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The first C2 selective halide substitution reaction of 2,3-epoxy alcohols by the use of $(CH_3O)_3B$–MX (X = I, Br, Cl) system

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Abstract—The first C2 selective halide substitution reactions of 2,3-epoxy alcohols have been realized by the use of the $(CH_3O)_3B$–MX (X = I, Br, Cl) system, which proceed through novel *endo*-mode epoxide-opening of intramolecular boron chelates to afford the corresponding C2 halohydrin derivatives with high regio- and stereoselectivity.

Since the discovery of the Katsuki–Sharpless asymmetric epoxidation,[1] stereoselective substitution reactions of 2,3-epoxy alcohols with various nucleophiles have been extensively studied,[2] particularly, in the context of chiral synthesis of biologically and/or medicinally important compounds. The utility of this type of reaction is critically dependent on its regioselectivity, and C3 selective substitution reactions of 2,3-epoxy alcohols with various nucleophiles have been reported so far. On the contrary, the C2 selective substitution reaction of epoxy alcohols has scarcely been developed despite its synthetic importance,[3] except for a few particular cases with the use of steric and/or electronic bias.[4]

Very recently, we discovered the first C2 selective substitution reactions of 2,3-epoxy alcohols with nucleophiles, e.g. N_3^-, PhS^-, and CN^-, by the combination with a trialkyl borate which proceed through the unprecedented *endo*-mode epoxide-opening of intramolecular boron chelates with remarkably high C2 selectivity.[5] The importance of this new synthetic methodology prompted us to investigate the boron-mediated substitution reaction of 2,3-epoxy alcohols with halogen nucleophiles (Fig. 1), since a variety of marine natural products containing halogen atom(s) have been found in nature;[6] however, only the C3 selective substitution reactions of epoxy alcohols with metal halides have been known.[7] If the C2 selective halide substitution reaction of 2,3-epoxy alcohols is realized, it should provide an extremely useful synthetic method for natural product synthesis.

At first, we examined the reaction of *trans*-2,3-epoxy-1-hexanol (**1**) with sodium iodide in the presence of trimethyl borate ($(CH_3O)_3B$) in acetone (Scheme 1).

However, the reaction was very sluggish and, moreover, a mixture of three substitution products, viz. C1, C2, and C3 iodohydrins, was formed in 28%, 17%, and 14% yields, respectively, along with 40% of the starting material. Thus, the boron-induced halide substitution reaction was found to be totally ineffective under the original conditions. However, we noticed that the C1 iodohydrin **4** was the major product, which was obvi-

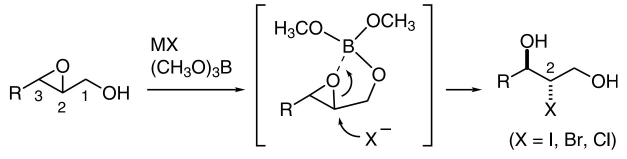
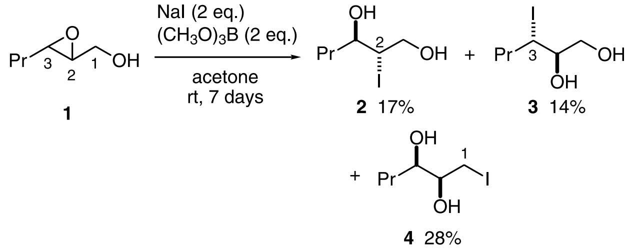


Figure 1. Design of the boron-induced C2 selective halide substitution reactions of 2,3-epoxy alcohols.



Scheme 1. Boron-induced substitution reaction of *trans*-2,3-epoxy-1-hexanol (**1**) with NaI.

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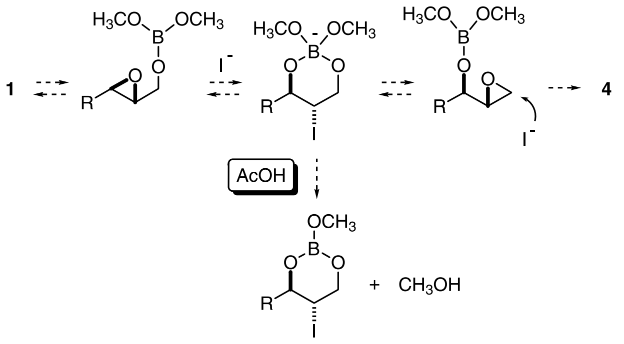
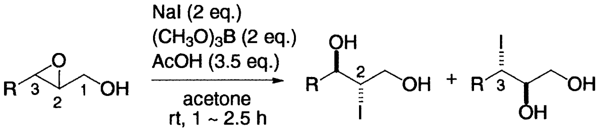
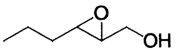
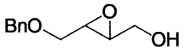
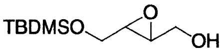
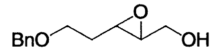
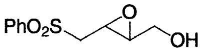


Scheme 2. Proposed reaction mechanism for the formation of **4** via Payne rearrangement.

Table 1. Boron-induced iodide substitution reactions of *trans*-epoxy alcohols



entry	substrate	isolated yield (%)	C2/ C3
1	 **1**	100	82 : 18
2		100	92 : 8
3		98	93 : 7
4		99	87 : 13
5		90	>99 : 1

ously derived via the Payne rearrangement,[8] and thence we assumed that the reaction media should be basic under these conditions. From the preliminary experimental results, we anticipated that the addition of AcOH would suppress the Payne rearrangement and probably accelerate the epoxide-opening reaction effectively by trapping the ate complex intermediate (Scheme 2).

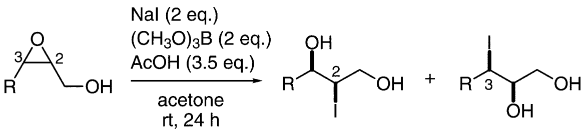
Indeed, the addition of AcOH to the boron-mediated substitution reaction of 2,3-epoxy alcohols with NaI dramatically changed not only the reaction path and the reaction rate, but also regioselectivity of the reaction, as shown in Table 1.

Thus, the reaction of **1** with NaI (2 equiv.) and $(CH_3O)_3B$ (2 equiv.) in acetone containing AcOH (3.5 equiv.) smoothly proceeded at room temperature and completed in 1 h to give an 82:18 mixture of the C2 iodohydrin **2** and the C3 iodohydrin **3** in quantitative yield (entry 1).[9] As we expected, the C2 iodohydrin **2** was obtained with remarkably high C2 selectivity and chemical yield. This outcome is in sharp contrast with those of the reactions of **1** and its alcohol derivatives with MgI_2 giving rise to the C3 iodohydrin derivatives regioselectively or exclusively.[7] In addition, it should be noted that the iodide substitution reactions of *trans*-2,3-epoxy alcohols having an ether oxygen on the side chain produced the C2 iodohydrin derivatives with extremely high regioselectivity (entries 2–4). Particularly, the epoxy alcohol having a benzenesulfonyl group furnished the C2 substitution product with complete regioselectivity (entry 5). These results unambiguously demonstrate that the boron-induced iodide substitution reaction of *trans*-epoxy alcohols occurs at the C2 position with high regioselectivity, whereas the reactions of *cis*-epoxy analogues were sluggish and resulted in decreased regioselectivity (Table 2), even though the substrate having a benzenesulfonyl group produced the C2 iodohydrin with almost complete regioselectivity (entry 3).

The exceptionally high C2 selectivity exhibited by the $(CH_3O)_3B$–NaI system led us to examine the scope of the boron-mediated halide substitution reaction of epoxy alcohols (Table 3).

Although the bromide substitution reactions of *trans*-epoxy alcohols with NaBr required longer reaction time than the previous iodide substitution reactions, the corresponding C2 bromohydrin derivatives were obtained with high regioselectivity and high yield, respectively (entries 1 and 3). The reaction of a *cis*-epoxy alcohol with LiBr furnished the C2 bromohydrin predominantly under similar conditions (entry 5). Similarly, the boron-induced chloride substitution reactions of *trans*-epoxy alcohols with LiCl also occurred predominantly at the C2 position (entries 2 and 4), although their regioselectivity and yields were some-

Table 2. Boron-induced iodide substitution reactions of *cis*-epoxy alcohols



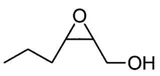
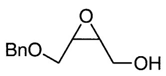
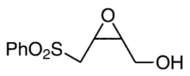
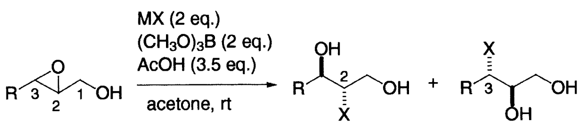
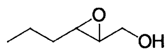
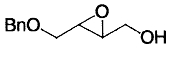
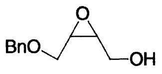
entry	substrate	isolated yield (%)	C2/ C3
1		93	28 : 72
2		100	76 : 24
3		84	>99 : 1

Table 3. Boron-induced bromide and chloride substitution reactions of epoxy alcohols



entry	substrate	MX	time (h)	yield (%)	C2/ C3
1		NaBr	24	94	80 : 20
2		LiCl	6	87	62 : 38
3		NaBr	24	94	92 : 8
4		LiCl	3	88	85 : 15
5		LiBr	20	97	74 : 26

what low in comparison with those of the corresponding iodide and bromide substitution reactions. It should be noted that all the bromide and chloride substitution reactions of the epoxy alcohols by the known methods have been reported to give the C3 substitution products predominantly or exclusively.[10]

In summary, we have realized the first C2 selective halide substitution reactions of 2,3-epoxy alcohols by the use of the $(CH_3O)_3B$–MX system, which proceed through novel *endo*-mode epoxide-opening of intramolecular boron chelates with high C2 selectivity. Since a variety of optically active epoxy alcohols are readily available, the present C2 selective halide substitution reaction of epoxy alcohols should provide an extremely useful methodology in natural product synthesis, inter alia, the synthesis of a variety of natural products containing halogen atom(s).

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9. *Typical procedure*: To a mixture of epoxy alcohol **1** (35 mg, 0.30 mmol), $(CH_3O)_3B$ (67 μL, 0.60 mmol), and NaI (90 mg, 0.60 mmol) in dry acetone (3 mL) was added acetic acid (60 μL, 1.05 mmol) at room temperature. After being stirred for 1 h, the mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over $MgSO_4$. Concentration under reduced pressure followed by purification by silica gel column chromatography afforded an 82:18 mixture of diols **2** and **3** (75 mg, 100%). The ratio of the isomers was determined by gas chromatography. Treatment of the product with $NaIO_4$ resulted in selective cleavage of 1,2-diol **3**, and the stereochemistry of 1,3-diol **2** was confirmed after conversion into the corresponding acetonide derivative.
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