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Desymmetrization of Cyclic *meso*-Epoxides with Silicon Tetrachloride Catalyzed by PINDOX, a Chiral Bipyridine Mono-*N*-oxide

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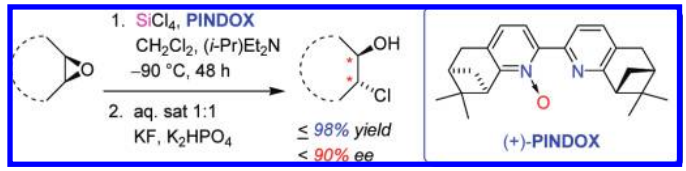
ABSTRACT

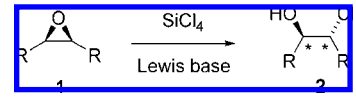


PINDOX 8 has been identified as a chiral organocatalyst for the enantioselective ring-opening of cyclic *meso*-epoxides with $SiCl_4$ to produce chlorohydrins in up to 90% ee. The catalyst is most effective with saturated cyclic substrates containing more than seven carbon units.

Epoxides constitute a class of versatile synthetic intermediates that offer a great deal of variability of the regio- and stereocontrolled ring cleavage, thus creating the space for subsequent synthetic transformations. In the case of symmetrical *meso*-epoxides, the ring opening generates two contiguous stereogenic centers.

The ability of various chlorosilanes to serve as the source of chloride ion in the epoxide cleavage was recognized half a century ago (Scheme 1).[1] Over the years, it has been demonstrated that the reaction can be dramatically accelerated by nucleophilic catalysts, such as phosphines and imidazole[2] and, most recently, by ferrocene-type phosphorus heterocycles[3] and HMPA.[4]

Scheme 1



Experimental and computational data[5] show that silanes act as weak Lewis acids toward neutral N and O Lewis bases. Stronger Lewis bases or stabilizing intermolecular forces in the solution can enhance the propensity of Si to the formation of relatively stable extracoordinate adducts.[6,7] However, when Lewis bases are to be employed as catalysts, it is

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(1) Malinovskii, M. S.; Romantsevich, M. K. *Zh. Obshch. Khim.* **1957**, *27*, 1873; *Chem. Abstr.* **1958**, *52*, 44711.
(2) Andrews, G. C.; Crawford, T. C.; Contillo, L. G. *Tetrahedron Lett.* **1981**, *22*, 3803.
(3) Carrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 4534.
(4) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428.
(5) Fleischer, H. *Eur. J. Inorg. Chem.* **2001**, 393.

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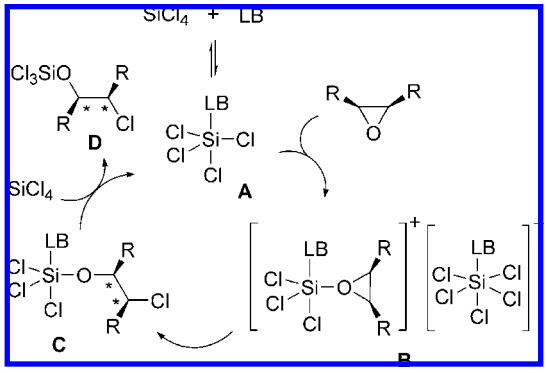
important that their adducts be sufficiently unstable to allow catalytic turnover.

A detailed investigation into the mechanism of the nucleophile-assisted opening of epoxides allowed Denmark[8] to formulate the following catalytic cycle (Scheme 2). Initially, tetrachlorosilane and a monodentate Lewis base (LB) form a pentacoordinate donor−acceptor complex **A**. The silicon center in the hypercoordinate derivatives, such as **A**, uniformly becomes more Lewis acidic due to the increased positive charge at Si,[5,7,9] which encourages interactions with the epoxide. Displacement of a chloride in the coordination sphere of silicon by the epoxide oxygen gives rise to complex **B**, where the Lewis base is present in both cationic and anionic species. Opening of the activated epoxide by a chloride ion, presumably generated from the silicate anion, proceeds in an S_N2 fashion to give intermediate **C**. Due to the reversible nature of the donor−acceptor interactions between the Lewis base and silicon, $SiCl_4$ then reacts with **C** to release the silylated chlorohydrin **D**, simultaneously generating complex **A**, which completes the catalytic cycle.

Scheme 2



The intermediacy of species **B** containing two molecules of the catalyst, each attached to a different silicon center, was proposed as the most plausible scenario, taking into account the nonlinear effect observed for monodentate chiral Lewis bases in conjuction with the inability of the corresponding bidentate catalysts to improve the enantioselectivity. Therefore, an alternative arrangement, where two molecules of the catalyst are coordinated to the same silicon atom, can be regarded as less likely.[8]

According to the latter mechanism (Scheme 2), the process is well suited to asymmetric modifications.[9,10] However, the existing enantioselective versions of the Lewis base-assisted desymmetrization of *meso*-epoxides with halosilanes are limited to the acyclic series, where a number of successful catalysts, in particular **3**−**7** (Figure 1), have been introduced:[4,11−14] The axially chiral phosphoramide **3**,[4] planar chiral pyridine *N*-oxide **4**,[11] helical pyridine *N*-oxide **5**,[12] bisisoquinoline *N*,*N*′-dioxide **6**,[13a] and BINAPO **7**[13b] exhibited high enantioselectivity in the opening of derivatives of *cis*-stilbene oxide **1** (R = Ar; 87−97% ee). By contrast, in the case of the less sterically demanding aliphatic substrates and, in particular, with cyclic epoxides, the enantioselectivity remains inadequate. Herein, we present the results of our investigation into the asymmetric catalytic opening of cyclic *meso*-epoxides.

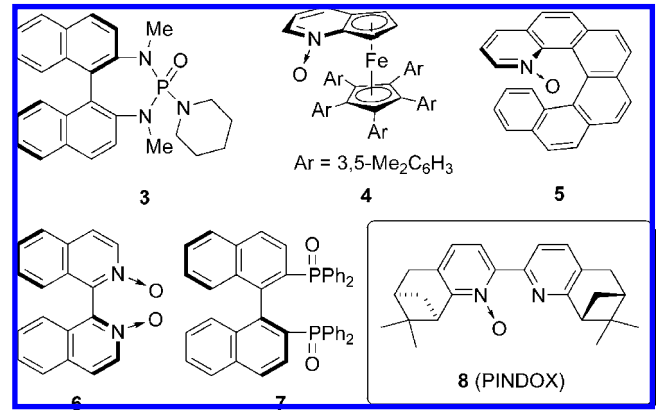


Figure 1

At the time of the first reports on desymmetrization of *cis*-stilbene oxide,[4,11] we introduced the bipyridine mono-*N*-oxide **8** (PINDOX) as an efficient catalyst for the asymmetric allylation of aromatic aldehydes with allyltrichlorosilanes.[15] When applied to the opening of noncyclic *meso*-epoxides, catalyst **8** proved ineffective: thus, *cis*-stilbene oxide and *cis*-oct-4-ene oxide produced the corresponding chlorohydrins in high yields but in only 16% and 8% ee, respectively. However, cyclooctene oxide, a particularly challenging substrate showing low reactivity and selectivity

(6) Brook, M. A. *Silicon in Organic, Organometallic and Polymeric Chemistry*; Wiley: New York, 2000; pp 133−136.

(7) Fester, G. W.; Wagler, J.; Brendler, E; Böhme, U.; Gerlach, D.; Kroke, E. *J. Am. Chem. Soc*. **2009**, *131*, 6855.

(8) (a) Denmark, S. E.; Barsanti, P. A.; Beutner, G. L.; Wilson, T. W. *Adv. Synth. Catal*. **2007**, *349*, 567. (b) See also footnote 13 in ref 11.

(9) For a comprehensive overview, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed*. **2008**, *47*, 1560.

(10) For overviews, see: (a) Kočovský, P.; Malkov, A. V. Chiral Lewis Bases as Catalysts. In *Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2007; p 255. (b) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem*. **2007**, 29.

(11) (b) Tao, B.; Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc*. **2001**, *123*, 353.

(12) Takenaka, N.; Sarangthem, R. S.; Captain, B. *Angew. Chem., Int. Ed*. **2008**, *47*, 9708.

(13) (a) Nakajima, M.; Saito, M.; Uemura, M.; Hashimoto, S. *Tetrahedron Lett*. **2002**, *43*, 8827. (b) Tokuoka, E.; Kotani, S.; Matsunaga, H.; Ishizuka, T.; Hashimoto, S.; Nakajima, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2391. For the most recent application of axially chiral allene-derived phosphine oxides, see: (c) Pu, X.; Qi, X.; Ready, J. M. *J. Am. Chem. Soc*. **2009**, *131*, 10364.

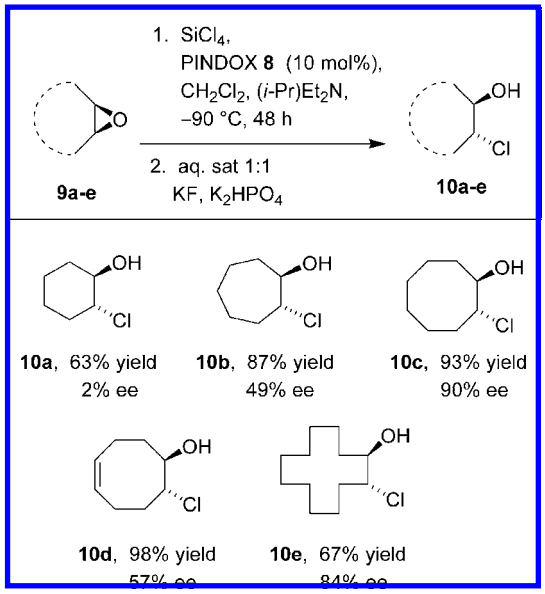
(14) (a) Paek, S. H.; Shim, S. C.; Cho, C. S.; Kim, T.-J. *Synlett* **2003**, 849. (b) Chelucci, G.; Baldino, S.; Pinna, G. A.; Benaglia, M.; Buffa, L.; Guizzetti, S. *Tetrahedron* **2008**, *64*, 7574. (c) Simonini, V.; Benaglia, M.; Benincorib, T. *Adv. Synth. Catal*. **2008**, *350*, 561.

(15) (a) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský, P. *Org. Lett*. **2002**, *4*, 1047. (b) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem*. **2003**, *68*, 9659.

with most of the Lewis bases **3**−**7**,[16] furnished the corresponding chlorohydrin in 85% ee (see footnote 25 in ref 15a). This prompted us to investigate PINDOX in the asymmetric opening of a series of cyclic epoxides **9a**−**e** (Scheme 3).

The opening of epoxides **9a**−**e** with $SiCl_4$, catalyzed by PINDOX **8** (10 mol %), was carried out in CH_2Cl_2 at −90 °C in the presence of (*i*-Pr)Et_2N (3 equiv) for 48 h. To ensure the accuracy and consistency of the results, the reaction mixtures were quenched with an aqueous saturated 1:1 KF/K_2HPO_4 solution, known to be highly effective in preventing the large quantities of acid released during the hydrolysis of Si−Cl bonds from entering the organic solution and causing a nonselective opening of the remaining unreacted epoxide.[8]

Scheme 3



The highest levels of selectivity (up to 90% ee) were attained for derivatives with the ring size of eight carbons or more (**10c** and **10e**).[17] Reduction of the ring size resulted in a dramatic drop in selectivity: thus, cycloheptane oxide **9b** afforded the corresponding chlorohydrin **10b** in good yield (87%) but with only 49% ee, whereas cyclohexane oxide **9a** furnished racemic product **10a**. The introduction of a double bond into the eight-membered ring system also had a negative effect, with **10d** showing a drop to 57% ee compared to the 90% ee for the corresponding saturated system **10c**. Note that to attain the highest enantioselectivity it is crucial to carry out the reaction at low temperature. Thus, opening of **9c** at −60 °C gave **10c** in 75% ee (a ∼15% drop in ee compared to −90 °C), whereas at −35 °C the product was racemic, as shown by chiral GC analysis. It is also pertinent to note that PINDOX (**8**) seems to be unique as a catalyst for these transformations. Its close analogues, such as the corresponding *N*,*N*′-dioxide[15] or METHOX,[18] were inefficient, giving practically racemic products.[19]

The tricyclic *exo*-norbornene oxide **9f** afforded the *syn*-*exo*-chloroalcohol **11** as the major product (53% yield and 90% ee), rather than the vicinal chlorohydrin (Scheme 4). The latter result is not surprising as the tendecy of **9f** to undergo Wagner−Meerwein rearrangements in the presence of hydrochloric or hydrobromic acids is well documented.[20,21]

The formation of **11** suggests that the epoxide opening does not strictly follow a bimolecular S_N2-type manifold but involves a substantial degree of the C−O bonds ionization in the initially formed complex **E**, generating the carbocation intermediate **F**/**G**. According to this scenario, the enantioselectivity of the process is determined by the selection of one of the two C−O bonds of the epoxide for ionization. It seems likely that the silicate counterion in the intermediate complex **B**, incorporating the chiral Lewis base (Scheme 2), exerts significant influence on the enantiodifferentiation.[22]

The syn relationship between the hydroxyl and chloride groups in the *syn*-*exo*-chlorohydrin **11** is noteworthy. Intrinsic preference for the nucleophile to form an *exo*-adduct, coupled with the close proximity of the hydroxy group, suggests that the delivery of the chloride ion may occur from the silicon atom coordinated to the oxygen, rather than from the silicate ion.

In conclusion, we have demonstrated that PINDOX **8** can catalyze an enantioselective formation of chlorohydrins from

(16) For a correction of erroneous reports, see: Denmark, S. E.; Wynn, T.; Jellerichs, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2255.

(17) (a) The absolute configuration of chlorohydrins **10** is unknown; the formulae shown here merely represent an arbitrarily chosen enantiomer. (b) The enantioselectivities shown in Scheme 3 were established by ^{19}F NMR analysis of the corresponding Mosher's esters, as most of the chlorohydrins **10** (except **10c**) proved difficult to separate by chiral chromatography. (c) The Mosher esterication was quantitative, as revealed by TLC analysis and by the ^1H NMR spectra of the crude products, which excludes a possible ee amplification during this derivatization. (d) The enantiopurity of Mosher's acid was independently verified to be >99% ee (see the Supporting Information). (d) Chiral GC analysis of the trifluoroacetate derived from **10c** revealed 87% ee, which is in good agreement with the the value obtained by the Mosher method (90% ee).

(18) (a) Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219. (b) Malkov, A. V.; Kabeshov, M. A.; Barłog, M.; Kočovský, P. *Chem.—Eur. J.* **2009**, *15*, 1570.

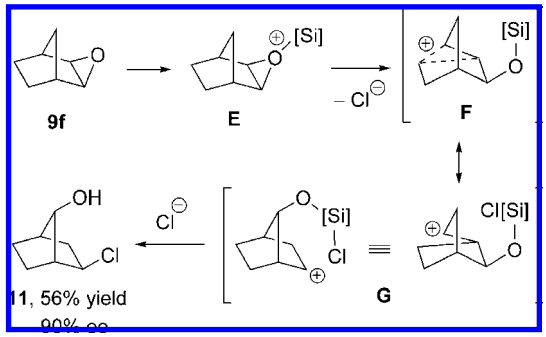
(19) The reaction rate observed for PINDOX (**8**) is equally unique, since all other catalysts (Figure 1) react considerably slower. In principle, the fast conversion of **9c** into chlorohydrin **10c** in the case of **8** could be attributed to the cleavage of the unreacted oxirane ring during the workup by the HCl released from $SiCl_4$. However, this process could hardly be expected to be enantioselective. Furthermore, the epoxide opening during the workup would not account for the variation of enantioselectivity with the reaction temperature. Note also that the reaction was quenched with a saturated aqueous solution of KF and K_2HPO_4 (1:1) to buffer the mixture and prevent the organic phase from becoming acidic (vide supra[8]).

(20) (a) Gerteisen, T. J.; Kleinfelter, D. C. *J. Org. Chem.* **1971**, *36*, 3255. (b) Loreto, M. A.; Pellacani, L.; Tardella, P. A. *Synth. Commun.* **1981**, *11*, 287. (c) Gargaro, G.; Loreto, M. A.; Pellacani, L.; Tardella, P. A. *J. Org. Chem.* **1983**, *48*, 2043. For a general discussion on the behavior of norbornyl cations, see the following: (d) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper and Row: New York, 1987; p 448. (e) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; p 662.

(21) Recently, Ready reported on the opening of epoxide **9f** with $SiCl_4$, catalyzed by an axially chiral allene-derived phosphine oxide, which occurred with 50% ee.[13c] However, he formulated the product as a vicinal chlorohydrin, which is apparently incorrect, as revealed by his NMR spectra that are compatible with those for **11** (as reported here and by Waegell: Chauvet, F.; Heumann, A.; Waegell, B. *J. Org. Chem.* **1987**, *52*, 1916.) but differ from those recorded for the vicinal chlorohydrin (also described by Waegell)

(22) Hamilton, G. L.; Kanai, T.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 14984.

Scheme 4



cyclic *meso*-epoxides **9** in up to 90% ee, which is unprecedented. The catalyst was most effective with cyclic saturated substrates containing more than seven carbon units. In the opening of the norbornene oxide, the major product resulting from the Wagner−Meerwein rearrangement was obtained in 90% ee. Since the existing catalysts (**3**−**7**) only exhibit high enantioselectivity with stilbene-type and related epoxides, PINDOX **8** can be regarded as a valuable addition to this collection as it fills a significant gap in the portfolio of substrates.

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Supporting Information Available: Experimental procedures; ^{1}H and ^{13}C NMR spectra for new compounds; ^{1}H and ^{19}F NMR spectra for Mosher's esters of chiral chlorohydrins and chiral GC analysis for **10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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