Palladium-Catalyzed Cross-Coupling of Ethyl α-Bromo-α-fluoroacetate with Arylboronic Acids: Facile Synthesis of α-Aryl-α-fluoroacetates

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Abstract: Palladium-catalyzed Suzuki–Miyaura coupling reactions of ethyl α-bromo-α-fluoroacetate with various structurally diverse arylboronic acids using a phosphine ligand proceeded smoothly to afford α-aryl-α-fluoroacetates in moderate to good yields. This method provides a practical and efficient route to diverse α-monofluorinated α-arylcarbonyl compounds.

Key words: cross coupling, fluorinated compounds, boronic acids

The α-arylacetic acid moiety is found in various important medicines, such as nonsteroidal anti-inflammatory drugs (NSAIDs) Naproxen and Flurbiprofen.[1] As a C–F bond is presented in numerous bioactive compounds due to its resistance to metabolism with minimal steric interference and other unique effects on the biological activity of compounds,[2] α-aryl-α-fluorocarbonyl compounds are expected to be useful in drug discovery and, thus, many different methods for their synthesis have been developed. Earlier, Chapman et al. described the synthesis of ethyl α-fluoro-α-phenylacetate in 53% yield from the reaction of ethyl α-bromo-α-phenylacetate with anhydrous potassium fluoride.[3] The anodic oxidation of benzylic ketones, esters, and nitriles using triethylamine trihydrofluoride as a fluorinating reagent allowed the regioselective introduction of a fluorine atom at the α-position of the electron-withdrawing group.[4] Direct conversion of a benzylic alcohol with *N*,*N*-diethylaminosulfur trifluoride (DAST)[5] into the corresponding fluoride has been one of the most effective approaches. Recently, Fasan and co-workers reported a strategy that combined cytochrome P450-catalyzed oxygenation with a deoxofluorination reaction in which the newly generated hydroxy group was substituted by fluorine using DAST. In this way, α-aryl-α-fluoroacetates could be prepared from the corresponding α-arylacetic esters with high enantioselectivity and in moderate yields.[6] Alternative strategies involve the introduction of fluorine into benzylcarbonyl compounds by electrophilic fluorination. Middleton et al. reported that initial conversion of carbonyl compounds into their enol silyl ethers and followed by treatment with trifluoromethyl hypofluorite gave the corresponding α-aryl-α-fluorocarbonyl compounds.[7] A versatile transition-metal-catalyzed[8] or organocatalytic[9] approach has also been developed using *N*-fluorobenzenesulfonimide as an electrophilic fluorination agent for the asymmetric α-fluorination of benzyl ester equivalents.

Recently, transition-metal-catalyzed arylation has become a useful and general synthetic method for the preparation of α-arylacetic acid derivatives.[10] Buchwald and Hartwig have successfully developed the palladium-catalyzed α-arylation of enolates of esters or amide using aryl halides as electrophiles (Scheme 1, path I).[11] An alternative arylation strategy employed α-haloacetic acid derivatives as electrophiles and ArM as nucleophiles (Scheme 1, path II). Utilizing path II, Goossen and Deng investigated the reactions of unsubstituted α-bromoacetic acid derivatives with arylboronic acid derivatives [$ArB(OH)_2$] under palladium catalysis,[12] and it was found that the bulky, moderately electron-donating phosphine ligand [$P(Nap)_3$][12a] and co-catalyst (Cu_2O)[12b] played key roles in the successful cross-coupling reaction. Lei et al. found that $Ni(PPh_3)_4$ served as a highly effective catalyst for the promotion of the direct arylation of α-halocarbonyl compounds with various arylboronic acids under mild conditions.[13] Fu et al. reported that a nickel(II) chloride/norephedrine-based catalyst accomplished the cross coupling of secondary α-bromo esters with aryltrifluorosilanes ($ArSiF_3$).[14] As fluorine is the most electronegative element, it is natural that α-fluorinated α-haloacetic acid derivatives will be more active in the cross-coupling reaction as shown in path II (Scheme 1). Actually, Kumadaki and co-workers found that in the presence of copper powder, ethyl α-bromo-α,α-difluoroacetate reacted with iodobenzene to give cross-coupling product (Scheme 1, equation 1) and this was a fairly facile process.[15] Inspired by these results, we anticipated that the cross-coupling reaction of α-bromo-α-fluoroacetates with ArM or ArI would be a practical and efficient route to α-aryl-α-fluoroacetates (Scheme 1, equation 2).

Our initial efforts focused on the reaction of ethyl α-bromo-α-fluoroacetate (**1**) with iodobenzene in the presence of copper powder;[15] to our disappointment, the starting material **1** remained intact. This failure led us to turn our attention to the palladium-catalyzed Suzuki–Miyaura cross-coupling of ethyl α-bromo-α-fluoroacetate (**1**) with arylboronic acids. Recently, it has been found that im-

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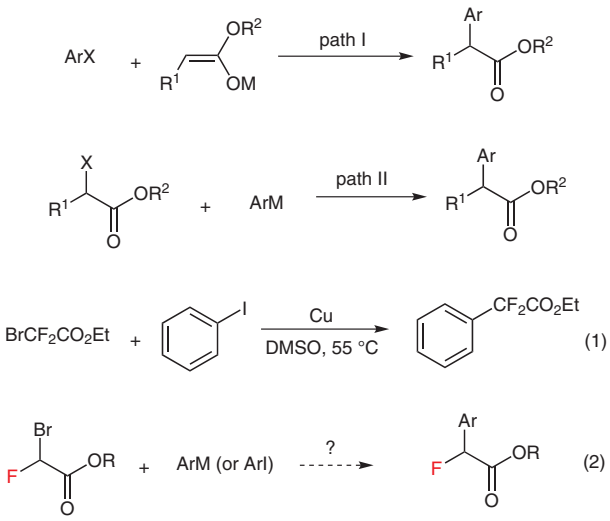


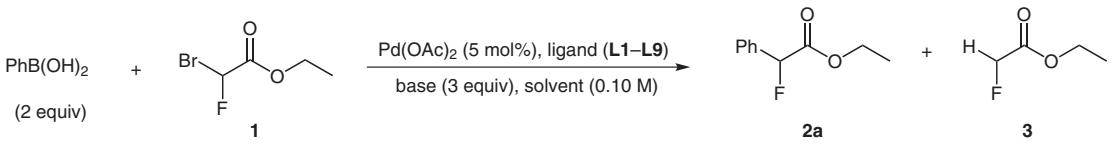
Scheme 1 α-Arylation of esters

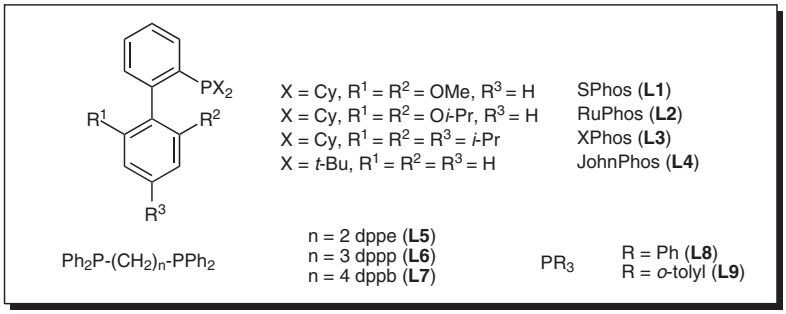
provements in Suzuki–Miyaura coupling reactions have relied a great deal on the increased reactivity and stability of the metal catalysts by use of increasing efficacious supporting ligands. Among these ligands, dialkylbiarylphosphines such as SPhos and RuPhos developed by Buchwald et al. presented unprecedented activities for various types of cross-coupling reactions.[16] Accordingly, we started by examining the reaction between **1** and phenylboronic acid under palladium(II) acetate catalysis using a series of Buchwald's ligands to see whether α-arylation would be achieved practically. As shown in Table 1, the reaction of **1** with phenylboronic acid (2.0 equiv) in the presence of palladium acetate and tripotassium phosphate with use of Buchwald's ligands **L1**–**L4** in toluene at 100 °C for 12 hours afforded the desired cross-coupling product **2a**, but byproduct **3** was also formed (entries 1–3) and the starting material **1** was not totally converted in the case of JohnPhos (**L4**) (entry 4). It was found that SPhos (**L1**) and RuPhos (**L2**) showed high catalytic effectiveness compared to XPhos (**L3**) and that **2a** and **3** were formed in a comparable ratio (entry 3). To achieve both total conversion of **1** and formation of **2a** as the sole product, we next turned our attention to diphosphine bidentate and monodentate phosphine ligands. When α,ω-diphosphine bidentate ligands **L5**–**L7** were employed, although compound **1** underwent complete conversion, a large amount of byproduct **3** was observed (entries 5–7). To our delight, when either triphenylphosphine (**L8**) or tri-2-methylphenylphosphine (**L9**) was used as the ligand, the coupling product **2a** was formed exclusively with full conversion of **1** (entries 8, 9). As triphenylphosphine (**L8**) is simple, stable, and inexpensive ligand, it was chosen as the ligand for this cross-coupling reaction. Furthermore, examination of the ^{19}F NMR of the reaction mixture every hour showed that compound **1** underwent total conversion in three hours (entry 10). Further investigation examining suitable bases showed that the use of sodium acetate, cesium carbonate, and cesium fluoride resulted in either no reaction or unavoidable formation of byproduct **3** (entries 11–13). Gratifyingly, tripotassium triphosphate trihydrate ($K_3PO_4 \cdot 3\ H_2O$) was an effective base for the coupling reaction (entry 14). As the handling of anhydrous tripotassium phosphate powder is troublesome due to its hygroscopic nature, tripotassium triphosphate trihydrate was used as the base instead of anhydrous tripotassium phosphate for the cross-coupling reaction. Toluene was by far the most effective solvent, the use of ether solvents resulted in simultaneous formation of byproduct **3** (entries 15, 16).

With these optimized conditions established, the scope of the cross-coupling reaction in terms of substrates was investigated. As illustrated in Table 2, The catalytic system was broadly applicable to a wide variety of *para*- and *meta*-substituted arylboronic acids (entries 2–15) to afford the corresponding α-aryl-α-fluoroacetates **2b–o** in moderate to good yields. Electron-withdrawing and electron-donating substituents on the aryl rings exhibited little effect on the yields (50–82%), except in the case of halogenated **2d**,**e** or extremely electron-deficient substrates **2o**. Arylboronic acids bearing *ortho*-substituents were also suitable coupling partners, however, the reaction yields were remarkably affected by the electronic and steric properties of their substituents (entries 16–21). When 2-methylphenylboronic acid was employed, small decrease in the yield of **2p** was noted compared to that for **2h** from 4-methylboronic acid (entry 16 vs 8, 69% cf. 82%). However, when an *ortho*-methoxy-, *ortho*-trifluoromethyl-, or *ortho*-fluoro group was present in the phenylboronic acid the yields of the corresponding products **2q–s** were dramatically reduced (entries 17–19). Surprisingly, sterically encumbered biphenyl-2-ylboronic acid took part in the coupling process smoothly with little difference in its reactivity compared to biphenyl-4-ylboronic acid (entry 20 vs 10), while reaction with 2,6-dimethylboronic acid did not proceed as efficiently as the reaction with 2-methylboronic acid (entry 21 vs 16). 6-Methoxynaphthalen-2-ylboronic acid reacted to afford the coupling product **2v** in reasonable yield (entry 22); **2v** has a similar scaffold to Naproxen. In addition, 2-heterocyclic boronic acids were suitable coupling partners, furnishing the products **2w**,**x** in lower yields and this was probably due to their inherent instability (entries 23 and 24).[17] It is noteworthy that an alternative catalytic system of $Pd(OAc)_2$/RuPhos (Table 1, entry 2), which was more active in the preparation of electron-deficient and hindered biaryls,[16] was found to be suitable for substrates where the $Pd(OAc)_2/PPh_3$ combination showed limited success, leading to the coupling products in higher yields (Table 2, entries 15, 17–19, 23, 24).

In conclusion, we report that by using a catalytic system of palladium(II) acetate and triphenylphosphine or RuPhos, the Suzuki–Miyaura cross-coupling reactions of various arylboronic acids with ethyl α-bromo-α-fluoroacetate proceed smoothly to afford α-aryl-α-fluoroacetates in moderate to good yields. To the best of our knowledge, this represents the first preparation of α-aryl-α-fluorocarbonyl scaffolds in a single step. All reagents used are readily available and easy to handle and the reaction con-

Table 1 Optimization of the Suzuki–Miyaura Cross-Couplings of **1** with Phenylboronic Acid under Palladium Catalysis[a]





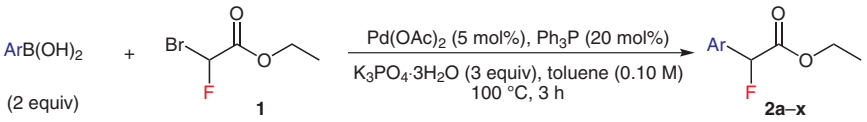
Entry	Ligand	Base	Solvent	Temp (°C), time (h)	Molar ratio[b] **1/2a/3**
1	SPhos (**L1**)	K_3PO_4	toluene	100, 12	–:1:0.17
2	RuPhos (**L2**)	K_3PO_4	toluene	100, 12	–:1:0.13
3	XPhos (**L3**)	K_3PO_4	toluene	100, 12	–:1:0.98
4	JohnPhos (**L4**)	K_3PO_4	toluene	100, 12	0.47:1:0
5	dppe (**L5**)	K_3PO_4	toluene	100, 12	–:1:4.9
6	dppp (**L6**)	K_3PO_4	toluene	100, 12	–:1:1.9
7	dppb (**L7**)	K_3PO_4	toluene	100, 12	–:1:2.1
8	PPh_3 (**L8**)	K_3PO_4	toluene	100, 12	only **2a**[c]
9	P(*o*-tolyl)$_3$ (**L9**)	K_3PO_4	toluene	100, 12	only **2a**[c]
10	PPh_3 (**L8**)	K_3PO_4	toluene	100, 3	only **2a**
11	PPh_3 (**L8**)	NaOAc	toluene	100, 3	n.r.[d]
12	PPh_3 (**L8**)	Cs_2CO_3	toluene	100, 3	–:1:0.07
13	PPh_3 (**L8**)	CsF	toluene	100, 3	–:1:0.19
14	PPh_3 (**L8**)	$K_3PO_4 \cdot 3\ H_2O$	toluene	100, 3	only **2a**[e]
15	PPh_3 (**L8**)	$K_3PO_4 \cdot 3\ H_2O$	THF	60, 3	–:1:0.58
16	PPh_3 (**L8**)	$K_3PO_4 \cdot 3\ H_2O$	diglyme	100, 3	–:1:0.31

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), ligand (**L1**–**L7**, 10 mol%) or ligand (**L8**, **L9**, 20 mol%), **1** (1.0 equiv), $PhB(OH)_2$ (2.0 equiv), base (3.0 equiv), solvent (0.10 mol L^{-1} of **1**).
[b] Determined by ^{19}F NMR of the reaction mixture.
[c] Isolated yield: 73%.
[d] No reaction, **1** remained intact.
[e] Isolated yield: 79%.

ditions are mild, hence, we believe that this method provides a practical and efficient route for the preparation of potentially bioactive α-monofluorinated α-arylcarbonyl compounds. The asymmetric version of the coupling reaction is ongoing in our laboratory.

All reactions were carried out under an argon atmosphere. All reagents were used as received from commercial sources, unless specified otherwise. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer and Varian MR-400, respectively. ^{19}F NMR spectra were recorded on a Bruker AM-300 spectrometer ($CFCl_3$ as outside standard and low field is positive). IR spectra were recorded on a Bio-Rad FTS-185 system. LRMS and HRMS analyses were performed on Agilent 5973N (EI, 70 eV) and Waters Micromass GCT Premier respectively.

Table 2 Suzuki–Miyaura Cross-Couplings of **1** with Structurally Diverse Aryl- and Heterocyclic Boronic Acids[a]



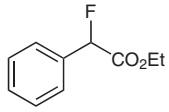
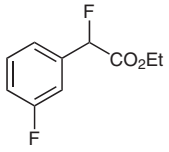
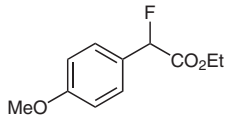
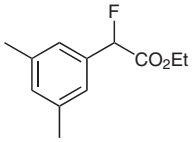
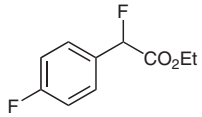
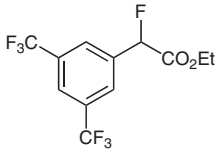
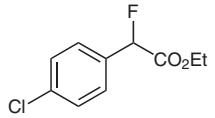
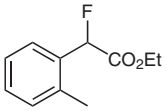
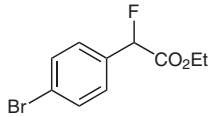
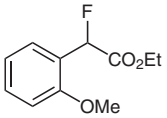
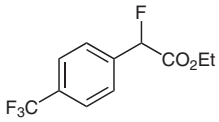
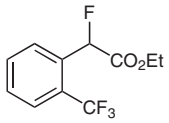
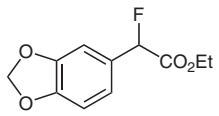
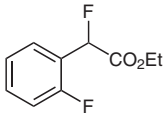
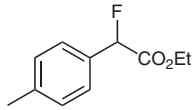
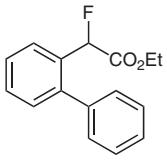
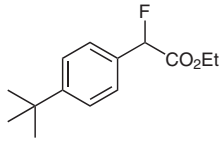
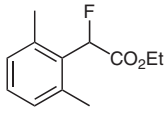
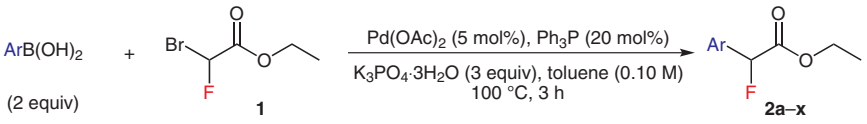
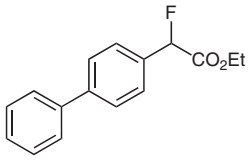
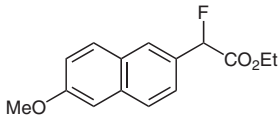
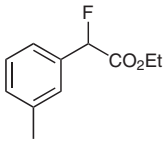
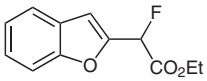
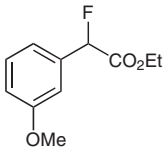
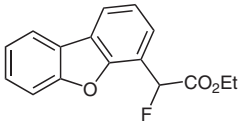
Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
1	 **2a**	79	13	 **2m**	64
2	 **2b**	81	14	 **2n**	50
3	 **2c**	66	15	 **2o**	26 (47[c])
4	 **2d**	37	16	 **2p**	69
5	 **2e**	38	17	 **2q**	19 (45[c])
6	 **2f**	61	18	 **2r**	35 (46[c])
7	 **2g**	77	19	 **2s**	–[d] (45[c])
8	 **2h**	82	20	 **2t**	68
9	 **2i**	65	21	 **2u**	32

Table 2 Suzuki–Miyaura Cross-Couplings of **1** with Structurally Diverse Aryl- and Heterocyclic Boronic Acids[a] (continued)



Entry	Product	Yield[b] (%)	Entry	Product	Yield[b] (%)
10	 **2j**	67	22	 **2v**	52
11	 **2k**	66	23	 **2w**	23 (38[c])
12	 **2l**	78	24	 **2x**	32 (45[c])

[a] Reaction conditions: $Pd(OAc)_2$ (5 mol%), PPh_3 (20 mol%), **1** (1.0 equiv), $ArB(OH)_2$ (2.0 equiv), $K_3PO_4 \cdot 3\,H_2O$ (3.0 equiv), toluene (0.10 mol L^{-1} of **1**), 100 °C, 3 h.
[b] Isolated yield.
[c] Isolated yield by the use of RuPhos (10 mol%) instead of PPh_3.
[d] No reaction when PPh_3 was used as ligand.

Ethyl α-Aryl-α-fluoroacetates 2a–x; General Procedure

An oven-dried Schlenk tube containing a magnetic stirrer bar was charged with $Pd(OAc)_2$ (5.6 mg, 0.025 mmol, 5 mol%), PPh_3 (26.2 mg, 0.10 mmol, 20 mol%), $ArB(OH)_2$ (1.0 mmol, 2.0 equiv), and $K_3PO_4 \cdot 3\,H_2O$ (400 mg, 1.5 mmol, 3.0 equiv). The Schlenk tube was capped with a rubber septum and then evacuated and backfilled with argon (this sequence was repeated 3 ×). Toluene (5.0 mL) was added through the septum via syringe and the resulting mixture was stirred at r.t. for 5 min. Ethyl α-bromo-α-fluoroacetate (**1**, 92.5 mg, 0.50 mmol, 1.0 equiv) was added dropwise via syringe. The Schlenk tube was sealed and the mixture was heated at 100 °C with vigorous stirring for 3 h. The mixture was then allowed to cool to r.t. and quenched with H_2O (10 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined organic phases were washed with brine (20 mL), dried (anhyd Na_2SO_4), filtered, and concentrated. The crude product was purified by flash chromatography (silica gel (petroleum ether–EtOAc, 50:1) to give the coupling compound.

Ethyl 2-Fluoro-2-phenylacetate (2a)[3,7,18]

IR (thin film): 1759 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.47 (m, 5 H), 5.78 (d, *J* = 48.0 Hz, 1 H), 4.22–4.28 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5 (d, *J* = 27.3 Hz), 134.3 (d, *J* = 20.3 Hz), 129.6 (d, *J* = 2.4 Hz), 128.8, 126.6 (d, *J* = 6.0 Hz), 89.3 (d, *J* = 184.3 Hz), 61.8, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –180.3 (d, *J* = 51.3 Hz).

MS (EI): *m*/*z* (%) = 182 (12) $[M]^+$, 109 (100) $[M - CO_2Et]^+$.

Ethyl 2-Fluoro-2-(4-methoxyphenyl)acetate (2b)[4a,b,18b,19]

IR (thin film): 1758 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 2 H), 6.93 (d, *J* = 8.4 Hz, 2 H), 5.71 (d, *J* = 48.0 Hz, 1 H), 4.21–4.27 (m, 2 H), 3.82 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.0 (d, *J* = 28.3 Hz), 160.8 (d, *J* = 2.2 Hz), 128.7 (d, *J* = 5.2 Hz), 126.5 (d, *J* = 20.9 Hz), 114.3, 89.3 (d, *J* = 183.1 Hz), 61.8, 55.4, 14.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –175.0 (d, *J* = 45.4 Hz).

MS (EI): *m*/*z* (%) = 212 (12) $[M]^+$, 139 (100) $[M - CO_2Et]^+$.

Ethyl 2-Fluoro-2-(4-fluorophenyl)acetate (2c)[4c,18d]

IR (thin film): 1761 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.48 (m, 2 H), 7.07–7.13 (m, 2 H), 5.75 (d, *J* = 47.4 Hz, 1 H), 4.22–4.27 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0 (d, *J* = 27.8 Hz), 163.1 (dd, *J* = 247.2, 2.3 Hz), 129.8 (dd, *J* = 20.8, 3.2 Hz), 129.0, 128.3 (dd, *J* = 8.5, 5.8 Hz), 126.8, 115.5 (d, *J* = 21.7 Hz), 88.3 (d, *J* = 184.7 Hz), 61.6, 13.6.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –111.9 (s, 1 F), –178.9 (d, *J* = 47.9 Hz, 1 F).

MS (EI): *m*/*z* (%) = 200 (9) $[M]^+$, 127 (100) $[M - CO_2Et]^+$.

Ethyl 2-(4-Chlorophenyl)-2-fluoroacetate (2d)[4c,18d,19]

IR (thin film): 1761 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.44 (m, 4 H), 5.75 (d, *J* = 47.4 Hz, 1 H), 4.22–4.27 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.3 (d, *J* = 26.8 Hz), 135.8 (d, *J* = 2.2 Hz), 132.9 (d, *J* = 20.9 Hz), 129.2, 128.1 (d, *J* = 6.0 Hz), 88.8 (d, *J* = 186.1 Hz), 62.2, 14.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –181.2 (d, *J* = 49.4 Hz).

MS (EI): *m*/*z* (%) = 216 (12) $[M]^+$, 143 (100) $[M - CO_2Et]^+$.

Ethyl 2-(4-Bromophenyl)-2-fluoroacetate (2e)[19]
IR (thin film): 1758 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, *J* = 8.1 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 5.73 (d, *J* = 47.7 Hz, 1 H), 4.22–4.27 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0 (d, *J* = 27.3 Hz), 133.2 (d, *J* = 20.8 Hz), 131.9, 128.1 (d, *J* = 6.5 Hz), 123.8 (d, *J* = 2.8 Hz), 88.7 (d, *J* = 185.6 Hz), 62.0, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –181.7 (d, *J* = 47.4 Hz, 1 F).

MS (EI): *m*/*z* (%) = 260, 262 (16) $[M]^+$, 187, 189 (100) $[M - CO_2Et]^+$.

Ethyl 2-Fluoro-2-[4-(trifluoromethyl)phenyl]acetate (2f)
IR (thin film): 1764, 1328 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.4 Hz, 2 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 5.85 (d, *J* = 47.7 Hz, 1 H), 4.24–4.29 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7 (d, *J* = 26.8 Hz), 138.0 (d, *J* = 19.5 Hz), 129.4, 128.9, 128.5, 127.2, 126.6 (d, *J* = 6.7 Hz), 125.7 (q, *J* = 7.5 Hz), 88.5 (d, *J* = 186.9 Hz), 62.2, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.3 (s, 3 F), –184.6 (d, *J* = 45.4 Hz, 1 F).

MS (EI): *m*/*z* (%) = 250 (2) $[M]^+$, 177 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{10}F_4O_2$: 250.0617; found: 250.0614.

Ethyl 2-(1,3-Benzodioxol-5-yl)-2-fluoroacetate (2g)[20]
IR (thin film): 1758, 1250 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.92–6.94 (m, 2 H), 6.80–6.83 (m, 1 H), 5.98 (s, 2 H), 5.65 (d, *J* = 47.7 Hz, 1 H), 4.21–4.27 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7 (d, *J* = 29.0 Hz), 148.9 (d, *J* = 3.0 Hz), 148.2, 128.0 (d, *J* = 20.8 Hz), 121.5 (d, *J* = 6.7 Hz), 108.5 (d, *J* = 1.5 Hz), 107.3 (d, *J* = 5.2 Hz), 101.6, 89.3 (d, *J* = 184.6 Hz), 62.0, 14.2.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –175.3 (d, *J* = 49.4 Hz).

MS (EI): *m*/*z* (%) = 226 (17) $[M]^+$, 153 (100) $[M - CO_2Et]^+$.

Ethyl 2-Fluoro-2-(4-methylphenyl)acetate (2h)[19,21]
IR (thin film): 1760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 7.2 Hz, 2 H), 7.21 (d, *J* = 8.1 Hz, 2 H), 5.73 (d, *J* = 48.0 Hz, 1 H), 4.20–4.26 (m, 2 H), 2.36 (s, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (d, *J* = 27.7 Hz), 139.5 (d, *J* = 2.3 Hz), 131.2 (d, *J* = 20.8 Hz), 129.3 (d, *J* = 0.9 Hz), 126.6 (d, *J* = 5.5 Hz), 89.2 (d, *J* = 183.8 Hz), 61.6, 21.1, 13.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –177.8 (d, *J* = 45.1 Hz, 1 F).

MS (EI): *m*/*z* (%) = 196 (18) $[M]^+$, 123 (100) $[M - CO_2Et]^+$.

Ethyl 2-(4-*tert*-Butylphenyl)-2-fluoroacetate (2i)
IR (thin film): 1762 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.45 (m, 4 H), 5.75 (d, *J* = 47.7 Hz, 1 H), 4.21–4.29 (m, 2 H), 1.32 (s, 9 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7 (d, *J* = 27.8 Hz), 152.7 (d, *J* = 2.3 Hz), 131.2 (d, *J* = 20.8 Hz), 126.5 (d, *J* = 5.6 Hz), 125.7, 89.2 (d, *J* = 183.8 Hz), 61.7, 34.7, 31.2, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –178.3 (d, *J* = 47.1 Hz, 1 F).

MS (EI): *m*/*z* (%) = 238 (23) $[M]^+$, 223 (85) $[M - CH_3]^+$, 165 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{19}FO_2$: 238.1369; found: 238.1375.

Ethyl 2-(Biphenyl-4-yl)-2-fluoroacetate (2j)
IR (thin film): 1760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.66 (m, 9 H), 5.83 (d, *J* = 48.0 Hz, 1 H), 4.25–4.31 (m, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (d, *J* = 27.5 Hz), 142.6 (d, *J* = 2.2 Hz), 140.3, 133.2 (d, *J* = 20.1 Hz), 128.9, 127.7, 127.5, 127.2, 127.1, 89.2 (d, *J* = 183.8 Hz), 61.9, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –179.9 (d, *J* = 49.4 Hz).

MS (EI): *m*/*z* (%) = 258 (21) $[M]^+$, 185 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{15}FO_2$: 258.1056; found: 258.1057.

Ethyl 2-Fluoro-2-(3-methylphenyl)acetate (2k)[19]
IR (thin film): 1759 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.19–7.32 (m, 4 H), 5.73 (d, *J* = 47.7 Hz, 1 H), 4.21–4.28 (m, 2 H), 2.37 (s, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (d, *J* = 27.3 Hz), 138.5, 134.1 (d, *J* = 19.9 Hz), 130.3 (d, *J* = 2.4 Hz), 128.6, 127.2 (d, *J* = 6.0 Hz), 123.7 (d, *J* = 6.0 Hz), 89.4 (d, *J* = 184.2 Hz), 61.7, 21.3, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –179.2 (d, *J* = 49.6 Hz, 1 F).

MS (EI): *m*/*z* (%) = 196 (20) $[M]^+$, 123 (100) $[M - CO_2Et]^+$.

Ethyl 2-Fluoro-2-(3-methoxyphenyl)acetate (2l)[4c]
IR (thin film): 1754 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.34 (m, 1 H), 7.01–7.05 (m, 2 H), 6.91–6.95 (m, 1 H), 5.74 (d, *J* = 47.4 Hz, 1 H), 4.21–4.27 (m, 2 H), 3.81 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.4 (d, *J* = 27.3 Hz), 159.8, 135.6 (d, *J* = 20.3 Hz), 129.8, 118.8 (d, *J* = 6.4 Hz), 115.3 (d, *J* = 2.3 Hz), 111.7 (d, *J* = 6.5 Hz), 89.2 (d, *J* = 184.8 Hz), 61.8, 55.2, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –180.3 (d, *J* = 49.4 Hz, 1 F).

MS (EI): *m*/*z* (%) = 212 (35) $[M]^+$, 139 (100) $[M - CO_2Et]^+$.

Ethyl 2-Fluoro-2-(3-fluorophenyl)acetate (2m)
IR (thin film): 1765 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.42 (m, 1 H), 7.18–7.24 (m, 2 H), 7.07–7.12 (m, 1 H), 5.77 (d, *J* = 47.4 Hz, 1 H), 4.20–4.32 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0 (d, *J* = 26.8 Hz), 162.8 (d, *J* = 246.3 Hz), 136.5 (q, *J* = 20.8, 7.4 Hz), 130.4 (d, *J* = 7.9 Hz), 122.1 (q, *J* = 6.5, 3.2 Hz), 116.5 (q, *J* = 21.3, 1.9 Hz), 113.5 (q, *J* = 23.2, 7.0 Hz), 88.5 (dd, *J* = 186.1, 2.3 Hz), 62.0, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –112.0 (q, *J* = 16.4, 8.2 Hz, 1 F), –182.2 (d, *J* = 49.6 Hz, 1 F).

MS (EI): *m*/*z* (%) = 200 (10) $[M]^+$, 127 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{10}F_2O_2$: 200.0649; found: 200.0648.

Ethyl 2-(3,5-Dimethylphenyl)-2-fluoroacetate (2n)
IR (thin film): 1760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.03–7.08 (m, 3 H), 5.69 (d, *J* = 48.0 Hz, 1 H), 4.21–4.29 (m, 2 H), 2.33 (s, 6 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.7 (d, *J* = 27.5 Hz), 138.4, 134.0 (d, *J* = 20.1 Hz), 131.2 (d, *J* = 2.9 Hz), 124.4 (d, *J* = 5.2 Hz), 89.4 (d, *J* = 183.9 Hz), 61.7, 21.2, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –178.7 (d, *J* = 49.6 Hz).

MS (EI): *m*/*z* (%) = 210 (16) $[M]^+$, 137 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}FO_2$: 210.1056; found: 210.1058.

Ethyl 2-[3,5-Bis(trifluoromethyl)phenyl]-2-fluoroacetate (2o)
IR (thin film): 1767, 1281 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.96 (m, 3 H), 5.92 (d, *J* = 46.8 Hz, 1 H), 4.28–4.31 (m, 2 H), 1.30 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0 (d, *J* = 26.1 Hz), 136.8 (d, *J* = 21.5 Hz), 132.2 (d, *J* = 33.5 Hz), 128.6, 126.3 (q, *J* = 7.4 Hz), 124.3, 123.3, 121.5, 87.7 (d, *J* = 189.1 Hz), 62.6, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –63.4 (s, 6 F), –186.6 (d, *J* = 45.1 Hz, 1 F).

MS (EI): *m*/*z* (%) = 299 (10) $[M - F]^+$, 245 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_9F_7O_2$: 318.0491; found: 318.0493.

Ethyl 2-Fluoro-2-(2-methylphenyl)acetate (2p)[19]
IR (thin film): 1761 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.20–7.41 (m, 4 H), 5.97 (d, *J* = 47.7 Hz, 1 H), 4.22–4.29 (m, 2 H), 2.44 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5 (d, *J* = 27.8 Hz), 136.2 (d, *J* = 3.7 Hz), 132.4 (d, *J* = 19.0 Hz), 130.5, 129.2 (d, *J* = 2.7 Hz), 127.0 (d, *J* = 6.5 Hz), 125.9 (d, *J* = 0.9 Hz), 86.9 (d, *J* = 183.3 Hz), 61.4, 18.8, 13.7.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –179.8 (d, *J* = 48.2 Hz).

MS (EI): *m*/*z* (%) = 196 (12) $[M]^+$, 123 (100) $[M - CO_2Et]^+$.

Ethyl 2-Fluoro-2-(2-methoxyphenyl)acetate (2q)
IR (thin film): 1759 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.39 (m, 2 H), 6.92–7.02 (m, 2 H), 6.09 (d, *J* = 47.7 Hz, 1 H), 4.24–4.28 (m, 2 H), 3.86 (s, 3 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (d, *J* = 27.5 Hz), 157.3 (d, *J* = 3.7 Hz), 131.3 (d, *J* = 3.7 Hz), 129.2 (d, *J* = 5.2 Hz), 122.9, 120.8 (d, *J* = 2.2 Hz), 111.2 (d, *J* = 1.5 Hz), 85.0 (d, *J* = 181.6 Hz), 61.6, 55.7, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –178.6 (d, *J* = 49.6 Hz).

MS (EI): *m*/*z* (%) = 212 (29) $[M]^+$, 139 (87) $[M - CO_2Et]^+$, 91 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{13}FO_3$: 212.0849; found: 212.0848.

Ethyl 2-Fluoro-2-[2-(trifluoromethyl)phenyl]acetate (2r)
IR (thin film): 1763 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.74 (m, 4 H), 6.16 (d, *J* = 47.1 Hz, 1 H), 4.19–4.31 (m, 2 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8 (d, *J* = 27.8 Hz), 132.5, 132.4 (t, *J* = 1.0 Hz), 129.8 (d, *J* = 2.8 Hz), 128.9, 128.8, 127.3, 126.1 (q, *J* = 10.2, 5.6 Hz), 85.0 (dq, *J* = 182.4, 5.1, 2.8 Hz), 62.0, 13.8.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –58.0 (s, 3 F), –174.9 (d, *J* = 49.6 Hz).

MS (EI): *m*/*z* (%) = 250 (1) $[M]^+$, 177 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{10}F_4O_2$: 250.0617; found: 250.0621.

Ethyl 2-Fluoro-2-(2-fluorophenyl)acetate (2s)
IR (thin film): 1761, 1021 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.49 (m, 2 H), 7.13–7.23 (m, 2 H), 6.06 (d, *J* = 47.1 Hz, 1 H), 4.24–4.30 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0 (d, *J* = 27.5 Hz), 160.3 (d, *J* = 244.9 Hz), 131.7 (dd, *J* = 8.2, 3.0 Hz), 128.8 (dd, *J* = 5.2, 3.0 Hz), 124.5 (dd, *J* = 3.7, 1.5 Hz), 115.9 (d, *J* = 22.3 Hz), 83.4 (dd, *J* = 183.1, 3.7 Hz), 62.0, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –118.0 (d, *J* = 15.8 Hz, 1 F), –181.3 (d, *J* = 51.6 Hz, 1 F).

MS (EI): *m*/*z* (%) = 200 (7) $[M]^+$, 127 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{10}F_2O_2$: 200.0649; found: 200.0650.

Ethyl 2-(Biphenyl-2-yl)-2-fluoroacetate (2t)
IR (thin film): 1760 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.60 (m, 9 H), 5.85 (d, *J* = 47.1 Hz, 1 H), 4.19–4.24 (m, 2 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (d, *J* = 29.1 Hz), 142.8 (d, *J* = 4.5 Hz), 139.5, 131.9 (d, *J* = 19.4 Hz), 130.5 (d, *J* = 1.5 Hz), 129.73 (d, *J* = 3.7 Hz), 129.67 (d, *J* = 1.5 Hz), 128.3, 128.0 (d, *J* = 2.2 Hz), 127.74, 127.69, 86.4 (d, *J* = 181.7 Hz), 61.7, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –169.5 (d, *J* = 45.4 Hz).

MS (EI): *m*/*z* (%) = 258 (24) $[M]^+$, 185 (34) $[M - CO_2Et]^+$, 165 (100) $[M - CO_2Et - HF]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{15}FO_2$: 258.1056; found: 258.1054.

Ethyl 2-(2,6-Dimethylphenyl)-2-fluoroacetate (2u)
IR (thin film): 1754 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.03–7.19 (m, 3 H), 6.19 (d, *J* = 46.2 Hz, 1 H), 4.20–4.29 (m, 2 H), 2.41 (s, 6 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 (d, *J* = 26.8 Hz), 137.5 (d, *J* = 3.3 Hz), 131.1 (d, *J* = 17.2 Hz), 129.3 (d, *J* = 0.9 Hz), 129.2 (d, *J* = 2.3 Hz), 128.9 (d, *J* = 1.9 Hz), 128.4, 127.1, 86.0 (d, *J* = 183.3 Hz), 61.6, 19.8 (d, *J* = 1.8 Hz), 13.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –183.7 (d, *J* = 45.4 Hz).

MS (EI): *m*/*z* (%) = 210 (20) $[M]^+$, 137 (100) $[M - CO_2Et]^+$.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{15}FO_2$: 210.1056; found: 210.1053.

Ethyl 2-Fluoro-2-(6-methoxynaphthalen-2-yl)acetate (2v)[22]
IR (thin film): 1758 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.86 (m, 3 H), 7.50–7.53 (m, 1 H), 7.13–7.19 (m, 2 H), 5.89 (d, *J* = 47.4 Hz, 1 H), 4.21–4.28 (m, 2 H), 3.90 (s, 3 H), 1.25 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6 (d, *J* = 28.2 Hz), 158.3 (d, *J* = 1.0 Hz), 134.9 (d, *J* = 1.4 Hz), 129.6 (d, *J* = 1.0 Hz), 129.1 (d, *J* = 20.8 Hz), 128.2, 127.4, 126.5 (d, *J* = 7.0 Hz), 124.0 (d, *J* = 4.6

Hz), 119.4, 105.5 (d, J = 1.0 Hz), 89.5 (d, J = 183.8 Hz), 61.7, 55.2, 13.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –177.4 (d, J = 45.1 Hz).

MS (ESI): m/z = 285 $[M + Na]^+$, 301 $[M + K]^+$.

Ethyl 2-(Benzofuran-2-yl)-2-fluoroacetate (2w)
IR (thin film): 1766 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.63 (m, 2 H), 7.25–7.39 (m, 2 H), 6.95–6.96 (m, 1 H), 5.94 (d, J = 48.0 Hz, 1 H), 4.33–4.38 (m, 2 H), 1.33 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1 (d, J = 27.6 Hz), 155.3 (d, J = 1.4 Hz), 148.9 (d, J = 20.9 Hz), 127.2 (d, J = 2.3 Hz), 125.8 (d, J = 1.5 Hz), 123.3, 121.8 (d, J = 2.2 Hz), 111.8 (d, J = 1.5 Hz), 108.7 (d, J = 5.9 Hz), 82.6 (d, J = 184.7 Hz), 62.4, 14.0.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –177.5 (d, J = 49.4 Hz).

MS (EI): m/z (%) = 222 (19) $[M]^+$, 149 (100) $[M – CO_2Et]^+$.

HRMS (EI): m/z $[M]^+$ calcd for $C_{12}H_{11}FO_3$: 222.0692; found: 222.0696.

Ethyl 2-(Dibenzo[*b*,*d*]furan-4-yl)-2-fluoroacetate (2x)
IR (thin film): 1759 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92–7.99 (m, 2 H), 7.32–7.61 (m, 5 H), 6.40 (d, J = 47.1 Hz, 1 H), 4.25–4.32 (m, 2 H), 1.24 (t, J = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2 (d, J = 27.8 Hz), 156.2, 153.7 (d, J = 3.7 Hz), 127.7, 125.9 (d, J = 4.7 Hz), 125.0 (d, J = 0.9 Hz), 123.8, 123.1, 123.0 (d, J = 1.4 Hz), 122.3 (d, J = 2.8 Hz), 120.8, 118.4 (d, J = 20.8 Hz), 111.9, 84.6 (d, J = 183.8 Hz), 62.0, 14.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –178.5 (d, J = 45.4 Hz).

MS (EI): m/z (%) = 272 (25) $[M]^+$, 199 (100) $[M – CO_2Et]^+$.

HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{13}FO_3$: 272.0849; found: 272.0846.

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