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An aryne triggered ring-opening fluorination of cyclic thioethers with potassium fluoride

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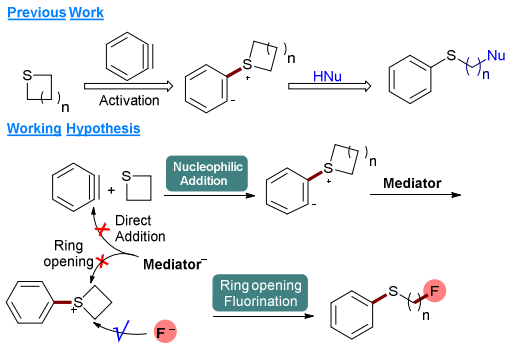
Rong Fan,[a] Binbin Liu,[a] Tianyu Zheng,[a] Kun Xu*[b], Chen Tan,[a] Tianlong Zeng,[a] shuaisong Su[a] and Jiajing Tan*[a]

Abstract: Herein, we reported an aryne triggered ring-opening fluorination protocol of a great variety of saturated sulfur heterocycles. A key factor for the success is to identify a suitable mediator. Compared to previous methods, this transition-metal free protocol employs low-cost potassium fluoride as the fluorine source. The operational simplicity and mild reaction conditions allow for the rapid synthesis of a wide range of aliphatic fluoride compounds in good yields.

Fluorinated organic compounds has recently emerged as the major focus in medicinal, agrochemical and materials chemistry field, as fluorine atoms could create a variety of unique properties.[1] For instance, the installment of fluorine atoms into pharmaceutical candidates can significantly improve their metabolic stability, lipophilicity, and overall bioactivity.[2] Fluorine could be also employed as biochemical probes to study biological processes via the in vivo magnetic resonance imaging of the ^{19}F nuclei.[3] Consequently, significant research efforts toward the invention of novel fluorination reaction has been witnessed during the past two decades.[4] While many protocols focus on the C_{sp2}-F bond formation, the synthetic method to enable C_{sp3}–F bond formation is still relatively underdeveloped.[5] Moreover, available methods often suffered from high cost and poor atom economy of fluorine source. In this case, developing alternative aliphatic fluoride synthesis protocol that employs readily available, inexpensive fluorine source remains an elusive task in organic synthesis.

Aryne chemistry has undergone a renaissance in recent years. As highly electrophilic species, arynes readily react with a great variety of nucleophiles to build molecule complexity in high efficacy.[6] Recently, our group disclosed a three-component aryne mediated ring-opening reaction of cyclic thioethers.[7] The sulfonium species formed in situ could deprotonate the pre-nucleophiles, which subsequently attacked the activated carbon-sulfur bond to provide the ring-opening products (Scheme 1a). During this project, the authors questioned if fluorides required for aryne generation could be also utilized to open the ring as the nucleophile. From a conceptual standpoint, our idea ought to be challenging, as literature studies revealed that the high electronegativity and low polarizability of fluoride often made itself a less reactive nucleophile but relatively strong base in organic reactions.[8]



Scheme 1. Working hypothesis

To this end, we proposed that the utilization of a mediator involving a transferable proton is necessary. The reactivity of the mediator must be "tailor-made" that besides being a proton donor to capture the ylide intermediate to form the key sulfonium ion, the deprotonated form of mediators would neither react with aryne directly, nor enable the competing ring-opening reaction as nucleophiles (Scheme 1b).[9] Due to the lower nucleophilicity of fluoride, side reactions including the ring-opening polymerization, decomposition of sulfonium intermediates as well as ring contraction also needed to be minimized or even obviated.[10] As such, a critical feature of this proposed transformation would be the identification of suitable mediators. Despite these challenges, we herein would like to report our recent efforts in developing an aryne triggered ring-opening fluorination reaction of cyclic thioethers

[a] Department of Organic Chemistry, Beijing Advanced Innovation Center for Soft Matter Science and Engineering, Beijing University of Chemical Technology, Beijing 100029, P. R. China. E-mail: tanjj@mail.buct.edu.cn
[b] College of Chemistry and Pharmaceutical Engineering, Nanyang Normal University, Nanyang, P. R. China. E-mail: xukun@nynu.edu.cn.
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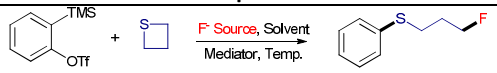
(four to six membered), which employs readily available potassium fluoride (KF). Given the importance of organofluorine compounds, this transition metal-free transformation should be of great interests to the community.

We began our investigation by exploring the suitable mediator in the model reaction of 2-(trimethylsilyl)aryl triflate (**1a**) and thietane (**2a**) in tetrahydrofuran with KF/18-C-6 as the fluoride source (Table 1). To our delight, the desired product **4a** was obtained in 57% yield in the presence of water, which confirmed our working hypothesis mentioned above (entry 1). Next, a series of well-designed mediators were thus examined (entries 2-8). The experimental results revealed that 2,3-dimethylindole was superior to give the desired fluorinated product **4a** in 80% yield (entry 7), while other additives gave inferior results (entries 2-6). The critical role of 2,3-dimethylindole was further demonstrated by the trace fluorinated product obtained, when the control reaction was performed without the utilization of mediators (entry 8). Lowering or increasing the reaction temperature proved to be detrimental, leading to decreased chemical yields (entries 9-12). When tetrabutylammonium fluoride (TBAF) or cesium fluoride (CsF) was utilized as the fluoride source instead, only trace amount of desired product was observed under otherwise identical reaction conditions (entries 13-14).

Table 1. Reaction Condition Optimization[a]

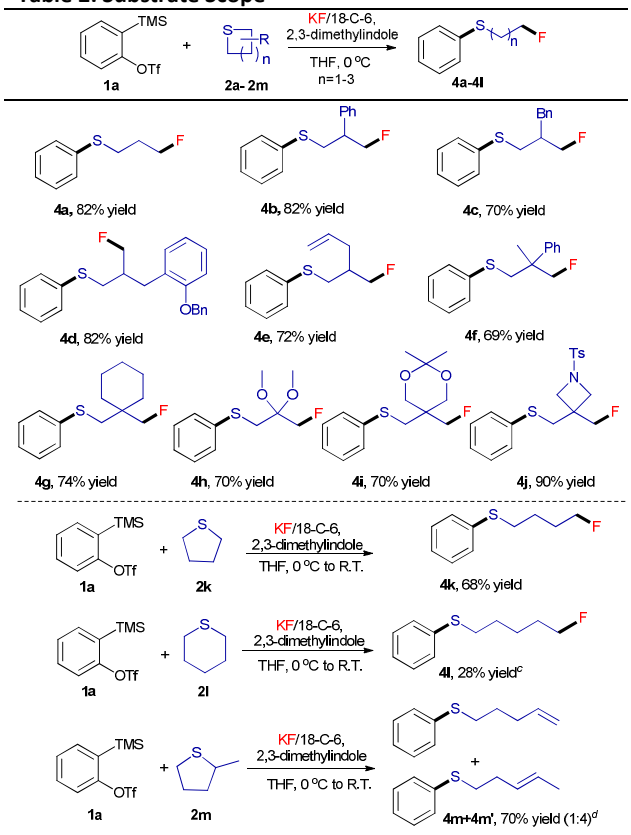


Entry	Fluoride source	Mediator	Temp.(°C)	Yield(%)[b]
1	KF/18-C-6	H_2O	0	57
2	KF/18-C-6	MeOH	0	64
3	KF/18-C-6	*i*-PrOH	0	67
4[c]	KF/18-C-6	TTBP	0	70
5	KF/18-C-6	carbazole	0	68
6	KF/18-C-6	tetrahydrocarbazole	0	66
7	KF/18-C-6	2,3-dimethylindole	0	80
8	KF/18-C-6	None	0	Trace
9	KF/18-C-6	2,3-dimethylindole	-10	67
10	KF/18-C-6	2,3-dimethylindole	10	60
11	KF/18-C-6	2,3-dimethylindole	30	52
12	KF/18-C-6	2,3-dimethylindole	50	25
13	TBAF	2,3-dimethylindole	0	Trace
14[d]	CsF	2,3-dimethylindole	0	Trace

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), KF (0.7 mmol), 18-Crown-6 (0.7 mmol), THF (2 ml), mediator (0.5 mmol, stirring for 5 minutes before adding), 24h. [b] Determined by ^{1}H NMR using an internal standard. [c] 48h instead of 24h. [d] Solvent: CH_3CN. TTBP: 2,4,6-Tri-*tert*-butylphenol.

By using the optimal fluorination reaction conditions described in Table 1, we explored the fluorination of a wide range of cyclic thioethers. As shown in Table 2, thietanes containing phenyl, benzyl and allyl substituent groups were all tolerated well under the optimized reaction conditions, giving fluorinated products **4b**-**4e** in 70-82% yields. Substrates with all-carbon quaternary center at 4-position were also viable that **4f** and **4g** proceeded in 69% and 74% yield, respectively. Furthermore, substrates bearing cyclic ketal moiety underwent the desired ring opening reactions smoothly to give corresponding products **4h** and **4i**. It is noteworthy that even the azetidinyl spirothietane proved to be viable substrate to afford the fluorinated product **4j** in 90% yield, while the medicinally relevant azetidine moiety kept intact. We believed that this result could be rationalized by the change in nucleophilicity between thietane and its nitrogen analogue. When tetrahydrothiophene and thiane were subjected to the reaction conditions, both of which formed the desired fluorinated sulfide products (**4k**-**4l**). As might be expected, the diminished yield and elevated reaction temperature were observed, which are probably due to their reduced ring strain. Under standard reaction conditions, the reaction of 2-methyltetrahydrothiophene **2m** gave exclusively the elimination products **4m** and **4m'** in 70% total yield with 1:4 ratio of regioisomers, demonstrating a limit of our protocol.

Table 2. Substrate Scope[a,b]



[a] Isolated yields. [b] **1a** (0.2 mmol), 2,3-dimethylindole (0.5 mmol), sulfur heterocycles (0.3 mmol), KF/18-C-6 (0.7 mmol), THF (2 mL) for 24 h at 0 °C. [c] KF/18-C-6 (0.14 mmol), 48 h. [d] Determined by ^{1}H NMR spectroscopic analysis.

We next turned our attention to determining the scope of aryne components that are amenable to this fluorination

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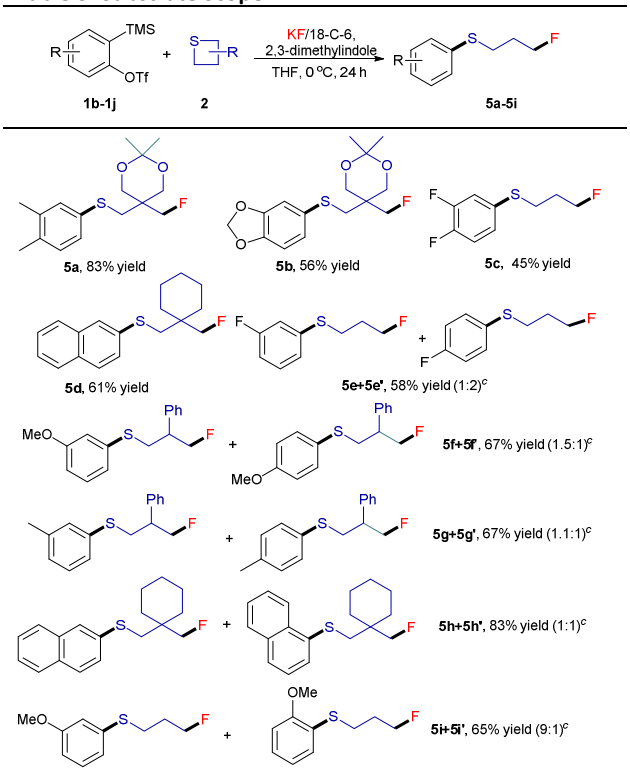
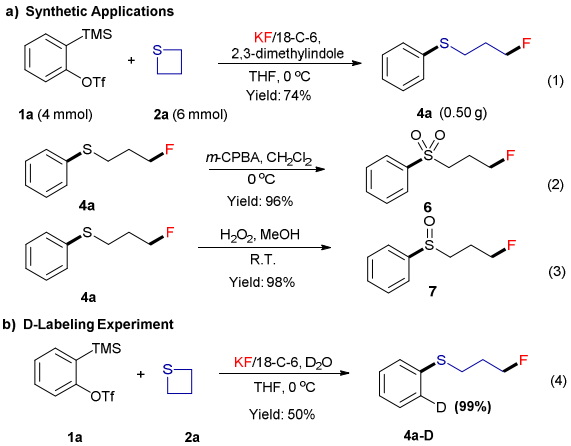
reaction. As shown in Table 3, symmetric aryne precursors that incorporate various functional groups are readily tolerated, affording the ring-opening fluorinated products (**5a**-**5d**) in good yields and great structural diversities. In general, arynes bearing electron-withdrawing groups gave less satisfying results than those with electron-donating groups. When unsymmetrical arynes were employed, the reactions proceeded as expected to give the corresponding products **5e**-**5h** in moderate yields although with poor regioselectivities. These observations were in accordance with the weak-biasing effects observed in previous reports.[11] It's important to note that 3-methoxy substituted benzyne gave ring-opening fluorinated product **5i** and **5i'** with a 9:1 ratio, which could be rationalized by the distortion/interaction model disclosed by Garg and Houk.[12]

Table 3. Substrate Scope[a,b]



[a] Isolated yields. [b] **2a** (0.3 mmol), 2,3-dimethylindole (0.5 mmol), substituted aryne (0.2 mmol), KF/18-C-6 (0.7 mmol), THF (2 mL) for 24 h at 0 ˚C. [c] Determined by NMR spectroscopic analysis.

To demonstrate the synthetic utility of this newly developed methodology, a gram-scale synthesis was carried out. As shown in Scheme 4, the authors reacted 4 mmol of **1a** with a slight excess (1.5 equivalents, 6 mmol) of the thietane. Under optimal conditions, the desired fluorinated product **4a** was produced in a slightly lower 74% yield (0.5 gram). Furthermore, sulfide **4a** could be readily transformed to fluorinated sulfone **6** and sulfoxide **7** selectively with excellent yields under oxidative conditions. To gain insights into the mechanism of this ring opening protocol, the deuterium-labeling experiment was carried out (Scheme 4b). Consistent with the proposed mechanism, the reaction proceeded in the presence of D_2O to give the fluorinated product **4a-D** in 50% yield and 99% deuterium incorporation at the *ortho*-position of the alkyl chain.



Scheme 4. Synthetic applications and D-labeling experiment

In conclusion, we successfully developed an aryne-triggered ring opening fluorination reaction with the aid of a "tailor-made" mediator. The operational simplicity and mild reaction conditions enable the synthesis of a diverse collection of valuable fluorinated products in good yields. Remarkably, this transition-metal free protocol proved to be not only scalable, but also easily possible for further functionalization. Given the importance of fluorine-containing compounds, we anticipate this method will find broad application in both the academic and industrial settings.

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Conflicts of interest

There are no conflicts to declare.

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