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Johan Guilbaud, Marine Labonde, Hélène Cattey, Sylvie Contal, Christian Montalbetti, et al.. N-(2-pyridyl)sulfonyl groups for ortho-directing palladium carbon-halogen bond formation at functionalized arenes. *Advanced Synthesis and Catalysis*, 2017, 359 (21), pp.3792-3804. 10.1002/adsc.201700858 . hal-04563455

HAL Id: hal-04563455

<https://hal.science/hal-04563455>

Submitted on 29 Apr 2024

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N-(2-pyridyl)sulfonyl groups for *ortho*-directing palladium carbon–halogen bond formation at functionalized arenes

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Abstract. We describe an efficient palladium-catalyzed selective C–H *ortho*-monohalogenation (X = I, Br, Cl, F) of various functionalized *N*-(2-pyridyl)arylsulfones. *Ortho*-, *meta*- and *para*-functionalization is tolerated at the arene group which undergoes C–H halogenation. Some modifications are also possible on the 2-(arylsulfonyl)heteroaryl directing groups.

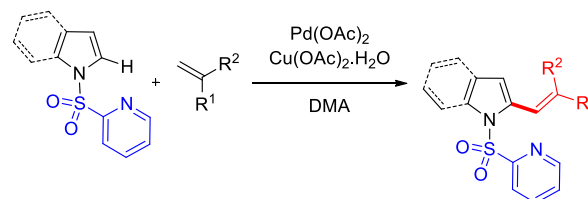
A comparison of the halogenation efficiency suggests that bromination is the practical method of choice, while chlorination and fluorination are possible but more challenging. Under forcing conditions *ortho*-dihalogenation can also be achieved.

Keywords: halogenation • fluorination • pyridylsulfone • palladium • arene C–H functionalization

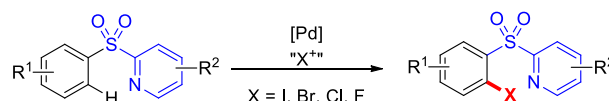
Introduction

Carbon–halogen C–X bond formation (X = I, Br, Cl, F) is central to organic chemistry since the resulting organic halides can be used as both synthetic precursors and target compounds for modern pharmaceutical and agrochemical synthesis, and in materials science.^[1] Transition metals catalyze the synthesis of organohalides and recently research focus shifted towards the selective use of C–H group as function towards C–X bond formation.^[2] From a synthetic viewpoint, C–H activation by transition metals using directing groups efficiently insure selectivity. When the target molecule does not contain directing functionality the introduction of efficient, possibly removable, directing groups is then recommended. Among such valuable directing groups for C–H activation,^[3] specifically *N*-(2-pyridyl)sulfonyl has been proved by Carretero and coworkers to exert complete and efficient C2 regiocontrol over the Pd(II)-catalyzed C–H alkenylation of the heteroarenes indoles and pyrroles (Scheme 1).^[4] Garcia-Manche o also described one example of C–H functionalization with acetate using *N*-(2-pyridyl)sulfonyl directing group.^[5]

(a) C–C coupling (Carretero 2009)



(b) C–X coupling (*this work*)



Scheme 1. *N*-(2-pyridyl)sulfonyl group used in Pd-catalyzed C–H activation/functionalization.

While the extension of this C–C bond formation chemistry employed with (hetero)arenes (Scheme 1a) to the formation of C–X bonds from functionalized arenes (Scheme 1b) could not be straightforward we envisioned its great potential. Indeed, organosulfur compounds have become widely used as bioactive products and in materials science, and for instance bioactive patented molecules of interest incorporating *N*-(2-pyridyl)sulfonyl group are known (Figure 1); these include any of the different halogens.^[6] In this

same context, the introduction of the parent sulfonamide directing group (and pharmacophore) has been reported as an attractive approach in medicinal chemistry for increasing pharmacologic potency.^[7]

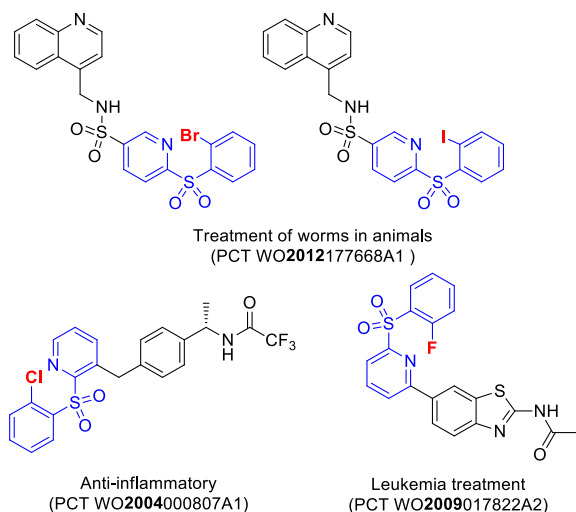


Figure 1. *Ortho*-halogenated 2-(arylsulfonyl)pyridine patented drugs.

Herein, we described the efficient palladium-catalyzed selective C–X *ortho*-monohalogenation of various functionalized 2-(arylsulfonyl)pyridines (X = I, Br, Cl, F). *Ortho*-, *meta*- and *para*-functionalization is tolerated on the aryl moiety where C–H halogenation occurs. Moreover, several modifications are possible on the 2-(arylsulfonyl)heteroaryl directing groups. A comparison of the halogenation efficiency suggests that bromination is the practical method of choice, while chlorination and fluorination are possible but more challenging. Under forcing conditions *ortho*-dihalogenation can be also achieved.

Results and Discussion

We previously reported a general protocol for palladium-catalyzed C–H mono- and difluorination of highly substituted arylpyrazoles and *s*-tetrazines.^[8] We showed that careful optimization of conditions was necessary for these halogenation reactions to efficiently proceed, especially regarding the palladium source, solvent, temperature conditions, as well as the nature and amount of halogen source. Herein, we started bromination of 2-(phenylsulfonyl)pyridine **1** in the presence of 1 equivalent of NBS, 10 mol% of [Pd⁰(dba)₂] in nitromethane at 110 °C (Table 1). While 2-(phenylsulfonyl)pyridine was found unreactive towards NBS in the absence of Pd (Table 1, entry 1), we were glad to observe in the presence of 10 mol% of [Pd⁰(dba)₂] a substrate conversion of 51%, fully selective in the monobrominated product **1a** (entry 2). A higher conversion to **1a** with a 78% yield was obtained from the use of [Pd^{II}(OAc)₂], instead of a Pd⁰ source (entry 3), however dibromination to **1b**

was also observed as traces (4%). Increasing the amount of NBS to 2 equivalents improved the conversion but mainly increased the formation of **1b** to 11% yield (entry 4). Solvent changes using PhCF₃ or acetic acid were found to be detrimental, respectively, for conversion rate (entry 5, 57% **1a**) and selectivity (entry 6, 21% **1b**). Further optimization of palladium amount (5 mol%) and NBS (1.2 equiv), as well as temperature adjustment (90 °C) allowed finally a full conversion with a fairly selective monobromination of 2-(phenylsulfonyl)pyridine to give **1a** in 85% yield (entry 7). In this case the formation of **1b** remained limited to 15% yield.

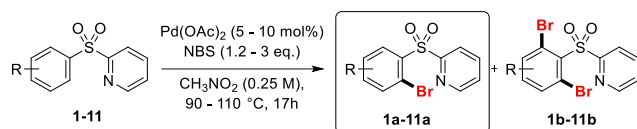
Table 1. Screening of conditions for 2-(phenylsulfonyl)pyridine bromination.^{a)}

Entry	[Pd] (mol%)	NBS (eq.)	Solvent	T °C	Conv. ^{b)}	1a ^{b)}	1b ^{b)}
1	-	NBS (1.0)	CH ₃ NO ₂	110	0	0	0
2	Pd(dba) ₂ (10)	NBS (1.0)	CH ₃ NO ₂	110	51	51	0
3	Pd(OAc) ₂ (10)	NBS (1.0)	CH ₃ NO ₂	110	82	78	4
4	Pd(OAc) ₂ (10)	NBS (2.0)	CH ₃ NO ₂	110	98 ^{c)}	80	11
5	Pd(OAc) ₂ (10)	NBS (2.0)	PhCF ₃	110	60 ^{c)}	57	0
6	Pd(OAc) ₂ (10)	NBS (2.0)	HOAc	110	100	79	21
7 ^{d), e)}	Pd(OAc) ₂ (5)	NBS (1.2)	CH ₃ NO ₂	90	100	85	15

^{a)} Conditions: 2-(phenylsulfonyl)pyridine (0.5 mmol, 1.0 equiv), NBS (1.2 equiv), [Pd(OAc)₂] (5 mol%), CH₃NO₂ (0.125 M), 110 °C, under argon, 17 h. ^{b)} ¹H NMR yield based on 2-(phenylsulfonyl)pyridine. ^{c)} Some unidentified products were observed. ^{d)} 2-(phenylsulfonyl)pyridine (1.5 mmol). ^{e)} CH₃NO₂ (0.25 instead of 0.125 M).

With these reaction conditions in hand we explored the scope of monobromination using arene-functionalized 2-(arylsulfonyl)pyridine (Table 2). In general the dibrominated products were formed in limited amounts and could be separated by silica column chromatography treatment. Thus, 2-(2-bromophenylsulfonyl)pyridine **1a** was isolated in good 75% yield (Table 2, entry 1).

Table 2. Palladium-catalyzed bromination of 2-(arylsulfonyl)pyridine.^{a)}



Entry	Sulfone	Conv. ^{b)}	a/b ratio ^{b)}	Y in a (%) ^{c)}
1		100	85/15	 1a: 75%
2		88	92/8	 2a: 61%
3		95	92/8	 3a: 56%
4		93	89/11	 4a: 72%
5		87	97/3	 5a: 66%
6 ^{e)}		83	100/0	 6a: 51%
7		99	100 ^{d)} /0	 7a: 85%
8 ^{e)}		63	100 ^{d)} /0	 8a: 49%
9		90	100/0	 9a: 69%
10 ^{e)}		91	100/0	 10a: 57%
11		37	100/0	 11a: 33%

^{a)} Conditions: 2-(arylsulfonyl)pyridine (1.0 equiv), NBS (1.2 equiv), [Pd(OAc)₂] (5 mol%), CH₃NO₂ (0.25 M), 90 °C, under argon, 17 h. ^{b)} ¹H NMR and GC yield based on 2-(arylsulfonyl)pyridine. ^{c)} Isolated yield. ^{d)} Less than 5% of brominated isomer in position 2 (near the substituent) was detected. ^{e)} NBS (3.0 equiv), [Pd(OAc)₂] (10 mol%), 110 °C.

Electron-donating substituents on the aryl moiety are tolerated like 4-Me or 4-*t*Bu, and bromination of **2** and **3**, respectively, gave a high conversion of 88% and 95% with a mono/dihalogenation ratio 92/8 (entries 2, 3). Workup to reach high purity (99%+) reduced the isolated yield to 61% of **2a** and 56% of **3a**. Halogenated 2-(arylsulfonyl)pyridines could be also further brominated: the *C*4-chlorinated **4** undergo *meta*-bromination without dechlorination to provide dihalogenated **4a** in 72% isolated yield (entry 4). Notably, reagent **4** does not undergo undesired side-reaction of oxidative addition to Pd(0). The fluorinated 2-(arylsulfonyl)pyridine **5** achieved bromination with a high selectivity 97/3:mono/dihalogenation. Again isolated yield is reduced (66%) when high purity 99%+ was achieved (entry 5). Sulfonylpyridine **6** bearing the electron-withdrawing 4-CF₃ group was more reluctant to bromination in the presence of 5 mol% in [Pd(OAc)₂] and conversion in **6a** reached 83% using 10 mol% of [Pd(OAc)₂] for an isolated yield of 51%, (entry 6).

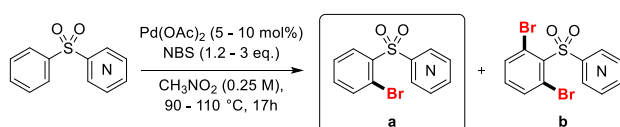
The substrates bearing electron-donor 3-Me and electron-withdrawing 3-Cl functions achieved highly selective monobromination to give *para*-brominated products (entries 7 and 8). Only traces of isomeric *ortho*-substitution were detected by GC-MS. The electronic effects previously observed were confirmed since methylated **7a** was isolated in excellent 85% yield (entry 7) while chlorinated **8a** was obtained in 49% yield due to lower conversion rate (entry 8).

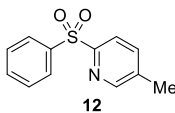
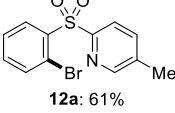
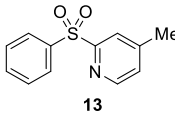
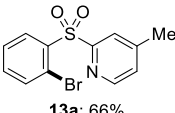
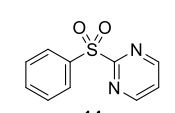
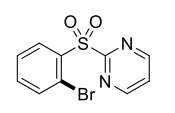
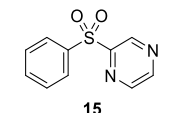
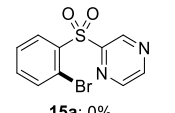
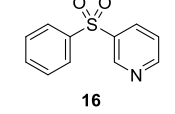
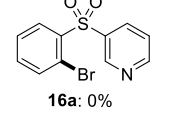
We also successively achieved monobromination of the 2-substituted sulfonyl pyridines **9-11** (Table 2, entries 9-11) bearing 2-Me, 2-Cl and 2-CF₃ groups respectively. Methylated **9a** was obtained in good 69% yield (starting material was found to be difficult to remove during work-up). Consistently, chlorinated **10a** was isolated in satisfactory 57% by using 10 mol% of catalyst: conversion was good but purification work-up by chromatography limited the isolated yield. In the presence of 2-CF₃, a moderate 37% conversion to **11a** was obtained (isolated yield 33%, entry 11) in the presence of 10 mol% catalyst, even with increased amounts of NBS. Thus, versatile selective bromination was achieved with this protocol, and notably unequally dihalogenated sulfones **4a**, **8a** and **10a** would be particularly suitable functionalized blocks to further build more sophisticated molecules.

We extended the scope of this bromination by using modified directing groups including various related sulfone substrates (Table 3). The presence of a methyl group on the pyridin-2-sulfonyl directing group is tolerated in *C*3 and *C*4 position and bromination of the phenyl moiety was achieved with high conversion (Table 3, entries 1 and 2). *C*3-methylated compound **12** converted in 86% yield with a 93/7 selectivity of monobrominated/dibrominated products, with **12a** isolated in satisfactory 61% yield (entry 1). Compound **13** *C*4-methylated gave a 84/16 ratio of **13a** and **13b** and monobrominated **13a** was isolated pure in 66% yield. The incorporation of a second nitrogen atom on the heteroaromatic directing

group decreases its global electron density, which was found detrimental for C–H bromination (entries 3-4). (1,3-)Pyrimidin-2-yl unit allowed C–Br bond formation in a low 26% yield under our standard conditions, and **14a** was isolated in 10% yield. (1,4-)Pyrazin-2-yl was inefficient for performing C–H bromination of the corresponding sulfone under our conditions. Unsurprisingly 3-pyridylsulfone **16** has no directing group effect to promote C–H bromination (entry 5).

Table 3. Palladium-catalyzed bromination of different 2-(phenylsulfonyl) heteroaryl.^{a)}



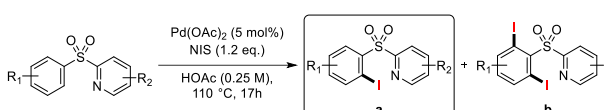
Entry	Sulfone	Conv. ^{b)}	a/b ratio ^{b)}	Y in a (%) ^{c)}
1		86	93/7	 12a: 61%
2		95	84/16	 13a: 66%
3		26	100/0	 14a: 10%
4		0	/	 15a: 0%
5		0	/	 16a: 0%

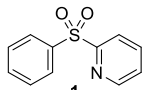
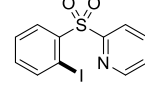
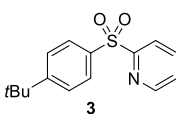
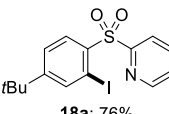
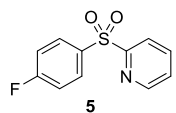
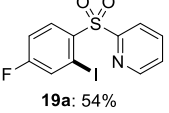
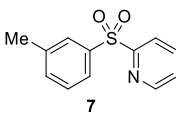
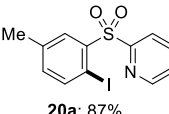
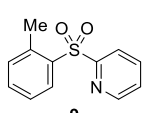
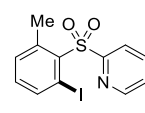
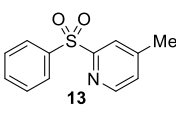
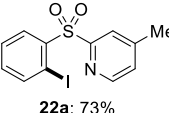
^{a)} Conditions: 2-(phenylsulfonyl) heteroaryl (1.0 equiv), NBS (1.2 equiv), [Pd(OAc)₂] (5 mol%), CH₃NO₂ (0.25 M), 90 °C, under argon, 17 h. ^{b)} ¹H NMR and GC yield based on 2-(phenylsulfonyl) heteroaryl. ^{c)} Isolated yield. ^{d)} NBS (3.0 eq.), [Pd(OAc)₂] (10 mol%), CH₃NO₂ (0.12 M), 110 °C.

The conditions for iodination of 2-(arylsulfonyl)pyridine were screened (see details in SI, Tables SI-2). The best protocol for *ortho*-C–H iodination of 2-(arylsulfonyl)pyridine was found fairly similar to the conditions used for C–H bromination with 5 mol% of Pd(OAc)₂ as the catalyst and NIS as iodine source (1.2 equiv). However, AcOH at 110 °C was a better reaction solvent. The 2-(phenylsulfonyl)pyridine **1** was successfully iodinated in a 93/7 ratio mono/dihalogen and a 61% yield was isolated for **17a** (Table 4, entry 1). 4-substituted aryl groups tolerate electron-donating and

electron-withdrawing substituents for selective monoiodination and *tert*-butylated **18a** was isolated in good 76% yield (entry 2). In the presence of electron-withdrawing fluorine the dihalide **19a** was obtained in lower 54% yield (entry 3). The protocol was successfully extended to 2-(arylsulfonyl)pyridine bearing 3-Me and 2-Me groups on aryl (**7** and **9**, entries 4 and 5, respectively). *Meta*- and *ortho*-methylated substrates achieved selective monoiodination with high to moderate yields, giving 87% yield for **20a** and 50% yield for **21a**. In the presence of 5-Me group on pyridyl the monoiodination takes place quantitatively, and **22a** was isolated in good 73% yield (entry 7).

Table 4. Palladium-catalyzed iodination of 2-(arylsulfonyl)pyridine.^{a)}



Entry	Sulfone	Conv. ^{b)}	a/b ratio ^{b)}	Y in a (%) ^{c)}
1		88	92/8	 17a: 61%
2		93	100/0	 18a: 76%
3		70	100/0	 19a: 54%
4		87	100/0	 20a: 87%
5		72	100/0	 21a: 50%
6		90	100/0	 22a: 73%

^{a)} Conditions: 2-(arylsulfonyl) heteroaryl (1.0 equiv), NIS (1.2 equiv), [Pd(OAc)₂] (5 mol%), HOAc (0.25 M), 110 °C, under argon, 17 h. ^{b)} ¹H NMR and GC yield based on 2-(arylsulfonyl) heteroaryl. ^{c)} Isolated yield.

While palladium-catalyzed iodination of 2-(arylsulfonyl)pyridine is a suitable alternative to C–H bromination, we also investigated the palladium-

catalyzed chlorination of 2-(arylsulfonyl)pyridine under analogous protocols (Table 5). The C–H chlorination using NCS as chlorine source was typically found more difficult, and we had to increase the amount of NCS to three equiv in order to achieve a satisfactory chlorination of 2-(arylsulfonyl)pyridines. Because of the excess of NCS, the chlorination of 2-(phenylsulfonyl)pyridine **1** was found less selective than iodination with a 88/12 ratio in mono/dichlorinated product. Thus, **23a** was isolated in 28% yield (Table 5, entry 1). Selective chlorination of functionalized sulfones **3**, **5**, **9** and **13** was successfully achieved in fairly good to high yield to give monochlorinated **24–27a** (78%, 67%, 83% and 82%, respectively, entries 2–5); however, purification work-up by chromatography limited the isolated yields.^[9]

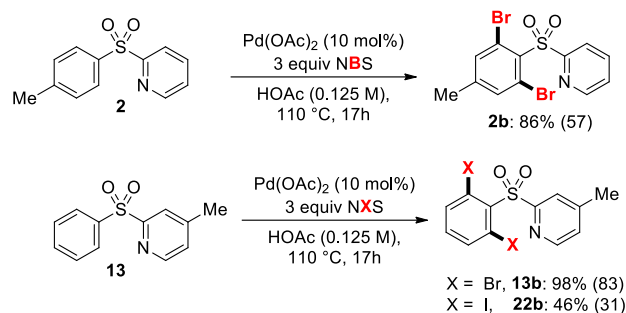
Table 5. Palladium-catalyzed chlorination of 2-(arylsulfonyl)pyridines.^{a)}

Entry	Sulfone	Conv. ^{b)}	a/b ratio ^{b)}	Yield in a (%) ^{c)}
1		56	100/0	 23a : 28%
2		78	100/0	 24a : 54%
3		67	100/0	 25a : 36%
4		83	100/0	 26a : 16%
5		82	100/0	 27a : 41%

^{a)} Conditions: 2-(arylsulfonyl) heteroaryl (1.0 equiv), NCS (3.0 equiv), [Pd(OAc)₂] (10 mol%), HOAc (0.25 M), 110 °C, under argon, 17 h. ^{b)} ¹H NMR and GC yield based on 2-(arylsulfonyl) heteroaryl. ^{c)} Isolated yield.

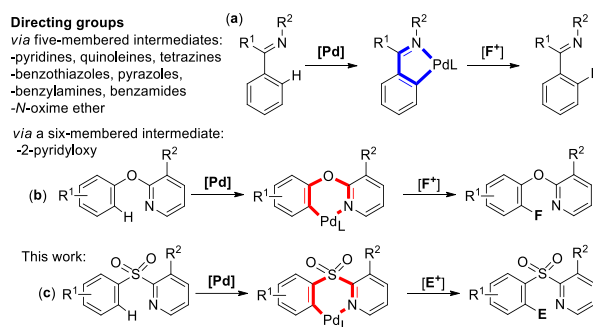
Conditions for dihalogenation of 2-(arylsulfonyl)pyridines were investigated using 2-(4-tolylsulfonyl)pyridine **2** (Scheme 2). In the presence of 10 mol% of Pd(OAc)₂ *ortho*-dibrominated **2b** formed in 57% isolated yield (86% conversion into **2b**) by using 3 equiv of *N*-bromosuccinimide. Accordingly, *ortho*-dibromination of the methylated 2-(phenylsulfonyl)-4-methylpyridine **13** also led to

isolate **13b** in 83% yield. Diiodination was found more difficult to achieve and by using NIS instead of NBS, the diiodo **22b** was obtained in moderate 31% yield.



Scheme 2. Pd-catalyzed *ortho*-dibromination and *ortho*-diiodination of methylated 2-(phenylsulfonyl)pyridines.

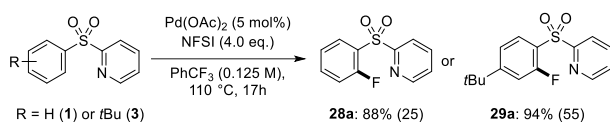
Finally, we also examined C–H fluorination reactions.^[8] Significant progress has been made in *ortho*-directed palladium-catalyzed C–F bond formation.^[10] From a mechanistic perspective, these reactions mostly involve a transient five-membered palladacycle (Scheme 3a). Examples of directing groups for which C–H fluorination proceeds *via* a six-membered palladacycle is limited to one very recent illustration in which a 2-pyridyloxy group is employed (Scheme 3b).^[11]



Scheme 3. Usual transient palladacycles formed in *ortho*-directed C–H fluorination.

On the other hand, potential fluorinating reagents have been already used by Carretero *et al.* in the olefination of carbazoles *ortho*-directed by *N*-(2-pyridyl)sulfonyl groups. *N*-fluoro-2,4,6-trimethylpyridinium triflates specifically reacted as oxidant without C–F bond formation reported.^[12] After the screening of several electrophile F⁺ sources (Me₃PyF.OTf, Selectfluor, Me₃PyF.BF₄, PyF.BF₄, details in SI, Table SI-4) we achieved the challenging selective monofluorination of 2-(phenylsulfonyl)pyridine **1** by using *N*-fluorobenzenesulfonimide (NFSI). In the presence of 5 mol% of Pd(OAc)₂ with four equiv of NFSI in trifluoromethylbenzene as solvent at 110 °C allowed forming **28a** in 88% conversion (Scheme 3). Unlike for bromination reactions, the purification of difluorinated products from starting material was

found to be troublesome and a limited yield of 25% only could be isolated to reach satisfactory high purity (99+%). We already reported on purification limitations with chromatography when a mixture of mono- and difluorinated compounds is obtained.^[8a] Nevertheless, fluorination of *tert*-butyl functionalized *N*-(2-pyridyl)sulfonyl **3** gave a 94/6 ratio for **29a** and consequently **29b** with a satisfactory 55% isolated yield.



Scheme 4. Fluorination of 2-(arylsulfonyl)-pyridines.

The solid state characterization of **28a** was achieved by XRD from single crystals grown by diffusion of dichloromethane in pentane (Ortep in Figure 2). The tetrahedral sulfur atom is embed in a three-dimensional environment in which the *ortho*-fluoroaryl moiety rotates freely after the C–H activation, which is assumed to occur through a six-membered palladacycle (Scheme 3c), to position the fluorine atom *anti* to the nitrogen of the pyridyl group.

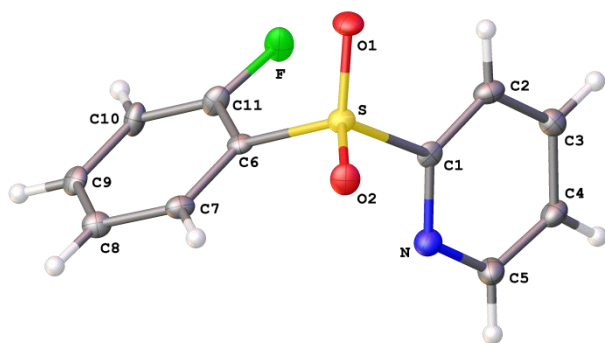


Figure 2. Ortep view of the **28a** with 50% probability ellipsoids.^[13]

Conclusion

Previously, (pyridyl)sulfonyl had been used as efficient *ortho*-C–H directing group for C–C bond formation. We now extended this reactivity to carbon–halogen C–X bond formation (X = Br, I, Cl, F). Palladium-catalyzed *ortho*-halogenation was optimized and generalized to selectively form at late-stage monohalogenated 2-(arylsulfonyl)heteroaryls. Thus, (arylsulfonyl)pyridines efficiently achieve catalyzed direct C–H halogenation. On the arylsulfonyl *para*-, *meta*- and *ortho*-substituents are tolerated (Me, *t*Bu, Cl, F, CF₃). While both electron-donating and electron-withdrawing groups on the arylsulfone are tolerated, substituents at *ortho*-position (CF₃, Me, Cl) reduced the yield. From selectivity perspective a function in *meta*-position of the arene allows a fully selective monobromination in the corresponding *para*-position. Besides effective

bromination and iodination, challenging selective C–H chlorination and fluorination were also achieved. A remarkable feature of the C–F coupling is the transient formation of a six-membered palladacycle necessary for *ortho*-selective functionalization while putative five-membered palladacycle intermediates were generally reported. Finally, dihalogenation conditions for the easier bromination and iodination reactions were determined.

These carbon–halogen bond formations, which are promoted by *N*-(2-pyridyl)sulfonyl groups, open new opportunities for further synthesis of sophisticated molecules usable for pharmaceutical, agrochemical or molecular materials application starting from (poly)halogenated precursor building blocks.

Experimental Section

General Conditions

All reagents were purchased from commercial suppliers and used without purifications. All reactions were performed in Schlenk tubes under argon. ¹H (300 MHz and 500 MHz), ¹³C (75 MHz and 125 MHz), ¹⁹F (282 MHz and 302 MHz) spectra were recorded on Bruker AVANCE III instrument in CDCl₃ solutions. Chemical shifts are reported in ppm relative to CDCl₃ (¹H: 7.26 and ¹³C: 77.16) and DMSO-*d*₆ (¹H: 2.5 and ¹³C: 39.52) coupling constants *J* are given in Hz. GC experiments were performed with a Shimadzu GC 2010 instrument. GC-MS experiments were performed with a Trace GC Ultra equipped with a mass-selective detector, high resolution mass spectra (HRMS) were obtained on a Thermo LTQ-Orbitrap XL with ESI source. Flash chromatography was performed on silica gel (230-400 mesh) or with PuriFlash 450 from Interchim. Elemental analysis experiments were performed Thermo Electron Flash EA 1112 Series.

All reactions were performed under an inert argon atmosphere using conventional vacuum-line and Schlenk techniques. 2-(arylsulfone)pyridine substrates were synthesized according literatures.

CCDC 1558706 (**28a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Catalytic bromination reactions

The sulfone derivative (0.5 mmol), NBS (1.2-3.0 equiv), and Pd(OAc)₂ (0.025-0.05 mmol) were introduced in a Schlenk tube, equipped with a magnetic stirring bar. Nitromethane (2-4 mL) was added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a pre-heated oil bath at 90 °C or 110 °C and reactants were allowed to stir for 17 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica and washed with dichloromethane. The solvent was removed in vacuum and the residue was analysed by NMR and gas chromatography to determine the conversion of the brominated product. Crude product

was purified by silica gel column chromatography using an appropriate ratio of the eluent.

Catalytic iodination reactions

The sulfone derivative (0.5 mmol), NIS (1.2-3 equiv), and Pd(OAc)₂ (0.025-0.05 mmol) were introduced in a Schlenk tube, equipped with a magnetic stirring bar. Acetic acid (2-4 mL) was added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a pre-heated oil bath at 110°C and reactants were allowed to stir for 17 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica and washed with dichloromethane. The solvent was removed in vacuum and the residue was analysed by NMR and gas chromatography to determine the conversion of the brominated product. Crude product was purified by silica gel column chromatography using an appropriate ratio of the eluent.

Catalytic chlorination reactions

The sulfone derivative (0.5 mmol), NCS (3 equiv), and Pd(OAc)₂ (0.025 mmol) were introduced in a Schlenk tube, equipped with a magnetic stirring bar. Acetic acid (4 mL) was added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a pre-heated oil bath at 110°C and reactants were allowed to stir for 17 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica and washed with dichloromethane. The solvent was removed in vacuum and the residue was analysed by NMR and gas chromatography to determine the conversion of the brominated product. Crude product was purified by silica gel column chromatography using an appropriate ratio of the eluent.

Catalytic fluorination reactions

The sulfone derivative (0.5 mmol), NFSI (4 equiv), and Pd(OAc)₂ (0.05 mmol) were introduced in a Schlenk tube, equipped with a magnetic stirring bar. Dry trifluoromethylbenzene (8 mL) was added, and the Schlenk tube purged several times with argon. The Schlenk tube was placed in a pre-heated oil bath at 110°C and reactants were allowed to stir for 17 h. After cooling to room temperature, the reaction mixture was filtered through a plug of silica and washed with dichloromethane. The solvent was removed in vacuum and the residue was analysed by NMR and gas chromatography to determine the conversion of the brominated product. Crude product was purified by semi preparative chromatography using an appropriate ratio of the eluent.

2-(2-bromophenylsulfonyl)pyridine (1a): The reaction of the corresponding sulfone (0.110 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **1a** in 75% (0.112 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.61 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.48 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.36 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.99 (td, *J* = 7.8, 1.7 Hz, 1H), 7.67 – 7.56 (m, 2H),

7.53 – 7.43 (m, 2H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 157.8, 150.1, 137.9, 137.8, 135.1, 135.0, 132.7, 127.9, 127.1, 123.7, 121.2.

2-(2-bromoparatoluensulfonyl)pyridine (2a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **2a** in 61% (0.095 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.60 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.39 – 8.26 (m, 2H), 7.97 (td, *J* = 7.8, 1.7 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.40 – 7.33 (ddd, *J* = 8.1, 1.7, 0.8 Hz, 1H), 2.39 (s, 3H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 158.1, 150.2, 146.6, 137.8, 135.7, 135.0, 132.7, 128.7, 127.1, 123.7, 121.0, 21.3. Elemental analysis: Calcd (%) for C₁₂H₁₀BrNO₂S: C 46.17 H 3.23, N 4.49. Found: C 46.83, H 3.44, N 4.43. HRMS + p ESI (*m/z*) [*M*+*H*⁺] Calcd for C₁₂H₁₀BrNO₂S: 311.968. Found: *m/z* = 311.968.

2-(2,6-dibromoparatoluensulfonyl)pyridine (2b):

The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-bromosuccinimide (0.267 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in nitromethane (4 mL) at 110 °C affords **2b** in 57% (0.112 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (500 MHz, DMSO-*d*6) δ (ppm) = 8.72 – 8.57 (m, 1H), 8.25 – 8.15 (m, 2H), 7.76 (d, *J* = 0.9 Hz, 2H), 7.72 (ddd, *J* = 6.8, 4.7, 2.0 Hz, 1H), 2.34 (s, 3H). ¹³C NMR (126 MHz, DMSO-*d*6) δ (ppm) = 158.2, 149.9, 149.8, 146.9, 139.0 (m), 136.5, 136.5, 132.0, 127.9, 127.9, 123.2, 121.7 (m), 19.8. Elemental analysis: Calcd (%) for C₁₂H₉BrNO₂S: C 36.86 H 2.32, N 3.58. Found: C 36.70, H 2.05, N 3.49. HRMS + p ESI (*m/z*) [*M*+*H*⁺] Calcd for C₁₂H₉Br₂NO₂S: 411.861. Found: *m/z* = 411.862.

2-(2-bromo-4-*tert*-butylphenylsulfonyl)pyridine (3a):

The reaction of the corresponding sulfone (0.138 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **3a** in 61% (0.095 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.62 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.42 – 8.28 (m, 2H), 7.97 (td, *J* = 7.8, 1.7 Hz, 1H), 7.67 – 7.54 (m, 2H), 7.49 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 1.32 (s, 9H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 159.5, 158.1, 150.2, 137.8, 135.0, 132.5, 132.5, 127.1, 125.2, 123.8, 121.0, 35.4, 31.0. Elemental analysis: Calcd (%) for C₁₅H₁₆BrNO₂S: C 50.86, H 4.55, N 3.95. Found: C 50.97, H 4.72, N 4.10. HRMS + p ESI (*m/z*) [*M*+*H*⁺] Calcd for C₁₅H₁₆BrNO₂S: 354.016. Found: *m/z* = 354.017.

2-(2-bromo-4-chlorophenylsulfonyl)pyridine (4a): The reaction of the corresponding sulfone (0.111 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **4a** in 72% (0.120 g) yield. White solid; (dichloromethane). ¹H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.61 (dq, *J* = 4.5, 0.7 Hz, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 8.37 – 8.32 (m, 1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.57 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.52 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 157.6, 150.3, 141.1, 138.0, 136.7, 134.9, 133.8, 128.4, 127.4, 123.8, 122.0. Elemental analysis: Calcd (%) for C₁₁H₇BrClNO₂S: C 39.72, H 2.12, N 4.21. Found: C 39.77, H 1.68, N 4.32. HRMS + p ESI

(m/z) [M+Na⁺] Calcd for C₁₁H₇BrClNO₂S: 353.896. Found: m/z = 353.897.

2-(2-bromo-4-fluorophenylsulfonyl)pyridine (5a): The reaction of the corresponding sulfone (0.119 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **5a** in 66% (0.104 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.61 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.49 (dd, *J* = 8.9, 5.8 Hz, 1H), 8.34 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.99 (td, *J* = 7.8, 1.7 Hz, 1H), 7.51 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.39 (dd, *J* = 7.9, 2.5 Hz, 1H), 7.33 – 7.22 (m, 1H). ¹⁹F NMR (282 MHz, Chloroform-*d*) δ (ppm) = –102.0. ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 165.4 (d, *J* = 260.5 Hz), 157.7, 150.3, 138.0, 135.1 (d, *J* = 9.9 Hz), 134.2 (d, *J* = 3.5 Hz), 127.3, 123.7, 122.8 (d, *J* = 25.3 Hz), 122.6 (d, *J* = 10.4 Hz), 115.4 (d, *J* = 21.6 Hz). Elemental analysis: Calcd (%) for C₁₁H₇BrFNO₂S: C 41.79, H 2.23, N 4.43. Found: C 41.47, H 2.25, N 4.51. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₁H₇BrFNO₂S: 315.944. Found: m/z = 315.943.

2-(2-bromo-4-trifluorophenylsulfonyl)pyridine (6a): The reaction of the corresponding sulfone (0.144 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **6a** in 66% (0.104 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.62 – 8.56 (m, 2H), 8.37 (dd, *J* = 7.9, 1.1 Hz, 1H), 8.02 (td, *J* = 8.0, 1.7 Hz, 1H), 7.89 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.58 – 7.49 (m, 1H). ¹⁹F NMR (470 MHz, Chloroform-*d*) δ (ppm) = –63.3. ¹³C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 157.4, 150.3, 141.8, 138.1, 136.6 (q, *J* = 33.7 Hz), 133.4, 132.3 (m, *J* = 3.7 Hz), 127.5, 124.9 (d, *J* = 3.6 Hz), 123.8, 122.4 (q, *J* = 273.1 Hz), 122.0. Elemental analysis: Calcd (%) for C₁₁H₇BrFNO₂S: C 39.36, H 1.93, N 3.83. Found: C 39.24, H 1.89, N 3.81. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₇BrF₃NO₂S: 365.940. Found: m/z = 315.940.

2-(2-bromo-5-methylphenylsulfonyl)pyridine (7a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **7a** in 85% with 6% of isomeric position product (0.104 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.62 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.36 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.29 (dd, *J* = 2.2, 0.8 Hz, 1H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.55 – 7.46 (m, 2H), 7.31 – 7.24 (m, 1H), 2.44 (d, *J* = 0.7 Hz, 3H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 158.0, 150.2, 138.6, 137.9, 137.5, 136.0, 135.0, 133.1, 127.1, 123.9, 117.7, 21.1. Elemental analysis: Calcd (%) for C₁₂H₁₀BrNO₂S: C 46.17, H 3.23. Found: C 45.71, H 3.19. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀BrNO₂S: 311.969. Found: m/z = 311.969.

2-(2-bromo-5-chlorophenylsulfonyl)pyridine (8a): The reaction of the corresponding sulfone (0.127 g, 0.5 mmol), *N*-bromosuccinimide (0.267 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in nitromethane (4 mL) at 110 °C affords **8a** in 49% (0.074 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.62 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.46 (d, *J* = 2.5 Hz, 1H), 8.35 (dt, *J* = 7.9, 1.0 Hz,

1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.61 – 7.49 (m, 2H), 7.44 (dd, *J* = 8.5, 2.5 Hz, 1H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 157.4, 150.3, 139.5, 138.0, 136.3, 135.1, 134.7, 132.7, 127.5, 123.9, 119.2. Elemental analysis: Calcd (%) for C₁₁H₇BrClNO₂S: C 39.72, H 2.12, N 4.21. Found: C 39.92, H 2.18, N 4.31. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀BrNO₂S: 333.913. Found: m/z = 333.913.

2-(2-bromo-6-methylphenylsulfonyl)pyridine (9a): The reaction of the corresponding sulfone (0.107 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **9a** in 69% (0.107 g) yield. White solid; (ethyl acetate-heptane = 3:7). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.58 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.26 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.96 (td, *J* = 7.8, 1.7 Hz, 1H), 7.55 – 7.41 (m, 2H), 7.39 – 7.21 (m, 2H), 2.93 (d, *J* = 0.7 Hz, 3H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 159.6, 149.8, 144.6, 137.7, 136.0, 133.9, 133.6, 132.9, 126.9, 123.1, 122.2, 23.7. Elemental analysis: Calcd (%) for C₁₂H₁₀BrNO₂S: C 46.17, H 3.23, N 4.49. Found: C 45.70, H 3.05, N 4.68. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀BrNO₂S: 311.969. Found: m/z = 311.969.

2-(2-bromo-6-chlorophenylsulfonyl)pyridine (10a): The reaction of the corresponding sulfone (0.127 g, 0.5 mmol), *N*-bromosuccinimide (0.267 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in nitromethane (4 mL) at 110 °C affords **10a** in 57% (0.95 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.61 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 8.35 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 7.57 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.52 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H). ¹³C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 159.1, 150.0, 138.0, 136.7, 135.5, 134.9, 134.0, 132.2, 127.3, 124.5, 122.2. Elemental analysis: Calcd (%) for C₁₁H₇BrClNO₂S: C 39.72, H 2.12, N 4.21. Found: C 40.29, H 2.18, N 4.23. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀BrNO₂S: 333.913. Found: m/z = 333.913.

2-(2-bromo-6-trifluorophenylsulfonyl)pyridine (11a): The reaction of the corresponding sulfone (0.144 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **11a** in 33% (0.060 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.54 (d, *J* = 4.7 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 1H), 8.05 – 7.93 (m, 2H), 7.89 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 8.0 Hz, 1H), 7.50 (ddd, *J* = 7.5, 4.7, 1.2 Hz, 1H). ¹⁹F NMR (470 MHz, Chloroform-*d*) δ (ppm) = –54.3. ¹³C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 159.5, 149.7, 139.8, 138.1, 138.0, 134.2 (d, *J* = 33.14 Hz), 133.7, 128.1 (q, *J* = 7.3 Hz), 127.2, 125.7, 123.4 (q, *J* = 275.5 Hz), 122.0. Elemental analysis: Calcd (%) for C₁₂H₁₀BrNO₂S: C 39.36, H 1.93, N 3.83. Found: C 40.13, H 1.24, N 3.82. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀BrF₃NO₂S: 365.941. Found: m/z = 365.941.

2-(2-bromophenylsulfonyl)-5-methylpyridine (12a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **12a** in 61% (0.095 g) yield. White solid; (dichloromethane-ethyl acetate = 95:5). ¹H NMR (500

MHz, Chloroform-*d*) δ (ppm) = 8.47 (dd, J = 7.9, 1.7 Hz, 1H), 8.42 (d, J = 1.9 Hz, 1H), 8.25 (d, J = 8.1 Hz, 1H), 7.76 (ddd, J = 8.1, 2.2, 0.9 Hz, 1H), 7.63 (dd, J = 8.0, 1.2 Hz, 1H), 7.58 (td, J = 7.7, 1.2 Hz, 1H), 7.46 (td, J = 7.7, 1.7 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 155.1, 150.8, 150.7, 138.3, 138.0, 135.2, 134.9, 132.7, 128.0, 123.7, 121.2, 18.8. Elemental analysis: Calcd (%) for $\text{C}_{12}\text{H}_{10}\text{BrNO}_2\text{S}$: C 46.17, H 3.23, N 4.49. Found: C 46.17, H 2.62, N 4.34. HRMS + p ESI (m/z) [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{12}\text{H}_{10}\text{BrNO}_2\text{S}$: 311.969. Found: m/z = 311.969.

2-(2-bromophenylsulfonyl)-4-methylpyridine (13a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-bromosuccinimide (0.107 g, 0.6 mmol) and $\text{Pd}(\text{OAc})_2$ (0.0056 g, 0.025 mmol) in nitromethane (2 mL) at 90 °C affords **13a** in 66% (0.104 g) yield. White solid; (dichloromethane-heptane = 9:1). ^1H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.47 (dd, J = 7.9, 1.7 Hz, 1H), 8.45 (d, J = 4.9 Hz, 1H), 8.19 – 8.17 (m, 1H), 7.65 (dd, J = 7.9, 1.2 Hz, 1H), 7.59 (td, J = 7.7, 1.3 Hz, 1H), 7.47 (td, J = 7.7, 1.7 Hz, 1H), 7.29 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 2.52 (d, J = 0.8 Hz, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 157.8, 149.9, 149.9, 138.2, 135.2, 135.0, 132.8, 128.0, 128.0, 124.4, 121.3, 21.5. Elemental analysis: Calcd (%) for $\text{C}_{12}\text{H}_{10}\text{BrNO}_2\text{S}$: C 46.17, H 3.23, N 4.49. Found: C 46.26 H 2.88, N 4.92. HRMS + p ESI (m/z) [$\text{M}+\text{Na}^+$] Calcd for $\text{C}_{12}\text{H}_{10}\text{BrNO}_2\text{S}$: 333.951. Found: m/z = 333.951.

2-(2,6-dibromophenylsulfonyl)-4-methylpyridine (13b): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-bromosuccinimide (0.267 g, 1.5 mmol) and $\text{Pd}(\text{OAc})_2$ (0.0112 g, 0.05 mmol) in nitromethane (4 mL) at 90 °C affords **13b** in 83% (0.161 g) yield. White solid; (dichloromethane-heptane = 9:1). ^1H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.43 (d, J = 4.9 Hz, 1H), 8.06 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.30 (dq, J = 2.8, 0.7 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 2.51 (s, 3H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 158.8, 149.9, 149.7, 136.1, 136.1, 134.1, 128.0, 124.5, 122.8, 21.5. Elemental analysis: Calcd (%) for $\text{C}_{12}\text{H}_9\text{Br}_2\text{NO}_2\text{S}$: C 36.86, H 2.32, N 3.58. Found: C 36.49 H 2.07, N 3.61. HRMS + p ESI (m/z) [$\text{M}+\text{Na}^+$] Calcd for $\text{C}_{12}\text{H}_9\text{Br}_2\text{NO}_2\text{S}$: 411.861. Found: m/z = 411.862.

2-(2-bromophenylsulfonyl)-pyrimidine (14a): The reaction of the corresponding sulfone (0.050 g, 0.23 mmol), *N*-bromosuccinimide (0.049 g, 0.276 mmol) and $\text{Pd}(\text{OAc})_2$ (0.0026 g, 0.011 mmol) in nitromethane (1 mL) at 90 °C affords **14a** in 10% (0.007 g) yield. White solid; (dichloromethane-heptane = 9:1). Recrystallization failed due to the low amount. ^1H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.91 (d, J = 4.8 Hz, 2H), 8.44 (dd, J = 7.9, 1.7 Hz, 1H), 7.69 (dd, J = 7.8, 1.2 Hz, 1H), 7.62 (td, J = 7.7, 1.3 Hz, 1H), 7.58 – 7.47 (m, 2H). ^{13}C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 166.3, 158.8, 137.6, 135.3, 135.1, 132.4, 128.1, 123.6, 121.8. HRMS + p ESI (m/z) [$\text{M}+\text{Na}^+$] Calcd for $\text{C}_{10}\text{H}_7\text{BrN}_2\text{O}_2\text{S}$: 320.930. Found: m/z = 320.931.

2-(2-iodophenylsulfonyl)pyridine (17a): The reaction of the corresponding sulfone (0.110 g, 0.5 mmol), *N*-iodosuccinimide (0.134 g, 0.6 mmol) and $\text{Pd}(\text{OAc})_2$ (0.0056 g, 0.025 mmol) in acetic acid (2 mL) at 110 °C affords **17a** in 61% (0.105 g) yield. White solid;

(dichloromethane-heptane = 9:1). ^1H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.59 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.49 (dd, J = 7.9, 1.7 Hz, 1H), 8.39 (dt, J = 7.9, 1.0 Hz, 1H), 8.05 – 7.92 (m, 2H), 7.66 – 7.57 (m, 1H), 7.49 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 7.26 (td, J = 7.6, 1.7 Hz, 1H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 157.2, 150.1, 142.4, 140.7, 137.7, 134.7, 132.6, 128.7, 127.1, 124.4, 93.4. Elemental analysis: Calcd (%) for $\text{C}_{11}\text{H}_8\text{INO}_2\text{S}$: C 38.28, H 2.34, N 4.06. Found: C 38.58, H 2.25, N 4.02. HRMS + p ESI (m/z) [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{11}\text{H}_8\text{INO}_2\text{S}$: 345.939. Found: m/z = 345.938.

2-(2-iodo-4-tert-butylphenylsulfonyl)pyridine (18a): The reaction of the corresponding sulfone (0.138 g, 0.5 mmol), *N*-iodosuccinimide (0.135 g, 0.6 mmol) and $\text{Pd}(\text{OAc})_2$ (0.0056 g, 0.025 mmol) in acetic acid (2 mL) at 110 °C affords **18a** in 76% (0.152 g) yield. White solid; (dichloromethane-heptane = 9:1). ^1H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.63 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.40 (d, J = 8.3 Hz, 2H), 8.05 – 7.93 (m, 2H), 7.62 (dd, J = 8.4, 1.9 Hz, 1H), 7.49 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 1.32 (s, 9H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 159.0, 157.6, 150.2, 139.9, 137.9, 137.7, 132.5, 127.0, 126.0, 124.6, 93.6, 35.2, 31.0. Elemental analysis: Calcd (%) for $\text{C}_{15}\text{H}_{16}\text{INO}_2\text{S}$: C 44.90, H 4.02, N 3.49. Found: C 45.27, H 2.37, N 3.66. HRMS + p ESI (m/z) [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{15}\text{H}_{16}\text{INO}_2\text{S}$: 402.002. Found: m/z = 402.003.

2-(2-iodo-4-fluorophenylsulfonyl)pyridine (19a): The reaction of the corresponding sulfone (0.119 g, 0.5 mmol), *N*-iodosuccinimide (0.135 g, 0.6 mmol) and $\text{Pd}(\text{OAc})_2$ (0.0056 g, 0.025 mmol) in acetic acid (2 mL) at 110 °C affords **19a** in 54% (0.097 g) yield. White solid; (dichloromethane-heptane = 9:1). NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.61 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.50 (dd, J = 8.9, 5.7 Hz, 1H), 8.40 – 8.36 (m, 1H), 7.99 (td, J = 7.8, 1.7 Hz, 1H), 7.72 (dd, J = 7.8, 2.5 Hz, 1H), 7.51 (ddd, J = 7.7, 4.7, 1.1 Hz, 1H), 7.32 (ddd, J = 8.9, 7.6, 2.5 Hz, 1H). ^{19}F NMR (282 MHz, Chloroform-*d*) δ (ppm) = -103.4. ^{13}C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 164.6 (d, J = 261.3 Hz), 157.2, 150.2, 137.9, 137.0 (d, J = 3.3 Hz), 134.9 (d, J = 9.6 Hz), 129.8 (d, J = 24.5 Hz), 127.3, 124.4, 116.0 (d, J = 21.5 Hz), 94.2 (d, J = 8.8 Hz). Elemental analysis: Calcd (%) for $\text{C}_{11}\text{H}_7\text{FINO}_2\text{S}$: C 36.38, H 1.94, N 3.86. Found: C 36.51, H 2.08, N 3.92. HRMS + p ESI (m/z) [$\text{M}+\text{H}^+$] Calcd for $\text{C}_{11}\text{H}_7\text{FINO}_2\text{S}$: 363.930. Found: m/z = 363.930.

2-(2-iodo-5-methylphenylsulfonyl)pyridine (20a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-iodosuccinimide (0.135 g, 0.6 mmol) and $\text{Pd}(\text{OAc})_2$ (0.0056 g, 0.025 mmol) in acetic acid (2 mL) at 110 °C affords **20a** in 90% (0.162 g) yield. White solid; (dichloromethane-heptane = 9:1). ^1H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.62 (ddd, J = 4.7, 1.7, 0.9 Hz, 1H), 8.41 (dt, J = 7.9, 1.0 Hz, 1H), 8.33 (dd, J = 2.2, 0.8 Hz, 1H), 7.98 (td, J = 7.8, 1.7 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.50 (ddd, J = 7.6, 4.7, 1.1 Hz, 1H), 7.08 (ddd, J = 8.0, 2.3, 0.8 Hz, 1H), 2.44 (d, J = 0.7 Hz, 3H). ^{13}C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 157.5, 150.2, 142.3, 140.4, 139.4, 137.7, 135.8, 133.3, 127.1, 124.6, 89.3, 21.2. Elemental analysis: Calcd (%) for $\text{C}_{12}\text{H}_{10}\text{INO}_2\text{S}$: C 40.13, H 2.81, N 3.90. Found: C 45.27, H 2.37, N 3.66. HRMS +

p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀INO₂S: 359.955. Found: m/z = 359.953.

2-(2-iodo-6-methylphenylsulfonyl)pyridine (21a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-iodosuccinimide (0.135 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in acetic acid (2 mL) at 110 °C affords **21a** in 50% (0.090 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.60 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.37 – 8.20 (m, 1H), 8.06 – 7.86 (m, 2H), 7.49 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 7.34 (ddd, *J* = 7.7, 1.4, 0.7 Hz, 1H), 7.05 (t, *J* = 7.7 Hz, 1H), 2.90 (d, *J* = 0.7 Hz, 3H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 159.1, 150.0, 144.5, 142.0, 138.6, 137.8, 133.9, 133.8, 127.1, 123.1, 95.8, 24.5. Elemental analysis: Calcd (%) for C₁₂H₁₀INO₂S: C 40.13, H 2.81, N 3.90. Found: C 42.55, H 3.38, N 3.88. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀INO₂S: 359.955. Found: m/z = 359.955.

2-(2-iodophenylsulfonyl)-4-methylpyridine (22a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-iodosuccinimide (0.107 g, 0.6 mmol) and Pd(OAc)₂ (0.0056 g, 0.025 mmol) in acetic acid (2 mL) at 110 °C affords **22a** in 73% (0.131 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.49 (d, *J* = 8.0 Hz, 1H), 8.45 (d, *J* = 4.9 Hz, 1H), 8.22 (s, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.31 – 7.24 (m, 2H), 2.51 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 157.3, 149.9, 149.7, 142.5, 141.0, 134.7, 132.7, 128.8, 127.9, 125.1, 93.5, 21.5. Elemental analysis: Calcd (%) for C₁₂H₁₀INO₂S: C 40.13; H 2.81, N 3.90. Found: C 39.17, H 2.40, N 3.81. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀INO₂S: 359.955. Found: m/z = 359.955.

2-(2,6-diiodophenylsulfonyl)-4-methylpyridine (22b): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-iodosuccinimide (0.337 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in acetic acid (4 mL) at 110 °C affords **22b** in 31% (0.075 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.44 (d, *J* = 4.9 Hz, 1H), 8.20 (d, *J* = 7.9 Hz, 2H), 8.11 (s, 1H), 7.29 (d, *J* = 5.1 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 2.50 (s, 3H). ¹³C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 157.5, 149.7, 149.6, 144.6, 140.0, 134.3, 128.0, 124.0, 94.6, 21.5. Elemental analysis: Calcd (%) for C₁₂H₉I₂NO₂S: C 29.71 H 1.87, N 2.89. Found: C 29.54 H 1.37, N 2.88. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₉I₂NO₂S: 485.852. Found: m/z = 485.852.

2-(2-chlorophenylsulfonyl)pyridine (23a): The reaction of the corresponding sulfone (0.110 g, 0.5 mmol), *N*-chlorosuccinimide (0.200 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in acetic acid (4 mL) at 110 °C affords **23a** in 28% (0.112 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.59 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.46 – 8.39 (m, 1H), 8.32 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.60 – 7.46 (m, 3H), 7.44 – 7.37 (m, 1H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 157.9, 150.2, 138.0, 136.4, 135.1, 132.9, 132.2, 131.7, 127.4, 127.3, 123.4. Elemental analysis: Calcd (%) for C₁₁H₈ClNO₂S: C 52.08, H 3.18, N 5.52. Found: C 52.26, H

3.37, N 5.30. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₁H₈ClNO₂S: 254.004. Found: m/z = 254.003.

2-(2-chloro-4-*tert*-butylphenylsulfonyl)pyridine (24a): The reaction of the corresponding sulfone (0.138 g, 0.5 mmol), *N*-chlorosuccinimide (0.200 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in acetic acid (4 mL) at 110 °C affords **24a** in 54% (0.084 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.63 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.37 – 8.29 (m, 2H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.41 (d, *J* = 1.9 Hz, 1H), 1.32 (s, 9H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 159.7, 158.3, 150.3, 137.9, 133.4, 132.6, 132.1, 129.0, 127.1, 124.7, 123.5, 35.5, 31.0. Elemental analysis: Calcd (%) for C₁₅H₁₆ClNO₂S: C 58.15, H 5.21, N 4.52. Found: C 58.14, H 5.51, N 4.36. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₅H₁₆ClNO₂S: 310.066. Found: m/z = 310.066.

2-(2-chloro-4-fluorophenylsulfonyl)pyridine (25a): The reaction of the corresponding sulfone (0.119 g, 0.5 mmol), *N*-chlorosuccinimide (0.200 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in acetic acid (4 mL) at 110 °C affords **25a** in 36% (0.048 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.61 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.46 (dd, *J* = 8.8, 5.8 Hz, 1H), 8.32 (dt, *J* = 7.9, 1.0 Hz, 1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.52 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.29 – 7.13 (m, 2H). ¹⁹F NMR (282 MHz, Chloroform-*d*) δ (ppm) = -101.63. ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 165.7 (d, *J* = 259.6 Hz), 157.8, 150.3, 138.1, 134.9 (d, *J* = 11.3 Hz), 134.7 (d, *J* = 10.2 Hz), 132.7 (d, *J* = 3.6 Hz), 127.4, 123.4, 119.4 (d, *J* = 25.5 Hz), 114.9 (d, *J* = 21.7 Hz). Elemental analysis: Calcd (%) for C₁₁H₇ClFNO₂S: C 48.63, H 2.60, N 5.16. Found: C 49.20, H 2.63, N 5.07. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₁H₇ClFNO₂S: 271.994. Found: m/z = 271.994.

2-(2-chloro-6-methylphenylsulfonyl)pyridine (26a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-chlorosuccinimide (0.200 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in acetic acid (4 mL) at 110 °C affords **26a** in 16% (0.021 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.58 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.24 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.96 (td, *J* = 7.8, 1.7 Hz, 1H), 7.48 (ddd, *J* = 7.6, 4.7, 1.2 Hz, 1H), 7.40 – 7.32 (m, 1H), 7.28 (dt, *J* = 2.1, 1.1 Hz, 1H), 7.25 (dt, *J* = 2.4, 0.9 Hz, 1H), 2.92 (s, 3H). ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 159.9, 150.0, 144.2, 137.9, 134.8, 134.5, 133.6, 132.4, 130.2, 127.0, 121.9, 23.3. Elemental analysis: Calcd (%) for C₁₂H₁₀ClNO₂S: C 53.84, H 3.77, N 5.23. Found: C 56.84, H 4.87, N 4.79. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀ClNO₂S: 268.019. Found: m/z = 268.019.

2-(2-chlorophenylsulfonyl)-4-methylpyridine (27a): The reaction of the corresponding sulfone (0.117 g, 0.5 mmol), *N*-chlorosuccinimide (0.200 g, 1.5 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in acetic acid (4 mL) at 110 °C affords **27a** in 41% (0.055 g) yield. White solid; (dichloromethane-heptane = 9:1). ¹H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.45 (d, *J* = 4.8 Hz, 1H), 8.44 – 8.41 (m, 1H), 8.16 (s, 1H), 7.59 – 7.49 (m, 2H), 7.43 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.30 (dq, *J* = 4.8, 0.7 Hz, 1H), 2.52 (d, *J* = 0.7 Hz, 3H). ¹³C NMR (75 MHz, Chloroform-*d*) δ

(ppm) = 158.0, 150.0, 150.0, 136.6, 135.0, 133.0, 132.3, 131.7, 128.0, 127.5, 124.0, 21.5. Elemental analysis: Calcd (%) for C₁₂H₁₀ClNO₂S: C 53.84, H 3.77, N 5.23. Found: C 53.19, H 3.54, N 5.22. RMS + p ESI (m/z) [M+H⁺] Calcd for C₁₂H₁₀ClNO₂S: 268.019. Found: m/z = 268.019.

2-(2-fluorophenylsulfonyl)pyridine (28a): The reaction of the corresponding sulfone (0.219 g, 1 mmol), NFSI (1.261 g, 4 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in trifluoromethylbenzene (8 mL) at 110 °C affords **28a** in 25% (0.021 g) yield. White solid; (acetonitrile-water = 2:8). ¹H NMR (300 MHz, Chloroform-*d*) δ (ppm) = 8.65 (ddd, *J* = 4.7, 1.7, 0.9 Hz, 1H), 8.31 (dq, *J* = 8.0, 0.9 Hz, 1H), 8.22 (ddd, *J* = 7.8, 7.0, 1.8 Hz, 1H), 8.00 (td, *J* = 7.8, 1.7 Hz, 1H), 7.72 – 7.57 (m, 1H), 7.52 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.38 (td, *J* = 7.7, 1.1 Hz, 1H), 7.11 (ddd, *J* = 9.6, 8.3, 1.1 Hz, 1H). ¹⁹F NMR (282 MHz, Chloroform-*d*) δ (ppm) = -108.2. ¹³C NMR (75 MHz, Chloroform-*d*) δ (ppm) = 159.6 (d, *J* = 257.2 Hz), 158.4, 150.4, 138.3, 136.6 (d, *J* = 8.5 Hz), 131.3, 127.5, 124.8 (d, *J* = 3.9 Hz), 122.9 (d, *J* = 2.1 Hz), 117.3, 117.0. Elemental analysis: Calcd (%) for C₁₂H₁₀ClNO₂S: C 55.69, H 3.40, N 5.90. Found: C 54.33, H 3.36, N 5.63. HRMS + p ESI (m/z) [M+H⁺] Calcd for C₁₁H₈FNO₂S: 238.033. Found: m/z = 238.033.

2-(2-fluoro-4-*tert*-butylphenylsulfonyl)pyridine (29a): The reaction of the corresponding sulfone (0.275 g, 1 mmol), NFSI (1.261 g, 4 mmol) and Pd(OAc)₂ (0.0112 g, 0.05 mmol) in trifluoromethylbenzene (8 mL) at 110 °C affords **29a** in 55% still contaminated by 7% of the difluorinated product **29b** (0.160 g) yield. White solid; (ethyl acetate-heptane = 5:5). ¹H NMR (500 MHz, Chloroform-*d*) δ (ppm) = 8.67 (d, *J* = 4.4 Hz, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 8.10 (t, *J* = 8.0 Hz, 1H), 7.98 (td, *J* = 7.8, 1.7 Hz, 1H), 7.51 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.37 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.10 (dd, *J* = 12.1, 1.7 Hz, 1H), 1.30 (d, *J* = 0.8 Hz, 9H). ¹⁹F NMR (470 MHz, Chloroform-*d*) δ (ppm) = -108.8. ¹³C NMR (126 MHz, Chloroform-*d*) δ (ppm) = 161.8 (d, *J* = 7.2 Hz), 160.5, 158.6 (d, *J* = 14.5 Hz), 150.4, 138.2, 130.8, 127.3, 123.8 (d, *J* = 14.1 Hz), 122.9 (d, *J* = 1.8 Hz), 121.9 (d, *J* = 3.1 Hz), 114.3 (d, *J* = 21.3 Hz), 35.6, 31.0. Elemental analysis: Calcd (%) for C₁₅H₁₆FNO₂S: C 61.42, H 5.50, N 4.77. Found: C 59.99, H 5.77, N 4.64. RMS + p ESI (m/z) [M+Na⁺] Calcd for C₁₅H₁₆FNO₂S: 316.078. Found: m/z = 316.077.

Acknowledgements

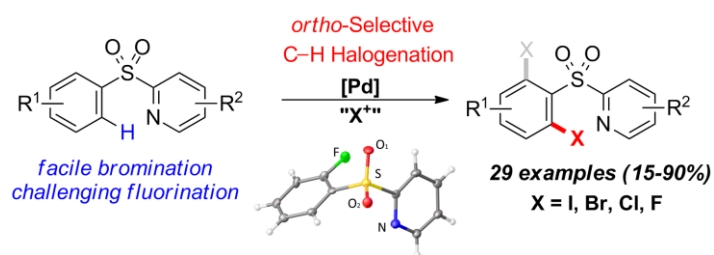
This work was funded by the Université de Bourgogne Franche-Comté, the CNRS, and the Conseil Régional de Bourgogne (PARI II CDEA and 3MIM program). The Conseil Régional de Bourgogne supported JG via the JCE program.

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N-(2-pyridyl)sulfonyl groups for *ortho*-directing palladium carbon-halogen C–X bond formation at functionalized arenes (X = I, Br, Cl, F)



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