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Regio- and stereospecific alkyl and alkynyl substitution reactions of epoxy selenides with organoaluminums via episelenonium ions

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Abstract—Regio- and stereospecific alkyl and alkynyl substitution reactions of epoxy selenides with organoaluminum reagents have been developed, which proceed via episelenonium ion intermediates to give the C2 alkyl substitution products with double inversion of the configuration and the C1 alkynyl substitution products with migration of the arylseleno group in high yields, respectively.

Stereoselective, epoxide-opening reactions are important transformations in organic synthesis and are widely used as the key reaction in natural product synthesis.[1] Although a variety of regio- and/or stereoselective epoxide-opening reactions via an S_N2 process have been reported so far,[2] the stereospecific alkyl or alkynyl substitution reaction of epoxides, which proceeds with retention of the configuration, is scarcely known. Recently, Saigo et al. and we have independently reported stereospecific alkyl[3,4] and alkynyl[4,5] substitution reactions of epoxy sulfides with organoaluminum reagents, which proceed via episulfonium ion intermediates to give the substitution products with double inversion of the configuration, that is, with retention of the configuration, respectively.[6,7] With a view to exploiting the stereospecific substitution reaction of epoxides with double inversion of the configuration, we examined the reaction of epoxy selenides with organoaluminum reagents. We report herein the regio- and stereospecific alkyl and alkynyl substitution reactions of epoxy selenides with organoaluminums, which proceed via episelenonium ion intermediates to afford the C2 alkyl substitution products with double inversion of the configuration and the C1 alkynyl substitution products with migration of the arylseleno group in high yields, respectively (Fig. 1).

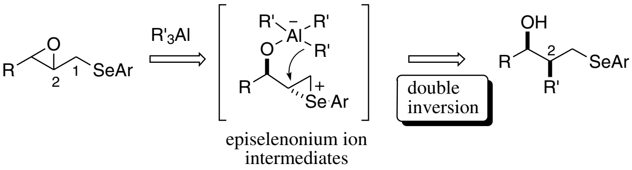
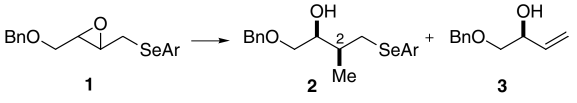


Figure 1. Substitution reaction of epoxy selenides with organoaluminum reagents.

To gain insight into the reaction of an epoxy selenide with organoaluminums, we initially examined the reaction of *trans*-1-arylseleno-4-benzyloxy-2,3-epoxybutane (**1**) with $(CH_3)_3Al$. For the purpose, three epoxy arylselenides, **1a**, **1b**, and **1c**, were prepared according to the Grieco–Nishizawa protocol.[8] As a result, remarkable discrepancy was observed depending on the aryl group on a selenium atom of **1** (Scheme 1).

Thus, the reaction of **1a** having a phenylseleno group with $(CH_3)_3Al$ afforded the allylic alcohol **3**, a reduction product, as the major product together with a minor amount of the methylation product **2** with double inversion of the configuration.[9] Notably, the reaction is



1a: Ar = phenyl		9%	90%
1b:	= *p*-nitrophenyl	86%	10%
1c:	= *o*-nitrophenyl	92%	trace

Scheme 1. Reactions of **1** with $(CH_3)_3Al$. The reactions were carried out with $(CH_3)_3Al$ (3 equiv) in CH_2Cl_2 at −30 °C for 30 min.

Keywords: Epoxide; Selenide; Substitution reaction; Organoaluminum.

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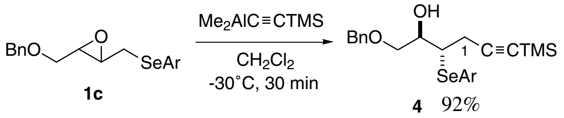
in contrast with that of the corresponding epoxy sulfide with $(CH_3)_3Al$ giving rise to the methylation product with double inversion of the configuration exclusively. Interestingly, we found that an aryl group bearing a strongly electron-withdrawing substituent improved the ratio of **2** and **3** dramatically. For example, the reaction of *p*-nitrophenylselenenyl epoxide **1b** with $(CH_3)_3Al$ afforded **2** and **3** in 86% and 10% yields, respectively, and *o*-nitrophenylselenenyl epoxide **1c** gave the methylation product **2** exclusively in 92% yield. These results suggest that a nitro group plays an important role to prevent the β-elimination pathway by destabilizing the $ArSe^+$ species. Thus, *o*-nitrophenylselenenyl epoxide was found to be best substrate for the present reaction.

The intriguing preliminary results led us to examine the reactions of various *trans*- and *cis*-*o*-nitrophenylselenenyl epoxides with $(CH_3)_3Al$. The results are summarized in Table 1.

As can be seen from the table, all the reactions proceeded stereospecifically to give the single methyl substitution products, respectively, with double inversion of the configuration in high yields. Thus, *syn*-substitution products are stereospecifically obtainable from *trans*-epoxy selenides, while *anti*-substitution products are exclusively produced from *cis*-epoxy selenides by the present method.

In turn, we focused on the alkynyl substitution reaction of epoxy selenides with alkynylaluminum reagents to explore another synthetic utility via episelenonium ions. First, we examined the reaction of **1c** with dimethyl[2-(trimethylsilyl)ethynyl]aluminum as a model reaction (Scheme 2).

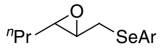
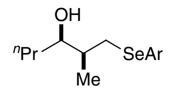
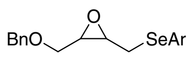
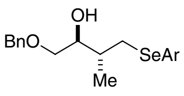
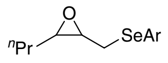
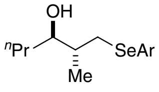
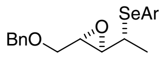
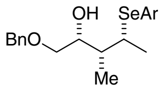


Scheme 2. The reaction of **1c** with an ethynylaluminum reagent.

Interestingly, the reaction occurred regioselectively at the C1 position through migration of the arylseleno group[10] to give the substitution product **4** in 92% yield. None of the C2 alkynyl substitution product with double inversion of the configuration was obtained. This result is in sharp contrast with that of the reaction of epoxy sulfides with the same aluminum reagent giving rise to the C2 alkynylation products stereoselectively.[5] Therefore, we investigated the reaction of various 1-*o*-nitrophenylselenenyl epoxides with dimethyl[2-(trimethylsilyl)ethynyl]aluminum. The results are summarized in Table 2.

As shown, all reactions other than entry 4 proceeded stereospecifically through migration of the arylseleno group to give the C1 alkynylation products as a single product, respectively, regardless of the stereochemistry of the epoxides. These results demonstrate that the reaction of an epoxy selenide with an organoaluminum reagent proceeds regio- and stereospecifically via an episelenonium ion intermediate and the reaction with $(CH_3)_3Al$ gives the C2 methyl substitution product with double inversion of the configuration, while the reaction with an alkynylaluminum reagent affords the C1 substitution product with migration of the arylseleno group, as a single product, respectively (Fig. 2).

Table 1. C2-selective alkyl substitution reactions of epoxy selenides with $(CH_3)_3Al$[a,b]

Entry	Substrate	Product[c]	Yield (%)[d]
1			89
2			92
3			77
4			82

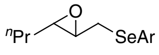
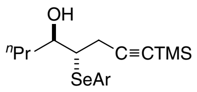
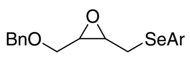
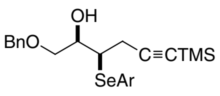
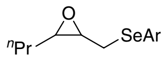
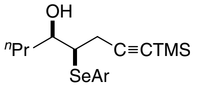
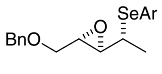
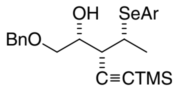
[a] An epoxy selenide was treated with $(CH_3)_3Al$ (3 equiv) in CH_2Cl_2 at −30 °C for 30 min.

[b] Ar = *o*-Nitrophenyl.

[c] All products were obtained as a single stereoisomer, respectively.

[d] Isolated yield.

Table 2. Alkynyl substitution reactions of epoxy selenides with dimethyl[2-(trimethylsilyl)ethynyl]aluminum[a,b]

Entry	Substrate	Product[c]	Yield (%)[d]
1			87
2			92
3			80
4			83

[a] An epoxy selenide was treated with the aluminum reagent (3 equiv) in CH_2Cl_2 at −30 °C for 30 min.

[b] Ar = *o*-Nitrophenyl.

[c] All products were obtained as a single stereoisomer, respectively.

[d] Isolated yield.

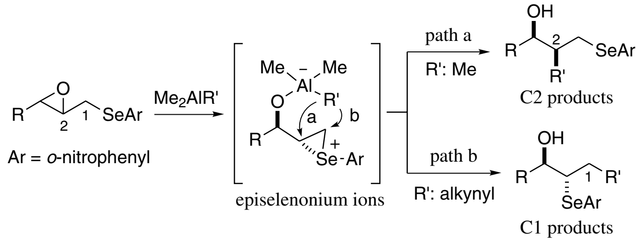
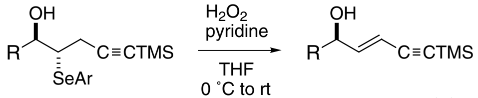


Figure 2. Substitution reaction of epoxy selenides with organoaluminum reagents.



4: R = BnOCH$_2$ 93% (E:Z = 95:5)
5: R = ^{n}Pr 92% (E:Z = 89:11)

Scheme 3. Conversion of the C1 alkynyl substitution products to enyne system.

Although the origin of the different behavior between $(CH_3)_3Al$ and an alkynylaluminum reagent is not clear, the exceptional result of entry 4 in Table 2 indicates that steric hindrance around the reaction site also has influence on the regioselectivity.

In order to demonstrate the synthetic potential of the products bearing a seleno group, the alkynyl substitution products were converted to a conjugated enyne system by elimination of the corresponding selenoxides.[11] Thus, the products **4** and **5** were treated with H_2O_2 in THF containing pyridine to afford the corresponding enyne compound in excellent yield, respectively (Scheme 3). As anticipated, the products having an E-olefin were produced predominantly.

In summary, we have developed new and stereospecific alkyl and alkynyl substitution reactions of epoxy selenides with organoaluminum reagents via episelenonium ion intermediates. The C1 alkynylation products were efficiently converted to a conjugated enyne system by elimination of selenoxides. Since a variety of optically active epoxy selenides are readily available from the corresponding epoxy alcohols, the present method provides an extremely useful methodology in organic synthesis including natural product synthesis.

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