

# Regioselective Alkyl and Alkynyl Substitution Reactions of Epoxy Alcohols by the Use of Organoaluminum Ate Complexes: Regiochemical Reversal of Nucleophilic Substitution Reactions

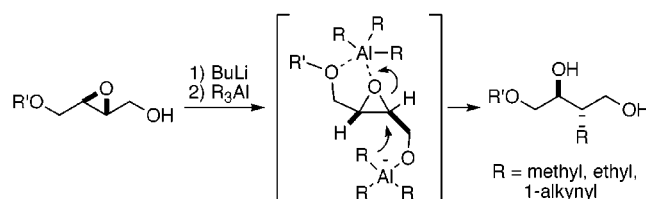
Minoru Sasaki, Keiji Tanino, and Masaaki Miyashita\*

Division of Chemistry, Graduate School of Science, Hokkaido University,  
Sapporo 060-0810, Japan

miyashita@sci.hokudai.ac.jp

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## ABSTRACT



Unprecedented nucleophilic substitution reactions of 2,3-epoxy-1-alkanols with alkyl- and alkynylaluminum ate complexes have been studied and demonstrated to occur at the C2 position with extremely high stereoselectivity, i.e., with exactly reversed regioselectivity to that obtained in the substitution reactions by normal organoaluminum reagents, resulting in the formation of the C2-alkyl and C2-alkynyl substitution products in excellent yields.

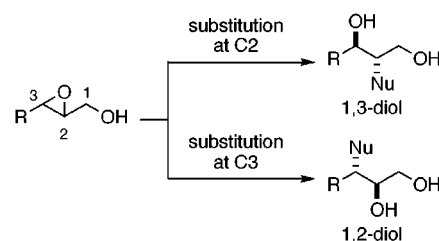
Nucleophilic substitution reactions of 2,3-epoxyalkanols, which are easily obtainable in an optically active form,<sup>1</sup> provide a powerful method for stereoselective construction of a carbon framework.<sup>2</sup> The utility of this type of C–C bond-forming reaction is critically dependent on regioselectivity,

and two methods have so far been developed on the basis of the characteristic features of organometallic compounds (Scheme 1). Thus, use of an organoaluminum reagent leads to a 1,2-diol via substitution at the C3 position,<sup>3</sup> while

(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. (c) For a review, see: Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 103–158.

(2) (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. J. *Org. Chem.* **1984**, *49*, 3928–3938. For a review, see: (b) Klunder, J. M.; Posner, G. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.5, pp 207–239. (c) Knight, D. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.6, pp 241–270. (d) Garratt, P. J. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.7, pp 271–292. (e) Posner, G. H. *Org. React.* **1975**, *22*, 253–400. (f) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–631.

Scheme 1

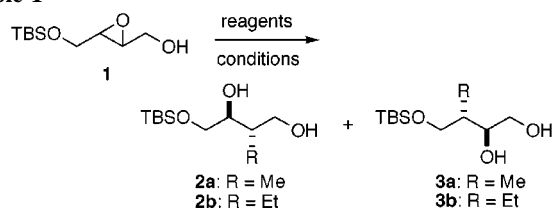


a Gilman-type reagent preferentially reacts at the C2 position to give a 1,3-diol.<sup>4</sup>

Although C–C bond formation at the C2 position has proved to be quite useful in the total synthesis of natural products, certain problems are incurred in the reactions using organocopper reagents: (1) the regioselectivity strongly depends on the structure of the substrates; (2) introduction of an alkynyl group seems to be extremely difficult because of the low reactivity of alkynylcopper reagents. The present Letter describes a new type of C2 selective nucleophilic substitution reaction of 2,3-epoxyalkanols using *alkyl- and alkynylaluminum ate complexes*.<sup>5</sup>

First, epoxy alcohol **1** was chosen as a substrate of the reactions with organoaluminum and organocopper reagents to compare the regioselectivity (Table 1).

**Table 1**



entry	reagents	conditions	R	2 : 3	yield (%)
1	Me <sub>3</sub> Al <sup>a</sup>	CH <sub>2</sub> Cl <sub>2</sub> 0 °C, 30 min	Me	8 : 92	87
2	BuLi <sup>b</sup> then Me <sub>3</sub> Al <sup>a</sup>	CH <sub>2</sub> Cl <sub>2</sub> -30 ~ 0 °C, 2 h	Me	92 : 8	93
3	Me <sub>2</sub> CuLi <sup>c</sup>	ether -40 °C, 1 h	Me	85 : 15	94
4	BuLi <sup>b</sup> then Et <sub>3</sub> Al <sup>a</sup>	CH <sub>2</sub> Cl <sub>2</sub> -30 ~ 0 °C, 2 h	Et	97 : 3	92

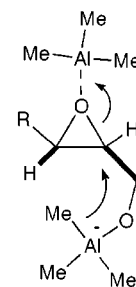
<sup>a</sup> 3 equiv. <sup>b</sup> 1.1 equiv. <sup>c</sup> 5 equiv.

While the reaction with Me<sub>3</sub>Al alone occurred selectively at the C3 position as was anticipated (entry 1),<sup>3a</sup> pretreatment of **1** with BuLi to generate a lithium alkoxide resulted in a dramatic change in the regioselectivity (entry 2). Thus, the ratio of diols **2a** and **3a** was completely reversed from 8:92 to 92:8 without any decrease in chemical yield. Similarly, successive treatment of **1** with BuLi and triethylaluminum produced a 97:3 mixture of **2b** and **3b** in 92% yield (entry 4). These results suggest an alternative reaction pathway involving an aluminum ate complex, which prefers a 5-exo

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(4) (a) Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 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. See also refs 2e and 2f.

(5) Intermolecular reactions of various epoxides with aluminum ate complexes have been reported. For example, see: (a) Boireau, G.; Abenhaim, D.; Bernardon, C.; Henry-Basch, E.; Sabourault, B. *Tetrahedron Lett.* **1975**, 2521–2524. (b) Pfaltz, V. A.; Mattenberger, A. *Angew. Chem Suppl.* **1982**, 161–168. (c) Boireau, G.; Abenhaim, D.; Henry-Basch, E. *Tetrahedron* **1980**, 36, 3061–3070. (d) Flippin, L. A.; Brown, P. A.; Jalali-Araghi, K. *J. Org. Chem.* **1989**, 54, 3588–3596. (e) Haddad, N.; Grishko, M.; Brik, A. *Tetrahedron Lett.* **1997**, 38, 6075–6078.



**Figure 1.** Reaction pathway involving an aluminum ate complex.

type substitution reaction at the C2 position (Figure 1). It should be noted that the C2 selectivity of the present method involving an organoaluminum ate complex is much higher than that of the conventional method using an organocuprate (entry 3).

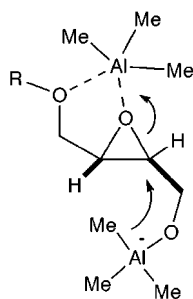
The excellent results of the preliminary experiments led us to examine the scope of the present method (Table 2).<sup>6</sup>

**Table 2.** Stereoselective Alkyl Substitution Reactions of Epoxy Alcohols by the Use of Trialkylaluminum Ate Complexes<sup>a</sup>

entry	substrate	products <sup>b</sup>	%yield (ratio <sup>c</sup> )
1	BnO-epoxy alcohol <b>4</b>	BnO-1,3-diol <b>11</b>	96 (>97:3)
2	<b>4</b>	BnO-1,3-diol <b>12</b>	96 (95:5)
3	BnO-epoxy alcohol <b>5</b>	BnO-1,3-diol <b>13</b>	96 (>98:<2)
4	<b>5</b>	BnO-1,3-diol <b>14</b>	95 (95:5)
5 <sup>d</sup>	TBSO-epoxy alcohol <b>6</b>	TBSO-1,3-diol <b>15</b>	95 (93:7)
6 <sup>d</sup>	Me-epoxy alcohol <b>7</b>	Me-1,3-diol <b>16</b>	90 (>98:<2)
7 <sup>d</sup>	BnO-epoxy alcohol <b>8</b>	BnO-1,3-diol <b>17</b>	88 (78:22)
8	Ph-epoxy alcohol <b>9</b>	Ph-1,3-diol <b>18</b>	94 (15:85)
9	PhSO <sub>2</sub> -epoxy alcohol <b>10</b>	PhSO <sub>2</sub> -1,3-diol <b>19</b>	80 (82:18)

<sup>a</sup> A mixture of an epoxy alcohol and 1.1 equiv of BuLi in CH<sub>2</sub>Cl<sub>2</sub> was treated with 3 equiv of R<sub>3</sub>Al at 0 °C to ~rt. <sup>b</sup> Structures of major isomers are depicted. <sup>c</sup> Ratio of 1,3-diol: 1,2-diol determined by proton NMR spectra. <sup>d</sup> Optically active substrate was used.

Treatment of *trans*-4-benzyloxy-2,3-epoxy-1-butanol **4** with BuLi (1.1 equiv) followed by Me<sub>3</sub>Al (3 equiv) induced introduction of a methyl group at the C2 position with net inversion of configuration in high selectivity (>97:<3) in 96% yield (entry 1).<sup>7</sup> Similarly, the reaction of the corresponding *cis*-epoxy alcohol **5** resulted in substitution at the C2 position to afford the *syn*-compound exclusively (entry 3).<sup>8</sup> It is noteworthy that the reaction with triethylaluminum also occurred in high yields without formation of any reduction products (entries 2 and 4). Furthermore, the present method is applicable to the stereoselective construction of three contiguous chiral centers (entries 5, 6, and 7). As can be seen in entry 6, a secondary hydroxyl group also serves as an anchor to control the regioselectivity. On the other hand, epoxy alcohol **9** having no alkoxy group on the side chain predominantly afforded 1,2-diol **18**, which is the same product arising from the reaction with trimethylaluminum alone (entry 8). These results suggest that chelation of the aluminum reagent with the oxygen atoms of the epoxide and the ether moiety plays an important role for achieving extremely high regioselectivity (Figure 2). In this connection,



**Figure 2.** Alternative reaction pathway involving an aluminum ate complex.

epoxy alcohol **10** having a phenylsulfonyl group underwent a selective substitution reaction at the C2 position (entry 9), which can be rationalized by a similar chelation model in Figure 2.

In turn, we examined the alkynyl substitution reaction by the use of alkynylaluminum ate complexes under similar conditions (Table 3). As shown, the alkynyl substitution reactions also occurred at the C2 position predominantly, though their regioselectivity was somewhat lower in comparison with that of the alkyl substitution reactions. It should be noted that the present method is the first case of a C2-selective alkynyl substitution reaction which is known to be inaccessible by organocopper reagents.

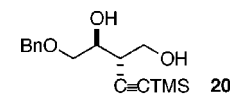
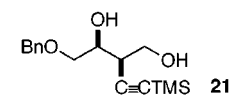
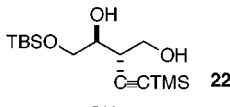
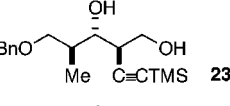
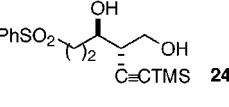
In conclusion, we have developed novel alkyl and alkynyl substitution reactions of epoxy alcohols by the use of

(6) Treatment of the crude products with sodium periodate followed by column chromatography afforded the 1,3-diols in pure form. The stereochemistry of the products was confirmed by comparison with authentic samples which were prepared by the reaction of organocopper reagents.

(7) It has been reported that treatment of the same substrate with Me<sub>3</sub>Al alone yielded a 16:84 mixture of the C2 and the C3 substitution products, while the reaction with dimethylcuprate in ether afforded a 86:14 mixture of the C2 and the C3 substitution products.<sup>3b</sup>

(8) This result was also found to be far better than that obtained in the reactions with dimethylcuprate (selectivity of C2/C3 = 70–82:18–30).

**Table 3.** Alkynyl Substitution Reaction of Epoxy Alcohols by the Use of Alkynylaluminum Ate Complexes<sup>a</sup>

entry	substrate	products <sup>b</sup>	%yield (ratio <sup>c</sup> )
1	<b>4</b>		94 (91:9)
2	<b>5</b>		94 (80:20)
3	<b>1</b>		93 (84:16)
4 <sup>d</sup>	<b>8</b>		93 (66:34)
5	<b>10</b>		86 (72:28)

<sup>a</sup> A mixture of an epoxy alcohol and 1.1 equiv of BuLi in CH<sub>2</sub>Cl<sub>2</sub> was treated with 3–4 equiv of Me<sub>2</sub>AlC≡CTMS at –78–0 °C. <sup>b</sup> Structures of major isomers are depicted. <sup>c</sup> Ratio of 1,3-diol:1,2-diol determined by proton NMR spectra. <sup>d</sup> Optically active substrate was used.

organoaluminum ate complexes which occurred with high stereoselectivity at the C2 position, i.e., with exactly reversed regioselectivity to that obtained in the substitution reactions with organoaluminum reagents alone. The present work is the first protocol of this type of transformation except for organocopper reagents. Although the reactions of epoxy alcohols **4** and **5** with dimethylcuprate have been widely used in the synthesis of various natural products, e.g., tautomycin,<sup>9</sup> ingramycin,<sup>10</sup> olygomycin,<sup>11</sup> rodularin,<sup>12</sup> FK-506,<sup>13</sup> etc., their stereoselectivity and chemical yields were not always satisfactory. Therefore, this new methodology provides an extremely useful tool for natural product synthesis.

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**Supporting Information Available:** Full characterization for **1–24**, IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL010062+

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