

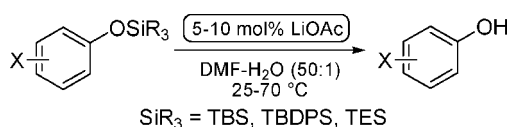
## LiOAc-Catalyzed Chemoselective Deprotection of Aryl Silyl Ethers under Mild Conditions

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An efficient and chemoselective deprotection protocol for aryl silyl ethers using LiOAc as a bifunctional Lewis acid–Lewis base catalyst was described. Acetates, epoxides, and aliphatic silyl ethers were preserved, whereas aryl TBS and TBDPS ethers can be differentiated.

Trialkylsilyls are popular protective groups for both alcoholic and phenolic hydroxyls.<sup>1</sup> Take *tert*-butyl-dimethylsilyl (TBS) as an example; since its introduction by Corey,<sup>2</sup> it has been one of the most widely used protective groups in modern organic synthesis. The cleavage of alkyl TBS ethers has been extensively investigated, leading to a wide array of deprotection methods.<sup>1</sup> In contrast, there are relatively fewer options available for the removal of phenolic TBS protections.<sup>1,3</sup> The latter usually required more than stoichiometric amounts of fluoride sources (TBAF,<sup>2,4a</sup> KF/18-C-6,<sup>4b</sup> KF/Al<sub>2</sub>O<sub>3</sub><sup>4c,d</sup>), acids (HF,<sup>5a,b</sup> CSA<sup>5c</sup>) or strong bases (alkoxides,<sup>6a–c</sup> carbonates<sup>6d–f</sup>). Recently, some

milder protocols have appeared, utilizing TMG,<sup>7a</sup> *N*-oxide,<sup>7b</sup> and DMSO–H<sub>2</sub>O.<sup>7c</sup> Because many biologically significant natural products such as vancomycin,<sup>8</sup> novobiocin,<sup>9</sup> and phenolic glycoconjugates<sup>10</sup> possess both phenol and alcohol functions, selective removal of phenolic TBS protection in the presence of aliphatic TBS ether (“aryl selectivity”) is of great value to total synthesis and medicinal chemistry.<sup>3,11</sup> To this end, the difference in the electronic nature of alkyl and aryl groups was to be exploited, for phenols are better leaving groups than alcohols, and thus aryl silyl ethers are more liable to base hydrolysis.<sup>4a</sup> Although this approach worked nicely in many cases, it involved prolonged exposure to excess basic reagents, which is apparently less desirable in multistep synthesis. Second, a closer examination revealed that catalytic procedure for the removal of phenolic silyl protection is uncommon, except one system using silica-gel-supported phosphomolybdic acid<sup>12</sup> and another using PdCl<sub>2</sub>(MeCN)<sub>2</sub>.<sup>13</sup> Unfortunately, both preferentially attack aliphatic TBS ethers, and the latter also removes acetone at room temperature.<sup>14</sup> A substoichiometric amount (0.2–0.4 equiv) of Verkade’s azaphosphatane also removes TBS protection from phenols; however, the “superbase” promoter is reactive toward many functional groups including alkenes.<sup>15</sup> Third, it should be noted that good chemoselectivity between two different aryl silyl ethers is not easy to achieve, whereas such protections for alcohols are readily differentiated.<sup>3</sup> For example, there are only two reports of preferential cleavage of phenolic TBS protection over TBDPS,<sup>4c,16</sup> although the steric bulk and acid/base stability of the two silyls are considerably varied. Herein we describe a highly efficient protocol using LiOAc as the catalyst to address all the aforementioned issues.

Since alkali hydroxides and carbonates are known to cleave aryl TBS ethers in a number of solvents,<sup>6</sup> we turned our attention to weaker bases in order to achieve deprotection under milder conditions with better chemoselectivity. The TBS ether of 4-*tert*-butylphenol was chosen as a benchmark substrate, for it reflected the true relative activity of the catalysts, while substrates bearing strong electron-withdrawing groups (EWGs) were too labile and thus exhibited a “leveling effect” for catalyst activity. We screened several acetates as the catalyst, and to our delight, LiOAc stood out as the most effective (Table 1).<sup>17</sup> Interestingly, the catalytic activity decreased rapidly when the cation went

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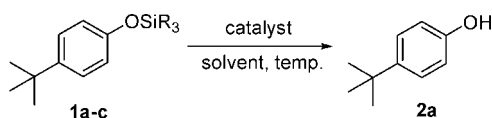
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TABLE 1. Optimization of Reaction Conditions<sup>a</sup>

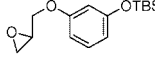


entry	SiR <sub>3</sub>	catalyst (mol %)	solvent	temp (°C)	time (h)	conversion (%)	2a (%) <sup>b</sup>
1	TBS (a)	LiOAc·2H <sub>2</sub> O (20)	DMF–H <sub>2</sub> O (50:1)	70	6	100	98
2	TBS (a)	NaOAc (20)	DMF–H <sub>2</sub> O (50:1)	70	8	35	33
3	TBS (a)	KOAc (20)	DMF–H <sub>2</sub> O (50:1)	70	2	trace	nd
4	TBS (a)	LiCl (200)	DMF–H <sub>2</sub> O (50:1)	70	8	0	
5	TBS (a)	LiOAc·2H <sub>2</sub> O (20)	THF–H <sub>2</sub> O (50:1)	70	8	0	
6	TBS (a)	LiOAc·2H <sub>2</sub> O (20)	MeCN–H <sub>2</sub> O (50:1)	70	8	0	
7	TBS (a)	LiOAc·2H <sub>2</sub> O (20)	EtOH–H <sub>2</sub> O (10:1)	70	8	trace	nd
8	TBS (a)	LiOAc (20)	DMF <sup>c</sup>	70	8	20	20
9	TBS (a)	LiOAc (120)	DMF <sup>c</sup>	70	2	100	96
10	TBS (a)	LiOAc·2H <sub>2</sub> O (200)	DMF–H <sub>2</sub> O (50:1)	25	8	10	10
11	TBS (a)	LiOAc·2H <sub>2</sub> O (5)	DMF–H <sub>2</sub> O (50:1)	70	18	100	94
12	TBS (a)	none	DMSO–H <sub>2</sub> O (5:1)	90	8	0	<i>d</i>
13	TBDPS (b)	LiOAc·2H <sub>2</sub> O (20)	DMF–H <sub>2</sub> O (50:1)	70	15	100	97
14	TES (c)	LiOAc·2H <sub>2</sub> O (20)	DMF–H <sub>2</sub> O (50:1)	25	4	100	99

<sup>a</sup> All reactions run on 0.5–1.0 mmol scale. <sup>b</sup> Isolated yields. <sup>c</sup> Anhydrous solvent. <sup>d</sup> No reaction when 20 mol % catalyst was added.

from Li<sup>+</sup> to K<sup>+</sup>. On the other hand, neutral lithium salts such as LiCl and LiBr<sup>18</sup> were inactive, even when used in excess. The solvent effect was then investigated, and DMF proved to be the only choice. In addition, an adequate amount of water was essential for catalyst regeneration to maintain the catalytic cycle; otherwise a stoichiometric amount of LiOAc is necessary (entries 8 and 9). This allowed the use of inexpensive LiOAc dihydrate as the catalyst, and no special care (drying and redistillation) is necessary with regard to the solvent. For electron-rich substrates, the deprotection was usually carried out at 70 °C; at room temperature the reaction of **1a** was sluggish. On the other hand, substrates activated with electron-withdrawing substitutions were readily deprotected at room temperature (vide infra). The loading of LiOAc could be lowered to 5 mol % without adverse effects, indicating it is a truly catalytic process. In comparison, it needs to be pointed out that DMSO–H<sub>2</sub>O failed to deprotect **1a** under literature conditions.<sup>7c</sup> For other representative aryl silyl ethers, we were pleased that our protocol could be extended to TBDPS and TES derivatives as well, and the reaction of the latter proceeded smoothly at rt.

Having established the standard conditions, the scope of this protocol was examined (Table 2). For TBS ethers derived from electron-rich or highly hindered phenols, the deprotection was complete within 2–24 h under heating (entries 1–6). Free amino group did not pose difficulty for the reaction (entry 2), and acid-sensitive *N*-Boc protection was preserved (entry 3). The highly hindered bis-TBS ether of 2,2'-biphenol (**1i**) was also smoothly cleaved. Notably, monosubstituted terminal epoxide was tolerated as well (entry 14). The deblocking of substrates bearing halogen or EWG substitutions can be carried out efficiently at room temperature to give excellent yields (entries 7–13). Meanwhile, TBS protections for heterocyclic substrates as well as enols were also cleanly removed under mild conditions (entries 15 and 16). Compared to protocols using stronger bases,<sup>6</sup> our method is remarkably efficient and mild.

TABLE 2. LiOAc-Catalyzed Deprotection of Aryl TBS Ethers<sup>a</sup>

entry	TBS ethers (I)	T (°C)	t (h)	2 (%) <sup>b</sup>
1	4-MeOC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1d</b> )	70	8	92
2 <sup>c</sup>	4-H <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1e</b> )	70	24	87
3	4-BocNHC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1f</b> )	70	8	98
4	2,4,6-Me <sub>3</sub> C <sub>6</sub> H <sub>2</sub> OTBS ( <b>1g</b> )	70	24	90
5	2,6-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> OTBS ( <b>1h</b> )	70	3	94
6	(2-TBSOC <sub>6</sub> H <sub>4</sub> ) <sub>2</sub> ( <b>1i</b> )	70	6	92
7	4-BrC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1j</b> )	25	10	93
8	2-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1k</b> )	25	1.5	98
9	2-OHCC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1l</b> )	25	4	91
10	3-OHCC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1m</b> )	25	8	96
11	4-OHCC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1n</b> )	25	3	95
12	2-AcC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1o</b> )	25	4	91
13	3-AcC <sub>6</sub> H <sub>4</sub> OTBS ( <b>1p</b> )	25	7	99
14 <sup>d</sup>	 ( <b>1q</b> )	25	11	93
15	 ( <b>1r</b> )	25	2.5	90
16	 ( <b>1s</b> )	25	8	90

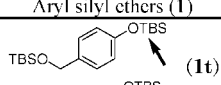
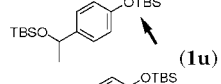
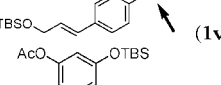
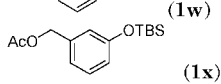
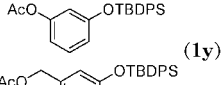
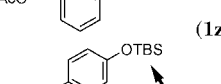
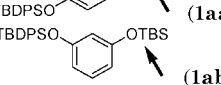
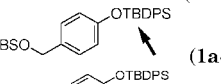
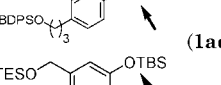
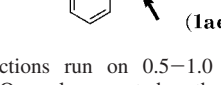
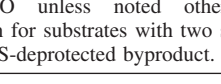
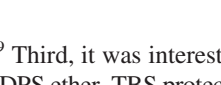
<sup>a</sup> All reactions run on 0.5–1.0 mmol scale using 5–10 mol % catalyst unless stated otherwise. <sup>b</sup> Isolated yields. <sup>c</sup> 30 mol % LiOAc·2H<sub>2</sub>O. <sup>d</sup> 20 mol % LiOAc·2H<sub>2</sub>O.

The issue of chemoselectivity between TBS and common protective groups for hydroxyl was next investigated as shown in Table 3. It was found that TBS-protected primary, secondary, benzylic, and allylic alcohols were completely inert under the present protocol (Table 3, entries 1–3). Furthermore, acetates of phenol and benzylic alcohol were also well-preserved (Table 3, entries 4–7). This is particularly noteworthy since phenol acetates are highly base-sensitive and thus cannot survive strong bases such as LiOH or even alkali carbonates in alcoholic

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(18) LiCl and LiBr were reported to deprotect alkyl TBS ethers: (a) Farras, J.; Serra, C.; Vilarasa, J. *Tetrahedron Lett.* **1998**, 39, 327. (b) Tandon, M.; Begley, T. P. *Synth. Commun.* **1997**, 27, 2953.

TABLE 3. Chemoselective Deprotection of Aryl Silyl Ethers<sup>a</sup>

entry	Aryl silyl ethers (1)	T (°C)	t (h)	2 (%) <sup>b</sup>
1	 (1t)	70	2	98
2	 (1u)	70	2	98
3	 (1v)	70	2.5	93
4	 (1w)	70	2	94
5	 (1x)	70	1.5	96
6	 (1y)	70	4	91
7	 (1z)	70	5	92
8	 (1aa)	35	48	91
9	 (1ab)	35	24	82 <sup>c</sup>
10	 (1ac)	70	8	90
11 <sup>d</sup>	 (1ad)	70	48	90
12 <sup>d</sup>	 (1ae)	25	16	86

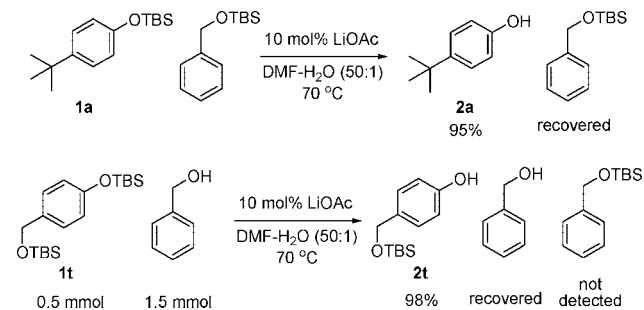
<sup>a</sup> All reactions run on 0.5–1.0 mmol scale using 5–10 mol % LiOAc·2H<sub>2</sub>O unless noted otherwise, arrows indicate site of deprotection for substrates with two silyl groups. <sup>b</sup> Isolated yields. <sup>c</sup> Up to 14% TBDPS-deprotected byproduct. <sup>d</sup> 40 mol % LiOAc·2H<sub>2</sub>O.

solvents.<sup>19</sup> Third, it was interesting to note that in the presence of aryl TBDPS ether, TBS protection was preferentially removed with good to excellent selectivity (Table 3, entries 8 and 9), despite the fact that in general *O*-TBDPS is intrinsically more susceptible to base-induced hydrolysis than *O*-TBS.<sup>20</sup> The selectivity concerning phenolic TBDPS and alcoholic silyl ethers was also investigated (Table 3, entries 10–12). As expected, the former was cleaved exclusively in the presence of the TBS ether of a primary alcohol (1ac). In addition, whereas there was only a single previous report of selective removal of phenolic TBDPS ether without affecting aliphatic TBDPS ether,<sup>7a</sup> this was also achieved using the present protocol (Table 3, entry 11). More significantly, we have demonstrated that selective deprotection of phenolic TBS ether in the presence of primary aliphatic TES ether was feasible at room temperature (Table 3, entry 12), whereas at elevated temperature (70 °C) global deprotection was achieved. To our knowledge, such chemoselectivity is unprecedented and highly desirable.

(19) For example, acetyl protection for phenol can be removed by NaHCO<sub>3</sub>, MeOH, room temperature, 45 min: Büchi, G.; Weinreb, S. M. *J. Am. Chem. Soc.* **1971**, *93*, 746.

(20) For selective base hydrolysis of TBDPS in the presence of TBS, see: (a) Hatakeyama, S.; Irie, H.; Shintani, T.; Noguchi, Y.; Yamada, H.; Nishizawa, M. *Tetrahedron* **1994**, *50*, 13369. (b) Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669. (c) Loh, T.-P.; Feng, L.-C. *Tetrahedron Lett.* **2001**, *42*, 3223. An independent study indicated that TBDPS is only slightly more stable than TBS toward NaOH but still quite base-labile ( $t_{1/2} \approx 6.5$  min). (d) Davies, J. S.; Higginbotham, C. L.; Tremeer, E. J.; Brown, C.; Treadgold, R. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3043.

SCHEME 1. Competition and Cross-over Experiments



To ascertain that the retaining of alkyl silyl ethers was not the result of possible silyl exchange or migration,<sup>21</sup> an intermolecular competition experiment and a cross-over experiment were carried out (Scheme 1). In an equimolar mixture of 1a and benzyl TBS ether, only the former underwent deprotection, while the latter was fully recovered. On the other hand, when the deprotection of compound 1t was conducted in the presence of excess benzyl alcohol, the absence of benzyl TBS ether excluded the possibility of silyl redistribution.

The counter-intuitive trend of catalyst activity within the series of acetates suggests that the mechanism of our deprotection protocol is not simply Lewis base induced hydrolysis analogous to that of aldol and related reactions of TMS enol ethers.<sup>17</sup> Unlike HO<sup>-</sup> or CO<sub>3</sub><sup>2-</sup>, the nucleophilicity of AcO<sup>-</sup> itself is probably too weak to effect direct attack of the bulky TBS to form hypervalent silicon species, whereas for the least hindered TMS, direct attack is viable.<sup>22</sup> Moreover, for the bulky TBS and TBDPS, further coordination of a neutral DMF molecule to the pentavalent silicon intermediates to form hexa-coordinated species seems unfavorable. Since Li<sup>+</sup> alone is ineffective, therefore both acetate anion (a Lewis base) and lithium cation (a Lewis acid) are essential to the desilylation. Presumably, the role of the latter is to coordinate with the phenolic oxygen with a 2-fold effect: first, it assists the cleavage of ArO-Si bond as the leaving of LiOAr is thermodynamically more favorable than that of a free phenoxide anion. This is confirmed by the fact that LiOAr cannot be silylated by TBSOAc (Table 1, entry 9), so the deprotection is irreversible even in neat anhydrous DMF.<sup>23</sup> Second, such coordination helps to bring the acetate anion to the proximity of the silyl, and the reaction is likely to proceed via a six-membered cyclic transition state<sup>24</sup> by a dual-activation mechanism (Figure 1). Thus, LiOAc represents a simple yet effective example of the concept of Lewis acid–Lewis base bifunctional catalysis.<sup>25</sup> The catalytic cycle was completed by facile hydrolysis of the resulting LiOAr and TBSOAc,

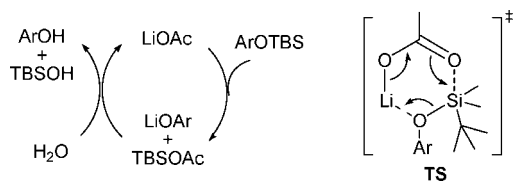
(21) Phenol to alcohol silyl migration: (a) Ku, T.-Y.; Grieme, T.; Raje, P.; Sharma, P.; King, S. A.; Morton, H. E. *J. Am. Chem. Soc.* **2002**, *124*, 4282. For a general survey of silyl migration, see: (b) ref 1, pp 166–171 and references therein.

(22) For systematic studies on the steric factors of silyl groups, see: (a) Shimizu, N.; Takesue, N.; Yamamoto, A.; Tsutsumi, T.; Yasuhara, S.; Tsuno, Y. *Chem. Lett.* **1992**, *21*, 1263. (b) Shimizu, N.; Takesue, N.; Yasuhara, S.; Inazu, T. *Chem. Lett.* **1993**, *22*, 1807. Informative qualitative comparison of acid/base stability of silyl ethers can also be found in ref 1, pp 166.

(23) In contrast, lithium aldolate (lithium alkoxide) was readily silylated by TMSOAc: Mukaiyama, T.; Fujisawa, H.; Nakagawa, T. *Helv. Chim. Acta* **2002**, *85*, 4518.

(24) Cyclic transition state has also been proposed for SbCl<sub>5</sub>-promoted deprotection of alkyl silyl ethers: Glória, P. M. C.; Prabhakar, S.; Lobo, A. M.; Gomes, M. J. S. *Tetrahedron Lett.* **2003**, *44*, 8819.

(25) For excellent reviews on Lewis acid–Lewis base bifunctional catalysis in asymmetric synthesis, see: (a) Shibasaki, M.; Kanai, M.; Funabashi, K. *Chem. Commun.* **2002**, 1989. (b) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566.



**FIGURE 1.** Catalytic cycle and plausible transition state.

followed by neutralization of LiOH and HOAc to regenerate LiOAc. The observed chemoselectivity in our protocol can also be rationalized by the above hypothesis. For aryl TBDPS ethers, the bulky phenyl substituents shielded the phenolic oxygen and the Si center so that both the O–Li and O–Si coordination (dashed lines in TS) was relatively weaker, resulting in lower reaction rate. Moreover, TBDPSOAc is appreciably more stable than its TBS analog, and thus its hydrolysis is slower and may also be part of the rate-limiting step.<sup>26</sup> The stability of alkyl silyl ethers could be attributed to thermodynamic reasons.<sup>23</sup>

In summary, we have developed an efficient and mild protocol for the selective removal of phenolic silyl protections using catalytic amount of LiOAc under near-neutral conditions. It displayed a wide substrate scope, consistently high yields, desirable functional group compatibility, and remarkable chemoselectivity between different silyl protections. Particularly, using this protocol, aryl silyl protections can be orthogonally removed in the presence of alkyl silyl ethers, acetates, carbamates, and epoxides. Operational simplicity and economy are additional benefits. A six-membered transition state wherein LiOAc serves

(26) TBDPS can be used to protect carboxylic acids; Schmidt, U.; Neumann, K.; Schumacher, A.; Weinbrenner, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1110.

as a Lewis acid–Lewis base bifunctional catalyst was proposed to rationalize the efficiency and selectivity. Our protocol complements existing desilylation methods, and we believe it would find wide applications in the synthesis of complex molecules.

## Experimental Section

**General Procedure.** To a solution of aryl silyl ether (1.0 mmol) in DMF–H<sub>2</sub>O (50:1, 5.0 mL) under argon was added LiOAc dihydrate (10.2 mg, 0.10 mmol, 10 mol %), and the solution was stirred at 25–70 °C until all the starting material has been consumed. The mixture was cooled to room temperature, diluted with ether, washed twice with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography.

**(E)-4-(3-(*tert*-Butyldimethylsilyloxy)prop-1-enyl)phenol (2v).** <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.26 (d, 2H, *J* = 8.7 Hz), 6.78 (d, 2H, *J* = 8.7 Hz), 6.51 (d, 1H, *J* = 15.6 Hz), 6.13 (dt, 1H, *J* = 15.6, 4.8 Hz), 4.96 (br s, 1H), 4.33 (d, 2H, *J* = 4.8 Hz), 0.94 (s, 9H), 0.11 (s, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 155.0, 130.0, 129.2, 127.7, 126.9, 115.4, 64.1, 26.0, 18.5, –5.1; HR-MS *m/z* calcd for C<sub>15</sub>H<sub>24</sub>O<sub>2</sub>Si 264.1546, found 264.1552.

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**Supporting Information Available:** Characterization data, <sup>1</sup>H and <sup>13</sup>C NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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