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Arenesulfonyl Fluoride Synthesis via Copper-Catalyzed Fluorosulfonylation of Arenediazonium Salts

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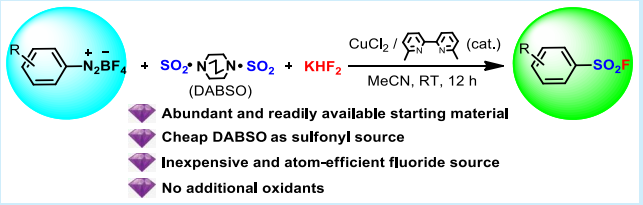
ABSTRACT: We report herein a general and practical copper-catalyzed fluorosulfonylation reaction of a wide range of abundant arenediazonium salts to smoothly prepare various arenesulfonyl fluorides using the 1,4-diazabicyclo[2.2.2]octane-bis(sulfur dioxide) adduct as a convenient sulfonyl source in combination with KHF_2 as an ideal fluorine source and without the need for additional oxidants. Interestingly, the electronic character of the arene ring in the starting arenediazonium salts has a significant impact on the reaction mechanistic pathway.



Organic compounds incorporating a sulfonyl fluoride functional group (SO_2F) have been attracting rapidly increasing attention since the introduction of sulfur(VI) fluoride exchange (SuFEx) as the latest powerful reaction for click chemistry by Sharpless and co-workers in 2014.[1] They have been widely applied in many fields, including medicinal chemistry and chemical biology,[2] organic synthesis,[3] polymer preparation,[4] etc. These applications may result from the unique properties observed with sulfonyl fluorides, including their special stability−reactivity pattern and proton-mediated reactivity that is sensitive to the microenvironment.[1a] However, the limited availability of sulfonyl fluorides seriously hinders their further development in these fields. The wide application of arenesulfonyl fluorides has drawn our attention to developing a mild and efficient method for their synthesis starting from abundant materials (Figure 1a). The conventional synthesis of arenesulfonyl fluorides was completed by classical chloride−fluoride exchange of the corresponding arenesulfonyl chlorides[1a,5] or oxidative fluorination of the alternative starting materials, including $ArSO_2NHNH_2$, $ArSO_2Na$, ArSH, ArSSAr, etc.[6] (Figure 1b). However, these methods commonly suffer from very limited sources of starting sulfur-containing compounds or require the use of costly and atom-inefficient fluoride sources. Consequently, a general and economic synthesis method for efficiently generating various arenesulfonyl fluorides from inexpensive and abundant starting materials is highly desired.

Very few new synthetic routes to arenesulfonyl fluorides from starting nonsulfur-containing compounds have been presented so far.[7,8] In 2017, an elegant palladium-catalyzed cross-coupling of aryl halides with the 1,4-diazabicyclo[2.2.2]-octane-bis(sulfur dioxide) adduct (DABSO)[9] in combination with electrophilic fluorinating reagents has been developed to efficiently generate the corresponding arenesulfonyl fluorides.[7] Despite their synthetic value, it is undesirable to use relatively expensive palladium catalysts and atom-inefficient electrophilic fluorinating reagents 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (Selectfluor) or *N*-fluorobenzenesulfonimide (NFSI) under relatively harsh reaction conditions (Figure 1c). On the other hand, arenediazonium salts with rich reactivity and diverse transformations are very important organic intermediates.[10] The conversion of aromatic amino groups into various fluorine-containing functional groups via fluoroalkylation of arenediazonium salts has recently been developed.[11] Notably, fluorination of arenediazonium salts, named the Balz−Schiemann reaction, is one of the most widely used methods for the preparation of aryl fluorides from anilines.[12] The reaction is supposed to proceed through thermal dediazotization of arenediazonium salts and subsequent nucleophilic fluorination with a fluorine ion to form a C_{Ar}−F bond. More recently, we developed an efficient method for the preparation of a number of alkyl sulfonyl fluorides via novel radical SO_2 insertion and in situ fluorination.[13] On the basis of these findings and as an extension of our interest in fluorosulfonylation, it is reasonable to conceive that the C_{Ar}−S(VI)−F bond construction might be achieved with arenediazonium salts in combination with sulfur dioxide and fluoride salt under appropriate reaction conditions (Figure 1c), which is a new mode of construction of arenesulfonyl fluorides. We report herein the first synthesis of various arenesulfonyl fluorides via copper-catalyzed fluorosulfonylation of arenediazonium salts.

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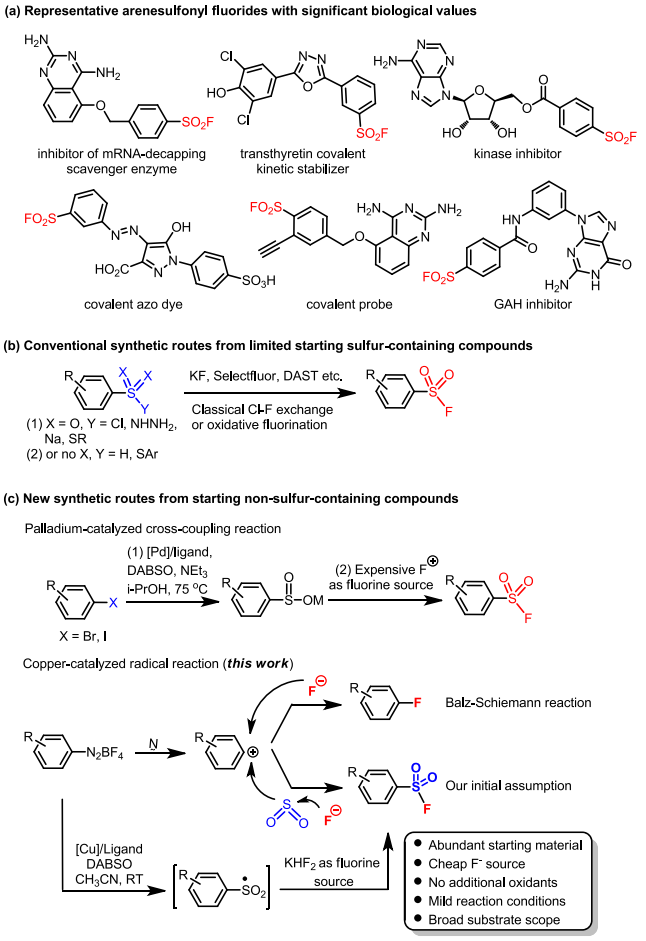
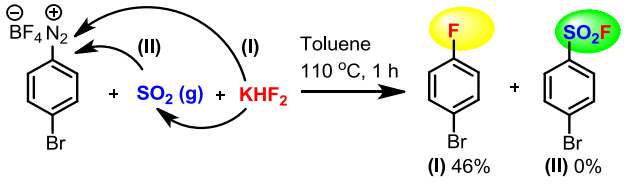


Figure 1. Representative arenesulfonyl fluorides with significant biological values and established synthetic methods for arenesulfonyl fluorides.

The very mild practical reaction conditions and the wide availability of the starting arenediazonium salts from various anilines allow for quick access to a broad range of highly valuable arenesulfonyl fluorides and will significantly promote their application in different research fields.

We commenced our study of the desired fluorosulfonylation of arenediazonium salts by using *p*-bromobenzenediazonium salt as the model substrate, SO_2 gas as received, and KHF_2 as an inexpensive and atom-efficient fluoride source (KHF_2 at ~$10/mol vs Selectfluor at ~$400/mol and NFSI at ~$110/mol)[14] in toluene at 110 °C for 1 h according to the novel concept presented in Figure 1c. No formation of the desired fluorosulfonylation product (**II**) was observed, but the competitive Balz−Schiemann fluorination byproduct (**I**) was produced in 46% ^{19}F NMR yield (Scheme 1). This result clearly demonstrates the challenge of the nucleophilic attack of fluorine ion at arenediazonium salt being much easier than at sulfur dioxide, which makes the desired fluorosulfonylation of arenediazonium salts via Balz−Schiemann-type nucleophilic reaction unlikely. To our delight, subsequent extensive screening of reaction conditions revealed that the combination of 1.0 equiv of DABSO and 5.0 equiv of KHF_2 in MeCN in the presence of catalytic amounts of $CuCl_2$ and 6,6′-dimethyl-2,2′-dipyridyl at room temperature provided suitable reaction conditions to generate the desired fluorosulfonylation product in good yield. Notably, both the copper catalyst and the halide in the catalyst played a very important role in the desired fluorosulfonylation reaction (also vide infra). A detailed screening of reaction conditions with regard to catalyst, ligand, solvent, and fluoride source is provided in the Supporting Information.

Scheme 1. Initial Fluorosulfonylation Attempt with *p*-Bromobenzenediazonium Salt via Balz-Schiemann-Type Nucleophilic Reaction



With the optimal reaction conditions successfully established, we next turned our attention to the generality of this copper-catalyzed fluorosulfonylation of various arenediazonium salts. As shown in Figure 2, a wide variety of arenediazonium salts with electron-donating, neutral, and electron-withdrawing substituents were effectively subjected to the optimal reaction conditions, affording the corresponding fluorosulfonylation products in good yields. Some polar and complicated byproducts were observed via TLC analysis and might be Sandmyer-type or azo byproducts. To the best of our knowledge, no fluorinated byproducts were observed in these reactions as expected. Most likely due to the mild reaction conditions employed, various functional groups were well tolerated, including ether (**2a−g**), halogen (**2n−r**), ketone (**2s−u**), ester (**2v−x**), amide (**2y−aa**), cyano (**2bb**), nitro (**2cc**), and heterocyclic (**2dd**) groups. In particular, substrates **1y** and **1aa** bearing an active N−H group provided the corresponding products in good yields. Additionally, the robustness of this transformation can be demonstrated by the successful application of this protocol to various heteroarenediazonium salts, thus affording the corresponding desired products in acceptable yields (**2ee−hh**). Next, several complex molecules, including aminoglutethimide (**1ii**), cabozantinib intermediate (**1jj**), menthol derivative (**1kk**), and sulfamethazine (**1ll**), were selected as suitable reaction partners for the current transformation, and all proceeded well to generate the corresponding products in satisfactory yields. Furthermore, gram-scale synthesis of **2a** was performed to illustrate the good viability of the transformation for scale-up.

We also decided to investigate derivatization reactions of the arenesulfonyl fluorides acquired to further expand the scope and utility of this protocol. As shown in Scheme 2, benefiting from the thermodynamic stability and relative stability toward nucleophilic substitution, bromo- and iodo-containing arenesulfonyl fluorides can undergo several orthogonal functionalizations at bromo or iodo sites, including trifluoromethylation with Chen's reagent,[16] Heck and Suzuki cross-coupling reactions, affording the corresponding products **3−5**, respectively, with the SO_2F group intact. Moreover, arenesulfonyl units frequently exist in many pharmaceuticals and herbicides, and the sulfonylation reaction of alcohol and amine is one of the top five widely applied reactions during pharmaceutical research.[17] Various arenesulfonyl fluorides obtained by this transformation may serve as good sulfonylation reagents. Facile reactions of arenesulfonyl fluoride **2a** with various oxygen- or nitrogen-containing nucleophiles give the corresponding sulfonate **6**, sulfonylamide **7**, and sulfonylazide **8** in excellent

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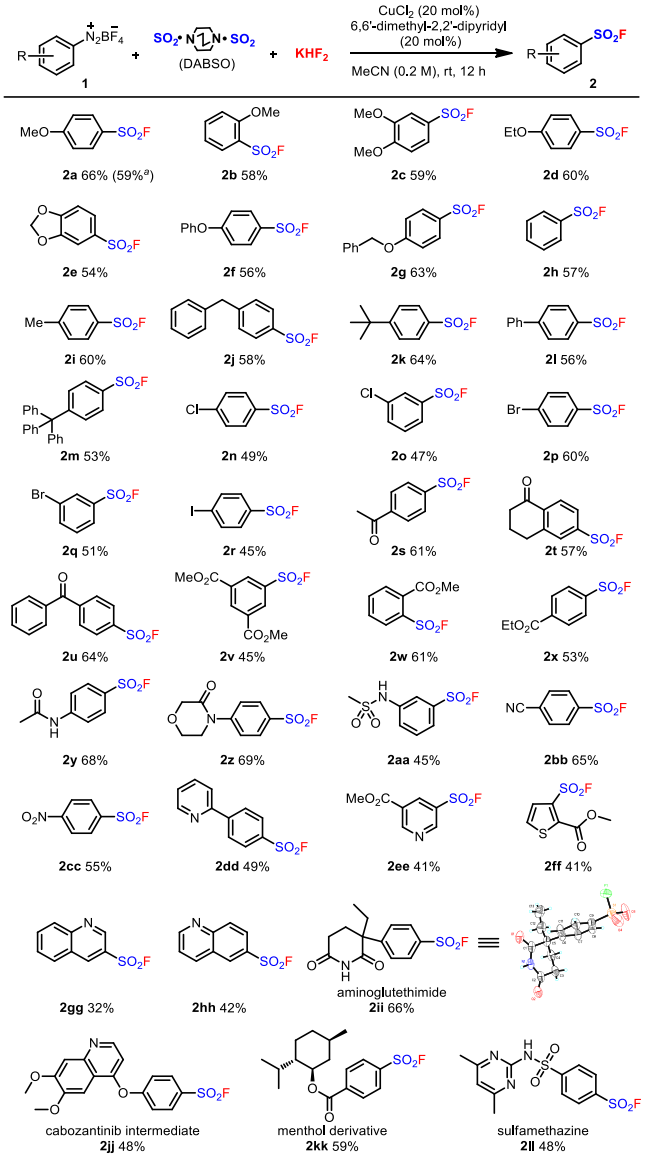
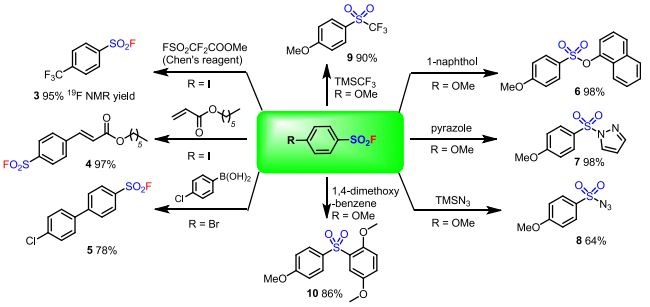


Figure 2. Substrate scope for the synthesis of arenesulfonyl fluorides via copper-catalyzed fluorosulfonylation of various arenediazonium salts. Standard reaction conditions: aryl diazonium salt (0.4 mmol), DABSO (0.4 mmol), KHF_2 (2.0 mmol), $CuCl_2$ (0.08 mmol), and 6,6′-dimethyl-2,2′-dipyridyl (0.08 mmol) in MeCN (2 mL) under an Ar atmosphere at room temperature for 12 h. Yields of isolated products are given. Thermal ellipsoids of the X-ray crystal structure[15] of **2ii** shown at 50% probability. [a]Reaction conditions: aryl diazonium salt (6.0 mmol), DABSO (6.0 mmol), and KHF_2 (18.0 mmol) in MeCN (30 mL) under an Ar atmosphere at room temperature for 12 h.

yields. Treatment of **2a** with $TMSCF_3$ smoothly results in good yields of the desired product **9**. Notably, **2a** could also be used as an electrophilic sulfonylation reagent to generate only sulfone **10** with the aid of stoichiometric $AlCl_3$ as a Lewis acid, which is in sharp contrast to the corresponding arenesulfonyl chloride.[1a]

On the basis of the experimental results mentioned above and previous reports,[18,19] we propose the following possible reaction mechanism. As demonstrated in Figure 3, the aryl radical readily generated from the corresponding arenediazonium salt **1** by Cu(I) species or DABSO by a single-electron transfer (SET) process under the reaction conditions is rapidly

Scheme 2. Derivatization Reactions of the Arenesulfonyl Fluorides Achieved via the Copper-Catalyzed Fluorosulfonylation of the Corresponding Arenediazonium Salts



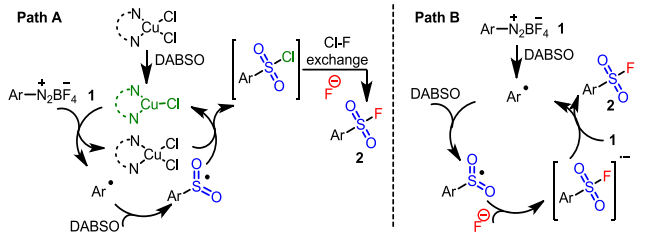


Figure 3. Proposed reaction mechanism.

trapped by SO_2 to produce the resulting relatively stabilized arenesulfonyl radical [$ArSO_2^•$]; its chlorine abstraction from $CuCl_2(L)$ regenerates the Cu(I) species and completes the corresponding $ArSO_2Cl$, and subsequent Cl−F exchange results in the desired product **2** (path A). Alternatively, [$ArSO_2^•$] can combine with the fluorine anion to afford the radical anion [$ArSO_2F^{-•}$]; its back-electron transfer with arenediazonium salt **1** regenerates the new aryl radical and leads to the final product **2** (path B).

Several control experiments were then conducted to gain more insight into the reaction mechanism described above (Figure 4). First, the results of several radical inhibition and radical probe experiments demonstrated the radical character of the reaction (Figure 4a). Second, replacement of KHF_2 with KCl under the standard reaction conditions resulted in the smooth formation of $ArSO_2Cl$ **13**, and using **13** as the reaction substrate instead of arenediazonium salts led to the desired arenesulfonyl fluoride **2a** in good yield (Figure 4b). These results suggest that path A in our proposed reaction mechanism is reasonable (Figure 3). Third, DFT calculations were carried out to rationalize the proposed reaction mechanism. The calculations suggest that both the radical trapping of an aryl radical with SO_2 and the combination of a fluorine anion with [$ArSO_2^•$] are almost energetically barrierless, and the overall reaction selectivity would not be affected even if a slow back-electron transfer process occurred. This process should be the key step and should be obviously influenced by the electron character of the arenediazonium salts used (Figure 4c). Indeed, the competition experiments between arenediazonium salt **1a** with an electron-donating OMe group and **1cc** with an electron-withdrawing NO_2 group under standard reaction conditions indicate that the reaction rate of **1cc** is markedly faster than that of **1a** probably due to a fast back-electron transfer process resulting from the strongly electron-withdrawing NO_2 group (Figure 4d, entry 1). Finally, three representative arenediazonium salts, **1a** (OMe), **1bb**

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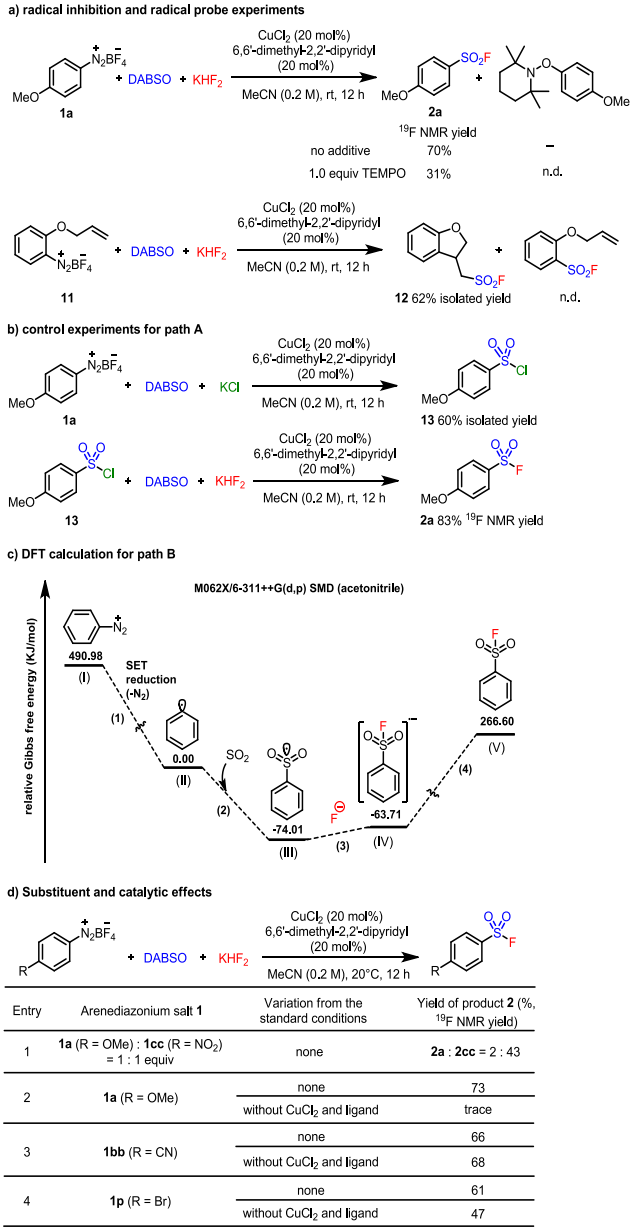

Entry	Arenediazonium salt **1**	Variation from the standard conditions	Yield of product **2** (%, ^{19}F NMR yield)
1	**1a** (R = OMe) : **1cc** (R = NO_2) = 1 : 1 equiv	none	**2a** : **2cc** = 2 : 43
2	**1a** (R = OMe)	none	73
		without $CuCl_2$ and ligand	trace
3	**1bb** (R = CN)	none	66
		without $CuCl_2$ and ligand	68
4	**1p** (R = Br)	none	61
		without $CuCl_2$ and ligand	47

Figure 4. Mechanistic investigation of the copper-catalyzed fluorosulfonylation of arenediazonium salts.

(CN), and **1p** (Br), were selected to investigate the substituent and catalytic effects on the reaction pathway (Figure 3c). In the case of **1a** with a typical electron-donating methoxyl group, only trace amounts of the desired product **2a** were formed in the absence of a copper catalyst and a ligand, while a good yield of **2a** was obtained under standard reaction conditions (Figure 4d, entry 2). This result demonstrates that the reaction fails to operate via path B possibly due to the unsuccessful oxidation of the [$ArSO_2F^{-\bullet}$] intermediate by **1a**. Then, path A becomes the main reaction pathway for the desired reaction. Interestingly, for **1bb** with a typical electron-withdrawing cyano group, similar yields of the target product **2bb** were observed in the presence or absence of a copper catalyst and a ligand, thus indicating that path B is the main reaction pathway in this case (Figure 4d, entry 3). As expected, without a catalyst and a ligand, the reaction of arenediazonium salt **1p** with a relatively neutral bromo substituent provided a lower yield of the desired product, thus showing that both path A and path B may be operative (Figure 4d, entry 4). All of these experimental results suggest that this copper-catalyzed fluorosulfonylation of various arenediazonium salts may proceed via different mechanistic pathways mainly depending on the electronic character of the aryl ring in the arenediazonium salts used.

In conclusion, the copper-catalyzed fluorosulfonylation of various arenediazonium salts described herein allows mild and effective transformation of widely available anilines to valuable arenesulfonyl fluorides. This method utilized inexpensive, safe, and atom-efficient KHF_2 as an ideal fluorine source and the readily available SO_2 surrogate DABSO as a sulfonyl source, and it does not require additional oxidants. In this context, this protocol will be highly valuable for expanding the toolkit of arenesulfonyl fluorides and be significantly advantageous for their further application in different fields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00484.

Full experimental details, characterization data, and copies of NMR spectra for new compounds (PDF)

Accession Codes

CCDC 1964881 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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