Enantioselective Ring Opening of Epoxides with Silicon Tetrachloride in the Presence of a Chiral Lewis Base

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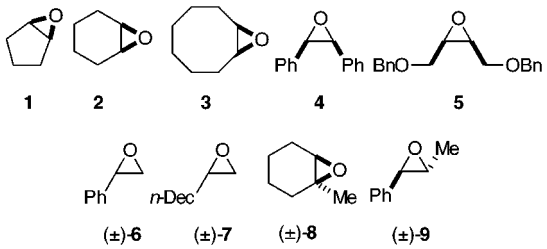
The facile ring opening of epoxides makes them extremely versatile intermediates for organic synthesis.[1] It is therefore not surprising that the enantioselective synthesis[2] and transformations[3] of epoxides are current topics of significant activity. Among the myriad of nucleophiles that have been employed in ring openings, halide ions (which afford the corresponding vicinal halohydrins) have received considerable attention.[4,5] The classical reagents for halohydrin synthesis are strong Lewis[4] or hydrohalic acids,[6] which provide powerful electrophilic activation. Methods for the asymmetric synthesis of chlorohydrins by enantioselective ring opening of epoxides have relied upon the use of stoichiometric amounts of chiral Lewis acid halides.[7] A conceptually distinct approach involves nucleophilic activation of Lewis acids (e.g., TMSCl) by Lewis bases (e.g., phosphines).[8,9] This method offers unique opportunities for asymmetric catalysis by disconnecting the roles of activator and nucleophile. Nevertheless, catalytic, enantioselective ring opening of epoxides to afford enantiomerically enriched chlorohydrins has yet to be reported.

In the context of our studies on Lewis base-promoted aldol additions of trichlorosilyl enolates,[10] we assayed the reaction of epoxides with these enolates. To our surprise, we found the exclusive formation of the corresponding chlorohydrins. Since the enolate was not formally involved, we felt that $SiCl_4$ should be a suitable source of chloride ion and, thus, initiated a program on the (chiral) Lewis base-promoted opening of epoxides with this and other chlorosilanes. In this paper, we wish to disclose the *first catalytic enantioselective ring opening of epoxides to afford optically active chlorohydrins*.

Our initial experiments with $SiCl_4$ employed HMPA and cyclohexene oxide. Since HCl (an obvious contaminant in $SiCl_4$) is known to open epoxides with ease,[6] it was essential to establish that the $SiCl_4$ was HCl free. Further, it was necessary to establish if $SiCl_4$ alone could open the epoxide and thus compete with the Lewis base-catalyzed pathway. To this end, we developed a strict protocol whereby, for each epoxide, freshly distilled $SiCl_4$ was employed in an uncatalyzed reaction, and the background was monitored by ^1H NMR spectroscopy. In all cases studied (vide infra), <5% conversion was detected even at room temperature. Thus assured that $SiCl_4$ could not affect ring opening, we then surveyed a number of Lewis bases for their ability to promote the opening of cyclohexene oxide as the test substrate. Low-temperature ^1H NMR studies indicated that as little as 10 mol % of HMPA, DMPU, or pyridine all promoted the reaction efficiently. Given our success with chlorosilane activation using phosphoramides we chose the combination of HMPA and $SiCl_4$ as our standard conditions. Thus, treatment of cyclohexene oxide with 1.1 equiv of $SiCl_4$ in the presence of 0.1 equiv of HMPA in CH_2Cl_2 at −78 °C cleanly afforded *trans*-2-chlorocyclohexanol in 89% yield.

With a functional protocol in hand, we next surveyed a variety of epoxide structures, Chart 1, to evaluate the steric and electronic contributions to rate and regioselectivity. The details of the ring-opening reactions are compiled in Table 1, and the product chlorohydrins are found in Chart 2.

Chart 1



Both cyclic and acyclic epoxides with various substitution patterns cleanly afford the corresponding chlorohydrins in excellent yields. Among the cyclic substrates, it was noticed that cyclooctene oxide (**3**) reacted at a considerably lower rate most likely due to hindered approach in the lowest energy boat−twist chair conformation.[11] Substrates **4** and **5**[12] also reacted slowly, presumably for electronic reasons. The opening of all epoxides was accompanied by inversion of configuration as verified by comparison with the known chlorohydrins.[13] The regioselectivity in reactions of unsymmetrical epoxides is governed by both steric and electronic effects.[14] This is illustrated in the high level but opposite sense of regioselectivity in the opening of terminal epoxides **6** and **7**. Surprisingly, both di- and trisubstituted epoxides

(1) (a) Erden, I. In *Comprehensive Heterocyclic Chemistry, 2nd ed.*; Padwa, A., Ed.; Pergamon Press: Oxford, 1996; Vol. 1A, Chapter 1.03. (b) Bartók, M.; Lang, K. L. In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1985; Vol. 42, Part 3, p 1. (c) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323.

(2) (a) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis, Vol. 7, Oxidation*; Ley, S. V., Ed.; Pergamon Press: Oxford, 1991; Chapter 3.2. (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; Chapter 4.1. (c) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993; Chapter 4.2.

(3) For leading references of enantioselective ring opening of epoxides, see: (a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, *114*, 2768. (b) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (c) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (d) 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. For a recent review see: (e) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.

(4) Bonini, C.; Righi, G. *Synthesis* **1994**, 225.

(5) Halohydrins also serve as important synthetic intermediates in their own right and are critical subunits for the synthesis of halogenated marine natural products. For reviews see: Fenical, W. *Marine Natural Products*; Scheuer, P. J., Ed.; Academic: New York, 1980; Vol. 2, p 174.

(6) Cross, A. D. *Quart. Rev. Chem Soc.* **1960**, *14*, 317.

(7) (a) Joshi, N. N.; Srebnik, M.; Brown, H. C. *J. Am. Chem. Soc.* **1988**, *110*, 6246. (b) Naruse, Y.; Esaki, T.; Yamamoto, H. *Tetrahedron* **1988**, *44*, 4747.

(8) (a) Andrews, G. C.; Crawford, T. C.; Contillo, L. G., Jr. *Tetrahedron Lett.* **1981**, *22*, 3803. (b) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1997**, *62*, 4534.

(9) Silicon tetrafluoride has been used together with Hünig base to open epoxides. Shimizu, M.; Yoshioka, H. *Tetrahedron Lett.* **1988**, *29*, 4101.

(10) (a) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, *118*, 7404. (b) Denmark, S. E.; Winter, S. B. D. *Synlett* **1997**, 1087. (c) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333. (d) Denmark, S. E.; Stavenger, R. A.; Wong, K.-T. *J. Org. Chem.* **1998**, *63*, 918.

(11) Calculated at the MM2* level (Macromodel 5.5), Monte Carlo search with 10^4 steps. The boat−twist chair was found to be the global minimum with six similar conformations within 1.6 kJ/mol.

(12) Garner, P.; Park, J. M. *Synth. Commun.* **1987**, *17*, 189.

(13) (a) For compounds **10**, **11**, **13**, **15**, and **16**, see ref 8b. (b) Compound **12**: Allinger, N. L.; Tushaus, L. A. *Tetrahedron* **1967**, *23*, 2051. (c) Compound **17**: Caputo, R.; Ferrer, C.; Noviello, S.; Palumbo, G. *Synthesis* **1986**, 499. (d) Compound **18**: Besse, P.; Renard, M. F.; Veschambre, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1249.

(14) The regiochemical assignment was confirmed by preparation of the trifluoroacetate of **17** and the acetate of **18**.

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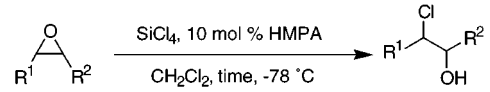
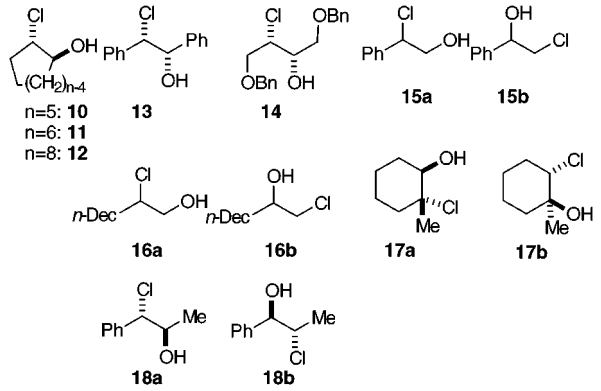
Table 1. Ring Opening of Epoxides with $SiCl_4$ in the Presence of HMPA[a]



epoxide	product (s)	ratio	time, min	yield,[b] %
1	**10**		20	85
2	**11**		20	89
3	**12**		120[c]	94
4	**13**		120	96
5	**14**		180[d]	93
6	**15a/15b**	17/1	20	94
7	**16a/16b**	1/18	20	91
8	**17a/17b**	2.2/1	20	88
9	**18a/18b**	1/1.5	20	92

[a] Conditions: 1.1 equiv of $SiCl_4$, 0.1 equiv of HMPA, 0.1 M in CH_2Cl_2, −78 °C. Regioisomeric mixture determined by ^1H NMR analysis. [b] Yields of analytically pure material. [c] Reaction run at room temperature/0.5 M. [d] Reaction run at 1.0 M.

Chart 2

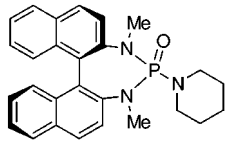


(**8** and **9**) gave poor regioselectivities despite the presence of an electronic bias.

The success of the HMPA-promoted reaction encouraged us to examine the opening of meso epoxides in the presence of chiral Lewis bases. The initial survey encompassed a range of Lewis basic promoters and $SiCl_4$ with **2** as the test substrate. Among those promoters examined, the enantiomerically pure phosphoramide **19** emerged as the most enantioselective promoter.[15] Next, a variety of chlorosilanes was investigated in conjunction with **19** again using **2**.[16] *Although reactions with all other chlorosilanes investigated proceeded satisfactorily, the corresponding chlorohydrins were essentially racemic.* Thus, to investigate the generality of opening of meso epoxides **1**−**5**, we employed $SiCl_4$ (1.1 equiv) in the presence of (*R*)-**19** (0.1 equiv), in CH_2Cl_2 (0.1 M) at −78 °C to afford the chlorohydrins **10**−**14**, (Table 2).

In all cases, the chlorohydrins were cleanly obtained in excellent yields; however, the enantioselectivity of the reaction was highly substrate dependent. For cyclic substrates, there is a dramatic dependence on ring size; only **2** reacted with significant enantioselectivity. Interestingly, the acyclic

Table 2. Catalytic Enantioselective Ring Opening of Epoxides[a]

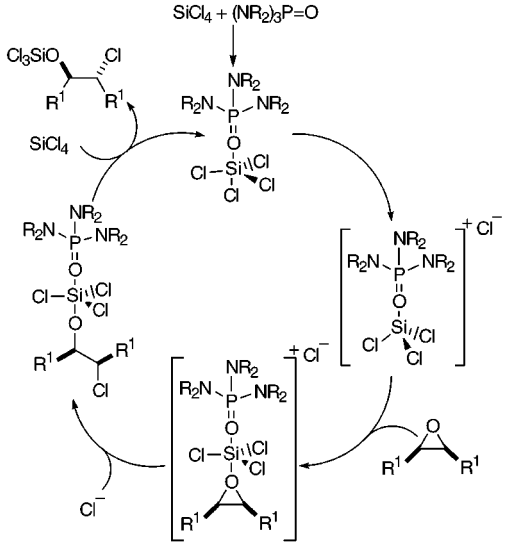


(*R*)-**19**

epoxide	time, h	product	yield,[b] %	er[c] (config)
1	0.3	**10**	87	53.6/46.4
2	0.3	(+)-**11**	90	75.8/24.2 (*S*,*S*)[d]
3	132	**12**	95	51.0/49.0
4	3	(+)-**13**	94	93.5/6.5 (*S*,*S*)[d]
5	4	(+)-**14**	95	85.6/14.4 (*S*,*S*)[e]

[a] Conditions: 1.1 equiv of $SiCl_4$, 0.1 equiv of (*R*)-**19**, in CH_2Cl_2, −78 °C. [b] Yields of analytically pure material. [c] Determined by CSP GC, SFC, or HPLC analysis; see the Supporting Information for details. [d] Established by comparison of optical rotation to literature values.[17] [e] Assigned by analogy.

Scheme 1



substrates afforded chlorohydrins with much higher levels of enantiomeric enrichment.

These reactions are mechanistically intriguing. Our working hypothesis is that a complex between $SiCl_4$ and the phosphoramide undergoes ionization to produce a highly reactive silicon cation and a chloride ion.[18] Nucleophilic opening occurs by activation of the epoxide through complexation of the phosphorus/silicon cation followed by attack with the chloride ion in an S_N2 fashion, Scheme 1. The origin of asymmetric induction is obscure at this time.

In summary, we have developed a synthetically useful and mild procedure for the preparation of chlorohydrins from epoxides with $SiCl_4$ and catalytic amounts of HMPA. In addition, the first catalytic enantioselective opening of meso epoxides to afford enantiomerically enriched chlorohydrins has been realized.

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Supporting Information Available: General procedure for the preparation of **10**−**18** and full characterization of all new chlorohyrins and their trifluoroacetates along with ^1H and ^{13}C NMR spectra of the known chlorohydrins and known trifluoroacetates (17 pages).

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(15) Other promoters examined include the following: phosphoramides based on the stilbenediamine and cyclohexane-1,2-diamine skeletons, sparteine, nicotine, cinchona alkaloids, chiral oxazolines, and assorted chiral tertiary amines and diamines.

(16) Other chlorosilanes examined include: $MeSiCl_3$, $PhSiCl_3$, Me_2SiCl_2, Me_3SiCl, $HSiCl_3$, $(CH_2)_3SiCl_2$, and $(CH_2)_3SiMeCl$.

(17) (a) (+)-(*S*,*S*)-**11**, $[\alpha]^{20}_D$ +27.7 (*c* = 4.7, $CHCl_3$): Sadozai, S. K.; Merckx, E. M.; Van de Wal, A. J.; Lemière, G. L.; Esmans, E. L.; Lepoivre, J. A.; Alderweireldt, F. C. *Bull. Chem. Soc. Belg.* **1982**, *91*, 163. (b) (−)-(*R*,*R*)-**13**, $[\alpha]^{20}_D$ −20.2 (*c* = 5.2, EtOH): Berti, G.; Bottari, F.; Ferrerini, P. L.; Macchia, B. *J. Org. Chem.* **1965**, *30*, 4091.

(18) Berrisford has demonstrated that CH_2Cl_2 solutions of allyltrichlorosilanes become conducting in the presence of Ph_3PO. Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351.