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R_3Al–R'_3SiOTf: Novel and Powerful Reagent System for Stereospecific Alkylation–Silylation Reactions of Epoxides

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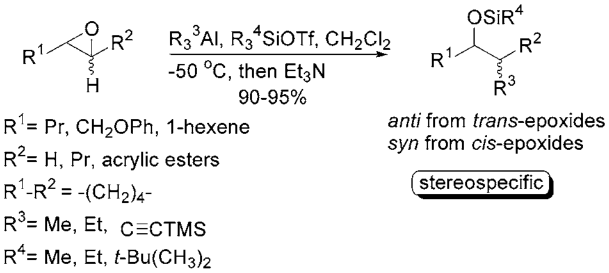
ABSTRACT



A novel and powerful reagent system R_3Al–R'_3SiOTf for the one-pot alkylation–silylation reaction of epoxides was discovered, and the reactions of various epoxides with the new reagent system have been demonstrated to occur stereospecifically giving rise to the corresponding alkylation–silylation products in excellent yields.

Stereoselective carbon−carbon bond-forming reactions of epoxides with carbon nucleophiles are one of the most important transformations in organic synthesis,[1] particularly in natural product synthesis.[2] Although various organoaluminum reagents have been used as carbon nucleophiles[3] for epoxide-opening reactions, this type of reaction is restricted to a structurally limited number of substrates such as 2,3-epoxy alcohols,[4] γ,δ-epoxy unsaturated esters,[5] epoxy sulfides,[6] and so on and not applicable to simple epoxy alkanes themselves.

For example, the reaction of *trans*-4-epoxyoctane (**1**) with trimethylaluminum (Me_3Al, 3 equiv) did not occur at −30

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[5] (a) Miyashita, M.; Hoshino, M.; Yoshikoshi, M. *J. Org. Chem.* **1991**, *56*, 6483. (b) Ishibashi, N.; Miyazawa, M.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 377.

[6] (a) Liu, C.; Hashimoto, Y.; Kudo, K.; Saigo, K. *Bull. Chem. Soc., Jpn.* **1996**, *69*, 2095. (b) Sasaki, M.; Tanino, K.; Miyashita, M. *J. Org. Chem.* **2001**, *66*, 5388.

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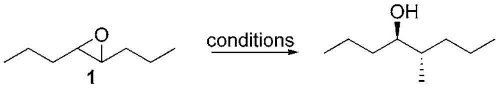
°C at all and the starting material was quantitatively recovered unchanged. Even with the use of the more active Me_3Al-H_2O system,[5,7] less than 10% of the product was formed (Scheme 1). The reaction with the Gillman reagent (Me_2CuLi, 2 equiv) furnished only 67% of the desired product.

Scheme 1. Reactions of *trans*-4-Epoxyoctane (**1**) with Me_3Al.



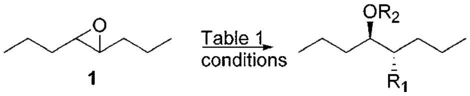
conditions	yield
Me_3Al, CH_2Cl_2, -30 °C, 3 h	No reaction
Me_3Al, H_2O, CH_2Cl_2, -30 °C, 3 h	10%
Me_2CuLi, dry ether, 0 °C, 3 h	67%

To overcome the synthetic limitation of organoaluminums and to realize efficient carbon−carbon bond-forming reactions of epoxides, we explored a new type of activation of organoaluminum reagents, although a few types of activations are known in the literature.[8] As a result, we discovered that the combination of trialkylaluminum (R_3Al) and trialkylsilyltriflate (R'_3SiOTf) serves as an excellent carbon nucleophile for epoxide-opening reactions. We report herein the powerful activation and enhancement in the reactivity of organoaluminums by the combination with R'_3SiOTf, which act as efficient and potentially useful alkylating reagents of various epoxides to afford the corresponding silylated products in the presence of Et_3N in a one-pot operation and in remarkably high yields.

We chose *trans*-4-epoxyoctane (**1**) as a model substrate for the present study. First, the epoxide **1** was treated with Me_3Al (1.5 equiv) and TMSOTf (1.5 equiv) in CH_2Cl_2 at −50 °C to afford the anti-methylated alcohol as a single product in 91% yield (Table 1, entry 1).[9]

Notably, we found that on the addition of Et_3N (1.5 equiv) to the reaction mixture after the disappearance of the starting material (TLC; ca. 30−40 min), the corresponding TMS−ether of the alcohol was formed in 93% yield (entry 2). We also examined the combination of Me_3Al and other triflates (TESOTf and TBSOTf) to demonstrate the scope and generality of the present method. Thus, the reaction of **1** with Me_3Al in the presence of TESOTf and Et_3N or TBSOTf and Et_3N afforded the corresponding silyl ethers with complete stereoselectivity in remarkably high yields (entries 3 and 4). We found that the reactivity of the triflates was TMSOTf >TESOTf > TBSOTf, probably due to the bulkiness of the reagents. Hence, the reaction of **1** with TIPSOTf furnished only the starting material even after prolonged reaction time and conditions. To get insight into the scope of the present method, other organoaluminum reagents such as Et_3Al and Me_2AlC•CTMS were examined. These reagents also served as excellent carbon nucleophiles to afford the corresponding substitution products in excellent yields (entries 5−7), although 4 mL/mmol concentration was required to minimize side products (e.g., ketones) in these reactions. All reactions in Table 1 proceeded smoothly, giving rise to a single product. It should be noted that the present method provides a variety of the alkylation−silylation products in one-pot operation with extremely high stereoselectivity.

Table 1. Alkylation−Silylation of **1** with $R_3Al-R'_3SiOTf$[a]



entry	conditions	product	isolated yield (%)
1	**A**,^{b} −50 °C,1 h	R_1 = Me, R_2 = H	91
2	**A**, −50 °C, 1 h	R_1 = Me, R_2 = TMS	93
3	**A**,^{c} −50 °C, 50 min	R_1 = Me, R_2 = TES	92
4	**A**,^{c} −50 °C, 50 min	R_1 = Me, R_2 = TBS	94
5	**B**,^{c,d} −50 °C, 1 h	R_1 = Et, R_2 = TMS	90
6	**B**,^{c,d} −50 °C, 75 min	R_1 = Et, R_2 = TES	95
7	**C**,^{f} −50 °C, 1 h	R_1 = C≡CTMS, R_2 = TMS	95^{e}

[a] All reactions were carried out in dichloromethane. **A**: Me_3Al (1.5 equiv), R_3SiOTf (1.5 equiv), Et_3N (1.5 equiv). **B**: Et_3Al (1.5 equiv), R_3SiOTf (1.5 equiv), Et_3N (1.5 equiv). **C**: Me_2AlC ≡ CTMS (2 equiv), R_3SiOTf (2 equiv), Et_3N (1.5 equiv). [b] Without Et_3N. [c] Performed with 1.3 equiv of the reagents. [d] Carried out with 4 mL/mmol concentration. [e] Isolated along with 8% of the reduction product. [f] Me_2AlC≡C-TMS was prepared by the treatment of Me_2AlOTf with Li C≡CTMS in CH_2Cl_2.

The excellent preliminary results prompted us to examine various epoxides under the optimized conditions. Thus, *cis*-4-epoxyoctane (**2**), cyclohexaneoxide (**3**), and *trans*- and *cis*-γ,δ-epoxy unsaturated esters (**4** and **5**, respectively) were examined and the results are summarized in Table 2. As shown, all the reactions proceeded stereospecifically giving rise to the corresponding silyl ethers of alkylation products as single products in excellent yields (entries 1−12). The configuration of the products was unambiguously confirmed by agreement with that of the products obtained by the reaction of **1** and **2** with the Gillman reagent (Me_2CuLi),[2a] although the later reactions gave lesser yields (40 and 67%, respectively) of products. It is noteworthy that the reactions of *trans*-γ,δ-epoxy unsaturated ester (**4**) having no particular oxygen function on the side chain also occurred smoothly

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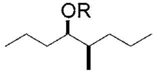
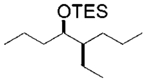
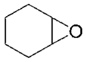
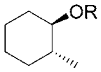
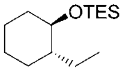
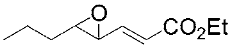
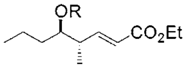
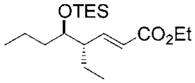
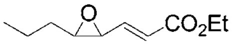
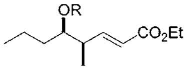
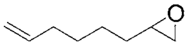
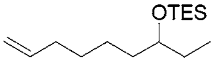
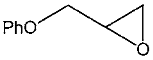
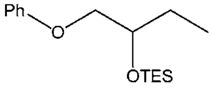
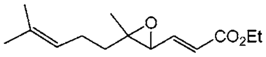
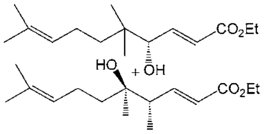
(8) (a) Zhou, H.; Campbell, E. J.; Nguyen, S. T. *Org. Lett.* **2001**, *3*, 2229. (b) Schneider, C.; Brauner, J. *Tetrahedron Lett.* **2000**, *41*, 3043. (c) Pfaltz, A.; Mattenberger, A. *Angew. Chem., Int, Ed. Engl.* **1982**, *21*, 71. (d) Inghardt, T.; Frejd, T. *Tetrahedron*, **1991**, *47*, 6483.

(9) **Representative Procedure.** To a solution of the epoxide **1** (100 mg, 0.78 mmol) in dry CH_2Cl_2 (2 mL) were added Me_3Al (1 M solution in hexane, 1.2 mL, 1.2 mmol) and TMSOTf (0.23 mL, 1.2 mmol) at −50 °C under an argon atmosphere. After the mixture was stirred for 45 min at the same temperature, Et_3N (0.16 mL, 1.2 mmol) was added and the mixture was further stirred for an additional 15 min at the same temperature. The reaction was quenched with 0.05 M HCl (2 mL), and the mixture was extracted with ethyl acetate (50 mL) and successively washed with water (4 × 25 mL) and brine (25 mL), dried (anhydrous $MgSO_4$), and concentrated in vacuo. The crude product was immediately purified by a silica gel column chromatography (5% hexanes−ethyl acetate) to give the pure trimethyl-(2-methyl-1-propylpentyloxy)-silane (159 mg, 93%). *It is critical to purify the crude products immediately to obtain the corresponding products in high yield.* The reaction was quenched with 1 M HCl (without adding Et_3N), followed by the same workup procedure, to afford the pure 5-methyl-oct-4-ol (93 mg, 91%).

Table 2. Alkylation−Silylation Reactions of Various Epoxides with $R_3Al-R'_3SiOTf-Et_3N$[a]

entry	substrate	conditions [b]	product	isolated yield (%)
1	 **2**	**A**, -50 °C, 1 h	 R= TMS	93
2		**A**, -50 °C, 40 min	R = TES	94
3		**A**, -50 °C, 40 min	R = TBS	94
4		**B**, -50 °C, 40 min		93
5	 **3**	**A**, -50 °C, 30 min	 R= TMS	90
6		**A**, -50 °C, 40 min	R = TES	90
7		**A**, -50 °C, 40 min	R = TBS	91
8		**B**, -50 °C, 40 min		96
9	 **4**	**C**, -50 °C, 1 h	 R= TMS	95
10		**C**, -40 °C, 2 h	R = TES	93
11		**C**, -30 °C, 2 h	R = TBS	82
12		**B**, -50 °C, 40 min		90
13	 **5**	**C**, -100 °C, 1 h	 R= TMS	96 (γ/δ=85:15)
14		**C**, -78 °C, 1 h	R = TES	94 (γ/δ=78:22)
15		**C**, -50 °C, 1 h	R = TBS	95 (γ/δ=79:21)
16	 **6**	**A**, -50 °C, 30 min		95 (α/β=92:8)
17	 **7**	**A**, -50 °C, 30 min		93
18	 **8**	**C**^{c}, -78 °C, 90 min.		90 (γ/δ=18:82)

[a] All reactions were carried out in dichloromethane. [b] **A**: Me_3Al (1.5 equiv), R_3SiOTf (1.5 equiv), Et_3N (1.5 equiv). **B**: Et_3Al (1.5 equiv), R_3SiOTf (1.5 equiv), Et_3N (1.5 equiv). **C**: Me_3Al (2 equiv), R_3SiOTf (2 equiv), Et_3N (1.3 equiv). [c] Without Et_3N.

with complete regioselectivity at the γ-position to give single γ-substitution products (entries 9−12), which were in contrast with the very sluggish reaction of **4** with the Me_3Al-H_2O system resulting in the formation of an 80:20 mixture of γ- and δ-methylation products.[5] Similarly, the corresponding cis-analogue **5** reacted cleanly to give an approximately 80:20 mixture of γ- and δ-substitution products (entries 13−15), while the reaction of **5** with Me_3Al-H_2O gave a complex mixture. As was anticipated, the reactions of terminal epoxides (**6** and **7**) produced the C1 substitution products regioselectively (entries 16 and 17) and reactions of a trisubstituted epoxide (**8**) gave a product bearing a quaternary carbon center predominantly (entry 18).

In conclusion, we have developed a novel and one-pot alkylation−silylation reaction of epoxides by the combination of R_3Al, $R_3'SiOTf$, and Et_3N. The present method involves the powerful activation of organoaluminums as carbon nucleophiles, which affords the alkylation−silylation products stereospecifically in excellent yields. Therefore, the present method should provide an extremely useful means in organic synthesis, including natural product synthesis. Further investigations on the new reagent system and its application to natural product synthesis are in progress in our laboratory.

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Note Added after ASAP Posting. The heading in ref 9 and the triple bond in entry 7 of Table 1 were missing in the version posted ASAP on August 9, 2003. The corrected version was posted on August 20, 2003.

Supporting Information Available: Typical experimental procedures, tabulated spectral details, and copies of ^{1}H and ^{13}C NMR spectra of selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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