Planar-Chiral Pyridine *N*-Oxides, a New Family of Asymmetric Catalysts: Exploiting an η^5-C_5Ar_5 Ligand to Achieve High Enantioselectivity[1]

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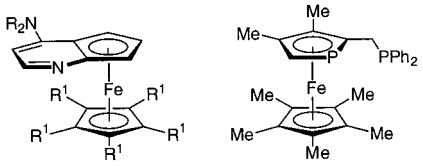
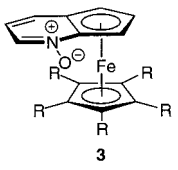
We have recently described a number of applications of planar-chiral heterocycles in asymmetric catalysis, both as enantioselective nucleophilic catalysts (e.g., **1**)[2] and as chiral ligands for transition metals (e.g., **2**).[3] In each case, nitrogen or phosphorus atoms served as nucleophilic/ligating sites.



NR_2 = NMe_2, pyrrolidino
R^1 = Me, Ph

Catalysts in which oxygen is the nucleophilic site effect a number of useful transformations.[4] For example, pyridine *N*-oxides catalyze the rearrangement of thiones, as well as the allylation of aldehydes.[5] In view of the utility of planar-chiral pyridine derivatives such as **1**, it occurred to us that the corresponding pyridine *N*-oxides (**3**) might also prove to be effective asymmetric catalysts. In this report, we describe the synthesis and structural characterization of several planar-chiral pyridine *N*-oxides, and we apply this new family of complexes to the catalytic enantioselective desymmetrization of meso epoxides (eq 1).

In contrast to catalysts in which the pyridine nitrogen serves as the nucleophilic site (e.g., **1**), we anticipated that, for pyridine *N*-oxide catalysts, an electron-donating 4-dialkylamino group should not be critical for reactivity. We therefore chose complexes



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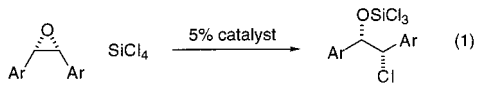
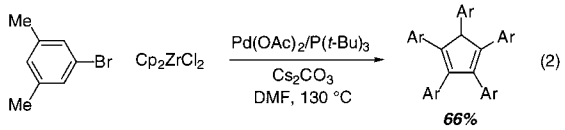


91-98% ee

3a and **3b** as our initial targets. As illustrated in Figure 1, these complexes are easily accessible.[6] Thus, one-pot treatment of $FeCl_2$ with C_5R_5Li, followed by pyrindinyl anion, affords ferrocenes **4a** and **4b**. Oxidation with dimethyldioxirane then furnishes the desired pyridine *N*-oxides **3a** and **3b**, the enantiomers of which are readily resolved by chiral HPLC. We have determined the absolute configuration of (−)-**3b** by X-ray crystallography (Figure 2).

As a test for our design, we chose to examine the effectiveness of this new family of planar-chiral catalysts in the desymmetrization of meso epoxides with chlorosilanes,[7] a reaction first studied by Denmark with a chiral phosphoramide catalyst.[8] We discovered that, although (−)-**3a** efficiently catalyzes the ring-opening of *cis*-stilbene oxide by $SiCl_4$, the product is formed in very modest enantiomeric excess (11% ee; Table 1, entry 1). Use of more sterically hindered (−)-**3b** provides somewhat higher selectivity (25% ee at room temperature; entry 2), which can be further enhanced by lowering the reaction temperature to −78 °C (60% ee; entry 3).[9]

Examination of the crystal structure of **3b** furnishes a clue to the origin of the moderate stereoselection that we observe: because the oxygen, not the nitrogen, of the catalyst is the nucleophilic site, the Fe(η^5-C_5Ph_5) group may not be sufficiently large to provide an effective chiral environment (Figure 2). Inspection of the structure further suggests that substitution in the meta position might be the best approach to extending the reach of the metal fragment. Fortunately, a method recently reported by Miura and Dyker provides ready access to the necessary cyclopentadiene derivative (eq 2).[10]



66%

Planar-chiral pyridine *N*-oxide **3c** can then be synthesized according to the general route described above (Figure 1; X-ray structure: Figure 3). It is evident from the crystal structures that, compared to the parent η^5-C_5Ph_5 ligand of **3b**, the meta-substituted

(1) Dedicated to Professor K. Barry Sharpless on the occasion of his 60th birthday.

(2) Kinetic resolution of alcohols: Bellemin-Laponnaz, S.; Tweddell, J.; Ruble, J. C.; Breitling, F. M.; Fu, G. C. *Chem. Commun.* **2000**, 1009−1010, and references therein. (b) Ring-opening/dynamic kinetic resolution of azlactones: Liang, J.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 3154−3155. (c) Rearrangement of *O*-acylated azlactones: Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532−11533. (d) Addition of alcohols to ketenes: Hodous, B. L.; Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1999**, *121*, 2637−2638.

(3) Amino alcohol-catalyzed addition of organozinc reagents to aldehydes: Dosa, P. I.; Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 444−445. (b) Rhodium-catalyzed hydrogenation of dehydroamino acids: Qiao, S.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 4168−4169. (c) Copper-catalyzed cyclopropanation of olefins: Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270−10271.

(4) For some examples of catalytic enantioselective processes, see: (a) Phosphoramide-catalyzed aldol reactions: Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432−440. (b) Overview of several X_3P═O-based reactions: Buono, G.; Chiodi, O.; Wills, M. *Synlett* **1999**, 377−388. (c) Formamide-catalyzed allenylations of aldehydes: Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2889−2894. (d) Phosphoramide-catalyzed allylations of aldehydes: Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161−6163.

(5) We are aware of only four reports of asymmetric catalysis using a chiral pyridine *N*-oxide: (a) Rearrangement of thiones: Diana, M. B.; Marchetti, M.; Melloni, G. *Tetrahedron: Asymmetry* **1995**, *6*, 1175−1179. (b) Allylation of aldehydes: Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S.-i. *J. Am. Chem. Soc.* **1998**, *120*, 6419−6420. (c) Reduction of ketones and addition of $ZnEt_2$ to aldehydes: Derdau, V.; Lachat, S.; Hupe, E.; König, W. A.; Dix, I.; Jones, P. G. *Eur. J. Inorg. Chem.* **1999**, 1001−1007. (d) Saito, M.; Nakajima, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **2000**, 1851−1852.

(6) These reactions have not been optimized.

(7) For a review of catalytic asymmetric ring-openings of epoxides, see: Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 35.

(8) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428−2429. (b) After our work was completed, Buono reported an effective phosphonamide catalyst: Brunel, J. M.; Legrannd, O.; Reymond, S.; Buono, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 2554−2557.

(9) We have found that, in the presence of $(i\text{-Pr})_2$NEt, we obtain higher enantioselectivities and more reproducible results. We believe that, in the absence of $(i\text{-Pr})_2$NEt, HCl that is produced through adventitious hydrolysis of $SiCl_4$ reacts directly with the epoxide to form the chlorohydrin in a nonstereoselective process. In a control reaction, we have determined that no ring-opening occurs upon treatment of an epoxide with $SiCl_4$ and $(i\text{-Pr})_2$NEt (no pyridine *N*-oxide) at room temperature.

(10) Miura, M.; Pivsa-Art, S.; Dyker, G.; Heiermann, J.; Satoh, T.; Nomura, M. *Chem. Commun.* **1998**, 1889−1890.

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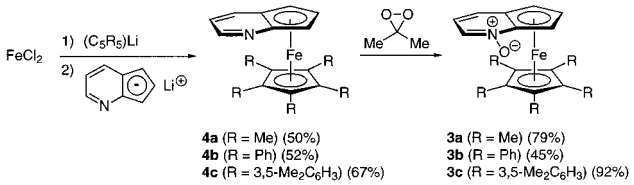


Figure 1. Synthesis of planar-chiral pyridine *N*-oxides.

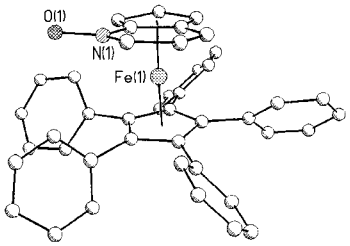
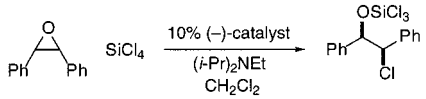


Figure 2. X-ray crystal structure of (−)-**3b**·MeOH (for clarity, the MeOH is omitted).

Table 1. Desymmetrization of *cis*-Stilbene Oxide Catalyzed by Planar-Chiral Pyridine *N*-Oxides



entry	catalyst	temperature	ee (%)
1	**3a**	rt	11
2	**3b**	rt	25
3	**3b**	−78 °C	60
4	**3c**	rt	68
5	**3c**	−78 °C	92

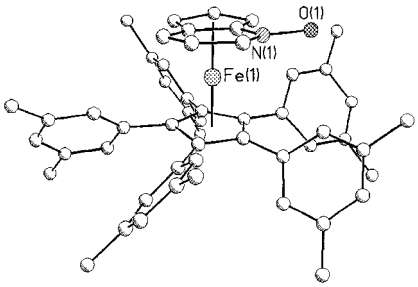


Figure 3. X-ray crystal structure of (+)-**3c**·TsOH (for clarity, the TsOH is omitted).

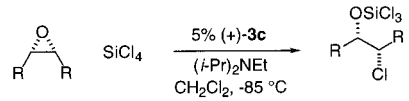
η^5-C_5Ar_5 ligand of **3c** more effectively occupies the space beneath the plane of the pyridine *N*-oxide (Figure 2 vs Figure 3).

Gratifyingly, this increased steric demand does indeed lead to increased enantioselectivity in the catalytic desymmetrization of meso epoxides with $SiCl_4$. Thus, whereas the parent complex (**3b**) furnishes 25% ee in the room-temperature ring-opening of *cis*-stilbene oxide (Table 1, entry 2), the more bulky derivative (**3c**) affords 68% enantiomeric excess (entry 4). Simply by decreasing the reaction temperature to −78 °C, we can now obtain the chlorohydrin with excellent stereoselection (92%, entry 5).

A lower catalyst loading can be employed without compromising enantioselectivity (Table 2, entry 1 vs Table 1, entry 5).[11]

(11) We have found that, even with a catalyst loading as low as 1%, we can obtain chlorohydrin in >90% ee for the reaction of *cis*-stilbene oxide. With chiral phosphonamides, Buono has reported a significant decrease in enantioselectivity at catalyst loadings less than 10% (ref 8b).

Table 2. Catalytic Enantioselective Desymmetrization of Meso Epoxides



entry	R	yield (%)	ee (%)
1	Ph	88	94
2	4-FC_6H_4	97	91
3	4-$CH_3C_6H_4$	94	93
4	4-$CF_3C_6H_4$	93	98
5	2-naphthyl	84	94
6	CH_2OBn	91	50

All data are the average of two runs.

Under these conditions (5% catalyst **3c**), a number of epoxides are desymmetrized in very good yield and high stereoselection (Table 2).[12] The enantiomeric excess of the chlorohydrin is modestly sensitive to electronic effects (entries 1−4), with the highest selectivity observed in the case of an electron-poor aromatic group (entry 4). The ring-opening proceeds in good ee with a naphthyl substituent (entry 5), but modest ee with an alkyl group (entry 6). At the end of these reactions, catalyst **3c** can be recovered nearly quantitatively (>90%).[13]

In summary, we have designed and synthesized a new family of chiral catalysts, planar-chiral pyridine *N*-oxides, and we have applied them to the catalytic, highly enantioselective ring-opening of meso epoxides. In the course of these studies, we have provided the first demonstration that appropriate incorporation of substituents on a C_5Ar_5 ring can serve as a powerful means for tuning catalyst enantioselectivity. In view of the widespread use of cyclopentadienylmetal complexes, particularly ferrocene derivatives,[14] in asymmetric catalysis, we anticipate that this strategy will prove to be broadly applicable. Ongoing studies are directed at providing support for this hypothesis and at developing additional applications of planar-chiral pyridine *N*-oxides as enantioselective catalysts.

Acknowledgment. We thank Dr. Jack Liang for furnishing C_5Ar_5H (Ar = 3,5-$Me_2C_6H_3$) and the Seeberger and Danheiser groups for sharing chemicals and equipment. Support has been provided by Bristol-Myers Squibb, Merck, the National Institutes of Health (National Institute of General Medical Sciences, R01-GM57034), Novartis, and Pfizer.

Supporting Information Available: Experimental procedures, compound characterization data, and X-ray crystallographic data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) General experimental (Table 2, entry 1): A solution of catalyst (+)-**3c** (11.6 mg, 0.015 mmol) in CH_2Cl_2 (1.0 mL), *cis*-stilbene oxide (58.9 mg, 0.30 mmol) in CH_2Cl_2 (1.0 mL), (*i*-Pr)$_2$NEt (60 μL, 0.34 mmol), and CH_2Cl_2 (4.0 mL) were added in turn to a Schlenk tube. The Schlenk tube was closed and then cooled to −80 °C. $SiCl_4$ (1.0 M solution in CH_2Cl_2; 0.36 mL, 0.36 mmol) was added by syringe to the reaction mixture over 5−10 min. After 24 h at ∼−85 °C, the reaction was quenched by the addition of a solution of saturated KF/1M KH_2PO_4 (1:1). The resulting mixture was extracted with EtOAc, and the organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (10% Et_2O in hexanes) afforded 60.8 mg (87%) of (*S*,*S*)-2-chloro-1,2-diphenylethan-1-ol. GC analysis (Chiraldex G-TA) showed 94% ee.

(13) We have begun to explore the mechanism of this catalytic enantioselective ring-opening process. Some of our preliminary observations include: (1) a positive nonlinear correlation between the ee of the catalyst and the ee of the chlorohydrin; (2) a rate that is zero-order in $SiCl_4$ and zero-order in (*i*-Pr)$_2$NEt; (3) ^{1}H and ^{29}Si NMR evidence (−70 °C) for an interaction between $SiCl_4$ and the catalyst, but not between $SiCl_4$ and either the epoxide or (*i*-Pr)$_2$NEt.

(14) *Ferrocenes*; Togni, A., Hayashi, T., Eds.; VCH: New York, 1995. (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377−2407.