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Nucleophilic Substitution

Rapid Deoxyfluorination of Alcohols with *N*-Tosyl-4-chlorobenzenesulfonimidoyl Fluoride (SulfoxFluor) at Room Temperature

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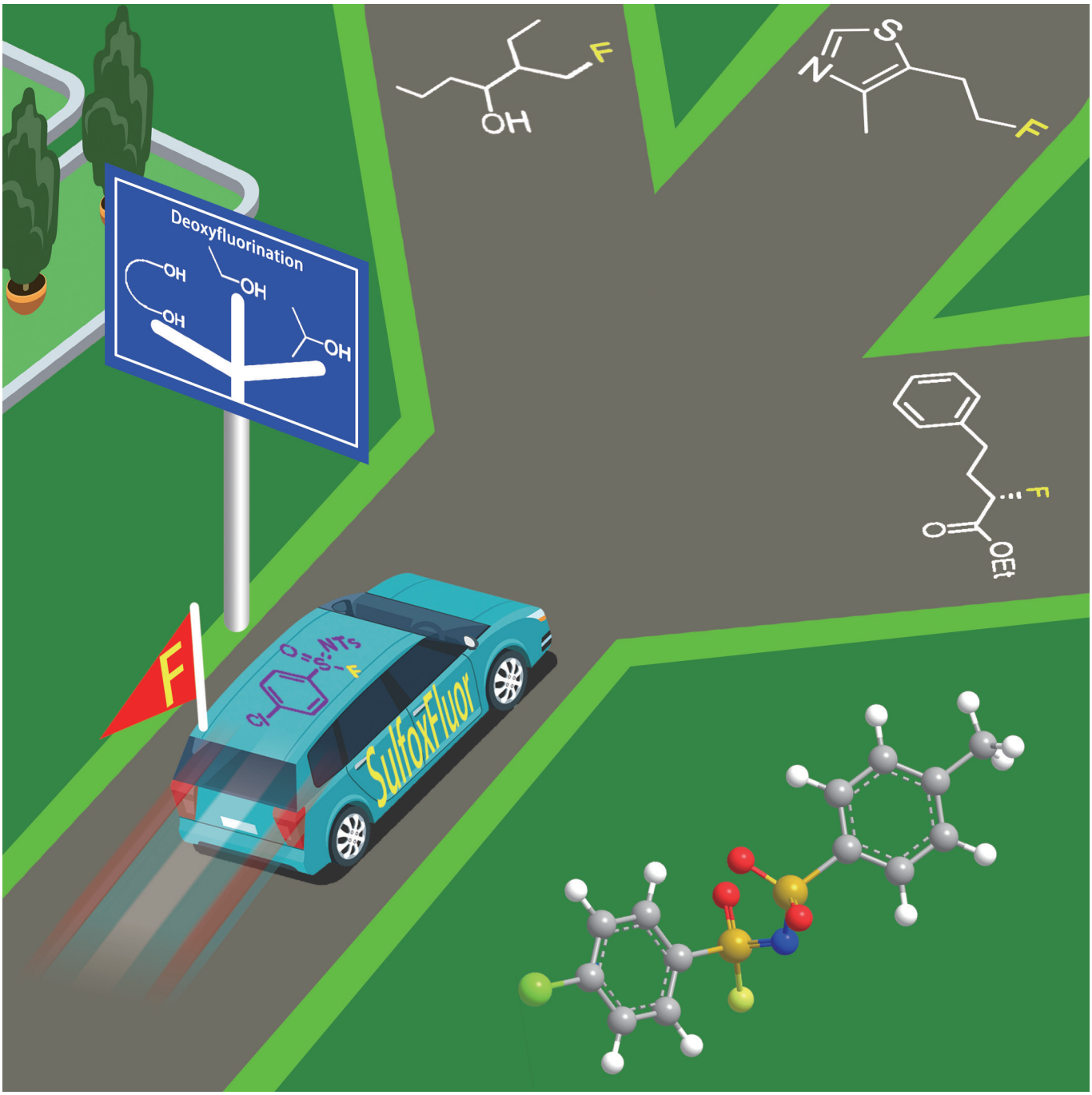
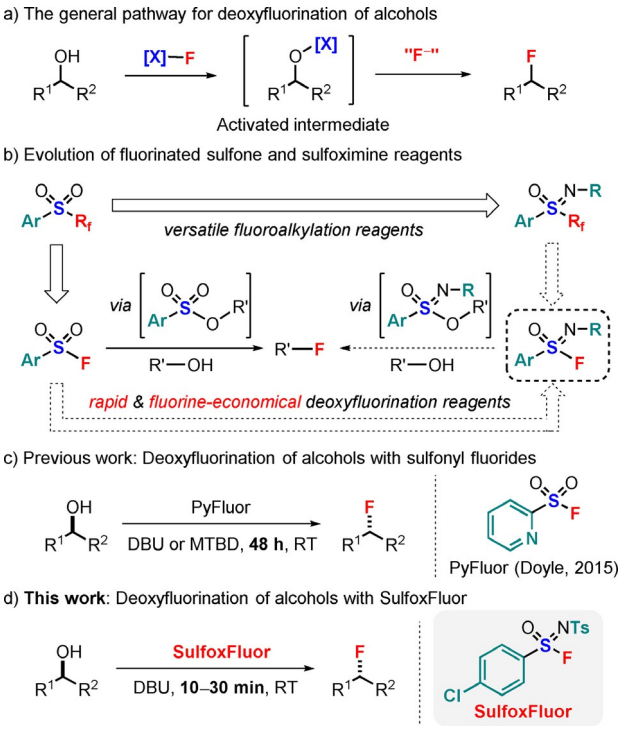
Dedicated to Professor Qing-Yun Chen on the occasion of his 90th birthday



Abstract: The deoxyfluorination of alcohols is a fundamentally important approach to access alkyl fluorides, and thus the development of shelf-stable, easy-to-handle, fluorine-economical, and highly selective deoxyfluorination reagents is highly desired. This work describes the development of a crystalline compound, *N*-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor), as a novel deoxyfluorination reagent that possesses all of the aforementioned merits, which is rare in the arena of deoxyfluorination. Endowed by the multi-dimensional modulating ability of the sulfonimidoyl group, SulfoxFluor is superior to 2-pyridinesulfonyl fluoride (PyFluor) in fluorination rate, and is also superior to perfluorobutanesulfonyl fluoride (PBSF) in fluorine-economy. Its reaction with alcohols not only tolerates a wide range of functionalities including the more sterically hindered alcoholic hydroxyl groups, but also exhibits high fluorination/elimination selectivity. Because SulfoxFluor can be easily prepared from inexpensive materials and can be safely handled without special techniques, it promises to serve as a practical deoxyfluorination reagent for the synthesis of various alkyl fluorides.



Scheme 1. Deoxyfluorination of alcohols with various reagents.

Alkyl fluorides constitute a valuable class of organofluorine compounds for pK_a modulation, lipophilicity tuning, and selective blocking of oxidative metabolism in medicinal chemistry, chemical biology and drug discovery.[1] As a consequence, many fluorination methods have been developed for their synthesis.[2] Among them, deoxyfluorination of alcohols, typically proceeding through in situ activation of the hydroxyl group followed by its displacement by a fluoride anion in a bimolecular nucleophilic substitution (S_N2) manner, represents the most straightforward method due to the abundance of both natural and synthetic alcohols (Scheme 1 a).[2,3] Since the first application of *N*,*N*-diethyl-2-chloro-1,1,2-trifluoroethylamine (Yarovenko's reagent) for deoxyfluorination of alcohols,[4] an arsenal of state-of-the art reagents, such as SF_4,[5] DAST,[6] Deoxo-Fluor,[7] XtalFluor,[8] 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead),[9] Ishikawa's reagent,[10] PhenoFluor,[11] AlkylFluor,[12] perfluorobutanesulfonyl fluoride (PBSF),[13] 2-pyridinesulfonyl fluoride (PyFluor),[14] and 3,3-difluoro-1,2-diarylcyclopropenes (CpFluors),[15] have been developed to achieve efficient transformation of alcohols. However, these efforts mainly focus on addressing the safety, the cost, and/or the selectivity problems associated with the deoxyfluorination reagents,[6–15] and very little attention has been devoted to improving the deoxyfluorination rate, which is of great significance to industry. A survey of literature showed that PBSF is an ideal deoxyfluorination reagent that fulfills the industrial requirements on safety, cost, and reaction rate,[13,14b] but the rising concern on the potential environment and health problems caused by its deoxyfluorination byproduct perfluorobutanesulfonate salt restricts its wide application.[16] Therefore, from the viewpoint of atom economy of fluorine (fluorine-economy),[17] the development of an operationally simple and highly effective alcohol deoxyfluorination reagent with low fluorine content is highly desirable.

Sulfonimidoyl compounds are the monoaza analogues of sulfonyl compounds; however, the former display much more diverse reactivity due to the additional modulation potential given by the nitrogen substituent.[18] In recent years, fluoroalkyl sulfoximines have been developed as more versatile and powerful fluoroalkylation reagents than their sulfone analogues and widely used for the incorporation of various fluoroalkyl groups into organic molecules by us and others (Scheme 1 b).[18c,19] Sulfonimidoyl fluorides can be easily prepared and generally possess the similar stability as sulfonyl fluorides,[20] but their application as deoxyfluorination reagents is still unknown. Furthermore, the nucleophilic displacement of the sulfonimidate group in an alkyl sulfonimidate ester is also rare.[21] Inspired by our previous studies on the synthetic application of fluorinated sulfones[22] and sulfoximines[19] as well as Doyle's elegant work on deoxyfluorination of alcohols with 2-pyridinesulfonyl fluoride (PyFluor) (Scheme 1 c),[14a] we envisioned that sulfonimidoyl fluorides might be able to serve as better deoxyfluorination reagents than sulfonyl fluorides because both the nitrogen and the sulfur substituents of the former can be modified (Scheme 1 b). Herein, we report our

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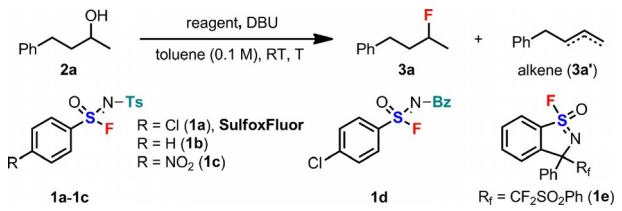
development and use of crystalline *N*-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor) (**1a**) as a new bench-stable, easy-to-prepare and highly reactive deoxyfluorination reagent, which can rapidly convert various alcohols into alkyl fluorides at room temperature (Scheme 1 d).[23]

We first evaluated the deoxyfluorination ability of sulfonimidoyl fluorides **1a**–**1e** with secondary alcohol **2a** as a model substrate, organic base 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) as activator,[13,14] and toluene as solvent at room temperature (Table 1; for details, see the Supporting Information). The preliminary results showed that the electronic nature of the substituents on both the sulfur atom and the nitrogen atom of a sulfonimidoyl fluoride could significantly influence the yield of the fluorination product **3a**, with *N*-tosyl-4-chlorobenzenesulfonimidoyl fluoride (SulfoxFluor, **1a**) being the most effective (Table 1, entry 1). Changing the *S*-substituent to an electron-neutral phenyl or more electron-deficient 4-nitrophenyl group resulted in a decrease of the yield of **3a** and an increase of the side product alkene **3a**′ (Table 1, entries 2 and 3). Replacing the *N*-substituent from tosyl to less electron-withdrawing benzoyl also led to an inferior result (Table 1, entry 4). Moreover, in the case of **1e** with an *N*-alkyl substituent, a full recovery of **1e** was observed (Table 1, entry 5). With SulfoxFluor (**1a**) as the optimal reagent, a further screening of the reaction conditions showed that a highest yield (74%) of **3a** could also be obtained in 30 min by performing the reaction with 1.2 equiv of **1a** and 1.6 equiv of DBU (Table 1, entries 6 and 7). For comparison, we conducted the deoxyfluorination of **2a** with PyFluor[14a] and perfluorobutanesulfonyl fluoride (PBSF)[13,14b] under similar conditions.[24] In the case of PyFluor, a stirring of the reaction mixture at room temperature for 30 min afforded only trace amount of **3a** (Table 1, entry 8), a result similar to previous report.[14a] When PBSF was used instead of SulfoxFluor (**1a**), although the reaction could be finished in 30 min, it afforded a little lower yield of **3a** (62%) and relatively higher yield of the elimination product **3a**′ (Table 1, entry 9). Despite its comparable reactivity, the high fluorine content of PBSF makes it fall short of the concept of fluorine-economy.[17] Clearly, SulfoxFluor (**1a**) is more suitable for both fluorine-economical and rapid deoxyfluorination of alcohols. Moreover, we found that the deoxyfluorination of primary alcohols could complete in 10 min by using only slightly excess amount of **1a** (1.2 equiv) and DBU (1.2 equiv) (see the Supporting Information).

Table 1. Screening of reaction conditions.[a]

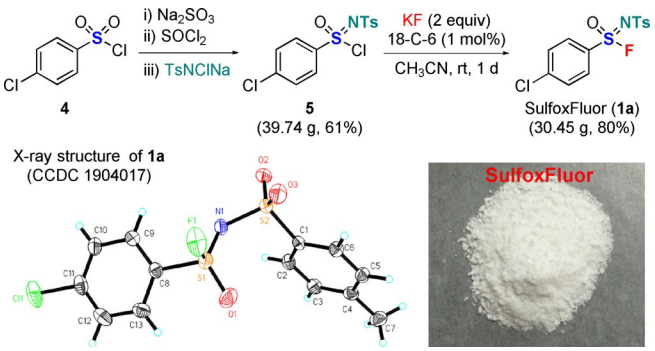


Entry	Reagent	2a/reagent/DBU	Time [min]	3a [%]	3a/3a′[b]
1	**1a**	1.0:1.1:1.1	720	74	20:1
2	**1b**	1.0:1.1:1.1	720	53	10:1
3	**1c**	1.0:1.1:1.1	720	56	7:1
4	**1d**	1.0:1.1:1.1	720	52	6:1
5	**1e**	1.0:1.1:1.1	720	0	ND[c]
6	**1a**	1.0:1.1:1.1	30	68	22:1
7	**1a**	1.0:1.2:1.6	30	74	22:1
8	PyFluor	1.0:1.2:1.6	30	<5	ND[c]
9	PBSF	1.0:1.2:1.6	30	62	9:1

[a] Reactions were conducted on 0.2-mmol scale. Yields of **3a** were determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard. [b] Detected by GC-MS analysis. [c] Not determined.

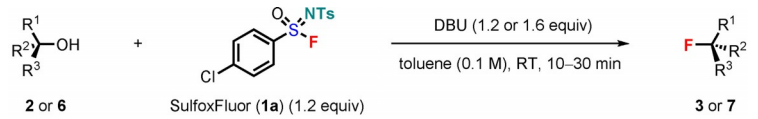
SulfoxFluor (**1a**) can be easily prepared in large scale from inexpensive 4-chlorobenzenesulfonyl chloride (**6**) through treatment with several readily available reagents including chloramine-T and potassium fluoride (Scheme 2).[25] We find that SulfoxFluor (**1a**) is a stable crystalline compound (m.p. 110–112 °C) that can be operated under air atmosphere and we have stored it in a rubber septa-sealed glass vial on the benchtop for over two years without decrease in reactivity. Differential scanning calorimetry (DSC) analysis showed that SulfoxFluor (**1a**) does not decompose in the range of 0–330 °C (see the Supporting Information), indicating its good safety feature for applications.

With the optimized reaction conditions in hand, we then examined the substrate scope by reacting SulfoxFluor (**1a**) with different alcohols (Table 2). Generally, a broad range of primary and secondary monoalcohols underwent rapid deoxyfluorination at room temperature to afford the corresponding alkyl fluorides in moderate to excellent yields (Table 2, **3b**–**3x**, and **7a**–**7j**). The reaction of enantioenriched secondary alcohols proceeded with inversion of configuration and high enantiospecificity (**3o**, **3p**, and **3s**). Many functional groups, such as alkene (**3l**), alkyne (**3m**), sulfonamide (**3n**), amide (**3o**), and carbamate (**3p** and **3q**), are compatible with this deoxyfluorination process. Heterocycles such as pyridine (**3r**), thiazole (**3v**), and benzofuran (**3w**) were also tolerated under the present conditions. Moreover, carbohydrate derivative (**3i**), steroid (**3j**), and idebenone (**3k**) were fluorinated in 58–90% yields, indicating the capability of this fluorination method for late-stage modification of complex biomolecules and their derivatives. The deoxyfluorination process is operationally simple and can be easily scaled up. For example, under the aforementioned optimized conditions, alcohol **2n** was deoxyfluorinated on 5 mmol scale in 88% yield. When multiple alcohols in

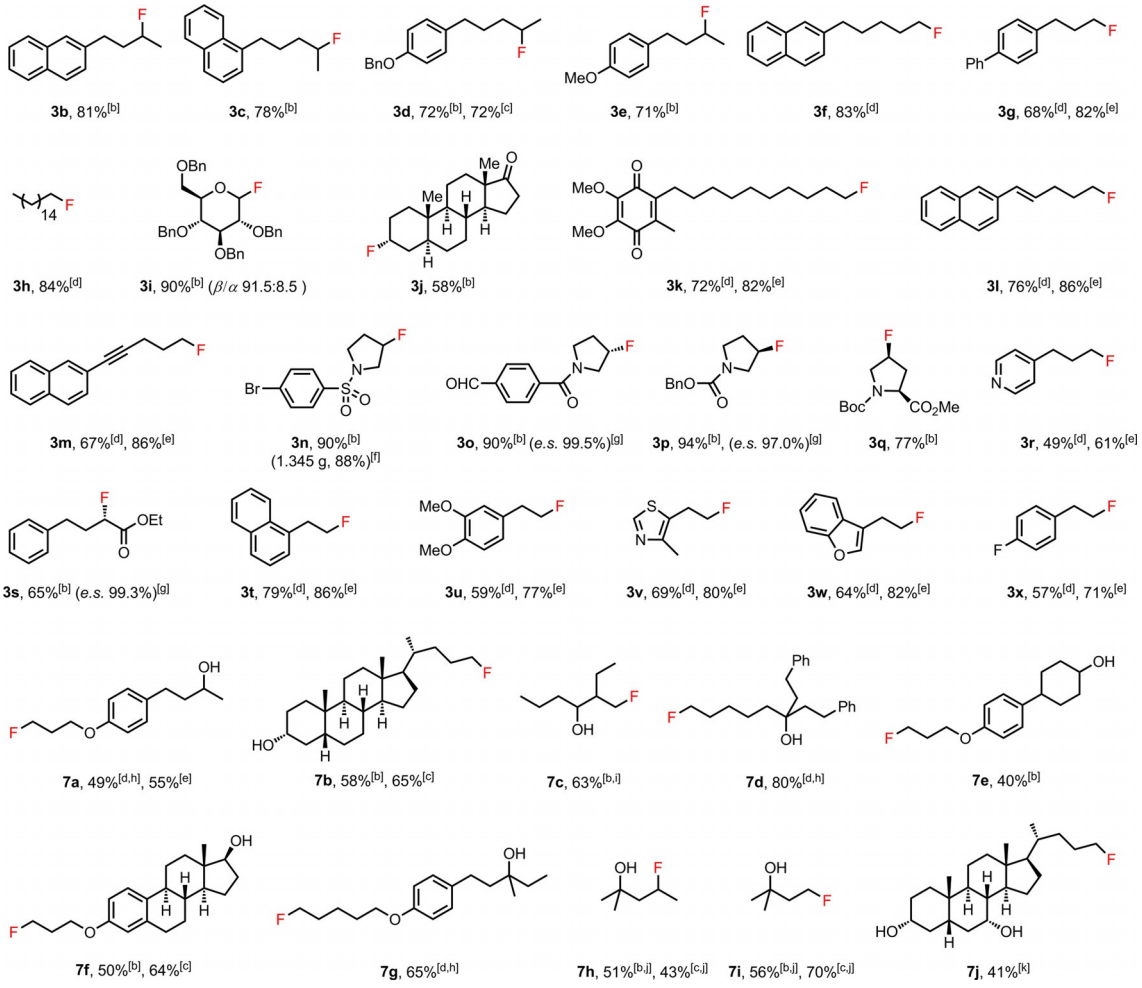


Scheme 2. Practical preparation of SulfoxFluor (**1a**)

Table 2. Scope of the deoxyfluorination with SulfoxFluor (**1a**).[a]



2 or **6** — SulfoxFluor (**1a**) (1.2 equiv) — **3** or **7**



3b, 81%[b] **3c**, 78%[b] **3d**, 72%[b], 72%[c] **3e**, 71%[b] **3f**, 83%[d] **3g**, 68%[d], 82%[e]

3h, 84%[d] **3i**, 90%[b] (β/α 91.5:8.5) **3j**, 58%[b] **3k**, 72%[d], 82%[e] **3l**, 76%[d], 86%[e]

3m, 67%[d], 86%[e] **3n**, 90%[b] (1.345 g, 88%)[f] **3o**, 90%[b] (*e.s.* 99.5%)[g] **3p**, 94%[b], (*e.s.* 97.0%)[g] **3q**, 77%[b] **3r**, 49%[d], 61%[e]

3s, 65%[b] (*e.s.* 99.3%)[g] **3t**, 79%[d], 86%[e] **3u**, 59%[d], 77%[e] **3v**, 69%[d], 80%[e] **3w**, 64%[d], 82%[e] **3x**, 57%[d], 71%[e]

7a, 49%[d,h], 55%[e] **7b**, 58%[b], 65%[c] **7c**, 63%[b,i] **7d**, 80%[d,h] **7e**, 40%[b]

7f, 50%[b], 64%[c] **7g**, 65%[d,h] **7h**, 51%[b,j], 43%[c,j] **7i**, 56%[b,j], 70%[c,j] **7j**, 41%[k]

[a] Unless otherwise noted, reactions were conducted on 0.2 mmol scale in a polytetrafluoroethylene (PTFE) tube, and isolated yields are given. [b] DBU (1.6 equiv), 30 min. [c] DBU (1.6 equiv), TBAF(*t*BuOH)$_4$ (1.0 equiv), 30 min. [d] DBU (1.2 equiv), 10 min. [e] DBU (1.2 equiv), TBAF(*t*BuOH)$_4$ (1.0 equiv), 30 min. [f] In parentheses: result of a 5.0 mmol scale reaction. [g] The abbreviation e.s. refers to enantiospecifity, e.s. = (*ee* of **3**)/(*ee* of **2**) × 100%. [h] Reaction time was 30 min. [i] Reaction was conducted on 0.5 mmol scale. [j] Yields were determined by ^{19}F NMR using 1-fluoronaphthalene as an internal standard. [k] **1a** (1.5 equiv), DBU (2.0 equiv), 80 °C, 30 min.

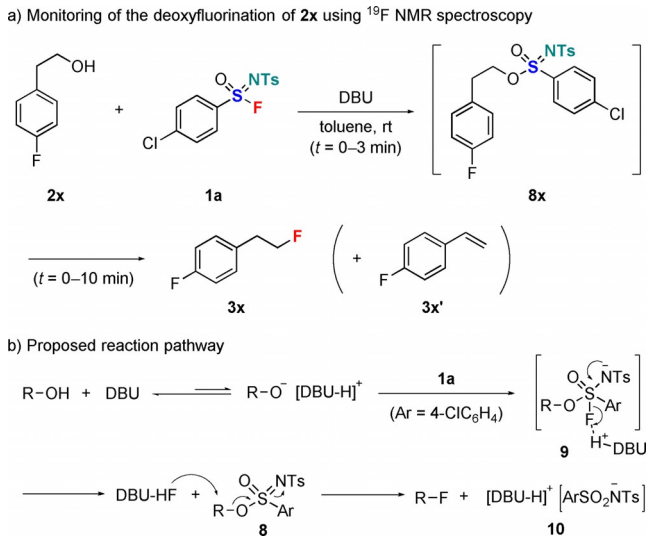
which the hydroxyl groups are separated by several carbon centers, were used as the substrates, the reaction selectively took place at the less sterically hindered position to afford the monofluorination products in synthetically useful yields in 30 min (Table 2, **7a**–**7j**). All these results showed that SulfoxFluor (**1a**) is a unique fluorination reagent for discriminating the steric hindrance of alcohols.

Moreover, deoxyfluorination with SulfoxFluor (**1a**) is highly selective against elimination, which can be especially beneficial for the purification of the fluorination products. The reaction of primary alcohols seldom generated the alkene side products, even in the cases of homobenzylic alcohols that highly tend to undergo elimination (**3t**–**3x**). Although 2-(4-fluorophenyl)ethanol (**2x**) is further activated by the electron-withdrawing *para*-fluoro substitute, its reaction with SulfoxFluor (**1a**) still afforded the fluorination product **3x** in 57% yield with a fluorination/elimination selectivity up to 15:1 (determined by ^{19}F NMR), which is much higher than the reaction with PyFluor (see the Supporting Information). We attribute this remarkable selectivity to the high electrophilicity of the sulfonimidate ester intermediates, which accelerates the nucleophilic fluorination. Most secondary alcohols also showed high selectivity of fluorination over elimination ($\geq$20:1); as an exception, the steroid *epi*-androsterone delivered **3j** as the single stereoisomer in 58% yield with a fluorination/elimination selectivity of 1.6:1.

In addition to its high reactivity and excellent selectivity, the byproduct of the reaction, that is, the ammonium salt of *N*-tosyl-4-chlorobenzenesulfonamide, which is formed as a precipitate, can be recovered by filtration (see the Supporting Information), thus simplifying the purification process. Moreover, the so-obtained salt is potentially useful for other synthetic application, such as preparing the analogue of the known electrophilic fluorination reagent NFSI.[26]

Nevertheless, the deoxyfluorination with SulfoxFluor (**1a**) in the absence of an external fluoride does have one disadvantage, that is, the high reactivity of the sulfonimidate ester intermediates can lead to the alkylation of DBU, especially in the cases of primary alcohol substrates, thus decreasing the yields of the desired alkyl fluorides to some extent. For example, the reaction of alcohol **2t** provided **3t** in only 79% yield, with the formation of the *N*-alkylation side product in about 16% yield. However, compared with the great conveniences brought by this method (short reaction time, operational simplicity, and high fluorination/elimination selectivity), this issue is trivial. Moreover, we found that the deoxyfluorination of primary alcohols could be improved by about 10–20% yields by adding 1.0 equiv of TBAF(*t*BuOH)$_4$[27] to override the side reaction (Table 2, **3g**, **3k**–**3m**, **3r**, **3t**–**3x**, **7a**, **7b**, **7f**, and **7i**). Note that even the phenethyl alcohol that is the most susceptible to undergo elimination reaction could be deoxyfluorinated with increased yield and fluorination/elimination selectivity (**3x**; see the Supporting Information). In contrast, the addition of external fluorides showed no positive effect on the reaction of the secondary alcohols (**3d** and **7h**).

Finally, to understand the mechanism, we monitored the reaction between 4-fluorophenethyl alcohol **2x** and SulfoxFluor (**1a**) in toluene using in situ ^{19}F NMR spectroscopy at room temperature (Scheme 3a; for details, see the Supporting Information). In the presence of DBU, an extremely fast reaction between **2x** and **1a** gave the intermediate 4-fluorophenethyl sulfonimidate **8x** quantitatively, which can be directly observed by ^{19}F NMR (t = 0–3 min). Meanwhile, a relatively slow consumption of the sulfonimidate **8x** afforded the alkyl fluoride **3x** (t = 0–10 min). However, in the absence of DBU, **2x** failed to react with **1a**. Compared with the reaction profile of PyFluor,[14a] it is obvious that the reactivity difference between these two reagents arises from the nucleophilic fluorination step rather than the activation step. The activation role of DBU was subsequently investigated. When mixing DBU and SulfoxFluor in the absence of the substrate alcohol, it was found that the reaction is very sluggish, so we ruled out the possibility of SulfoxFluor activation by DBU via the formation of a σ-complex.[28]



Scheme 3. Mechanistic considerations.

We envisioned that DBU may serve as a base to deprotonate the alcohol, thus promoting the formation of the sulfonimidate ester by replacing the fluorine atom in SulfoxFluor, which is similar to previously reported reaction of PyFluor.[14a]

According to above results and rationalization, a proposed reaction pathway for the deoxyfluorination of alcohols with SulfoxFluor is shown in Scheme 3b. First, DBU deprotonates the alcohol to generate the alcoholate anion, which undergoes very fast nucleophilic addition to the SulfoxFluor to afford a pentacoordinated intermediate **9**. Then the stabilization effect of the protonated DBU on fluoride promotes the quick release of the fluorine substituent from intermediate **9** to afford the sulfonimidate ester **8**. Finally, the nucleophilic displacement of the sulfonimidate group by DBU-HF provided the alkyl fluoride products and the salt **10**. We believe that the excellent leaving ability of the sulfonimidate group can be attributed to the electron-withdrawing nature of the *N*-substituent. The activation of the leaving group by protonation on nitrogen[21d] is less likely due to the weak acidity of the DBU-HF complex.

In summary, we have developed a bench-stable and crystalline sulfonimidoyl fluoride compound, SulfoxFluor, as a safe and practical reagent for rapid and efficient deoxyfluorination of alcohols. SulfoxFluor can be easily accessed from inexpensive materials and handled without special techniques. Its reaction with alcohols not only tolerates a wide range of functionalities, but also shows high selectivity against elimination. Therefore, this new deoxyfluorination protocol with SulfoxFluor reagent promises to find many practical applications. Further investigation on the synthetic application of SulfoxFluor by utilizing its unique activation ability is underway in our laboratory.

Acknowledgements

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Conflict of interest

The authors declare the following financial interest: J.H., J.G. and C.N. have filed a patent application with the China National Intellectual Property Administration based on the results of this study.

Keywords: alcohols · deoxyfluorination · fluorine · fluorination · SulfoxFluor

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