

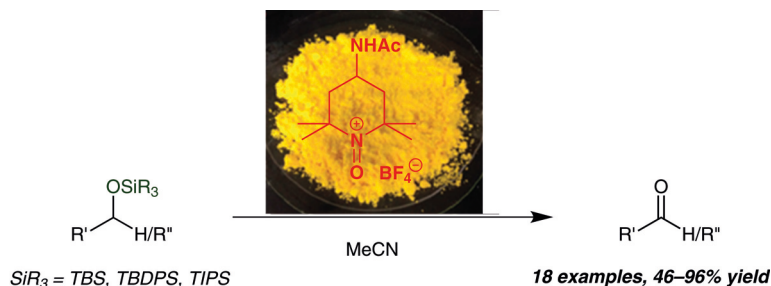
Oxidative Cleavage of Silyl Ethers by an Oxoammonium Salt

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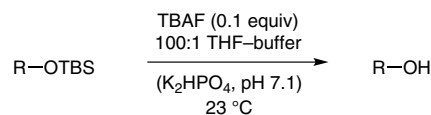
Abstract A method for the oxidative cleavage of silyl ethers to their corresponding carbonyl species mediated by an oxoammonium salt is described. The resulting aldehydes and ketones are obtained under mild reaction conditions with no observed overoxidation. For robust substrates, heating to reflux temperatures significantly reduces the reaction time.

Key words protecting groups, silicon, oxidation, oxoammonium salt, aldehydes, ketones

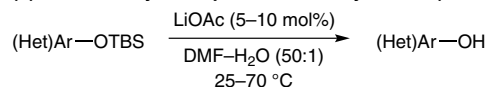
Silyl ethers are ubiquitous protecting groups in organic synthesis.¹ They are easily installed, and the relative stability of the resulting masked alcohols is a function of the structure of the silyl moiety. Depending on the silyl ether, these Si–O linkages are stable to a wide range of reaction conditions and thus the underlying hydroxyl group can be revealed when required. Of the silyl protecting groups commonly utilized, the trimethylsilyl (TMS) is certainly the most commonly seen but is also the most labile. Less labile groups including the *tert*-butyldimethylsilyl (TBS), triisopropylsilyl (TIPS), and *tert*-butyldiphenylsilyl (TBDPS) which are more utilized in synthesis. Due to their popularity, numerous deprotection strategies have been developed for these less labile silyl ethers (Scheme 1),^{2–4} with the most popular being fluoride-mediated desilylation, capitalizing on the known fluorophilicity of silicon.

In some cases, direct cleavage of silyl ethers to their corresponding carbonyl species may be desirable. In such cases, an oxidative cleavage protocol would be advantageous because it would reduce the required number of chemical steps, thus likely improving overall yield. Oxidative cleavage of silyl ethers has been reported previously.^{5–7} However, the

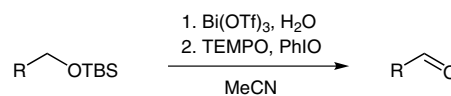
(a) Fluoride-mediated cleavage (78–96%)³



(b) LiOAc-catalyzed deprotection of silyl ethers (87–99%)⁴



(c) Two-step one-pot oxidative cleavage via TEMPO (51–85% yield)⁷

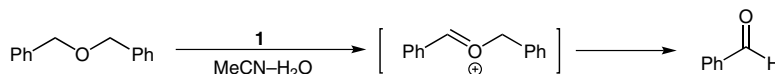


Scheme 1 Alternative silyl ether deprotection strategies

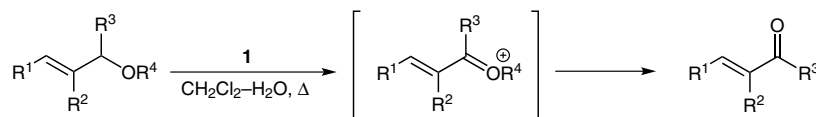
majority of the examples reported involve scission of the TMS–O bond and, in spite of relatively labile nature of this bond, harsh reaction conditions or expensive/toxic transition-metal catalysts were still required.^{5,6} This likely is not a consequence of the cleavage but rather of the subsequent oxidation, a task which still can prove difficult even for alcohol oxidation alone.

Recently, Vatèle reported a method for cleaving TBS ethers using catalytic amounts of TEMPO with a metal triflate co-catalyst in the presence of a Lewis acid.⁷ Based on this report and our recent synthesis of nitriles from aldehydes,⁸ we envisioned that 4-NHAc-TEMPO⁺BF₄[−] (Bobbitt's salt, **1**) could be used to facilitate oxidative desilylation. That is, this species can serve as an oxidant as well as a fluoride source and potentially a Lewis acid source (both of which can mediate in situ deprotection) and thus would be ideally suited for the dual task of oxidation and cleavage of

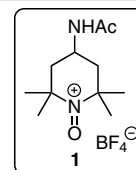
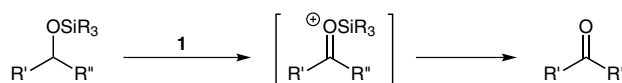
(a) Cleavage of benzyl ethers



(b) Cleavage of allyl ethers



(c) Envisioned cleavage of silyl ethers (this work)

Scheme 2 Oxidative cleavage of ethers using oxoammonium salt **1**

the Si–O bond. Additionally, **1** is a recyclable oxidant that can be synthesized at relatively low cost.⁹ The strategy of oxidative functionalisation using **1** has previously been employed successfully by Garcia-Mancheño,¹⁰ Bailey,¹¹ and us.¹² Representative examples of this concept are the cleavage of benzyl and allyl ethers via treatment with **1** (Scheme 2, a and b).^{11,13} These reactions have potential value as mild deprotection strategies for alcohols. With these encouraging precedents in mind, we explored the feasibility of this strategy for oxidative desilylation. We report our results on the cleavage of TBS, TIPS, and TBDPS ethers here.

Initially, 1-(*tert*-butyldimethylsilyloxy)-3-phenylpropane **2a** was selected as a representative silyl ether for determining the propensity of **1** to engage in silyl ether cleavage. Modeling after other previously reported methods for oxoammonium salt mediated oxidative cleavage, we first performed the reaction at room temperature in dichloromethane as the solvent using 2.5 equivalents of **1** and 2.5 equivalents of 2,6-lutidine (**4**) as an additive. Under these conditions, no cleavage to **3a** was observed (Table 1, entry 1). The same was true when we performed the reaction using 1 equivalent of **1** at 40 °C in the absence of the additive (entry 2). However, by simply changing the solvent to CH₂Cl₂–MeCN (8:2), a 60% conversion into **3a** was observed after heating at 40 °C for 72 hours (entry 3). Using acetonitrile as the sole solvent proved beneficial, improving the conversion to 81% under otherwise identical reaction conditions (entry 4). Both these improvements in conversion are likely a consequence of a combination of factors: increased oxidant solubility, stabilization of the polar transition state required for oxidation, and improve cation/anion separation. Performing the reaction at room temperature proved significantly less effective, even when using an increased loading of **1** (entries 5 and 6). While after extended periods the reaction would reach completion, we hoped to

substantially reduce the reaction time by heating to 40 °C. For this reason, and because no overoxidation was observed using our revised conditions, reactions were allowed to run for 72 hours in order to obtain the highest isolated yields. Increasing the reaction temperature had a marked effect on increasing reaction rate, with 88% conversion observed after four hours at reflux (entry 7). However, in the interest of pursuing a methodology that would be suitable for potentially thermally delicate substrates, we opted to move forward with our milder, albeit longer, reaction conditions.

Table 1 Optimization of Reaction Conditions for the Oxidative Cleavage of TBS Ethers^a

Entry	Solvent	Temp	Time (h)	1a (equiv)	3a (%) ^b
1 ^c	CH ₂ Cl ₂	r.t.	72	2.5	–
2	CH ₂ Cl ₂	40 °C	72	1.0	–
3 ^d	CH ₂ Cl ₂ –MeCN (8:2)	40 °C	72	1.0	60
4	MeCN	40 °C	72	1.0	81
5	MeCN	r.t.	72	1.0	38
6	MeCN	r.t.	72	2.1	33
7	MeCN	reflux	4	1.0	88

^a Conditions unless otherwise noted: **2a** (1.0 mmol, 1 equiv), solvent (5.0 mL, 0.2 M in **2a**). Reaction progress monitored by ¹H NMR spectroscopy for consumption of starting material and formation of aldehyde peak.

^b Conversion determined by ¹H NMR spectroscopy.

^c Using 2.5 equiv 2,6 lutidine as an additive.

^d Solvent ratio by volume.

We next explored the scope of the reaction in the context of various TBS ethers. The results are shown in Table 2.¹⁴ Silyl ethers bearing α -aryl and α -heteroaryl substrates (entries 3–9) were very amenable to oxidative desilylation. The reaction could readily be extended to allylic (entries 10–12) and propargylic (entry 13) systems in addition to the initial aliphatic example (entry 1). In the case of the aliphatic substrate, while the aldehyde **3a** was the dominant product, other side reactions occurred. These undesired pathways were oxidative esterification, thus furnishing its dimer, and what appeared to be oxidative dehydrogenation

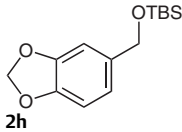
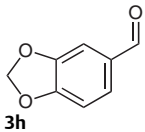
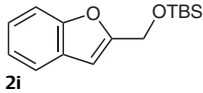
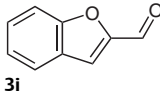
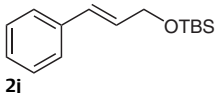
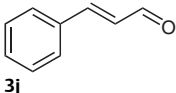
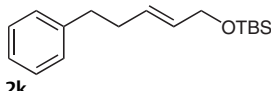
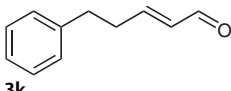
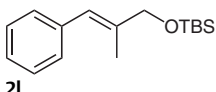
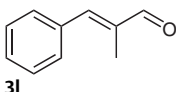
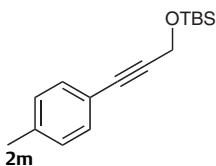
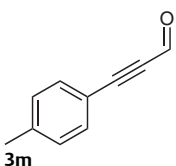
yielding cinnamaldehyde. This mixture of products, along with the silyl fluoride byproduct, was not highly amenable to separation thus explaining the low isolated yield in this case. This unexpected difficulty in isolation was not encountered with the other substrates. In general, cleavage of primary ethers proceeded more effectively than that of secondary ethers (cf. Table 2, entries 4 and 6). Finally, as predicted, cleavage of the TBS ethers was likely a result of fluoride-mediated desilylation as the major byproduct detected was TBS-F.

Table 2 Substrate Scope for the Oxidative Cleavage of TBS Ethers^a

Reaction scheme: $\text{R}-\text{CH}(\text{OTBS})-\text{R}' \xrightarrow[\text{MeCN, 40 }^\circ\text{C, 72 h}]{1} \text{R}-\text{C}(=\text{O})-\text{R}'$

Entry	Silyl ether	Product	Yield (%) ^b
1			81 ^c
2			46
3			59
4			75
5			81
6			64
7			81

Table 2 (continued)

Entry	Silyl ether	Product	Yield (%) ^b
8			96
9			81
10			61
11			60
12			44
13			81

^a Conditions: silyl ether (1.0 equiv), **1** (1.0 equiv), MeCN (0.2 M in silyl ether), 40 °C, 72 h.

^b Isolated yields unless otherwise noted.

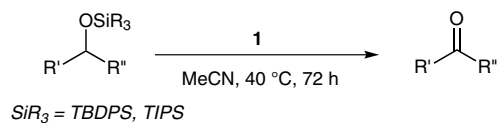
^c Conversion by NMR spectroscopy.

Representative TIPS and TBDPS silyl ethers were also assessed as substrates. As shown in Table 3, the results match the trends observed for the corresponding TBS substrates. However, while TBS ether cleavage resulted in aldehyde or ketone formation and a silyl fluoride byproduct, TIPS and TBDPS ethers gave the corresponding silanols (R₃SiOH) as the major reaction byproduct. These silanols proved surprisingly difficult to separate from the desired aldehyde product. However, the oxidative deprotection itself is a viable strategy should the target substrate be amenable to isolation from a silanol byproduct.

Based on the byproducts obtained and the observed reactions trends, we devised a plausible mechanism for the reaction (Scheme 3). In this mechanism, we posit that the first step is oxidation via the known hydride transfer pathway to the hydridophilic oxygen atom of the oxoammonium cation.^{12c} The fate of the resulting silylated oxonium ion depends on the identity of the silyl group. The unstabilized (and hence more reactive), sterically unimpeded TBS group is subject to rapid fluoride-mediated desilylation via fluoride transfer from BF₄⁻. Using more stabilizing or sterically

hindered silyl groups favors ionization followed by capture by residual water in the solvent or in the oxidant. While we cannot completely rule out a mechanism involving initial deprotection via the BF₄⁻ anion followed by oxidation to the carbonyl, the observed silanol formation in reactions involving TIPS or TBDPS protecting groups suggests the sequence proceeds in the order shown in Scheme 1. To elude further mechanistic insight and the role of the tetrafluoroborate anion, we performed a test oxidation of **2c** using an analogous oxoammonium salt to **1** possessing a perchlorate (ClO₄⁻) counterion. Oxidative deprotection was still observed. In the absence of [BF₄]⁻, residual water serves as the nucleophilic agent for capturing the electrophilic silicon species that results upon oxidation. A mechanism involving formal hydride abstraction as the initial step also concurs with our previous investigations into chemistry of **1** in the presence of silylated species.⁸

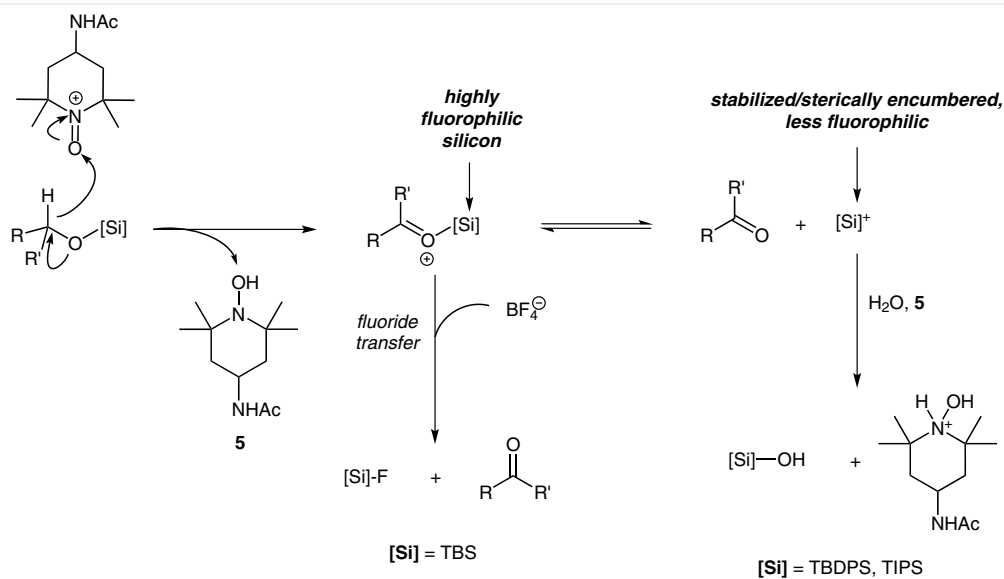
In summary, we present a strategy for one-step oxidative deprotection of silyl ethers using a recyclable oxoammonium salt as a stoichiometric oxidant and desilylating agent. A range of silyl ethers (TBS, TBDPS, TIPS) were

Table 3 Substrate Scope for the Oxidative Cleavage of TIPS and TBDPS Ethers^a

Entry	Silyl ether	Product	Conversion (%) ^b
1			74
2			39
3			59
4			47
5			60
6			70

^a Conditions: silyl ether (1.0 equiv), **1** (1.0 equiv), MeCN (0.2 M), 40 °C, 72 h.

^b Conversion determined by ¹H NMR spectroscopy.



amendable to oxidative cleavage in this fashion and both ketones and aldehydes could be prepared. Likewise, the reaction tolerated a number of functional groups and oxidation could be accomplished under relatively mild conditions.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1561498>.

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- (14) **Representative Procedure**
To a 100 mL round-bottom flask equipped with a stir bar was added the silyl ether **2c** (1.95 g, 7.0 mmol, 1 equiv) and the oxoammonium salt **1** (2.10 g, 7.0 mmol, 1 equiv), followed by MeCN (35 mL, 0.2 M in the silyl ether). The solution was heated to 40 °C while stirring for 72 h. After this time, the crude mixture was diluted with Et₂O (200 mL) and deionized water (200 mL). The phases were separated, and the aqueous layer was extracted with Et₂O (3 × 50 mL). The combined organic layers were washed with deionized water (ca. 100 mL), brine (ca. 100 mL), and dried with Na₂SO₄. The solvent was removed in vacuo by rotary evaporation, and the resulting crude mixture was adhered to silica gel using 1.5 wt equiv of SiO₂ (relative to the theoretical yield). The dry-packed material was gently added atop a silica gel plug. The plug was washed with an excess of hexanes (ca. 5 column volumes). The desired product was eluted off the plug via a 95:5 by volume mixture of hexanes–EtOAc (3–4 column volumes). The solvent was removed in vacuo by rotary evaporation affording the pure aldehyde **3c** (0.67 g, 59%) as a clear yellow liquid. ¹H NMR (400 MHz, CDCl₃): δ = 9.98 (s, 1 H), 7.88–7.77 (m, 2 H), 7.61–7.48 (m, 2 H), 1.36 (s, 9 H) ppm. ¹³C NMR (100 MHz, CDCl₃): δ = 192.05 (CH), 158.53 (C), 134.30 (C), 129.84 (CH), 126.13 (CH), 35.49 (C), 31.23 (CH₃) ppm.