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Electrochemical Trifluoromethylation of Thiophenols with Sodium Trifluoromethanesulfinate

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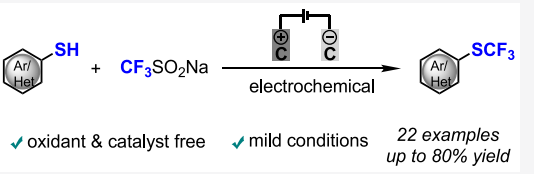
ABSTRACT: We developed an electrochemical trifluoromethylation of thiophenols without the use of metal catalysts and oxidants. This reaction features mild reaction conditions, readily available substrate, as well as moderate to good yields. In addition, this protocol can be easily scaled up with moderate efficiency.



Because of the unique ability of the fluorine atom, the introduction of fluorine atoms into organic molecules will significantly change the dipole moment, acidity, lipophilicity, and chemical and metabolic stability of the molecule.[1] Today fluorinated drugs account for ~25% of all drug molecules and even up to 30% of pesticide chemicals.[2] In the organofluorine family, the trifluoromethylthio group (-SCF_3) has very high lipophilicity and hydrophobic parameters.[3] Introducing -SCF_3 into drug molecules can greatly enhance the lipophilicity and biological permeability of drugs.[4] Therefore, organic molecules containing -SCF_3 groups have great potential application value in medicine, pesticides, and other fields. Examples of trifluoromethylthiolated drugs including Toltrazuril,[5] Losartan analogues,[6] Adrenergic agent,[7] and Tiforex[8] are shown in Figure 1.

In recent decades, significant progress has been made in the synthesis of trifluoromethyl aryl sulfide; many novel methods and effective reagents have emerged.[9−14] In 2007, Togni and co-workers disclosed a trifluoromethylation of thiophenols by using electrophilic hypervalent iodine(III)-CF_3 reagent (Togni reagent) as a CF_3 source (Scheme 1a).[12a] In 2014, Wang and Noël developed a photocatalytic trifluoromethylation of thiophenols, respectively (Scheme 1a).[12b] In 2016, Yi et al. reported the trifluoromethylation of thiophenols with sodium trifluoromethanesulfinate using iodine pentoxide and as an oxidant (Scheme 1a).[12c,d] Since organic electrosynthesis has the advantages of less pollution, short process flow, and mild reaction conditions, organic electrosynthesis has emerged as an eco-friendly synthetic tool in synthetic chemistry.[15] Inspired by these works and as a continuation of our studies on electrochemical reactions,[16] we describe an electrochemical trifluoromethylation of thiophenols under metal- and oxidant-free undivided electrosynthetic conditions (Scheme 1b).

Initially, a model reaction of 4-methoxythiophenol (**1a**) with CF_3SO_2Na (**2a**) was chosen to optimize the reaction conditions (Table 1). The initial reaction was performed in an undivided cell with graphite plates as electrodes under 10 mA constant current at room temperature using $^nBu_4NBF_4$ as the supporting electrolyte and CH_3CN as the solvent under argon atmosphere. We chose NaBr as the mediator according to a previous report,[17] which proved that bromide can mediate the electrochemical trifluoromethylation. To our delight, the desired product **3a** was obtained in 76% yield (Table 1, entry 1). With $LiClO_4$ as the supporting electrolyte, the yield decreases slightly (Table 1, entry 2). But with other supporting electrolytes such as $^nBu_4NPF_6$ and $NaBF_4$, only a trace amount of **3a** was observed (Table 1, entries 3 and 4). Subsequently, a series of solvents was examined, and replacement of CH_3CN with CH_2Cl_2 gave a significantly decreased yield (Table 1, entry 5). When dimethylformamide (DMF) was used as the reaction solvent, none of the desired product was formed (Table 1, entry 6). In addition, NaBr was proved to be the best mediator for the reaction (Table 1, entries 7 and 8). Only 43% yield of **3a** was obtained in the absence of NaBr (Table 1, entry 9). Other current systems can also proceed the reaction, but the yields were significantly reduced (Table 1, entries 10 and 11). When the reaction was performed under air atmosphere, a significantly reduced yield of **3a** was obtained (Table 1, entry 12). Note that the nature of the electrode material has a great influence on the reaction;[18] with platinum and nickel as the anode, the yields reduced to 26% and 68%, respectively (Table 1, entries 13 and 14). Finally, control experiments demonstrated that an electric current was indispensable for the reaction (Table 1, entry 15).

With the optimized reaction conditions established, we began to evaluate the substrate scope. As summarized in Scheme 2, a variety of thiophenols with *ortho*, *meta*, or *para* substituents on the benzene ring are well-tolerated, and no

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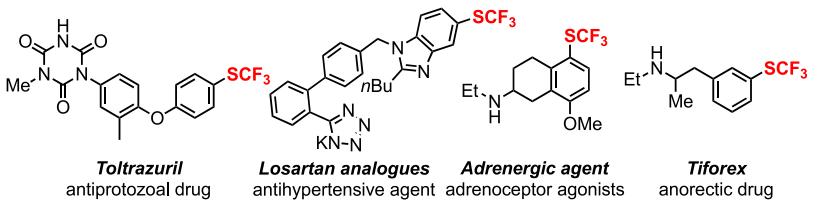


Figure 1. Examples of SCF_3-containing biologically active compounds.

Scheme 1. Approaches for Trifluoromethylation of Thiophenols

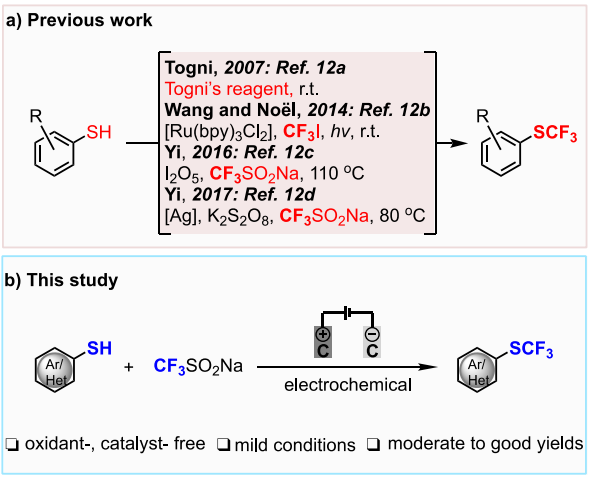
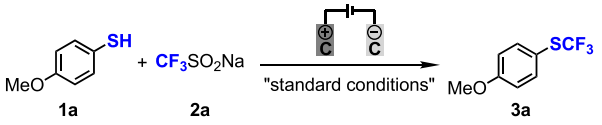


Table 1. Optimization of the Reaction Conditions[a]

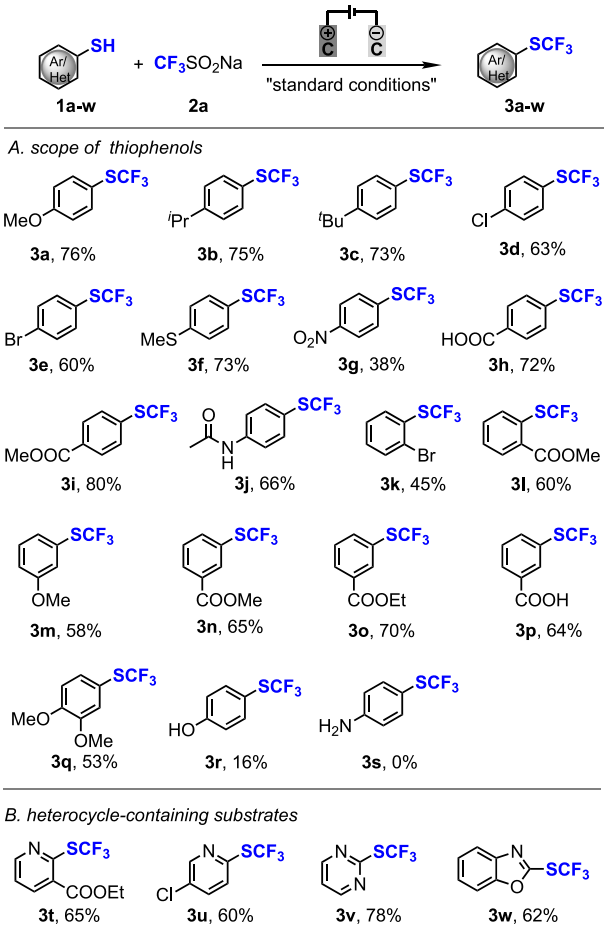


entry	variation from the standard conditions	yield[b] (%)
1	none	76
2	$LiClO_4$ instead of $^nBu_4NBF_4$	70
3	$NaBF_4$ instead of $^nBu_4NBF_4$	trace
4	$^nBu_4NPF_6$ instead of $^nBu_4NBF_4$	trace
5	CH_2Cl_2 instead of CH_3CN	23
6	DMF instead of CH_3CN	n.r.
7	KBr instead of NaBr	68
8	Et_4NBr instead of NaBr	45
9	no NaBr	43
10	under air	21
11	8 mA instead of 10 mA, 12.5 h	47
12	14 mA instead of 10 mA, 7 h	34
13	platinum instead of graphite as the anode	26
14	nickel instead of graphite as the cathode	68

[a]Standard conditions: graphite plate anode: (10 mm × 15 mm), constant current: 10.0 mA, **1a** (0.5 mmol, 1.0 equiv), **2a** (1.5 mmol, 3.0 equiv), NaBr (0.5 mmol, 1.0 equiv), $^nBu_4NBF_4$ (0.63 mmol, 1.25 equiv), CH_3CN (10 mL) in an undivided cell under Ar atmosphere, 10 h at room temperature. [b]Isolated yield. n.r. = no reaction.

matter whether the benzene ring had an electron-donating group or an electron-withdrawing group, it could be successfully converted to the corresponding trifluoromethylthio product (Scheme 2A). Alkyl (isopropyl, *tert*-butyl, e.g., **3b** and **3c**), halide (Cl, Br, e.g., **3d**, **3e**, and **3k**), ester (**3i**, **3l**, **3n**, and **3o**), and carboxyl (**3h** and **3p**) functional groups were all untouched, providing potential reactive sites for further

Scheme 2. Substrate Scope[a]



[a]Standard conditions: Undivided cell, graphite plate anode: (10 mm × 15 mm), constant current: 10.0 mA, **1a**−**1w** (0.5 mmol, 1.0 equiv), **2a** (1.5 mmol, 3.0 equiv), NaBr (0.5 mmol, 1.0 equiv), $^nBu_4NBF_4$ (0.63 mmol, 1.25 equiv), CH_3CN (10 mL), Ar, r.t., 10 h.

derivatization. Versatile functional groups such as ether (**3a**, **3f**, and **3m**), nitro (**3g**), or amide (**3j**) groups were well-tolerated. Furthermore, the disubstituted thiols could undergo the reaction smoothly to afford the desired product (**3q**) in 53% yield. Unfortunately, 4-aminothiophenol failed in this transformation, and 4-mercaptophenol was poorly tolerated; the desired product **3r** was only obtained in 16% yield. The next step in the research on the scope of substrates was focused on substrates containing heterocycles (Scheme 2B). The results showed that pyridine (**3t** and **3u**), pyrimidine (**3v**), and benzoxazole (**3w**) derivatives obtained the target product with moderate 60−78% yields.

To illustrate the synthetic practicability of this electrochemical trifluoromethylation of thiols, a gram-scale (2.8 g, 20 mmol) reaction was also conducted under the optimum

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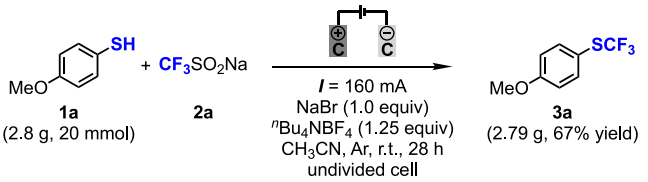
conditions (Scheme 3). The desired product **3a** was obtained with 67% yield (2.79 g) after 28 h of constant-current electrolysis.

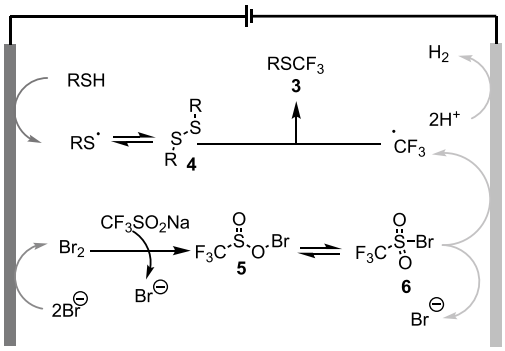
Scheme 3. Gram-Scale Synthesis of 3a



To elucidate the mechanism insight into this electrochemical transformation, a series of control experiments was conducted (Scheme 4). First, we performed free-radical trapping experiments. We observed that radical scavengers such as tetramethylpiperidinoxyl (TEMPO), 2,6-di-*tert*-butyl-4-methylphenol (BHT), and 1,1-diphenylethylene inhibited the electrochemical conversion, and the corresponding free radicals were captured (see the Supporting Information for more details); this result indicated that electrocatalysis was gone through the free radical pathway. Subsequently, with the replacement of thiophenol **1a** with sulfide **4** under standard conditions, the desired product of **3a** was obtained in 73% yield, which indicated that the sulfide **4** may be the intermediate involved in this reaction.

On the basis of the preliminary experiments and literature reports,[17,19] a possible mechanism is proposed in Scheme 5. Initially thiol undergoes hydrogen evolution in the anode to generate a thiol radical; subsequently, the thiol radical generates the disulfide **4** in situ. Meanwhile, bromide ions produced by sodium bromide (NaBr) in the reaction solution are oxidized to produce molecular Br_2, followed by a reaction with CF_3SO_2Na to afford sulfonyl hypobromide **5**, which is in equilibrium with intermediate **6**. The intermediate **5** or **6** is reduced or homolytically cleaved at the cathode to release SO_2 gas, regenerate bromide ions, and generate free radicals at the same time. Once the CF_3 free radical is formed, it reacts with **4**

Scheme 5. Proposed Reaction Mechanism

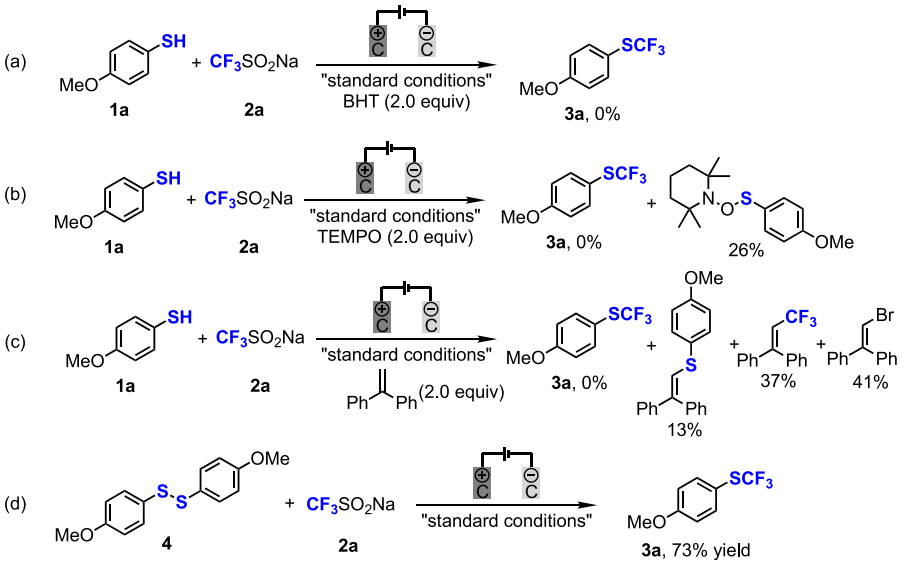


to generate the desired product **3**. Finally, the hydrogen ions at the cathode are reduced to release hydrogen.

In summary, an electrochemical trifluoromethylation of thiol has been developed that avoids the use of metal catalysts and oxidants. Mild reaction conditions, readily available substrate, as well as moderate to good yields made this reaction, providing an alternative electrochemical trifluoromethylation manner for the functionalization of biological molecules.

Experimental Section. *General Information*. All solvents and reagents were used as received from commercial sources. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a Bruker Advance 400 or 600 spectrometer at the ambient temperature in $CDCl_3$ or deuterated dimethyl sulfoxide (DMSO-d_6). Chemical shifts (δ) are reported in parts per million (ppm) using tetramethylsilane (TMS) as internal standard (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = triplet of doublets, m = multiplet). Data for the ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. Chemical shifts were referenced to internal TMS at δ 0.00 ppm or to the signal of residual proton solvent peak: $CDCl_3$ at δ 7.26 ppm. Data for the ^{13}C NMR are reported in terms of chemical shift (δ ppm). Chemical shifts were referenced to the residual solvent peak: $CDCl_3$ at δ 77.2 ppm. Data for the ^{19}F NMR are reported in terms of chemical shift (δ ppm). Chemical shifts were referenced to internal or external $CFCl_3$

Scheme 4. Control Experiments



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at δ 0.00 ppm. In DMSO-d_6, the chemical shifts in the ^{1}H NMR and ^{13}C NMR spectra were determined based on the chemical shift of DMSO-d_6 (δ = 2.50 ppm and δ = 39.52 ppm, respectively). Gas chromatography-mass spectrometry (GC-MS) analyses were performed on a Thermo Scientific AS 3000 Series GC-MS system. Analytical thin-layer chromatography (TLC) was done on precoated silica gel plates. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Flash column chromatographic purification of products was accomplished using forced-flow chromatography on silica gel (200−300 mesh).

General Procedure. To a 25 mL tube were sequentially added the substrate **1** (0.5 mmol, 1.0 equiv), CF_3SO_2Na (1.5 mmol, 3.0 equiv, 234 mg), NaBr (0.5 mmol, 1.0 equiv, 51.5 mg), ^{n}Bu$_4$NBF$_4$(0.63 mmol, 1.25 equiv, 208 mg), and CH_3CN (10 mL). The tube was equipped with two graphite plate electrodes (10 mm × 15 mm). The electrolysis was performed at r.t. under Ar atmosphere with a constant current of 10.0 mA for 10 h. After the completion of the reaction, the mixture was concentrated and subjected to flash chromatography on silica gel eluting with petroleum ether/ethyl acetate to afford the desired product.

Gram-Scale Reaction. In a 500 mL container equipped with a stir bar, **1a** (2.80 g, 20 mmol), **2a** (9.36 g, 60 mmol), NaBr (2.04 g, 20 mmol), and ^{n}Bu$_4$NBF$_4$ (8.22 g, 25 mmol) were dissolved in CH_3CN (200 mL), followed by graphite plates as anode and cathode (5 cm × 4 cm × 2 mm each, ∼2 cm immersed in the solution) under an argon atmosphere (operated in glovebox). Then the electrolysis system was stirred at a constant current of 160 mA at r.t. for 28 h. Then the solvent was removed with a rotary evaporator, and the desired product was purified by column chromatography (silica gel) using petroleum ether as eluent. The desired product was obtained as a colorless oil with 67% yield (2.79 g).

Characterization data for all products. (4-Methoxyphenyl)(trifluoromethyl)sulfane (**3a**). Purified by flash column chromatography (petroleum ether) as a colorless oil (78.9 mg, 76% yield).[12b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 8.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.1, 138.5, 129.8 (q, C−F, $^1J_{C-F}$ = 308.1 Hz), 115.2, 115.1 (d, C−F, $^3J_{C-F}$ = 2.1 Hz), 55.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ −43.95 (s, 3F).

(4-Isopropylphenyl)(trifluoromethyl)sulfane (**3b**). Purified by flash column chromatography (petroleum ether) as a colorless oil (82.5 mg, 75% yield).[13j] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.1 Hz, 2H), 2.98−2.93 (m, 1H), 1.28 (s, 1H), 1.27 (s, 1H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 152.3, 136.6, 129.9 (q, C−F, $^1J_{C-F}$ = 307.9 Hz), 127.8, 121.3 (d, C−F, $^3J_{C-F}$ = 2.3 Hz), 34.2, 23.9. ^{19}F NMR (565 MHz, $CDCl_3$) δ −43.01 (s, 3F).

(4-(*tert*-Butyl)phenyl)(trifluoromethyl)sulfane (**3c**). Purified by flash column chromatography (petroleum ether) as a colorless oil (85.4 mg, 73% yield).[12b] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, J = 8.8 Hz, 2H), 7.45 (d, J = 8.8 Hz, 2H), 1.35 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 154.6, 136.3, 129.9 (q, C−F, $^1J_{C-F}$ = 309.3 Hz), 126.8, 121.1 (d, C−F, $^3J_{C-F}$ = 2.3 Hz), 35.1, 31.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −42.89 (s, 3F).

(4-Chlorophenyl)(trifluoromethyl)sulfane (**3d**). Purified by flash column chromatography (petroleum ether) as a colorless oil (66.8 mg, 63% yield).[12b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.58 (m, 2H), 7.42−7.39 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.8, 132.9, 130.0, 129.5 (q, C−F, $^1J_{C-F}$ = 308.3 Hz), 123.0 (q, C−F, $^3J_{C-F}$ = 2.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −43.03 (s, 3F).

1-Bromo-4-[(trifluoromethyl)thio]benzene (**3e**). Purified by flash column chromatography (petroleum ether) as a colorless oil (76.8 mg, 60% yield).[12b] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57−7.56 (m, 2H), 7.52−7.51 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 137.9, 133.0, 129.4 (q, C−F, $^1J_{C-F}$ = 308.2 Hz), 126.2, 123.6 (d, C−F, $^3J_{C-F}$ = 2.3 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ −42.64 (s, 3F).

1-Methylthio-4-[(trifluoromethyl)thio]benzene (**3f**). Purified by flash column chromatography (petroleum ether) as a colorless oil (81.8 mg, 73% yield).[12b] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H). 2.50 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.4, 136.8, 129.7 (q, C−F, $^1J_{C-F}$ = 308.3 Hz), 126.5, 119.9 (d, C−F, $^3J_{C-F}$ = 2.5 Hz), 15.1. ^{19}F NMR (565 MHz, $CDCl_3$) δ −43.15 (s, 3F).

1-Nitro-4-[(trifluoromethyl)thio]benzene (**3g**). Purified by flash column chromatography (petroleum ether) as a colorless oil (42.4 mg, 38% yield).[12b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 7.83 (d, J = 8.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.3, 136.3, 132.8 (d, C−F, $^3J_{C-F}$ = 2.1 Hz), 129.1 (q, C−F, $^1J_{C-F}$ = 308.8 Hz), 124.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.32 (s, 3F).

4-[(Trifluoromethyl)thio]benzoic acid (**3h**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 2:1) as a light yellow solid (79.9 mg, 72% yield).[12b] ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.02 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 7.8 Hz, 2H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 172.3, 135.5, 130.4, 129.6, 129.5 (q, C−F, $^1J_{C-F}$ = 307.8 Hz), 125.6. ^{19}F NMR (564 MHz, DMSO-d_6) δ −46.00 (s, 3F).

Methyl-4-[(trifluoromethyl)thio]benzoate (**3i**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 50:1) as a colorless oil (94.4 mg, 80% yield).[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.2, 135.7, 132.3, 130.6, 130.0 (d, C−F, $^3J_{C-F}$ = 2.0 Hz), 129.4 (q, C−F, $^1J_{C-F}$ = 308.4 Hz), 52.6. ^{19}F NMR (564 MHz, $CDCl_3$) δ −41.89 (s, 3F).

N-[4-[(Trifluoromethyl)thio]phenyl]acetamide (**3j**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 5:1) as a white solid (77.6 mg, 66% yield).[12b] ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.26 (s, 1H), 7.74−7.72 (m, 2H), 7.65−7.62 (m, 2H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 168.9, 142.3, 137.3, 129.6 (q, C−F, $^1J_{C-F}$ = 308.1 Hz), 119.8, 115.5 (d, C−F, $^3J_{C-F}$ = 2.3 Hz), 24.1. ^{19}F NMR (565 MHz, DMSO-d_6) δ −42.79 (s, 3F).

1-Bromo-2-[(trifluoromethyl)thio]benzene (**3k**). Purified by flash column chromatography (petroleum ether) as a colorless oil (57.6 mg, 45% yield).[20] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78−7.72 (m, 2H), 7.39−7.31 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.2, 134.2, 132.3, 129.4 (q, C−F, $^1J_{C-F}$ = 309.9 Hz), 130.8, 128.4, 126.5 (d, C−F, $^3J_{C-F}$ = 2.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.91 (s, 3F).

Methyl-2-[(trifluoromethyl)thio]benzoate (**3l**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 50:1) as a colorless oil (70.8 mg, 60% yield).[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (dd, J = 7.8, 1.1 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.54 (td, J = 7.9, 1.3 Hz, 1H), 7.44 (t, J = 7.7 Hz, 1H), 3.94 (s, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.8, 132.8, 132.7, 132.6, 131.1, 129.7 (q, C−F, $^1J_{C-F}$ = 309.1 Hz), 128.8, 128.5 (d, C−F, $^3J_{C-F}$ = 1.6 Hz), 52.8. ^{19}F NMR (564 MHz, $CDCl_3$) δ −41.39 (s, 3F).

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1-Methoxy-3-[(trifluoromethyl)thio]benzene (**3m**). Purified by flash column chromatography (petroleum ether) as a colorless oil (60.3 mg, 58% yield).[21] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34−7.32 (m, 1H), 7.24 (d, J = 7.7 Hz, 1H), 7.19−7.18(m, 1H), 7.04−7.02 (m, 1H), 3.83 (s, 3H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 160.1, 130.3, 129.8 (q, C−F, $^1J_{C-F}$ = 308.0 Hz), 128.5, 125.4 (d, C−F, $^3J_{C-F}$ = 1.8 Hz), 121.3, 117.0, 55.6. ^{19}F NMR (564 MHz, $CDCl_3$) δ −42.59 (s, 3F).

Methyl-3-[(trifluoromethyl)thio]benzoate (**3n**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 30:1) as a light yellow solid (72.2 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 7.52 (t, J = 7.8 Hz, 1H), 3.95 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.9, 140.5, 137.4, 132.1, 131.8, 129.7, 129.6 (q, C−F, $^1J_{C-F}$ = 308.2 Hz), 125.3 (d, C−F, $^3J_{C-F}$ = 2.2 Hz), 52.6. ^{19}F NMR (564 MHz, $CDCl_3$) δ −42.48 (s, 3F). High-resolution mass spectrometry (electrospray ionization) (HRMS (ESI)): Calcd for $C_9H_8F_3O_2S$ ([M + H]$^+$): 237.0192, found: 237.0201.

Ethyl-3-[(trifluoromethyl)thio]benzoate (**3o**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 20:1) as a colorless oil (82.6 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.16 (d, J = 7.7 Hz, 1H), 7.84 (d, J = 7.7 Hz, 1H), 7.51 (t, J = 7.8 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.43−1.39 (m, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.4, 140.4, 137.4, 132.2, 132.0, 129.7, 129.6 (q, C−F, $^1J_{C-F}$ = 308.2 Hz), 125.2 (d, C−F, $^3J_{C-F}$ = 2.1 Hz), 61.7, 14.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ −42.50 (s, 3F). HRMS (ESI): Calcd for $C_{10}H_{10}F_3O_2S$ ([M + H]$^+$): 250.0348, found: 251.0355.

3-[(Trifluoromethyl)thio]benzoic acid (**3p**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 2:1) as a colorless oil (80.1 mg, 64% yield).[9b] ^{1}HNMR (600 MHz, DMSO-d_6) δ 8.18 (s, 1H), 8.15−8.13 (m, 1H), 7.97 (d, J = 7.8 Hz, 1H), 7.72−7.65 (m, 1H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 166.0, 140.2, 136.4, 132.5, 132.1, 130.5, 129.5 (q, C−F, $^1J_{C-F}$ = 308.2 Hz), 123.8 (d, C−F, $^3J_{C-F}$ = 2.4 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ −41.92 (s, 3F).

1,2-Dimethoxy-4-[(trifluoromethyl)thio]benzene (**3q**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 50:1) as a colorless oil (63.1 mg, 53% yield).[13j] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 11.5 Hz, 1H), 7.09 (d, J = 22.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.91 (d, J = 3.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 151.7, 149.4, 130.3, 125.9 (d, C−F, $^1J_{C-F}$ = 309.1 Hz), 119.1, 116.2, 111.6, 56.4, 56.3. ^{19}F NMR (565 MHz, $CDCl_3$) δ −43.61 (s, 3F).

4-((Trifluoromethyl)thio)phenol (**3r**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 5:1) as a brown solid (15.5 mg, 16% yield).[12b] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, J = 8.6 Hz, 2H), 6.88−6.86 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 158.1, 138.7, 129.7 (q, C−F, $^1J_{C-F}$ = 308.1 Hz), 116.7, 115.5 (d, C−F, $^3J_{C-F}$ = 2.4 Hz). ^{19}F NMR (565 MHz, $CDCl_3$) δ −43.21 (s, 3F).

2-[(Trifluoromethyl)thio]nicotinic acid ethyl ester (**3t**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 20:1) as a light yellow solid (81.6 mg, 65% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.66 (dd, J = 4.7, 1.9 Hz), 8.29 (dd, J = 7.9, 1.9 Hz), 7.25 (dd, J = 7.9, 4.7 Hz), 4.42 (q, J = 7.1 Hz), 1.41 (t, J = 7.2 Hz). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 164.87, 156.06 (d, C−F, $^3J_{C-F}$ = 2.6 Hz), 152.60, 138.99, 128.85 (q, C−F, $^1J_{C-F}$ = 309.3 Hz), 120.94, 62.35, 14.30. ^{19}F NMR (565 MHz, $CDCl_3$) δ. −41.18 (s, 3F). HRMS (ESI): Calcd for $C_9H_9F_3NO_2S$ ([M + H]$^+$): 252.0301, found: 252.0311.

2-[(Trifluoromethyl)thio]-5-(chloro)pyridine (**3u**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 20:1) as a colorless oil (63.9 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, J = 2.4 Hz, 1H), 7.71 (dd, J = 8.4, 2.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 149.8, 147.3 (d, C−F, $^3J_{C-F}$ = 2.7 Hz), 137.5, 133.2, 129.2 (q, C−F, $^1J_{C-F}$ = 308.7 Hz), 129.1 (d, C−F, $^4J_{C-F}$ = 1.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ −40.29 (s, 3F). HRMS (ESI): Calcd for $C_6H_4ClF_3NS$ ([M + H]$^+$): 213.9700, found: 213.9709.

[(Trifluoromethyl)thio]pyrimidine (**3v**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1) as a colorless oil (70.2 mg, 78% yield).[12b] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 4.9 Hz, 2H), 7.18 (t, J = 4.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 166.0, 158.1, 128.4 (q, C−F, $^1J_{C-F}$ = 307.8 Hz), 119.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ −41.07 (s, 3F).

2-((Trifluoromethyl)thio)benzo[d]oxazole (**3w**). Purified by flash column chromatography (petroleum ether/ethyl acetate = 10:1) as a colorless oil (67.9 mg, 62% yield).[12a] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79−7.78 (m, 1H), 7.60−7.58 (m, 1H), 7.45−7.39 (m, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 152.9 (d, C−F, $^3J_{C-F}$ = 3.6 Hz), 152.5, 141.5, 127.8 (q, C−F, $^1J_{C-F}$ = 311.2 Hz), 126.6, 125.4, 120.6, 111.0. ^{19}F NMR (565 MHz, $CDCl_3$) δ −38.54 (s, 3F).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02659.

Mechanism study, gram-scale reaction and NMR spectra of the products (PDF)

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Notes

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■ REFERENCES

(1) (a) Schlosser, M. CF_3-Bearing Aromatic and Heterocyclic Building Blocks. *Angew. Chem., Int. Ed.* **2006**, *45*, 5432−5446. (b) Muller, K.; Faeh, C.; Diederich, F. Fluorine in Pharmaceuticals: Looking Beyond Intuition. *Science* **2007**, *317*, 1881−1886. (c) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. Fluorine in medicinal chemistry. *Chem. Soc. Rev.* **2008**, *37*, 320−330. (d) Bégué, J. P.; Bonnet-Delpon, D. In *Bioorganic and Medicinal Chemistry of Fluorine;* Wiley-VCH: Weinheim, Germany, 2008. (e) Uneyama, K. In *Organofluorine Chemistry;* Blackwell Publishing: Oxford, UK, 2006.

(2) Jiang, L.; Yi, W.; Liu, Q. Direct Phosphorus-Induced Fluoroalkylthiolation with Fluoroalkylsulfonyl Chlorides. *Adv. Synth. Catal.* **2016**, *358*, 3700−3705. (b) Begue, J.-P.; Bonnet-Delpon, D. Recent advances (1995−2005) in fluorinated pharmaceuticals based on natural products. *J. Fluorine Chem.* **2006**, *127*, 992−1012. (c) Isanbor, C.; O'Hagan, D. Fluorine in medicinal chemistry: A review of anti-cancer agents. *J. Fluorine Chem.* **2006**, *127*, 303−319. (d) Kirk, K. Fluorine in medicinal chemistry: Recent therapeutic applications of fluorinated small molecules. *J. Fluorine Chem.* **2006**, *127*, 1013−1029.

(3) (a) Hansch, C.; Leo, A. *Substituent constants for correlation analysis in chemistry and biology;* Wiley: New York, 1979; p 339. (b) Filler, R. *Biomedical Aspests of Fluorine Chemsitry;* Kodansha: Tokyo, Japan, 1982. (c) Yagupol'skii, L. M.; Il'chenko, A. Y.; Kondratenko, N. V. The Electronic Nature of Fluorine-containing Substituents. *Russ. Chem. Rev.* **1974**, *43*, 32−47.

(4) (a) Hagmann, W. K. The Many Roles for Fluorine in Medicinal Chemistry. *J. Med. Chem.* **2008**, *51*, 4359−4369. (b) Meanwell, N. A. Synopsis of Some Recent Tactical Application of Bioisosteres in Drug Design. *J. Med. Chem.* **2011**, *54*, 2529−2591. (c) Wang, J.; Sánchez-Roselló, M.; Aceña, J.; del Pozo, C.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (d) Landelle, G.; Panossian, A.; Leroux, F. R. Trifluoromethyl Ethers and − Thioethers as Tools for Medicinal Chemistry and Drug Discovery. *Curr. Top. Med. Chem.* **2014**, *14*, 941−951.

(5) Laczay, P.; Voros, G.; Semjen, G. Comparative studies on the efficacy of sulphachlorpyrazine and toltrazuril for the treatment of caecal coccidiosis in chickens. *Int. J. Parasitol.* **1995**, *25*, 753−756.

(6) (a) Yagupolskii, L. M.; Maletina, I. I.; Petko, K. I.; Fedyuk, D. V. *Fluorinated Bio-Active Compounds in the Agricultural and Medical Fields*, Chemical & Polymer, Brussels, Belgium, September 13−15, 1999; Paper No 17. (b) Yagupolskii, L. M.; Maletina, I. I.; Petko, K. I.; Fedyuk, D. V.; Handrock, R.; Shavaran, S. S.; Klebanov, B. M.; Herzig, S. New fluorine-containing hypotensive preparations. *J. Fluorine Chem.* **2001**, *109*, 87−94. (c) Jouvin, K.; Matheis, C.; Goossen, L. J. Synthesis of Aryl Tri- and Difluoromethyl Thioethers via a C−H-Thiocyanation/Fluoroalkylation Cascade. *Chem. - Eur. J.* **2015**, *21*, 14324−14327.

(7) Holz, W. C.; Hieble, J. P.; Gill, C. A.; De Marinis, R. M.; Pendleton, R. G. α-Adrenergic agents. 3. Behavioral effects of 2-aminotetralins. *Psychopharmacology* **1982**, *77*, 259−267.

(8) Silverstone, T.; Fincham, J.; Plumley, J. B. An evaluation of the anorectic activity in man of a sustained release formulation of tiflorex. *J. Clin. Pharmacol.* **1979**, *7*, 353−356.

(9) For selected trifluoromethylthiolation of aryldiazonium salts, see: Adams, D. J.; Goddard, A.; Clark, J. H.; Macquarrie, D. J. Trifluoromethylthiodediazoniation: a simple, efficient route to trifluoromethyl aryl sulfides. *Chem. Commun.* **2000**, 987−988. (b) Danoun, G.; Bayarmagnai, B.; Grünberg, M. F.; Goossen, L. J. Sandmeyer trifluoromethylthiolation of arenediazonium salts with sodium thiocyanate and Ruppert-Prakash reagent. *Chem. Sci.* **2014**, *5*, 1312−1316. (c) Zhao, X.; Zheng, X.; Tian, M.; Tong, Y.; Yang, B.; Wei, X.; Qiu, D.; Lu, K. Visible-light photocatalytic trifluoromethylthiolation of aryldiazonium salts: conversion of amino group into trifluoromethylthiol group. *Org. Chem. Front.* **2018**, *5*, 2636−2640.

(10) For selected trifluoromethylthiolation of halogenated aromatics, see: Adams, D. J.; Clark, J. H. Preparation of Trifluoromethyl Aryl Sulfides Using Silver(I) Trifluoromethanethiolate and an Inorganic Iodide. *J. Org. Chem.* **2000**, *65*, 1456−1460. (b) Teverovskiy, G.; Surry, D. S.; Buchwald, S. L. Pd-Catalyzed Synthesis of Ar-SCF_3 Compounds under Mild Conditions. *Angew. Chem., Int. Ed.* **2011**, *50*, 7312−7314. (c) Zhang, C.-P.; Vicic, D. A. Nickel-Catalyzed Synthesis of Aryl Trifluoromethyl Sulfides at Room Temperature. *J. Am. Chem. Soc.* **2012**, *134*, 183−185. (d) Weng, Z.; He, W.; Chen, C.; Lee, R.; Tan, D.; Lai, Z.; Kong, D.; Yuan, Y.; Huang, K.-W. An Air-Stable Copper Reagent for Nucleophilic Trifluoromethylthiolation of Aryl Halides. *Angew. Chem., Int. Ed.* **2013**, *52*, 1548−1552. (e) Rueping, M.; Tolstoluzhsky, N.; Nikolaienko, P. Copper-Catalyzed Trifluoromethyl Thiolation-Mild and Efficient Synthesis of Trifluoromethyl Thioethers. *Chem. - Eur. J.* **2013**, *19*, 14043−14046.

(11) For selected trifluoromethylthiolation of aryl boronic acids, see: Chen, C.; Xie, Y.; Chu, L.-L.; Wang, R.-W.; Zhang, X.-G.; Qing, F.-L. Copper-Catalyzed Oxidative Trifluoromethylthiolation of Aryl Boronic Acids with $TMSCF_3$ and Elemental Sulfur. *Angew. Chem., Int. Ed.* **2012**, *51*, 2492−2495. (b) Zhang, C.-P.; Vicic, D. A. Oxidative Trifluoromethylthiolations of Aryl Boronic Acids Using a Copper/O_2-Based Protocol. *Chem. - Asian J.* **2012**, *7*, 1756−1758. (c) Zhai, L.; Li, Y.; Yin, J.; Jin, K.; Zhang, R.; Fu, X.; Duan, C. Copper-mediated oxidative trifluoromethylthiolation of aryl boronic acids with CF_3CO_2Na and elemental sulfur. *Tetrahedron* **2013**, *69*, 10262−10266.

(12) For selected trifluoromethylation of thiols, see: (a) Kieltsch, I.; Eisenberger, P.; Togni, A. Mild Electrophilic Trifluoromethylation of Carbon- and Sulfur-Centered Nucleophiles by a Hypervalent Iodine(III)-CF_3 Reagent. *Angew. Chem., Int. Ed.* **2007**, *46*, 754−757. (b) Straathof, N. J. W.; Tegelbeckers, B. J. P.; Hessel, V.; Wang, X.; Noël, T. A mild and fast photocatalytic trifluoromethylation of thiols in batch and continuous-flow. *Chem. Sci.* **2014**, *5*, 4768−4773. (c) Ma, J.-J.; Yi, W.-B.; Lu, G.-P.; Cai, C. Trifluoromethylation of thiophenols and thiols with sodium trifluoromethanesulfinate and iodine pentoxide. *Catal. Sci. Technol.* **2016**, *6*, 417−421. (d) Ma, J.-J; Liu, Q.-R.; Lu, G.-P.; Yi, W.-B. Silver-catalyzed fluoroalkylation of thiols using fluoroalkanesulfinates. *J. Fluorine Chem.* **2017**, *193*, 113−117. (e) Xu, C.; Song, X.; Guo, J.; Chen, S.; Gao, J.; Jiang, J.; Gao, F.;

Li, Y.; Wang, M. Synthesis of Chloro(phenyl)trifluoromethyliodane and Catalyst-Free Electrophilic Trifluoromethylations. *Org. Lett.* **2018**, *20*, 3933−3937.

(13) For selected trifluoromethylthiolation of arenes with electrophilic trifluoromethylthiolating reagents, see: Toulgoat, F.; Alazet, S.; Billard, T. Direct trifluoromethylthiolation reactions: the "renaissance" of an old concept. *Eur. J. Org. Chem.* **2014**, *2014*, 2415−2428. (b) Chu, L.; Qing, F.-L. Oxidative trifluoromethylation and trifluoromethylthiolation reactions using (trifluoromethyl)-trimethylsilane as a nucleophilic CF_3 source. *Acc. Chem. Res.* **2014**, *47*, 1513−1522. (c) Shao, X.; Xu, C.; Lu, L.; Shen, Q. Shelf-stable electrophilic reagents for trifluoromethylthiolation. *Acc. Chem. Res.* **2015**, *48*, 1227−1236. (d) Xu, X.-H.; Matsuzaki, K.; Shibata, N. Synthetic Methods for Compounds Having CF_3−S Units on Carbon by Trifluoromethylation, Trifluoromethylthiolation, Triflylation, and Related Reactions. *Chem. Rev.* **2015**, *115*, 731−764. (e) Ferry, A.; Billard, T.; Bacque, E.; Langlois, B. R. Electrophilic trifluoromethanesulfanylation of indole derivatives. *J. Fluorine Chem.* **2012**, *134*, 160−163. (f) Xu, C.; Shen, Q. Palladium-Catalyzed Trifluoromethylthiolation of Aryl C-H Bonds. *Org. Lett.* **2014**, *16*, 2046−2049. (g) Xu, C.; Ma, B.; Shen, Q. *N*-Trifluoromethylthiosaccharin: An Easily Accessible, Shelf-Stable, Broadly Applicable Trifluoromethylthiolating Reagent. *Angew. Chem., Int. Ed.* **2014**, *53*, 9316−9320. (h) Shao, X.; Xu, C.; Lu, L.; Shen, Q. Structure-Reactivity Relationship (SAR) of Trifluoromethanesulfenates: Discovery of An Electrophilic Trifluoromethylthiolating Reagent. *J. Org. Chem.* **2015**, *80*, 3012−3021. (i) Wang, Q.; Qi, Z.; Xie, F.; Li, X. Lewis Acid-Catalyzed Electrophilic Trifluoromethylthiolation of (Hetero)Arenes. *Adv. Synth. Catal.* **2015**, *357*, 355−360. (j) Wang, D.; Carlton, C. G.; Tayu, M.; McDouall, J. J. W.; Perry, G. J. P.; Procter, D. J. Trifluoromethyl Sulfoxides: Reagents for Metal-Free C-H Trifluoromethylthiolation. *Angew. Chem., Int. Ed.* **2020**, *59*, 15918−15922.

(14) For selected trifluoromethylthiolation of other compounds, see: Chen, C.; Chu, L.-L.; Qing, F.-L. Metal-Free Oxidative Trifluoromethylthiolation of Terminal Alkynes with CF_3SiMe_3 and Elemental Sulfur. *J. Am. Chem. Soc.* **2012**, *134*, 12454−12457. (b) Tran, L. D.; Popov, I.; Daugulis, O. Copper-Promoted Sulfenylation of sp^2 C−H Bonds. *J. Am. Chem. Soc.* **2012**, *134*, 18237−18240. (c) Wang, K.-P.; Yun, S. Y.; Mamidipalli, P.; Lee, D. Silver-mediated fluorination, trifluoromethylation, and trifluoromethylthiolation of arynes. *Chem. Sci.* **2013**, *4*, 3205−3211. (d) Wu, H.; Xiao, Z.; Wu, J.; Guo, Y.; Xiao, J.-C.; Liu, C.; Chen, Q.-Y. Direct Trifluoromethylthiolation of Unactivated C(sp^3)-H Using Silver(I) Trifluoromethanethiolate and Potassium Persulfate. *Angew. Chem., Int. Ed.* **2015**, *54*, 4070−4074. (e) Li, Y.; Ye, Z.; Bellman, T. M.; Chi, T.; Dai, M. Efficient Synthesis of beta-CF_3/SCF_3-Substituted Carbonyls via Copper-Catalyzed Electrophilic Ring-Opening Cross-Coupling of Cyclopropanols. *Org. Lett.* **2015**, *17*, 2186−2189.

(15) For reviews and selected recent examples, see: Yoshida, J.; Kataoka, K.; Horcajada, R.; Nagaki, A. Modern Strategies in Electroorganic Synthesis. *Chem. Rev.* **2008**, *108*, 2265−2299. (b) Sperry, J. B.; Wright, D. L. The Application of Cathodic Reductions and Anodic Oxidations in the Synthesis of Complex Molecules. *Chem. Soc. Rev.* **2006**, *35*, 605−621. (c) Frontana-Uribe, B. A.; Little, R. D.; Ibanez, J. G.; Palma, A.; Vasquez-Medrano, R. Organic electrosynthesis: a promising green methodology in organic chemistry. *Green Chem.* **2010**, *12*, 2099−2119. (d) Francke, R.; Little, R. D. Redox Catalysis in Organic Electrosynthesis: Basic Principles and Recent Developments. *Chem. Soc. Rev.* **2014**, *43*, 2492−2521. (e) Yan, M.; Kawamata, Y.; Baran, P. S. Synthetic Organic Electrochemical Methods Since 2000: On the Verge of a Renaissance. *Chem. Rev.* **2017**, *117*, 13230−13319. (f) Song, C.; Liu, K.; Dong, X.; Chiang, C.-W.; Lei, A. Recent Advances in Electrochemical Oxidative Cross-Coupling for the Construction of C-S Bonds. *Synlett* **2019**, *30*, 1149−1163.

(16) (a) Dai, J.-J.; Huang, Y.-B.; Fang, C.; Guo, Q.-X.; Fu, Y. Electrochemical Synthesis of Adiponitrile from the Renewable Raw Material Glutamic Acid. *ChemSusChem* **2012**, *5*, 617−620. (b) Tao, X.-Z.; Dai, J.-J.; Zhou, J.; Xu, J.; Xu, H.-J. Electrochemical C-O Bond Formation: Facile Access to Aromatic Lactones. *Chem. - Eur. J.* **2018**, *24*, 6932−6935. (c) Zhou, J.; Tao, X.-Z.; Dai, J.-J.; Li, C.-G.; Xu, J.; Xu, H.-M.; Xu, H.-J. Electrochemical synthesis of 1,2-diketones from alkynes under transition-metal-catalyst-free conditions. *Chem. Commun.* **2019**, *55*, 9208−9211. (d) Yang, C.-H.; Wu, C.; Zhang, J.-M.; Tao, X.-Z.; Xu, J.; Dai, J.-J.; Xu, H.-J. Electrochemical Oxidative Esterification of Thiophenols: Efficient Access to Sulfinic Esters. *Curr. Org. Synth.* **2020**, *17*, 540−547.

(17) (a) Jiang, Y.-Y.; Dou, G.-Y.; Xu, K.; Zeng, C.-C. Bromide-catalyzed electrochemical trifluoromethylation/cyclization of *N*-arylacrylamides with low catalyst loading. *Org. Chem. Front.* **2018**, *5*, 2573−2577. (b) Dou, G.-Y.; Jiang, Y.-Y.; Xu, K.; Zeng, C.-C. Electrochemical Minisci-type trifluoromethylation of electron-deficient heterocycles mediated by bromide ions. *Org. Chem. Front.* **2019**, *6*, 2392−2397.

(18) *Preparative Electrolysis on the Laboratory Scale, Organic Electrochemistry,* 5th ed.; Jörissen, J., Speiser, B., Eds.; CRC Press, 2015; pp 263−330.

(19) (a) Huang, P.; Wang, P.; Tang, S.; Fu, Z.; Lei, A. Electro-Oxidative S-H/S-H Cross-Coupling with Hydrogen Evolution: Facile Access to Unsymmetrical Disulfides. *Angew. Chem., Int. Ed.* **2018**, *57*, 8115−8119. (b) Mo, Z.-Y.; Swaroop, T. R.; Tong, W.; Zhang, Y.-Z.; Tang, H.-T.; Pan, Y.-M.; Sun, H.-B.; Chen, Z.-F. Electrochemical sulfonylation of thiols with sulfonyl hydrazides: a metal- and oxidant-free protocol for the synthesis of thiosulfonates. *Green Chem.* **2018**, *20*, 4428−4432. (c) Li, Y.; Yang, Q.; Yang, L.; Lei, N.; Zheng, K. A scalable electrochemical dehydrogenative cross-coupling of P(O)H compounds with RSH/ROH. *Chem. Commun.* **2019**, *55*, 4981−4984. (d) Ai, C.; Shen, H.; Song, D.; Li, Y.; Yi, X.; Wang, Z.; Ling, F.; Zhong, W. Metal- and oxidant-free electrochemical synthesis of sulfinic esters from thiols and alcohols. *Green Chem.* **2019**, *21*, 5528−5531.

(20) Harsányi, A.; Dorkó, É.; Csapó, Á.; Bakó, T.; Peltz, C.; Rábai, J. Convenient synthesis and isolation of trifluoromethylthio-substituted building blocks. *J. Fluorine Chem.* **2011**, *132*, 1241−1246.

(21) Matheis, C.; Wagner, V.; Goossen, L. G. Sandmeyer-Type Trifluoromethylthiolation and Trifluoromethylselenolation of (Hetero)Aromatic Amines Catalyzed by Copper. *Chem. - Eur. J.* **2016**, *22*, 79−82.

https://dx.doi.org/10.1021/acs.joc.0c02659
J. Org. Chem. XXXX, XXX, XXX−XXX