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Stereospecific interconversion of *cis*- and *trans*-γ,δ-epoxy α,β-unsaturated ester systems

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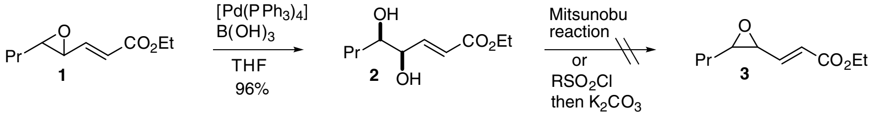
The unprecedented, stereospecific interconversion of *cis*- and *trans*-γ,δ-epoxy α,β-unsaturated ester systems has been realized, which involves the palladium-catalyzed stereospecific alkoxy or hydroxy substitution reaction with double inversion of configuration at the γ-position as the key step. The new methodology is not only applicable to various disubstituted and trisubstituted epoxy unsaturated esters, but also these interconversions proceed with an extremely high degree of stereoselectivity and efficiency.

Stereoselective, epoxide-opening reactions with nucleophiles have played very important roles in organic synthesis, particularly in the stereoselective synthesis of biologically important target molecules in natural product and in medicinal research.[1] It is well known that the epoxide-opening reaction via an S_N2 process occurs stereospecifically, that is, the reaction of a *trans*-epoxide with a nucleophile gives an *anti*-product stereoselectively, while that of a *cis*-epoxide produces a *syn*-product exclusively. Therefore, if stereospecific interconversion between *cis*-epoxides and *trans*-epoxides is realized, both *anti* and *syn* products should be available from the same epoxide in a highly stereoselective manner. However, such transformation has been known to be methodologically very difficult, although cis–trans isomerization of epoxides in a few particular cases such as thermal isomerization of α-cyanostilbene oxide,[2] ruthenium-catalyzed isomerization,[3] and that of α,β-epoxy amides[4] have been reported, most of which produced the thermodynamically more stable *trans*-isomers predominantly.

As a program of acyclic stereocontrol based on the stereospecific epoxide-opening reactions, we already reported the highly stereoselective interconversion between *cis*- and *trans*-epoxy sulfides.[5] Our recent studies on a number of stereospecific substitution reactions of γ,δ-epoxy α,β-unsaturated esters with carbon,[6] nitrogen,[7] and oxygen nucleophiles[8] call for an efficient and highly stereoselective interconversion of *cis*- and *trans*-epoxy unsaturated ester systems, which would provide very useful transformations in organic synthesis.

We first explored an interconversion route via the palladium-catalyzed stereospecific hydroxy substitution reaction of γ,δ-epoxy α,β-unsaturated esters with boric acid ($B(OH)_3$) which was recently developed by us[8b] (Scheme 1). Thus, the palladium-catalyzed reaction of ethyl *trans*-4,5-epoxy-2-octenecarboxylate (**1**) with $B(OH)_3$ in THF smoothly occurred giving rise to *syn*-diol **2** with double inversion of configuration at the γ-position in excellent yield. We presumed that stereoselective interconversion of *cis*- and



Scheme 1. Attempts to convert *trans*-epoxy unsaturated ester **1** to *cis*-congener **3** via *vic*-diol **2**.

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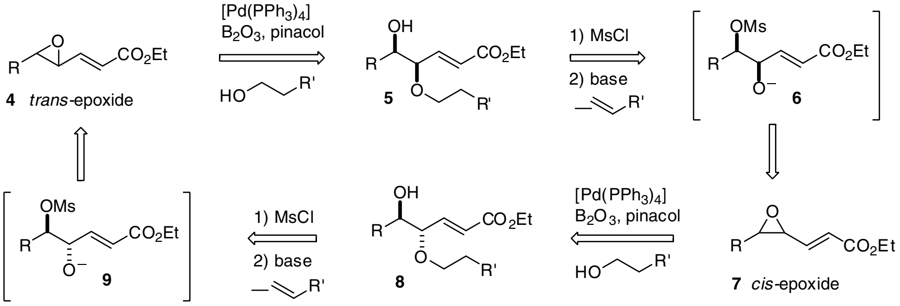
trans-γ,δ-epoxy α,β-unsaturated esters might be possible, if the diol **2** was to be stereoselectively converted to the corresponding *cis*-epoxide **3**. However, neither the Mitsunobu dehydration reaction[9] of **2** nor the two-step reaction sequence via mono-sulfonate followed by treatment with a base was fruitless under various conditions (Scheme 1). These results suggest that ingenuity to differentiate vicinal hydroxyl groups in **2** is of critical importance for interconversion of the *trans*-epoxide **1** and the *cis*-epoxide **3**.

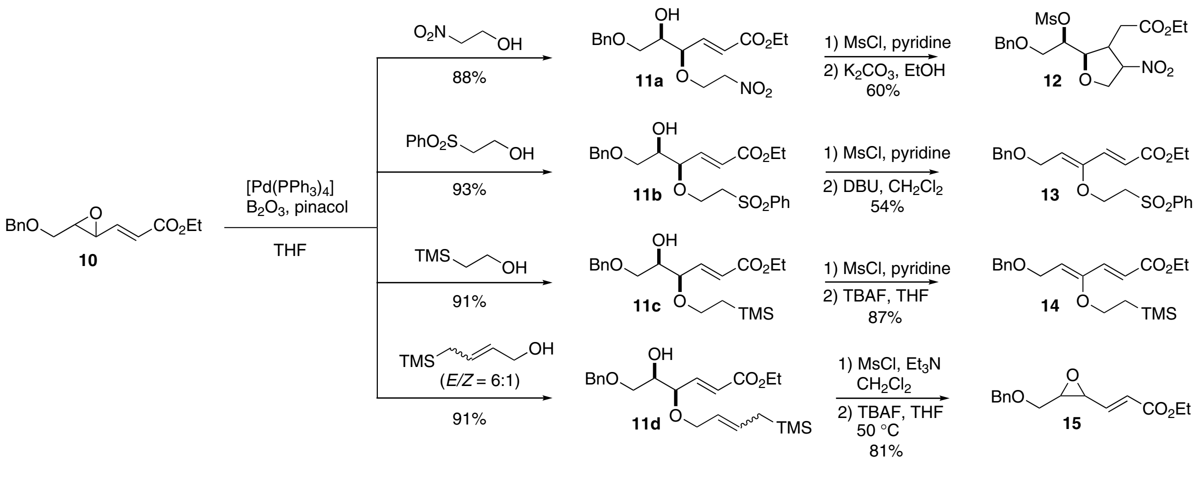
Very recently, we developed the novel palladium-catalyzed alkoxy substitution reaction by combination of a γ,δ-epoxy α,β-unsaturated ester, boron oxide, and pinacol, which proceeds with double inversion of the configuration at the γ-position to afford a γ-alkoxy-δ-hydroxy-α,β-unsaturated ester in a stereospecific manner and in high yield.[10] Since a variety of γ-alkoxy-δ-hydroxy-α,β-unsaturated esters **5** are easily obtainable by this method, we envisioned that stereospecific interconversion between *cis*- and *trans*-epoxy unsaturated esters might be possible, if the key alkoxide ion **6** could effectively be generated in situ by use of a γ-alkoxy substituent after introduction of a mesyloxy group at the δ-position, as shown in Scheme 2. Based on this concept, we studied the following three-step reaction sequence, which involves the palladium-catalyzed stereospecific alkoxy substitution reaction of a *trans*-epoxy unsaturated ester **4**, mesylation of the resulting alcohol **5** followed by the key generation of the alkoxide ion **6** leading to a *cis*-epoxide **7**.

Initially, a number of alcohol nucleophiles were examined to find out which type of an alkoxy substituent in **5** is most suitable for in situ generation of the alkoxide ion **6**. For this purpose, we selected 2-nitroethanol, 2-(phenylsulfonyl)ethanol, 2-trimethylsilylethanol, and 4-(trimethylsilyl)-2-buten-1-ol[11,12] as alcohol counterparts, and carried out the palladium-catalyzed alkoxy substitution reactions of ethyl 6-benzyloxy-*trans*-4,5-epoxy-2-hexenoate (**10**) with these alcohols. The substitution reactions smoothly occurred at room temperature to afford *syn*-γ-alkoxy-δ-hydroxy-α,β-unsaturated esters **11a–d**, the products with retention of configuration, in excellent yields, as shown in Scheme 3. After each product was treated with methanesulfonyl chloride, the crude mesylate was subjected to the key epoxide-forming reaction. Upon treatment of the mesylate derived from **11a** with K_2CO_3 in EtOH, only tetrahydrofuran derivative **12**[14] was formed, and the *cis*-epoxide **15** was not detected at all. On the other hand, treatment of the mesylate prepared from **11b** with DBU resulted in formation of the elimination product **13**. Next, we focused on the reactions of **11c** and **11d** in expectation to generate of alkoxide ions by treatment with a mild fluoride ion. Thus, treatment of the mesylate derived from **11c** with TBAF in THF merely resulted in formation of diene **14**. On the contrary, upon treatment of the mesylate prepared from **11d** with TBAF in THF at 50 °C, much to our pleasure, the *cis*-epoxide **15** was produced as a single product in 81% isolated yield. These outcomes demonstrate that only 4-(trimethylsilyl)-2-buten-1-ol serves as the alcohol counterpart for this particular transformation that allows efficient generation of the key alkoxide ion by elimination of 1,3-butadiene from the 4-(trimethylsilyl)-2-butenyl ether moiety on treatment with TBAF.

Efficient conversion of the *trans*-epoxide **10** to the *cis*-congener **15** with complete diastereoselectivity prompted us to investigate the scope of this methodology. To our expectation, the opposite transformation from the *cis*-epoxide **15** to the *trans*-isomer **10** also occurred stereospecifically in three steps in 80% overall yield (Scheme 4). Similarly, interconversion of *cis*- and *trans*-epoxy unsaturated esters **3** and **1** that bear no ether oxygen atom on the side chain was performed with complete stereoselectivity, as



Scheme 2. Strategy for stereospecific interconversion of *cis*- and *trans*-epoxy unsaturated esters.



Scheme 3. Pd(0)-catalyzed substitution reactions of **10** with various alcohols and subsequent epoxide-forming reactions.