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Deoxyfluorination of alcohols with aryl fluorosulfonates†

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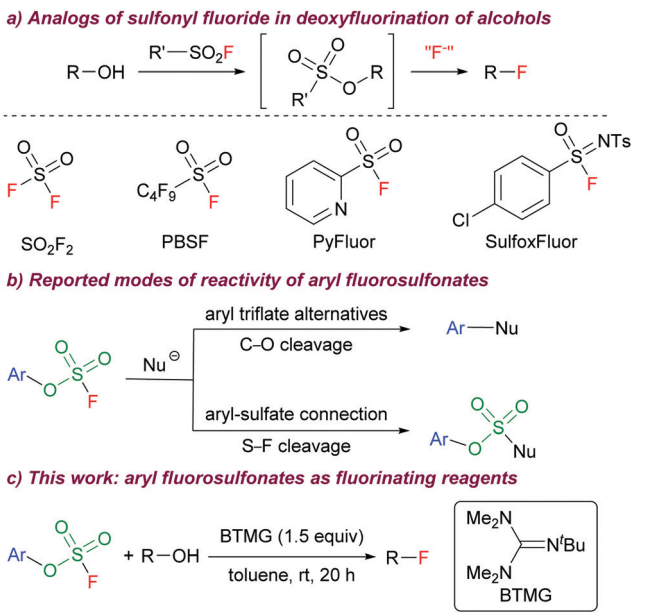
Aryl fluorosulfonates are developed as a deoxyfluorinating reagent in the transformation of primary and secondary alcohols into the corresponding alkyl fluorides. These reagents feature easy availability, low-cost, high stability and high efficiency. Diverse functionalities including aldehyde, ketone, ester, halogen, nitro, alkene, and alkyne are well tolerated under mild reaction conditions.

The introduction of a fluorine atom confers unique chemical, physical and biological properties on organic molecules, and has become a standard routine to discover new candidates of materials and pharmaceuticals.[1] In terms of aliphatic carbon–fluorine-bond formation, the deoxyfluorination of alcohols is recognized as a straightforward and efficient approach, due to the abundant and readily available alcohol-containing precursors.[2] Conventional fluorinating reagents for deoxyfluorination of alcohols include DAST,[3] Deoxo-Fluor,[4] XtalFluor,[5] and Fluolead,[6] which are limited by their thermally instability, high cost, and/or poor functional-group tolerance. Subsequently, representative α-fluorinated alkylamines such as PhenoFluor,[7] AlkylFluor,[8] and carbon-based CpFluor[9] were developed, which improved the substrate scope and selectivity to a large extent. Besides, a sulfur-based reagent is another indispensable category in deoxyfluorination of alcohols, especially for the analogs of sulfonyl fluoride (Scheme 1a). Only one example was described that uses gaseous sulfuryl fluoride (SO_2F_2) as a fluorination reagent.[10] PBSF,[11] PyFluor,[12] and SulfoxFluor[13] were distinguished by their good balance between high reactivity and great stability. However, they still suffered from safety concerns,[14] unsatisfactory results with benzylic alcohols, multistep synthesis, and/or the poor fluorine atom economy (especially the PBSF reagent). Therefore, readily available, bench-stable, easy-to-handle and inexpensive fluorinating reagents are still highly desired.

Aryl fluorosulfonates could be easily synthesized from the reaction of phenols and sulfuryl fluoride (SO_2F_2) in high yields under mild reaction conditions.[15] They are conventionally used as aryl electrophile alternatives to aryl triflates and well documented in various transformations (Scheme 1b).[16–22] The OSO_2F unit could not only function as a good leaving group, but a stable sulfate connector applied in click chemistry (Scheme 1b).[23] To date, the use of aryl fluorosulfonates as



Scheme 1 Deoxyfluorination of alcohols and applications of aryl fluorosulfonates.

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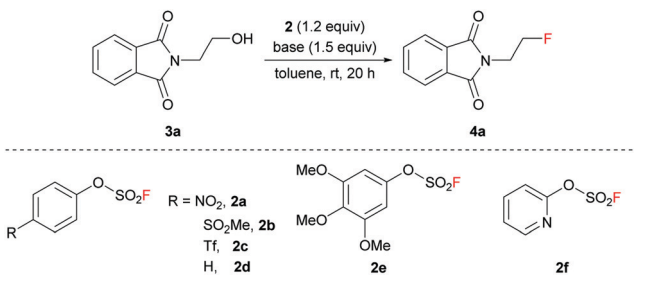
halogenating agents has not been reported.[23b] Herein, we reported the novel application of $ArOSO_2F$ in deoxyfluorination of alcohols, which constitutes a practical method for the synthesis of alkyl fluorides, due to their easy availability, low cost, and high stability towards air and moisture (Scheme 1c).

Initially, *N*-hydroxyethyl phthalimide (**3a**) and aryl fluorosulfonate bearing a nitro group (**2a**) were chosen as the model reaction substrates. Various reaction parameters including solvent (Table S1, ESI†), amount of aryl fluorosulfonate (**2a**) and base (Table S2, ESI†) were systematically evaluated. As a result, 73% yield of the desired product **4a** was obtained with 1 equivalent of **3a** and 1.2 equivalent of **2a** activated by 1.5 equivalent of 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in toluene at room temperature for 20 h (Table 1, entry 1). Other organic bases such as 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), and 1,1,3,3-tetramethylguanidine (TMG) were also tested, and all of them were proved to be less efficient in the present transformation (entries 2–4). The effect of the electronic nature of aryl fluorosulfonates on the fluorinating ability of aryl fluorosulfonate was further studied, and electron-deficient functional groups incorporated into phenyl sulfurofluoridate including nitro (**2a**), mesyl (**2b**), and triflyl (**2c**) displayed moderate to good yields. In particular, **4a** was obtained with 80% yield when 4-(methylsulfonyl)phenyl sulfurofluoridate (**2b**) was used (entry 5). In contrast, electron-neutral **2d** and electron-rich **2f** showed poor reactivity, along with target product **4a** in 16% and 12% yields, respectively (entries 7 and 8). Hetero-atom-containing aryl fluorosulfonates (**2f**) also led to inferior results (entry 9). On the other hand, the yield of **4a** was further increased to 88% when 2-*tert*-butyl-1,1,3,3-tetramethylguanidine (BTMG) was used instead of DBU under the identical reaction conditions (entry 10).

Table 1 Optimization of the reaction conditions[a]



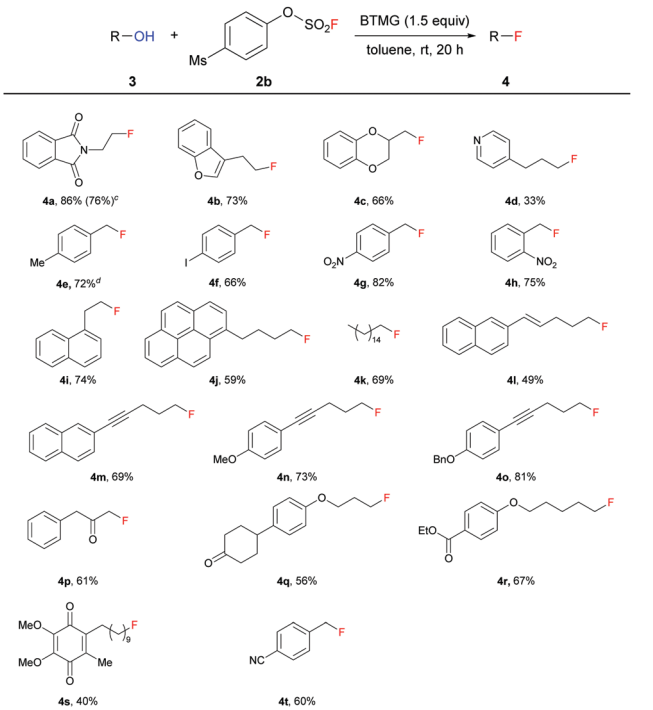
Entry	2	Base	4a[b] (%)
1	**2a**	DBU	73
2	**2a**	DBN	9
3	**2a**	TBD	34
4	**2a**	TMG	28
5	**2b**	DBU	80
6	**2c**	DBU	55
7	**2d**	DBU	16
8	**2e**	DBU	12
9	**2f**	DBU	34
10	**2b**	**BTMG**	**88 (86)**

[a] Reaction conditions: **3a** (0.5 mmol), **2** (1.2 equiv.), base (1.5 equiv.), toluene (5 mL), r.t., 20 h. [b] Determined by ^{19}F NMR analysis of the crude mixture, using fluorobenzene as an internal standard. An isolated yield is given in parentheses.

The performance of **2b** with primary alcohols under the optimized reaction conditions was evaluated as shown in Table 2. Pharmaceutically important heterocycles such as phthalimide (**3a**), benzofuran (**3b**), and benzodioxine (**3c**) could proceed smoothly, affording the corresponding fluoroalkanes **4a–4c** in 66–86% yields; whereas pyridine and benzoquinone-containing compounds provided **4d** and **4s** in 33% and 40% yields, respectively. Notably, 20 mmol scale synthesis of **4a** was tested with 76% (2.9 g) isolated yield, which demonstrated the practicability and effectiveness of this methodology, as well as its value and prospects in industry. Unhindered benzylic alcohols bearing methyl, iodo, nitro and cyano groups regardless of the steric effect delivered fluorinated products **4e–4h** and **4t** in good yields, which showed the advantages of our method over PyFluor.[12] Fused aromatic rings such as naphthyl (**3i**), pyrene (**3j**) or long alkyl chain (**3k**) containing primary alcohols could also be fluorinated in this transformation. The present protocol was highlighted by various functionalities including alkene (**4l**), alkynes (**4m–4o**), ketone (**4p**, **4q**), and ester (**4r**), which proved that **2b** is a practical alternative to other fluorinating reagents.

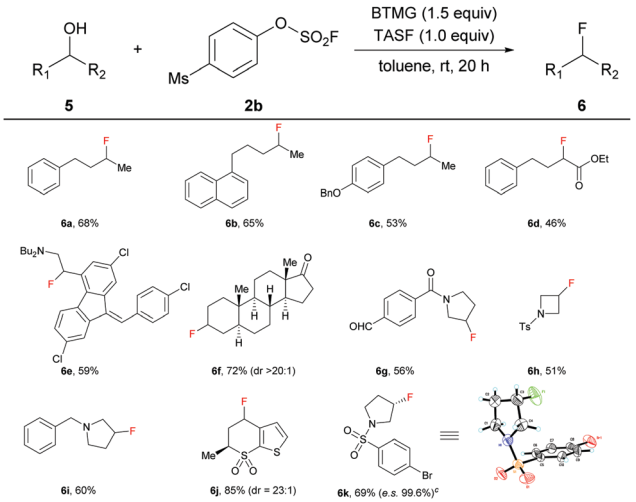
Deoxyfluorination of secondary alcohols was also accomplished with the assistance of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) under the optimized reaction conditions (Table 3). Acyclic secondary alcohols were reliable for the generation of fluorinated products **6a–6e**. Good selectivity was demonstrated by the substrates with ketone (**5f**) or

Table 2 Deoxyfluorination of primary alcohols[ab]



[a] Reaction conditions: **3** (0.5 mmol), **2b** (0.6 mmol), BTMG (0.75 mmol), toluene (5 mL), r.t., 20 h. [b] Isolated yields. [c] Isolated yield in a 20 mmol scale reaction. [d] ^{19}F NMR yield using fluorobenzene as an internal standard.

Table 3 Deoxyfluorination of secondary alcohols[ab]

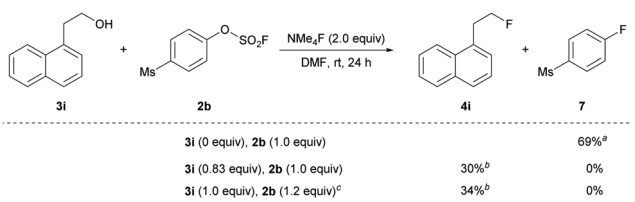


[a] Reaction conditions: **5** (0.5 mmol), **2b** (1.0 mmol), BTMG (0.75 mmol), TASF (0.5 mmol), toluene (5 mL), r.t., 20 h. [b] Isolated yields. [c] The abbreviation e.s. refers to enantiospecifity, e.s. = (ee of **6**)/(ee of **5**) × 100%.

aldehyde (**5g**) groups, which are prone to form geminal difluorides.[24] Other heterocyclic secondary alcohols were investigated and transformed into the desired products **6h–6j** with moderate to good yields. Deoxyfluorination of chiral secondary alcohol (**5k**) gave inverted product **6k** with 69% yield and 99.6% enantiospecificity.

A set of control experiments were conducted to illustrate the high selectivity of **2b** (Scheme 2). Based on the research of Sanford and co-workers, aryl fluorosulfonates could be directly reacted with tetramethylammonium fluoride (Me_4NF) to give out aryl fluorides.[22] Thus, deoxyfluorination of **2b** was tried with their standard reaction conditions, and fluorinated product **7** was obtained in 69% isolated yield. Unexpectedly, only the deoxyfluorination of alcohol **3i** occurred in the presence of **3i**, **2b**, and an external fluorine source (NMe_4F), and similar yields of **4i** were obtained under Sanford's or the present conditions.

To gain insights into the advantages of **2b** as a deoxyfluorinating reagent, pointwise estimates on the reactivity, selectivity, stability, and synthetic method of **2b** were investigated. Initially, time course experiments of **2b** with **3a** or **3g** under the identical reaction conditions disclosed that the present deoxyfluorination process was essentially completed within 2 h, and the yields of **3g** reached a maximum within 10 h (Fig. S1 and S2, ESI†). Subsequently, differential scanning calorimetry (DSC) analysis showed that no exothermic decomposition was observed in the range of 0–330 °C (Scheme S1, ESI†). In addition, thermo gravimetric analysis (TGA) pointed out that **2b** was hardly decomposed below 127 °C (Scheme S2, ESI†). Both DSC and TGA data proved that **2b** is a safe and stable deoxyfluorinating reagent with considerable thermal stability. Furthermore, **2b** could be stored in a glass vial on the benchtop and handled under an air atmosphere. Notably, a gram-scale synthesis of **2b** could be easily achieved *via* the reaction of commercially available phenol and sulfuryl fluoride (SO_2F_2), an inexpensive commodity chemical which is widely used as an insecticide. Given the above, **2b** is distinguished by high reactivity and selectivity, great stability, simple operation and low-cost.



Scheme 2 Control experiments. [a]Isolated yields. [b]Determined by ^{19}F NMR analysis of the crude mixture, using fluorobenzene as an internal standard. [c]Toluene was used instead of DMF for 20 h.

In summary, we discovered the fluorinating ability of 4-(methylsulfonyl)phenyl sulfurofluoridate in deoxyfluorination of alcohols for the first time. A wide range of primary and secondary alcohols were efficiently fluorinated with 4-(methylsulfonyl)phenyl sulfurofluoridate, especially benzylic, aldehyde or ketone-substituted alcohols. The merits of high reactivity and selectivity, great stability, low-cost and mild reaction conditions made the 4-(methylsulfonyl)phenyl sulfurofluoridate a promising deoxyfluorinating reagent.

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Conflicts of interest

There are no conflicts to declare.

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