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On-Water Synthesis of Biaryl Sulfonyl Fluorides

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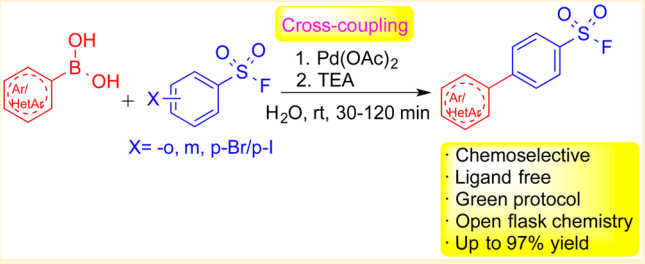
Supporting Information

ABSTRACT: Herein, we report an efficient, ligand-free, and additive-free Suzuki–Miyaura coupling that is compatible with the aromatic sulfonyl fluoride functional group. The protocol proceeds at room temperature, on water, and offers facile access to a wide range of biaryl sulfonyl fluorides as bioorthogonal "click" reagents.



Compounds containing a sulfur–fluoride bond are receiving escalating attention in both the chemical and the biological literature. Expanding on the very fruitful concept of "click-chemistry", the Sharpless laboratory recently added sulfonyl fluorides ($-SO_2F$) and fluorosulfates ($-OSO_2F$) to the list of potential "click" reagents.[1] These sulfur(VI) fluoride compounds are expected to be chemically stable until exposed to "H^+" or "R_3Si^+" ions in the presence of a suitably placed nucleophile to affect a sulfur fluoride exchange (SuFEx) process.

The need to activate the S–F bond through formation of a hydrogen bond ("H^+") in the presence of a proximal nucleophile forms the basis for sulfonyl fluorides to be used as privileged biocompatible orthogonal electrophiles in biological systems. Sulfonyl fluoride electrophiles have long been used as reactive war heads/chemical probes in chemical biology and molecular pharmacology (target identification, target validation, cellular pathway identification, and off-target identification) as recently reviewed by Jones et al.[2]

Sulfonyl fluoride reagents such as PMSF (Figure 1) are used as unselective protease inhibitors,[3] while FSBA (Figure 1) was designed to be a selective inhibitor of ATP-binding proteins.[4] Sulfonyl fluoride probes for the covalent modification of active site serine/threonine,[2,5] lysine,[2,6] tyrosine,[7] cysteine,[2,5b,6a,8] and histidine residues[2,9] have also been reported.

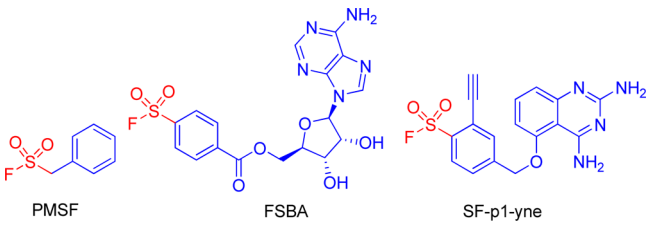


Figure 1. Some protease inhibitors encompassing a sulfonyl fluoride war head.

Given the large interest in sulfonyl fluoride-containing molecules as bioorthogonal "click" reagents, we wanted to establish robust synthetic procedures for the preparation of such derivatives. With one notable exception, these probes were so far prepared through traditional (esters, amides, nucleophilic substitution reactions, etc.) coupling between the reactive sulfonyl fluoride and the molecular framework that brings specificity to the chemical probe.[10] Very recently, the group of Jones at Pfizer reported the probe SF-p1-yne (Figure 1) in which the alkyne handle was installed as the last step through a Stille reaction.[7a] To the best of our knowledge, this is the only example where sulfonyl fluoride containing compounds have been subjected to metal-catalyzed (Pd) cross-coupling conditions that are the workhorse reactions among medicinal chemists. As a part of our continued interest in the area of sulfur chemistry method development,[11] we herein report a systematic study of sulfonyl fluoride containing substrates in the Suzuki–Miyaura (SM) reaction. Such compounds would be of interest for the development of sulfonyl fluoride chemical probes with higher selectivity toward specific protein classes and could serve as interesting reagents for chemical biology studies.[12]

Hitherto, only two methods are available in the literature for the synthesis of biaryl sulfonyl fluorides. One uses a Cu-mediated Ulmann coupling (Scheme 1a),[13] while the other employs an aromatic electrophilic substitution (Scheme 1b)[14] under high temperature; both methods have limitations such as harsh experimental conditions and low substrate scope. In this aspect, this is the first method for the preparation of substituted

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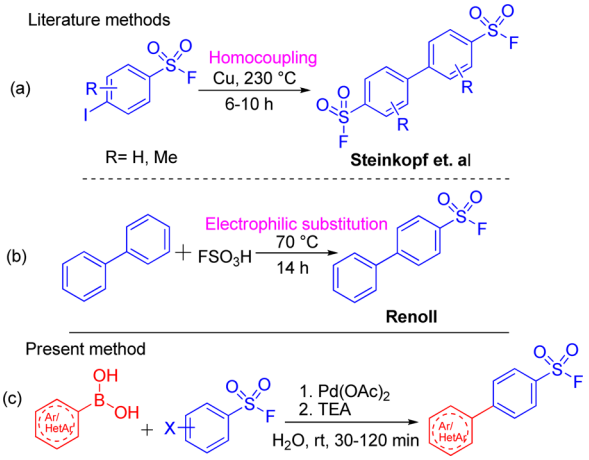
Scheme 1. Synthesis of Biaryl Sulfonyl Fluorides



biaryl sulfonyl fluorides under very mild conditions with a high substrate scope (Scheme 1c).

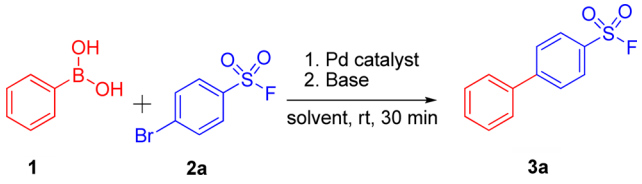
An initial attempt to prepare biaryl sulfonyl fluorides from 4-bromo sulfonyl chloride and phenylboronic acid (**1**) under Suzuki–Miyaura conditions failed. Instead, we prepared the substrate 4-bromo sulfonyl fluoride (**2a**) from 4-bromo sulfonyl chloride as described by Sharpless.[1] To investigate the sulfonyl fluoride functional group's tolerability/compatibility under Suzuki–Miyaura conditions, we set up a model reaction with phenylboronic acid (**1**, 1.5 equiv) and 4-bromo sulfonyl fluoride (**2a**, 1 equiv) in the presence of Pd/C (1 mol %); use of isopropanol as the solvent and K_2CO_3 (3 equiv) as a base under open air conditions afforded the product (**3a**) in moderate yield (Table 1, entry 1). As desired, the coupling reaction took place chemoselectively at the bromide, thus sparing the sulfonyl fluoride group (Scheme 2). It should be noted that Sharpless and Jian, and Hanley, recently reported the use of fluorosulfonates as an alternative to the halogen leaving group in an SM reaction; in these cases, the −OS(O)2F was expelled without decomposition of the S−F bond.[15]

Table 1. Evaluation of Different Pd Catalysts for Biaryl Coupling of Compounds 1 and 2a

entry	Pd catalyst (mol %)[a]	solvent (mL)[b]	base (equiv)[c]	time (min)	yield (%)
1	Pd/C	*i*-PrOH	K_2CO_3	60	52
2	$Pd(PPh_3)_4$	*i*-PrOH	K_2CO_3	60	66
3	$Pd_2(dba)_3$	*i*-PrOH	K_2CO_3	60	63
4	$Pd(PPh_3)_2Cl_2$	*i*-PrOH	K_2CO_3	60	41
5	RuPhosPd	*i*-PrOH	K_2CO_3	60	10
6	$Pd(OAc)_2$	*i*-PrOH	K_2CO_3[d]	60	81

[a]In all cases, 1 mol % various Pd catalysts were used in each reaction. [b]1 mL of solvent *i*-PrOH was used. [c]3 equiv of base K_2CO_3 was used. [d]Biaryl sulfonic acid formed as a side product through hydrolysis.

Scheme 2. General Scheme for Biaryl Sulfonyl Fluorides Synthesis



Having preliminary results in hand, we screened diverse Pd catalysts such as $Pd(PPh_3)_4$, $Pd_2(dba)_3$, $Pd(PPh_3)_2Cl_2$, RuPhos Pd(II) phenyl ethylamine chloride (1:1 MTBE solvate), and $Pd(OAc)_2$ to improve the reaction yield. All catalysts produced the product **3a** in moderate to good yield (Table 1 entries 1–5). $Pd(OAc)_2$ appeared to give the highest yield (81% yield) (Table 1, entry 6), despite the fact that we noted some degree of hydrolysis of the sulfonyl fluoride to sulfonic acid with the base.

Continuing to optimize the reaction conditions, we next evaluated the effect of different organic solvents and bases. Henceforth, we carried out a series of experiments using different bases such as TEA, DIPEA, Cs_2CO_3, NaOAc, and phosphate buffer along with a control reaction without any base. The organic bases TEA and DIPEA gave the best yields (also within 60 min reaction time) (Table 2, entries 1 and 2). In the case of inorganic bases (K_2CO_3, Cs_2CO_3, NaOAc), moderate yields were observed (57–83%) (Table 2, entries 3 and 4) after 60 min, and we noted some remaining unreacted starting material. Prolonging the reaction time further led to formation of diary sulfonic acid for some of the substrates (**3a**, **3k**, **3l**, etc.) in approximately 39%. We could not observe a clear trend for this hydrolysis depending on the electronic properties of the reactants, but we could establish that this byproduct formation depended on the strength of the inorganic base used, i.e., Cs_2CO_3 > K_2CO_3 > NaOAc, by resubmitting the products (**3a**, **3k**, **3l**, etc.) to the reaction conditions. Phosphate buffer, and the control reaction without any base, gave sluggish reactions (Table 2, entries 5 and 6). The results are summarized in Table 2. The organic bases were probably more efficient in this reaction, since they could reduce Pd(II) species more efficiently than the water-soluble bases under ligand-free condition.[16]

Next, we studied how various solvents influenced reaction time, yield, and the sulfonyl fluoride functional group compatibility. Henceforth, we again carried out a series of experiments using different solvent systems such as MeOH, MeOH:H_2O, H_2O, CH_3CN, CH_2Cl_2, and toluene. Interestingly, we found that H_2O offered a clean formation of the biaryl sulfonyl fluoride product (97%) within 30 min (Table 3, entry 3). Further overnight stirring did not affect biaryl sulfonyl fluoride hydrolysis. The other solvent systems evaluated gave moderate to good yields (61–96%). The results are summarized in Table 3. Water has been reported to enhance the reaction rate of Suzuki–Miyaura reactions due to increased solubility of the arylboronic acid.[17] However, we observed that the reaction mixture was cloudy at the start due to limited solubility of the reactants in water, then the reaction mixture cleared up during the course of reaction, and subsequently formed a precipitate of the product. That is, the reaction proceeded on water and the sulfonyl fluoride product was protected from hydrolysis through the precipitation.[18] The unique characteristic of the *on-water* reaction made us conclude that the optimal conditions were obtained with water as a solvent, TEA as a base, and $Pd(OAc)_2$ as a catalyst.

To establish the substrate scope, the optimized reaction conditions were then applied to a wide range of aryl, heteroarylboronic acids, and halo phenyl sulfonyl fluorides to deliver the corresponding biaryl sulfonyl fluorides (Figure 2). The effect of different electron-donating as well as electron-withdrawing groups on arylboronic acids was studied, and no

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Table 2. Evaluation of Different Bases for Pd-Catalyzed Biaryl Coupling for Compounds 1 and 2a

entry	Pd catalyst (mol %)[a]	solvent (mL)[b]	base (equiv)[c]	time (min)	yield (%)
1	$Pd(OAc)_2$	*i*-PrOH	TEA	60	91
2	$Pd(OAc)_2$	*i*-PrOH	DIPEA	60	90
3	$Pd(OAc)_2$	*i*-PrOH	Cs_2CO_3[d]	60	83
4	$Pd(OAc)_2$	*i*-PrOH	NaOAc	60	57
5	$Pd(OAc)_2$	*i*-PrOH	phosphate buffer	60	50
6	$Pd(OAc)_2$	*i*-PrOH	none	60	30

[a]In all cases, 1 mol % catalyst was used in each reaction. [b]1 mL of *i*-PrOH was used. [c]3 equiv of various bases was used. [d]Biaryl sulfonic acid formed as a side product through hydrolysis.

Table 3. Evaluation of Different Bases for Pd-Catalyzed Biaryl Coupling for Compounds 1 and 2a

entry	Pd catalyst (mol %)[a]	solvent (mL)[b]	base (equiv)[c]	time (min)	yield (%)
1	$Pd(OAc)_2$	MeOH	TEA	30	61
2	$Pd(OAc)_2$	MeOH:H_2O	TEA	30	68
3	$Pd(OAc)_2$	H_2O	TEA	30	97
4	$Pd(OAc)_2$	CH_3CN	TEA	60	83
5	$Pd(OAc)_2$	CH_2Cl_2	TEA	60	96
6	$Pd(OAc)_2$	toluene	TEA	60	95

[a]In all cases, 1 mol % catalyst was used in each reaction. [b]1 mL of various solvents was used. [c]3 equiv of TEA base was used.

remarkable difference was observed on reaction yield under aerobic conditions. In general, the reaction proceeded efficiently with *para*- and *meta*-substituted aryl boronic acids. In the case of *ortho*-disubstituted boronic acid, the yield was drastically reduced to 67% (**3n**), due to steric hindrance during the transmetalation step.[19] In the case of *ortho*-monosubstituted boronic acids, the reaction yield was unaffected, offering 90% and 97% yields for **3g** and **3m**, respectively. Heteroaromatic (**3b**) and alkenyl (**3j**) analogues also furnished good yields. Gratifyingly, 2-naphthylboronic acid also gave a good yield. It is also worth noting that, with this catalytic system, only an insignificant amount of homocoupling product was formed under these conditions. Figure 2 illustrates that the contemporary method is applicable for a vast range of boronic acids.

An attempt to extend the current method to benzylic sulfonyl fluorides, i.e., 4-bromo benzyl sulfonyl fluoride (4-Br PMSF), unfortunately failed (even at room temperature) due to decomposition of the benzylic substrate through sulfene formation—a known liability of these kinds of substrates.[1,20]

In summary, we have developed a robust method to access substituted biaryl sulfonyl fluorides under mild reaction conditions using a Suzuki–Miyaura coupling protocol on water. The reported method applies to *p*-iodo and *p*/*m*/*o*-bromo sulfonyl fluorides, and the reactivity order is I-Ar-SO_2F > Br-Ar-SO_2F. The reaction proceeds smoothly at room temperature and offers good yields within a short reaction time using 1 mol % catalyst and 3 mol % base. The present method works well for a variety of aryl-, heteroaryl-, and alkenylboronic acids. Given the wide utility of sulfonyl fluorides as covalent enzyme inhibitors, and more recently as postulated new "click"

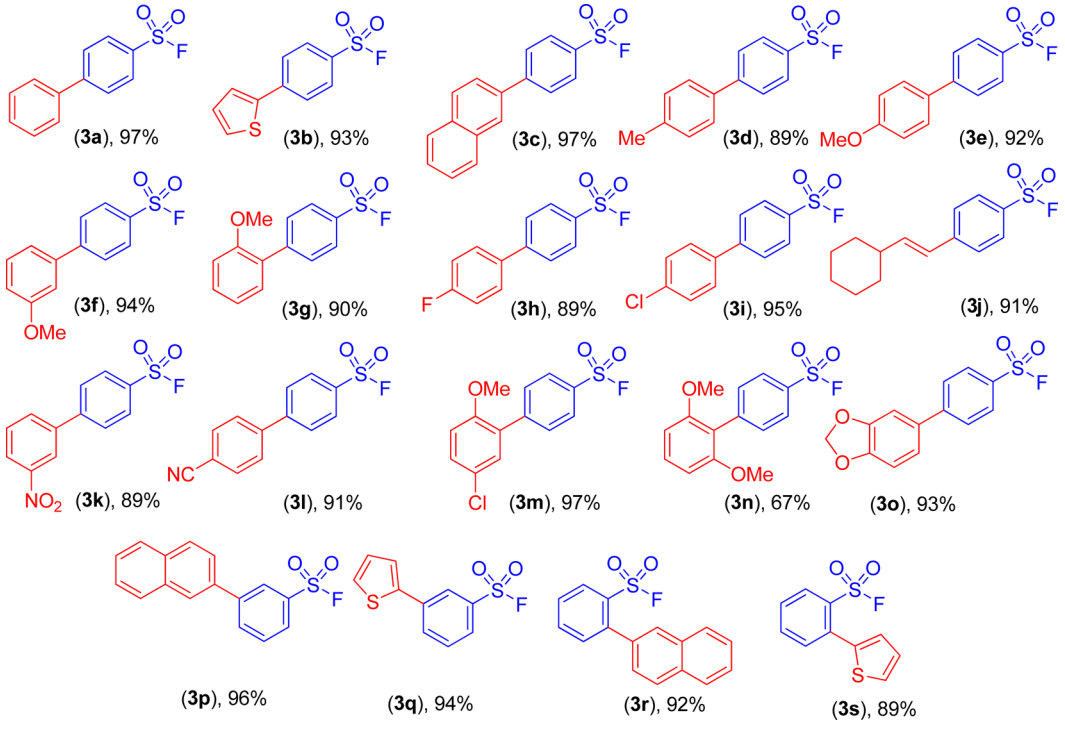

Figure 2. Substrate scope for the Suzuki–Miyaura coupling reaction of 4-bromo/iodo phenyl sulfonyl fluoride with various aryl/alkenyl boronic acids.

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reagents, we anticipate that the current protocol will find broad utility for the synthesis of sulfonyl fluoride derivatives with specifically tuned properties (e.g., selectivity, solubility, reactivity, etc.).

EXPERIMENTAL SECTION

General Information. All commercially available starting materials (Pd catalysts, ligands, sulfonyl chlorides, and alkenyl/arylboronic acids) were purchased from various suppliers and used as received. Solvents were of reagent grade and dried prior to use. Chemical reactions were monitored with thin-layer chromatography using precoated silica gel plates. Flash column chromatography was performed on silica gel 60−120. ^{1}H, ^{19}F, and ^{13}C spectra were recorded on 400 and 600 MHz instruments in $CDCl_3$, using the residual signals from $CDCl_3$ (^{1}H: δ = 7.26 ppm; ^{13}C: δ = 77.16 ppm) as internal standard. IR spectra were recorded on an ATR-IR spectrometer. GC−MS were recorded on an Ultra spectrometer. Melting points were uncorrected.

General Procedure for the Synthesis of Biaryl Sulfonyl Fluorides. 4-Br-sulfonyl fluoride (100 mg, 0.41 mmol, 1.0 equiv), aryl/alkenylboronic acid (0.62 mmol, 1.5 equiv), $Pd(OAc)_2$ (1.0 mg, 1 mol %), triethylamine (175 μL, 1.2 mmol, 3.0 equiv), and water (5.0 mL) were added to a pear-shaped round-bottom flask equipped with a magnetic stir bar. The resulting reaction mixture was stirred at room temperature in open air. The reaction progress was monitored using TLC. Upon completion, the reaction mixture was diluted with ethyl acetate/dichloromethane (20 mL) and washed with water (3 × 15 mL), followed by brine solution (3 × 15 mL). The organic layer was dried over anhydrous $MgSO_4$ and concentrated under vacuum. The crude product was purified by column chromatography using 2−4% of ethyl acetate in hexane as the eluent.

*Biphenyl-4-sulfonyl Fluoride (**3a**).* (Prepared from 4-Br-sulfonyl-fluoride) White solid (96 mg, 97% yield), R_f = 0.30 (4% ethyl acetate/hexane), mp 65−66 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (2H, d, J = 8.50 Hz), 7.82 (2H, d, J = 8.50 Hz), 7.64−7.60 (2H, m), 7.53−7.44 (3H, m) ppm. ^{19}F NMR: δ 66.45 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 148.8, 138.7, 131.7 (d, J = 24.73 Hz), 129.39 (2CH), 129.32, 129.1 (2CH), 128.3 (2CH), 127.6 (2CH) ppm. IR (ATR): ν = 2922, 1735, 1587, 1562, 1460, 1405, 1319, 1186, 673, 588 cm^{-1}. HRMS (EI): m/z calcd for $C_{12}H_9FO_2S$ [M]$^{+\cdot}$ 236.0307, found 236.0299.

*4-(Thiophen-2-yl) Benzene-1-sulfonyl Fluoride (**3b**).* (Prepared from 4-Br-sulfonylfluoride) White solid (94 mg, 93% yield), R_f = 0.30 (4% ethyl acetate/hexane), mp 117−118 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.0 (2H, d, J = 8.60 Hz), 7.82 (2H, d, J = 8.60 Hz), 7.49 (1H, dd, J = 3.92, 1.5 Hz), 7.45 (1H, d, J = 5.4 Hz), 7.17−7.15 (1H, m) ppm. ^{19}F NMR: δ 66.46 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 141.6, 141.4, 131.2 (d, J = 26.97 Hz), 129.3 (2CH), 128.8, 128.1, 126.5 (2CH), 126.1 ppm. IR (ATR): ν = 2196, 2109, 1942, 1699, 1559, 1488, 1352, 1189, 650, 584 cm^{-1}. HRMS (APCI): m/z calcd for $C_{10}H_8FO_2S_2$ [M + H]$^{+}$ 242.9944, found 242.9946.

*4-(Naphthalen-2-yl) Benzene-1-sulfonyl Fluoride (**3c**).* (Prepared from 4-Br-sulfonylfluoride) White solid (116 mg, 97% yield), R_f = 0.30 (4% ethyl acetate/hexane), mp 99−100 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.12−8.10 (3H, m), 7.99−7.89 (5H, m), 7.73 (1H, d, J = 8.31 Hz), 7.57−7.55 (2H, m) ppm. ^{19}F NMR: δ 66.54 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 148.7, 135.9, 133.6, 133.5, 131.7 (d, J = 24.09 Hz), 129.3, 129.2 (2CH), 128.6, 128.5 (2CH), 127.9, 127.2, 127.1, 127.0, 124.9 ppm. IR (ATR): ν = 3052, 2360, 1589, 1437, 1396, 1184, 1147, 641, 614, 566 cm^{-1}. HRMS (APCI): m/z calcd for $C_{16}H_{12}FO_2S$ [M + H]$^{+}$ 287.0537, found 287.0528.

*4′-Methylbiphenyl-4-sulfonyl Fluoride (**3d**).* (Prepared from 4-Br-sulfonylfluoride) White solid (93 mg, 89% yield), R_f = 0.35 (4% ethyl acetate/hexane), mp 120−121 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (2H, d, J = 8.54 Hz), 7.80 (2H, d, J = 8.55 Hz), 7.53 (2H, d, J = 8.04 Hz), 7.31 (2H, d, J = 8.05 Hz), 2.43 (3H, s) ppm. ^{19}F NMR: δ 66.49 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 148.7, 139.5, 135.7, 131.2 (d, J = 24.37 Hz), 130.1 (2CH), 129.0 (2CH), 128.0 (2CH), 127.4 (2CH), 21.34 ppm. IR (ATR): ν = 2338, 1921, 1590, 1558, 1517, 1479, 1189, 634, 566, 521 cm^{-1}. HRMS (EI): m/z calcd for $C_{13}H_{11}FO_2S$ [M]$^{+\cdot}$250.0464, found 250.0474.

*4′-Methoxy-[1,1′-biphenyl]-4-sulfonyl Fluoride (**3e**).* (Prepared from 4-Br-sulfonylfluoride) White solid (102 mg, 92% yield), R_f = 0.30 (5% ethyl acetate/hexane), mp 84−85 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.03 (2H, d, J = 8.52 Hz), 7.77 (2H, d, J = 8.46 Hz), 7.57 (2H, d, J = 8.64), 7.02 (2H, d, J = 8.88 Hz), 3.87 (3H, s) ppm. ^{19}F NMR: δ 66.52 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 160.8, 148.3, 130.9, 130.8 (d, J = 23.41 Hz), 129.1 (2CH), 128.8 (2CH), 127.6 (2CH), 114.8 (2CH), 55.6 ppm. IR (ATR): ν = 2364, 1588, 1558, 1440, 1135, 663, 634, 621, 577, 556 cm^{-1}. HRMS (APCI): m/z calcd for $C_{13}H_{12}FO_3S$ [M + H]$^{+}$ 267.0486, found 267.0483.

*3′-Methoxy-[1,1′-biphenyl]-4-sulfonyl Fluoride (**3f**).* (Prepared from 4-Br-sulfonylfluoride) White solid (104 mg, 94% yield), R_f = 0.30 (5% ethyl acetate/hexane), mp 52−53 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.06 (2H, d, J = 8.34 Hz), 7.80 (2H, d, J = 8.34 Hz), 7.41 (1H, d, J = 8.3 Hz), 7.19 (1H, d, J = 7.59 Hz), 7.13 (1H, d, J = 2.25 Hz), 7.0 (1H, dd, J = 8.3, 2.35 Hz), 3.88 (3H, s) ppm. ^{19}F NMR: δ 66.45 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 160.4, 148.6, 140.1, 131.6 (d, J = 24.10 Hz), 130.4, 129.0 (2CH), 128.4 (2CH), 120.0, 114.5, 113.5, 55.5 ppm. IR (ATR): ν = 2967, 2841, 1590, 1563, 1436, 1320, 1117, 633, 540, 502 cm^{-1}. HRMS (APCI): m/z calcd for $C_{13}H_{12}FO_3S$ [M + H]$^{+}$ 267.0486, found 267.0482.

*2′-Methoxy-[1,1′-biphenyl]-4-sulfonyl Fluoride (**3g**).* (Prepared from 4-Br-sulfonylfluoride) White solid (100 mg, 90% yield), R_f = 0.30 (5% ethyl acetate/hexane), mp 82−83−00 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.03 (2H, d, J = 8.40 Hz), 7.80 (2H, d, J = 8.40 Hz), 7.43−7.40 (1H, m), 7.32 (1H, dd, J = 7.58, 1.49 Hz), 7.08 (1H, d, J = 7.5 Hz), 7.03 (1H, d, J = 8.25 Hz), 3.84 (3H, s) ppm. ^{19}F NMR: δ 66.35 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 156.5, 146.6, 131.1, 131.0 (d, J = 24.09 Hz), 130.8 (2CH), 130.5 (2CH), 128.2 (2CH), 121.3, 111.6, 55.7 ppm. IR (ATR): ν = 2940, 2837, 1590, 1501, 1437, 1398, 1187, 633, 549, 516 cm^{-1}. HRMS (APCI): m/z calcd for $C_{13}H_{12}FO_3S$ [M + H]$^{+}$ 267.0486, found 267.0484.

*4′-Fluorobiphenyl-4-sulfonyl Fluoride (**3h**).* (Prepared from 4-Br-sulfonylfluoride) White solid (94 mg, 89% yield), R_f = 0.41 (4% ethyl acetate/hexane), mp 87−88 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (2H, d, J = 8.53 Hz), 7.78 (2H, d, J = 8.48 Hz), 7.62−7.57 (2H, m), 7.23−7.17 (2H, m) ppm. ^{19}F NMR: δ 66.44 (1F, s), −112.25 (m) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 163.66 (d, J = 248 Hz), 147.7, 134.8, 131.7 (d, J = 24.15 Hz), 129.4, 129.3, 129.1 (2CH), 128.1 (2CH), 116.5, 116.3 ppm. IR (ATR): ν = 2918, 1592, 1515, 1481, 1186, 1162, 633, 568, 554, 523 cm^{-1}. HRMS (EI): m/z calcd for $C_{12}H_8F_2O_2S$ [M]$^{+\cdot}$254.0213, found 254.0212.

*4′-Chlorobiphenyl-4-sulfonyl Fluoride (**3i**).* (Prepared from 4-Br-sulfonylfluoride) White solid (107 mg, 95% yield), R_f = 0.40 (4% ethyl acetate/hexane), mp 133−134 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.07 (2H, d, J = 8.52 Hz), 7.78 (2H, d, J = 8.59 Hz), 7.57−7.54 (2H, m), 7.49−7.46 (2H, m) ppm. ^{19}F NMR: δ 66.43 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 147.5, 137.1, 135.7, 131.9 (d, J = 23.83 Hz), 129.6 (2CH), 129.2 (2CH), 128.8 (2CH), 128.2 (2CH) ppm. IR (ATR): ν = 2850, 1588, 1559, 1473, 1403, 1387, 1304, 1188, 608, 556 cm^{-1}. HRMS (EI): m/z calcd for $C_{12}H_8ClFO_2S$ [M]$^{+\cdot}$269.9918, found 269.9910.

*(E)-4-(2-Cyclohexylvinyl) Benzene-1-sulfonyl Fluoride (**3j**).* (Prepared from 4-Br-sulfonylfluoride) White solid (102 mg, 91% yield), R_f = 0.30 (4% ethyl acetate/hexane), mp 56−57 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.9 (2H, d, J = 8.39 Hz), 7.53 (2H, d, J = 8.39 Hz), 6.40 (2H, dd, J = 16, 4.24 Hz), 2.21−2.16 (1H, m), 1.83−1.77 (4H, m), 1.72−1.68 (1H, m), 1.37−1.30 (2H, m), 1.25−1.17 (3H, m) ppm. ^{19}F NMR: δ 66.44 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 145.7, 142.8, 130.5 (d, J = 24.16 Hz), 128.9 (2CH), 126.8 (2CH), 125.7, 41.4, 32.6, ($3CH_2$), 26.1, 26.0 ppm. IR (ATR): ν = 2923, 1566, 1489, 1464, 1364, 1182, 794, 693, 630, 560 cm^{-1}. HRMS (EI): m/z calcd for: $C_{14}H_{17}FO_2S$ [M]$^{+\cdot}$268.0933, found 268.0942.

*3′-Nitro-[1,1′-biphenyl]-4-sulfonyl Fluoride (**3k**).* (Prepared from 4-Br-sulfonylfluoride) White solid (100 mg, 89% yield), R_f = 0.30 (5% ethyl acetate/hexane), mp 108−109 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.49 (1H, d, J = 2.20 Hz), 8.33 (1H, dd, J = 8.33, 1.75 Hz), 8.15 (2H, d, J = 8.33 Hz), 7.95 (1H, d, J = 7.72 Hz), 7.87 (2H, d, J =

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8.4 Hz), 7.71 (1H, d, J = 8.1 Hz) ppm. ^{19}F NMR: δ 66.41 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 149.1, 146.0, 140.3, 133.3, 133.0 (d, J = 25.21 Hz), 130.5, 129.5 (2CH), 128.5 (2CH), 123.9, 122.5 ppm. IR (ATR): ν = 2924, 1593, 1527, 1474, 1349, 1192, 656, 629, 595, 541 cm^{-1}. HRMS (EI): m/z calcd for $C_{12}H_8FNO_4S$ [M]$^{+\bullet}$281.0158, found 281.0168.

*4′-Cyano-[1,1′-biphenyl]-4-sulfonyl Fluoride (**3l**).* (Prepared from 4-Br-sulfonylfluoride) White solid (99 mg, 91% yield), R_f = 0.40 (6% ethyl acetate/hexane), mp 129−130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (2H, d, J = 8.0 Hz), 7.84−7.80 (4H, m), 7.73 (2H, d, J = 7.84 Hz) ppm. ^{19}F NMR: δ 66.37 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 146.5, 142.9, 133.1 (2CH), 132.8 (d, J = 20.64 Hz), 129.3 (2CH), 128.6 (2CH), 128.3 (2CH), 118.3, 113.0 ppm. IR (ATR): ν = 2918, 2850, 2224, 1591, 1484, 1312, 1111, 647, 570, 554 cm^{-1}. HRMS (APCI): m/z calcd for $C_{13}H_9FNO_2S$ [M + H]$^+$ 262.0333, found 262.0334.

*5′-Chloro-2′-methoxy-[1,1′-biphenyl]-4-sulfonyl Fluoride (**3m**).* (Prepared from 4-Br-sulfonylfluoride) White solid (122 mg, 97% yield), R_f = 0.30 (5% ethyl acetate/hexane), mp 57−58 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.03 (2H, d, J = 8.38 Hz), 7.74 (2H, d, J = 8.38 Hz), 7.35 (1H, d, J = 8.9, 2.9 Hz), 7.29 (1H, d, J = 2.66 Hz), 6.94 (1H, d, J = 8.64 Hz), 3.82 (3H, s) ppm. ^{19}F NMR: δ 66.28 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 155.2, 145.1, 131.8 (d, J = 24.48 Hz), 130.7 (2CH), 130.5, 130.0, 129.6, 128.3 (2CH), 126.3, 112.9, 56.1 ppm. IR (ATR): ν = 2971, 2840, 1592, 1561, 1439, 1386, 1175, 680, 644, 531 cm^{-1}. HRMS (EI): m/z calcd for $C_{13}H_{10}ClFO_3S$ [M]$^{+\bullet}$300.0023, found 300.0027.

*2′,6′-Dimethoxy-[1, 1′-biphenyl]-4-sulfonyl Fluoride (**3n**).* (Prepared from 4-Br-sulfonylfluoride) White solid (83 mg, 67% yield), R_f = 0.30 (6% ethyl acetate/hexane), mp 128−129 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.91 (2H, d, J = 8.24 Hz), 7.6 (2H, d, J = 8.24 Hz), 7.34 (1H, d, J = 8.34 Hz), 6.67 (2H, d, J = 8.34 Hz), 3.75 (6H, s) ppm. ^{19}F NMR: δ 66.15 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 157.5 (2C), 142.8, 132.5 (2CH), 130.9 (d, J = 24.57 Hz), 130.3, 127.7 (2CH), 117.1, 104.3 (2CH), 56.0 (2CH3) ppm. IR (ATR): ν = 2935, 2839, 1599, 1590, 1432, 1301, 1181, 643, 583, 555 cm^{-1}. HRMS (APCI): m/z calcd for $C_{14}H_{14}FO_4S$ [M + H]$^+$ 297.0591, found 297.0591.

*4-(Benzo[d][1,3]dioxol-5-yl)benzene-1-sulfonyl Fluoride (**3o**).* (Prepared from 4-Br-sulfonylfluoride) White solid (109 mg, 93% yield), R_f = 0.30 (5% ethyl acetate/hexane), mp 104−105 °C. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.03 (2H, d, J = 8.64 Hz), 7.73 (2H, d, J = 8.46 Hz), 7.12−7.08 (2H, m), 6.93 (1H, d, J = 8.04 Hz), 6.04 (2H, s) ppm. ^{19}F NMR: δ 66.49 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz): δ 148.89, 148.83, 148.4, 132.8, 131.1 (d, J = 24.09 Hz), 129.1 (2CH), 127.8 (2CH), 121.7, 109.1, 107.7, 101.7 ppm. IR (ATR): ν = 2918, 1592, 1566, 1439, 1309, 1154, 670, 619, 562, 544 cm^{-1}. HRMS (APCI): m/z calcd for $C_{13}H_{10}FO_4S$ [M + H]$^+$ 281.0276, found 281.0278.

*3-(Naphthalen-2-yl)benzene-1-sulfonyl Fluoride (**3p**).* (Prepared from 3-Br-sulfonylfluoride) Semisolid (114 mg, 96% yield), R_f = 0.30 (3% ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (1H, m), 8.09 (1H, d, J = 8.14 Hz), 8.07 (1H, s), 8.01 (1H, d, J = 8.14 Hz), 7.97 (1H, d, J = 8.55 Hz), 7.94−7.88 (2H, m), 7.75−7.70 (2H, m), 7.58−7.52 (2H, m) ppm. ^{19}F NMR: δ 66.04 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 143.2, 135.6, 134.3, 134.0, 133.8, 133.6(d, J = 24.15 Hz), 133.2, 130.3, 129.2, 128.4, 127.8, 127.1, 126.9, 126.9, 126.6, 124.8 ppm. IR (ATR): ν = 2921, 1796, 1482, 1412, 1311, 1232, 821, 788, 656, 527 cm^{-1}. HRMS (APCI): m/z calcd for $C_{16}H_{12}FO_2S$ [M + H]$^+$ 287.0537, found 287.0534.

*3-(Thiophen-2-yl)benzene-1-sulfonyl Fluoride (**3q**).* (Prepared from 3-Br-sulfonylfluoride) Semisolid (95 mg, 94% yield), R_f = 0.50 (2.5% ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.2−8.19 (1H, m), 7.96 (1H, d, J = 8.0 Hz), 7.89 (1H, d, J = 8.0 Hz), 7.65−7.61 (1H, m), 7.43−7.39 (2H, m), 7.15−7.13 (1H, m) ppm. ^{19}F NMR: δ 65.82 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 141.11, 136.58, 133.91 (d, J = 24.15 Hz), 132.62, 130.39, 128.67, 127.04, 126.73, 125.32, 125.24 ppm. IR (ATR): ν = 2922, 1726, 1564, 1399, 1207, 761, 723, 583, 541, 485 cm^{-1}. HRMS (APCI): m/z calcd for $C_{10}H_8FO_2S_2$ [M + H]$^+$ 242.9944, found 242.9946.

*2-(Naphthalen-2-yl)benzene-1-sulfonyl Fluoride (**3r**).* (Prepared from 2-Br-sulfonylfluoride) Semisolid (109 mg, 92% yield), R_f = 0.30 (3% ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.22 (1H, dd, J = 8.10, 1.06 Hz), 7.93−7.86 (4H, m), 7.8−7.76 (1H, m), 7.64−7.60 (1H, m), 7.56−7.54 (1H, m), 7.50 (1H, dd, J = 8.51, 1.02 Hz) ppm. ^{19}F NMR: δ 67.38 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 143.1, 135.4, 134.8, 133.4, 133.1, 132.8, 132.5 (d, J = 22.13 Hz), 130.17, 130.16, 128.44, 128.42, 128.4, 127.9, 127.7, 126.8, 126.7 ppm. IR (ATR): ν = 2923, 1590, 1483, 1209, 1103, 859, 820, 762, 670, 529 cm^{-1}. HRMS (APCI): m/z calcd for $C_{16}H_{12}FO_2S$ [M + H]$^+$ 287.0532, found 287.0537.

*2-(Thiophen-2-yl)benzene-1-sulfonyl Fluoride (**3s**).* (Prepared from 2-Br-sulfonylfluoride) Semisolid (90 mg, 89% yield), R_f = 0.50 (2.5% ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.19 (1H, d, J = 8.0 Hz), 7.76−7.72 (1H, m), 7.63−7.57 (2H, m), 7.47 (1H, d, J = 4.0 Hz), 7.29−7.28 (1H, m), 7.14−7.11 (1H, m) ppm. ^{19}F NMR: δ 65.49 (1F, s) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 137.27, 135.43, 134.65, 134.20, 133.11, 132.90 (d, J = 21.13 Hz), 130.48, 129.3, 127.48, 127.33 ppm. IR (ATR): ν = 2921, 1803, 1561, 1400, 1265, 850, 762, 701, 660, 584 cm^{-1}. HRMS (APCI): m/z calcd for $C_{10}H_8FO_2S_2$ [M + H]$^+$ 242.9933, found 242.9946.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02770.

Full characterization data (^{1}H, ^{19}F, ^{13}C, GC−MS, and HRMS) with copies of spectra for all the compounds (PDF)

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Notes

The authors declare no competing financial interest.

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