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# Copper-free Sandmeyer-type Reaction for the Synthesis of Sulfonyl Fluorides

Tao Zhong, Meng-Ke Pang, Zhi-Da Chen, Bin Zhang, Jiang Weng,* and Gui Lu

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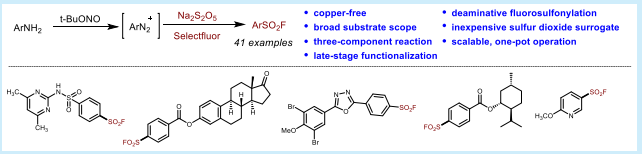
**ABSTRACT:** A copper-free Sandmeyer-type fluorosulfonylation reaction is reported. Utilizing $Na_2S_2O_5$ and Selectfluor as the sulfur dioxide and fluorine sources, respectively, aryldiazonium salts were transformed into sulfonyl fluorides. The one-pot direct synthesis of sulfonyl fluorides from aromatic amines was also realized via in situ diazotization. The practicality of this method was demonstrated by the broad functional group tolerance, gram-scale synthesis, and late-stage fluorosulfonylation of natural products and pharmaceuticals.






Since the concept of sulfur(VI) fluoride exchange (SuFEx) was first introduced by Sharpless and coworkers in 2014,[1] this new-generation click chemistry has emerged as an efficient and reliable tool for creating modular intermolecular connections and has quickly found extensive applications in diverse fields,[2] including organic synthesis, drug discovery, chemical biology, and material science. Among sulfur(VI) fluoride species that can undergo SuFEx reactions, sulfonyl fluorides are of essential importance and have attracted much attention, owing to their unique reactivity−stability balance. Sulfonyl fluorides have been used in drug discovery as privileged covalent inhibitors and reactive probes by targeting specific amino acid residues of enzyme binding sites (Figure 1).[3] Moreover, sulfonyl fluorides have been widely used as

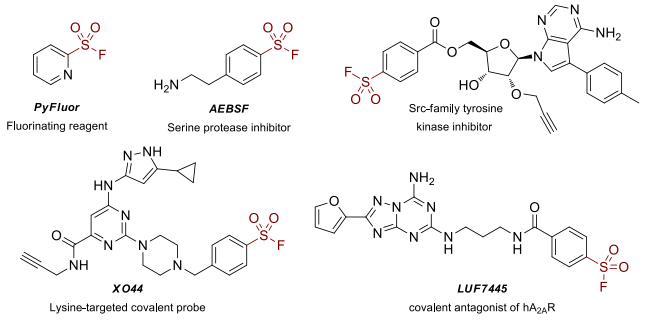



**Figure 1.** Selected biologically or synthetically useful arylsulfonyl fluorides.

alternative intermediates instead of sulfonyl chlorides for the synthesis of sulfonyl-containing compounds.[4] Besides, sulfonyl fluorides have recently been demonstrated as a new class of selective and thermal-stable fluorinating reagents (Figure 1, PyFluor) for deoxy-fluorination[5] and $^{18}F$ radiolabeling.[6] Despite great progress, the SuFEx click chemistry is still in its early stage, and the development in this field is partly hampered by the limited accessibility of sulfur(VI) fluoride species.

Given their great importance in widespread applications, considerable efforts have been devoted to the development of new methods for the synthesis of sulfonyl fluorides. Conventionally, sulfonyl fluorides are synthesized via the fluoride−chloride exchange of sulfonyl chlorides with fluoride salts.[3g,6b,7] However, sulfonyl chlorides as highly reactive electrophiles, which are generally of limited availability and sensitive to various nucleophiles and reductants, are not suitable for use in late-stage functionalization. Alternatively, several groups have developed the synthesis of sulfonyl fluorides from other aromatic sulfur compounds, including thiols,[8] disulfides,[8a,b] sodium sulfonates or sulfinates,[9] sulfonic acids,[9c,10] sulfonyl hydrazides,[11] and sulfonamides.[12] For example, Noël and coworkers have recently reported an elegant electrochemical oxidative approach to prepare sulfonyl fluorides from thiols or disulfides with KF as the fluoride source.[13] Apart from these organic sulfur precursors, readily available aryl halides have also been realized as good substrates to access sulfonyl fluorides via a metal-mediated cross-coupling strategy.[14] In this context, the groups of Willis[14a] and Ball[14b] have pioneered the palladium-catalyzed synthesis of sulfonyl fluorides from the corresponding aryl halides in combination with 1,4-diazabicyclo[2.2.2]octane bis(sulfur dioxide) (DABSO) and an electrophilic fluorinating reagent. Recently, Sammis and Ball disclosed the syntheses of sulfonyl fluorides from the preformed Grignard reagents and sulfuryl fluoride ($SO_2F_2$)

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gas.[14d] Despite the fact that these methods are powerful, the utilization of toxic metal might contaminate the final click reagents, which is a particular concern regarding the application of click chemistry in biological systems.[15]

Aromatic amines are ubiquitous and cheap substrates in research laboratories and industry. Recently, we embarked on a project to convert the aromatic $NH_2$ group into a $SO_2F$ group in the late stage of the development of novel covalent inhibitors. We envisaged that this goal might be achieved by combining several known transformations (Figure 2c), which

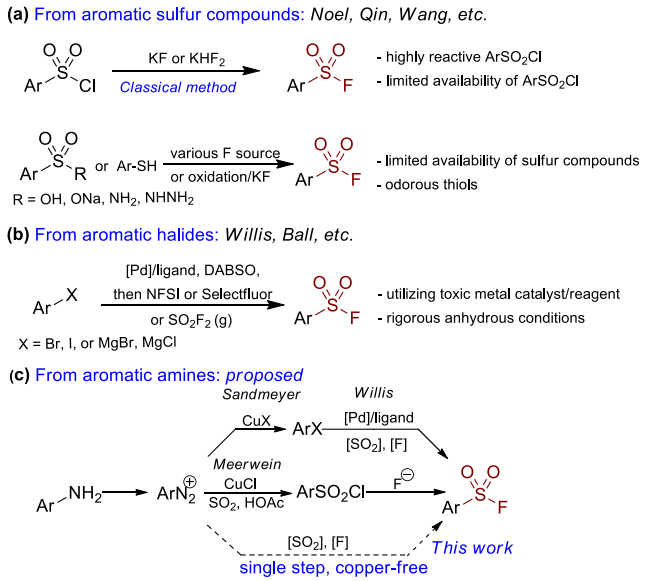
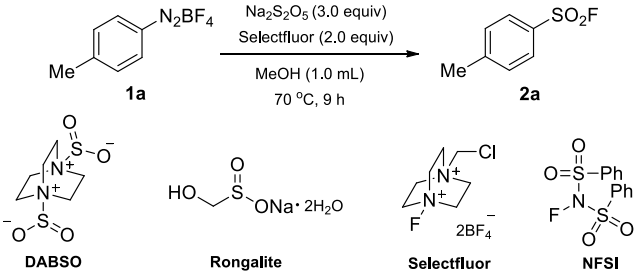



**Figure 2.** Strategies for the synthesis of arylsulfonyl fluorides.

involved (1) a Sandmeyer halogenation reaction[16] followed by Willis's Pd-catalyzed cross-coupling strategy[14a] or (2) a Meerwein chlorosulfonylation reaction[17] followed by the fluoride−chloride exchange.[7] However, these two-step procedures generally suffer from the use of stoichiometric copper salts and the tedious separation of intermediates. Thus we wondered whether the synthesis of sulfonyl fluorides could be directly achieved from aryldiazonium salts in a single step under copper-free conditions. Surprisingly, in contrast with its counterpart sulfonyl chlorides, the synthesis of sulfonyl fluorides via Sandmeyer-type fluorosulfonylation remains underexplored,[18] which is probably due to the high reactivity of diazonium salts and the lack of appropriate sulfur dioxide and fluorine sources. Herein we report a copper-free Sandmeyer-type fluorosulfonylation reaction of aryldiazonium salts using readily available sodium metabisulfite and Selectfluor as the sulfur dioxide surrogate and fluorine source, respectively.[19]

Initially, 4-methylbenzenediazonium tetrafluoroborate (**1a**) was chosen as the model substrate to optimize the reaction conditions. Inspired by recent progress[20] in the synthesis of sulfonyl functionalities utilizing sulfur dioxide surrogates instead of toxic $SO_2$ gas, we first examined a range of solid sulfur dioxide surrogates (Table 1, entries 1−7), including sodium metabisulfite ($Na_2S_2O_5$), sodium dithionite ($Na_2S_2O_4$), DABSO, Rongalite,[21] Langlois reagent ($CF_3SO_2Na$), sodium sulfite ($Na_2SO_3$), and potassium metabisulfite ($K_2S_2O_5$). To our delight, utilizing cheap sodium metabisulfite as the sulfur dioxide surrogate and Selectfluor as

**Table 1. Selected Optimization Studies**[a]




| entry | variation from the standard conditions | yield (%)[b] |
|---|---|---|
| 1 | none | 65 (66)[c] |
| 2 | $Na_2S_2O_4$ instead of $Na_2S_2O_5$ | 48 |
| 3 | DABSO instead of $Na_2S_2O_5$ | 24 |
| 4 | Rongalite instead of $Na_2S_2O_5$ | trace |
| 5 | $CF_3SO_2Na$ instead of $Na_2S_2O_5$ | N.D. |
| 6 | $Na_2SO_3$ instead of $Na_2S_2O_5$ | 10 |
| 7 | $K_2S_2O_5$ instead of $Na_2S_2O_5$ | <5 |
| 8 | NFSI instead of Selectfluor | 53 |
| 9 | KF instead of Selectfluor | N.D. |
| 10 | 4.0 equiv of $Na_2S_2O_5$ | 42 |
| 11 | 2.0 equiv of $Na_2S_2O_5$ | 46 |
| 12 | 25 °C instead of 70 °C | 15 |
| 13 | 60 °C instead of 70 °C | 58 |
| 14 | 2 mL of MeOH | 63 |
| 15 | EtOH instead of MeOH | 32 |
| 16 | DMF instead of MeOH | 20 |
| 17 | under air atmosphere | 32 |

[a]Reaction conditions: **1a** (0.2 mmol), $Na_2S_2O_5$ (0.6 mmol, 3.0 equiv), Selectfluor (0.4 mmol, 2.0 equiv), MeOH (1 mL), 70 °C, under $N_2$, 9 h. [b]$^{19}F$ NMR yield calculated with $PhCF_3$ as internal standard. [c]Isolated yield.

the fluorine source, 4-methylbenzene-1-sulfonyl fluoride (**2a**) could be obtained in 66% isolated yield after 9 h at 70 °C (Table 1, entry 1). When the $SO_2$ source was switched from sodium metabisulfite to others, the yields decreased (Table 1, entries 2−7). In addition, using NFSI as the fluorine source instead of Selectfluor led to a slight decrease in reaction yield (Table 1, entry 8), whereas no desired product was detected when replacing Selectfluor with KF (Table 1, entry 9). Notably, the amount of sodium metabisulfite was found to be vital because either increasing or reducing the loading provided less efficient reactions (Table 1, entries 10 and 11). The examination of temperature, solvents, and concentration identified 70 °C and MeOH (1 mL) as optimal reaction parameters (Table 1, entries 12−16). Moreover, the control experiment indicated that the nitrogen atmosphere is necessary for this reaction (Table 1, entry 17). For full details of the reaction optimization, see the Supporting Information.

Having identified the optimal reaction conditions, we next investigated the scope of the aryldiazonium salts, and the results are summarized in Scheme 1. To our delight, aryldiazonium tetrafluoroborates with electron-donating groups at the para position on the benzene ring gave the corresponding sulfonyl fluorides **2a−g** in good to excellent yield (66−85%). However, lower yields were obtained for the substrates with electron-withdrawing groups under the same conditions. For example, 4-nitrobenzenediazonium salt gave the desired product in 34% yield, whereas nitrobenzene was isolated as the major byproduct in 45% yield. After further investigation of the reaction condition using the *para*-nitro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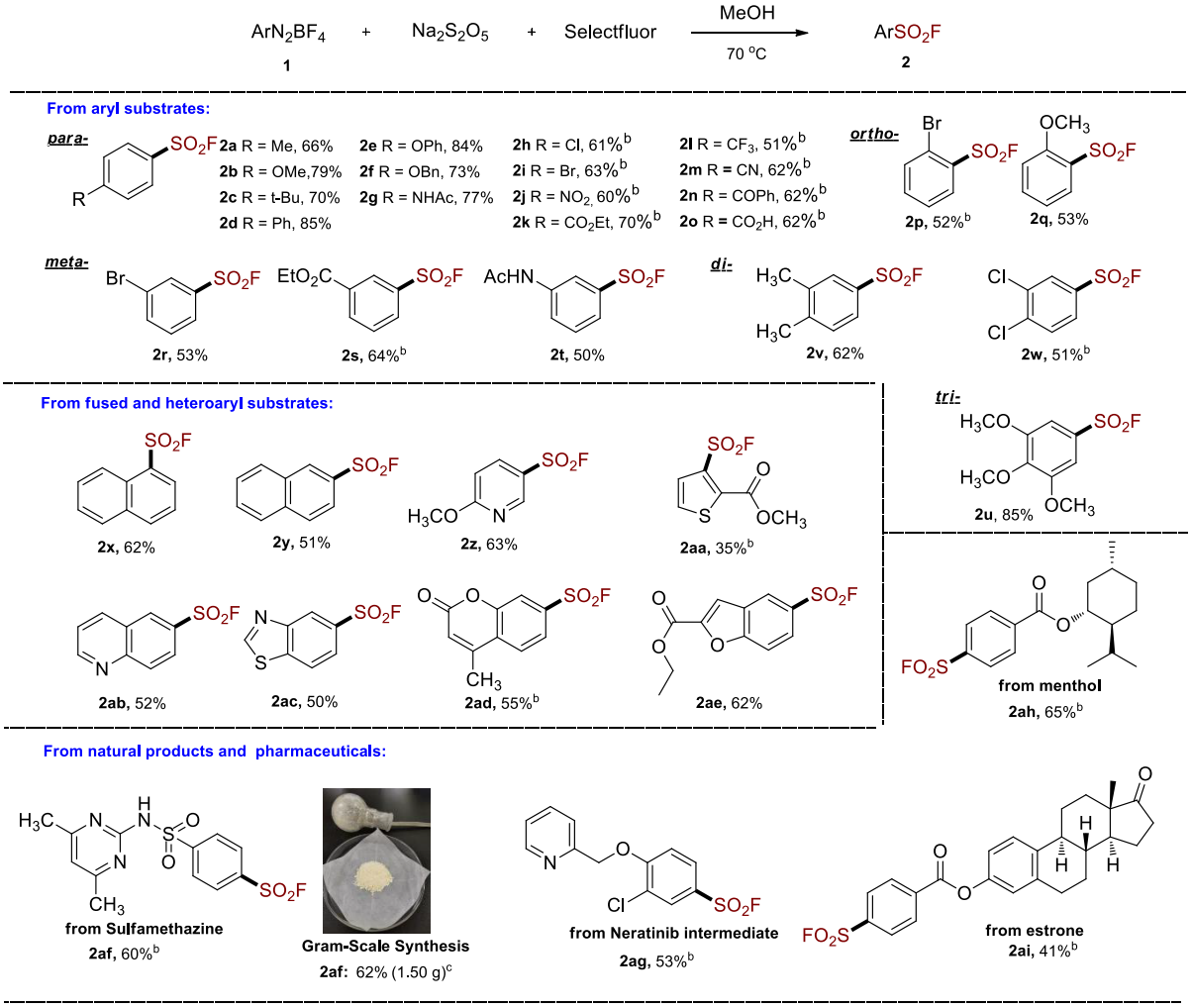
**Scheme 1. Substrate Scope for Fluorosulfonylation of Aryldiazonium Salts**[a]




[a]Reaction conditions: 1 (0.2 mmol, 1.0 equiv), $Na_2S_2O_5$ (0.6 mmol, 3.0 equiv), Selectfluor (0.4 mmol, 2.0 equiv), MeOH (1.0 mL), 70 °C, under $N_2$, 9h, isolated yield. [b]$Na_2S_2O_5$ (0.3 mmol, 1.5 equiv). [c]See the Supporting Information for details.

-substituted substrate, the unwanted reduction (Ar−H) was easily suppressed by simply reducing the loading of $Na_2S_2O_5$ to 1.5 equiv. (See Table S6 for optimization.) Then, a range of substrates with electron-withdrawing groups at the para position was explored under this condition. Sulfonyl fluorides **2h−o** were smoothly obtained in good yield (51−70%). Various functional groups including halogen (**2h**, **2i**), nitro (**2j**), ester (**2k**), trifluoromethyl (**2l**), cyano (**2m**), ketone (**2n**), and carboxylic acid groups (**2o**) were well compatible with the reaction conditions. Notably, fluorosulfonylation could be performed smoothly for the bromo-substituted aryl diazonium salts, which was incompatible with previous metal-mediated strategies. In addition, products containing reactive groups such as $-NO_2$, −Br, −CN, and $-CO_2H$ are useful for further synthetic elaboration. The ortho- and meta-substituted products (**2p−t**) were also obtained in slightly lower yields than their para-substituted analogues. Di- and trisubstituted substrates were well tolerated (**2u−w**). The condensed aromatic substrates were also proved to be compatible (**2x**, **2y**). Then, the substrate scope of heteroarenediazonium tetrafluoroborates was also investigated. A wide range of heteroarene sulfonyl fluorides including pyridine, thiophene, quinoline, benzothiazole, coumarin, and benzofuran derivatives were accessed in reasonable yield (**2z−ae**). Furthermore, the potential of this reaction was evaluated by more challenging substrates derived from pharmaceutical and natural products. The diazonium salts derived from sulfamethazine (antibacterial) and a neratinib (anticancer) intermediate were subjected to the standard reaction conditions, affording the corresponding sulfonyl fluorides **2af** and **2ag** in 60% and 53% yield, respectively. Notably, **2af** could be obtained in 62% isolated yield on a gram scale. Likewise, menthol and estrone derivatives were well tolerated to provide the desired products **2ah** and **2ai**, respectively.

To further simplify the operation process, we attempted to carry out the one-pot straightforward synthesis of sulfonyl fluorides from aromatic amines. To our delight, this goal was realized via in situ diazotization without separation of the diazonium salt intermediates. As illustrated in Scheme 2, aromatic amines bearing either electron-donating or electron-withdrawing substituents proceeded smoothly to deliver the desired products without obvious loss of yield. Therefore, this approach represents an attractive synthetic tool for the direct conversion of anilines into sulfonyl fluorides.

To highlight the practicability of this methodology, we applied the established one-pot deaminative fluorosulfonyla-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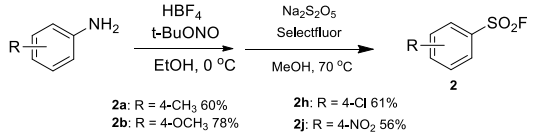
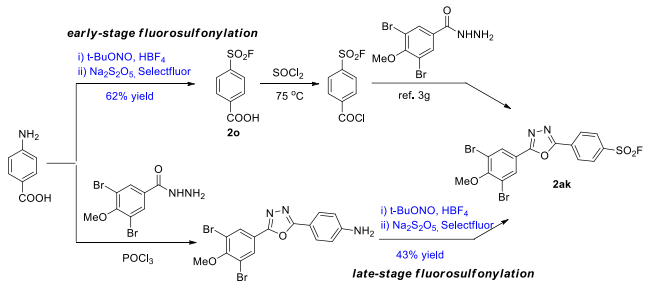
**Scheme 2. One-Pot Synthesis of Sulfonyl Fluorides from Anilines**




tion protocol in the synthesis of a covalent kinetic stabilizer of transthyretin (**2ak** in Scheme 3), which shows potential for

**Scheme 3. Synthetic Application**

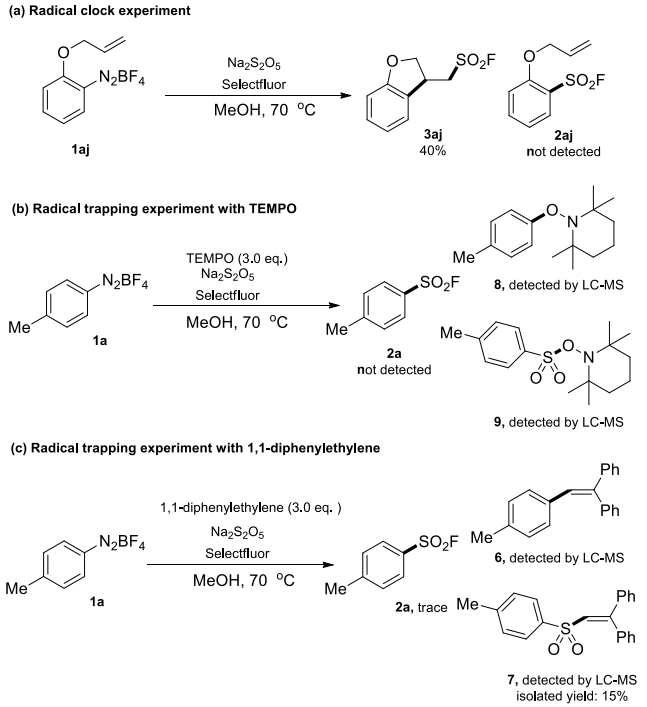



preventing amyloid fibril formation.[3g] Previously, **2ak** and analogues were synthesized from the corresponding sulfonyl chlorides in a three-step sequence involving the fluoride−chloride exchange as the first step. As depicted in Scheme 3, we could access the desired sulfonyl fluorides intermediate **2o** in 62% yield from 4-aminobenzoic acid in the early stage of the synthetic sequence. Alternatively, the current method could also be used for late-stage functionalization. Under the standard reaction conditions, the $SO_2F$ motif could be installed from the free amine intermediate in the last step. Therefore, this strategy represents a flexible and versatile tool for early- and late-stage structural modification.

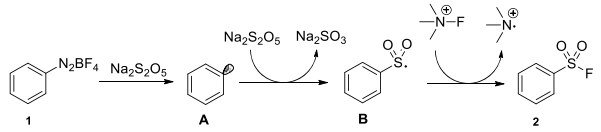
To gain mechanistic insight into this reaction, several preliminary control experiments were carried out (Scheme 4). First, when utilizing 2-(allyloxy)-benzenediazonium tetrafluoroborate **1aj** in this transformation (Scheme 4a), the cyclized alkyl sulfonyl fluoride **2aj** was obtained in 40% yield, and the acyclic sulfonyl fluoride product was not detected, which suggested that an aryl radical is generated in this transformation. Then, the formation of **2a** was completely suppressed when 3.0 equiv of the radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) was added to the reaction (Scheme 4b). Furthermore, a trace amount of **2a** was detected when 3.0 equiv of a milder radical scavenger 1,1-diphenylethylene was introduced into this reaction, and the radical coupling products **6** and **7** were detected by LC-MS (Scheme 4c; **7** was isolated in 15% yield), which indicated the existence of both an aryl radical and an arylsulfonyl radical in this transformation.

On the basis of the above control experiments and related literature reports,[22] a plausible Sandmeyer-type reaction mechanism is proposed (Scheme 5). Aryl radical **A** is generated from aryldiazonium salt **1** through single-electron reduction. Then, trapping of the aryl radical **A** with $SO_2$ affords an arylsulfonyl radical **B**. Subsequent fluorine atom transfer from Selectfluor provides the sulfonyl fluoride product **2**. It should be mentioned that herein sodium metabisulfite might act as both the reductant and the $SO_2$ source, which enabled this copper-free Sandmeyer-type fluorosulfonylation reaction.

**Scheme 4. Control Experiments**




**Scheme 5. Proposed Mechanism**




In conclusion, we have developed a Sandmeyer-type fluorosulfonylation approach for the synthesis of arylsulfonyl fluorides through C−N cleavage. This method employs easy-to-handle $Na_2S_2O_5$ and Selectfluor as the sulfur dioxide surrogate and fluorine sources, respectively, proceeding smoothly under operational simple and copper-free conditions without any other additives. The reaction tolerates a wide range of functional groups and is even effective for sulfonyl fluorides containing sensitive groups (−$CO_2H$, −CN, −Br, etc.) that are not easily accessible by the previously reported methods. Furthermore, the two-step, one-pot synthesis of sulfonyl fluorides directly from aromatic amines has also been realized without a loss of yield. The applicability of this method has been demonstrated by the gram-scale synthesis and the late-stage fluorosulfonylation of numerous natural products and pharmaceuticals. Preliminary mechanistic studies suggest that a Sandmeyer-type radical process is involved in this reaction. We believe that this method for the conversion of the aromatic $NH_2$ group into a $SO_2F$ group will find further applications.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00823.

Experiment procedures, compounds characterizations data, copies of NMR spectra(PDF)



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## AUTHOR INFORMATION


### Corresponding Author

**Jiang Weng** − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China;* orcid.org/0000-0002-4117-4686; Email: wengj2@mail.sysu.edu.cn

### Authors

**Tao Zhong** − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China*

**Meng-Ke Pang** − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China*

**Zhi-Da Chen** − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China*

**Bin Zhang** − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China*

**Gui Lu** − *Guangdong Provincial Key Laboratory of Chiral Molecule and Drug Discovery, School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, P. R. China;* orcid.org/0000-0003-0089-0907

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c00823


### Notes

The authors declare no competing financial interest.

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