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A mild and efficient cleavage of *tert*-butyldimethylsilyl (TBS) and tetrahydropyranyl (THP) ethers using a catalytic amount of $TBPA^{+\cdot}SbCl_6^-$

Yanfen Xu [a], Shouchu Tang [a], Junjie Han [a], Xuegong She [a,b,*], Xinfu Pan [a]

[a] *Department of Chemistry, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, PR China*
[b] *State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PR China*

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Abstract

A mild and efficient method for the deprotection of the TBS and THP ethers is described. A wide variety of TBS ethers as well as THP ethers can be easily deprotected to the corresponding parent hydroxyl compounds by employing a catalytic amount of tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^{+\cdot}SbCl_6^-$) in methanol at room temperature in good yield.

The *tert*-butyldimethylsilyl (TBS)[1a] and tetrahydropyranyl (THP)[1b] ethers are frequently employed as protective groups for hydroxyl functionalities in multi-step synthesis due to their ease of preparation and stability under a wide variety of reaction conditions as well as their subsequent ease of removal. In general, fluoride ion[2] and aqueous acids[1a] are the most popular reagents for the deprotection of TBS ether. Recently, some reducing[3] and oxidizing[4] reagents have also been developed for the cleavage of TBS ethers. However, these methods have drawbacks such as the requirement for long reaction times, harsh reaction conditions, and large amounts of reagents. Although numerous synthetic methods[5] have been developed for the deprotection of TBS and THP ethers in recent years, there is still a need for a catalytically efficient method under mild reaction conditions. $TBPA^{+\cdot}SbCl_6^-$ (Fig. 1),[6] normally used as a single electron transfer reagent and a relatively stronger oxidant,[7] to the best of our knowledge, has not been used in the cleavage of any protecting groups. Herein, we disclose a new mild method for the cleavage of TBS and THP ethers using a catalytic amount of $TBPA^{+\cdot}SbCl_6^-$ in methanol at room temperature.

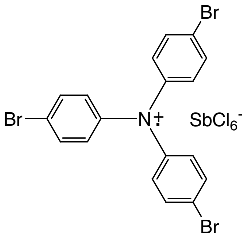

Fig. 1. The structure of $TBPA^{+\cdot}SbCl_6^-$.

Initially, the TBS ether of dodecan-1-ol was chosen as a model substrate to optimize the reaction conditions and the results are summarized in Table 1. As shown in Table 1, the best result was obtained using 5 mol % of $TBPA^{+\cdot}SbCl_6^-$ in methanol. When the amount of catalyst was reduced to 1 mol %, a longer reaction time was required for completion of the reaction (entry 7).

With the optimized conditions[8] in hand, varieties of TBS ethers were synthesized and tested (Table 2). It has been observed that in the case of the TBS ethers of primary alcohol (entries 1–4 and 6–8), the reactions were fast and the

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[*] Corresponding author. Tel.: +86 09318912582.
E-mail address: shexg@lzu.edu.cn (X. She).

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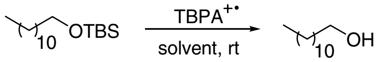
yields were high. We have also found that this method can selectively remove TBS ethers in the presence of TBDPS ethers[9] and benzyl ethers (entries 2–6). When the TBS ethers of secondary alcohols were tested (entries 5 and 9–11), the reactions required longer times to obtain satisfactory yields due to steric effects. However, there was no reaction when TBS ethers of phenols were tested (entries 13–16). This led us to explore the possibility of selective removal of alkyl TBS ethers in the presence of aryl TBS ethers. As expected, when entries 15 and 16 were tested, the TBS ether of the alcohol was cleaved cleanly while the TBS ether of phenol remained unaffected.

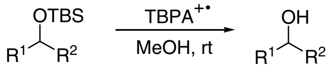
Table 1
Deprotection of the TBS Ether of dodecan-1-ol

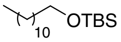
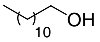
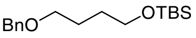
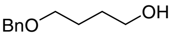
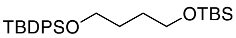
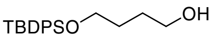
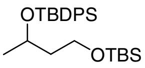
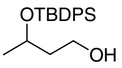
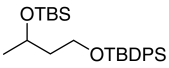
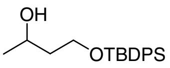
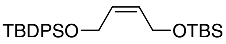
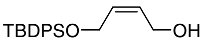
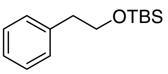
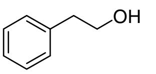
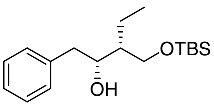
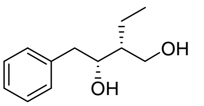
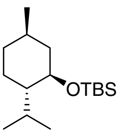
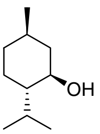
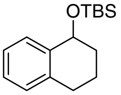
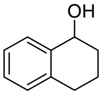
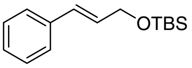
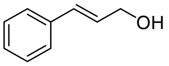
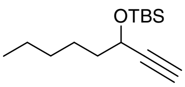
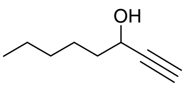


Entry	Equiv of TBPA$^{+\cdot}$	Solvent	Time (h)	Yield[a] (%)
1	0.05	CH_2Cl_2	18	71
2	0.05	$CHCl_3$	12	86
3	0.10	MeCN	12	94
4	0.10	DMF	8	<5
5	0.10	THF	6	61
6	0.05	MeOH	0.5	99
7	0.01	MeOH	1.5	95

[a] Isolated yields.

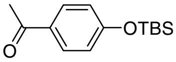
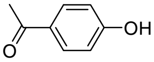
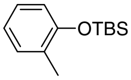
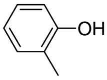
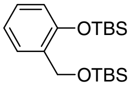
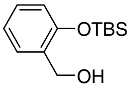
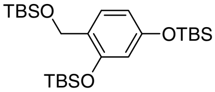
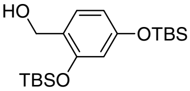
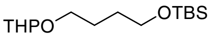
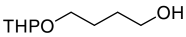
Table 2
Deprotection of various TBS ethers



Entry	Substrate	Equiv of TBPA$^{+\cdot}$	Time (h)	Product	Yield[a] (%)
1		0.05	0.5		99
2		0.05	0.5		99
3		0.05	0.5		93
4		0.05	1		99
5		0.05	2		97
6		0.05	1		99
7		0.10	0.5		74
8		0.05	1		96
9		0.05	2.5		87
10		0.05	2		83
11		0.05	1		99
12		0.10	3		70

(*continued on next page*)

Table 2 (*continued*)

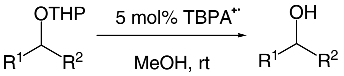
Entry	Substrate	Equiv of TBPA$^{+\cdot}$	Time (h)	Product	Yield[a] (%)
13		0.05	4		NR[b]
14		0.05	4		NR[b]
15		0.05	1		97
16		0.05	1		92
17		0.05	1		45[c]

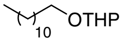
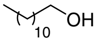
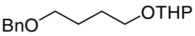
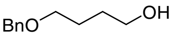
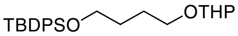
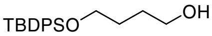
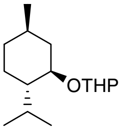
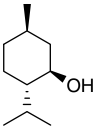
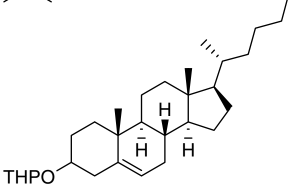
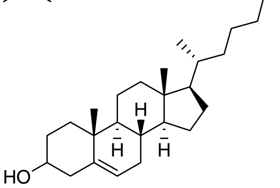
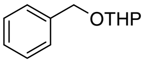
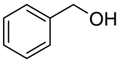
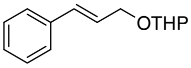
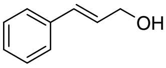
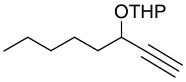
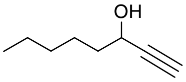
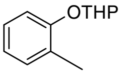
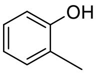
[a] Isolated yields.

[b] No reaction.

[c] Butane-1,4-diol was obtained in 20% yield.

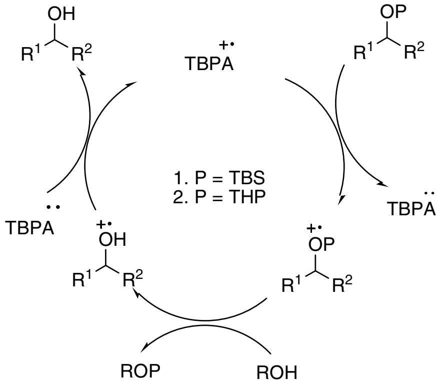
Table 3
Deprotection of various THP ethers



Entry	Substrate	Time (h)	Product	Yield[a] (%)
1		2		99
2		2		96
3		2.5		91
4		2.5		93
5		3		90[b]
6		3		86
7		1.5		90
8		2		66
9		1		81

[a] Isolated yields.

[b] The reaction was conducted in mixed solvent (MeOH/$CHCl_3$, 1/1, v/v).



Scheme 1. The plausible mechanism.

When entry 17 was tested, we found that the THP ether was partially cleaved at the same time. So, we wondered whether this reagent could be applied for the deprotection of the THP ethers. Thus, several THP ethers were prepared and subjected to these reaction conditions and the results are summarized in Table 3. The reactions proceeded smoothly and the corresponding alcohols were obtained in high yields within 2–3 h. However, we noticed that the THP ether of cholesterol could not be deprotected even after long reaction times, due to the poor solubility in methanol. But replacing methanol as the solvent with a 1:1 mixture of methanol and $CHCl_3$ allowed the reaction to proceed at a satisfactory rate and in high yield (entry 5). Interestingly, THP ether of phenol could be cleaved in a short time (entry 9).

The plausible mechanism of the reaction is proposed (Scheme 1). A single electron transfer process may be involved.

In conclusion, we have developed a simple, inexpensive, and mild procedure for the cleavage of TBS and THP ethers which will have a wide scope in view of the tremendous usefulness in organic synthesis.

Acknowledgments

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References and notes

1. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4rd ed.; John Wiley & Sons: New York, 2007; p 89; (b) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 4rd ed.; John Wiley & Sons: New York, 2007; p 59.
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8. *General procedure*: $TBPA^{+\cdot}SbCl_6^{-}$ (0.05 mmol) was added to a solution of TBS or THP ether (1 mmol) in methanol (5 mL). The resulting mixture was stirred at room temperature and monitored by TLC. After the reaction was complete, the mixture was diluted with water (5 mL) and extracted with CH_2Cl_2 (10 mL × 3). The organic extracts were collected, washed with brine and dried with anhydrous Na_2SO_4. When the solvent was removed in vacuum, the residue was purified by column chromatography on silica gel to afford the corresponding alcohol or phenol.
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