TEMPO Improves Generality and Decreases Oxidative Deboronation in Chan–Lam Couplings of Primary Sulfonamides

Supporting Information

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1. General information

Materials. Reagents and substrates were purchased from commercial sources (BLD, Sigma Aldrich, Molport) and used without further purification.

Methods.

Purification: Flash column chromatography was performed using silica gel cartridges (RediSep Gold Silica Disposable columns, 4 gram, 20-40 μm particle size), on CombiFlash NextGen 300+ System with 200–800 nm UV-Vis variable wavelength detector.

Analysis: Samples were analyzed using Avantor 50 x 2.1 mm ACE Excel 1.7 C18-PFP column (cat. EXL-1710-0502U), equipped with a guard column, on Shimadzu LCMS-2020. Water with 0.1 % FA was used as mobile phase A and acetonitrile with 0.1% FA as phase B. Samples were dissolved in the acetonitrile containing caffeine as internal standard, filtered and injected at 0.5 ul volume. Two methods were developed: short and long, with different gradients but the same MS and PDA settings.

Short Method gradient: 3% B from 0 min. to 0.05 min, 3% to 97% B from 0.05 to 1.80 min., 97% B from 1.8 to 2.00 min, 3%B from 2.01 min. to 3 min., with flow at 0.8 ml/min.

Long Method gradient: 3% B from 0 min. to 0.05 min. (B.Curve: -1), 3% to 97% B from 0.05 to 4.5 min. (B.Curve: -1), 97% B from 4.5 to 4.8 min., 3%B from 4.81 min. to 5.70 min.

All results reported in this work were obtained using the Short analytical Method. A subset of reactions - those performed under the optimized TEMPO conditions (2 eq., 20 mol% copper loading) and the corresponding no-oxidant controls - were reanalyzed using the Long Method for data quality assurance. No significant differences were observed between the conclusions drawn from the two methods.

The temperature of the column was set to 45 ºC. Shimadzu MS 2020 detector, equipped with ESI, was set to collect data in the positive and negative mode with m/z ranging from 50 to 1000u and scan speed of 3750 u/sec. DL temperature: 300 ºC, Nebulizing Gas Flow: 1.5 ml/min, Heat Block: 480 ºC, Drying Gas Flow 20 L/min., Detector Voltage: Relative to the Tuning Result, Interface voltage: 4.5 kV, DL Voltage: 3 V, Quarray DC Voltage: Default, Quarray RF Voltage: Tuning File. PDA was set to collect data in the range from 210 nm to 500 nm. Cell temperature was set to 40 ºC and Slit Width to 1.2 nm.

PDA spectra analysis: From each post-reaction chromatogram, two types of peak area are taken: the caffeine area at 254 nm (A_std) and, for each product or side product, its area is integrated over the full PDA wavelength range (A_prod). Where peaks are reported directly by the chromatography software, their integrated areas are used as measured and evaluated alongside peaks integrated in-house, which boundaries are set at half of each peak's prominence and the area is computed as the sum of the signal intensities between the left and right boundaries.

Absorption prediction (confidential): Omitted. May be shared confidentially upon request.

Yield estimation (confidential): Omitted. May be shared confidentially upon request.

Instrumentation. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on Bruker Avance II Plus 700 MHz spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$ δ 7.26 ppm, DMSO δ 2.50 ppm). All NMR spectra were taken at 25 °C.

Abbreviations. DMA = N,N-dimethylacetamide

2. High-Throughput Experiments (HTE) in a microliter scale

2.1. General information

Stock solutions were prepared in 4.0 mL clear borosilicate glass vials (VWR, Catalog#: 548-0051A) equipped with ND13 screw caps (VWR, Catalog#: 548-0054A, PP with silicone/PTFE septa). Solutions were stored at -20 °C under an inert atmosphere when not in use.

Reactions were performed in ROTH Roti-labo® 96-well polypropylene plate (Cat#: CEL3.1). Microliter-scale transfers of starting materials and reagents were carried out using an Opentrons® OT-2 automated liquid-handling robot equipped with a P20 multi-channel pipette and a P300 multi-channel pipette.

Due to the hygroscopic nature of the inorganic bases deposited on chembeads, all initial reagent additions were performed inside an argon-filled glovebox. The inorganic bases were dispensed as chembeads using a solid dispenser, while liquid reagents were added as solutions using the OT-2 liquid handler. After reagent addition, the 96-well plates were sealed with aluminium foil under ambient atmosphere.

2.2. General procedure: High-Throughput Screening (HTE) of Chan-Lam couplings.

Caveat: The experimental procedures outlined below describe reactions run at a microliter scale. For milligram-scale procedures see SI, 3.1-4.

2.2.1. Experimental procedure, first High-Throughput Experimentation campaign:

Stock solutions of sulfonamide (200 mM in DMA, 2 µL, 0.4 µmol, 1eq.), and boronic acid (200 mM in DMA, 2.58 µL, 0.516 µmol, 1.29 eq.) were dosed into the reaction plate, followed by the addition of the respective solvent (DMA, dioxane, diglyme or H_2O) needed to achieve the final reaction volume, , as per design of this particular condition set (see: SI, Table S3). Catalyst was dispensed as a stock solution in DMA (20–40 mM) to achieve loadings of 10, 20 or 40 mol% (see: SI, Table S3). Oxidants (0.5–1.0 eq.) were dispensed as stock solutions in their respective solvents (dioxane, DMA, diglyme, or H_2O), according to the design (see: SI, Table S3). Finally, bases (2.0 eq.) were added either as 2,6-lutidine (400 mM in DMA or 44 mM in dioxane) or as K_2CO_3 and CsF pre-loaded onto chembeads (see: SI, Table S3). Reaction plates were stirred at 60°C for 18 h at 160 rpm in the thermoshaker.

2.2.2. Experimental procedure, second High-Throughput Experimentation campaign:

Stock solutions of sulfonamide (200 mM in DMA, 2 µL, 0.4 µmol, 1eq.), and boronic acid (200 mM in DMA, 1 eq./1.29 eq./2 eq.) were dosed into the reaction plate, followed by the addition of the respective solvent (DMA, dioxane, or diglyme) needed to achieve the final reaction volume, as per design of this particular condition set (see: SI, Table S4). Catalyst was dispensed as a stock solution in DMA (2.5–40 mM) to achieve loadings of 2.5–40 mol% (see: SI, Table S4). Oxidants (0.05–2.0 eq.) were dispensed as stock solutions in their respective solvents (dioxane, *n*-BuOH, diglyme), according to the design (see: SI, Table S4). Bases (1–4 eq.) were added pre-loaded onto chembeads (see: SI, Table S4). Plates were stirred at 60°C or 80°C (see: SI, Table S4) for 18 h at 160 rpm in the thermoshaker.

2.2.2.A. Experimental procedure, optimized High-Throughput Experimentation conditions

Stock solutions of sulfonamide (200 mM in DMA, 2 µL, 0.4 µmol, 1 eq.), and boronic acid (200 mM in DMA, 2.58 µL, 0.516 µmol, 1.29 eq.) were dosed into the reaction plate, followed by addition of DMA (2µL) and diglyme (16 µL). $Cu(OAc)_2 \cdot H_2O$ was dispensed as a stock solution (40 mM in DMA, 2 µL, 0.08 µmol) to achieve loading of 20 mol%. TEMPO were dispensed as a stock solution (200mM in diglyme, 4 µL, 0.8 µmol, 2.0 eq). K_2CO_3 (0.8 µmol, 2.0 eq) was added pre-loaded onto chembeads. Plates were stirred at 60°C for 18 h at 160 rpm in the thermoshaker.

2.2.3. Work-up (Common to Experiments 1 & 2):

Reaction mixtures were cooled to room temperature and treated with 190 µL of caffeine stock solution (0.526 mM in MeCN, 0.25 eq.) as an external standard, followed by scavenger EDTA (aqueous solution, 5.0 eq. relative to Cu). Quenched mixtures were stirred for 1.5 h at RT (130 rpm), then transferred to 96-well filter plates (preloaded with 10 µL isopropanol) and filtered through a 0.45 µm filter (4 °C, 1 min, 3000 rpm). Filtrates were collected in analytical plates for LCMS analysis.

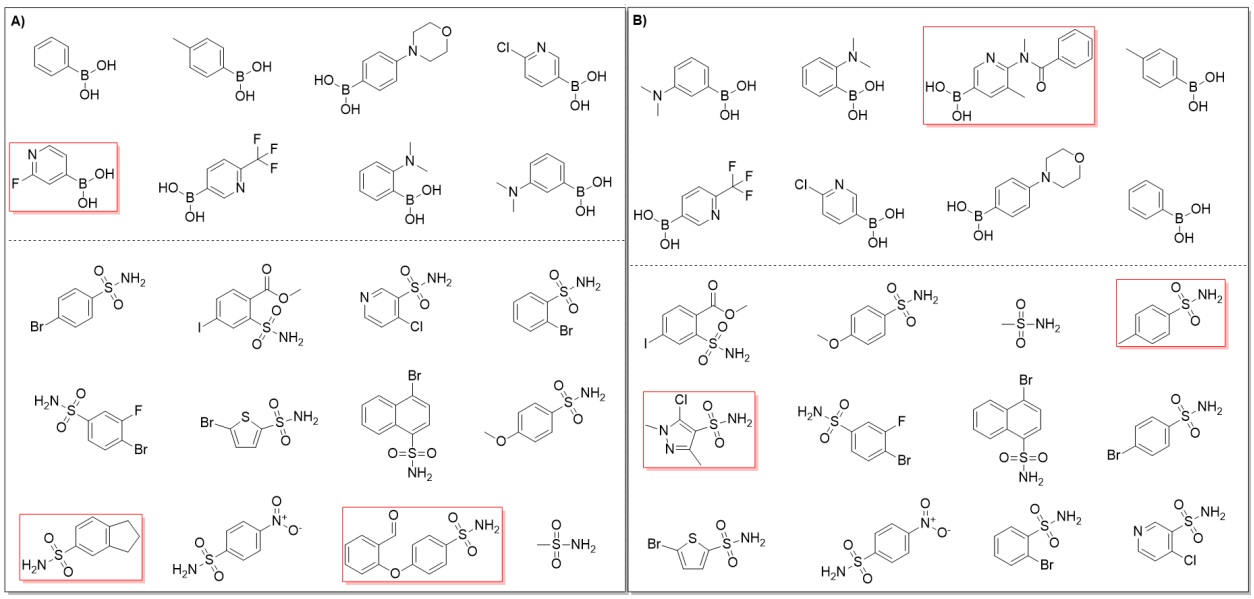


Figure S1. Comparison of substrate sets used in the first and second HTE campaigns. A) Substrate set used in the first HTE campaign. B) Substrate set used in the second HTE campaign. Substrates highlighted in red indicate the one boronic acid and two sulfonamides that differed between the two campaigns.

Table S1. Comparison of oxidant performance under fixed copper loading of 10 mol%.

cond_id*	oxidant	oxidant (mol %)	base (2 eq.)	$Cu(OAc)_2 \cdot H_2O$ (mol %)	solvent (volume ratio)
51	TEMPO	100	K_2CO_3	10	DMA/Diglyme (3:7)
48	*tert*-Butyl peroxide	50	K_2CO_3	10	DMA/Diglyme (3:7)
11	No oxidant		CsF	10	DMA/Dioxane (3:7)
46	NMO	100	K_2CO_3	10	DMA/Diglyme (3:7)
50	H_2O_2, 30%	50	K_2CO_3	10	DMA/Diglyme (3:7)
30	Selectfluor	100	K_2CO_3	10	DMA/Dioxane/Water (2.3:7.3:0.7)
47	*p*-benzoquinone	100	K_2CO_3	10	DMA/Diglyme (3:7)
33	Oxone	50	K_2CO_3	10	DMA/Dioxane/Water (2.3:7.3:0.7)
27	Sodium percarbonate	50	CsF	10	DMA/Dioxane/Water (2.3:7.3:0.7)
39	DMP	100	CsF	10	DMA/Diglyme (3:7)
19	Ammonium persulfate	50	2,6-Lutidine	10	DMA/Dioxane/Water (3:6.3:0.7)

Mean estimated yield and percentage of reactions achieving >30% yield across 96 substrate pairs are shown for representative condition sets in which $Cu(OAc)_2 \cdot H_2O$ loading was fixed at 10 mol%. These conditions correspond to the best-performing 10 mol% copper condition identified for each oxidant; oxidant loading, base identity, and solvent composition were allowed to vary, while base loading was kept constant at 2 equivalents. All reactions used 1 equivalent of primary sulfonamide and 1.29 equivalents of aryl boronic acid in a 28.58 µL reaction volume, with heating at 60 °C for 18 h. TEMPO remains the top-performing oxidant under this comparison, consistent with its superior overall performance. *Full condition set details corresponding to each *cond_id* are provided in Table S3 in this Supporting Information.

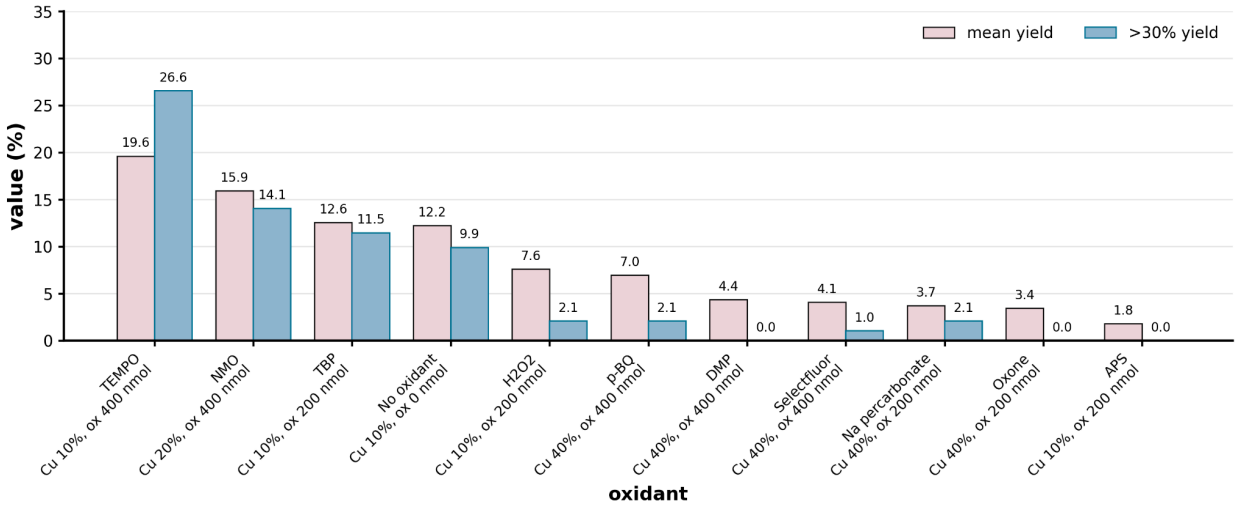


Figure S2. Comparison of oxidant performance under best-performing condition. Mean estimated yield and percentage of reactions achieving >30% yield across 96 substrate pairs are shown for the best-performing condition identified for each oxidant. TEMPO remains the top performer, even when each oxidant is evaluated under its own best observed condition from the 53-condition screen, in which solvent, reagent loading, copper loading, and base were varied.

Table S2. Comparison of oxidant performance under best-performing conditions.

cond_id*	oxidant	oxidant (mol %)	base (2 eq.)	$Cu(OAc)_2 \cdot H_2O$ (mol %)	solvent (volume ratio)
51	TEMPO	100	K_2CO_3	10	DMA/Diglyme (3:7)
48	*tert*-Butyl peroxide	50	K_2CO_3	10	DMA/Diglyme (3:7)
53	No oxidant		K_2CO_3	40	DMA/Diglyme (3:7)
52	NMO	100	K_2CO_3	20	DMA/Diglyme (3:7)
50	H_2O_2, 30%	50	K_2CO_3	10	DMA/Diglyme (3:7)
34	Selectfluor	100	K_2CO_3	40	DMA/Dioxane/Water (3:6.3:0.7)
16	*p*-benzoquinone	100	K_2CO_3	40	DMA/Dioxane (3:7)
33	Oxone	50	K_2CO_3	10	DMA/Dioxane/Water (2.3:7.3:0.7)
24	Sodium percarbonate	50	2,6-Lutidine	40	DMA/Dioxane/Water (3:6.3:0.7)
44	DMP	100	CsF	40	DMA/Diglyme (3:7)
19	Ammonium persulfate	50	2,6-Lutidine	10	DMA/Dioxane/Water (3:6.3:0.7)

Mean estimated yield and percentage of reactions achieving >30% yield across 96 substrate pairs are shown for the best-performing condition identified for each oxidant across the 53-condition screen. All reactions used 1 equivalent of primary sulfonamide and 1.29 equivalents of aryl boronic acid in a 28.58 µL reaction volume, with heating at 60 °C for 18 h. TEMPO remains the top-performing oxidant, demonstrating that its superior performance is maintained even when each oxidant is evaluated under its own best observed condition.

*Full condition set details corresponding to each *cond_id* are provided in Table S3 in this Supporting Information.

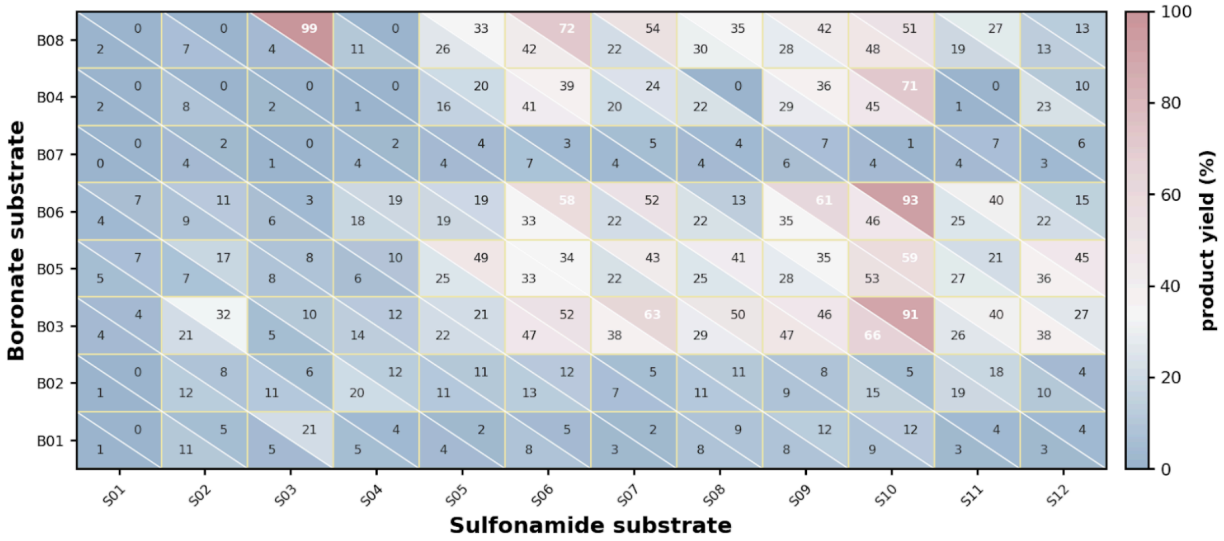


Figure S3. Comparison of TEMPO and 4-hydroxy-TEMPO in primary sulfonamide Chan-Lam coupling. Estimated product yields are shown for each sulfonamide/boronic acid substrate pair tested (n=96). Each cell compares the yields obtained with TEMPO (lower-left triangle) and 4-hydroxy-TEMPO (upper-right triangle) for the same substrate pair.

3. Bench scale Chan-Lam coupling with HTE-identified conditions

3.1. No oxidant procedure:

An oven-dried 10 mL vial equipped with a magnetic stir bar was charged with the appropriate sulfonamide (0.225 mmol, 1.0 eq.), the corresponding boronic acid (0.290 mmol, 1.29 eq.), $Cu(OAc)_2 \cdot H_2O$ (18.0 mg, 0.090 mmol, 0.40 eq.), and K_2CO_3 (62.2 mg, 0.450 mmol, 2.00 eq.). DMA (1.61 mL) and diglyme (3.75 mL) were added. The vial was capped with a septum pierced with a syringe needle to allow access to air, and the reaction mixture was heated with stirring at 60 °C for 18 h.

3.2. Oxidant (TEMPO) procedure:

An oven-dried 10 mL vial equipped with a magnetic stir bar was charged with the appropriate sulfonamide (0.225 mmol, 1.00 eq.), the corresponding boronic acid (0.290 mmol, 1.29 eq.), $Cu(OAc)_2 \cdot H_2O$ (4.5 mg, 0.0225 mmol, 0.10 eq.), K_2CO_3 (62.2 mg, 0.450 mmol, 2.00 eq.), and TEMPO (35.2 mg, 0.225 mmol, 1.00 eq.). DMA (1.61 mL) and diglyme (3.75 mL) were added. The vial was capped with a septum pierced with a syringe needle to allow access to air, and the reaction mixture was heated with stirring at 60 °C for 18 h.

3.3. No oxidant procedure (20 mol% Cu):

An oven-dried 10 mL vial equipped with a magnetic stir bar was charged with the appropriate sulfonamide (0.225 mmol, 1.0 eq.), the corresponding boronic acid (0.290 mmol, 1.29 eq.), $Cu(OAc)_2 \cdot H_2O$ (9.0 mg, 0.045 mmol, 0.20 eq.), and K_2CO_3 (62.2 mg, 0.450 mmol, 2.00 eq.). DMA (1.61 mL) and diglyme (3.75 mL) were added. The vial was capped with a septum pierced with a syringe needle to allow access to air, and the reaction mixture was heated with stirring at 60 °C for 18 h.

3.4. Oxidant (TEMPO) procedure (20 mol% Cu):

An oven-dried 10 mL vial equipped with a magnetic stir bar was charged with the appropriate sulfonamide (0.225 mmol, 1.00 eq.), the corresponding boronic acid (0.290 mmol, 1.29 eq.), $Cu(OAc)_2 \cdot H_2O$ (9.0 mg, 0.045 mmol, 0.20 eq.), K_2CO_3 (62.2 mg, 0.450 mmol, 2.00 eq.), and TEMPO (35.2 mg, 0.225 mmol, 1.00 eq.). DMA (1.61 mL) and diglyme (3.75 mL) were added. The vial was capped with a septum pierced with a syringe needle to allow access to air, and the reaction mixture was heated with stirring at 60 °C for 18 h.

3.5. Work-up & purification (Common to procedures 3.1-4):

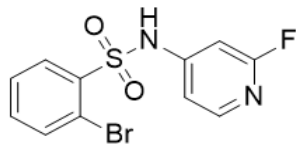
The crude reaction mixture was filtered through a 22 μm syringe filter. DMA and diglyme were evaporated on rotavap at 50 °C. To the residue, EtOAc and saturated aqueous solution of disodium EDTA were added and the solution was stirred for 15 min. After the separation of the phases, the product was extracted two times with EtOAc. The organic phase was washed with saturated brine, dried over Na_2SO_4, filtered and evaporated. The residue was purified on FC using regular SiO_2 using **Solvent A** and **Solvent B** mixture.

3.6 qNMR yields measurements:

^{1}H qNMR measurements were performed using 4-fluoro-2-methoxy-5-nitrobenzoic acid (BLD Pharm, confirmed purity 97.6%) as an internal standard. Samples were prepared from weighed portions of the sufficiently purified analyte and the internal standard. Quantification was based on the ratio of the integrated signal intensities of the analyte and the internal standard, corrected for the respective masses and corresponding molar amounts.

Solvent A: DCM, **Solvent B**: DCM / MeOH / HCOOH, ratio: 90:9:1 solvent mixture.
Gradient: 1 min 0% of B, 13 min 0-100% of B, 10 min 100% of B.

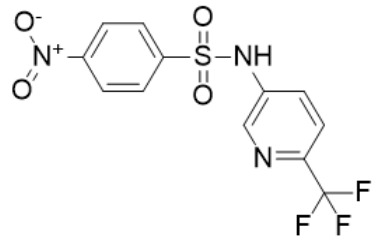
2-Bromo-*N*-(2-fluoropyridin-4-yl)benzenesulfonamide (Table 1, Entries 1-2)



The title compound was prepared according to the Procedures 3.1. and 3.2. from 2-bromobenzene-1-sulfonamide (53.1 mg, 0.225 mmol) and (2-fluoropyridin-4-yl)boronic acid (40.9 mg, 0.290 mmol). Purification afforded the title compound as a solid.

^{1}H NMR (700 MHz, DMSO) δ 11.81 (s, 1H), 8.25 (dd, J = 7.9, 1.7 Hz, 1H), 8.02 (d, J = 5.7 Hz, 1H), 7.88 (dd, J = 7.8, 1.2 Hz, 1H), 7.67 (td, J = 7.7, 1.3 Hz, 1H), 7.61 (td, J = 7.6, 1.7 Hz, 1H), 6.97 (dt, J = 5.9, 1.6 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H) ppm.

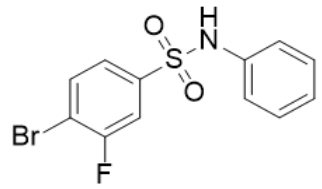
4-nitro-N-[6-(trifluoromethyl)pyridin-3-yl]benzenesulfonamide (Table 1, Entries 3-4)



The title compound was prepared according to the Procedures 3.1. and 3.2. from 4-nitrobenzene-1-sulfonamide (45.5 mg, 0.225 mmol) and (6-(trifluoromethyl)pyridin-3-yl)boronic acid (55.4 mg, 0.290 mmol). Purification afforded the title compound as a solid.

^{1}H NMR (700 MHz, DMSO) δ 11.52 (s, 1H), 8.50 (d, J = 2.5 Hz, 1H), 8.42 – 8.39 (m, 2H), 8.13 – 8.09 (m, 2H), 7.84 (d, J = 8.6 Hz, 1H), 7.78 (dd, J = 8.6, 2.6 Hz, 1H) ppm.

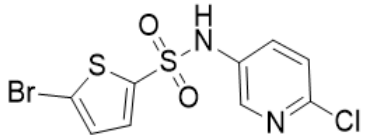
4-Bromo-3-fluoro-*N*-phenylbenzenesulfonamide (Table 1, Entries 5-6)



The title compound was prepared according to the Procedures 3.1. and 3.2. from 4-bromo-3-fluorobenzene-1-sulfonamide (57.2 mg, 0.225 mmol) and phenylboronic acid (35.4 mg, 0.290 mmol). Purification afforded the title compound as a solid.

^{1}H NMR (700 MHz, DMSO) δ 10.42 (s, 1H), 7.93 (dd, J = 8.4, 6.8 Hz, 1H), 7.66 (dd, J = 8.2, 2.1 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.28 – 7.24 (m, 2H), 7.11 – 7.05 (m, 3H) ppm.

5-Bromo-*N*-(6-chloropyridin-3-yl)thiophene-2-sulfonamide (Table 1, Entries 7-8)



The title compound was prepared according to the Procedures 3.1. and 3.2. from 5-bromothiophene-2-sulfonamide (54.5 mg, 0.225 mmol) and (6-chloropyridin-3-yl)boronic acid (45.6 mg, 0.290 mmol). Purification afforded the title compound as a solid.

^{1}H NMR (700 MHz, DMSO) δ 11.00 (s, 1H), 8.15 (dd, J = 2.8, 0.6 Hz, 1H), 7.62 (dd, J = 8.6, 2.9 Hz, 1H), 7.49 (dd, J = 8.6, 0.6 Hz, 1H), 7.45 (d, J = 4.0 Hz, 1H), 7.33 (d, J = 4.1 Hz, 1H) ppm.

4. Full High Throughput Experimentation conditions tables

Table S3. Conditions tested in the First High-throughput Campaign

cond_id	temperature (°C)	R-SO2-NH2 (eq.)	Ar-BOH (eq.)	base	base (eq.)	catalyst	catalyst (mol %)	oxidant	oxidant (mol %)	solvent (volume ratio)	reaction volume [µL]
1	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	none		DMA/Dioxane (3:7)	28.58
2	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	4-Methylmorpholine *N*-oxide, NMO	100	DMA/Dioxane (3:7)	28.58
3	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	*p*-Benzoquinone	100	DMA/Dioxane (3:7)	28.58
4	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	*tert*-Butyl peroxide	50	DMA/Dioxane (3:7)	28.58
5	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	H2O2	50	DMA/Dioxane (3:7)	28.58
6	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Dioxane (3:7)	28.58
7	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	20	none		DMA/Dioxane (3:7)	28.58
8	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	20	Dess-Martin Periodinane, DMP	100	DMA/Dioxane (3:7)	28.58
9	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	20	H2O2	50	DMA/Dioxane (3:7)	28.58
10	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	20	TEMPO	100	DMA	28.58
11	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	none		DMA/Dioxane (3:7)	28.58
12	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA	28.58
13	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	40	none		DMA/Dioxane (3:7)	28.58
14	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	40	*tert*-Butyl peroxide	50	DMA/Dioxane (3:7)	28.58
15	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	40	TEMPO	100	DMA/Dioxane (3:7)	28.58
16	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	40	*p*-Benzoquinone	100	DMA/Dioxane (3:7)	28.58
17	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	40	*tert*-Butyl peroxide	50	DMA/Dioxane (3:7)	28.58

18	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	Selectfluor	100	DMA/Dioxane/Water (3:6.3:0.7)	28.58
19	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	Ammonium persulfate	50	DMA/Dioxane/Water (3:6.3:0.7)	28.58
20	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	Sodium percarbonate	50	DMA/Dioxane/Water (3:6.3:0.7)	28.58
21	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	10	Oxone	50	DMA/Dioxane/Water (3:6.3:0.7)	28.58
22	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	40	Selectfluor	100	DMA/Dioxane/Water (3:6.3:0.7)	28.58
23	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	40	Ammonium persulfate	50	DMA/Dioxane/Water (3:6.3:0.7)	28.58
24	60	1	1.29	2,6-Lutidine	2	$Cu(OAc)_2 \cdot H_2O$	40	Sodium percarbonate	50	DMA/Dioxane/Water (3:6.3:0.7)	28.58
25	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	Selectfluor	100	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
26	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	Ammonium persulfate	50	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
27	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	Sodium percarbonate	50	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
28	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	Oxone	50	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
29	80	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	40	Ammonium persulfate	50	DMA/Dioxane/Water (3:6.3:0.7)	28.58
30	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	Selectfluor	100	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
31	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	Ammonium persulfate	50	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
32	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	Sodium percarbonate	50	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
33	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	Oxone	50	DMA/Dioxane/Water (2.3:7.3:0.7)	28.58
34	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	40	Selectfluor	100	DMA/Dioxane/Water (3:6.3:0.7)	28.58
35	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	40	Oxone	50	DMA/Dioxane/Water (3:6.3:0.7)	28.58
36	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	4-Methylmorpholine *N*-oxide, NMO	100	DMA/Diglyme (3:7)	28.58
37	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	*p*-Benzoquinone	100	DMA/Diglyme (3:7)	28.58

38	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	*tert*-Butyl peroxide	50	DMA/Diglyme (3:7)	28.58
39	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	Dess-Martin Periodinane, DMP	100	DMA/Diglyme (3:7)	28.58
40	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	H2O2	50	DMA/Diglyme (3:7)	28.58
41	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
42	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	20	*p*-Benzoquinone	100	DMA/Diglyme (3:7)	28.58
43	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	40	4-Methylmorpholine *N*-oxide, NMO	100	DMA/Diglyme (3:7)	28.58
44	60	1	1.29	CsF	2	$Cu(OAc)_2 \cdot H_2O$	40	Dess-Martin Periodinane, DMP	100	DMA/Diglyme (3:7)	28.58
45	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	none		DMA/Diglyme (3:7)	28.58
46	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	4-Methylmorpholine *N*-oxide, NMO	100	DMA/Diglyme (3:7)	28.58
47	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	*p*-Benzoquinone	100	DMA/Diglyme (3:7)	28.58
48	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	*tert*-Butyl peroxide	50	DMA/Diglyme (3:7)	28.58
49	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	Dess-Martin Periodinane, DMP	100	DMA/Diglyme (3:7)	28.58
50	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	H2O2	50	DMA/Diglyme (3:7)	28.58
51	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
52	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	20	4-Methylmorpholine *N*-oxide, NMO	100	DMA/Diglyme (3:7)	28.58
53	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	40	none		DMA/Diglyme (3:7)	28.58

Table S4. Conditions tested in the Second High-throughput Campaign

cond_id	temperature (°C)	R-SO2-NH2 (eq.)	Ar-BOH (eq.)	base	base (eq.)	catalyst	catalyst (mol %)	oxidant	oxidant (mol %)	solvent (volume ratio)	reaction volume [µL]
1	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	20	none		DMA/Diglyme (3:7)	28.58
2	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	200	DMA/Diglyme (3:7)	28.58

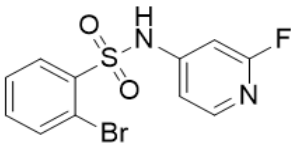
3	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	2.5	none		DMA/Diglyme (3:7)	28.58
4	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	2.5	TEMPO	25	DMA/Diglyme (3:7)	28.58
5	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	2.5	TEMPO	100	DMA/Diglyme (3:7)	28.58
6	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	2.5	TEMPO	200	DMA/Diglyme (3:7)	28.58
7	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	none		DMA/Diglyme (3:7)	28.58
8	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	4-hydroxy-TEMPO	100	DMA/Diglyme (3:7)	28.58
9	60	1	1.29	K_2CO_3	1	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
10	60	1	1.29	Na_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
11	60	1	1.29	KOAc	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
12	60	1	1.29	CsF	4	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
13	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
14	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	25	DMA/Diglyme (3:7)	28.58
15	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	20	TEMPO	100	DMA/Diglyme (3:7)	28.58
16	60	1	1.29	$KHCO_3$	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
17	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO + NMO	75 (each)	DMA/Diglyme (3:7)	28.58
18	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/*n*-BuOH (3:7)	28.58
19	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	20	TEMPO	25	DMA/Diglyme (3:7)	28.58
20	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	5	DMA/Diglyme (3:7)	28.58
21	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	5	none		DMA/Diglyme (3:7)	28.58
22	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	5	TEMPO	25	DMA/Diglyme (3:7)	28.58
23	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	5	TEMPO	100	DMA/Diglyme (3:7)	28.58
24	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	2.5	TEMPO	5	DMA/Diglyme (3:7)	28.58
25	60	1	1.29	K_3PO_4	4	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
26	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	1,2,2,6,6-pentamethylpiperidine	100	DMA/Diglyme (3:7)	28.58
27	60	1	1.29	K_2CO_3	4	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
28	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	4-oxo-TEMPO	100	DMA/Diglyme (3:7)	28.58

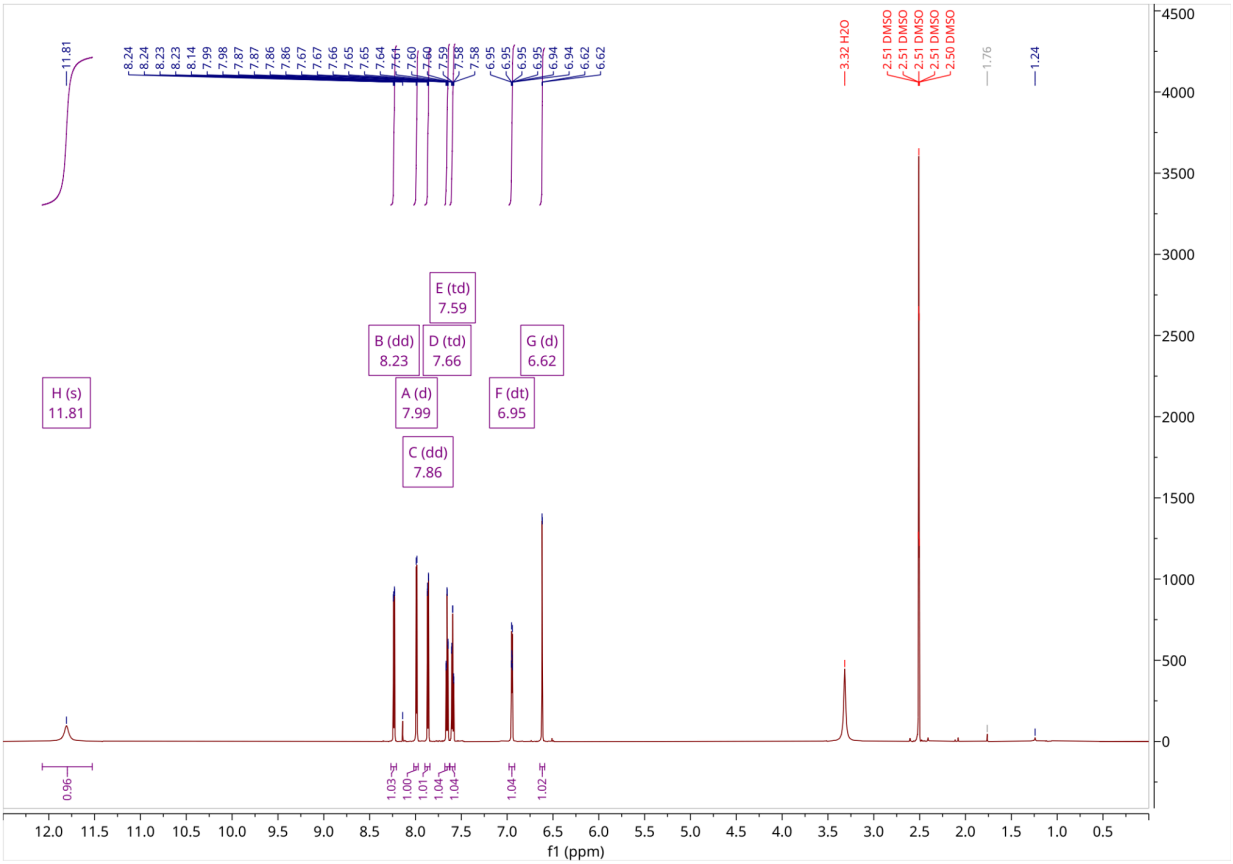
29	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO + *p*-Benzoquinone	50 (each)	DMA/Diglyme (3:7)	28.58
30	80	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
31	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/*n*-BuOH/Water (3:6:1)	28.58
32	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/diglyme/Water (3:6:1)	28.58
33	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	20	TEMPO	200	DMA/Diglyme (3:7)	28.58
34	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme/Water (3:5:2)	28.58
35	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	50	DMA/Diglyme (3:7)	28.58
36	60	1	1	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28
37	60	1	1.29	Cs_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
38	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	5	TEMPO	5	DMA/Diglyme (3:7)	28.58
39	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	5	TEMPO	200	DMA/Diglyme (3:7)	28.58
40	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	20	TEMPO	5	DMA/Diglyme (3:7)	28.58
41	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Dioxane (3:7)	28.58
42	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	20	NMO	100	DMA/Diglyme (3:7)	28.58
43	60	1	1.29	K_2CO_3	2	$Cu(OTf)_2$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
44	60	1	1.29	K_2CO_3	2	$Cu(MeCN)_4PF_6$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
45	60	1	1.29	K_2CO_3	2	$CuCl_2$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
46	60	1	1.29	CsF	4	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
47	60	1	1.29	K_3PO_4	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3:7)	28.58
48	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	40	none		DMA/Diglyme (3:7)	28.58
49	60	1	2	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA/Diglyme (3.5:6.5)	28.58
50	60	1	1.29	KO*t*-Bu	2	$Cu(OAc)_2 \cdot H_2O$	20	none		DMA/*n*-BuOH/Water (3:6:1)	28.58
51	60	1	1.29	KO*t*-Bu	2	$Cu(OAc)_2 \cdot H_2O$	20	TEMPO	25	DMA/*n*-BuOH/Water (3:6:1)	28.58
52	60	1	1.29	K_2CO_3	2	$Cu(OAc)_2 \cdot H_2O$	10	TEMPO	100	DMA	28.58

5. ^{1}H NMR spectra

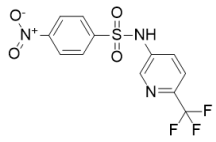
Unless otherwise noted, the recorded NMR spectra correspond to the isolated materials obtained after purification. In some cases, minor residual impurities remained detectable in the spectra; however, these did not preclude unambiguous structural assignment.

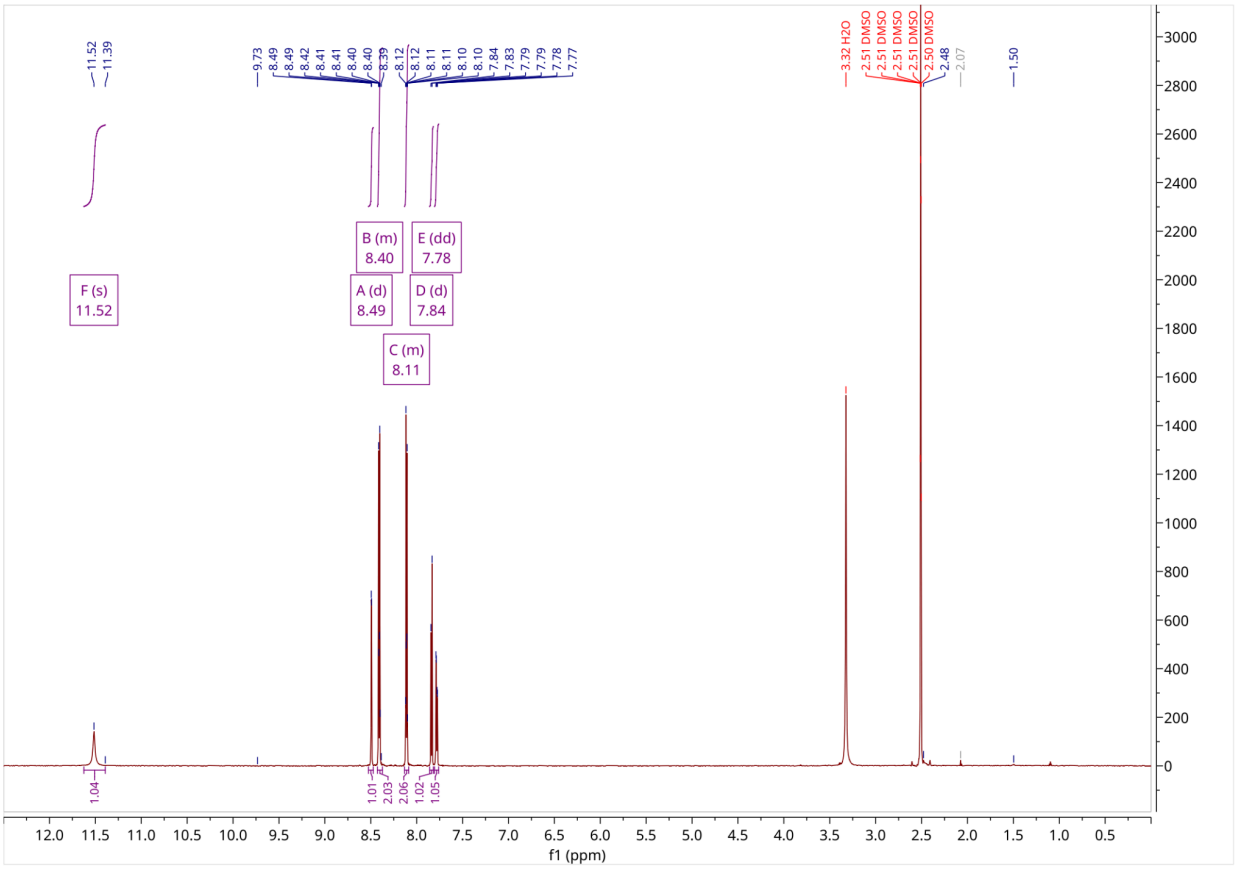
^{1}H NMR of **2-Bromo-*N*-(2-fluoropyridin-4-yl)benzenesulfonamide**



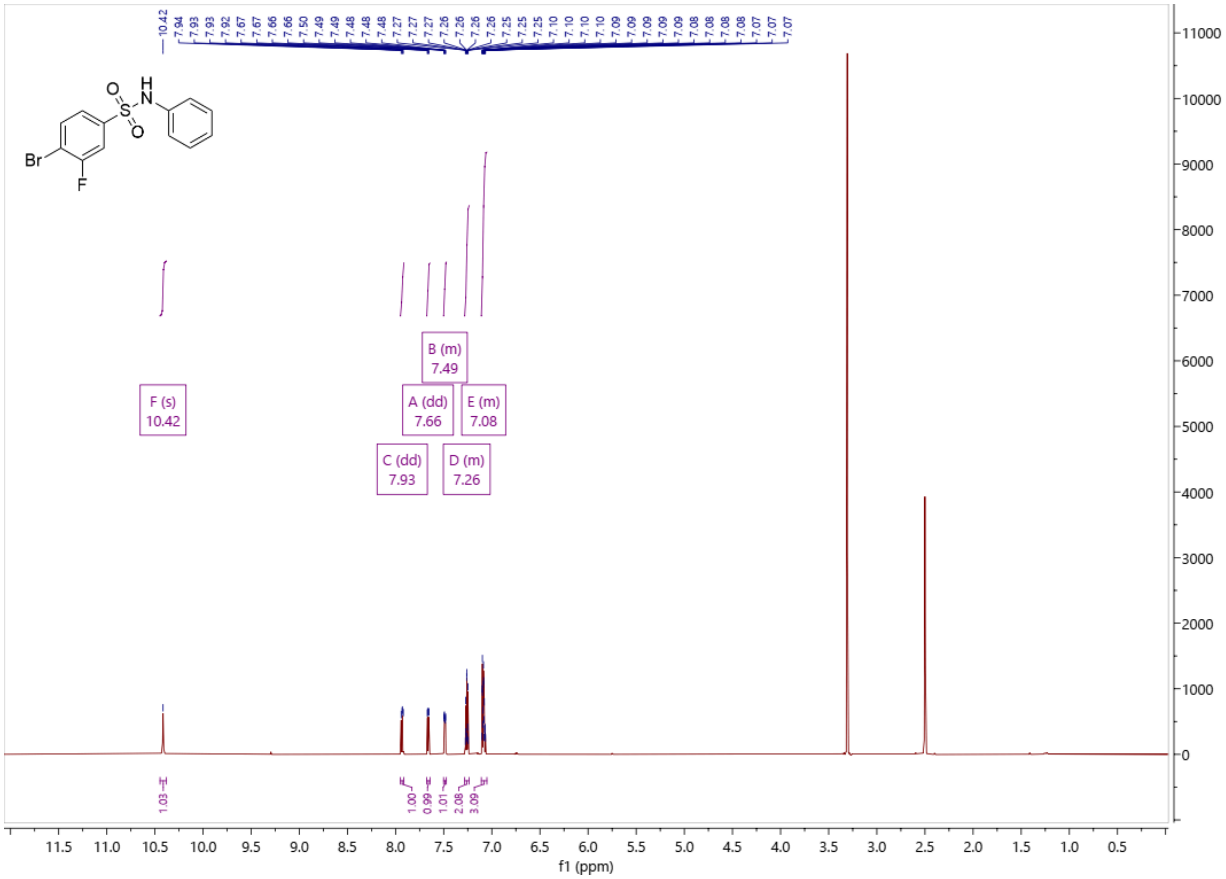


^{1}H NMR of **4-nitro-N-[6-(trifluoromethyl)pyridin-3-yl]benzenesulfonamide**





^{1}H NMR of **4-Bromo-3-fluoro-*N*-phenylbenzenesulfonamide**



^{1}H NMR of **5-Bromo-N-(6-chloropyridin-3-yl)thiophene-2-sulfonamide**