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# Stereospecific epoxide-opening reactions of 1,1-dibromo-3,4-epoxy-1-alkenes with carbon nucleophiles

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ABSTRACT

The stereospecific epoxide-opening reactions of 1,1-dibromo-3,4-epoxy-1-alkenes with allyltributylstannane and with ketene silyl acetals in the presence of a Lewis acid are described. Both the reactions occurred regioselectively at the allylic position via an $S_N2$ process giving rise to a single product, respectively. Treatment of the products by the latter reaction with *p*-TsOH afforded various 3,4-*anti*- and 3,4-*syn*-disubstituted γ-lactones in a highly stereoselective manner and high yields.

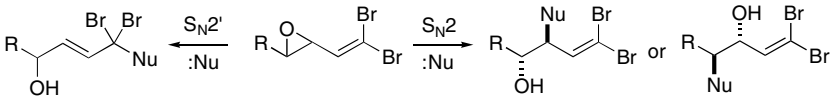


The stereoselective carbon-carbon bond-forming reaction of an epoxide with a carbon nucleophile is one of the most important transformations in organic synthesis, *inter alia,* in the synthesis of biologically important target molecules in natural product and pharmaceutical research.[1] In this context, the substitution reactions of vinyl epoxides and their analogues with carbon nucleophiles have been particularly focused upon due to the merit of the ease to control regioselectivity in the epoxide-opening reactions.

In connection with our studies of new acyclic stereocontrol based on the stereospecific epoxide-opening reactions,[2] we were interested in the reaction of 1,1-dibromo-3,4-epoxy-1-alkenes with carbon nucleophiles and its reaction mode (Scheme 1), because not only such a substitution reaction is unknown,[3] but also 1,1-dibromo-1-alkenes themselves are extremely useful synthetic intermediates in organic synthesis. For example, 1,1-dibromo-1-alkenes can be easily converted to alkyne derivatives by treatment with a base,[4] to (*Z*)-1-bromo-1-alkenes by the use of $Pd[(PPh_3)_4]$ catalyst and $Bu_3SnH$,[5] to (*E*)-1-bromo-1-alkenes with methyllithium,[6] and further to various functionalized alkenes by combination of organometallics or cross-coupling reactions.[7] Therefore, if the stereoselective epoxide-opening reaction of 1,1-dibromo-3,4-epoxy-1-alkenes with a carbon nucleophile is newly developed, it will probably provide a potentially useful methodology in organic synthesis.

We report herewith two types of stereospecific epoxide-opening reactions of 1,1-dibromo-3,4-epoxy-1-alkenes with allyltributylstannane and with ketene silyl acetals in the presence of a Lewis acid.

Initially, we chose *trans*-5-benzyloxy-1,1-dibromo-3,4-epoxy-1-pentene (**1**) as a model substrate and examined the allylation reaction of **1** with an allylmetal reagent in the presence of a Lewis acid. As a result, although the reaction of **1** with allyltrimethylsilane was unsuccessful in the presence of various Lewis acids,




**Scheme 1.** Possible modes in the substitution reaction of a 1,1-dibromo-3,4-epoxy-1-alkene with a carbon nucleophile.

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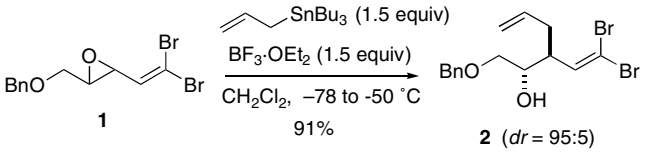



**Scheme 2.** The Lewis acid-mediated reaction of **1** with allyltributylstannane.

the substitution reaction of **1** with allyltributylstannane (1.5 equiv) was found to occur successfully in the presence of a Lewis acid, same as the reaction of vinyl epoxides with allyltrimethylstannane reported by Naruta and Maruyama.[8] Toward the new reaction, various Lewis acids such as $TiCl_4$, $TiCl_2(OEt)_2$, $Ti(OEt)_4$, $Me_2AlCl$, $BF_3{\cdot}OEt_2$, and $MgBr_2{\cdot}OEt_2$ were surveyed and $BF_3{\cdot}OEt_2$ (1.5 equiv) proved to be the reagent of choice for this particular reaction (Scheme 2).[9]

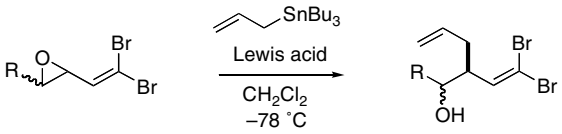
The excellent preliminary result prompted us to investigate the scope of the methodology and the results are summarized in Table 1. It is noteworthy that $BF_3{\cdot}OEt_2$ gave the best results in the case of epoxides bearing an alkoxy side chain (Scheme 2 and Table 1, entry 1),[9] while $Me_2AlCl$ was the reagent of choice for the substrates without an alkoxy substituent (entries 2 and 3). The results imply that the epoxide-opening reaction of the substrates bearing an alkoxy side chain occurred more smoothly in higher yield due to chelation of the Lewis acid by the oxygen atoms of the epoxide and the ether moiety, whereas the epoxides without an alkoxy substituent required a stronger Lewis acid than $BF_3{\cdot}OEt_2$ for completion of the reaction. As shown in Scheme 2 and Table 1, the Lewis acid-mediated allylation reaction of 1,1-dibromo-3,4-epoxy-1-alkenes with allyltributylstannane occurred regioselectively at the allylic position, regardless of the stereochemistry of the epoxides, giving rise to the corresponding 3-allyl-4-hydroxy derivatives stereospecifically in high yields. These results are in contrast to those of the allylation reaction of vinyl epoxides with allyltrimethylstannane by Naruta and Maruyama, which occurred via an $S_N2$ or $S_N2'$ process depending on the substituents at the olefinic terminus.[8]

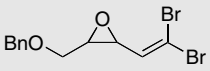
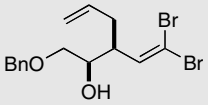
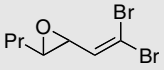
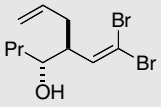
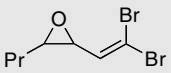
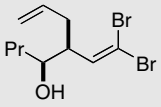
The extremely high regioselectivity in the present reaction is evidently due to the effect of the dibromoethylene group to stabilize cationic species at the allylic position by its remarkable electron-donating character, because the $Me_2AlCl$-mediated allylation reaction of ethyl *trans*-4,5-epoxy-(*E*)-2-octen-1-carboxylate with allyltributylstannane did not occur under similar conditions and the starting material was recovered unchanged.

Next, we focused on the reaction of 1,1-dibromo-3,4-epoxy-1-alkenes with a ketene silyl acetal to synthesize 3,4-disubstituted γ-butyrolactones bearing a dibromoethylene side chain in a stereoselective manner.[10] Toward this end, upon treatment of the *trans*-epoxide **1** with ketene silyl acetal **3** (5 equiv)[11] in the presence of $BF_3{\cdot}OEt_2$ (1.5 equiv) in $CH_2Cl_2$ at −78 °C, *anti*-4-hydroxy ester **4** was produced as a single product in quantitative yield (Scheme 3). As anticipated, the reaction occurred regioselectively at the allylic position, and interestingly, $BF_3{\cdot}OEt_2$ gave the best result in this case, too. When the product **4** was warmed with a catalytic amount of *p*-TsOH in $(CH_2Cl)_2$ at 40 °C, 3,4-*syn*-disubstituted γ-butyrolactone **5** with a dibromoethylene side chain was formed in nearly quantitative yield.

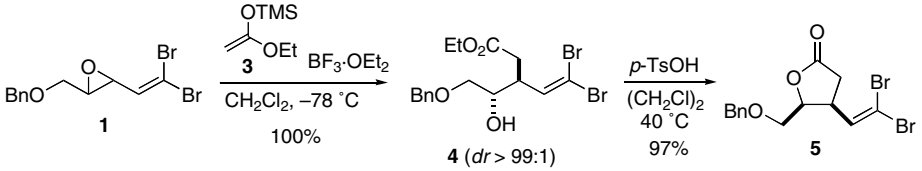
Similarly, the substitution reactions of other 1,1-dibromo-3,4-epoxy-1-alkenes with the ketene silyl acetal **3** proceeded stereospecifically as shown in Table 2, wherein the reactions of *cis*-epoxides gave a mixture of 4-hydroxy ester and 3,4-*anti*-disubstituted γ-butyrolactone (entries 1 and 3). Therefore, the crude products

**Table 1**
The reaction of 1,1-dibromo-3,4-epoxy-1-alkenes with allytributylstannane[a]



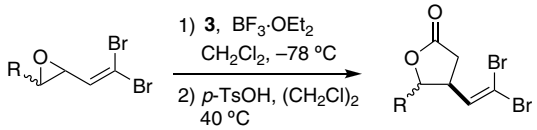

| Entry | Substrate | Lewis acid | Product | Yield[b] (%) | *dr* |
|---|---|---|---|---|---|
| 1 |  | $BF_3{\cdot}OEt_2$ |  | 95 | 96:4 |
| 2 |  | $Me_2AlCl$ |  | 92 | >99:1 |
| 3 |  | $Me_2AlCl$ |  | 77 | >99:1 |

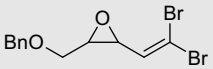
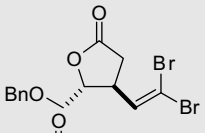
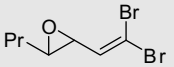
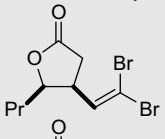
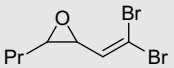
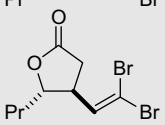
[a] The reaction was carried out with allytributylstannane (1.5 equiv) and Lewis acid (1.5 equiv).
[b] Isolated yield by silica gel column chromatography.




**Scheme 3.** The Lewis acid-promoted reaction of **1** with ketene silyl acetal **3** followed by lactonization.

**Table 2**
The reaction of 1,1-dibromo-3,4-epoxy-1-alkenes with **3** leading to γ-butyrolactones[a]




| Entry | Substrate | Product | Yield[b] (%) | *dr* |
|---|---|---|---|---|
| 1 |  |  | 100 | >99:1 |
| 2[c] |  |  | 64 | >99:1 |
| 3[c] |  |  | 63 | >99:1 |

[a] The reaction was carried out with **3** (5 equiv) and $BF_3{\cdot}OEt_2$ (1.5 equiv).
[b] The yield for two steps.
[c] The reaction temperature with **3** was −78 to −50 °C, and that with *p*-TsOH was 50 °C.

obtained by the latter reactions were directly converted to γ-butyrolactones by treatment with *p*-TsOH.

It should be noted that all the $BF_3{\cdot}OEt_2$-mediated allylation reactions of 1,1-dibromo-3,4-epoxy-1-alkenes with the ketene silyl acetal **3** exclusively occurred at the allylic position. It is also noteworthy that the substrates bearing an alkoxy substituent gave much higher yield of the products in comparison with those having no alkoxy substituent (Scheme 3 and entry 1 vs entries 2 and 3). These results apparently demonstrate that chelation of the Lewis acid by the oxygen atoms of the epoxide and the ether moiety promoted the epoxide-opening reaction very effectively.

To gain an insight into the reaction of 1,1-dibromo-3,4-epoxy-1-alkenes with an alkyl-substituted ketene silyl acetal, we examined the reaction of **1** with ketene silyl acetal **6** derived from ethyl propionate in the presence of $BF_3{\cdot}OEt_2$. As shown in Scheme 4, the two-step reaction sequence proceeded very efficiently, although the stereochemistry of the new asymmetric carbon center at the α-position of the ester group was not controlled well.

In order to demonstrate the synthetic potential of the new methods, further transformation of the products was examined (Scheme 5). Thus, the chemoselective cross olefin-metathesis reaction of **2** with methyl acrylate leading to unsaturated ester **7** was successfully performed by the use of the Grubbs' 2nd-generation catalyst (**8**).[12] On the other hand, conversion of **5** to γ-butyrolactone **9** having a (*Z*)-vinylbromide moiety[5] and that to γ-butyrolactone **10** with a terminal alkynyl group was achieved, respectively, in high yields.

In summary, we have developed the stereospecific epoxide-opening reactions of 1,1-dibromo-3,4-epoxy-1-alkenes with allyltributylstannane and with ketene silyl acetals in the presence of a Lewis acid. Both the reactions occurred regioselectively at the allylic position via an $S_N2$ process giving rise to a single product, respectively. Treatment of the crude products by the latter reaction with *p*-TsOH afforded various 3,4-*anti*- and 3,4-*syn*-disubstituted γ-lactones in a highly stereoselective manner and high yields. To the best of our knowledge, this is the first report on the stereospecific substitution reactions of 1,1-dibromo-3,4-epoxy-1-alkenes with carbon nucleophiles. The new methods will provide useful tools in organic synthesis including natural product synthesis.

## Acknowledgement

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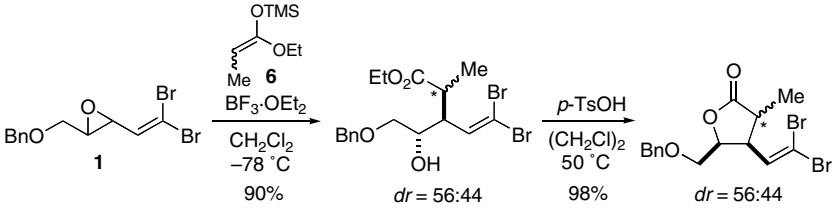
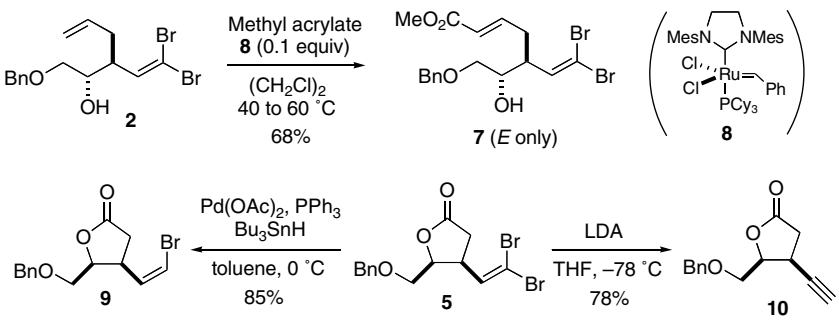
## Supplementary data

Typical experimental procedures and spectral data of the products are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.09.115.




**Scheme 4.** The Lewis acid-mediated reaction of **1** with ketene silyl acetal **6**.




**Scheme 5.** Further transformation of the products **2** and **5**.

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9. When an excess amount of allyltributylstannane (5 equiv) was used in the allylation reaction, better diastereoselectivity (*dr* > 99:1) was observed.
10. The $TiCl_4$-mediated substitution reaction of epoxides with ketene silyl acetals leading to γ-butyrolactones has been reported, although the presence of halogen atoms at the vicinal positions of epoxides was indispensable for the conversion except for ethylene oxide, see: Maslak, V.; Matović, R.; Saičić, R. N. *Tetrahedron* **2004**, *60*, 8957–8966.
11. Five equiv of ketene silyl acetal **3** were required for completion of the reaction, because **3** prepared by the Mikami protocol: Mikami, K.; Matsumoto, S.; Ishida, A.; Takamuku, S.; Suenobu, T.; Fukuzumi, S. *J. Am. Chem. Soc.* **1995**, *117*, 11134–11141. consisted of an inseparable mixture of ketene silyl acetal and ethyl (2-trimethylsilyl)acetate as well as because of its high susceptibility to Lewis acids.
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