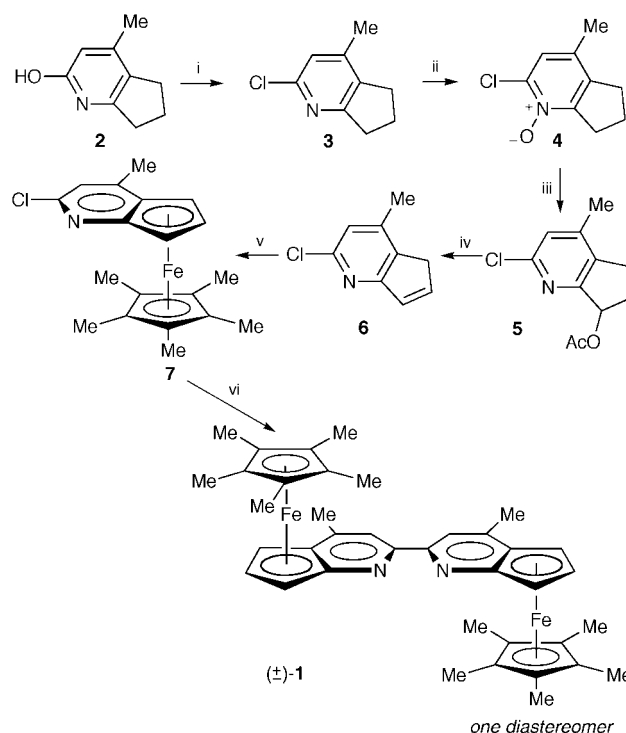


Our synthesis of ligand **1** begins with previously reported pyridine derivative **2**,¹¹ which is available in one step from commercially available materials (Scheme 1). Chlorination with $POCl_3$ affords compound **3** in 74% yield, and a standard sequence of oxidation, acetoxylation and elimination then furnishes pyridine **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%.

Table 1 Scope of the Cu^I/1-catalyzed enantioselective cyclopropanation of olefins^a

Entry	R	<i>trans</i> : <i>cis</i>	Ee (%) (<i>trans</i>)	Yield (%)
1	Ph	97:3	87	78
2	<i>p</i> -(MeO)C ₆ H ₄	95:5	75	71
3	<i>p</i> -(F ₃ C)C ₆ H ₄	94:6	94	83
4	<i>n</i> -Hexyl	94:6	78	78
5	Et ₃ Si	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)]PF₆[†] clearly shows that bidentate complexation of ligand 1 to copper furnishes a well-defined C₂-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 C₂-symmetric planar-chiral bipyridine ligands, and we have demonstrated the effectiveness of our ligand design through a study of 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* → FeC₅Ph₅^{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 com-

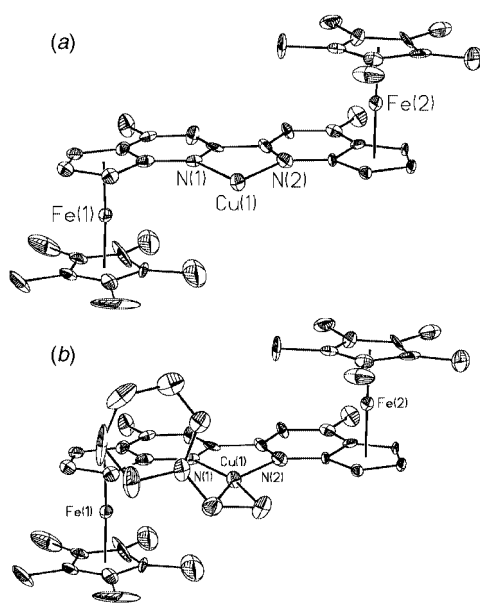


Fig. 1 X-Ray crystal structure of [Cu(–)1(styrene)]PF₆ (the non-coordinating PF₆ counter ion has been omitted for clarity): (a) without styrene; (b) with styrene.

plexes provides a wealth of opportunities for applications of these ligands in asymmetric catalysis.

Support has been provided by the Alfred P. Sloan Foundation, the American Cancer Society, Bristol-Myers Squibb, the Camille and Henry Dreyfus Foundation, Merck, the National Science Foundation, Novartis, Pfizer, Pharmacia & Upjohn, Procter & Gamble, the Spanish Ministry of Education, and Union Carbide.

Notes and references

[†] Crystal data for [Cu((*R,R*)-1)(PhCH=CH₂)]PF₆ (green): C₁₆H₁₂CuF₆Fe₂N₂P, *M* = 953.11, orthorhombic, space group *P*2₁2₁2₁, μ = 1.315 mm⁻¹, *a* = 7.8830(16), *b* = 20.670(4), *c* = 25.167(5) Å, *V* = 4100.8(14) Å³, *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* > 2σ(*I*)], Flack parameter = –0.02(2). CCDC 182/1534.

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Communication a909457a