A Novel Method for Inside Selective Silylation of 1,2-Diols

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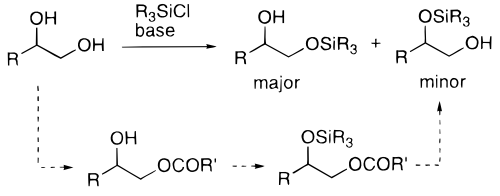
Silyl groups are of great importance for protection of a hydroxy group,[1] and site-selective silylation of polyols has frequently been used in organic synthesis. Since usual silylation conditions always effect selective protection of the less hindered hydroxy group,[2] inside selective silylation of a 1,2-alkanediol generally requires multistep transformations. For example, a 2-siloxy-1-alkanol can be prepared from the corresponding diol through esterification of the 1-OH group, silylation of the 2-OH group, and hydrolysis of the ester moiety (Scheme 1). In the present paper, we describe a novel method for one-pot silylation of the internal hydroxy group of a 1,2-alkanediol.

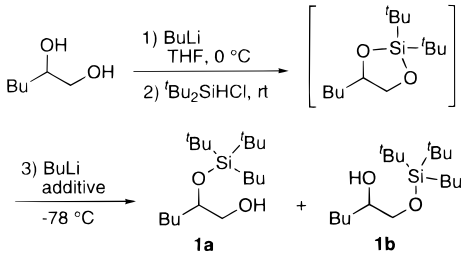
There are several reports concerning inside selective protection of 1,2-alkanediols by benzyl ethers,[3] *tert*-butyl ethers,[4] methoxymethyl ethers,[5] or benzoates.[6] It is noteworthy that all of these examples involve regioselective cleavage of five-membered intermediates, namely, cyclic acetals, ortho esters, or phospholanes. On the other hand, in relation to the chemistry of 1-oxa-2-silacyclopentane derivatives described previously,[7] we became intrigued by ring-cleavage reactions of cyclic silyl ethers induced by nucleophiles. We envisioned that treatment of a 1,3-dioxa-2-silacyclopentane derivative with a nucleophile might effect regioselective ring cleavage to give the corresponding 2-siloxy-1-alkanol.[8]

Since five-membered cyclic silyl ethers easily undergo hydrolysis by silica gel column chromatography,[9] it was desired to carry out both the preparation and ring cleavage reaction of these ethers in one pot. The conventional methods for silylation of 1,2-alkanediols by using dialkylsilyl dichloride[10] or ditriflate[11] and amines are unsuitable for this purpose because the resulting ammonium salt would serve as a proton donor. We found that the reaction of 1,2-hexanediol with 1 equiv of butyllithium followed by di-*tert*-butylchlorosilane in THF affords the desired cyclic silyl ether with the evolution of hydrogen. Treatment of the solution with butyllithium at −78 °C resulted in cleavage of the Si−O bond to yield 2-siloxy-1-hexanol as the major product.[12] Interestingly, the isomeric ratio was enhanced in the presence of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), while use of hexamethylphosphoramide (HMPA) gave somewhat lower selectivity (Scheme 2).

Scheme 1

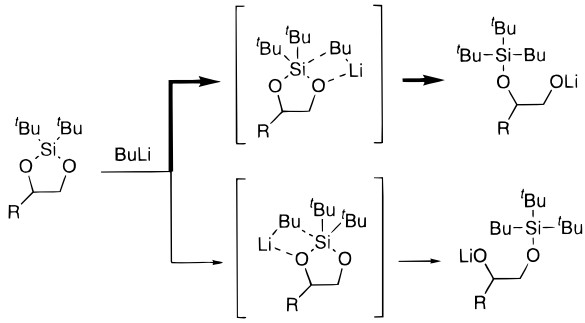


Scheme 2. Regioselective Cleavage of a Cyclic Silyl Ether

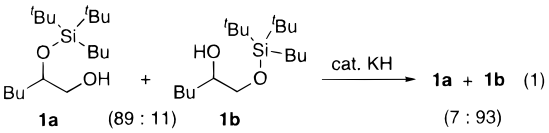


additive	%yield	**1a** : **1b**
none	99	89 : 11
HMPA	99	79 : 21
TMEDA	84	94 : 6

Scheme 3



The regioselectivity observed in these reactions would come from kinetically controlled ring cleavage because the 2-siloxy-1-alkanol seems less stable than the corresponding 1-siloxy-2-alkanol. Indeed, **1a** underwent isomerization to **1b** under the influence of a catalytic amount of potassium hydride (eq 1). Therefore, the preferential formation of 2-siloxy-1-alkanols could be attributable to complexation of lithium at the sterically less hindered oxygen as depicted in Scheme 3.



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(8) It has been reported that treatment of a dimethylsilylene derivative of a 1,3-diol with *tert*-butyllithium induced regioselective cleavage of the less hindered Si−O bond to yield the corresponding siloxy alcohol: Mukaiyama, T.; Shiina, I.; Kimura, K.; Akiyama, Y.; Iwadare, H. *Chem. Lett.* **1995**, 229.
(9) Dialkyl silylene derivatives of 1,2-diols are much less stable than those of 1,3-diols. See ref 11.
(10) (a) Trost, B. M.; Caldwell, C. G. *Tetrahedron Lett.* **1981**, *22*, 4999. (b) Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.
(11) Corey, E. J.; Hopkins, P. B. *Tetrahedron Lett.* **1982**, *23*, 4871.

(12) Treatment of 2-(butyldi-*tert*-butylsiloxy)-1-hexanol (**1a**) with tetrabutylammonium fluoride in THF at room temperature overnight effected smooth removal of the bulky silyl group.

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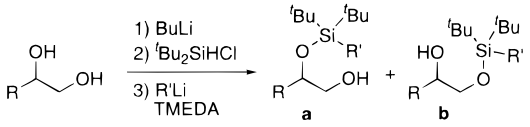
Table 1. One-Pot Silylation of 1,2-Diols



entry	R	R′	product	% yield[a]	**a**/**b**[b]
1	C_4H_9	C_4H_9	**1**	84	94:6
2	C_4H_9	C_6H_5	**2**	89	94:6
3	C_4H_9	$C{\equiv}CC_6H_{13}$	**3**	96	93:7
4	*c*-C_6H_{11}	C_4H_9	**4**	94	99:1
5	*c*-C_6H_{11}	$C{\equiv}CC_4H_9$	**5**	76	99:1
6	$BnOCH_2$	C_4H_9	**6**	83	95:5
7	C_6H_5	C_4H_9	**7**	85	99:1
8	C_6H_5	C_6H_5	**8**	89	98:2

[a] Combined isolated yield of **a** and **b**. [b] Determined by GLC analysis.

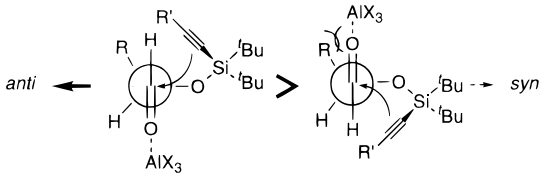
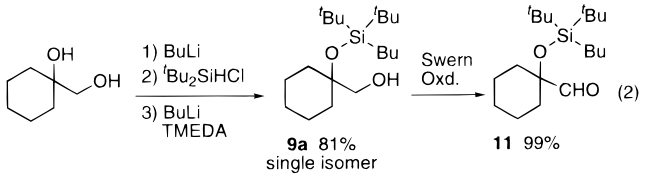
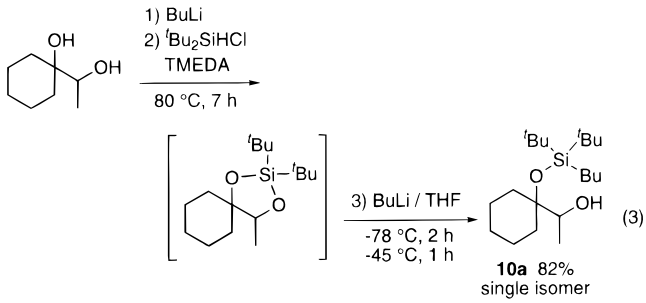


Figure 1.

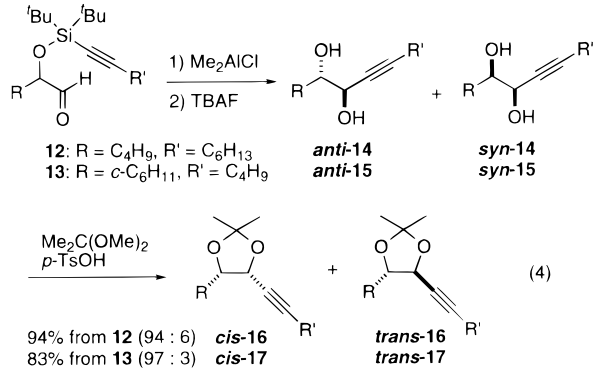
This method is applicable to various kinds of 1,2-diols as shown in Table 1. Use of phenyllithium or an alkynyllithium as a nucleophile also gave the corresponding 2-siloxy-1-alkanols in high selectivity (entries 2 and 3). Steric hindrance around the inside hydroxy group seems to enhance the regioselectivity (entries 4 and 7), and the effect was typically observed in the reaction of 1-(hydroxymethyl)-cyclohexanol, which has an inside tertiary hydroxy group (eq 2). Distinction between a tertiary hydroxy group and a secondary hydroxy group by the one-pot silylation method was also examined (eq 3). Although formation of the cyclic silyl ether required higher temperature and a prolonged reaction period in this case, the cyclic ether underwent smooth ring cleavage to give siloxy alcohol **10a** as a single isomer.[13]

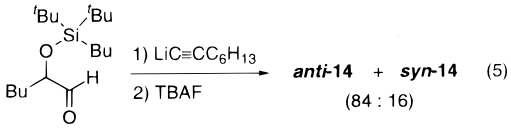




As shown in eq 2, the position of the silyl group was confirmed by converting these silyl ethers into the corresponding α-siloxy aldehydes by Swern oxidation. A variety of α-siloxy aldehydes, including optically active ones that are important building blocks in organic synthesis, can be easily prepared by this methodology. For example, (*S*)-1-phenyl-1,2-ethanediol was converted into (*S*)-2-(butyldi-*tert*-butylsiloxy)-2-phenylacetaldehyde (>95% ee, 80% overall yield) by two-step transformations.[14]

Furthermore, α-siloxy aldehydes with a functionalized silyl group show promise for stereoselective C−C bond formations. For example, in the presence of Me_2AlCl, α-(alkynylsiloxy) aldehydes **12** and **13** underwent rearrangement of the alkynyl group to yield an anti diol predominantly (eq 4).[15] It is noteworthy that a similar non-chelation-type





adduct was obtained, albeit in lower selectivity, by the intermolecular reaction of 2-(butyldi-*tert*-butylsiloxy)hexanal and the corresponding alkynyllithium (eq 5).[16] The high stereoselectivity of the intramolecular reaction can be rationalized by transition-state models in which the siloxy group is perpendicular to the carbonyl group (Figure 1).[17] The reaction would proceed mainly through TS-1 because TS-2 suffers from steric repulsion between the alkyl substituent and the carbonyl oxygen.

In conclusion, a novel method for selective silylation of an internal hydroxy group of 1,2-diols was developed. To our knowledge, the present method is the first example of this type of transformation that is feasible in one pot. We are currently investigating synthetic reactions using 2-siloxy-1-alkanols or α-siloxy aldehydes having a functionalized silyl group.

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Supporting Information Available: Experimental procedures and characterization data for **1**−**17** and the α-siloxy aldehydes (8 pages).

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(13) The same product was also obtained by treating aldehyde **11** with methyllithium.

(14) Treatment of the aldehyde with DIBAL afforded alcohol **6a**, which was then converted into the corresponding MTPA ester. HPLC analysis of the MTPA ester indicated that the diastereomeric excess is >95%.

(15) Diastereoselective intramolecular allylation reaction of a *β*-(allylsiloxy)aldehyde promoted by a Lewis acid has been reported: Reetz, M. T.; Jung, A.; Bolm, C. *Tetrahedron* **1988**, *44*, 3889.

(16) It has been reported that the reaction of [2-(trimethylsilyl)ethynyl-]lithium and 2-(*tert*-butyldiphenylsiloxy)heptanal afforded the corresponding adduct as an 84:16 mixture of anti and syn isomers: Alami, M.; Crousse, B.; Linstrumelle, G.; Mambu, L, Larchevêque, M. *Synlett* **1993**, 217.

(17) Crossover experiments were performed by using a 1:1 mixture of α-(alkynylsiloxy) aldehydes **12** and **13**, and no product arising from an intermolecular addition reaction was observed. See the Supporting Information.