# **Supporting Information**

## Copper-Catalyzed ortho-Halogenation of Protected Anilines

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# Experimental procedures and data

**General Methods.** The corresponding starting materials were synthetized using ovendried glassware under a nitrogen atmosphere containing a teflon-coated stirrer bar and dry septum. All halogenation reactions were performed at ambient  $O_2$  pressure in ovendried 20 mL vessel containing a teflon-coated stirrer bar and dry septum. All reactions were monitored by GC using *n*-hexadecane as an internal standard. Response factors of the products with regard to *n*-hexadecane were obtained experimentally by analyzing known quantities of the substances. GC analyses were carried out using an HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3) and a time program beginning with 2 min at 60 °C followed by 30 °C/min ramp to 300 °C, then 3 min at this temperature. Flash column chromatography was performed using 230-400 mesh ultra-pure silica gel. NMR spectra were obtained on Bruker AC-300 or on Bruker AMX-500 systems using acetone-d<sub>6</sub> and CDCl<sub>3</sub> as solvents, with proton and carbon resonances at 300/500 MHz and 75/125 MHz, respectively. Mass spectral data were acquired on a VG *AutoSpec* mass spectrometer.

Solvents were purified by standard procedures prior to use. Copper salts were dried *in vacuo* at 60 °C prior to use.  $O_2$  was supplied with a purity of 99.99%. All other compounds are commercially available and were used without further purification.

All oxidation reactions involving sodium hypochlorite were carried out with rapid continuous magnetic stirring in Erlenmeyer flasks open to the atmosphere. Sodium hypochlorite was commercial "ultra" laundry bleach containing a stated concentration of 6% NaOCl.

Hydrochloric acid (ca. 1 M) containing 25 wt % of calcium chloride was prepared by dissolving 125 g of anhydrous calcium chloride in 350 mL of water and cooling to room temperature. Once the solution had cooled, 42 mL of concentrated hydrochloric acid were added and the solution was diluted to 500 mL with water.

#### 1. Optimization studies

#### 1.1 Confirmation of Cl<sub>2</sub>CHCHCl<sub>2</sub> as source of chlorine

To confirm that the solvent was the source of chlorine in the reactions shown in the Scheme 1 of the manuscript, we replaced  $Cl_2CHCHCl_2$  (Table S1, entry 1) by  $ClCH_2CH_2Cl$  (DCE, entry 2) as solvent. When the reaction was thus performed in DCE, only 26% of the chlorinated aniline **1-Cl** was detected by GC analysis (entry 2). This percentage of chlorinated aniline could be attributed to the 20 mol% of CuCl<sub>2</sub> used as catalyst. Therefore, it was confirmed that tetrachloroethane was serving as the *in situ* source of the chlorine in our model reaction. In accordance with this hypothesis, in the presence of NCS as chlorinating agent (1.2 equiv), the reactivity was restored and the desired product **1-Cl** was obtained with high *ortho*-regiocontrol after 1 h at 130 °C (entry 3).

	NHSO <sub>2</sub> Py	CuCl <sub>2</sub> (20 mo O <sub>2</sub> (1 atm) solvent 130 °C, 24 h	⊃l%) ——►	NHSO <sub>2</sub> Cl	Py I +		Ру +	NHSO <sub>2</sub> Py Cl Cl 2.4-di-Cl	
	-					<b>U</b> - <b>y</b>		_,	
Entry	solvent		1-CI (%)	[a]	<i>(p)</i> -1	<b>-CI</b> (%) <sup>[a]</sup>		<b>2,4-di-Cl</b> (%) <sup>[a]</sup>	
1	Cl <sub>2</sub> CHCH	ICI <sub>2</sub>	62 (78) <sup>[b</sup>	]					
2	DCE		26						
3 <sup>[c]</sup>	DCE		91		8			traces	

#### Table S1: First optimization studies

[a] GC yields (*n*-hexadecane as internal standard). [b] Isolated yield after column chromatography. [c] Using 1.2 equiv of NCS as chlorine source and with a reaction time of 1h.

#### **1.2** Evaluation of inorganic chlorine sources

Next, a study of the chlorine source was performed using DCE as solvent (Table S2). Unfortunately, inorganic chlorides such as LiCl, NaCl, CsCl or NH<sub>4</sub>Cl proved to be inefficient for the *ortho*-chlorination reaction (entries 2-5). Only upon prolonging the reaction time to 24 h, the *ortho*-halogenated product **1-Cl** could be detected in 16% conversion by GC (18% isolated yield, 78% of the starting material recovered) when LiCl was used (entry 6). As stated before, this percentage of product is attributable to

the 20 mol% of  $CuCl_2$  catalyst present, the catalyst acting as the chlorine-source (see also Table S1, entry 2).

	NHSO <sub>2</sub> Py CuCl O <sub>2</sub> ( Cl-so DCE	₂ (20 mol%) l atm) purce (1.2 equiv) , 130 ºC	NHSO <sub>2</sub> Py Cl	NHSO <sub>2</sub> Py	NHSO <sub>2</sub> Py
	1		1-CI	( <i>p</i> )-1-Cl	2,4-di-Cl
Entry	Reaction time (h)	CI-source	<b>1-Cl</b> (%) <sup>[a]</sup>	<b>1-(p)-Cl</b> (%) <sup>[a]</sup>	<b>2,4-di-Cl</b> (%) <sup>[a]</sup>
1	1	NCS	91	8	traces
2	1	NH₄CI	2	-	-
3	1	LiCI	2	-	-
4	1	NaCl	3	-	-
5	1	CsCl	-	-	-
6	24	LiCl	16	-	-

#### **Table S2: Examination of inorganic chlorine sources**

[a] GC yields (*n*-hexadecane as internal standard).

#### **1.3** Reaction temperature: change from DCE to CH<sub>3</sub>CN

The temperature was found out to be a critical factor. When we tried to reduce the temperature of the model NCS-chlorination reaction of sulfonamide **1** from 130 °C to 100 °C, we observed that the reaction mixture became heterogeneous. In the search for a more polar solvent to ensure the solubility of all the reactants, MeCN was found to be an optimal solvent for this transformation (Table S3). The results observed in the chlorination of **1** with NCS in MeCN at 130 °C nicely parallels those obtained when using DCE as solvent (entry 1, compare with entry 3 of Table S1). The reaction temperature could be reduced to 100 °C without appreciable changes in reactivity or selectivity (entry 2). However, further decrease of the temperature to 80 °C resulted in a loss of the regiocontrol, affording a mixture of three products (**1-Cl**, **1-(p)-Cl** and **2,4di-Cl**) in similar ratios (entry 3). This result could be rationalized assuming that the Cucatalyzed directed *ortho*-chlorination reaction becomes too slow at temperatures below 100 °C, then being competitive the alternative uncatalyzed electrophilic aromatic substitution pathway, thereby resulting in a non-selective transformation.

NHSO <sub>2</sub> F H	<sup>•</sup> Y + NCS (1.2 equiv)	CuCl <sub>2</sub> (10 NCS (1.2 $O_2$ (1 atm CH <sub>3</sub> CN, <b>t</b> 1	) mol%) equiv) ) emperature h	NHSO <sub>2</sub> Py	+ (p)-1-Cl	D₂Py +	NHSO <sub>2</sub> Py Cl 2,4-di-Cl
Entry	Temperat	ure (ºC)	1-CI (%) <sup>[a]</sup>	( <i>p</i> )-1-C	l (%) <sup>[a]</sup>	2,4-di-C	l (%) <sup>[a]</sup>
1	130		83	<5		traces	
2	100		79(95) <sup>[b]</sup>	<5		-	
3	80		39	28		33	

#### **Table S3: Evaluation of reaction conditions**

[a] Conversion yield (GC). [b] Isolated yield after column chromatography.

#### **1.4** Importance of aerobic conditions

Aerobic conditions (O<sub>2</sub> atmosphere) proved to be determinant for achieving high levels of reactivity and selectivity (Table S4). The CuCl<sub>2</sub>-catalyzed reaction of the model sulfonamide **1** with NCS under anaerobic conditions (N<sub>2</sub> atmosphere) resulted in a loss of regioselectivity affording a mixture of three products (**1-Cl**, **1-**(p)-**Cl** and **2,4di-Cl**) (entry 1). This result can be rationalized assuming that O<sub>2</sub> accelerates the Cucatalyzed *ortho*-regiocontrolled reaction and, consequently, in its absence the competitive chlorination through a non-catalyzed electrophilic substitution operates in a competitive fashion resulting in mixture of products. In fact, at identical reaction time, the reaction under O<sub>2</sub> provides a higher conversion towards the *ortho*-chlorinated product with virtually complete regiocontrol (entry 2). Prolonging the reaction time to 1 h under aerobic conditions resulted in full conversion to **1-Cl** while maintaining the regiocontrol.

NHSO <sub>2</sub> I	<sup>⊃</sup> y + NCS (1.2 equiv)	CuCl <sub>2</sub> (10 mol%) <u>O<sub>2</sub> or N<sub>2</sub> (1 atm)</u> MeCN 100 ℃, time		HSO <sub>2</sub> Py CI +	NHSO <sub>2</sub> Py + Cl (p)-1-Cl	NHSO <sub>2</sub> Py Cl Cl 2,4-di-Cl
Entry	aerobic/anaerobi	c time (min)	<b>1</b> (%) <sup>[a]</sup>	<b>1-Cl</b> (%) <sup>[a]</sup>	<b>1-(<i>p</i>)-Cl</b> (%) <sup>[a]</sup>	<b>2,4-di-Cl</b> (%) <sup>[a]</sup>
1	N <sub>2</sub>	45	traces	50	25	22
2	O <sub>2</sub>	45	23	69	<5	traces
3	O <sub>2</sub>	60	traces	79(95) <sup>[b]</sup>	<5	traces

#### Table S4: Influence of aerobic/anaerobic conditions

[a] GC yields (*n*-hexadecane as internal standard). [b] Isolated yield after column chromatography.

#### **1.5** Use of CuCl<sub>2</sub> as stoichiometric chlorinating agent

As expected, the stoichiometric use of  $CuCl_2$  proved to be an alternative to the use of NCS as the chlorinating agent (see Scheme below). Thus, when the reaction was performed under oxygen atmosphere with stoichiometric amount of  $CuCl_2$  (1.0 equiv) in the absence of NCS under otherwise optimized conditions, the reaction proceeded with very high selectivity to produce the *ortho*-chlorinated product **1-Cl** in a 58% GC-yield.



# 1.6 Control Experiments: electrophilic halogenations IN THE ABSENCE OF Cu-CATALYST

No reaction was observed in the *NCS*-halogenation of the deactivated p-CF<sub>3</sub>substituted aniline derivative (**3**), the starting material being recovered unaltered. Meanwhile, control *NBS*-halogenations in the absence of Cu-catalysis of substrates with electron-releasing substituents such as the *p*-MeO- and *p*-Me-substituted derivatives (**2**  and  $\mathbf{8}$ , respectively) led to very low reactivity and selectivity. In the case of aniline  $\mathbf{1}$ , the *p*-Br derivative was formed with excellent regiocontrol.



[a] GC yields (n-hexadecane as internal standard).

#### **1.7** Bromination of aniline 1

While the NBS-uncatalyzed bromination of 1 led to the formation of the *p*-Br derivative with excellent regiocontrol, the CuBr<sub>2</sub>-catalyzed NBS-bromination of 1 provided a mixture of *o*- and *p*-substitution.

NHSO <sub>2</sub> Py	[CuBr <sub>2</sub> ] NBS (1.2 equiv) MeCN, 100 °C, 4 h	► NHSO <sub>2</sub> Py + Br <b>1-(</b> <i>p</i> )-Br	NHSO <sub>2</sub> Py Br 1-Br
		1-( <i>p</i> )-Br (%) <sup>[a]</sup>	1-Br (%) <sup>[a]</sup>
	no copper	90	n.d.
	10 mol% CuBr <sub>2</sub>	46	42

[a] GC yields (n-hexadecane as internal standard).

#### 2 Typical procedure for the *N*-sulfonylation of anilines

# Synthesis of *N*-phenylpyridine-2-sulfonamide (1).<sup>1</sup> To a solution of aniline (364 $\mu$ L,

NHSO<sub>2</sub>Py 4.00 mmol, 1.00 equiv) in THF (40 mL), pyridine (388  $\mu$ L, 4.80 mmol, 1.20 equiv) and 2-pyridylsulfonyl chloride (852 mg, 4.80 mmol, 1.20 equiv) were successively added dropwise at 0 °C

and under N<sub>2</sub> atmosphere. The mixture was warmed to room temperature and stirred overnight. During this time, a gradual formation of a precipitate was observed. The resulting mixture was then suction filtered through a 6-cm fritted glass funnel (coarse) into a round-bottomed flask, and the filter cake was rinsed with THF (3 x 10 mL). To the resulting filtrate and the washes, water (20 mL) was added and the THF was removed by evaporation at reduced pressure, yielding a suspension of a white solid in the aqueous medium. This solid was collected by filtration, washed sequentially with toluene (2 x 5 mL) and diethyl ether (2 x 5 mL). Then it was transferred to a round-bottomed flask, and dried at 1.0 mmHg to provide 1 as a white powder; yield: 862 mg (92%); mp = 170-172 °C. The analytical data (NMR, HRMS analysis) matched those reported in the literature for *N*-phenylpyridine-2-sulfonamide [CAS: 103863-00-9]. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.19 (s, 1H), 8.69 (dd, *J* = 3.6, 1.2, 1H), 8.06 – 7.98 (m, 1H), 7.98 – 7.91 (m, 1H), 7.59 (ddd, *J* = 7.2, 4.8, 1.5, 1H), 7.33 – 7.14 (m, 4H), 7.03 (t, *J* = 7.2 Hz, 1H). ESI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>S (M+H)<sup>+</sup>: 235.0535; Found: 235.0537.

N-(4-Methoxyphenyl)pyridine-2-sulfonamide (2). Compound 2 was preparedfollowing the typical procedure from 4-methoxyaniline(493 mg, 4.00 mmol) to give 2 as a white solid; yield: 951 mg(90%); mp = 167-168 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)

δ: 8.93 (s, 1H), 8.71 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 7.98 (td, J = 7.7, 1.7 Hz, 1H), 7.86 (dt, J = 7.9, 1.1 Hz, 1H), 7.58 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.15 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 9.0 Hz, 2H), 3.70 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz) δ: 158.3, 158.1, 150.8, 139.0, 130.8, 127.7, 125.5, 123.5, 114.9, 55.6. ESI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>O<sub>3</sub>S (M+H)<sup>+</sup>: 265.0641; Found: 265.0649.

<sup>&</sup>lt;sup>[1]</sup> A. García-Rubia, B. Urones, R. Gómez Arrayás, J. C. Carretero, *Angew. Chem. Int. Ed.* **2011**, *50*, 10927.

*N*-(*p*-Tolyl)pyridine-2-sulfonamide (8). Compound 8 was prepared following the typical procedure from *p*-toluidine (440 µL, 4.00 mmol) to give 8 as a white solid; yield: 934 mg (94%); mp = 196-197 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.04 (s, 1H), 8.69 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.00 (td, J = 7.7, 1.7 Hz, 1H), 7.92 (dt, J = 7.8, 1.1 Hz, 1H), 7.58 (ddd, J = 7.5, 4.7, 1.3 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.08 – 6.98 (m, 2H), 2.20 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 158.1, 150.9, 139.0, 135.9, 135.0, 130.3, 127.8, 123.5, 122.6, 20.7. ESI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>S (M+H)<sup>+</sup>: 249.0692; Found: 249.0691.

*N*-(4-Iodophenyl)pyridine-2-sulfonamide (9). Compound 9 was prepared following the typical procedure from 4-iodoaniline (876 mg, 4.00 mmol) to give 9 as a white solid; yield: 1.28 g (89%); mp = 193-194 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.34 (s, 1H), 8.69 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.05 (td, J = 7.6, 1.7 Hz, 1H), 7.98 (ddd, J = 7.9, 1.5, 0.9 Hz, 1H), 7.67 – 7.55 (m, 3H), 7.12 (d, J = 8.7 Hz, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 157.8, 151.0, 139.2, 138.8, 128.1, 123.7, 123.6, 123.5, 88.3. ESI<sup>+</sup> calcd. for  $C_{11}H_{10}N_2O_2SI (M+H)^+$ : 360.9502; Found: 360.9492.

N-(4-Bromophenyl)pyridine-2-sulfonamide(10). Compound10waspreparedNHSO2Pyfollowing the typical procedure from 4-bromoaniline(688 mg,4.00 mmol) to give 10 as a white solid; yield:1.09 g (87%); mp= 192-193 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ :9.34 (s, 1H),

8.69 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.04 (td, J = 7.6, 1.7 Hz, 1H), 7.98 (dt, J = 7.9, 1.2 Hz, 1H), 7.61 (ddd, J = 7.4, 4.7, 1.4 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 157.8, 151.0, 139.2, 138.2, 138.1, 132.8, 128.1, 123.6, 123.6, 123.5, 117.7. ESI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>SBr (M+H)<sup>+</sup>: 312.9640; Found: 312.9645.

N-(4-Chlorophenyl)pyridine-2-sulfonamide(11).Compound11waspreparedNHSO2Pyfollowing the typical procedure from 4-chloroaniline(510 mg,4.00 mmol) to give 11 as a white solid; yield:817 mg (76%); mp= 182-184 °C.<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ :9.33 (s, 1H),

8.69 (dd, J = 4.5, 1.0 Hz, 1H), 8.10 – 8.00 (m, 1H), 8.00 – 7.94 (m, 1H), 7.61 (ddd, J = 7.3, 4.7, 1.4 Hz, 1H), 7.37 – 7.20 (m, 4H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ :

157.8, 151.0, 139.2, 137.6, 130.1, 129.8, 128.1, 123.5, 123.4, 123.4. **ESI**<sup>+</sup> calcd. for  $C_{11}H_{10}N_2O_2SCl (M+H)^+$ : 269.0146; Found: 269.0155.

N-(4-Fluorophenyl)pyridine-2-sulfonamide (12). Compound 12 was prepared here following the typical procedure from 4-fluoroaniline (379 μL, 4.00 mmol) to give 12 as a white solid; yield: 797 mg (79%); mp = 156-157 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz) δ: 9.21 (s, 1H), 8.70 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.02 (td, J = 7.7, 1.7 Hz, 1H), 7.92 (dt, J = 7.9, 1.1Hz, 1H), 7.60 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.36 – 7.22 (m, 2H), 7.01 (t, J = 8.8 Hz, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz) δ: 160.9 (d,  $J_{C-F} = 242.0$  Hz), 157.9, 150.9, 139.1, 134.7 (d,  $J_{C-F} = 2.7$  Hz), 127.9, 124.8 (d,  $J_{C-F} = 8.3$  Hz), 123.5, 116.4 (d,  $J_{C-F} = 22.8$  Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz) δ: 57.8. ESI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>FS (M+H)<sup>+</sup>: 253.0441; Found: 253.0437.

N-[4-(Trifluoromethyl)phenyl]pyridine-2-sulfonamide (3). Compound 3 wasprepared following the typical procedure from 4-(trifluoromethyl)aniline (502 µL, 4.00 mmol) to give 3 as awhite solid; yield: 919 mg (76%); mp = 179-180 °C. <sup>1</sup>H NMR

(acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.69 (s, 1H), 8.69 (d, J = 4.7 Hz, 1H), 8.07 (d, J = 3.4 Hz, 2H), 7.72 – 7.46 (m, 5H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 157.7, 151.1, 142.6, 139.4, 128.9 (q,  $J_{C-F} = 270.7$  Hz), 128.3, 127.1 (q,  $J_{C-F} = 3.8$  Hz), 126.0 (q,  $J_{C-F} = 32.5$  Hz), 123.5, 120.52. <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz)  $\delta$ : 114.9. ESI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub>S (M+H)<sup>+</sup>: 303.0409; Found: 303.0413.

N-(4-Acetylphenyl)pyridine-2-sulfonamide (13). Compound 13 was prepared following the typical procedure from 1-(4-aminophenyl)ethanone (541 mg, 4.00 mmol) to give 13 as a white solid; yield: 869 mg (79%); mp = 231-232 °C.

<sup>1</sup>**H NMR (acetone-d<sub>6</sub>, 300 MHz)** δ: 8.68 (dt, J = 4.7, 1.3 Hz, 1H), 8.09 (dd, J = 1.3, 0.8 Hz, 1H), 8.07 (dd, J = 1.3, 0.6 Hz, 1H), 7.87 (d, J = 9.1 Hz, 2H) 7.70 – 7.58 (m, 1H), 7.40 (d, J = 9.1 Hz, 2H), 2.48 (s, 3H). <sup>13</sup>**C NMR (acetone-d<sub>6</sub>, 75 MHz)** δ: 157.9, 151.1, 143.2, 139.4, 135.5, 133.7, 130.4, 128.2, 123.5, 119.6, 26.4. **EI**<sup>+</sup> calcd. for C<sub>13</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>S (M)<sup>+</sup>: 276.0569; Found: 276.0566.

Methyl 4-[N-(2-pyridyl)sulfonylamino]benzoate (14). Compound 14 was prepared

the typical procedure from methyl following aminobenzoate (605 mg, 4.00 mmol) to give 14 as a white solid; yield: 748 mg (64%); mp = 222-224 °C. The

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analytical data (NMR, GC-MS analysis) matched those reported in the literature for methyl 4-[N-(2-pyridyl)sulfonylamino]benzoate [CAS: 1352965-44-6]. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.66 (s, 1H), 8.68 (d, J = 4.6 Hz, 1H), 8.07 (d, J = 3.5 Hz, 2H), 7.88 (d, J = 8.8 Hz, 2H), 7.70 – 7.52 (m, 1H), 7.41 (d, J = 8.7 Hz, 2H), 3.82 (s, 3H). **ESI**<sup>+</sup> calcd. for  $C_{13}H_{13}N_2O_4S$  (M+H)<sup>+</sup>: 293.0590; Found: 293.0594.

N-(4-Cyanophenyl)pyridine-2-sulfonamide (15). Compound 15 was prepared following the typical procedure from 4-cyanoaniline (473 mg, .NHSO<sub>2</sub>Pv 4.00 mmol) to give 15 as a white solid; yield: 842 mg (81%); NC mp = 240-241 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.83 (s,

1H), 8.69 (dt, J = 4.7, 1.2 Hz, 1H), 8.11 (t, J = 1.4 Hz, 1H), 8.09 (d, J = 1.3 Hz, 1H), 7.77 – 7.54 (m, 3H), 7.56 – 7.43 (m, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz) δ: 157.6, 151.2, 143.3, 139.5, 134.2, 128.4, 123.5, 120.3, 119.1, 107.7. EI<sup>+</sup> calcd. for  $C_{12}H_9N_3O_2S$  (M)<sup>+</sup>: 259.0415; Found: 259.0403.

N-(4-Nitrophenyl)pyridine-2-sulfonamide (16). Compound 16 was prepared following the typical procedure from 4-nitroaniline (552 mg, NHSO<sub>2</sub>Py 4.00 mmol) to give 16 as a white solid; yield: 801 mg (72%); O<sub>2</sub>N mp = 253-254 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.69 (dt, J = 4.7 Hz, 1.3, 1H), 8.16 (d, J = 9.3 Hz, 2H), 8.13 (d, J = 1.4 Hz, 1H), 8.12 (t, J = 1.4 Hz, 100 Hz)J = 1.4 Hz, 1H), 7.72 – 7.62 (m, 1H), 7.55 (d, J = 9.3 Hz, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, **125 MHz**) δ: 157.5, 151.2, 145.1, 144.4, 139.6, 128.6, 125.8, 123.5, 119.6. **EI**<sup>+</sup> calcd. for  $C_{11}H_9N_3O_4S(M)^+$ : 279.0314; Found: 279.0301.

N-(3-Fluorophenyl)pyridine-2-sulfonamide (17). Compound 17 was prepared NHSO<sub>2</sub>Py following the typical procedure from 3-fluoroaniline (384 µL, 4.00 mmol) to give 17 as a white solid; yield: 837 mg (83%); mp = 164-165 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 9.53 (s, 1H), 8.70 (d, J = 4.7 Hz, 1H), 8.06 (td, J = 7.6, 1.7 Hz, 1H), 8.03 (dt, J = 7.9, 1.3 Hz, 1H), 7.63 (ddd, J = 7.4, 4.7, 1.4 Hz, 1H), 7.26 (td, J = 8.3, 6.6 Hz, 1H), 7.16 – 7.07 (m, 2H), 6.80 (td, J = 8.5, 2.2 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 163.7 (d,  $J_{C-F} = 243.4$  Hz), 157.7, 151.0, 140.6 (d,  $J_{C-F} = 10.6$  Hz), 139.3, 131.4 (d,  $J_{C-F} = 9.5$  Hz), 128.2, 123.5, 116.9 (d,  $J_{C-F} =$  3.0 Hz), 111.5 (d,  $J_{C-F} = 21.3$  Hz), 108.1 (d,  $J_{C-F} = 25.8$  Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)  $\delta$ : -113.3. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>FS (M)<sup>+</sup>: 252.0369; Found: 252.0359.

N-(3-Isopropylphenyl)pyridine-2-sulfonamide (18). Compound 18 was preparedfollowing the typical procedure from 3-isopropylaniline(541 mg, 4.00 mmol) to give 18 as a white solid; yield: 884 mg $(80%); mp = 185-186 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz) <math>\delta$ :

9.11 (s, 1H), 8.70 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.01 (td, J = 7.7, 1.7 Hz, 1H), 7.95 (dt, J = 7.9, 1.1 Hz, 1H), 7.59 (ddd, J = 7.6, 4.7, 1.3 Hz, 1H), 7.16 – 7.09 (m, 2H), 7.07 (ddd, J = 8.0, 2.2, 1.2 Hz, 1H), 6.93 (dt, J = 7.6, 1.5 Hz, 1H), 2.78 (h, J = 6.9 Hz, 1H), 1.13 (d, J = 6.9 Hz, 6H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.1, 150.9, 150.6, 139.0, 138.5, 129.7, 127.8, 123.6, 123.4, 120.0, 119.5, 34.6, 24.1. EI<sup>+</sup> calcd. for C<sub>14</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S (M)<sup>+</sup>: 276.0932; Found: 276.0940.

N-[3-(Trifluoromethyl)phenyl]pyridine-2-sulfonamide (19). Compound 19 was  $F_{3}C \longrightarrow NHSO_{2}Py \qquad prepared following the typical procedure from 3-$ (trifluoromethyl)aniline (575 µL, 4.00 mmol) to give 19 as awhite solid; yield: 883 mg (73%); mp = 190-191 °C. <sup>1</sup>H NMR

(acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 9.57 (s, 1H), 8.70 (ddd, J = 4.7, 1.8, 1.0 Hz, 1H), 8.11 – 8.05 (m, 1H), 8.05 – 8.00 (m, 1H), 7.68 – 7.61 (m, 2H), 7.61 – 7.55 (m, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.39 (dt, J = 7.6, 0.8 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 157.7, 151.1, 139.7, 139.4, 131.6 (q,  $J_{C-F} = 32.3$  Hz), 131.0, 128.2, 124.9, 124.9 (q,  $J_{C-F} = 271.7$  Hz), 123.4, 121.6 (q,  $J_{C-F} = 3.9$  Hz), 117.8 (q,  $J_{C-F} = 4.0$  Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)  $\delta$ : -63.4. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub>S (M)<sup>+</sup>: 302.0337; Found: 302.0324.

*N*-(3-Chloro-4-iodophenyl)pyridine-2-sulfonamide (20). Compound 20 was prepared following the typical procedure from 3-chloro-4-iodoaniline (1.01 g, 4.00 mmol) to give 20 as a white solid; yield: 1.10 g (70%); mp = 205-206 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ :

9.54 (s, 1H), 8.70 (ddd, J = 4.7, 1.7, 1.0 Hz, 1H), 8.08 (td, J = 7.6, 1.7 Hz, 1H), 8.03 (dt, J = 7.8, 1.1 Hz, 1H) 7.79 (d, J = 8.6 Hz, 1H), 7.64 (ddd, J = 7.5, 4.7, 1.3 Hz, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.06 (dd, J = 8.7, 2.5 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 157.6, 151.1, 141.5, 140.6, 139.4, 139.2, 128.3, 123.4, 121.6, 121.2, 91.6. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SCII (M)<sup>+</sup>: 393.9040; Found: 393.9031.

N-(4-Bromo-3-chlorophenyl)pyridine-2-sulfonamide (21). Compound 21 was

prepared following the typical procedure from 4-bromo-3chloroaniline (826 mg, 4.00 mmol) to give **21** as a white solid; yield: 1.15 g (83%); mp = 195-197 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>,

**500 MHz**)  $\delta$ : 9.54 (s, 1H), 8.70 (ddd, J = 4.7, 1.6, 0.9 Hz, 1H), 8.08 (td, J = 7.6, 1.7 Hz, 1H), 8.03 (dt, J = 7.8, 1.1 Hz, 1H), 7.64 (ddd, J = 7.5, 4.7, 1.3 Hz, 1H), 7.59 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 2.6 Hz, 1H), 7.21 (dd, J = 8.7, 2.6 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 157.6, 151.1, 139.6, 139.4, 135.0, 134.9, 128.3, 123.4, 122.7, 121.3, 117.2. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SBrCl (M)<sup>+</sup>: 345.9178; Found: 345.9162.

 $N-(3,4-\text{Dichlorophenyl}) \text{pyridine-2-sulfonamide} (22). \text{ Compound } 22 \text{ was prepared} \\ Cl \rightarrow NHSO_2Py \\ following the typical procedure from 3,4-dichloroaniline (648 mg, 4.00 mmol) to give 22 as a white solid; yield: 1.03 g (85%); mp = 183-184 °C. <sup>1</sup>H NMR (acetone-d_6, 500 MHz) \\ \delta: 9.54 (s, 1H), 8.70 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.08 (td, J = 7.6, 1.7 Hz, 1H), 8.03 (dt, J = 7.8, 1.1 Hz, 1H), 7.65 (ddd, J = 7.6, 4.7, 1.3 Hz, 1H), 7.53 (d, J = 2.6 Hz, 1H),$  $7.44 (d, J = 8.7 Hz, 1H), 7.28 (dd, J = 8.8, 2.5 Hz, 1H). <sup>13</sup>C NMR (acetone-d_6, 125 MHz) \\ \delta: 157.6, 151.1, 139.4, 139.0, 132.9, 131.7, 128.3, 127.9, 123.4, 122.9, 121.3. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SCl<sub>2</sub> (M)<sup>+</sup>: 301.9684; Found: 301.9689.$ 

*N*-(Benzo[d][1,3]dioxol-5-yl)pyridine-2-sulfonamide (23). Compound 23 was prepared following the typical procedure from 1,3-benzodioxol-5amine (547 mg, 4.00 mmol) to give 23 as a white solid; yield: 945 mg (85%); mp = 178-179 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.00 (s, 1H), 8.72 (ddd, *J*=4.7, 1.7, 0.9, 1H), 8.07 –

7.98 (m, 1H), 7.96 – 7.86 (m, 1H), 7.61 (ddd, *J*=7.6, 4.7, 1.2, 1H), 6.81 (t, *J*=1.3, 1H), 6.67 (d, *J*=1.3, 2H), 5.93 (s, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 157.9, 150.9, 148.7, 146.1, 139.1, 132.2, 127.8, 123.5, 116.9, 108.7, 105.4, 102.4. **EI**<sup>+</sup> calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>4</sub>S (M)<sup>+</sup>: 278.0361; Found: 278.0370.

4-Methyl-*N*-phenylbenzenesulfonamide (4). Compound 4 was prepared following the NHTs typical procedure from aniline (364 μL, 4.00 mmol) and 4-methylbenzenesulfonyl chloride (915 mg, 4.80 mmol, 1.2 equiv) to give 4 as a white solid; yield: 752 mg (76%); mp = 96-97 °C. The analytical data (NMR, GC-MS analysis) matched those reported in the literature for 4-methyl-*N*-phenylbenzenesulfonamide [CAS: 68-34-8]. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz) δ: 8.90

(s, 1H), 7.67 (d, *J*=8.3, 2H), 7.31 (d, *J*=7.9, 2H), 7.26 – 7.16 (m, 4H), 7.13 – 7.00 (m, 1H), 2.35 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz) δ: 144.0, 136.7, 136.2, 129.8, 129.4, 127.4, 125.4, 121.6, 21.6.

*N*-Methyl-*N*-phenylpyridine-2-sulfonamide (7). Compound 7 was prepared from *N*-Me methylaniline (433 µL, 4.00 mmol), according to the already described protocol by our group,<sup>1</sup> to give 7 as a white solid; yield: 844 mg (85%); mp = 100-102 °C. The analytical data (NMR, HRMS analysis) matched those reported in the literature for *N*-methyl-*N*-phenylpyridine-2-sulfonamide [CAS: 1352965-24-2]. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.78 (dd, *J* = 4.7, 0.8 Hz, 1H), 8.01 (td, *J* = 7.8, 1.7 Hz, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.66 (ddd, *J* = 7.7, 4.7, 1.2 Hz, 1H), 7.36 – 7.15 (m, 5H), 3.48 (s, 3H). EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>S (M)<sup>+</sup>: 248.0619; Found: 248.0630.

#### 3. Typical procedure for the synthesis of *N*-(pyrimidyl)sulfonyl anilines

#### Synthesis of N-(4-chloro-2-fluorophenyl)pyrimidine-2-sulfonamide (26-Cl). A

F

in a mixture of  $CH_2Cl_2$  (25 mL) and a 1 M solution of HCl having 25 wt % of  $CaCl_2$  (25 mL) was stirred in a 125-mL Erlenmeyer flask for 10 min at -30 to -25 °C (internal

solution of 2-mercaptopyrimidine (0.561 g, 5 mmol, 1.00 equiv)

temperature, maintained by intermittent cooling with a dry ice-acetone bath). Then calcium chloride 6-hydrate (19 g) was dissolved in sodium hypochlorite (6% solution, 0.74 M, 24 mL, 18 mmol, 3.3 equiv), and the resulting clear solution was added dropwise with *very rapid* stirring to the original solution of 2-mercaptopyrimidine while maintaining the internal temperature at -30 to -25 °C. The resulting mixture was stirred for 15 min at -30 to -25 °C (internal temperature) before it was diluted with of ice/water (25 mL) and transferred to a separatory funnel (pre-cooled with ice water). The organic phase was rapidly separated and collected in a clean 125-mL Erlenmeyer flask cooled in a dry ice-acetone bath. 2-Chloro-4-fluoroaniline (1.49 mL, 12.5 mmol, 2.5 equiv) was added with stirring, whereupon the mixture became a white suspension. The flask was moved to an ice-water bath and the suspension was stirred for 30 min at 0 °C. To the resulting suspension was added 1 M phosphoric acid and the organic phase was dried

(MgSO<sub>4</sub>) and concentrated under reduced pressure. The residue was purified by flash chromatography (*n*-hexane-EtOAc 2:1) to afford **26-Cl** as a pale yellow solid; yield: 1.15 g (80%); mp = 139-140 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.99 (d, J = 4.8 Hz, 2H), 8.89 (s, 1H), 7.77 (t, J = 4.8 Hz, 1H), 7.66 (dd, J = 9.0, 5.6 Hz, 1H), 7.29 (dd, J = 8.4, 2.9 Hz, 1H), 7.13 (ddd, J = 9.0, 8.0, 2.9 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 166.5, 161.1 (d,  $J_{C-F} = 246.7$  Hz), 159.7, 131.7, 130.8 (d,  $J_{C-F} = 10.7$  Hz), 129.2 (d,  $J_{C-F} = 8.9$  Hz), 124.9, 117.6 (d,  $J_{C-F} = 26.2$  Hz), 115.5 (d,  $J_{C-F} = 22.4$  Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz)  $\delta$ : 61.9. EI<sup>+</sup> calcd. for C<sub>10</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>FSC1 (M)<sup>+</sup>: 286.9932; Found: 286.9924.

*N*-(2-Bromo-4-methylphenyl)pyrimidine-2-sulfonamide (27). Compound 27 was prepared following the typical procedure from 2-bromo-4methylaniline (1.55 mL, 12.5 mmol), to give 27 as a white solid; yield: 1.21 g (74%); mp = 127-129 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.98 (d, *J* = 4.9 Hz, 2H), 7.75 (t, *J* = 4.9 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.41 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.14 (ddd, *J* = 8.3, 2.0, 0.8 Hz, 1H), 2.28 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 166.5, 159.7, 138.7, 134.0, 133.6, 129.8, 127.0, 124.8, 119.2, 20.4. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>3</sub>O<sub>2</sub>SBr (M)<sup>+</sup>: 326.9677; Found: 326.9682.

*N*-(4-Fluorophenyl)pyrimidine-2-sulfonamide (26). Compound 26 was prepared following the typical procedure from 4-fluoroaniline (1.18 mL, 12.5 mmol), to give 26 as a white solid solid; yield: 670 mg (54%); mp = 145-147 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 9.32 (s, 1H), 8.97 (d, *J* = 4.9 Hz, 2H), 7.72 (t, *J* = 4.9 Hz, 1H), 7.38 (dd, *J* = 9.2 Hz, 4.8, 2H), 7.16 – 6.87 (m, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 166.3, 160.7 (d, *J<sub>C</sub>*-*<sub>F</sub>* = 241.9 Hz), 159.7, 134.7 (d, *J<sub>C</sub>*-*<sub>F</sub>* = 2.9 Hz), 124.8, 124.7, 116.4 (d, *J<sub>C</sub>*-*<sub>F</sub>* = 22.9 Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz)  $\delta$ : 57.8. EI<sup>+</sup> calcd. for C<sub>10</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub>FS (M)<sup>+</sup>: 253.0321; Found: 253.0314.

N-(p-Tolyl)pyrimidine-2-sulfonamide (29). Compound 29 was prepared following the



typical procedure from *p*-toluidine (1.38 mL, 12.5 mmol), to give **29** as a white solid; yield: 1.02 g (82%); mp = 134-135 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 9.23 (s, 1H), 8.96 (d,

J = 4.8 Hz, 2H), 7.70 (t, J = 4.9 Hz, 1H), 7.22 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 2.22 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz) \delta: 166.4, 159.6, 135.9, 135.0,

130.3, 124.6, 122.5, 20.7. **EI**<sup>+</sup> calcd. for  $C_{11}H_{11}N_3O_2S$  (M)<sup>+</sup>: 249.0572; Found: 249.0569.

Methyl 4-(pyrimidine-2-sulfonamido)benzoate (30). Compound 30 was prepared  $NHSO_2Pyr$  following the typical procedure from methyl 4-amino benzoate (1.89 g, 12.5 mmol), to give 30 as a white solid; yield: 1.20 mg (82%); mp = 189-190 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.98 (d, J = 4.9 Hz, 2H), 7.90 (d, J = 9.0 Hz, 2H), 7.74 (t, J = 4.9 Hz, 1H), 7.44 (d, J = 9.0 Hz, 2H), 3.83 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 166.6, 166.1, 159.8, 143.4, 131.4, 126.4, 125.0, 119.8, 52.2. EI<sup>+</sup> calcd. for C<sub>15</sub>H<sub>7</sub>N<sub>3</sub>O<sub>4</sub>S (M)<sup>+</sup>: 293.0470; Found: 293.0482.

#### 3.1. Synthesis of *N*-(4-chloro-2-methylphenyl)pyrimidine-2-sulfonamide (28)



*N*-(*o*-Tolyl)pyrimidine-2-sulfonamide (I). Compound I was prepared following the typical procedure from *ortho*-toluidine (1.33 mL, 12.5 mmol), to give I as a white solid; yield: 797 mg (64%); mp = 99-101 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)  $\delta$ : 8.90 (d, J = 4.9 Hz, 2H), 7.49 (t, J = 4.9 Hz, 1H), 7.38 (dd, J = 7.8, 1.5 Hz, 1H), 7.16 – 7.11 (m, 1H), 7.11 – 7.02 (m, 2H), 6.84 (s, 1H), 2.31 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$ : 165.6, 158.8, 158.7, 134.2, 131.2, 131.1, 127.1, 126.3, 123.5, 123.3, 18.0. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>O<sub>2</sub>S (M)<sup>+</sup>: 249.0572; Found: 249.0576.

N-(4-Chloro-2-methylphenyl)pyrimidine-2-sulfonamide (28). An oven-dried, nitrogen-flushed 20 mL vessel was charged with the corresponding *N*-protected aniline **I** (0.40 mmol, 1.00 equiv) and NCS (64.0 mg, 0.48 mmol, 1.2 equiv). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed

with oxygen three times. Under the atmosphere of oxygen, MeCN (2 mL) was added *via* syringe and the resulting mixture was stirred at 100 °C for 1 h. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by

column chromatography (*n*-hexane-EtOAc 5:1), yielding the corresponding chlorinated product **28** as a white solid; yield: 107 mg (94%); mp = 103-104 °C. <sup>1</sup>H NMR (acetoned<sub>6</sub>, **500** MHz)  $\delta$ : 9.00 (dd, J = 4.9, 0.7 Hz, 2H), 8.81 (s, 1H), 7.75 (td, J = 4.9, 0.6 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.25 (d, J = 2.7 Hz, 1H), 7.12 (dd, J = 8.6, 2.5 Hz, 1H), 2.38 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, **125** MHz)  $\delta$ : 166.8, 159.7, 136.8, 135.1, 131.8, 131.2, 127.7, 127.8, 127.1, 124.7, 18.2. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>10</sub>ClN<sub>3</sub>O<sub>2</sub>S (M)<sup>+</sup>: 283.0182; Found: 283.0181.

#### 4. Synthesis of *N*-phenyl-2-pyridinecarboxamide (6)

NHCOPy Compound **6** was synthetized in a 10.0 mmol-scale following the literature procedure,<sup>2</sup> to give **6** as a pale yellow solid; yield: 1.05 g (53%); mp = 76-77 °C. The analytical data (NMR, HRMS analysis)

matched those reported in the literature for *N*-phenyl-2-pyridinecarboxamide [CAS: 10354-53-7]. <sup>1</sup>**H NMR (acetone-d<sub>6</sub>, 300 MHz)**  $\delta$ : 10.23 (s, 1H), 8.68 (ddd, *J* = 4.8, 1.7, 1.0 Hz, 1H), 8.25 (dt, *J*=7.9, 1.1 Hz, 1H), 8.05 (td, *J* = 7.7, 1.7 Hz, 1H), 7.94 (dd, *J* = 8.6, 1.1 Hz, 2H), 7.63 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 7.44 – 7.34 (m, 2H), 7.21 – 7.09 (m, 1H). **EI**<sup>+</sup> calcd. for C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O (M)<sup>+</sup>: 198.0793; Found: 198.0794.

#### 5. General procedures for the copper-catalyzed *ortho*-halogenation

# 5.1. METHOD A: *ortho*-Chlorination using 1,1,2,2-tetracloroethane as chlorine source

An oven-dried, nitrogen-flushed 20 mL vessel was charged with the corresponding *N*-(2-pyridyl)sulfonyl aniline (**1-3**) (0.20 mmol) and copper(II) chloride (5.38 mg, 0.04 mmol, 20 mol%). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen,  $Cl_2CHCHCl_2$  (1 mL) and the internal standard *n*-hexadecane (50 µL) were added *via* syringe. After stirring the reaction mixture at 130 °C for 24 h, it was diluted with 5 mL of  $CH_2Cl_2$  and filtered through a pad of Celite. The filtrate was washed twice with brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum.

<sup>&</sup>lt;sup>[2]</sup> M. D. Markey, Y. Fu, T. R. Kelly, Org. Lett. 2007, 9, 3255.

The residue was purified by column chromatography (SiO<sub>2</sub>, *n*-hexane-ethyl acetate 5:1), yielding the corresponding *ortho*-chlorinated product.

*N*-(2-Chlorophenyl)pyridine-2-sulfonamide (1-Cl). Compound 1-Cl was prepared following Method A from *N*-phenylpyridine-2-sulfonamide 1 (46.9 mg, 0.20 mmol), to give 1-Cl as a white solid; yield: 41.9 mg (78%); mp = 105-106 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.70 (ddd, *J* = 4.6, 1.7, 1.0 Hz, 1H), 8.59 (s, 1H), 8.05 (tt, *J* = 7.8, 1.6 Hz, 1H), 8.00 – 7.90 (m, 1H), 7.69 – 7.59 (m, 2H), 7.38 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.28 (ddd, *J* = 8.1, 7.4, 1.5 Hz, 1H), 7.20 – 7.12 (m, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 158.2, 151.0, 139.2, 135.0, 130.5, 128.5, 128.2, 127.9, 127.5, 125.9, 123.2. ESI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>SCl (M+H)<sup>+</sup>: 269.0146; Found: 269.0144.

Compound **1-Cl** was also prepared following Method A on a 1.00-mmol scale, using *N*-phenylpyridine-2-sulfonamide (**1**) (234 mg, 1.0 mmol, 1.00 equiv), NCS (160 mg, 1.20 mmol, 1.2 equiv) and CuCl<sub>2</sub> (13.4 mg, 0.10 mmol, 10 mol%) in MeCN (4 mL). The title compound **1-Cl** was isolated in 79% yield (213 mg). Under these conditions, compound **1-(***p***)-Cl** was also isolated in 12% yield (33.0 mg).

N-(2-Chloro-4-methoxyphenyl)pyridine-2-sulfonamide (2-Cl). Compound 2-Cl was following prepared Method А from N-(4-NHSO<sub>2</sub>Py methoxyphenyl)pyridine-2-sulfonamide 2 (52.9 mg, MeO 0.20 mmol) to give 2-Cl as a white solid; yield: 56.1 mg (94%): mp = 131-132 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.72 (ddd, J = 4.7, 1.9,0.9 Hz, 1H), 8.53 (s, 1H), 8.03 (td, J = 7.8, 1.7 Hz, 1H), 7.86 (dt, J = 7.9, 1.0 Hz, 1H), 7.65 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.42 (d, J = 8.9 Hz, 1H), 6.93 (d, J = 2.9 Hz, 1H), 6.86 (dd, J = 8.9, 2.9 Hz, 1H), 3.79 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 159.5, 158.5, 151.0, 139.1, 131.3, 129.6, 128.0, 127.4, 123.2, 115.5, 114.2, 56.1. **EI**<sup>+</sup> calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>SCl (M)<sup>+</sup>: 298.0179; Found: 298.0173.

#### N-(2-Chloro-4-(trifluoromethyl)phenyl)pyridine-2-sulfonamide (3-Cl). Compound



**3-Cl** was prepared following Method A from *N*-[4-(trifluoromethyl)phenyl]pyridine-2-sulfonamide **3** (60.5 mg, 0.20 mmol) to give **3-Cl** as a white solid; yield: 60.0 mg (89%);

mp = 109-110 °C. <sup>1</sup>**H NMR (acetone-d<sub>6</sub>, 500 MHz)** δ: 9.01 (s, 1H), 8.71 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.12 (td, *J* = 7.7, 1.7 Hz, 1H), 8.05 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.97 (dd,

J = 8.7, 1.0 Hz, 1H), 7.76 (d, J = 1.9 Hz, 1H), 7.69 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.67 - 7.64 (m, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.0, 151.2, 139.6, 139.1, 128.6, 127.9 (q,  $J_{C-F} = 33.4$  Hz), 127.6 (q,  $J_{C-F} = 32.5$  Hz), 126.9, 125.6 (q,  $J_{C-F} = 3.7$  Hz), 124.6, 124.4 (q,  $J_{C-F} = 271.4$  Hz), 123.2. <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz)  $\delta$ : 114.5. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>2</sub>F<sub>3</sub>O<sub>2</sub>SCl (M)<sup>+</sup>: 335.9947; Found: 335.9945.

#### 5.2. METHOD B: ortho-Chlorination using NCS as a source of chlorine

An oven-dried, nitrogen-flushed 20 mL vessel was charged with the corresponding *N*-protected aniline (**1-23**) (0.20 mmol, 1.00 equiv), NCS (32.0 mg, 0.24 mmol, 1.2 equiv) and CuCl<sub>2</sub> (2.69 mg, 0.02 mmol, 10 mol%). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen, MeCN (1 mL) and the internal standard *n*-hexadecane (50  $\mu$ L) were added *via* syringe. The resulting mixture was stirred at 100 °C for 4-8 h, depending on the reactivity of the substrate (indicated for each case). After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (*n*-hexane-EtOAc 5:1), yielding the corresponding chlorinated products.

N-(2-Chlorophenyl)pyridine-2-sulfonamide (1-Cl). Compound 1-Cl was preparedfollowing Method B (reaction time: 4 h) from*N*-phenylpyridine-2sulfonamide 1 (46.9 mg, 0.20 mmol), to give 1-Cl as a white solid;yield: 51.0 mg (95%); mp = 105-106 °C. For the analytical data

(NMR, HRMS analysis) see compound 1-Cl described in Method A.

*N*-(4-Chlorophenyl)-4-methylbenzenesulfonamide (4-Cl). Compound 4-Cl was prepared following Method B (reaction time: 4 h) from 4-methyl-*N*phenylbenzenesulfonamide 4 (49.5 mg, 0.20 mmol) to give 4-Cl as a white solid; yield: 55.0 mg (97%). <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)

δ: 9.06 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.27 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.1 Hz, 2H), 2.35 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz) δ: 144.6, 137.8, 137.7, 130.5, 130.1, 129.9, 128.0, 123.0, 21.36.

N-(2,6-Dichlorophenyl)acetamide (5-Cl). Compound 5-Cl was detected when Nphenylacetamide 5 (27.0 mg, 0.20 mmol) was used following Method B (reaction time: 4 h). This compound showed very similar  $R_f$  than the starting acetanilide. MS: m/z (%) = 203 (100), 205(64), 207 (13), 204 (9), 206 (5).

N-(4-Chlorophenyl)-2-pyridinecarboxamide (6-Cl). Compound 6-Cl was prepared following Method B (reaction time: 4 h) from N-phenyl-2pyridinecarboxamide 6 (39.6 mg, 0.20 mmol) to give 6-Cl as a white solid; yield: 32.0 mg (69%). <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz) δ: 10.34 (s, 1H), 8.68 (ddd, J = 4.7, 1.7, 1.0 Hz, 1H), 8.24 (dt, J = 7.8, 1.1 Hz, 1H), 7.99 (d, J = 8.9 Hz, 2H), 7.64 (ddd, J = 7.6, 4.8, 1.3 Hz, 1H), 7.41 (d, J = 8.9Hz, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz) δ: 163.1, 150.7, 149.2, 138.9, 138.4, 129.6,

129.1, 127.7, 123.1, 122.2.

N-Methyl-N-(4-chlorophenyl)pyridine-2-sulfonamide (7-Cl). Compound 7-Cl was Me prepared following Method В (reaction time: 4 h: NSO<sub>2</sub>Py chromatography eluents: n-hexane-EtOAc 5:1) from N-methyl-Nphenylpyridine-2-sulfonamide 7 (49.7 mg, 0.20 mmol) to give 7-Cl as a white solid; yield: 51.0 mg (90%). <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.77 (ddd, J = 4.6, 1.7, 0.9 Hz, 1H), 8.04 (td, J = 7.8, 1.7 Hz, 1H), 7.79 (dt, J = 7.8, 1.1 Hz, 1H), 7.67 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 7.37 – 7.26 (m, 4H), 3.46 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz) δ: 157.7, 151.0, 141.6, 139.2, 132.9, 129.7, 129.2, 128.1, 123.9, 40.0.

N-(2-Chloro-4-methoxyphenyl)pyridine-2-sulfonamide (2-Cl). Compound 2-Cl was

MeO CI

prepared following Method B (reaction time: 4 h) from N-(4methoxyphenyl)pyridine-2-sulfonamide 2 (52.9 mg, 0.20 mmol) to give 2-Cl as a white solid; yield: 53.1 mg

(89%). For the analytical data (NMR, HRMS analysis), see compound **2-Cl** in Method A.

N-(2-Chloro-4-methylphenyl)pyridine-2-sulfonamide (8-Cl). Compound 8-Cl wasNHSO2Pyprepared following Method B (reaction time: 4 h) from N-(p-<br/>tolyl)pyridine-2-sulfonamide 8 (49.7 mg, 0.20 mmol) to give 8-<br/>Cl as a white solid; yield: 44.0 mg (78%); mp = 128-129 °C.<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.74 – 8.67 (m, 1H), 8.53 (s, 1H), 8.04 (td, J = 7.7,

1.8 Hz, 1H), 7.91 (dt, J = 7.6, 1.1 Hz, 1H), 7.64 (ddd, J = 7.4, 4.6, 1.2 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 2.1 Hz, 1H), 7.08 (dd, J = 8.2, 2.0 Hz, 1H), 2.26 (s, 3H).

<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.3, 151.0, 139.1, 138.1, 132.2, 130.7, 129.1, 128.5, 128.0, 126.6, 123.2, 20.5. **EI**<sup>+</sup> calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>SCl (M)<sup>+</sup>: 282.0230; Found: 282.0233.

N-(2-Chloro-4-iodophenyl)pyridine-2-sulfonamide (9-Cl). Compound 9-Cl was



prepared following Method B (reaction time: 4 h); from N-(4-iodophenyl)pyridine-2-sulfonamide **9** (72.0 mg, 0.20 mmol) to give **9-Cl** as a white solid; yield: 46.0 mg (58%); mp = 102-

103 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.79 (s, 1H), 8.70 (ddd, J = 4.6, 1.8, 0.9 Hz, 1H), 8.07 (td, J = 7.8, 1.7 Hz, 1H), 7.97 (dt, J = 7.9, 1.0 Hz, 1H), 7.74 (d, J = 2.0 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.46 (d, J = 8.6 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.0, 151.0, 139.3, 138.5, 137.6, 135.3, 129.0, 128.3, 127.6, 123.2, 89.6. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SCII (M)<sup>+</sup>: 393.9040; Found: 393.9048.

N-(4-Bromo-2-chlorophenyl)pyridine-2-sulfonamide (10-Cl). Compound 10-Cl wasNHSO2Pyprepared following Method B (reaction time: 4 h) from N-(4-<br/>bromophenyl)pyridine-2-sulfonamide 10 (62.6 mg, 0.20 mmol)<br/>to give 10-Cl as a white solid; yield: 42.0 mg (61%); mp = 163-

165 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.76 (s, 1H), 8.71 (d, J = 3.6 Hz, 1H), 8.09 (tt, J = 7.5, 1.7 Hz, 1H), 7.98 (d, J = 7.4 Hz, 1H), 7.73 – 7.60 (m, 1H), 7.65 – 7.56 (m, 2H), 7.49 (dt, J = 8.7, 2.0 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.1, 151.1, 139.4, 134.7, 132.8, 131.6, 129.3, 128.3, 127.7, 123.2, 119.1. **EI**<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SClBr (M)<sup>+</sup>: 345.9178; Found: 345.9169.

N-(2,4-Dichlorophenyl) pyridine-2-sulfonamide (11-Cl). Compound 11-Cl was prepared following Method B (reaction time: 4 h) from N-(4-chlorophenyl) pyridine-2-sulfonamide 11 (53.7 mg, 0.20 mmol) to give 11-Cl as a white solid; yield: 46.0 mg (76%); mp = 110-

111 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.79 (s, 1H), 8.70 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.08 (td, J = 7.8, 1.7 Hz, 1H), 7.96 (dt, J = 7.8, 1.0 Hz, 1H), 7.70 – 7.64 (m, 2H), 7.47 (d, J = 2.4 Hz, 1H), 7.35 (dd, J = 8.8, 2.4 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.1, 151.1, 139.4, 134.3, 131.8, 130.0, 129.2, 128.7, 128.3, 127.5, 123.2. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SCl<sub>2</sub> (M)<sup>+</sup>: 301.9684; Found: 301.9681.

prepared following Method B (reaction time: 4 h) from *N*-(4-fluorophenyl)pyridine-2-sulfonamide **12** (50.5 mg, 0.20 mmol) to give **12-Cl** as a white solid; yield: 46.0 mg (80%); mp = 97-98 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.75 – 8.68 (m, 2H), 8.06 (td, *J* = 7.8, 1.7 Hz, 1H), 7.91 (dd, *J* = 7.9, 2.5 Hz, 1H), 7.70 – 7.59 (m, 2H), 7.25 (dt, *J* = 8.4, 2.7 Hz, 1H), 7.13 (ddt, *J* = 9.0, 7.9, 2.7 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, **125 MHz**)  $\delta$ : 161.1 (d, *J<sub>C-F</sub>* = 161.1 Hz), 158.31 (s), 151.0, 139.3, 131.6 (d, *J<sub>C-F</sub>* = 3.4 Hz), 130.5 (d, *J<sub>C-F</sub>* = 10.9 Hz), 129.1 (d, *J<sub>C-F</sub>* = 9.2 Hz), 128.2, 123.1, 117.5 (d, *J<sub>C-F</sub>* = 26.2 Hz), 115.5 (d, *J* = 22.4 Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, **471 MHz**)  $\delta$ : -115.7. **EI**<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>FSCl (M)<sup>+</sup>: 285.9979; Found: 285.9991.

N-(2-Chloro-4-fluorophenyl)pyridine-2-sulfonamide (12-Cl). Compound 12-Cl was

N-(2-Chloro-4-(trifluoromethyl)phenyl)pyridine-2-sulfonamide (3-Cl). Compound



NHSO<sub>2</sub>Py **3-Cl** was prepared following Method B (reaction time: 4 h) from N-[4-(trifluoromethyl)phenyl]pyridine-2-sulfonamide **3** (60.5 mg, 0.20 mmol) to give **3-Cl** as a white solid; yield:

54.0 mg (80%). For the analytical data (NMR, HRMS analysis) see compound **3-Cl** in Method A.

N-(4-Acetyl-2-chlorophenyl)pyridine-2-sulfonamide (13-Cl). Compound 13-Cl was prepared following Method B (reaction time: 4 h) from*N* $-(4-acetylphenyl)pyridine-2-sulfonamide 13 (55.3 mg, 0.20 mmol) to give 13-Cl as a white solid; yield: 45.3 mg (73%); mp = 136-138 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz) <math>\delta$ : 8.95 (bs, 1H), 8.70 (d, *J* = 4.1 Hz, 1H), 8.15 - 8.08 (m, 1H), 8.08 - 8.04 (m, 1H), 7.95 (d, *J* = 1.9 Hz, 1H), 7.93 - 7.87 (m, 1H), 7.87 - 7.83 (m, 1H), 7.68 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 1H), 2.55 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 195.9, 158.0, 151.1, 139.5, 139.4, 135.3, 130.3, 128.6, 128.5, 126.2, 123.3, 26.5. EI<sup>+</sup> calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>SCl (M)<sup>+</sup>: 310.0179; Found: 310.0170.

Methyl 3-chloro-4-(pyridine-2-sulfonamido)benzoate (14-Cl). Compound 14-Cl was

MeO<sub>2</sub>C Cl prepared following Method B (reaction time: 4 h) from methyl 4-[N-(2-pyridyl)sulfonylamino]benzoate 14 (58.5 mg, 0.20 mmol) to give 14-Cl as a white solid; yield:

56.0 mg (86%); mp = 129-130 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.94 (s, 1H), 8.70 (d, J = 4.6 Hz, 1H), 8.10 (td, J = 7.7, 1.7 Hz, 1H), 8.05 (dt, J = 7.9, 1.1 Hz, 1H),

7.94 (d, J = 1.8 Hz, 1H), 7.89 (dd, J = 8.6, 1.8 Hz, 1H), 7.85 (d, J = 8.6 Hz, 1H), 7.67 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 3.86 (s, 3H). <sup>13</sup>**C NMR** (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 165.6, 157.8, 151.1, 139.5, 139.5, 131.3, 129.5, 128.5, 128.3, 126.0, 123.4, 123.3, 52.6. **EI**<sup>+</sup> calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub>SCl (M)<sup>+</sup>: 326.0128; Found: 326.0116.

 $N-(2-Chloro-4-cyanophenyl)pyridine-2-sulfonamide (15-Cl). Compound 15-Cl was prepared following Method B (reaction time: 4 h) from N-(4-cyanophenyl)pyridine-2-sulfonamide 15 (51.8 mg, 0.20 mmol) to give 15-Cl as a white solid; yield: 48.0 mg (82%); mp = 143-146 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz) <math>\delta$ : 9.10 (s, 1H), 8.71 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.16 – 8.10 (m, 1H), 8.10 – 8.05 (m, 1H), 7.97 (d, J = 8.6 Hz, 1H), 7.88 (d,

J = 1.9 Hz, 1H), 7.76 – 7.67 (m, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 157.8, 151.2, 140.0, 139.6, 134.1, 132.5, 128.6, 126.4, 123.9, 123.3, 117.9, 109.6. **EI**<sup>+</sup> calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub>SCl (M)<sup>+</sup>: 293.0026; Found: 293.0037.

N-(2-Chloro-4-nitrophenyl)pyridine-2-sulfonamide (16-Cl). Compound 16-Cl was



prepared following Method B (reaction time: 4 h) from *N*-(4nitrophenyl)pyridine-2-sulfonamide **16** (55.8 mg, 0.20 mmol) to give **16-Cl** as a white solid; yield: 54.0 mg (86%); mp =

176-177 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.68 (dt, J = 4.7, 1.3 Hz, 1H), 8.23 (d, J = 2.7 Hz, 1H), 8.15 – 8.06 (m, 3H), 7.97 (d, J = 9.2 Hz, 1H), 7.66 (ddd, J = 6.2, 4.7, 2.5 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.8, 150.9, 144.4, 143.5, 139.4, 128.2, 125.8, 125.7, 123.9, 123.1, 122.2. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>3</sub>O<sub>4</sub>SCl (M)<sup>+</sup>: 312.9924; Found: 312.9923.

*N*-(2-Chloro-3-fluorophenyl)pyridine-2-sulfonamide (17-Cl). Compound 17-Cl was prepared following Method B (reaction time: 8 h) from *N*-(3fluorophenyl)pyridine-2-sulfonamide 17 (50.5 mg, 0.20 mmol) to give 17-Cl as a white solid; yield: 45.0 mg (78%); mp = 114-

116 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.81 (s, 1H), 8.72 (ddd, J = 4.7, 1.8, 0.9 Hz, 1H), 8.10 (td, J = 7.7, 1.7 Hz, 1H), 8.03 (dt, J = 7.9, 1.1 Hz, 1H), 7.68 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.55 (dd, J = 10.4, 3.0 Hz, 1H), 7.43 (dd, J = 8.9, 5.7 Hz, 1H), 6.97 (ddd, J = 8.9, 7.9, 3.0 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 162.1 (d,  $J_{C-F} = 244.3$  Hz), 157.9, 151.1, 139.5, 136.6 (d,  $J_{C-F} = 11.3$  Hz), 131.6 (d,  $J_{C-F} = 9.4$  Hz), 128.4, 123.2, 122.2 (d,  $J_{C-F} = 3.5$  Hz), 113.9 (d,  $J_{C-F} = 23.3$  Hz), 112.0 (d,  $J_{C-F} = 27.6$ 

Hz). <sup>19</sup>**F NMR (acetone-d<sub>6</sub>, 471 MHz)**  $\delta$ : -114.4. **EI**<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>FSCl (M)<sup>+</sup>: 285.9979; Found: 285.9989.

N-(2-Chloro-5-isopropylphenyl)pyridine-2-sulfonamide (18-Cl). Compound 18-Cl was prepared following Method B (reaction time: 8 h) from N-NHSO<sub>2</sub>Py iPr (3-isopropylphenyl)pyridine-2-sulfonamide 18 (55.3 mg, 0.20 mmol) to give 18-Cl as a white solid; yield: 32.0 mg (52%); mp = 136-137 °C. This compound could not be completely purified from presumably minor chlorinated side products. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz) δ: 8.72 (ddd, J = 4.7, 1.6, 0.9 Hz, 1H), 8.57 (s, 1H), 8.11 - 8.02 (m, 1H), 7.96 (dt, J = 7.8, 1.0)Hz, 1H), 7.65 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.47 (d, J = 2.2 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.04 (dd, J = 8.3, 2.1 Hz, 1H), 2.78 (s, 1H), 1.16 (d, J = 6.9 Hz, 6H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz) δ: 158.2, 151.0, 149.5, 139.2, 134.7, 130.2, 128.1, 125.7, 125.2, 124.0, 123.4, 34.3, 24.0. **EI**<sup>+</sup> calcd. for  $C_{14}H_{15}N_2O_2SCI$  (M)<sup>+</sup>: 310.0543; Found: 310.0536.

*N*-[2-Chloro-3-(trifluoromethyl)phenyl]pyridine-2-sulfonamide and *N*-[2-chloro-5-(trifluoromethyl)phenyl]pyridine-2-sulfonamide (19-Cl). Following Method B

 $\begin{array}{c} \label{eq:reaction time: 8 h) from $N$-[3-(trifluoro-methyl)phenyl]pyridine-2-sulfonamide $19$ (60.4 mg, 0.20 mmol) a mixture of regioisomers 19-Cl was obtained in a 1:1 ratio, as a white solid; yield: 39.0 mg (58%). $$^{1}H NMR (acetone-d_6, 300 MHz) [(19a+19b)-Cl] $$^{\circ} 9.02 (s, 1H), $$^{8.85} - $$^{8.52} (m, 1H), $$^{8.31} - 7.91 (m, 3H), $7.87 - 7.58 (m, 2H), $7.58 - 7.36 (m, 1H). $$MS(19a-Cl): m/z (%) 336 (4), 301 (64), $237 (28), $78 (100). $$MS(19b-Cl): m/z (%) 336 (12), 301 (13), $237 (49), $78 (100). $$$ 

*N*-(2,3-Dichloro-4-iodophenyl)pyridine-2-sulfonamide (20-Cl). Compound 20-Cl was prepared following Method B (reaction time: 8 h) from *N*-(3-chloro-4-iodophenyl)pyridine-2-sulfonamide 20 (78.9 mg, 0.20 mmol) to give 20-Cl as a white solid; yield: 50.0 mg (58%); mp = 152-154 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 9.73 (s, 1H), 9.49 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.88 (td, *J* = 7.7, 1.7 Hz, 1H), 8.79 (dt, *J* = 7.9, 1.1 Hz, 1H), 8.69 (d,

J = 8.8 Hz, 1H), 8.47 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 8.26 (d, J = 8.7 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.0, 151.1, 139.5, 139.1, 137.5, 137.4, 128.4, 126.3, 125.0, 123.2, 94.4. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub>SCl<sub>2</sub>I (M)<sup>+</sup>: 427.8650; Found: 427.8645.

## N-(4-Bromo-2,3-dichlorophenyl)pyridine-2-sulfonamide (21-Cl). Compound 21-Cl

was prepared following Method B (reaction time: 8 h) from *N*-Cl NHSO<sub>2</sub>Py (4-bromo-3-chlorophenyl)pyridine-2-sulfonamide **21** (69.5 mg, 0.20 mmol) to give **21-Cl** as a white solid; yield: 46.0 mg (60%); mp = 144-145 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ :9.00 (s, 1H), 8.70 (ddd, *J* = 4.5, 1.6, 0.8 Hz, 1H), 8.09 (td, *J* = 7.8, 1.7 Hz, 1H), 8.00 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.80 – 7.66 (m, 2H), 7.63 (d, *J* = 8.9 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.0, 151.1, 139.5, 136.6, 133.8, 132.7, 128.4, 128.0, 125.0, 123.2, 119.9. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub>SCl<sub>2</sub>Br (M)<sup>+</sup>: 379.8789; Found: 379.8797.

*N*-(2,3,4-Trichlorophenyl)pyridine-2-sulfonamide (22-Cl). Compound 22-Cl was prepared following Method B (reaction time: 8 h) from *N*-(3,4dichlorophenyl)pyridine-2-sulfonamide 22 (78.9 mg, 0.20 mmol) to give 22-Cl as a white solid; yield: 55.0 mg (64%); mp = 131-132 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.97 (s, 1H), 8.70 (ddd, *J* = 4.7, 1.8, 1.0 Hz, 1H), 8.10 (td, *J* = 7.8, 1.7 Hz, 1H), 7.99 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.75 – 7.61 (m, 2H), 7.55 (td, *J* = 9.0 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.0, 151.1, 139.5, 135.9, 132.0, 131.5, 130.8, 129.4, 128.4, 124.8, 123.2. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub>SCl<sub>3</sub> (M)<sup>+</sup>: 335.9294; Found: 335.9305.

N-(6-Chlorobenzo[d][1,3]dioxol-5-yl)pyridine-2-sulfonamide (23-Cl). Compound23-Cl was prepared following Method B (reaction time: 8 h)from N-(benzo[d][1,3]dioxol-5-yl)pyridine-2-sulfonamide 23(55.6 mg, 0.20 mmol) to give 23-Cl as a white solid; yield:

46.2 mg (74%); mp = 169-171 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.72 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.52 (s, 1H), 8.10 – 7.99 (m, 1H), 7.95 – 7.87 (m, 1H), 7.65 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.08 (s, 1H), 6.86 (s, 1H), 6.05 (s, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 158.3, 151.0, 147.9, 147.5, 139.2, 128.3, 128.0, 123.2, 121.9, 109.8, 108.4, 103.4. **EI**<sup>+</sup> calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>4</sub>SCl (M)<sup>+</sup>: 311.9972; Found: 311.9983.

#### 5.3. METHOD C: ortho-Bromination using NBS as a source of bromine

An oven-dried, nitrogen-flushed 20 mL vessel was charged with the corresponding *N*-protected aniline (**2-3**, **8-17**, **22** and **23**) (0.20 mmol, 1.00 equiv), NBS (42.7 mg, 0.24 mmol, 1.2 equiv) and CuBr<sub>2</sub> (4.47 mg, 0.02 mmol, 10 mol%). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with

oxygen three times. Under the atmosphere of oxygen, MeCN (1 mL) and the internal standard *n*-hexadecane (50  $\mu$ L) were added *via* syringe. The resulting mixture was stirred at 100 °C for 4-8 h, depending on the reactivity of the substrate (indicated for each case). After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (*n*-hexane-EtOAc 5:1), yielding the corresponding brominated products.

#### N-(2-Bromo-4-methoxyphenyl)pyridine-2-sulfonamide (2-Br). Compound 2-Br was



prepared following Method C (reaction time 16 h) from N-(4methoxyphenyl)pyridine-2-sulfonamide **2** (52.9 mg, 0.20 mmol), copper(II) bromide (8.94 mg, 0.04 mmol,

20 mol%) and DMF (1.00 mL) at 150 °C, to give **2-Br** as a white solid; yield: 60.3 mg (88%); mp = 136-137 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 8.71 (ddd, J = 4.6, 1.7, 0.8 Hz, 1H), 8.38 (s, 1H), 8.10 – 7.94 (m, 1H), 7.86 (dt, J = 7.9, 1.0 Hz, 1H), 7.64 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.40 (dd, J = 8.9, 1.0 Hz, 1H), 7.10 (d, J = 2.8 Hz, 1H), 6.90 (ddd, J = 8.9, 2.8, 1.0 Hz, 1H), 3.79 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 159.5, 158.6, 151.0, 139.1, 129.5, 128.9, 127.9, 123.2, 121.5, 118.7, 114.8, 56.1. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>SBr (M)<sup>+</sup>: 341.9674; Found: 341.9675.

*N*-(2-Bromo-4-methylphenyl)pyridine-2-sulfonamide (8-Br). Compound 8-Br was prepared following Method C (reaction time: 8 h) from *N*-(*p*-tolyl)pyridine-2-sulfonamide 8 (49.7 mg, 0.10 mmol) to give 8-Br Br as a white solid; yield: 35.0 mg (71%); mp = 120-121 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.71 (dd, *J* = 3.8, 1.0 Hz, 1H), 8.36 (s, 1H), 8.04 (td, *J* = 7.8, 1.7 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.65 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.2, 3.4 Hz, 1H), 7.37 (s, 1H), 7.13 (dd, *J* = 8.3, 2.0 Hz, 1H), 2.27 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.3, 151.0, 139.2, 138.5, 134.0, 133.6, 129.8, 128.1, 126.7, 123.3, 119.0, 20.40. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>2</sub>SBr (M)<sup>+</sup>: 325.9725; Found: 325.9738.

*N*-(2-Bromo-4-iodophenyl)pyridine-2-sulfonamide (9-Br). Compound 9-Br was prepared following Method C (reaction time: 8 h) from *N*-(4iodophenyl)pyridine-2-sulfonamide 9 (72.0 mg, 0.20 mmol) to give 9-Br as a white solid; yield: 50.0 mg (57%); mp = 111-112 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.70 (ddd, *J* = 4.7, 1.6, 0.8, 1H), 8.56 (s, 1H), 8.13 – 8.03 (m, 1H), 8.01 – 7.94 (m, 1H), 7.91 (d, *J* = 2.0 Hz, 1H), 7.75 – 7.62 (m, 2H), 7.45 (d, *J* = 8.6 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.1, 151.1, 141.5, 139.4, 138.3, 136.7, 128.3, 127.8, 123.24, 119.4, 100.9, 90.1. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SBrI (M)<sup>+</sup>: 437.8535; Found: 437.8553.

*N*-(2,4-Dibromophenyl)pyridine-2-sulfonamide (10-Br). Compound 10-Br was prepared following Method C (reaction time: 8 h) from *N*-(4bromophenyl)pyridine-2-sulfonamide 10 (62.6 mg, 0.2 mmol) to give 10-Br as a white solid; yield: 67.0 mg (85%); mp = 101-102 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.71 (ddd, *J* = 4.7, 1.6, 0.9 Hz, 1H), 8.59 (s, 1H), 8.08 (td, *J* = 7.8, 1.7 Hz, 1H), 7.96 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.75 (d, *J* = 2.2 Hz, 1H), 7.67 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.60 (d, *J* = 8.7 Hz, 1H), 7.53 (dd, *J* = 8.7, 2.3 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.1, 151.1, 139.4, 136.0, 135.8, 132.2,

128.3, 127.9, 123.2, 119.5, 119.5. **EI**<sup>+</sup> calcd. for  $C_{11}H_8N_2O_2SBr_2$  (M)<sup>+</sup>: 389.8673; Found: 389.8684.

N-(2-Bromo-4-chlorophenyl)pyridine-2-sulfonamide (11-Br). Compound 11-Br was

NHSO<sub>2</sub>Py prepared following Method C (reaction time: 8 h) from N-(4chlorophenyl)pyridine-2-sulfonamide **11** (53.7 mg, 0.20 mmol)

F<sub>3</sub>C

to give **11-Br** as a white solid; yield: 31.0 mg (45%); mp = 103-104 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.71 (ddd, J = 4.7, 1.6, 0.8 Hz, 1H), 8.60 (s, 1H), 8.08 (td, J = 7.8, 1.7 Hz, 1H), 7.96 (dt, J = 7.8, 1.0 Hz, 1H), 7.68 (d, J = 1.1 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.62 (d, J = 2.4 Hz, 1H), 7.40 (dd, J = 8.7, 2.4 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.1, 151.1, 139.4, 135.6, 133.1, 132.1, 129.2, 128.3, 127.7, 123.2, 119.4. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SClBr (M)<sup>+</sup>: 345.9178; Found: 345.9180.

N-(2-Bromo-4-fluorophenyl)pyridine-2-sulfonamide (12-Br). Compound 12-Br was

NHSO<sub>2</sub>Py Br prepared following Method C (reaction time: 8 h) from N-(4fluorophenyl)pyridine-2-sulfonamide **12** (50.5 mg, 0.20 mmol) to give **12-Br** as a white solid; yield: 52.0 mg (79%); mp = 111-

112 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.71 (ddd, J = 4.7, 1.8, 1.0 Hz, 1H), 8.58 (s, 1H), 8.06 (td, J = 7.8, 1.7 Hz, 1H), 7.92 (dd, J = 7.9, 1.1 Hz, 1H), 7.67 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.62 (dd, J = 9.0, 5.5 Hz, 1H), 7.41 (dd, J = 8.2, 2.9 Hz, 1H), 7.17 (ddd, J = 9.1, 8.0, 2.9 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 161.1 (d,  $J_{C-F} = 248.2$  Hz), 158.3, 151.1, 139.3, 133.0 (d,  $J_{C-F} = 3.3$  Hz), 129.2 (d,  $J_{C-F} = 8.9$  Hz), 128.2, 123.2, 120.6 (d,  $J_{C-F} = 25.8$  Hz), 120.5, 116.0 (d,  $J_{C-F} = 22.4$  Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)  $\delta$ : -115.6. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>FSBr (M)<sup>+</sup>: 329.9474; Found: 329.9463.

### N-(2-Bromo-4-(trifluoromethyl)phenyl)pyridine-2-sulfonamide (3-Br). Compound

NHSO<sub>2</sub>Py Br  $NHSO_2$ Py 3-Br was prepared following Method C (reaction time: 8 h) from N-(4-(trifluoromethyl)phenyl)pyridine-2-sulfonamide **3** (60.5 mg, 0.20 mmol) to give **3-Br** as a white solid; yield:

71.0 mg (83%); mp = 88-89 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.78 (s, 1H), 8.74 – 8.69 (m, 1H), 8.12 (td, J = 7.8, 1.7 Hz, 1H), 8.05 (dd, J = 7.9, 1.3 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 7.92 (s, 1H), 7.73 – 7.67 (m, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 157.9, 151.2, 140.4, 139.6, 130.8 (q,  $J_{C-F}$  = 3.8 Hz), 128.6, 128.4 (q,  $J_{C-F}$  = 33.4 Hz), 126.3 (q,  $J_{C-F}$  = 3.8 Hz), 124.9, 124.2 (q,  $J_{C-F}$  = 271.5 Hz), 123.3, 117.0. <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)  $\delta$ : -62.9. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub>SBr (M)<sup>+</sup>: 379.9442; Found: 379.9423.

N-(4-Acetyl-2-bromophenyl) pyridine-2-sulfonamide (13-Br). Compound 13-Br was  $NHSO_2Py \quad \text{prepared following Method C (reaction time: 8 h) from } N-(4-acetylphenyl) pyridine-2-sulfonamide \quad 13 \qquad (55.3 \text{ mg}, 13-Br) = 0$ 

0.20 mmol) to give **13-Br** as a white solid; yield: 60.1 mg (85%); mp = 111-113 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.71 (dd, J = 4.7, 1.0 Hz, 1H), 8.68 (s, 1H), 8.16 – 8.09 (m, 2H), 8.06 (d, J = 7.9 Hz, 1H), 7.97 – 7.91 (m, 1H), 7.86 – 7.79 (m, 1H), 7.69 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 2.55 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 195.8, 157.8, 151.2, 140.5, 139.5, 135.8, 133.7, 129.3, 128.5, 123.6, 123.4, 116.4, 26.5. EI<sup>+</sup> calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>SBr (M)<sup>+</sup>: 353.9674; Found: 353.9676.

## Methyl 3-bromo-4-(pyridine-2-sulfonamido)benzoate (14-Br). Compound 14-Br

MeO<sub>2</sub>C NHSO<sub>2</sub>Py Br NHSO<sub>2</sub>Py Br 4-[N-(2-pyridy])sulfonylamino]benzoate 14 (58.5 mg, 0.20 mmol) to give 14-Br as a white solid; yield: 64.0 mg (86%); mp = 145-146 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.70 (ddd, J =

4.7, 1.7, 0.9 Hz, 1H), 8.67 (s, 1H), 8.14 – 8.08 (m, 2H), 8.05 (dt, J = 7.9, 1.1 Hz, 1H), 7.93 (dd, J = 8.6, 1.9 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.68 (ddd, J = 7.5, 4.7, 1.2 Hz, 1H), 3.87 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 165.4, 157.8, 151.2, 140.7, 139.5, 134.7, 130.2, 128.8, 128.5, 123.7, 123.4, 116.2, 52.6. EI<sup>+</sup> calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub>SBr (M)<sup>+</sup>: 369.9623; Found: 369.9638.

N-(2-Bromo-4-cyanophenyl)pyridine-2-sulfonamide (15-Br). Compound 15-Br wasNCprepared following Method C (reaction time: 8 h) from N-(4-cyanophenyl)pyridine-2-sulfonamide 15 (51.8 mg, 0.20 mmol)NCbrNCto give 15-Br as a white solid; yield: 49.8 mg (74%); mp = 142-

143 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.84 (s, 1H), 8.71 (d, J = 4.3 Hz, 1H), 8.18 – 8.09 (m, 1H), 8.10 – 8.05 (m, 1H), 8.04 (d, J = 1.9 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.77 (dd, J = 8.6, 1.9 Hz, 1H), 7.71 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 157.8, 151.2, 141.1, 139.6, 137.3, 133.1, 128.7, 124.2, 123.3, 117.7, 116.4, 110.2. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>3</sub>O<sub>2</sub>SBr (M)<sup>+</sup>: 336.9521; Found: 336.9505.

N-(2-Bromo-4-nitrophenyl) pyridine-2-sulfonamide (16-Br). Compound 16-Br was prepared following Method C (reaction time: 8 h) from N-(4-nitrophenyl) pyridine-2-sulfonamide 16 (55.8 mg, 0.20 mmol) to give 16-Br as a yellow solid; yield: 52.1 mg (73%); mp = 1

153-155 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz) δ: 8.71 (ddd, J = 4.7, 1.7, 1.0 Hz, 1H), 8.42 (d, J = 2.6 Hz, 1H), 8.23 – 8.20 (dd, J = 9.1, 2.6 Hz, 1H), 8.18 – 8.07 (m, 2H), 8.03 (d, J = 9.1 Hz, 1H), 7.71 (ddd, J = 7.1, 4.7, 1.7 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, **75 MHz**) δ: 157.8, 151.2, 145.1, 143.1, 139.7, 129.1, 128.7, 124.5, 123.3, 123.2, 115.6. **EI**<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>3</sub>O<sub>4</sub>SBr (M)<sup>+</sup>: 356.9419; Found: 356.9415.

#### N-(2-Bromo-3-fluorophenyl)pyridine-2-sulfonamide (17-Br). Compound 17-Br was

F\_\_\_\_\_NHSO<sub>2</sub>Py

prepared following Method C (reaction time: 16 h) from N-(3-fluorophenyl)pyridine-2-sulfonamide **17** (50.5 mg, 0.20 mmol) to give **17-Br** as a white solid; yield: 42.0 mg (64%). This

compound could not be completely purified from presumably minor brominated side products. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 9.59 (s, 1H), 8.70 (ddd, J = 4.7, 1.7, 0.9Hz, 1H), 8.13 – 8.06 (m, 1H), 8.06 – 8.02 (m, 1H), 7.65 (ddd, J = 7.4, 4.7, 1.4 Hz, 1H), 7.52 (dd, J = 8.7, 7.9 Hz, 1H), 7.27 (dd, J = 10.6, 2.5 Hz, 1H), 7.09 (ddd, J = 8.8, 2.5,1.0 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 159.7 (d,  $J_{C-F} = 244.7$  Hz), 157.6, 140.2 (d,  $J_{C-F} = 9.7$  Hz), 139.4, 137.0, 128.5, 128.3, 123.5, 118.3 (d,  $J_{C-F} = 3.3$  Hz), 113.3 (d,  $J_{C-F} = 27.9$  Hz), 109.2 (d,  $J_{C-F} = 26.6$  Hz), 103.5 (d,  $J_{C-F} = 20.9$  Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)  $\delta$ : -107.3. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>FSBr (M)<sup>+</sup>: 329.9474; Found: 329.9472.

N-(2-Bromo-5-isopropylphenyl)pyridine-2-sulfonamide (18-Br). Compound 18-Br

iPr NHSO<sub>2</sub>Py Br was prepared following Method C (reaction time: 8 h) from *N*-(3-isopropylphenyl)pyridine-2-sulfonamide 18 (55.3 mg, 0.20 mmol) to give 18-Br as a white solid; yield: 36.9 mg

(52%); mp = 185-186 °C. This compound could not be completely purified from a minor unidentified side product. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 9.26 (s, 1H), 8.71 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.09 – 8.02 (m, 1H), 8.01 – 7.96 (m, 1H), 7.62 (ddd, J = 7.6, 4.7, 1.2 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 7.28 (d, J = 2.7 Hz, 1H), 7.05 (dd, J = 8.6, 2.7 Hz, 1H), 3.22 (dt, J = 13.7, 6.9 Hz, 1H), 1.13 (d, J = 6.8 Hz, 6H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 157.8, 151.0, 148.7, 139.2, 138.6, 133.9, 128.1, 123.6, 121.1, 120.4, 119.4, 33.6, 22.9. ESI<sup>+</sup> calcd. for C<sub>14</sub>H<sub>15</sub>N<sub>2</sub>O<sub>2</sub>SBr (M+H)<sup>+</sup>: 355.0110; Found: 355.0121.

#### N-[2-bromo-5-(trifluoromethyl)phenyl]pyridine-2-sulfonamide (19-Br). Compound

F<sub>3</sub>C NHSO<sub>2</sub>Py

**19-Br** was prepared following Method C (reaction time: 8 h) from N-[3-(trifluoromethyl)phenyl]pyridine-2-sulfonamide **19** (60.4 mg, 0.20 mmol) to give **19-Br** as a white solid; yield:

44.8 mg (59%); mp = 138-139 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz) [19-Br] δ: 8.82 (s,

1H), 8.72 (d, J = 3.8 Hz, 1H), 8.17 – 8.09 (m, 1H), 8.07 (d, J = 2.0 Hz, 1H), 8.02 (d, J = 7.9 Hz, 1H), 7.84 (dd, J = 8.4, 1.0 Hz, 1H), 7.70 (ddd, J = 7.6, 4.6, 1.1 Hz, 1H), 7.45 (dd, J = 8.3, 1.9 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.2, 151.1, 139.5, 137.8, 135.0, 131.0, 129.5 (q,  $J_{C-F} = 294.1$  Hz), 128.5, 124.0 (q,  $J_{C-F} = 3.9$  Hz), 123.2, 122.7 (q,  $J_{C-F} = 4.4$  Hz), 122.5 (q,  $J_{C-F} = 1.3$  Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)  $\delta$ : - 63.4. ESI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>2</sub>F<sub>3</sub>SBr (M+H)<sup>+</sup>: 380.9514; Found: 380.9509.

*N*-(2-Bromo-3,4-dichlorophenyl)pyridine-2-sulfonamide (22-Br). Compound 22-Br was prepared following Method C (reaction time: 16 h) from *N*-(3,4-dichlorophenyl)pyridine-2-sulfonamide 22 (60.6 mg, 0.20 mmol) to give 22-Br as a white solid; yield: 46.0 mg (60%); mp = 176-178 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.76 (s, 1H), 8.70 (ddd, *J* = 4.6, 1.8, 1.0 Hz, 1H), 8.09 (td, *J* = 7.8, 1.7 Hz, 1H), 7.99 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.73 - 7.65 (m, 2H), 7.60 (d, *J* = 8.8 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.1, 151.1, 139.5, 137.7, 133.9, 130.6, 130.1, 128.4, 125.1, 123.2, 120.76. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>7</sub>N<sub>2</sub>O<sub>2</sub>SCl<sub>2</sub>Br (M)<sup>+</sup>: 379.8789; Found: 379.8788.

N-(6-Bromobenzo[d][1,3]dioxol-5-yl)pyridine-2-sulfonamide (23-Br). Compound23-Br was prepared following Method B (reaction time: 8 h)from N-(benzo[d][1,3]dioxol-5-yl)pyridine-2-sulfonamide 23(55.6 mg, 0.20 mmol) to give 23-Br as a white solid; yield:

56.9 mg (80%); mp = 160-162 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.72 (ddd, J = 4.6, 1.8, 0.9 Hz, 1H), 8.39 (s, 1H), 8.05 (td, J = 7.7, 1.7 Hz, 1H), 7.91 (dt, J = 7.9, 1.1 Hz, 1H), 7.66 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 7.08 (s, 1H), 7.02 (s, 1H), 6.06 (s, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 158.3, 151.0, 148.5, 147.8, 139.2, 129.8, 128.1, 123.2, 112.6, 111.2, 108.7, 103.5. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>2</sub>O<sub>4</sub>SBr (M)<sup>+</sup>: 355.9466; Found: 355.9468.

# 5.4. METHOD D: *N*-(2-pyrimidyl)sulfonyl-directed copper-catalyzed *ortho*-chlorination

An oven-dried, nitrogen-flushed 20 mL vessel was charged with the corresponding N-(pyrimidyl)sulfonyl aniline (26, 26-Cl, 27-30) (0.20 mmol, 1.00 equiv), NCS and CuCl<sub>2</sub> (8.1 mg, 0.06 mmol, 30 mol%). The reaction vessel was

sealed with a Teflon lined cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen, the solvent (1 mL) and the internal standard *n*-hexadecane (50 µL) were added *via* syringe. The resulting mixture was stirred at the appropriate temperature 16 h. The solvent used [MeCN or DMF (1.00 mL)], the temperature (130 °C or 150 °C) and the exact amount of NCS would be specified in each case. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (*n*-hexane-EtOAc 2:1), yielding the corresponding *N*-(2-chlorophenyl)pyrimidine-2-sulfonamides.

*N*-(2,6-Dichloro-4-fluorophenyl)pyrimidine-2-sulfonamide (26-Cl<sub>2</sub>). Compound Cl 26-Cl<sub>2</sub> was prepared following Method D from *N*-(4-chloro-2fluorophenyl)pyrimidine-2-sulfonamide 26-Cl (65.6 mg, 0.20 mmol) and NCS (32.0 mg, 0.24 mmol, 1.2 equiv), in MeCN at 130 °C, to give 26-Cl<sub>2</sub> as a white solid; yield: 56.6 mg (78%); mp = 187-188 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz) δ: 9.00 (d, *J* = 4.8 Hz, 2H), 7.77 (t, *J* = 4.9 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz) δ: 167.1, 161.6 (d, *J*<sub>C-F</sub> = 252.1 Hz), 159.5, 138.0 (d, *J*<sub>C-F</sub> = 12.4 Hz), 129.8 (d, *J*<sub>C-F</sub> = 4.3 Hz), 124.7, 117.2 (d, *J*<sub>C-F</sub> = 25.7 Hz). <sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz) δ: 66.3. EI<sup>+</sup> calcd. for Cl<sub>10</sub>H<sub>6</sub>N<sub>3</sub>O<sub>2</sub>FCSCl<sub>2</sub> (M)<sup>+</sup>: 320.9542; Found: 320.9527.

*N*-(2-Bromo-6-chloro-4-methylphenyl)pyrimidine-2-sulfonamide (27-Cl). Com-Br pound 27-Cl was prepared following Method D from *N*-(2bromo-4-methylphenyl)pyrimidine-2-sulfonamide 27 (65.6 mg, 0.20 mmol) and NCS (32.0 mg, 0.24 mmol, 1.2 equiv), in DMF at 150 °C, to give 27-Cl as a white solid; yield: 58.0 mg (80%); mp = 198-200 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz) δ: 9.89 (s, 1H), 8.99 (d, *J* = 4.8 Hz, 2H), 7.75 (t, *J* = 4.9 Hz, 1H), 7.45 (d, *J* = 1.1 Hz, 1H), 7.30 (dd, *J* = 1.8, 0.8 Hz, 1H), 2.33 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz) δ: 178.9, 167.2, 159.4, 142.1, 136.3, 133.4, 131.3, 130.7, 126.9, 124.6, 20.4. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>SClBr (M)<sup>+</sup>: 360.9287; Found: 360.9304.

N-(2,4-Dichloro-6-methylphenyl)pyrimidine-2-sulfonamide (28-Cl). Compound 28-

186 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ: 8.92 (d, J = 4.8 Hz, 2H), 7.54 (t, J = 4.8 Hz, 1H), 7.20 (d, J = 2.2 Hz, 1H), 7.11 (d, J = 2.3 Hz, 1H), 6.88 (s, 1H), 2.52 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ: 165.1, 158.8, 142.7, 134.2, 133.4, 130.5, 130.0, 127.0, 123.7, 20.0. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>SCl<sub>2</sub> (M)<sup>+</sup>: 316.9793; Found: 316.9794.

N-(2,6-Dichloro-4-methylphenyl)pyrimidine-2-sulfonamide (29-Cl<sub>2</sub>). Compound 29-

Cl<sub>2</sub> was prepared following Method D from *N*-(*p*-tolyl)pyrimidine-2-sulfonamide **29** (49.9 mg, 0.20 mmol) and NCS (64.1 mg, 0.48 mmol, 2.4 equiv), in MeCN at 130 °C, to give **29-Cl<sub>2</sub>** as a pale yellow oil; yield: 58.0 mg (85%). <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.99 (d, *J* = 4.8 Hz, 2H), 7.75 (t, *J* = 4.8 Hz, 1H), 7.27 (s, 2H), 2.33 (s, 3H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 167.2, 159.4, 141.7, 136.5, 130.1, 129.9, 124.5, 20.6. EI<sup>+</sup> calcd. for C<sub>11</sub>H<sub>9</sub>N<sub>3</sub>O<sub>2</sub>SCl<sub>2</sub> (M)<sup>+</sup>: 316.9793; Found: 316.9803.

Methyl 3,5-dichloro-4-(pyrimidine-2-sulfonamido)benzoate (30-Cl<sub>2</sub>). Compound 30-

Cl<sub>2</sub> was prepared following Method D from methyl 4-(pyrimidine-2-sulfonamido)benzoate **30** (58.6 mg, 0.20 mmol) and NCS (64.1 mg, 0.48 mmol, 2.4 equiv), in MeCN at 130 °C, to give **30-Cl<sub>2</sub>** as a white solid; yield: 43.0 mg (60%); mp = 164-167 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 9.31 (s, 1H), 9.02 (d, *J* = 4.8 Hz, 2H), 7.97 (s, 2H), 7.79 (t, *J* = 4.8 Hz, 1H), 3.92 (s, 2H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)  $\delta$ : 166.9, 164.6, 159.6, 136.9, 136.8, 132.2, 130.1, 124.8, 53.2. EI<sup>+</sup> calcd. for C<sub>12</sub>H<sub>9</sub>N<sub>3</sub>O<sub>4</sub>SCl<sub>2</sub> (M)<sup>+</sup>: 360.9691; Found: 360.9686. 5.6. METHOD E: *ortho*-halogenation using 1,3-dichloro-5,5-dimethylhydantoin as source of chlorine or 1,3-dibromo-5,5-dimethylhydantoin as source of bromine



Compound **8-Cl** was isolated when following Method B (reaction time: 1 h) from *N*-(*p*-tolyl)pyridine-2-sulfonamide **8** (49.7 mg, 0.20 mmol) and 1,3-dichloro-5,5-dimethylhydantoin (23.6 mg, 0.12 mmol, 0.6 equiv); yield: 45.7 mg (81%).



Likewise, compound **8-Br** was isolated when following Method C (reaction time: 1 h) from *N*-(*p*-tolyl)pyridine-2-sulfonamide **8** (49.7 mg, 0.20 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (34.3 mg, 0.12 mmol, 0.6 equiv); yield: 34.0 mg (69%).

#### 6. Mechanistic Investigations

#### 6.1. Intramolecular isotopic kinetic effect

a) Synthesis of the deuterated aniline derivative **1(D)**.



Following the literature procedure,<sup>3</sup> 1.00 g (5.82 mmol) of 2-bromoaniline was treated with several portions of MeOD to give 2-bromoaniline- $d_2$  (amino group exchange). The 2-bromoaniline- $d_2$  was the added to 2.0 g (0.03 mmol) of zinc dust in 20 mL of 10% NaOD in D<sub>2</sub>O and the slurry heated under reflux for 72 h, after which time the 2-deuteroaniline was isolated as a colorless oil, after filtration, extraction and drying.

Following the typical procedure for N-sulfonylation, pyridine (388 µL, 4.80 mmol, 1.20 equiv) and 2-pyridylsulfonyl chloride (852 mg, 4.80 mmol, 1.20 equiv) were successively added dropwise at 0  $^{\circ}$ C to a solution of 2-deuteroaniline (364  $\mu$ L, 4.00 mmol, 1.00 equiv) in THF (40 mL), under N<sub>2</sub> atmosphere. The mixture was warmed to room temperature and stirred overnight. During this time, a gradual formation of a precipitate was observed. The resulting mixture was then suction filtered through a 6-cm fritted glass funnel (coarse) into a round-bottomed flask, and the filter cake was rinsed with THF (3 x 10 mL). To the resulting filtrate and the washes, water (20 mL) was added and the THF was removed by evaporation at reduced pressure, yielding a suspension of a white solid in the aqueous medium. This solid was collected by filtration, washed sequentially with toluene (2 x 5 mL) and diethyl ether (2 x 5 mL). Then it was transferred to a round-bottomed flask, and dried at 1.0 mmHg to provide 1(D) as a white powder; yield: 862 mg (92%); mp = 170-172 °C. <sup>1</sup>H NMR (acetone- $d_6$ , **300 MHz**)  $\delta$ : 9.23 (s, 1H), 8.68 (dt, J = 4.7, 1.3 Hz, 1H), 8.10 – 7.92 (m, 2H), 7.58 (ddd, J = 7.2, 4.8, 1.6 Hz, 1H), 7.37 - 7.16 (m, 3H), 7.11 - 6.98 (m, 1H). <sup>13</sup>C NMR (acetoned<sub>6</sub>, 75 MHz) δ: 158.0, 150.9, 139.1, 138.6, 129.8, 129.7, 127.9, 125.2, 123.5, 121.9, 121.8. **ESI**<sup>+</sup> calcd. for  $C_{11}H_{10}DN_2O_2S$  (M+H)<sup>+</sup>: 235.0535; Found: 235.0537.

b) Determining the intramolecular isotopic kinetic effect when using  $(Cl_2CH)_2$ 



An oven-dried, nitrogen-flushed 20 mL vessel was charged with the deuterated aniline derivative 1(D) (0.20 mmol) and copper(II) chloride (5.38 mg, 0.04 mmol,

<sup>&</sup>lt;sup>3</sup> Huang, S.-H.; Keith, J. M.; Hall, M. B.; Richmond, M. G. Organometallics 2010, 29, 4041.

20 mol%). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen,  $Cl_2CHCHCl_2$  (1 mL) and the internal standard *n*-hexadecane (50 µL) were added *via* syringe. After stirring the reaction mixture at 130 °C for 38 h, it was diluted with 5 mL of  $CH_2Cl_2$  and filtered through a pad of Celite. The filtrate was washed twice with brine. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under vacuum. The residue was purified by column chromatography (SiO<sub>2</sub>, *n*-hexane-ethyl acetate 5:1), yielding a mixture of **1-Cl** and **1(D)-Cl** in a ratio 1:1. The GC analysis showed that the conversion was 49% and the ratio of *ortho*-proton product (**1-Cl**) to *ortho*-deuterium product (**1(D)-Cl**) is 1:1 as deduced from the comparison with the standard <sup>1</sup>H NMR spectrum of **1-Cl**: the integration of the peak at the multiplet at 7-68-7.62 ppm was 1.5 instead of 2.

c) Determining the intramolecular isotopic kinetic effect when using NCS



An oven-dried, nitrogen-flushed 20 mL vessel was charged with the corresponding *N*-protected aniline (**1(D**)) (0.20 mmol, 1.00 equiv), NCS (32.0 mg, 0.24 mmol, 1.2 equiv) and CuCl<sub>2</sub> (2.69 mg, 0.02 mmol, 10 mol%). The reaction vessel was sealed with a Teflon lined cap, then evacuated and flushed with oxygen three times. Under the atmosphere of oxygen, MeCN (1 mL) and the internal standard *n*-hexadecane (50  $\mu$ L) were added *via* syringe. The resulting mixture was stirred at 100 °C for 1 h. After the reaction was complete, the volatiles were removed *in vacuo* and the residue was purified by column chromatography (*n*-hexane-EtOAc 5:1), yielding a mixture of **1-Cl** and **1(D)-Cl** in a ratio 1:1. The GC analysis showed that the conversion was 65% and the ratio of *ortho*-proton product (**1-Cl**) to *ortho*-deuterium product (**1(D)-Cl**) is 1:1 as we can deduced from the comparison with the standard <sup>1</sup>H NMR spectrum of **1-Cl**: the integration of the peak at the multiplet at 7-68-7.62 ppm was 1.5 instead of 2.






#### 6.2. Electronic Effect

Substrates **8** and **3** were chlorinated following the general procedure of METHOD B: *ortho*-chlorination using NCS as a source of chlorine. The reaction was monitored by GC analysis to measure the conversion over time. The result described in Figure 1 shows the reaction rate of **3** is slower than that of **8**.



Figure 1. Plot of conversion *versus* time; Serie 1: substrate 8; Serie 2: substrate 3.

#### 7. Typical procedure for the Mg-promoted *N*-desulfonylation

Synthesis of 2-chloroaniline (31). To a solution of *N*-(2-chlorophenyl)pyridine-2sulfonamide 1-Cl (53.5 mg, 0.2 mmol, 1.00 equiv) in dry MeOH (10 mL) was added magnesium (turnings, 48.6 mg, 2.00 mmol, 10 equiv). The reaction mixture was sonicated at room temperature until complete conversion of the starting material (TLC monitoring). Equal volumes of diethyl ether and saturated aq. NH<sub>4</sub>Cl were added, and the organic phase was separated. The aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases were dried (MgSO<sub>4</sub>) and concentrated to dryness to give pure **31** as colourless oil; yield: 22.0 mg (85%). The analytical data (NMR, GC-MS analysis) are in agreement with those of the commercial available 2-chloroaniline [CAS: 95-51-2]. **2,6-Dichloro-4-fluoraniline** (32). *N*-(2,6-Dichloro-4-fluorophenyl)pyrimidine-2sulfonamide **26-Cl<sub>2</sub>** (64.4 mg, 0.20 mmol) was deprotected following the above described typical procedure for Mg-promoted *N*desulfonylation to give **32** as a white solid; yield: 28.1 mg (78%); mp = 50-52 °C. The analytical data (NMR, GC-MS analysis) are in

agreement with those of the commercial available 2,6-dichloro-4-fluoraniline [CAS: 344-19-4].

8. Typical procedure for the synthesis of 2-substituted *NH*-indoles from *ortho*bromo-substituted *N*-(2-pyridyl)sulfonyl anilines: Sonogashira coupling/cyclization/deprotection.



#### a) Sonogashira coupling-cyclization:

Ph

#### Synthesis of 2-benzyl-1-(pyridin-2-ylsulfonyl)-5-(trifluoromethyl)-1H-indole (33a).

F<sub>3</sub>C

An oven-dried, nitrogen-flushed 20 mL vessel was charged with sulfonamide **3-Br** (76.2 mg, 0.20 mmol, 1.00 equiv),  $Pd(PPh_3)_4$  (23.1 mg, 0.02 mmol, 10 mol%) and CuI (7.6 mg, 0.04 mmol,

20 mol%). The reaction vessel was then evacuated and flushed with nitrogen three times. Under nitrogen atmosphere, *p*-xylene (2 mL), prop-2-yn-1-ylbenzene (50.2  $\mu$ L, 0.40 mmol, 2.00 equiv) and triethylamine (55.8  $\mu$ L, 0.4 mmol, 2.00 equiv) were added *via* syringe. The resulting mixture was stirred at 110 °C for 16 h before the volatiles were removed *in vacuo*. The residue was purified by column chromatography (*n*-hexane-EtOAc 10:1), to give indole **33a** as a white solid; yield: 75 mg (90%); mp = 126-127 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>, **500 MHz**)  $\delta$ : 8.58 (ddd, *J* = 4.7, 1.5, 0.9 Hz, 1H), 8.26 (d, *J* = 8.8 Hz, 1H), 7.85 – 7.82 (m, 1H), 7.81 – 7.76 (m, 1H), 7.65 (s, 1H), 7.49 (dd, *J* = 8.8, 1.8 Hz, 2H), 7.44 (ddd, *J* = 7.5, 4.7, 1.3 Hz, 2H), 7.34 – 7.26 (m, 3H), 7.25 – 7.22 (m, 3H), 6.21 (d, *J* = 1.0 Hz, 1H), 4.56 (s, 2H). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)  $\delta$ : 155.8, 150.5, 144.3, 139.1, 138.2, 138.0, 129.5, 129.3, 128.6, 127.7, 126.8, 126.0 (q, *J*<sub>C-F</sub> =

32.2 Hz), 124.7 (q,  $J_{C-F} = 271.7$  Hz), 122.0, 120.8 (q,  $J_{C-F} = 3.5$  Hz), 117.7 (q,  $J_{C-F} = 4.1$  Hz), 115.3, 110.5, 35.3. <sup>19</sup>F NMR (CDCl<sub>3</sub>, 471 MHz)  $\delta$ : -61.3. ESI<sup>+</sup> calcd. for C<sub>21</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>SF<sub>3</sub> (M+H)<sup>+</sup>: 417.0879; Found: 417.0890.

2-Phenyl-5-(trifluoromethyl)-N-(2-pyridyl)sulfonyl indole (33b). An oven-dried, nitrogen-flushed 20 mL vessel was charged with sulfonamide 3-Br F<sub>3</sub>C (76.2 mg, 0.20 mmol, 1.00 equiv),  $Pd(PPh_3)_4$ (23.1 mg, ŚO₂Py 0.02 mmol, 10 mol%) and CuI (7.6 mg, 0.04 mmol, 20 mol%). The reaction vessel was then evacuated and flushed with nitrogen three times. Under nitrogen atmosphere, p-xylene (2 mL), ethynylbenzene (26.3 µL, 0.24 mmol, 1.20 equiv) and triethylamine (55.8 µL, 0.4 mmol, 2.00 equiv) were added via syringe. The resulting mixture was stirred at 110 °C for 16 h before the volatiles were removed in vacuo. The residue was purified by column chromatography (n-hexane-EtOAc 10:1), to give indole **33b** as a white solid; yield: 77.2 mg (96%); mp = 118-122 °C. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$ : 8.57 (ddd, J = 4.5, 1.7, 0.9 Hz, 1H), 8.42 - 8.33 (m, 1H), 8.04 (td, J = 7.8, 1.7 Hz, 1H), 7.98 (dd, J = 1.7, 0.8 Hz, 1H), 7.80 (dt, J = 7.9, 1.0 Hz, 1H), 7.72 – 7.62 (m, 2H), 7.50 – 7.42 (m, 3H), 7.42 – 7.35 (m, 2H), 6.85 (s, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz) δ: 156.3, 151.3, 145.1, 140.8, 139.5, 132.6, 131.4, 130.7, 129.7, 129.3, 128.3, 126.5 (q,  $J_{C-F} = 32.1$ ), 125.7 (q,  $J_{C-F} = 271.2$  Hz) 123.4, 121.8 (q,  $J_{C-F} = 3.6$  Hz), 119.1 (q,  $J_{C-F} = 4.1$  Hz), 117.3, 112.5. <sup>19</sup>F NMR (acetone-d<sub>6</sub>, **471 MHz**)  $\delta$ : -61.7. **EI**<sup>+</sup> calcd. for C<sub>20</sub>H<sub>13</sub>N<sub>2</sub>O<sub>2</sub>SF<sub>3</sub> (M)<sup>+</sup>: 402.0650; Found: 402.0658.

b) Deprotection: synthesis of 2-phenyl-5-(trifluoromethyl)-1H-indole (34). The

F<sub>3</sub>C

indole 33b (80.4 mg, 0.20 mmol, 1.00 equiv) was deprotectedPh following the above described typical procedure for Mg-promoted *N*-desulfonylation to give indole 34 as a white solid;

yield: 43 mg (81%); mp = 132-135 °C. The analytical data (NMR, HRMS analysis) matched those reported in the literature for 2-phenyl-5-(trifluoromethyl)-1*H*-indole [CAS: 491601-38-8]. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)  $\delta$ : 7.95 (s, 1H), 7.90 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.60 (dd, *J* = 8.7, 0.9 Hz, 1H), 7.54 – 7.45 (m, 2H), 7.43 – 7.33 (m, 3H), 7.07 (d, *J* = 1.1 Hz, 1H). <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)  $\delta$ : 141.2, 139.8, 132.8, 129.9, 129.6, 129.0, 126.7 (q, *J*<sub>C-F</sub> = 126.3 Hz), 122.4 (q, *J*<sub>C-F</sub> = 31.4 Hz), 119.0 (q, *J*<sub>C-F</sub> = 3.6 Hz), 118.7 (q, *J*<sub>C-F</sub> = 4.4 Hz), 112.6, 100.7. EI<sup>+</sup> calcd. for C<sub>15</sub>H<sub>10</sub>NF<sub>3</sub> (M)<sup>+</sup>: 261.0765; Found: 261.0778.

#### 9. Regioselectivity in the *ortho*-chlorination process

In order to ensure the correct regio-position of the new halogen-carbon bond, a series of *para*-substituted anilines bearing a chlorine in the *ortho*- or *meta*-position were N-protected with (2-pyridyl)sulfonyl chloride. Thus, 2-chloro-4-iodoaniline, 2-chloro-4-fluoraniline and methyl 4-amino-3-chlorobenzoate were derivatized to the corresponding protected substrates **36**, **37** and **38**, respectively (vide infra). The NMR spectra recorded for the corresponding N-(2-pyridyl)sulfonyl anilines matched those reported for the Cu-catalyzed *ortho*-chlorinated products.

For the non-comercially available *ortho*-chloro anilines, the *meta*-regioisomer was *N*-protected with (2-pyridyl)sulfonyl chloride. This is the case for 3-chloro-4-methoxyaniline (substrate **39**), 3-chloro-4-iodoaniline (**20**), 4-bromo-3-chloroaniline (**21**) and 3,4-dichloroaniline (**22**). The NMR spectra recorded for the corresponding *N*-(2-pyridyl)sulfonyl anilines did not match those reported for the Cu-catalyzed *ortho*-chlorinated products. Anilines **20**, **21** and **22** have been already described because they were used as starting materials. The corresponding <sup>1</sup>H NMR spectra of both regioisomers, *ortho*- and *meta*-, can be compared in NMR spectra section, see pp. S137-S144.



N-(2-Chloro-4-iodophenyl)pyridine-2-sulfonamide (36). Compound 36 was prepared following the typical procedure for the *N*-sulfonylation of anilines from 2-chloro-4-iodoaniline (1.01 g, 4.00 mmol) to give 36 as a white solid; yield: 1.28 g (81%); mp = 102-103 °C. The analytical

data (NMR, HRMS analysis) matched those obtained for the *ortho*-chlorinated product **9-Cl**. The NMR spectra did not match those reported for the *meta*-chlorinated product **17**. <sup>1</sup>**H** NMR (acetone-d<sub>6</sub>, **500** MHz)  $\delta$ : 8.75 (s, 1H), 8.70 (ddd, J = 4.6, 1.8, 0.9 Hz, 1H), 8.08 (td, J=7.8, 1.7, 1H), 7.97 (dt, J=7.9, 1.1, 1H), 7.75 (d, J=2.0, 1H), 7.71 – 7.62 (m, 2H), 7.47 (d, J=8.6, 1H). **EI**<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>SCII (M)<sup>+</sup>: 393.9040; Found: 393.9022. N-(2-Chloro-4-fluorophenyl)pyridine-2-sulfonamide (37). Compound 37 was

prepared following the typical procedure for the *N*-sulfonylation of anilines from 2-chloro-4-fluoroaniline (0.448 mL, 4.00 mmol) to give **37** as a white solid; yield: 0.91 g (79%); mp = 97-98 °C.

The analytical data (NMR, HRMS analysis) matched those obtained for the *ortho*chlorinated product **12-Cl**. <sup>1</sup>**H NMR (acetone-d<sub>6</sub>, 500 MHz)**  $\delta$ : 8.79 – 8.66 (m, 2H), 8.06 (td, *J*=7.8, 1.7, 1H), 7.91 (dt, *J*=7.9, 1.0, 1H), 7.72 – 7.60 (m, 2H), 7.25 (dd, *J*=8.4, 2.9, 1H), 7.13 (ddd, *J*=9.1, 8.0, 2.9, 1H). **EI**<sup>+</sup> calcd. for C<sub>11</sub>H<sub>8</sub>N<sub>2</sub>O<sub>2</sub>FSCl (M)<sup>+</sup>: 285.9972; Found: 285.9991.

Methyl 3-chloro-4-(pyridine-2-sulfonamido)benzoate (38). Compound 38 was  $MeO_2C$   $NHSO_2Py$  prepared following the typical procedure for the *N*sulfonylation of anilines from methyl 4-amino-3chlorobenzoate (724 mg, 4.00 mmol) to give 38 as a white solid; yield: 1.07 g (82%); mp = 127-128 °C. The analytical data (NMR, HRMS analysis) matched those obtained for the *ortho*-chlorinated product 13-Cl. <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)  $\delta$  8.94 (s, 1H), 8.70 (ddd, *J*=4.7, 1.7, 1.0, 1H), 8.12 (td, *J* = 7.7, 1.7 Hz, 1H), 8.04 (dt, *J* = 7.9, 1.1 Hz, 1H), 7.95 (d, *J*=1.9, 1H), 7.89 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.68 (ddd, *J*=7.5, 4.7, 1.2, 1H), 3.87 (s, 3H). EI<sup>+</sup> calcd. for C<sub>13</sub>H<sub>11</sub>N<sub>2</sub>O<sub>4</sub>SCl (M)<sup>+</sup>: 326.0125; Found: 326.0116.

*N*-(3-chloro-4-methoxyphenyl)pyridine-2-sulfonamide (39). Compound 39 was prepared following the typical procedure for the *N*sulfonylation of anilines from 3-chloro-4-methoxyaniline (630 mg, 4.00 mmol) to give **39** as a white solid; yield: 1.06 g (89%); mp = 208-209 °C. The NMR spectra did not match

those obtained for the *ortho*-chlorinated product **2-Cl**. <sup>1</sup>**H NMR (acetone-d<sub>6</sub>, 500 MHz)**  $\delta$ : 9.11 (s, 1H), 8.72 (ddd, *J*=4.7, 1.7, 0.9, 1H), 8.23 – 7.97 (m, 1H), 7.91 (dt, *J*=7.8, 1.0, 1H), 7.62 (ddd, *J*=7.7, 4.7, 1.1, 1H), 7.31 (d, *J*=2.6, 1H), 7.17 (dd, *J*=8.9, 2.6, 1H), 6.98 (d, *J*=8.9, 1H), 3.82 (s, 3H). <sup>13</sup>**C NMR (acetone-d<sub>6</sub>, 125 MHz)**  $\delta$ : 157.9, 153.6, 151.0, 139.2, 131.6, 128.0, 125.3, 123.5, 123.3, 122.6, 113.5, 56.6. **EI**<sup>+</sup> calcd. for C<sub>12</sub>H<sub>11</sub>N<sub>2</sub>O<sub>3</sub>SCl (M)<sup>+</sup>: 298.0179; Found: 298.0173.

#### 10. NMR Spectra

#### N-Phenylpyridine-2-sulfonamide (1)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



### *N*-(4-Methoxyphenyl)pyridine-2-sulfonamide (2)







#### *N*-(*p*-Tolyl)pyridine-2-sulfonamide (8)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)



#### N-(4-Iodophenyl)pyridine-2-sulfonamide (9)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



## <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)



20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 f1 (ppm)

#### N-(4-Bromophenyl)pyridine-2-sulfonamide (10)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)





#### *N*-(4-Chlorophenyl)pyridine-2-sulfonamide (11)





## <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)



f1 (ppm) i

#### *N*-(4-Fluorophenyl)pyridine-2-sulfonamide (12)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)



20 210 140 130 110 100 f1 (ppm) Ó -10 

<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz)



--- 57.8

#### , 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -4( f1 (ρρm)

### *N*-(4-(Trifluoromethyl)phenyl)pyridine-2-sulfonamide (3)





<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz)

\_\_\_\_ 114.9

. 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -4( f1 (ppm)

#### *N*-(4-Acetylphenyl)pyridine-2-sulfonamide (13)





120 110 100 f1 (ppm) . 190 . 160 140 130 . 30 

## Methyl 4-[N-(2-pyridyl)sulfonylamino]benzoate (14)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



#### *N*-(4-Cyanophenyl)pyridine-2-sulfonamide (15)





#### N-(4-Nitrophenyl)pyridine-2-sulfonamide (16)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



#### *N*-(3-Fluorophenyl)pyridine-2-sulfonamide (17)





# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



0 -10

-20

-30 -40 -50

-60 -70

-80

<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)

-90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 f1 (ppm)

### N-(3-Isopropylphenyl)pyridine-2-sulfonamide (18)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



## <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



### *N*-[3-(Trifluoromethyl)phenyl]pyridine-2-sulfonamide (19)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



## <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)



0 -10

-20

-30 -40 -50

-60 -70

-80

<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)

-90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 fl (ppm)

#### N-(3-Chloro-4-iodophenyl)pyridine-2-sulfonamide (20)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



### <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



120 110 100 f1 (ppm) 210 200 150 140 - 1

### *N*-(4-Bromo-3-chlorophenyl)pyridine-2-sulfonamide (21)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



#### *N*-(3,4-Dichlorophenyl)pyridine-2-sulfonamide (22)





## <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



f1 (ppm) 

### *N*-(Benzo[d][1,3]dioxol-5-yl)pyridine-2-sulfonamide (23)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)





<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz)



### N-(4-Chloro-2-fluorophenyl)pyrimidine-2-sulfonamide (26-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)



<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 282 MHz)



### *N*-(2-Bromo-4-methylphenyl)pyrimidine-2-sulfonamide (27)





## <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



#### *N*-(4-Fluorophenyl)pyrimidine-2-sulfonamide (26)





## <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)


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# *N-(p-Tolyl)*pyrimidine-2-sulfonamide (29)







## Methyl 4-(pyrimidine-2-sulfonamido)benzoate (30)





<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)





## N-(o-Tolyl)pyrimidine-2-sulfonamide (I)

# <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)









<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)













<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



<sup>19</sup>F NMR (acetone-d<sub>6</sub>,282 MHz)

190 180 170 160 150

140 130 120 110 100 90



80 70 f1 (ppm) 60 50

40

30 20

10 0 -10 -20 -30 -4

## N-(4-Chlorophenyl)-4-methylbenzenesulfonamide (4-Cl)





<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)







### *N*-(4-Chlorophenyl)-2-pyridinecarboxamide (6-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)





# N-Methyl-N-(4-chlorophenyl)pyridine-2-sulfonamide (7-Cl)

<sup>1</sup>H NMR (acetone- $d_6$ , 300 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)



120 110 100 f1 (ppm) . 160 

## *N*-(2-Chloro-4-methylphenyl)pyridine-2-sulfonamide (8-Cl)





## *N*-(2-Chloro-4-iodophenyl)pyridine-2-sulfonamide (9-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



20 210 f1 (ppm) ĺ 

#### N-(4-Bromo-2-chlorophenyl)pyridine-2-sulfonamide (10-Cl)



#### *N*-(2,4-Dichlorophenyl)pyridine-2-sulfonamide (11-Cl)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



120 110 100 f1 (ppm) 

# N-(2-Chloro-4-fluorophenyl)pyridine-2-sulfonamide (12-Cl)









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Ó

-10 -20

-30 -40

-50 -60

-70 -80

-90 -100 f1 (ppm) -120 -130 -140

-110

-150

-160 -170

-180 -190

-200

<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)

#### *N*-(4-Acetyl-2-chlorophenyl)pyridine-2-sulfonamide (13-Cl)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



<sup>120 110 100</sup> f1 (ppm) . 190 . 160 . 30 

## Methyl 3-chloro-4-(pyridine-2-sulfonamido)benzoate (14-Cl)



#### N-(2-Chloro-4-cyanophenyl)pyridine-2-sulfonamide (15-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)







<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)







<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)





#### N-(2-Chloro-5-isopropylphenyl)pyridine-2-sulfonamide (18-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)





N-(2-Chloro-3-(trifluoromethyl)phenyl)pyridine-2-sulfonamide and N-(2-chloro-5-

### (trifluoromethyl)phenyl)pyridine-2-sulfonamide (19-Cl).



#### *N*-(2,3-Dichloro-4-iodophenyl)pyridine-2-sulfonamide (20-Cl).

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



120 110 100 f1 (ppm) 

#### N-(4-Bromo-2,3-dichlorophenyl)pyridine-2-sulfonamide (21-Cl)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



120 110 100 f1 (ppm) - 1

#### N-(2,3,4-Trichlorophenyl)pyridine-2-sulfonamide (22-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



120 110 100 f1 (ppm) 

# *N*-(4-Acetyl-2-chlorophenyl)pyridine-2-sulfonamide (23-Cl)





150 140 130 120 110 100 f1 (ppm) 210 200 . 190 . 30 

#### *N*-(2-Bromo-4-methoxyphenyl)pyridine-2-sulfonamide (2-Br)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)





 $N\-(2-Bromo-4-methylphenyl) pyridine-2-sulfonamide~(8-Br)$ 



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



#### 20 210 200 f1 (ppm)

i

*N*-(2-Bromo-4-iodophenyl)pyridine-2-sulfonamide (9-Br)







20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 N-(2,4-Dibromophenyl)pyridine-2-sulfonamide (10-Br)



 $^{13}$ C NMR (acetone-d<sub>6</sub>, 125 MHz)



20 210 200 190 180 170 160 f1 (ppm) N-(2-Bromo-4-chlorophenyl)pyridine-2-sulfonamide (11-Br)

- i


<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



-i

#### f1 (ppm) N-(2-Bromo-4-fluorophenyl)pyridine-2-sulfonamide (12-Br)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)

20 210 200 190 180 170









<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)





# *N*-(2-Bromo-4-(trifluoromethyl)phenyl)pyridine-2-sulfonamide (3-Br)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)





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<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)





# *N*-(4-Acetyl-2-bromophenyl)pyridine-2-sulfonamide (13-Br)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)





#### Methyl 3-bromo-4-(pyridine-2-sulfonamido)benzoate (14-Br)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



## *N*-(2-Bromo-4-cyanophenyl)pyridine-2-sulfonamide (15-Br)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)





--- 2.05 Acetone-d6

#### N-(2-Bromo-4-nitrophenyl)pyridine-2-sulfonamide (16-Br)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)







#### N-(2-Bromo-3-fluorophenyl)pyridine-2-sulfonamide (17-Br)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



120 110 100 f1 (ppm)  Electronic Supplementary Material (ESI) for Chemical Communications This journal is C The Royal Society of Chemistry 2013

<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)

		1													· · · ·	
-50	-55	-60	-65	-70	-75	-80	-85	-90 f1 (ppm)	-95	-100	-105	-110	-115	-120	-125	-13

#### *N*-(2-Bromo-5-isopropylphenyl)pyridine-2-sulfonamide (18-Br).

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



#### *N*-[2-bromo-5-(trifluoromethyl)phenyl]pyridine-2-sulfonamide (19-Br).

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



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<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)



#### *N*-(2-Bromo-3,4-dichlorophenyl)pyridine-2-sulfonamide (22-Br)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



120 110 100 f1 (ppm) 

## *N*-(6-Bromobenzo[d][1,3]dioxol-5-yl)pyridine-2-sulfonamide (23-Br)





<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)













# N-(2-Bromo-6-chloro-4-methylphenyl)pyrimidine-2-sulfonamide (27-Cl)



# <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)

# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



120 110 100 f1 (ppm) 

# *N*-(2,4-Dichloro-6-methylphenyl)pyrimidine-2-sulfonamide (28-Cl)





<sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)





<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 75 MHz)





<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz)



<sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz)



#### 2-Phenyl-5-(trifluoromethyl)-N-(2-pyridyl)sulfonyl indole (33b)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



# <sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



20 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 f1 (pom) Electronic Supplementary Material (ESI) for Chemical Communications This journal is C The Royal Society of Chemistry 2013

<sup>19</sup>F NMR (acetone-d<sub>6</sub>, 471 MHz)

0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 fl (ppm)

#### 2-Phenyl-5-(trifluoromethyl)-1*H*-indole (34)



120 110 100 f1 (ppm) 210 200 

#### REGIOSELECTIVITY

#### *N*-(2-Chloro-4-iodophenyl)pyridine-2-sulfonamide (9-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



#### *N*-(2-Chloro-4-iodophenyl)pyridine-2-sulfonamide (36)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



# N-(2-Chloro-4-fluorophenyl)pyridine-2-sulfonamide (12-Cl)





# N-(2-Chloro-4-fluorophenyl)pyridine-2-sulfonamide (37)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



#### Methyl 3-chloro-4-(pyridine-2-sulfonamido)benzoate (14-Cl)

<sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



### Methyl 3-chloro-4-(pyridine-2-sulfonamido)benzoate (38)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz) ---- 2.05 Acetone-d6 - 8.94 NHSO<sub>2</sub>Py MeO<sub>2</sub>C CI ſſ // // / H00.1 3.16-≖ 5.0 f1 (ppm) S139 ).0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5

#### N-(2-Chloro-4-iodophenyl)pyridine-2-sulfonamide (9-Cl)



#### *N*-(3-Chloro-4-iodophenyl)pyridine-2-sulfonamide (20)

#### <sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



0.5 0.

### N-(4-Bromo-2-chlorophenyl)pyridine-2-sulfonamide (10-Cl)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 300 MHz)



#### *N*-(4-Bromo-3-chlorophenyl)pyridine-2-sulfonamide (21)

<sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



# *N*-(2,4-Dichlorophenyl)pyridine-2-sulfonamide (11-Cl)





#### *N*-(3,4-Dichlorophenyl)pyridine-2-sulfonamide (22)

#### <sup>1</sup>H NMR (acetone-d<sub>6</sub>, 500 MHz)



#### *N*-(2-Chloro-4-methoxyphenyl)pyridine-2-sulfonamide (2-Cl)





#### *N*-(3-Chloro-4-methoxyphenyl)pyridine-2-sulfonamide (39)

#### <sup>1</sup>H NMR (acetone- $d_6$ , 500 MHz)



<sup>13</sup>C NMR (acetone-d<sub>6</sub>, 125 MHz)



130 120 110 100 f1 (ppm) 210 200 190 180 170 , i