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Exploration of the Fluoride Reactivity of Aryltrifluoroborate on Selective Cleavage of Diphenylmethylsilyl Group

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Abstract: The first known report on the fluoride catalytic reactivity of potassium aryltrifluoroborate is described. The fluoride reactivity of phenyltrifluoroborate was controlled by substituents on the trifluoroborate-attached benzene, such as the methoxy group at the para-position and the methyl group at the ortho-position. In addition, the selective aryltrifluoroborate-catalyzed cleavage of the diphenylmethylsilyl group was achieved.

Potassium organotrifluoroborate is an important and promising surrogate of organoboronic acid for use in metal-catalyzed cross-coupling reactions due to its excellent bench stability. Since Molander reported Suzuki-Miyaura cross-coupling reactions with potassium aryl, alkenyl, alkynyl, and alkyltrifluoroborates in 2001,[1] much effort has been devoted to the development of a wide variety of transition-metal-catalyzed cross-coupling reactions by using potassium trifluoroborate.[2] In addition, potassium trifluoroborate-incorporated compounds have been developed as useful reaction substrates in organic reactions such as transition-metal-free coupling,[3] epoxidation,[4] orthogonal borylation,[5] and total synthesis.[6] As well, unique chemoselective amide bond-forming reactions combining potassium acyltrifluoroborate and azide,[7] *O*-carbonylated hydroxylamine,[8] or primary amine and amide under acidic conditions,[9] were developed.

In chemical biology, electron poor potassium aryltrifluoroborate has been studied in the development of a [^{18}F]-labeled radiotracer for positron emission tomography (PET) imaging.[10] Keller and Overall et al. developed the 2,4,6-trifluoro-3-[^{18}F]trifluoroborylbenzoyl group as an electron poor aryltrifluoroborate and applied it to the synthesis of in vivo, stable [^{18}F]trifluoroborate-labeled marimastat, which is a noncovalent matrix metalloproteinase (MNP) inhibitor (Figure 1a).[11] The three fluorines on the benzene ring led to an electron deficit, thereby suppressing the release of fluoride from trifluoroborate to generate difluoroborane, which is easily hydrolyzed in a water solution and decomposes to boronic acid.[12] On the basis of the design of the electron poor aryltrifluoroborate, [^{18}F]trifluoroborate-substituted pyridine with an electron poor skeleton and bearing bromine as an electron withdrawing group was developed and the [^{18}F]trifluoroborate-modified cyclic RGD peptide was synthesized (Figure 1a).[13]

Inspired by the extensive application of aryltrifluoroborate to organic synthesis and molecular probes, we began to explore the unique reactivity of aryltrifluoroborate. Based on the effect of the substituent on the trifluoroborate-attached arene, which affects the stability of the trifluoroborate reported by Perrin,[12] we anticipated that substitution of an electron-donating group to the trifluoroborate-attached arene would enhance the fluoride reactivity of the aryltrifluoroborate (Figure 1b). Herein, we report the fluoride reactivity of the potassium phenyltrifluoroborate derivatives electronically enriched by the substituent on the benzene, enabling a selective desilylation reaction of the diphenylmethylsilyl ($MePh_2Si$) group.

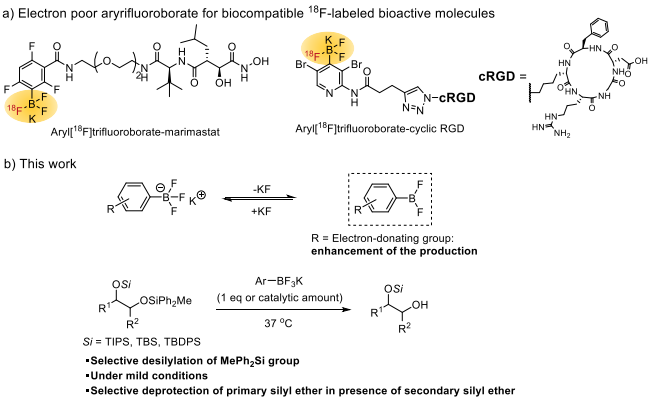

Figure 1. (a) Application of electron poor aryltrifluoroborate to the biocompatible ^{18}F-labeled bioactive molecule. (b) Reactivity of electron rich aryltrifluoroborate as a fluoride reagent and its catalytic selective desilylation.

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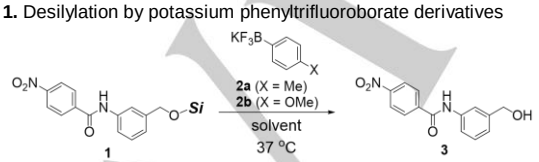
To examine the fluoride reactivity of aryltrifluoroborate, we first chose potassium *p*-tolyltrifluoroborate **2a**, which is commercially available, as the electron neutral phenyltrifluoroborate, and we attempted to promote a desilylation reaction with a series of benzyl silyl ethers (Table 1). The silyl ethers **1a**-**c**, which are derived from 3-[(4-nitrobenzoyl)amino]benzyl alcohol and protected by TIPS, TBS, and TBDPS groups for each, were treated with 100 mol% trifluoroborate **2a** in DMSO at 37 °C. The resulting desilylation reaction gave the alcohol **3** in negligible yield (Entry 1-3). We then tried the desilylation reaction on **1a**,**b** by using potassium *p*-methoxyphenyltrifluoroborate **2b** as the electron rich phenyltrifluoroborate, which is also commercially available, producing **3** in improved yields, 10% and 8%, respectively (Entry 4 and 5). As a moderately fluoride-sensitive silyl group, the $MePh_2Si$ group-protected benzyl alcohol derivative **1d** was subjected to this desilylation reaction. Treatment of the silyl ether **1d** with trilfluoroborate **2a** in DMSO at 37 °C cleaved the $MePh_2Si$ group to give the alcohol **3** in 88% yield after 4 h (Entry 6). The desilylation was performed at lower concentration (5 mM) to avoid overreaction of the desilylated product with trifluoroborate. When the reaction was carried out with 0.56 mmol of **1** and **2a**, according to monitoring by TLC, it was confirmed that the desilylation under this conditions was also compatible with large scale. Moreover, when a catalytic amount (16.7 mol%) of trifluoroborate **2a** was loaded, the desilylation was completed and the corresponding alcohol **3** was obtained in 86% yield (Entry 7). The catalytic desilylation of **1d** was investigated in 50, 33, and 25 mol% loading of **2a**, the product **3** was obtained in 88% after reaction for 6 h, 84% after reaction for 10 h, and 77% after reaction for 24 h by HPLC ananlysis, for each. However, $CHCl_3$ and THF were not applicable to this desilylation due to the poor solubility of potassium aryltrifluoroborate in these organic solvents, giving the alcohol **3** in 3% and 7% yields, respectively (Entry 8 and 9). In order to neutralize the hydrogen fluoride that was likely to be generated by the hydrolysis of potassium trifluoroborate, the desilylation was performed in phosphate buffer saline containing DMSO (pH 7.4) (Entry 10). Although it was expected that the electron neutral aryltrifluoroborate **2a** would not be not stable in aqueous solution and appeared to be nonreactive, the desilylation of **1d** proceeded and the alcohol **3** was obtained in 38% yield. However, the trifluoroborate **2a** demonstrated poor reactivity in anhydrous DMSO, producing **3** in trace amounts (Entry 11). This suggested that a small amount of water works as a reactant in this desilylation reaction.

Table 1. Desilylation by potassium phenyltrifluoroborate derivatives



Entry	*Si*	$ArBF_3K$	Solvent	Time (h)	Yield of **3** (%)[f]
1[a]	TIPS (**1a**)	**2a** (100 mol%)	DMSO	24	1
2[a]	TBS (**1b**)	**2a** (100 mol%)	DMSO	24	1
3[a]	TBDPS (**1c**)	**2a** (100 mol%)	DMSO	24	3
4[b]	TIPS (**1a**)	**2b** (100 mol%)	DMSO	24	10
5[b]	TBS (**1b**)	**2b** (100 mol%)	DMSO	24	8
6[b]	$MePh_2Si$ (**1d**)	**2a** (100 mol%)	DMSO	4	88
7[c]	$MePh_2Si$ (**1d**)	**2a** (16.7 mol%)	DMSO	33	86
8[b]	$MePh_2Si$ (**1d**)	**2a** (100 mol%)	$CHCl_3$[e]	24	3
9[b]	$MePh_2Si$ (**1d**)	**2a** (100 mol%)	THF[e]	24	7
10[d]	$MePh_2Si$ (**1d**)	**2a** (100 mol%)	DMSO/PBS (1:2)	24	38
11[b]	$MePh_2Si$ (**1d**)	**2a** (100 mol%)	Anhydrous DMSO	24	Trace

[a] The reaction was performed with a 50 mM solution of **1**. [b] The reaction was performed with a 5 mM solution of **1**. [c] The reaction was performed with a 30 mM solution of **1** and 5 mM solution of **2a**. [d] The reaction was performed with a 10 mM solution of **1**. [e] The solvent contained 1% DMSO. [f] Yield was calculated by HPLC analysis.

To further explore the unique fluoride reactivity of the electron neutral *p*-tolyltrifluoroborate **2a** and the electron rich *p*-methoxyphenyltrifluoroborate **2b**, a substrate analysis of various $MePh_2Si$ ethers was carried out (Table 2). Although this desilylation in 50 mol% loading of trifluoroborate **2a** also gave the alcohol **3** excellent yield (Table 1), the desilylation was carried out by using 100 mol% of **2**, by considering low reactive substrates, including amino acid derivatives and secondary silyl ethers. The 2-naphthylmethyl silyl ether **4** reacted with 100 mol% electron neutral trifluoroborate **2a** in DMSO at 37 °C. After 33 h, the alcohol **PD4** was obtained in 71% yield. Subsequently, desilylation was examined under the same conditions. The (*E*)-cinnamyl silyl ether **5** could be desilylated by **2a** to give the alcohol **PD5** in excellent yield. The liner alkyl silyl ethers **6** and **7** were treated with **2a**, giving the corresponding alcohols **PD6** and **PD7** in 80% and 18% yields, respectively. It was expected that **PD7** would be trapped by the boron after quenching the reaction with brine. Thus, isolation of **PD7** by silica gel column chromatography led to decrease the yield. In addition, it was difficult to calculate the yield by HPLC analysis due to the low UV absorption. Treatment of **8**, which has a pyrene and is a useful fluorophore, with **2a** afforded the alcohol **PD8** in 60% yield. Use of the electron rich trifluoroborate **2b** completed the desilylation of **8** within 2 h and **PD8** was obtained in quantitative yield. This desilylation reaction of **9**, which has a free aromatic amino group, produced **PD9** in 68% yield, without interfering with the trifluoroborate. The heteroaromatic ring-containing silyl ether **10**, and the amide bond-embedded silyl ether **11** were compatible with this desilylation, giving **PD10** in 98% yield and **PD11** in 96% yield. The desilylation of the $MePh_2Si$ group-protected *N*-Fmoc-L-serine **12** and **13** resulted in the production of **PD12** and **PD13** in low yields, due to the cleavage of the Fmoc group. The $MePh_2Si$ group-protected *N*-Boc-L-serine **14** tolerated this desilylation to afford **PD14** in 39% yield with recovery of **14** in 48% yield. The desilylation by using

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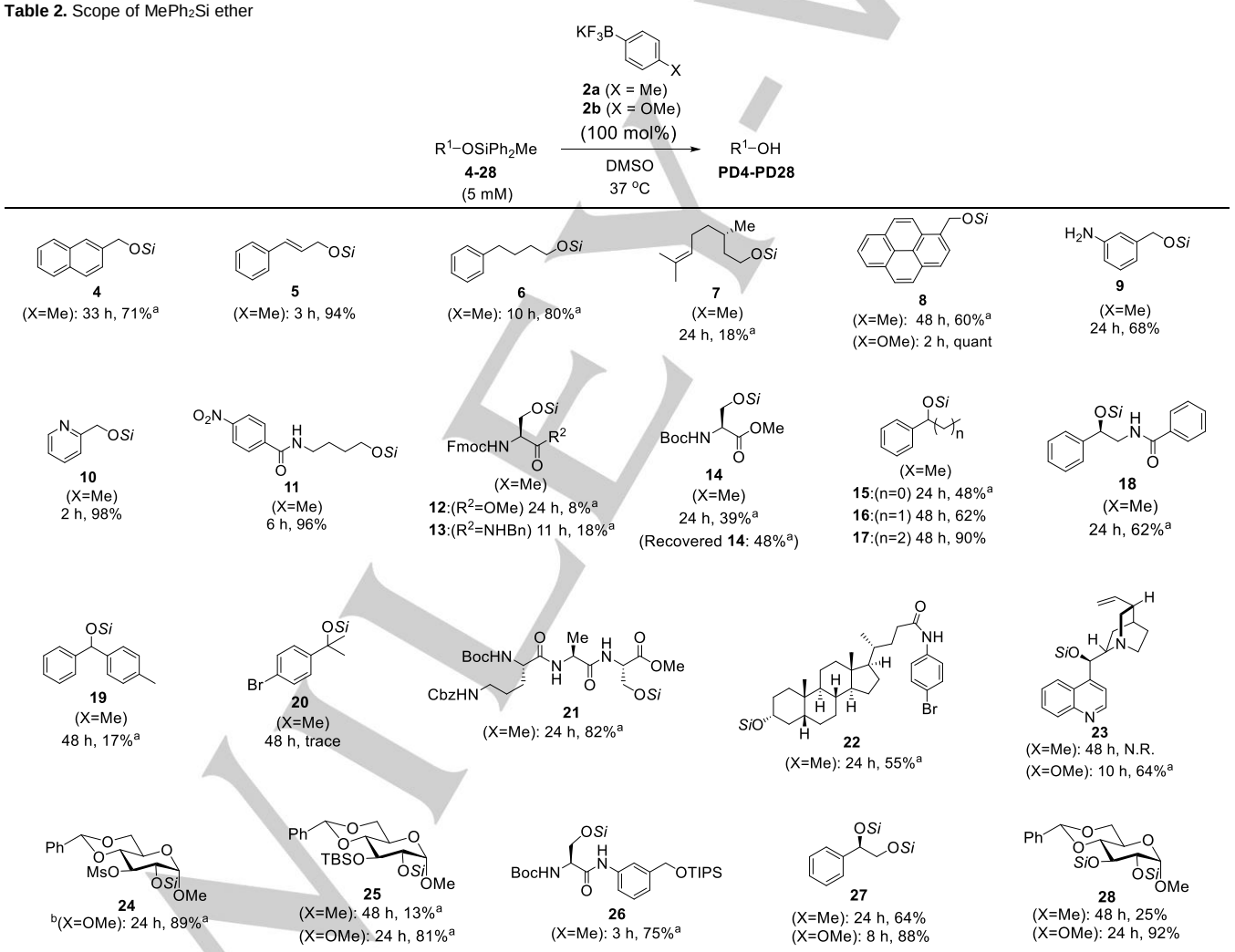
2b was examined, but the yield was not imporved so much. It was expected that this low reactivity attributes to the adjacent bulky Boc group. The secondary silyl ethers **15**-**18** were permitted for this desilylation and the corresponding alcohols were obtained in modest to good yields (48–90%). The bulky alkyl silyl ethers **19** and **20** were less reactive, giving **PD19** in 17% yield and **PD20** in trace amounts. The yield was not improved due to the bulky structure of **19** and **20**, even though the more reactive **2b** was used. The $MePh_2Si$ groups on the complex compounds were examined in the desilylation reaction. The $MePh_2Si$ group on the tripeptide, *N*-Boc-ornithine(Cbz)-alanine-serine($OSiPh_2Me$)-COOMe **21**, was cleaved by **2a** to afford **PD21** in 82% yield after 24 h. The silyl ether **22**, derived from lithocholic acid, was treated with **2a** to give **PD22** in 55% yield. The more reactive **2b** was examined on **22**, but improvement of the yield was traceless. The unique structure consisting of the fused ring would interfere with reactivity of the pheyltrifluoroborate. The $MePh_2Si$ group-protected cinchonidine **23**, which contains two nitrogen atoms such as quinoline and tertiary aliphatic amine, did not react with **2a**. When **2b** was employed, efficient desilylation of **23** occurred and **PD23** was obtained in 64% yield. The $MePh_2Si$ group at the 2-position of the protected D-glucose **24** was cleaved by **2b** in 89% yield, without impairing the nucleophile-reactive methylsulfonyl group even at concentration of 50 mM for **24** and **2b**. Selective cleavage of the $MePh_2Si$ group on D-glucose **25**, which is protected by the $MePh_2Si$ and TBS groups at the 2- and 3-positions, was performed by using **2a** and **PD25** was obtained in 13% yield. Utilization of **2b** improved the yield of **PD25** up to 81%. The selective desilylation of the $MePh_2Si$ group on **26** by **2a** was successful and **PD26** was obtained in 75% yield. The double $MePh_2Si$ group-protected substrates **27** and **28** were evaluated on this desilylation. The trifluoroborate **2a** and **2b** could cleave both primary and secondary $MePh_2Si$ groups on **27** and the dialcohol **PD27** was obtained in 64% and 88% yields, respectively. The two $MePh_2Si$ groups at the 2- and 3-positions of the D-glucose **28** could be removed by **2a** or **2b**, yielding **PD28** in 25% or 92% yields, respectively.

Table 2. Scope of $MePh_2Si$ ether



Yield was calculated by HPLC analysis. [a] Isolated yield. [b] The reaction was performed with a 50 mM solution of **24**. *Si* = $MePh_2Si$.

To clarify the synthetic advantage of trifluoroborate as a fluoride reagent, selective desilylation of the primary $MePh_2Si$ ether **6** in the presence of the secondary $MePh_2Si$ ether **17** was investigated (Scheme 1a). The selective desilylation of the primary $MePh_2Si$ ether **6** with 1 equivalent of **2b** was successful and **PD6** was observed as the primary product with a 72% yield

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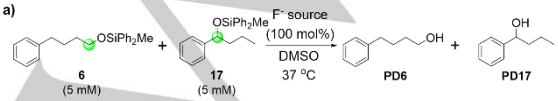
and **PD17** as a minor product in 13% yield (Entry 1). However, selective desilylation of **6** in the presence of **17** by utilizing 1 equivalent of potassium fluoride (KF) or tetrabutylammonium fluoride (TBAF) as conventional fluoride reagents was not successful to afford **PD6** in 84% and **PD17** in 99% (Entry 2), **PD6** in 78% and **PD17** in 94% (Entry 3). In addition, the desilylation of the $MePh_2Si$ group-protected L-serine **29** containing a 2,2,2-trichloroethoxycarbonyl (Troc) group, which is a fluoride-labile protective group,[14] was conducted (Scheme 1b). The trifluoroborate **2a** enabled the desilylation of **29** without harming the Troc group to afford **PD29** in 53% yield (Entry 1). The treatment of TBAF gave a complex mixture and no **PD29** was obtained (Entry 2).

Further investigation of the substituent effect, especially at the *ortho*-position of the trifluoroborate-substituted benzene, on the reactivity of the desilylation was carried out. With various phenyltrifluoroborates **2c**-**e**, which are substituted with electron-donating or neutral groups at the *ortho*-position, desilylation of two $MePh_2Si$ groups containing substrate **27** was performed (Scheme 1c). When the potassium 2-methoxyphenyltrifluoroborate **2c** was employed, no desilylation occurred. In addition, the more electron rich potassium 2,6-dimethoxyphenyltrifluoroborate **2d** showed low reactivity in the desilylation reaction. From these results, steric hindrance by the *ortho*-substituted methoxy groups of **2c** and **2d** greatly prohibited the trifluoroborate from approaching the $MePh_2Si$ groups. This supports the hypothesis that the cleavage of the Si-O bond occurs directly through fluoride acting on trifluoroborate, and not by the potassium fluoride generated in situ by the hydrolysis of trifluoroborate. The 2,6-dimethylphenyltrifluoroborate **2e** showed excellent reactivity and the desilylation of **27** was completed in 2 h with **PD27** obtained in 85% yield. This attributed to less hindrance of the methyl groups at *ortho* position. We also tested the relative reactivity of **2a** and **2b**. The yield of **PD27** was negligible with **2a**, and **PD27** was obtained in 32% yield by HPLC analysis, after 2 h. We attempted selective cleavage of the primary silyl ether on **27**, but any selectively-cleaved product was not obtained, even in catalytic loading of **2a**-**e**. It was expected that the two silyl groups at 1,2-positions of substrate **27** would be activated by forming cyclic intermediate with two fluorines of aryltrifluoroborate. In addition, the selective cleavage of **28** would also be difficult based on same activation mechanism as **27**.

The mechanism of the trifluoroborate-catalyzed desilylation reaction was discussed (Scheme 1d). According to the results in scheme 1a and 1c, cleavage of the Si-O bond would occur through fluoride acting on the trifluoroborate. From the ^{19}F NMR analysis of the desilylation reaction of **6** by **2b** in DMSO-d_6, only the fluorine peak of **2b** was observed during the reaction (Figure S11). Therefore, it was expected that the silane-trifluoroborate complex **A** would be formed by Si-F interaction. The activated silyl ether on the complex **A** would be reactive with a water molecule as electrophile, as shown in entry 11 in Table 1, to give the desired alcohol and the silanol.

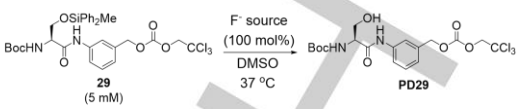
a)



Entry	F⁻ source	Time (h)	Yield (%) PD6	Yield (%) PD17
1	**2b**	6	72	13
2	KF	2	84	99
3	TBAF	0.5	78	94

Yield was calculated by HPLC analysis.

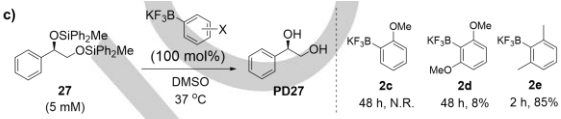
b)



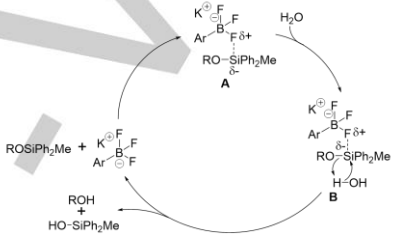
Entry	F⁻ source	Time (h)	Yield (%)
1	**2a**	3	53
2	TBAF	3	complex mixture

Isolated yield.

c)



d)



Scheme 1. Selective desilylation on (a) primary and secondary $MePh_2Si$ ethers and (b) other fluoride-labile protective group-containing $MePh_2Si$ ethers. (c) Effect of other substituents on aryltrifluoroborate to fluoride reactivity. Yield was calculated by HPLC analysis. (d) Proposed mechanism.

In conclusion, through this study, we documented a new fluoride reactivity of trifluoroborate, which is electronically controlled by electron neutral or donating groups on the benzene ring. By using various phenyltrifluoroborates, selective desilylation reactions of the $MePh_2Si$ group, such as the desilylation of the primary $MePh_2Si$ ether in the presence of a secondary silyl ether or the desilylation of the $MePh_2Si$ ether in the presence of other silyl groups and the fluoride-labile Troc group, were achieved under mild conditions. Further synthetic applications of aryltrifluoroborate, such as the development of a more electron rich and mild reactive aryltrifluoroborate to enable desilylation of robust silyl groups and the design of a chiral skeleton-incorporated trifluoroborate to enable asymmetric reactions, are currently being studied in our laboratory.

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Conflict of interest

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The authors declare no conflict of interest.

Keywords: Trifluoroborate • Fluoride reagent • Desilylation • Diphenylmethylsilyl group • Organocatalyst

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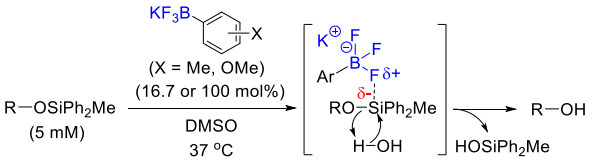

R = primary silyl ethers, secondary silyl ethers, tripeptide, carbohydrates, etc

The unique fluoride reactivity of phenyltrifluoroborate controlled by substituents on the benzene on the desilylation of the diphenylmethylsilyl groups is described. The fluorine on trifluoroborate interacts with silicone and activates the Si-O bond to enable selective desilylation of diphenylmethylsilyl group. Selective desilylation of primary silyl ether in the presence of secondary silyl ether by the trifluoroborate was also successful.

Key topic: Potassium trifluoroborate reagent for selective desilylation of diphenylmethylsilyl group