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Use of Catalytic Fluoride under Neutral Conditions for Cleaving Silicon−Oxygen Bonds†

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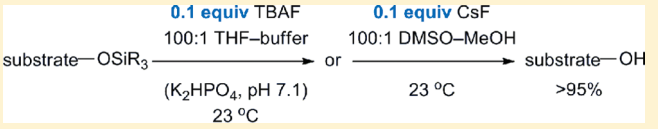
Supporting Information

ABSTRACT: This Article describes the development of conditions for cleaving silicon−oxygen bonds using catalytic quantities of fluoride at neutral pH in mixed organic−aqueous solutions that contain buffer. A variety of silicon protecting groups can be removed under these conditions, which show tolerance for acid- and base-sensitive groups. A modified procedure also is presented using catalytic fluoride in anhydrous dimethyl sulfoxide−methanol, which generates primarily volatile silicon byproducts.



INTRODUCTION

During our studies on analyte-responsive polymers, a *tert*-butyldimethylsilyl (TBS) end-capped poly(phthalaldehyde) polymer was designed to depolymerize upon exposure to fluoride via fluoride-mediated cleavage of the TBS protecting group from the end of the polymer (Figure 1).[1] We were surprised, however, to find that the polymer depolymerized completely when exposed to only 0.5 equiv of tetrabutylammonium fluoride (TBAF) in 1000:1 THF−phosphate-buffered water (K_2HPO_4, pH 7.1).[1] Traditionally, conditions for cleaving a silyl ether use stoichiometric fluoride to obtain complete cleavage of the silicon−oxygen bond;[2−4] these conditions also typically use pure organic solvents, not organic−aqueous solutions such as those used in our polymer studies.[1] Thus, we reasoned that perhaps the water was playing a crucial role in enabling complete deprotection using substoichiometric quantities of fluoride, as noted by Higashibayashi et al. in their paper on the use of acetic acid to effect selective cleavage of silyl ethers.[5]

The aim of this study was to evaluate whether the catalytic, neutral silyl ether bond cleavage reaction in Figure 1 could be made into a general procedure for removing silicon protecting groups. Herein, we describe new conditions for removing silicon protecting groups using catalytic fluoride.[6] These conditions employ commercially available reagents, do not require exclusion of air, operate under neutral pH (e.g., pH 7.1) at 23 °C under buffered conditions, and provide the product of the reaction cleanly and in high yield. We believe that these conditions will find use in a variety of contexts, particularly for deprotecting acid- and base-sensitive substrates and in large-scale reactions where the cost of the fluoride reagent and/or the effort to remove the spent fluoride reagent from the product becomes burdensome.

Background on Fluoride-Mediated Cleavage of Silyl Ethers. Silicon−oxygen bonds can be cleaved under a variety of conditions, including those that use acid, base, Lewis acids, heat, and/or a source of fluoride.[2,3] Fluoride-mediated cleavage is one of the most common methods for effecting this transformation,[2,3] and TBAF (available commercially as a solution in tetrahydrofuran (THF) and as the solid hydrate) is frequently the first reagent explored.[4] Anhydrous TBAF also can be prepared, but in addition to requiring the use of an inert atmosphere box, it is both strongly basic and nucleophilic, which can be an advantage or disadvantage depending on the substrate.[7]

For silyl ether cleavage reactions, commercial sources of TBAF are used more often than anhydrous TBAF, but both the solid and solution forms of commercial TBAF contain water. The quantity of this water depends on the batch of TBAF, the age of the reagent, and the conditions under which the reagent is stored.[2,3,8] As a consequence, solutions of TBAF (whether made from solid TBAF or purchased as a solution) often are treated with molecular sieves to reduce the water content of the solution.[8]

Neutral conditions for cleaving silyl ethers are desirable when dealing with sensitive substrates, yet most examples of deprotection conditions are either acidic or basic. TBAF is particularly troublesome in this regard, since the presence of water in TBAF creates a basic solution.[9,10] Acetic acid frequently is added to reactions that employ TBAF in an effort to neutralize the base,[2,11] but the addition of acetic acid often has the effect of substantially decreasing the rate of cleavage of the Si−O bond.[5,12] Moreover, the quantity of acetic acid needed to neutralize the solution depends on the amount of base present in the TBAF, which, like the concentration of water, varies from bottle to bottle. If rigorously neutral reaction conditions are necessary, then experimentation is required to determine the correct quantity of acetic acid needed.[2] In most cases, however, this level of rigor is not implemented, and instead the reaction solution remains either basic or acidic depending on whether too little or too much acetic acid was added.

Other fluoride-based reagents, such as hydrofluoric acid and HF·pyridine, also are used for effecting Si−O bond cleaving reactions,[2,3] but these reagents render the reaction conditions

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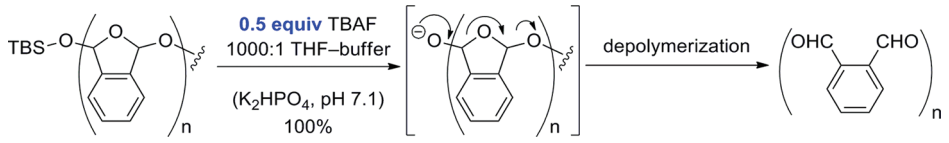

Figure 1. An analyte-responsive polymer that depolymerizes completely when exposed to 0.5 equiv of TBAF in mixtures of THF and buffered water.[1]

either acidic or basic. Nonacidic or nonbasic reagents are available for removing silicon protecting groups (e.g., tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF),[13−15] tetrabutylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride (TBAF(*t*BuOH)$_4$),[16] and tetrabutylammonium triphenyldifluorosilicate (TBAT)[10,17]), with the caveat that such reagents either must be freshly prepared, require refluxing reaction conditions, are hygroscopic, and/or are expensive when purchased commercially.

This latter point on the cost of reagents is especially important when reactions are conducted on large scale because a stoichiometric quantity of a fluoride reagent is used to effect complete deprotection. Moreover, the use of stoichiometric reagents leads to the presence of stoichiometric byproducts that must be separated from the product of the reaction. This purification process can be laborious, especially when phase-transfer reagents such as tetraalkylammonium reagents (e.g., TBAF) are used.[18] Hence, the catalytic deprotection conditions described herein may be of value in a variety of contexts.

RESULTS

Deprotection of R$_3$SiOR Using Catalytic TBAF. To test whether the conditions in Figure 1 could be made more general for small molecules, we dissolved *tert*-butyldimethylsilyl[4] (TBS)-protected benzyl alcohol (**1**) (0.1 M) in THF−phosphate buffer (pH 7.1, 0.1 M) at 23 °C and exposed it to various quantities of TBAF, ranging from 0 equiv to 1.1 equiv (Figure 2). Figure 2 shows that complete removal of the silicon protecting group can be effected even with substoichiometric quantities of fluoride. In addition, the time required for complete conversion of **1** to **2** is inversely proportional to the number of equivalents of fluoride added to the reaction mixture. Background hydrolysis of the Si−O bond by buffered water does not account for these observations (Figure 2b).

Effect of pH, Buffer Concentration, and the Quantity of Water on the Deprotection Reaction. The reaction mixtures depicted in Figure 2 remained at approximately pH 7 throughout the course of the reaction.[19] We found that solutions of TBAF in 0.0 M, 0.1 M, 0.25 M, and 0.5 M phosphate buffer (pH 7.1) can be used instead of solutions of TBAF in 0.1 M phosphate buffer with no noticeable effect on the rate of the deprotection reaction (Figure S1, Supporting Information); such conditions may be necessary for substrates that are particularly sensitive to fluctuations in pH. Likewise, different pH values (e.g., pH 6.5, 7.0, 7.5, and 8.0) provide rates of reaction that are identical to the standard pH 7.1 conditions, making this reaction useful for substrates that are especially sensitive to either acid or base (Figure S2, Supporting Information).

The presence of phosphate buffer would do little to control the pH of the reaction mixture in the absence of water, and we found that there is a threshold level of water that is necessary for an

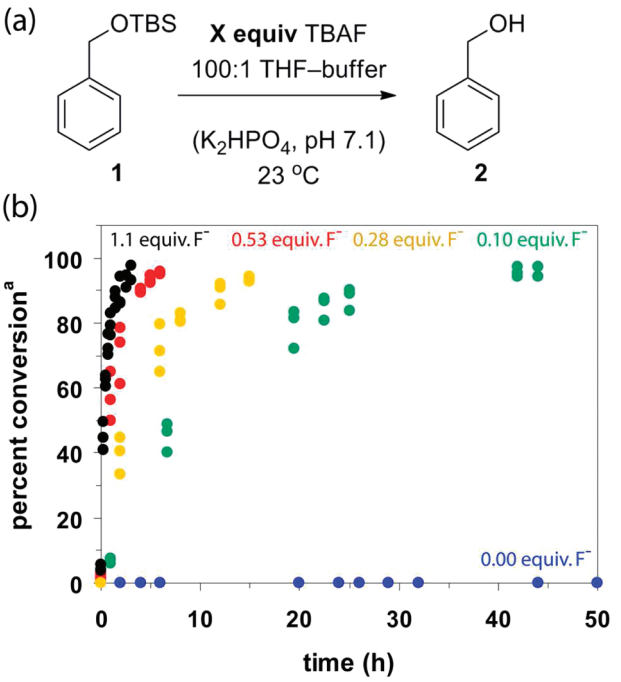

Figure 2. Demonstration of the catalytic effects of TBAF on (a) the conversion of **1** to **2** under neutral reaction conditions. (b) The relationship between reaction time and the quantity of **1** remaining in the reaction mixture. The experiments were performed in triplicate and all data are included on the graph. The percent conversion of **1** to **2** was determined by integrating peak areas in HPLC chromatograms. Percent conversion = (area$_{\text{compound 1}}$/(area$_{\text{compound 1}}$ + area$_{\text{compound 2}}$)) × 100%.

efficient deprotection reaction (Figure 3). For example, when **1** is treated with 0.5 equiv of TBAF for 6 h under the reaction conditions, conversion to **2** occurs equally well when water is present in quantities ranging from 0.6−1.2% in THF.[20,21] However, as the quantity of water in the reaction mixture increases to ≥1.4%, the percent conversion at 6 h decreases dramatically.[22]

Effect of the Reaction Vessel on the Deprotection Reaction. Because the reaction conditions employ only a catalytic quantity of fluoride, the type of reaction vessel becomes important to the success of the reaction. The results shown in Figures 2 and 3 were obtained from reactions run in polypropylene centrifuge tubes, which, unlike glass, should not sequester trace quantities of fluoride from solution. When deprotection reactions of **1** were conducted using 0.1 equiv of TBAF in typical Pyrex round-bottomed flasks, the results were inconsistent: several experiments showed decreased rates of deprotection of **1** in comparison to identical reactions run in polypropylene centrifuge tubes, while others showed indistinguishable rates. Because of this variation in reaction rates, we recommend using polypropylene reaction vessels for catalytic cleavage reactions of Si−O bonds.

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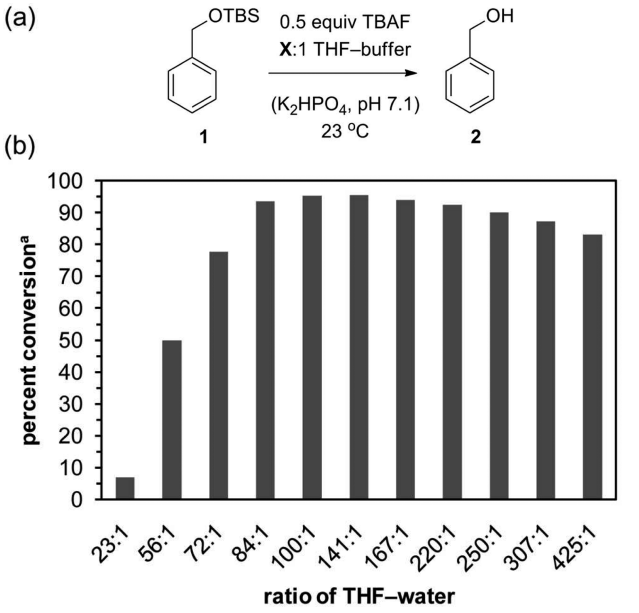
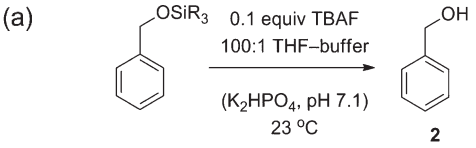


Figure 3. Effect of the ratio of THF−water on the percent conversion of **1** to **2** after 6 h of reaction time.[21] Percent conversion of **1** to **2** was determined by integration of peak areas in HPLC chromatograms. Percent conversion = $(\text{area}_{\text{compound 1}}/(\text{area}_{\text{compound 1}} + \text{area}_{\text{compound 2}})) \times 100$.

A General Deprotection Procedure. Taken together, the results above have led to the following general silyl ether cleavage procedure:[23] (a) Preparation of a 3.3 M buffered TBAF solution: Tetrabutylammonium fluoride hydrate (0.24 g, 0.90 mmol) was dissolved in anhydrous tetrahydrofuran (90 μL). The resulting solution was sonicated for 10 min. Aqueous dibasic potassium phosphate (K_2HPO_4) (0.1 M, pH 7.1, 180 μL) was added to the TBAF solution, and the resulting mixture was sonicated for an additional 3 min. No precautions were employed to exclude air. (b) Deprotection of **1**: Buffered tetrabutylammonium fluoride solution (50 μL, 3.3 M, 0.16 mmol, 0.5 equiv) was added to a solution of TBS-protected benzyl alcohol (**1**) (73 mg, 0.33 mmol, 1 equiv) in tetrahydrofuran (3.3 mL, anhydrous) in a 15-mL polypropylene tube. The polypropylene tube was capped, and the reaction mixture was stirred at 23 °C for 6 h, at which point the solvent was removed under reduced pressure. The product was purified using silica gel flash column chromatography (20% ethyl acetate in hexanes) to provide benzyl alcohol (**2**) as a colorless oil (35 mg, 98%).

Application to Other Silicon Protecting Groups. These neutral, catalytic conditions for cleaving Si−O bonds extend to other silicon protecting groups as well. Deprotection reactions using 0.1 equiv of TBAF in 100:1 THF−buffered water (K_2HPO_4, pH 7.1) (0.1 M in substrate, 23 °C) followed pseudo-first-order kinetics with rate constants that are consistent in relative magnitude to known rates of fluoride-mediated deprotection of triethylsilyl (TES),[24] TBS, triisopropylsilyl (TIPS),[25] and *tert*-butyldiphenylsilyl (TBDPS)[26] groups (Figure 4).[1,27] Diphenylmethylsilyl (DPMS) (**6**)-[28] and triphenylsilyl (TPS) (**7**)-protected benzyl alcohol were deprotected completely under the same reaction conditions in less than 5 min. The disadvantage of the catalytic reaction conditions, particularly when only 0.1 equiv of TBAF are used, is the slow reaction time for bulky silicon protecting groups; for example, removal of the TBDPS protecting group required ~4 days to reach completion.

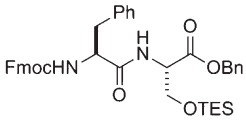
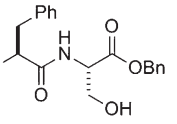
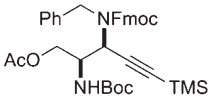
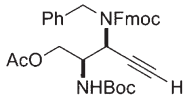
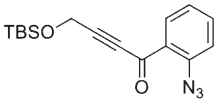
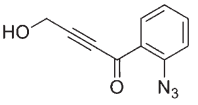
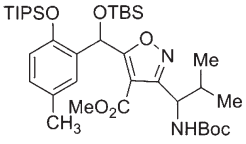
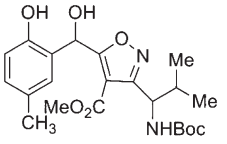
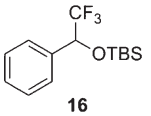
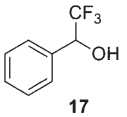


(b)

substrate	reaction rate (s^{-1})	relative rxn rate
$PhCH_2OTES$ (**3**)	$5.44 \pm 0.16 \times 10^{-4}$	56.2
$PhCH_2OTIPS$ (**4**)	$3.03 \pm 0.24 \times 10^{-5}$	3.13
$PhCH_2OTBS$ (**1**)	$2.11 \pm 0.25 \times 10^{-5}$	2.18
$PhCH_2OTBDPS$ (**5**)	$9.68 \pm 0.68 \times 10^{-6}$	1

Figure 4. Effect of the silicon protecting group on the rate of cleavage of the Si−O bond. (a) The reaction conditions for deprotection of different silicon protecting groups. The concentration of the protected benzyl alcohol was 0.1 M in 100:1 THF−buffer (K_2HPO_4, pH 7.1). (b) Reaction rates were determined using HPLC by measuring the consumption of the starting material relative to the formation of product. The experiments were repeated three times.

Table 1. Deprotection of Silyl Ether Protecting Groups in Complex Substrates[a]

Starting Material	Product	Yield
 **8**	 **9**	63%
 **10**	 **11**	95%
 **12**	 **13**	78%
 **14**	 **15**	95%
 **16**	 **17**	96%

[a] The compounds (0.1 M) were deprotected at 23 °C using 0.5 equiv of TBAF in 100:1 THF−buffered water (K_2HPO_4, pH 7.1).

Application to Complex Substrates. These Si−O cleavage conditions were evaluated in the context of more complex substrates as well (Table 1). The data in Table 1 demonstrates that these neutral, catalytic deprotection conditions are capable

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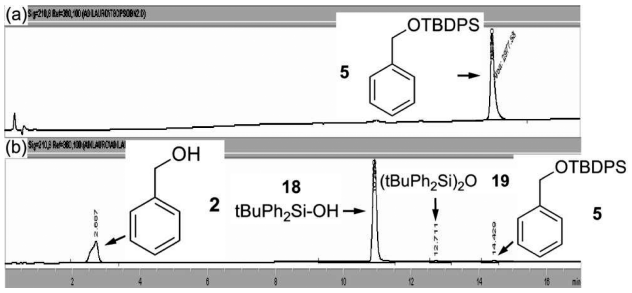

Figure 5. HPLC chromatograms of (a) TBDPS-protected benzyl alcohol (**5**) and (b) the UV-active products at >95% deprotection of **5**. Compound **5** was deprotected at 23 °C using 0.1 equiv of TBAF in 100:1 THF-buffered water (K_2HPO_4, pH 7.1).

of cleaving Si−O bonds selectively in the presence of functional groups that are sensitive to base (**8**, **10**)[29] and acid (**10**, **14**).

Improving the Deprotection Reaction

a. Determining the Fate of Silicon. We used HPLC to probe the fate of silicon during the deprotection of TBDPSOBn (**5**); our goal was to devise a straightforward strategy for separating the desired product from the silicon byproducts once they were known. Figure 5 shows that the dominant silicon byproduct of this reaction is silanol **18** (TBDPSOH); no silyl fluoride was observed by HPLC, and only a trace quantity of $TBDPS_2O$ (**19**) was present. To determine whether the observed silanol **18** was the result of HPLC-mediated hydrolysis, we prepared an authentic sample of $TBDPS_2O$ and demonstrated that it does not hydrolyze under the HPLC conditions used for analysis (Figure S5). This observation indicates that the HPLC chromatogram in Figure 5 is an accurate representation of the quantities of $TBDPS_2O$ and silanol **18** in the reaction mixture and not a result of the conditions used for analysis.

b. A Modified Procedure That Generates Volatile Silicon Byproducts. As demonstrated in Figure 3, water is crucial to the success of this catalytic deprotection reaction; therefore, we suspected that an alcohol could serve the same purpose. By using an alcohol (e.g., methanol) instead of water, we reasoned that the resulting silyl ether byproducts would be volatile and hence could be separated easily from the product of the reaction. To test this theory, we conducted the following experiment: TBDPSOBn (**5**) (0.1 M) in 100:1 anhydrous DMSO−anhydrous MeOH was exposed to 0.1 equiv of CsF at 23 °C. After 20 h, HPLC analysis revealed that >95% of **5** had been converted to BnOH (**2**).[30] This reaction time is approximately 4.8× shorter than that observed with the TBAF under THF-buffered water conditions (Figure 4). The silicon byproducts for the deprotection of **5** in DMSO−MeOH are $tBuPh_2SiOMe$ (which is volatile and easily removed by rotary evaporation), $tBuPh_2SiOH$ (which likely was formed from the presence of trace quantities of water), and $(tBuPh_2)_2SiO$. TBSOBn (**1**) was also tested under these conditions and provided similar results.

As an added advantage, CsF is easier to work with than solid TBAF because CsF can be flame-dried under vacuum, stored in a 160 °C oven, and manipulated in air. Solid, anhydrous TBAF can be prepared but is extremely hygroscopic and typically requires the use of inert atmosphere boxes and rigorously anhydrous reaction conditions to avoid adsorption of water.[7] Likewise, commercial TBAF cannot be dried at elevated temperatures under vacuum, because it undergoes a Hoffman elimination to yield butene, tributylamine, and bifluoride.[7,9,31] The disadvantage of our modified anhydrous conditions is that base arising from adventitious water is not buffered, and therefore the conditions may not be compatible with all base-sensitive substrates.

CONCLUSION

The new silyl ether cleavage conditions described in this Article are mild (pH 7.1, 23 °C) and use as little as 0.1 equiv of either TBAF or CsF. These catalytic deprotection conditions should prove useful both for acid- and base-sensitive substrates and for large-scale reactions in which cost and ease of purification (i.e., removal of the source of fluoride) are both a primary concern. Moreover, the studies described herein may have implications in standard TBAF-mediated deprotection reactions that use commercial sources of $TBAF\cdot xH_2O$. Mechanistic studies to investigate this catalytic Si−O bond cleavage reaction are in progress.

EXPERIMENTAL SECTION

General Experimental Methods. All reactions were performed in polypropylene copolymer centrifuge tubes under air unless otherwise noted. Air- and moisture-sensitive liquids were transferred by syringe. Organic solutions were concentrated by rotary evaporation (24−40 mmHg) at ambient temperature, unless otherwise noted. Benzyl alcohol, tetrabutylammonium fluoride hydrate, potassium phosphate dibasic, and all other reagents were purchased commercially and were used as received unless otherwise noted. Residual water was removed from cesium fluoride according to the procedure of Corriu, Moreau, and Pataud-Sat.[32] The silicon-protected benzyl alcohols were prepared according to the following known procedures: TBS-protected benzyl alcohol (**1**), Corey and Venkateswarlu;[4] TES-protected benzyl alcohol (**3**), Oppolzer, Snowden, and Simmons;[24] TIPS-protected benzyl alcohol (**4**), Cunico and Bedell;[25] TBDPS-protected benzyl alcohol (**5**), Hanessian and Lavallee;[26] DPMS-protected benzyl alcohol (**6**), Denmark, Hammer, Weber, and Habermas;[28] TPS-protected benzyl alcohol (**7**), Kocienski.[3] Flash column chromatography was performed as described by Still, Kahn, and Mitre,[33] employing silica gel (60-Å pore size, 32−63 μm, standard grade, Dynamic Adsorbents). Thin layer chromatography was carried out on Dynamic Adsorbents silica gel TLC (20 × 20 w/h, F-254, 250 μm).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded at 25 °C. Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to tetramethylsilane ($(CH_3)_4Si$, 0.00 ppm) or to residual protium in the solvent (C_4HD_7O, 3.58 ppm and 1.73 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), integration, and coupling constant (*J*) in hertz. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 25 °C. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0, or tetrahydrofuran-d_8, δ 67.6 ppm and 25.4 ppm).

HPLC analysis was performed using a reversed-phase phenyl-hexyl column. The column was equilibrated at 1:9 acetonitrile−water at 1 mL/min flow rate, and, after injection of the sample, the gradient was ramped to 9:1 acetonitrile−water over 15 min. This solvent ratio was then run for an additional 3 min for a total run time of 18 min.

General Procedure for Preparing Buffered TBAF Solutions. *a. Preparation of a 6.7 M Buffered TBAF Solution.* Tetrabutylammonium fluoride hydrate (0.48 g, 1.8 mmol) was dissolved in anhydrous tetrahydrofuran (90 μL). The resulting solution was sonicated for 10 min. Potassium phosphate buffer (0.1 M, pH 7.1, 180 μL) was added to the TBAF solution, and the entire mixture was sonicated for an additional 3 min. No precautions were employed to exclude air.

Table 2

molarity of buffered TBAF solution, M	mass (and millimoles) of tetrabutylammonium fluoride hydrate used
12.8	0.90 g (3.3 mmol)
9.1	0.65 g (2.5 mmol)
7.5	0.54 g (2.1 mmol)
5.0	0.36 g (1.4 mmol)
4.3	0.30 g (1.1 mmol)
3.3	0.24 g (0.9 mmol)
2.5	0.18 g (0.69 mmol)
2.1	0.15 g (0.57 mmol)
1.7	0.12 g (0.45 mmol)
0.67	0.048 g (0.18 mmol)
0	0 g (0 mmol)

b. Preparation of 12.8 M, 9.1 M, 7.5 M, 5.0 M, 4.3 M, 3.3 M, 2.5 M, 2.1 M, 1.7 M, 0.7 M, and 0 M Buffered TBAF Solutions. Identical procedures were used as described above for the preparation of a 6.7 M buffered TBAF solution, with the exception that the quantity of tetrabutylammonium fluoride hydrate used to make each solution varied as shown in Table 2.

c. Preparation of 3.3 M Buffered TBAF Solution with 0.0 M, 0.25 M, and 0.50 M Buffer. Identical procedures were used as described above for the preparation of a 3.3 M buffered TBAF solution, with the exception that the initial concentration of the potassium phosphate buffer solution used were 0.0 M, 0.25 M, and 0.5 M.

d. Preparation of 3.3 M Buffered TBAF Solution with pH 6.5, 7.0, 7.5, and 8.0 Buffer. Identical procedures were used as described above for the preparation of a 3.3 M buffered TBAF solution, with the exception that the initial pH values of the potassium phosphate buffer solution used were pH 6.5, 7.0, 7.5, and 8.0.

General Procedure for the Deprotection of TBSOBn (1). *a. Deprotection of TBSOBn (**1**) Using 1.1 Equiv of TBAF.* To a 15-mL polypropylene tube charged with a magnetic stirrer were added TBS-protected benzyl alcohol (**1**) (66 mg, 0.3 mmol, 1.0 equiv) and anhydrous tetrahydrofuran (3.3 mL). The buffered tetrabutylammonium fluoride solution (50 μL from the 6.7 M solution, 0.33 mmol fluoride, 1.1 equiv fluoride) was added to the THF solution, the screw cap was added to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was monitored by HPLC and was performed in triplicate.

*b. Deprotection of TBSOBn (**1**) Using 0.53, 0.28, 0.1, and 0 Equiv of TBAF.* Identical procedures were used as described above in part a, with the exception that different solutions of buffered TBAF were used as follows: 0.53 equiv (3.3 M buffered TBAF); 0.28 equiv (1.7 M buffered TBAF; 0.10 equiv (0.67 M buffered TBAF); 0 equiv (0 M buffered TBAF).

*c. Deprotection of TBSOBn (**1**) Using THF–Buffer Ratios of 425:1, 307:1, 250:1, 220:1, 167:1, 141:1, 84:1, 72:1, 56:1, and 23:1.* Identical procedures were used as described above in part a, with the exception that 0.5 equiv (0.15 mmol) of TBAF was used, and different volumes and different concentrations of buffered TBAF solutions were used as shown in Table 3.

Procedure for Measuring the pH of the Deprotection Reaction Mixture. Tetrabutylammonium fluoride hydrate (0.48 g, 1.8 mmol) was dissolved in 1.8 mL of potassium phosphate buffer (0.1 M, pH 7.1, 180 μL). The pH of the solution was found to be 7.1 using a pH meter.

To a 50-mL polypropylene tube charged with a magnetic stirrer were added TBS-protected benzyl alcohol (**1**) (0.95 g, 4.3 mmol, 1 equiv) and anhydrous tetrahydrofuran (43 mL). The buffered tetrabutylammonium fluoride solution (650 μL from the 0.67 M solution, 0.43 mmol fluoride, 0.1 equiv fluoride) was added to the THF solution, the screw cap was added to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was complete after 42 h, at which point the reaction vessel was cooled to −78 °C to freeze the water in the mixture. The THF was decanted, and the remaining aqueous reaction mixture was then warmed to 23 °C. The pH of the aqueous solution was measured using pH paper and was found to be in a range of pH 6.9–7.2.

Table 3

THF–buffer ratio	solution molarity, M	volume of solution used, μL
425:1	12.8	11.7
307:1	9.1	16.2
250:1	7.5	20.1
220:1	6.67	22.5
167:1	5.0	30
141:1	4.25	35.4
84:1	2.5	60
72:1	2.13	70.5
56:1	1.67	90
23:1	0.67	222

General Procedure for Deprotecting R_3SiOBn Using 0.1 Equiv TBAF. The procedure described above for deprotecting TBSOBn (**1**) using 0.1 equiv of TBAF was repeated for TESOBn (**3**), TIPSOBn (**4**), TBDPSOBn (**5**), DPMSOBn (**6**), and TPSOBn (**7**). The progress of the reaction was monitored by ^{1}H NMR.

Synthesis of Complex Substrate 8. To a flame-dried round-bottom flask charged with a magnetic stirrer were added *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine (0.60 g, 1.6 mmol, 1.1 equiv), L-serine benzyl ester hydrochloride (0.33 g, 1.4 mmol, 1 equiv), *O*-benzotriazole-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) (0.70 g, 1.8 mmol, 1.3 equiv), and anhydrous methylene chloride (15 mL). The flask was placed under an atmosphere of nitrogen, and *N*,*N*-diisopropylethylamine (1.2 mL, 7.1 mmol, 5 equiv) was added. The reaction mixture was stirred at 23 °C overnight and then was diluted with ethyl acetate and washed with 0.1 M HCl, followed by 10% aqueous sodium bicarbonate solution and brine. The organic layer was collected and dried over magnesium sulfate, and the solution was filtered and concentrated. The product was purified using silica gel flash column chromatography using 50% ethyl acetate in hexanes to provide *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine-L serine benzyl ester (**9**)[34] as a white solid (0.72 g, 1.3 mmol, 90%). mp 234–239 °C; IR (cm^{-1}) 3300, 1740, 1690, 1640; ^{1}H NMR (THF-d_8) δ 7.76 (d, 2H, J = 7.5), 7.59 (t, 2H, J = 5.3), 7.38–7.16 (m, 14H), 6.87 (d, 1H, J = 8.6), 5.16 (s, 2H), 4.61 (s, 1H), 4.53 (m, 1H), 4.20–4.15 (m, 3H), 3.87 (m, 1H), 3.74 (m, 1H), 3.11 (m, 1H), 2.90 (m, 1H); ^{13}C NMR (THF-d_8) δ 172.1, 171.1, 156.8, 145.3, 145.3, 142.2, 138.7, 137.3, 129.1–126.0, 120.5, 63.1, 56.8, 55.8, 54.9, 48.2; TOF MS (ESI) m/z 565 (100 MH^+). HRMS (ESI) Calcd for $C_{34}H_{33}N_2O_6$ ($M + H^+$): 565.2339. Found: 565.2341.

To a flame-dried round-bottom flask were added *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine-L-serine benzyl ester (**9**) (0.33 g, 0.58 mmol, 1 equiv), imidazole (0.10 g, 1.5 mmol, 2.5 equiv), and anhydrous dimethylformamide (15 mL). The flask was placed under an argon atmosphere, and the reaction mixture was cooled to 0 °C. Chlorotriethylsilane (0.11 g, 0.70 mmol, 1.2 equiv) was added to the flask dropwise via syringe, and the reaction mixture was warmed to 23 °C over 1 h and then allowed to stir overnight. The reaction mixture was diluted with dichloromethane, and the organic layer was washed with 0.1 M HCl (1 × 30 mL), followed by water (1 × 30 mL) and brine (1 × 30 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated. The crude product was purified using silica gel flash

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column chromatography using 20% ethyl acetate in hexanes to yield *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine-*O*-(triethylsilyloxy)-L-serine benzyl ester (**8**) as a white solid (0.25 g, 0.37 mmol, 63%). mp: 137−140 °C; IR (cm^{-1}) 3290, 1740, 1690, 1650; ^1H NMR ($CDCl_3$) δ 7.75 (d, 2H, J = 7.1), 7.52 (t, 2H, J = 7.6), 7.40−7.20 (m, 14H), 6.61 (br s, 1H), 5.48 (br s, 1H), 5.16 (s, 2H), 4.65 (d, 2H, J = 5.4), 4.51 (s, 1H), 4.40 (t, 1H, J = 7.0), 4.27 (s, 1H), 4.16 (t, 1H, J = 6.1), 4.05 (d, 1H, J = 9.8), 3.76 (d, 1H, J = 10), 3.09 (s, 2H), 0.85 (t, 9H, J = 5.3) 0.49 (q, 6H, J = 5.3); ^{13}C NMR ($CDCl_3$) δ 170.7, 169.8, 155.8, 150.6, 143.9, 141.4, 136.4, 135.4, 129.6, 128.6, 128.5, 128.2, 125.2, 120.0, 107.3, 67.4, 63.1, 56.9, 54.5, 47.1, 38.9, 6.7, 4.3; TOF MS (ESI) m/z 679 (100 MH^+). HRMS (ESI) Calcd for $C_{40}H_{47}N_2O_6Si$ ($M + H^+$): 679.3203. Found: 679.3207.

Synthesis of Complex Substrate 16. To a flame-dried round-bottom flask charged with a magnetic stirrer was added 2,2,2-trifluoro-1-phenylethanol (**17**) (0.20 g, 1.4 mmol), imidazole (0.19 g, 2.8 mmol), *tert*-butyl(chloro)dimethylsilane (0.21 g, 1.4 mmol), and anhydrous acetonitrile (1 mL). The flask was placed under an argon atmosphere and allowed to stir overnight. The reaction mixture was partitioned over dichloromethane (10 mL) and 0.1 M HCl (10 mL). The aqueous layer was separated and washed with dichloromethane (2 × 10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated. The crude product was purified with silica gel flash column chromatography using 100% pentane to yield *tert*-butyldimethyl-(2,2,2-trifluoro-1-phenylethoxy)silane (**16**) as a clear oil (0.20 g, 0.69 mmol, 62%). IR (cm^{-1}) 1260, 1170, 1120, 850; ^1H NMR ($CDCl_3$) δ 7.44 (m, 2H), 7.38 (m, 3H), 4.91 (q, 1H, J = 7.2), 0.89 (s, 9H), 0.11 (s, 3H), −0.03 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 135.7, 129.2, 128.4, 127.8, 73.8, 25.6, 18.3, −5.0, −5.2; TOF MS (ESI) m/z 233 (29 [M − *t*Bu]$^+$). HRMS (ESI) Calcd for $C_{10}H_{12}F_3OSi$ ([M − *t*Bu]$^+$): 233.0610. Found: 233.0619.

Deprotection of Complex Substrates. *a. Deprotection of* ***8***. To a 1.7-mL polypropylene microcentrifuge tube charged with a magnetic stirrer were added *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine-*O*-(triethylsilyloxy)-L-serine benzyl ester (**8**) (0.04 g, 0.06 mmol, 1 equiv) and anhydrous tetrahydrofuran (0.65 mL). Buffered tetrabutylammonium fluoride solution (9.7 μL from the 3.3 M solution, 0.05 mmol fluoride, 0.5 equiv) was added to the THF solution, the cap was affixed to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was complete after 3 h, at which point the crude material was loaded directly onto a silica gel flash column. Chromatography (30:70 ethyl acetate−hexanes, increasing to 50:50 ethyl acetate−hexanes) provided *N*-(9-fluorenylmethoxycarbonyl)-L-phenylalanine-L-serine benzyl ester (**9**)[34] (0.02 g, 0.04 mmol, 63%).

b. Deprotection of ***10***. To a 1.7-mL polypropylene microcentrifuge tube charged with a magnetic stirrer were added acetic acid 3*S*-[benzyl-(9*H*-fluoren-9-ylmethoxycarbonylamino)-2*R*-*tert*-butyloxy-carbonylamino-5-trimethylsilylpent-4-ynyl] ester (**10**)[35] (10 mg, 16 μmol, 1 equiv) and anhydrous tetrahydrofuran (0.2 mL). Buffered tetrabutylammonium fluoride solution (2.3 μL from a 3.3 M solution, 7.6 μmol fluoride, 0.5 equiv) was added to the THF solution, the cap was affixed to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was complete after 5 min, at which point the crude material was loaded directly onto a silica gel flash column. Chromatography (80:20 hexanes−ethyl acetate) provided acetic acid 3*S*-[benzyl-(9*H*-fluoren-9-yl-methoxycarbonylamino)-2*R*-*tert*-butyloxycarbonylaminopent-4-ynyl] ester (**11**) as a white solid (8.4 mg, 15 μmol, 95%). mp: 226−231 °C; IR (cm^{-1}) 3280, 2120, 1705; ^1H NMR ($CDCl_3$) δ 7.67 (d, 2H J = 7.4), 7.30 (s, 8H), 7.12−7.08 (m, 3H), 5.33 (d, 1H, J = 9), 5.04 (d, 1H, J = 9.8), 4.62−4.00 (m, 8H), 2.33 (s, 1H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 170.8, 158.2, 155.5, 143.8, 141.2, 138.1, 128.6−125.0, 120.0, 98.0, 80.0, 78.5, 68.8, 64.4, 49.9, 48.6, 47.2, 28.5, 21.0; TOF MS (ESI) m/z 569 (88 MH^+). HRMS (ESI) Calcd for $C_{34}H_{37}N_2O_6$ ($M + H^+$): 569.2652. Found: 569.2660.

c. Deprotection of ***12***. To a 1.7-mL polypropylene microcentrifuge tube charged with a magnetic stirrer were added 1-(2-azidophenyl)-4-(*tert*-butyldimethylsilyloxy)-2-butyn-1-one (**12**) (11 mg, 36 μmol, 1 equiv) and anhydrous tetrahydrofuran (0.35 mL). Buffered tetrabutylammonium fluoride solution (5.3 μL from the 3.3 M solution, 18 μmol fluoride, 0.5 equiv) was added to the THF solution, the cap was affixed to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was complete after 18 h, at which point the crude material was loaded directly onto a silica gel flash column. Chromatography (20:80 ethyl acetate−hexanes, increasing to 50:50 ethyl acetate−hexanes) provided 1-(2-azidophenyl)-4-(hydroxy)-2-butyn-1-one (**13**) as an orange solid (5.6 mg, 0.03 mmol, 78%). mp 164−167 °C; IR (cm^{-1}) 3260, 2290, 2120, 1720; ^1H NMR ($CDCl_3$) δ 7.77 (m, 2H), 7.70 (t, 1H, J = 7.3), 7.42 (t, 1H, J = 7.7), 4.98 (s, 2H), 2.69 (b, 1H); ^{13}C NMR ($CDCl_3$) δ 176.3, 148.1, 141.2, 136.1, 129.2, 128.5, 126.3, 113.3, 57.0, 32.1; TOF MS (API) 202.1 (100, MH^+). HRMS (ESI) Calcd for $C_{10}H_8N_3O_2$ ($M + H^+$): 202.0590. Found: 202.0599.

d. Deprotection of ***14***. To a 1.7-mL polypropylene microcentrifuge tube charged with a magnetic stirrer were added 3-methyl 3-(1-(*tert*-butoxycarbonylamino)-2-methylpropyl)-5-((*tert*-butyldimethylsilyloxy)-(5-methyl-2-(triisopropylsilyloxy)phenyl)methyl)isoxazole-4-carboxylate (**14**) (18 mg, 26 μmol, 1 equiv) and anhydrous tetrahydrofuran (0.25 mL). Buffered tetrabutylammonium fluoride solution (3.9 μL from a 3.33 M solution, 0.013 mmol fluoride, 0.5 equiv) was added to the THF solution, the cap was affixed to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was complete after 24 h, at which point the crude material was purified directly using silica gel flash chromatography (15:85 ethyl acetate−hexanes, increasing to 30:70 ethyl acetate−hexanes) to provide methyl 3-(1-(*tert*-butoxycarbonylamino)-2-methylpropyl)-5-((hydroxy)(2-hydroxy-5-methylphenyl)methyl)-isoxazole-4-carboxylate (**15**) as a clear oil (10 mg, 24 μmol, 95%). IR (cm^{-1}) 3250, 1710, 1680; ^1H NMR ($CDCl_3$) δ 7.98 (b, 1H), 7.02 (d, 1H, J = 8.1), 6.78 (m, 2H), 6.39 (b, 1H), 5.32 (m, 1H), 5.17 (m, 1H), 3.91 (s, 3H), 2.22 (s, 3H), 2.07 (m, 1H), 1.42 (s, 9H), 0.98−0.83 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 178.0, 163.7, 163.2, 155.8, 153.2, 130.9, 129.7, 128.0, 122.4, 117.3, 108.3, 80.1, 68.2, 52.8, 32.6, 28.5, 20.7, 20.0, 17.1; TOF MS (ESI) m/z 435 (100 MH^+). HRMS (ESI) Calcd for $C_{22}H_{31}N_2O_7$ ($M + H^+$): 435.2131. Found: 435.2150.

e. Deprotection of ***16***. To a 1.7-mL polypropylene microcentrifuge tube charged with a magnetic stirrer was added *tert*-butyldimethyl(2,2,2-trifluoro-1-phenylethoxy)silane (**16**) (41 mg, 0.14 mmol, 1 equiv) and anhydrous tetrahydrofuran (1.4 mL). Buffered tetrabutylammonium fluoride solution (21 μL from 3.3 M solution, 0.07 mmol) was added to the THF solution, the cap was affixed to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was complete after 2 h, at which point the crude material was loaded directly onto a silica gel flash column. Chromatography (10:90 ethyl acetate−hexanes) provided 2,2,2-trifluoro-1-phenylethanol[36] (**17**) as a clear oil (24 mg, 0.14 mmol, 96%).

Cesium Fluoride Deprotection Conditions. *a. Preparation of a 0.67 M Cesium Fluoride Solution.* Cesium fluoride (27 mg, 0.18 mmol) was dissolved in anhydrous dimethyl sulfoxide (90 μL). The resulting solution was sonicated for 10 min. Anhydrous methanol (180 μL) was added to the CsF solution, and the entire mixture was sonicated for an additional 3 min. No precautions were employed to exclude air.

*b. Deprotection of TBSOBn (****1****).* To a 15-mL polypropylene tube charged with a magnetic stirrer were added TBS-protected benzyl alcohol (**1**) (73 mg, 0.33 mmol, 1 equiv) and anhydrous dimethyl sulfoxide (3.3 mL). The cesium fluoride solution (50 μL from a 0.67 M solution, 33 μmol fluoride, 0.1 equiv) was added to the DMSO solution, the screw cap was added to the polypropylene tube, and the reaction mixture was stirred at 23 °C. The reaction was monitored by HPLC. Note: The procedure for deprotecting TBDPSOBn (**5**) is identical to the procedure for deprotecting **1**.

■ ASSOCIATED CONTENT

Supporting Information. Characterization data for all new compounds, and tables of data for reaction rates. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

†This Article is dedicated to Professor Steven M. Weinreb on the occasion of his 70th birthday.

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(19) The pH value of the aqueous portion of the solution before deprotection of **1** was 7.1 (measured using a pH meter). After **1** was converted completely to **2**, the pH value of the aqueous portion of the reaction mixture was 6.9−7.2 (measured using pH paper; see Experimental Section for details).
(20) We used a single batch of solid TBAF·$x$$H_2O$ for the experiments shown in Figures 2 and 3. This batch contained TBAF·1.8H_2O, as determined by elemental analysis.
(21) The total quantity of water in each experiment shown in Figure 3 was calculated from the sum of the number of moles of water in: TBAF + THF + water added with the phosphate buffer. Since 0.5 equiv of TBAF were used in each experiment, the TBAF contributed 299 μmol of water. Karl Fischer titration of the THF used in the experiments revealed 11.41 ppm water, which indicates that the THF contributed 2.1 μmol of water. These sources of water provided a baseline level to which we added more water by varying the concentration and volume of buffered TBAF solution that was added to the reaction mixture.
(22) A similar observation was noted by Hogrefe et al. in ref 8 when using stoichiometric quantities of TBAF to effect deprotection of a silicon protecting group.
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