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The C2 Selective Nucleophilic Substitution Reactions of 2,3-Epoxy Alcohols Mediated by Trialkyl Borates: The First *endo*-Mode Epoxide-Opening Reaction through an Intramolecular Metal Chelate

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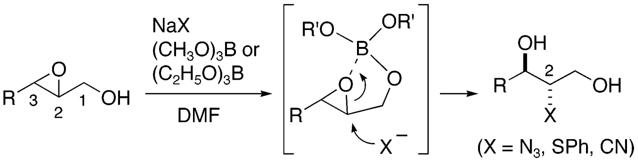
ABSTRACT



Highly efficient C2 selective substitution reactions of 2,3-epoxy alcohols with nucleophiles were developed by using NaN_3–$(CH_3O)_3B$, NaSPh–$(CH_3O)_3B$, or NaCN–$(C_2H_5O)_3B$ system. The reaction proceeds through novel *endo*-mode epoxide opening of an intramolecular boron chelate, which was suggested from both experimental and quantum mechanic studies.

Since the discovery of the Katsuki−Sharpless asymmetric epoxidation in 1980,[1] reactions of 2,3-epoxy alcohols with various nucleophiles[2] have been extensively studied in the context with the chiral synthesis of biologically important natural compounds. The utility of this type of reaction is dependent on its regioselectivity, and the C3 selective substitution reactions via an intramolecular metal chelate (Figure 1, path a) have been widely used in organic synthesis.[3−5] On the contrary, it has been known that the C2 selective substitution reaction of a 2,3-epoxy alcohol is extremely difficult, despite its synthetic importance,[6] although a few particular cases with use of steric and/or electronic bias have been reported.[7]

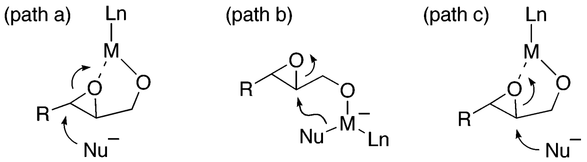


Figure 1. The pathways of the reactions of a 2,3-epoxy alcohol with nucleophiles.

Recently, we have reported that the combined use of NaN_3 and $PhB(OH)_2$ effected the C2 azide substitution reaction of a *trans*-2,3-epoxy alcohol,[8] which was originally designed

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[1] (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976. (b) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1−299.

[2] (a) Caron, M.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 1560−1563. (b) Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437−475.

[3] For C3 selective reactions with azide ion equivalents. (a) Maruoka, K.; Sano, H.; Yamomoto, H. *Chem. Lett.* **1985**, 599−602. (b) Onaka, M.; Sugita, K.; Izumi, Y. *Chem. Lett.* **1986**, 1327−1328. (c) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5187−5189. (d) Benedetti, F.; Berit, F.; Norbedo, S. *Tetrahedron Lett.* **1998**, *39*, 7971−7974. (e) Martin, R.; Islas, G.; Moyano, A.; Pericas, M. A.; Riera, A. *Tetrahedron.* **2001**, *57*, 6367−6374. See also ref 2.

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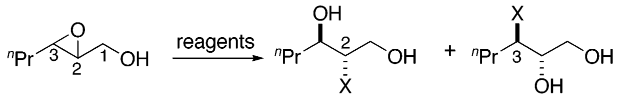
by assuming an intramolecular ate complex (Figure 1, path b), the same as the reactions of an epoxy alcohol with Red-Al[9] or organocopper reagents.[6a−d] The synthetic potential of the reaction prompted us to investigate the boron-induced substitution reaction in detail. We now report the new findings that the boron-mediated substitution reaction of 2,3-epoxy alcohols proceeds via an intramolecular boron chelate through an unprecedented *endo*-mode epoxide opening with extremely high C2 selectivity (Figure 1, path c).

Initially, the reactions of *trans*-2,3-epoxy-1-hexanol (**1**) with several reagents were examined to compare the regioselectivity (Table 1).

Table 1. Substitution Reaction of *trans*-2,3-Epoxyhexanol



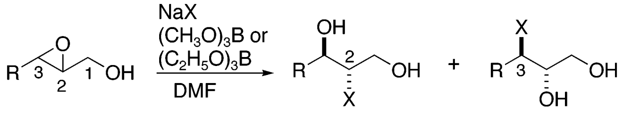
entry	reagents	X	C2:C3	yield,[e] %
1[a]	NaN_3, $(CH_3O)_3B$	N_3	82:18	97
2[b]	NaN_3,NH_4Cl	N_3	15:85	95
3[c]	$Ti(O^iPr)_2(N_3)_2$	N_3	3:97	88
4[d]	Me_2CuLi	Me	41:59	93

[a] The reaction was carried out in DMF at 50 °C. [b] Reference 2. [c] Reference 3c. [d] The reaction was carried out in ether at −30 °C. [e] Combined isolated yield.

Use of a new combination $(CH_3O)_3B-NaN_3$ instead of the previous system $(PhB(OH)_2-NaN_3)$ was found to enhance both the reaction rate and the regioselectivity, and an 82:18 mixture of the azido diols was obtained in quantitative yield (entry 1). The remarkable C2 selectivity of the boron-mediated substitution reaction is apparent in comparison with that of conventional azide substitution reactions[3] (entries 2 and 3). It should be noted that even the reaction of **1** with the Gilman reagent, which would involve an ate complex intermediate (Figure 1, path b), does not proceed regioselectively (entry 4).

The exceptionally high C2 selectivity exhibited by the $(CH_3O)_3B-NaN_3$ system led us to examine the scope of the boron-mediated substitution reaction (Tables 2 and 3). The reactions of *trans*-epoxy alcohols **2** and **3** with NaN_3, NaSPh, or NaCN produced the corresponding C2 substitution products with extremely high regioselectivity (>92:8) and chemical yields, respectively (Table 2, entries 1−6).

Table 2. Substitution Reactions of *trans*-Epoxy Alcohols

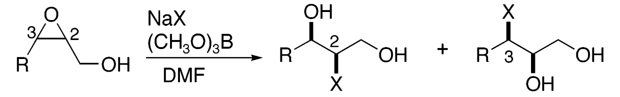


entry	epoxide (R)	X	C2:C3	yield,[d] %
1[a]	**2** ($BnOCH_2$)	N_3	92:8	96
2[b]		SPh	95:5	97
3[c]		CN	92:8	96
4[a]	**3** ($TBSOCH_2$)	N_3	92:8	99
5[b]		SPh	95:5	98
6[c]		CN	93:7	89
7[b]	**1** (*n*Pr)	SPh	85:15	97
8[c]		CN	84:16	83

[a] With 2 equiv of NaN_3 and 1.5 equiv of $(CH_3O)_3B$ at 50 °C. [b] With 1.5 equiv of NaSPh and 1.3 equiv of $(CH_3O)_3B$ at room temperature. [c] With 4 equiv of NaCN and 3 equiv of $(C_2H_5O)_3B$ at 70 °C. [d] Combined isolated yield.

Similarly, the *trans*-epoxy alcohol **1** having no particular oxygen function on the side chain produced the C2-substitution products predominantly (Table 2, entries 7 and 8). These results unambiguously demonstrate that the boron-mediated substitution reaction of *trans*-epoxy alcohols generally occurs at the C2 position with high regioselectivity, whereas the reactions of *cis*-epoxy analogues were far more sluggish and resulted in decreased regioselectivity (Table 3).

Table 3. Substitution Reactions of *cis*-Epoxy Alcohols.



entry	epoxide (R)	X	C2:C3	yield,[c] %
1[a]	**4** ($BnOCH_2$)	N_3	73:27	96
2[b]		SPh	76:24	90
3[a]	**5** (*n*Pr)	N_3	31:69	89
4[b]		SPh	48:52	85

[a] With 3 equiv of NaN_3 and 3.5 equiv of $(CH_3O)_3B$ at 50 °C. [b] With 1.5 equiv of NaSPh and 1.3 equiv of $(CH_3O)_3B$ at room temperature. [c] Combined isolated yield.

In turn, we focused on the mechanism of the present boron-induced substitution reactions. Contrary to our assumption involving the ate complex intermediate (Figure 2, **B**), the transition structures proposed by calculation strongly suggested the intermediary of an intramolecular boron chelate (C).

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(4) For a C3 selective reaction with a thiolate ion equivalent: Onaka, M.; Sugita, K.; Takeuti, H.; Izumi, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 1173−1174. See also ref 2.

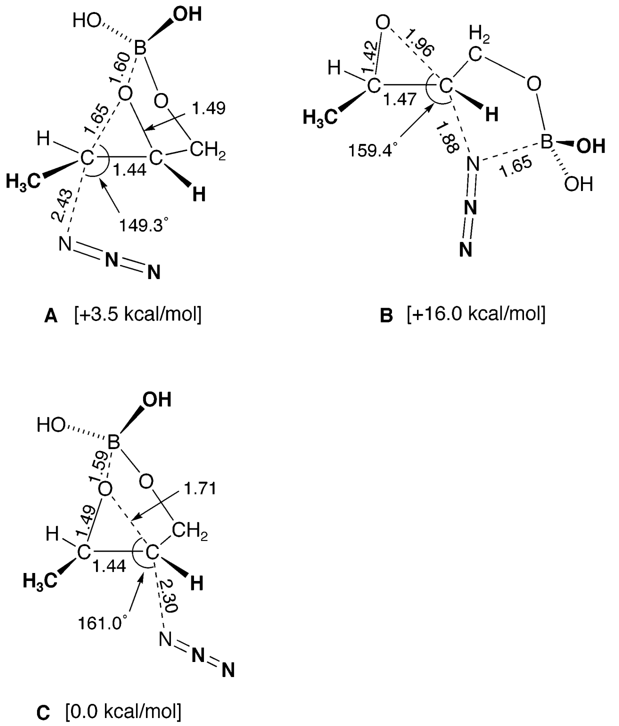
(5) For C3 selective reactions with carbon nucleophiles. (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597−3600. (b) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377−1380. (c) Takatsuto, S.; Yazawa, N.; Ishiguro, M.; Morisaki, M.; Ikekawa, N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 139−146.

(6) For C2 selective reactions with carbon nucleophiles. (a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, *20*, 4343−4346. (b) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131−4132. (c) Chong, J. M.; Cyr, D. R.; Mar, E. K. *Tetrahedron Lett.* **1987**, *28*, 5009−5012. (d) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135−631. (e) Sasaki, M.; Tanino, K.; Miyashita, M. *Org. Lett.* **2001**, *3*, 1765−1767.

(7) (a) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696−5704. (b) Chakraborty, T. K.; Reddy, G. V. *Tetrahedron Lett.* **1991**, *32*, 679−682.

(8) Hayakawa, H.; Okada, N.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1999**, *40*, 4589−4592.

(9) (a) Ma, P.; Martin, V, S.; Masamune, S.; Sharpless, K. B.; Viti, S, M. *J. Org. Chem.* **1982**, *47*, 1378−1380. (b) Finan, J. M.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2719−2722. (c) Viti, S. M. *Tetrahedron Lett.* **1982**, *23*, 4541−4544.



A [+3.5 kcal/mol]

B [+16.0 kcal/mol]

C [0.0 kcal/mol]

Figure 2. Optimized transition structures of boron-mediated substitution reactions of *trans*-2,3-epoxybutanol and azide ion.[10] Bond lengths are shown in Å. Energies relative to **C** are shown in brackets.

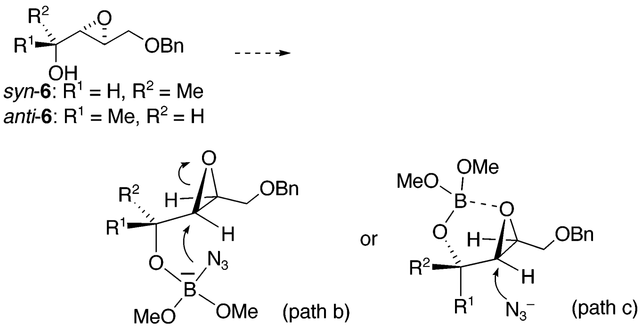
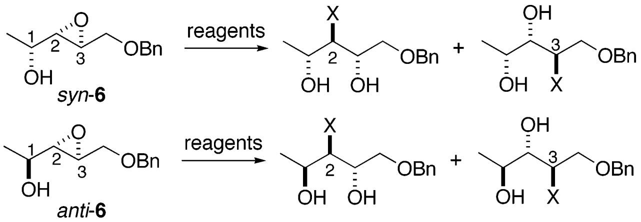


Figure 3. A probe to discriminate between the two reaction mechanisms.

Since this type of substitution reaction has never been reported, we designed two epoxy alcohols *syn*-**6** and *anti*-**6** as probes to discriminate between the two reaction mechanisms (Figure 3). In the case of the reaction involving an ate complex intermediate (path b), *syn*-**6** would exhibit lower reactivity and selectivity than *anti*-**6** owing to steric repulsion between the methyl group and the epoxide ring. On the contrary, if the reaction proceeds under chelation control (path c), *syn*-**6** would react faster than *anti*-**6** with higher selectivity because of severe steric hindrance between the methyl and a nucleophile in the latter.

Indeed, the reaction of *anti*-**6** with Me_2CuLi gave the C2 substitution product predominantly (Table 4, entry 2), while *syn*-**6** afforded a 1:1 mixture of regioisomers in lower yield. These outcomes are consistent with the reaction mechanism involving an ate complex intermediate. On the other hand, the reaction of *syn*-**6** with $(CH_3O)_3B-NaN_3$ produced the C2 substitution product with high regioselectivity and chemical yield (entry 3), whereas the reaction of *anti*-**6** under the same conditions resulted in the formation of an almost equal amount of regioisomers in poor yield (entry 4). These results clearly demonstrate that the boron-induced substitution reaction of epoxy alcohols does proceed via a novel *endo*-mode epoxide opening of an intramolecular boron chelate (path c).

Table 4. Substitution Reactions of *syn*-**6** and *anti*-**6**



entry	epoxide	reagents	X	C2:C3	yield,[c] %
1[a]	*syn*-**6**	Me_2CuLi	Me	50:50	76
2[a]	*anti*-**6**	Me_2CuLi	Me	79:21	83
3[b]	*syn*-**6**	NaN_3, $(CH_3O)_3B$	N_3	89:11	92
4[b]	*anti*-**6**	NaN_3, $(CH_3O)_3B$	N_3	46:54	30[d]

[a] The reaction was carried out in ether at −30 °C. [b] The reaction was carried out in DMF at 50 °C. [c] Combined isolated yield of the isomers. [d] Ca. 70% of *anti*-**6** was recovered.

In conclusion, we have realized the first C2 selective substitution reactions of epoxy alcohols with nucleophiles which proceed through novel *endo*-mode epoxide opening of intramolecular boron chelates with extremely high selectivity. The boron-induced substitution reaction of epoxy alcohols should provide a powerful methodology in organic synthesis, including natural product synthesis.

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Supporting Information Available: Spectroscopic data, experimental details, and Cartesian coordinates of transition structures **A**−**C** at the B3LYP/6-31G*//HF/3-21G level. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Calculations were performed with the GAUSSIAN 98 program at the B3LYP/6-31G*//HF/3-21G level. For details, see the Supporting Information.