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New Strategies for Protecting Group Chemistry: Synthesis, Reactivity, and Indirect Oxidative Cleavage of *para*-Siletanylbenzyl Ethers

Sami F. Tlais, Hubert Lam,[†] Sarah E. House,[‡] and Gregory B. Dudley*

Department of Chemistry and Biochemistry, Florida State University, Tallahassee, Florida 32306-4390

gdudley@chem.fsu.edu

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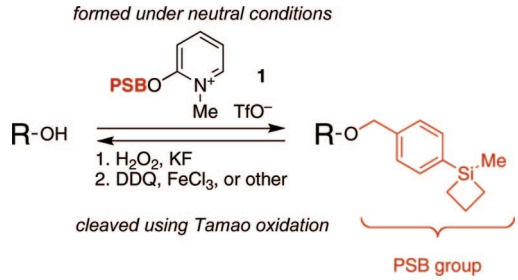

Reported herein is a new entry in the growing arsenal of arylmethyl ether protecting groups. The *para*-siletanylbenzyl (PSB) ether is electronically similar to the benzyl ether. Cleavage of the PSB ether is accomplished under mild conditions—involving alkaline hydrogen peroxide—that are unique among cleavage protocols for arylmethyl ethers. Furthermore, the PSB group affords the user new flexibility in the implementation of protecting group strategies that revolve around multiple arylmethyl ether protecting groups. In addition to hydrogen peroxide-based cleavage protocols, conversion of a PSB ether into a *para*-methoxybenzyl (PMB) ether and assembly of a PSB ether from a pre-existing *para*-bromobenzyl (PBB) ether are described. Finally, a new reagent for installing PSB ethers under neutral "mix and heat" conditions is reported.

Protecting Group Strategies

Protecting group strategies[1] are indispensable to the general pursuit of synthetic polyketides,[2] oligosaccharides,[3] peptides,[4] and other complex small molecule structures[5] of potential relevance to human health. A desirable protecting group satisfies three main criteria: (1) the installation (formation) of the protecting group must occur easily and in high yield; (2) the installed protecting group must render inert an otherwise reactive site during a synthetic sequence aimed at affecting other regions of the molecular system; and (3) the removal (cleavage) of the protecting group must occur easily and under mild conditions at the appropriate point in the synthetic scheme. Orthogonal reactivity with other common protecting groups is especially valuable for highly functionalized systems.

Arylmethyl Protecting Groups

Benzyl and modified benzyl ethers are among the most common and important protecting groups in synthetic chemistry. Benzyl ethers are robust, yet they provide cleavage mechanisms unique among alkyl ethers, including hydrogenolysis, dissolving metal reduction, electron-transfer oxidation (i.e., DDQ oxidation), and acidic cleavage under a range of experimental conditions. Electronic tuning of the aromatic ring provides an expanded range of valuable properties, resulting in a series of arylmethyl protecting groups that includes *para*-methoxybenzyl

[†] Current address: General Electric Company-GE Global Research, One Research Circle, Niskayuna, NY.

[‡] Current address: Department of Chemistry, Latimer Hall, University of California, Berkeley, CA.

(1) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*; 4th ed.; John Wiley and Sons: Hoboken, NJ, 2007. Kocienski, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, Germany, 2003.

(2) Mickel, et al, S. J. Large-Scale Synthesis of the Anti-Cancer Marine Natural Product (+)-Discodermolide. Part 1: Synthetic Strategy and Preparation of a Common Precursor. *Org. Process Res. Dev.* **2004**, *8*, 92–100. Part 2: Synthesis of Fragments C1−6 and C9−14, 101−106. Part 3: Synthesis of Fragment C15−21, 107−112. Part 4: Preparation of Fragment C7−24, 113−121. Part 5: Linkage of Fragments C1−6 and C7−24 and finale, 122−130.

(3) (a) *Preparative Carbohydrate Chemistry*; Hanessian, S. , Ed.; Marcel Dekker: New York, 1997. (b) *The Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; Taylor & Francis: Boca Raton, FL, 2006.

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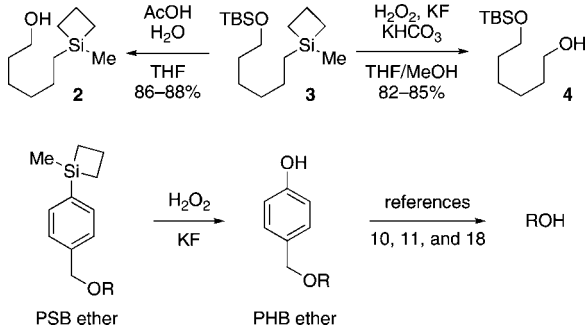
SCHEME 1. Tamao-type Oxidation of Organosiletanes



(PMB), dimethoxybenzyl (DMB), napthylmethyl (NAP), *para*-bromobenzyl (PBB),[6] and many others.

Not included in this list is the relatively unstable *para*-hydroxybenzyl (PHB) group, which decomposes to release the unprotected substrate under very mild conditions.[7] Jobron and Hindsgaul recently drew attention to the advantage of employing protected-PHB ethers in carbohydrate synthesis by introducing *para*-acetoxybenzyl (PAB) and *para*-(*tert*-butyldimethylsilyl)-oxybenzyl protecting groups, the cleavage of which is promoted by first cleaving the acetate ester or silyl ether, respectively.[8] The use of protected-PHB ethers is well suited to carbohydrate synthesis. Arylmethyl protecting groups offer minimal electronic impact on glycosyl donors, in contrast to the more electron-withdrawing acetate esters and silyl ethers.[9] Outside of glycosylation reactions, however, it is unclear how much is gained by employing protected-PHB protecting groups over direct use of an acetyl or silyl moiety, especially as formation of protected-PHB ethers has thus far only been demonstrated on primary alcohols.[8]

Arylsiletane Oxidations

Earlier methodology from these laboratories[10] illustrated the Tamao-type oxidation[11] of silacyclobutanes (siletanes),[12] in which the strained organosiletane undergoes a rapid ring-opening reaction promoted by aqueous fluoride to set the stage for eventual oxidation of the carbon−silicon bonds. Organosiletanes are stable to routine purification, handling, and even acidic hydrolysis of silyl ethers. Because hydrolytic opening of the siletane ring occurs rapidly under the mildest of Tamao oxidation conditions,[13] organosiletanes undergo carbosilane oxidations without affecting a pendant silyl ether (Scheme 1) and at rates comparable to even the most activated Tamao substrates.[10] Notably, arylsiletanes provide convenient access to phenols without requiring the separate "priming" step of the Tamao−Fleming reaction, which often involves cleavage of an aryl−silicon bond.[14] When functionalized at the *para*-position with an alkoxymethyl substituent, the arylsiletane oxidation provides easy access to labile PHB ethers.[15] From the perspective of protecting group strategies, the aforementioned *para*-(alkoxymethyl)-arylsiletane is more appropriately referred to as an alkyl PSB ether (PSB = *para*-siletanylbenzyl).

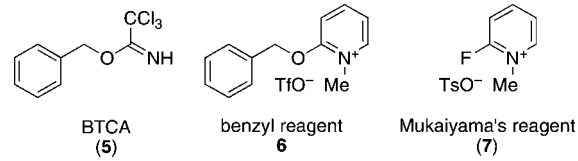


FIGURE 1. Benzyl transfer reagent **6** and related reagents.

Formation of Arylmethyl Ethers

Traditionally, preparation of arylmethyl ethers from alcohols is accomplished by one of two strategies: Williamson ether synthesis under basic conditions or under acidic conditions using trichloroacetimidates.[16] Neither strategy was found, generally, to be appropriate for making the PSB ethers that are the subject of this article.[15] Upon exposure to alkali metal alkoxides, such as are employed in the Williamson ether synthesis protocol, siletanes undergo ring-opening polymerization to give rise to carbosilane polymers.[17] Under acidic conditions, arylsilanes are subject to protiodesilylation.[18]

A new arylmethylation strategy had to be developed in order to address these limitations, with an aim of eventually identifying a general method for making PSB ethers. Because trichloroacetimidates require acidic conditions that were not compatible with the aryl−silicon subunit, a search began for a reagent analogous to benzyl trichloroacetimidate (BTCA, Figure 1) that could be activated by *N*-alkylation rather than *N*-protonation. Initial efforts, focusing on the preparation of simple benzyl ethers,[19] revealed that *N*-methylation of 2-benzyloxypyridine[20]

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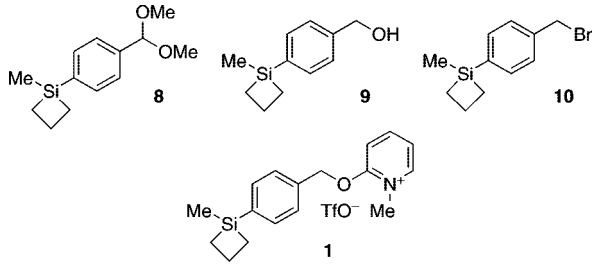

FIGURE 2. Reagents for the synthesis of PSB ethers.

leads to a reagent—2-benzyloxy-1-methylpyridinium triflate (**6**)[21]—that converts alcohols into benzyl ethers upon warming.[23] Thus emerged a new benzyl ether synthesis, which has since been extended to include reagents for the preparation of PMB[24−26] and halobenzyl ethers.[27] Importantly, the new arylmethyl ether synthesis involves neutral conditions that are applicable to the formation of PSB ethers (vide infra). This methodology was inspired in part by Mukaiyama's success with acylation reactions using *N*-methylpyridinium salts as coupling reagents.[28]

This article provides a detailed account of the development of the PSB ether as an arylmethyl protecting group for alcohols and phenols, with an emphasis on the synthesis of PSB ethers. The direct formation of alkyl PSB ethers was not appropriately addressed in previously reported studies,[15,29] which instead relied mostly on two-step protocols for preparing a limited range of PSB ethers. Four different reagents with complementary scope and limitations are now available for the synthesis of PSB ethers (Figure 2): *para*-siletanylbenzaldehyde dimethyl acetal **8**, *para*-siletanylbenzyl alcohol **9** (PSB-OH), *para*-siletanylbenzyl bromide **10** (PSB-Br), and *para*-siletanylbenzyl-oxypyridinium triflate **1**, referred to herein as PSB-OPT.

Two convenient peroxide oxidation methods for converting PSB ethers into PHB ethers are outlined, along with relevant applications of known protocols for cleaving PHB ethers. Competition experiments illustrate the degree to which the PSB ethers are orthogonally compatible with other common protecting groups, including MOM, TBS, PMB, and others.

Finally, the synthesis of PSB-OPT (**1**) is described in detail as it is capable of delivering the PSB group onto the widest range of alcohol substrates, including carbohydrates and secondary alcohols. The optimized synthesis of PSB-OPT features an innovative technique for initiating the formation of Grignard reagents.

Results and Discussion

1. Formation of PSB Ethers. The first aspect of the development of the *para*-siletanylbenzyl protecting group relates to the synthesis of PSB ethers from a collection of representative alcohols (Figure 3). This collection comprises primary and secondary alcohols and phenols, which offers insight that can be extrapolated to a wide range of potential substrates. Additional specific substrates (carbohydrate and carboxylic acid) are included as well.

1.1. Formation of Aryl PSB Ethers Using PSB-OH. Conversion of phenols to the corresponding PSB ethers was best accomplished under Mitsunobu conditions (Scheme 2) using PSB-OH (**9**), providing ethers **17** (74%) and **18** (96%). Arylmethylation using PSB-Br under basic conditions was less effective due to competing siletane polymerization.

1.2. Formation of PSB Ethers Using PSB-Br. Silver oxide-mediated etherification protocols delivered PSB ethers with limited efficiency (Table 1). Of the representative alcohols screened, only the simple primary alcohol (**13**) gives rise to the corresponding PSB ether in good yield (up to 83%). Arylmethylation of phenol **11** was reasonably efficient at best (70%), whereas PSB ethers of secondary alcohols **20** and **21** were obtained in only up to 50% and 38% yields, respectively. Furthermore, these reactions were capricious, difficult to conduct successfully, and required freshly prepared silver oxide for best results. We concluded that PSB-Br **10** could not provide the general solution that we sought for the synthesis of PSB ethers.

1.3. Formation of Secondary Alkyl PSB Ethers by Reduction of Dioxane Acetals. Regioselective reduction of benzylidene acetals with DIBAL provides indirect access to secondary arylmethyl ethers, including PSB ethers (Scheme 3).[29] Condensation of 1,3-butanediol with acetal **8** provided 1,3-dioxane **23** (quantitative yield), the reduction of which with DIBAL furnished PSB ether **24** in 97% yield. Glucopyranoside **25** was readily protected as acetal **26** (Scheme 4). DIBAL reductive ring opening of acetal **26** yielded a mixture of PSB ethers **27a** (81%) and **27b** (15%).

1.4. Formation of Alkyl PSB Ethers from Alkyl PBB Ethers. In light of difficulties associated with the direct conversion of alcohols into PSB ethers using PSB-Br (section 1.1, above), a two-step process was developed to access PSB ethers indirectly from *para*-bromobenzyl (PBB) ethers, which are amenable to preparation using the Williamson ether synthesis. First, the alcohol was treated with sodium hydride and PBB-Br. With the PBB ether thus installed, conversion of the aryl bromide moiety to the corresponding arylsiletane was achieved under Barbier conditions to furnish the desired PSB ethers (**19**−**21**, Scheme 5).

This approach provided the compounds needed to advance our initial studies on the cleavage of PSB ethers.[15] In a more general context, this sequence represents conversion of a PBB ether into a PSB ether on synthetic intermediates that can tolerate the aforementioned Barbier conditions, which provides valuable

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(23) Dudley Benzylation Reagent. *ChemFiles* **2007**, *7* (3), 3. Sigma-Aldrich product number: 679674.

(24) Nwoye, E. O.; Dudley, G. B. A Method for the Synthesis of *Para*-Methoxybenzyl (PMB) Ethers Under Effectively Neutral Conditions. *Chem. Commun.* **2007**, 1436–1437.

(25) Stewart, C. A.; Peng, X.; Paquette, L. A. An Efficient Means for Generating *P*-Methoxybenzyl (PMB) Ethers under Mildly Acidic Conditions. *Synthesis* **2008**, 433–437.

(26) Also now commercially available: Sigma-Aldrich product number 701440.

(27) Albiniak, P. A.; Amisial, S. M.; Dudley, G. B.; Hernandez, J. P.; House, S. E.; Matthews, M. E.; Nwoye, E. O.; Reilly, M. K.; Tlais, S. F. Stable Oxypyridinium Triflate (OPT) Salts for the Synthesis of Halobenzyl Ethers. *Synth. Commun.* **2008**, *38*, 656–665.

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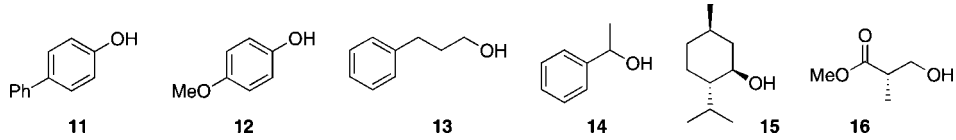
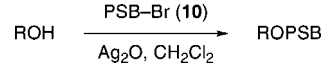
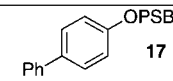
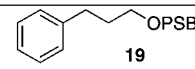
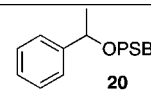
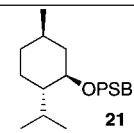


FIGURE 3. Representative alcohols employed as test substrates.

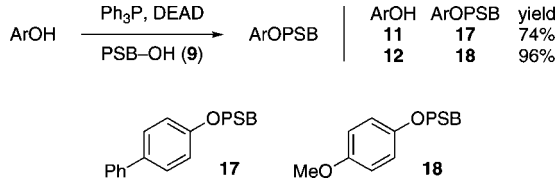
TABLE 1. Formation of PSB Ethers Using PSB-Br[a]



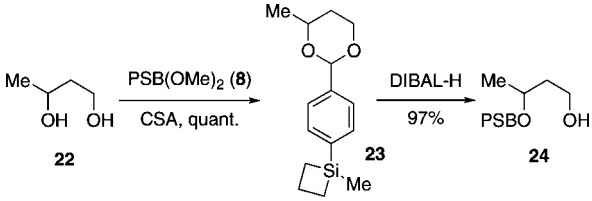
entry	ROH	ROPSB	yield[a]
1	**11**		up to 70%
2	**13**		up to 83%
3	**14**		up to 50%
4	**15**		up to 38%

[a] Yield of individual experiments highly dependent on the quality of **10**, silver oxide, and other reaction variables.

SCHEME 2. Synthesis of PSB Ethers Using the Mitsunobu Reaction



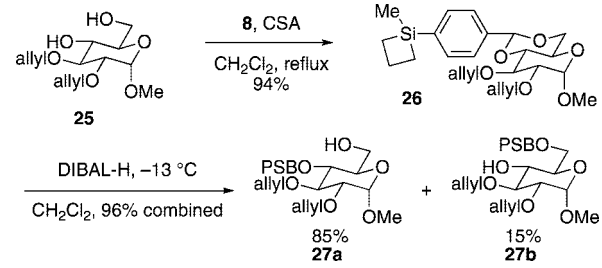
SCHEME 3. Synthesis of a Secondary PSB Ether via a 1,3-Dioxane Acetal



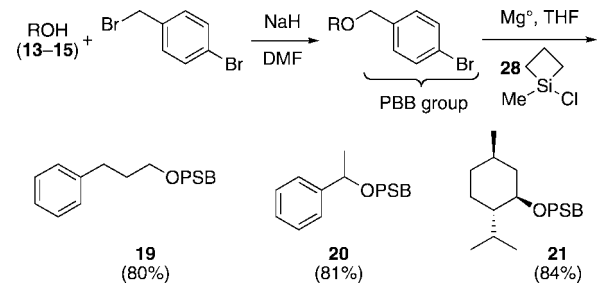
flexibility to arylmethyl protecting group strategies. For example, Murai employed a conceptually similar sequence to remove a PBB ether via an arylborane in a synthetic approach to ciguatoxin.[7] The corresponding arylsiletane could be cleaved under similar conditions or advanced through unrelated synthetic operations prior to releasing the free alcohol. Despite potential value in such highly specialized applications, we continued to work toward alternative, general methods for preparing PSB ethers.

1.5. Formation of Alkyl PSB Ethers Using PSB-OPT. The viability of PSB-OPT and its immediate precursor, PSB-OP **29**, as general reagents for the synthesis of PSB ethers is the key finding of this article. Given the lability of siletanes to sodium

SCHEME 4. Formation and Reductive Ring Opening of Glucopyranoside Dioxane Acetal 26



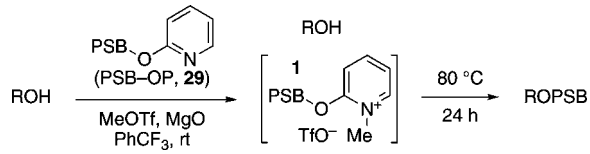
SCHEME 5. Two-Step Assembly of PSB Ethers via PBB Ethers

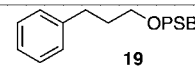
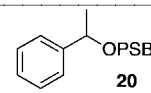
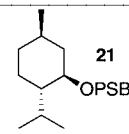
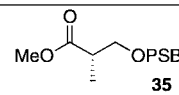
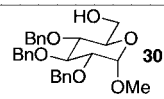
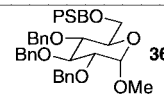
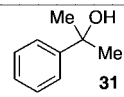
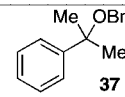
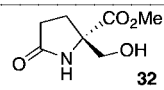
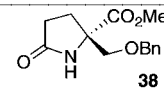
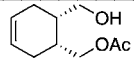
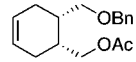
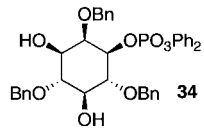
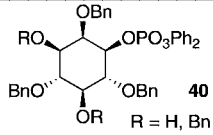


alkoxide nucleophiles and the general incompatibility of arylsiletanes to strong acid, the ideal method for preparing PSB ethers involves neutral conditions. PSB-OPT and PSB-OP enable such a method. Our findings using benzyl-transfer reagent **6** (Figure 1) guided the development of PSB-OPT.

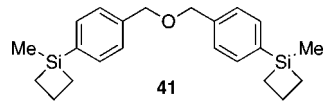
A range of representative primary and secondary alcohols give way to PSB ethers upon warming in the presence of PSB-

TABLE 2. Formation of Alkyl PSB Ethers Using PSB-OPT (1)[a]



Entry	alcohol	ether	Yield[b,c]
1	**13**	 **19**	90% (>95%)[ref. 22]
2	**14**	 **20**	88% (83%)[ref. 22]
3	**15**	 **21**	88% (88%)[ref. 22]
4	**16**	 **35**	71%[d] (76–82%)[ref. 22]
5[e]	 **30**	 **36**	91%[d]
6[f]	 **31**	 **37**	(44%)[ref. 22]
7[f]	 **32**	 **38**	(75%)[ref. 30]
8[f]	 **33**	 **39**	(96%)[ref. 31]
9[f]	 **34**	 **40** R = H, Bn	(18%)[ref. 32]

[a] See Supporting Information for details. Unless otherwise indicated, 2.0 equiv of **28**, MeOTf, and MgO employed relative to ROH. [b] Estimated by ^{1}H NMR, unless otherwise noted; isolated material contaminated with varying amounts of di-PSB ether **41**.

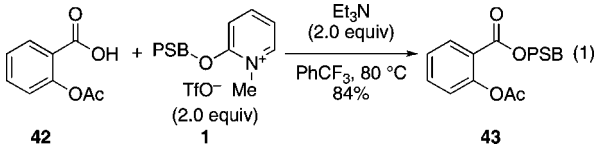

41

[c] Yield in parentheses refers to synthesis of the corresponding benzyl ether using benzyl reagent **6**, as reported in the literature. [d] Isolated yield of pure material judged to be >95% pure by ^{1}H NMR. [e] For this experiment, triflate **1** was prepared and isolated prior to use, and 3.0 equiv of **28** and MgO were employed relative to ROH. [f] Reported synthesis of the benzyl ether, included for the sake of comparison, using benzyl reagent **6** and MgO. [g] Obtained as a mixture of mono- and dibenzylated products. No other benzylation protocols were more effective for this transformation, and the authors ultimately changed their protecting group strategy.

OPT (Table 2, entries 1−5). Analogous benzylation reactions are recounted for comparison (yields given in parentheses), along with a few additional examples from the recent literature (entries 7−9). 3-Phenylpropanol, a simple primary alcohol, was converted into the corresponding PSB ether in 90% by heating it at 80 °C in the presence of 2 equiv of PSB-OPT (formed in situ from PSB-OP and methyl triflate) and magnesium oxide for 24 h (entry 1). PSB protection of secondary alcohols

1-phenylethanol and menthol each proceeded in 88% yield (entries 2 and 3). The Roche ester, which is susceptible to β-elimination of its oxygen functionality, was protected as a PSB ether (**11** → **35**, entry 4) in 71% yield. Additionally, glucose derivative **30** was prepared in 91% yield using a slightly larger excess (3.0 equiv) of preformed PSB-OPT **1** (entry 5).

The experiments described in entries 1−4 mirror previously reported findings on the synthesis of benzyl ethers using reagent **6**, so limitations of the arylmethyl transfer method are alluded to in entries 6 and 9. Recently reported transformations for which benzyl reagent **6** was uniquely successful (entries 7 and 8) are also recounted for reference. We suggest that one can extrapolate from these representative results to predict with confidence the likely reactivity of various alcohols toward PSB-OPT under similar conditions.



1.5. Formation of Akyl PSB Esters Using PSB-OPT. Benzyl reagent **6** gives rise to benzyl esters upon reaction with carboxylic acids.[30] Similar reactivity of oxypyridinium **1** is illustrated by the PSB esterification of acetylsalicylic acid in 84% yield (eq 1.5).

2. Cleavage of PSB Ethers. The cleavage of PSB ethers was described in detail in our preliminary account of this work.[15] The salient features are recounted here. Tamao-type oxidation of the arylsiletane generates an intermediate PHB ether. In the cases of protected phenols, the alkaline oxidation conditions promote expulsion of the free phenols. In cases of protected aliphatic alcohols, the intermediate PHB ethers are sufficiently stable to be isolated prior to cleavage. A separate step is then employed to release the free alcohol from the PHB ether.

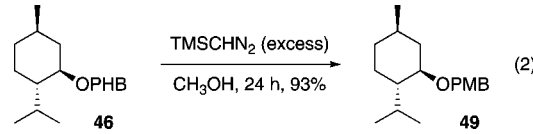
Conditions for cleaving PHB ethers have been reported elsewhere[7,8] and include DDQ, iron trichloride, sodium methoxide, and others. Of these, we focused on the use of DDQ (conditions D) and iron trichloride (conditions E).

The PSB ethers prepared in this study were thus cleaved in one- or two-step protocols (Table 3) that involved standard Tamao conditions (conditions A). Alternatively, Woerpel's method[31] (conditions B) provided PHB ethers faster and in higher yield (compare entries 3 and 6 with 4 and 7), so this protocol is recommended for substrates that can withstand the more forcing conditions. PHB ethers release the original alcohols upon subsequent treatment with either iron trichloride or DDQ. Finally, as seen in entry 5, catalytic hydrogenolysis (conditions C) efficiently removed PSB ethers, as expected by analogy to electronically similar benzyl ethers.

3. Orthogonality and Reactivity Experiments. In order to determine orthogonality with other common protecting groups, a series of competition experiments were performed (Table 4). The PSB ether of 3-phenylpropanol (**19**) was mixed with protected versions of 3-(*p*-anisyl)propanol (**47**) and treated under various protocols designed to cleave one protecting group or the other. The anisyl and phenyl tags are easily distinguishable by NMR spectroscopy, and we assume that their *n*-propyl chains provide essentially equivalent chemical platforms for studying the cleavage of the respective ethers. Entries 1 and 2 describe orthogonal reactivity of PSB and PMB ethers under oxidative conditions. The alkaline nucleophilic peroxide oxidation affects only PSB ether **19**, whereas the charge-transfer oxidation of DDQ occurs preferentially at the electron-rich aromatic ring of the PMB ether. Similarly, MOM ether **47b** withstands the Tamao oxidation but succumbs to aqueous hydrochloric acid, which does not affect the PSB ether (entries 3 and 4). As we showed in our original siletane oxidation study,[10] TBS ethers survived the mild Tamao conditions, and they cleaved under acidic hydrolysis conditions to which the PSB group is inert (entries 5 and 6). Finally, PSB ether **19** was recovered unchanged from a reaction mixture that cleaved the Troc carbonate of **47d** (entry 8), but Troc carbonate **47d** partially hydrolyzed on exposure to alkaline peroxide (entry 7).

Implicit in this study is the assumption that these other protecting groups will equally survive removal of the intermediate PHB ethers. We consider this assumption to be quite sound in general because each of these protecting groups (with the obvious exception of the PMB ether) can withstand conditions that cleave arylmethyl ethers. PMB ethers are known[32] to be stable to $FeCl_3$ under the conditions that we used to cleave PHB ethers, so we chose to look specifically at cleavage of the PHB ether in the presence of the PMB ether using DDQ (Scheme 6). By controlling the reaction stoichiometry and temperature, we quickly obtained evidence to validate our assumption: The PHB ether was removed in 82% yield, whereas the PMB ether (**47a**) was recovered 85% yield.

Although not directly related to this orthogonality study, it is interesting to note that PSB ethers can be converted into PMB ethers (eq 4) under mild conditions that would not impact most other protected or unprotected alcohols. The ability to convert a given protecting group into an orthogonal protecting group during multistep synthesis—as opposed to employing a deprotection/reprotection sequence—adds valuable flexibility to protecting group strategies based on the PSB ether.



4. Synthesis of PSB Reagents. The arylsiletanes employed in this methodology were prepared by coupling 1-chloro-1-methylsiletane (**28**) with the requisite aryl Grignard reagent or, similarly, with the aryl halide under Barbier conditions. The applicability of Barbier conditions illustrates that arylsiletanes are stable to organomagnesium nucleophiles even at elevated temperature (refluxing THF). In contrast, organolithium reagents

(30) Legeay, J.-C.; Langlois, L. Nitrone [2 + 3]-Cycloadditions in Stereocontrolled Synthesis of a Potent Proteasome Inhibitor: (−)-Omuralide. *J. Org. Chem.* **2007**, *72*, 10108–10113. Caubert, V.; Massé, J.; Retailleau, P.; Langlois, N. Stereoselective Formal Synthesis of the Potent Proteasome Inhibitor: Salinosporamide A. *Tetrahedron Lett.* **2007**, *48*, 381–384.

(31) Schmidt, J. P.; Beltrân-Rodil, S.; Cox, R. J.; McAllister, G. D.; Reid, M.; Taylor, R. J. K. The First Synthesis of the Abc-Ring System of 'Upenamide. *Org. Lett.* **2007**, *9*, 4041–4044.

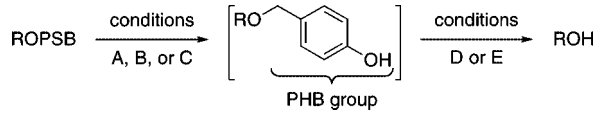
(32) Kayser-Bricker, K. J.; Jordan, P. A.; Miller, S. J. Catalyst-Dependent Syntheses of Phosphatidylinositol-5-Phosphate-Dic8 and Its Enantiomer. *Tetrahedron* **2008**, *64*, 7015–7120.

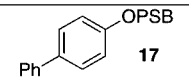
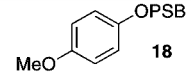
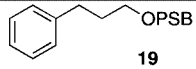
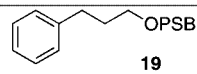
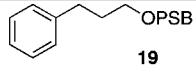
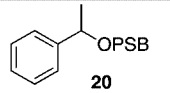
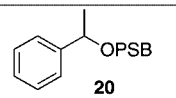
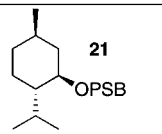
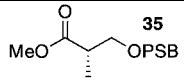
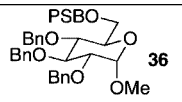
(33) Tummatorn, J.; Albiniak, P. A.; Dudley, G. B. Synthesis of Benzyl Esters Using 2-Benzyloxy-1-Methylpyridinium Triflate. *J. Org. Chem.* **2007**, *72*, 8962–8964.

(34) Smitrovich, J. H.; Woerpel, K. A. Oxidation of Sterically Hindered Alkoxysilanes and Phenylsilanes under Basic Conditions. *J. Org. Chem.* **1996**, *61*, 6044–6046.

(35) Sharma, G. V. M.; Reddy, C. G.; Krishna, P. R. Zirconium(IV) Chloride Catalyzed New and Efficient Protocol for the Selective Cleavage of *P*-Methoxybenzyl Ethers. *J. Org. Chem.* **2003**, *68*, 4574–4575.

TABLE 3. One- and Two-Step Cleavage of PSB Ethers



entry	PSB ether	conditions[a]	PHB ether (yield)	Alcohol (yield)
1	 **17**	A	—	**11** (89%)
2	 **18**	A	—	**12** (86%)
3	 **19**	A; D	**44** (87%)	**13** (90%)
4	 **19**	B; E	**44** (99%)	**13** (99%)
5	 **19**	C	—	**13** (88%)
6	 **20**	A; E	**45** (84%)	**14** (97%)
7	 **20**	B; E	**45** (99%)	**14** (97%)
8	 **21**	A; E	**46** (85%)	**15** (94%)
9	 **35**	A; D	—	**16** (83%)[b]
10	 **36**	A; D	—	**30** (72%)[b]

[a] See Supporting Information for details. Conditions A: 30% aqueous H_2O_2, KF, K_2CO_3, THF/MeOH, 50 °C. Conditions B: *t*-BuOOH, TBAF, DMF, 70 °C. Conditions C: H_2, 10% Pd/C, EtOH. Conditions D: DDQ, CH_2Cl_2; Conditions E: $FeCl_3$, CH_2Cl_2. [b] Overall yield for two steps.

are not suitable for the preparation of arylsiletanes because even substoichiometric amounts of most organolithium reagents promote anionic ring-opening polymerization of organosiletanes.[17]

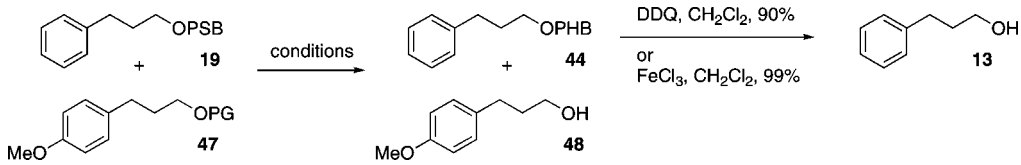
PSB-OPT **1**, like other oxypyridinium triflate reagents prepared in these laboratories, arises by *N*-methylation of 2-PSBO-pyridine (**29**). However, the standard method for preparing 2-pyridyl ethers—potassium hydroxide-promoted nucleophilic aromatic substitution of 2-chloropyridine—is not compatible with the siletane ring. Therefore, alternative synthetic protocols were developed (vide infra).

4.1. Synthesis of PSB-Br (10) via 8 and 9. A straightforward series of reactions sequentially provided PSB dimethyl acetal **8**, PSB-OH **9**, and PSB-Br **10**, as described previously (Scheme 7).[29] *para*-Bromobenzaldehyde dimethyl acetal (**50**) undergoes Barbier coupling with **28** to furnish *para*-siletanylbenzaldehyde dimethyl acetal (**8**) in 86−91% yield. Hydrolysis of **8** and reduction with DIBAL provides PSB-OH **9** in 87−95% yield over two steps. Finally, PSB-Br is available in 95% yield by treating PSB-OH with Appel's conditions (Ph_3P, CBr_4, CH_2Cl_2).[36]

4.2. Synthesis of PSB-OPT (1) from *para*-Iodobenzyl Alcohol. The standard method employed in these laboratories

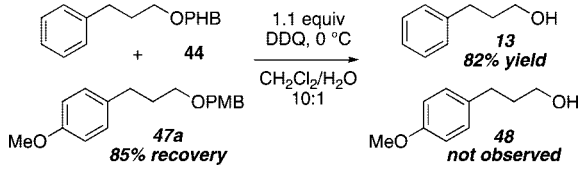
(36) Appel, R. Tertiary Phosphane/Tetrachloromethane, A Versatile Reagent for Chlorination, Dehydration, And P−N Linkage. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 801–811.

TABLE 4. Orthogonality in the Cleavage of PSB Ethers with Other Common Protecting Groups

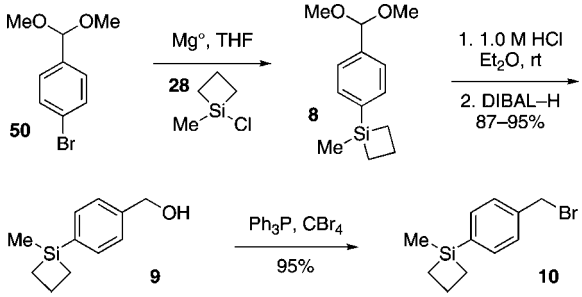


entry	PG (**47**)	conditions	recovered PSB **19** (%)	recovered PG **47** (%)	yield of PHB **44** (%)	yield of **48** (%)
1	PMB (**47a**)	H_2O_2, KF	—	96 (**47a**)	82	—
2	PMB (**47a**)	DDQ	94	—	—	96
3	MOM (**47b**)	H_2O_2, KF	—	90 (**47b**)	85	—
4	MOM (**47b**)	6N HCl	85	—	—	86
5	TBS (**47c**)	H_2O_2, KF	—	88 (**47c**)	72	—
6	TBS (**47c**)	AcOH, H_2O	90	—	—	98
7	Troc (**47d**)	H_2O_2, KF	—		N.D.	N.D.
8	Troc (**47d**)	Zn, AcOH	92	—	—	90

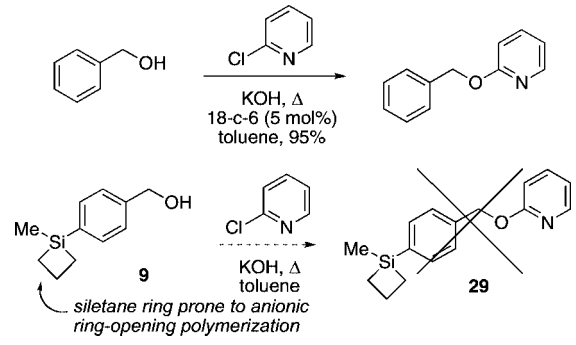
SCHEME 6. DDQ Oxidation of PHB Ether 44 in the Presence of a PMB Ether



SCHEME 7. Synthesis of PSB Reagents 8−10



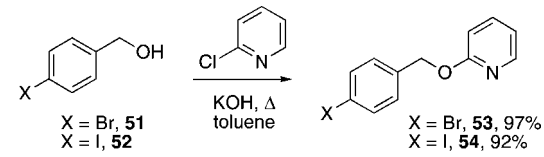
SCHEME 8. Nucleophilic Substitution of 2-Chloropyridine



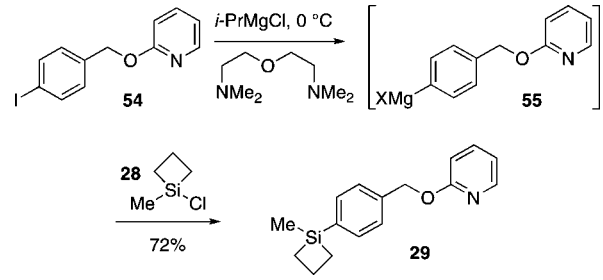
for preparing 2-pyridyl ethers is to heat 2-chloropyridine with the corresponding alcohol in the presence of potassium hydroxide (Scheme 8). Siletanes do not withstand such conditions, so for the synthesis of 2-PSBO-pyridine **29** the siletane moiety must be introduced last.

Thus, nucleophilic aromatic substitution of 2-chloropyridine with *para*-bromobenzyl alcohol (**51**) and *para*-iodobenzyl alcohol (**52**) was employed to provide aryl bromide **53** (97% yield) and aryl iodide **54** (92% yield), respectively (Scheme 9). Inclusion of 18-crown-6 in the reaction mixture increases the efficiency of this coupling process,[20,22,27] but this additive can be excluded without suffering a significant drop in the reaction

SCHEME 9. Preparation of *para*-Halogenated 2-Benzyloxypyridines



SCHEME 10. Synthesis of PSB-OP 29 from Aryl Iodide 54

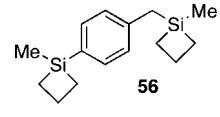


yield if the potassium hydroxide pellets are thoroughly ground with a mortar and pestle prior to use. Aryl halides **53** and **54** were converted to the corresponding Grignard reagents for trapping with chlorosiletane **28**.

Initial attempts to generate aryl Grignard reagent **55** were unsuccessful using either aryl bromide **53** or iodide **54**,[37] but magnesium-iodide exchange[38] furnished **55** (Scheme 10). Subsequent addition of chlorosiletane **28** afforded PSBO-pyridine **29** in 72% yield.

4.3. Synthesis of PSB-OPT from *para*-Bromobenzyl Alcohol. A weakness in the synthesis of **1**, as outlined in Scheme 10, is that *para*-iodobenzyl alcohol is prohibitively expensive[39] compared to *para*-bromobenzyl alcohol.[40,41] Although standard methods for preparing Grignard reagents[42] failed for this

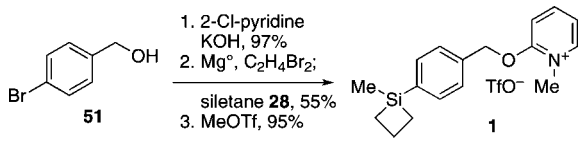
(37) Multiple attempts to prepare Grignard **55** using activated magnesium turnings under standard conditions were unsuccessful. Insertion does not occur at room temperature, and it appears as though magnesium insertion into the benzylic carbon-oxygen bond occurs upon prolonged heating, based on recovery of bis-siletane **56** from the crude reaction mixture.



(38) Wang, X.-j.; Xu, Y.; Zhang, L.; Krishnamurthy, D.; Senanayake, C. H. Mild Iodine-Magnesium Exchange of Iodoaromatics Bearing a Pyrimidine Ring with Isopropylmagnesium Chloride. *Org. Lett.* **2006**, *8*, 3141–3144.

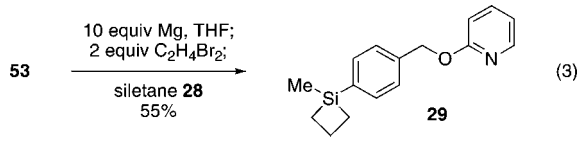
(39) Sigma-Aldrich list pricing: Catalog number: 523496−5g; List price: $104.00 ($4.87/mmol); see http://www.sigmaaldrich.com.

SCHEME 11. Preferred Synthesis of PSB-OPT 1



substrate (**53** → **55**),[37] we identified a new protocol for activating magnesium turnings that enabled us to generate **55** from aryl bromide **53**.

The reaction protocol that provided reproducible amounts of arylsiletane **29** from **53** involved premixing aryl bromide **53** with a large excess (10 equiv) of unactivated magnesium turnings in THF[43] and then injecting dibromoethane (2 equiv) rapidly by syringe. Bubbles of gas emanated from the surface of the magnesium metal for approximately 30 min, after which time the formation of Grignard **55** was complete. Addition of chlorosiletane **28** then provided arylsiletane **29** in 55% yield (eq 3).



(3)

This protocol may be successful because of localized heating that occurs selectively at the magnesium surface promoting Grignard formation, but not bimolecular reactions between combinations of aryl species (**53** and **55**). The localized heat then dissipates to the solvent and eventually to external cooling elements (water bath and reflux condenser).[44] Such a procedure is likely scale-dependent and would have to be monitored and optimized carefully prior to preparing larger quantities of material, but in our hands it provided **29** reproducibly on a ca. 1 mmol scale.[45]

5. Generation and Recrystallization of PSB-OPT. Pyridyl ether **29** was dissolved in trifluorotoluene and treated with methyl triflate. After 30 min, the volatiles were removed in vacuo to leave crude PSB-OPT **1** as an oily residue. The residue was dissolved in trifluorotoluene and left standing in the freezer at −20 °C to provide crystalline **1** (mp 65 °C) in 95% yield (Scheme 11). Alternatively, as outlined above in Table 2, the activation of PSB-OP **29** with methyl triflate can be performed in situ, thus obviating the need to isolate PSB-OPT **1**.

5. Conclusion

Electronically, PSB ethers are similar to benzyl ethers. What differentiates PSB ethers from benzyl ethers is the siletane ring. Therefore, a thorough understanding of siletane reactivity will guide optimal incorporation of the PSB group in protecting group strategies for multistep synthesis.

Based on our recent review of the siletane literature[12] and studies from the Denmark,[46] Oshima,[47] and other[17,48] research laboratories as well as our own,[10] we have outlined a chart of siletane reactivity (Table 5). This table is an abridged version of (and follows the same layout as) the reactivity profile chart published in *Greene's Protective Groups in Organic Synthesis*.[1] The entries for benzyl and TBS are reproduced for comparison.

In conclusion, we provide full details of the development of the *para*-siletanylbenzyl (PSB) ether as a new protecting group for alcohols. PSB ethers are conveniently prepared using the "mix-and-heat" protocol that we reported previously for the synthesis of benzyl and *para*-halobenzyl ethers. PSB ethers are electronically similar to benzyl ethers, but cleavage occurs under conditions that are unique among benzyl ether derivatives. The methodology described herein broadens the utility of arylmethyl ethers as protecting groups for alcohols.

Experimental Section

2-(4-(1-Methyl-1-siletanyl)-benzyloxy)-pyridine (PSB-OP, 29). A stirred solution of bis[2-(*N*,*N*-dimethylamino)ethyl] ether (2.66 mL, 14 mmol) in 15 mL of THF under nitrogen was cooled at 0 °C, and *i*-PrMgCl (1.0 M, 14 mL, 14 mmol) was added dropwise. After 30 min, iodide **52** (1.22 g, 3.93 mmol) in 5 mL of THF was added over 1.5 h at 0 °C. The solution was allowed to warm to rt over 1 h. After recooling the mixture to 0 °C, 1-chloro-1-methylsiletane (**28**, 1.7 mL, 14 mmol) was added, the reaction mixture was warmed to room temperature and stirred for an additional 4 h. The reaction mixture was diluted with 20 mL of diethyl ether, extracted with 5 mL of H_2O, and washed with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. 2-Benzyloxypyridine (a byproduct of this reaction) was removed by bulb-to-bulb distillation at reduced pressure (0.1 mmHg, bath temp 100 °C), and the residual oil was further purified using silica gel chromatography (elution with 10% EtOAc in hexane) to give 760 mg (72%) of **29** as a white solid: mp 30 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.55 (s, 3H), 1.11−1.34 (m, 4H), 2.18 (m, 2H), 5.39 (s, 2H), 6.81 (d, 1H, J = 8.36 Hz), 6.88 (m, 2H), 7.49 (apparent d, 2H, J = 7.87 Hz), 7.65 (apparent d, 2H, J = 7.9 Hz), δ 8.18 (d-d, 1H, J = 5.03, 1.36 Hz). ^{13}C NMR (300 MHz, $CDCl_3$) δ −1.71, 14.3, 18.2, 67.3, 111.2, 116.8, 127.3, 133.6, 138.0, 138.5, 138.6, 146.7, 163. HRMS (ESI+) calcd for $C_{16}H_{21}NOSi^+$ 270.1314, found 270.1317.

1-Phenylethanol, PSB Ether (20): Typical Procedure for the Synthesis of Alkyl PSB Ethers. An ice-cold mixture of PSB-OP **29** (211 mg, 0.78 mmol), $PhCF_3$ (2 mL), MgO (32 mg, 0.6 mmol, dried in an oven), and alcohol **13** (48 mg, 0.39 mmol) was treated dropwise with methyl triflate (89 μL, 0.6 mmol). After 30 min, the reaction mixture was warmed to room temperature and then stirred at 80−85 °C for 12 h until TLC analysis showed

TABLE 5. Reactivity of PSB, Bn, and TBS Ethers under Various Reaction Conditions[a]

conditions	Bn	PSB	TBS	conditions	Bn	PSB	TBS	conditions	Bn	PSB	TBS
pH 1, H_2O	*L*	*L*	H	Zn/AcOH	*L*	*L*	*L*	$AlCl_3$, rt	*H*	H	*M*
NaOMe	*L*	*R*	*L*	Na/NH_3	*H*	H	*L*	Br_2	M	M	L
R_3N	*L*	*L*	*L*	$LiAlH_4$	*L*	*R*	*L*	H_2O_2, pH 10	*L*	*R*[c]	*L*
RLi	*L*	*R*	*L*	DIBAL-H	*L*	*L*	*L*	Quinone	*L*	*L*	*L*
RMgX	*L*	*L*	*L*	$NaBH_4$	*L*	*R*	*L*	150 °C	*L*	*L*	L
H_2/Pd	*H*	*H*	H[b]	$Zn(BH_4)_2$	*L*	L	*L*	N_2CHCO_2R, Cu	L	*R*	L

[a] Key: *L*: Low reactivity; protecting group is stable under the reaction conditions. *M*: Marginal reactivity; depends on exact reaction parameters. *H*: Protecting group is removed. *R*: Protecting group reacts, but the original functionality is not necessarily restored. Letters in italics are based on direct experimental evidence. Letters not in italics are based on circumstantial evidence. [b] In reference 1, TBS ethers are estimated to be highly reactive toward H_2/Pd. We transcribed this estimation to remain true to the source but consider TBS ethers to be stable to these conditions. [c] These conditions, along with potassium fluoride, are recommended for converting PSB ethers into PHB ethers for ensuing cleavage.

consumption of alcohol **13**. The reaction mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated under vacuum and purified on silica gel to yield 140 mg of a light yellow oil, which based on ^{1}H NMR analysis comprises 102 mg (88%) of **29** and 38 mg $(PSB)_2O$ of (**41**). Characterization data for **29**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.56 (s, 3H), 1.14−1.31 (m, 4H), 1.48 (d, 3H, J = 6.6 Hz), 4.52 (q, 1H, J = 6.4 Hz), 4.48 (d, 1 H, J = 12.0 Hz), 4.32 (d, 1H, J = 12.0 Hz), 7.30−7.42 (m, 7H), 7.62 (apparent d, 2H, J = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.5, 14.5, 18.5, 24.4, 70.4, 126.6, 127.4, 127.7, 127.9, 128.7, 133.8, 138.0, 140.2, 143.9. IR (neat) 2971, 2928, 2864, 1451. HRMS (ESI+) calcd for $C_{19}H_{24}OSi^+$ 296.1596, found 296.1601.

Standard Procedure for the Oxidation of Alkyl PSB Ethers (Conditions A).[10,15] $KF\cdot 2H_2O$ (2.5 equiv) and K_2CO_3 (2.5 equiv) were added to a 0.12 M solution of PSB ether (1 equiv) in THF/CH_3OH (1:1). The resulting mixture was cooled in an ice bath, and H_2O_2 (30% in H_2O, 25 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min and at 50 °C for 2 h. The reaction mixture then was extracted with CH_2Cl_2. The combined organic phases were sequentially washed with a 1.0 M aqueous $Na_2S_2O_3$ and brine. The combined aqueous phases were extracted with CH_2Cl_2 (3x). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification by flash column chromatography on silica gel (EtOAc/hexanes) provided the PHB ether. See Table 3 for yields, and see Supporting Information for characterization data.

Standard Procedure for the Cleavage of Alkyl PHB Ethers (Conditions E).[8] A 0.35 M solution of PHB ether (1 equiv) in Et_2O was added to a 0.2 M solution of $FeCl_3$ (1.5 equiv) in CH_2Cl_2 dropwise over 5 min under argon. The reaction was stirred from 0.5−3 h and then extracted with 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by column chromatography on silica gel (EtOAc/hexanes) gave the corresponding alcohols. Spectroscopic data matched with the commercially available samples. See Table 3 for yields.

Menthol, PMB Ether (49): Conversion of a PHB Ether into a PMB Ether. PHB-menthol **46** (39 mg, 0.14 mmol) was dissolved in 0.3 mL of methanol at 0 °C. $TMSCHN_2$ (2 M in Et_2O, 0.34 mL, 0.68 mmol) was added to the solution, which was then stirred at room temperature for 24 h. After the solvent was evaporated under reduced pressure, the residue was purified by column chromatography on silica gel (5% EtOAc/hexanes) to give 38 mg (93%) of PMB-menthol **49**.

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Note Added in Proof. Additional data recently appeared regarding the utility of oxypyridinium reagent **6** for addressing difficulties associated with the synthesis of benzyl ethers.[49] By extension, such information is relevant to making the appropriate choice of reagent for making PSB ethers.

Supporting Information Available: Detailed experimental procedures, characterization data, and 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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(40) Sigma-Aldrich list pricing: Catalog number: 187054−50g; List price: $151.50 ($0.57/mmol); see http://www.sigmaaldrich.com.

(41) Note that the Sigma-Aldrich list price of siletane **28** (catalog number: 411582−5g, list price: $145.50, $3.54/mmol) is comparable to that of TBS-OTf (catalog number: 226149−5g, list price: $52.60, $2.78/mmol); see http://www.sigmaaldrich.com.

(42) Garst, J. F.; Easton Lawrence, K.; Batlaw, R.; Boone, J. R.; Ungváry, F. Magnesium Bromide in Grignard Reagent Formation. *Inorg. Chim. Acta* **1994**, *222*, 365–375. Jing, L.; Xiangjun, L.; Hua, L.; Qinglan, X.; Zhun, L.; Xilin, H. a New Way to Prepare Grignard Reagent from Rx (X=Cl, Br) Using the Mixture of $Brch_2Ch_2Br$ and I_2 As an Initiator. *Synth. Commun.* **1999**, *29*, 1037–1039. Bogdanovic, B.; Schwickardi, M. Transition Metal Catalyzed Preparation of Grignard Compounds. *Angew. Chem., Int. Ed.* **2000**, *39*, 4610–4612.

(43) Grignard formation does not initiate spontaneously even when using magnesium turnings that were preactivated with iodine and/or dibromoethane.

(44) A reflux condenser was included in the experimental setup as a precaution; solvent reflux was never definitively observed in this experiment.

(45) The authors thank Ms. Cecelia C. O'Leary, an undergraduate research student in the Dudley Lab, for providing independent verification of this new and unusual procedure for making Grignard reagents. Further exploration of this protocol is underway and will be reported in due course.

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