Fluorination

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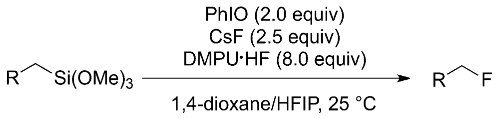
Hypervalent Iodine(III)-Mediated Oxidative Fluorination of Alkylsilanes by Fluoride Ions

Peng Xu, Feng Wang, Guilan Fan, Xiufang Xu, and Pingping Tang**

Abstract: *The first example of a hypervalent iodine(III)-mediated oxidative fluorination of alkylsilanes by fluoride ions without the use of transition metals is demonstrated. This reaction is operationally simple, scalable, and proceeds under mild reaction conditions. Mechanistic studies suggest the involvement of a single-electron transfer resulting from the interaction of an organopentafluorosilicate and aryliodonium difluoride, which were generated in situ from the corresponding alkylsilane and iodosobenzene, respectively, in the presence of fluoride ions.*

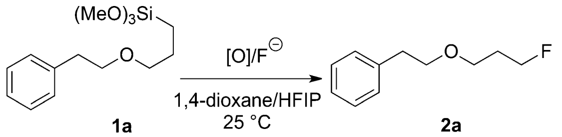
Organofluorine compounds are extremely rare in nature, as only five natural fluorinases have been discovered.[1] Fluorine substitution is becoming increasingly popular because it can improve the properties of different classes of functional molecules, including pharmaceuticals, agrochemicals, and materials.[2] For example, the incorporation of fluorine atoms into pharmaceuticals can increase metabolic stability, lipophilicity, and overall biological activity, and approximately 20% of commercially available pharmaceuticals contain at least one fluorine atom. Therefore, the development of new methods for the introduction of fluorine into small molecules has received extensive attention.[3] Organosilanes are useful intermediates in organic synthesis and reactions,[4] such as the Hiyama coupling reaction. However, the fluorination of organosilanes with fluoride ions is uncommon because fluoride ions interact with silicon atoms to form Si–F bonds, which have high bond dissociation energies.[5]

The conventional methods for the fluorination of arylsilanes use relatively strong fluorinating reagents, such as fluorine gas, cesium fluoroxysulfate, and xenon difluoride.[6] Recently, the group of Ritter reported the silver-mediated fluorination of arylsilanes with Selectfluor as the fluorinating agent.[7] In addition to recent advances in the fluorination of vinylsilanes and allenylsilanes,[8] methods for the fluorination of alkylsilanes have also been developed.[9] Gouverneur and co-workers reported the regio- and enantioselective synthesis of allylic fluorides by electrophilic fluorodesilylation of allylsilanes with Selectfluor.[10] The fluorination of allenylmethylsilanes with Selectfluor has also been investigated, and enabled the preparation of 2-fluoro-1,3-dienes.[11] Despite the advances of these methods with electrophilic fluorinating reagents, the fluorination of alkylsilanes with fluoride ions remains virtually unexplored. Only one example has been reported: the electrochemical fluorination of 4-trimethylsilylazetidine-2-ones in the presence of $Et_3N{\cdot}3HF$ affords 4-fluoroazetidin-2-ones.[12] Given that fluoride is stable and abundant in nature,[13] the development of a general and practical fluorination of alkylsilanes with fluoride is highly desirable. Herein, we present the first example of a hypervalent iodine(III)-mediated oxidative fluorination of alkylsilanes by fluoride ions without the use of a transition metal. This protocol is operationally simple, scalable, and proceeds under mild reaction conditions (Scheme 1).



Scheme 1. Hypervalent iodine(III)-mediated oxidative fluorination of alkylsilanes by fluoride ions without transition metals. DMPU = 1,3-dimethyltetrahydropyrimidin-2-one, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Table 1: Screening of reaction conditions.



Entry	[O][a]	Fluoride ions[b]	Yield [%][d]
1	PhIO	KF	0
2	PhIO	CsF	0
3	PhIO	AgF	0
4	PhIO	$Et_3N{\cdot}3HF$	15
5	PhIO	Py·HF	0
6	PhIO	DMPU·HF	0
7[c]	PhIO	CsF, $Et_3N{\cdot}3HF$	43
8[c]	PhIO	CsF, Py·HF	53
9[c]	PhIO	CsF, DMPU·HF	87
10[c]	PhIO	KF, DMPU·HF	0
11[c]	$PhI(OAc)_2$	CsF, DMPU·HF	62
12[c]	$PhI(O_2CCF_3)_2$	CsF, DMPU·HF	0

[a] 2.0 equiv of oxidants were used. [b] 8.0 equiv of fluoride ions were used. [c] 2.5 equiv of metal fluorides and 8.0 equiv of HF-based fluorinating reagents were used. [d] Yields were determined by ^{19}F NMR spectroscopy with 1-bromo-5-fluoropentane as a standard.

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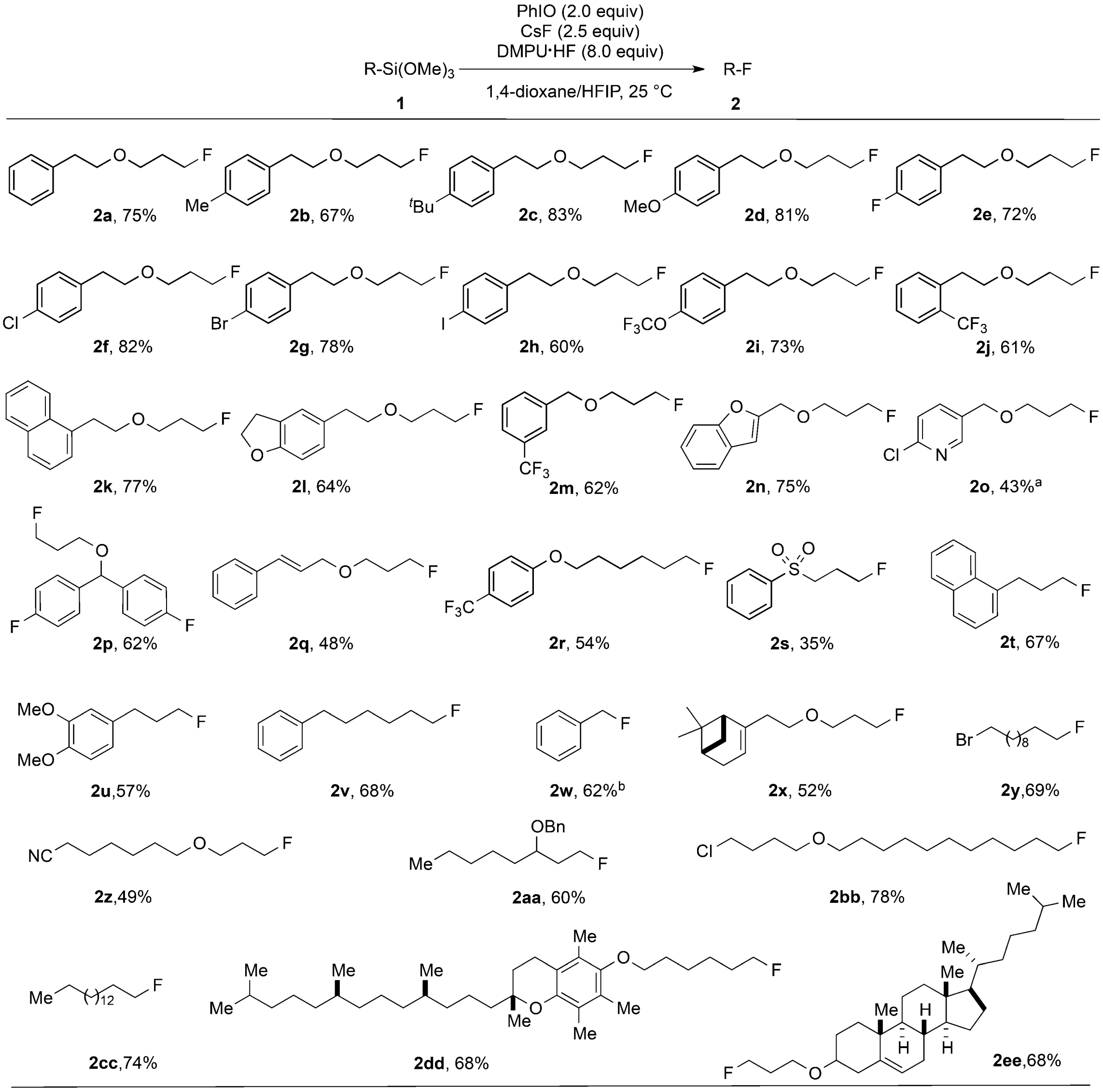
Radical fluorination reactions have received much attention in $C(sp^3)$–F bond formations.[14] Many methodologies utilizing a number of radical precursors to access radical intermediates have been reported. Among these radical intermediates, primary radicals are the most difficult to access.[15] We were inspired by the work of the group of Kumada on the oxidative generation of organic radicals from organopentafluorosilicates.[16] Thus, we envisioned that the oxidative radical fluorination of alkylsilanes by fluoride ions could be achieved by the in situ generation of radical intermediates derived from organopentafluorosilicates. Initial investigations focused on the reaction of the alkylsilane **1a** with various oxidants and fluoride salts (Table 1; see more details in the Supporting Information). With iodosobenzene (PhIO) as the oxidant, no desired fluorinated product **2a** was observed when either KF, CsF, or AgF was used as the fluorinating reagent (entries 1–3). HF-based fluorinating reagents were subsequently evaluated (entries 4–6), and triethylamine trihydrofluoride ($Et_3N{\cdot}3HF$) gave the desired fluorinated product **2a** in 15% yield. No product was observed when either 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone hydrofluoride (DMPU·HF)[17] or pyridine hydrofluoride (Py·HF) was used. A further improvement was observed when CsF and HF-based fluorinating reagents were used together. A yield of 43% was achieved in the presence of 2.5 equivalents CsF and 8.0 equivalents $Et_3N{\cdot}3HF$, and the yield increased to 53% when 8.0 equivalents Py·HF was used (entries 7 and 8). The highest yield was obtained when CsF and DMPU·HF were used together as the fluorinating agents (entry 9). The main byproduct of the reaction was from elimination to give an alkene. After extensive screening with various solvents, oxidants, and temperatures (see more details in the Supporting Information), the ideal reaction conditions of 2.0 equivalents of PhIO,

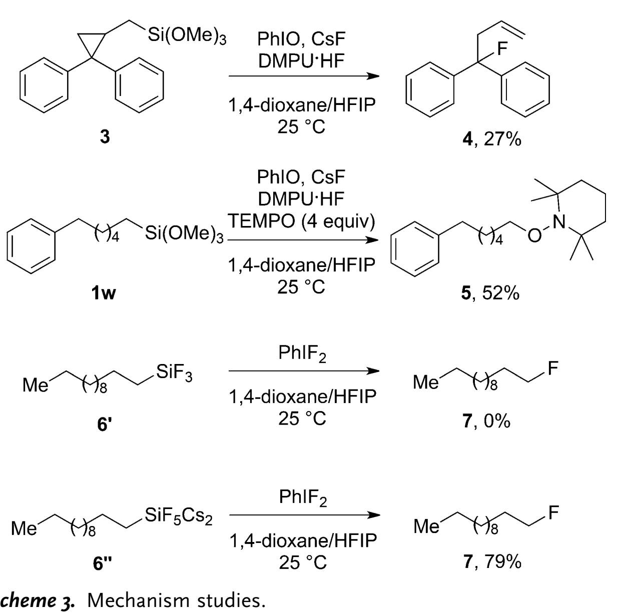


Scheme 2. Substrate scope for oxidative fluorination of alkylsilanes by fluoride ions. Reaction conditions: **1** (1.0 equiv), PhIO (2.0 equiv), DMPU·HF (8.0 equiv), CsF (2.5 equiv), 1,4-dioxane/HFIP (*v*/*v* 10:1), N_2 atmosphere, 25 °C, 12 h. Yields of isolated products are given. [a] 4 equiv of CsF was used. [b] Benzyltriethoxysilane was used. Yield was determined by ^{19}F NMR spectroscopy with 1-bromo-5-fluoropentane as a standard.

2.5 equivalents of CsF, and 8.0 equivalents of DMPU·HF in 10:1 (v:v) 1,4-dioxane/HFIP under N_2 atmosphere at 25 °C, were found to produce the highest yields. No fluorination products were detected in control experiments where either the fluoride ion or oxidant was omitted. The roles of 1,4-dioxane and HFIP are unclear.[18]

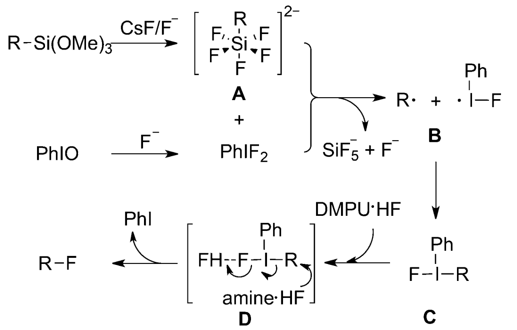
Having established the optimum reaction conditions, we explored the substrate scope of the transformation (Scheme 2). First, various primary alkylsilanes bearing electron-donating and electron-withdrawing substituents on aryl rings (**1a**–**w**) and primary alkylsilanes without aryl rings (**1x**–**cc**) were successfully converted into the desired products with good yields. Notably, the heteroaromatic substrates **1l**, **1n**, and **1o** were also successfully employed to provide the corresponding products (**2l**, **2n**, and **2o**). A good range of functional groups including ether, nitrile, sulfonyl, chloride, bromide, and even iodide and alkene were well tolerated under the mild reaction conditions. These results encouraged the application of this method to more complex small molecules, **1dd** and **1ee**, which gave the corresponding fluorination products **2dd** and **2ee** in moderate yields. In addition, we prepared the compound **2g**, on gram scale under the standard reaction conditions, in 83 %, thus demonstrating the scalability of this method. No desired fluorination product was observed with secondary alkylsilanes, such as cyclohexyltrimethoxysilane, and the major byproducts were an alkene and a ketone. Our attempts to test more secondary or tertiary alkyltrimethoxysilanes, especially functionalized compounds, were hampered by their difficult preparation.

Although the mechanistic details of this transformation are not yet clear, preliminary observations provide some insights (Scheme 3). First, a radical clock experiment was performed with substrate **3**, and the ring-opening product **4** was obtained in 27 % yield, as determined by ^{19}F NMR analysis of the crude reaction mixture. When 4.0 equivalents of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) were added, the TEMPO adduct **5** was isolated in 52 % yield. Together, these observations provide solid evidence for a carbon-centered radical intermediate in the reaction, and it was also supported by density-functional theory (DFT) calculations (see the Supporting Information for details). In addition, monitoring of the reaction by ^{19}F NMR spectroscopy revealed that $PhIF_2$ ($\delta = -176$ ppm) was generated in the reaction.[19] In the presence of $PhIF_2$, the fluorinated product **7** was formed in 79 % yield with the cesium organopentafluorosilicate **6″**, whereas no product was formed with the organotrifluorosilane **6′**. These results demonstrate that the in situ generated organopentafluorosilicate can react productively with $PhIF_2$.



Scheme 3. Mechanism studies.

On the basis of these mechanistic investigations and associated DFT calculations (see the Supporting Information for details), we proposed the mechanism depicted in Scheme 4. In the presence of CsF and DMPU·HF, the organopentafluorosilicate **A** and $PhIF_2$ are generated from alkylsilane and PhIO, respectively. Next, single-electron transfer from **A** to $PhIF_2$ generates a carbon radical intermediate and iodoarene radical (**B**), which subsequently form the stable hypervalent iodine(III) species **C**. The formation of this species facilitates an activation-displacement sequence by the transition-state **D** with the aid of DMPU·HF to produce the final product.[20]



Scheme 4. Proposed mechanism.

In conclusion, we have developed the first transition-metal-free hypervalent iodine(III)-mediated fluorination of alkylsilanes with fluoride. Compared to conventional methods for the preparation of alkyl fluorides by S_N2-type reactions of alkyl (pseudo)halides or alcohols,[3] this method enables the facile replacement of various primary aliphatic silanes with fluoride ions under mild reaction conditions and tolerates a wide range of functional groups, including alkyl halides. Additionally, preliminary mechanistic studies and DFT calculations suggest that the reaction may proceed through a radical mechanism. Although secondary alkylsilanes do not give the desired fluorinated products under these reaction conditions, this reaction provides a complementary method for the synthesis of primary alkyl fluorides. Furthermore, these studies provide a solution to the challenge of fluorination of alkylsilanes by fluoride while also open a new path for the design of intermolecular radical reactions of alkylsilanes.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: fluorination · hypervalent compounds · radicals · silanes · synthetic methods

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Communications

Fluorination

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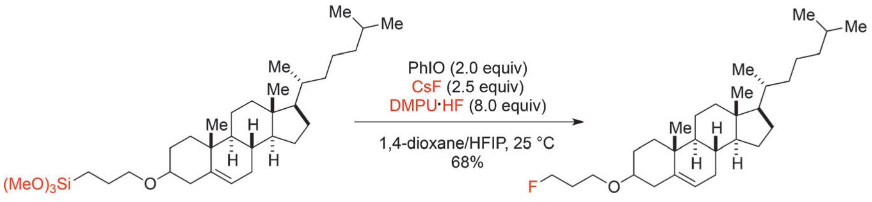
Hypervalent Iodine(III)-Mediated Oxidative Fluorination of Alkylsilanes by Fluoride Ions



Tip the scale: A hypervalent iodine(III)-mediated fluorination of alkylsilanes in the absence of transition metals is reported for the first time. The reaction is operationally simple and amenable to gram-scale synthesis. Mechanistic studies and DFT calculations suggest that the reaction may proceed through a radical mechanism.