

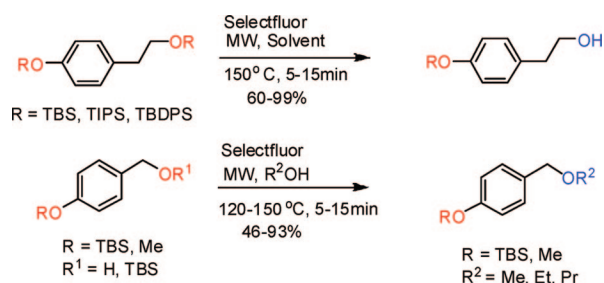
A Novel, Chemoselective and Efficient Microwave-Assisted Deprotection of Silyl Ethers with Selectfluor

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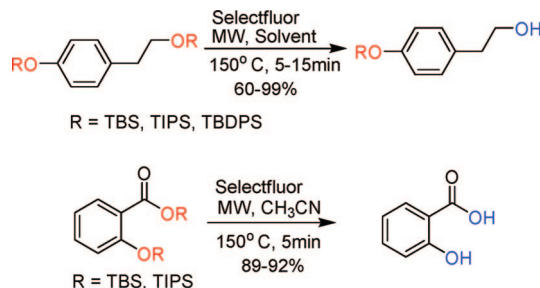


A novel microwave-assisted, chemoselective and efficient method for the cleavage of silyl ethers (aliphatic and aromatic) catalyzed by Selectfluor is reported. A wide range of TBS-, TIPS-, and TBDPS-protected alkyl silyl ethers can be chemoselectively cleaved in high yield in the presence of aryl silyl ethers. The chemoselective deprotection of phenolic TBS ethers, and not the TIPS- or TBDPS-protected phenolic ethers, and the deprotection of silyl esters were also achieved under these reaction conditions. In addition, the transesterification and etherification of benzylic hydroxy groups in alcoholic solvents is observed.

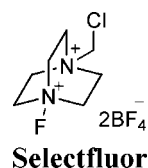
Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate)) is a commercially available, user-friendly electrophilic fluorinating reagent for a wide variety of electron-rich carbon centers.^{1,2} Due to its electrophilic and oxidative characteristics Wong has reported its use in the cleavage of electron-rich protecting groups, such as *p*-methoxybenzylidene (PMP) and tetrahydropyranyl (THP) ethers and 1,3-dithianes.³

Silyl esters and ethers are among the most frequently used protecting groups for acid and alcohol functionalities.⁴ A number of Lewis acids and other reagents have been reported to be effective in promoting cleavage of silyl-protected acids and

SCHEME 1



alcohols and examples from the recent literature include the following: BF₃,⁵ BCl₃,⁶ sulfated SnO₂,⁷ silica triflate,⁸ CuBr₂,⁹ ZnBr₂,¹⁰ NIS,¹¹ TMSBr,¹² and TMSCl.¹³ Many of these reagents provide the added advantage of promoting selective desilylation of bis-silyl ethers.^{14,15}



We recently reported the chemoselective and efficient deprotection of silyl ethers using catalytic quantities of TMSBr.^{16a} We have also reported the use of ZrCl₄ as an efficient catalyst for one-pot protection/deprotection synthetic methodology.^{16b}

Considering the electrophilic and oxidative characters of Selectfluor, we envisioned that this reagent could be used in the cleavage of more commonly used, electron-rich silyl ether protecting groups. In this communication, we wish to report the desilylation of a wide range of silyl-protected primary, secondary, and aromatic hydroxy and acid groups using microwave irradiation in the presence of a substoichiometric amount of Selectfluor in organic solvents such as acetonitrile, methanol, and ethanol without any added reagent (Scheme 1).

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TABLE 1. The Deprotection of Silyl-Protected Hydroxy Groups Catalyzed by Selectfluor in Acetonitrile^a

Entry	Substrate	Eq	Time min	Product	Yield %	
1						
	a R = TES	0.1	3		82	
	b R = TBS	0.1	3		97	
	c R = TIPS	0.4	10		95	
2		0.1	10		82	
3		0.1	3		92	
4		0.1	5		83	
5		0.2	10		94	
6		a R = TBS	0.4	10		97
		b R = TMS	0.1	2		93
7		0.2	10		54	
8		0.1	20		—	

^a 150 °C, 150 W max; all products were characterized from spectral (¹H NMR, ¹³C NMR, and MS) data and by comparison with the parent alcohols.

To our knowledge, studies exploiting this catalyst for such transformations have not been previously reported.

Since 1986 microwave irradiation has become an increasingly popular method for accelerating synthetic transformations.¹⁷ This technology offers a clean, effective, and convenient method of heating, which often results in higher yields, almost always shorter reaction times, and easier workup. Organic reactions that are assisted by microwave irradiation have attracted considerable attention.¹⁸ The deprotection of silyl groups, particularly chemoselective deprotection, assisted by microwave heating has so far been described in a limited number of publications.¹⁹

By using microwave heating a wide range of silyl-protected hydroxy groups were cleaved within minutes in high to excellent yields by using substoichiometric quantities of Selectfluor in acetonitrile, Table 1. The silyl-protecting group employed has a significant effect on the reaction rate, entries 1a–c. The deprotection of monoprotected silyl ethers proceeded in 54% to 97% yields, all in short reaction times (3–10 min), entries 1–5. The deprotection methodology proceeds cleanly, even in the presence of secondary and allylic alcohols, entries 3 and 6. Several functional groups such as ester, ketone, acetate, and acetal (entries 7 and 8) remained intact, under these reactions conditions.

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In conjunction with an ongoing total synthesis project in our laboratory, we have prepared a bis-*tert*-butyldimethylsilyl (TBS) ether (5*S*,6*R*)-methyl 5,6-bis(*tert*-butyldimethylsilyloxy)oct-7-enoate as a key synthetic intermediate.²⁰ With this compound at hand we applied our new deprotection methodology to afford the corresponding diol in 97% yield after 10 min at 150 °C, entry 6a. In addition, we observed that the corresponding bis-trimethylsilyl (TMS) ether was also effectively cleaved in 93% yield using 0.1 equiv of Selectfluor, entry 6b.

Alcoholic and phenolic hydroxy groups are present in many complex natural products such as vancomycin and teicoplanin, and the chemoselective deprotection of alcoholic and phenolic silyl ethers is of considerable interest.²¹ In this context, we were pleased to find that we could develop a mild and efficient methodology in which by controlling the reaction conditions, alkyl silyl ethers were chemoselectively deprotected in the presence of aryl silyl ethers using a substoichiometric amount of Selectfluor, Tables 2 and 3.

To explore the generality of this reagent system for desilylation, we examined the solvent effect by employing bis-TBS ether **1** as substrate (Table 2). Use of Selectfluor in organic solvents such as acetonitrile, ethanol and dimethylformamide provides a chemoselective means of removing alkyl TBS ethers in the presence of aryl TBS ethers. When acetonitrile was employed, desilylation went smoothly within 10 min in 94% yield, entry 1. The use of an acetonitrile/water mixture gave an 88% yield, entry 2. Ethanol afforded a high yield (95%) of desilylated product but required an excess of Selectfluor and longer reaction time of 15 min, entry 6. Other alcoholic solvents

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TABLE 2. The Chemoselective Desilylation of Bis-Silyl Ether Catalyzed by Selectfluor in Various Solvents^a

Entry	R	Solvent	Eq	Time min	Yield, %	
					2	3
1	H	CH ₃ CN	0.1	10	94	
2	H	CH ₃ CN+H ₂ O	0.1	5	88	
3	H	DMF	0.1	15	73	
4	H	CH ₃ NO ₂	0.1	5	81	
5	H	isopropanol	0.5	25	74	
6	H	EtOH	0.6	15	95	
7	H	MeOH	1.0	12 h ^{b,c}	85	
8	H	MeOH	0.1	5		81
9	Br	MeOH	0.1	5		92
10	OMe	MeOH	0.1	5		99

^a 150 °C, 150 W max initial MW power. ^b Room temperature. ^c Reflux 4 h 87%.

TABLE 3. The Chemoselective Deprotection of Bis-Silyl Protected Hydroxy Groups Catalyzed by Selectfluor

Entry	Substrate	Eq	Time min	Product	Yield %	
1		a R = TIPS	0.1	15		92 ^a (99) ^b
		b R = TBDPS	0.3	10		82 ^a
		c R = DPMS	0.2	10		—
2		R = TBS	0.1	5		72 ^a
3		a R = TBS	0.1	5		87 ^a
		b R = TIPS	0.2	15		74 ^a (60) ^b
		c R = TBDPS	0.2	10		95 ^a (79) ^b

^a Temperature 150 °C, 150 W max initial MW power, CH₃CN. ^b Percent yield in MeOH; all products were characterized from spectral (¹H NMR, ¹³C NMR, and MS) data and by comparison with the parent alcohols.

such as isopropanol did afford the desilylation product but the reaction was much slower as a longer reaction time of 25 min was required. The reaction was successful in the polar aprotic solvent dimethylformamide although the reaction was slower than in acetonitrile, entry 3.

In the preliminary results using methanol as solvent we also noted that the reaction at room temperature afforded the alkyl silyl ether deprotected product. However, when the reaction was performed in methanol with microwave heating, aryl TBS ethers were chemoselectively cleaved in the presence of alkyl TBS ethers in 81–99% yield, entries 8–10. This clearly indicates another potential use of this method in the rapid and chemoselective deprotection of phenolic TBS ethers in methanol by using microwave heating.

To generalize the utility of this method we further investigated the deprotection of bis-silyl ethers in acetonitrile, which resulted in the cleavage of alkyl silyl ethers in 72–95% yield, Table 3. Surprisingly, when the bulkier bis-silyl ethers such as TIPS and TBDPS were heated in methanol the alkyl TIPS and TBDPS ethers were cleaved instead of the aryl TIPS and TBDPS ethers, in contrast to results we obtained with the bis-TBS ethers (Table

TABLE 4. The Transesterification and Etherification of Benzylic Hydroxy Groups Catalyzed by Selectfluor

Entry	Substrate	Eq	Time min	Product	Yield %
1		0.25	10		93
		0.25	10		88
		0.50	15		92
2		0.25	10		92
		0.25	10		91
		0.50	15		91
3		0.4	5		98
4		0.2	5		90
		0.2	10		85
5		0.1	10		82 ^b
		0.2	10		90 ^b
6		0.1	10		85 ^b
7		0.1	10		70 ^b
8		0.1	10		76 ^{b,c}
9		0.1	5		40 ^b

^a Temperature 150 °C, 150 W max initial MW power. ^b Temperature 120 °C, 150 W max initial MW power. ^c Stereochemistry conformed by chiral HPLC; all products were characterized from spectral data and by comparison with the parent alcohols.

2, entries 8–10). Similarly, in the cases of bulkier silyl ethers such as TIPS and TBDPS, the chemoselective deprotection required a higher catalyst loading of Selectfluor and longer reaction times. This chemoselective silyl cleavage procedure is much faster than the previously reported methods such as TMSCl.¹⁷

Collington and co-workers have used aqueous HF in acetonitrile for the selective deprotection of alkyl silyl ethers in the presence of aryl silyl ethers.²² We believe that our method is superior to several other methods such as Collington's as they use HF which is hazardous, toxic, and also requires special care for its use whereas we have introduced a simple, rapid, and inexpensive method.

We wished to extend the substrate range to include benzylic silyl ethers and found that the use of substoichiometric quantities of Selectfluor in alcoholic solvents led, not to the expected benzylic alcohol, but instead to the products of trans-etherification in 88–98% yield, entries 1–3 in Table 4; however, transesterification of allylic alcohols was not achieved, entries 3 and 6 in Table 1. We performed the etherification reaction in

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TABLE 5. The Deprotection of Silyl Protected Acid Groups Catalyzed by Selectfluor^a

Entry	Substrate	Eq	Time min	Product	Yield %
1		0.4	10		93
2		a R = TBS 0.2	5		96
		b R = TBDPS 0.4	5		89

^a Temperature 150 °C, 150 W max initial MW power; all products were characterized from spectral (¹H NMR, ¹³C NMR, and MS) data and by comparison with the parent alcohols.

deuterated solvent on the enantiomerically pure benzylic substrate and the product formed was a racemic mixture (Table 4, entry 8).

To further explore the utility of this novel desilylation procedure we have also investigated the cleavage of silyl protected esters, Table 5. This proceeded in high yields (89–93%) for aromatic esters, entries 1 and 2. However, chemoselective cleavage of silyl esters in the presence of silyl ethers was not achieved, entry 2. Since Selectfluor is a fluorinating reagent,^{1,2} we obtained the fluorine spectra (¹⁹F NMR) of our products and they did not show any peaks. The ¹⁹F NMR of our crude reaction mixtures in deuterated solvents showed formation of the silyl fluorides, TBSF and TBDPSF (−172.2 and −182.7 ppm, respectively; entry 8, Table 2; entry 1b, Table 3; entry 1a, Table 4). We think that there is the possibility of the formation of reactive species MeOF, EtOF, *i*-PrOF or HF or HOF under nonanhydrous conditions.

In conclusion, the use of Selectfluor with microwave-assisted heating provides a mild, efficient, and chemoselective means of removing alkyl silyl ethers such as TBS, TIPS, and TBDPS in the presence of aryl silyl ethers. The advantages of this procedure over earlier reported processes include its functional group compatibility, simplicity, the nonrequirement of additional reagents, and the clean and rapid reactions it promotes. This methodology is equally applicable to thermal and room temperature conditions.

By controlling the reaction conditions, selective desilylation can be accomplished in the presence of bulkier silyl groups and other acid-sensitive protecting groups. In addition, high yields of etherification and transesterification of benzylic hydroxy

groups were achieved by using this procedure. Nonetheless, the facile conditions, high yields, and demonstrated applicability to complex, highly functionalized molecules suggest that this protocol will find widespread utility in synthesis.

Experimental Section

General Procedure for the Deprotection of Silyl-Protected Hydroxy Groups Catalyzed by Selectfluor. A 10-mL reaction vessel was charged with a magnetic stir bar, 1 mmol of silyl ether, and 0.1 mmol of Selectfluor, in organic solvent (acetonitrile or methanol). A septum cap was affixed, the vessel was placed in the microwave cavity of a CEM Discover microwave reactor, and the pressure sensor was attached. The stirring reaction mixture was irradiated at 150 °C (MW power 150 W) for 2–15 min for TMS, TES, and TBS silyl ethers (10–20 min for TBDPS and TIPS ethers). After cooling to room temperature, TLC indicated the disappearance of starting material. Most of the products were separated on preparative silica gel plates without any extraction by elution with diethyl ether:pentane (1:4). In some cases the reaction mixture was diluted with Et₂O and water. The layers were separated, and the aqueous phase was extracted with Et₂O. The combined organic layers were washed three times with saturated NaHCO₃ and three times with water, dried over MgSO₄, filtered, and concentrated. Column chromatography afforded the pure alcohol. All products were spectrally identical with authentic alcohols.

Microwave Irradiation Experiments. All microwave experiments were performed with the CEM Discover Synthesizer possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in standard microwave process Pyrex vials (capacity 10 mL) using the high absorbance level. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

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Supporting Information Available: Characterization data and ¹H and ¹³C NMR spectra of the products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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