JOC The Journal of Organic Chemistry

Article

Two ligands transfer from Ag to Pd: En Route to (SIPr)Pd(CF2H)(X) and its Application in One-pot C-H Borylation/Difluoromethylation

Haiwei Zhao, Simon Herbert, Tom Kinzel, Wei Zhang, and Qilong Shen

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b03296 • Publication Date (Web): 23 Jan 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Two ligands transfer from Ag to Pd: En Route to (SIPr)Pd(CF_2H)(X) and its Application in One-pot C-H Borylation/Difluoromethylation

Haiwei Zhao,[†] Simon Herbert,[‡] Tom Kinzel,[§] Wei Zhang[⊥] and Qilong Shen[†,*]

[†]*Key Laboratory of Organofluorine Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, P. R. China*

[‡]*Bayer AG, Research & Development, Pharmaceuticals, 178 Müllerstraße, Berlin, 13342, Germany*

[§]*Bayer Pharmaceuticals, Open Innovation Center China, Bayer Center, Bei Dong San Han 27, Beijing 100020, P. R. China*

[⊥]*Centre for Green Chemistry and Department of Chemistry, University of Massachusetts Boston, 100 Morrissey Boulevard, Boston, Massachusetts 02125, United States*

ABSTRACT: A process for the concurrent transfer of both the NHC ligand and difluoromethyl group from [(SIPr)Ag(CF_2H)] to PdX_2 (X = Cl, OAc and OPiv) for the preparation [(SIPr)Pd(CF_2H)X] complexes is described. These complexes were air-stable and easily underwent transmetalation with aryl pinacol boronate/reductive elimination to generate $ArCF_2H$ in high yields. Based on this discovery, the first one-pot C-H borylation and difluoromethylation for the preparation of difluoromethylated (hetero)arenes was developed.

Introduction

Mainly due to its unique physicochemical properties, the difluoromethyl group (-CF_2H) is generally considered by medicinal chemists as one of the privileged functional groups that may bring beneficial effects to the pharmacological and pharmacokinetic properties of lead compounds.[1] 1) The proton in the difluoromethyl group is slightly acidic, which is able to act as hydrogen bonding donor to interact with the targeted protein.[2] It is now commonly accepted that the difluoromethyl group is an isosteric and isopolar functional group to hydroxyl (OH) and thiol (SH) units in drug design;[3] 2) The Hammett constant (σ_p) of the difluoromethyl group is 0.32, which is slightly lower than that of an ester (σ_p = 0.45) but much higher than that of a hydroxy (σ_p = -0.37) or thiol groups (σ_p = 0.15),[4] suggesting that the difluoromethyl group is a moderate electron-withdrawing group. Thus, replacement of hydroxy or thiol groups with difluoromethyl in a drug molecule may effectively decrease its overall electron density potentially preventing its oxidation by cytochrome P450, and consequently, improving the drug

molecule's metabolic stability. These beneficial effects of the difluoromethyl group have promoted organic chemists to develop efficient methods for its incorporation. As a result, in the past few years, numerous difluoromethylative methods for the preparation of difluoromethylated arenes have emerged, especially those mediated with transition metal catalysis (Figure 1).[5]

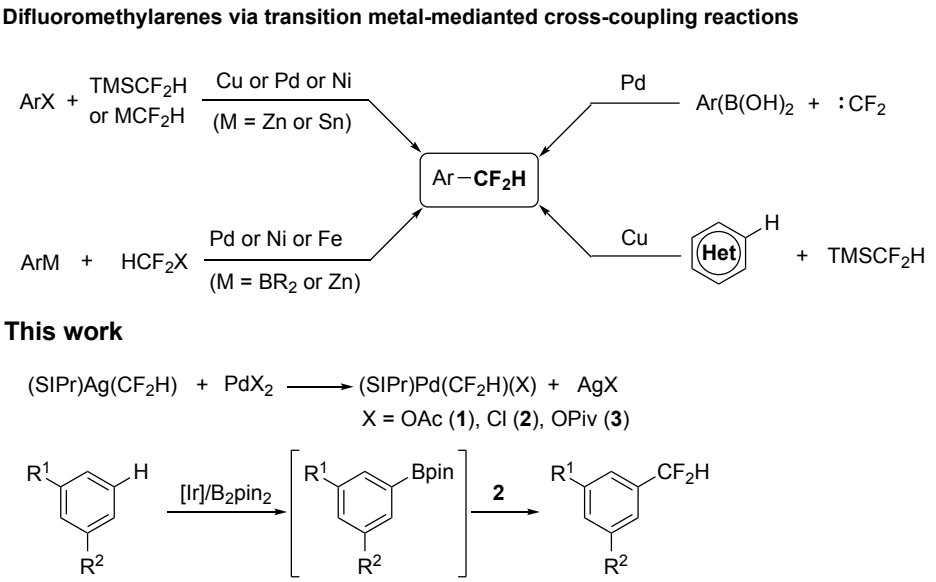


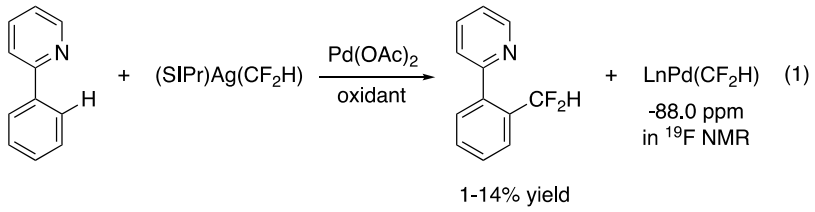
Figure 1. Methods for preparation of difluoromethylarenes via transition metal catalysis.

Among these methods, transition metals including copper,[6] nickel[7] or palladium[8]-mediated or -catalyzed coupling of an aryl halide with a nucleophilic difluoromethyl reagent represents an attractive strategy, with potentially broad applications. For example, in 2014, we reported the first transition metal-catalyzed direct difluoromethylation of aryl bromides/iodides with $TMSCF_2H$ by employing a cooperative bimetallic Pd/Ag catalyst, which could be easily applied in the preparation of many bioactive difluoromethylated arene derivatives.[8a] In addition, by using the key intermediate [(SIPr)Ag(CF_2H)] (SIPr = 1,3-bis(2,6-di*iso*propyl-phenylimidazolin-2-ylidene) as a nucleophilic difluoromethylating reagent, we further developed several Pd-catalyzed difluoromethylation protocols that are able to difluoromethylate a broad scope of aryl electrophiles including aryl chlorides and triflates,[9] heteroaryl chlorides, bromides and iodides.[10] Nevertheless, these methods typically required the use of prefunctionalized arene substrates that limits their applications in the late-stage modification of drug candidates for structure-activity studies. A more efficient and atom-economical difluoromethylation method that could direct convert the arene C-H

bond to C-CF_2H bond under certain conditions, is thus highly desirable. Previously, Qing and coworkers reported a copper-mediated C-H difluoromethylation of heteroarenes. Nevertheless, the scope of substrates was limited to heteroarenes.[11]

Results and Discussion

During the studies of $Pd(OAc)_2$-catalyzed C-H bond activation/difluoromethylation of 2-phenylpyridine with [(SIPr)Ag(CF_2H)], we discovered that even though the desired C-H difluoromethylative product can be observed in about 10% yield, a new species with a chemical shift at -88.0 ppm in ^{19}F NMR spectroscopy was also detected. Further studies showed that this species was [(SIPr)Pd(CF_2H)(OAc)], which was resulted from concurrently transferring both difluoromethyl group and *N*-heterocyclic carbene ligand SIPr from Ag to Pd. In addition, not only $Pd(OAc)_2$ but also $PdCl_2$ or $Pd(OPiv)_2$ (OPiv = pivalate) also reacted similarly to give [(SIPr)Pd(CF_2H)(X)]$_2$ (X = Cl or OPiv) in high yield. We also discovered that these new complexes could serve as efficient difluoromethylating reagents when reacted with aryl boronic acids or their derivatives under basic conditions. Based on these findings, we developed a one-pot C-H borylation difluoromethylation protocol for the preparation of difluoromethylated arenes and heteroarenes. Herein, we report these discoveries.



Initially, we investigated direct C-H difluoromethylation by examining the reaction of 2-phenylpyridine with [(SIPr)Ag(CF_2H)] using 10 mol% $Pd(OAc)_2$ as the catalyst in the presence of various oxidants such as AgOAc, Ag_2CO_3, $Cu(OAc)_2$, 1,4-benzoquinone (BQ) or oxygen.[12,13] Interestingly, while the desired difluoromethylated product 2-(2-(difluoromethyl)phenyl)pyridine was generated in 1-14% yield, a new signal which is a doublet with a chemical shift at -88.0 ppm in ^{19}F NMR spectroscopy appeared. We suspected that the new signal was a difluoromethylated palladium complex (Eq. 1). Since we were unable to improve the yield of the C-H difluoromethylated product by optimizing the reaction parameters such as the solvent, the reaction temperature and the oxidant, we speculated that the unknown difluoromethylated species observed in various reaction conditions might serve as a

dormant palladium catalyst or a palladium catalyst reservoir. We then decided to isolate this species to probe whether our speculation was correct.

After a quick screen of the reaction conditions, we identified a high-yielding method for the preparation of the target difluoromethylated palladium complex. Stoichiometric reaction of [(SIPr)Ag(CF_2H)] with $Pd(OAc)_2$ in THF at 80 °C overnight generated the identical signal in ^{19}F NMR spectroscopy as the catalytic reaction in 80% yield (Eq. 2).

$$(SIPr)Ag(CF_2H) + PdX_2 \xrightarrow[80\ ^oC,\ overnight]{THF} (SIPr)Pd(CF_2H)(X) + AgX \quad (2)$$

X = OAc **1**, 80%
Cl **2**, 70%
OPiv **3**, 82%

^1H NMR spectroscopic study of the isolated complex showed that the complex bears an SIPr ligand, an acetate and a difluoromethyl group, which indicates that the structure of the complex is [(SIPr)Pd(OAc)(CF_2H)] **1** in which the acetate group coordinated in κ^2-binding modes. The structure was further ambiguously confirmed by X-ray diffraction of its single crystals (Figure 2). In addition, other Pd(II) complexes such as $PdCl_2$ or $Pd(OPiv)_2$ also reacted with [(SIPr)Ag(CF_2H)] to give crystalline solids [(SIPr)Pd(Cl)(CF_2H)]$_2$ **2** and [(SIPr)Pd(OPiv)(CF_2H)] **3** in 70% and 82% yield, respectively (See SI for their single crystal structures). In all cases, we observed that both NHC ligand the difluoromethyl group were transferred from Ag to Pd.[14]

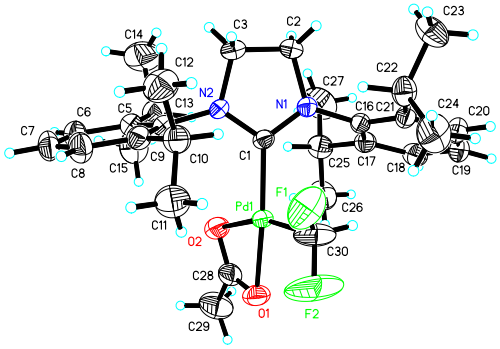
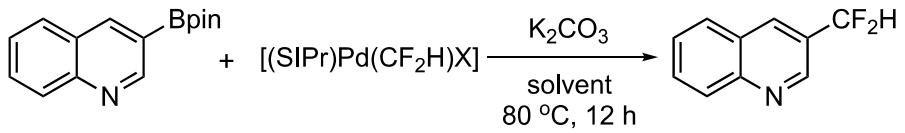


Figure 2. ORTEP diagram of complex [(SIPr)Pd(OAc)(CF_2H)] **1**. Ellipsoids are shown at the 30% probability level.

With these complexes in hand, we then subjected them to the palladium-catalyzed arene C-H difluoromethylation conditions. The formation of C-H difluoromethylation product 2-(2-(difluoromethyl)phenyl)pyridine was not observed when the three complexes were used as catalysts. These observations confirm our initial assumption that the difluoromethylated complexes were dormant palladium complexes that suppressed the catalytic reaction.

Scheme 1. Rapid Optimization of Conditions for Reaction of Quinoline-3-boronic Acid Pinacol Ester with Complexes 1-3[a]



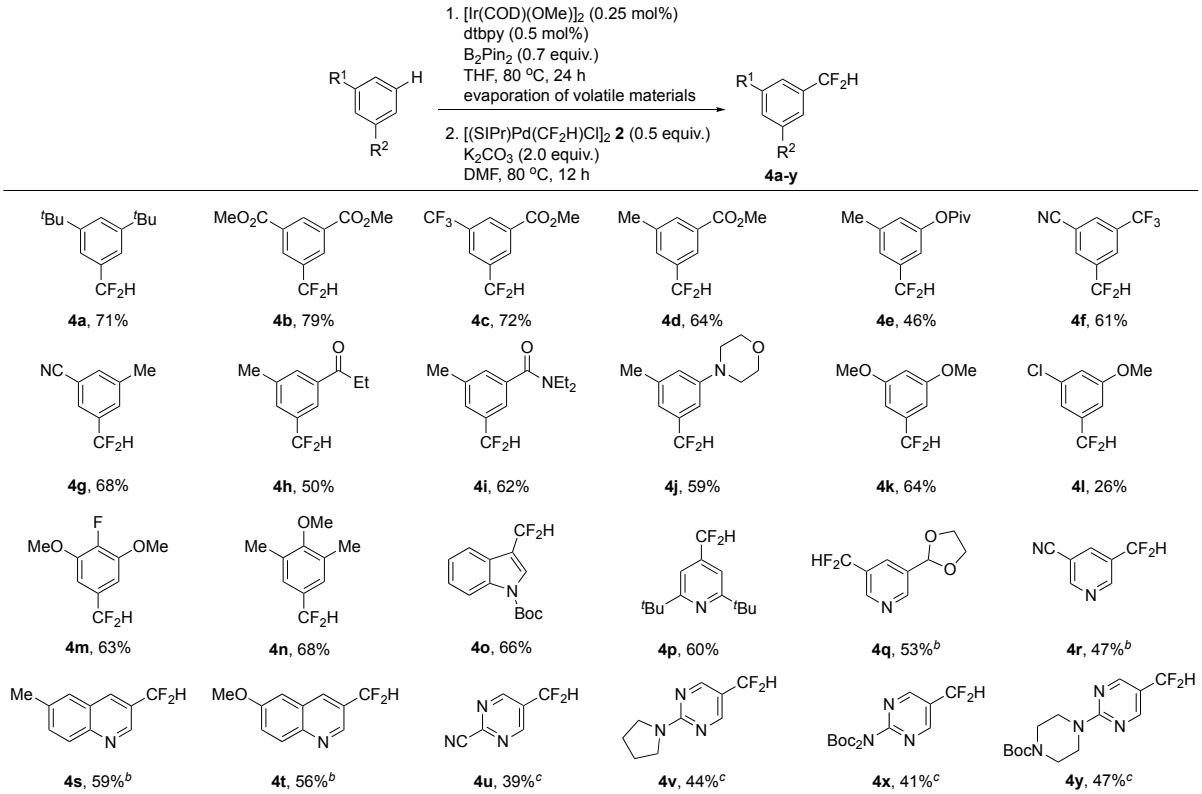
entry	[Pd]	solvent	yield (%)
1	[(SIPr)Pd(CF_2H)OAc] **1**	THF	68
2	[(SIPr)Pd(CF_2H)OPiv] **3**	THF	10
3	[(SIPr)Pd(CF_2H)Cl]$_2$ **2**	THF	76
4	[(SIPr)Pd(CF_2H)Cl]$_2$ **2**	PhMe	72
5	[(SIPr)Pd(CF_2H)Cl]$_2$ **2**	DMF	88

[a]Reaction conditions: quinoline-3-boronic acid pinacol ester (0.05 mmol), [(SIPr)Pd(CF_2H)(X)] **1**-**3** (0.05 mmol) and K_2CO_3 (0.1 mmol) in specified solvent (1.0 mL). [b]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with benzotrifluoride as an internal standard.

The lack of success in the development of the Pd-catalyzed arene C-H difluoromethylation method promoted us to seek an alternative protocol. Previously, Hartwig, Marder, Smith, Maleczka and co-workers have independently reported an efficient iridium-catalyzed borylation of arene C-H bonds and they have demonstrated that the borylated products can be efficiently converted to other functionalized arenes such as aryl halides, phenol or amine derivatives and trifluoromethylated arenes in high yields.[15] We therefore envisaged that if the aryl pinacol boronates resulting from the Ir-catalyzed C-H borylation could react with complexes **1**-**3**, a tandem C-H activation borylation/difluoromethylation protocol would be developed. This would provide a method for late-stage difluoromethylation, with previously inaccessible regioselectivity, which could be applied to drug-like molecules. The key for such a strategy is the successful difluoromethylation of aryl pinacol boronates with complexes **1**-**3** which we next quickly examined. It was found that reaction of quinoline-3-boronic acid pinacol ester with complexes **1-3** occurred smoothly at 80 °C after 12 h to give 3-difluoromethylquinoline in 10-76% yield, whereas [(SIPr)Pd(CF_2H)Cl]$_2$ **2** showed higher reactivity than [(SIPr)Pd(CF_2H)(OAc)] **1** and [(SIPr)Pd(CF_2H)(OPiv)] **3** was much less reactive. Further optimizations showed that DMF was a better solvent than THF or toluene.

With the optimized conditions for the difluoromethylation of aryl pinacol boronates in hand, the tandem reaction of 1,3-disubstituted arenes or heteroarenes to the corresponding difluoromethyl (hetero)arenes was studied, as shown in Scheme 2.

Scheme 2. Scope of One-Pot C-H Borylation/Difluoromethylation[a]



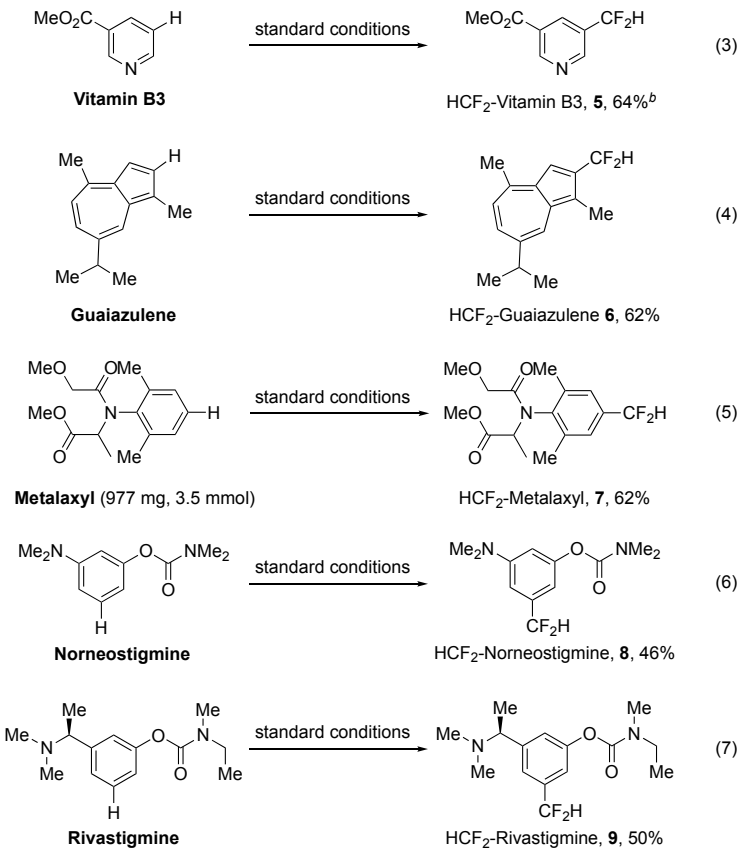
[a]Isolated yields; [b][Ir(cod)OMe]$_2$ (1.0 mol%) and dtbpy (2.0 mol%) were used; [c][Ir(COD)(OMe)]$_2$ (3.0 mol%) and Me_4Phen (6.0 mol%) were used.

Generally, we conducted the well-known process of borylation of 1,3-disubstituted arenes or heteroarenes with 0.7 equivalents of bis(pinacolato)diboron (B_2pin_2) in the presence of 0.25 mol% of [Ir(COD)OMe]$_2$ (COD = 1,5-cyclooctadiene) and 0.54 mol% of di-*tert*-butylbipyridine (dtbpy) in THF at 80 °C for 24 h. After evaporation of the volatile materials, [(SIPr)Pd(CF_2H)Cl]$_2$ **2**, K_2CO_3 and DMF were sequentially added and the resulting mixture was heated at 80 °C for another 12 h. Using this one-pot protocol, a variety of 5-difluoromethylated 1,3-disubstituted (hetero)arenes were obtained in moderate to high yields, as summarized in Scheme 1. In general, arenes containing esters (**4b**-**d**), protected phenolic hydroxy (**4e**), cyano (**4f-g**), enolizable ketone (**4h**), amide (**4i**) and tertiary amine (**4j**) were compatible with the reaction conditions. However, bromine and iodine are not tolerated since the halogenated arenes further reacted with aryl pinacol boronates. Chlorinated substrate (**4l**) was successfully difluoromethylated, albeit in slightly lower yield. Heteroarenes, including protected indole (**4o**), pyridine (**4p**-**r**) and quinoline (**4s**-**t**) were successfully difluoromethylated, even though slightly higher loadings of [Ir-(COD)OMe]$_2$ and dtbpy were required. Reactions of pyrimidine derivatives, however, required the use a more

reactive catalyst, generated by using Me_4Phen (3,4,7,8-tetramethyl-1,10-phenanthroline) as the ligand. Under these conditions, a few pyrimidine derivatives successfully underwent the one-pot C-H borylation/difluoromethylation to give the corresponding difluoromethylated pyrimidine derivatives in moderate yields (**4u**-**x**).

Finally, to demonstrate the applicability of the one-pot borylation/difluoromethylation protocol, we attempted the late-stage difluoromethylation of drug and agrochemical derivatives (Scheme 3). For example, Vitamin B3 and Guaiazulene,[16] a cosmetic color additive, were successfully difluoromethylated in 64% and 62% yields, respectively, under the standard protocol conditions (Eqs. 3-4). In addition, Metalaxyl,[17] a marketed fungicide used in mixtures as a foliar spray for tropical and subtropical crops and as a seed treatment to control downy mildews was successfully difluoromethylated in gram-scale in 62% yield (Eq 5). Furthermore, two other drug molecules Neostigmine,[18] a medication to treat myasthenia gravis and ogilvie syndrome, and Rivastigmine,[19] a drug used to treat confusion related to Alzheimer/Parkinson's disease, were also successfully difluoromethylated in 46-50% yield, respectively (Eqs. 6-7). Considering the importance of the difluoromethyl group in medicinal chemistry which often is considered as a bioisostere of the hydroxy or thio group,[2] these examples exhibit great potential of the one-pot C-H borylation/difluoromethylation protocol in the preparation of more complicated drug-like molecules.

Scheme 3. Late-stage difluoromethylation of drug and agrochemical derivatives



In summary, we reported a concurrent ligand transfer process that transfers both NHC ligand and CF_2H group from [(SIPr)Ag(CF_2H)] to PdX_2 (X = Cl, OAc, OPiv) for the preparation [(SIPr)Pd(CF_2H)X] complexes. These complexes were then applied in one-pot Ir-catalyzed C-H borylation and difluoromethylation access 5-difluoromethylated 1,3-difunctionalized (hetero)arenes in high yields. Even though a stoichiometric amount of difluoromethylated palladium complex was used as the difluoromethylating reagent, from the viewpoint of medicinal chemists, this protocol represents an efficient method for the direct late-stage preparation of previously inaccessible difluoromethylated arenes and heteroarenes. Studies toward the use of complex **1**-**3** as the catalyst for catalyzed difluoromethylation are undergoing currently in our laboratory.

Experimental Section

General information. All solvents were purified by standard method. ^1H, ^{19}F and ^{13}C NMR spectra were acquired on 400 MHz; 376 MHz; 101, 126, 151 MHz spectrometer (400 MHz for ^1H ; 376 MHz for ^{19}F; 101, 126 151 MHz for ^{13}C). ^1H NMR and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0 ppm and ^{19}F NMR chemical shifts were determined relative to $CFCl_3$ as inter standard. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in hertz (Hz).

The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. All reactions were monitored by TLC or ^{19}F NMR. Flash column chromatograph was carried out using 300-400 mesh silica gel at medium pressure.

Materials. All reagents were received from commercial sources. Solvents were freshly dried and degassed according to the purification handbook *Purification of Laboratory Chemicals* before using.

Synthesis of [(SIPr)Pd(CHF_2)(OAc)] 1. In a glovebox, $Pd(OAc)_2$ (448 mg, 2.00 mmol, 1.00 equiv.) and (SIPr)Ag(CF_2H) (1.1 g, 2.0 mmol, 1.0 equiv.) were placed in a 250 mL sealed tube that was equipped with a stirrer. Then 20 mL of anhydrous THF was added and the reaction mixture was stirred at 80 ^oC in an oil bath overnight. The mixture was then filtered through a short plug of Celite. The solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (petroleum / ethyl acetate = 20/1) to give [(SIPr)Pd(CF_2H)(OAc)] as a white solid (973 mg, 80%). Colorless crystals of **1** suitable for single-crystal X-ray diffraction study were obtained by standing its THF solution at room temperature via slow evaporation of THF. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.7 Hz, 2 H), 7.28 (m, 4 H), 5.87 (t, *J* = 52.8 Hz, 1 H), 4.01 (s, 3 H), 3.23 (m, 4 H), 1.45 (d, *J* = 6.6 Hz, 12 H), 1.26 (d, *J* = 6.8 Hz, 12 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -87.95 (d, *J* = 52.8 Hz); $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 198.7 (t, *J* = 9.8 Hz), 187.5, 147.4, 134.8, 129.6, 124.8, 120.2 (t, *J* = 304.2 Hz), 53.8, 28.8, 26.5, 23.6, 23.4 ppm. Anal. Calcd for $C_{30}H_{42}PdO_2F_2N_2$: C, 59.35; H, 6.97; N, 4.61. Found: C, 59.74; H, 7.24; N, 4.42.

Synthesis of [(SIPr)Pd(CHF_2)Cl]$_2$ 2. In a glovebox, $Pd(CH_3CN)_2Cl_2$ (520 mg, 2.00 mmol, 1.00 equiv.) and (SIPr)Ag(CF_2H) (1.1 g, 2.0 mmol, 1.0 equiv.) were placed in a 250 mL sealed tube that was equipped with a stirrer. Then 20 mL of anhydrous THF was added and the reaction mixture was stirred at 80 ^oC in an oil bath overnight. The mixture was then filtered through a short plug of Celite. The solution was reduced to a minimum volume of THF, and a white solid (817 mg, 70%) was precipitated by the addition of ether to the concentrated solution. Colorless crystals of **2** suitable for single crystal X-ray diffraction study were obtained by diffusing n-pentane into its THF solution at room temperature. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.6 Hz, 2 H), 7.21 (m, 4 H), 5.53 (t, *J* = 52.8 Hz, 1 H), 3.84 (d, *J* = 3.9 Hz, 4 H), 3.19 (m, 4 H), 1.33 (d, *J* = 6.3 Hz, 12 H), 1.21 (d, *J* = 6.1 Hz, 6 H), 1.10 (d, *J* = 5.8 Hz, 6 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -85.05 (d, *J* = 52.8 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 200.1 (t, *J* =

12.9 Hz), 147.6, 146.8, 135.6, 129.0, 124.6, 124.4, 120.8 (t, *J* = 304.0 Hz), 28.9, 28.1, 27.0, 26.8, 24.1, 24.0 ppm. Anal. Calcd for $C_{33}H_{48}PdO_2F_2N_2$: C,61.06; H, 7.45; N, 4.32. Found: C, 60.66; H, 7.41; N, 3.46.

Synthesis of [(SIPr)Pd(CHF_2)(OPiv)] 3. In a glovebox, $Pd(OPiv)_2$ (154 mg, 0.500 mmol, 1.00 equiv.) and (SIPr)Ag(CF_2H) (275 mg, 0.500 mmol, 1.00 equiv.) were placed in a 25 mL sealed tube that was equipped with a stirrer. Then 5 mL of anhydrous THF was added and the reaction mixture was stirred at 80 °C in an oil bath overnight. The mixture was then filtered through a short plug of Celite. The solvent was removed under vacuum. The residue was purified by flash chromatography on silica gel (petroleum / ethyl acetate = 20/1) to give [(SIPr)Pd(CF_2H)(OPiv)] as a white solid (533 mg, 82%). Colorless crystals of **3** suitable for single-crystal X-ray diffraction study were obtained by standing its THF solution at room temperature via slow evaporation of THF. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 7.7 Hz, 2 H), 7.28 (m, 4 H), 5.87 (t, *J* = 52.8 Hz, 1 H), 4.01 (s, 4 H), 3.23 (m, 4 H), 1.45 (d, *J* = 6.6 Hz, 12 H), 1.26 (d, *J* = 6.8 Hz, 12 H), 0.86 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -87.95 (d, *J* = 52.8 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 198.7 (t, *J* = 9.8 Hz), 187.5, 147.4, 134.8, 129.6, 124.8, 120.2 (t, *J* = 304.2 Hz), 53.8, 28.8, 26.5, 23.6 ppm. Anal. Calcd for $C_{56}H_{78}Pd_2Cl_2F_4N_4$: C,57.64; H, 6.74. Found: C, 57.64; H, 6.81.

General procedure for one-pot C-H borylation/difluoromethylation.

Procedure A. In an argon-filled glove box, arene (0.3 mmol) and B_2pin_2 (53 mg, 0.21 mmol) were placed into a sealed tube. To this tube was added anhydrous THF (1.5 mL) containing $[Ir(COD)(OMe)]_2$ (0.25 mol%) and dtbpy (0.54 mol%). The reaction was stirred at 80 °C in an oil bath and monitored by TLC until the disappearance of the arene (24 h). After evaporation of volatile materials under vacuum, K_2CO_3 (83 mg, 0.60 mmol), $[(SIPr)Pd(CF_2H)Cl]_2$ (175 mg, 0.150 mmol) and dry DMF (3.0 mL) were added under argon. The mixture was stirred at 80 °C in an oil bath overnight. The solution was diluted with Et_2O (5.0 mL), and filtered through a short plug of silica gel, washed with Et_2O (20.0 mL). The organic layer was washed with water (20.0 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

Procedure B. In an argon-filled glove box, arene (0.3 mmol) and B_2pin_2 (53 mg, 0.21 mmol) were placed into a sealed tube. To this tube was added anhydrous THF (1.5 mL) containing $[Ir(COD)(OMe)]_2$ (1.0 mol%) and dtbpy (2.0 mol%). The reaction was stirred at 80 °C in an oil bath and monitored by TLC until the disappearance of the

arene (24 h). After evaporation of volatile materials under vacuum, K_2CO_3 (83 mg, 0.60 mmol), $[(SIPr)Pd(CF_2H)Cl]_2$ (175 mg, 0.150 mmol) and dry DMF (3.0 mL) were added under argon. The mixture was stirred at 80 °C in an oil bath overnight. The solution was diluted with Et_2O (5.0 mL), and filtered through a short plug of silica gel, washed with Et_2O (20.0 mL). The organic layer was washed with water (20.0 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

Procedure C. In an argon-filled glove box, arene (0.3 mmol) and B_2pin_2 (53 mg, 0.21 mmol) were placed into a sealed tube. To this tube was added anhydrous THF (1.5 mL) containing $[Ir(COD)(OMe)]_2$ (3.0 mol%) and Me_4Phen (6.0 mol%). The reaction was stirred at room teperature and monitored by TLC until the disappearance of the arene (24 h). After evaporation of volatile materials under vacuum, K_2CO_3 (83 mg, 0.60 mmol), $[(SIPr)Pd(CF_2H)Cl]_2$ (175 mg, 0.150 mmol) and dry DMF (3.0 mL) were added under argon. The mixture was stirred at 80 °C in an oil bath overnight. The solution was diluted with Et_2O (5.0 mL), and filtered through a short plug of silica gel, washed with Et_2O (20.0 mL). The organic layer was washed with water (20.0 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel.

1,3-Di-*tert*-butyl-5-(difluoromethyl)benzene 4a. The general **procedure A** conducted with 1,3-di-tert-butylbenzene (57 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 51 mg (71%) product as a yellow oil. Eluent: petroleum ether, R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1 H), 7.33 (s, 2 H), 6.63 (t, *J* = 56.7 Hz, 1 H), 1.34 (s, 18 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.42 (d, *J* = 56.7 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.4, 133.6 (t, *J* = 21.5 Hz), 124.9, 119.7 (t, *J* =5.67 Hz), 115.6 (t, *J* = 238.4 Hz), 35.0, 31.4 ppm. The physical and spectral data were consistent with those previously reported.[8b]

Dimethyl 5-(difluoromethyl)isophthalate 4b. The general **procedure A** conducted with dimethyl isophthalate (58 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 58 mg (79%) product as a yellow solid. Mp: 60.8-62.2 °C. Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1 H), 8.38 (s, 2 H), 6.74 (t, *J* = 55.9 Hz, 1 H), 3.98 (s, 6 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.78 (d, *J* = 55.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.38, 135.35 (t, *J* = 23.1 Hz), 132.74, 131.42, 130.92 (t, *J* = 6.0 Hz), 113.47 (t, *J* = 240.4 Hz), 52.70 ppm. MS (EI): 213 (100), 244 (19.38); HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_{10}O_4F_2$: 244.0553;

Found: 244.0547. IR (KBr): ν_{max} = 2956, 1723, 1617, 1434, 1384, 1328, 1242, 1207 cm^{-1}.

Methyl 3-(difluoromethyl)-5-(trifluoromethyl)benzoate 4c. The general **procedure A** conducted with methyl 3-(trifluoromethyl)benzoate (61 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 54 mg (72%) product as a yellow oil. Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 16.9 Hz, 2 H), 7.97 (s, 1 H), 6.75 (t, *J* = 55.8 Hz, 1 H), 3.99 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.01 (s, 3 F), -112.32 (d, *J* = 55.8 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.8, 135.9 (t, *J* = 23.5 Hz), 132.4 – 131.3 (m), 130.0 (t, *J* = 6.1 Hz), 128.6, 128.6, 126.6 (dt, *J* = 9.5, 4.8 Hz), 123.1 (q, *J* = 272.8 Hz), 113.1 (t, *J* = 240.8 Hz), 52.8 ppm. MS (EI): 223 (100), 254 (43.79). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_7O_2F_5$: 254.0366; Found: 254.0371. IR (KBr): ν_{max} = 2960, 1731, 1617, 1439, 1345, 1255, 1131, 1039, 988, 767, 720 cm^{-1}.

Methyl 3-(difluoromethyl)-5-methylbenzoate 4d. The general **procedure A** conducted with methyl 3-methylbenzoate (45 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 38 mg (64%) product as a colorless oil. Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 2 H), 7.52 (s, 1 H), 6.65 (t, *J* = 56.3 Hz, 1 H), 3.93 (s, 3 H), 2.45 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.20 (d, *J* = 56.3 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 166.5, 139.3, 134.9 (t, *J* = 22.5 Hz), 132.6, 130.9, 130.6 (t, *J* = 5.5 Hz), 124.3 (t, *J* = 6.3 Hz), 114.4 (t, *J* = 239.3 Hz), 52.4, 21.4 ppm. MS (EI): 169 (100), 200 (75.44). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{10}H_{10}O_2F_2$: 200.0649; Found: 200.0653. IR (KBr): ν_{max} = 2956, 1723, 1612, 1437, 1386, 1311, 1221, 1171, 1028, 881, 766 cm^{-1}.

3-(Difluoromethyl)-5-methylphenyl pivalate 4e. The general **procedure A** conducted with methyl *m*-tolyl pivalate (58 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 33 mg (46%) product as a colorless oil. Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 1 H), 7.00 (d, *J* = 12.5 Hz, 2 H), 6.59 (t, *J* = 56.4 Hz, 1 H), 2.40 (s, 3 H), 1.36 (s, 9 H);^{19}F NMR (376 MHz, $CDCl_3$) δ -111.20 (d, *J* = 56.4 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 177.1, 151.3, 140.4, 135.7 (t, *J* = 22.4 Hz), 124.7, 123.6 (t, *J* = 6.0 Hz), 116.1 (t, *J* = 6.1 Hz), 114.2 (t, *J* = 239.1 Hz), 39.2, 27.2, 21.4 ppm. MS (EI): 116 (100), 167 (99.81), 242 (1.99). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{13}H_{16}O_2F_2$: 242.1118; Found:

242.1125. IR (KBr): ν_{max} = 2976, 1752, 1600, 1463, 1371, 1273, 1110, 1029, 888, 741 cm^{-1}.

3-(Difluoromethyl)-5-(trifluoromethyl)benzonitrile 4f. The general **procedure A** conducted with 3-(trifluoromethyl)benzonitrile (51 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 40 mg (61%) product as a colorless oil. Eluent: ethyl acetate/petroleum ether (1/10), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1 H), 8.01 (s, 2 H), 6.75 (t, *J* = 55.5 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.29 (s, 3 F), -113.40 (d, *J* = 55.5 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 136.5 (t, *J* = 23.7 Hz), 132.5 (dd, *J* = 68.2, 33.3 Hz), 132.1 (t, *J* = 6.0 Hz), 130.6, 126.5 – 126.2 (m), 121.9 (q, *J* = 273.2 Hz), 116.0, 114.0, 111.8 (t, *J* = 241.8 Hz) ppm. MS (EI): 152 (100), 221 (86.84). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_9H_4NF_5$: 221.0264; Found: 221.0260. IR (KBr): ν_{max} = 2240, 1617, 1462, 1386, 1281, 1225, 1136, 1114, 1044, 899, 748 cm^{-1}.

3-(Difluoromethyl)-5-methylbenzonitrile 4g. The general **procedure A** conducted with 3-methylbenzonitrile (35 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 34 mg (68%) product as a colorless oil. Eluent: ethyl acetate/petroleum ether (1/10), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1 H), 7.58 (s, 1 H), 7.55 (s, 1 H), 6.63 (t, *J* = 55.7 Hz, 1 H), 2.46 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.26 (d, *J* = 55.7 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 140.4, 135.8 (t, *J* = 23.1 Hz), 134.8, 130.7 (t, *J* = 5.6 Hz), 126.6 (t, *J* = 6.3 Hz), 118.1, 113.4 (t, *J* = 240.5 Hz), 113.2, 21.3 ppm. MS (EI): 116 (100), 167 (79.18). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_9H_7NF_2$: 167.0547; Found: 167.0546. IR (KBr): ν_{max} = 2926, 2235, 1604, 1464, 1376, 1293, 1175, 1093, 1033, 874, 730 cm^{-1}.

1-(3-(Difluoromethyl)-5-methylphenyl)propan-1-one 4h. The general **procedure A** conducted with 1-(m-tolyl)propan-1-one (44 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 30 mg (50%) product as a yellow oil. Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.2. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 2 H), 7.51 (s, 1 H), 6.66 (t, *J* = 56.2 Hz, 1 H), 3.01 (q, *J* = 7.2 Hz, 2 H), 2.46 (s, 3 H), 1.23 (t, *J* = 7.2 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.97 (d, *J* = 56.2 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 200.2, 139.4, 137.6, 135.0 (t, *J* = 22.3 Hz), 130.9, 130.5 (t, *J* = 5.8 Hz), 122.6 (t, *J* = 6.2 Hz), 114.4 (t, *J* = 239.3 Hz), 32.1, 21.5, 8.3 ppm. MS (EI): 169 (100), 198 (10.17). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_{12}OF_2$: 198.0856;

Found: 198.0859. IR (KBr): ν_{max} = 2980, 2942, 1688, 1605, 1350, 1184, 1165, 1026, 880, 806, 739 cm^{-1}.

3-(Difluoromethyl)-*N*,*N*-diethyl-5-methylbenzamide 4i. The general **procedure A** conducted with *N*,*N*-diethyl-3-methylbenzamide (57 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 45 mg (62%) product as a yellow oil. Eluent: ethyl acetate/petroleum ether (1/4), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (s, 1 H), 7.30 (s, 2 H), 6.62 (t, *J* = 56.3 Hz, 1 H), 3.55 (s, 2 H), 3.24 (s, 2 H), 2.42 (s, 3 H), 1.25 (s, 3 H), 1.11 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.24 (d, *J* = 56.3 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 170.5, 139.2, 138.0, 134.7 (t, *J* = 22.7 Hz), 129.3, 126.9 (t, *J* = 6.1 Hz), 120.7 (t, *J* = 6.2 Hz), 114.4 (t, *J* = 239.3 Hz), 43.4, 39.4, 21.4, 14.3, 13.0 ppm. MS (ESI): 242.1 $[M+H]^+$; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{13}H_{17}ONF_2$: 242.1351; Found: 242.1349. IR (KBr): ν_{max} = 2976, 2934, 2874, 1626, 1430, 1383, 1318, 1255, 1218, 1171, 1085, 1021, 875, 811, 758, 729 cm^{-1}.

4-(3-(Difluoromethyl)-5-methylphenyl)morpholine 4j. The general **procedure A** conducted with 4-(m-tolyl)morpholine (53 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 40 mg (59%) product as a pale green oil. Eluent: ethyl acetate/petroleum ether (1/10), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1 H), 6.82 (s, 2 H), 6.56 (t, *J* = 56.7 Hz, 1 H), 3.91 – 3.82 (m, 4 H), 3.23 – 3.13 (m, 4 H), 2.36 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.42 (d, *J* = 56.7 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.7, 139.7, 135.3 (t, *J* = 21.9 Hz), 118.6, 117.9 (t, *J* = 6.1 Hz), 115.2 (t, *J* = 238.8 Hz), 109.7 (t, *J* = 6.1 Hz), 67.0, 49.2, 21.8 ppm. MS (EI): 169 (100), 227 (47.59). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{12}H_{15}NOF_2$: 227.1122; Found: 227.1132. IR (KBr): ν_{max} = 2966, 2860, 2824, 1602, 1450, 1388, 1263, 1121, 1089, 1014, 844, 728 cm^{-1}.

1-(Difluoromethyl)-3,5-dimethoxybenzene 4k.[5f] The general **procedure A** conducted with 1,3-dimethoxybenzene (41 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 36 mg (64%) product as a colorless oil. Eluent: ethyl acetate/petroleum ether (1/100), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 2 H),6.56 (t, *J* = 56.5 Hz, 1 H), 6.54 (s, 1 H), 3.82 (s, 6 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.90 (d, *J* = 56.5 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 161.0, 136.4 (t, *J* = 22.4 Hz), 114.5 (t, *J* = 239.1 Hz), 103.4 (t, *J* = 6.5 Hz), 102.7, 55.5 ppm. The physical and spectral data were consistent with those previously reported.

Methyl 3-chloro-5-(difluoromethyl)benzoate 4l. The general **procedure A** conducted with 1-chloro-3-methoxybenzene (43 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 17 mg (26%) product as a colorless oil. Eluent: petroleum ether (1/100), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, 1 H), 6.99 (s, 1 H), 6.92 (s, 1 H), 6.56 (t, *J* = 56.1 Hz, 1 H), 3.83 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.77 (d, *J* = 56.1 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.7, 136.9 (t, *J* = 22.8 Hz), 135.6, 118.2 (t, *J* = 6.4 Hz), 116.7, 113.8 (t, *J* = 240.3 Hz), 109.8 (t, *J* = 6.3 Hz), 55.8 ppm. MS (EI): 192 (100). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_8H_7OF_2Cl$: 192.0153; Found: 192.0156. IR (KBr): ν_{max} = 2972, 2840, 1583, 1466, 1435, 1368, 1279, 1170, 1106, 1031, 947, 843, 732 cm^{-1}.

5-(Difluoromethyl)-2-fluoro-1,3-dimethoxybenzene 4m. The general **procedure A** conducted with 2-fluoro-1,3-dimethoxybenzene (47 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 39 mg (63%) product as a colorless oil. Eluent: ethyl acetate/petroleum ether (1/100), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, *J* = 6.8 Hz, 2 H), 6.57 (t, *J* = 56.6 Hz, 1 H), 3.91 (s, 6 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.76 (dd, *J* = 56.6, 3.1 Hz, 2 F), -154.59 (tt, *J* = 6.8, 3.4 Hz, 1 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 148.8 (d, *J* = 9.2 Hz), 143.8 (dt, *J* = 248.6, 2.1 Hz), 129.7 (td, *J* = 22.6, 5.0 Hz), 114.4 (t, *J* = 239.4 Hz), 103.4 (t, *J* = 6.3 Hz), 56.7 ppm. MS (EI): 206 (100). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_9H_9O_2F_3$: 206.0555; Found: 206.0550. IR (KBr): ν_{max} = 2976, 1619, 1522, 1466, 1426, 1380, 1341, 1244, 1130, 1020, 974, 841, 733 cm^{-1}.

5-(Difluoromethyl)-2-methoxy-1,3-dimethylbenzene 4n. The general **procedure A** conducted with 2-methoxy-1,3-dimethylbenzene (41 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 38 mg (69%) product as a yellow oil. Eluent: ethyl acetate/petroleum ether (1/20), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 2 H), 6.54 (t, *J* = 56.7 Hz, 1 H), 3.74 (s, 3 H), 2.32 (s, 6 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.16 (d, *J* = 56.7 Hz). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.0, 131.7, 129.8 (t, *J* = 22.2 Hz), 126.2 (t, *J* = 5.7 Hz), 115.0 (t, *J* = 237.9 Hz), 59.8, 16.3 ppm. MS (EI): 186 (100). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{10}H_{12}OF_2$: 186.0856; Found: 186.0858. IR (KBr): ν_{max} = 2940, 1611, 1487, 1371, 1228, 1150, 1089, 1006, 881, 782, 756 cm^{-1}.

***tert*-Butyl 3-(difluoromethyl)-1*H*-indole-1-carboxylate 4o**. The general **procedure B** conducted with *tert*-butyl 1*H*-indole-1-carboxylate (65 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 53 mg (66%) product as a yellow solid.

Mp: 66.0-67.5 °C. Eluent: ethyl acetate/petroleum ether (1/30), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.3 Hz, 1 H), 7.81 (t, *J* = 2.3 Hz, 1 H), 7.72 (d, *J* = 7.8 Hz, 1 H), 7.42 – 7.36 (m, 1 H), 7.31 (td, *J* = 7.8, 1.0 Hz, 1 H), 6.89 (t, *J* = 55.6 Hz, 1 H), 1.68 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.65 (dd, *J* = 55.6, 2.4 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 149.4, 135.7, 126.5, 125.6 (t, *J* = 8.9 Hz), 125.5, 123.5, 120.1, 115.6, 115.3 (t, *J* = 25.9 Hz), 112.4 (t, *J* = 234.0 Hz), 84.8, 28.3 ppm. MS (EI): 57 (100), 267 (13.64). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{14}H_{15}NO_2F_2$: 267.1071; Found: 267.1077. IR (KBr): ν_{max} = 2982, 1740, 1452, 1396, 1345, 1259, 1155, 1094, 1016, 852, 746 cm^{-1}.

2,6-Di-*tert*-butyl-4-(difluoromethyl)pyridine 4p. The general **procedure A** conducted with 2,6-di-*tert*-butylpyridine (57 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 43 mg (60%) product as a yellow oil. Eluent: ethyl acetate/petroleum ether (1/10), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 2 H), 6.58 (t, *J* = 56.1 Hz, 1 H), 1.36 (s, 18 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -114.17 (d, *J* = 56.1 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 169.0, 142.3 (t, *J* = 22.4 Hz), 114.2 (t, *J* = 240.3 Hz), 111.9 (t, *J* = 6.0 Hz), 38.0, 30.2 ppm. MS (EI): 226 (100), 241 (25.92). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{14}H_{21}NF_2$: 241.1642; Found: 241.1651. IR (KBr): ν_{max} = 2959, 1608, 1577, 1479, 1420, 1374, 1207, 1099, 1043, 901, 875, 729 cm^{-1}.

3-(Difluoromethyl)-5-(1,3-dioxolan-2-yl)pyridine 4q.[10] The general **procedure B** conducted with 3-(1,3-dioxolan-2-yl)pyridine (45 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 32 mg (53%) product as a yellow oil. Eluent: ethyl acetate/petroleum ether (1/2), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1 H), 8.72 (s, 1 H), 7.92 (s, 1 H), 6.70 (t, *J* = 55.7 Hz, 1 H), 5.87 (s, 1 H), 4.69 – 3.78 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.59 (d, *J* = 55.7 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.5 (t, *J* = 1.9 Hz), 147.7 (t, *J* = 6.6 Hz), 134.0, 131.5 (t, *J* = 5.6 Hz), 129.8 (t, *J* = 23.1 Hz), 113.2 (t, *J* = 239.7 Hz), 101.3, 65.5 ppm. The physical and spectral data were consistent with those previously reported.

5-(Difluoromethyl)nicotinonitrile 4r.[10] The general **procedure B** conducted with nicotinonitrile (31 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 21 mg (47%) product as a yellow solid. Mp: 58.1-59.4 °C. Eluent: ethyl acetate/petroleum ether (1/2), R_f = 0.4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1 H), 8.93 (s, 1 H), 8.11 (s, 1 H), 6.75 (t, *J* = 55.3 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.91 (d, *J* = 55.3 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 154.3 (t, *J* = 1.7 Hz),

150.4 (t, *J* = 6.4 Hz), 136.7 (t, *J* = 5.8 Hz), 130.5 (t, *J* = 23.9 Hz), 115.6, 112.0 (t, *J* = 241.8 Hz), 110.4 ppm. The physical and spectral data were consistent with those previously reported.

3-(Difluoromethyl)-6-methylquinoline 4s. The general **procedure B** conducted with 6-methylquinoline (43 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 34 mg (59%) product as a yellow solid. Mp: 41.6-43.0 ^{o}C. Eluent: ethyl acetate/petroleum ether (1/4), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 8.19 (s, 1 H), 8.05 (d, *J* = 9.1 Hz, 1 H), 7.63 (d, *J* = 3.6 Hz, 2 H), 6.86 (t, *J* = 55.9 Hz, 1 H), 2.55 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.47 (d, *J* = 55.9 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 147.8, 146.3 (t, *J* = 5.3 Hz), 137.8, 133.5, 133.3 (t, *J* = 6.7 Hz), 129.2, 127.4, 127.2, 127.0, 113.9 (t, *J* = 239.3 Hz), 21.7 ppm. MS (EI): 193 (100). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_9NF_2$: 193.0703; Found: 193.0701. IR (KBr): ν_{max} = 3024, 1614, 1573, 1440, 1383, 1333, 1181, 1027, 919, 829 cm^{-1}.

3-(Difluoromethyl)-6-methoxyquinoline 4t. The general **procedure B** conducted with 6-methoxyquinoline (48 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 35 mg (56%) product as an orange oil. Eluent: ethyl acetate/petroleum ether (1/2), R_f = 0.5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (s, 1 H), 8.20 (s, 1 H), 8.06 (d, *J* = 9.2 Hz, 1 H), 7.46 (dd, *J* = 9.2, 2.6 Hz, 1 H), 7.14 (d, *J* = 2.5 Hz, 1 H), 6.87 (t, *J* = 55.5 Hz, 1 H), 3.95 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.89 (d, *J* = 55.5 Hz); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 158.7, 145.5, 144.8 (t, *J* = 5.3 Hz), 132.6 (t, *J* = 6.4 Hz), 131.1, 128.3, 127.6 (t, *J* = 22.8 Hz), 124.1, 113.9 (t, *J* = 239.7 Hz), 105.7, 55.8 ppm. MS (EI): 209 (100). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{11}H_9NOF_2$: 209.0652; Found: 209.0657. IR (KBr): ν_{max} = 2954, 2926, 1613, 1504, 1379, 1235, 1221, 1027, 916, 837, 731 cm^{-1}.

5-(Difluoromethyl)pyrimidine-2-carbonitrile 4u.[10] The general **procedure C** conducted with pyrimidine-2-carbonitrile (32 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 18 mg (39%) product as a yellow oil. Eluent: ethyl acetate/petroleum ether (1/3), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 2 H), 6.85 (t, *J* = 56.4 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -115.91 (d, *J* = 56.4 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 150.6(t, *J* = 7.5 Hz), 141.3(t, *J* = 2.5 Hz), 124.8 (t, *J* = 30.0 Hz), 109.8, 105.8 (t, *J* = 243.2 Hz) ppm. The physical and spectral data were consistent with those previously reported.

5-(Difluoromethyl)-2-(pyrrolidin-1-yl)pyrimidine 4v.[10] The general **procedure C** conducted with 2-(pyrrolidin-1-yl)pyrimidine (45 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 26 mg (44%) product as a yellow solid. Mp: 71.2-72.0 °C. Eluent: ethyl acetate/petroleum ether (1/2), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 2 H), 6.56 (t, *J* = 56.4 Hz, 1 H), 3.60 (t, *J* = 6.0 Hz, 4 H), 2.01 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.45 (d, *J* = 56.4 Hz, 2 F); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.0, 155.8 (t, *J* = 5.0 Hz), 115.5 (t, *J* = 23.8 Hz), 113.8 (t, *J* = 235. 5 Hz), 46.8, 25.4 ppm. The physical and spectral data were consistent with those previously reported.

***tert*-Butyl-N-*tert*-butoxycarbonyl-N-[5-(difluoromethyl)pyrimidin-2-yl]carbamate 4x.**[10] The general **procedure C** conducted with 2-(di-(*tert*-butoxycarbonyl)amino)pyrimidine (88 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 42 mg (41%) product as a yellow solid. Mp: 67.0-68.1 °C. Eluent: ethyl acetate/petroleum ether (1/8), R_f = 0.3.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 2 H), 6.77 (t, *J* = 56.4 Hz, 1 H), 1.48 (s, 18 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.82 (d, *J* = 56.4 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 160.2, 156.4 (t, *J* = 6.3 Hz), 150.4, 125.4, 111.9 (t, *J* = 239.2 Hz), 84.0, 27.8 ppm. The physical and spectral data were consistent with those previously reported.

***tert*-Butyl 4-(5-(difluoromethyl)pyrimidin-2-yl)piperazine-1-carboxylate 4y**. The general **procedure C** conducted with *tert*-butyl 4-(pyrimidin-2-yl)piperazine-1-carboxylate (79 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 44 mg (47%) product as a white solid. Mp: 62.9-64.6 °C. Eluent: ethyl acetate/petroleum ether (1/3), R_f = 0.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 2 H), 6.57 (t, *J* = 56.0 Hz, 1 H), 3.92 – 3.81 (m, 4 H), 3.55 – 3.44 (m, 4 H), 1.49 (s, 9 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.11 (d, *J* = 56.0 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 162.4, 156.1 (t, *J* = 5.5 Hz), 154.9, 116.7 (t, *J* = 24.3 Hz), 113.6 (t, *J* = 237.0 Hz), 80.3, 43.8, 28.6 ppm. MS (ESI): 337.1 $[M+Na]^+$; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{14}H_{20}O_2N_4F_2$: 315.1627; Found: 315.1625. IR (KBr): ν_{max} = 2977, 2868, 1681, 1610, 1526, 1236, 1167, 1122, 1076, 955, 742 cm^{-1}.

Methyl 5-(difluoromethyl)nicotinate 5. The general **procedure B** conducted with *tert*-butyl 4-(pyrimidin-2-yl)piperazine-1-carboxylate (41 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 36 mg (66%) product as a yellow solid. Mp: 94.6-96.3 °C. Eluent: ethyl acetate/petroleum ether (1/3), R_f = 0.4. ^{1}H NMR (400

MHz, $CDCl_3$) δ 9.30 (s, 1 H), 8.90 (s, 1 H), 8.43 (s, 1 H), 6.76 (t, *J* = 55.5 Hz, 1 H), 3.97 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.95 (d, *J* = 55.5 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.0, 152.9, 150.8 (t, *J* = 6.11 Hz), 134.6 (t, *J* = 5.9 Hz), 130.2 (t, *J* = 23.6 Hz), 126.2, 112.9 (t, *J* = 240.4 Hz), 52.8 ppm. MS (EI): 156 (100), 187 (81.97). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_8H_7NO_2F_2$: 187.0445; Found: 187.0451. IR (KBr): ν_{max} = 3057, 1721, 1587, 1442, 1374, 1298, 1216, 1111, 1084, 1036, 925, 901, 768, 726 cm^{-1}.

2-(Difluoromethyl)-7-isopropyl-1,4-dimethylazulene 6. The general **procedure C** conducted with Guaiazulene (60 mg, 0.30 mmol) in dry n-hexane (1.5 mL) at 100 °C and then in dry DMF (3.0 mL) gave 46 mg (62%) product as a blue oil. Eluent: petroleum ether, R_f = 0.4. ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1 H), 7.51 (d, *J* = 10.5 Hz, 1 H), 7.40 (s, 1 H), 7.11 (t, *J* = 55.9 Hz, 1 H), 7.10 (d, *J* = 9.8 Hz, 1 H),3.18 – 3.05 (m, 1 H), 2.86 (s, 3 H), 2.70 (s, 3 H), 1.39 (d, *J* = 6.9 Hz, 6 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.80 (d, *J* = 55.8 Hz). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 147.3, 141.3, 139.3 – 138.7 (m), 137.0, 136.4, 135.4, 126.4, 122.4 (t, *J* = 5.7 Hz), 113.8 (t, *J* = 235.0 Hz), 110.4 (t, *J* = 5.8 Hz), 38.4, 24.84, 24.3, 10.5 ppm. MS (EI): 233 (100), 248 (79). HRMS (EI-TOF) m/z: $[M]^+$ Calcd for $C_{16}H_{18}F_2$: 248.1377; Found: 248.1368. IR (KBr): ν_{max} = 2960, 2924, 2870, 1560, 1461, 1361, 1126, 1031, 819, 793 cm^{-1}.

Gram-scale synthesis of HCF_2-Metalaxyl 7. In an argon-filled glove box, Metalaxyl (977 mg, 3.50 mmol) and B_2pin_2 (630 mg, 2.48 mmol) were placed into a sealed tube. To this tube was added anhydrous THF (10 mL) containing $[Ir(COD)(OMe)]_2$ (5.8 mg, 0.25 mol%) and dtbpy (6.4 mg, 0.50 mol%). The reaction was stirred at 80 °C in an oil bath and monitored by TLC until the disappearance of Metalaxyl (24 h). After evaporation of volatile materials under vacuum, K_2CO_3 (966 mg, 7.00 mmol), $[(SIPr)Pd(CF_2H)Cl]_2$ (2.04 g, 1.75 mmol) and dry DMF (35 mL) were added under argon. The mixture was stirred at 80 °C in an oil bath overnight. The solution was diluted with Et_2O (50 mL), and filtered through a short plug of silica gel, washed with Et_2O (100 mL). The organic layer was washed with water (100 mL × 3), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 1/3, v/v) to afford HCF_2-Metalaxyl (714 mg, 62%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (s, 2 H), 6.55 (t, *J* = 56.2 Hz, 1 H), 4.46 (q, *J* = 7.4 Hz, 1 H), 3.74 (s, 3 H), 3.53 (d, *J* = 15.4 Hz, 1 H), 3.41 (d, *J* = 15.4 Hz, 1 H), 3.27 (s, 3 H), 2.46 (s, 3 H), 2.15 (s, 3 H), 0.94 (d, *J* = 7.4 Hz, 3 H); ^{19}F

NMR (376 MHz, $CDCl_3$) δ -111.02 (d, *J* = 56.2 Hz); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.7, 169.8, 139.9, 138.6, 137.8, 135.1 (t, *J* = 22.4 Hz), 126.7 (t, *J* = 5.7 Hz), 125.9 (t, *J* = 5.5 Hz), 114.1 (t, *J* = 239.5 Hz), 70.7, 59.5, 55.4, 52.4, 18.8, 18.5, 14.8 ppm. MS (ESI): 330.1 $[M+H]^+$; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{16}H_{21}O_4NF_2$: 330.1511; Found: 330.1508. IR (KBr): ν_{max} = 2988, 2952, 1747, 1673, 1454, 1381, 1200, 1171, 1091, 1024, 881, 742 cm^{-1}.

3-(Difluoromethyl)-5-(dimethylamino)phenyl dimethylcarbamate 8. The general **procedure A** conducted with Norneostigmine (62 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 35 mg (46%) product as a brown oil. Eluent: ethyl acetate/petroleum ether (1/4), R_f = 0.4. ^1H NMR (400 MHz, $CDCl_3$) δ 6.64 (s, 1 H), 6.59 (s, 1 H), 6.56 (t, *J* = 56.7 Hz, 1 H), 6.52 (s, 1 H), 3.09 (s, 3 H), 3.01 (s, 3 H), 2.97 (s, 6 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.14 (d, *J* = 56.7 Hz). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.9, 152.8, 151.7, 136.0 (t, *J* = 22.1 Hz), 114.8 (t, *J* = 239.5 Hz), 107.8, 106.9 (t, *J* = 5.9 Hz), 106.1 (t, *J* = 6.2 Hz), 40.6, 36.8, 36.6 ppm. MS (ESI): 259.1 $[M+H]^+$; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{12}H_{17}O_2N_2F_2$: 259.1253; Found: 259.1255. IR (KBr): ν_{max} = 2927, 1718, 1615, 1497, 1373, 1238, 1159, 1088, 877, 756, 741 cm^{-1}.

(S)-3-(Difluoromethyl)-5-(1-(dimethylamino)ethyl)phenyl ethyl(methyl) carbamate 9. The general **procedure A** conducted with Rivastigmine (75 mg, 0.30 mmol) in dry THF (1.5 mL) and then in dry DMF (3.0 mL) gave 45 mg (50%) product as a yellow oil. Eluent: dichloromethane/methanol (20/1), R_f = 0.4. ^1H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1 H), 7.20 (m, 2 H), 6.62 (t, *J* = 56.5 Hz, 1 H), 3.41 (m, 3 H), 3.03 (d, *J* = 29.5 Hz, 3 H), 2.22 (s, 6 H), 1.38 (d, *J* = 6.6 Hz, 3 H), 1.20 (m, 3 H).^{19}F NMR (376 MHz, $CDCl_3$) δ -110.96 (d, *J* = 56.4, rotamer 1), -110.98 (d, *J* = 56.4, rotamer 2). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 154.2 (rotamer 1), 154.0 (rotamer 2), 151.7 (d, *J* = 4.1 Hz), 146.9 (d, *J* = 10.9 Hz), 135.4 (t, *J* = 22.7 Hz), 123.1 (d, *J* = 8.5 Hz), 121.2 (q, *J* = 6.2 Hz), 117.7 (t, *J* = 6.1 Hz), 114.2 (t, *J* = 239.5 Hz), 65.5, 44.1, 43.2, 34.3 (rotamer 1), 33.8 (rotamer 2), 20.0, 13.2 (rotamer 1), 12.4 (rotamer 2) ppm. MS (ESI): 301.2 $[M+H]^+$; HRMS (ESI-Orbitrap) m/z: $[M+H]^+$ Calcd for $C_{15}H_{23}O_2N_2F_2$: 301.1722; Found: 301.1724. IR (KBr): ν_{max} = 2979, 2770, 1721, 1453, 1376, 1278, 1164, 1089, 1027, 968, 883, 755 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. ^{1}H, ^{19}F and ^{13}C NMR spectra of complexes **1**-**3**, **4a**-**y** and **5**-**7** (PDF); cif files of for single crystals of complexes **1**-**3** (cif)

AUTHOR INFORMATION

Corresponding Author

*shenql@sioc.ac.cn

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

The authors gratefully acknowledge the financial support from National Natural Science Foundation of China (21625206, 21632009, 21572258, 21421002) and the Strategic Priority Research Program of the Chinese Academy of Sciences (XDB20000000).

REFERENCES

1. Selected reviews for difluoromethylation: (a) Hu, J.-B.; Zhang, W.; Wang, F. Selective difluoromethylation and monofluoromethylation reactions. *Chem. Commun.* **2009**, 7465-7478; (b) Chen, B.; Vicic, D. A. Transition-Metal-Catalyzed Difluoromethylation, Difluoromethylylenation and Polydifluoromethylenation Reactions. *Top. Organometallic Chem.* **2015**, *52*, 113; (c) Lu, Y.; Liu, C.; Chen, Q.-Y. Recent Advances in Difluoromethylation Reaction. *Current Org. Chem*. **2015**, *19*, 1638; (d) Ni, C.-F.; Zhu, L.-G.; Hu, J.-B. Advances in Transition-Metal-Mediated Di- and Monofluoroalkylations. *Acta Chim. Sinica* **2015**, *73*, 90-115; (e) Belhomme, M.-C.; Besset, T.; Poisson, T.; Pannecoucke, X. Recent Progress toward the Introduction of Functionalized Difluoromethylated Building Blocks onto C(sp^2) and C(sp) Centers. *Chem. Eur. J.* **2015**, *21*, 12836-12865; (f) Rong, J.; Ni, C.-F.; Hu, J.-B. Mrtal-catalyze Direct Difluoromethylation Reactions. *Asian J. Org. Chem.* **2017**, *6*, 139-152.
2. (a) Sessler, C. D.; Rahm, M.; Becker, S.; Goldberg, J. M.; Wang, F.; Lippard, S. J. CF_2H, a Hydrogen Bond Donor. *J. Am. Chem. Soc.* **2017**, *139*, 9325-9332; (b) Zafrani, Y.; Yeffet, D.; Sod-Moriah, G.; Berliner, A.; Amir, D.; Marciano, D.; Gershonov, E.; Saphier, S. Difluoromethyl Bioisostere: Examining the "Lipophilic Hydrogen Bond Donor" Concept. *J. Med. Chem.* **2017**, *60*, 797-804.

3. (a) Meanwell. N. A. Fluorine and Fluorinated Motifs in the Design and Application of Bioisosteres for Drug Design. *J. Med. Chem.* **2018**, *61*, 5822-5880; (b) Narjes, F.; Koehler,K. F.; Koch, U.; Gerlach, B.; Colarusso, S.; Steinkühler, C.; Brunetti, M.; Sergio Altamura, S.; De Francesco, R.; Matassa, V. G. A designed P1 cysteine mimetic for covalent and non-covalent inhibitors of HCV NS3 protease. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 701-704.
4. Hansch, C.; Leo, A.; Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. *Chem. Rev.* **1991**, *91*, 165-195.
5. Selected reports for the formation of difluoromethylated arenes: (a) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. A New Method for Aromatic Difluoromethylation: Copper-Catalyzed Cross-Coupling and Decarboxylation Sequence from Aryl Iodides. *Org. Lett.* **2011**, *13*, 5560-5563; (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D.; Rodriguez, R. A.; Baxter, R. D.; Herlé, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. Practical and innate carbon–hydrogen functionalization of heterocycles. *Nature* **2012**, *492*, 95-99; (c) Xia, J.-B., Zhu, C.; Chen, C. Visible Light-Promoted Metal-Free C−H Activation: Diarylketone-Catalyzed Selective Benzylic Mono- and Difluorination. *J. Am. Chem. Soc.* **2013**, *135*, 17494-17500; (d) Xu, P.; Guo, S.; Wang, L.-Y.; Tang, P.-P. Silver-Catalyzed Oxidative Activation of Benzylic C_H Bonds for the Synthesis of Difluoromethylated Arenes. *Angew. Chem. Int. Ed.* **2014**, *53*, 5955-5958; (e) Deng, X.-Y.; Lin, J.-H.; Xiao, J.-C. Pd-Catalyzed Transfer of Difluorocarbene. *Org. Lett.* **2016**, *18*, 4384-4387; (f) Feng, Z.; Min, Q.-Q.; Fu, X.-P.; An, L.; Zhang, X.-G. Chlorodifluoromethane-triggered formation of difluoromethylated arenes catalysed by palladium. *Nat. Chem.* **2017**, *9*, 918-923; (g) Miao, W.-J.; Zhao, Y.-C.; Ni, C.-F.; Gao, B.; Zhang, W.; Hu, J.-B. Iron-Catalyzed Difluoromethylation of Arylzincs with Difluoromethyl 2-Pyridyl Sulfone. *J. Am. Chem. Soc.* **2018**, *140*, 880-883; (h) Pan, F.; Boursalian, G. B.; Ritter, T. Palladium-Catalyzed Decarbonylative Difluoromethylation of Acid Chlorides at Room Temperature. *Angew. Chem. Int. Ed.* **2018**, *57*, 16871-16876; (i) Zeng, X.; Yan, W.; Zacate, S. B.; Chao, T.-H.; Sun, X.; Cao, Z.; Bradford, K. G. E.; Paeth, M.; Tyndall, S. B.; Yang, K.; Kuo, T.-C.; Cheng, M.-J.; Liu, W. Copper-Catalyzed Decarboxylative Difluoromethylation. *J. Am. Chem. Soc.* **2019**, *141*, 11398-11403.
6. (a) Fier, P. S.; Hartwig, J. F. Copper Mediated Difluoromethylation of Aryl and Vinyl Iodides. *J. Am. Chem. Soc.* **2012**, *134*, 5524-5527; (b) Prakash, G. K. S.;

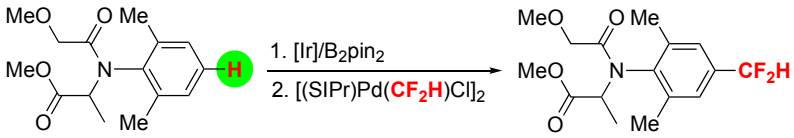
Ganesh, S. K.; Jones, J. P.; Kulkarni, A.; Masood, K.; Swabeck, J. K.; Olah, G. A. Copper-Mediated Difluoromethylation of (Hetero)aryl Iodides and β-Styryl Halides with Tributyl(difluoromethyl)stannane. *Angew. Chem., Int. Ed.* **2012**, *51*, 12090-12094; (c) Jiang, X.-L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. Copper-mediated difluoromethylation of electron-poor aryl iodides at room temperature. *Org. Chem. Front.* **2014**, *1*, 774-776; (d) Matheis, C.; Jouvin, K.; Goossen, L. Sandmeyer Difluoromethylation of (Hetero-)Arenediazonium Salts. *Org. Lett.* **2014**, *16*, 5984-5987; (e) Belhomme, M.-C.; Poisson, T.; Pannecoucke, X. Copper Catalyzed Direct C-2 Difluoromethylation of Furans and Benzofurans: Access to C-2-CF_2H Derivatives. *J. Org. Chem.* **2014**, *79*, 7205-7211; (f) Gu, Y.; Chang, D.-L.; Leng, X.-B.; Gu, Y.-C.; Shen. Q. Well-Defined, Shelf-Stable (NHC)Ag(CF_2H) Complexes for Difluoromethylation. *Organometallics* **2015**, *34*, 3065-3071; (g) Serizawa, H.; Ishii, K.; Aikawa, K.; Mikami, K. Copper-Catalyzed Difluoromethylation of Aryl Iodides with (Difluoromethyl)zinc Reagent. *Org. Lett.* **2016**, *18*, 3686-3689; (h) Li, X.-J.; Zhao, J.-W.; Hu, M.-Y.; Chen, D.-B.; Ni, C.-F.; Wang, L.-M.; Hu, J.-B. Copper-mediated aerobic (phenylsulfonyl)difluoromethylation of arylboronic acids with difluoromethyl phenyl sulfone. *Chem. Commun.* **2016**, *52*, 3657-3660; (i) Bour. J. R., Kariofillis. S. K., Sanford. M. S. Synthesis, Reactivity, and Catalytic Applications of Isolable. (NHC)Cu(CHF_2) Complexes. *Organometallics* **2017**, *36*, 1220-1223.

7. (a) Xu, L.; Vicic, D. A. Direct Difluoromethylation of Aryl Halides via Base Metal Catalysis at Room Temperature. *J. Am. Chem. Soc.* **2016**, *138*, 2536-2539; (b) Sheng, J.; Ni, H.-Q.; Bian, K.-J.; Li, Y.; Wang, Y.-N.; Wang, X.-S. Nickel-Catalyzed Direct Difluoromethylation of Aryl Boronic Aids with $BrCF_2H$. *Org. Chem. Front.* **2018**, *5*, 606-610; (c) Motohashi, H.; Mikami, K. Nickel-Catalyzed Aromatic Cross-Coupling Difluoromethylation of Grignard Reagents with Difluoroiodomethane. *Org. Lett.* **2018**, *20*, 5340-5343; (d) Bacauanu, V.; Cardinal, S.; Yamauchi, M.; Kondo, M.; Fernandez, D. F.; Remy, R.; MacMillan, D. W. C. Metallaphotoredox Difluoromethylation of Aryl Bromides. *Angew. Chem. Int. Ed.* **2018**, *57*, 12543-12548; (e) Gao, X.; He, X.; Zhang, X.-G. Nickel-Catalyzed Difluoromethylation of Arylboronic Acids with Bromodifluoromethane. *Chin. J. Org. Chem.* **2019**, *39*, 215-222.

8. (a) Gu, Y.; Leng, X.-B.; Shen, Q. Cooperative Dual Palladium/Silver Catalyst for Direct Difluoromethylation of aryl Bromides and Iodides. *Nat. Commun.* **2014**, *5*, 6405, 10.1038/ncomms6405; (b) Ge, S.-Z. ; Chaladaj, W. ; Hartwig, J. F. Pd-Catalyzed α-Arylation of α,α-Diflouroketones with Aryl Bromides and Chlorides. A Route to Difluoromethylarenes. *J. Am. Chem. Soc.* **2014**, *136*, 4149-4152; (c) Chang, D.-L.; Gu, Y.; Shen, Q. Pd-Catalyzed difluoromethylation of Vinyl Bromides, Tosylates and Nonaflates. *Chem. Eur. J.* **2015**, *21*, 6074-6078; (d) Aikawa, K.; Serizawa, H.; Mikami, K. Palladium-Catalyzed Negishi Cross-Coupling Reaction of Aryl Halides with (Difluoromethyl)zinc Reagent. *Org. Lett.* **2016**, *18*, 3690-3693; (e) Ferguson, D. M.; Malapit, C. A.; Bour, J. R.; Sanford, M. S. Palladium-Catalyzed Difluoromethylation of Aryl Chlorides and Bromides with $TMSCF_2H$. *J. Org. Chem.* **2019**, *84*, 3735-3740; (f) Nitta, J. Motohashi, H.; Aikawa, K.; Mikami, K. Palladium-Catalyzed Negishi Cross-Coupling Reaction of Difluoroiodomethane with Arylzinc Reagents. *Asian J. Org. Chem.* **2019**, *8*, 698-701.
9. Lu, C.-H.; Lu, H.; Wu, J.; Shen, C. H.; Hu, T.; Gu. Y.-C.; Shen. Q. Palladium-Catalyzed Difluoromethylation of Aryl Chlorides and Triflates and Its Applications in the Preparation of Difluoromethylated Derivatives of Drug/Agrochemical Molecules. *J.* Org. *Chem.* **2018**, *83*, 1077-1083.
10. Lu. C.-H.; Gu. Y.; Wu. J.; Gu. Y.-C.; Shen. Q. Palladium-catalyzed difluoromethylation of heteroaryl chlorides, bromides and iodides. *Chem. Sci.* **2017**, *8*, 4848-4852.
11. Zhu, S-Q.; Liu, Y.-L.; Li, H.; Xu, X.-H.; Qing, F.-L. Direct and Regioselective C−H Oxidative Difluoromethylation of Heteroarenes. *J. Am. Chem. Soc.* **2018**, *140*, 11613-11617.
12. Selected reviews for transition metal-catalyzed C-H functionalization: (a) Lyons, T. W.; Sanford, M. S. Palladium-Catalyzed Ligand-Directed C−H Functionalization Reactions. *Chem. Rev.* **2012**, *110*, 1147-1169; (b) Kuhl, N.; Hoplinson, M. N.; Wencel-Delord, J.; Glorius, F. Beyond Directing Groups: Transition-Metal-Catalyzed C-H Activation of Simple Arenes. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236-10254.

13. Dick, A. R.; Hull, K. L.; Sanford, M. S. A Highly Selective Catalytic Method for the Oxidative Functionalization of C−H Bonds.*J. Am. Chem. Soc.* **2004**, *126*, 2300-2301.
14. For an example of trasferring both ligands from Ag to Cu, see: Kaplan, P. T.; Vicic, D. A. Versatile Route to Arylated Fluoroalkyl Bromide Building Blocks. *Org. Lett.* **2016**, *18*, 884-886.
15. (a) Mkhalid, I. A.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. C−H Activation for the Construction of C−B Bonds. *Chem. Rev.* **2010**, *110*, 890-931; b) Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr; Smith, M. R., III, Remarkably Selective Iridium Catalysts for the Elaboration of Aromatic C-H Bonds. *Science* **2002**, *295*, 305–308.
16. Guarrera, M; Turbino, L; Rebora, A. The anti-inflammatory activity of azulene. *J. Eur. Acad. Dermatol. Venereol.* **2001**, *15*, 486-487.
17. Kimmel, E. C.; Casida, J. E.; Ruzo, L. O. Formamidine insecticides and chloroacetanilide herbicides: disubstituted anilines and nitrosobenzenes as mammalian metabolites and bacterial mutagens. *J. Agri. Food Chem.* **1986**, *34*, 157-161.
18. Hodgson, P. S.; Liu, S. S. New developments in spinal anesthesia. Clin. North America **2000**, 18, 235-249.
19. Jann, M. W. Rivastigmine, a New-Generation Cholinesterase Inhibitor for the Treatment of Alzheimer's Disease. *Pharmacotherapy* **2000**, *20*, 1-12.

Table of Content



Metalaxyl (977 mg) **HCF_2-Metalaxyl**, 62%