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Asymmetric construction of quaternary carbon centers by titanium-mediated stereospecific allylation of 2,3-epoxy alcohol derivatives

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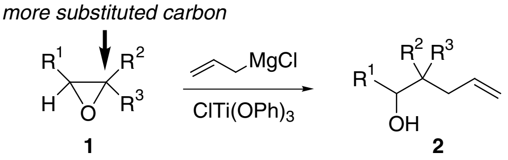
Abstract—A general procedure for the asymmetric construction of a quaternary carbon center from readily available 2,3-epoxy alcohol derivatives was developed. Ring-opening reaction of 2-substituted 2,3-epoxy alcohol derivatives with a reagent prepared from allylmagnesium halide and chlorotitanium triphenoxide affords allylated 1,3-diols having a chiral quaternary carbon as a single isomer by the *anti* pathway.

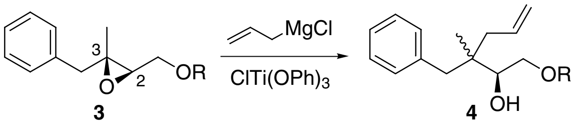
The asymmetric construction of quaternary carbon stereocenters represents an attractive area of research in organic synthesis.[1] For the formation of chiral quaternary carbons, ring-opening reaction of chiral epoxides is a promising methodology. However, such stereospecific ring-opening reaction of epoxides to create chiral quaternary carbons is relatively rare,[2] except for intramolecular reactions[3] including rearrangement.[4] Both regioselective cleavage at the more hindered tertiary carbon atom of epoxides and suppression of the S_N1 reaction to form tertiary carbocation are essential for such conversion.

We previously reported that an allyltitanium reagent prepared from chlorotitanium triphenoxide and allylmagnesium chloride selectively cleaves the more substituted carbon atom of epoxides **1** to give an allylated product **2** having a quaternary carbon center (Scheme 1).[5] This allyltitanium reagent prevents the formation of the undesired reduction product, which can be formed in the reaction of epoxides with a titanium reagent derived from chlorotitanium triisopropoxide[6] by Meerwein–Ponndorf–Verley reaction. In this communication, we present an allyltitanium-mediated asymmetric construction of quaternary carbons from readily available chiral 2-substituted 2,3-epoxy alcohol derivatives utilizing this chemistry. To the best of our knowledge, this is the first example to construct chiral quaternary carbons by stereospecific titanium-mediated ring-opening reaction of acyclic epoxides,[7] although some stereoselective reactions forming tertiary carbons were already reported.[8,9]



Scheme 1.

First, we prepared chiral protected 2,3-epoxy alcohols **3a** and **3b** through Sharpless asymmetric epoxidation[10] and investigated the allyltitanium-mediated ring-opening reaction (Scheme 2). Treatment of **3** with allylmagnesium chloride (3 equiv) in the presence of chlorotitanium triphenoxide (3 equiv) afforded allylated product **4** in good yields (70–79%) but without stereoselectivity (50:50–54:46). This is presumably due to the



epoxide	time	stereoselectivity	yield
3a (R = MOM)	2 h	50:50	70%
3b (R = Bn)	2 h	54:46	79%

Scheme 2.

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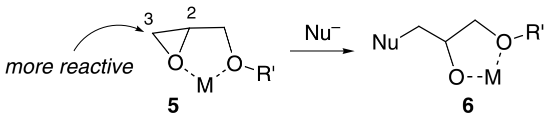
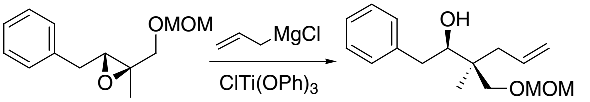
Lewis acidity of the titanium reagent causing the undesired S_N1 reaction. The reaction with allylmagnesium bromide and chlorotitanium triphenoxide gave almost the same results.

It is well documented that ring-opening reaction of 2,3-epoxy alcohol derivatives **5** with a nucleophilic metal reagent such as titanium,[8] aluminum,[11] and other nucleophiles[12] regioselectively proceeds at the 3-position to form 1,2-diols such as **6** (Eq. 1).[13] If the substituents at the highly reactive 3-position of 2,3-epoxy alcohol **3** might assist the S_N1 ring-opening reaction to form the tertiary carbocation, the low stereoselectivity of the reaction is understandable. Accordingly, we then turned our attention to the ring-opening reaction of 2,3-disubstituted 2,3-epoxy alcohol **7** (Eq. 2). Fortunately, the reaction of **7** with the allyltitanium reagent yielded 1,3-diol derivative **8** bearing a quaternary carbon center as a single isomer. Although the yield was moderate (54%),[14] the ring-opening reaction has proven to proceed through a stereospecific *anti* pathway.[15]



5 **6** (1)

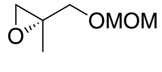
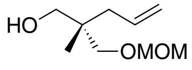
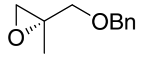
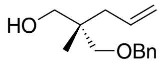
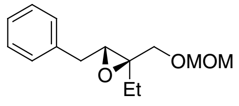
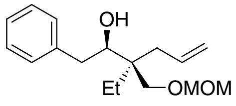
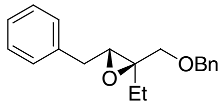
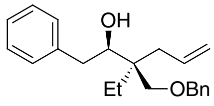
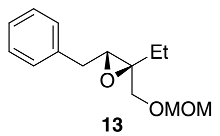
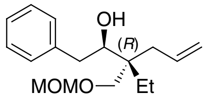
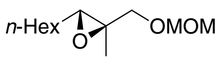
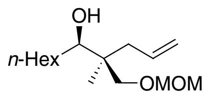
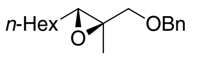
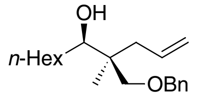


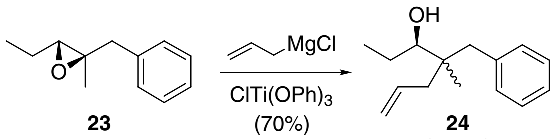
7 **8** (54%, single isomer) (2)

We next investigated the ring-opening reaction of 2,3-disubstituted 2,3-epoxy alcohol derivatives **9**–**15** with allylmagnesium chloride in the presence of chlorotitanium triphenoxide for the asymmetric construction of quaternary carbon centers.[16] The results are summarized in Table 1. Although the yields are moderate, the *anti* products **16**–**22** were exclusively obtained in all cases examined. 2,3-Epoxy alcohols **9** and **10** without a substituent at C-3 also gave the allylated products **16** and **17**, respectively, having a quaternary carbon (entries 1 and 2). The reaction of epoxy alcohol **13** (entry 5) derived from (*Z*)-allylic alcohol afforded the desired product **20** with (*R*)-configuration, which is opposite to that obtained with (*E*)-allylic alcohol derivatives **11**, **12**, **14**, and **15** (entries 3, 4, 6, and 7), both via the *anti* pathway. We also investigated the allylation reaction using allylmagnesium bromide in place of allylmagnesium chloride and the similar results were obtained.

It should be clearly noted that the reaction of epoxide **23** without the hydroxy functionality gave the allylated product **24** as an almost 1:1 diastereomixture (Eq. 3) presumably through the S_N1 pathway. Therefore, it is apparent that the protected hydroxy group of the 2-substituted epoxy alcohols plays a significant role in the stereospecific ring-opening reaction.

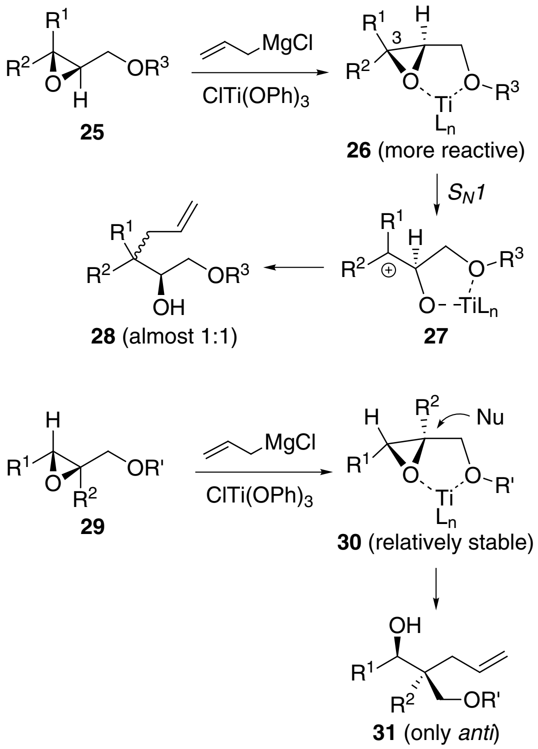
Table 1. Allyltitanium-mediated asymmetric construction of quaternary carbons from epoxides

Entry	Epoxy alcohol	Product (yield)
1	 **9**	 **16** (46%)
2	 **10**	 **17** (41%)
3	 **11**	 **18** (42%)
4	 **12**	 **19** (34%)
5	 **13**	 **20** (37%)
6	 **14**	 **21** (49%)
7	 **15**	 **22** (33%)



23 **24** (55:45) (3)

One possible rationalization for the observed stereoselectivity is depicted in Scheme 3. Both the above-mentioned high reactivity of the 3-position[8,11,12] and the substituent at C-3 of the 2,3-epoxy alcohols **25** would assist the S_N1-type ring-opening reaction by the allyltitanium reagent to form the tertiary carbocationic species **27** via the coordinated structure **26**,[8] that promotes the formation of the allylated product **28** as a 1:1 diastereomixture. In contrast, the corresponding coordinated structure **30** derived from 2,3-disubstituted epoxy alcohol **29** would be relatively stable and suppress the undesired S_N1 reaction, yielding the *anti* product **31**. The moderate yields of the stereospecific ring-opening reaction would be attributed to the stability of **30**.



Scheme 3.

In conclusion, we have developed an asymmetric construction of quaternary carbon centers by ring-opening reaction of readily available chiral 2,3-epoxy alcohol derivatives. Although the yields are moderate, this is the first example of the asymmetric construction of quaternary carbon centers by a stereospecific ring-opening reaction of readily available chiral acyclic epoxides using a titanium reagent. Since the products obtained have three distinguishable functional groups around the chiral quaternary stereocenter, this reaction would serve as an extremely useful method for the synthesis of complex molecules having a chiral quaternary carbon.

Acknowledgements

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14. Halohydrin is one of the representative side products irrespective of the Grignard reagent used, the stereochemistry of which is not determined. No regioisomer of the allylated product was detected in the reaction mixture.
15. The stereochemistry of **8** was determined by NOE analysis of the corresponding lactone, which was obtained by ozonolysis followed by oxidation.
16. Typical procedure is as follows: a solution of $ClTi(OPh)_3$ (7 equiv) in THF was added dropwise to allylmagnesium chloride (7 equiv) or bromide in THF at −78 °C. The mixture was stirred for 30 min at −50 °C, and a solution of a protected epoxy alcohol in THF was added to the above reagent at −78 °C. The mixture was stirred overnight, and saturated aqueous KF was added to the mixture. After the mixture was stirred for 30 min, precipitates were removed by filtration. The filtrate was washed with 2 N NaOH, water, and brine, and dried over $MgSO_4$. After purification by silica gel chromatography, 1,3-diol having a chiral quaternary carbon center was obtained.