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Palladium-Catalyzed *para*-Selective Difluoromethylation of Arene Esters

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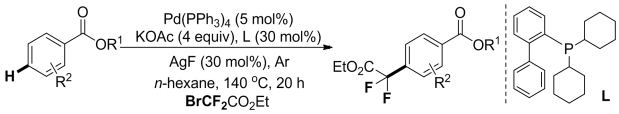
ABSTRACT: A highly efficient, palladium-catalyzed, *para*-selective difluoromethylation of arene esters has been developed using [1,1'-biphenyl]-2-dicyclohexylphosphine as the effective ligand. A wide variety of arene esters bearing various functional groups were all compatible with the reaction conditions, leading to *para*-difluoromethylated products in moderate to good yields. Moreover, benzoylamide and benzenesulfonamide were also well-tolerated, suggesting this novel catalyst system has broad application to a variety of substrates.



INTRODUCTION

Arene esters are key structural motifs that exist in a vast range of bioactive molecules and drugs such as benzyl benzoate, cocaine, hexylcaine, flavoxate, and bopindolol (shown in Figure 1). More importantly, the ester group is not only widely available but also easily converted into other functional groups, including amides, alcohols, or other carbonyl compounds.[1] The development of a novel method to functionalize arene esters directly is highly important. Although ester assisted, *ortho*-selective C-H reactions have been extensively explored in recent years,[2-7] *para*-selective C-H functionalization of arene esters remains rare (Scheme 1). Several strategies have selectively functionalized *para* C-H bonds of general aromatic compounds,[8] such as the use of electronic or spatial effects of substrates and the design of D-shaped targeting groups. However, most of these strategies do not apply to arene esters. Only recently, the Chattopadhyay group reported an effective strategy for the *para*-selective borylation of aromatic esters.[9] It has been proposed that the noncovalent interaction between the iridium catalyst, L-shaped ligand, and the substrate controls the selectivity. Recently, Nakao and co-workers pioneered *para*-selective alkylation of benzamide, diaryl ketones, and aryl sulfone using cooperative nickel/aluminum catalysis.[10] In 2018, our group successfully developed a method that resulted in selective difluoromethylation of acetophenone and benzophenone derivatives at the *para* position using tetrakis(triphenylphosphine) palladium as the catalyst.[11]

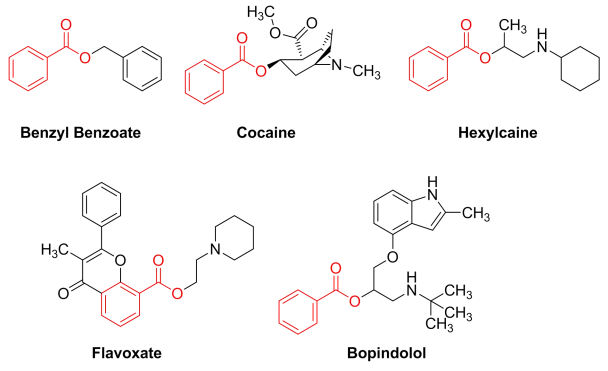


Figure 1. Examples of drugs containing the arene ester moiety (highlighted in red).

Subsequently, the directed *para*- difluoromethylation of various aromatic carbonyls with ethyl bromodifluoroacetate in the presence of a palladium (II) catalyst was also reported by the Xu group.[12] However, only limited examples of methyl benzoate were reported with low yields. In 2020, the Li group developed an effective visible-light-induced iridium-catalyzed *para*-difluoroalkylation of aromatic carbonyl compounds.[13] Unfortunately, the applicability of these substrates to aromatic esters leads to very poor reaction results.

The difluoromethyl group is a special fluorine-containing functional group with unique physicochemical properties and has been incorporated in many scientific fields, from medicinal chemistry to materials science.[14] Thus, based on research into the site-selective C-H difluoromethylation of arenes,[15-17] the development of a novel method to introduce difluoromethyl groups to the *para*-position of arene esters is highly attractive and in great demand. Herein, we report our recent results on the [1,1'-biphenyl]-2-dicyclohexylphosphin assisted tetrakis(triphenylphosphine)palladium-catalyzed *para*-selective difluoromethylation of arene esters. This new approach is compatible with a variety of arene esters, leading to highly *para*-selective difluoromethylated products in moderate to good yields. A preliminary mechanistic study revealed the reaction undergoes a free radical pathway.

Scheme 1. C-H Functionalization of Arene Esters.

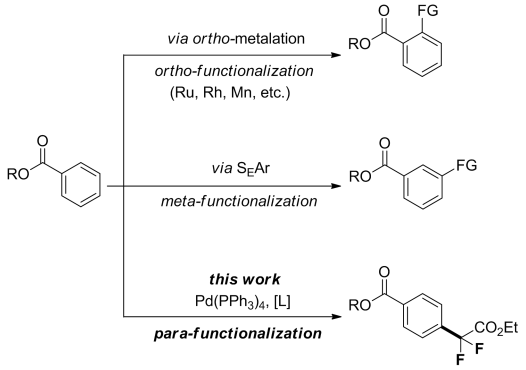
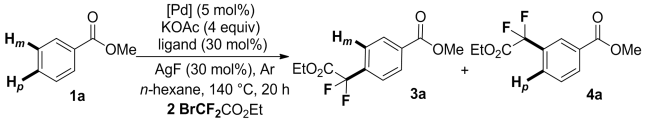


Table 1. Optimization of Reaction Conditions.[a]



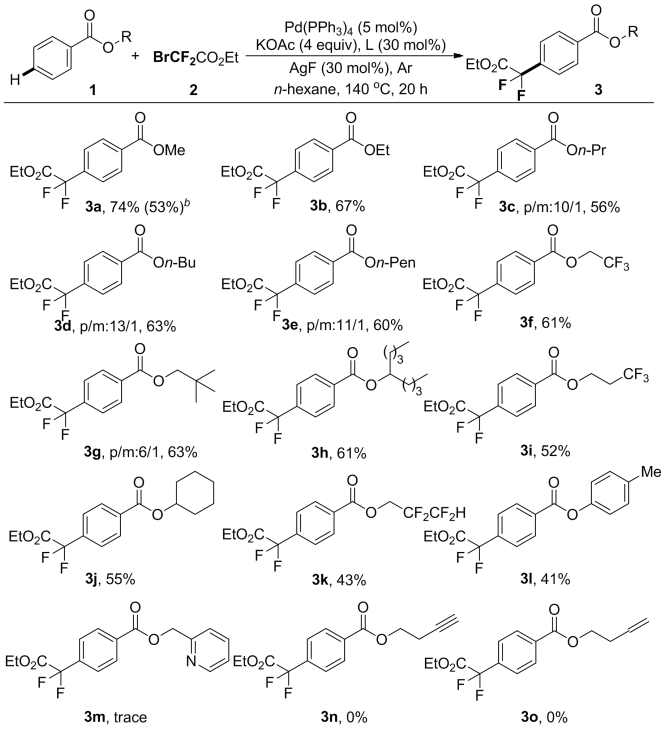
entry	catalyst	ligand	(**3a** + **4a**) yield (%)	**3a**/**4a** (*p*/*m*)[b]
1	$Pd(PPh_3)_4$	PPh_3	46	35/1
2	$Pd(dba)_2$	PPh_3	26	12/1
3	$Pd(PPh_3)_2Cl_2$	PPh_3	41	20/1
4	$Pd(OAc)_2$	PPh_3	34	15/1
5	$PdCl_2$	PPh_3	<5	-
6	$Pd(PPh_3)_4$	P(*t*-Bu)$_3$	<5	-
7	$Pd(PPh_3)_4$	P(*n*-Bu)$_3$	<5	-
8	$Pd(PPh_3)_4$	P(Cy)$_3$	<5	-
9	$Pd(PPh_3)_4$	P(4-OMePh)$_3$	59	32/1
10	$Pd(PPh_3)_4$	P(4-CF_3Ph)$_3$	53	13/1
11	$Pd(PPh_3)_4$	dppf	36	12/1
12	$Pd(PPh_3)_4$	dppp	40	16/1
13	$Pd(PPh_3)_4$	DPEPhos	61	44/1
14	$Pd(PPh_3)_4$	L	74	19/1
15	$Pd(PPh_3)_4$	-	<5	-
16	$Pd(PPh_3)_4$	L	54[c]	25/1
17	$Pd(PPh_3)_4$	L	48[d]	16/1
18	$Pd(PPh_3)_4$	L	57[e]	15/1
19	$Pd(PPh_3)_4$	L	63[f]	10/1
20	$Pd(PPh_3)_4$	L	46[g]	21/1
21	$Pd(PPh_3)_4$	L	51[h]	17/1
22	$Pd(PPh_3)_4$	L	25[i]	13/1
23	none	L	<5	-

[a]Reaction performed on 0.2 mmol scale with **2** (1 mmol). [b]The selectivity ratio determined by ^{1}H NMR analysis. [c]O_2 atmosphere. [d]KF instead of AgF. [e]AgOAc instead of AgF. [f]no AgF. [g]Cyclohexane. [h]Petroleum ether. [i]Toluene. Key: 1,1'-bis(diphenylphosphino)ferrocene (dppf), 1,3-Bis(diphenylphosphino)propane (dppp), bis[(2-diphenylphosphino)phenyl] ether (DPEphos), L = [1,1'-biphenyl]-2-yldicyclohexylphosphine.

RESULTS AND DISCUSSION

Initially, ethyl benzoate (1a) was treated with ethyl bromodifluoroacetate (2) in the presence of $Pd(PPh_3)_4$ (5 mol %), KOAc (4 equiv), PPh_3 (30 mol %), and AgF (30 mol %) at 140 °C for 20 h in n-hexane which afforded *para*-difluoromethylated methyl benzoate in 46 % yield along with a trace amount of meta-difluoromethylated methyl benzoate (p/m = 35/1). Several palladium precursors including $Pd(dba)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(OAc)_2$, and $PdCl_2$ were investigated; all of these palladium precursors did not perform as well as $Pd(PPh_3)_4$ (Table 1, entries 1-5). The ligand normally plays an important role in palladium-catalyzed *para*-selective difluoromethylation reactions, therefore, a variety of phosphine ligands were screened. Electronic rich phosphine ligands such as tri-tert-butylphosphine, tributylphosphine, and tricyclohexylphosphine all yield the difluoromethylated product 3a in yields of less than 5 %, along with the recovery of methyl benzoate (Table 1, entries 6-8). Interestingly, tris(4-methoxyphenyl)phosphine and tris(4-trifluoromethylphenyl)phosphine have a promoting effect, affording products in greater than 50 % yield (Table 1, entries 9-10). [1,1'-biphenyl]-2-yldicyclohexylphosphine gave the *para*-difluoromethylated methyl benzoate, **3a**, in 74 % yield (Table 1, entry 14), whereas a small amount of meta-difluoromethylated product was observed (p/m = 19/1). Further studies revealed bidentate phosphine ligands all resulted in poorer yields relative to [1,1'-biphenyl]-2-yldicyclohexylphosphine (Table 1, entries 11-13). As a result, we found the phosphine ligand was indispensable for this reaction (Table 1, entry 15). When an oxygen atmosphere was used instead of argon under the optimal conditions, a significant decrease in yield was observed (Table 1, entry 16). Next, using potassium fluoride and silver acetate as additives instead of silver fluoride, it was found that the reaction yields were greatly reduced (Table 1, entry 17-18). When silver fluoride was not added, the yield was 63 %, and poor selectivity was obtained (Table 1, entry 19). Although the specific role of silver fluoride is unclear, it may be acted as a lewis acid to assist the palladium complex, further activating the aromatic ring. Also, it was found that the reaction can proceed smoothly with non-polar solvents, but none of them were comparable to the effect of *n*-hexane (Table 1, entry 20-22). Control experiments revealed the palladium catalyst was essential in the reaction (Table 1, entry 23).

Table 2. Various protecting groups of benzoic acid.[a]

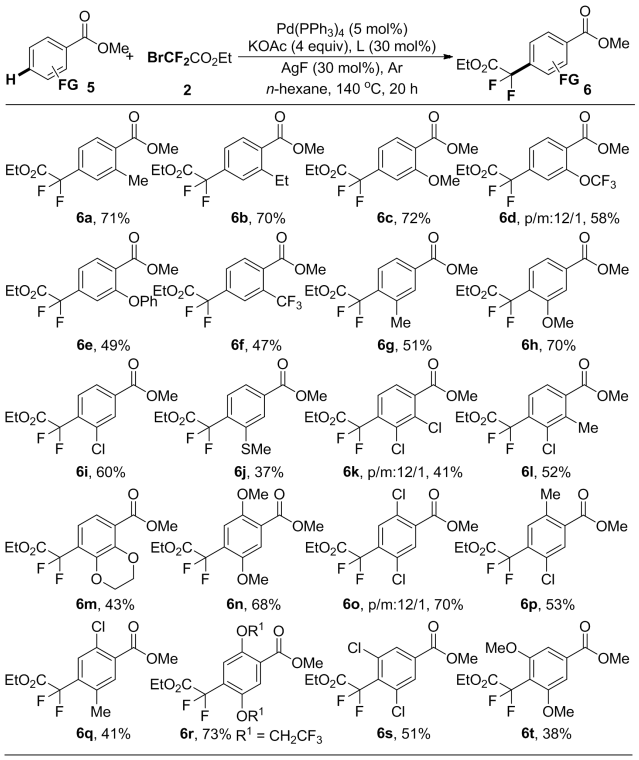


[a]Reaction performed on 0.2 mmol scale with **2** (1 mmol) in a sealed tube. L= [1,1'-biphenyl]-2-yldicyclohexylphosphine. [b]1 mmol scale synthesis. *n*-hexane (1 mL), 30 h.

After optimizing the reaction conditions, the protecting group tolerance of benzoic acid was investigated (Table 2). Changing the alkoxy moiety of the benzoate, including increasing the number of linear carbons or adjusting the steric hindrance did not reduce the reaction efficiency but resulted in similar product yields (**3a-j**). Among those, substrates **1c-e** indicated that as the number of linear carbon atoms increased, the *para*-selectivity of difluoromethylation decreases slightly (*p*/*m* ≈ 10/1). Unfortunately, even though the neopentyl benzoate (**1g**) substrate

provided good yields, site selectivity was relatively poor (*p*/*m* = 6/1). The reaction of the substrate methyl benzoate was scaled up to 1 mmol, providing product **3a** with a yield of 53%. When 1,1,2,2-tetrafluoroethanol and *p*-cresol were employed as the protecting groups, the 1,1,2,2-tetrafluoroethyl benzoate (**3k**) and p-tolyl benzoate (**3l**) substrates afforded the corresponding products in only moderate yields. Also, when using pyridin-2-ylmethylbenzoate as a substrate, only a trace amount of difluoromethylated product was obtained. It is believed that the nitrogen atom in the pyridine can interact with the palladium catalyst, which reduced the effect of carbonyl oxygen, making the yield drop sharply (**3m**). Finally, when there is an olefin or alkyne in the benzoic acid protecting group, the corresponding difluoromethylated product cannot be obtained (**3n-3o**). It might be the unsaturated group can direct trap difluoromethyl radical, which can shut down the *para*-selective C-H difluoromethylation.

Table 3. Functional group tolerance on methyl benzoate.[a]

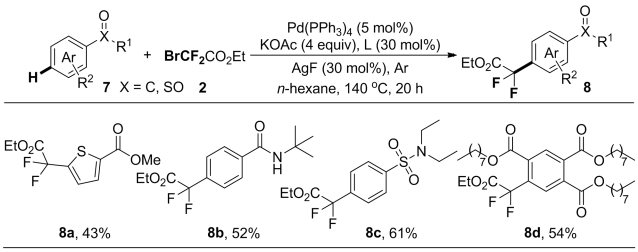


[a]Reaction performed on 0.2 mmol scale with **2** (1 mmol) in a sealed tube. L= [1,1'-biphenyl]-2-yldicyclohexylphosphine.

The substrate range applicability using benzoate compounds was also examined (Table 3). *Ortho*-substituted benzoates with various functional groups such as Me, Et, OMe, OCF_3, OPh, and CF_3 were all well-tolerated and yielded the *para*-difluoromethylated products (**6a-f**) in moderate to good yields (47–72 %). All reactions with *meta*-substituted substrates proceeded smoothly under this condition as well (**6g-j**; 37–70 %). Further study indicated that the disubstituted arene esters all performed well and yielded corresponding products in acceptable yields. (**6k-t**; 38–73 %). Impressively, the substrate **5r** was also tolerated, yielding the corresponding product in 73 % yield with high *para*-selectivity.

Subsequently, the diversity of aryl carbonyl substrates was explored under the optimized reaction conditions (Table 4). All reactions, including methyl thiophene-2-carboxylate (**7a**), N-(tert-butyl)benzamide (**7b**) and N,N-diethylbenzenesulfonamide (**7c**), reacted smoothly with bromodifluoroacetate (**2**) to afford the corresponding difluoromethylated products (**8a–8c**) in moderate to good yields (43 %, 52 %, and 61 %, respectively); unreacted starting materials were also recovered. Notably, trioctyl 1,2,4-benzenetricarboxylate (**7d**), a commonly used plasticizer for polyvinyl chloride, reacted well and selectively afforded 8c in 54 % yield.

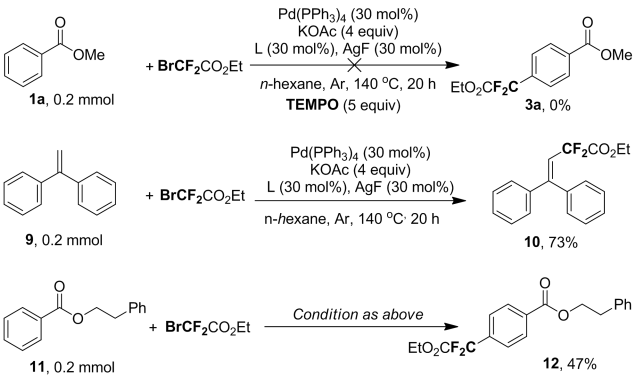
Table 4. Examples of other aromatic substrates.[a]



[a]Reaction performed on 0.2 mmol scale with **2** (1 mmol) in a sealed tube. L= [1,1'-biphenyl]-2-yldicyclohexylphosphine.

To understand the reaction pathway, a series of control experiments were performed (Scheme 2). For example, the radical scavenger TEMPO completely shut down the reaction. Meanwhile, when 1,1-diphenylethylene was treated with $BrCF_2CO_2Et$ under standard reaction conditions, product **10** was obtained in 73 % yield. These results strongly supported the idea that this difluoromethylation reaction involved a free-radical pathway. The palladium complex can release a $\cdot CF_2CO_2Et$ radical through a single-electron transfer process. Finally, compound **11** reacts in moderate yield with high selectivity at the benzoyl ring to give a single *para*-difluoromethylated result, which indicates that the interaction of the arene-bound ester carbonyl group and the palladium catalyst is a key factor for realizing the *para*-difluoromethylation reaction.

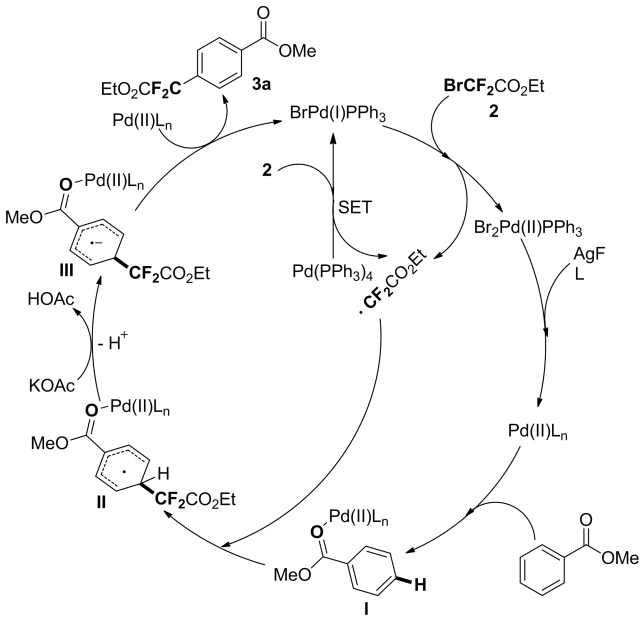
Scheme 2. Reaction Pathway Control Experiments.



Based on these results and previous reports[11,18], a plausible reaction pathway was proposed and is shown in Scheme 3. First, palladium(0) interacts with ethyl bromodifluoroacetate in the form of a single-electron transfer (SET) to generate $BrPd(I)PPh_3$ and releases a portion of ethyl difluoroacetate free radicals. Next, a palladium(II) complex was derived from the combination of palladium(I) and ethyl bromodifluoroacetate. Under the action of the large hindered phosphine ligand L and silver fluoride, ligand exchange occurs to regenerate palladium(II), which further plays an important role in coordination with the carbonyl oxygen to improve the reactivity of the aromatic ring of the arene ester. The difluoromethyl radical can be trapped by the active aromatic ring at the less hindered para position to produce the complex **II**. Subsequent potassium acetate takes away the proton hydrogen to

get complex **III**, followed by a SET process by the palladium(II) complex and aromatization to release **3a**.

Scheme 3. Plausible Mechanism.



CONCLUSIONS

In summary, we have developed an efficient method for the *para*-selective difluoromethylation of arene esters based on tetrakis(triphenylphosphine)palladium as the catalyst and [1,1'-biphenyl]-2-dicyclohexylphosphine as the ligand. Diverse arene esters bearing various functional groups were well tolerated under the optimized conditions, providing the *para*-difluoromethylated products in moderate to good yields. Moreover, benzoylamide and benzenesulfonamide are also suitable for this reaction strategy, which provides the possibility for the synthesis of biologically active molecules and drugs.

EXPERIMENTAL SECTION

General. Unless otherwise noted, all reagents were purchased from commercial suppliers and used without further purification. Column chromatography purifications were performed using 200–300 mesh silica gel. NMR spectra were recorded on Varian Inova–400 MHz, Inova–300 MHz, Bruker DRX–400 or Bruker DRX–500 instruments and calibrated using residual solvent peaks as internal reference. Multiplicities are recorded as: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, td = triplet of doublets, m = multiplet. HRMS analysis were carried out using a Bruker micrOTOF–Q instrument or a TOF–MS instrument.

General Procedure for the Benzoate Derivatives.[19] To a solution of alcohols (12 mmol, 1.2 equiv) and Et_3N (1.75 ml, 12.5 mmol) in CH_2Cl_2 (25 ml) cooled in an ice bath was added benzoyl chloride (1.16 ml, 10 mmol, 1 equiv) dropwise over 2 min with stirring. After stirring for 20 minutes, the ice bath was removed, stirring was continued for 12 hours at room temperature, and then quenched with 1 N HCl. The resulting mixture was extracted with CH_2Cl_2 (3 × 5 mL), and the mixed organic layer was washed with saturated $NaHCO_3$ and brine successively, and finally dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purifified by column chromatography (PE/EA = 30/1) on silica gel to give the product. These compound **1f**[20], **1g**[21], **1h**[22], **1k**[23], **5b**[24] and **5j**[25] were known.

*3,3,3-trifluoropropyl benzoate (**1i**).* Colorless oil, 80%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.02 (m, 2H), 7.61 – 7.55 (m, 1H), 7.49 – 7.43 (m, 2H), 4.55 (t, J = 6.3 Hz, 2H), 2.67 – 2.55 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.23, 133.40, 129.79, 129.7, 26.0 (q, J_{C-F} = 276.7 Hz), 128.6, 57.8 (q, J_{C-F} = 3.7 Hz), 33.6 (q, J_{C-F} = 29.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ -65.0 (t, J_{C-F} = 10.4 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{10}H_9F_3O_2Na$ 241.0447; Found: 241.0441.

General Procedure for p-tolyl benzoate (**1l**).[26] To a solution of *p*-cresol (1.08 g, 10 mmol, 1 equiv) in pyridine (10 mL) cooled in an ice bath was added benzoyl chloride (1.38 mL, 12 mmol, 1.2 equiv) dropwise over 10 min with stirring. After stirring for 60 minutes, the ice bath was removed, and then quenched with 1 N HCl. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the mixed organic layer was washed with water, and finally dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purifified by column chromatography (PE/EA = 10/1) on silica gel to give the product.

*p-tolyl benzoate (**1l**).* White solid, 95%, mp 63-64 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.8 Hz, 2H), 7.63 – 7.54 (m, 1H), 7.52 – 7.40 (m, 2H), 7.23 – 7.13 (m, 2H), 7.07 (dd, J = 8.5, 2.3 Hz, 2H), 2.34 (d, J = 2.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.5, 148.8, 135.6, 133.6, 130.3, 130.1, 129.8, 128.6, 121.5, 21.0.

General Procedure for n-(Tert-butyl)benzamide (**7a**). To a solution of *Tert-butylamine* (1.6 mL, 15 mmol, 1.5 equiv) and Et_3N (2.0 ml, 15 mmol) in CH_2Cl_2 (25 ml) cooled in an ice bath was added benzoyl chloride (1.16 mL, 10 mmol, 1 equiv) dropwise over 2 min with stirring. After stirring for 20 minutes, the ice bath was removed, stirring was continued for 12 hours at room temperature, and then quenched with saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), and dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting residue was purifified by column chromatography (PE/EA = 5/1) on silica gel to give the product.

N-*(tert-butyl)benzamide (**7a**)*.[27] White solid, 92%, mp 130-131 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 2H), 7.48 – 7.42 (m, 1H), 7.42 – 7.35 (m, 2H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.0, 136.0, 131.1, 128.5, 126.8, 51.7, 29.0.

General procedures for 1 mmol-Scale Synthesis. A mixture of **1a** (136 mg, 1 mmol, 1.0 equiv), $BrCF_2CO_2Et$ (650 μL, 5 mmol, 5.0 equiv), $Pd(PPh_3)_4$ (57.8 mg, 0.05 mmol, 0.05 equiv), KOAc (392.5 mg, 4 mmol, 4.0 equiv), L (105.1 mg, 0.3 mmol, 0.3 equiv), AgF (38.1 mg, 0.3 mmol, 0.3 equiv) and *n*-hexane (1 mL) in a 15 mL glass vial sealed under argon atmosphere was heated at 140 °C oil bath for 30 hours. The reaction mixture cooled to room temperature and concentrated in vacuo. The resulting residue was purified by column chromatography (PE / EA = 50 / 1) on silica gel to give the product **3**a (Colorless oil, 136.8 mg, 53% yield).

General procedures for para-Difluoromethylation of Benzoate. A mixture of **1** or **5** (0.2 mmol, 1.0 equiv), $BrCF_2CO_2Et$ (130 μL, 1 mmol), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 0.05 equiv), KOAc (78.5 mg, 0.8 mmol, 4 equiv), L (21.0 mg, 0.06 mmol, 0.3 equiv), AgF (7.6 mg, 0.06 mmol, 0.3 equiv) and *n*-hexane (0.25 mL) in a 15 mL glass vial sealed under argon atmosphere was heated at 140 °C oil bath for 20 hours. The reaction mixture cooled to room temperature and concentrated in vacuo. The resulting residue was purified by column chromatography (PE / EA = 50 / 1 – 10 / 1) on silica gel to give the product **3** or **6**.

*methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate (**3a**)*. Colorless oil, 38.2mg, 74%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 163.8 (t, J_{C-F} = 34.8 Hz), 137.1 (t, J_{C-F} = 25.5 Hz), 132.8 (t, J_{C-F} = 1.5 Hz), 130.0, 125.8 (t, J_{C-F} = 6.1 Hz),

113.1 (t, J_{C-F} = 252.8 Hz), 63.5, 52.6, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{12}F_2O_4Na$ 281.0596; Found: 281.0588.

ethyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3b)***. Colorless oil, 36.5mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 4.40 (q, J = 7.1 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 163.8 (t, J_{C-F} = 34.8 Hz), 137.0 (t, J_{C-F} = 25.5 Hz), 133.1, 130.0, 125.7 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.8 Hz), 63.5, 61.5, 14.4, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{14}F_2O_4Na$ 295.0752; Found: 295.0751.

propyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3c)***. Colorless oil, 32.0mg, 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 4.33 – 4.27 (m, 4H), 1.87 – 1.73 (m, 2H), 1.29 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 163.8 (t, J_{C-F} = 34.8 Hz), 137.0 (t, J_{C-F} = 25.6 Hz), 133.1, 130.0, 125.8 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.8 Hz), 67.1, 63.5, 22.2, 14.0, 10.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{17}F_2O_4$ 287.1089; Found: 287.1094.

butyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3d)***. Colorless oil, 37.8mg, 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 4.37 – 4.27 (m, 4H), 1.81 – 1.71 (m, 2H), 1.53 – 1.42 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H), 0.98 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 163.8 (t, J_{C-F} = 34.8 Hz), 137.0 (t, J_{C-F} = 25.5 Hz), 133.1, 130.0, 125.8 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.8 Hz), 65.4, 63.5, 30.8, 19.4, 14.0, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{19}F_2O_4$ 301.1246; Found: 301.1245.

pentyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3e)***. Colorless oil, 37.7mg, 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 2H), 7.69 (d, J = 8.4 Hz, 2H), 4.36 – 4.26 (m, 4H), 1.82 – 1.73 (m, 2H), 1.45 – 1.35 (m, 4H), 1.30 (t, J = 7.1 Hz, 3H), 0.93 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 163.8 (t, J_{C-F} = 34.9 Hz), 137.0 (t, J_{C-F} = 25.6 Hz), 133.2, 130.0, 125.8 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.7 Hz), 65.7, 63.5, 28.5, 28.3, 22.5, 14.1, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}F_2O_4$ 315.1402; Found: 315.1405.

2,2,2-trifluoroethyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3f)***. Colorless oil, 39.8mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.7 Hz, 2H), 4.72 (q, J = 8.3 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.2, 163.7 (t, J_{C-F} = 34.7 Hz), 138.2 (t, J_{C-F} = 25.6 Hz), 131.0, 130.5, 126.1 (t, J_{C-F} = 6.1 Hz), 124.5 (t, J_{C-F} = 277.1 Hz), 113.0 (t, J_{C-F} = 253.0 Hz), 63.6, 61.2 (q, J_{C-F} = 36.9 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.9, -104.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{13}H_{12}F_5O_4$ 327.0650; Found: 327.0648.

neopentyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3g)***. Colorless oil, 39.6mg, 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.7 Hz, 2H), 7.70 (d, J = 8.6 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.04 (s, 2H), 1.30 (t, J = 7.2 Hz, 3H), 1.04 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.8, 163.9 (t, J_{C-F} = 34.9 Hz), 137.1 (t, J_{C-F} = 25.5 Hz), 133.2, 130.0, 125.8 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.7 Hz), 74.8, 63.5, 31.8, 26.7, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{21}F_2O_4$ 315.1402; Found: 315.1401.

nonan-5-yl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3h)***. Colorless oil, 45.2mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.6 Hz, 2H), 7.69 (d, J = 8.6 Hz, 2H), 5.20 – 5.09 (m, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.76 – 1.60 (m, 4H), 1.38 – 1.27 (m, 11H), 0.92 – 0.85 (m, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 163.9 (t, J_{C-F} = 34.9 Hz), 136.9 (t, J_{C-F} = 25.6 Hz), 133.5, 130.0, 125.8 (t, J = 6.1 Hz), 113.2 (t, J_{C-F} = 252.7 Hz), 75.9, 63.5, 34.0, 27.7, 22.8, 14.1, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.4. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{20}H_{28}F_2O_4Na$ 393.1848; Found: 393.1848.

3,3,3-trifluoropropyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3i)***. Colorless oil, 35.4mg, 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.6 Hz, 2H), 7.70 (d, J = 8.5 Hz, 2H), 4.57 (t, J = 6.2 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 2.68 – 2.55 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.3, 163.8 (t, J_{C-F} = 34.6 Hz), 137.6 (t, J_{C-F} = 25.7 Hz), 132.2, 130.1, 125.9 (t, J_{C-F} = 6.0 Hz), 125.9 (q, J_{C-F} = 278.0 Hz), 113.1 (t, J_{C-F} = 252.9 Hz), 63.6, 58.2 (q, J_{C-F} = 3.6 Hz), 33.6 (q, J_{C-F} = 29.3 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -64.9 (t, J_{C-F} = 10.9 Hz), -104.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{14}F_5O_4$ 341.0807; Found: 341.0811.

cyclohexyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3j)***. Colorless oil, 35.9mg, 55%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 2H), 7.68 (d, J = 8.6 Hz, 2H), 5.09 – 4.99 (m, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.99 – 1.90 (m, 2H), 1.85 – 1.74 (m, 2H), 1.64 – 1.54 (m, 4H), 1.51 – 1.40 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.9 (t, J_{C-F} = 25.5 Hz), 133.6, 130.0, 125.7 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.7 Hz), 73.8, 63.5, 31.7, 25.6, 23.8, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{20}F_2O_4Na$ 349.1222; Found: 349.1223.

2,2,3,3-tetrafluoropropyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3k)***. Colorless oil, 30.8mg, 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.7 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H), 5.94 (tt, J = 53.1, 3.3 Hz, 1H), 4.75 (tt, J = 12.8, 1.2 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 163.7 (t, J_{C-F} = 34.7 Hz), 138.1 (t, J_{C-F} = 25.7 Hz), 131.2, 130.4, 126.1 (t, J_{C-F} = 6.1 Hz), 114.3 (t, J_{C-F} = 253.6 Hz), 112.9 (t, J_{C-F} = 255.1 Hz), 109.6 (t, J_{C-F} = 37.6 Hz), 63.6, 60.3 (t, J_{C-F} = 29.0 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.7, -122.7 (t, J_{C-F} = 1.9 Hz), -136.6 (t, J_{C-F} = 1.9 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{12}F_6O_4Na$ 381.0532; Found: 381.0537.

p-tolyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(3l)***. Colorless oil, 27.4mg, 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 8.5 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.6, 163.8 (t, J_{C-F} = 34.7 Hz), 148.7, 137.7, 136.0, 132.4, 130.6, 130.2, 126.0 (t, J_{C-F} = 6.1 Hz), 121.4, 113.1 (t, J_{C-F} = 253.1 Hz), 63.6, 21.1, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{18}H_{17}F_2O_4$ 335.1089; Found: 335.1095.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-methylbenzoate ***(6a)***. Colorless oil, 38.6mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.7 Hz, 1H), 7.48 – 7.47 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 2.63 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.4, 163.9 (t, J_{C-F} = 34.9 Hz), 140.8, 136.0 (t, J_{C-F} = 25.5 Hz), 132.3, 131.0, 128.7 (t, J_{C-F} = 6.0 Hz), 123.0 (t, J_{C-F} = 6.1 Hz), 113.0 (t, J_{C-F} = 252.7 Hz), 63.5, 52.3, 21.8, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.7. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{14}F_2O_4Na$ 295.0752; Found: 295.0752.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-ethylbenzoate ***(6b)***. Colorless oil, 40.1mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 1H), 7.51 (s, 1H), 7.48 (dd, J = 8.2, 1.5 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 3.00 (q, J = 7.5 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.6, 164.0 (t, J_{C-F} = 34.9 Hz), 146.6, 136.1 (t, J_{C-F} = 25.5 Hz), 132.2, 130.9, 127.3 (t, J_{C-F} = 6.0 Hz), 123.0 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.6 Hz), 63.5, 52.4, 27.6, 15.8, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.6. HRMS (ESI)

m/z: [M + Na]$^+$ Calcd for $C_{14}H_{16}F_2O_4Na$ 309.0908; Found: 309.0908.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-methoxybenzoate ***(6c)***. Colorless oil, 41.5mg, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 7.24 – 7.18 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 3.90 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 163.8 (t, $J_{C\text{-}F}$ = 34.8 Hz), 159.1, 137.6 (t, $J_{C\text{-}F}$ = 25.6 Hz), 132.0, 122.8, 117.3 (t, $J_{C\text{-}F}$ = 6.1 Hz), 112.9 (t, $J_{C\text{-}F}$ = 253.2 Hz), 109.2 (t, $J_{C\text{-}F}$ = 6.3 Hz), 63.6, 56.4, 52.5, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.7. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{14}F_2O_5Na$ 311.0701; Found: 311.0692.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-(trifluoromethoxy)benzoate ***(6d)***. Colorless oil, 39.7mg, 58%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 1H), 7.63 (dd, J = 8.2, 1.5 Hz, 1H), 7.58 (s, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.2, 163.0 (t, $J_{C\text{-}F}$ = 34.4 Hz), 147.6, 138.1 (t, $J_{C\text{-}F}$ = 26.4 Hz), 132.5, 127.5, 124.2 (t, $J_{C\text{-}F}$ = 6.1 Hz), 120.3 (t, $J_{C\text{-}F}$ = 6.2 Hz), 120.2 (q, $J_{C\text{-}F}$ = 259.1 Hz), 112.0 (t, $J_{C\text{-}F}$ = 253.9 Hz), 63.7, 52.8, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -57.6, -104.6. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{11}F_5O_5Na$ 365.0419; Found: 365.0417.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-phenoxybenzoate ***(6e)***. Colorless oil, 34.3mg, 49%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.2 Hz, 1H), 7.40 (dd, J = 8.2, 1.6 Hz, 1H), 7.37 – 7.33 (m, 2H), 7.20 (d, J = 1.4 Hz, 1H), 7.17 – 7.11 (m, 1H), 6.99 – 6.96 (m, 2H), 4.27 (q, J = 7.1 Hz, 2H), 3.84 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.7, 163.5 (t, $J_{C\text{-}F}$ = 34.6 Hz), 156.8, 156.6, 137.9 (t, $J_{C\text{-}F}$ = 25.9 Hz), 132.4, 130.1, 125.6, 124.1, 120.2 (t, $J_{C\text{-}F}$ = 6.0 Hz), 118.7, 117.6 (t, $J_{C\text{-}F}$ = 6.2 Hz), 112.5 (t, $J_{C\text{-}F}$ = 253.2 Hz), 63.6, 52.6, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.4. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{18}H_{16}F_2O_5Na$ 373.0857; Found: 373.0853.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-(trifluoromethyl)benzoate ***(6f)***. Colorless oil, 30.6mg, 47%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.87 – 7.86 (m, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.96 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 163.1 (t, $J_{C\text{-}F}$ = 34.4 Hz), 135.9 (t, $J_{C\text{-}F}$ = 26.4 Hz), 133.3 (q, $J_{C\text{-}F}$ = 1.7 Hz), 130.7, 129.5 (q, $J_{C\text{-}F}$ = 33.3 Hz), 129.1 (t, $J_{C\text{-}F}$ = 6.1 Hz), 124.2 (q, $J_{C\text{-}F}$ = 5.8 Hz), 122.7 (q, $J_{C\text{-}F}$ = 273.7 Hz), 112.2 (t, $J_{C\text{-}F}$ = 253.7 Hz), 63.8, 53.2, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.0, -104.6. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{11}F_5O_4Na$ 349.0470; Found: 349.0472.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3-methylbenzoate ***(6g)***. Colorless oil, 27.8mg, 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 – 7.88 (m, 2H), 7.66 (d, J = 8.1 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 2.46 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.4, 163.8 (t, $J_{C\text{-}F}$ = 34.7 Hz), 137.0 (t, $J_{C\text{-}F}$ = 3.0 Hz), 135.5 (t, $J_{C\text{-}F}$ = 23.3 Hz), 133.0, 132.4 (t, $J_{C\text{-}F}$ = 1.3 Hz), 127.2, 126.5 (t, $J_{C\text{-}F}$ = 8.9 Hz), 113.9 (t, $J_{C\text{-}F}$ = 252.4 Hz), 63.5, 52.5, 19.8 (t, $J_{C\text{-}F}$ = 2.7 Hz), 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.0. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{14}F_2O_4Na$ 295.0752; Found: 295.0747.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3-methoxybenzoate ***(6h)***. Colorless oil, 40.3mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.1, 1.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.60 (s, 1H), 4.33 (q, J = 7.1 Hz, 1H), 3.94 (s, 1H), 3.88 (s, 1H), 1.29 (t, J = 7.1 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.3, 163.7 (t, $J_{C\text{-}F}$ = 33.5 Hz), 156.8 (t, $J_{C\text{-}F}$ = 4.8 Hz), 134.1 (t, $J_{C\text{-}F}$ = 1.5 Hz), 126.7 (t, $J_{C\text{-}F}$ = 7.5 Hz), 126.4 (t, $J_{C\text{-}F}$ = 24.1 Hz), 122.0, 112.2, 63.0, 56.1, 52.7, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.5. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{14}F_2O_5Na$ [M+Na$^+$]: 311.0701, Found: 311.0697.

*methyl 3-chloro-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate****(6i)***. Colorless oil, 35.0mg, 60%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.04 (dd, J = 8.2, 1.2 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.1, 162.7 (t, $J_{C\text{-}F}$ = 33.5 Hz), 135.4 (t, $J_{C\text{-}F}$ = 24.4 Hz), 134.0, 132.5 (t, $J_{C\text{-}F}$ = 4.2 Hz), 131.7, 128.1, 127.7 (t, $J_{C\text{-}F}$ = 8.5 Hz), 112.0 (t, $J_{C\text{-}F}$ = 251.7 Hz), 63.7, 52.9, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.9. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{11}ClF_2O_4Na$ 315.0206; Found: 315.0203.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3-(methylthio)benzoate ***(6j)***. Colorless oil, 22.5mg, 37%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.95 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.2 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 2.48 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.0, 163.5 (t, $J_{C\text{-}F}$ = 33.5 Hz), 137.9 (t, $J_{C\text{-}F}$ = 3.7 Hz), 137.0 (t, $J_{C\text{-}F}$ = 23.3 Hz), 133.0, 131.1, 127.2, 126.7 (t, $J_{C\text{-}F}$ = 8.8 Hz), 112.8 (t, $J_{C\text{-}F}$ = 251.3 Hz), 63.4, 52.7, 18.2, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.9. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{14}F_2O_4SNa$ 327.0472; Found: 327.0475.

methyl 2,3-dichloro-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(6k)***. Colorless oil, 26.7mg, 41%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.77 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 1.32 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.3, 162.5 (t, $J_{C\text{-}F}$ = 33.2 Hz), 135.8 (t, $J_{C\text{-}F}$ = 24.8 Hz), 135.2, 133.4, 132.6 (t, $J_{C\text{-}F}$ = 3.7 Hz), 128.7, 125.2 (t, $J_{C\text{-}F}$ = 8.9 Hz), 111.6 (t, $J_{C\text{-}F}$ = 252.3 Hz), 63.9, 53.2, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.7. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{10}Cl_2F_2O_4Na$ 348.9816; Found: 348.9821.

methyl 3-chloro-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-methylbenzoate ***(6l)***. Colorless oil, 31.8mg, 52%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.93 (s, 3H), 2.61 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.38, 163.1 (t, $J_{C\text{-}F}$ = 33.4 Hz), 138.6, 135.0, 134.6 (t, $J_{C\text{-}F}$ = 24.1 Hz), 133.7, 128.3, 124.5 (t, $J_{C\text{-}F}$ = 9.0 Hz), 112.1 (t, $J_{C\text{-}F}$ = 251.1 Hz), 63.6, 52.7, 17.5, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.7. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{13}H_{13}ClF_2O_4Na$ 329.0362; Found: 329.0370.

methyl 8-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2,3-dihydrobenzo[b][1,4]dioxine-5-carboxylate ***(6m)***. Colorless oil, 27.2mg, 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.3 Hz, 1H), 7.22 (d, J = 8.3 Hz, 1H), 4.41 – 4.26 (m, 6H), 3.90 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 165.5, 163.5 (t, $J_{C\text{-}F}$ = 33.8 Hz), 144.0, 141.9 (t, $J_{C\text{-}F}$ = 4.8 Hz), 125.4 (t, $J_{C\text{-}F}$ = 24.9 Hz), 123.1, 122.5, 117.5 (t, $J_{C\text{-}F}$ = 7.6 Hz), 111.6 (t, $J_{C\text{-}F}$ = 249.9 Hz), 64.5, 64.1, 63.1, 52.5, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.1. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{16}F_2O_6Na$ 341.0807; Found: 341.0815.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2,5-dimethoxybenzoate ***(6n)***. Colorless oil, 43.3mg, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.28 (s, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.91 (s, 6H), 3.80 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.1, 163.5 (t, $J_{C\text{-}F}$ = 33.5 Hz), 153.2, 150.1 (t, $J_{C\text{-}F}$ = 4.8 Hz), 126.5 (t, $J_{C\text{-}F}$ = 23.9 Hz), 123.0, 114.8, 111.7 (t, $J_{C\text{-}F}$ = 250.7 Hz), 111.2 (t, $J_{C\text{-}F}$ = 7.8 Hz), 63.1, 57.0, 56.6, 52.6, 14.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.1. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{14}H_{16}F_2O_6Na$ 341.0807; Found: 341.0802.

methyl 2,5-dichloro-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(6o)***. Colorless oil, 45.6mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.82 (s, 1H), 4.36 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 164.3, 162.2 (t, $J_{C\text{-}F}$ = 33.3 Hz), 135.2 (t, $J_{C\text{-}F}$ = 24.8 Hz), 133.3, 132.8, 130.4 (t, $J_{C\text{-}F}$ = 4.2 Hz), 130.3 (t, $J_{C\text{-}F}$ = 8.9 Hz), 111.2 (t, $J_{C\text{-}F}$ = 252.8 Hz), 63.9, 53.2, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.2. HRMS (ESI) m/z: [M + Na]$^+$ Calcd for $C_{12}H_{10}Cl_2F_2O_4Na$ 348.9816, Found: 348.9821.

methyl 5-chloro-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2-methylbenzoate ***(6p)***. Colorless oil, 32.4mg, 53%. ^{1}H NMR (400

MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.62 (s, 1H), 4.35 (q, J = 7.1 Hz, 2H), 3.92 (s, 3H), 2.62 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.2, 162.9 (t, J_{C-F} = 33.5 Hz), 139.3, 134.0 (t, J_{C-F} = 24.1 Hz), 133.1, 132.6, 130.7 (t, J_{C-F} = 8.4 Hz), 129.1 (t, J_{C-F} = 4.1 Hz), 111.9 (t, J_{C-F} = 251.6 Hz), 63.7, 52.5, 21.4, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -103.0. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{13}ClF_2O_4Na$ 329.0363; Found: 329.0373.

methyl 2-chloro-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-5-methylbenzoate ***(6q)***. Colorless oil, 25.1mg, 41%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 2.39 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.6, 163.3 (t, J_{C-F} = 34.3 Hz), 135.4 (t, J_{C-F} = 23.9 Hz), 135.2 (t, J_{C-F} = 3.1 Hz), 134.6, 132.1, 131.3, 129.0 (t, J_{C-F} = 9.4 Hz), 113.0 (t, J_{C-F} = 253.3 Hz), 63.7, 52.8, 19.2, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{13}ClF_2O_4Na$ 329.0363, Found: 329.0374.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2,5-bis(2,2,2-trifluoroethoxy)benzoate ***(6r)***. Colorless oil, 66.3mg, 73%. 1H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.36 (s, 1H), 4.44 (q, J = 8.1 Hz, 2H), 4.38 (q, J = 7.9 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.94 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.9, 162.9 (t, J_{C-F} = 32.9 Hz), 152.2, 149.6 (t, J_{C-F} = 4.5 Hz), 128.0 (t, J_{C-F} = 24.7 Hz), 125.6, 123.1 (q, J_{C-F} = 278.2 Hz), 122.8 (q, J_{C-F} = 277.8 Hz), 116.5 (t, J_{C-F} = 7.8 Hz), 116.2, 111.2 (t, J_{C-F} = 252.0 Hz), 69.0 (q, J_{C-F} = 35.8 Hz), 66.9 (q, J_{C-F} = 36.6 Hz), 63.5, 52.9, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -73.9 (t, J_{C-F} = 7.7 Hz), -74.1 (t, J_{C-F} = 8.1 Hz), -103.2. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{16}H_{14}F_8O_6Na$ 477.0554; Found: 477.0559.

methyl 3,5-dichloro-4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(6s)***. Colorless oil, 33.3mg, 51%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 2H), 4.37 (q, J = 7.1 Hz, 2H), 3.96 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 164.1, 162.5 (t, J_{C-F} = 32.5 Hz), 135.2 (t, J_{C-F} = 2.7 Hz), 133.4, 132.2 (t, J_{C-F} = 22.9 Hz), 131.3, 112.9 (t, J_{C-F} = 256.1 Hz), 63.9, 53.2, 13.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ -97.6. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{12}H_{10}Cl_2F_2O_4Na$ 348.9819; Found: 348.9822.

methyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)-3,5-dimethoxybenzoate ***(6t)***. Colorless oil, 24.2mg, 38%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20 (s, 2H), 4.27 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.81 (s, 6H), 1.26 (t, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.1, 164.3 (t, J_{C-F} = 32.7 Hz), 159.16 (t, J_{C-F} = 2.6 Hz), 134.0, 113.8 (t, J_{C-F} = 23.5 Hz), 112.9 (t, J_{C-F} = 250.4 Hz), 106.0, 62.8, 56.6, 52.7, 14.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.0. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{16}F_2O_6Na$ 341.0807; Found: 341.0814.

methyl 5-(2-ethoxy-1,1-difluoro-2-oxoethyl)thiophene-2-carboxylate (***8a***). Colorless oil, 22.7mg, 43%. ^1H NMR (400 MHz, CDCl3) δ 7.72 (d, J = 3.9 Hz, 1H), 7.37 (d, J = 3.9 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl3) δ 162.8 (t, J_{C-F} = 34.5 Hz), 162.0, 140.1 (t, J_{C-F} = 30.0 Hz), 136.9, 133.0, 128.7 (t, J_{C-F} = 5.5 Hz), 111.2 (t, J_{C-F} = 252.0 Hz), 63.9, 52.7, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -94.5. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{10}H_{11}F_2O_4S$ 265.0346; Found: 265.0343.

ethyl 2-(4-(tert-butylcarbamoyl)phenyl)-2,2-difluoroacetate ***(8b)***. Colorless oil, 31.1mg, 52%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.6 Hz, 2H), 7.65 (d, J = 8.6 Hz, 2H), 5.94 (br, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.47 (s, 9H), 1.29 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.9 (t, J_{C-F} = 35.0 Hz), 138.6, 135.5 (t, J_{C-F} = 25.6 Hz), 127.2, 125.9 (t, J_{C-F} = 6.1 Hz), 113.1 (t, J_{C-F} = 252.6 Hz), 63.5, 52.1, 29.0, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.4. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}F_2NO_3$ 300.1406; Found: 300.1408.

ethyl 2-(4-(N,N-diethylsulfamoyl)phenyl)-2,2-difluoroacetate ***(8c)***. Yellow oil, 40.9mg, 61%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.4 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 3.26 (q, J = 7.2 Hz, 4H), 1.31 (t, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.6 (t, J_{C-F} = 34.7 Hz), 143.5, 136.7 (t, J_{C-F} = 25.7 Hz), 127.4, 126.6 (t, J_{C-F} = 6.1 Hz), 112.8 (t, J_{C-F} = 253.7 Hz), 63.7, 42.3, 14.3, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.3. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{14}H_{20}F_2NO_4S$ 336.1076; Found: 336.1080.

trioctyl 5-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzene-1,2,4-tricarboxylate ***(8d)***. Colorless viscous oil, 72.2mg, 54%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.16 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 4.32 – 4.19 (m, 6H), 1.76 – 1.64 (m, 3H), 1.48 – 1.22 (m, 27H), 0.97 – 0.84 (m, 18H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.4, 166.1, 164.8, 162.7 (t, J_{C-F} = 30.5 Hz), 136.6, 135.9, 134.4, 131.5 (t, J_{C-F} = 3.3 Hz), 131.4, 127.7 (t, J_{C-F} = 10.3 Hz), 112.5 (t, J_{C-F} = 249.4 Hz), 69.1, 68.8, 68.8, 63.2, 38.9, 38.9, 38.8, 30.5, 30.5, 29.1, 29.0, 23.9, 23.9, 23.1, 23.1, 14.2, 14.2, 14.0, 11.1, 11.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.6. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{37}H_{59}F_2O_8$ 669.4173; Found: 669.4178.

General procedures for TEMPO inhibition experiments. A mixture of **1a** (0.2 mmol, 1.0 equiv), $BrCF_2CO_2Et$ (130 μL, 1 mmol), $Pd(PPh_3)_4$ (11.6 mg, 0.01 mmol, 0.05 equiv), KOAc (78.5 mg, 0.8 mmol, 4 equiv), L (15.7 mg, 0.06 mmol, 0.3 equiv), AgF (7.6 mg, 0.06 mmol, 0.3 equiv), TEMPO (5 equiv) and *n*-hexane (0.25 mL) in a 15 mL glass vial sealed under argon atmosphere was heated at 140 °C for 20 hours. Totally no reaction.

ethyl 2,2-difluoro-4,4-diphenylbut-3-enoate ***(10)***. Yellow oil, 44.1mg, 73%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.29 (m, 6H), 7.29 – 7.24 (m, 2H), 7.24 – 7.17 (m, 2H), 6.28 (t, J = 11.8 Hz, 1H), 3.92 (q, J = 7.2 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, cdcl3) δ -91.1 (d, J_{C-F} = 11.9 Hz). HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{18}H_{16}F_2O_2Na$ 325.1011; Found: 325.1010.

phenethyl benzoate ***(11)***. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 – 7.90 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.37 – 7.17 (m, 5H), 4.53 (t, J = 7.0 Hz, 2H), 3.08 (t, J = 7.0 Hz, 2H).

phenethyl 4-(2-ethoxy-1,1-difluoro-2-oxoethyl)benzoate ***(12)***. Colorless oil, 32.7mg, 47%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.2 Hz, 2H), 7.68 (d, J = 8.3 Hz, 2H), 7.38 – 7.22 (m, 5H), 4.56 (t, J = 7.0 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 3.09 (t, J = 6.9 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 165.7, 163.8 (t, J_{C-F} = 34.7 Hz), 137.8, 137.2 (t, J_{C-F} = 25.5 Hz), 132.9, 130.0, 129.1, 128.8, 126.9, 125.8 (t, J_{C-F} = 6.0 Hz), 113.1 (t, J_{C-F} = 252.9 Hz), 66.0, 63.5, 35.3, 14.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.5. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{19}H_{18}F_2O_4Na$ 371.1065; Found: 371.1068.

ASSOCIATED CONTENT

Supporting Information

This material is available free of charge via the internet at http://pubs.acs.joc.

^1H, ^{13}C and ^{19}F NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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