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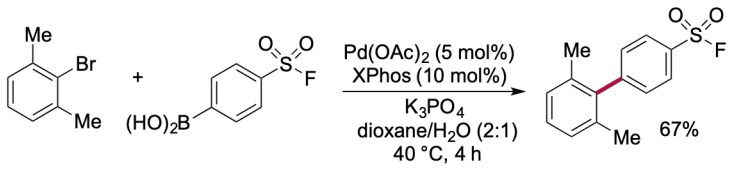

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Arylsulfonyl fluoride boronic acids: Preparation and coupling reactivity

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This paper is dedicated to Professor Steve Davies in recognition of his contributions to organic chemistry

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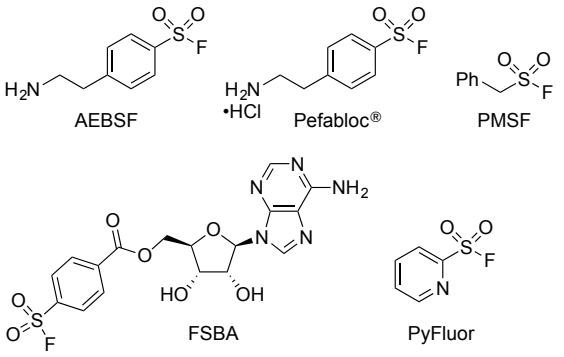
ABSTRACT

We report the efficient and practical syntheses of *ortho*-, *meta*, and *para*-sulfonyl fluoride substituted benzene boronic acids. The syntheses of the *para*- and *meta*-isomers commence with the appropriate bromo-substituted benzenesulfonyl chlorides, and the *ortho*-isomer is prepared from benzenesulfonyl fluoride. The *para*- and *meta*-substituted boronic acids undergo efficient Sukuki-Miyaura coupling reactions with a range of aryl halides. We also report an efficient Rh(I)-catalyzed conjugate addition reaction using the *para*-substituted boronic acid.

1. Introduction

The balance of reactivity and stability available in sulfonyl fluorides has made them popular motifs in medicinal chemistry[1] and chemical biology.[2] Their stability to physiological hydrolysis, their utility in SuFEx click chemistry,[3] and the ability to act as fluorinating reagents, has resulted in a variety of applications. Scheme 1 illustrates this with examples of serine protease inhibitors (AEBSF, Pefabloc and PMSF),[4] the probe reagent FBSA,[5] and Doyle's PyFluor[6] fluorinating reagent.

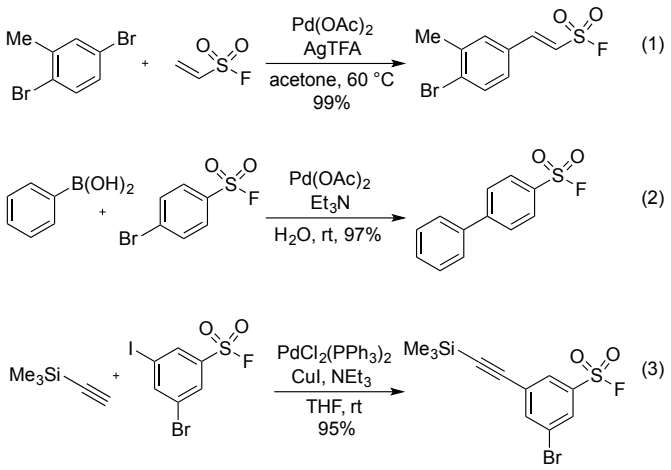


Scheme 1. Sulfonyl fluorides in medicinal chemistry, as chemical probes, and as fluorinating reagents.

The most common method to prepare sulfonyl fluorides is by chloride to fluoride exchange using the corresponding sulfonyl chlorides. These reactions typically use toxic potassium bifluoride, or potassium fluoride in combination with 18-crown-6. In addition, sulfonyl chlorides can often show limited stability, and can be challenging to prepare and purify.[7] Sulfonates, and various sulfonate-derivatives such as sulfonylhydrazides,[8] can also be transformed into sulfonyl flourides, although these approaches can be limited by the availability of the required substrates. Aryl halides and alkenyl triflates have been exploited as sulfonyl fluoride precursors *via* palladium-catalyzed sulfination chemistry, using sulfur dioxide surrogates,[9] followed by electrophilic fluorination.[10] Sulfonyl fluoride synthesis by the electrochemical oxidation of thiols has recently been reported.[11]

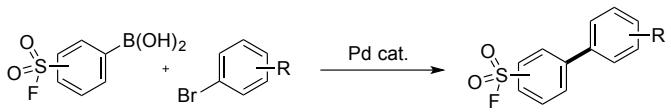
The chemical stability present in sulfonyl flourides has allowed alternative approaches to these motifs based on the functionalization of molecules containing a pre-existing sulfonyl fluoride functional group. A useful example of this is the use of ethenesulfonyl fluoride (ESF) in a variety of conjugate addition-type processes.[12] The stability of sulfonyl fluorides has also been exploited in a number of transition metal-catalyzed reactions, and this chemistry has recently been reviewed by Chinthakindi and Arvidsson.[13] Reaction 1 of Scheme 2 is illustrative, and shows ESF being employed as the alkene component in a Heck coupling with an aryl halide.[14] Related Heck-type reactions using aryl boronic acids,[15] and also aryl diazonium salts,[16] both in combination with ESF and palladium catalysts have also been reported. Aryl halides substituted with sulfonyl fluorides have been used as cross-coupling partners in Suzuki-Miyaura reactions (reaction 2, Scheme 2),[17] in Sonogashira coupling reactions (reaction 3, Scheme 2),[2a] in Stille coupling,[2d] and in a Negishi cross-coupling reaction with diethylzinc.[17b] In addition to these palladium-catalyzed processes, sulfonyl fluorides have also been shown to be

tolerant to certain copper-,[18] iridium-,[2a] and rhodium-catalyzed reactions.[19]



Scheme 2. Sulfonyl fluorides containing molecules in palladium-catalyzed reactions.

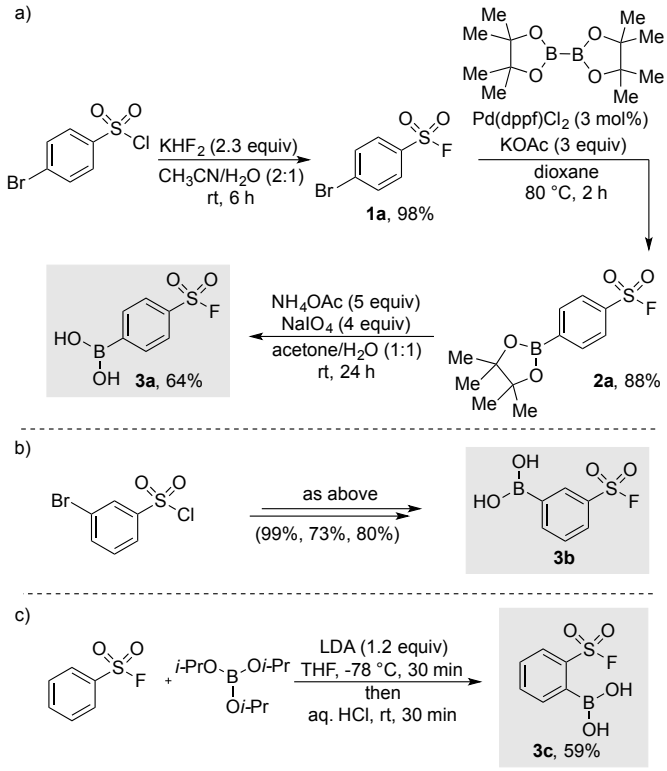
Although sulfonyl fluoride-substituted aryl halides have been used in Suzuki-Miyaura cross-coupling reactions (reaction 1, Scheme 2), the corresponding sulfonyl fluoride-substituted aryl boronic acids have not been reported, although one example of a boronic ester is known.[2a] Given the tolerance of sulfonyl fluorides to a variety of palladium-catalyzed reactions, as well as other metal-mediated processes, together with the widespread use of Suzuki-Miyaura reactions in synthetic chemistry, we reasoned that such boronic acids would be useful reagents, and would add to the repertoire of methods available for the introduction of a sulfonyl fluoride group. Introducing sulfonyl fluorides by way of an aryl boronic acid reagent would also allow combination with the vast number of commercially available aryl halides. In this paper we report the efficient preparation of *ortho*-, *meta*-, and *para*-benzenesulfonyl fluoride boronic acids, together with their reactivity in coupling reactions (Scheme 3).



Scheme 3. **This work:** Benzenesulfonyl fluoride boronic acids and their coupling chemistry.

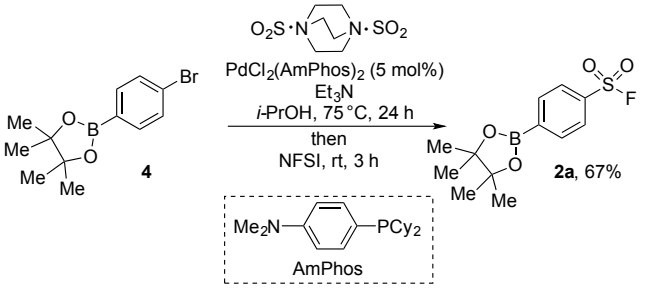
2. Results and discussion

The synthesis of the *para*-benzenesulfonyl fluoride boronic acid starts from *para*-bromobenzenesulfonyl chloride, selected for its ready availability and low-cost. Conversion of the sulfonyl chloride group into the corresponding sulfonyl fluoride was achieved by treatment with KHF_2 in aqueous acetonitrile at room temperature,[3a] and provided sulfonyl fluoride **1a** in 98% yield (Scheme 4a). Miyaura borylation using B_2pin_2 with $Pd(dppf)Cl_2$ as catalyst delivered boronic ester **2a** in 88% yield.[20] Hydrolysis of the boronic ester to liberate the target boronic acid (**3a**) was achieved using ammonium acetate and sodium periodate in 64% yield.[21] *para*-Benzenesulfonyl fluoride boronic acid **3a** was purified by trituration with a hexane/dichloromethane mixture. An identical sequence was completed starting from the *meta*-sulfonyl chloride, ultimately providing *meta*-benzenesulfonyl fluoride boronic acid **3b** (Scheme 4b). The *ortho*-isomer required an alternative route, and the developed synthesis started with commercially available benzenesulfonyl fluoride. *Ortho*-lithiation of benzenesulfonyl fluoride was achieved using LDA, and *in situ* quenching with isopropyl borate then provided the corresponding boronic ester,[22] which was treated directly with aqueous HCl to provide *ortho*-benzenesulfonyl fluoride boronic acid (**3c**) in 59% yield for this one-pot operation (Scheme 4c).



Scheme 4. Preparation of benzenesulfonyl fluoride boronic acids **3a-c**.

The routes presented in Scheme 4 employ readily available starting materials and allowed gram-scale quantities of the targeted sulfonyl fluoride boronic acids to be obtained. However, we also wanted to explore a route based on the catalytic sulfination of a substrate featuring an intact boron-substituent. Accordingly, *para*-bromo-substituted aryl pinocolate boronic ester **4** was subjected to palladium-catalyzed sulfination conditions,[10] followed by trapping with the electrophilic fluorinating reagent NFSI, to provide boronic ester substituted sulfonyl fluoride **2a** in 67% yield. This complementary route to boronic ester **2a** provides an alternative entry to these sulfonyl fluorides, and could find application when late-stage introduction of the sulfur functional group is needed.

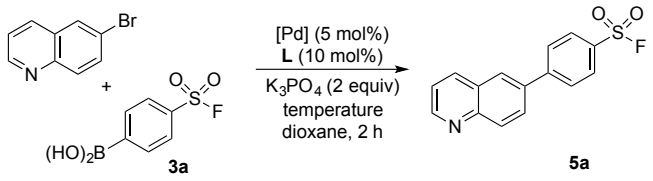


Scheme 5. Sulfonyl fluoride synthesis starting from pinocolate boronic ester **5**.

With the three key sulfonyl fluoride substituted boronic acids available, we next explored their use in Suzuki-Miyaura coupling

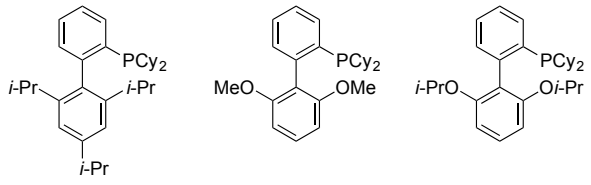
reactions. We optimized reaction conditions using the coupling between *para*-substituted boronic acid **3a**, and 6-bromoquinoline (Table 1). We evaluated a range of phosphine ligands, using $Pd(OAc)_2$ as the palladium source, and K_3PO_4 as base, using dioxane as solvent, initially at 60 °C. Yields were recorded after 2 hours, and 22 hours, with the latter being used to gauge any decomposition of the product under the reaction conditions. Entries 1-7 show that XPhos, SPhos, RuPhos and AmPhos (in this case used as a preformed complex) all performed well under these conditions. XPhos and AmPhos were then evaluated at lower temperatures, with both performing well at 40 °C (entries 8 and 9). At 25 °C only XPhos was effective, with the AmPhos system delivering only a low conversion (entries 10 and 11). All entries to this point had used 2.0 equivalents of boronic acid; entry 12 shows that using 1.5 equivalents of boronic acid can achieve good conversion after 4 hours reaction at 40 °C, with minimal decomposition being observed after 22 hours. This final entry represents the conditions that were taken forward.

Table 1. Optimization of the coupling between boronic acid **3a** and 6-Br-quinoline.[a]



Entry	[Pd]	L	Temp.	Yield[b] (2 h)	Yield[b] (22 h)
1	$Pd(OAc)_2$	-	60 °C	40%	38%
2	$Pd(OAc)_2$	XPhos	60 °C	92%	85%
3	$Pd(OAc)_2$	SPhos	60 °C	95%	85%
4	$Pd(OAc)_2$	RuPhos	60 °C	96%	75%
5	$Pd(OAc)_2$	PCy_3	60 °C	69%	60%
6	$Pd(PPh_3)_4$	-	60 °C	29%	53%
7	$PdCl_2(AmPhos)_2$	-	60 °C	99%	92%
8	$Pd(OAc)_2$	XPhos	40 °C	99%	98%
9	$PdCl_2(AmPhos)_2$	-	40 °C	99%	93%
10	$Pd(OAc)_2$	XPhos	25 °C	81%[c]	99%
11	$PdCl_2(AmPhos)_2$	-	25 °C	10%	-
12	**$Pd(OAc)_2$**	**XPhos**	**40 °C**	**94%[d]**	**93%**

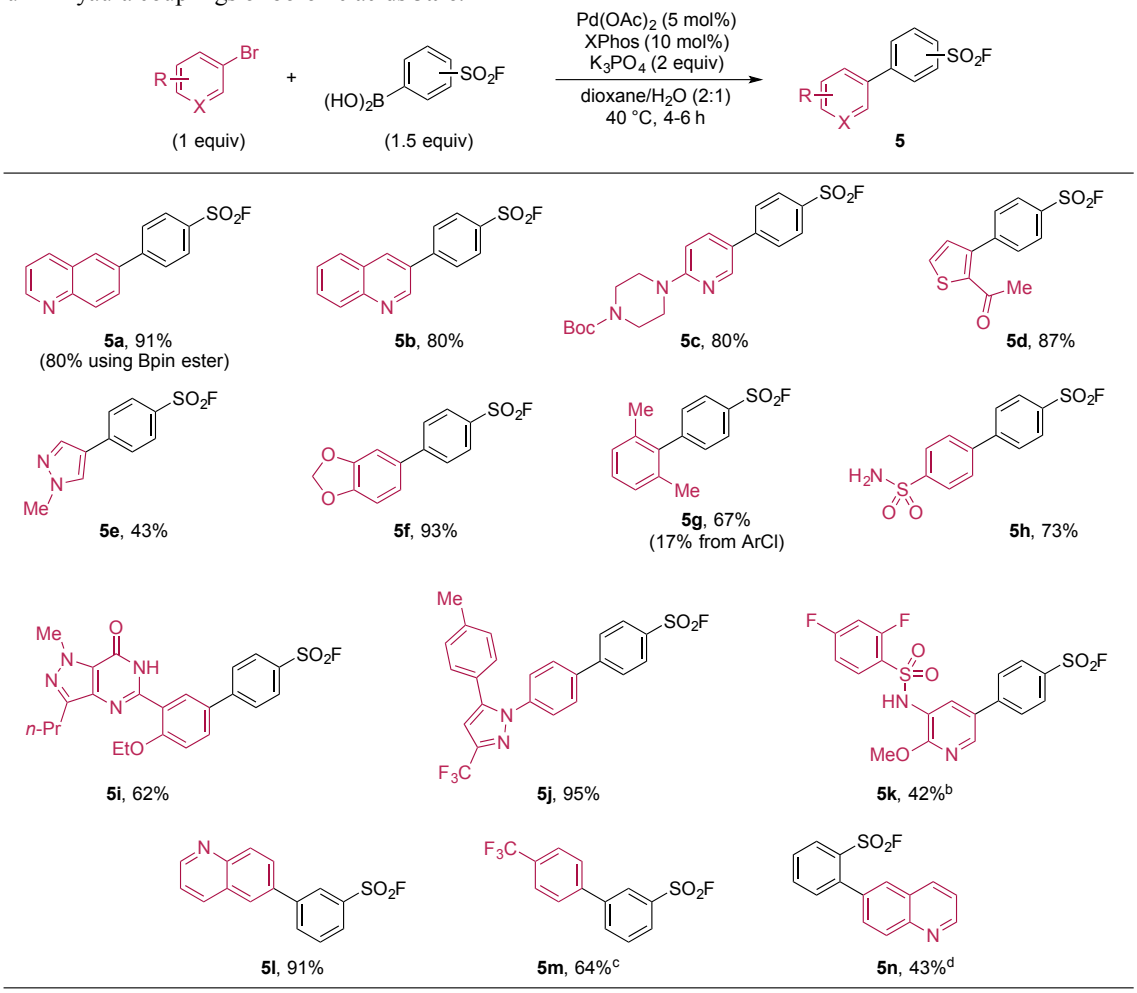
a. Reaction conditions: Aryl halide (0.075 mmol, 1.0 equiv), boronic acid (2.0 equiv), [Pd] (5 mol%), **L** (10 mol%), K_3PO_4 (1 M *aq*) (2.0 equiv), dioxane [0.25 M], at given temperature. b. Yield determined by HPLC against internal standard. c. 24 hours reaction. d. 4 hours reaction, using 1.5 equiv of boronic acid.



The optimized reaction conditions were then applied to a range of aryl halide coupling partners, initially using *para*-substituted boronic acid **3a** as the fixed component (Table 2). As can be seen, in addition to 6-bromoquinoline (**5a**), a range of alternative heterocycles could also be successfully employed, including 3-bromoquinoline (**5b**), a 3-bromopyridine (**5c**), a 3-bromothiophene (**5d**), and a 4-bromopyrazole (**5e**). Electron-rich and sterically demanding aryl bromides (**5f** and **5g**) could be employed, as could a 4-sulfonamide-substituted example (**5h**). We then employed several more complex aryl halide coupling partners of established worth in medicinal chemistry. For example, the aryl fragments in products **5i**, **5j** and **5k** (a 3-bromopyridine) are present in Sildenafil, Celecoxib, and Omipalisib,[23] respectively. *Meta*-sulfonyl fluoride substituted boronic acid **3b** could be used in coupling reactions under identical reaction conditions, and products **5l** and **5m** were obtained in good yields in this way. Product **5m** was obtained using the aryl chloride as the coupling partner, demonstrating that these less reactive aryl halides can be employed providing that an activating substituent, such as trifluoromethyl in this case, is present. The final example in Table 2 shows that the *ortho*-substituted boronic acid (**3c**) was significantly more challenging to engage in coupling chemistry than the corresponding *para*- and *meta*-isomers. Using the conditions that were successful for the *para*- and *meta*-isomers resulted in rapid decomposition of the *ortho*-sulfonyl fluoride substituted boronic acid. However, the use of KF as base in THF as solvent at room temperature (initial addition at 40 °C),[24] along with an increased amount of palladium catalyst, did restore some reactivity; after 12 hours reaction with 6-bromoquinoline, coupled product **5n** was obtained in 43% yield.

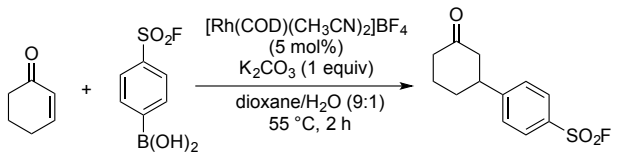
Para-substituted sulfonyl fluoride boronic ester **2a** could also be used as a reaction partner in Suzuki-Miyaura coupling processes, although reduced reactivity, relative to the boronic acid was observed. For example, using the standard conditions, a reaction time of 20 hours was needed to achieve an 80% yield of biaryl **5a**. In contrast, boronic acid **3a** delivered coupled product **5a** in 91% yield after 4 hours reaction.

Table 2. Suzuki-Miyaura couplings of boronic acids **3a-c**.[a]



a. Reaction conditions: Aryl halide (1.0 equiv), boronic acid (1.5 equiv), $Pd(OAc)_2$ (5 mol%), XPhos (10 mol%), K_3PO_4 (1 M *aq*) (2.0 equiv), dioxane, 40 °C, 4-6 h. Isolated yields. b. 24 hours. c. Using aryl chloride substrate. d. Aryl halide (1.0 equiv), boronic acid (1.5 equiv), $Pd(OAc)_2$ (20 mol%), XPhos (40 mol%), KF (3.3 equiv), THF, 40 °C, 0.5 h, then 25 °C, 12 h.

The rhodium(I)-catalyzed conjugate addition of aryl boronic acids to electron-poor alkenes represents a further useful C-C bond-forming reaction that employs boronic acids,[25] and accordingly, we were interested in whether sulfonyl fluoride substituted examples would engage in these types of reactions. Scheme 6 shows that *para*-substituted boronic acid **3a** was a competent nucleophile in the addition to cyclohexenone using a simple Rh(I) catalyst, providing the β-substituted ketone **6** in 74% yield.



Scheme 6. Rhodium(I)-catalyzed addition of boronic acid **3a** to cyclohexenone.

3. Conclusions

We have reported efficient and practical syntheses of *ortho*-, *meta*, and *para*-sulfonyl fluoride substituted benzene boronic acids. These boronic acids undergo efficient Sukuki-Miyaura coupling reactions, and we have also achieved an efficient Rh(I)-catalyzed conjugate addition reaction. These syntheses and reactions provide new methods for the installation of arylsulfonyl fluoride groups and should find applications in medicinal chemistry and chemical biology.

4. Experimental

4.1. General information

^{1}H, ^{11}B, ^{13}C, and ^{19}F NMR spectra were obtained on a Brüker AVIII400 (400 MHz) or AVII (500 MHz) spectrometer. Proton-decoupled spectra are denoted as $\{^{1}H\}$. Chemical shifts (δ) were reported in parts per million (ppm) using the residual solvent signal as an internal standard ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.16 ppm). All coupling constants (*J* values) were reported in Hertz (Hz). Multiplicities were reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; quin., quintet; m, multiplet. High-resolution mass spectrometry (HRMS) measurements were recorded on a Bruker Daltronics microTOF (ESI) spectrometer. Infrared spectra were recorded as thin films on a Bruker Tensor 27 FT-IR spectrometer. Flash chromatography was carried out using matrix 60 silica.

4.2. Synthesis of bromobenzenesulfonyl fluorides

4.2.1. General procedure

To a solution of KHF_2 (2.3 equiv) in deionized water (2 M) was added a solution of bromobenzenesulfonyl chloride (1 equiv) in CH_3CN (1 M). The reaction was stirred at ambient temperature for 24 h. The two phases were separated and the aqueous layer was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was further purified by flash column chromatography if required to afford the corresponding bromobenzenesulfonyl fluoride.

*4.2.2. 4-Bromobenzenesulfonyl fluoride (**1a**)*

Prepared according to general procedure, using 4-bromobenzenesulfonyl chloride (10.0 g, 39.1 mmol, 1.0 equiv), KHF_2 (7.0 g, 90 mmol, 2.3 equiv), deionized water (20 mL) and CH_3CN (40 mL) to afford the corresponding *sulfonyl fluoride* **1a** as a white solid (9.16 g), 98% yield. ***mp*** 66–67 °C (EtOAc); $\mathbf{R}_f$ 0.46 (10% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 133.3, 132.1 (d, J = 25.6 Hz), 131.5, 130.0; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.4; **IR** ν_{max} (neat)/cm^{-1} 3097, 1574, 1406, 1393, 1211, 825, 779, 736; **HRMS** (EI^+) *m/z* calc. for $C_6H_4{}^{79}BrFO_2S^+$ $[M]^+$ 237.9094, found 237.9092.

*4.2.3. 3-Bromobenzenesulfonyl fluoride (**1b**)*

Prepared according to general procedure, using 3-bromobenzenesulfonyl chloride (2.0 g, 7.8 mmol, 1.0 equiv), KHF_2 (1.4 g, 18 mmol, 2.3 equiv), deionized water (4 mL) and CH_3CN (8 mL) to afford the corresponding *sulfonyl fluoride* **1b** as a pale yellow oil (1.78 g), 99% yield. $\mathbf{R}_f$ 0.38 (10% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.15 (t, J = 1.9 Hz, 1H), 7.98–7.94 (m, 1H), 7.93–7.89 (m, 1H), 7.53 (td, J = 8.0, 1.1 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 138.8, 134.8 (d, J = 25.8 Hz), 131.4, 131.3, 127.1, 123.7; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.3; **IR** ν_{max} (neat)/cm^{-1} 3091, 1410, 1209, 801, 786, 747; **HRMS** (EI^+) *m/z* calc. for $C_6H_4{}^{79}BrFO_2S^+$ $[M]^+$ 237.9094, found 237.9077.

4.3. Synthesis of benzenesulfonyl fluoride boronic acid pinacol esters from bromobenzenesulfonyl fluorides

4.3.1. General procedure

A round bottom flask was charged with 4-bromobenzenesulfonyl fluoride **1a** (1 equiv), $B_2(pin)_2$ (1.1 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (3 mol%) and KOAc (3 equiv), evacuated and back-filled with N_2 three times. Degassed anhydrous 1,4-dioxane (0.33 M) was added and the reaction was stirred at 80 °C for 16 h, then cooled to ambient temperature and concentrated *in vacuo*. The mixture was diluted with EtOAc, washed sequentially with water and brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography rapidly to afford the corresponding benzenesulfonyl fluoride boronic acid pinacol ester.

*4.3.2. 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonyl fluoride (**2a**)*

Prepared according to general procedure, using 4-bromobenzenesulfonyl fluoride **1a** (4.78 g, 20.0 mmol, 1.0 equiv), $B_2(pin)_2$ (5.59 g, 22.0 mmol, 1.1 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (0.49 g, 0.60 mmol, 3 mol%), KOAc (5.88 g, 60.0 mmol, 3.0 equiv) and 1,4-dioxane (60 mL). The crude product was purified by flash column chromatography (10–30% EtOAc in petrol) to afford the corresponding *sulfonyl fluoride* **2a** as a white solid (5.06 g), 88% yield. ***mp*** 129–130 °C (Et_2O); $\mathbf{R}_f$ 0.23 (10% EtOAc in hexane) [$KMnO_4$/UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05–8.02 (m, 2H), 8.00–7.96 (m, 2H), 1.36 (s, 12H); **^{11}B {^{1}H} NMR** (128 MHz, $CDCl_3$) δ 30.3; **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 135.8, 135.2 (d, $^2J_{CF}$ = 23.9 Hz), 127.4, 84.9, 25.0 (1C missing); **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 65.7; **IR** ν_{max} (neat)/cm^{-1} 2976, 1396, 1357, 1213, 1140, 1080, 853, 768; **HRMS** (ESI/APCI/EI) not found.

*4.3.3. 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonyl fluoride (**2b**)*

Prepared according to general procedure using 3-bromobenzenesulfonyl fluoride (1.67 g, 7.0 mmol, 1.0 equiv), $B_2(pin)_2$ (1.96 g, 7.7 mmol, 1.1 equiv), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (172 mg, 0.21 mmol, 3 mol%), KOAc (2.06 g, 21 mmol, 3.0 equiv) and 1,4-dioxane (25 mL). The crude product was purified by flash column chromatography (5–20% EtOAc in petrol) to afford the corresponding *sulfonyl fluoride* **2b** as a white solid (1.47 g), 73% yield. ***mp*** 83–85 °C (pentane); $\mathbf{R}_f$ 0.21 (10% EtOAc in hexane) [$KMnO_4$/UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.44 (t, J = 1.4 Hz, 1H), 8.17 (d, J = 7.4 Hz, 1H), 8.07 (dt, J = 8.0, 1.6 Hz, 1H), 7.62 (t, J = 7.7 Hz, 1H), 1.36 (s, 12H); **^{11}B {^{1}H} NMR** (128 MHz, $CDCl_3$) δ 30.2; **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 141.7, 134.6, 132.9 (d, J = 23.9 Hz), 130.7, 129.1, 84.9, 25.0 (1C missing);; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 65.8; **IR** ν_{max} (neat)/cm^{-1} 2980, 1600, 1406, 1353, 1208, 1142; **HRMS** (ESI) not found.

*4.4. Pd-catalyzed synthesis of benzenesulfonyl fluoride boronic ester **2a** from bromophenylboronic acid pinacol ester, DABSO and NFSI*

A reaction tube was charged with 4-bromophenylboronic acid pinacol ester (85 mg, 0.30 mmol, 1.0 equiv), DABSO (72 mg, 0.30 mmol, 1.0 equiv) and $PdCl_2(AmPhos)_2$ (10.6 mg, 0.015 mmol, 5.0 mol%), sealed with a rubber septum, evacuated and back-filled with N_2 three times. Anhydrous degassed isopropanol (1.2 mL) and anhydrous triethylamine (0.13 mL, 0.90 mmol, 3.0 equiv) were added subsequently, and the reaction mixture was stirred under positive pressure of N_2 in a preheated aluminium heating block at 75 °C for 24 h. After cooling to ambient temperature, NFSI (104 mg, 0.33 mmol, 1.1 equiv) was added. The reaction mixture was stirred at ambient temperature for 3 h until completion. The reaction mixture was then diluted with EtOAc, filtered through a plug of Celite® and concentrated *in vacuo* to yield the crude product which was then purified by flash column chromatography (10–30% EtOAc in petrol), affording the *sulfonyl fluoride* **2a** as a white solid (57 mg), 67% yield.

4.5. Synthesis of arylsulfonyl fluoride boronic acids from the corresponding pinacolate boronic esters

4.5.1. General procedure

4-(Fluorosulfonyl)phenylboronic acid pinacol ester (1 equiv) was dissolved in acetone (0.2 M). A solution of NH_4OAc (5 equiv) in water (0.2 M) was then added, followed by $NaIO_4$ (4 equiv). The mixture was stirred rigorously at ambient temperature for 24 h, volatiles were then removed *in vacuo* and the residue was extracted with EtOAc. The organic layer was washed with brine, and the combined aqueous extracts were further extracted with EtOAc three times. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The

resultant solid was then triturated with a mixture of hexane/CH_2Cl_2, followed by pentane to afford the corresponding arylsulfonyl fluoride boronic acid.

*4.5.2. 4-(Fluorosulfonyl)phenylboronic acid (**3a**)*

Prepared according to general procedure, using 4-(fluorosulfonyl)phenylboronic acid pinacol ester **2a** (1.2 g, 4.2 mmol, 1.0 equiv), NH_4OAc (1.64 g, 21 mmol, 5.0 equiv), $NaIO_4$ (3.64 g, 17 mmol, 4.0 equiv), acetone (20 mL) and water (20 mL). The crude product was triturated with hexane/CH_2Cl_2 (2:1), followed by pentane to afford the *boronic acid* **3a** as a white solid (0.55 g), 64% yield. ***mp*** 240 °C (decomp.) (CH_2Cl_2); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.58 (s, 2H), 8.14–8.07 (m, 4H); **^{11}B {^{1}H} NMR** (126 MHz, DMSO-d_6) δ 27.7; **^{13}C {^{1}H} NMR** (101 MHz, DMSO-d_6) δ 143.9 (br.), 135.5, 132.6 (d, J = 22.7 Hz), 127.0; **^{19}F {^{1}H} NMR** (377 MHz, DMSO-d_6) δ 66.1; **IR** ν_{max} (neat)/cm^{-1} 2160, 1405, 1349, 1304, 1209, 1108, 1075, 1015, 803, 785, 741; **LRMS** (ESI$^-$) m/z 203.0 ([M−H]$^-$); **HRMS** (ESI$^-$) m/z calc. for $C_6H_5BFO_4S^-$ [M−H]$^-$ 202.9991, found 202.9990.

*4.5.3. 3-(Fluorosulfonyl)phenylboronic acid (**3b**)*

Prepared according to general procedure, using 3-(fluorosulfonyl)phenylboronic acid pinacol ester **2b** (1.45 g, 5.1 mmol, 1.0 equiv), NH_4OAc (1.93 g, 25 mmol, 5.0 equiv), $NaIO_4$ (4.28 g, 20 mmol, 4.0 equiv), acetone (25 mL) and water (25 mL). The crude product was triturate with hexane/CH_2Cl_2 (4:1), followed by pentane to afford the *boronic acid* **3b** as a white solid (0.83 g, 80%); ***mp*** 240 °C (decomp.) (CH_2Cl_2); **^{1}H NMR** (400 MHz, DMSO-d_6) 8.58 (s, 2H), 8.46 (app. s, 1H), 8.29 (d, J = 7.5 Hz, 1H), 8.15 (ddd, J = 8.0, 2.2, 1.2 Hz, 1H), 7.76 (t, J = 7.7 Hz, 1H); **^{11}B {^{1}H} NMR** (128 MHz, DMSO-d_6) δ 27.0; **^{13}C {^{1}H} NMR** (126 MHz, DMSO-d_6) δ 142.0, 137.0 (d, J = 20.8 Hz), 133.3, 131.1 (d, J = 22.3 Hz), 129.72, 129.70; **^{19}F {^{1}H} NMR** (377 MHz, DMSO-d_6) δ 66.4; **IR** ν_{max} (neat)/cm^{-1} 1598, 1568, 1401, 1344, 1203, 1091, 841, 762, 721; **HRMS** (ESI$^-$) m/z calc. for $C_6H_5BFO_4S^-$ [M−H]$^-$ 202.9991, found 202.9988.

*4.6. Synthesis of 2-(fluorosulfonyl)phenylboronic acid (**3c**) through ortho-lithiation/borylation of benzenesulfonyl fluoride*

Preparation of LDA solution

Diisopropylamine (0.92 mL, 6.6 mmol, 1.32 equiv) was dissolved in anhydrous THF (6 mL) under N_2 atmosphere and the solution was cooled to 0 °C. A solution of *n*-BuLi (2.4 M in hexane) (2.5 mL, 6.0 mmol, 1.2 equiv) was then added dropwise and the mixture was stirred at 0 °C for 15 min.

Ortho-lithiation/borylation

Under N_2 atmosphere, benzenesulfonyl fluoride (0.60 mL, 5.0 mmol, 1.0 equiv) was dissolved in anhydrous THF (5 mL) and the solution was cooled to -78 °C. Triisopropyl borate (2.8 mL, 12 mmol, 2.4 equiv) was added to the solution, followed by the slow addition of LDA solution prepared as described above over 10 min and the reaction was stirred at -78 °C for 30 min. The reaction mixture was then warmed to ambient temperature, 10% (v/v) *aq.* HCl (9 mL) was added and the reaction was stirred at ambient temperature for 30 min. The mixture was then diluted with EtOAc and the two phases were separated. The aqueous extract was further extracted with EtOAc three times and the combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (30–50% EtOAc in petrol). The resultant oil was added with hexane and sonicated to induce precipitation, which was then subsequently triturated with hexane, hexane/CH_2Cl_2 (5:1) and pentane to afford the *boronic acid* **3c** as a white solid (599 mg), 59% yield. ***mp*** 70–72 °C (CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 5.58 (br. s, 2H); **^{11}B {^{1}H} NMR** (128 MHz, $CDCl_3$) δ 28.7; **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 136.2, 135.9 (d, J = 21.6 Hz), 135.0, 131.2 (br.), 130.8, 129.4; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 63.8; **IR** ν_{max} (neat)/cm^{-1} 3387, 1394, 1332, 1207, 790, 763, 749; **HRMS** (ESI$^-$) m/z calc. for $C_6H_5BFO_4S^-$ [M−H]$^-$ 202.9991, found 202.9991.

4.7. Suzuki-Miyaura Coupling (SMC) reactions

4.7.1. General procedure

A reaction tube was charged with benzenesulfonyl fluoride boronic acid **3** (61 mg, 0.30 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.3 mg, 0.010 mmol, 5.0 mol%) and XPhos (9.5 mg, 0.020 mmol, 10 mol%), sealed with a rubber septum, evacuated and back-filled with N_2 three times. Degassed 1,4-dioxane (0.8 mL), degassed 1.0 M aq. K_3PO_4 solution (0.4 mL, 0.40 mmol, 2.0 equiv) and aryl halide* (0.20 mmol, 1.0 equiv) were added subsequently, and the reaction mixture stirred under positive pressure of N_2 in a preheated aluminium heating block at 40 °C for 4 h (**5a**, **b**, **f**, **g**, **h**, **l**), 6 h (**5c**, **d**, **e**, **i**, **j**, **m**) or 24 h (**5k**). After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, dried with anhydrous $MgSO_4$, filtered over Celite® and concentrated *in vacuo*. The crude product was purified by flash column chromatography to afford the biarylsulfonyl fluoride**.**

*In the case where aryl halide is a solid, it was added to the vessel before evacuating and back-filling.

*4.7.2. 4-(Quinolin-6-yl)benzenesulfonyl fluoride (**5a**)*

White solid, 91% yield. ***mp*** 135–136 °C (CH_2Cl_2); **R_f** 0.26 (30% EtOAc in hexane) [$KMnO_4$/UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (dd, J = 4.2, 1.7 Hz, 1H), 8.28–8.23 (m, 2H), 8.15–8.12 (m, 2H), 8.07 (d, J = 2.1 Hz, 1H), 7.99–7.93 (m, 3H), 7.49 (dd, J = 8.3, 4.2 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 151.6, 148.4, 147.9, 136.7, 136.6, 132.1 (d, J = 24.9 Hz), 130.9, 129.3, 128.7, 128.6, 128.5, 126.9, 122.2; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.5; **IR** ν_{max} (neat)/cm^{-1} 3071, 1591, 1406, 1212, 1193, 1097; **LRMS** (ESI$^+$) m/z 288.0 ([M+H]$^+$); **HRMS** (ESI$^+$) m/z calc. for $C_{15}H_{11}FNO_2S^+$ [M+H]$^+$ 288.0489, found 288.0490.

Using boronic ester **2a**: The general procedure was followed with benzenesulfonyl fluoride boronic ester **2a** (86 mg, 0.30 mmol, 1.5 equiv) used in place of boronic acid **3a**, and the reaction mixture was stirred at 40 °C for 20 h. Upon purification, biarylsulfonyl fluoride **5a** was afforded as a white solid (45.7 mg), 80% yield. Data as above.

*4.7.3. 4-(Quinolin-3-yl)benzenesulfonyl fluoride (**5b**)*

White solid, 80% yield. ***mp*** 161–163 °C (CH_2Cl_2); **R_f** 0.42 (30% EtOAc in hexane) [$KMnO_4$/UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.19 (d, J = 2.4 Hz, 1H), 8.39 (dd, J = 2.4, 0.8 Hz, 1H), 8.21–8.14 (m, 3H), 7.99–7.95 (m, 2H), 7.95–7.92 (m, 1H), 7.81 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.65 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 149.1, 148.3, 145.5, 134.6, 132.5 (d, J = 25.4 Hz), 131.4, 130.7, 129.6, 129.5, 128.6, 128.4,

127.8, 127.8; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.5; **IR** ν_{max} (neat)/cm^{-1} 3606, 1595, 1403, 1216, 1097; **LRMS** (ESI$^+$) *m/z* 288.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{15}H_{11}FNO_2S^+$ [M+H]$^+$ 288.0489, found 288.0490.

*4.7.4. tert-Butyl 4-(5-(4-(fluorosulfonyl)phenyl)pyridin-2-yl)piperazine-1-carboxylate (**5c**)*

White solid, 80% yield. ***mp*** 198–200 °C ($CHCl_3$); R_f 0.42 (30% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.49 (dd, *J* = 2.6, 0.7 Hz, 1H), 8.04 (dt, *J* = 8.5, 2.1 Hz, 2H), 7.77 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.75–7.72 (m, 2H), 6.74 (dd, *J* = 9.0, 0.8 Hz, 1H), 3.69–3.60 (m, 4H), 3.61–3.50 (m, 4H), 1.49 (s, 9H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 159.3, 154.9, 147.0, 145.9, 136.3, 130.6 (d, *J* = 24.8 Hz), 129.3, 126.8, 123.4, 107.0, 80.3, 44.9, 43.3 (br.), 28.6; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.6; **IR** ν_{max} (neat)/cm^{-1} 2981, 2923, 1673, 1605, 1589, 1424, 1403, 1243, 1212, 1190, 1172; **LRMS** (ESI$^+$) *m/z* 422.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{20}H_{25}FN_3O_4S^+$ [M+H]$^+$ 422.1544, found 422.1548.

*4.7.5. 4-(2-Acetylthiophen-3-yl)benzenesulfonyl fluoride (**5d**)*

Off-white solid, 87% yield. ***mp*** 127–129 °C ($CHCl_3$); R_f 0.44 (30% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.05 (dt, *J* = 8.5, 1.8 Hz, 2H), 7.66 (dtd, *J* = 8.8, 1.9, 0.8 Hz, 2H), 7.61 (d, *J* = 5.1 Hz, 1H), 7.09 (d, *J* = 5.0 Hz, 1H), 2.39 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 190.5, 144.3, 144.1, 138.9, 132.6 (d, *J* = 25.3 Hz), 131.9, 131.2, 130.7, 128.5, 29.9; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.2; **IR** ν_{max} (neat)/cm^{-1} 3105, 1672, 1402, 1274, 1209, 1186, 1095; **LRMS** (ESI$^+$) *m/z* 285.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{12}H_{10}FO_3S_2^+$ [M+H]$^+$ 285.0050, found 285.0051.

*4.7.6. 4-(1-Methyl-1H-pyrazol-4-yl)benzenesulfonyl fluoride (**5e**)*

White solid, 43% yield. ***mp*** 85–86 °C ($CHCl_3$); R_f 0.29 (50% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (dt, *J* = 8.5, 1.9 Hz, 2H), 7.85 (d, *J* = 0.9 Hz, 1H), 7.75 (d, *J* = 0.8 Hz, 1H), 7.67 (dtd, *J* = 8.8, 2.1, 1.0 Hz, 2H), 3.99 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 140.5, 137.5, 130.0 (d, *J* = 24.3 Hz), 129.4, 128.3, 126.0, 121.1, 39.5; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.5; **IR** ν_{max} (neat)/cm^{-1} 3101, 2948, 1597, 1564, 1402, 1206, 1192, 1097; **LRMS** (ESI$^+$) *m/z* 241.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{10}H_{10}FN_2O_2S^+$ [M+H]$^+$ 241.0442, found 241.0443.

*4.7.7. 4-(Benzo[d][1,3]dioxol-5-yl)benzenesulfonyl fluoride (**5f**)*

White solid, 93% yield. ***mp*** 104–105 °C ($CHCl_3$); R_f 0.45 (20% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03 (dtd, *J* = 8.8, 2.0, 0.5 Hz, 2H), 7.74 (dtd, *J* = 8.8, 2.1, 0.9 Hz, 2H), 7.12 (dd, *J* = 8.0, 1.9 Hz, 1H), 7.09 (dd, *J* = 1.9, 0.4 Hz, 1H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.05 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 148.9, 148.8, 148.4, 132.8, 131.0 (d, *J* = 24.6 Hz), 129.1, 127.9, 121.7, 109.1, 107.8, 101.8; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.5; **IR** ν_{max} (neat)/cm^{-1} 3079, 2922, 1594, 1505, 1477, 1442, 1405, 1223, 1209, 1186, 1100, 1033; **HRMS** (ESI) not found.

*4.7.8. 2',6'-Dimethyl-[1,1'-biphenyl]-4-sulfonyl fluoride (**5g**)*

White solid, 67% yield. ***mp*** 133–134 °C ($CHCl_3$); R_f 0.56 (10% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (dtd, *J* = 8.2, 2.0, 0.4 Hz, 2H), 7.44 (dtd, *J* = 8.6, 1.9, 0.9 Hz, 2H), 7.23 (dd, *J* = 8.4, 6.7 Hz, 1H), 7.16–7.13 (m, 2H), 2.01 (s, 6H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 149.6, 139.4, 135.4, 131.6 (d, *J* = 24.6 Hz), 130.8, 128.9, 128.3, 127.9, 20.9; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.1; **IR** ν_{max} (neat)/cm^{-1} 3088, 2966, 2923, 1590, 1464, 1403, 1208, 1179, 1163, 1092; **HRMS** (ESI) not found.

*4.7.9. 4'-Sulfamoyl-[1,1'-biphenyl]-4-sulfonyl fluoride (**5h**)*

White solid, 73% yield. ***mp*** 181–183 °C (EtOAc); R_f 0.14 (30% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.25 (d, *J* = 8.6 Hz, 2H), 8.14 (d, *J* = 8.1 Hz, 2H), 8.02–7.95 (m, 4H), 7.49 (s, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 146.4, 144.6, 140.7, 130.9 (d, *J* = 23.9 Hz), 129.2, 128.9, 128.1, 126.5; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.6; **IR** ν_{max} (neat)/cm^{-1} 3367, 3263, 1594, 1404, 1329, 1215, 1153, 1097; **LRMS** (ESI$^-$) *m/z* 313.9 ([M−H]$^-$); **HRMS** (ESI$^-$) *m/z* calc. for $C_{12}H_9FNO_4S_2^-$ [M−H]$^-$ 313.9963, found 313.9961.

*4.7.10. 4'-Ethoxy-3'-(1-methyl-7-oxo-3-propyl-6,7-dihydro-1H-pyrazolo[4,3-d]pyrimidin-5-yl)-[1,1'-biphenyl]-4-sulfonyl fluoride (**5i**)*

5-(5-Bromo-2-ethoxyphenyl)-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo[4,3-*d*]pyrimidin-7-one (39.1 mg, 0.10 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **3a** (31 mg, 0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (1.1 mg, 5.0 µmol, 5.0 mol%), XPhos (4.8 mg, 10 µmol, 10 mol%), 1.0 M aq. K_3PO_4 solution (0.2 mL, 0.20 mmol, 2.0 equiv) and 1,4-dioxane (0.4 mL) were used. *Sulfonyl fluoride* **5i** was isolated as a white solid (29.0 mg), 62% yield. ***mp*** 176–178 °C ($CHCl_3$); R_f 0.26 (50% EtOAc in hexane) [$KMnO_4$/UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.67 (d, *J* = 2.5 Hz, 1H), 8.08–8.00 (m, 2H), 7.80 (dd, *J* = 8.9, 0.8 Hz, 2H), 7.65 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 4.35–4.26 (m, 2H), 4.21 (s, 3H), 2.87 (dd, *J* = 8.0, 7.1 Hz, 2H), 1.80 (h, *J* = 7.4 Hz, 2H), 1.58 (t, *J* = 7.0 Hz, 3H), 0.96 (t, *J* = 7.4 Hz, 3H) (recorded as a mixture of tautomers at ratio of 82:13:5); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 157.3, 153.9, 147.8, 147.4, 146.9, 138.6, 132.2, 131.5 (d, *J* = 24.7 Hz), 131.2, 130.3, 129.3, 128.0, 124.7, 121.2, 113.9, 65.9, 38.4, 27.9, 22.5, 14.8, 14.2; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.5; **IR** ν_{max} (neat)/cm^{-1} 3310, 2959, 2932, 1697, 1593, 1566, 1486, 1473, 1406, 1213, 1159, 1031; **LRMS** (ESI$^+$) *m/z* 471.2 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{23}H_{24}FN_4O_4S^+$ [M+H]$^+$ 471.1497, found 471.1496.

*4.7.11. 4'-(5-(p-Tolyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)-[1,1'-biphenyl]-4-sulfonyl fluoride (**5j**)*

1-(4-Bromophenyl)-5-(*p*-tolyl)-3-(trifluoromethyl)-1*H*-pyrazole (38.1 mg, 0.10 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **3a** (31 mg, 0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (1.1 mg, 5.0 µmol, 5.0 mol%), XPhos (4.8 mg, 10 µmol, 10 mol%), 1.0 M aq. K_3PO_4 solution (0.2 mL, 0.20 mmol, 2.0 equiv) and 1,4-dioxane (0.4 mL) were used. *Sulfonyl fluoride* **5j** was isolated as an off-white solid (43.5 mg), 95% yield. ***mp*** 121–123 °C ($CHCl_3$); R_f 0.41 (10% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (ddt, *J* = 103.1, 8.5, 2.0 Hz, 2H), 7.82 (dtd, *J* = 8.9, 2.1, 0.8 Hz, 2H), 7.62 (dt, *J* = 8.7, 2.5 Hz, 2H), 7.47 (dt, *J* = 8.8, 2.2 Hz, 2H), 7.19–7.15 (m, 4H), 6.75 (s, 1H), 2.38 (s, 3H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 147.3, 145.1, 143.8 (d, *J* = 38.9 Hz), 140.2, 139.6, 138.4, 132.1 (d, *J* = 24.7 Hz), 129.7, 129.2, 128.9, 128.3, 128.2, 126.3, 126.1, 121.4 (d, *J* = 269.5 Hz), 106.0, 21.5; **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.5 (s, 1F), -62.3 (s, 3F); **IR** ν_{max} (neat)/cm^{-1} 3061, 2925, 1595, 1472, 1408, 1376, 1236, 1213, 1161, 1133, 1097; **LRMS** (ESI$^+$)

m/z 461.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{21}H_{17}F_4N_2O_2S^+$ [M+H]$^+$ 461.0941, found 461.0938.

*4.7.12. 4-(5-((2,4-Difluorophenyl)sulfonamido)-6-methoxypyridin-3-yl)benzenesulfonyl fluoride (**5k**)*

N-(5-Bromo-2-methoxypyridin-3-yl)-2,4-difluorobenzenesulfonamide (37.9 mg, 0.10 mmol, 1.0 equiv), 4-(fluorosulfonyl)phenylboronic acid **3a** (31 mg, 0.15 mmol, 1.5 equiv), $Pd(OAc)_2$ (1.1 mg, 5.0 µmol, 5.0 mol%), XPhos (4.8 mg, 10 µmol, 10 mol%), 1.0 M aq. K_3PO_4 solution (0.2 mL, 0.20 mmol, 2.0 equiv) and 1,4-dioxane (0.4 mL) were used. *Sulfonyl fluoride* **5k** was isolated as an off-white solid (19.4 mg), 42% yield. ***mp*** 152–154 °C ($CHCl_3$); $\mathbf{R}_f$ 0.52 (50% EtOAc in hexane) [UV]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.3 Hz, 1H), 8.08 (dt, *J* = 8.6, 2.0 Hz, 2H), 7.99 (d, *J* = 2.3 Hz, 1H), 7.91–7.86 (m, 1H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.28 (br. s, 1H), 6.98–6.93 (m, 2H), 3.98 (s, 3H); **^{13}C {^{1}H,^{19}F} NMR** (126 MHz, $CDCl_3$) δ 166.4, 160.0, 155.0, 144.7, 140.9, 132.5, 129.4, 128.5, 127.9, 126.3, 123.5, 121.0, 112.2, 106.0, 54.6 (1C missing); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.4 (s, 1F), -98.5 (m, 1F), -103.8 (m, 1F); **IR** ν_{max} (neat)/cm^{-1} 3285, 3103, 2929, 2856, 1602, 1480, 1407, 1347, 1213, 1178, 1149; **LRMS** (ESI$^+$) *m/z* 459.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{18}H_{14}F_3N_2O_5S_2^+$ [M+H]$^+$ 459.0291, found 459.0291.

*4.7.13. 3-(Quinolin-6-yl)benzenesulfonyl fluoride (**5l**)*

White solid, 91% yield. ***mp*** 111–113 °C ($CHCl_3$); $\mathbf{R}_f$ 0.24 (30% EtOAc in hexane) [UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.34 (t, *J* = 1.9 Hz, 1H), 8.27–8.22 (m, 2H), 8.12–8.08 (m, 1H), 8.06–8.02 (m, 2H), 7.96 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.77 (t, *J* = 7.9 Hz, 1H), 7.48 (dd, *J* = 8.3, 4.2 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 151.4, 148.2, 142.5, 136.5, 136.4, 134.4, 134.1 (d, *J* = 24.6 Hz), 130.8, 130.5, 128.5 (2C), 127.4, 127.2, 126.5, 122.1; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.1; **IR** ν_{max} (neat)/cm^{-1} 3067, 1593, 1480, 1404, 1208; **LRMS** (ESI$^+$) *m/z* 288.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{15}H_{11}FNO_2S^+$ [M+H]$^+$ 288.0489, found 288.0489.

*4.7.14. 4'-(Trifluoromethyl)-[1,1'-biphenyl]-3-sulfonyl fluoride (**5m**)*

Off-white solid, 64% yield. ***mp*** 50–51 °C ($CHCl_3$); $\mathbf{R}_f$ 0.70 (30% EtOAc in hexane) [UV/$KMnO_4$]; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (t, *J* = 1.9 Hz, 1H), 8.06 (dt, *J* = 7.9, 1.5 Hz, 1H), 8.00 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.78–7.71 (m, 5H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 141.9, 141.9, 134.3, 134.2 (d, *J* = 24.6 Hz), 131.1 (app. d, *J* = 32.7 Hz), 130.6, 127.9, 127.8, 127.2, 126.4 (q, *J* = 3.7 Hz), 124.1 (app. d, *J* = 272.5 Hz); **^{19}F NMR** (377 MHz, $CDCl_3$) δ 66.1 (s, 1F), -62.7 (s, 3F); **IR** ν_{max} (neat)/cm^{-1} 3076, 1619, 1409, 1325, 1210, 1167, 1125, 1071; **LRMS** (ESI$^-$) *m/z* 339.1 ([M+Cl]$^-$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{13}H_8F_4O_2SNa^+$ [M+Na]$^+$ 327.0073, found 327.0080.

*4.7.15. 2-(Quinolin-6-yl)benzenesulfonyl fluoride (**5n**)*

A reaction tube was charged with KF (48 mg, 0.83 mmol, 3.3 equiv), $Pd(OAc)_2$ (11.2 mg, 0.050 mmol, 0.20 equiv) and XPhos (48 mg, 0.10 mmol, 0.40 equiv), sealed with a rubber septum, evacuated and back-filled with N_2 three times. Degassed anhydrous THF (0.25 mL) and 6-bromoquinoline (34 µL, 0.25 mmol, 1.0 equiv) were added subsequently, the mixture was stirred at ambient temperature for 5 min, then warmed to 40 °C and a solution of 2-(fluorosulfonyl)phenyl boronic acid **3c** (76 mg, 0.37 mmol, 1.5 equiv) in degassed THF (1 mL) was added over a period of 30 min. The reaction mixture was stirred at 40 °C for an additional 30 min, then stirred at ambient temperature for 12 h. The reaction was then diluted with EtOAc, filtered over Celite and concentrated *in vacuo*. The crude product was purified by flash column chromatography (40–50% EtOAc in petrol) to afford an off-white solid (30.5 mg), 43% yield. ***mp*** 95–96 °C ($CHCl_3$); $\mathbf{R}_f$ 0.31 (50% EtOAc in hexane) [$KMnO_4$/UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.3 Hz, 3H), 8.21–8.17 (m, 2H), 7.86–7.84 (m, 1H), 7.81 (td, *J* = 7.6, 1.4 Hz, 1H), 7.72 (ddd, *J* = 8.7, 2.0, 0.9 Hz, 1H), 7.66 (ddt, *J* = 9.1, 7.7, 1.4 Hz, 1H), 7.55 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.47 (dd, *J* = 8.3, 4.2 Hz, 1H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 151.3, 147.9, 142.3, 136.6, 136.3, 135.0, 133.3, 132.6 (d, *J* = 22.4 Hz), 130.5, 130.3, 129.4, 128.7, 128.4, 127.7, 122.0; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 67.5; **IR** ν_{max} (neat)/cm^{-1} 3064, 1478, 1404, 1210, 763; **LRMS** (ESI$^+$) *m/z* 288.0 ([M+H]$^+$); **HRMS** (ESI$^+$) *m/z* calc. for $C_{15}H_{11}FNO_2S^+$ [M+H]$^+$ 288.0489, found 288.0488.

*4.8. Rh(I)-catalyzed conjugate addition for the synthesis of 4-(3-oxocyclohexyl)benzenesulfonyl fluoride (**6**)*

A reaction tube was charged with 4-(fluorosulfonyl)-phenylboronic acid **3a** (61 mg, 0.30 mmol, 2.0 equiv), $[Rh(COD)(CH_3CN)_2]BF_4$ (2.9 mg, 7.5 µmol, 5.0 mol%) and K_2CO_3 (21 mg, 0.15 mmol, 1.0 equiv), sealed with a rubber septum, evacuated and back-filled with N_2 three times. Degassed 1,4-dioxane (1.35 mL), degassed water (0.15 mL) and 2-cyclohexen-1-one (14.5 µL, 0.15 mmol, 1.0 equiv) were added sequentially, and the reaction mixture stirred under positive pressure of N_2 in a preheated aluminium heating block at 55 °C for 2 h. After cooling to ambient temperature, the reaction mixture was diluted with EtOAc, washed with water and then brine, dried with anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by flash column chromatography (20–40% EtOAc in petrol) to afford a white solid (28.5 mg), 74% yield. ***mp*** 61–62 °C (CH_2Cl_2); $\mathbf{R}_f$ 0.38 (30% EtOAc in hexane) [$KMnO_4$/UV]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (dt, *J* = 8.4, 2.0 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 3.15 (tt, *J* = 11.6, 4.0 Hz, 1H), 2.62 (ddt, *J* = 14.0, 4.2, 1.9 Hz, 1H), 2.59–2.45 (m, 2H), 2.47–2.34 (m, 1H), 2.25–2.13 (m, 1H), 2.16–2.09 (m, 1H), 1.97–1.74 (m, 2H); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 209.4, 152.8, 131.5 (d, *J* = 24.7 Hz), 129.1, 128.1, 48.2, 44.7, 41.1, 32.4, 25.4; **^{19}F {^{1}H} NMR** (377 MHz, $CDCl_3$) δ 66.1; **IR** ν_{max} (neat)/cm^{-1} 2980, 2884, 1712, 1597, 1404, 1211, 1186, 804, 771; **HRMS** (APCI$^+$) *m/z* calc. for $C_{12}H_{14}FO_3S^+$ [M+H]$^+$ 257.0642, found 257.0641.

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Appendix A. Supplementary data

Supplementary data relating to this article (NMR spectra) may be found at.

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