C–F Activation **Hot Paper**

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Single C–F Bond Cleavage of Trifluoromethylarenes with an *ortho*-Silyl Group

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Abstract: *The transformation of a single C–F bond of trifluoromethylarenes bearing a hydrosilyl group at the ortho position was achieved. The activation of the hydrosilyl group with a trityl cation in the presence of nucleophiles allowed for selective C–F bond functionalization, for example, by allylation, carboxylation, or chlorination. Further derivatization of the resulting fluorosilylarenes afforded various aromatic difluoromethylene compounds.*

Organofluorine compounds are an important class of molecules that are widely used in various fields, including the pharmaceutical sciences, agrochemistry, and materials science.[1] The increasing demand for fluorinated compounds has prompted the development of a variety of methods for introducing a fluorine atom or a fluorinated functional group into organic frameworks. In particular, with the increasing availability of convenient reagents in recent years, various methods for fluorination and trifluoromethylation have been developed.[2,3] However, methods for synthesizing complex fluorinated compounds are still limited, and new approaches are highly sought-after.

In principle, a diverse range of fluorinated compounds can be straightforwardly prepared from trifluoromethylated compounds by the selective transformation of one of the three C–F bonds of the trifluoromethyl group. However, the high stability of the C–F bond has rendered this transformation difficult to achieve (Figure 1 A).[4–7] Furthermore, previous studies regarding the transformation of C–F bonds stressed the difficulty of performing single C–F bond cleavage with an aromatic trifluoromethyl group; all of the three C–F bonds of the trifluoromethyl group were cleaved in these cases.[8–10] The reason behind this difficulty is that the C–F bonds of the di- and monofluorinated intermediates are likely to be more reactive than those of the trifluoromethyl-substituted starting material (Figure 1 B). For example, Ozerov and co-workers reported the reduction of an aromatic trifluoromethyl group to the corresponding methyl group by C–F bond cleavage with a silylium species (Figure 1 C).[8b] We assumed that a pinpoint transformation of the aromatic trifluoromethyl group could be achieved through a single C–F bond cleavage that is triggered by the generation of a silyl cation at the *ortho* position in the presence of an appropriate nucleophile (Figure 1 D). We also anticipated that the resulting products could be transformed into a wide range of difluoromethylene compounds because the hydrosilyl group of the starting material is converted into a base-activatable fluorosilyl group during this transformation.[11]

A

	length (Å)	energy (kcal/mol)
C–H	1.10	105
C–F	1.38	110
C–Cl	1.78	84
C–Br	1.94	70

B

	length (Å)	energy (kcal/mol)
H_3C–F	1.38	110
H_2FC–F	1.36	120
HF_2C–F	1.33	128
F_3C–F	1.32	131

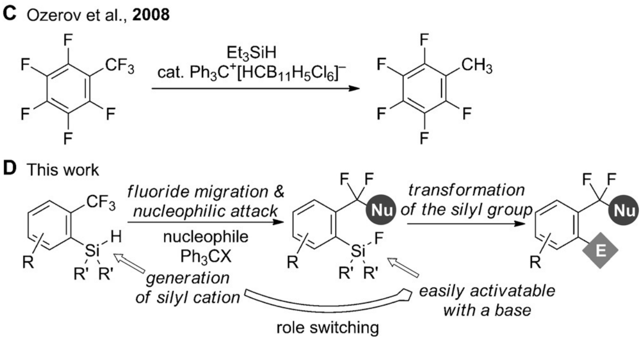

Figure 1. Transformation of an aromatic trifluoromethyl group by C–F bond cleavage. A) Bond lengths and dissociation energies of C–X bonds for homolytic bond cleavage.[4] B) Bond lengths and dissociation energies of C–F bonds in $H_{4-n}CF_n$ (n = 1–4) for homolytic bond cleavage.[5] C) Reported transformation of an aromatic trifluoromethyl group with a silylium intermediate.[8a] D) Strategy proposed herein.

After an extensive screening of reaction conditions for the transformation of trifluoromethylarenes by single C–F bond cleavage, we found that defluorinative mono-allylation of 2-(diphenylsilyl)benzotrifluoride (**1a**)[12] proceeded upon treatment with a trityl cation source in the presence of allyltrimethylsilane (**3a**) to afford *gem*-difluorinated **2a** (Table 1). The best result was obtained when a mixture of **1a** and **3a** was treated with triphenylmethylium tetrafluoroborate in a 1:1 mixture of dichloromethane and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) at 0 °C for 10 minutes, which afforded **2a** in 86 % yield (entry 6). The diallylated product, which would result from further C–F bond cleavage, was not detected. Product **2a** contains a fluorosilyl group, which indicates that the reaction proceeded by hydride abstraction from the silyl group in **1a** with the trityl cation,[13] followed by migration of a fluoride to the silyl group. Performing the reaction in dichloromethane, toluene, acetonitrile, or nitromethane furnished a complex mixture that included triphenylmethane (entries 1–4). These results indicate that using

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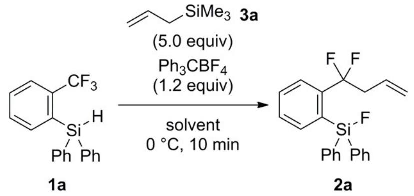
Table 1: C–F bond allylation of **1a** in various solvents.



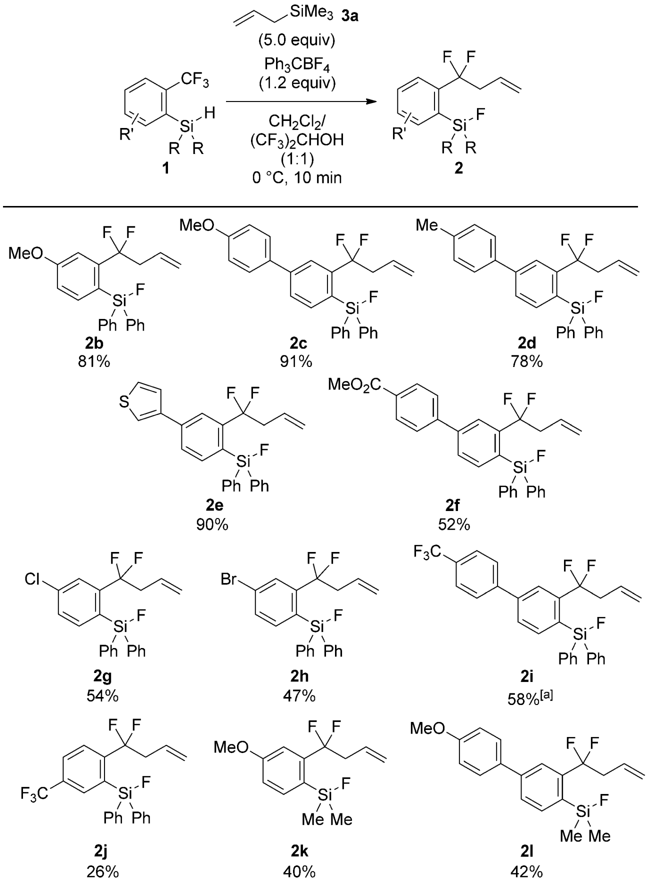
Entry	Solvent	**2a** [%][a]
1	CH_2Cl_2	trace
2	toluene	0
3	CH_3CN	0
4	CH_3NO_2	0
5	$CH_2Cl_2/(CF_3)_2CHOH$ (9:1)	34
6	$CH_2Cl_2/(CF_3)_2CHOH$ (1:1)	86[b]
7	$CH_2Cl_2/(CF_3)_2CHOH$ (1:9)	58

[a] Yields determined by ^1H NMR analysis, unless otherwise noted. [b] Yield of isolated product.

a solvent such as HFIP that strongly stabilizes cationic intermediates was crucial to the efficiency of this transformation.[14]

The optimized conditions were applicable to the defluorinative allylation of various benzotrifluorides **1** (Table 2). Benzotrifluorides bearing electron-rich substituents, such as methoxy, *para*-anisyl, *para*-tolyl, or 3-thienyl groups, were smoothly allylated to afford the corresponding products **2b**–**2e** in high yields. The allylation of substrates bearing electron-deficient groups also afforded difluoromethylated products **2f**–**2j**, some of which contained chloro, bromo, or ester moieties for further transformation. Notably, as demonstrated by the synthesis of **2i** and **2j**, the C–F bond cleavage of substrates having two trifluoromethyl groups occurred only at the trifluoromethyl group adjacent to the silyl group. 2-(Dimethylsilyl)benzotrifluorides also participated in the reaction, providing the allylated products, such as **2k** and **2l**, in moderate yields.

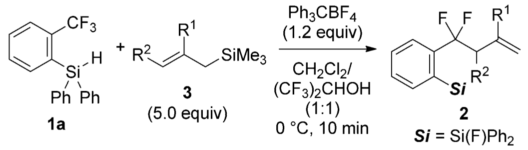
Table 2: C–F bond allylation of various benzotrifluorides.

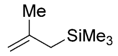
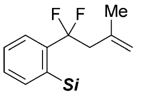
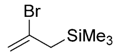
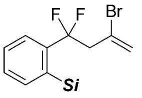
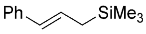
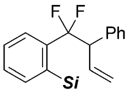
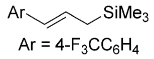
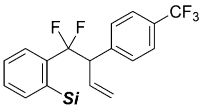


[a] Allylsilane (10 equiv) was used.

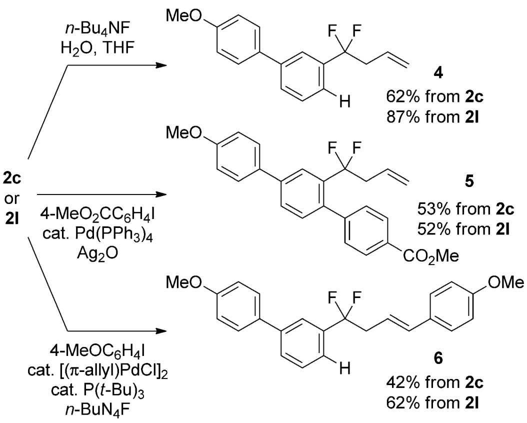
A variety of substituted allylsilanes, such as **3b**–**3e**, were also suitable for this transformation (Table 3). Methallylation and 2-bromoallylation afforded the corresponding products **2m** and **2n** in moderate yields (entries 1 and 2). In the case of γ-substituted allylsilanes **3d** and **3e**, C–C bond formation selectively occurred at the γ-position (entries 3 and 4).[15] Notably, 4,4-difluoro-1-butene derivative **2p** was obtained by C–F bond cleavage of the trifluoromethyl group of benzotrifluoride **1a** without damaging the trifluoromethyl group of allylsilane **3e**.

Table 3: C–F bond allylation using various allylsilanes.



Entry	Allylsilane	**3**	Product	**2**	Yield [%]
1		**3b**		**2m**	42
2		**3c**		**2n**	61
3		**3d**		**2o**	50
4	 Ar = 4-$F_3CC_6H_4$	**3e**		**2p**	41

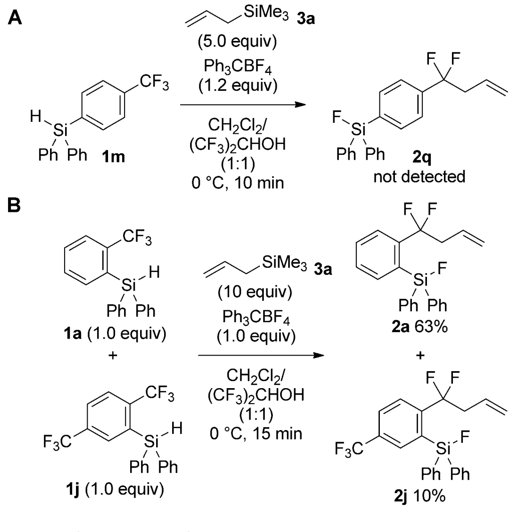
The fluorodiphenylsilyl and fluorodimethylsilyl groups in the allylated products are more reactive than the corresponding hydrosilyl groups, thereby allowing for further transformations into a diverse range of difluorinated compounds (Scheme 1). For example, desilylprotonation of **2c** or **2l** with tetra(*n*-butyl)ammonium fluoride (TBAF) smoothly proceeded to afford **4** in high yields. C–C bond formation by Hiyama cross-coupling with an iodoarene using silver(I) oxide as an activator afforded *para*-terphenyl derivative **5**.[16,17] Modification of the allyl group under Heck arylation conditions in the presence of TBAF afforded desilylprotonated styrene derivative **6**.



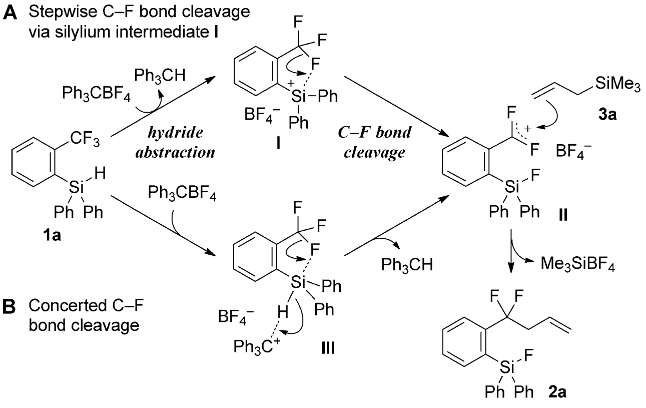
Scheme 1. Further transformations of the fluorosilyl group.

To gain insight into the mechanism of the defluorinative allylation reaction, we performed several experiments. The reaction of benzotrifluoride **1m**, which bears a hydrosilyl group at the *para* position, did not afford the desired allylated product **2q**; a complex mixture was obtained, and the formation of triphenylmethane was observed (Scheme 2 A). This result indicates the importance of the proximity of the hydrosilyl and trifluoromethyl groups to achieve the transformation, which most likely proceeds by intramolecular fluoride migration. Furthermore, a competition experiment using equimolar amounts of **1a**, **1j**, and a trityl cation source resulted in the preferential production of **2a** over **2j**, indicating that more electron-rich substrates are favored by this reaction (Scheme 2 B).

On the basis of the experimental results, we currently believe that the reaction is triggered by hydride abstraction from the hydrosilyl group of benzotrifluoride **1a** with a trityl cation, followed by the transfer of one fluoride of the trifluoromethyl group to generate carbocationic intermediate **II** (Scheme 3 A). Subsequent allylation of carbocation **II** with allylsilane **3a** would then furnish the desired product **2a** by a mechanism similar to that of the Hosomi–Sakurai allylation. However, a concerted mechanism involving hydride abstraction and C–F bond cleavage without generation of silylium intermediate **I** cannot be excluded (Scheme 3 B).

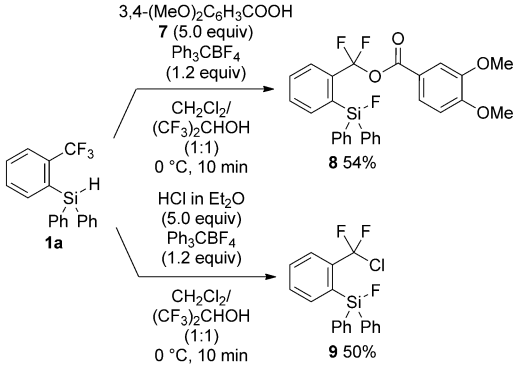


Scheme 2. Mechanistic studies.



Scheme 3. Plausible reaction mechanisms.

Nucleophiles other than allylsilane were also applicable to the defluorinative transformation (Scheme 4). For example, using benzoic acid **7** or anhydrous hydrogen chloride as the nucleophile, carboxylation and chlorination of benzotrifluoride **1a** took place to afford ester **8** and chlorodifluoromethylarene **9**, respectively.



Scheme 4. C–F bond carboxylation and chlorination.

In summary, we have described the transformation of a single C–F bond of benzotrifluorides with an *ortho*-hydrosilyl group upon treatment with a trityl cation in the presence of various nucleophiles. Through further transformations of the resulting fluorosilylarenes, this method allows for the synthesis of various difluoromethylene compounds. Further studies to expand the scope of this reaction are currently underway.

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Keywords: allylation · C—F Activation · fluorine · silanes · trityl cation

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