Improved Protocols for the Selective Deprotection of Trialkylsilyl Ethers Using Fluorosilicic Acid

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Improvements for the application of aqueous fluorosilicic acid to the selective cleavage of *tert*-butyldimethylsilyl ethers in the presence of triisopropylsilyl ethers are described. Deprotection conditions have been optimized for cleavage selectivity, tolerance by acid-labile compounds, and cleavage rate. Mechanistic features of the desilylation reaction are discussed.

Introduction

Silyl ethers have attained a position of prominence in the area of hydroxyl group protection due to their ease of formation and removal and their stability to a wide range of reagents and reaction conditions.[1] The *tert*-butyldimethylsilyl (TBDMS) and triisopropylsilyl (TIPS) ethers are among the most popular protecting groups for hydroxyl functions in synthetic chemistry as they are generally readily introduced and are robust to a variety of reaction conditions. The fact that either of these two silyl ethers can be attached regioselectively[1] further increases their utility.

One limitation of silicon-based protecting groups is that, although a variety of methods have been developed for the cleavage of the silicon–oxygen bond,[2] few of these methods allow for effective differentiation between two trialkylsilyl moieties[3] and none are capable of reliably differentiating between a TBDMS and a TIPS ether. Selective deprotecting agents could be applied to advantage in complex synthetic sequences in which two protected hydroxyl groups must be unmasked at different stages of a synthesis.

During the course of the total synthesis of tirandamycin B, it was noted that aqueous HF solutions *that had come in contact with glass* were able to selectively remove a TBDMS group while in the presence of a TIPS moiety.[4] Solutions of HF *which had not been exposed to glass* were unreactive under identical conditions. This remarkable observation indicated that the reaction of *HF and glass* provided the active cleaving reagent. In subsequent experiments,[5] we demonstrated that fluorosilicic acid (H_2SiF_6) served as a selective cleaving agent for trialkylsilyl ethers.[6] Specifically, a TBDMS ether was deprotected in the presence of a TIPS ether (81% selectivity[7]) or a *tert*-butyldiphenylsilyl (TBDPS) ether (100% selectivity). Presumably, fluorosilicic acid is the active cleaving reagent formed *in situ* by the reaction of HF with glass. To our knowledge, this is the first reagent with the general ability to effectively differentiate between a TBDMS and TIPS group in a cleavage reaction. In addition to selectivity, this reagent has additional advantages over other silicon–oxygen cleaving agents. For example, unlike tetraalkylammonium or alkali fluorides or NaH,[3c] H_2SiF_6 is not a threat to base-sensitive compounds. Also, fluorosilicic acid does not have the oxidizing properties of NBS[2k] nor the strong nucleophilic character of NaN_3.[3b] The deprotection reaction conditions employing H_2SiF_6 are catalytic and, therefore, are not as acidic as those using HF[2j] or HCl.[2i] As a result, certain acid-labile moieties are retained during the deprotection. These features of the H_2SiF_6-based cleavage protocol indicated that it was a superior reagent for the removal of silyl ether functions. Accordingly, we believed that a thorough investigation of the scope and limitations of this hypervalent silicon reagent was warranted. In this paper, we provide three new sets of deprotection protocols which are superior to those initially reported.[5] Each protocol is tailored for different experimental situations. For example, a stoichiometric amount of H_2SiF_6 in *t*-BuOH is employed to obtain optimum selectivity between two different trialkylsilyl ether protecting groups. When the acid sensitivity of other functionalities is a concern, a catalytic amount of H_2SiF_6 in 9/1 CH_3CN/*t*-BuOH is the reagent of choice. Finally, when selectivity is not a concern, H_2SiF_6 in CH_3CN gives the fastest cleavage while maintaining tolerance by acid-sensitive groups. In addition to the discussion of reaction protocols, several mechanistic features of the cleavage reaction with fluorosilicic acid are discussed.

Results and Discussion

The mechanism that was previously[5] proposed for the cleavage of silylethers using H_2SiF_6 is outlined in Scheme I. In this mechanism, reversible loss of fluoride ion from hexafluorosilicate dianion 1 provides a pentacoordinate

[•] Abstract published in *Advance ACS Abstracts,* August 15, 1993.

(1) Lalonde, M.; Chan, T. H. *Synthesis* **1985**, 817.

(2) (a) Green, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1991; pp 80–83. (b) Otera, J.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 5743. (c) Olsson, L. I. *Acta Pharm. Suec.* **1986**, *23*, 370. (d) Otera, J.; Niibo, Y.; Nozaki, H.; Chikada, S. *Synthesis* **1988**, 328. (e) Solladé-Cavallo, A.; Khiar, N. *Synth. Commun.* **1989**, *19*, 1335. (f) Bou, V.; Vilarrasa, J. *Tetrahedron Lett.* **1990**, *31*, 567. (g) Cort, A. D. *Synth. Commun.* **1990**, *20*, 757. (h) Cormier, J. F. *Tetrahedron Lett.* **1991**, *32*, 187. (i) Cunico, R. F.; Bedell, L. *J. Org. Chem.* **1980**, *45*, 4797. (j) Newton, R. F.; Reynolds, D. P. *Tetrahedron Lett.* **1979**, *41*, 3981. (k) Batten, R. J.; Dixon, A. J.; Taylor, R. J. K.; Newton, R. F. *Synthesis* **1980**, 234.

(3) (a) Prakash, C.; Samir, S.; Blair, I. A. *Tetrahedron Lett.* **1989**, *30*, 19. (b) Monger, S. J.; Parry, D. M.; Roberts, S. M. *J. Chem. Soc., Chem. Commun.* **1989**, 381. (c) Shekhani, M. S.; Khan, K. M.; Mahmood, K.; Shah, P. M.; Malik, S. *Tetrahedron Lett.* **1990**, *31*, 1669. (d) Corey, E. J.; Yi, K. Y. *Ibid.* **1992**, *33*, 2289.

(4) Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 791.

(5) Pilcher, A. S.; Hill, D. K.; Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Org. Chem.* **1992**, *57*, 2492.

(6) It is probable that previous investigators have inadvertently employed solutions of aqueous fluorosilicic acid by using aqueous HF in glass vessels or transferring aqueous HF solutions in glass pipettes. In these investigations, all manipulations employed appropriate polymer containers (see Experimental Section for details).

(7) Selectivity in these competitive deprotection reactions is defined as percent of the desired protected alcohol minus percent of the undesired protected alcohol.

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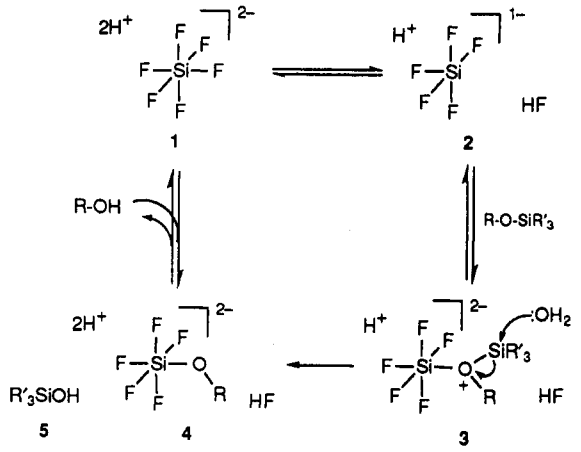
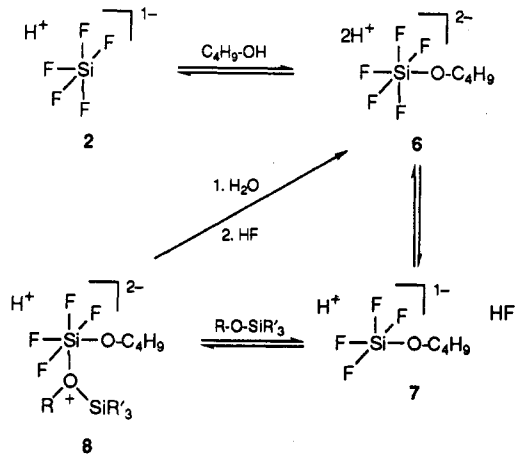
Scheme I



Scheme II



silicate monoanion intermediate **2** which serves as a Lewis acid and binds the silyl ether to give hypervalent silicate derivative **3**. This activates the silicon–oxygen bond of the silyl ether for cleavage. Under the aqueous acidic conditions, water attacks the silicon group of **3**, resulting in formation of hexavalent silicate **4** and trialkylsilanol **5**. Hydrolysis of **4** releases the alcohol and regenerates hexafluorosilicate **1**.

Evidence to support the mechanism outlined in Scheme I is that the initial product of desilylation is trialkylsilanol **5** and not the trialkylsilyl fluoride, the product anticipated from fluoride attack on anion **3**.[8,9] Also, addition of either additional water or alcohols such as 2-propanol and *t*-BuOH, which serve as Lewis bases and compete with the silyl ether for binding to silicate **2**, dramatically retard the rate of desilylation under standard conditions.

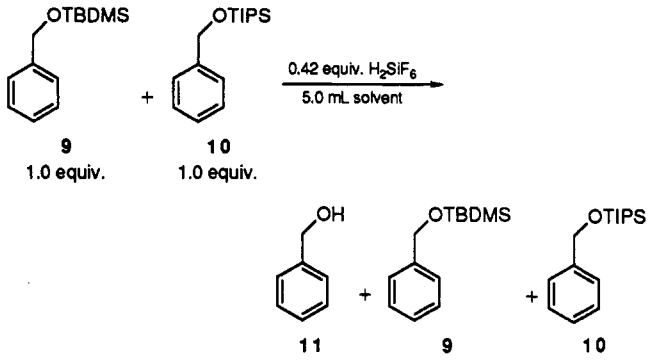
This mechanistic hypothesis for desilylation suggests that other potential Lewis bases present in the reaction mixture, besides the silyl ether substrate, will compete with the silyl ether for binding to fluorosilicate derivative **2** and slow the deprotection reaction rate. First, replacement of fluorine by another ligand in the SiL_6^{2-} complex should reduce the Lewis acidity of the silicon atom, and second, other ligands also act as competitive binders (*vide supra*). These two effects are expected to be equal for silyl ether substrates independent of steric bulk of the alkyl groups residing on silicon. However, any ligand that is larger than fluorine will also slow the deprotection reaction by increasing steric crowding in the octahedral ligand sphere around silicon as shown in Scheme II. This steric hindrance of an alcoholate ligand attached to the hypervalent silicon species (i.e., **6** and **7**) should affect the binding of the silyl ether with bulkier substituents, leading to enhanced selectivity between TBDMS and TIPS cleavage. According to this hypothesis, using an alcohol as the solvent instead of acetonitrile would result in increased selectivity with regard to cleavage.

Table I. Deprotection Solvent Comparison

entry	solvent	temp (°C)	time (h)	% 9[a]	% 10[a]	% selectivity[7]
1	acetonitrile	0	0.17	1	70	69
2	ethanol	0	8.0	1.5	89	87
3	2-propanol	0	~71	0	89	89
4	2-methyl-2-propanol	23	~82	0	100	100

[a] Yields determined by GC analysis (±2%); see Experimental Section for details.

In a competitive deprotection study between BnOTBDMS (**9**) and BnOTIPS (**10**), the use of H_2SiF_6 in alcohols



led to improved selectivity for removal of TBDMS, although longer reaction times were required. In addition, selectivity and reaction time increased as the steric bulk of the alcohol increased, as anticipated by the hypothesis (*vide supra*). The results are summarized in Table I.

As indicated in Table I, utilization of *t*-BuOH as solvent gave complete selectivity for the removal of the TBDMS ether, but the protracted reaction time was a drawback. By increasing the quantity of H_2SiF_6 to 1.0 molar equiv, the reaction time was reduced to 6.3 h, while selectivity was only slightly decreased (95%). This protocol was employed to selectively deprotect bis-silyl ether **12** *on a preparative scale* affording a 91% yield of alcohol **13** and demonstrating the usefulness of the method.

(8) Control experiments have shown that trialkylsilanol **5** is slowly transformed to silyl fluoride as the deprotection proceeds. Under the reaction conditions, trialkylsilyl fluoride does not hydrolyze to provide silanol **5**.

(9) An alternative mechanism involving attack by silicate dianion **1** at the silicon of the silyl ether to produce a fluoride-bridged intermediate (see: Damrauer, R.; Simon, R. A.; Kanner, B. *Organometallics* **1988**, *7*, 1161. Corriu, R. J. P.; Perg, R.; Reye, C. *Tetrahedron* **1983**, *3*, 999) is not viable in this process since silyl fluoride, not silanol, would be the product of cleavage.

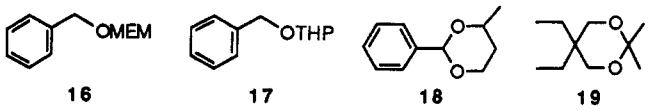
(10) The pH of 0.01 M solutions of H_2SiF_6 and HF are comparable (pH 2–3).

Table II. Determination of Substrate Steric Effects

entry	compd A	compd B	solvent[a]	temp (°C)	mmol of H_2SiF_6	time (h)	% A[b] (±2%)	% B[b] (±2%)	selectivity
1	20	21	*t*-BuOH	rt	0.500	3.3	4	62	58
2	20	21	90/10 CH_3CN/*t*-BuOH	0	0.125	3.0	4	52	48
3	20	23	90/10 CH_3CN/*t*-BuOH	0	0.125	3.0	0.3	100	100
4	21	23	90/10 CH_3CN/*t*-BuOH	0	0.250	8.0	2	99	97
5	21	22	90/10 CH_3CN/*t*-BuOH	0	0.250	24	2	65	63

[a] In each experiment, 0.5 mmol of each compound, A and B, was used in 5.0 mL of solvent. [b] Yields determined by GC analysis; see Experimental Section for details.

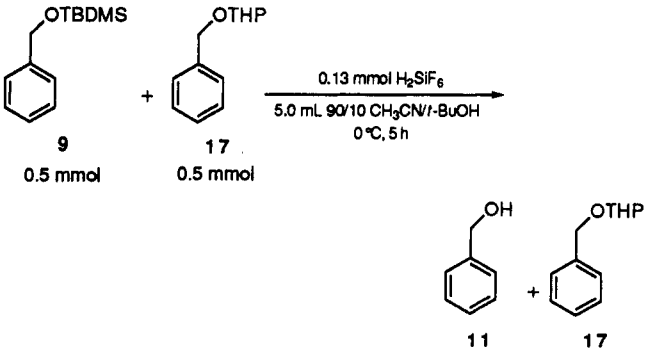
These reaction conditions offer a compromise between selectivity of cleavage and the rate of desilylation. Although this protocol is a significant improvement in selectivity over the original protocol, acid-sensitive compounds such as protected alcohols **16–19** do not withstand



16 17 18 19

these conditions due to the increased fluorosilicic acid concentration.[10] Accordingly, another deprotection protocol was sought in which acid-labile functionalities were retained.

The second set of reaction protocols was developed for compatibility with acid-sensitive moieties. In an effort to reduce the amount of H_2SiF_6 required while maintaining both high selectivity and short reaction times, various mixtures of CH_3CN and *t*-BuOH were investigated. After extensive experimentation, it was established that a 9/1 ratio of CH_3CN/*t*-BuOH provided the best results in a competitive deprotection reaction between BnOTBDMS (**9**) and BnOTIPS (**10**). This solvent mixture gave 90% selectivity after 1.5 h at 0 °C using 0.42 molar equiv of H_2SiF_6. In this solvent system, the quantity of fluorosilicic acid could be reduced to 0.25 molar equiv without significantly altering the efficiency of the deprotection. Moreover, a variety of acid-labile protecting groups such as MEM ethers (**16**, 100%), tetrahydropyranyl ethers (**17**, 85%), and benzylidene groups (**18**, 76%) survived these conditions. On the other hand, acetonide **19** was not retained in this protocol.

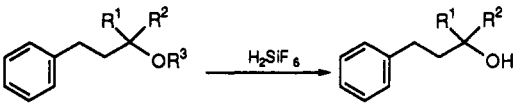


9 0.5 mmol + 17 0.5 mmol → 11 + 17

The final desilylation protocol that was developed maximizes the rate of desilylation at the expense of selectivity. These conditions are recommended for situations when it is desirable to efficiently cleave all silyl ethers present in the molecule. Acetonitrile is used as the solvent at room temperature with 0.2 molar equiv of H_2SiF_6. Under these conditions, TBDMS ethers are generally cleaved in 20 min. This protocol is significantly faster than the traditional method of deprotection employing HF in CH_3CN.[2j]

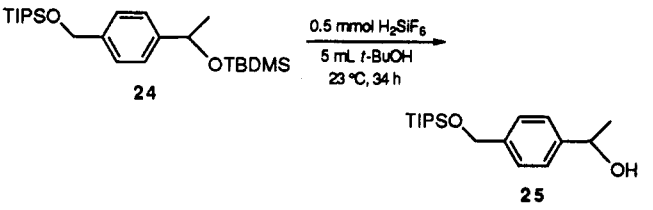
To increase the tolerance of acid-labile groups under these more stringent conditions, the amount of H_2SiF_6 can be reduced to catalytic quantities (4 mol %). For example, the deprotection of primary silyl ether **20** was 95% complete in less than 2 h using only 4 mol % of H_2SiF_6. To diminish the reaction time or to cleave very hindered silyl ethers such as a TBDPS ether, the amount of H_2SiF_6 should be increased.

In order to compare the selective desilylation of primary vs secondary vs tertiary silyl ethers, compounds **20–23** were investigated. The compounds were paired and



	R_1	R_2	R_3
20	H	H	TBDMS
21	H	CH_3	TBDMS
22	H	CH_3	TIPS
23	CH_3	CH_3	TBDMS

treated with H_2SiF_6 as shown in the equation below, providing the results listed in Table II. Excellent selectivity was observed in the deprotection of primary TBDMS vs tertiary TBDMS and secondary TBDMS vs tertiary TBDMS derivatives. On the other hand, selectivity was fair for primary TBDMS vs secondary TBDMS and secondary TBDMS vs secondary TIPS. As observed before, *t*-BuOH provided greater selectivity than *t*-BuOH/CH_3CN solvent mixtures. The potential of this methodology is illustrated in the experiment in which bis-silyl ether **24** was deprotected to give 68% yield of the TIPS alcohol **25**.



24 → 25

Spectroscopic Studies

The proposal that fluorosilicic acid is the product of HF and SiO_2 (*vide supra*) has ample precedent in the literature; however, we provide our own NMR evidence.[11] When the product of the glass/HF preparation was analyzed by ^{19}F NMR spectroscopy, broad singlets were observed at δ −50.0 ppm and δ −51.3 ppm (relative to external trifluoroacetic acid in CD_3CN). An authentic sample of aqueous fluorosilicic acid under identical conditions gave a broad singlet

(11) (a) Palmer, W. G. *J. Chem. Soc.* **1930**, 1656. (b) Blumberg, A. A.; Stavrinou, S. C. *J. Phys. Chem.* **1960**, *64*, 1438. (c) Nielsen, H.; Hackleman, D. *J. Electrochem. Soc.* **1983**, *130*, 708.

at δ −51.8 ppm.[12] Considering the large chemical shift changes that result because of temperature and concentration effects in ^{19}F systems, these chemical shift values are identical within experimental error. The broadness of the peaks is due to dynamic fluorine exchange.[13] The peak at δ −50.0 ppm in the NMR spectra is attributed to an unidentified boron fluoride species.[14] Hydrofluoric acid gave a sharp singlet at δ −81.2 ppm.

To eliminate interference by boron-containing impurities, HF and silicic acid were allowed to react, and in this case, the products were studied by ^{29}Si NMR spectroscopy. Since silicic acid can be considered a glass monomer, we anticipated that this reaction would yield the same fluorosilicate species as the HF-glass reaction. The silicic acid/HF solution gave a broad singlet at δ −186.4 ppm; while fluorosilicic acid gave a broad singlet at δ −185.4 ppm (relative to external TMS in CD_3CN). When the two samples were mixed, a single peak was observed at δ −186.7 ppm. The conclusion based on this data is that H_2SiF_6 is generated when HF reacts with either glass or silicic acid.

Conclusions

We have demonstrated the utility of fluorosilicic acid for the selective deprotection of a variety of silyl ether derivatives. The modifications to the original desilylation protocol have greatly improved the selectivity of deprotection while maintaining tolerance by acid-labile moieties. Fluorosilicic acid is highly selective, effects silyl ether cleavage much faster than HF, and can be used catalytically for reduced acidity.

Experimental Section

General Experimental Procedures. Proton, carbon, fluorine, and silicon magnetic spectra (NMR) were recorded on a Bruker WP-200, AF-200, or AM-400 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from TMS except for ^{19}F NMR where trifluoroacetic acid in CD_3CN was used as an external standard. Coupling constants (J values) are given in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). NMR data are presented as follows: chemical shift in δ (multiplicity, number of protons, assignment, coupling constants). Deuterated NMR solvents contained 99.0–99.8% deuterium in the indicated position.

Infrared spectra were recorded on a Nicolet 5DXC FT-IR spectrophotometer. Band positions are given in reciprocal centimeters (cm^{-1}), and relative intensities are listed as follows: br (broad), vs (very strong), s (strong), m (medium), or w (weak).

Mass spectral data were obtained on a HP 5988A spectrometer using EI at 70 eV unless otherwise indicated. Data are given in the following format: m/z (relative intensity).

Flash chromatography was performed using thick-walled glass columns and "medium-pressure" silica (Merck, 230–400 mesh).

All solvents were distilled from calcium chloride prior to use unless noted otherwise. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone ketyl while triethylamine (Et_3N), pyridine, and methylene chloride (CH_2Cl_2) were distilled from calcium hydride. All reagents were distilled, recrystallized, or chromatographed prior to use unless otherwise noted. Spectrophotometric-grade acetonitrile was used as the solvent in the deprotection protocols.

Gas chromatography was performed on a Hewlett-Packard Model 5890 gas chromatograph equipped with a flame ionization detector using a 25-m capillary column coated with crosslinked phenyl–methyl silicone.

The synthesis and characterization of compounds **9**, **10**, **12**, **16**, **17**, **18**, and **19** were described previously.[5]

Fluorosilicic acid (H_2SiF_6) was purchased as a 31% aqueous solution from Fisher and was used without further purification. All reactions employing either HF or H_2SiF_6 were performed in polyethylene, polypropylene, or Teflon vessels. No glass items of any sort were allowed to come in contact with the deprotection reagents or reaction mixtures.

A typical desilylation experimental protocol involves the addition of the appropriate quantity of a 31% aqueous solution of H_2SiF_6 to a solution of the substrate(s) in the indicated dry solvent.

Deprotection Procedure Using Fluorosilicic Acid in *t*-BuOH. Stock solutions of the silylated alcohols and naphthalene were made to be 0.10 M in hexane. In a typical selective deprotection reaction using aqueous H_2SiF_6 in t-BuOH, 5.0 mL of the BnOTBDMS (**9**) solution (0.50 mmol), 5.0 mL of the BnOTIPS (**10**) solution (0.50 mmol), and 5.0 mL of the naphthalene solution (0.50 mmol) were mixed in a heavy walled polypropylene centrifuge tube. The hexane was removed at reduced pressure, and 2-methyl-2-propanol (5.0 mL) was added. The mixture was stirred magnetically until homogeneous, and three 0.2-μL GC injections were made to determine the response factors. Fluorosilicic acid (185.1 μL, 0.50 mmol, 1.0 molar equiv of a ~31% aqueous solution, d = 1.256) was added *via* a micropipette with a polyethylene tip. The course of the reaction was monitored by GC. A 200-μL sample was neutralized in 1.5 mL of saturated Na_2CO_3 solution and then extracted with 1.5 mL of ether. The organic phase was assayed by GC using naphthalene as an internal standard.

Preparative-Scale Deprotection of Bis-silyl Ether 12. Ether **12** (10.0 mmol, 4.09 g) and 100 mL of t-BuOH were mixed in a 175-mL polyethylene bottle and cooled in an ice bath. Fluorosilicic acid (10 mmol, 3.7 mL of a ~31% aqueous solution, 1.0 molar equiv) was added, and the progress of the reaction was monitored by GC. At 99% completion as determined by GC (7 h), 10 mL of saturated $NaHCO_3$ solution was added. After the t-BuOH was evaporated at reduced pressure, the residue was diluted with 100 mL of EtOAc and washed with 3 × 50 mL of brine. The organic phase was dried ($MgSO_4$) and evaporated at reduced pressure to give 2.76 g (92%) of a colorless oil which was identified by NMR as alcohol **13** (98% pure by GC): IR (CCl_4) 3617 (w), 2944 (s), 2867 (s), 1117 (m), 1096 (m), 1069 (m), 1014 (m), 883 (m); ^1H NMR ($CDCl_3$) 7.32 (s, 4H, ArH), 4.82 (s, 2H, $ArCH_2OSi$–), 4.66 (s, 2H, $ArCH_2OH$), 1.67 (s, 1H, –OH), 1.13–1.03 (m, 21H, –Si-*i*-Pr).

Deprotection Procedure Using Fluorosilicic Acid in 9/1 CH_3CN/*t*-BuOH. This procedure is the same as that for t-BuOH except that 9/1 CH_3CN/t-BuOH is used in place of t-BuOH and the amount of fluorosilicic acid is reduced to 0.13 mmol (0.26 molar equiv).

Deprotection Procedure Using Fluorosilicic Acid in CH_3CN. This procedure is the same as that for t-BuOH except that CH_3CN is used in place of t-BuOH and the amount of fluorosilicic acid is reduced to 0.10 mmol (0.20 molar equiv).

[3-(*tert*-Butyldimethylsiloxy)propyl]benzene (20). Primary silyl ether **20** was prepared by Corey's procedure[15] using TBDMS-Cl to protect (3-hydroxypropyl)benzene (11.44 g, 84.00 mmol) giving 20.26 g (99% pure by GC, 100% yield) of the silyl ether as a clear, colorless oil: IR (CCl_4) 2957 (s), 2932 (s), 2857 (s), 1497 (m), 1472 (m), 1254 (s), 1101 (vs), 962 (m); ^1H NMR ($CDCl_3$) 7.32–7.14 (m, 5H, ArH), 3.63 (t, 2H, $-CH_2OTBDMS$, J

(12) ^{19}F data on hexafluorosilicates given in: (a) *Bruker Almanac* **1990**, 83. (b) Happe, J. A.; Walkup, C. M.; Morgan, R. J. *Polymer* **1985**, *26*, 827.

(13) (a) Kennedy, J. D.; McFarlane, W. In *Multinuclear NMR*; Mason, J., Ed.; Plenum Press: New York, 1987; Chapter 11. Refer to the following for information on the structure and reactivity of fluorosilicates: (b) Klanberg, F.; Muetterties, E. L. *Inorg. Chem.* **1968**, *7*, 155. (c) Rochow, E. G. In *Comprehensivie Inorganic Chemistry*; Trotman-Dickenson, A. F., Ed.; Pergamon Press: New York, 1973; Vol. 1, pp 1465–1466. (d) Driesen, R. A. J.; Hulsbergen, F. B.; Vermin, W. J.; Reedijk, J. *Inorg. Chem.* **1982**, *21*, 3594. (e) Schomburg, D.; Krebs, R. *Inorg. Chem.* **1984**, *23*, 1378. (f) Corriu, R. J. P. *J. Organomet. Chem.* **1990**, *400*, 81.

(14) Powdered borosilicate glass was employed in this experiment; hence, the boron impurities. ^{19}F chemical shift of BF_3 (vs trifluoroacetic acid) is ca. δ −53.[12a]

(15) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190. A modified procedure utilizing acetonitrile as the reaction solvent in place of DMF was used.

= 6), 2.68 (t, 2H, $PhCH_2$–, J = 8), 1.91–1.76 (m, 2H, $BnCH_2$–), 0.91 (s, 9H, t-Bu), 0.05 (s, 6H, $SiMe_2$).

[3-(*tert*-Butyldimethylsiloxy)butyl]benzene (21). 4-Phenyl-2-butanone (20.01 g, 135.0 mmol) was reduced to the alcohol using $NaBH_4$ as in the synthesis of bis-silyl ether **12**.[4] 4-Phenyl-2-butanol was obtained in quantitative yield as a clear, colorless oil (20.77 g, 100% by GC): IR (CCl_4) 3630 (s), 3030 (s), 2968 (vs), 2928 (vs), 2865 (s), 1605 (m), 1497 (s), 1455 (vs), 1377 (m), 1115 (m), 1052 (s), 952 (m), 904 (m); ^1H NMR ($CDCl_3$) 7.34–7.14 (m, 5H, ArH), 3.83 (sextet, 1H, BnCCC*H*Me–, J = 6), 2.72 (octet, 2H, $PhCH_2$–, J = 8), 1.77 (m, 2H, $BnCH_2$–), 1.23 (d, 3H, $-CH_3$, J = 6).

4-Phenyl-2-butanol (12.02 g, 80.02 mmol) was protected by Corey's procedure[15] using TBDMS-Cl to give 20.97 g (99% pure by GC, 98%) of silyl ether **21** as a clear, colorless oil: IR (CCl_4) 2957 (vs), 2929 (vs), 2858 (s), 1605 (w), 1472 (m), 1255 (s), 1136 (s), 1091 (m), 1062 (m); ^1H NMR ($CDCl_3$) 7.32–7.13 (m, 5H, ArH), 3.85 (sextet, 1H, BnCC*H*Me–, J = 6), 2.76–2.50 (m, 2H, $PhCH_2$–), 1.80–1.67 (m, 2H, $BnCH_2$–), 1.17 (d, 3H, BnCCHCH_3–, J = 6), 0.91 (s, 9H, t-Bu), 0.06 (s, 6H, $SiMe_2$, J = 6).

[3-(Triisopropylsiloxy)butyl]benzene (22). 4-Phenyl-2-butanol from above (7.794 g, 51.88 mmol) was protected by Corey's procedure[15] using TIPS-Cl to give 16.54 g (97% pure by GC, 100%) of silyl ether **22** as a clear colorless oil: IR (CCl_4) 2962 (s), 2946 (vs), 2867 (vs), 1464 (m), 1136 (m), 1062 (m); ^1H NMR ($CDCl_3$) 7.31–7.12 (m, 5H, ArH), 4.00 (q, 1H, BnCC*H*Me–, J = 6), 2.68 (t, 2H, $PhCH_2$–, J = 8), 1.79 (m, 2H, $BnCH_2$–), 1.23 (d, 3H, BnCCCHCH_3–, J = 6), 1.13–1.06 (m, 21H, i-Pr).

[3-(*tert*-Butyldimethylsiloxy)-3-methylbutyl]benzene (23). Silyl ether **23** was prepared by Corey's procedure[15] using TBDMS-Cl to protect 2-methyl-4-phenyl-2-butanol (13.14 g, 80.00 mmol) with the exception that the reaction mixture was refluxed for 4 d. After workup and purification by flash column chromatography (hexane), 18.63 g (98% pure by GC, 82% yield) of TBDMS derivative **23** was obtained as a clear colorless oil: IR (CCl_4) 2956 (vs), 2930 (vs), 2858 (s), 1605 (m), 1472 (m), 1365 (m), 1253 (s), 1209 (m), 1074 (m), 1046 (vs); ^1H NMR ($CDCl_3$) 7.32–7.12 (m, 5H, ArH), 2.74–2.65 (m, 2H, $PhCH_2$–), 1.76–1.67 (m, 2H, $BnCH_2$–), 1.26 (s, 6H, $BnCCC(CH_3)_2OTIPS$), 0.89 (s, 9H, t-Bu), 0.10 (s, 6H, $SiMe_2$).

4-[1-(*tert*-Butyldimethylsiloxy)ethyl]-1-[(triisopropylsiloxy)methyl]benzene (24). Ethyl 4-acetylbenzoate (3.84 g, 20.0 mmol) was diluted with 35 mL of absolute ethanol in a 100-mL three-neck flask. A solution of sodium borohydride (386 mg, 10.0 mmol) in 40 mL of absolute ethanol was added from an additional funnel over 7 min while stirring under N_2. The solution was then heated to reflux over 30 min and then cooled, concentrated at reduced pressure, diluted with 100 mL of ether, and washed with 4 × 50 mL of brine. The organic phase was dried ($MgSO_4$) and then concentrated at reduced pressure to give 3.85 g (99% pure by GC, 99% yield) of ethyl 4-(1-hydroxy)-ethylbenzoate as a clear, colorless oil: IR (CCl_4) 3618 (m), 2980 (s), 2868 (s), 1722 (vs), 1612 (m), 1276 (vs), 1107 (s), 1090 (m), 1021 (m); ^1H NMR ($CDCl_3$) 8.02 (d, 2H, ArH, J = 8), 7.43 (d, 2H, ArH, J = 8), 4.98 (q, 1H, ArC*H*OHMe, J = 6), 4.37 (q, 2H, $-OCH_2$-CH_3, J = 7), 1.95 (br s, 1H, –OH), 1.50 (d, 3H, $ArCCH_3$, J = 6), 1.39 (t, 3H, $-OCH_2CH_3$, J = 7).

Ethyl 4-(1-hydroxy)ethylbenzoate (3.75 g, 19.2 mmol) was protected using TBDMS-Cl by Corey's procedure[15] to give 6.28 g (92% pure by GC, 96% yield) of ethyl 4-[1-(*tert*-butyldimethylsiloxy)ethyl]benzoate as a clear, colorless oil: IR (CCl_4) 2957 (m), 2930 (m), 2857 (m), 1220 (s), 1274 (s), 1256 (m), 1103 (m), 1095 (m); ^1H NMR ($CDCl_3$) 7.99 (d, 2H, ArH, J = 8), 7.37 (d, 2H, ArH, J = 8), 4.88 (q, 1H, ArCH–, J = 6), 4.35 (q, 2H, $-OCH_2CH_3$, J = 7), 1.38 (d, 3H, $ArCCH_3$, J = 6), 1.37 (t, 3H, $-OCH_2CH_3$, J = 7), 0.88 (s, 9H, t-Bu), –0.01 (m, 6H, $SiMe_2$).

Ethyl 4-[1-(*tert*-butyldimethylsiloxy)ethyl]benzoate (6.028 g, 19.54 mmol) was diluted with 20 mL of ether in a 50-mL flask. Lithium aluminum hydride (9.77 mL of a 1 M ether solution, 9.77 mmol) was added *via* syringe at a rate which maintained a gentle reflux. After 3 h, the flask was cooled in an ice bath and the reaction was quenched with water (4 mL). The alkali salts were removed by filtration and rinsed with ether. The combined filtrate and rinse were washed with 3 × 25 mL of pH 3 phosphate buffer and then with 25 mL of saturated $NaHCO_3$ solution. The organic phase was dried ($MgSO_4$) and concentrated at reduced pressure to give 5.050 g (87% pure by GC, 87%) of 4-[1-(*tert*-butyldimethylsiloxy)ethyl]-1-(hydroxymethyl)benzene as a clear colorless oil: IR (CCl_4) 3617 (m), 2960 (s), 2930 (s), 2858 (s), 1258 (s), 1096 (s), 1033 (m), 959 (m); ^1H NMR ($CDCl_3$) 7.30 (s, 4H, ArH), 4.85 (q, 1H, ArC*H*OTBDMSMe), 4.66 (s, 2H, $ArCH_2$–), 1.60 (s, 1H, –OH), 1.38 (d, 3H, $-CH_3$, J = 6), 0.88 (s, 9H, t-Bu), –0.04 (m, 6H, $SiMe_2$).

4-[1-(*tert*-butyldimethylsiloxy)ethyl]-1-(hydroxymethyl)benzene (4.176 g, 15.67 mmol) was protected with TIPS-Cl by Corey's procedure[15] to give 6.205 g (99% pure by GC, 93%) of disilyl ether **24** as a clear colorless oil after purification by flash column chromatography (hexane): IR (CCl_4) 2946 (s), 2866 (s), 1472 (m), 1461 (m), 1257 (m), 1091 (s), 1032 (m), 961 (m); ^1H NMR ($CDCl_3$) 7.27 (s, 4H, ArH), 4.84 (d, 1H, ArC*H*OTBDMSMe, J = 6), 4.80 (s, 2H, $ArCH_2OTIPS$), 2.12 (d, 3H, $ArCCH_3$, J = 6), 1.09 (s, 18H, i-Pr), 1.06 (s, 3H, i-Pr), 0.88 (s, 9H, t-Bu), –0.03 (m, 6H, $SiMe_2$); MS 422 (M^+, 0.05), 407 (0.7), 379 (2), 365 (5), 291 (2), 261 (1), 247 (4), 233 (3), 219 (4), 177 (4), 145 (8), 117 (100).

Selective Deprotection of Bis-silyl Ether (24). Substrate **24** (211.4 mg, 0.5 mmol) was weighed into a polypropylene centrifuge tube, and 5.0 mL of a 0.1 M solution of napthalene in hexane was added. The hexane was removed at reduced pressure and replaced with 5.0 mL of t-BuOH. Fluorosilicic acid (185.1 μL, 0.50 mmol) was added using a micropipette with a polyethylene tip, and the reaction was monitored by GC. After 34 h, 68% of the cleavage products was TIPS derivative **25**; the remainder consisted of starting material (11%), the monoprotected TBDMS derivative (3%), and the diol (17%).

Synthesis of H_2SiF_6 from Silicic Acid or Glass. A 100-mL polypropylene bottle containing 40 mL of ~49% aqueous HF was chilled in an ice bath. Silicic acid was slowly added while stirring (strongly exothermic) until no more would dissolve (~15.4 g). The slurry was stirred for 1 h and then filtered through filter paper to give a clear, colorless solution that is indistinguishable from aqueous H_2SiF_6 by ^{29}Si NMR (CD_3CN, Teflon NMR tube, TMS was used as an external standard); δ –186.6 (s, 0.6 ppm at half height).

The same procedure was followed using powdered borosilicate glass instead of silicic acid. The resulting solution was studied by ^{19}F NMR in a Teflon-lined NMR tube using CD_3CN as the solvent and TFA in CD_3CN as an external standard: δ –51.3 (s, 2.2 ppm at half height).

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