Journal of Fluorine Chemistry 167 (2014) 231–236

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

# Radical (2-pyridylsulfonyl)difluoromethylation of terminal alkenes with iododifluoromethyl 2-pyridyl sulfone

Wenjun Miao, Chuanfa Ni, Yanchuan Zhao, Jinbo Hu *

*Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China*

ARTICLE INFO

*Article history:*
Received 21 April 2014
Received in revised form 20 May 2014
Accepted 27 May 2014
Available online 1 July 2014

Dedicated to Dr. Teruo Umemoto on the occasion of his receipt of the ACS Award for Creative Work in Fluorine Chemistry 2014.

*Keywords:*
Radical reactions
(2-Pyridylsulfonyl)difluoromethylation
Triethylborane
Iododifluoromethyl 2-pyridyl sulfone
Difluoromethylation

ABSTRACT

An efficient radical (2-pyridylsulfonyl)difluoromethylation of terminal alkenes with 2-$PySO_2CF_2I$ has been successfully achieved by using catalytic amount of $Et_3B$/air as initiating system. This methodology was also further extended to the synthesis of 2-$PySO_2CF_2$-substituted alkanes and alkenes.



## 1. Introduction

The introduction of fluorine atoms and fluorinated moieties into organic compounds has become an important and widely adopted strategy in the design of biologically active molecules and high-performance materials [1]. In the past decades, many approaches have been devised to incorporate fluorine or fluorinated moieties into organic molecules by selective fluorination and fluoroalkylation, as well as by the clever design and manipulation of fluorinated building blocks [2]. In this context, substantial progress has been made in the difluoromethylation and difluoromethylenation reactions in recent years [3]. For instance, Baran and co-workers reported a new reagent ($Zn(SO_2CF_2H)_2$, DFMS) for the innate difluoromethylation of heteroarenes under mild conditions via a radical process [4]. The Reutrakul group developed a Pd-mediated Heck-type reaction between $PhSO_2CF_2Br$ and styrene [5]. Wang and co-workers described a Pd(0)-catalyzed intramolecular aryldifluoromethylation of activated alkenes with $PhSO_2CF_2I$ [6]. It is known that (phenylsulfonyl)difluoromethyl group could serve as a "chemical chameleon" in various difluoromethylation reactions, which showed great power in the synthesis of many difluoromethyl-, difluoromethylene-, and difluoromethylidene-containing organic molecules [2a,3c]. Previously, we used both difluoromethyl phenyl sulfone ($PhSO_2CF_2H$) and difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) as robust and efficient nucleophilic difluoromethylation reagents [3d]. In particular, 2-$PySO_2CF_2H$ was found to act as a novel and efficient *gem*-difluoroolefination reagent for preparing *gem*-difluoroalkenes from both aldehydes and ketones via a Julia–Kocienski protocol [7]. Furthermore, the (2-pyridyl)sulfonyl group exhibited versatile chemical behaviors in fluoroalkylation reactions [8]. Moreover, fluoroalkyl 2-pyridyl sulfones (2-$PySO_2R_f$) are important potential precursors for fluorinated sulfinate salts by depyridination [9], which have recently emerged as promising reagents for the direct incorporation of fluoroalkyl groups onto heteroaromatic systems by a formal C–H functionalization through a radical addition process [10]. Previously, we reported an unprecedented radical (phenylsulfonyl)difluoromethylation of terminal alkenes with iododifluoromethyl phenyl sulfone ($PhSO_2CF_2I$) by using $Et_3B$/air as an initiator [11]. We envisioned that it should also be possible to achieve an efficient transfer of 2-$PySO_2CF_2$ group under mild conditions by using a similar approach. Herein, we report our

* Corresponding author. Tel.: +86 21 54925174; fax: +86 21 64166128.
*E-mail addresses:* jinbohu@sioc.ac.cn, jinbohu2007@yahoo.com.cn (J. Hu).

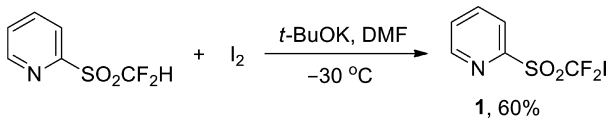
http://dx.doi.org/10.1016/j.jfluchem.2014.05.012
0022-1139/

recent discovery of $Et_3B$/air-initiated radical (2-pyridylsulfonyl)difluoromethylation of terminal alkenes with iododifluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2I$).

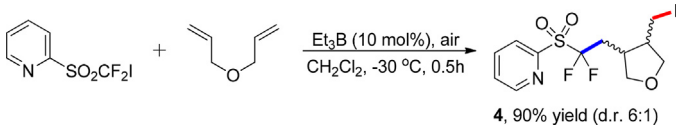
## 2. Results and discussion

Our research commenced with the preparation of iododifluoromethyl 2-pyridyl sulfone **1** following a similar procedure for the preparation of $PhSO_2CF_2I$ (Scheme 1) in 60% isolated yield [12]. Based on our previous studies on radical (phenylsulfonyl)difluoromethylation of terminal alkenes with $PhSO_2CF_2I$, we investigated the reaction of 2-$PySO_2CF_2I$ and 1-hexene (**2a**). Firstly, we tried several radical initiators and found that Cu, $Pd(PPh_3)_4$ and $Na_2S_2O_4$ were not efficient in initiating this reaction (Table 1, entries 1–4). Then we conducted these reactions with equal molar amounts of $Et_3B$/air as the radical initiating system [13], and found that the reactions afforded the corresponding radical atom-transfer products **3a** in 29–70% yields in different solvents (Table 1, entries 5–15). Regarding the amount of $Et_3B$, the reaction with 0.1 equiv of $Et_3B$ performed better than that with 1.0 equiv (Table 1, entry 16). To further improve the yield, we also screened the reaction temperature and the amount of alkene, which turned out to be crucial to this radical atom-transfer process (Table 1, entries 17 and 18). The use of 0.1 equiv of $Et_3B$ gave the optimal yield (92%) when the reaction was carried out in $CH_2Cl_2$ at −30 °C with 1.2 equiv of alkene **2a** (Table 1, entry 17).

With the optimized reaction conditions in hand, we explored the scope of the $Et_3B$/air-initiated radical (2-pyridylsulfonyl)difluoromethylation reactions of various substituted terminal alkenes with 2-$PySO_2CF_2I$ (Table 2). A wide range of substrates bearing various functional groups (including free alcohol, phenol, carbonyl, carboxylic acid, ester and epoxide) were found to be compatible with the reaction, and the corresponding regioselective products were formed in good yields. It is noteworthy to mention that, allylbenzenes were less reactive in the reaction when 0.1 equiv of $Et_3B$ was used. Nevertheless, increasing the amount of $Et_3B$ to 0.5 equiv resulted in the improvement of the chemical yields of **3f** and **3g** (70% and 64%, respectively). The sterically hindered disubstituted alkene **2e** provided the desired radical addition product **3e** in 51% yield. Styrenes proved to be ineffective alkene substrates.




**Scheme 1.** Preparation of compound **1**.

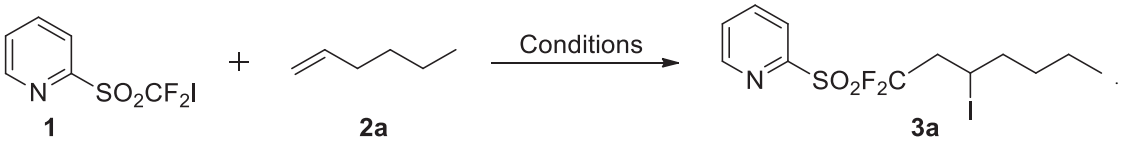



**Scheme 2.** $Et_3B$/air-initiated radical cyclization reaction.

Diallyl ether served to trap the 2-$PySO_2CF_2^{\bullet}$ radical intermediate in this reaction. Under the reaction conditions in the presence of 0.1 equiv $Et_3B$, the cyclized product **4** was obtained in a 90% yield (Scheme 2).

It has been reported that tributyltinhydride can be used as an efficient reagent for deiodination reaction to obtain the corresponding alkanes from the iodoalkanes (Scheme 3). When tributyltinhydride was applied in the deiodination reaction of **3a**, the reaction proceeded smoothly to give in 75% isolated yield. Furthermore, the intermediate compound **3a** can undergo dehydroiodination reactions in the presence of a base, affording the (2-pyridylsulfonyl)difluoromethylated alkenes. We found that 1,5-diazabicyclo[4,3,0]non-5-ene (DBU) served to be an excellent base in toluene at 0 °C, giving a remarkable *E*/*Z* ratio (75:1) of 6 in 93% isolated yield (Scheme 3).

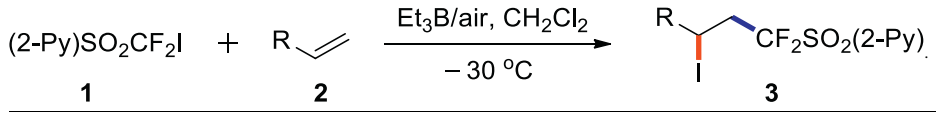
**Table 1**
Optimization of reaction conditions.

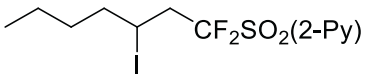



| Entry | Initiator (equiv)[a] | Molar ratio (**1**:**2a**) | Solvent | Temperature (°C) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Cu (0.5) | 1:2.0 | DMF | 60 | 1 | 0 |
| 2 | $Pd(PPh_3)_4$ (0.1) | 1:2.0 | Toluene | 60 | 1 | Trace |
| 3[c] | $Na_2S_2O_4$ (1.5) | 1:2.0 | $CH_3CN/H_2O$ | 24 | 1 | 10 |
| 4[c,d] | $Na_2S_2O_4/NaHCO_3$ (0.1) | 1:2.0 | $CH_3CN/H_2O$ | 24 | 1 | 0 |
| 5 | $Et_3B$ (1.0)/air | 1:2.0 | Toluene | −30 | 1 | 56 |
| 6 | $Et_3B$ (1.0)/air | 1:2.0 | DCE | −30 | 1 | 62 |
| 7 | $Et_3B$ (1.0)/air | 1:2.0 | THF | −30 | 1 | 60 |
| 8 | $Et_3B$ (1.0)/air | 1:2.0 | $CH_3CN$ | −30 | 1 | 63 |
| 9 | $Et_3B$ (1.0)/air | 1:2.0 | $CHCl_3$ | −30 | 1 | 56 |
| 10 | $Et_3B$ (1.0)/air | 1:2.0 | DMF | −30 | 1 | 58 |
| 11 | $Et_3B$ (1.0)/air | 1:2.0 | $CH_3OH$ | −30 | 1 | 29 |
| 12 | $Et_3B$ (1.0)/air | 1:2.0 | EtOAc | −30 | 1 | 62 |
| 13 | $Et_3B$ (1.0)/air | 1:2.0 | $CH_2Cl_2$ | −30 | 1 | 63 |
| 14 | $Et_3B$ (1.0)/air | 1:2.0 | $CH_2Cl_2$ | 0 | 1 | 70 |
| 15 | $Et_3B$ (1.0)/air | 1:2.0 | $CH_2Cl_2$ | 24 | 1 | 63 |
| 16 | $Et_3B$ (0.1)/air | 1:2.0 | $CH_2Cl_2$ | −30 | 1 | 73 |
| 17 | $Et_3B$ (0.1)/air | 1:1.2 | $CH_2Cl_2$ | −30 | 0.5 | 92 |
| 18 | $Et_3B$ (0.1)/air | 1:1.2 | $CH_2Cl_2$ | 24 | 1 | 79 |

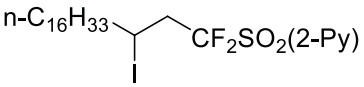
[a] The molar equivalent of the initiator was calculated relative to the amount of compound **1**.
[b] Determined by $^{19}F$ NMR spectroscopy.
[c] $CH_3CN/H_2O$ = 1:1 (v/v = 1:1).
[d] The molar ratio of $Na_2S_2O_4/NaHCO_3$ = 1:1.

**Table 2**
$Et_3B/O_2$-initiated radical atom transfer reactions between **1** and alkenes **2**.

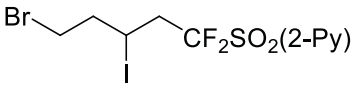


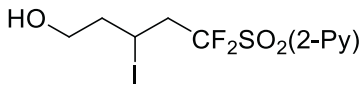

**3a**, 89%[a]



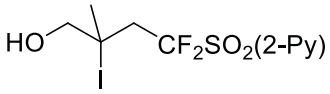

**3b**, 82%[a]



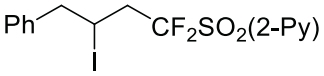

**3c**, 84%[a]



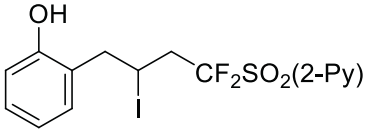

**3d**, 82%[a]



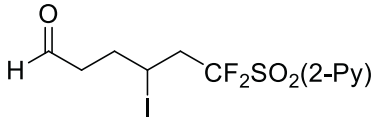

**3e**, 51%[a]



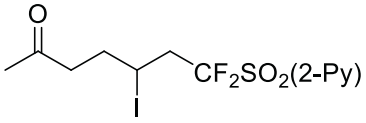

**3f**, 70%[b]



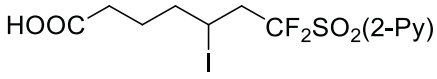

**3g**, 64%[b]



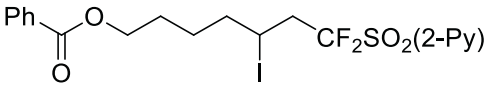

**3h**, 87%[a]



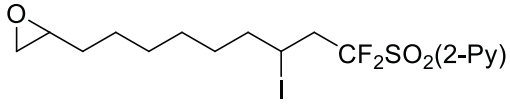

**3i**, 93%[a]



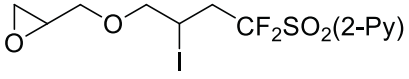

**3j**, 85%[a]




**3k**, 90%[a]

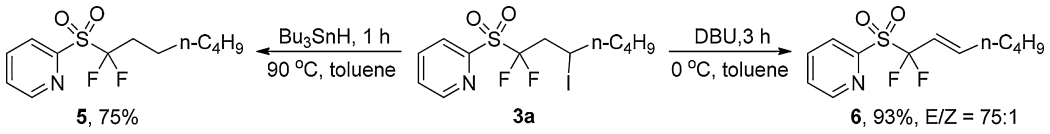



**3l**, 80%[a] (d.r. = 1:1)[c]




**3m**, 90%[a] (d.r. = 1:1)[c]

[a] Reaction conditions: **1** (1.0 mmol), **2** (1.2 mmol), $Et_3B$ (0.1 mmol), $CH_2Cl_2$ (3.0 mL), 0.5 h, −30 °C, air. Isolated yield.
[b] 0.5 mmol of $Et_3B$ was used.
[c] The diastereomeric ratio was determined by HPLC.




**5**, 75% **3a** **6**, 93%, E/Z = 75:1

**Scheme 3.** Transformation of compound **3a**.

## 3. Conclusions

We have developed a $Et_3B$/air-initiated free radical (2-pyridylsulfonyl)difluoromethylation of 2-$PySO_2CF_2I$ with terminal alkenes. The radical reactions were efficient and compatible with plenty of functionalities. This synthetic methodology was also extended to the synthesis of (2-pyridylsulfonyl)difluoromethylated alkanes and alkenes with high *E*/*Z* ratio. We believe that this methodology may become a very useful tool in organic synthesis. Further studies on taking advantage of the behavior of the 2-pyridylsulfonyl group, such as the preparation of fluorinated sulfinate salts by depyridination are underway in our laboratory.

## 4. Experimental

### 4.1. General

Unless otherwise mentioned, solvents and reagents were purchased from commercial sources and used as received. Column chromatography was performed on silica gel 300–400 mesh. $^1H$ NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at $\delta$ 0.0 or to the signal of a residual protonated solvent: $CDCl_3$ $\delta$ 7.26. $^{13}C$ NMR chemical shifts were determined relative to internal TMS at $\delta$ 0.0. $^{19}F$ NMR chemical shifts were determined relative to $CFCl_3$ at $\delta$ 0.0. Chemical shifts of common trace $^1H$ NMR

impurities (ppm): $H_2O$: 1.56, $CHCl_3$: 7.26. All coupling constants (*J* values) were reported in Hertz (Hz). The data is being reported as s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, and m = multiplet. Low-resolution mass spectra were obtained on a low-resolution mass spectrometer. High-resolution mass data were recorded on a high-resolution mass spectrometer in the MALDI mode. Melting points are uncorrected.

### 4.2. Typical procedure for the radical addition of iododifluoromethyl 2-pyridyl sulfone with terminal alkenes

Open to the air, into a 30-mL Schlenk flask containing iododifluoromethyl 2-pyridyl sulfone (**1**) (318.9 mg, 1.0 mmol) and 1-hexene (**2a**) (101 mg, 1.2 mmol) in 3.0 mL of $CH_2Cl_2$ at −30 °C was added $Et_3B$ (100 μL, 1.0 M in hexane) via a syringe. The reaction mixture was stirred at this temperature for 0.5 h. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography to give product **3a** as an oily liquid, yield 89%.

#### 4.2.1. 2-[(Difluoroiodomethyl)sulfonyl]pyridine (*1*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.89 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1H), 8.22 (d, *J* = 7.9 Hz, 1H), 8.07 (td, *J* = 7.8, 1.7 Hz, 1H), 7.74 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −50.63 (s). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.3, 148.4, 138.5, 129.2, 127.3, 102.3 (t, *J* = 357.2 Hz). MS (ESI, *m*/*z*): 319.8 ($M+H^+$), 341.7 ($M+Na^+$). HRMS (MALDI): calcd. for $C_6H_5NO_2F_2SI^+$ ($M+H^+$) 319.9048, found 319.9054.

#### 4.2.2. 2-[(1,1-Difluoro-3-iodoheptyl)sulfonyl]pyridine (*3a*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.82 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1H), 8.13 (d, *J* = 7.9 Hz, 1H), 8.03 (td, *J* = 7.8, 1.7 Hz, 1H), 7.67 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 4.36–4.29 (m, 1H), 3.27–3.04 (m, 2H), 1.84–1.68 (m, 2H), 1.51–1.21 (m, 4H), 0.86 (t, *J* = 7.2 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −100.54 (ddd, *J* = 229.2, 26.8, 10.1 Hz, 1F), −102.13 (ddd, *J* = 229.2, 24.8, 10.4 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.9, 138.3, 128.8, 126.3, 123.9 (t, *J* = 290.9 Hz), 40.7 (t, *J* = 18.6 Hz), 39.8, 31.3, 21.5, 20.9, 13.7. MS (ESI, *m*/*z*): 404.0 ($M+H^+$). HRMS (MALDI): calcd. for $C_{12}H_{16}F_2INNaO_2S^+$ ($M+Na^+$) 425.9807, found 425.9808.

#### 4.2.3. 2-[(1,1-Difluoro-3-iodononadecyl)sulfonyl]pyridine (*3b*)

White solid. m.p.: 57–58 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.03 (td, *J* = 7.8, 1.7 Hz, 1H), 7.67 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 4.34 (dt, *J* = 14.7, 6.4 Hz, 1H), 3.29–3.05 (m, 2H), 1.85–1.69 (m, 2H), 1.54–1.22 (m, 28H), 0.84 (t, *J* = 6.8 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −100.51 (ddd, *J* = 229.1, 26.9, 9.9 Hz, 1F), −102.09 (ddd, *J* = 229.1, 24.9, 10.4 Hz, 1F). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.9, 150.9, 138.3, 128.8, 126.4, 124.0 (t, *J* = 290.9 Hz), 40.8 (t, *J* = 18.6 Hz), 40.2, 31.8, 29.61, 29.60, 29.59, 29.58, 29.56, 29.5 (d, *J* = 2.1 Hz), 29.44, 29.33, 29.29, 29.28, 28.4, 22.6, 21.0 (t, *J* = 1.8 Hz), 14.1. MS (ESI, *m*/*z*): HRMS (MALDI): calcd. for $C_{24}H_{40}NO_2F_2SINa^+$ ($M+Na^+$) 594.1685, found 594.1698.

#### 4.2.4. 2-[(5-Bromo-1,1-difluoro-3-iodopentyl)sulfonyl]pyridine (*3c*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.5 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.04 (td, *J* = 7.8, 1.6 Hz, 1H), 7.68 (ddd, *J* = 7.6, 4.7, 0.9 Hz, 1H), 4.52–4.45 (m, 1H), 3.59–3.54 (m, 1H), 3.48–3.41 (m, 1H), 3.38–3.09 (m, 2H), 2.35–2.27 (m, 1H), 2.24–2.15 (m, 1H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −100.02 (ddd, *J* = 230.1, 28.3, 8.4 Hz, 1F), −101.96 (ddd, *J* = 230.1, 26.0, 9.0 Hz, 1F). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.6, 150.9, 138.4, 128.9, 126.3, 123.7 (t, *J* = 291.1 Hz), 42.0, 40.7 (t, *J* = 18.8 Hz), 32.8, 18.0. MS (ESI, *m*/*z*): 453.9 ($M+H^+$). HRMS (MALDI): calcd. for $C_{10}H_{11}NO_2F_2SBrINa^+$ ($M+Na^+$) 475.8599, found 475.8597.

#### 4.2.5. 5,5-Difluoro-3-iodo-5-(pyridin-2-ylsulfonyl)pentan-1-ol (*3d*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, *J* = 4.4, 1H), 8.14 (d, *J* = 7.9 Hz, 1H), 8.03 (td, *J* = 7.8, 1.7 Hz, 1H), 7.67 (ddd, *J* = 7.6, 4.7, 1.1 Hz, 1H), 4.54–4.47 (m, 1H), 3.84–3.79 (m, 1H), 3.73–3.67 (m, 1H), 3.32–3.12 (m, 2H), 2.20 (s, 1H), 2.02–1.98 (m, 2H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −100.42 (ddd, *J* = 229.6, 23.2, 13.2 Hz, 1F), −101.45 (ddd, *J* = 229.7, 21.9, 13.4 Hz, 1F). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.6, 150.9, 138.4, 128.9, 126.4, 123.8 (t, *J* = 291.1 Hz), 62.1, 42.3, 41.0 (t, *J* = 18.6 Hz), 16.8 (t, *J* = 2.2 Hz). MS (ESI, *m*/*z*): 391.9 ($M+H^+$). HRMS (MALDI): calcd. for $C_{10}H_{12}NO_3F_2SINa^+$ ($M+Na^+$) 413.9443, found 413.9449.

#### 4.2.6. 4,4-Difluoro-2-iodo-2-methyl-4-(pyridin-2-ylsulfonyl)butan-1-ol (*3e*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.88 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.07 (td, *J* = 7.8, 1.7 Hz, 1H), 7.71 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 3.73 (d, *J* = 12.4 Hz, 1H), 3.57 (d, *J* = 12.5 Hz, 1H), 3.45–3.24 (m, 2H), 2.54 (s, 1H), 2.11 (s, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −99.76 (t, *J* = 19.9 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 151.6, 150.9, 138.4, 128.9, 126.5, 124.4 (t, *J* = 292.7 Hz), 73.8, 46.6, 41.5 (t, *J* = 17.6 Hz), 31.2. MS (ESI, *m*/*z*): 391.9 ($M+H^+$). HRMS (MALDI): calcd. for $C_{10}H_{12}NO_3F_2SINa^+$ ($M+Na^+$) 413.9443, found 413.9447.

#### 4.2.7. 2-[(1,1-Difluoro-3-iodo-4-phenylbutyl)sulfonyl]pyridine (*3f*)

$^1$H NMR (400 MHz, $CDCl_3$) 8.80 (ddd, *J* = 4.6, 1.6, 0.8 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.01 (td, *J* = 7.8, 1.7 Hz, 1H), 7.65 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.33–7.18 (m, 5H), 4.56–4.49 (m, 1H), 3.32–3.15 (m, 4H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −100.26 (ddd, *J* = 229.4, 22.1, 13.2 Hz, 1F), −101.38 (ddd, *J* = 230.1, 20.2, 15.3 Hz, 1F). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.6, 150.8, 138.3, 138.3, 128.8, 128.8, 128.4 (d, *J* = 0.6 Hz), 127.0, 126.2, 123.7 (t, *J* = 290.8 Hz), 46.6, 40.2 (t, *J* = 18.7 Hz), 19.9. MS (ESI, *m*/*z*): 437.9 ($M+H^+$), 459.9 ($M+Na^+$). HRMS (MALDI): calcd. for $C_{15}H_{14}NO_2F_2SINa^+$ ($M+Na^+$) 459.9650, found 459.9651.

#### 4.2.8. 2-[4,4-Difluoro-2-iodo-4-(pyridin-2-ylsulfonyl)butyl]phenol (*3g*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.81 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 8.02 (td, *J* = 7.8, 1.7 Hz, 1H), 7.66 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 7.17–7.11 (m, 2H), 6.88 (td, *J* = 7.5, 1.0 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 5.25 (br, s, 1H), 4.75–4.68 (m, 1H), 3.38–3.14 (m, 4H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −101.16 to −101.28 (m, 2F). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 153.7, 151.7, 150.9, 138.4, 131.4, 128.9, 128.6, 126.4, 125.4, 123.9 (t, *J* = 290.9 Hz), 120.7, 115.6, 42.4, 40.1 (t, *J* = 18.7 Hz), 18.6. MS (ESI, *m*/*z*): 454.0 ($M+H^+$), 475.9 ($M+Na^+$). HRMS (MALDI): calcd. for $C_{15}H_{14}NO_3F_2SINa^+$ ($M+Na^+$) 475.9599, found 475.9603.

#### 4.2.9. 5,5-Difluoro-3-iodo-5-(pyridin-2-ylsulfonyl)pentanal (*3h*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 8.88 (ddd, *J* = 4.7, 1.6, 0.8 Hz, 1H), 8.19 (d, *J* = 7.9 Hz, 1H), 8.09 (td, *J* = 7.8, 1.7 Hz, 1H), 7.73 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H), 4.47–4.40 (m, 1H), 3.37–3.11 (m, 2H), 2.82–2.66 (m, 2H), 2.27–2.18 (m, 1H), 2.13–2.04 (m, 1H). $^{19}$F NMR (376 MHz, $CDCl_3$) δ −100.33 (ddd, *J* = 230.2, 27.6, 8.9 Hz, 1F), −102.17 (ddd, *J* = 230.2, 25.3, 9.5 Hz, 1F). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 199.8, 151.4, 150.8, 138.4, 128.9, 126.3, 123.5 (t, *J* = 291.0 Hz), 43.7, 40.8 (t, *J* = 18.8 Hz), 32.2, 19.4 (t, *J* = 2.1 Hz). MS (ESI, *m*/*z*): 404.0 ($M+H^+$). HRMS (MALDI): calcd. for $C_{11}H_{12}NO_3F_2SINa^+$ ($M+Na^+$) 425.9443, found 425.9448.

#### 4.2.10. 7,7-Difluoro-5-iodo-7-(pyridin-2-ylsulfonyl)heptan-2-one (*3i*)

$^1$H NMR (400 MHz, $CDCl_3$) δ 8.79 (ddd, *J* = 4.7, 1.7, 0.8 Hz, 1H), 8.10 (d, *J* = 7.9 Hz, 1H), 8.01 (td, *J* = 7.8, 1.7 Hz, 1H), 7.65 (ddd,

$J$ = 7.7, 4.7, 1.2 Hz, 1H), 4.37–4.30 (m, 1H), 3.26–3.01 (m, 2H), 2.69–2.53 (m, 2H), 2.09 (s, 3H), 2.07–1.88 (m, 2H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −100.47 (ddd, $J$ = 230.0, 27.5, 9.3 Hz, 1F), −102.09 (ddd, $J$ = 230.0, 25.3, 9.6 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 206.4, 151.5, 150.8, 138.4, 128.9, 126.3, 123.6 (t, $J$ = 291.0 Hz), 43.2, 40.8 (t, $J$ = 18.7 Hz), 33.8, 29.9, 19.9. MS (ESI, $m/z$): 417.9 ($M+H^+$), 439.8 ($M+Na^+$). HRMS (MALDI): calcd. for $C_{12}H_{15}NO_3F_2SI^+$ ($M+H^+$) 417.9780, found 417.9782.

#### 4.2.11. 7,7-Difluoro-5-iodo-7-(pyridin-2-ylsulfonyl)heptanoic acid (**3j**)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 10.81 (brs, 1H) 8.84 (d, $J$ = 3.9 Hz, 1H), 8.14 (d, $J$ = 7.8 Hz, 1H), 8.04 (td, $J$ = 7.8, 1.6 Hz, 1H), 7.68 (ddd, $J$ = 7.6, 4.7, 1.1 Hz, 1H), 4.36–4.30 (m, 1H), 3.29–3.05 (m, 2H), 2.42–2.30 (m, 2H), 1.90–1.67 (m, 4H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −100.34 (ddd, $J$ = 229.9, 26.5, 9.7 Hz, 1F), −101.93 (ddd, $J$ = 230.0, 24.6, 10.5 Hz, 1F). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 178.8, 151.5, 150.9, 138.5, 128.9, 126.4, 123.7 (t, $J$ = 290.9 Hz), 40.7 (t, $J$ = 18.7 Hz), 39.1, 32.6, 24.5, 19.5. MS (ESI, $m/z$): 434.0 ($M+H^+$). HRMS (MALDI): calcd. for $C_{12}H_{14}NO_4F_2SINa^+$ ($M+Na^+$) 455.9548, found 455.9546.

#### 4.2.12. 7,7-Difluoro-5-iodo-7-(pyridin-2-ylsulfonyl)heptyl benzoate (**3k**)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87 (ddd, $J$ = 4.7, 1.6, 0.8 Hz, 1H), 8.17 (d, $J$ = 7.9 Hz, 1H), 8.07–8.02 (m, 3H), 7.69 (ddd, $J$ = 7.7, 4.7, 1.1 Hz, 1H), 7.58–7.54 (m, 1H), 7.46–7.42 (m, 2H), 4.44–4.31 (m, 3H), 3.36–3.11 (m, 2H), 1.97–1.69 (m, 5H), 1.66–1.55 (m, 1H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −100.10 (ddd, $J$ = 229.6, 27.1, 9.3 Hz, 1F), −101.91 (ddd, $J$ = 229.6, 25.0, 10.1 Hz, 1F). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 166.3, 151.7, 150.8, 138.3, 132.7, 130.1, 129.4, 128.8, 128.2, 126.3, 123.8 (t, $J$ = 290.9 Hz), 64.3, 40.8 (t, $J$ = 18.7 Hz), 39.5, 27.5, 26.0, 20.4 (d, $J$ = 2.1 Hz). MS (ESI, $m/z$): 524.0 ($M+H^+$). HRMS (MALDI): calcd. for $C_{19}H_{20}NO_4F_2SINa^+$ ($M+Na^+$) 546.0018, found 546.0013.

#### 4.2.13. 2-[(1,1-Difluoro-3-iodo-9-(oxiran-2-yl)nonyl)sulfonyl]pyridine (**3l**)

A 1:1 mixture of diastereomers (determined by HPLC). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.78 (d, $J$ = 4.6 Hz, 1H), 8.09 (d, $J$ = 7.9 Hz, 1H), 7.99 (td, $J$ = 7.8, 1.6 Hz, 1H), 7.63 (ddd, $J$ = 7.6, 4.7, 1.1 Hz, 1H), 4.32–4.25 (m, 1H), 3.22–2.99 (m, 2H), 2.82–2.78 (m, 1H), 2.64 (dd, $J$ = 4.9, 4.1 Hz, 1H), 2.36 (dd, $J$ = 5.0, 2.7 Hz, 1H), 1.80–1.64 (m, 2H), 1.46–1.13 (m, 10H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −100.50 (ddd, $J$ = 36.6, 27.2, 10.1 Hz, 1F), −102.04 (ddd, $J$ = 229.6, 24.5, 10.8 Hz, 1F). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 151.6, 150.7, 138.3, 128.7, 126.2, 123.7 (t, $J$ = 290.8 Hz), 51.9, 46.7, 40.6 (t, $J$ = 18.7 Hz), 39.9, 32.1, 29.0, 28.8, 28.0 (d, $J$ = 1.2 Hz), 25.5, 20.9.MS (ESI, $m/z$): 474.0 ($M+H^+$). HRMS (MALDI): calcd. for $C_{16}H_{23}NO_3F_2SI^+$ ($M+H^+$) 474.0406, found 474.0407.

#### 4.2.14. 2-[(1,1-Difluoro-3-iodo-4-(oxiran-2-ylmethoxy)butyl)sulfonyl]pyridine (**3m**)

A 1:1 mixture of diastereomers (determined by HPLC). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.84 (d, $J$ = 4.5 Hz, 1H), 8.14 (d, $J$ = 7.9 Hz, 1H), 8.03 (td, $J$ = 7.8, 1.6 Hz, 1H), 7.67 (dd, $J$ = 6.8, 4.9 Hz, 1H), 4.42–4.36 (m, 1H), 3.84–3.65 (m, 3H), 3.46–3.32 (m, 2H), 3.14–3.10 (m, 1H), 3.08–2.92 (m, 1H), 2.77–2.75 (m, 1H), 2.60 (td, $J$ = 4.7, 2.8 Hz, 1H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −100.80 to −102.33 (m, 2F). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 151.8, 150.9, 138.4, 128.8, 126.3, 123.7 (t, $J$ = 290.5 Hz), 75.8 (d, $J$ = 8.9 Hz), 71.4 (d, $J$ = 11.4 Hz), 50.5 (d, $J$ = 5.1 Hz), 43.9 (d, $J$ = 4.4 Hz), 37.0 (td, $J$ = 19.0, 2.3 Hz), 14.9 (dt, $J$ = 10.2, 2.1 Hz). MS (ESI, $m/z$): 434.0 ($M+H^+$), 455.9 ($M+Na^+$). HRMS (MALDI): calcd. for $C_{12}H_{14}NO_4F_2SINa^+$ ($M+Na^+$) 455.9548, found 455.9553.

#### 4.2.15. 2-[(1,1-Difluoro-2-(4-(iodomethyl)tetrahydrofuran-3-yl)ethyl)sulfonyl]pyridine (**4**)

A 6:1 mixture of diastereomers (determined by $^{19}$F NMR). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87–8.86 (m, 1H), 8.18 (d, $J$ = 7.9 Hz, 1H), 8.05 (td, $J$ = 7.8, 1.7 Hz, 1H), 7.68 (ddd, $J$ = 7.7, 4.7, 1.1 Hz, 1H), 4.02–3.97 (m, 2H), 3.74 (dd, $J$ = 9.1, 4.6 Hz, 1H), 3.64 (t, $J$ = 8.0 Hz, 1H), 3.24 (dd, $J$ = 9.8, 4.9 Hz, 1H), 3.08 (t, $J$ = 10.1 Hz, 1H), 2.83–2.63 (m, 3H), 2.50–2.29 (m, 1H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −100.10 to −103.18 (m, 2F). $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 152.0, 151.0, 138.4, 128.8, 126.4, 124.6 (t, $J$ = 288.5 Hz), 73.4, 71.5 (d, $J$ = 3.1 Hz), 45.1, 36.2, 27.8 (t, $J$ = 19.6 Hz), 2.9. MS (ESI, $m/z$): 417.9 ($M+H^+$). HRMS (MALDI): calcd. for $C_{12}H_{14}NO_3F_2SINa^+$ ($M+Na^+$) 439.9599, found 439.9596.

#### 4.2.16. 2-[(1,1-Difluoroheptyl)sulfonyl]pyridine (**5**)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.82 (ddd, $J$ = 4.7, 1.7, 0.8 Hz, 1H), 8.12 (d, $J$ = 7.9 Hz, 1H), 8.00 (td, $J$ = 7.8, 1.7 Hz, 1H), 7.63 (ddd, $J$ = 7.7, 4.7, 1.1 Hz, 1H), 2.42–2.28 (m, 2H), 1.65–1.57 (m, 2H), 1.39–1.22 (m, 6H), 0.84 (t, $J$ = 7.0 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ -102.29 (t, $J$ = 18.8 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.3, 150.7, 138.2, 128.5, 126.2, 125.3 (t, $J$ = 287.2 Hz), 31.1, 30.0 (t, $J$ = 19.8 Hz), 28.6, 22.2, 20.5 (t, $J$ = 3.2 Hz), 13.8. MS (ESI, $m/z$): 277.9 ($M+H^+$). HRMS (MALDI): calcd. for $C_{12}H_{18}NO_2F_2S^+$ ($M+H^+$) 278.1021, found 278.1022.

#### 4.2.17. 2-[(1,1-Difluorohept-2-en-1-yl)sulfonyl]pyridine (**6**)

$^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.87 (d, $J$ = 4.7 Hz, 1H), 8.17 (d, $J$ = 7.9 Hz, 1H), 8.03 (td, $J$ = 7.8, 1.7 Hz, 1H), 7.67 (ddd, $J$ = 7.7, 4.7, 1.1 Hz, 1H), 6.58–6.50 (m, 1H), 5.88–5.78 (m, 1H), 2.29–2.23 (m, 2H), 1.50–1.30 (m, 4H), 0.92 (t, $J$ = 7.2 Hz, 3H). $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −100.14 (dd, $J$ = 11.9, 2.5 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 152.7, 150.8, 147.0, 138.2, 128.5, 126.4, 121.5 (t, $J$ = 283.4 Hz), 114.8 (t, $J$ = 21.6 Hz), 32.0, 29.9, 22.0, 13.7. MS (ESI, $m/z$): 275.9 ($M+H^+$), 297.9 ($M+Na^+$). HRMS (MALDI): calcd. for $C_{12}H_{15}NO_2F_2SNa^+$ ($M+Na^+$) 298.0684, found 298.0685.


## Acknowledgements

This work was supported by the National Basic Research Program of China (2012CB215500 and 2012CB821600), the National Natural Science Foundation of China (21372246 and 21202189), Shanghai QMX program (13QH1402400), and the Chinese Academy of Sciences.


## References


[1] (a) J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, John Wiley & Sons, New York, 1991;
(b) P. Krish, Modern Fluorooganic Chemistry, Wiely-VCH, Weinheim, 2004;
(c) K. Uneyama, Organofluorine Chemistry, Blackwell Publishing, Oxford, 2006;
(d) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330;
(e) K. Müller, C. Faeh, F. Diederich, Science 317 (2007) 1881–1886.

[2] (a) G.K.S. Prakash, J. Hu, Acc. Chem. Res. 40 (2007) 921–930;
(b) T. Furuya, A.S. Kamlet, T. Ritter, Nature 473 (2011) 470–477;
(c) T. Besset, C. Schneider, D. Cahard, Angew. Chem. Int. Ed. 51 (2012) 5048–5050;
(d) A. Studer, Angew. Chem. Int. Ed. 51 (2012) 8950–8958;
(e) T. Liang, C.N. Neumann, T. Ritter, Angew. Chem. Int. Ed. 52 (2013) 8214–8264.

[3] (a) J. Hu, W. Zhang, F. Wang, Chem. Commun. (2009) 7465–7478;
(b) W. Zhang, C. Ni, J. Hu, Top. Curr. Chem. 308 (2012) 25–44;
(c) J. Hu, J. Fluorine Chem. 130 (2009) 1130–1139;
(d) C. Ni, J. Hu, Synlett (2011) 770–782.

[4] (a) Y. Fujiwara, J.A. Dixon, R.A. Rodriguez, R.D. Baxter, D.D. Dixon, M.R. Collins, D.G. Blackmond, P.S. Baran, J. Am. Chem. Soc. 134 (2012) 1494–1497;
(b) Y. Fujiwara, J.A. Dixon, F. O'Hara, E.D. Funder, D.D. Dixon, R.A. Rodriguez, R.D. Baxter, B. Herle, N. Sach, M.R. Collins, Y. Ishihara, P.S. Baran, Nature 492 (2012) 95–99.

[5] N. Surapanich, C. Kuhakarn, M. Pohmakotr, V. Reutrakul, Eur. J. Org. Chem. (2012) 5943–5952.

[6] J.-Y. Wang, Y.-M. Su, F. Yin, Y. Bao, X. Zhang, Y.-M. Xu, X.-S. Wang, Chem. Commun. 50 (2014) 4108–4111.

[7] (a) Y. Zhao, W. Huang, L. Zhu, J. Hu, Org. Lett. 12 (2010) 1444–1447;
(b) B. Gao, Y. Zhao, M. Hu, C. Ni, J. Hu, Chem. Eur. J. 20 (2014) 7803–7810.
[8] (a) Y. Zhao, B. Gao, C. Ni, J. Hu, Org. Lett. 14 (2012) 6080–6083;
(b) Y. Zhao, C. Ni, F. Jiang, B. Gao, X. Shen, J. Hu, ACS Catal. 3 (2013) 631–634;
(c) Y. Zhao, B. Gao, J. Hu, J. Am. Chem. Soc 134 (2012) 5790–5793;
(d) Y. Zhao, L. Zhang, G. Xu, J. Zheng, J. Hu, Sci. Sin. Chim 41 (2011) 1833–1839.
[9] (a) G.K.S. Prakash, C. Ni, F. Wang, J. Hu, G.A. Olah, Angew. Chem. Int. Ed. 50 (2011) 2559–2563;
(b) G.K.S. Prakash, C. Ni, F. Wang, Z. Zhang, R. Haiges, G.A. Olah, Angew. Chem. Int. Ed. 52 (2013) 10835–10839.
[10] (a) Y. Ji, T. Brueckl, R.D. Baxter, Y. Fujiwara, I.B. Seiple, S. Su, D.G. Blackmond, P.S. Baran, Proc. Natl. Acad. Sci. U.S.A. 108 (2011) 14411–14415;
(b) Q. Zhou, J. Gui, C.-M. Pan, E. Albone, X. Cheng, E.M. Suh, L. Grasso, Y. Ishihara, P.S. Baran, J. Am. Chem. Soc. 135 (2013) 12994–12997;
(c) Q. Zhou, A. Ruffoni, R. Gianatassio, Y. Fujiwara, E. Sella, D. Shabat, P.S. Baran, Angew. Chem. Int. Ed. 52 (2013) 3949–3952.
[11] (a) Y. Li, J. Liu, L. Zhang, L. Zhu, J. Hu, J. Org. Chem 72 (2007) 5824–5827;
(b) Y. Li, H. Li, J. Hu, Tetrahedron 65 (2009) 478–483.
[12] G.K.S. Prakash, J. Hu, Y. Wang, G.A. Olah, Org. Lett. 6 (2004) 4315–4317.
[13] (a) K. Nozaki, K. Oshima, K. Uchimoto, J. Am. Chem. Soc. 109 (1987) 2547–2549;
(b) C. Ollivier, P. Renaud, Chem. Rev. 101 (2001) 3415–3434.