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The *para*-siletanylbenzyl (PSB) ether: a peroxide-cleavable protecting group for alcohols and phenols

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Abstract—A novel arylmethyl protecting group that is electronically similar to benzyl (Bn) but that can be cleaved under mild oxidizing conditions in the presence of *para*-methoxybenzyl (PMB) is described herein. *para*-Siletanylbenzyl (PSB) ethers are formed in one or two steps from the corresponding alcohols and cleaved in one or two steps with basic peroxide. Alcohols and phenols have been protected in good yields and deprotected cleanly under mild oxidative conditions.

The complexities of natural product synthesis and of the rapidly developing field of carbohydrate synthesis create a demand for chemically differentiable protecting groups (PGs) for vulnerable functionality. Benzyl ethers are among the most popular alcohol PGs due to their ease of formation, stability to a wide range of reaction conditions, and mild cleavage protocols. Modified arylmethyl PGs have been tailored for use in more complex systems.[1]

Several arylmethyl PGs are cleaved by initial transformation into a *para*-hydroxybenzyl (PHB) ether. Jobron and Hindsgaul first reported the use of *O*-protected 4-*O*-benzyl PGs for carbohydrate chemistry.[2] Removal of the arene 4-*O*-PG[3] under the appropriate conditions reveals the PHB ether, which is then easily hydrolyzed. Cross-coupling of *para*-bromobenzyl (PBB) ethers provides a similar effect: palladium-catalyzed amination of the PBB group yields a labile *para*-aminobenzyl ether,[4] whereas palladium-catalyzed borylation of PBB followed by oxidation afforded a PHB ether in a synthetic approach to ciguatoxin.[5]

These efforts reflect the importance of diverse arylmethyl PGs and highlight the need for orthogonality and functional group compatibility in the cleavage event.

We recently reported that aryl-siletanes (silacyclobutanes) react with hydrogen peroxide under mild conditions to afford phenols.[6] The oxidation reaction (silylarene→phenol) dramatically increases the oxidation potential (electron density) of the arene ring.

Seeking to take advantage of this change, we set out to develop a new arylmethyl PG for alcohols, the cleavage of which would be triggered by hydrogen peroxide. Unlike masked PHB ethers,[2] latent PHB ethers offer greater promise in terms of orthogonality with a range of other common PGs. For example, revealing the PHB intermediate does not involve cleavage of a different protecting group.

This letter describes preliminary results on the synthesis and applications of a siletane-substituted benzyl PG for alcohols and phenols (Scheme 1). *para*-Siletanylbenzyl (PSB) derivatives **1a** and **b** were prepared from commercially available **7** (Scheme 2).

Arylmagnesium bromide **6**[7] couples with siletane **7** to provide **8** in excellent yield. The silyl ether is then selectively removed in acidic methanol to afford PSB alcohol **1a**.[6] The fact that the arylsiletane is unaffected by these conditions is encouraging with respect to the potential utility of PSB ethers. PSB–OH (**1a**) then yields PSB–Br (**1b**) upon treatment with CBr_4 and PPh_3.[2]

We selected a representative sample of aromatic and aliphatic alcohols to serve as test cases for the formation and cleavage of PSB ethers (Fig. 1).

Keywords: Benzyl; Protecting group; Siletane; Oxidation; Strained silacycle.

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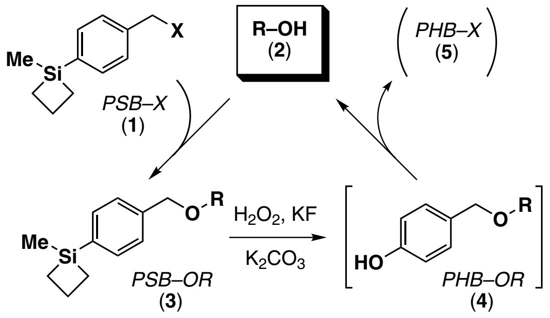
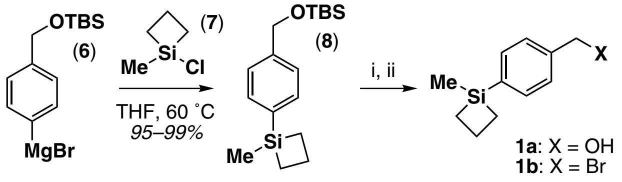


Scheme 1. Overview of protection/deprotection of alcohols using the *para*-siletanylbenzyl protecting group.



Scheme 2. Preparation of **1a** and **b**. Reagents and conditions: (i) HCl, MeOH, 3 h, 94% (**1a**); (ii) CBr_4, PPh_3, 12 h, 95% (**1b**).

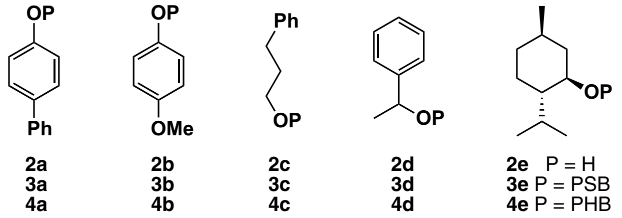
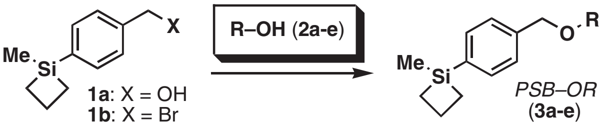


Figure 1. Alcohols and PSB ethers described in Tables 1 and 2.

Protection of phenols can be achieved using PSB–OH (**1a**) under Mitsunobu conditions (Table 1, entries 1 and 4).[8] Attempts to alkylate potassium, cesium, or sodium salts with **1b** were unsuccessful (entries 2 and 6).[9] Arylmethylation of primary alcohols (i.e., **2c**) occurs smoothly with PSB–Br (**1b**) using freshly prepared Ag_2O;[10] this afforded the corresponding PSB ether in 80–83% yield (entry 5). However, secondary alcohols could not be protected efficiently using the same method even after prolonged reaction times (entries 7 and 8). Side products and/or low conversions were observed. We adopted a two-step protection strategy for such substrates (Scheme 3). The alcohol is first derivatized as a PBB ether,[4] which is then silylated via the corresponding Grignard reagent. This circumvents the independent synthesis of **1** and increases the scope of PSB-protected alcohols. The alternative protocol may be useful for protection of alcohols prior to introducing sensitive functionality.

Table 1. Protection of phenols and alcohols as PSB ethers

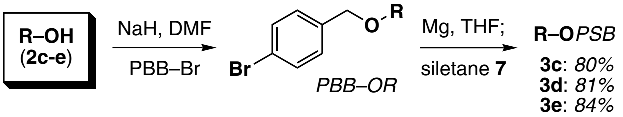


Entry	PSB–X	Alcohol	Conditions[a]	PSB ether (% yield)
1	**1a**	**2a**	A	**3a** (74)
2	**1b**	**2a**	B	—
3	**1b**	**2a**	C	**3a** (70)
4	**1a**	**2b**	A	**3b** (96)
5	**1b**	**2c**	C	**3c** (80–83)
6	**1b**	**2c**	B	—
7	**1b**	**2d**	C	**3d** (50)
8	**1b**	**2e**	C	**3e** (38)

[a] Conditions. A: PPh_3, DEAD, CH_2Cl_2; B: K_2CO_3/TBAI, Cs_2CO_3, or NaH, DMF; C: Ag_2O, CH_2Cl_2.

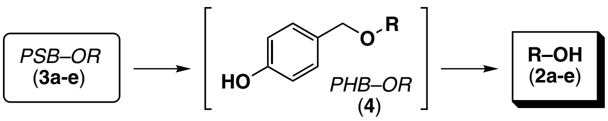
With PSB ethers in hand, we proceeded to the deprotection using conditions identified previously in our laboratory.[6] Tamao-type oxidation of aryl ethers **3a** and **b** provides the deprotected phenols (**2a** and **b**)[11] in one step (Table 2, entries 1 and 2). Intermediate PHB ethers **4a** and **b** presumably undergo solvolysis during the course of the reaction.[12]

In the aliphatic ether cases (**3c–e**), the labile PHB ethers (**4c–e**) were isolated and then cleaved[2] using $FeCl_3$ (entries 3–5 and 7) or DDQ (entry 6) to give alcohols **2c–e**. Alternatively, Smitrovich and Woerpel's more rigorous carbosilane oxidation protocol also affords the PHB ethers (**4c** and **d**, entries 6 and 7).[13] Such conditions are not expected to tolerate pendant silyl ether PGs,[14] but they do afford excellent yields after a relatively simple purification.[15] PSB ethers can also be removed by hydrogenolysis (entry 8). PSB ethers are presumably similar to benzyl ethers in terms of arene oxidation potential, yet they cleave under mild oxidizing conditions that are unique among the common arylmethyl PGs. We illustrate this attractive feature through competition experiments with *para*-methoxybenzyl (PMB) ether **10**.



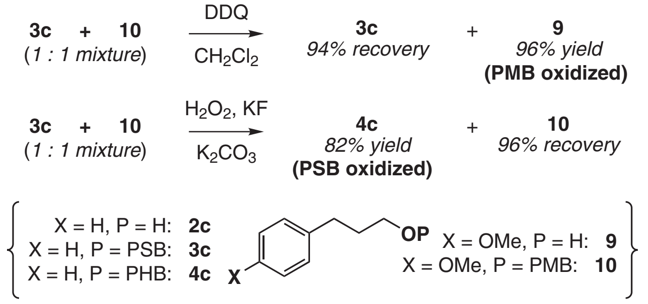
Scheme 3. Two-step protection of alcohols (and overall yields).

Table 2. Cleavage of PSB ethers



Entry	PSB ether	Conditions[a]	PHB ether	Alcohol
			(% yield)	(% yield)
1	**3a**	D	—	**2a** (89)
2	**3b**	D	—	**2b** (86)
3	**3c**	(i) D (ii) $FeCl_3$	**4c** (87)	**2c** (99)
4	**3d**	(i) D (ii) $FeCl_3$	**4d** (84)	**2d** (97)
5	**3e**	(i) D (ii) $FeCl_3$	**4e** (85)	**2e** (94)
6	**3c**	(i) E; (ii) DDQ	**4c** (99)	**2c** (90)
7	**3d**	(i) E; (ii) $FeCl_3$	**4d** (99)	**2d** (97)
8	**3c**	F	—	**2c** (88)

[a] Conditions: D: K_2CO_3, $KF{\cdot}2H_2O$, 30% aqueous H_2O_2, THF/MeOH, 50 °C;[16] E: TBAF, *t*-BuOOH, DMF, 70 °C; F: H_2, 10% Pd/C.



Scheme 4. Orthogonality in the oxidative cleavage of *para*-siletanylbenzyl (PSB) and *para*-methoxybenzyl (PMB) ethers.

PMB ethers can be removed oxidatively with DDQ in the presence of Bn ethers;[1] the same orthogonality is seen with PSB ethers (Scheme 4). Alternatively, treating an equimolar mixture of **3c** and **10** with basic peroxide affects only the PSB ether, leaving the PMB group intact.

In conclusion, the *para*-siletanylbenzyl PG has been shown to protect phenols and primary alcohols cleanly. Its easy removal under mild oxidative conditions as well as its orthogonality with the PMB group can be advantageous in multi-step synthesis. Our on-going efforts are aimed at developing new and improved methods for the arylmethylation of secondary alcohols in order to address this limitation in the current protocol.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.03.110. Experimental procedures (for the preparation of compounds **1**–**4** and **8**) and characterization data for new compounds are published alongside the on-line version of this letter.

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11. Note that hydroquinone **2b** is stable under these conditions.
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14. For siletane oxidation in the presence of a TBS ether, see Ref. 6.
15. A by-product believed to result from oxidation of THF is observed following the Tamao protocol.
16. The oxidations described in Ref. 6 were conducted at ambient temperature using $KHCO_3$ as the base. The mild heating employed in conditions D provides shorter reaction times and, in the case of aryl ethers, promotes in situ solvolysis of the PHB intermediate (**4**).