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Chemoselective deprotection of silyl ethers by DIBALH

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ABSTRACT

The first examples of highly selective deprotection of silyl ethers by DIBALH are reported. Its selectivity enabled us to remove a primary TBS group and a primary TBDPS group in the presence of a secondary TES group.

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Protection and deprotection of functional groups, especially hydroxy groups, are important steps in organic synthesis, and numerous protective groups have been reported with their formation and cleavage methods.[1]

Silyl ethers, such as the TES (triethylsilyl) group, the TBS (*tert*-butyldimethylsilyl) group, and the TBDPS (*tert*-butyldiphenylsilyl) group are the most widely used protective groups for alcohols because of the facility for selective protection and deprotection. Selective introduction of silyl ethers is achieved by controlling the reaction conditions, for example, the solvent, temperature, reaction time, base, amount of the reagents, and so on. Similarly, many groups reported selective deprotection of silyl ethers by proper choice of the conditions.[2] The steric hindrance around the silicon atom and the alcohol influences the reactivity of protection and cleavage.

In general, silyl ethers are effectively cleaved by acid, base, or a fluoride anion. On the other hand, a lot of unexpected deprotections of silyl ethers also have been reported. For example, many groups reported the deprotection of silyl ethers by DIBALH (diisobutylaluminium hydride)[3] as unexpected side-reactions from the use of this electrophilic reducing agent.[4]

In our synthetic studies, we also have experienced this undesired deprotection of silyl ethers by DIBALH even at low temperatures. However, we found that this undesired deprotection occurred mainly for primary silyl ethers, while secondary silyl ethers were often stable even at higher temperatures (0 °C to rt). Based on these observations, we investigated the use of DIBALH for the selective deprotection of primary silyl ethers in the presence of secondary silyl ethers.

Firstly, we examined the deprotection of silyl ethers by DIBALH under various conditions (Table 1). Treatment of primary silyl ethers **1a–c** with DIBALH at −20 °C afforded primary alcohol **2** in good yields[5] (entries 1–3). Originally, the deprotection of the TBS group at room temperature was reported though, the primary TES group, TBS group, and TBDPS group were also smoothly cleaved at lower temperature. On the other hand, the secondary TES ethers **3**[6] and **5**[7] were not cleaved and their benzylidene acetals were reduced regioselectively[8] with DIBALH at higher temperature (0 °C to rt, entries 4 and 5). These differences in reactivity between primary silyl ethers and secondary silyl ethers encouraged us to use DIBALH for selective deprotection.

Next, we investigated the selective deprotection of 1,3-bis-silyl ethers, which were synthesized from a known diol **7**[9,10] (Table 2). Treatment of bis-TBS ether **8a** with 5 equiv of DIBALH afforded 78% yield of the primary alcohol **9a**. It is noteworthy that the selective deprotection of **8a** under the usual conditions failed. Selective deprotections using acids (CSA, PPTS, and AcOH) failed because of the competitive deprotection of the benzylidene acetal. Low selectivity was observed in the deprotection using TBAF. The benzylidene acetal was more stable than the primary TBS group under this condition. Similarly bis-TES ether **8b** was converted to the primary alcohol **9b** in 80% yield (entry 2).

Next, we investigated the deprotection of a primary TBS group and a primary TBDPS group in the presence of a secondary TES group. It is well known that the TBS ether and the TBDPS ether are more stable than the TES ether under the usual deprotection reaction conditions. For this reason, no general method of selective deprotections of a primary TBS group and a primary TBDPS group in the presence of a secondary TES group had been previously reported.[3] Interestingly, when the silyl ethers **8c** and **8d** were treated with DIBALH, primary alcohol **9b** was afforded in good yield (entries 3 and 4). The secondary TES ether remained unaltered under these conditions even though a primary TBS group and a primary TBDPS group were smoothly removed. When the reaction was run with 2 equiv of DIBALH, a longer reaction time was required (entry 5). Although we conducted the reactions in CH_2Cl_2, we did not find any remarkable difference using toluene (entry 6).

We then studied the scope and limitations of this efficient selective deprotection (Table 3). The deprotection of 1,4-bis-silyl ethers **10a–d**[11] (entries 1–4) and 1,2-bis-silyl ether **14**[12] (entry 5) are shown in table 3. Treatment of bis-TBS ether **10a** with DIBALH at −20 °C gave the desired primary alcohol **11a** in 57% yield with

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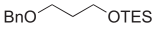
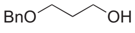
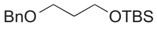
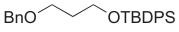
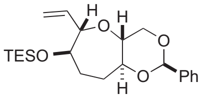
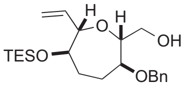
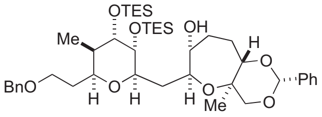
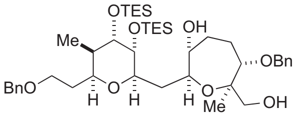
Table 1
Treatment of primary and secondary silyl ethers with DIBALH

Entry	**SM**[a]	Temperature (°C)	Time (h)	Product and yield
1	 **1a**	−20	1	 **2** 84%[b]
2	 **1b**	−20	3.5	**2** 97%[b]
3	 **1c**	−20	9	**2** 84%[b]
4	 **3**	0 to rt	4	 **4** 67%[c]
5	 **5**	0 to rt	4	 **6** 73%[d]

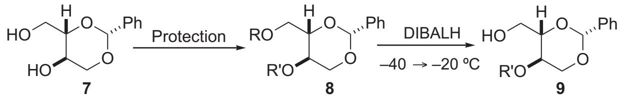
[a] Starting material.

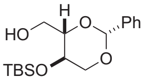
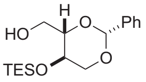
[b] Reactions were run with 5 equiv of DIBALH (1 M hexane solution) in CH_2Cl_2 (0.1 M).

[c] Reaction was run with 5 equiv of DIBALH (1 M hexane solution) in CH_2Cl_2 (0.2 M).

[d] Reaction was run with 10 equiv of DIBALH (1 M hexane solution) in CH_2Cl_2 (0.07 M).

Table 2
Chemoselective deprotection of 1,3-bis-silyl ethers by DIBALH



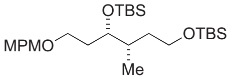
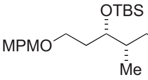
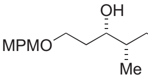
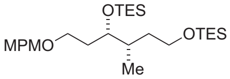
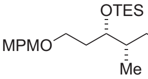
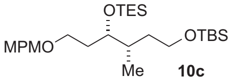
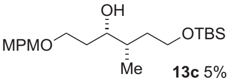
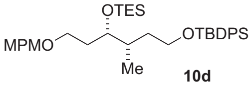
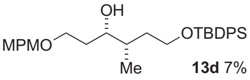
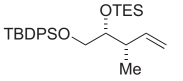
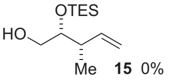
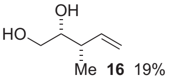
Entry	SM	R	R′	Time (h)	Product and yield	
1	**8a**	TBS	TBS	1	 **9a**	78%[a]
2	**8b**	TES	TES	1	 **9b**	80%[a]
3	**8c**	TBS	TES	1.2		87%[a]
4	**8d**	TBDPS	TES	1.5		81%[a]
5	**8d**			6		67%[b]
6	**8d**			1		72%[c]

[a] Reactions were run with 5 equiv of DIBALH (1 M hexane solution) in CH_2Cl_2 (0.1 M).

[b] Reaction was run with 2 equiv of DIBALH (1 M hexane solution) in CH_2Cl_2 (0.1 M).

[c] Reaction was run with 5 equiv of DIBALH (1 M toluene solution) in toluene (0.1 M).

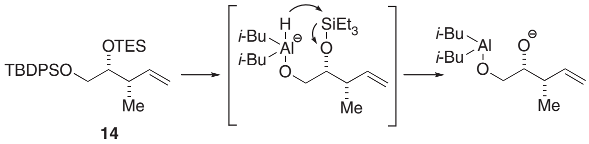
Table 3
Deprotection of 1,4-bis-silyl ethers and 1,2-bis-silyl ether by DIBALH[a]

Entry	SM	Time	Product and yield
1	 **10a**	22 h	**SM** 57%  **11a** 57%  **12** 17%
2	 **10b**	12 h	 **11b** 73% **12** 26%
3	 **10c**	16 h	**SM** 13% **11b** 73%  **13c** 5%
4	 **10d**	13 h	**SM** 26% **11b** 31% **12** 29%  **13d** 7%
5	 **14**	12 h	**SM** 64%  **15** 0%  **16** 19%

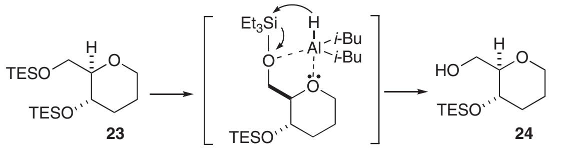
[a] Reactions were run with 5 equiv of DIBALH (1 M hexane solution) in CH_2Cl_2 (0.1 M).

recovered starting material (11%) and undesired diol **12** (17%). Even when for the reaction time was increased to 22 h, a small amount of the starting material was recovered. Bis-TES ether **10b** could be converted into primary alcohol **11b** in 73% yield with 26% yield of the diol **12**. A primary TBS group and a primary TBDPS group were also cleaved in the presence of secondary TES ethers (entries 3 and 4) with small amount of secondary alcohols **13c** and **13d**. Although selective deprotection was achieved, the deprotection of bis-silyl ethers **10a–d** required longer reaction times relative to those of **8a–d** and gave over-deprotected products. Furthermore, the selective deprotection failed in the case of a 1,2-bis-silyl ether (entry 5). Interestingly when the 1,2-bis-silyl ether **14** was treated with DIBALH, diol **15** and starting material were isolated, though no mono-silyl ether **16** was observed. This over-deprotection can be rationalized by Scheme 1. Once the primary TBDPS group is removed, the intermediate reacts with another molecule of DIBALH faster than the first step. Then the neighboring TES group is reductively cleaved, similar to the reported selective deprotection using $LiAlH_4$.[13]

In order to rationalize the differences of the reaction rate between **8** and **10**, we then investigated the deprotection of other bis-TES ethers, which have similar structures to **8b**. First we at-



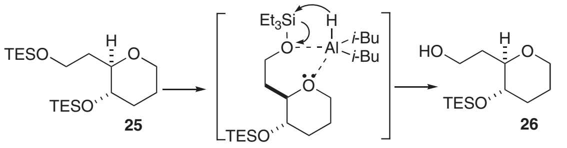
Scheme 1.



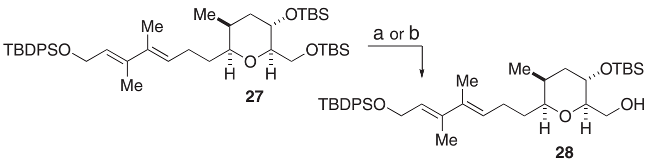
Scheme 2.

tempted the deprotection of one or two-carbon elongated compounds **17** and **19** by the same condition as the deprotection of **8b** (Table 4). When bis-TES ethers **17** and **19** were treated with DIBALH at −20 °C for 1 h, although selectively deprotected products **18** and **20** were observed, large amounts of starting materials also were recovered (entries 1 and 2). Next, we conducted the deprotection of bis-TES ether **21**[14] which possesses no cyclic ether structure. Similar to **17** and **19**, selective deprotection was achieved though, the deprotection of **21** required a longer reaction time (entries 3 and 4). Thus the distance between the silyl ether and the oxygen atom is important. In addition to that, the smooth deprotections of **23** and **25**[15] suggest that the interactions between DIBALH and the neighboring oxygen atoms accelerate the deprotection through cyclic intermediates as depicted in Schemes 2 and 3. However, comparison of **8b** with **23** and comparison of **17** with **25** indicate that the benzylidene acetals interrupt the deprotection.

Finally, an application of this method to natural products synthesis was demonstrated (Scheme 4). Recently, we reported the synthesis of the cyclic-ether-amide brevisamide.[16] In our synthetic study, although the primary TBS group of a synthetic intermediate **27** was selectively cleaved by acid, the reaction had to be stopped before consuming the starting material because of the competitive cleavage of the allylic TBDPS group. On the other hand, when **27** was treated with DIBALH at −40 °C, the selective deprotection of the primary TBS group proceeded smoothly and the primary alcohol **28** was afforded in better yield.[17]



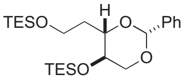
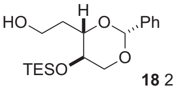
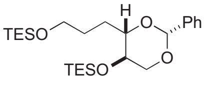
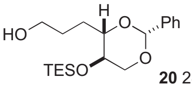
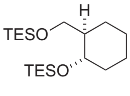
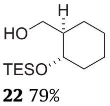
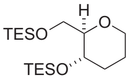
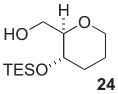
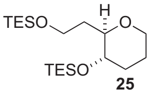
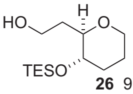
Scheme 3.



Scheme 4. Reagents and conditions: (a) CSA, CH_2Cl_2/MeOH, 0 °C, 65% (85% brsm); (b) DIBALH, CH_2Cl_2, −40 °C, 93%.

In conclusion, the first examples of highly selective deprotection of the primary silyl ethers in the presence of the secondary silyl ethers using DIBALH are reported.[18] We consider that the selectivity is generated from the bulkiness of DIBALH especially at lower temperature. Furthermore when the reactions proceed through a five-membered ring intermediate (Scheme 2), the silyl ethers are rapidly cleaved even in the presence of the benzylidene acetal. It is noteworthy that its high selectivity enabled us to remove a primary TBS group and a primary TBDPS group in the presence of a secondary TES group, and this method will be very useful for organic synthesis involving multiple hydroxy groups.

Table 4
Treatment of various bis-TES ethers with DIBALH[a]

Entry	SM	Temperature (°C)	Time	Product and yield
1	 **17**	−20	1 h	**SM** 69%  **18** 25%
2	 **19**	−20	1 h	**SM** 61%  **20** 28%
3	 **21**	−20	1 h	**SM** 64%  **22** 15%
4	**21**	−20	6 h	**22** 79%
5	 **23**	−40	30 min	 **24** 94%
6	 **25**	−40	30 min	 **26** 97%

[a] Reactions were run with 5 equiv of DIBALH (1 M hexane solution) in CH_2Cl_2 (0.1 M).

Acknowledgments

This work was financially supported by KAKENHI (No. 2061102) and the Global COE Program for Chemistry Innovation, the University of Tokyo. T.K. is grateful for a SUNBOR Scholarship. We thank Dr. P. T. Holland, Cawthron Institute, NZ for critical reading of the Letter.

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4. Selected undesired deprotections by DIBALH: (a) Nyavanandi, V. K.; Nanduri, S.; Dev, V.; Naidu, A.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 6667; (b) Aiguade, J.; Hao, J.; Forsyth, C. J. *Tetrahedron Lett.* **2001**, *42*, 817.
5. All yields in this Letter are isolated yields.
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8. Takano, S.; Akiyama, Y.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, *12*, 1593.
9. Selected one-pot protection procedure: To a solution of the diol **7** (149 mg, 0.706 mmol) in CH_2Cl_2 (7 mL) were added triethyl amine (0.50 mL, 3.5 mmol), DMAP (25.7 mg, 0.21 mmol), and TBDPSCl (0.36 mL, 1.4 mmol) at 0 °C. After stirring for 3.5 h at room temperature, TESOTf (0.18 mL, 0.80 mmol) was added at 0 °C. After usual workup, bis-silyl ether **8d** was obtained (393 mg, 99%).
10. Tanabe, G.; Yoshikai, K.; Hatanaka, T.; Yamamoto, M.; Shao, Y.; Minematsu, T.; Muraoka, O.; Wang, T.; Matsuda, H.; Yoshikawa, M. *Bioorg. Med. Chem.* **2007**, *15*, 3926.
11. Compounds **10a–d** were synthesized from known homoallylic alcohol: Shirai, T.; Kuranaga, T.; Wright, J. L. C.; Baden, D. G.; Satake, M.; Tachibana, K. *Tetrahedron Lett.* **2010**, *51*, 1394.
12. Compound **14** was synthesized from known homoallylic alcohol: Kuranaga, T.; Shirai, T.; Baden, D. G.; Wright, J. L. C.; Satake, M.; Tachibana, K. *Org. Lett.* **2009**, *11*, 217.
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14. Racemic compound. Compound **21** was synthesized from known benzoate: Vina, D.; Santana, L.; Uriarte, E.; Teran, C. *Tetrahedron* **2005**, *61*, 473.
15. Compounds **23** and **25** were synthesized from known diol: Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; De Frees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040.
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17. Selected experimental procedure for the deprotection: A solution of **27** (19.6 mg, 0.0260 mmol) in CH_2Cl_2 (1.0 mL) was treated with DIBALH (1.04 M in hexane, 0.13 mL, 0.13 mmol) at −40 °C. After stirring for 30 min, usual workup afforded the alcohol **28** (15.4 mg, 93%).
18. A referee pointed out the lack of urgency and novelty, however, this is the first report of selective deprotection of silyl ethers by DIBALH and its application for natural products synthesis. We believe that rapid publication of the present result will promote natural products synthesis.