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Short Communication

Oxidative fluorination of *N*-arylsulfonamides

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ABSTRACT

We report a late stage oxidative nucleophilic fluorination of *N*-arylsulfonamides, a class of compounds so far not considered as precursors to 4-fluorophenyl sulfonamides. By installing a *para*-positioned *tert*-butyl substituent on the aniline, oxidative fluorination takes place regioselectively in the presence of HF·pyridine and PIDA. This methodology has been shown to give good yields for a variety of *ortho*- and *meta*-functionalised *N*-arylsulfonamides and has been adapted for radiofluorination to give 4-[^{18}F]fluorophenyl sulfonamides under carrier added conditions.

1. Introduction

Amongst the many functional groups frequently found in pharmaceutical drugs, sulfonamides are well represented in a number of antibacterial, anti-migraine, anti-inflammatory and anti-diabetic agents as well as diuretics [1]. The benefits of fluorine substitution in drug discovery [2] have encouraged the development of methods to access fluorinated sulfonamide analogues. In this context, methods to access *N*-arylsulfonamides with fluorine substitution on the aryl sub-motif are in demand, especially approaches that avoid sulfonyl chloride, which is known to be genotoxic [3]. We opted for a synthesis based on late stage fluorination with a fluoride source since this chemistry is attractive for ^{18}F-labelling and its application for Positron Emission Tomography (PET) [4]. To date, ^{11}C-labelled sulfonanilides have been developed as potential PET agents for imaging of aromatase in breast cancer [5]. Recently, our laboratory reported a method for the oxidative ^{18}F-fluorination of phenols mediated by hypervalent iodine [6]. This metal free reaction, inspired by the seminal work of Feiring [7], Yoneda [8] and Langlois et al. [9], employs PhI(OAc)$_2$ (PIDA) to impose a reactivity switch on electron rich phenols, which become responsive to nucleophilic attack with [^{18}F]fluoride [10]. Herein, we report that this umpolung approach can be successfully applied to *N*-arylsulfonamide precursors allowing direct access to various fluorinated analogues. This advance is significant since no example of direct fluorination of arylsulfonamides leading to 4-fluorophenyl sulfonamides is known; in fact, a recent study conducted by Meng, Li and co-workers showed that *N*-tosyl and *N*-mesylanilines are not suitable substrates for oxidative fluorination with hypervalent iodine reagents [11].

2. Results and discussion

This work began with a study probing the effect on reactivity of *N*-sulfonylation versus *N*-acylation with four representative anilines (Table 1). Based on our previous success with the oxidative fluorination of phenols [6], we selected the sulfonanilide **1a** and the *N*-benzanilide **2a** both substituted with a *para*-located *tert*-butyl group on the aniline ring. The corresponding *N*-phenyl-4-methylbenzenesulfonamide **3a** and *N*-benzanilide **4a** that are not substituted at the *para* position were also subjected to oxidative fluorination for comparison. The reaction was conducted using 1 eq. of PIDA and 4 eq. of HF·pyridine in DCM for 15 min at room temperature, followed by addition of trifluoroacetic acid (TFA). Collectively, the data assembled in Table 1 demonstrate that the presence of the *tert*-butyl group is critical for the oxidative

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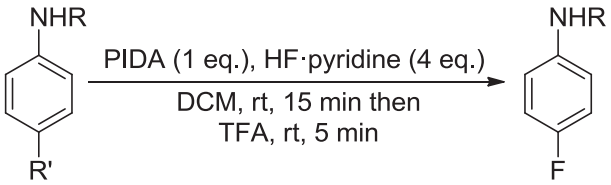
0022-1139/

Table 1
Fluorination of *N*-arylsulfonamides versus *N*-benzanilides.



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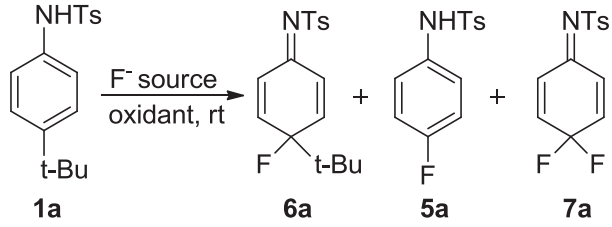
Entry	R	R′	Substrate	Product	Yield (%)[a,b]
1	Tos	*t*-Bu	**1a**	**5a**	46 (33)
2	COPh	*t*-Bu	**2a**	**6a**	66(69)
3	Tos	H	**3a**	**5a**	9 (0)
4	COPh	H	**4a**	**6a**	46

[a] Determined by ^{19}F NMR integration with 1-fluoro-3-nitrobenzene as internal standard.
[b] Values in parenthesis refer to yield of isolated product.

fluorination of sulfonamides to proceed. Pleasingly, the fluorination of **1a** was successful affording isolated **5a** in 33% yield under unoptimised reaction conditions (entry 1). When using *N*-phenyl-4-methylbenzenesulfonamide **3a**, the fluorinated sulfonanilide **5a** was detectable (<10%) prior to purification but could not be isolated (entry 3). In contrast, *para*-substitution with the *tert*-butyl group is not essential for the fluorination of *N*-acylated anilines [11], although beneficial based on comparative ^{19}F NMR yields (entries 2 and 4).

Having established that the oxidative fluorination of the *tert*-butylated sulfonanilide **1a** is possible, further optimisation was carried out (Table 2). Analysis of the crude reaction mixture indicated that three fluorinated products were formed upon fluorination of **1a**: the dearomatised *tert*-butylated fluoro-intermediate **6a** (^{19}F NMR, δ = −160.4 ppm), the desired sulfonanilide **5a** (^{19}F NMR, δ = −116.6 ppm) and **7a** resulting from further

Table 2
Oxidative fluorination of **1a**: optimisation.



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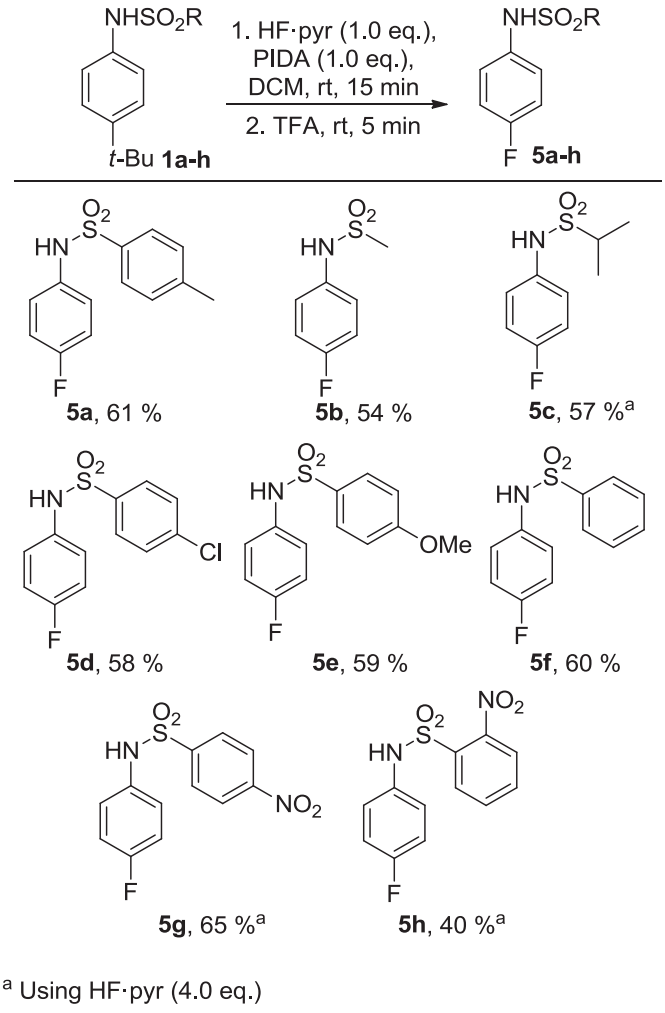
Entry	F^- (eq.)	Ox. (eq.)	Solvent	TFA[a] (min)	Yield (%)[b] **6a**, **5a**, **7a**
1	HF·pyr (4.0)	PIDA (1.0)	DCM	–	0, **44**, 20
2	HF·pyr (4.0)	PIDA (1.0)	DCM	5	0, **46**, 6
3	HF·pyr (4.0)	$PhI(OPiv)_2$ (1.0)	DCM	5	0, **52**, 0
4	HF·pyr (4.0)	PIFA (1.0)	DCM	–	0, **34**, 6
5	HF·pyr (4.0)	PIDA (1.0)	DCE	–	0, **43**, 13
6	HF·pyr (4.0)	PIDA (1.0)	THF	–	0, **0**, 0
7	HF·pyr (4.0)	PIDA (1.0)	Et_2O	–	8, **0**, 0
8	$3HF·NEt_3$ (4.0)	PIDA (1.0)	DCM	–	85, **0**, 0
9	$3HF·NEt_3$ (4.0)	PIDA (1.0)	DCM	5	0, **42**, 9
10	$TBAF·3H_2O$ (1.0)	PIDA (1.0)	DCM	5	0, **12**, 0
11	HF·pyr (1.0)	PIDA (1.0)	DCM	–	68, **19**, 6
12	HF·pyr (1.0)	PIDA (1.0)	DCM	5	0, **94**, 2
13	HF·pyr (1.0)	$PhI(OPiv)_2$ (1.0)	DCM	5	0, **92**, 3
14	HF·pyr (1.0)	PIDA (2.0)	DCM	5	0, **0**, 43

[a] TFA added after 15 min.
[b] Yields determined by ^{19}F NMR by integration relative to 1-fluoro-3-nitrobenzene as the internal standard.

oxidative fluorination of **5a** (^{19}F NMR, δ = −96.6 ppm). At first, we employed 4 equivalents of HF·pyridine since the use of an excess of the fluoride source was advantageous for the oxidative fluorination of 4-*tert*-butylphenol (Table 2, entries 1–7) [6]. Yields were comparable replacing PIDA with $PhI(OPiv)_2$ but were lower with PIFA (Table 2, entries 1–4). Dichloromethane and dichloroethane emerged as the optimum solvents; tetrahydrofuran or diethylether led to recovered starting material or very low conversion of **1a** into **6a** (Table 2, entries 5–7). Only HF based reagents were suitable (entry 10). In the absence of trifluoroacetic acid (TFA), $3HF·NEt_3$ did not allow for aromatisation of **6a** (Table 2, entries 8 and 9). Better results were obtained using only one equivalent of HF·pyridine in the presence of TFA, which is in contrast to the oxidative fluorination of 4-*tert*-butylphenol (Table 2, 11–13). As expected, an excess of PIDA led mainly to the difluorinated dienimine **7a** resulting from further oxidative fluorination of **5a** (Table 2, entry 14) [12]. The addition of TFA facilitates the conversion of the fluorinated dienimine **6a** into **5a** (Table 2, entries 11–12). For this model substrate, the oxidative fluorination is therefore best performed with 1 eq. of HF·pyridine and 1 eq. of PIDA in DCM at room temperature followed by treatment with TFA. Under these conditions, **5a** was formed in 94% yield (^{19}F NMR) and isolated in 61% yield.

Various *N*-arylsulfonamides participated in the oxidative fluorination effectively. In the first instance, we studied the reactivity of substrates *N*-substituted with alkyl- and arylsulfonyl groups (Scheme 1). All reactions were first conducted using our

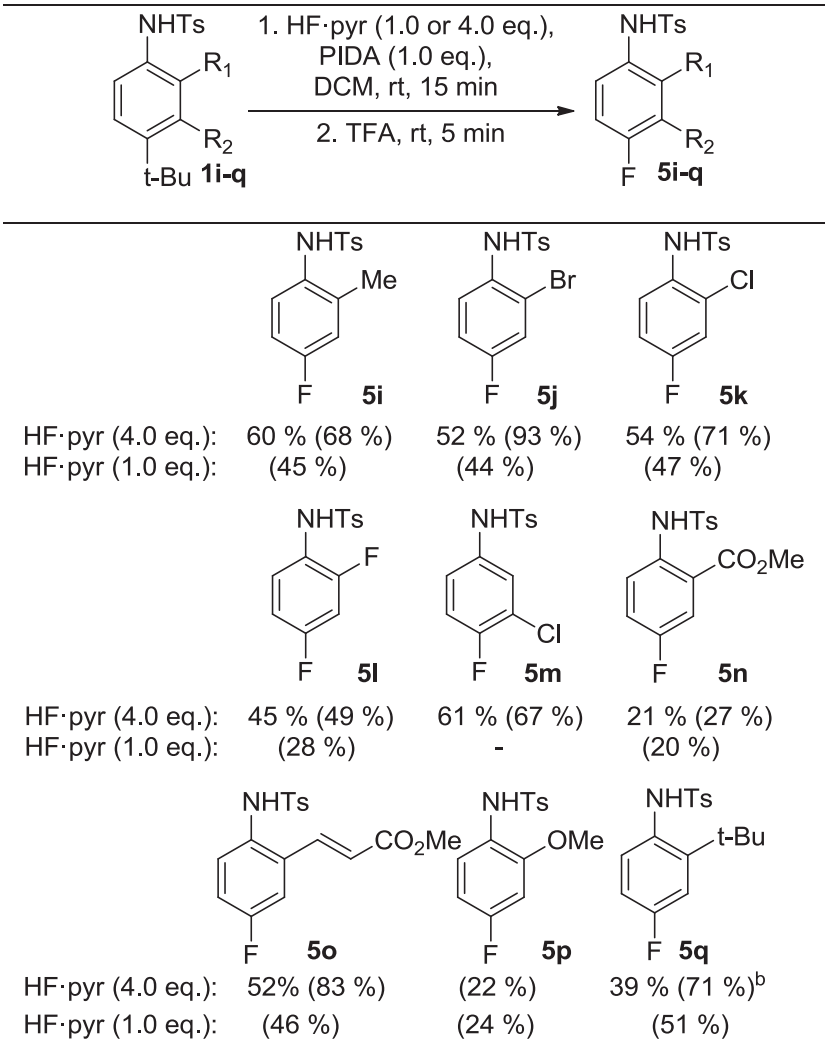


[a] Using HF·pyr (4.0 eq.)

Scheme 1. Influence of the sulfonyl substituent on reactivity.

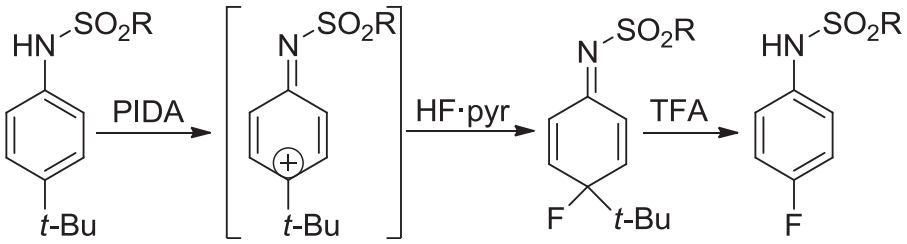
standard reaction conditions and completed in less than 30 min. For some substrates, better yields were obtained with 4 eq. of HF·pyridine. The yields of isolated *para*-fluoroanilines **5a–g** were comparable ranging from 54% to 65%. This observation suggests that the electronic profile of the *N*-sulfonyl substituent remotely positioned from the aryl motif subjected to oxidative fluorination, has little influence on the efficacy of the reaction. However, the yield dropped for the sulfonamide **5h** suggesting that *ortho*-substitution of arylsulfonyl with the electron withdrawing NO_2 group impeded activation with PIDA. For this substrate, the yield of fluorination did not exceed 40% despite using 4 eq. of HF·pyridine. Advantageously, the cleavage of 2- or 4-nitrosulfonylbenzene (nosyl) and mesylsulfonyl (mesyl) protecting groups is known to occur under mild conditions when compared to the tosyl protecting group [13].

Next, we examined how the substitution pattern of the *N*-aryl sub-motif undergoing sequential oxidation–fluorination impacts on reactivity (Scheme 2). For this study, we selected *N*-tosylated aniline precursors. All reactions were performed using stoichiometric amount or an excess of HF·pyridine. The best yields were obtained with an excess of fluoride, which is contrasting with the optimisation performed on the model aniline **1a**. The reaction was tolerant to a selection of *ortho* or *meta* positioned functional groups including alkyl, halogen and esters. Electron withdrawing groups located *ortho* to the *N*-tosyl substituent have a detrimental effect on the reaction due to lack of reactivity. This is illustrated with the low isolated yield of the ester-substituted aniline **5n**. Distancing the ester functionality from the aniline ring was beneficial as demonstrated with the successful synthesis of **5o**. The reaction led to the formation of the methoxy-substituted aniline **5p**, but with low conversion. The corresponding substrate, 2-methoxy-4-tert-butyl-*N*-tosylaniline, is easier to oxidise than 4-*tert*-butyl-*N*-tosylaniline **1a**; however, it is possible that a competitive fluorination pathway occurs; fluoride attack on the oxidised intermediate could indeed take place at the methoxy group with concomitant release of methyl fluoride. The fluorination of 2-*tert*-butyl-*N*-tosylaniline is chemoselective occurring exclusively at the *para* position. For this substrate, the presence of the *para* located *tert*-butyl group is not necessary to allow for oxidative fluorination. The reaction gave aniline **5q** (^{19}F NMR, $\delta = -115.7$ ppm) that was isolated in 39% yield. 2-Fluoro-*N*-tosylaniline (^{19}F NMR, $\delta = -129.7$ ppm) and 2.4-difluoro-*N*-tosylaniline (^{19}F NMR, $\delta = -112.0$ ppm and -123.4 ppm), both easily identifiable by ^{19}F NMR, could not be detected in the crude reaction mixture. Typically,

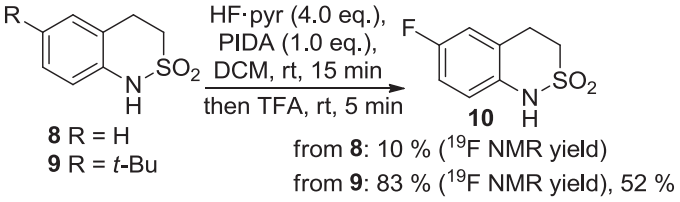


[a] Yields of isolated products; values under parenthesis refer to yields determined by ^{19}F NMR by integration relative to 1-fluoro-3-nitrobenzene as the internal standard. [b] Aniline **5q** was prepared from 2-*tert*-butyl-*N*-tosylaniline.

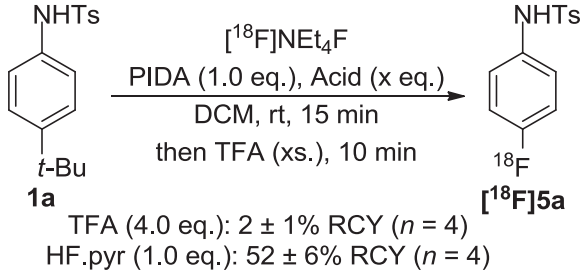
Scheme 2. Synthesis of *N*-tosylsulfonamides **5i–q**.[a]



Scheme 3. Mechanism of the fluorination of *N*-arylsulfonamides.



Scheme 4. Oxidative fluorination of benzosultams **8** and **9**.



Scheme 5. Oxidative fluorination with [^{18}F]fluoride. *n* = number of experiments.

the outcome of these reactions correlates well with the ability of the substrates to undergo oxidation [14].

Mechanistically [15], this reaction transits via an aryl-stabilised *N*-sulfonylnitrenium [16] amenable to nucleophilic fluorination. Addition of TFA facilitates aromatisation of the resulting fluorodienimine with concomitant loss of the *tert*-butyl carbocation (Scheme 3).

Pleasingly, 3.4-dihydro-2.1-benzothiazine 2.2-dioxide **9** activated with the *tert*-butyl group at C-6 underwent fluorination with PIDA and 4 eq. of HF·pyridine. This reaction gave **10** in 52% yield. A control experiment performed with the unsubstituted benzosultam **8** confirmed that the presence of the *tert*-butyl group on the substrate is advantageous for reactivity. In its absence, conversion remained low even after extended reaction time (Scheme 4).

As late-stage radiofluorination reactions are favoured for the synthesis of PET tracers, extension of this methodology to employ [^{18}F]fluoride was highly desirable. In the first instance, conditions from previous work from our research group on the oxidative ^{18}F-fluorination of phenols [6] were adapted for this system, using [^{18}F]NEt_4F as the [^{18}F]fluoride source, and applied to the model substrate **1a**. However, under these conditions only low yields of 4-[^{18}F]fluoro-*N*-tosylaniline (**[^{18}F]5a**) were observed (RCY = 2 ± 1% (*n* = 4)) (Scheme 5). The addition of HF·pyridine (1.0 eq.) as the acid was more successful, leading to the synthesis **[^{18}F]5a** in good yields (RCY = 52 ± 6% (*n* = 4)). This carrier added approach is however unfavourable in terms of specific activity and work is ongoing to find suitable alternative conditions.

3. Conclusions

In summary, we have developed a direct method for the fluorination of *N*-arylsulfonamides that are *para* substituted with a *t*-butyl group on the aniline. Using PIDA and an excess of HF·pyridine, regioselective fluorination occurred by ipso substitution of the *tert*-butyl group. The reaction also allows access to a representative fluorinated benzosultam. This study unveils an important difference of reactivity for sulfonamides versus anilides towards oxidative nucleophilic fluorination. Furthermore, we have demonstrated that this methodology can be applied as a novel route to the radiofluorination of *N*-arylsulfonamides, a useful transformation in the production of PET tracers.

4. Experimental

4.1. General

All NMR spectra were recorded on Bruker AVIII400 and AVII500 spectrometers. Proton and carbon-13 NMR spectra are reported as chemical shifts (δ) in parts per million (ppm) relative to the solvent peak using the Bruker internal referencing procedure (edlock). Fluorine-19 NMR spectra are referenced relative to $CFCl_3$ in $CDCl_3$. Coupling constants (*J*) are reported in units of hertz (Hz) to the nearest 0.1 Hz. The following abbreviations are used to describe multiplicities – s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sept (septet), m (multiplet), brs (broad singlet). High resolution mass spectra (HRMS, *m/z*) were recorded on a Bruker MicroTOF spectrometer using positive/negative electrospray ionisation (ESI) or on a Micromass GCT spectrometer using field ionisation (FI+). Infrared spectra were recorded either as the neat compound or in a solution using a Bruker Tensor 27 FT-IR spectrometer. Absorptions are reported in wavenumbers (cm^{-1}) and only peaks of interest are reported. Melting points of solids were measured on a Gryphon apparatus and are uncorrected. All reaction solvents were dried on a column of alumina prior to use. Flash column chromatography was performed over Merck silica gel C60 (40–60 μm). Chemicals were purchased from Acros, Alfa Aesar, Fisher Scientific, Fluorochem and Sigma–Aldrich and used as received. Reactions were monitored by thin-layer chromatography (TLC) carried out on Merck Kiesegel 60 F254 plates.

4.2. General procedure for oxidative fluorination reaction

To a solution of *N*-arylsulfonamide (1.0 eq.) in DCM (0.5 M) in a Falcon tube was added HF·pyridine (70%) (1.0/4.0 eq.) followed by PIDA (1.0 eq.). The reaction was stirred at room temperature for 15 min before the addition of TFA (1.0 mL). After stirring for a further 5 min the reaction was quenched with saturated aqueous sodium bicarbonate and extracted into DCM. The combined organic phases were washed with brine, dried over magnesium sulphate and the solvent removed under reduced pressure. Purification was performed by flash chromatography on silica gel.

To obtain ^{19}F NMR yields, the reaction was performed on a 0.50 mmol scale. The crude residue was fully dissolved in $CDCl_3$ before the addition of 1-fluoro-3-nitrobenzene (53 μL, 0.50 mmol, 1.0 eq.) as an internal standard. An aliquot of the resulting solution was taken for NMR analysis.

N-(4-Fluorophenyl)-4-methylbenzenesulfonamide (5a). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 9:1–4:1) afforded the title compound as a white solid (162 mg, 0.61 mmol, 61% yield). Data consistent with literature [17].

N-(4-Fluorophenyl)benzamide (6a). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 19:1–9:1) afforded the title compound as a white solid (148 mg, 0.69 mmol, 69% yield). Data consistent with literature [18].

N-(4-Fluorophenyl)methanesulfonamide (5b). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 4:1) afforded the title compound as an off-white solid (102 mg, 0.54 mmol, 54% yield). Data consistent with literature [19].

N-(4-Fluorophenyl)propane-2-sulfonamide (5c). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 17:3) afforded the title compound as a pale orange solid (125 mg, 0.57 mmol, 57% yield). MP: 74–76 °C; IR (ν, cm^{-1}): 3257 (w, NH), 1506 (s, C=C_{Ar}), 1322 (m, S=O), 1140 (s, S=O), 1099 (w, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (6H, d, J = 6.8 Hz), 3.27 (1H, sept., J = 6.8 Hz), 6.60 (1H, brs), 7.00–7.08 (2H, m), 7.21–7.27 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 16.5, 52.5, 116.4 (d, J = 22.3 Hz), 123.1 (d, J = 9.5 Hz), 132.8 (d, J = 3.2 Hz), 160.3 (d, J = 244.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ = −117.1; HRMS (ESI^+, m/z): $[C_9H_{12}FNNaO_2S]^+$ (M+Na)$^+$ calcd. 240.0465, found 240.0474.

4-Chloro-N-(4-fluorophenyl)benzenesulfonamide (5d). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 9:1–7:3) afforded the title compound as an off-white solid (166 mg, 0.58 mmol, 58% yield). MP: 106–108 °C; IR (ν, cm^{-1}): 3261 (w, NH), 1507 (s, C=C_{Ar}), 1332 (m, S=O), 1163 (s, S=O), 1094 (m, C–F), 755 (s, C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.04–7.15 (4H, m), 7.61–7.66 (2H, m), 7.67–7.74 (2H, m), 10.31 (1H, brs); ^{13}C NMR (126 MHz, DMSO-d_6): δ = 116.0 (d, J = 21.9 Hz), 123.2 (d, J = 8.6 Hz), 128.6, 129.4, 133.5 (d, J = 2.9 Hz), 137.8, 138.0, 159.3 (d, J = 242.2 Hz); ^{19}F NMR (471 MHz, DMSO-d_6) δ = −115.5; HRMS (ESI^+, m/z): $[C_{12}H_9ClFNNaO_2S]^+$ (M+Na)$^+$ calcd. 307.9199, found 307.9906.

N-(4-Fluorophenyl)-4-methoxybenzenesulfonamide (5e). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 17:3–7:3) afforded the title compound as a white solid (176 mg, 0.59 mmol, 59% yield). MP: 72–74 °C; IR (ν, cm^{-1}): 3246 (m, NH), 1449 (w, C=C_{Ar}), 1333 (m, S=O), 1149 (s, S=O), 1090 (m, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (3H, s), 6.58 (1H, brs), 6.90 (2H, d, J = 8.8 Hz), 6.92–6.97 (2H, m), 7.01–7.06 (2H, m), 7.66 (1H, d, J = 8.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 51.2, 109.9, 111.7 (d, J = 24.0 Hz), 120.1 (d, J = 9.6 Hz), 125.1, 125.7, 128.1 (d, J = 3.2 Hz), 156.2 (d, J = 244.5 Hz), 158.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ = −116.6; HRMS (ESI^+, m/z): $[C_{13}H_{12}FNNaO_3S]^+$ (M+Na)$^+$ calcd. 304.0414, found 304.0403.

N-(4-Fluorophenyl)benzenesulfonamide (5f). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 9:1) afforded the title compound as a white solid (151 mg, 0.60 mmol, 60% yield). MP: 106–108 °C; IR (ν, cm^{-1}): 3259 (w, NH), 1507 (s, C=C_{Ar}), 1328 (m, S=O), 1157 (s, S=O), 1091 (m, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.87–6.99 (2H, m), 7.03–7.11 (2H, m), 7.19 (1H, brs), 7.40–7.51 (2H, m), 7.52–7.60 (1H, m), 7.75–7.79 (2H, m); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 116.1 (d, J = 22.3 Hz), 124.7 (d, J = 9.5 Hz), 127.3, 129.1, 132.1 (d, J = 3.2 Hz), 133.2, 138.6, 160.7 (d, J = 246.4 Hz); ^{19}F NMR (471 MHz, $CDCl_3$) δ = −116.1; HRMS (ESI^+, m/z): $[C_{12}H_{10}FNNaO_2S]^+$ (M+Na)$^+$ calcd. 274.0308, found 274.0302.

N-(4-Fluorophenyl)-4-nitrobenzenesulfonamide (5g). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 17:3–7:3) afforded the title compound as a yellow solid (193 mg, 0.65 mmol, 65% yield). Data consistent with literature [20].

N-(4-Fluorophenyl)-2-nitrobenzenesulfonamide (5h). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 17:3–7:3) afforded the title compound as a yellow solid (118 mg, 0.40 mmol, 40% yield). Data consistent with literature [21].

N-(4-Fluoro-2-methylphenyl)-4-methylbenzenesulfonamide (5i). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 17:3) afforded the title compound as an off-white solid (100 mg, 0.36 mmol, 60% yield). MP: 95–96 °C; IR (ν, cm^{-1}): 3270 (w, NH), 1497 (m, C=C_{Ar}), 1329 (m, S=O), 1161 (s, S=O), 1092 (w, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (3H, s), 2.41 (3H, s), 6.65 (1H, brs), 6.81 (1H, d, J = 8.8 Hz), 6.82–6.85 (1H, m), 7.18–7.23 (1H, m), 7.24 (2H, d, J = 8.2 Hz), 7.60 (2H, d, J = 8.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 17.8, 21.6, 113.5 (d, J = 22.3 Hz), 117.3 (d, J = 22.3 Hz), 127.2, 127.7 (d, J = 9.5 Hz), 129.7, 130.2 (d, J = 3.2 Hz), 135.6 (d, J = 7.9 Hz), 136.5, 143.9, 161.0 (d, J = 246.4 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ = −115.5; HRMS (ESI^+, m/z): $[C_{14}H_{14}FNNaO_2S]^+$ (M+Na)$^+$ calcd. 302.0621, found 302.0620.

N-(2-Bromo-4-fluorophenyl)-4-methylbenzenesulfonamide (5j). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 19:1–9:1) afforded the title compound as a pale orange solid (179 mg, 0.52 mmol, 52% yield). MP: 92–93 °C; IR (ν, cm^{-1}): 3260 (w, NH), 1486 (s, C=C_{Ar}), 1334 (m, S=O), 1161 (s, S=O), 1090 (m, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (3 H, s), 6.80 (1H, brs), 7.03 (1H, ddd, J = 8.9 Hz, J = 7.9 Hz, J = 2.9 Hz), 7.16 (1H, dd, J = 7.7 Hz, J = 2.8 Hz), 7.22 (2H, d, J = 8.3 Hz), 7.60 (2H, d, J = 8.3 Hz), 7.68 (1H, dd, J = 9.0 Hz, J = 5.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.8, 115.9 (d, J = 22.3 Hz), 117.1 (d, J = 9.5 Hz), 119.8 (d, J = 25.4 Hz), 125.2 (d, J = 8.7 Hz), 127.5, 129.9, 131.3 (d, J = 3.2 Hz), 135.8, 144.5, 160.0 (d, J = 249.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ = −114.2; HRMS (ESI^+, m/z): $[C_{13}H_{11}{}^{79}BrFNNaO_2S]^+$ (M+Na)$^+$ calcd. 365.9570, found 365.9570.

N-(2-Chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (5k). Purification by flash chromatography on silica gel (SiO_2, hexane:EtOAc 9:1–4:1) afforded the title compound as a pale orange solid (162 mg, 0.54 mmol, 54% yield). MP: 102–103 °C; IR (ν, cm^{-1}): 3250 (m, NH), 1490 (s, C=C_{Ar}), 1339 (m, S=O), 1165 (s, S=O), 1091 (m, C–F), 729 (s, C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (3H, s), 6.89 (1H, brs), 6.95–7.02 (1H, m), 7.22 (1H, d, J = 8.1 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.61 (2H, d, J = 8.2 Hz), 7.66 (1H, dd, J = 9.1 Hz, J = 5.4 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7, 115.2 (d, J = 22.3 Hz), 116.7 (d, J = 26.2 Hz), 125.2 (d, J = 8.7 Hz), 127.0 (d, J = 10.3 Hz), 127.4, 129.7, 129.9 (d, J = 3.2 Hz), 135.8, 144.5, 159.7 (d, J = 249.5 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ = −114.2; HRMS (ESI^+, m/z): $[C_{13}H_{11}ClFNNaO_2S]^+$ (M+Na)$^+$ calcd. 322.0075, found 322.0075.

N-(2.4-Difluorophenyl)-4-methylbenzenesulfonamide (5l). Purification by flash chromatography on silica gel (SiO_2, hexane:EtOAc 9:1) afforded the title compound as an orange solid (77 mg, 0.27 mmol, 45% yield). MP: 102–103 °C; IR (ν, cm^{-1}): 3250 (w, NH), 1506 (s, C=C_{Ar}), 1335 (m, S=O), 1160 (s, S=O), 1092 (m, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (3H, s), 6.71 (1H, ddd, J = 10.2 Hz, J = 8.3 Hz, J = 2.8 Hz), 6.81–6.88 (2H, m), 7.23 (2H, d, J = 8.2 Hz), 7.56 (1H, td, J = 9.0 Hz, J = 5.8 Hz), 7.63 (2H, d, J = 8.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7, 104.2 (dd, J = 27.0 Hz, J = 23.8 Hz), 111.9 (dd, J = 22.3 Hz, J = 4.8 Hz), 120.8 (dd, J = 12.7 Hz, J = 4.0 Hz), 126.1 (dd, J = 9.5 Hz, J = 1.6 Hz), 127.3, 129.9, 135.8, 144.4, 155.0 (dd, J = 248.8 Hz, J = 11.9 Hz), 160.2 (dd, J = 248.8 Hz, J = 11.1 Hz; ^{19}F NMR (377 MHz, $CDCl_3$): δ = −123.4 (1F, d, J = 5.7 Hz), −112.0 (1F, d, J = 5.7 Hz); HRMS (ESI^+, m/z): $[C_{13}H_{11}F_2NNaO_2S]^+$ (M+Na)$^+$ calcd. 306.0371, found 306.0368.

N-(3-Chloro-4-fluorophenyl)-4-methylbenzenesulfonamide (5m). Purification by flash chromatography on silica gel (SiO_2, hexane:EtOAc 9:1–4:1) afforded the title compound as an orange solid (91 mg, 0.30 mmol, 61% yield). MP: 110–112 °C; IR (ν, cm^{-1}):

3251 (m, NH), 1499 (s, C=C_{Ar}), 1326 (m, S=O), 1161 (s, S=O), 1091 (m, C–F), 669 (m, C–Cl); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.41 (3H, s), 6.94–7.03 (2H, m), 7.15 (1H, brs), 7.19 (1H, dd, J = 6.3 Hz, J = 2.5 Hz), 7.27 (2H, d, J = 8.2 Hz), 7.67 (2H, d, J = 8.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6, 117.0 (d, J = 22.3 Hz), 121.6 (d, 19.1 Hz), 121.9 (d, J = 7.2 Hz), 124.3, 127.3, 129.2, 133.1 (d, J = 3.4 Hz), 135.4, 144.4, 156.0 (d, J = 247.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ = −118.9; HRMS (ESI$^+$, m/z): $[C_{13}H_{11}ClFNNaO_2S]^+$ $(M+Na)^+$ calcd. 322.0075, found 322.0075.

Methyl 5-fluoro-2-(4-methylphenylsulfonamido)benzoate (5n). Purification by flash chromatography on silica gel (SiO_2, hexane:EtOAc 9:1–4:1) afforded the title compound as a white solid (52 mg, 0.16 mmol, 21% yield). MP: 65–67 °C; IR (ν, cm^{-1}): 3184 (w, NH), 1691 (m, C=O), 1494 (m, C=C_{Ar}), 1342 (m, S=O), 1229 (m, C–O), 1162 (s, S=O), 1121 (m, C–O), 1090 (w, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (3H, s), 3.87 (3H, s), 7.16–7.22 (1H, m), 7.22 (2H, d, J = 8.1 Hz), 7.58 (1H, dd, J = 9.0 Hz, J = 3.2 Hz), 7.68 (2H, d, J = 8.3 Hz), 7.72 (1H, dd, J = 9.2 Hz, J = 4.8 Hz), 10.28 (1H, brs); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.5, 52.9, 117.3 (d, J = 25.4 Hz), 117.5 (d, J = 6.4 Hz), 121.9 (d, J = 22.3 Hz), 122.0 (d, J = 4.8 Hz), 127.4, 129.8, 136.3, 136.8 (d, J = 3.2 Hz), 144.2, 158.0 (d, J = 246.4 Hz), 167.3 (d, J = 3.2 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ = −118.3; HRMS (ESI$^+$, m/z): $[C_{15}H_{14}FNNaO_4S]^+$ $(M+Na)^+$ calcd. 346.0520, found 346.0513.

(E)-Methyl 3-(5-fluoro-2-(4-methylphenylsulfonamido)phenyl)acrylate (5o). Purification by flash chromatography on silica gel (SiO_2, petroleum ether 30–40:EtOAc 17:3) afforded the title compound as a white solid (80 mg, 0.23 mmol, 52% yield). MP: 152–155 °C; IR (ν, cm^{-1}): 3244 (w, NH), 1700 (m, C=O), 1632 (w, C=C), 1490 (m, C=C_{Ar}), 1328 (m, S=O), 1161 (s, S=O), 1092 (w, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.37 (3H, s), 3.79 (3H, s), 6.08 (1H, d, J = 15.9 Hz), 7.03 (1H, brs), 7.04–7.10 (1H, m), 7.15 (1H, dd, J = 9.0 Hz, J = 2.9 Hz), 7.20 (2H, d, J = 8.2 Hz), 7.36 (1H, dd, J = 9.0 Hz, J = 5.1 Hz), 7.48–7.55 (1H, m), 7.53 (2H, d, J = 8.2 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.5, 52.0, 113.3 (d, J = 23.8 Hz), 117.9 (d, J = 22.3 Hz), 121.1, 127.4, 129.7, 130.6 (d, J = 3.2 Hz), 130.7 (d, J = 9.5 Hz), 133.4 (d, J = 7.9 Hz), 135.5, 138.3, 144.2, 161.5 (d, J = 246.4 Hz), 166.6; ^{19}F NMR (377 MHz, $CDCl_3$): δ = −113.0; HRMS (ESI$^+$, m/z): $[C_{17}H_{16}FNNaO_4S]^+$ $(M+Na)^+$ calcd. 372.0676, found 372.0663.

N-(2-(tert-Butyl)-4-fluorophenyl)-4-methylbenzenesulfonamide (5q). Purification by flash chromatography on silica gel (SiO_2, hexane:EtOAc 9:1) afforded the title compound as a purple solid (125 mg, 0.39 mmol, 39% yield). MP: 82–84 °C; IR (ν, cm^{-1}): 3281 (w, NH), 1481 (m, C=C_{Ar}), 1326 (m, S=O), 1186 (s, S=O), 1093 (m, C–F); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (9H, s), 2.38 (3H, s), 6.54 (1H, brs), 6.77 (1H, ddd, J = 8.8 Hz, J = 7.1 Hz, J = 2.9 Hz), 7.01 (1H, dd, J = 11.5 Hz, J = 2.9 Hz), 7.22–7.26 (3H, m), 7.68 (2H, d, J = 8.3 Hz); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.7, 30.9, 34.9, 113.4 (d, J = 22.3 Hz), 114.6 (d, J = 23.8 Hz), 126.0 (d, J = 8.7 Hz), 127.5, 129.8, 130.9 (d, J = 2.4 Hz), 137.4, 144.1, 145.2 (d, J = 7.2 Hz), 160.5 (d, J = 244.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$): δ = −115.7; HRMS (ESI$^+$, m/z): $[C_{17}H_{20}FNNaO_2S]^+$ $(M+Na)^+$ calcd. 344.1091, found 344.1086.

6-Fluoro-3.4-dihydro-1H-2.1-benzothiazine 2.2-dioxide (10). Purification by flash chromatography on silica gel (SiO_2, DCM:MeOH 9:1) afforded the title compound as an off-white solid (97 mg, 0.48 mmol, 52% yield). MP: 135–137 °C; IR (ν, cm^{-1}): 3185 (w, NH), 1324 (s, S=O), 1155 (s, S=O); ^{1}H NMR (400 MHz, MeOD): δ = 3.23 (2H, t, J = 7.0 Hz), 3.37 (2H, t, J = 7.0 Hz), 6.74 (1H, dd, J = 8.8 Hz, J = 5.0 Hz), 6.88 (1H, dd, J = 8.0 Hz, J = 3.0 Hz), 6.94 (1H, dd, J = 8.8, 3.0 Hz); ^{13}C NMR (101 MHz, MeOD): δ = 29.3, 45.9, 115.5 (d, J = 23.1 Hz), 116.7 (d, J = 23.1 Hz), 121.4 (d, J = 7.9 Hz), 124.7 (d, J = 7.2 Hz), 135.6 (d, J = 2.4 Hz), 160.0 (d, J = 240.8 Hz); ^{19}F NMR (471 MHz, MeOD): δ = −122.8; HRMS (ESI$^-$, m/z): $[C_8H_7FNO_2S]^-$ $(M-H)^-$ calcd. 201.0187, found 200.0184.

4.3. Radiochemistry

Procedure for [^{18}F]fluorination reactions: [^{18}F]fluoride was trapped on an anion exchange cartridge, released with 6 × 100 μL of a solution of NEt_4HCO_3 in MeCN:H_2O (7 mg in 1 mL (4:1)) and azeotropically dried with MeCN. Dried [^{18}F]fluoride was resolubilised in anhydrous DCM (1000 μL) to give a stock solution of [^{18}F]NEt_4F. This was used to dispense [^{18}F]NEt_4F (15–30 MBq) into a v-vial containing a stirrer bar and **1a** (12 mg, 40 μmol, 1.0 eq.). PIDA (13 mg, 40 μmol, 1.0 eq.) in DCM (150 μL) was added, followed by the acid (HF·pyridine (1 μL, 40 μmol, 1.0 eq.) or TFA (12 μL, 160 μmol, 4.0 eq.)) in DCM (50 μL). The reaction mixture was stirred for 15 min before TFA (22 μL) was added and left for a further 10 minutes prior to radioHPLC and radioTLC analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2015.07.030.

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