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Palladium-Catalyzed Difluoromethylation of Aryl Chlorides and Triflates and Its Applications in the Preparation of Difluoromethylated Derivatives of Drug/Agrochemical Molecules

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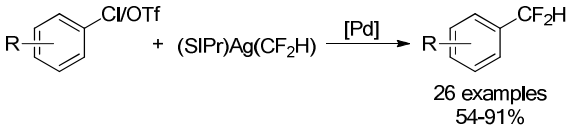


ABSTRACT: A palladium-catalyzed difluoromethylation of a series of aryl chlorides and triflates under mild conditions was described. A variety of common functional groups were tolerated. In addition, by using this protocol, several drug molecules containing an aryl chloride unit were successfully diflurometylated, thus enabling medicinal chemists to rapidly access novel drug derivatives with potentially improved properties via late-stage functionalization.

Modern drug discovery is a highly challenging, costly, laborious and time-consuming yet potentially highly rewarding process.[1] In general, drug discovery process involves different stages such as target identification and validation, lead generation, and lead optimization, which precedes clinical trials. In the lead generation and optimization stages, high-throughput screening (HTS) and structure-activity relationship study (SAR) of compounds are crucial to the success of a drug discovery program. It is the SAR stage in which the organofluorine chemistry may play an important role in facilitating the search of the lead compounds and preclinical candidates. Typically, by selective incorporation of a fluorine or a fluoroalkyl group into a specific position of a pharmacophore, the pharmacological and pharmacokinetic properties of the compound may be significantly improved in order to obtain an ideal profile of a preclinical candidate.[2] In this regard, introduction of a difluoromethyl group into the an biologically active compound has attracted considerable interest from both synthetic and medicinal chemists recently,[3-6] mainly due to the difluoromethyl group's unique physicochemical properties which could be translated into biological consequences. As such, in the past few years, a variety of methods for the introduction of difluoromethyl group (CF_2H) to small molecules have been reported.[7]

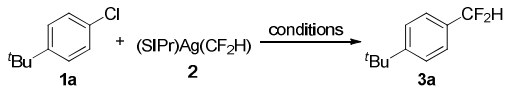
Among these methods, coupling of an aryl halide with a nucleophilic difluoromethyl reagent in the presence of a transition metal catalyst represents an attractive strategy with potentially broad applications.[8] In this regard, a number of copper,[8] nickel[9] or palladium-catalyzed difluoromethylation reactions[10] of aryl bromides or iodides have been reported recently. Nevertheless, the analogous coupling of aryl chlorides, to the best of our knowledge, has not been disclosed previously.[11] Comparing with aryl bromides and iodides, aryl chlorides are advantageous since they are much cheaper and more broadly commercially available.[12] Moreover, aryl chloride unit is a common drug fragment in many drug molecules such as desloratadine, montelukast sodium and fenofibrate, which allows for further derivatization and biological activity assessment.

Recently, we reported the preparation of a *N*-heterocyclic carbene (NHC) ligated difluoromethylated silver complex [(SIPr)Ag(CF_2H)] **2** (SIPr = 1,3-bis(2,6-diisopropylphenyl) imidazolin-2-ylidene),[13] which reacted efficiently with aryl bromides or iodides in the presence of a palladium catalyst. However, efforts to extend the difluoromethylation toward less reactive aryl chlorides were only partially successful. While activated heteroaryl chlorides such as 2-chloropyridine or its derivatives[11] reacted with [(SIPr)Ag(CF_2H)] **2** in the presence of a combination of $Pd(dba)_2$/Xantphos to give the corresponding difluoromethylated pyridine derivatives in acceptable yields, unactivated aryl chlorides did not react at all.

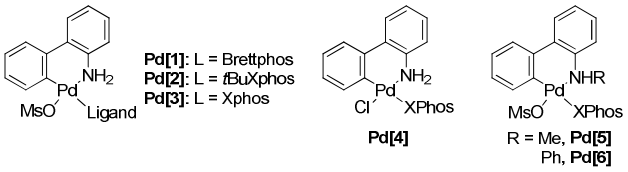
It was known that, to activate the strong aryl chloride bond, a catalyst derived from an electron-rich, sterically bulky phosphine is generally required.[12] Guided by these observations, to enable the direct difluoromethylation of unactivated aryl chlo-

rides, we then turned our attention to a palladium catalyst containing an electron-rich, sterically bulky phosphine ligand. Herein, we report the realization of such a cross-coupling reaction by employing a combination of Buchwald' precatalyst[14] with Xphos as the catalyst. Under these conditions, a variety of aryl chlorides and triflates reacted with reagent **2** to give the corresponding difluoromethylarenes in high yields. More importantly, drug molecules such as desloratadine, montelukast sodium and fenofibrate could also be successfully difluoromethylated in high yields.

Scheme 1. Optimization of the palladium-catalyzed difluoromethylation of 4-*tert*-butyl-chlorobezene.[a,b]



entry	[Pd]	ligand	yield (%)[b]	entry	[Pd]	ligand	yield (%)[b]
1	$Pd(dba)_2$	Xantphos	< 5%	8	**Pd[3]**	-	49%
2	$Pd(dba)_2$	dppe	< 5%	9	**Pd[4]**	-	23%
3	$Pd(dba)_2$	Xphos	< 5%	10	**Pd[5]**	-	< 5%
4	$Pd(dba)_2$	Brettphos	< 5%	11	**Pd[6]**	-	< 5%
5	$Pd(dba)_2$	DPEphos	< 5%	12	**Pd[3]**	XPhos	67%[c]
6	**Pd[1]**	-	30%	13	**Pd[3]**	Xphos	85%[d]
7	**Pd[2]**	-	20%	14	**Pd[3]**	Xphos	90%[e]

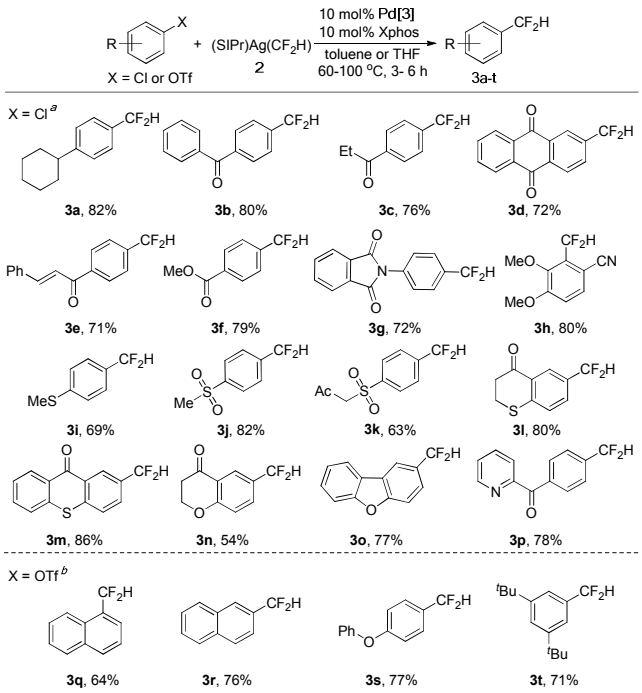


[a]Reaction condition: **1a** (16.8 mg, 0.100 mmol), (SIPr)Ag(CF_2H) **2** (72 mg, 0.13 mmol), [Pd] (5.0 mol %) and ligand (10.0 mol %) in toluene (1.0 mL) at 100 °C for 6 h under Ar atmosphere; [b]Yields were determined by ^{19}F NMR analysis of the crude reaction mixture with trifluorotoluene as an internal standard; [c][Pd] (5.0 mol %) and ligand (5.0 mol %) were used; [d][Pd] (7.0 mol %) and ligand (7.0 mol %) were used; [e][Pd] (10.0 mol %) and ligand (10.0 mol %) were used.

Initially, we chose the reaction of 4-*tert*-butyl-chlorobenzene **1a** with [(SIPr)Ag(CF_2H)] **2** in the presence of a palladium catalyst as a model reaction to optimize the reaction conditions. Our first attempts by using a combination of $Pd(dba)_2$ with a bidentate or monodendate ligand, such as DPPE, Xantphos, DPEphos, Xphos and Brettphos were unsuccessful, generally giving the corresponding difluoromethylarene in less than 10% yields (Scheme 1, entries 1-5). To our delight, the yields were improved significantly when Buchwald's precatalysts **Pd[1]**-**Pd[4]** were employed as the catalyst and much higher yields were obtained when **Pd[3]** was used (Scheme 1, entries 6-9). Replacement of the proton of the amino group in precatalyst **Pd[3]** by a methyl or phenyl group resulted in a dramatically decreased catalytic reactivity of **Pd[3]** (Scheme 1, entries 10-11). On the other hand, the yield of the reaction can be further improved to 67% by the addition of 5.0 mol% of Xphos (Scheme 1, entry 12). Finally, the yield was increased to 85% when 7.0 mol% **Pd[3]** and 7.0 mol% Xphos were used (Scheme 1, entry 13). Further increasing the catalyst loading to 10 mol% led to a slight yield increase to 90% (Scheme 1, entry 14).

Under the optimized condition described in entry 13 of Scheme 1, we investigated the generality of the palladium-catalyzed difluoromethylation of aryl chlorides. As summarized in Scheme 2, both electron-rich (**3a**, **3j, 3o**) and electron-

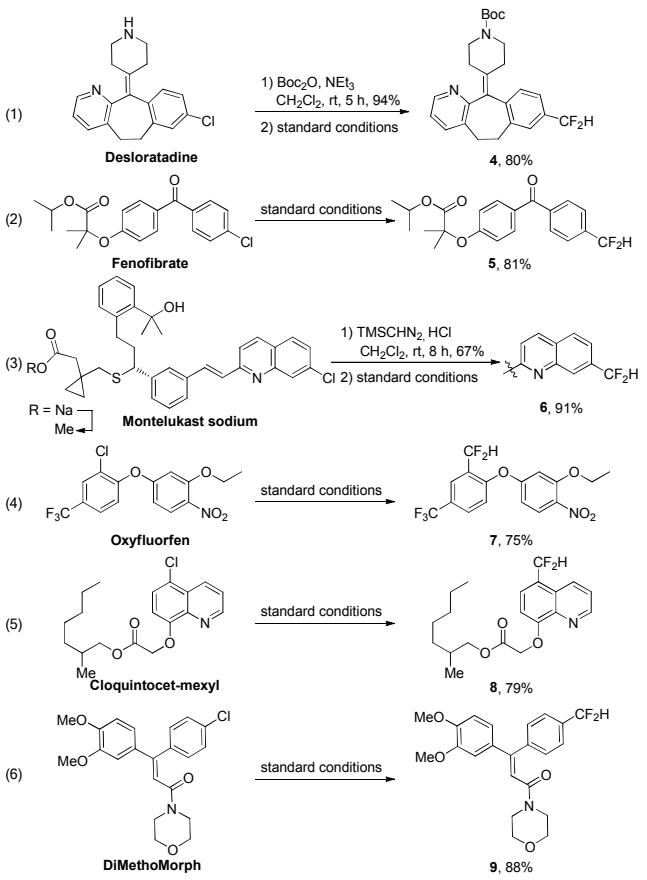
Scheme 2. Scope of the palladium-catalyzed difluoromethylation of aryl chlorides or triflates



[a]Reaction condition: aryl chloride (0.5 mmol), (SIPr)Ag(CF_2H) **2** (358 mg, 0.65 mmol), **Pd[3]** (29 mg, 7.0 mol %) and Xphos (17 mg, 7.0 mol %) in toluene (5.0 mL) at 100 °C for 3-6 h under Ar atmosphere. [b]Aryl triflate (0.5 mmol), (SIPr)Ag(CF_2H) **2** (358 mg, 0.65 mmol), **Pd[2]** (39 mg, 10.0 mol %) in THF (5.0 mL) at 70 °C for 8 h under Ar atmosphere.

poor in Scheme 2, both electron-rich (**3a**, **3j, 3o**) and electron-poor aryl chlorides (**3b**-**h**, **3j**-**n**, **3t**) reacted with reagent **2** to give the corresponding difluoromethylated compounds in high yields. Sterically hinder aryl chloride **1h** also reacted under the optimized conditions to give compound **3h** in 80% yield. Because the reactions were conducted under neutral conditions, a variety of base-sensitive functional groups such as enolizable ketone, ester, α,β-unsaturated ketone, cyano and sulfonyl groups were tolerant of the reaction conditions. In addition, heteroaryl chlorides bearing medicinally important heteroaryl moiety such as thiochromanone, 9*H*-thioxanthen-9-one, 4*H*-chromen-4-one, dibenzo[b,d]furan or pyridine were also compatible with the reaction conditions. It was found that reactions of electron-rich aryl triflates with reagent **2** in the presence of 10 mol% **Pd[2]** in THF took place with a full conversion after 8 h at 70 °C under a slightly modified conditions (See Table S1 in the supporting information for details). A few electron-rich aryl triflates were then successfully difluoromethylated in good yields (Scheme 2, **3q**-**t**). Reactions of electron-poor aryl triflates, however, were low yielding, although the reason is unclear at the moment.

To demonstrate the applicability of this difuoromethylating protocol, we chose to difluoromethlate a series of drug or agrochemical compounds that contain an aryl chloride or phenol moiety, as showing in Scheme 3. For example, Desloratadine,[15] which is used to treat allergic rhinitis and nasal congestion, can be successfully difluoromethylated to give compound **4** in 80% yield after the amino group was protected by a Boc group (Scheme 3, Eq. 1). Likewise, Fenofibrate,[16] a drug for treatment of high cholesterol and



Scheme 3. Difluoromethylation of drug or agrochemical compounds that contain an aryl chloride moiety.

high triglyceride levels, reacted with reagent **2** under standard conditions to give the difluoromethylated derivative **5** in 72% yield in **gram quantity** (Scheme 3, Eq. 2). Furthermore, Montelukast sodium,[17] the active ingredient of a blockbuster drug Singular for the treatment of asthma and to relieve symptoms of seasonal allergies, can be difluoromethylated in 91% yield after methylation of the carboxylic acid group (Scheme 3, Eq. 3).

Agrochemical compounds that containing an aryl chloride moiety can also be directly difluoromethylated in high yields. For example, Oxyfluorfen,[19] a selective pre- and post-emergence herbicide used to control certain annual broadleaf and grassy weeds in vegetables, was successfully difluoromethylated in 75% yield (Scheme 3, Eq. 4). Likewise, Cloquintocet-mexyl,[20] a herbicide safener, was difluoromethylated in 79% yield (Scheme 3, Eq. 5). In addition, DiMethoMorph,[21] a broad-spectrum fungicide, which contains an α,β-unsaturated amide unit, can be directly difluoromethylated in 88% yield (Scheme 3, Eq. 6). These results clearly domonstrate the power and potential of our new difluoromethylating protocol in the late stage modification of pharmaceutical or argochemical molecules.

In summary, we have developed a palladium-catalyzed direct difluoromethylation of aryl chlorides and triflates with (SIPr)Ag(CF_2H) **2** by employing an interesting combination of Buchwald's precatalyst and Xphos. Applications in the difluoromethylation of a couple of pharmaceutical and agrochemical molecules were demonstrated, thus providing the medicinal chemists a powerful tool in the late stage modification of drug compounds. Efforts to elucidation of the reaction mechanism and expand the scope of the reaction toward heteroaryl chlorides is currently undergoing in our lab.

EXPERIMENTAL SECTION

General information. All solvents were purified by standard method. All solvents were purified by standard method. ^{1}H , ^{13}C and ^{19}F NMR spectra were acquired on 400 MHz, 125 MHz, 100 MHz, 375 MHz spectrometer (400 MHz for ^{1}H ; 100 MHz or 125 MHz for ^{13}C; 375 MHz for ^{19}F). ^{1}H NMR and ^{13}C NMR chemical shifts were determined relative to internal standard TMS at δ 0.0 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, br = broad. Flash column chromatograph was carried out using 300-400 mesh silica gel at medium pressure.

All reagents were received from commercial sources. Solvents were freshly dried and degassed according to the purification handbook Purification of Laboratory Chemicals before using. [(SIPr)Ag(CF_2H)] **2** was prepared according to reported procedure.[10a]

General Procedure for palladium-catalyzed difluoromethyl -ation of aryl chlorides and triflates.

Method A

In an argon-filled glove box, aryl chlorides (0.50 mmol, 1.0 equiv), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), and [(SIPr)Ag(CF_2H)] **2** (357 mg, 1.30 equiv) were added in a Schlenk tube. Anhydrous toluene (2.0 mL) was added and the Schlenk tube was sealed and took out from the glove box. The mixture was stirred at 100 °C for 6~12 h. The brown solution was diluted with Et_2O (10.0 mL), and filtered through a short plug of silica gel, washed with Et_2O (20.0 mL). The organic layer was combined and concentrated under vacuum. The crude product was purified by column chromatography on silica gel with pentane/ethyl acetate (50/1) as the eluent to give the product.

Method B

Phenyl trifluoromethanesulfonate (0.5 mmol, 1.0 equiv), [(SIPr)Ag(CF_2H)] (358 mg, 0.65 mmol, 1.3 equiv), **Pd[2]** (39.7 mg, 0.05 mmol, 0.1 equiv) were added in a 20 mL Schlenk tube under argon. To the tube was added 7.5 mL of anhydrous THF and the mixture was stirred at 70 °C for 1.5 h. The dark solution was diluted with Et_2O (15.0 mL). The mixture was filtered through a short plug of silica gel, washed with Et_2O (100 mL). The organic layer was combined, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel with pentane as the eluent to give the product.

1-Cyclohexyl-4-(difluoromethyl)benzene 3a.[10b] The general procedure A conducted with 1-(*tert*-butyl)-4-chlorobenzene (97 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 50/1, R_f = 0.7) gave 1-cyclohexyl-4-(difluoromethyl)benzene **3a** (86 mg, 82%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 6.63 (t, *J* = 56.7 Hz, 1 H), 1.88

(s, 4 H), 1.78 (d, *J* = 12.4 Hz, 1 H), 1.52-1.34 (m, 4 H), 1.34-1.18 (m, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.70 (d, *J* = 56.7 Hz); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 150.9, 131.9 (t, *J* = 22.4 Hz), 127.2, 125.6 (t, *J* = 6.0 Hz), 114.97 (t, *J* = 238.0 Hz), 44.5, 34.3, 26.8, 26.1 ppm.

4-(Difluoromethyl)phenyl)(phenyl)methanone 3b.[10b] The general procedure A conducted with (4-chlorophenyl) (phenyl)methanone (108 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 30/1, R_f = 0.5) gave (4-(difluoromethyl)phenyl)(phenyl)methanone **3b** (93 mg, 80%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2 H), 7.80 (d, *J* = 7.3 Hz, 2 H), 7.61 (m, 3 H), 7.49 (t, *J* = 7.7 Hz, 2 H), 6.72 (t, *J* = 56.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.97 (d, *J* = 56.1 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 195.8, 139.7, 137.8 (t, *J* = 22.4 Hz), 137.0, 132.9, 130.2, 130.1, 128.4, 125.6 (t, *J* = 6.0 Hz), 114.1 (t, *J* = 239.7 Hz) ppm. MS (EI): 232 (100). HRMS (EI) *m/z*: [M^+] Calcd for: 232.0700; Found: 232.0695. IR (KBr): ν_{max} = 1649, 1597 cm^{-1}. Mp: 64.5 – 66.3 °C.

1-(4-(Difluoromethyl)phenyl)propan-1-one 3c.[22] The general procedure A conducted with 1-(4-chlorophenyl)propan-1-one (84 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 30/1, R_f = 0.6) gave 1-(4-(difluoromethyl)phenyl) propan-1-one **3c** (70 mg, 69%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.1 Hz, 2 H), 7.59 (d, *J* = 8.1 Hz, 2 H), 6.67 (t, *J* = 56.1 Hz, 1 H), 3.01 (q, *J* = 7.2 Hz, 2 H), 1.22 (t, *J* = 7.2 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.26 (d, *J* = 56.1 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 200.0, 138.7 (t, *J* = 1.9 Hz), 138.3 (t, *J* = 22.4 Hz), 128.3, 125.9 (t, *J* = 6.1 Hz), 114.0 (t, *J* = 239.7 Hz), 32.1, 8.1 ppm. Mp: 36.1 – 37.2 °C.

2-(Difluoromethyl)anthracene-9,10-dione 3d. The general procedure A conducted with 2-chloroanthracene-9,10-dione (121 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 20/1, R_f = 0.6) gave 2-(difluoromethyl)anthracene-9,10-dione **3d** (93 mg, 72%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 8.38 (d, *J* = 8.0 Hz, 1 H), 8.34 – 8.24 (m, 2 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.82 (dd, *J* = 5.8, 3.3 Hz, 2 H), 6.79 (t, *J* = 55.8 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.94 (d, *J* = 55.8 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 182.4, 182.2, 139.7 (t, *J* = 23.0 Hz), 134.9, 134.8, 134.5, 133.8, 133.3, 130.8 (t, *J* = 5.6 Hz), 128.0, 127.4, 127.4, 124.8 (t, *J* = 6.4 Hz), 113.5 (t, *J* = 240.8 Hz), 100.0 ppm. MS (EI): 258 (100). HRMS (EI) *m/z*: [M^+] Calcd for $C_{15}H_8F_2O_2$: 258.0492; Found: 258.0495. IR (KBr): ν_{max} = 3343, 1682, 1612 cm^{-1}. Mp: 130.6 – 131.2 °C.

(*E*)-1-(4-(Difluoromethyl)phenyl)-3-phenylprop-2-en-1-one 3e. The general procedure A conducted with (E)-1-(4-chlorophenyl)-3-phenylprop-2-en-1-one (121 mg, 0.500 mmol), Pd[5] (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 40/1, R_f = 0.6) gave (*E*)-1-(4-(difluoromethyl)phenyl)-3-phenylprop-2-en-1-one **3e** (91 mg, 71%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.1 Hz, 2 H), 7.83 (d, *J* = 15.7 Hz, 1 H), 7.66 (d, *J* = 8.1 Hz, 4 H), 7.51 (d, *J* = 15.7 Hz, 1 H), 7.46 – 7.41 (m, 3 H), 6.72 (t, *J* = 56.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.18 (d, *J* = 56.1 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 189.9, 145.7, 140.2 (t, *J* = 1.8 Hz), 138.1 (t, *J* = 22.3 Hz), 134.6, 130.8, 129.0, 128.8, 128.5, 125.9 (t, *J* = 6.0 Hz), 121.8, 114.0 (t, *J* = 239.8 Hz) ppm. HRMS (EI) *m/z*: [M^+] Calcd for $C_{16}H_{12}F_2O$: 258.0856; Found: 258.0854. IR (KBr): ν_{max} = 1943, 1683 cm^{-1}. Mp: 90.1 – 91.2 °C.

Methyl 4-(difluoromethyl)benzoate 3f.[13a] The general procedure A conducted with methyl 4-chlorobenzoate (85 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 40/1, R_f = 0.5) gave methyl 4-(difluoromethyl)benzoate **3f** (73 mg, 79%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 2 H), 7.58 (d, *J* = 8.0 Hz, 2 H), 6.69 (t, *J* = 56.1 Hz, 1 H), 3.94 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.30 (d, *J* = 56.1 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.2, 138.4 (t, *J* = 22.4 Hz), 132.3 (t, *J* = 1.8 Hz), 129.9, 125.6 (t, *J* = 6.0 Hz), 114.0 (t, *J* = 239.8 Hz), 52.4 ppm.

2-(4-(Difluoromethyl)phenyl)isoindoline-1,3-dione 3g. The general procedure A conducted with 2-(4-chlorophenyl) isoindoline-1,3-dione (128 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 10/1, R_f = 0.5) gave 2-(4-(difluoromethyl)phenyl)isoindoline -1,3-dione **3g** (98 mg, 72%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 5.3, 3.1 Hz, 2 H), 7.80 (dd, *J* = 5.3, 3.1 Hz, 2 H), 7.64 (d, *J* = 8.3 Hz, 2 H), 7.57 (d, *J* = 8.4 Hz, 2 H), 6.68 (t, *J* = 56.3 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.13 (d, *J* = 56.3 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.9, 134.6, 133.9 (t, *J* = 2.1 Hz), 133.8 (t, *J* = 22.6 Hz), 131.6, 126.6, 126.4 (t, *J* = 6.1 Hz), 123.9, 114.2 (t, *J* = 239.3 Hz) ppm. MS (EI): 273 (100). HRMS (EI) *m/z*: [M^+] Calcd for $C_{15}H_9F_2O_2N$: 273.0601; Found: 273.0599. IR (KBr): ν_{max} = 1712, 1616 cm^{-1}. Mp: 202.1 – 203.2 °C.

2-(Difluoromethyl)-3,4-dimethoxybenzonitrile 3h. The general procedure A conducted with 2-chloro-3,4-dimethoxy benzonitrile (98 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 30/1, R_f= 0.7) gave 2-(difluoromethyl)-3,4-dimethoxybenzonitrile **3h** (85 mg, 80%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.6 Hz, 1 H), 7.06 (s, 1 H), 7.04 (t, *J* = 53.9 Hz, 1 H), 3.96 (s, 3 H), 3.91 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.35 (d, *J* = 53.9 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.5, 148.2 (t, *J* = 5.3 Hz), 131.3, 129.9 (t, *J* = 22.9 Hz), 116.4, 114.1, 110.5 (t, *J* = 238.4 Hz), 101.7, 62.0, 56.2 ppm. MS (EI): 213 (100). HRMS (EI) *m/z*: [M^+] Calcd for $C_{10}H_9F_2NO_2$: 213.0601; Found: 213.0605. IR (KBr): ν_{max} = 2228, 1599 cm^{-1}. Mp: 73.2 – 73.2 °C.

(4-(Difluoromethyl)phenyl)(methyl)sulfane 3i.[10b] The general procedure A conducted with (4-chlorophenyl)(methyl) thioether (78 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 100/1, R_f =

0.5) gave 60 mg (69%) of (4-(difluoromethyl)phenyl)(methyl)sulfane as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.4 Hz, 2 H), 6.61 (t, *J* = 56.6 Hz, 1 H), 2.50 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.92 (d, *J* = 56.6 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 142.3 (t, *J* = 2.1 Hz), 130.8 (t, *J* = 22.7 Hz), 126.0 (t, *J* = 6.1 Hz), 125.9, 114.7 (t, *J* = 238.2 Hz), 15.2 ppm.

1-(Difluoromethyl)-4-(methylsulfonyl)benzene 3j. The general procedure B conducted with 1-chloro-4-(methylsulfonyl) benzene (94 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 40/1, R_f = 0.6) gave 1-(difluoromethyl)-4-(methylsulfonyl)benzene **3j** (84 mg, 82%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2 H), 7.72 (d, *J* = 8.1 Hz, 2 H), 6.72 (t, *J* = 55.8 Hz, 1 H), 3.07 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.82 (d, *J* = 55.8 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 142.8, 139.5 (t, *J* = 22.7 Hz), 128.0, 126.8 (t, *J* = 6.0 Hz), 113.4 (t, *J* = 240.6 Hz), 44.4 ppm. MS (EI): 127 (100), 206 (36.57). HRMS (EI) *m/z*: [M^+] Calcd for $C_8H_8F_2O_2S$: 206.0213; Found: 206.0216. Mp: 51.1 – 52.2 °C.

1-((4-(Difluoromethyl)phenyl)sulfonyl)propan-2-one 3k. The general procedure B conducted with 1-((4-chlorophenyl) sulfonyl)propan-2-one (116 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 30/1, R_f = 0.5) gave 1-((4-(difluoromethyl)phenyl)sulfonyl) propan-2-one **3k** (78 mg, 63%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2 H), 7.72 (d, *J* = 8.0 Hz, 2 H), 6.71 (t, *J* = 55.8 Hz, 1 H), 4.18 (s, 2 H), 2.39 (s, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.18 (d, *J* = 55.8 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 195.7, 140.9, 140.0 (t, *J* = 21.8 Hz), 128.9, 126.7 (t, *J* = 6.1 Hz), 113.3 (t, *J* = 240.9 Hz), 67.3, 31.5 ppm. MS (EI): 127 (100), 248 (4.18). HRMS (EI) *m/z*: [M^+] Calcd for $C_{10}H_{10}F_2O_3S$: 248.0319; Found: 248.0317. IR (KBr): ν_{max} = 3422, 1934, 1717 cm^{-1}. Mp: 67.2 – 68.1 °C.

6-(Difluoromethyl)thiochroman-4-one 3l. The general procedure A conducted with 6-chlorothiochroman-4-one (99 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 40/1, R_f = 0.5) gave 6-(difluoromethyl)thiochroman-4-one **3l** (85.6 mg, 80%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1 H), 7.54 (d, *J* = 8.2 Hz, 1 H), 7.39 (d, *J* = 8.3 Hz, 1 H), 6.63 (t, *J* = 56.2 Hz, 1 H), 3.29 (dd, *J* = 7.5, 5.5 Hz, 2 H), 3.02 (dd, *J* = 7.5, 5.5 Hz, 2 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.71 (d, *J* = 56.2 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 193.1, 145.4, 131.3 (t, *J* = 23.2 Hz), 130.8, 129.7 (t, *J* = 5.2 Hz), 128.3, 126.8 (t, *J* = 6.8 Hz), 114.0 (t, *J* = 239.0 Hz), 39.1, 26.5 ppm. MS (EI): 186 (100), 214 (45.06). HRMS (EI) *m/z*: [M^+] Calcd for $C_{10}H_8F_2OS$: 214.0264; Found: 214.0266. IR (KBr): ν_{max} = 1672, 1604 cm^{-1}. Mp: 79.3 – 80.2 °C.

2-(Difluoromethyl)-9*H*-thioxanthen-9-one 3m. The general procedure A conducted with 2-chloro-9*H*-thioxanthen-9-one (123 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 20/1, R_f = 0.7) gave 2-(difluoromethyl)-9*H*-thioxanthen-9-one **3m** (113 mg, 86%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.73 (s, 1 H), 8.64 (d, *J* = 8.1 Hz, 1 H), 7.79 (d, *J* = 8.3 Hz, 1 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.66 (d, *J* = 7.0 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 7.53 (t, *J* = 7.5 Hz, 1 H), 6.78 (t, *J* = 56.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -106.56 (d, *J* = 56.1 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 179.2, 139.9, 136.8, 132.7, 130.0, 129.1, 129.1, 128.6 (t, *J* = 4.9 Hz), 127.7 (t, *J* = 7.0 Hz), 126.9, 126.8, 126.1, 114.1 (t, *J* = 238.1 Hz), 110.0 ppm. MS (EI): 179 (100), 262 (42.29). HRMS (EI) *m/z*: [M^+] Calcd for $C_{14}H_8F_2SO$: 262.0266; Found: 262.0265. IR (KBr): ν_{max} = 1949, 1636 cm^{-1}. Mp: 155 – 157 °C.

6-(Difluoromethyl)chroman-4-one 3n. The general procedure A conducted with 6-chlorochroman-4-one (91 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 30/1, R_f = 0.6) gave 6-(difluoromethyl)chroman-4-one **3n** (53 mg, 54%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1 H), 7.64 (d, *J* = 9.5 Hz, 1 H), 7.07 (d, *J* = 8.7 Hz, 1 H), 6.61 (t, *J* = 56.3 Hz, 1 H), 4.58 (t, *J* = 6.4 Hz, 2 H), 2.85 (t, *J* = 6.4 Hz, 2 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.60 (d, *J* = 56.3 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 190.9, 163.3, 145.4, 132.6 (t, *J* = 5.0 Hz), 125.3 (t, *J* = 6.8 Hz), 120.9, 118.8, 114.1 (t, *J* = 238.4 Hz), 67.2, 37.5 ppm. HRMS (EI) *m/z*: [M^+] Calcd for $C_{10}H_8F_2O_2$: 198.0492; Found: 198.0487. IR (KBr): ν_{max} = 3367, 1691 cm^{-1}. Mp: 62.3 – 63.7 °C.

2-(Difluoromethyl)dibenzo[*b*,*d*]furan 3o.[11] The general procedure A conducted with 2-chlorodibenzo[b,d]furan (101 mg, 0.500 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 50/1, R_f = 0.7) gave 2-(difluoromethyl)dibenzo[*b*,*d*] furan **3o** (84 mg, 77%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1 H), 7.98 (d, *J* = 7.6 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.61 (d, *J* = 4.0 Hz, 2 H), 7.51 (t, *J* = 7.7 Hz, 1 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 6.82 (t, *J* = 56.7 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.84 (d, *J* = 56.6 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 156.7, 127.9, 124.6 (t, *J* = 5.9 Hz), 124.6, 123.6, 123.2, 123.2, 121.1, 120.9, 118.4 (t, *J* = 6.3 Hz), 115.0 (t, *J* = 238.6 Hz), 112.0, 111.9 ppm.

(4-(Difluoromethyl)phenyl)(pyridin-2-yl)methanone 3p. The general procedure A conducted with (4-chlorophenyl) (pyridin-2-yl)methanone (108 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 10/1, R_f = 0.7) gave (4-(difluoromethyl)phenyl)(pyridin-2-yl)methanone **3p** (91 mg, 78%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (d, *J* = 4.6 Hz, 1 H), 8.16 (d, *J* = 8.1 Hz, 2 H), 8.10 (d, *J* = 7.9 Hz, 1 H), 7.92 (t, *J* = 7.7 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.51 (dd, *J* = 7.5, 4.8 Hz, 1 H), 6.71 (t, *J* = 56.1 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.32 (d, *J* = 56.1 Hz, 2 F); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 193.0, 154.4, 148.6, 138.4 (t, *J* = 2.0 Hz), 138.1 (t, *J* = 22.4 Hz), 137.2, 131.3, 126.6, 125.3 (t, *J* = 6.1 Hz), 124.7, 114.1 (t, *J* = 239.7 Hz) ppm. MS (EI): 205 (100), 233 (33.46). HRMS (EI)

m/z: [M$^+$] Calcd for $C_{13}H_9F_2NO$: 233.0652; Found: 233.0648. IR (KBr): ν_{max} = 1669, 1615 cm^{-1}.

1-(Difluoromethyl)naphthalene 3q.[13a] The general procedure B conducted with naphthalen-1-yl trifluoromethanesulfonate (138 mg, 0.500 mmol), **Pd[2]** (39.7 mg, 0.05 mmol, 0.1 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol) in dry THF (7.5 mL), purified by column chromatography (petroleum ether/ethyl acetate = 60/1, R_f = 0.7) gave 1-(difluoromethyl)naphthalene **3q** (57 mg, 64%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.1 Hz, 1 H), 7.96 (dd, *J* = 16.3, 8.1 Hz, 2 H), 7.73 (d, *J* = 6.9 Hz, 1 H), 7.69-7.56 (m, 2 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.17 (t, *J* = 55.2 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.77 (d, *J* = 55.2 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 133.8, 131.5, 129.8-129.7(m), 129.6, 128.8, 127.2, 126.4, 124.8 (t, *J* = 8.7 Hz), 124.7, 123.6, 115.5 (t, *J* = 238.4 Hz) ppm.

2-(Difluoromethyl)naphthalene 3r.[10a] The general procedure B conducted with naphthalen-2-yl trifluoromethanesulfonate (138 mg, 0.500 mmol), **Pd[2]** (39.7 mg, 0.05 mmol, 0.1 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol) in dry THF (7.5 mL), purified by column chromatography (petroleum ether/ethyl acetate = 80/1, R_f = 0.5) gave 1-(difluoromethyl)naphthalene **3r** (67 mg, 76%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03-7.82 (m, 4 H), 7.57 (tdd, *J* = 9.2, 8.1, 1.4 Hz, 3 H), 6.81 (t, *J* = 56.4 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.90 (d, *J* = 56.4 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 134.3, 132.6, 131.6 (t, *J* = 22.3 Hz), 128.9, 128.5, 127.9, 127.4, 126.8, 125.9 (t, *J* = 7.5 Hz), 122.0 (t, *J* = 4.8 Hz), 115.0 (t, *J* = 238.5 Hz) ppm.

1-(Difluoromethyl)-4-phenoxybenzene 3s.[8e] The general procedure B conducted with 4-phenoxyphenyl trifluoromethane sulfonate (159 mg, 0.500 mmol), **Pd[2]** (39.7 mg, 0.0500 mmol, 0.100 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol) in dry THF (7.5 mL), purified by column chromatography (petroleum ether/ethyl acetate = 60/1, R_f = 0.6) gave 1-(difluoromethyl)-4-phenoxybenzene **3s** (85 mg, 77%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.7 Hz, 2 H), 7.42 – 7.33 (m, 2 H), 7.16 (t, *J* = 7.4 Hz, 1 H), 7.04 (d, *J* = 8.0 Hz, 4 H), 6.62 (t, *J* = 56.6 Hz, 1 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.99 (d, *J* = 56.6 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 159.6 (t, *J* = 1.9 Hz), 156.2, 130.0, 128.9 (t, *J* = 22.7 Hz), 127.4 (t, *J* = 6.0 Hz), 124.1, 119.7, 118.3, 114.6 (t, *J* = 238.0 Hz) ppm.

1,3-Di-*tert*-butyl-5-(difluoromethyl)benzene 3t.[10b] The general procedure B conducted with 3,5-di-*tert*-butylphenyl trifluoro methanesulfonate (169 mg, 0.500 mmol), **Pd[2]** (39.7 mg, 0.0500 mmol, 0.100 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol) in dry THF (7.5 mL), purified by column chromatography (petroleum ether/ethyl acetate = 100/1, R_f = 0.8) gave 1,3-di-*tert*-butyl-5-(difluoromethyl)benzene **3t** (120 mg, 71%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1 H), 7.37 (d, *J* = 0.5 Hz, 1 H), 6.65 (t, *J* = 56.7 Hz, 2 H), 1.37 (s, 18 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -109.36 (d, *J* = 56.7 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 151.5, 133.7 (t, *J* = 21.6 Hz), 124.9, 119.7 (t, *J* = 6.0 Hz), 115.6 (t, *J* = 238.4 Hz), 35.0, 31.4 ppm.

Preparation of *N*-Boc desloraradine. In a 500 mL round-bottom flask, Desloratadine (310 mg, 1.00 mmol) and NEt_3 (202 mg, 2.00 mmol) were dissolved in dichloromethane (10.0 mL). Boc_2O (436 mg, 2.00 mmol) was added dropwise to the solution. The mixture was stirred at room temperature for 5 h. The mixture was concentrated in vacuo. The resulting residue was purified by flash chromatography (eluent: hexane / EtOAc = 4:1) to give the desired *N*-Boc desloratadine as a white solid (388 mg, 94 %). ***N*-Boc desloratadine.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (d, *J* = 3.6 Hz, 1 H), 7.43 (d, *J* = 7.7 Hz, 1 H), 7.16 (s, 1 H), 7.14 – 7.03 (m, 3 H), 3.76 (s, 2 H), 3.37 (dd, *J* = 14.5, 11.9 Hz, 2 H), 3.08 (dd, *J* = 10.8, 5.0 Hz, 2 H), 2.82 (dd, *J* = 16.7, 11.2 Hz, 2 H), 2.45 (dd, *J* = 11.6, 7.1 Hz, 2 H), 2.31 (dd, *J* = 14.9, 9.8 Hz, 2 H), 1.45 (s, 9 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 157.2, 154.8, 146.7, 139.5, 137.8, 137.7, 137.5, 134.0, 133.3, 132.9, 130.6, 129.0, 126.2, 122.2, 79.6, 31.7, 31.5, 30.8, 30.6, 28.4 ppm. MS (EI): 57 (100), 410 (34.9). HRMS (EI) *m/z*: [M$^+$] Calcd for $C_{24}H_{27}N_2O_2Cl$: 410.1761; Found: 410.1765. IR (KBr): ν = 1691, 1648 cm^{-1}. Mp: 157 – 160 °C.

Difluoromethylation derivertives of Boc protected Desloratadine 4. The general procedure A conducted with *N*-Boc desloratadine (205 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 4/1, R_f = 0.6) gave compound **4** (170 mg, 80%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 4.8 Hz, 1 H), 7.40 (d, *J* = 7.7 Hz, 1 H), 7.29 (s, 1 H), 7.26 (s, 2 H), 7.06 (dd, *J* = 7.7, 4.8 Hz, 1 H), 6.55 (t, *J* = 56.5 Hz, 1 H), 3.75 (s, 2 H), 3.52 – 3.27 (m, 2 H), 3.06 (dd, *J* = 9.5, 6.9 Hz, 2 H), 2.84 (d, *J* = 13.0 Hz, 2 H), 2.46 (t, *J* = 9.2 Hz, 1 H), 2.37 – 2.17 (m, 3 H), 1.42 (s, 9 H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.28 (d, *J* = 56.6 Hz, 2 F). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.9, 154.8, 146.7, 142.0, 138.4, 138.0, 137.6, 134.3, 133.4, 133.4 (t, *J* = 22.3 Hz), 129.6, 126.1 (t, *J* = 5.9 Hz), 123.3 (t, *J* = 6.0 Hz), 122.3, 114.7 (t, *J* = 238.5 Hz), 79.6, 31.8, 31.6, 30.8, 30.6, 28.4 ppm. MS (EI): 57 (100), 426 (27.2). HRMS (EI) *m/z*: [M$^+$] Calcd for $C_{25}H_{28}N_2O_2F_2$: 426.2119; Found: 426.2116. IR (KBr): ν_{max} = 3366, 1689 cm^{-1}.

Isopropyl 2-(4-(4-(difluoromethyl)benzoyl)phenoxy)-2-methylpropanoate 5. The general procedure A conducted with Fenofibrate (180 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 20/1, R_f = 0.5) gave isopropyl 2-(4-(4-(difluoromethyl)benzoyl) phenoxy)-2-methylpropanoate **5** (152 mg, 81%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 2 H), 7.73 (d, *J* = 8.6 Hz, 2 H), 7.58 (d, *J* = 7.7 Hz, 2 H), 6.85 (d, *J* = 8.6 Hz, 2 H), 6.68 (t, *J* = 56.1 Hz, 1 H), 5.54 – 4.33 (m, 1H), 1.64 (s, 6 H), 1.17 (d, *J* = 6.2 Hz, 6 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -111.85 (d, *J* = 56.1 Hz, 2 F). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 194.5, 173.0, 159.9, 140.3 (t, *J* = 1.6 Hz), 137.3 (t, *J* = 22.5 Hz), 132.0, 130.0, 129.8, 125.5 (t, *J* = 6.0 Hz), 117.2, 114.1 (t, *J* = 239.5 Hz), 79.4, 69.3, 25.3, 21.5 ppm. MS (EI): 121 (100), 376 (7.26). HRMS (EI) *m/z*: [M$^+$] Calcd for $C_{21}H_{22}F_2O_4$: 376.1486; Found: 376.1481. IR (KBr): ν = 1941, 1728, 1654 cm^{-1}. Mp: 83.1 – 83.6 °C.

Gram scale preparation of difluoromethylated methyl Montelukast 5. The general procedure A conducted with Fenofibrate (1.8 g, 5 mmol), **Pd[3]** (290 mg, 0.070 equiv), Xphos (170 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (3.57 g, 6.50 mmol), in dry toluene (25.0 mL) gave isopropyl 2-(4-(4-(difluoromethyl)benzoyl) phenoxy)-2-methylpropanoate **5** (1.35 g, 72%) as a yellow solid.

Montelukast sodium (607 mg, 1.00 mmol) was dissolved in CH_2Cl_2 (10.0 mL), then 10% HCl aqueous solution was added dropwise and the mixture was stirred at room temperature for 1 h. $TMSCHN_2$ in hexane (1 mL, 2 M) was then added dropwise at room temperature. Nitrogen was released gradually. After 8 h, the reaction was completed as monitored by TLC. The mixture was concentrated in *vacuo*. The residue was redissolved in dichloromethane (50.0 mL) and the solution was washed successively with 10 % aqueous NaCl solution (2 × 30 mL). The organic phase was combined, dried over anhydrous Na_2SO_4, filtered and then concentrated in *vacuo*. The resulting residue was purified by flash chromatography (eluent: hexane / EtOAc = 20:1 to 5:1) to give the methyl Montelukast as a yellow oil (510 mg, 67%).

Methyl Montelukast. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.01 (m, 2 H), 7.80 – 7.59 (m, 4 H), 7.52 (d, *J* = 7.6 Hz, 1 H), 7.47 – 7.27 (m, 4 H), 7.23 – 7.01 (m, 4 H), 5.27 (s, 2 H), 5.12 (s, 1 H), 4.80 (s, 1 H), 3.97 – 3.76 (m, 1 H), 3.61 (s, 3 H), 2.96 – 2.66 (m, 1 H), 2.67 – 2.55 (m, 1 H), 2.45 (dd, *J* = 29.9, 9.7 Hz, 3 H), 2.31 – 2.07 (m, 3 H), 1.96 (s, 3 H), 0.45 (dt, *J* = 22.3, 8.0 Hz, 4 H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 172.6, 156.9, 148.6, 145.4, 143.7, 143.5, 138.0, 136.5, 136.2, 135.6, 135.1, 129.3, 129.0, 128.7, 128.6, 128.3, 128.2, 127.1, 127.0, 126.9, 126.2, 125.9, 125.7, 119.6, 115.1, 53.5, 51.4, 49.9, 39.9, 39.2, 38.8, 31.3, 25.1, 16.9, 12.8, 12.4 ppm. HRMS (MALDI-FT) *m/z*: [M^+] Calcd for $C_{36}H_{38}ClNO_3S$: 600.2334; Found: 600.2330. IR (KBr): ν_{max} = 1734, 1607, 1594 cm^{-1}.

Difluoromethylated Methyl Montelukast 6. The general procedure A conducted with methyl Montelukast (300 mg, 0.50 mmol), **Pd[3]** (29 mg, 0.070 equiv), Xphos (17 mg, 0.070 equiv), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), in dry toluene (2.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 10/1, R_f = 0.4) gave Difluoromethylated Methyl Montelukast **6** (280 mg, 91%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.05 (m, 2 H), 7.88 (d, *J* = 8.4 Hz, 1 H), 7.80 – 7.70 (m, 2 H), 7.63 (d, *J* = 7.4 Hz, 2 H), 7.53 (d, *J* = 7.6 Hz, 1 H), 7.47 – 7.27 (m, 3 H), 7.13 (ddd, *J* = 23.9, 18.5, 7.6 Hz, 4 H), 6.84 (t, *J* = 56.1 Hz, 1 H), 5.29 (s, 1 H), 5.11 (s, 1 H), 4.79 (s, 1 H), 3.94 – 3.79 (m, 1 H), 3.61 (s, 3 H), 2.66 (dd, *J* = 40.5, 5.5 Hz, 2 H), 2.55 – 2.29 (m, 4 H), 2.15 (dd, *J* = 25.2, 13.1 Hz, 3 H), 1.96 (s, 3 H), 1.78 (s, 1 H), 0.60 – 0.29 (m, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.66 (d, *J* = 56.1 Hz); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 172.7, 156.9, 147.7, 145.4, 143.7, 143.5, 138.0, 136.5, 136.2, 135.5 (t, *J* = 22.6 Hz), 135.2, 129.2, 128.6 (t, *J* = 33.4 Hz), 128.6, 128.4, 127.3 (t, *J* = 7.4 Hz), 126.9, 126.9, 125.9, 122.3 (t, *J* = 4.8 Hz), 120.7, 115.0, 114.6 (t, *J* = 239.3 Hz), 53.4, 51.4, 49.9, 39.9, 39.2, 38.7, 31.3, 25.1, 16.9, 12.7, 12.4 ppm. HRMS (MAILDIFT_DHB) *m/z*: [M+H]$^+$ Calcd for $C_{37}H_{39}SO_3NF_2$: 615.2619; Found: 616.2691. IR (KBr): ν_{max} = 1734, 1636 cm^{-1}.

1-Nitro-4-(2-(difluoromethyl)-4-(trifluoromethyl)phenoxy)-2-ethoxybenzene 7. The general procedure A was conducted with Cloquintocet-mexyl (180 mg, 0.500 mmol), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), **Pd[3]** (42 mg, 10 mol%), Xphos (24 mg, 10 mol%) in dry toluene (5.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 40/1, R_f = 0.5) gave 1-nitro-4-(2-(difluoromethyl)-4-(trifluoromethyl)phenoxy)-2-ethoxybenzene **7** (142 mg, 75%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.93 (d, *J* = 8.9 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 6.74 (s, 1 H), 6.58 (d, *J* = 8.9 Hz, 1 H), 4.13 (dd, *J* = 13.7, 6.7 Hz, 2 H), 1.48 (t, *J* = 6.8 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.33 (s, 3 F), -115.56 (d, *J* = 54.8 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 160.2, 156.1 (t, *J* = 5.5 Hz), 154.7, 136.2, 129.6, 128.0, 127.2 (dd, *J* = 67.3, 33.4 Hz), 126.4 (t, *J* = 23.4 Hz), 124.9 (td, *J* = 9.4, 3.4 Hz), 122.0, 120.4 – 117.5 (m), 110.4 (t, *J* = 238.6 Hz), 109.6, 105.1, 65.8, 14.4 ppm. MS (EI): 377 (100). HRMS (EI) *m/z*: [M^+] Calcd for $C_{16}H_{12}NO_4F_5$: 377.0686; Found: 377.0678. IR (KBr): ν_{max} = 1621, 1520 cm^{-1}. Mp：96 – 97 °C.

Heptan-2-yl-2-((5-(difluoromethyl)quinolin-8-yl)oxy) acetate 8. The general procedure A was conducted with Cloquintocet-mexyl (174 mg, 0.500 mmol), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), **Pd[3]** (42 mg, 10 mol%), Xphos (24 mg, 10 mol%) in dry toluene (5.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 20/1, R_f = 0.6) gave heptan-2-yl 2-((5-(difluoromethyl)quinolin-8-yl)oxy) acetate **8** (145 mg, 79%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.95 (s, 1 H), 8.46 (d, *J* = 8.5 Hz, 1 H), 7.56 – 7.43 (m, 1 H), 6.85 (d, *J* = 8.0 Hz, 2 H), 4.98 (dd, *J* = 12.7, 6.4 Hz, 1 H), 4.89 (d, *J* = 11.0 Hz, 2 H), 2.62 (s, 1 H), 1.56 – 1.44 (m, 1 H), 1.39 (d, *J* = 7.9 Hz, 1 H), 1.26 – 1.03 (m, 9 H), 0.77 (t, *J* = 6.3 Hz, 3 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -107.94 (d, *J* = 54.9 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 167.9, 155.9, 149.8, 140.2, 132.4, 126.3, 126.2 (t, *J* = 9 Hz), 122.8, 122.5, 115.6 (t, *J* = 237.9 Hz), 107.3, 72.9, 66.1, 35.6, 31.4, 24.9, 22.4, 19.8, 13.9 ppm. MS (EI): 208 (100), 351 (0.12). HRMS (DART POSITIVE Ion Mode) *m/z*: [M^+] Calcd for $C_{19}H_{24}NO_3F_2$: 352.1719; Found: 352.1715. IR (KBr): ν = 3449, 1732, 1605, cm^{-1}.

(*E*)-3-(4-(Difluoromethyl)phenyl)-3-(3,4-dimethoxyphenyl) -1-morpholinoprop-2-en-1-one 9. The general procedure A was conducted with DiMethoMorph (E/Z isomers = 1:1.8) (194 mg, 0.500 mmol), [(SIPr)Ag(CF_2H)] **2** (357 mg, 0.650 mmol), **Pd[3]** (42 mg, 10 mol%), Xphos (24 mg, 10 mol%) in dry toluene (5.0 mL), purified by column chromatography (petroleum ether/ethyl acetate = 10/1, R_f = 0.6) gave (*E,Z*)-3-(4-(difluoromethyl)phenyl)-3-(3,4-dimethoxyphenyl)-1-morpholinoprop-2-en-1-one **9** (E/Z isomers = 1:1.8) (178 mg, 88%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.0 Hz, 1 H), 7.37 (d, *J* = 8.1 Hz, 1 H), 7.27 (dd, *J* = 16.4, 8.8 Hz, 2 H), 6.66 (dddd, *J* = 97.1, 65.3, 33.5, 8.6 Hz, 4 H), 6.19 (d, *J* = 35.2 Hz, 1 H), 3.78 (d, *J* = 9.0 Hz, 3 H), 3.70 (d, *J* = 4.1 Hz, 3 H), 3.44 (d, *J* = 5.1 Hz, 2 H), 3.39 (d, *J* = 4.7 Hz, 2 H), 3.24 – 2.96 (m, 4 H). (td, *J* = 8.7, 2.2 Hz, 4 H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -110.98 (dd, *J* = 74.3, 56.4 Hz, 2 F); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.9 (d, *J* = 33.1 Hz), 149.8, 149.6, 148.8, 146.9, 146.3, 143.3, 141.4, 134.5 (td, *J* = 22.4, 4.5 Hz), 132.9, 130.7, 129.7, 128.5, 126.7 – 125.0 (m), 122.2, 121.2, 120.7, 119.7, 114.4 (d, *J* = 6.6 Hz), 114.4 (td, *J* = 238.8, 6.6 Hz), 112.5, 110.9 (t, *J* = 3.2 Hz), 66.3 (d, *J* = 4.7 Hz), 55.9 (dd, *J* = 6.3, 3.0 Hz), 46.6, 41.4 (d, *J* = 7.9 Hz) ppm. MS (EI): 317 (100), 403 (24.53). HRMS (EI) *m/z*: [M^+] Calcd for $C_{22}H_{23}O_4NF_2$: 403.1595; Found: 403.1599. IR (KBr): ν_{max} = 3480, 2251, 1628 cm^{-1}.

ASSOCIATED CONTENT

Supporting Information

Spectroscopic data of compounds **3a-t**, **4-10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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