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Base-Catalyzed Intramolecular Defluorination/O-Arylation Reaction for the Synthesis of 3-Fluoro-1,4-oxathiine 4,4-Dioxide

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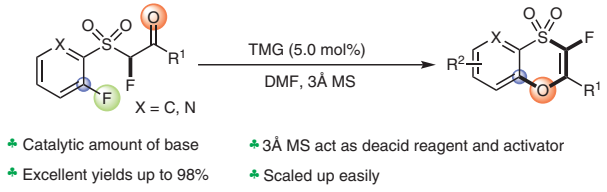

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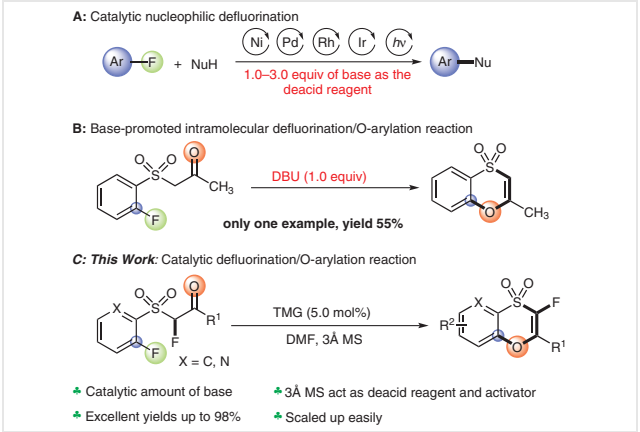
Abstract A novel process involving base-catalyzed intramolecular defluorination/O-arylation of readily available α-fluoro-β-one-sulfones was realized and provided a series of 3-fluoro-1,4-oxathiine 4,4-dioxide derivatives in good to excellent yields. Unlike traditional defluorination reactions with stoichiometric base as the deacid reagent, this process is triggered by a catalytic amount of base (TMG: tetramethylguanidine) and molecular sieves serve as both an adsorbent to remove HF acid and an activator to assist C–F bond cleavage.

Key words base catalysis, defluorination, O-arylation, metal-free reactions, 1,4-oxathiines

Organofluorines are an important class of industrial chemicals, accounting for 30% of agrochemicals and 10% of pharmaceuticals.[1] The implantation of fluorine atoms into organic molecules can alter the biological properties of lipophilicity, bioavailability, and metabolic stability. However, environmental persistence and toxicity to human health are motivating efforts to develop processes that efficiently degrade organofluorines.[2] The development of new methods for their decomposition and emission reduction are significant for environmental conservation and public health. Carbon–fluorine bonds are among the most chemically robust bonds (for example, the Ph–F bond energy is 127.2 kcal/mol), which makes bond activation relatively challenging.[3] In addition, it takes great effort to avoid fluoride waste. Some significant achievements have been made in the defluorination of aryl fluorides under mild reaction conditions (Scheme 1A), but all of the strategies need excess base as the deacid reagent.[4–9] Recently, transition-metal-catalyzed transformations of carbon–fluorine bonds have been developed under mild reaction conditions (Scheme 1A) by using tailored transition-metal- or organophotocatalysts, such as nickel,[4] cobalt,[5] palladium,[6] rhodium[7] xanthylium,[8] and ruthenium.[7a,9] The results show that C–F bond activation remains challenging and excess base seems to be necessary for neutralizing the released HF acid.



Scheme 1 Methods for defluorination; TMG: tetramethylguanidine

Base-promoted intramolecular defluorination/O-arylation reactions have not attracted much attention, and only one example has been reported by Drushlyak's group[10] (Scheme 1B). The possibility of using a catalytic amount of base to access the defluorination/O-arylation reaction has not been realized. Herein, we report a novel synthesis of 3-fluoro-1,4-oxathiine 4,4-dioxides by base-catalyzed defluorination/O-arylation reactions of α-fluoro-β-one-sulfones (Scheme 1C). This would be useful for the exploitation of pharmacologically active candidates and fluorine-containing compounds in materials science because monofluoroalkenes usually function as stable bioisosteres of amide bonds and sulfones are frequently applied in pharmaceuticals and synthetic chemistry.[11] Preliminary experiments

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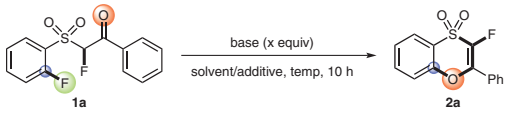
and related literature reports suggest that molecular sieves would serve as both an adsorbent to remove HF acid and an activator to assist C–F bond cleavage.

Initially, we selected 2-fluoro-2-((2-fluorophenyl)sulfonyl)-1-phenylethan-1-one (**1a**) as the model substrate to explore reaction conditions (Table 1). The desired reaction took place smoothly in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Cs_2CO_3, and Na_2CO_3 with MeCN as the solvent at 80 °C in 10 h to form **2a** in moderate yields (entries 1–3).

Table 1 Optimization of Reaction Conditions[a]



Entry	Base/*x*	Solvent/additive	Temp (°C)	Yield (%)[b]
1	DBU/1.2	MeCN	80	55
2	Cs_2CO_3/1.2	MeCN	80	46
3	Na_2CO_3/1.2	MeCN	80	37
4	pyridine/1.2	MeCN	80	nr
5	NEt_3/1.2	MeCN	80	nr
6	DABCO/1.2	MeCN	80	nr
7	DIPEA/1.2	MeCN	80	nr
8	TMG/1.2	MeCN	80	12
9	DBU/1.2	THF	80	65
10	DBU/1.2	dioxane	80	43
11	DBU/1.2	toluene	80	40
12	DBU/1.2	DMF	80	64
13	DBU/1.2	DMSO	80	55
14	DBU/1.2	DCM	80	58
15	DBU/1.0	THF	80	63
16	DBU/0.8	THF	80	66
17	DBU/0.5	THF	80	61
18	DBU/0.2	THF	80	27
19	DBU/0.8	THF	25	56
20	DBU/0.8	THF	50	54
21	DBU/0.8	THF	65	59
22	DBU/0.8	THF	95	65
23	DBU/0.8	THF[c]	80	56
24	DBU/0.8	THF/3Å MS	80	71
25	DBU/0.8	THF/4Å MS	80	57
26	DBU/0.8	DMF/3Å MS	80	79
27	TMG/0.8	DMF/3Å MS	80	89
28	TMG/0.5	DMF/3Å MS	80	88
29	TMG/0.1	DMF/3Å MS	80	90
30	TMG/0.05	DMF/3Å MS	80	92 (90)[d]
31	TMG/0.01	DMF/3Å MS	80	18
32	TMG/0.05	THF/3Å MS	80	decomposed
33	TMG/0.05	DMSO/3Å MS	80	69
34	TMG/0.05	EtOAc/3Å MS	80	nr
35	TMG/0.05	DMF	80	47
36	DBU/0.05	DMF/3Å MS	80	81
37	–	DMF/3Å MS	80	nr

[a] Reaction conditions: **1a** (0.1 mmol) and base in anhydrous solvent (0.5 mL) were mixed at 25–95 °C for 10 h.
[b] Yields as measured by ^{19}F NMR spectroscopy with $PhCF_3$ as an internal standard; nr means no reaction.
[c] THF instead of anhydrous THF.
[d] The isolated yield is given in parentheses.

No reaction occurred if pyridine, triethylamine (NEt_3), 1,4-diazabicyclo[2.2.2]octane (DABCO), or *N*,*N*-diisopropylethylamine (DIPEA) was employed (entries 4–7). With DBU as the catalyst, changing the solvent from MeCN to THF accelerated the formation of **2a** to 65% yield (entry 9). Other solvents such as dioxane, toluene, DMF, DMSO, and DCM did not improve the results (entries 10–14). Reducing the amount of DBU to 0.8 equiv gave **2a** in 66% yield (entry 16). Examination of the reaction temperature revealed that 80 °C is optimal (entries 19–23). The yield of **2a** could be increased to 79% by adding 3Å molecular sieves (3Å MS) as a dehydrating reagent (entries 24–26). With tetramethylguanidine (TMG) as the catalyst, the outcome was further improved (entries 27–29). Remarkably, even a reduced TMG loading of 5.0 mol% led to a good yield (92%; isolated yield 90%; entry 30). In addition, under the same conditions but with THF, DMSO, or EtOAc as the solvent, the reaction was not further optimized (entries 32–34). The yield of **2a** dropped sharply when the 3Å MS were removed (entry 35). When 5.0 mol% DBU was used as the catalyst under the standard conditions, the transformation still resulted in 81% yield (entry 36). We believe that the 3Å MS might act as not only a dehydrating reagent but also a deacid reagent and activator in this base-catalyzed intramolecular defluorination/O-arylation reaction. Unsurprisingly, the reaction was shut down entirely without the base catalyst (entry 37).

With the optimized reaction conditions in hand, we then investigated the scope of substrates. As shown in Scheme 2, electron-neutral, -donating, or -withdrawing substituents on the phenyl unit were generally well tolerated, affording the desired products **2a–h** in 65–98% yields. Naphthyl (**1i**), pyridyl (**1j**) and furanyl (**1k**) groups were compatible and provided **2i–k** in 54–85% yields. Substrates with cyclopropyl (**1l**) and biphenyl (**1m**) groups successfully gave **2l** and **2m** in 45% and 87% yields, respectively. The substituted 2-fluorophenylsulfone substrates **1n–s** were

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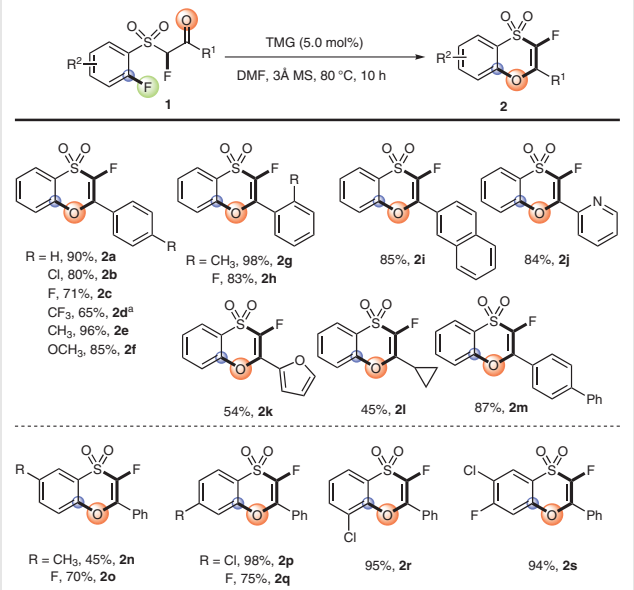
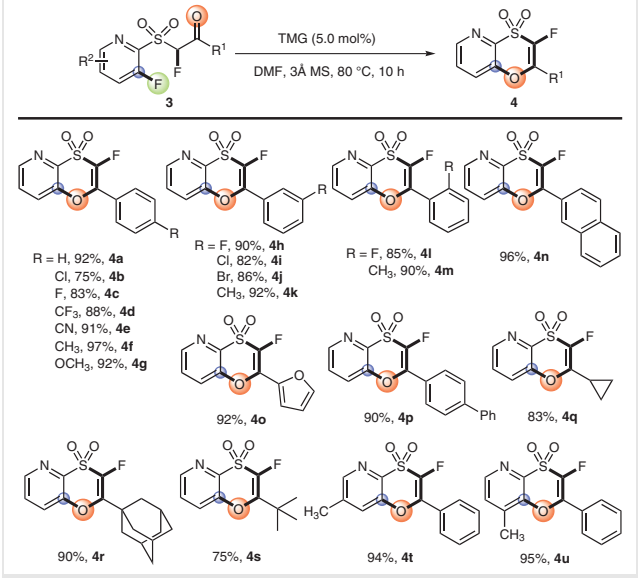


Scheme 2 Scope of 2-fluorophenylsulfone substrates. *Reagents and conditions*: **1** (0.2 mmol), TMG (5.0 mol%), and 3Å MS (50 mg) in DMF (1 mL), 80 °C, 10 h. Molecular sieves need to be activated at 180 °C for 5 h. Yields of isolated product are given. [a] The loading of TMG was increased to 10.0 mol%.



Scheme 3 Scope of 3-fluoro-2-sulfonylpyridine substrates. *Reagents and conditions*: **3** (0.2 mmol), TMG (5.0 mol%), and 3Å MS (50 mg) in DMF (1 mL), 80 °C, 10 h. Yields of isolated product are given.

also suitable for the reaction and produced **2n–s** in 45–98% yields.

Next, we turned our attention to the scope with substituted 2-fluoro-2-((3-fluoropyridin-2-yl)sulfonyl)-1-phenylethan-1-ones (**3**). As shown in Scheme 3, products **4a–m** were furnished in good to excellent yields (75–97%). Among these, Cl and Br groups were tolerated; these products possess a useful feature with respect to further synthetic manipulations. Moreover, heteroaryl- and alkyl-substituted substrates **3n–s** afforded the corresponding products **4n–s** in 75–96% yields. Substrates with challenging bulky adamantyl and tertiary butyl groups smoothly formed **4r** and **4s** in 90% and 75% yields, respectively. 3-Fluoro-2-sulfonylpyridine substrates with methyl groups at different positions furnished desired products **4t** and **4u** in 94% and 95% yields.

Practically, the transformations of **1a** and **3u** could be run on a gram scale without appreciable decrease in their yields. Accordingly, under the standard reaction conditions, products **2a** and **4u** could be readily isolated in 90% (2.48 g) and 94% (2.74 g) yields, respectively.

As shown in Figure 1, the structures of 3-fluoro-2-phenylbenzo[*b*][1,4]oxathiine 4,4-dioxide (**2a**) and 3-fluoro-2-phenyl[1,4]oxathiino[3,2-*b*]pyridine 4,4-dioxide (**4a**) were confirmed by X-ray diffraction analysis.

To gain more mechanistic insights into the current TMG-catalyzed desulfonylation/O-arylation reaction, control experiments were performed (Scheme 4A). With 1.0 equiv of pyridine as the deacid reagent, the yield of **2a** decreased sharply. This suggests that the 3Å MS might not only act as a deacid reagent but also assist in the C–F bond cleavage during the O-arylation process. If 2-((2-chlorophenyl)sulfonyl)-2-fluoro-1-phenylethan-1-one (**5**) and 2-((2-bromophenyl)sulfonyl)-2-fluoro-1-phenylethan-1-one (**6**) were employed under the standard reaction conditions, product **2a** was obtained in trace yields and substrates **5** and **6** decomposed completely. These results indicate that the fluorine and the 3Å MS are necessary to this transformation. With this in mind, a proposed mechanism is shown in Scheme 4B. When TMG reacts with α-fluoro-β-ketosulfone **1**, α-fluorosulfonyl carbanion **A** is easily obtained. Then, carbanion **A** undergoes a keto–enol tautomerism reaction to generate oxyanion **B**, and subsequently, an intramolecular nucleophilic attack to the Ar–F carbon atom gen-

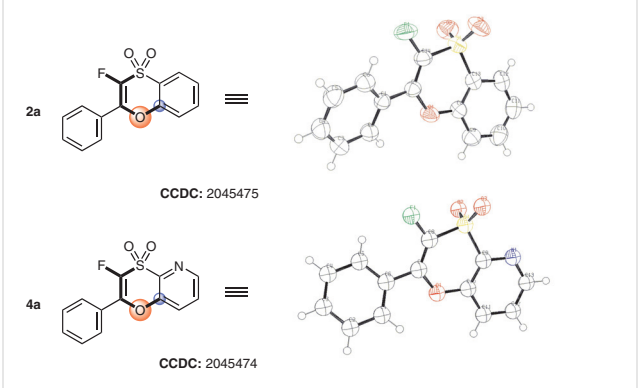


Figure 1 X-ray crystal structures of products **2a** and **4a**

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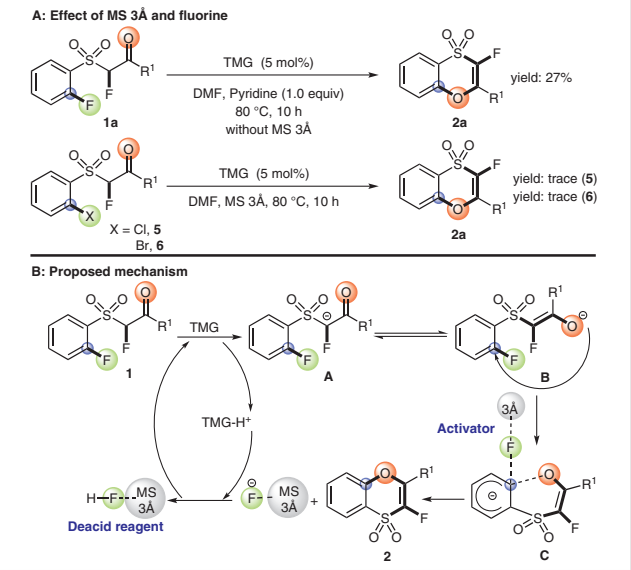
erates six-membered ring anion **C**. After defluorination, adduct **2** is generated and the released HF acid can be trapped by the 3Å MS to assist with base-catalyst regeneration.[12]



Scheme 4 Mechanistic hypothesis

In summary, we have developed a novel base-catalyzed defluorination/O-arylation that streamlines the synthesis of 3-fluoro-1,4-oxathiine 4,4-dioxide derivatives from readily accessible substituted α-fluoro-β-one-sulfones,[13] which might be valuable for the exploitation of fluorine-containing pharmaceutical molecules and materials. Unlike traditional defluorination reactions with transition-metal catalysis or with stoichiometric base as the deacid reagent, our process is triggered by a catalytic amount of base and molecular sieves act as the deacid reagent and activator. This method, is complementary and contradistinctive to the classical transformations of defluorination reactions and represents a valuable method for organofluorine chemistry.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1387-8862.

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(13) **3-Fluoro-2-phenylbenzo[*b*][1,4]oxathiine 4,4-dioxide (2a); Typical Procedure**

Substrate **1a** (0.2 mmol, 1.0 equiv), tetramethylguanidine (TMG, 0.01 mmol, 100 μL of 0.1 M TMG in DMF), and 3 Å molecular sieves (100 mg, 3 Å molecular sieves were activated at 180 °C for 5 h) were mixed in anhydrous DMF (1.0 mL) at 80 °C for 10 h. After the reaction was complete, the solvent was evaporated and the crude mixture was purified by flash chromatography on silica gel (PE/EtOAc/DCM = 12:1:1) to afford the desired compound **2a** in 90% yield; white solid; mp 131–133 °C. ^{1}H NMR (400 MHz, chloroform-*d*): δ = 8.04–7.97 (m, 1 H), 7.80 (dd, *J* = 6.7, 2.9 Hz, 2 H), 7.72–7.64 (m, 1 H), 7.53 (dd, *J* = 5.0, 1.9 Hz, 3 H), 7.48–7.38 (m, 2 H). ^{13}C NMR (100 MHz, chloroform-d): δ = 150.0, 144.4 (d, *J* = 21.1 Hz), 141.6 (d, *J* = 276.7 Hz), 134.2, 131.6, 128.9, 128.0, 127.9, 126.2 (d, *J* = 6.2 Hz), 125.6, 123.2 (d, *J* = 2.6 Hz), 119.2. ^{19}F NMR (376 MHz, chloroform-*d*): δ = –175.89. HRMS (ESI): *m*/*z* calcd for $C_{14}H_9FNaO_3S$ [M + Na]$^+$: 299.0149; found: 299.0145.

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