Brief Communication

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.6b02723 • Publication Date (Web): 03 Dec 2016

Nucleophilic 1,1-difluoroethylation with fluorinated phosphonium salt

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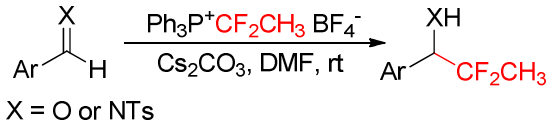


The fluorinated phosphonium salt ($Ph_3P^+CF_2CH_3$ BF_4^-) was shown to act as a nucleophilic 1,1-difluoroethylation agent to enable difluoroethylation of aldehydes and imines.

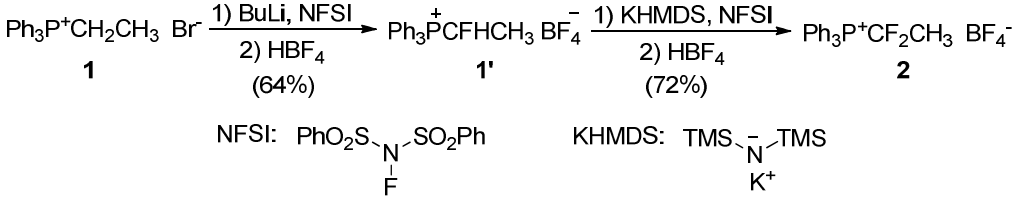
The 1,1-difluoroethyl group (CF_2CH_3) has proved to be a valuable pharmacophore, as it is not only an isostere of a methoxy group, but may also improve the bioactivity of the target molecules.[1] Consequently, significant efforts have been directed towards the exploration of general methods for the incorporation of this functionality. The traditional methods such as deoxyfluorination of carbonyl compounds suffer from harsh reaction conditions and a narrow substrate scope.[2] C-H fluorination is an operationally simple

approach for the installation of CF_2CH_3 moiety,[3] and fluorination of terminal alkynes can also smoothly construct the CF_2CH_3 group.[4] Direct difluoroethylation may serve as an efficient alternative to the fluorination strategies, but the studies in this area remains largely unexplored. Baran and co-workers disclosed that sodium difluoroethylsulfinate ($CH_3CF_2SO_2Na$) could be successfully applied to radical difluoroethylation reactions.[5] Although CH_3CF_2Br was found to be able to undergo difluoroethylation with aryl Grignard agents catalyzed by cobalt complex, the high volatility of CH_3CF_2Br results in operational inconveniences.[6] Recently, it was found that $TMSCF_2CH_3$ was an effective nucleophilic difluoroethylation agent,[7] but this agent is volatile and its synthesis requires a multi-step procedure. Therefore, the development of mild protocols for 1,1-difluoroethylation is still highly desirable.

Phosphonium salts have played an increasingly important role in a variety of research areas. The positively charged phosphorus increases the acidity of the adjacent C-H bond due to an inductive effect, and can readily interact with a counter anion because of Coulombic interaction. Therefore, phosphonium salts have been widely used as ylide precursors,[8] phase-transfer catalysts,[9] Lewis-acid catalysts,[10] and so on. Apparently, these successful applications of phosphonium salts arise from the high electrophilicity of the cation. From this high electrophilicity it may be inferred that the cation or a substituent on the cation cannot act as a nucleophile to construct C-C bond. However, we recently discovered that a substituent on the phosphorus can be turned into a

nucleophile, a process which was developed as a synthetic tool to carry out arylation[11] and difluoromethylation[12] reactions. The unprecedented findings opened up new perspectives for the chemistry of phosphonium salts, and prompted us to develop their applications further. We found that 1,1-difluoroethyl phosphonium salt ($Ph_3P^+CF_2CH_3$ BF_4^-) can be used as a nucleophilic difluoroethylation agent to enable difluoroethylation of aldehydes and imines.[13] The preliminary results are described herein.

Phosphonium salt **2** ($Ph_3P^+CF_2CH_3$ BF_4^-) could be readily prepared from ethyl phosphonium salt **1** by a stepwise fluorination process (Scheme 1). Salt **2** is shelf-stable and could be purified simply by washing with organic solvents, allowing for its easy access.

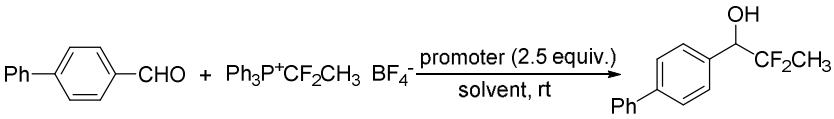


Scheme 1. The preparation of 1,1-difluoroethyl phosphonium salt **2**

With a reliable approach for the synthesis of salt **2** established, optimization of difluoroethylation of aldehyde **3a** with salt **2** was conducted as shown in Table 1. As it has been previously shown that Cs_2CO_3 was a suitable promoter for the nucleophilic reactions with phosphonium salts,[11-12] the effect of Cs_2CO_3 was firstly examined in our initial attempts at this difluoroethylation conversion. To our delight, the product was given by using THF as the solvent albeit in a low yield (Table 1, entry 1). A brief survey of the reaction solvents (Table 1, entries 2-6) revealed that a higher yield could be obtained in DMF (entry 6).

Interestingly, the slow addition of a solution of salt **2** instead of adding the agent in one portion significantly increased the yield to 90% (entry 7 vs. entry 6), which was similar to our previous observations.[11-12] A series of other promoters were also screened, but no better results were obtained (Table 1, entries 8-11 vs. 7). Increasing the reaction scale did not lead to a decrease in the yield (Table 1, entry 12 vs. 7).

Table 1. Screening reaction conditions[a]

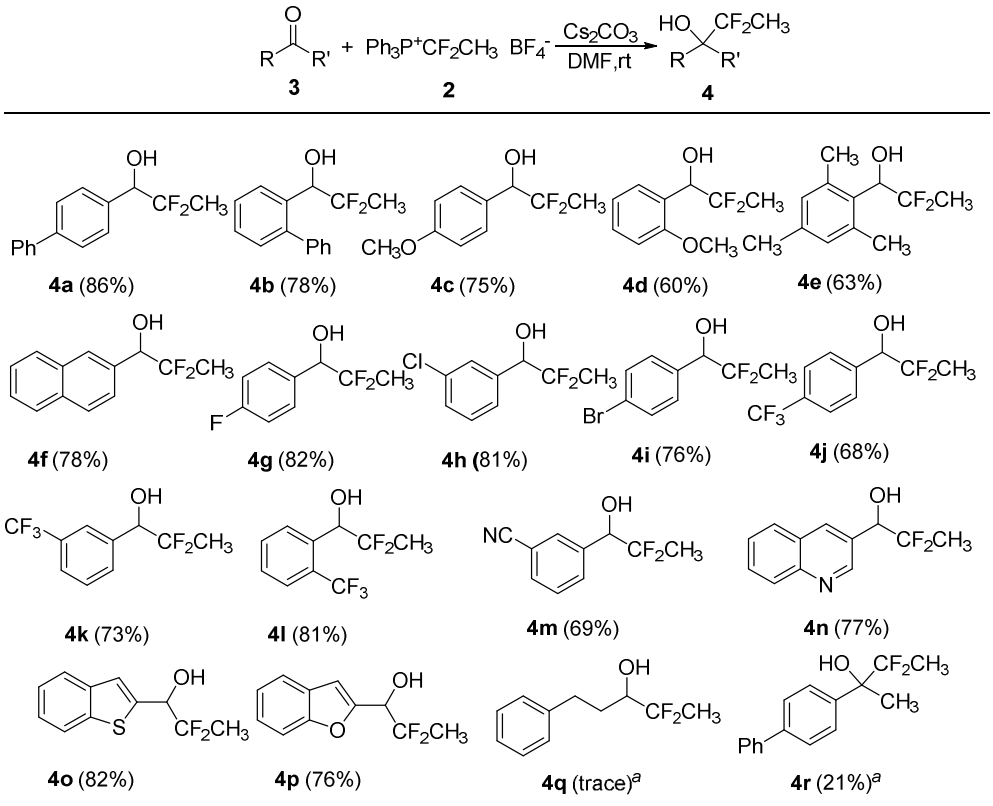


3a (0.2 mmol) **2** (0.4 mmol) **4a**

Entry	solvent	promoter	**4a**, yield (%)[b]
1	THF	Cs_2CO_3	28
2	Cyclohexane	Cs_2CO_3	4
3	Toluene	Cs_2CO_3	0
4	EtOAc	Cs_2CO_3	23
5	CH_3CN	Cs_2CO_3	8
6	DMF	Cs_2CO_3	56
7[c]	DMF	Cs_2CO_3	90
8[c]	DMF	K_2CO_3	49
9[c]	DMF	AcOCs	31
10[c]	DMF	$PhCO_2K$	17
11[c,d]	DMF	CsF	43
12[c,e]	DMF	Cs_2CO_3	90

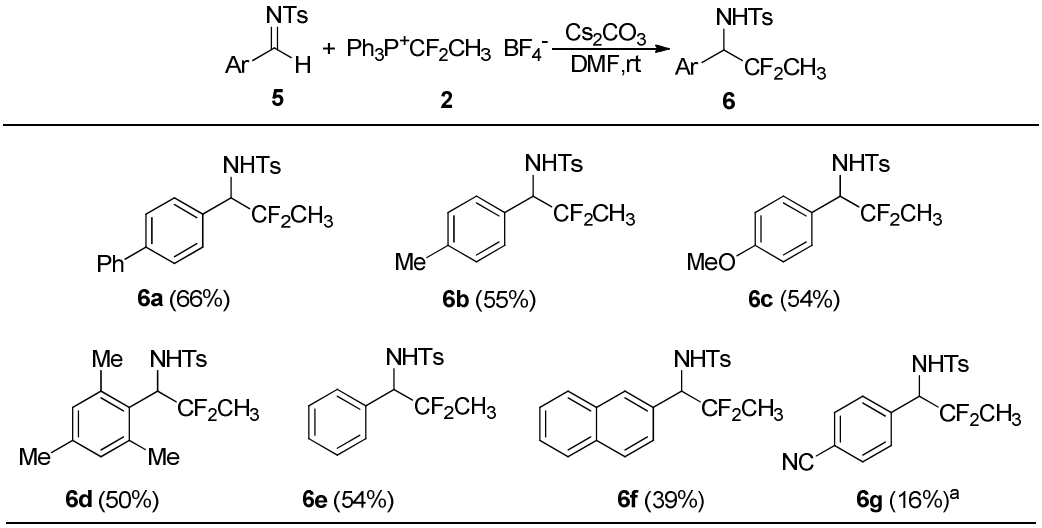
[a]Conditions: **3a** (0.2 mmol), salt **2** (0.4 mmol) and promoter (2.5 equiv) in solvent at rt for 2 h; [b]Determined by ^{19}F NMR by using $PhCF_3$ as an internal standard; [c]A solution of salt **2** in DMF (1 mL) was added slowly into the solution of **3a** and promoter in DMF (1 mL) in 30 min; [d]5 equiv of CsF was used; [e]The reaction scale was increased to 0.5 mmol (substrate **3a**).

With the optimized reaction conditions in hand (Table 1, entry 7)，we then investigate the substrate scope for the nucleophilic difluoroethylation of carbonyls with salt **2**. As shown in Scheme 2, the examination of electronic effects showed that neither the electron-donating groups nor the electron-withdrawing groups had side effects for the conversion of aryl aldehydes (**4a-4m**). The transformation was moderately sensitive to steric effects, as evidenced by the moderate yield of **4e**. Heteroaryl aldehydes were also well tolerated and could be converted smoothly into the expected products in good yields (**4n**–**4p**). Enolizable aldehyde was found to be inert towards difluoroethylation under these reaction conditions (**4q**). For the conversion of ketone, the yield was decreased dramatically (**4r**). Due to the lower reactivity of aliphatic aldehyde and ketone, the corresponding difluoroethylation products (**4q-4r**) were obtained in very low yields. The attempts to increase their yields by reoptimizing the reaction conditions such as increasing the loading of reagent or elevating the reaction temperature were not successful.



Scheme 2. Substrate scope for the difluoroethylation of carbonyls. Isolated yields; [a]The yields were determined by ^{19}F NMR.

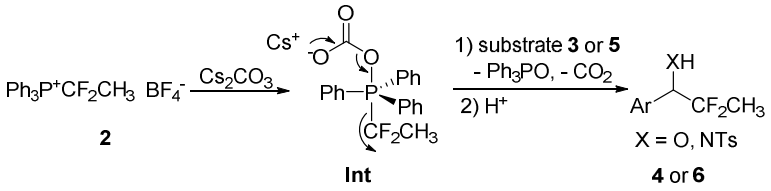
The successful conversion of aryl aldehydes encouraged us to examine the difluoroethylation of imines. Compared with aldehydes, *N*-Ts imines exhibited lower reactivity and only moderate yields were obtained (Scheme 3). The substrates containing electron-donating groups could be well converted (**6a-6f**). Although it may be expected that the aryl substrates containing electron-withdrawing group might be well transformed due to their higher electrophilicity, the difluoroethylation of 4-cyano phenyl imine gave the desired product only in a very low yield (**6g**). That should be partially because the substrate would readily undergo hydrolysis with cesium carbonate under these reaction conditions.



Scheme 3. Substrate scope for the difluoroethylation of imines. Isolated yields. [a]The yield was determined by ^{19}F NMR.

On the basis of above results and our previous studies towards nucleophilic reactions with phosphonium salts,[11-12] the difluoroethylation conversion is proposed to occur through initial attack of Cs_2CO_3 at phosphonium salt **2** (Scheme 4). Since the attack of a nucleophile at the positively charged phosphorus would usually be along the axial direction and the subsequent pseudorotation would place the electronegative substituent in the other axial position,[14] the trigonal bipyramidal phosphorus species **Int** would be readily generated from this nucleophilic addition process. Intermediate **Int** is highly reactive and its decarboxylation would occur rapidly, giving Ph_3PO and resulting in the cleavage of P-CF_2 bond. The bond breaking may proceed concurrently with the nucleophilic addition of CH_3CF_2 group to the substrate. Hydrolysis gives the final product. Considering that cyano group (in **4m** in Scheme 2) was compatible with the reaction conditions, we believe that the free $CH_3CF_2^-$ ion may not be produced. The proposed mechanism was

further supported by the almost full conversion of salt **2** into Ph_3PO detected by ^{31}P NMR spectroscopy, the observation of CH_3CF_2H and $CH_3CF_2CO_2^-$ determined by ^{19}F NMR spectroscopy. CH_3CF_2H and $CH_3CF_2CO_2^-$ should be formed via the nucleophilic attack of CH_3CF_2 moiety in **Int** at proton or CO_2, respectively.



Scheme 4. Proposed reaction mechanism

Conclusions

In summary, we have disclosed that 1,1-difluoroethyl phosphonium salt ($Ph_3P^+CF_2CH_3$ BF_4^-) can be successfully applied to 1,1-difluoroethylation of aldehydes and imines under mild conditions. This phosphonium salt is shelf stable and easy to access, and therefore is reasonably expected to become an efficient 1,1-difluoroethylation agent. This work offers new opportunities to explore valuable applications of phosphonium salts in the chemistry of C-C bond construction. The strategy for nucleophilic fluoroalkylation with phosphonium salts may find synthetic utility in other research areas.

Experimental Section

All solvents were obtained from commercial available and were extra dry grade. All glassware used was dried in a 120°C oven and cooled in a desiccator before use. High resolution mass data were recorded on a high resolution mass spectrometer in

the EI or ESI mode. ^{1}H, ^{19}F, ^{31}P and ^{13}C NMR spectra were recorded on a 400 MHz NMR or 500 MHz NMR spectrometer. ^{1}H NMR and ^{13}C NMR chemical shifts were determined relative to internal $(CH_3)_4Si$ (TMS) at δ 0.0 ppm. ^{19}F NMR chemical shifts were determined relative to internal $CFCl_3$ at 0.0 ppm. ^{31}P NMR chemical shifts were determined relative to internal H_3PO_4 at 0.0 ppm.

The procedure for the synthesis of 1,1-difluoroethyl phosphonium salt:

(1) The synthesis of ethyl phosphonium salt **1**:

Under N_2 atmosphere, the mixture of Ph_3P (8.5 g, 33 mmol), EtBr (3.3 g, 30 mmol) and p-xylene (20 mL) was stirred at 110 ^{o}C for 3 h. The mixture was cooled to room temperature. After filtration, the residue was washed with dry Et_2O (60 mL) and then dried under reduced pressure to afford the pure product.

Ethyl triphenylphosphonium bromide (**1**)[15]: 7.1g, 63% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 - 7.72 (m, 9H), 7.65 (td, *J* = 8.1, 3.5 Hz, 6H), 3.84 - 3.74 (m, 2H), 1.34 (dt, *J* = 20.1, 7.4 Hz, 3H). ^{31}P NMR (162 MHz, $CDCl_3$) δ 26.28 (s, 1P).

(2) The synthesis of 1-fluoroethyl phosphonium salt **1'**:

Under argon atmosphere, into the mixture of **1** (3.9 g, 10 mmol) and THF (16 mL) at 0 ^{o}C was added the solution of BuLi (2.5 M, 11 mmol) in hexane (4.4 mL) dropwise via a syringe for 30 min. Upon the completion of addition, the resulting mixture was warmed to room temperature and was further stirred for 30 min to give the phosphonium ylide ($Ph_3P^{+}CH^{-}Me$). The solution of this ylide was stored in ice bath before use.

Under argon atmosphere, into the solution of NFSI (*N*-fluoro-dibenzene-sulfonimide) (10.6 g, 33 mmol) in THF (30 mL) at 0 ^{o}C was added slowly the solution of the phosphonium ylide in 30 min. Upon the completion of addition, the resulting mixture was warmed to room temperature and was further stirred for 30 min. The reaction mixture was then poured into the aqueous solution of HBF_4 (1 M, 100 mL), and extracted with CH_2Cl_2 (50 mL X 6). The combined organic phase was concentrated to afford a viscous liquid. Enough Et_2O (500 mL) was added into the liquid to precipitate the crude product, which was contaminated by NFSI, salt **1** and salt **2**. After filtration, the solid was dissolved in CH_2Cl_2 (20 mL) to give a saturated solution. Enough Et_2O (500 mL) was added into the solution to precipitate the product. The solid was collected by filtration. The dissolving-precipitate process by CH_2Cl_2/Et_2O was repeated once more to afford a solid. The solid was dissolved in CH_2Cl_2 (about 20 mL) to give a saturated solution. The solutions was stirred at 80 ^{o}C and ethyl acetate (EA, 200 mL) was added slowly to precipitate the crude product. The crude product was collected by filtration. This dissolving-precipitate process by CH_2Cl_2/EA was repeated for 3-4 times until the product was pure detected by ^{31}P NMR. The product was then dissolved in CH_2Cl_2 (80 mL), and the solution was then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by concentration to give the pure product as a white solid (64%).

1-Fluoroethyl triphenylphosphonium tetrafluoroborate (**1'**): 2.67 g. 64% yield, white solid. M.P.: 155 - 156 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (td, *J* = 7.2, 1.6 Hz, 3H), 7.78 - 7.67 (m, 12H), 6.98 - 6.78 (m, 1H), 1.91 - 1.72 (m, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -152.89 (s, 1F),

-152.95 (s, 3F), -193.71 (ddq, J = 69.6, 43.7, 25.9 Hz, 1F). ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.28 (d, J = 69.6 Hz, 1P). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 136.0 (d, J = 2.4 Hz), 134.2 (d, J = 9.7 Hz), 130.8 (d, J = 12.7 Hz), 114.7 (d, J = 84.2 Hz), 86.1 (dd, J = 191.7, 64.5 Hz), 16.4 (d, J = 21.1 Hz). IR(KBr): 3066, 2967, 1587, 1486, 1382, 1320, 1283, 1193, 1168, 1113, 1060, 997, 887, 754, 728, 711, 690, 541, 526, 498 cm^{-1}. HRMS (ESI): calcd. for $[C_{20}H_{19}FP]^+$ $[M - BF_4^-]^+$ 309.1203, found 309.1203.

(3) The synthesis of 1,1-difluoroethyl phosphonium salt **2**:

Under argon atmosphere, into the mixture of salt **1'** (3.96 g, 10 mmol) and THF (40 mL) at -78 ^oC was added dropwise the solution of KHMDS [Potassium bis(trimethylsilyl)amide] (1.0 M, 15 mmol) in THF (15 mL) via a syringe for 30 min. Upon the completion of addition, the resulting mixture was further stirred at 0 ^oC until the solid disappeared (about 20 min) to give the fluorinated phosphonium ylide ($Ph_3P^+CF^-Me$). The solution of this ylide was unstable and needed to be stored at -78 ^oC before use.

Under argon atmosphere, into the solution of NFSI (14.2 g, 45 mmol) in THF (40 mL) at 0 ^oC was added the solution of the fluorinated ylide slowly in 30 min. Upon the completion of addition, the resulting mixture was warmed to room temperature and was further stirred for 10 min. The reaction mixture was then poured into the aqueous solution of HBF_4 (200 mL), and extracted with CH_2Cl_2 (50 mL X 6). The combined organic phase was concentrated to afford a viscous liquid. Enough Et_2O (500 mL) was added into the liquid to precipitate the crude product, which was contaminated by NFSI and salt **1'**. After filtration under air atmosphere, the solid was

dissolved in CH_2Cl_2 (about 20 mL) to give a saturated solution. Enough Et_2O (500 mL) was added into the solution to precipitate the product. The solid was collected by filtration under air atmosphere. The dissolving-precipitate process by CH_2Cl_2/Et_2O was repeated once more to afford a solid. The solid was dissolved in CH_2Cl_2 (about 20 mL) to give a saturated solution. The solutions was stirred at 80 ^oC and EA (200 mL) was added slowly to precipitate the crude product. The crude product was collected by filtration. This dissolving-precipitate process by CH_2Cl_2/EA was repeated for 3-4 times until the product was pure detected by ^{31}P NMR. The product was then dissolved in CH_2Cl_2 (100 mL), and the solution was then dried over anhydrous $MgSO_4$. After filtration, the solvent was removed by concentration to give the pure product as a white solid (3.0 g, 72%).

1,1-difluoroethyl triphenylphosphonium tetrafluoroborate (**2**): 3.0 g, 72% yield, white solid. M.P.: 153 - 154 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (t, J = 7.3 Hz, 3H), 7.84 - 7.70 (m, 12H), 2.19 [td, J = 21.8 (CH_3-CF_2), 9.7 Hz, 3H]. ^{19}F NMR (376 MHz, $CDCl_3$) δ -86.85 (dq, J = 95.8, 21.8 Hz, 2F), -153.27 (s, 1F), -153.33 (s, 3F). ^{31}P NMR (162 MHz, $CDCl_3$) δ 25.15 (t, J = 95.8 Hz, 1P). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 136.9 (d, J = 3.2 Hz), 134.6 (d, J = 10.3 Hz), 131.3 (d, J = 13.1 Hz), 124.0 (td, J = 270.4, 92.4 Hz), 112.3 (d, J = 83.5 Hz), 22.7 (dt, J = 36.2, 18.1 Hz). IR(KBr): 3069, 1587, 1485, 1441, 1389, 1284, 1142, 1109, 1055, 997, 936, 899, 753, 729, 689, 544, 526, 494 cm^{-1}. HRMS (ESI): calcd. For $[C_{20}H_{18}F_2P]^+$ [M - BF_4^-]$^+$ 327.1105, found 327.1105.

General procedure for 1,1-difluoroethylation of aldehydes and imines

In a glove box, into a 25 mL Schlenk tube were added substrate (0.5 mmol), Cs_2CO_3 (407.3 mg, 1.25 mmol) and DMF (1 mL). The tube was sealed and then taken out from the glove box. Into this mixture under argon atmosphere at room temperature, the solution of **2** (414 mg, 1.0 mmol) in DMF (2.0 mL) was added dropwise via a syringe for 30 min. Upon the completion of addition, the resulting mixture was further stirred at the same temperature for 10 minutes. The reaction was quenched by 3 N HCl (0.5 mL). The resulting mixture was diluted with water (40 mL) and extracted with DCM (4 × 40 mL). The combined organic phase was dried over Na_2SO_4. After filtration, the solvent was removed by concentration, and the residue was subjected to column chromatography (ethyl acetate and petroleum ether as the eluent) to afford the pure product.

1-([1,1'-biphenyl]-4-yl)-2,2-difluoropropan-1-ol (**4a**): 106.3 mg, 86% yield, white solid. M.P.: 89 -90 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 - 7.58 (m, 4H), 7.52 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.4 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 4.91 (td, J = 9.5, 3.8 Hz, 1H), 2.48 (d, J = 3.8 Hz, 1H), 1.58 (t, J = 18.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.66 ((ABq)qd, δ_{AB} = 267.0 Hz, J_{AB} = 241.9 Hz, J = 18.8, 9.5 Hz, 2F). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 141.6 (s), 140.6 (s), 135.6 (s), 128.9 (s), 127.7 (s), 127.5 (s), 127.2 (s, Hz), 127.1 (s), 123.4 (t, J = 243.1 Hz), 75.6 (t, J = 28.6 Hz), 18.9 (t, J = 26.3 Hz). IR(KBr): 3612, 3457, 2922, 1489, 1449, 1394, 1232, 1186, 1126, 1058, 964, 924, 845, 802, 759, 738, 692, 610, 592, 524, 497 cm^{-1}. HRMS (EI): calcd. for $[C_{15}H_{14}OF_2]$ $[M^+]$ 248.1007, found 248.1008.

1-([1,1'-biphenyl]-2-yl)-2,2-difluoropropan-1-ol (**4b**): 93.4 mg, 78% yield, colorless oil. M.P.: 49 - 50 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.4 Hz, 1H), 7.45 - 7.33 (m, 5H), 7.30 (d, J = 7.3 Hz, 2H), 7.25 (d, J = 7.4 Hz, 1H), 4.96 (dd, J = 11.8, 10.2 Hz, 1H), 2.13 (br, 1H), 1.42 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.67 ((ABq)qd, δ_{AB} = 609.2 Hz, J_{AB} = 244.3 Hz, J = 18.8, 10.2 Hz, 2F). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 142.8 (s), 140.8 (s), 134.5 (s), 130.3 (s), 129.4 (s), 128.5 (s), 128.3 (s), 127.9 (s), 127.5 (s), 127.4 (s), 123.3 (t, J = 244.0 Hz), 71.8 (t, J = 27.2 Hz), 20.4 (t, J = 26.4 Hz). IR(KBr): 3430, 3060, 3026, 2930, 1597, 1480, 1439, 1389, 1285, 1236, 1184, 1129, 1110, 1057, 1047, 1009, 925, 878, 850, 775, 755, 704, 658, 612, 592, 573, 537 cm^{-1}. HRMS (EI): calcd. for [$C_{15}H_{14}OF_2$] [M^+] 248.1007, found 248.1012.

2,2-difluoro-1-(4-methoxyphenyl)propan-1-ol (**4c**): 82.4 mg, 75% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 4.78 (t, J = 9.6 Hz, 1H), 3.80 (s, 3H), 2.44 (br, 1H), 1.49 (t, J = 18.9 Hz, 3H).^{19}F NMR (376 MHz, $CDCl_3$) δ -101.11 (qd, J = 18.9, 9.6 Hz, 2F). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.8 (s), 128.9 (s), 128.5 (s), 123.4 (t, J = 242.9 Hz), 113.8 (s), 75.4 (t, J = 28.8 Hz), 55.3 (s), 18.9 (t, J = 26.4 Hz). IR(KBr): 3462, 3005, 2920, 2841, 1614, 1587, 1516, 1465, 1444, 1391, 1305, 1251, 1177, 1127, 1068, 1032, 963, 924, 859, 839, 802, 789, 774, 645, 628, 616, 571, 520 cm^{-1}. HRMS (EI): calcd. for [$C_{10}H_{12}O_2F_2$] [M^+] 202.0800, found 202. 0807.

2,2-difluoro-1-(2-methoxyphenyl)propan-1-ol (**4d**): 71.0 mg, 60% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 6.98

(t, J = 7.6 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 5.13 (td, J = 11.1, 6.7 Hz, 1H), 3.85 (s, 3H), 3.26 (d, J = 6.7 Hz, 1H), 1.57 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.51 ((ABq) qd, δ_{AB} = 364.5 Hz, J_{AB} = 241.8 Hz, J = 18.9, 11.1 Hz, 2F)). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 157.3 (s), 129.7 (s), 129.2 (s), 124.9 (s), 123.4 (t, J = 244.1 Hz), 120.9 (s), 111.1 (s), 75.4 (t, J = 28.8 Hz), 55.6 (s), 20.0 (t, J = 26.4 Hz). IR(KBr): 3444, 3006, 2945, 2841, 1603, 1589, 1494, 1465, 1441, 1390, 1289, 1245, 1185, 1128, 1050, 1026, 962, 924, 853, 814, 785, 757, 734, 658, 608, 581, 566, 506 cm^{-1}. HRMS (EI): calcd. for $[C_{10}H_{12}O_2F_2]$ $[M^+]$ 202.0800, found 202.0800.

2,2-difluoro-1-mesitylpropan-1-ol (**4e**): 68.8 mg, 63% yield, white solid. M.P.: 49 - 50 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 2H), 5.31 (td, J = 11.3, 4.6 Hz, 1H), 2.43 (s, 6H), 2.28 (d, J = 4.6 Hz, 1H), 2.25 (s, 3H), 1.68 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.31 ((ABq)qd, δ_{AB} = 614.4 Hz, J_{AB} = 245.4 Hz, J = 18.9, 11.3 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 137.8 (s), 129.6 (s) , 124.40 (s), 124.39 (t, J = 243.4 Hz), 73.7 (dd, J = 30.0, 28.1 Hz), 21.3 (t, J = 3.3 Hz), 21.0 (s), 20.7 (s). IR(KBr): 3462, 3004, 2925, 1611, 1576, 1450, 1387, 1232, 1186, 1124, 1068, 1022, 954, 938, 917, 853, 821, 791, 727, 645, 635, 587, 522 cm^{-1}. HRMS (EI): calcd. for $[C_{12}H_{16}OF_2]$ $[M^+]$ 214.1164, found 214.1163.

2,2-difluoro-1-(naphthalen-2-yl)propan-1-ol (**4f**): 86.6 mg, 78% yield, white solid. M.P.: 53 – 54 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.88 - 7.81 (m, 3H), 7.54 (d, J = 8.6 Hz, 1H), 7.52 - 7.46 (m, 2H), 5.02 (td, J = 9.5, 3.7 Hz, 1H), 2.55 (d, J = 3.7 Hz, 1H), 1.52 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.18 - -100.41 (m, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 134.2 (s), 133.5 (s), 133.0 (s),

128.2(s), 128.1 (s), 127.7 (s), 126.7 (s), 126.5 (s), 126.4 (s), 124.8 (s), 123.5 (t, J = 243.3 Hz), 75.9 (t, J = 28.8 Hz), 19.0 (t, J = 26.3 Hz). IR(KBr): 3442, 3059, 3007, 2923, 1602, 1509, 1442, 1391, 1365, 1271, 1236, 1190, 1123, 1067, 963, 927, 886, 861, 824, 805, 758, 744, 654, 564, 545, 501, 480 cm^{-1}. HRMS (EI): calcd. for $[C_{13}H_{12}OF_2]$ $[M^+]$ 222.0851, found 222.0861.

2,2-difluoro-1-(4-fluorophenyl)propan-1-ol (**4g**): 79.6 mg, 82% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 8.3, 5.6 Hz, 2H), 7.05 (t, J = 8.3 Hz, 2H), 4.82 (t, J = 9.6 Hz, 1H), 2.14 (s, 1H), 1.48 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.93 ((ABq)qd, δ_{AB} = 219.1 Hz, J_{AB} = 247.8 Hz, J = 18.9, 9.6 Hz, 2F), -113.35 – -113.47 (m, 1F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.9 (d, J = 247.1 Hz), 132.4 (s), 129.0 (d, J = 8.2 Hz), 123.2 (t, J = 243.0 Hz), 115.3 (d, J = 21.6 Hz), 75.1 (t, J = 29.2 Hz), 18.7 (t, J = 26.3 Hz). IR(KBr): 3442, 2992, 1607, 1514, 1393, 1228, 1129, 1068, 927, 844, 804, 562 cm^{-1}. HRMS (EI): calcd. for $[C_9H_9OF_3]$ $[M^+]$ 190.0600, found 190.0607.

1-(3-chlorophenyl)-2,2-difluoropropan-1-ol (**4h**): 83.8 mg, 81% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.35 - 7.25 (m, 3H), 4.81 (t, J = 9.2 Hz, 1H), 2.37 (br, 1H), 1.49 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.42 ((ABq)qd, δ_{AB} = 356.60 Hz, J_{AB} = 249.1 Hz, J = 18.9, 9.2 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 138.6 (d, J = 4.3 Hz), 134.4 (s), 129.6 (s), 128.8 (s), 127.4 (s), 125.5 (s), 123.1 (t, J = 242.7 Hz), 75.0 (dd, J = 28.7, 29.8 Hz), 18.7 (t, J = 26.2 Hz). IR(KBr): 3589, 3437, 3071, 3007, 2923, 1600, 1576, 1475, 1432 , 1392, 1288, 1234,

1188, 1129, 1102, 1063, 964, 929, 819, 803, 776, 728, 707, 692, 656, 595, 514, 480 cm^{-1}. HRMS (EI): calcd. for $[C_9H_9ClOF_2]$ $[M^+]$ 206.0305, found 206.0309.

1-(4-bromophenyl)-2,2-difluoropropan-1-ol (**4i**): 95.4 mg, 76% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 4.81 (t, J = 9.4 Hz, 1H), 2.47 (s, 1H), 1.48 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.65 ((ABq)qd, δ_{AB} = 333.9 Hz, J_{AB} = 246.8 Hz, J = 18.9, 9.4 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 135.6 (dd, J = 1.3, 4.4 Hz), 131.5 (s), 128.9 (t, J = 1.4 Hz), 123.1 (t, J = 244.0 Hz), 122.8 (s), 75.1 (dd, J = 28.4, 29.9 Hz), 18.6 (t, J = 26.3 Hz). IR(KBr): 3589, 3435, 3006, 2924, 2853, 1595, 1488, 1392, 1234, 1187, 1128, 1074, 1012, 964, 927, 849, 836, 794, 779, 634, 622, 599, 564, 551, 502 cm^{-1}. HRMS (EI): calcd. for $[C_9H_9BrOF_2]$ $[M^+]$ 249.9799, found 249.9804.

2,2-difluoro-1-(4-(trifluoromethyl)phenyl)propan-1-ol (**4j**): 82.6 mg, 68% yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.3 Hz, 2H), 7.56 (d, J = 8.2 Hz, 2H), 4.90 (t, J = 9.2 Hz, 1H), 2.68 (br, 1H), 1.48 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.75 (s, 3F), -100.32 ((ABq)qd, δ_{AB} = 522.3 Hz, J_{AB} = 250.3 Hz, J = 18.9, 9.2 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.5 (s), 130.9 (q, J = 32.5 Hz), 127.6 (s), 125.2 (q, J = 3.8 Hz), 124.0 (q, J = 273.4 Hz), 123.0 (t, J = 243.4 Hz), 75.1 (t, J = 29.4 Hz), 18.6 (t, J = 26.2 Hz). IR(KBr): 3608, 3447, 2924, 2361, 2341, 1622, 1420, 1394, 1327, 1234, 1167, 1126, 1068, 1019, 956, 929, 851, 788, 804, 766, 734, 679, 623, 609, 501 cm^{-1}. HRMS (EI): calcd. for $[C_{10}H_9OF_5]$ $[M^+]$ 240.0568, found 240.0570.

2,2-difluoro-1-(3-(trifluoromethyl)phenyl)propan-1-ol (**4k**): 88.5 mg, 73% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.49 (t, *J* = 8.0 Hz, 1H), 4.91 (t, *J* = 9.0 Hz, 1H), 2.40 (br, 1H), 1.49 (t, *J* = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.71 (s, 3F), -100.47 ((ABq)qd, δ_{AB} = 532.2 Hz, J_{AB} = 248.4 Hz, *J* = 18.9, 9.0 Hz, 2F). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 137.6 (d, *J* = 4.6 Hz), 130.8 (q, *J* = 32.5 Hz), 130.7 (s), 128.8 (s), 125.5 (q, *J* = 3.7 Hz), 124.1 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 272.4 Hz), 123.0 (t, *J* = 244.4 Hz), 75.1 (dd, *J* = 30.1, 29.0 Hz), 18.6 (t, *J* = 26.2 Hz). IR(KBr): 3603, 3439, 3011, 2923, 1619, 1494, 1451, 1394, 1330, 1234, 1167, 1127, 1075, 1003, 965, 928, 813, 193, 758, 704, 683, 654, 613, 613, 590, 555, 506 cm^{-1}. HRMS (EI): calcd. for [$C_{10}H_9OF_5$] [M^+] 240.0568, found 240.0578.

2,2-difluoro-1-(2-(trifluoromethyl)phenyl)propan-1-ol (**4l**): 98.1 mg, 81% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.61 (t, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 5.25 (t, *J* = 10.5 Hz, 1H), 2.18 (br, 1H), 1.57 (t, *J* = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.21 (t, *J* = 4.0 Hz, 3F), -101.00 - -102.05 (m, 1F), -102.59 - -103.73 (m, 1F). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 135.6 (s), 132.2 (s), 129.5 (t, *J* = 2.9 Hz), 128.9 (q, *J* = 30.1 Hz), 128.9 (s), 125.8 (q, *J* = 5.8 Hz), 124.1 (q, *J* = 274.5 Hz), 122.5 (t, *J* = 244.5 Hz), 70.8 (tq, *J* = 27.5, 2.6 Hz), 20.6 (t, *J* = 26.4 Hz). IR(KBr): 3604, 3433, 3011, 1894, 1609, 1588, 1457, 1392, 1313, 1235, 1167, 1123, 1070, 1054, 1035, 964, 931, 855, 817, 771, 750, 677, 678, 613, 599 cm^{-1}. HRMS (EI): calcd. for [$C_{10}H_9OF_5$] [M^+] 240.0568, found 240.0576.

3-(2,2-difluoro-1-hydroxypropyl)benzonitrile (**4m**): 66.0 mg, 69% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 4.86 (t, *J* = 9.1 Hz, 1H), 3.14 (br, 1H), 1.48 (t, *J* = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.56 - -99.48 (m, 1F), -101.04 - -101.99 (m, 1F). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5 (s), 132.2 (s), 131.9 (s), 131.0 (s), 129.1 (s), 122.9 (t, *J* = 243.6 Hz), 118.6 (s), 112.3 (s), 74.5 (t, *J* = 29.9 Hz), 18.7 (t, *J* = 26.1 Hz). IR(KBr): 3453, 3007, 2234, 1585, 1484, 1438, 1391, 1275, 1259, 1235, 1190, 1141, 1066, 966, 927, 787, 750, 692, 613, 588, 538 cm^{-1}. HRMS (EI): calcd. for [$C_{10}H_9ONF_2$] [M^+] 197.0647, found 197.0654.

2,2-difluoro-1-(quinolin-3-yl)propan-1-ol (**4n**): 82.6 mg, 77% yield, white solid. M.P.: 126 – 127 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 8.27 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.72 (t, *J* = 7.7 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 5.08 (t, *J* = 9.2 Hz, 1H), 3.49 (br, 1H), 1.57 (t, *J* = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.30 ((ABq)qd, δ_{AB} = 747.1 Hz, J_{AB} = 251.2 Hz,, *J* = 18.9, 9.2 Hz, 2F). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 149.5 (s), 147.4 (s), 135.4 (s), 130.8 (s), 130.1 (s), 128.4 (s), 128.1 (s), 127.6 (s), 127.1 (s), 123.3 (t, *J* = 243.4 Hz), 73.5 (t, *J* = 30.3 Hz), 19.0 (t, *J* = 26.2 Hz). IR(KBr): 3061, 2958, 1991, 1652, 1595, 1391, 1260, 1238, 1187, 1123, 1091, 1014, 964, 919, 818, 775, 758, 616, 593, 550 cm^{-1}. HRMS (EI): calcd. for [$C_{12}H_{11}NOF_2$] [M^+] 223.0803, found 223.0811.

1-(benzo[b]thiophen-2-yl)-2,2-difluoropropan-1-ol (**4o**): 90.9 mg, 82% yield, yellow solid. M.P.: 65 – 66 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 1H), 7.75 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.40 - 7.29 (m, 3H), 5.16 (t, *J* = 9.1 Hz, 1H), 2.60 (br, 1H),

1.63 (t, J = 18.9 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.59 ((ABq)qd, δ_{AB} = 349.4 Hz, J_{AB} = 249.9 Hz, J = 18.9, 9.1 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.0 (s), 139.8 (s), 139.2 (s), 124.7 (s), 124.5 (s), 123.8 (s), 123.2 (s), 122.8 (t, J = 244.3 Hz), 122.4 (s), 73.0 (t, J = 30.6 Hz), 19.0 (t, J = 25.9 Hz). IR(KBr): 3430, 3059, 3000,5, 2924, 1458, 1437, 1391, 1334, 1308, 1260, 1234, 1186, 1126, 1046, 927, 862, 839, 804, 747, 726, 632, 609, 562 cm^{-1}. HRMS (EI): calcd. for [$C_{11}H_{10}OSF_2$] [M^+] 228.0415, found 228.0421.

1-(benzofuran-2-yl)-2,2-difluoropropan-1-ol (**4p**): 81.4 mg, 76% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 6.82 (s, 1H), 4.97 (t, J = 9.4 Hz, 1H), 2.56 (br, 1H), 1.71 (t, J = 18.8 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.89 - -100.84 (m, 1F), -100.95 - -101.88 (m, 1F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.9 (s), 152.3 (s), 127.7 (s), 124.9 (s), 123.2 (s), 122.2 (t, J = 244.4 Hz), 121.4 (s), 111.5 (s), 106.1 (s), 70.9 (t, J = 31.0 Hz), 19.7 (t, J = 26.0 Hz). IR(KBr): 3428, 2992, 1476, 1454, 1393, 1238, 1138, 1061, 1009, 931, 885, 805, 751 cm^{-1}. HRMS (EI): calcd. for [$C_{11}H_{10}O_2F_2$] [M^+] 212.0643, found 212.0644.

N-(1-([1,1'-biphenyl]-4-yl)-2,2-difluoropropyl)-4-methylbenzenesulfonamide (**6a**): 130.6 mg, 66% yield, white solid. M.P.: 188 - 189 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 - 7.31 (m, 9H), 7.12 (d, J = 8.0 Hz, 2H), 7.05 (d, J = 8.0 Hz, 2H), 5.27 (d, J = 8.5 Hz, 1H), 4.59 (td, J = 13.3, 8.5 Hz,, 1H), 2.27 (s, 3H), 1.61 (t, J = 18.7 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.35 - -101.08 (m, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.4 (s), 141.4 (s), 140.3 (s), 137.2 (s), 133.1 (s), 129.3 (s), 128.8 (s), 128.6

(s), 127.6 (s), 127.1 (s), 127.0 (s), 122.3 (t, J = 245.8 Hz), 62.1 (t, J = 26.8 Hz), 21.7 (t, J = 26.4 Hz), 21.4 (s). IR(KBr): 3278, 3035, 2972, 2925, 1920, 1600, 1568, 1489, 1451, 1410, 1389, 1306, 1236, 1192, 1151, 1118, 1083, 1021, 1006, 963, 949, 911, 864, 853, 812, 763, 739, 696, 670, 611571, 552, 544, 511 cm^{-1}. HRMS (ESI): calcd. for $[C_{22}H_{22}O_2NSF_2]$ $[M + H^+]$ 402.1333, found 402.1334.

N-(2,2-difluoro-1-(p-tolyl)propyl)-4-methylbenzenesulfonamide (**6b**): 93.2 mg, 55% yield, white solid. M.P.: 196 - 197 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.2 Hz, 2H), 7.07 (d, J = 8.2 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 8.4 Hz, 2H), 5.24 (d, J = 8.0 Hz, 1H), 4.49 (td, J = 13.0, 8.0 Hz, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 1.54 (t, J = 18.7 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.71 ((ABq)qd, δ_{AB} = 613.7 Hz, J_{AB} = 244.3 Hz, J = 18.7, 13.0 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.3 (s), 138.4 (s), 137.3 (s), 131.3 (s), 129.3 (s), 129.1 (s), 128.0 (s), 127.1 (s), 122.3 (t, J = 245.0 Hz), 62.1 (dd, J = 25.6, 27.4 Hz), 21.6 (t, J = 26.3 Hz), 21.4 (s), 21.1 (s). IR(KBr): 3269, 3041, 3008, 2981, 1922, 1741, 1598, 1519, 1496, 1455, 1389, 1331, 1308, 1287, 1236, 1213, 1194, 1165, 1128, 1090, 1025, 961, 937, 911, 846, 813, 802, 781, 721, 705, 670, 645, 627, 582, 559, 545 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{20}O_2NSF_2]$ $[M + H^+]$ 340.1177, found 340.1177.

N-(2,2-difluoro-1-(4-methoxyphenyl)propyl)-4-methylbenzenesulfonamide (**6c**): 96.0 mg, 54% yield, white solid. M.P.: 156 - 157 ^oC. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 6.99 (d, J = 8.6 Hz, 2H), 6.68 (d, J = 8.6 Hz, 2H), 5.32 (d, J = 8.8 Hz, 1H), 4.49 (td, J = 12.6, 8.8 Hz, 1H), 3.74 (s, 3H), 2.32 (s, 3H), 1.54 (t, J = 18.6 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.84 ((ABq)qd,

δ_{AB} = 618.3 Hz, J_{AB} = 246.6 Hz, J = 18.6, 12.6 Hz, 2F). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.6 (s), 143.2 (s), 137.3 (s), 129.31 (s), 129.28 (s), 127.0 (s), 126.4 (s), 122.4 (t, J = 243.9 Hz), 113.8 (s), 61.8 (dd, J = 25.8, 27.9 Hz), 55.2 (s), 21.5 (t, J = 26.3 Hz), 21.4 (s). IR(KBr): 3279, 3066, 3010, 2978, 2939, 2844, 1616, 1599, 1585, 1519, 1496, 1457, 1390, 1323, 1320, 1285, 1259, 1233, 1198, 1185, 1164, 1128, 1090, 1035, 956, 940, 912, 868, 845, 812, 727, 705, 670, 642, 626, 580, 559, 547 cm^{-1}. HRMS (ESI): calcd. for $[C_{17}H_{20}O_3NSF_2]$ $[M + H^+]$ 356.1126, found 356.1126.

N-(2,2-difluoro-1-mesitylpropyl)-4-methylbenzenesulfonamide (**6d**): 92.1 mg, 50% yield, white solid. M.P.: 160 - 161 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, J = 8.3 Hz, 2H), 7.00 (d, J = 8.3 Hz, 2H), 6.73 (s, 1H), 6.56 (s, 1H), 5.31 (d, J = 9.2 Hz, 1H), 5.24 - 5.06 (m, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.17 (s, 6H), 1.63 (t, J = 18.7 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -93.22 - -94.16 (m, 1F), -94.43 - -95.35 (m, 1F). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 143.2 (s), 137.8 (s), 137.7 (s), 137.0 (s), 136.3 (s), 131.4 (s), 129.3 (s), 129.1 (s), 127.7 (d, J = 2.4 Hz), 126.6 (s), 123.4 (t, J = 245.1 Hz), 58.4 (dd, J = 29.5, 26.0 Hz), 22.2 (t, J = 26.9 Hz), 21.4 (s), 21.2 (s), 21.1 (t, J = 5.9 Hz), 20.7 (s). IR(KBr): 3335, 2971, 1613, 1600, 1577, 1498, 1441, 1386, 1336, 1289, 1230, 1189, 1168, 1148, 1084, 1028, 971, 948, 919, 903, 857, 835, 819, 805, 726, 707, 670, 629, 595, 573, 549 cm^{-1}. HRMS (ESI): calcd. for $[C_{19}H_{24}O_2NSF_2]$ $[M + H^+]$ 368.1490, found 368.1490.

N-(2,2-difluoro-1-phenylpropyl)-4-methylbenzenesulfonamide (**6e**): 88.3 mg, 54% yield, white solid. M.P.: 175 - 176 ^{o}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 2H), 7.24 - 7.14 (m, 3H), 7.08 - 7.04 (m, 4H), 5.24 (d, J = 8.9 Hz, 1H), 4.64 -

4.44 (m, 1H), 2.31 (s, 3H), 1.56 (t, J = 18.7 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.84 ((Abq)qd, δ_{AB} = 522.9 Hz, J_{AB} = 244.8 Hz, J = 18.7, 13.5 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.3 (s), 137.2 (s), 134.3 (d, J = 2.7 Hz), 129.3 (s), 128.5 (s), 128.4 (s), 128.1 (s), 127.0 (s), 122.3 (t, J = 245.0 Hz), 62.3 (dd, J = 27.7, 25.4 Hz), 21.6 (t, J = 26.4 Hz), 21.4 (s). IR(KBr): 3266, 3069, 3013, 2974, 1600, 1497, 1459, 1448, 1389, 1332, 1309, 1269, 1234, 1190, 1166, 1127, 1095, 1070, 936, 953, 911, 861, 831, 813, 752, 703, 676, 643, 580, 558, 548 cm^{-1}. HRMS (ESI): calcd. For $[C_{16}H_{18}O_2NSF_2]$ $[M + H^+]$ 326.1020, found 326.1021.

N-(2,2-difluoro-1-(naphthalen-2-yl)propyl)-4-methylbenzenesulfonamide (**6f**): 74.2 mg, 39% yield, white solid. M.P.: 134 - 135 ^oC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 - 7.72 (m, 1H), 7.67 - 7.61 (m, 2H), 7.49 - 7.38 (m, 5H), 7.20 (d, J = 8.4 Hz, 1H), 6.86 (d, J = 8.0 Hz, 2H), 5.41 (d, J = 6.5 Hz, 1H), 4.74 - 4.63 (m, 1H), 2.09 (s, 3H), 1.61 (t, J = 18.7 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.42 ((ABq)qd, δ_{AB} = 516.3 Hz, J_{AB} = 244.6 Hz, J = 18.7, 13.0 Hz, 2F). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.3 (s), 137.0 (s), 133.0 (s), 132.8 (s), 131.3 (s), 129.1 (s), 128.4 (s), 128.2 (s), 128.0 (s), 127.5 (s), 127.0 (s), 126.5 (s), 126.3 (s), 125.0 (s), 122.4 (t, J = 245.7 Hz), 62.6 (dd, J = 27.9, 25.7 Hz), 21.7 (t, J = 26.2 Hz), 21.2 (s). IR(KBr): 3273, 3062, 3007, 2953, 1921, 1594, 1511, 1492, 1452, 1432, 1395, 1335, 1308, 1270, 1247, 1202, 1165, 1126, 1086, 1040, 1017, 975, 936, 910, 866, 816, 806, 781, 766, 752, 705, 670, 603, 564, 543 cm^{-1}. HRMS (ESI): calcd. for $[C_{20}H_{20}O_2NSF_2]$ $[M + H^+]$ 376.1177, found 376.1175. Elem. Anal. Calcd for $C_{20}H_{19}O_2NSF_2$: C, 63.98; H, 5.10; N, 3.73; F, 10.12; S, 8.54; found C, 63.60; H, 5.13; N, 3.54; F, 10.34; S, 8.59.

N-(1-(4-cyanophenyl)-2,2-difluoropropyl)-4-methylbenzenesulfonamide (**6g**): 16% yield determined by ^{19}F NMR. In order to isolate this product to get the full characterization data, the reaction scale was increased (1.25 mmol of substrate). 54.6 mg, 12%; White solid. M.P.: 152 - 153 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 8.1 Hz, 2H), 7.46 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 6.11 (d, J = 9.2 Hz, 1H), 4.63 (dt, J = 15.1, 9.2 Hz, 1H), 2.36 (s, 3H), 1.61 (t, J = 18.3 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -97.74 - -100.50 (m, 2F).^{13}C NMR (101 MHz, $CDCl_3$) δ 144.0 (s), 139.3 (d, J = 1.7 Hz), 136.7 (s), 132.0 (s), 129.5 (s), 129.1 (s), 126.9 (s), 121.8 (t, J = 249.7 Hz), 118.2 (s), 112.3 (s), 61.8 (dd, J = 29.6, 25.8 Hz), 21.47 (t, J = 26.2 Hz), 21.44 (s). IR (neat) ν = 3271, 1418, 1330, 1235, 1184, 1164, 1089, 911, 668, 585 cm^{-1}; HRMS (ESI) Calcd for $C_{17}H_{15}O_2N_2F_2S$ $[M-H]^-$: 349.0822, Found: 349.0828.

Acknowledgements

We thank National Basic Research Program of China (2015CB931900, 2012CBA01200), the National Natural Science Foundation (21421002, 21472222, 21502214, 21672242), the Chinese Academy of Sciences (XDA02020105, XDA02020106), and the Science and Technology Commission of Shanghai Municipality (15DZ1200102, 14ZR1448800) for financial support.

Supporting Information: Copies of ^{1}H, ^{19}F, ^{31}P and ^{13}C NMR spectra of products.

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