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Article

Electrochemical Conversions of Sulfenamides into Sulfonimidoyl- and Sulfondiimidoyl Fluorides

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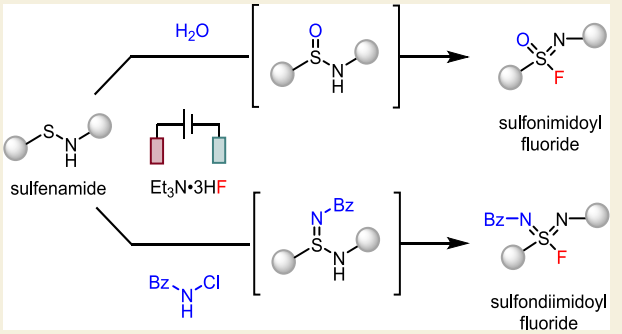
ABSTRACT: The invention of versatile linkage agents provides the chemical basis for SuFEx chemistry. Sulfonimidoyl fluorides and sulfondiimidoyl fluorides are aza-isosteres of sulfonyl fluorides with diverse reactivity through the fine-tuning of *N*-substituents. However, limited synthetic approaches impede their wide applications in SuFEx chemistry. Herein, we develop a straightforward electrochemical strategy for sulfonimidoyl- and sulfondiimidoyl fluorides through sequential oxidations of the readily available sulfenamides via sulfinamide and iminosulfinamide intermediates, respectively. The previously rarely investigated (bis)sulfondiimidoyl fluorides are now easily accessible and readily participate in SuFEx chemistry with diverse oxygen and nitrogen nucleophiles, macrocyclization, and polymerization.



KEYWORDS: *electrochemistry, SuFEx, sulfenamides, sulfonimidoyl fluorides, sulfondiimidoyl fluorides*

INTRODUCTION

The sulfur(VI) fluoride exchange reaction (SuFEx)[1] is a type of click chemistry used for connecting molecules with high fidelity and is widely adopted in organic synthesis, drug discovery, and life and materials science.[2,3] The most notable feature of SuFEx chemistry is that while S^{VI}−F bonds are typically inert under most reaction conditions, they exhibit orthogonal high reactivity and selectivity in the fluoride-to-oxygen, nitrogen, and carbon exchange processes. In this context, the invention of versatile SuFEx linkage agents lays the chemical basis for SuFEx chemistry.[4]

Sulfonyl fluorides and their aza-isosteres, i.e., sulfonimidoyl- and sulfondiimidoyl fluorides, are the most notable sulfur (VI) fluoride linkage agents (Scheme 1A). Compared with sulfonyl fluorides, the nitrogen atom(s) of sulfonimidoyl- and sulfondiimidoyl fluorides provide extra handles to tune their reactivity by installing N-substituents.[5] In addition, the sulfur chirality makes them potentially chiral linkage agents that should find broad applications in asymmetric catalysis,[6,7] pharmaceutical,[8] and agrochemical designs.[9]

Unlike the readily accessible sulfonyl fluorides,[10] synthetic approaches to their monoaza-isosteres, sulfonimidoyl fluorides, are limited and typically require sulfur agents in high oxidation states. For instance, sulfonimidoyl fluorides are often prepared via S^{VI}−Cl to S^{VI}−F exchange reaction using the *in situ* generated sulfonimidoyl chlorides lacking long-term stability.[11] Stoichiometric chemical oxidants are necessary to convert S^{IV} compounds such as sulfinamides and *N*-sulfinylamines,[12−15] and even the divalent sulfenamides to sulfonimidoyl chlorides. Notably, Nandi and co-workers[16] recently developed a one-step synthesis of sulfonimidoyl fluorides from sulfenamides using *N*-chlorosuccinimide (NCS) and tetrabutylammonium fluoride (TBAF) without the isolation of sulfonimidoyl chlorides. Li and co-workers[17] further achieved the chiral phosphoric acid catalyzed enantioselective synthesis of chiral sulfonimidoyl fluorides from sulfenamides facilitating stereospecific SuFEx click chemistry. Alternative methods include SuFEx chemistry with the highly toxic and corrosive thionyl tetrafluoride (SOF_4)[18−20] and sulfinyl trifluoride ($ArSOF_3$),[21] or (electro)chemical oxidative fluorination of the S^{IV} sulfinamide derivatives (Scheme 1B).[22,23] However, the preparation of diverse aza-isosteres of sulfonyl fluorides employing low-valent sulfur reagents still remains underexplored.

Synthetic accessibility to the bisaza-isosteres, sulfondiimidoyl fluorides, is more challenging and thus has been sparsely explored. Existing methods require either unattractive agents or multiple-step preparations. For instance, Yagupolskii et al.[24] treated diphenyl disulfide with superstoichiometric amounts of the unfavorable agent, *N*,*N*-dichlorotrifluoromethanesulfonamide (Tf-NCl_2), to first generate ditriflyl sulfondiimidoyl

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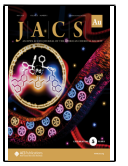

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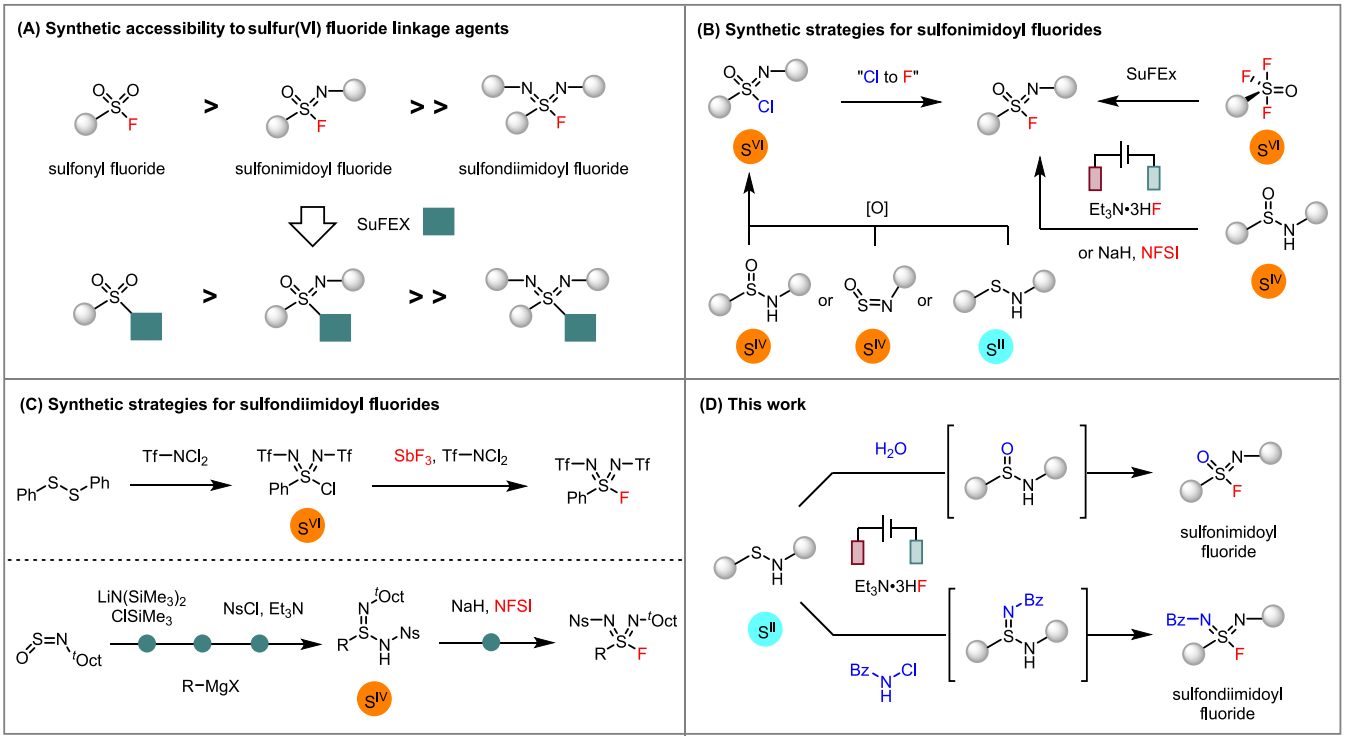
Scheme 1. Sulfonimidoyl- and Sulfondiimidoyl Fluorides



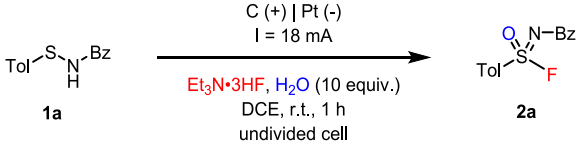
chloride, followed by a chloride-to-fluoride exchange with antimony(III) fluoride and Tf-NCl_2 to afford the sulfondiimidoyl fluoride. Willis et al.[25,26] recently developed a modular approach for sulfondiimidoyl fluorides via oxidative fluorination with iminosulfinamides and NFSI (Scheme 1C). This approach profoundly facilitates the investigation of the previously underexplored reactivity of sulfondiimidoyl fluorides. However, access to the key iminosulfinamide intermediates is not trivial as it requires lengthy operations and uses pyrophoric magnesium agents. The lack of straightforward and efficient access to the monoaza- and bisaza-isosteres of sulfonyl fluorides hinders the in-depth investigations of these promising linkage agents in SuFEx chemistry.

We envision that synthetic electrochemistry[27] should provide alternative, straightforward, and sustainable solutions for SuFEx linkers.[23,28,29] Indeed, we found the electrolysis of the readily available and stable sulfenamides[30] with $Et_3N{\cdot}3HF$ and water readily affords diverse sulfonimidoyl fluorides (Scheme 1D). Straightforward access for the synthetically challenging sulfondiimidoyl fluorides is also readily achieved by simply changing H_2O with *N*-chlorobenzamide under slightly modified electrolytic conditions. As a novel linkage agent, sulfondiimidoyl fluorides readily participate in SuFEx reactions with diverse oxygen and nitrogen nucleophiles, macrocyclization, and polymerization. Mechanistic investigations suggest sulfenamides are first (electro)chemically oxidized to their S^{IV} intermediates,[31,32] i.e., sulfinamides and iminosulfinamides, and then undergo further electrochemical oxidation to form sulfonimidoyl- and sulfondiimidoyl fluorides, respectively.

RESULTS AND DISCUSSION

N-(*p*-Tolylthio)benzamide (**1a**), $Et_3N{\cdot}3HF$, and H_2O in 1,2-dichloroethane were subjected to constant-current electrolysis (I = 18 mA) with a carbon felt anode and a platinum cathode to give sulfonimidoyl fluoride (**2a**) in 72% isolated yield

Table 1. Optimization of Reaction Conditions



Entry	Deviation from standard conditions	**2a**, Yield (%)[a]
1	none	72
2	Py·9HF	15
3	TBAF	9
4	KF or KHF_2	<5
5	H_2O (5 equiv)	65
6	H_2O (20 equiv)	47
7	I = 10 mA	27
8	I = 25 mA	60
9	without electricity	n.d.

[a]Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), $Et_3N{\cdot}3HF$ (6.2 mmol, 31.0 equiv), DCE, carbon felt anode, platinum cathode, undivided cell, I = 18 mA, r.t., 1 h; Isolated yield. n.d. (not detected).

(Table 1, entry 1). $Et_3N{\cdot}3HF$ is a commercially available and easy-to-handle ionic liquid[33,34] that is widely used in electrochemical fluorination[35] because it can serve both as the supporting electrolyte and fluorinating agent. The use of $Et_3N{\cdot}3HF$ was pivotal because other fluorinating agents, either organic (Py·9HF and TBAF, entries 2−3) or inorganic (KF and KHF_2, entry 4), were all deleterious to this reaction. Reducing the loading of $Et_3N{\cdot}3HF$ led to incomplete consumption of the starting material and the resultant sulfinamide intermediate resulting in lower yields (*vide infra*). The addition of 10 equiv of H_2O gave the highest yield of **2a** (entries 5−6). The O^{18} isotopic labeling experiment confirmed that oxygen atoms in **2a** originated from water (see Supporting Information). Screening of passing

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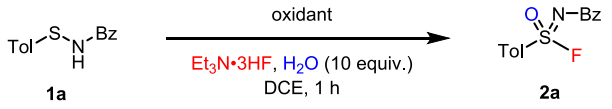
Table 2. Examining Chemical Oxidants *In Lieu Of* Electrochemical Oxidation[a]



Entry	Oxidant	2a, Yield (conv., %)[a]
1	anode oxidation	72[b] (99)
2	TBHP	n.d. (58)
3	CAN	n.d. (99)
4	*m*-CPBA	n.d. (99)
5	DDQ	n.d. (42)
6	$Mn(OAc)_3$	n.d. (54)
7	$AgNO_3$	n.d. (99)
8	$PhI(OAc)_2$	57[b] (99)

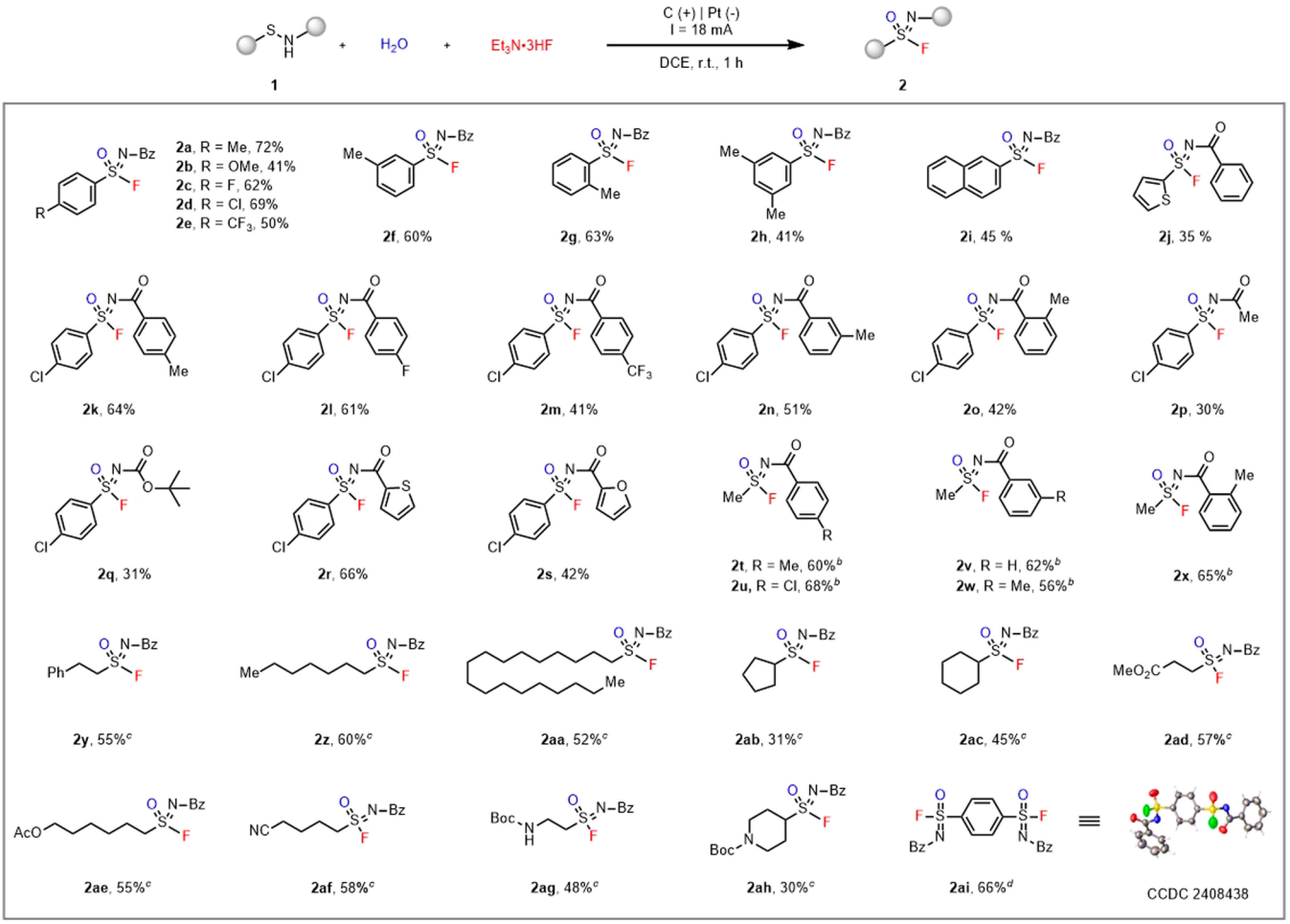
[a]Conversions were determined by ^1H NMR analysis of the crude reaction mixture with CH_2Br_2 as the internal standard. [b]Isolated yield. n.d. (not detected).

current revealed that 10 mA only resulted in a low conversion while increasing the current to 25 mA was not beneficial to reaction yield (entries 7−8). The fact that the sulfur atom was oxidized from S^{II} to S^{IV} necessitated the participation of electricity (entry 9).

We also examined the possibility of replacing electricity by using chemical oxidants (Table 2). Although moderate to good conversions of **1a** were typically realized, the formation of the desired sulfonimidoyl fluoride (**2a**) was not detected (entries 2−7). The only exception was the reaction with $PhI(OAc)_2$ as the oxidant, which afforded **2a** in 57% yield (entry 8). However, superstoichiometric amounts of $PhI(OAc)_2$ (2.0 equiv) were needed in this reaction which was also accompanied by the generation of several side products, i.e., sufinamide and sulfonamide.[36]

Under the optimal electrolytic conditions (Table 1, entry 1), the substrate scope of sulfonimidoyl fluorides was investigated (Scheme 2). *N*-benzoyl sulfonimidoyl fluorides bearing a wide array of phenyls with different electronic and steric substituents (**2a−2h**), naphthyl (**2i**), and thiophenyl (**2j**) were all readily obtained. Besides various substituted *N*-benzoyl sulfonimidoyl fluorides (**2k−2o**), the commonly used *N*-protecting groups, including acetyl (**2p**), *tert*-butoxycarbonyl (**2q**), thiophenyl, and furanyl carboxamides (**2r−2s**), were also well tolerated. In addition, facile preparation of sulfonimidoyl fluorides derived from *N*-benzoyl sulfenamides with linear (**2t−2aa**) and cyclic

Scheme 2. Substrate Scope of Sulfonimidoyl Fluorides[a]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), H_2O (2.0 mmol, 10.0 equiv), DCE/$Et_3N{\cdot}3HF$ = 10:1, carbon felt anode, Pt cathode, undivided cell, r.t. [b] E_{cell} = 3.5 V, TFA (0.1 mL), 35 min, Q = 3.0 F·mol^{-1}. [c]E_{cell} = 3.5 V, TFA (0.1 mL), 1 h, Q = 7.1 F·mol^{-1}. [d]*N,N′*-(1,4-phenylenebis(sulfanediyl))dibenzamide (0.1 mmol, 1.0 equiv), H_2O (2.0 equiv), TFA (0.1 mL), 1.5 h, Q = 10.1 F·mol^{-1}.

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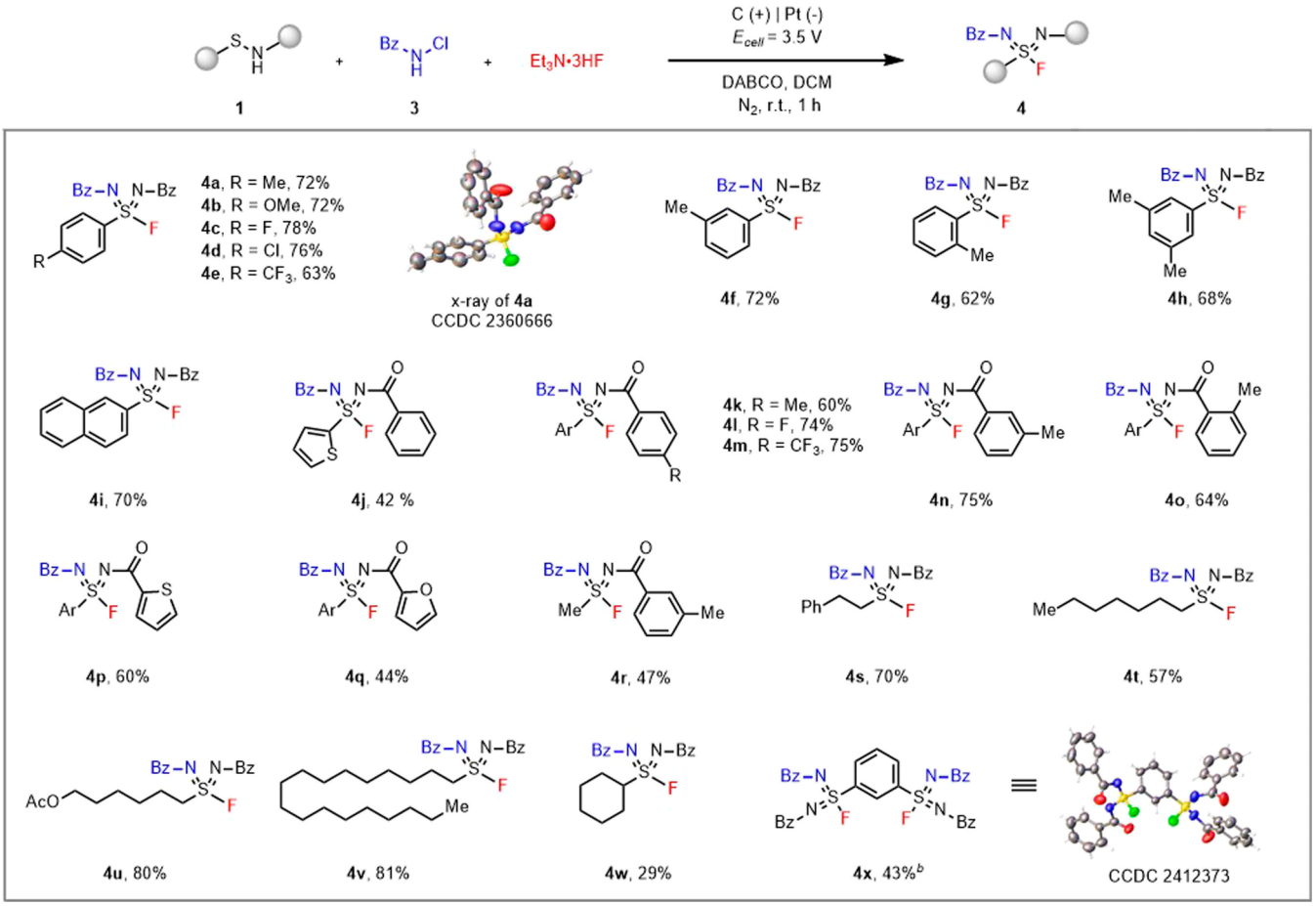
Scheme 3. Substrate Scope of Sulfondiimidoyl Fluorides[a]



[a]Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **3** (0.4 mmol, 2.0 equiv), DABCO (0.4 mmol, 2.0 equiv), DCM/Et_3N·3HF = 4:1, carbon felt anode, Pt cathode, undivided cell, r.t., N_2, E_{cell} = 3.5 V, 1 h, Q = 5.8 F·mol^{-1}, isolated yield, Ar = 4-ClC_6H_4. [b] From the corresponding bis-sulfinamidine (0.1 mmol, 1.0 equiv), DCM/Et_3N·3HF = 10:1, Q = 4.7 F·mol^{-1}.

(**2ab**−**2ac**) aliphatic chains was successful. It is worth noting that constant-cell-potential electrolysis (E_{cell} = 3.5 V), i.e., the applied potential between the working and counter electrodes without a reference electrode, in the presence of trifluoroacetic acid (TFA) was beneficial for those alkyl sulfenamides. The mild electrolytic conditions allowed compatibility with a variety of functionalities, including ester (**2ad**), acetate (**2ae**), nitrile (**2af**), secondary (**2ag**), and tertiary (**2ah**) *tert*-butyl carbamates. The bis-sulfonimidoyl fluoride (**2ai**) was also readily obtained starting from *N*,*N*′-(1,4-phenylenebis-(sulfanediyl))dibenzamide in 66% yield as confirmed by X-ray diffraction analysis.[37]

In addition, synthetic electrochemistry also served as a straightforward protocol to access the previously challenging sulfondiimidoyl fluorides with the replacement of H_2O by *N*-chlorobenzamide (**3**). Compared with existing approaches, we employed the readily available and stable sulfenamides and *N*-chlorobenzamides as the starting materials to conveniently access diverse sulfondiimidoyl fluorides. As illustrated in Scheme 3, constant-cell-potential electrolysis (E_{cell} = 3.5 V) with **1a**, Et_3N·3HF, and **3** in dichloromethane afforded the sulfondiimidoyl fluoride (**4a**) in 72% yield and its structure was confirmed by X-ray diffraction analysis, too. The addition of 1,4-diaza[2.2.2]bicyclooctane (DABCO) accelerated the formation of iminosulfinamide via the chemical reaction between **1a** and **3** before electrolysis (*vide infra*). Under the optimal reaction conditions, diverse sulfondiimidoyl fluorides were conveniently prepared. It is worth noting that *N*-protecting groups at the two nitrogen atoms of sulfondiimidoyl fluorides can be the same (**4b**−**4j** and **4s**−**4w**) or varied (**4k**−**4r**). Similar to sulfonimidoyl fluorides, both the aryl and alkyl sulfenamides proceeded with the anticipated reactivity. Compared with the existing literature, this electrochemical approach for sulfondiimidoyl fluorides features a straightforward preparation, obviates unfavorable reagents, and eliminates the need for tedious isolation of reaction intermediates. Notably, the formation of bis-sulfondiimidoyl fluoride (**4x**) was obtained in 43% yield from the corresponding bis-iminosulfinamide of 1,3-benzenedithiol. By contrast, directly subjecting 1,3-benzenedithiol to the above one-pot synthesis only resulted in a complex reaction mixture. In addition, the bis-iminosulfinamide of 1,4-benzenedithiol was only partially soluble in dichloromethane, which prevented its further transformation.

Recent studies suggest that sulfondiimidoyl moiety is a promising pharmacophore in agrochemical and pharmaceutical discovery.[38,39] Unfortunately, limited synthetic accessibility is the major obstacle preventing their in-depth studies. We demonstrated that a gram-scale reaction proceeded smoothly to afford sulfondiimidoyl fluoride (**4a**, 3.71 g) in 81% yield

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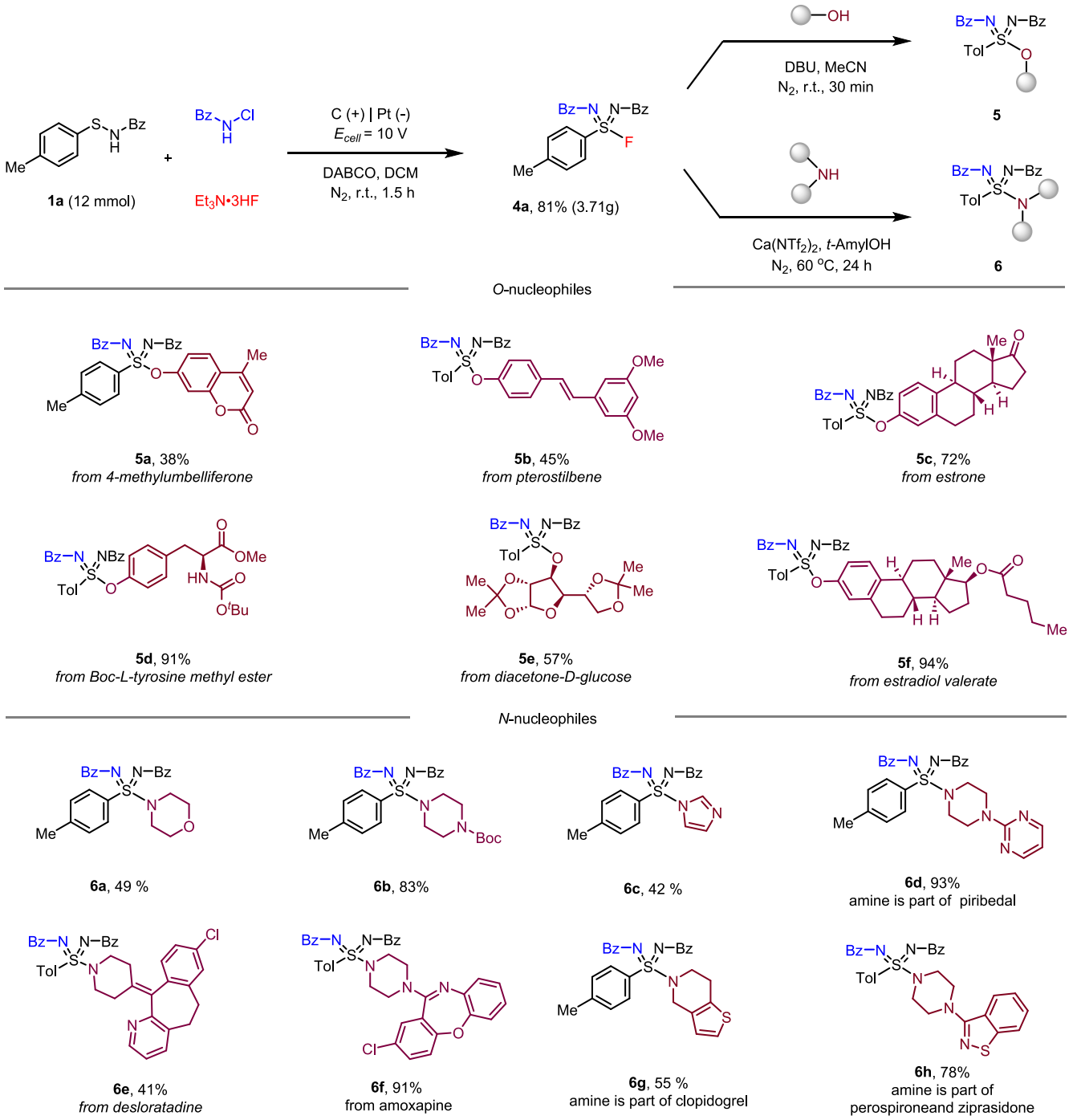
Scheme 4. SuFEx Reactivity of Sulfondiimidoyl Fluoride (4a)



(Scheme 4). The ready accessibility of sulfondiimidoyl fluorides facilitated their investigations in SuFEx reactions with diverse nucleophiles. For instance, sulfondiimidoyl fluoride (**4a**) underwent a facile exchange reaction with various oxygen nucleophiles in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) to give the corresponding sulfondiimidate esters.[40] These included the antitumor and antimetastasis 4-methylumbelliferone (**5a**), the antioxidant pterostilbene (**5b**), the reproduction hormone estrone (**5c**), Boc-L-tyrosine methyl ester (**5d**), diacetone-D-glucose (**5e**), and the estradiol prodrug estradiol valerate (**5f**).

In addition, various sulfondiimidamides were readily prepared through the reaction of sulfondiimidoyl fluoride (**4a**) and secondary nitrogen nucleophiles in the presence of $Ca(NTf_2)_2$.[41−43] Many nitrogen-containing heterocycles, including morpholine (**6a**), piperazine (**6b**), and imidazole (**6c**) were well tolerated. The *N*-containing pharmaceuticals or their amine parts also underwent SuFEx reactions with sulfondiimidoyl fluoride (**4a**). For instance, the amine part of the anti-Parkinson drugs piribedal (**6d**), desloratadine (**6e**), the antidepressant amoxapine (**6f**), the amine part of the antiplatelet drug clopidogrel (**6g**), and the amine part of the atypical antipsychotics perospirone and ziprasidone (**6h**) were all amenable substrates.

As illustrated in Scheme 5, this electrosynthesis was readily integrated with a continuous-flow setup for the scaled

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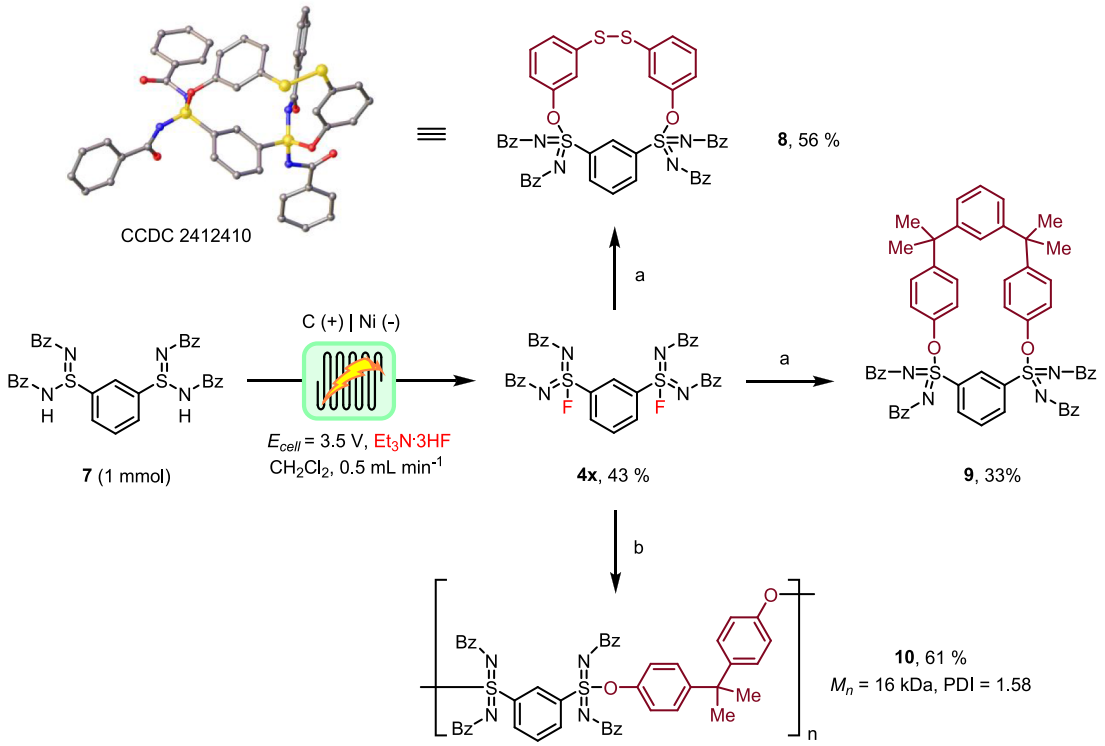
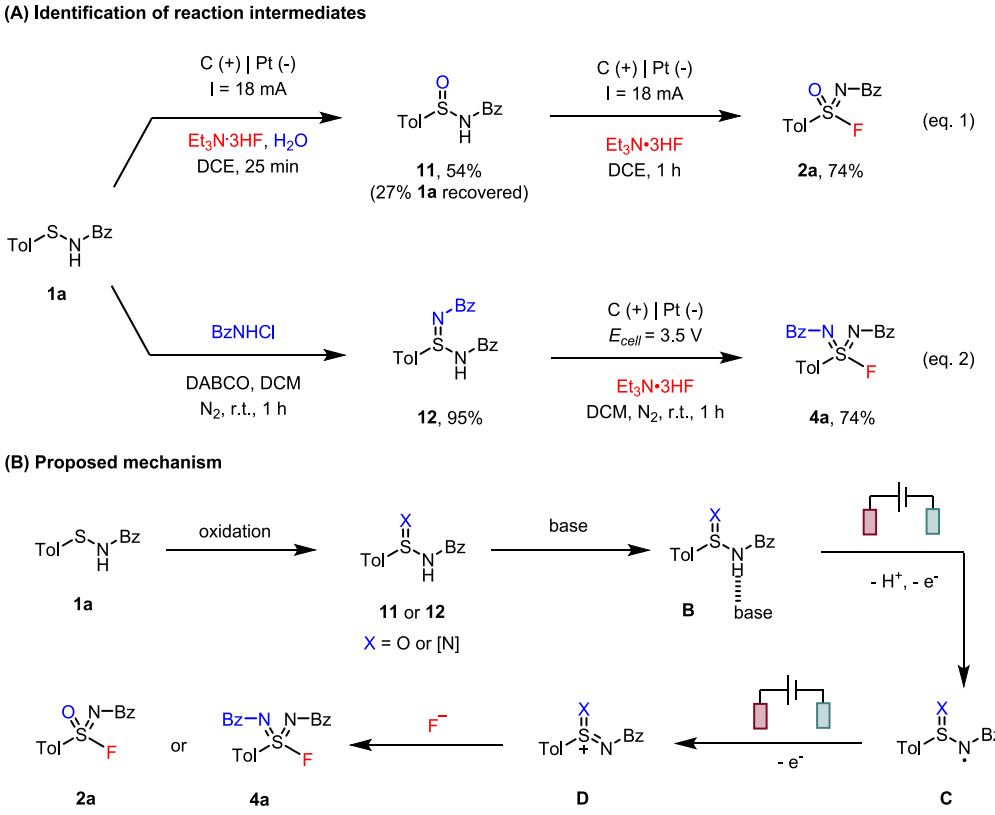
Scheme 5. Macrocyclization and Polymerization of Bis-Sulfondiimidoyl Fluoride (4x)[a]



[a]Conditions: (a) **4x** (0.1 mmol, 1.0 equiv), bisphenols (0.1 mmol, 1.0 equiv), DBU (0.21 mmol, 2.1 equiv), MeCN, r.t., N_2, 30 min; (b) **4x** (0.2 mmol, 1.0 equiv), bisphenol A (0.2 mmol, 1.0 equiv), DBU (0.22 mmol, 1.1 equiv), MeCN, r.t., N_2, 36 h.

Scheme 6. Mechanistic Rationale



preparation of bis-sulfondiimidoyl fluoride (**4x**) from bis-sulfinamidine (**7**) in a slightly higher yield (43%) than the batch reaction (see Supporting Information for details). When **4x** was treated with 3,3′-dihydroxydiphenyl disulfide or 1,3-

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bis[2-(4-hydroxyphenyl)-2-propyl]benzene in the presence of DBU in acetonitrile at ambient temperature, 15-membered macrocycle **8** (CCDC 2412410) and 20-membered macrocycle **9** were formed in 56% and 33% yields, respectively.[44] Polymerization of **4x** with bisphenol A readily formed the corresponding polysulfondiimidate esters (**10**, Mn = 16 kDa, PDI = 1.58) in 61% yield.[45] These diverse transformations imply the synthetic potentials of sulfondiimidoyl fluorides both in pharmaceutical and materials sciences.

To provide more mechanistic insights, several mechanistic experiments were performed. First, reaction intermediates of sulfonimidoyl- and sulfondiimidoyl fluorides were identified (Scheme 6A). Electrolysis of sulfenamide (**1a**) for 25 min only resulted in a moderate conversion to give sulfinamide (**11**) in 54% yield, which was a competent intermediate for the follow-up electrochemical synthesis of sulfonimidoyl fluoride **2a** (eq 1). An analogous iminosulfinamide (**12**)[46] was generated when **1a** was treated with readily available and stable *N*-chlorobenzamide (**3**) and DABCO (1,4-diaza[2.2.2]-bicyclooctane). Similarly, **12** proved to be the synthetic intermediate for the subsequent electrochemical synthesis of sulfondiimidoyl fluoride **4a** (eq 2).

According to cyclic voltammetry studies (see Supporting Information), the oxidation potential of sulfenamide (E_{1a}, 1.42 V) was much lower than that of sulfinamide (E_{11}, 2.16 V) and iminosulfinamide (E_{12}, 1.89 V). When transferred to their sodium salts upon treatment with NaH, **11**[**Na**] (0.79 V) and **12**[**Na**] (1.19 V) were more readily accessible to electrochemical oxidation. The presence of $Et_3N{\cdot}3HF$ also exhibited similar effects on the facilitation of electrochemical oxidations of **11** (pK_a = 11.7) and **12** (pK_a = 15.9),[47] which is in line with an electrochemically proton-coupled electron transfer process.[48−50] In addition, the kinetic isotope effect (KIE) of the analog electrochemical oxygenation of sulfinamide was also determined to further substantiate that the electrochemical oxidation of the acid−base complex is likely via a PCET pathway (see Supporting Information for details).

As illustrated in the proposed mechanism (Scheme 6B), the sulfenamide (**1a**) is electrochemically or chemically oxidized to the corresponding sulfinamide (**11**) and iminosulfinamide (**12**), respectively. In the presence of $Et_3N{\cdot}3HF$, this S^{IV} species undergoes an electrochemical proton-coupled electron transfer process to form an amidyl radical (**C**). Successive electrochemical oxidation then affords a trigonal planar S^{VI} centered cation (**D**),[5,23] which is readily intercepted by fluoride to deliver sulfonimidoyl-(**2a**) and sulfondiimidoyl (**4a**) fluorides, respectively.

CONCLUSION

In summary, we have developed a straightforward electrochemical preparation of two SuFEx linkage agents, i.e., sulfonimidoyl- and sulfondiimidoyl fluorides. It features sequential oxidations of sulfenamides to sufinamides and iminosulfinamides, and ultimately to their S^{VI} fluorides, respectively. The ready accessibility of previously synthetically challenging sulfonimidoyl- and sulfondiimidoyl fluorides enables their broad applications in versatile SuFEx reactions. We anticipate synthetic electrochemistry should find more applications for the preparation of diverse SuFEx linkage agents and thus facilitate discoveries in life and materials science.

METHODS

General Procedure for the Electrosynthesis of Aryl Sulfonimidoyl Fluorides

In an undivided three-necked glassware (25 mL) equipped with a stirring bar, S-aryl sulfenamide **1** (0.2 mmol, 1.0 equiv) was added. The glassware was equipped with carbon felt (15 mm × 15 mm × 2 mm) as the anode and platinum plate (15 mm × 15 mm × 0.3 mm) as the cathode. $Et_3N{\cdot}3HF$ (1.0 mL, 6.2 mmol, 31.0 equiv), DCE (10.0 mL), and H_2O (36 μL, 2.0 mmol, 10.0 equiv) were injected into the glassware via syringes. The reaction mixture was stirred and electrolyzed at a constant current of 18 mA at r.t. for 1 h. After completion, the resultant reaction mixture was concentrated in vacuo, and the crude residue was subjected to flash column chromatography on silica gel to yield the desired product **2**.

General Procedure for the Electrosynthesis of Alkyl Sulfonimidoyl Fluorides

In an undivided three-necked glassware (25 mL) equipped with a stirring bar, S-alkyl sulfenamide **1** (0.2 mmol, 1.0 equiv) was added. The glassware was equipped with carbon felt (15 mm × 15 mm × 2 mm) as the anode and platinum plate (15 mm × 15 mm × 0.3 mm) as the cathode. $Et_3N{\cdot}3HF$ (1.0 mL, 6.2 mmol, 31.0 equiv), DCM (10.0 mL), TFA (0.1 mL, 1.3 mmol, 6.5 equiv), and H_2O (36 μL, 2.0 mmol, 10.0 equiv) were injected into the glassware via syringes. The reaction mixture was stirred and electrolyzed at a constant voltage of 3.5 V at room temperature. After completion, the resultant reaction mixture was concentrated in vacuo, and the crude residue was subjected to flash column chromatography on silica gel to yield the desired product **2**.

General Procedure for the Electrosynthesis of Sulfondiimidoyl Fluorides

In an undivided three-necked glassware (25 mL) equipped with a stirring bar, sulfenamide **1** (0.2 mmol, 1.0 equiv), *N*-chlorobenzamide **3** (62.0 mg, 0.4 mmol, 2.0 equiv), DABCO (44.8 mg, 0.4 mmol, 2.0 equiv) were added. The glassware was equipped with carbon felt (15 mm × 15 mm × 2 mm) as the anode and platinum plate (15 mm × 15 mm × 0.3 mm) as the cathode. Under the N_2 atmosphere, $Et_3N{\cdot}3HF$ (1.0 mL, 6.2 mmol, 31.0 equiv) and DCM (4.0 mL) were injected into the glassware via syringes. The reaction mixture was stirred and electrolyzed at a constant current of 3.5 V at r.t. for 1 h. After completion, the resultant reaction mixture was concentrated in vacuo, and the crude residue was subjected to flash column chromatography on silica gel to yield the desired product **4**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.5c00374.

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Optimizations, synthetic procedures, mechanism experiments, cyclic voltammetry studies, characterization data, and NMR spectra of synthesized compound (PDF)
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Author Contributions

K.Y. and Y.L. conceived the concept and directed the investigations. B.Z. developed the electrolytic system, performed the experiments, and analyzed the data. D.Z. synthesized the substrates. X.H. and J.L. performed X-ray crystal structure determination and analyses. All authors contributed to the formulation of this manuscript.

Notes

The authors declare no competing financial interest.

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