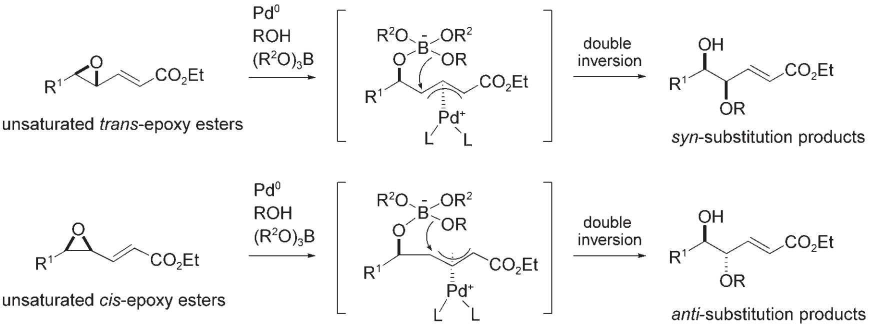
Homogeneous Catalysis

DOI: 10.1002/anie.200703889

Palladium-Catalyzed Stereospecific Substitution of α,β-Unsaturated γ,δ-Epoxy Esters by Alcohols with Double Inversion of Configuration: Synthesis of 4-Alkoxy-5-hydroxy-2-pentenoates**

*Xiao-Qiang Yu, Fumihiko Yoshimura, Fumito Ito, Minoru Sasaki, Atsushi Hirai, Keiji Tanino, and Masaaki Miyashita**

In memory of Yoshihiko Ito



Scheme 1. Pd^0-catalyzed stereospecific alkoxy substitution reaction of α,β-unsaturated γ,δ-epoxy esters with double inversion of configuration. L = ligand.

Stereoselective, epoxide-opening reactions have played very important roles in organic synthesis, particularly in the stereoselective synthesis of biologically important target molecules in natural product and pharmaceutical research.[1] Although a variety of regio- and stereoselective substitution reactions of epoxides by an S_N2 mechanism have so far been reported,[1] the stereospecific substitution reaction which proceeds with double inversion of configuration, that is, retention of configuration, is only limited.[2,3] As part of a program to develop such types of reactions, we recently reported the palladium-catalyzed stereospecific azide substitution reaction of α,β-unsaturated γ,δ-epoxy esters with trimethylsilylazide with double inversion of configuration.[4] We have also developed palladium-catalyzed stereospecific hydroxy substitution reactions of α,β-unsaturated γ,δ-epoxy esters with alkylboronic acid[5] and with boric acid[6] to give cyclic alkyl boronates and γ,δ-vicinal diol derivatives, respectively, with double inversion of configuration.[7] From mechanistic analyses of these reactions and the precedent report by Trost et al.,[8] we anticipated that the palladium-catalyzed stereospecific substitution reaction of an α,β-unsaturated γ,δ-epoxy ester with an alcohol nucleophile might occur in the presence of an appropriate boron reagent to afford a γ-alkoxy substitution product with double inversion of configuration (Scheme 1). A new type of palladium-catalyzed substitution reaction of epoxides with alcohols should have the following synthetic advantages: 1) Overcome the extremely poor reactivity of alcohols as nucleophiles; 2) realize fast and stereoselective interconversion of the π-allylpalladium intermediates with alcohol nucleophiles; and 3) various alcohols may serve as nucleophiles to provide a variety of 4-alkoxy-5-hydroxy-2-pentenoate systems with a high stereoselectivity that reflects the stereochemistry of the epoxides.

Initially, we chose ethyl *trans*-6-benzyloxy-4,5-epoxy-2(*E*)-hexenoate (**1a**)[5] as a model substrate and examined its palladium-catalyzed reactions with $(MeO)_3B$, $(EtO)_3B$, and $(PhO)_3B$ to confirm whether such reactions indeed take place. Thus, the substitution reaction of **1a** with $(MeO)_3B$ (1.3 equiv) and a palladium catalyst ($[Pd(PPh_3)_4]$, 10 mol%) in THF occurred smoothly at 0 °C to afford *syn*-δ-hydroxy-γ-methoxy ester **2a** as a single product in 92% yield (Scheme 2). Similarly, the palladium(0)-catalyzed reaction of **1a** with $(EtO)_3B$ gave **2b** exclusively in 90% yield, whereas the reaction of **1a** with $(PhO)_3B$ did not take place at all and the starting material was recovered unchanged (Scheme 2).

To realize the palladium-catalyzed alkoxy substitution reaction of epoxy unsaturated esters with various alcohols, the preparation of the requisite borate reagents, preferably in situ, is of critical importance, since such boron reagents are not commercially available. From the result of the reaction of **1a** with $(PhO)_3B$, we anticipated that $(PhO)_3B$ could be used as a boron-tether reagent for this particular

---

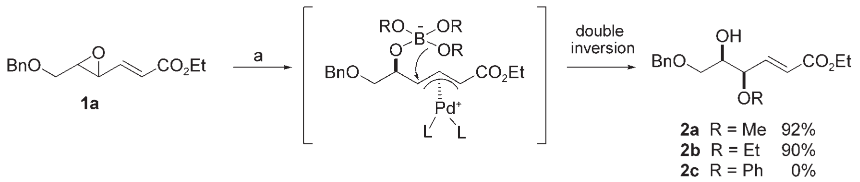
[*] Dr. X.-Q. Yu, Dr. F. Yoshimura, Dr. M. Sasaki, Dr. A. Hirai, Prof. Dr. K. Tanino, Prof. Dr. M. Miyashita[+]
Division of Chemistry, Graduate School of Science
Hokkaido University, 060-0810 Sapporo (Japan)
Fax: (+81) 11-706-4920
E-mail: bt13149@ns.kogakuin.ac.jp

[+] Present address:
Department of Applied Chemistry
Kogakuin University, 192-0015 Tokyo (Japan)
Fax: (+81) 42-628-4870

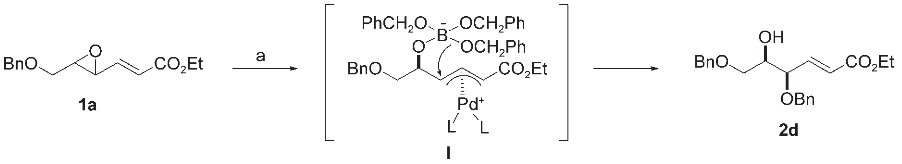
[**] Financial support from the Ministry of Education, Culture, Sports, Science, and Technology (Japan) (a Grant-in-Aid for Scientific Research (B) (no. 16350049)) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

substitution reaction. Indeed, the palladium-catalyzed reaction of **1a** with benzyl alcohol (4.5 equiv) and $(PhO)_3B$ (1.5 equiv) did occur at 0 °C, thereby giving rise to the single product **2d** in 89 % yield (Scheme 3), while phenoxy substitution product **2c** was not detected at all. The use of Et_3B, which was employed in the protocol developed by Trost et al.,[8] resulted in a lower yield (43 %) of the product.



Scheme 2. Pd^0-catalyzed substitution reactions of **1a** with trimethyl, triethyl, and triphenyl borates: a) $[Pd(PPh_3)_4]$ (10 mol %),$(RO)_3B$ (1.3 equiv), THF, 0 °C.



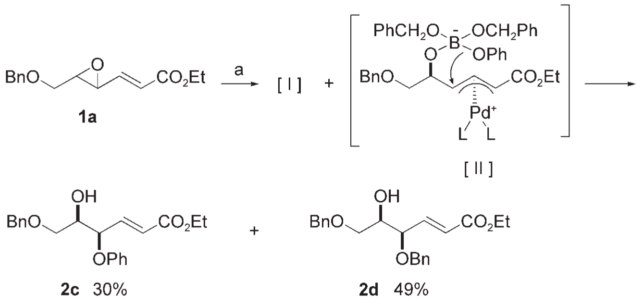
Scheme 3. Pd^0-catalyzed substitution reaction of **1a** with benzyl alcohol in the presence of triphenyl borate: a) $[Pd(PPh_3)_4]$ (10 mol %), $PhCH_2OH$ (4.5 equiv), $(PhO)_3B$ (1.5 equiv), THF, 0 °C, 4.5 h, 89 %. Bn = benzyl.

These results clearly demonstrate that $(PhO)_3B$ played the crucial role of a boron tether in this substitution reaction. The role of $(PhO)_3B$ may be rationalized as follows: A rapid alcohol-exchange reaction probably occurs between $(PhO)_3B$ and benzyl alcohol which results in the formation of tribenzyl borate $(PhCH_2O)_3B$ in situ, and the π-allyl palladium species [I] involving the tribenzyl borate complex smoothly undergoes a benzyloxy substitution reaction as a consequence of the electron-donating character of the three alkoxy groups (Scheme 3). In contrast, the corresponding π-allyl palladium species involving the triphenyl borate does not undergo a phenoxy substitution reaction, presumably because of the stabilization of the ate complex by the electron-withdrawing character of three phenoxy groups.

These excellent preliminary results led us to examine the scope of the new synthetic methodology with various epoxides and alcohol nucleophiles (Table 1). The substitution reactions of **1a** with a variety of alcohols, including allyl and propargyl alcohols, proceeded cleanly in the presence of $(PhO)_3B$ to give the *syn*-δ-hydroxy-γ-alkoxy unsaturated esters **2e–g** with remarkably high stereoselectivity and chemical yields (Table 1, entries 1–3). It should be noted that not only primary alcohols but also a sterically crowded secondary alcohol reacted smoothly to give rise to the corresponding product **2h** in high yield (Table 1, entry 4). It is also noteworthy that base-sensitive 2-bromoethanol as well as chemically labile 2-trimethylsilylethanol also served as substrates because of the mild reaction conditions (Table 1, entries 5 and 2, respectively), although formation of by-products was observed to a lesser extent in the former reaction.

Similarly, the reactions of *cis*-epoxy unsaturated ester **1b** with various alcohols proceeded stereospecifically under the same conditions to furnish the *anti*-substitution products **3a–c** in high yields (Table 1, entries 6–8). Also, *trans*- and *cis*-epoxy unsaturated esters **1c** and **1d**, which bear no ether oxygen atom in the side chain, produced the corresponding substitution products **4a**,**b** and **5a**,**b**, respectively, with complete stereoselectivity (Table 1, entries 9–12). The configuration of the products in Table 1 was determined unambiguously based on the ^1H NMR spectroscopic analyses of the δ-lactone derived from **4b**.[9]

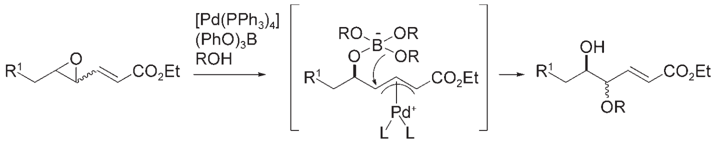
Next, we turned our attention to the phenoxy substitution reaction of epoxy unsaturated esters, since the reaction of **1a** with $(PhO)_3B$ gave none of the expected product **2c** (Scheme 1). Concerning this reaction, we observed the unexpected but important phenomenon that the reaction of **1a** with benzyl alcohol (1.2 equiv), $[Pd(PPh_3)_4]$ (5 mol %), and a catalytic amount of $(PhO)_3B$ (0.1 equiv) gave a mixture of **2c** (30 %) and **2d** (49 %; Scheme 4). This result probably indicates that the reaction proceeded via borate complexes **I** and **II** to give **2d** and **2c**, respectively, and that the latter reaction was much faster than the former reaction, since all phenoxide ions were consumed completely, regardless of their minor amounts.

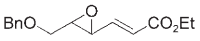
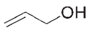
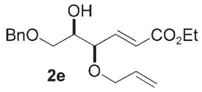
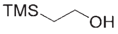
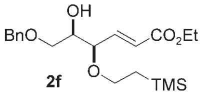
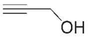
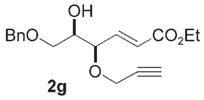
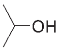
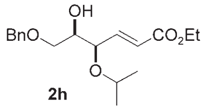
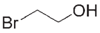
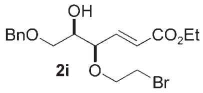
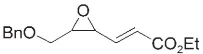
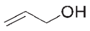
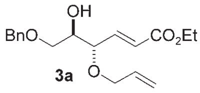
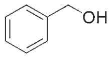
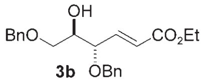
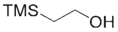
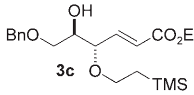
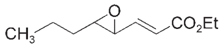
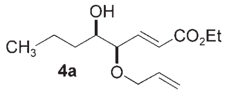
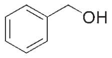
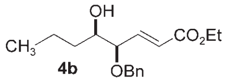
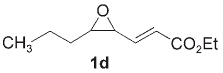
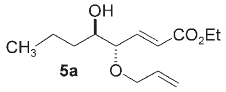
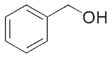
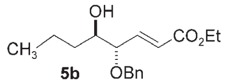


Scheme 4. Pd^0-catalyzed reaction of **1a** with benzyl alcohol in the presence of a catalytic amount of triphenyl borate: a) $[Pd(PPh_3)_4]$ (5 mol %), $(PhO)_3B$ (0.1 equiv), $PhCH_2OH$ (1.2 equiv), THF, 0 °C, 30 min.

These outcomes led us to use pinacol as a non-nucleophilic boron tether and this idea was proved to be very effective for this particular reaction. Thus, the reactions of **1a–d** with $(PhO)_3B$ (2 equiv) and pinacol (2 equiv) occurred smoothly in the presence of $[Pd(PPh_3)_4]$ (10 mol %) in THF to give rise to the corresponding phenoxy substitution products **2c** and **6a–c**, respectively, in high yield (Table 2).

Table 1: Pd^0-catalyzed stereospecific alkoxy substitution reactions of α,β-unsaturated γ,δ-epoxy esters with various alcohols in the presence of triphenyl borate.

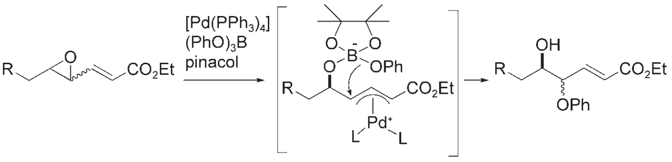


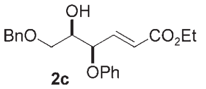
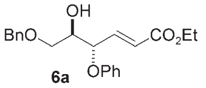
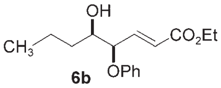
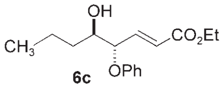
Entry	Substrate	ROH	Product	Yield [%][b]	*anti*:*syn*
1	 **1a**		 **2e**	86	> 1:99
2	**1a**		 **2f**	84	> 1:99
3	**1a**		 **2g**	81	> 1:99
4	**1a**		 **2h**	81	> 1:99
5	**1a**		 **2i**	56[c]	14:86
6	 **1b**		 **3a**	86	> 99:1
7	**1b**		 **3b**	90	> 99:1
8	**1b**		 **3c**	82	> 99:1
9	 **1c**		 **4a**	91	> 1:99
10	**1c**		 **4b**	92	> 1:99
11	 **1d**		 **5a**	86	> 99:1
12	**1d**		 **5b**	91	> 99:1

[a] The reaction was carried out with [Pd(PPh$_3$)$_4$] (10 mol%), (PhO)$_3$B (1.5 equiv), and ROH (4.5 equiv) in THF at 0 °C (10 min–4 h). [b] Yield of isolated product. [c] A mixture of keto esters was formed as by-products. TMS = trimethylsilyl.

Furthermore, the combination of pinacol (0.5 equiv) and boric anhydride (B_2O_3, 1 equiv)[10] also proved to be very effective for the palladium(0)-catalyzed substitution reaction of α,β-unsaturated γ,δ-epoxy esters with various alcohols (Table 3). Thus, the reactions of **1a** with a variety of alcohols, including base-sensitive 2-bromoethanol and 2-nitroethanol, proceeded quite smoothly by using the combination of pinacol and B_2O_3[10] to afford the corresponding γ-substitution products **2d**, **2i**, and **2j** with a high degree of stereoselectivity and in high yields (Table 3, entries 1–3). It is noteworthy that the reaction of **1a** with 2-bromoethanol in the presence of this new combination gave **2i** in much higher yield than when triphenyl borate was used (Table 3, entry 2 versus Table 1 entry 5). In addition, the trisubstituted epoxy ester **1e** also furnished the desired γ-alkoxy substitution products **7a** and **7b** stereospecifically (Table 3, entries 4 and 5).

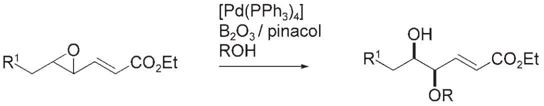
Table 2: Pd^0-catalyzed phenoxy substitution reactions of **1a–d** in the presence of pinacol.

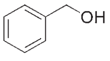
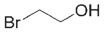
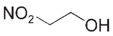
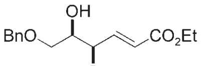
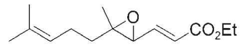
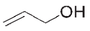
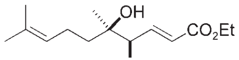
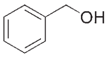
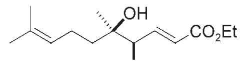


Entry	Substrate	Product	Yield [%][b]	*anti*:*syn*
1	**1a**	 **2c**	89	3:97
2	**1b**	 **6a**	93	96:4
3	**1c**	 **6b**	95	4:96
4	**1d**	 **6c**	91	95:5

[a] The reaction was carried out with [Pd(PPh$_3$)$_4$] (10 mol%), (PhO)$_3$B (2 equiv), and pinacol (2 equiv) in THF at room temperature (10 min–2 h). [b] Yield of isolated product.

Table 3: Pd^0-catalyzed alkoxy substitution reactions of α,β-unsaturated γ,δ-epoxy esters with various alcohols by the combination of pinacol and boric anhydride.



Entry	Substrate	ROH	Product	Yield[%][b]	*anti*:*syn*
1	**1a**		**2d**	96	>1:99
2	**1a**		**2i**	93	3:97
3	**1a**		 **2j**	88	3:97
4	 **1e**		 **7a**	75	6:94
5	**1e**		 **7b**	76	6:94

[a] The reaction was carried out with [Pd(PPh$_3$)$_4$] (5 mol%), ROH (2 equiv), pinacol (0.5 equiv), and B$_2$O$_3$ (1.0 equiv) in THF at room temperature. The reaction time was 5 min for entries 1–3, 90 min for entry 4, and 20 min for entry 5. [b] Yield of isolated product.

The highly functionalized compounds shown in Tables 1–3 (which were previously inaccessible) can be readily obtained in a highly stereoselective manner, in high yields, and even in chiral forms. In addition, these products serve as versatile synthetic intermediates for further chemical transformations.

In summary, we have developed a new palladium-catalyzed stereospecific substitution reaction of α,β-unsaturated γ,δ-epoxy esters with various alcohols that proceeds with double inversion of configuration to afford a variety of 4-alkoxy-5-hydroxy-2-pentenoate derivatives in high yields. Since the new methods are applicable to various substrates and alcohols, and since the products thus obtained serve as versatile synthetic intermediates for further transformations, these methodologies should have great potential in organic synthesis, particularly, in the context of the stereoselective synthesis of biologically active target molecules in the natural product and pharmaceutical research areas. Further investigations into the synthetic applications of these methodologies are on going.

Received: August 24, 2007

Keywords: alcohols · esters · homogeneous catalysis · palladium · synthetic methods

---

[1] a) J. M. Klunder, G. H. Posner in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, chap. 1.5, pp. 207–239; b) D. W. Knight in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, chap. 1.6, pp. 241–270; c) P. J. Garratt in *Comprehensive Organic Synthesis*, *Vol. 3* (Eds.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, chap. 1.7, pp. 271–292; d) G. H. Posner, *Org. React.* **1975**, *22*, 253; e) R. M. Hanson, *Chem. Rev.* **1991**, *91*, 437; f) B. H. Lipshutz, S. Sengupta, *Org. React.* **1992**, *41*, 135; g) C. Bonini, G. Righi, *Synthesis* **1994**, 225.

[2] For the substitution reactions of epoxy sulfides with double inversion of configuration, see a) C. Liu, Y. Hashimoto, K. Kudo, K. Saigo, *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2095; b) H. Hayakawa, N. Okada, M. Miyashita, *Tetrahedron Lett.* **1999**, *40*, 3191; c) M. Sasaki, K. Tanino, M. Miyazawa, M. Miyashita, *Tetrahedron Lett.* **1999**, *40*, 9267; d) M. Sasaki, K. Tanino, M. Miyashita, *J. Org. Chem.* **2001**, *66*, 5388; e) A. Hirai, T. Tonooka, K. Wakatsuki, T. Tanino, M. Miyashita, *Angew. Chem.* **2002**, *114*, 847; *Angew. Chem. Int. Ed.* **2002**, *41*, 819.

[3] For other substitution reactions of epoxides with double inversion of configuration, see a) C. Liu, Y. Hashimoto, K. Saigo, *Tetrahedron Lett.* **1996**, *37*, 6177; b) M. Sasaki, M. Hatta, K. Tanino, M. Miyashita, *Tetrahedron Lett.* **2004**, *45*, 1911.

[4] M. Miyashita, T. Mizutani, G. Tadano, Y. Iwata, M. Miyazawa, K. Tanino, *Angew. Chem.* **2005**, *117*, 5224; *Angew. Chem. Int. Ed.* **2005**, *44*, 5094.

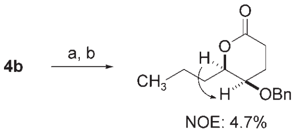
[5] A. Hirai, X.-Q. Yu, T. Tonooka, M. Miyashita, *Chem. Commun.* **2003**, 2482.

[6] X.-Q. Yu, A. Hirai, M. Miyashita, *Chem. Lett.* **2004**, *33*, 764.

[7] Pd^0-catalyzed cross-coupling reactions of vinyl epoxides with organoboronic acids in an S$_N$2 process has recently been reported, see J. Kjellgren, J. Aydin, O. A. Wallner, I. V. Saltanova, K. J. Szabó, *Chem. Eur. J.* **2005**, *11*, 5260.

[8] B. M. Trost, E. J. McEachern, F. D. Toste, *J. Am. Chem. Soc.* **1998**, *120*, 12702.

[9] The configuration of **4b** was determined by its conversion into a δ-lactone and its ^{1}H NMR analyses.



a) H_2, $Pd(OH)_2/C$, AcOEt; b) pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2, reflux.

[10] The use of absolutely dry boric anhydride (B_2O_3) is of critical importance for this type of reaction. Dry B_2O_3 was prepared by heating the commercially available reagent in an oven at 100 °C for 3 h in vacuo prior to use.