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A Mild and Chemoselective Method for the Deprotection of Tertbutyldimethylsilyl (Tbdms) Ethers Using Iron(III) Tosylate as a Catalyst

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ABSTRACT

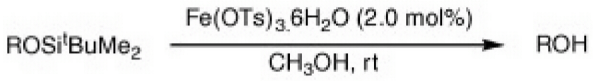
The most common method for the deprotection ofTBDMS ethers utilizes stoichiometric amounts of tetrabutylammonium fluoride, n-Bu4N+F (TBAF), which is highly corrosive and toxic. We have developed a mild and chemoselective method for the deprotection ofTBDMS, TES, and TIPS ethers using iron(III) tosylate as a catalyst. Phenolic TBDMS ethers, TBDPS ethers and the BOC group are not affected under these conditions. Iron(III) tosylate is an inexpensive, commercially available, and non-corrosive reagent.

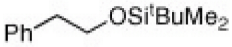
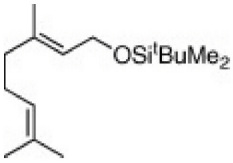
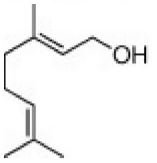
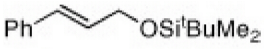
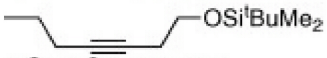
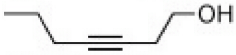
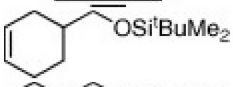
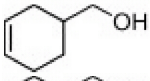
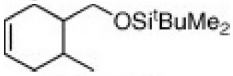
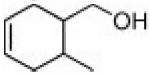
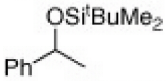
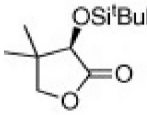
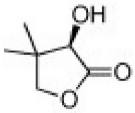
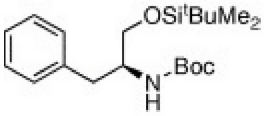
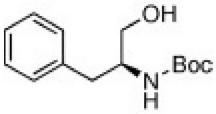
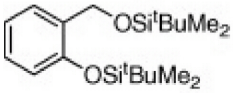
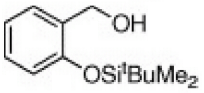
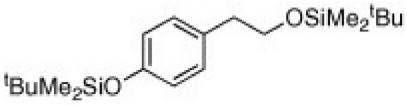
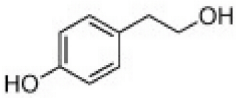
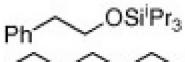
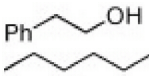
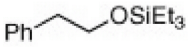
The tert-butyldimethylsilyl (TBDMS) protecting group, introduced by Corey and coworkers,[l] is one of the most common silylprotecting groups for alcohols and phenols. The TBDMS group owes its popularity to several facts such as ease of introduction, stability to a variety of reagents, and ease of selective deprotection. The most common methods for the deprotection of the TBDMS group utilize reagents containing fluoride ion with n-$Bu_4N^+F^-$ often being the reagent of choice.[1] However, n-$Bu_4N^+F^-$ is very basic, a property that can lead to side reactions with base-sensitive substrates[2] In addition, n-$Bu_4N^+F^-$ is extremely corrosive to the mucosa and the upper respiratory tract[3], a problem compounded by the fact that n-BU_4N^+F is required in stoichiometric amounts. Several alternative methods have also been developed for the deprotection of TBDMS ethers. These include Selectfluor (10.0 mol %),[4] LiOAc (20.0 mol %),[5] pyridinium tribromide (Py·Br_3) (5.0-100.0 mol %),[6] $ZrCl_4$ (20.0 mol %),[7] tris(4-bromophenyl)aminium hexachloroantimonate ($TBPA^+$ ·$SbCl_6$ -) (5.0-10.0 mol %),[8] sulfated $Sn0_2$ (1.0% by weight),[9] silica supported $NaHS0_4$, lOTiCl4-Lewis base complexes (1.2 equiv),[11] sulfonic acid-functionalized nanoporous silica,[12] phosphomolybdic acid,[13] NiCb in 1,2-ethanediol (20.0 mol %),[14] N-iodosuccinimide (5.0

mol %),[15] BiOCl04 (50.0-200.0 mol %),[16] SbCl5 (10.0 mol %),[17] $ZnBr_2$ (5.0 equiv),[18] $Ce(OTf)_4$ (10.0 mol %),[19] ceric ammonium nitrate (10.0 mol %),[20] tetrabutylammonium tribromide (10.0 mol %),[21] TMSOTf (2.0 equiv),[22] $Zn(BF_4h$ (4.0 equiv),[23] and DMSO-H_20 (excess DMSO)[24] Methods for the de protection of TBDMS ethers under acidic conditions have also been developed. These include aqueous HF,[25] CF_3COOH/H_20 (9:1),[26] and CH_3COOH in aqueous THF (13:7:3).[27] As can be seen from these examples, most of these reagents are not highly catalytic. Many of these reagents are quite corrosive (N-iodosuccinimide, $ZrCl_4$, $ZnBr_2$> and $SbCl_5$) and difficult to handle, while some must be synthesized in lab (sulfated $Sn0_2$> phosphomolybidic acid on silica gel). Our continued interest in developing environmentally friendly synthetic methodology prompted us to investigate a mild and highly catalytic method for the deprotection of TBDMS ethers utilizing inexpensive commercially available reagents. Herein, we wish to report that iron(III) tosylate[28] is an efficient, inexpensive, easy to handle available catalyst for the deprotection of TBDMS, TES, and TIPS ethers. Iron(III) tosylate is commercially available as the hexahydrate and was used as such. The experimental procedure is very simple and consists of stirring the silyl ether in methanol as the catalyst is added. The product is isolated by the removal of methanol and filtration of the residue through a short silica column, thus avoiding an aqueous waste stream. Products can also be isolated using an aqueous work up followed by purification through silica gel chromatography.

The results of this study are summarized in Table 1. The best results were obtained with a catalyst loading of 2.0 mol % in methanol as the solvent at room temperature. As can be seen from Table 1, a wide range of silyl ethers underwent smooth deprotection to yield the corresponding alcohol. Although deprotection was observed in ethanol as well as in THF/H20 (80/20, v/v), the reactions in these solvents were somewhat sluggish and often did not go to completion. While detailed mechanistic studies were not carried out, a few points merit comment. In the synthesis of the lactone fragment of lankacidin antibiotics, the use of p-TsOH (10.0 mol %) has been reported for the deprotection of a TBDMS ether.29 A solution of iron(III) tosylate in CH_30H is acidic (pH rv 3) and hence not surprisingly, we were successfully able to cleave the TBDMS ether of phenethyl alcohol using 6.0 mol % p-TsOH. The same de protection was unsuccessful when carried out using 2.0 mol % Fe(OTsh and a proton scavenger, proton sponge® (7.0 mol %), [1,8-(dimethylamino)naphthalene].30 Although these observations suggest that the true catalyst is pTsOH, the use of Fe(OTsh is preferable to p-TsOH because the latter compound is much more toxic and its handling poses a greater health hazard.[31] The use of protic acids such as HCl or H_2S0_4 is less desirable due to their corrosive nature. In addition, it is much more difficult to control the pH of the solution with small amounts of protic acid.

Table 1: Deprotection ofTBDMS Ethers using $Fe(OTs)_3 \cdot 6H_20$ as a catalyst



Entry	Substrate[a]	Product	T[b]	Yield[c] (%)
1			1 h 45 min	77
2	*p*-$NO_2C_6H_4CH_2OSi^tBuMe_2$	*p*-$NO_2C_6H_4CH_2OH$	4 h 30 min	77
3			1 h 45 min	79
4			2 h 15 min	86
5			2 h 50 min	82
6			1 h	82
7			2 h 30 min	81
8			3 h	73
9			5 h	72
10[d]			27 h 35 min	84
11			2 h	79
12			2 h	91
13[d]			26 h	84
14	$Me_2{}^tBuSiO$ OSi^tBuPh_2	HO OSi^tBuPh_2	1 h 40 min	80
15[d]			2 h 50 min	72
16			2 h 15 min	67
17			20 min	80
18[e]	*p*-$Me_2{}^tBuSiOC_6H_4CH(OMe)_2$	*p*-$Me_2{}^tBuSiOC_6H_4CHO$	2 h 15 min	86

a All silyl ethers were prepared from the corresponding alcohol or phenol using the literature methods.[1b,35]
b Reaction progress was followed by gas chromatography or TLC, and reactions were worked up when <1 % starting material remained.
C Refers to the yield of isolated and purified product. All products are commercially available compounds and were characterized by ^1H & ^{13}C NMR, and GC analysis.
d Reaction was heated at reflux.
e The starting material was synthesized by the protection of p-hydroxybenzaldehyde as the TBDMS ether followed by acetalization following a literature procedure.36

The selective deprotection of functional groups is especially desirable during the course of a total synthesis. A variety of chemoselective de protections could be achieved under the reaction conditions. Alkenes and alkynes remained unaffected (entries 4-8). A TBDMS ether could be cleaved in the presence of a lactone (entry 10) and a Boc group (entry 11). The stability of the Boc group under TBDMS deblocking conditions suggests potential useful application to solid phase peptide synthesis. The selective cleavage of an alkyl TBDMS ether in the presence of a phenolic TBDMS has received considerable attention in the literature.[32] Under our reaction conditions, at room temperature a phenolic TBDMS ether was unaffected while an alkyl TBDMS group was cleaved (entry 12). Both phenolic and alkyl TBDMS groups were cleaved under reflux conditions (entry 13). The selective cleavage of a 2° TBDMS ether in the presence of a 1° TBDPS (tert-butyldiphenylsilyl) ether using pyridinium p-toluenesulfonate (30.0 mol %) in ethanol has been described in the literature.[33] A mixture of water and lithium chloride (50 equiv) in DMF at 90°C (an environmentally unfriendly solvent) has also been used to cleave a TBDMS group in the presence of a TBDPS group.[34] Under our reaction conditions, we were able to cleave a 10 TBDMS ether in the presence of a 10 TBDPS ether (entry 14). As can be seen by comparing the literature examples, iron(III) tosylate is much more efficient in effecting such chemoselective deprotections. Although the deprotection of triisopropylsilyl ether (entry 15) was slow at room temperature, heating the reaction mixture at reflux resulted in complete deprotection. At room temperature, an acetal group could be cleaved in the presence of a phenolic TBDMS ether (entry 18).

In conclusion, a mild, chemoselective, and highly catalytic method for the deprotection of tert-butyldimethylsilyl (TBDMS) ethers using iron(III) tosylate has been developed. The resistance of TBDPS and BOC groups to the reaction conditions should prove especially useful in the course of total synthesis.

Representative procedure for the deprotection of TBDMS ethers. Method A: A solution of (S)-tert-butyll-(tert-butyldimethylsilyloxy)- 3-phenylpropan-2-ylcarbamate (entry 11) (0.50 g, 1.4 mmol) in CH_30H (5.0 mL) was stirred at room temperature as $Fe(OTs)_3{\cdot}6H_20$ (0.0185 g, 0.0274 mmol, 2.0 mol %) was added. Reaction progress was followed by TLC. At 2 h, the reaction was taken up in EtOAc (20 mL), washed with aqueous saturated $NaHC0_3$ (10 mL) and aqueous saturated NaCl (10 mL), dried (Na_2S0_4) and concentrated on the rotary evaporator to yield 0.370 g of a white solid. The crude product was purified by flash chromatography on 20 g of silica gel (EtOAc/heptane, 40/60 v/v). Forty fractions (4 mL) were collected and fractions 23-38 were concentrated to yield 0.27 g (79%) of (S)-tert-butyl 1-hydroxy-3-phenylpropan-2-ylcarbamate product as a white solid.[13] ^{1}H NMR: δ 1.40 (s, 9H), 2.05 (s, lH), 2.81-2.84 (d, 2H, J = 7.2 Hz), 3.51-3.68 (m, 2H), 3.85 (s, lH), 4.73 (s, lH), 7.18-7.32 (m, 5H). BC (10 peaks) <5 28.28, 37.48, 53.75, 63.92,79.68,126.39,128.44,129.26,137.86,156.13.

Method B: A solution of tert-butyl(2-tert-butyldimethylsilyloxy) benzyloxy)dimethylsilane (entry 12) (0.50 g, 1.4 mmol) in CH_30H (5.0 mL) was stirred at room temperature as $Fe(OTs)_3{\cdot}6H_20$ (0.0192 g, 0.0284 mmol, 2.0 mol %) was added. Reaction progress was followed by GC and TLC. At 1 h 55 min, CH30H was removed on the rotary evaporator. The residue (0.3 705 g) was purified by flash chromatography on 25 g of silica gel

(EtOAc/heptane, 20/80 v/v). Twenty four fractions (8 mL) were collected and fractions 7 - 22 were combined and concentrated to yield 0.3084 g (91 %) of (2-(tert - butyldimethylsilyloxy) phenyl)methanol as a colorless liquid.13 The product was determined by GC and NMR to be >99% pure. 1 H NMR: <50.26 (s, 6H), 1.02 (s, 9H), 2.37 (s, 1 H), 4.65 (s, 2H), 6.80-6.83 (dd,J 8.2 Hz, 1.0 Hz, 1 H), 6.92-6.97 (td, 1 H), 7.14-7.20 (td,] = 7.4 Hz, 2.0 Hz, 1 H), 7.29-7.32 (dd, lH). 13C (10 peaks) <5 -4.3, 18.1, 25.7, 61.7, 118.3, 121.3,128.5,128.7,131.4,153.3.

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