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# Synthesis of a New Chiral Nonracemic $C_2$-Symmetric 2,2′-Bipyridyl Ligand and Its Application in Copper(I)-Catalyzed Enantioselective Cyclopropanation Reactions

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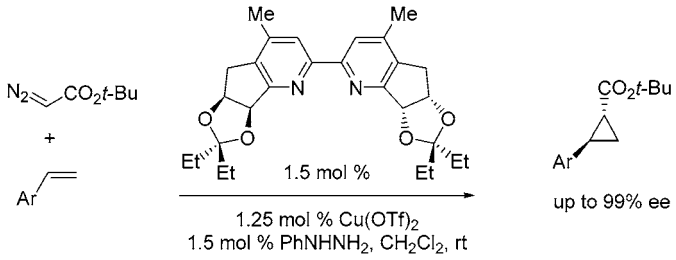
## ABSTRACT




**An efficient synthesis of a low molecular weight, chiral nonracemic and $C_2$-symmetric bipyridyl ligand is reported. The ligand was prepared using a catalytic asymmetric dihydroxylation reaction of a pyrindine as a key step. The ligand was evaluated in the asymmetric copper(I)-catalyzed cyclopropanation reactions of a series of alkenes and diazoesters. Very high diastereoselectivities and enantioselectivities were observed (>95:5 dr and up to 99% ee). These are the highest reported stereoselectivities for a chiral bipyridyl ligand.**

Of the many types of chiral ligands that have been developed for catalytic asymmetric synthesis, chiral nonracemic 2,2′-bipyridines and 1,10-phenanthrolines have received considerable recent attention.[1,2] The 2,2′-bipyridine unit offers the potential for a broad range of structural modifications that include the incorporation of stereogenic centers as well as elements of planar and axial chirality.[1] In addition, the electronic properties of this type of ligand may be adjusted by appropriate functionalization of the pyridine moieties. This class of bidentate ligand complements the prominent class of chiral ligands, the bis(oxazolines) that have been employed to a great degree of success in many asymmetric transformations.[3] In this paper, we report an efficient synthesis of the low molecular weight, chiral nonracemic and $C_2$-symmetric bipyridyl ligand (+)-**1** (Figure 1). The asymmetry of this novel chiral ligand was installed by the use of a catalytic asymmetric reaction that negated the use of chiral pool starting materials or resolution procedures. The evaluation of this chiral ligand as a highly effective chiral director in the asymmetric copper(I)-catalyzed cyclopropanation reactions of a series of alkenes and diazoesters is also described.

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(2) For discussions on the coordination chemistry of 2,2′-bipyridines and 1,10-phenanthrolines, see: (a) Reedijk, J. In *Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon Press: Oxford, 1987; Vol. 2, pp 73−98. (b) Kaes, C.; Katz, A.; Hosseini, M. W. *Chem. Rev.* **2000**, *100*, 3553.

(3) For a recent review on chiral bis(oxazolines) in asymmetric transition metal catalyzed reactions, see for example: (a) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

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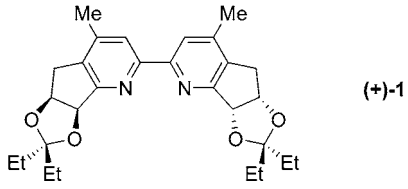
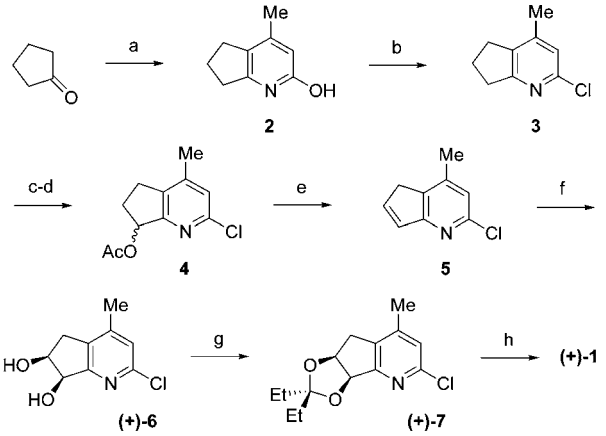



(+)-1

**Figure 1.** Chiral nonracemic $C_2$-symmetric 2,2′-bipyridyl ligand (+)-**1**.

The synthesis of the bipyridyl ligand (+)-**1** began from the 2-hydroxypyridine (pyridinone) **2**, which can be prepared on a multigram scale from cyclopentanone and ethyl acetoacetate (Scheme 1).[4] This compound was converted to the 2-chloropyridine **3** on heating with phenylphosphonic dichloride.[5,6] Subsequent oxidation with hydrogen peroxide afforded the corresponding pyridine *N*-oxide, which was converted to the acetate **4** on heating with acetic anhydride. The pyrindine **5** was prepared, as a single regioisomeric product (>30:1), on briefly heating the acetate **4** in concentrated sulfuric acid.[7] Asymmetric dihydroxylation (AD) of the pyrindine **5** with AD-mix-$\beta$ afforded the diol (+)-**6** (assigned 6*S*,7*R* stereochemistry), which on subsequent condensation with 3-pentanone afforded the acetal (+)-**7** in reasonable overall yield (57%) and in very high enantiomeric excess (90%).[8,9] To the best of our knowledge, this is the highest reported catalytic AD reaction of a cyclic *cis*-alkene.[10,11] The absolute stereochemistry of the diol (+)-**6** has not yet been determined definitively but was assigned on the basis of the well-established predictability of the Sharpless AD reaction and the sense of the following asymmetric cyclopropanation (AC) reactions.[1,8] Repeating the above two-step procedure with AD-mix-α afforded the acetal (−)-**7** in 48% yield and in 82% ee. To improve the yield and rate of the AD reaction, it was modified and performed with 1 mol % of potassium osmate dihydrate and 5 mol % of the chiral ligand $(DHQD)_2PHAL$.[12] This afforded the corresponding acetal (+)-**7** in 81% overall yield and in 90% ee. The rate of the AD reaction was also significantly improved. Employing *N*-methylmorpholine-*N*-oxide in place of potassium ferricyanide, as the stoichiometric oxidant in the latter two-step procedure, afforded the acetal (+)-**7** in 89% overall yield.[13] However, the required reaction time was longer, and the enantioselectivity of this AD reaction was significantly compromised (61% ee).

**Scheme 1.** Synthesis of 2,2′-Bipyridyl Ligand (+)-**1**[a]




[a] Reagents and conditions: (a) ethyl acetoacetate, $NH_4OAc$ (ref 4); (b) $PhP(O)Cl_2$, 160 °C, 16 h, 83%; (c) $H_2O_2$, $H_2O$, AcOH, 80 °C, 16 h; (d) $Ac_2O$, rt, 1 h then 100 °C, 4 h, 60% (over two steps); (e) $H_2SO_4$, 120 °C, 10 min, 81%; (f) AD-mix-$\beta$, *t*-BuOH/$H_2O$ (1:1), 0 °C, 12 h *or* 1 mol % $K_2OsO_4 \cdot 2H_2O$, 5 mol % $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, $K_2CO_3$, *t*-BuOH/$H_2O$ (1:1), 0 °C, 2 h; (g) 3-pentanone, PhH, *p*-TsOH (cat.), reflux, 16 h, 57% *and* 81%, respectively (over two steps); (h) $NiCl_2(H_2O)_6$, $PPh_3$, Zn, DMF, 60 °C, 4 h, 84%.

It was determined by analytical chiral HPLC and found to be greater than 99% ee. This indicated that significant enrichment of the enantiomeric purity of the chiral material had occurred in this coupling reaction. The enantiomeric bipyridyl ligand (−)-**1** was prepared accordingly in 53% yield (unoptimized) and was also found to have an enantiomeric excess that was greater than 99%.

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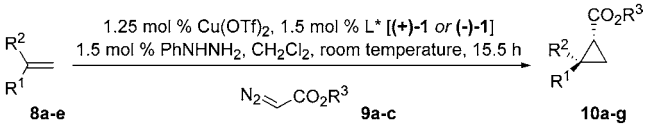
(7) On heating the acetate **4** with concentrated sulfuric acid for an extended period of time (1 h) the regioselectivity of this elimination reaction was compromised (9:1). Ruble and Fu have reported a related example in which a functionalized pyrindine is formed as a mixture of regioisomers (2:1): Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230 (Supporting Information).
(8) For a review on AD reactions, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
(9) The enantioselectivity of this AD reaction was determined by analytical chiral HPLC (Daicel Chiracel OD column).
(10) For comparison, AD of indene with AD-mix-$\beta$ affords the corresponding diol (6*S*,7*R* stereochemistry) in 33−40% ee; see: Spivey, A. C.; Hanson, R.; Scorah, N.; Thorpe, S. J. *J. Chem. Ed*. **1999**, *76*, 655. Hanessian and co-workers have reported that indene can be dihydroxylated with a simple $C_2$-symmetric chiral ligand derived from (1*R*,2*R*)-*trans*-1,2-diaminocyclohexane in 80% ee (70% yield). However, the chiral ligand and osmium tetroxide are used stoichiometrically in this reaction; see: Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-Y.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991.
(11) Interestingly, the overall yield of the corresponding quinoline derivative of the acetal (+)-**7** that has been prepared from cyclohexanone by the same procedures was significantly greater. However, the enantiomeric purity of this acetal was poor (~5% ee).
(12) The rate and yield of this process was not improved by the addition of methanesulfonamide. Sharpless and co-workers have reported an improvement in the rate of the AD reaction of indene with the chiral ligand $(DHQD)_2PHAL$ using methanesulfonamide as an additive and 1 mol % of potassium osmate dihydrate: (a) Wang, Z.-M.; Kakiuchi, K., Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 6895. (b) Wang, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7568.
(13) Wang, Z.-M.; Sharpless, K. B. *J. Org. Chem.* **1994**, *59*, 8302.
(14) (a) Dehmlow, E. V.; Sleegers, A. *Liebigs Ann. Chem.* **1992**, 953. (b) Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn*. **1990**, *63*, 80.

**Table 1.** Asymmetric Cyclopropanation of Alkenes **8a**−**e**




| entry | L* | $R^1$ | $R^2$ | $R^3$ | product | *trans*:*cis*[a] | yield (%)[b] | ee[c] (*trans*) |
|---|---|---|---|---|---|---|---|---|
| 1 | (+)-**1** | Ph | H | Et | **10a** | 80:20 | 74 | 82 |
| 2 | (+)-**1** | Ph | H | Bn | **10b** | 92:8 | 49 | 84 |
| 3 | (+)-**1** | Ph | H | *t*-Bu | **10c** | 93:7 | 67 | 92 |
| 4 | (−)-**1** | Ph | H | *t*-Bu | *ent*-**10c** | 92:8 | 68 | 93[d] |
| 5 | (+)-**1** | *p*-$MeOC_6H_4$ | H | *t*-Bu | **10d** | >95:5 | 69 | 71 |
| 6 | (+)-**1** | *p*-$FC_6H_4$ | H | *t*-Bu | **10e** | 92:8 | 73 | 99 |
| 7 | (+)-**1** | $PhCH_2CH_2$ | H | *t*-Bu | **10f** | >95:5 | 82 | 83 |
| 8 | (+)-**1** | Ph | Ph | *t*-Bu | **10g** | | 81 | 72 |

[a] Determined by analysis of the $^1$H NMR spectra of the crude reaction products. [b] Combined yield of chromatographically separated *trans*- and *cis*-cyclopropanes. [c] Determined by analytical chiral HPLC (Daicel Chiracel OD column) following reduction to the corresponding primary alcohols with lithium aluminum hydride. The reactions were also performed in the absence of the chiral ligand to provide reference samples for these analytical measurements. [d] The product is the enantiomer of that indicated in the reaction scheme.

The bipyridine (+)-**1** was evaluated as a chiral ligand for use in catalytic asymmetric synthesis by undertaking a series of copper(I)-catalyzed AC reactions (Table 1).[15]

The active copper(I)-catalyst was generated by reduction of the complex formed between 1.25 mol % of copper(II) triflate and 1.50 mol % of the ligand (+)-**1** with phenylhydrazine. The AC reactions were carried out at room temperature in dichloromethane and involved the slow addition of the diazoesters **9a**−**c** (over ∼3 h) to a solution of alkenes **8a**−**e** and the preformed catalyst according to standard procedures.[16] Of note, the diazoesters **9a**−**c** were employed as the limiting reagent. The AC reaction of styrene **8a** with ethyl diazoacetate **9a** afforded the cyclopropane **10a** in good yield, diastereoselectivity and enantioselectivity.[1,17] This result compares favorably with several other known chiral 2,2′-bipyridyl ligands.[1] Improved diastereoselectivity of this reaction was observed when benzyl and *tert*-butyl diazoacetate **9b**−**c** were used to prepare the corresponding cyclopropanes **10b**−**c**.[1,17,18] Very high enantioselectivity was also recorded for the reaction of styrene **8a** with *tert*-butyl diazoacetate **9c**.[1,17] The enantiomeric ligand (−)-**1** was used to prepare cyclopropane *ent*-**10c**, which also illustrates the observed reproducibility of these AC reactions. It is known that the enantioselectivity of AC reactions of styrene derivatives with bipyridyl complexes are susceptible to electronic effects.[5,19] It was found that the AC reaction of electron-rich *p*-methoxystyrene **8b** afforded cyclopropane **10d** in moderate enantiomeric excess (71%). However, the electron-poor *p*-fluorostyrene **8c** afforded cyclopropane **10e** in exceptionally high enantiomeric excess (99%). The latter result is, to the best of our knowledge, the highest reported enantioselectivity for an AC reaction with a chiral bipyridyl ligand. The ligand (+)-**1** was also used to cyclopropanate a terminal alkene, 4-phenyl-1-butene **8d**, and a 1,1-disubstituted alkene, 1,1-diphenylethene **8e**, in good to moderate enantiomeric excess.[19,20]

The stereochemical outcome of these AC reactions can be rationalized in terms of minimization of steric interactions between the reacting species and the copper(I) complex of the bipyridyl ligand (+)-**1**.[19,21] The high enantioselectivities can be rationalized in terms of the structural rigidification that is provided by the chiral acetal moieties of the $C_2$-symmetric bipyridyl ligand.[22]

In conclusion, an efficient synthesis of a low molecular weight, chiral nonracemic and $C_2$-symmetric 2,2′-bipyridyl ligand (+)-**1** has been achieved from readily available starting materials. The chirality of the ligand was installed by an enantioselective catalytic AD reaction. This ligand was found to be highly effective in the AC reactions of a variety of alkenes with *tert*-butyl diazoacetate **9c**. Very high diastereoselectivities (>95:5) and enantioselectivities (99% ee) were observed. Current investigations are focused on the use of the bipyridyl ligand (+)-**1** in other catalytic asymmetric processes and on the preparation of derivatives of this ligand by condensation of the diol (+)-**6** with a variety of symmetrical ketones.

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**Supporting Information Available:** Detailed experimental procedures and product characterization data for all of the compounds synthesized and $^1$H and $^{13}$C NMR spectra for compounds (+)-**1**, **2**−**5** and (+)-**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049853C

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(17) The absolute stereochemistry of cyclopropane **10a** was assigned as 1*R*,2*R* by comparison of the optical rotation with literature values; see for example: Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Adv. Synth. Catal.* **2001**, *343*, 79 and references therein.

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(22) Of note, disubstituted chiral bis(oxazoline) ligands provide improved enantioselection in AC reactions; see: Doyle, M. P. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 5.