Pergamon

Tetrahedron Letters 43 (2002) 8827–8829

TETRAHEDRON
LETTERS

Enantioselective ring opening of *meso*-epoxides with tetrachlorosilane catalyzed by chiral bipyridine *N*,*N*′-dioxide derivatives

Makoto Nakajima,* Makoto Saito, Michinao Uemura and Shunichi Hashimoto

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

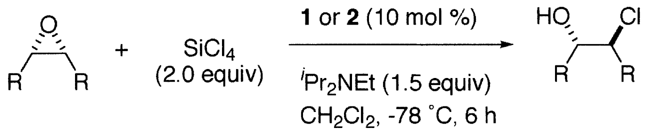
Received 25 September 2002; revised 4 October 2002; accepted 7 October 2002

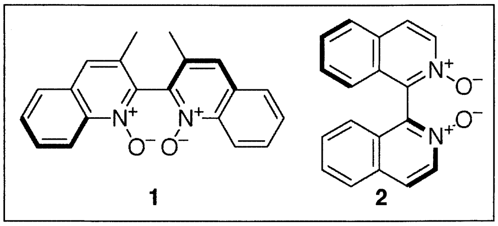
Abstract—An enantioselective ring opening of *meso*-epoxides with tetrachlorosilane in the presence of diisopropylethylamine exploiting chiral bipyridine *N*,*N*′-dioxides as catalysts affords the corresponding chlorohydrins in high enantioselectivities of up to 90% ee. © 2002 Elsevier Science Ltd. All rights reserved.

The asymmetrization of *meso*-epoxides via enantioselective addition of nucleophiles is an attractive strategy for asymmetric synthesis since it simultaneously establishes two contiguous stereogenic centers.[1,2] Among various nucleophiles employed in epoxide opening, halide ions have currently received considerable attention.[3] Recently, Denmark and co-workers reported the formation of optically active chlorohydrin by ring opening of *meso*-epoxide with tetrachlorosilane in the presence of a chiral phosphoramide as a Lewis base via a pentacoordinate silicate complex as an intermediate.[4–6] More recently, Fu and co-workers reported that planar-chiral pyridine *N*-oxide-catalyzed epoxide opening with tetrachlorosilane afforded the corresponding chlorohydrin in high enantioselectivity of up to 98% ee.[7] As part of our program directed at the development of *N*-oxide-mediated reactions,[8] we reported an enantioselective allylation of aldehydes with allyltrichlorosilanes via hexacoordinate silicate complexes as intermediates utilizing chiral bipyridine *N*,*N*′-dioxide **1** as a catalyst.[8a] We were intrigued by the reaction mechanism of Lewis base-catalyzed activation of tetrachlorosilane and the beneficial effect of bidentate *N*,*N*′-dioxide on reactivity and enantioselectivity. Herein, we describe an epoxide opening with tetrachlorosilane employing *N*,*N*′-dioxides as chiral catalysts.

Initial studies examined the addition of tetrachlorosilane to *cis*-stilbene oxide (**3**) using 10 mol% of chiral *N*,*N*′-dioxide **1** as a catalyst in the presence of diisopropylethylamine (1.5 equiv.) in dichloromethane. The reaction proceeded smoothly at −78°C to afford the corresponding chlorohydrin in 94% yield but the observed enantioselectivity (56%) was not satisfactory. Among the various chiral *N*-oxides surveyed, we were gratified to find that the corresponding chlorohydrin was obtained in 95% yield with 90% ee by employing **2** as a catalyst (Table 1, entry 1), which were less effective in the enantioselective allylation previously reported.[8a]

The reaction was optimized by varying the solvent and the nucleophile using **2** as a catalyst. Dichloromethane appears be to the best solvent in terms of enantioselectivity (propionitrile: 89%, 8% ee; tetrahydrofuran: 93%, 3% ee; toluene: 91%, 2% ee). The use of methyl-, allyl-, or phenyltrichlorosilane as a nucleophile gave racemic





1 **2**

---

* Corresponding author. Tel.:+81-11-706-3766; fax: +81-11-706-4981; e-mail: nakajima@pharm.hokudai.ac.jp

PII: S0040-4039(02)02229-3

Table 1. Enantioselective ring opening of *meso*-epoxide catalyzed by chiral bipyridine *N*,*N*′-dioxide **2**[9]

Entry	Epoxide	Yield, %[a]	ee, %[b] (confgn)[c]	$[\alpha]_D$ (*c*, solvent)
1	**3**: R = Ph	95	90 (1*S*,2*S*)	+21.4 (1.4, EtOH)
2	**4**: R = CH_2OCH_2Ph	98	74 (2*S*,3*S*)	+3.4 (1.1 EtOH)
3	**5**: R = $CH_2O(CH_2)_3Ph$	95	70 (2*S*,3*S*)[d]	+4.0 (1.0 EtOH)
4	**6**: R, R = $(CH_2)_4$	83	0	–

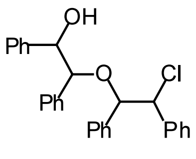
[a] Isolated yield.

[b] Determined by HPLC analysis employing a Daicel Chiralcel OD-H or Chiralpak AD-H.

[c] Configuration assignment by comparison to literature values of optical rotations.

[d] Assignment by analogy.

chlorohydrin in high yield. The effect of addition of diisopropylethylamine is essential for both chemical and optical yields.[10] The reaction in the absence of amine produced the chlorohydrin in only 31% ee and in 73% yield, accompanied by dimer **7**. 1.5 Equivalents of diisopropylethylamine were sufficient for optimum chemical and optical yields. It is reasonable to assume that diisopropylethylamine traps hydrogen chloride which was produced through adventitious hydrolysis of tetrachlorosilane and reacts directly with the epoxide to form chlorohydrin in a nonstereoselective process.[11]

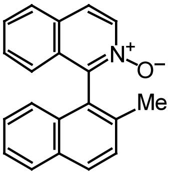


7

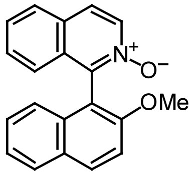
Ring opening of other epoxides with the present method was also examined. Epoxides derived from 2-butene-1,4-diols (**4** and **5**) produced the corresponding chlorohydrins in good enantioselectivity (entries 2 and 3), while cyclohexene oxide (**6**) gave a racemic product (entry 4).

The mechanism of the present reaction is intriguing. Denmark and co-workers suggested that the reaction mechanism involves a pentacoordinate silicate complex with monodentate phosphoramide and epoxide. However, Fu and co-workers observed a positive nonlinear correlation between the enantiomeric excess of their catalyst and the enantiomeric excess of the product in the epoxide opening reaction catalyzed by their planar-chiral pyridine oxide. This result suggests the possibility of the coordination of the second *N*-oxide molecule to silicon atom forming a hexacoordinate silicate. Analogous to the enantioselective allylation previously reported,[8a] **1** and **2** are expected to act as a bidentate ligand to form a hexacoordinate silicate intermediate.

To test this hypothesis, we examined an epoxide opening using monodentate *N*-oxides **8** and **9**,[13] wherein one of the *N*-oxide moieties in **2** is substituted with a methyl or methoxy group. Catalytic activity of **8** and **9** were so low that the reaction of stilbene oxide with tetrachlorosilane did not proceeded at all at −78°C. In the case of 1,4-dibenzyloxy-2-butene epoxide (**4**), the corresponding chlorohydrin was obtained in low chemical and optical yield (**8**: 35% yield with 62% recovery of epoxide, 27% ee, **9**: 75% yield with 15% recovery of epoxide, 6% ee) in otherwise identical conditions. The significant decrease in reactivity and enantioselectivity may be explained by invoking the hexacoordinate silicate intermediate, though the details are not clear at present.



8



9

In conclusion, we have demonstrated the effectiveness of chiral *N*,*N*′-dioxide as a catalyst for enantioselective ring opening of *meso*-epoxide with tetrachlorosilane via a hexacoordinate silicate intermediate. Studies on the mechanism as well as the design of chiral bipyridine *N*,*N*′-dioxides to enhance enantioselectivity are currently in progress.

Acknowledgements

This work was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan, Novartis Foundation for the Promotion Science, and the Akiyama Foundation. The authors thank the Japan Society for the Promotion of Science for Research Fellowships for Young Scientists (to M.S.).

References

1. For a review, see: Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361–14384.
2. For recent successful approaches, see: (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768–2769; (b) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898; (c) Cole, B. M.; Shimizu, K. D.; Krueger, C. A.; Harrity, J. P. A.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1668–1671; (d) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784; (e) Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 9023–9026.

3. (a) Andrews, G. C.; Crawford, T. C.; Contillo, L. G. *Tetrahedron Lett.* **1981**, *22*, 3803–3806; (b) Bonini, C.; Righi, G. *Synthesis* **1994**, 225–238; (c) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 4534–4535.
4. Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428–2429.
5. For enantioselective allylations via silicate complexes catalyzed by chiral Lewis bases, see: (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161–6163; (b) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *37*, 5149–5150; (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1999**, *39*, 2767–2770; (d) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett.* **2002**, *4*, 2799–2801; (e) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, *4*, 1047–1049.
6. For enantioselective aldol reactions via silicate complexes catalyzed by chiral Lewis bases, see: Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432–440.
7. Tao, B.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 353–354.
8. (a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419–6420; (b) Nakajima, M.; Saito, M.; Hashimoto, S. *Chem. Pharm. Bull.* **2000**, *48*, 306–307; (c) Saito, M.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2000**, 1851–1852; (d) Nakajima, M.; Yamaguchi, Y.; Hashimoto, S. *Chem. Commun.* **2001**, 1596–1597.
9. *Representative procedure*: To a stirred solution of **2** (7.5 mg, 10 mol%), *cis*-stilbene oxide **3** (50 mg) and diisopropylethylamine (33 mg, 1.5 equiv.) in dichloromethane (1 mL) was added 1 M tetrachlorosilane in dichloromethane (0.50 mL, 2.0 equiv.) at −78°C under an argon atmosphere. The mixture was stirred at the same temperature for 6 h. After the reaction was quenched with satd sodium bicarbonate aq. (2 mL), the aqueous layer was treated with potassium fluoride/potassium dihydrogenphosphate aq., and extracted with ethyl acetate (50 mL). The organic layer was washed with brine (20 mL), dried over sodium sulfate and concentrated. The crude material was purified by column chromatography (silica gel, 5 g, hexane/AcOEt = 10:1) to give 2-chloro-1,2-diphenylethanol (57 mg, 96%). HPLC (AD-H, hex/2-propanol = 29:1): t_R (1*S*,2*S*)-(+)-isomer, 22.0 min (95.1%); (1*R*,1*R*)-(−)-isomer, 24.0 min (4.9%).
10. Fu and co-workers reported that the presence of diisopropylethylamine is important for higher enantioselectivity and more reproducible results.
11. In our early work on allylation of aldehyde with allyltrichlorosilane catalyzed by **1**, addition of diisopropylethylamine was effective for rate acceleration wherein the amine promotes a dissociation of *N*-oxide from the silicon atom in the product by ligand exchange to regenerate *N*-oxide. In the present reaction, little rate acceleration was observed. An NMR study[12] revealed that dissociation of *N*-oxide from the product is so fast that the benefit of ligand exchange by diisopropylethylamine is negligible.
12. In the case of the allylation, the complex of the silyl ether of the allylated product with the *N*,*N*′-dioxide was observed in ^{1}H NMR spectrum before the addition of diisopropylethylamine and the signals of the free *N*,*N*′-dioxide appeared upon the addition of amine. On the other hand, the free *N*,*N*′-dioxide was observed in the epoxide opening even in the absence of amine.
13. Racemic *N*-oxides were prepared by palladium-catalyzed coupling of 2-chloroisoquinoline and 2-methyl- or 2-methoxy-1-naphthylborate followed by oxidation with *m*CPBA. Optical resolution through the hydrogen complex with homochiral binaphthol ((*R*)-binaphthol for **8** and (*S*)-binaphthol for **9**) afforded optically pure **8** (mp 213.5–214.5°C, $[\alpha]_D^{21} = -30.8$ (*c* 1.0, CHCl$_3$)) and **9** (mp 180.5°C, $[\alpha]_D^{21} = +132.1$ (*c* 0.9, CHCl$_3$)). Absolute configurations of **8** and **9** have not been determined.