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Copper-Catalyzed Direct C-2 Difluoromethylation of Furans and Benzofurans: Access to C-2 CF_2H Derivatives

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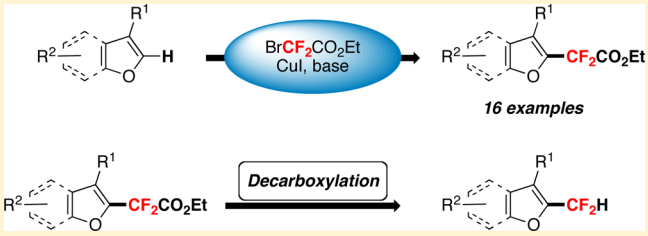
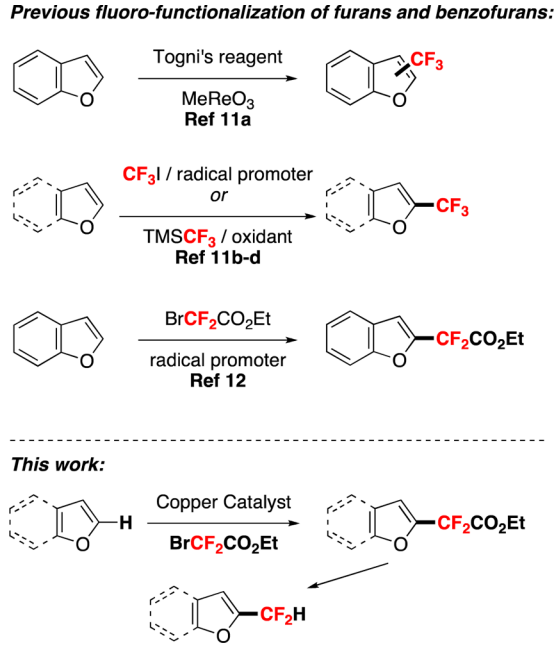
Supporting Information

ABSTRACT: We report herein the first copper-catalyzed C-2 difluoromethylation of furans and benzofurans. The developed methodology allows the selective introduction of the CF_2CO_2Et moiety at C-2 using CuI as a catalyst. This process was applied to a broad range of furans and benzofurans, giving the functionalized products in moderate to good yields. The resulting products were then decarboxylated to afford the highly valuable C-2-CF_2H-substituted furans and benzofurans in good yields.



Fluorine atom is very popular for modifying the properties of bioactive compounds. Indeed, the electronegativity and size of the F atom and the high energy of the C−F bond provide to the fluorine atom a significant ability to modify the biological and physical properties of a molecule.[1] Hence, it is not surprising to find this intriguing atom on more than 20% of pharmaceuticals and 30% of agrochemicals.[2] Thus, several methodologies have been developed to introduce fluorinated building blocks and particularly the CF_3 group.[3] Among all of these methodologies, the introduction of fluorinated moieties by means of direct C−H bond functionalization has become one of the most popular approaches.[3d−h] Besides, furans and benzofurans are an important class of heterocycles. Those two oxygenated rings are encountered in several bioactive and natural compounds[4] and are versatile building blocks in organic chemistry and materials science.[5] Therefore, it is not surprising that a lot of effort has been devoted to accessing highly functionalized derivatives in order to improve the molecular diversity.[6] The usual way to access these backbones mainly focuses on the construction of the oxygenated ring, and the most popular strategies remain (1) base-promoted dehydrative cyclization of functionalized ethers[7] and (2) transition-metal-catalyzed cyclization of arylacetylene derivatives.[8] Recently, several interesting and elegant methodologies involving C−H bond functionalization have been reported to offer a new access to these valuable highly functionalized products. This reaction manifold mainly focuses on the introduction of aryl[9] and alkyne[10] derivatives at either the C-2 or C-3 position. Quite surprisingly, among these elegant methodologies, only a few reports dealing with the direct introduction of fluorinated building blocks onto furan and benzofuran derivatives have been described to date (Scheme 1). Most of these reports focus on the radical introduction of the CF_3 moiety on furans and benzofurans.[11] Moreover, only three reports depict the radical introduction of the CF_2CO_2Et moiety on the benzofuran ring (Scheme 1).[12]

Scheme 1. Fluorofunctionalization of Furans and Benzofurans—State of the Art



As part of our research program devoted to the development of new straightforward access to fluorinated molecules,[13] we report herein our contribution toward the copper-catalyzed direct and selective C-2 introduction of the difluoromethyl motif, a potential CF_2H precursor for instance, on furans and benzofurans.

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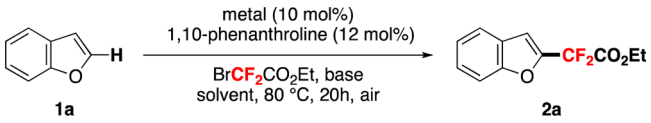
At the outset of the study, benzofuran (**1a**) was chosen as a model substrate to optimize the reaction conditions (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

entry	metal	base	solvent	yield (%)[b]
1	$Pd(PPh_3)_4$	K_2CO_3	DMF	–
2	CuI	K_2CO_3	DMF	51 (50[c])
3	CuI	K_2CO_3	NMP	21
4	CuI	K_2CO_3	dioxane	8
5	CuI	Cs_2CO_3	DMF	23
6	CuI	KH_2PO_4	DMF	43
7	CuI	2,6-lutidine	DMF	17
8	CuCl	K_2CO_3	DMF	45
9	$[Cu(OTf)]_2.C_6H_6$	K_2CO_3	DMF	33
10	$Cu(OTf)_2$	K_2CO_3	DMF	33
11	–	K_2CO_3	DMF	NR
12	CuI	–	DMF	NR
13[d]	CuI	K_2CO_3	DMF	NR

[a]Conditions: **1a** (0.24 mmol), metal catalyst (0.024 mmol), **3** (mmol), $BrCF_2CO_2Et$ (1.92 mmol), base (0.48 mmol), solvent (1.2 mL), 80 °C, 20 h, air atmosphere. [b]Yields were determined by ^{19}F NMR using α,α,α-trifluorotoluene as an internal standard. NR = no reaction. [c]Isolated yield. [d]Reaction was performed without 1,10-phenanthroline.

First, the reaction was carried out in the presence of palladium catalysts such as $Pd(PPh_3)_4$ (entry 1). Unfortunately, despite all our attempts, no traces of the product were observed. To tackle this lack of reactivity, we turned our attention to copper catalysts. Indeed, we envisioned that the reaction might proceed through an electrophilic metalation. Thus, copper catalysts might be more efficient than palladium catalysts through the formation of highly electrophilic Cu(III) species. After extensive investigations, we were pleased to find that the CuI/1,10-phenanthroline (**3**) system gave the C-2-CF_2-substituted benzofuran **2a** in 50% isolated yield (entry 2). Next, a survey of solvents revealed that DMF is the most adequate solvent for this transformation. For instance, when the reaction was performed in NMP or dioxane, the product was obtained in 21% or 8% yield, respectively (entries 3 and 4). The nature of the base also played an important role in this reaction. Among all of the inorganic bases tested, K_2CO_3 was the most efficient for this reaction (entries 2, 5, and 6). In addition, lower yields were observed with organic bases such as 2,6-lutidine (entry 7). Next, different copper catalysts were examined. CuCl led to the formation of **2a** in a yield comparable to that with CuI (45%; entry 8), whereas both $[Cu(OTf)]_2{\cdot}C_6H_6$ and $Cu(OTf)_2$ gave lower yields (33%; entries 9 and 10). The effectiveness of Cu(I) and Cu(II) indicated that Cu(I) might be the active catalyst, probably involving a Cu(I)/Cu(III) catalytic cycle.[14] As expected, control experiments revealed that no reaction occurred in the absence of the copper catalyst or the base (entries 11 and 12). Finally, it was noted that 1,10-phenanthroline (**3**) plays a crucial role in this reaction, as no product was observed in the absence of this ligand (entry 13).

With these optimized conditions in hand, we moved on the extension of the scope of the reaction to several benzofurans and furans (Scheme 2). First, benzofuran derivatives were placed under our reaction conditions. 3-Methylbenzofuran (**1b**) reacted smoothly to afford the difluorinated benzofuran **2b** in 61% yield, while 2-methylbenzofuran was unreactive under our reaction conditions, thus highlighting the C-2 selectivity of our process. Benzofuran **1c** bearing a phenyl substituent at C-5 gave the corresponding product **2c** in modest yield (36%). 3-Phenylbenzofuran (**1d**) was tested and gave **2d** in 67% isolated yield. When the reaction was performed on a larger scale (2.5 g, 12.7 mmol), similar results were obtained, highlighting the efficiency of the difluoromethylation process. The 4-bromophenyl derivative **1e** gave fluorinated benzofuran **2e** in similar yield (62%). It is noteworthy that no alteration of the bromine substituent was observed, showing the compatibility of our process with brominated substrates. Finally, the difluoromethylation reaction was carried out with benzofuran **1f** providing the polysubstituted benzofuran **2f** in a decent 62% yield and a 68% yield on a gram scale. It is worthy of note that the crystal structure of **2f** was determined by X-ray crystallographic analysis and confirmed the C-2 selectivity of the reaction.[15]

Next, we turned our attention to the furan backbone. First, the reaction with furan (**1g**) was carried out under slightly modified conditions (60 °C instead of 80 °C) and gave fluorinated furan **2g** in 52% yield, despite the high volatility of the product. 2-Methylfuran (**1h**) and 2,3-dimethylfuran (**1i**) reacted smoothly to afford the difluoromethylated products **2h** and **2i** in 61% and 52% yield, respectively. Then, several *O*-protected 2-hydroxymethylfurans were screened, and the reaction proceeded well with all of the protecting groups. The *O*-benzyl derivative **2j** was isolated in 64% yield, while the *O*-MOM derivative **2k** was obtained in 65% yield. One should note that reaction performed with **1j** on a 2 g scale (10 mmol) gave the desired product in 70% yield. The acetyl moiety was also compatible, and fluorinated furan **2l** was obtained in 63% yield. Then, C-3-substituted furan **2m** was tested and gave a 66:34 mixture of the C-2 and C-5 regioisomers in 45% yield (66% based on the recovered starting material). This result might be explained by the stability of the putative carbocation resulting from the nucleophilic attack of the aromatic ring on a highly electrophilic Cu(III) species (vide infra). Finally, furans bearing aromatic substituents were tested. 2-Phenylfuran (**1n**) gave the C-5-difluoromethylated furan **2n** in 58% yield. Similarly, furans **1o** and **1p** reacted nicely to give the corresponding fluorinated furans **2o** and **2p** in 59% and 61% yield, respectively.

To gain insight into the reaction pathway, the reaction was carried out in the presence of radical inhibitors or scavengers (Scheme 3). When the reaction was performed with 1 equiv of TEMPO under the standard conditions, no deleterious effect was observed, and benzofuran **2a** was obtained in a slightly decreased yield (40%); *tert*-butylhydroxytoluene (TBHT) led to similar observations. It is noteworthy that no trace of the TEMPO–CF_2CO_2Et adduct was detected in the crude reaction mixture. Thus, taking into account these observations, we envisaged the following reaction pathway: The Cu(I) catalyst reacts with ethyl bromodifluoroacetate to form the Cu(III) species **A**.[13a,16] The furan or benzofuran **1** undergoes nucleophilic addition to the metal center to give the most stabilized carbocation **B**. The base reacts with **B** to form intermediate **C**, which undergoes reductive elimination to deliver compound **2** and release the copper catalyst.[17]

Finally, to highlight the versatility of these fluorinated scaffolds, we turned our attention to transformation of the ester into the valuable CF_2H moiety.[18] Indeed, the CF_2H moiety is well-appreciated in isostere-based drug design. The CF_2H group is recognized as a bioisostere of alcohol and thiol moieties

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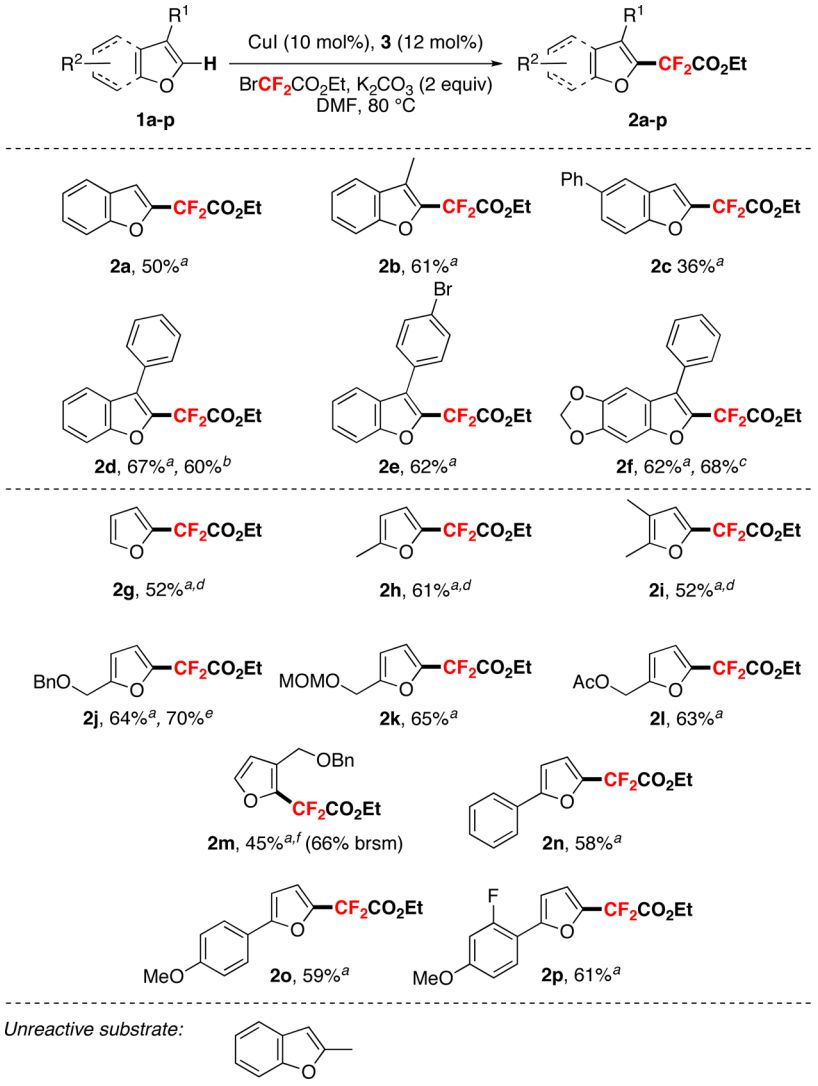
Scheme 2. Scope of the Reaction



[a]Isolated yield. [b]Reaction was performed on a 2.5 g scale (12.7 mmol). [c]Reaction was performed on a 1 g scale (4.1 mmol). [d]Reaction was performed at 60 °C. [e]Reaction was performed on a 2 g scale (10 mmol). [f]**2m** was obtained as a 66:34 mixture of the C-2 and C-5 isomers; the major isomer is shown.

and might behave as a lipohilic hydrogen-bond donor.[19] Therefore, increasing attention has been recently paid to the design of new access to these relevant CF_2H compounds,[20] and several commercial pharmaceuticals[21a,b] and a drug candidate[21c] bearing this motif have recently appeared. Thus, we decided to convert the difluoroacetyl group into the CF_2H moiety through a saponification/decarboxylation sequence (Scheme 4). To achieve the formation of the CF_2H moiety from the CF_2CO_2Et group, benzofuran **2a** was first converted into the corresponding acid **3a** in quantitative yield, and **3a** was directly engaged in a CsF-mediated decarboxylation reaction.[22] Pleasingly, the C-2-CF_2H-substituted benzofuran **4a** was isolated in 65% yield. Then the decarboxylation process was successfully applied to benzofurans **3b** and **3c**, giving the decarboxylated products **4b** and **4c** in 85% and 64% yield, respectively. Finally, this process was applied to furan **3d**, providing the C-2-CF_2H-substituted furan **4d** in 47% isolated yield; the modest yield was due to the high volatility of the product.

In summary, we have reported the first copper-catalyzed direct introduction of the CF_2CO_2Et moiety onto furan and benzofuran skeletons. This reaction proved to be C-2-selective, and the resulting products were obtained in moderate to good yields. Moreover, the reaction proved to be efficient on larger scales (up to 2.5 g). In addition, several functional groups were tolerated under our conditions. Subsequently, the difluoroacetyl group was readily converted into the valuable CF_2H group by decarboxylation, affording a unique access to the CF_2H-substituted furan and benzofuran derivatives.

■ EXPERIMENTAL SECTION

Residual $CHCl_3$ served as the internal standard for ^1H NMR (δ 7.26), and $CFCl_3$ served as the internal standard for ^{19}F NMR (δ 0.0); $CDCl_3$ was used as the internal standard for ^{13}C NMR (δ 77.0). Flash chromatography was performed with silica gel (0.063−0.200 mm). Analytical thin-layer chromatography (TLC) was performed on silica gel aluminum plates with F-254 indicator and visualization by UV fluorescence and/or staining with $KMnO_4$ or PMA. HRMS analyses were performed under ESI conditions with a micro-TOF detector. All experiments were conducted in oven-dried glassware with magnetic stirring. 5-Phenylbenzofuran,[10b] 3-phenylbenzofuran,[10b,23] 3-(4-bromophenyl)benzofuran,[24] 2-(benzyloxymethyl)furan,[25] 2-

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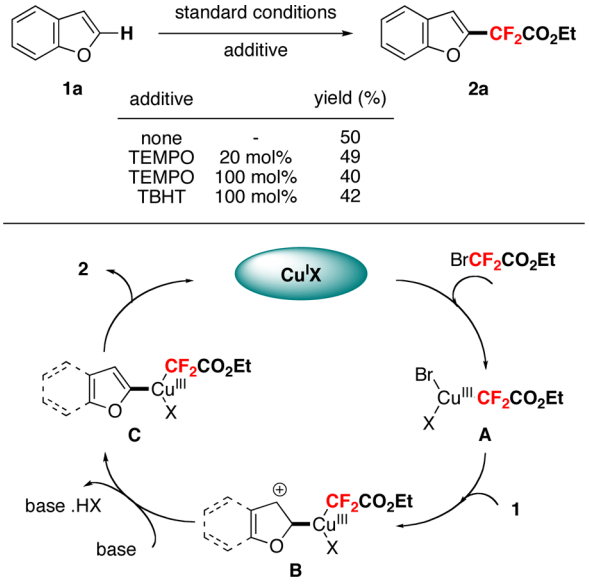
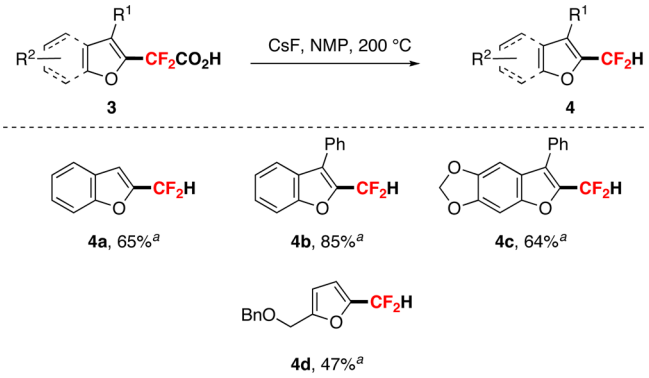
Scheme 3. Mechanistic Experiments and Proposed Mechanism



Scheme 4. Decarboxylation Reaction—Easy Access to the CF_2H Derivatives



[a]Isolated yield.

((methoxymethoxy)methyl)furan,[26] 3-(benzyloxymethyl)furan,[27] 2-phenylfuran,[28] and 2-(4-methoxyphenyl)furan[24] were prepared according to the known procedures.

***α-O*-(3,4-Dioxal)acetophenone.** A solution of 2-bromoacetophenone (4.1 g, 21 mmol), sesamol (2.9 g, 21 mmol), and potassium carbonate (4.3 g, 31 mmol) in acetone (30 mL) was refluxed for 6 h. The reaction mixture was cooled to room temperature, poured into water, and extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL) and dried over $MgSO_4$. The solvent was removed under vacuum, and the solid was recrystallized from 2-propanol to afford α-*O*-(3,4-dioxal)acetophenone as a yellow solid in 65% yield (3.5 g). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 8.02−7.98 (m, 2H, Ph), 7.63 (tt, 1H, Ph, J = 7.2, 2.3 Hz), 7.53−7.48 (m, 2H, Ph), 6.69 (d, 1H, J = 8.3 Hz), 6.58 (d, 1H, J = 2.6 Hz), 6.36 (dd, 1H, J = 8.3, 2.6 Hz), 5.92 (s, 2H), 5.21 (s, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 194.5, 153.4, 148.3, 142.3, 134.4, 133.8, 128.7 (2C), 128.0 (2C), 107.8, 106.0, 101.2, 98.5, 71.7. **IR** (neat, cm^{-1}): 2904, 1701, 1486, 1184. **HRMS** (EI): calcd for [M] $C_{15}H_{12}O_4$, 256.0736; found, 256.0732 (−1.6 ppm). Mp: 75−76 °C.

7-Phenylfuro[2,3-*f*]-1,3-benzodioxole (1f). BCl_3 (1.4 mL, 1.40 mmol, 1 M in DCM) was added dropwise to a solution of α-*O*-(3,4-dioxal)acetophenone (300 mg, 1.17 mmol) in DCM (10.5 mL) at −78 °C. After 30 min at room temperature, the reaction mixture was quenched with cold water and extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine (30 mL) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate 19:1, R_f = 0.44) to afford **1f** as a colorless oil in 39% yield (109 mg). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.70 (s, 1H), 7.61−7.58 (m, 2H, Ph), 7.50−7.45 (m, 2H, Ph), 7.40−7.34 (m, 1H, Ph), 7.19 (s, 1H), 7.04 (s, 1H), 6.02 (s, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 150.9, 146.3, 144.8, 140.7, 132.0, 128.9 (2C), 127.30, 127.25 (2C), 122.6, 119.6, 101.3, 98.7, 93.7. **IR** (neat, cm^{-1}): 2910, 1553, 1463, 1150. **HRMS** (EI): calcd for [M] $C_{15}H_{10}O_3$, 238.0630; found, 238.0637 (+2.9 ppm).

2-(2-Fluoro-4-methoxyphenyl)furan (1p). A sealed tube was charged with 2-fluoro-4-methoxyphenylboronic acid (277 mg, 1.63 mmol), $P(PPh_3)_4$ (157 mg, 0.14 mmol), K_2CO_3 (376 mg, 2.72 mmol), DMF (5 mL), and H_2O (2 mL). After the mixture was degassed with N_2, 2-bromofuran (200 mg, 1.36 mmol) was added, and the tube was sealed. The resulting mixture was heated at 80 °C for 12 h. The solution was cooled, filtered through a plug of Celite, and extracted with Et_2O (3 × 15 mL). The organic layer was washed with water (2 × 15 mL) and brine (2 × 15 mL) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography (petroleum ether/ethyl acetate 19:1, R_f = 0.44) to afford **1p** as a colorless oil in 46% yield (119 mg). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.73 (t, 1H, J = 8.7 Hz), 7.47 (d, 1H, J = 1.5 Hz), 6.78−6.67 (m, 3H), 6.50 (dd, 1H, J = 3.4, 1.5 Hz), 3.84 (s, 3H, OMe). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 159.7 (d, J_{CF} = 11.0 Hz), 159.2 (d, J_{CF} = 249.8 Hz), 148.2 (d, J_{CF} = 3.3 Hz), 141.2, 126.6 (d, J_{CF} = 4.9 Hz), 112.1 (d, J_{CF} = 13.2 Hz), 111.7, 110.1 (d, J_{CF} = 2.8 Hz), 108.0 (d, J_{CF} = 10.6 Hz), 102.0 (d, J_{CF} = 25.9 Hz), 55.5 (d, J_{CF} = 3.9 Hz). **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −112.6 (s, 1F). **IR** (neat, cm^{-1}): 2842, 1629, 1287, 1024. **HRMS** (EI): calcd for [M] $C_{11}H_9FO_2$, 192.0587; found, 192.0592 (+2.6 ppm).

General Procedure A: Copper-Catalyzed Difluoromethylation Reaction of Benzofurans and Furans. Under an air atmosphere, CuI (5 mg, 0.024 mmol), 1,10-phenanthroline (5 mg, 0.029 mmol), and K_2CO_3 (66 mg, 0.48 mmol) were dissolved in DMF (1.2 mL). Then the benzofuran or furan derivative (0.24 mmol) and ethyl bromodifluoroacetate (0.25 mL, 1.92 mmol) were added, and the tube was sealed. The resulting mixture was heated at 80 °C for 20 h. The solution was cooled and extracted with Et_2O (3 × 10 mL). The organic layer was washed with water (2 × 10 mL) and brine (2 × 10 mL) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography (SiO_2, petroleum ether/ethyl acetate or pentane/diethyl ether).

*Ethyl 2-(Benzofuran-2-yl)-2,2-difluoroacetate (**2a**).* Prepared following general procedure A from benzofuran **1a**. Compound **2a** was obtained as a colorless oil in 50% yield (29 mg) after flash chromatography (SiO_2, petroleum ether/ethyl acetate 19:1, R_f = 0.57). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.66 (d, 1H, J = 7.7 Hz), 7.56 (d, 1H, J = 8.3 Hz), 7.42 (t, 1H, J = 7.7 Hz), 7.32 (t, 1H, J = 8.3 Hz), 7.16 (s, 1H), 4.42 (q, 2H, J = 7.2 Hz), 1.38 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.1 (t, J_{CF} = 33.7 Hz), 155.4 (t, J_{CF} = 1.1 Hz), 146.5 (dd, J_{CF} = 33.4, 33.4 Hz), 126.5, 126.4, 123.7, 122.3, 112.0, 108.9 (t, J_{CF} = 249.2 Hz), 108.1 (t, J_{CF} = 3.9 Hz), 63.7, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −104.6 (s, 2F). **IR** (neat, cm^{-1}): 2986, 1770, 1292, 1105. **HRMS** (ESI+): calcd for $[M + H]^+$ $C_{12}H_{11}F_2O_3$, 241.0676; found, 241.0686 (+4.1 ppm).

*Ethyl 2,2-Difluoro-2-(3-methylbenzofuran-2-yl)acetate (**2b**).* Prepared following general procedure A from 3-methylbenzofuran (**1b**). Compound **2b** was obtained as a colorless oil in 61% yield (37 mg) after flash chromatography (SiO_2, petroleum ether/ethyl acetate 49:1, R_f = 0.38). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.60 (d, 1H, J = 7.7 Hz), 7.50 (d, 1H, J = 8.1 Hz), 7.41 (t, 1H, J = 7.7 Hz), 7.32 (t, 1H, J = 8.1 Hz), 4.41 (q, 2H, J = 7.2 Hz), 2.43 (s, 3H), 1.37 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.5 (t, J_{CF} = 34.1 Hz), 154.2, 140.9 (t, J_{CF} = 32.5 Hz), 128.9, 126.3, 123.1, 120.3, 118.1 (t, J_{CF} = 2.2 Hz), 111.8, 110.4 (t, J_{CF} = 249.8 Hz), 63.6, 13.9, 7.7. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −103.9 (s, 2F). **IR** (neat, cm^{-1}): 2987, 1767, 1287, 1093. **HRMS** (AP+): calcd for $[M + H]^+$ $C_{13}H_{13}F_2O_3$, 255.0833; found, 255.0834 (+0.4 ppm).

*Ethyl 2,2-Difluoro-2-(5-phenylbenzofuran-2-yl)acetate (**2c**).* Prepared following general procedure A from 5-phenylbenzofuran (**1c**),

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except that the reaction mixture was heated at 80 °C for 15 h instead of 20 h. Compound **2c** was obtained as a colorless oil in 36% yield (27 mg) after flash chromatography (SiO_2, petroleum ether/ethyl acetate 19:1, R_f = 0.35). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.84 (s, 1H), 7.66−7.60 (m, 4H), 7.48 (t, 2H, J = 7.6 Hz), 7.38 (tt, 1H, J = 7.6, 1.3 Hz), 7.21 (s, 1H), 4.43 (q, 2H, J = 7.2 Hz), 1.40 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.1 (t, J_{CF} = 33.0 Hz), 155.0, 147.0 (t, J_{CF} = 33.6 Hz), 141.0, 137.6, 128.8 (2C), 127.4 (2C), 127.2, 127.1, 126.2, 120.6, 112.1, 108.8 (t, J_{CF} = 249.2 Hz), 108.3 (t, J_{CF} = 3.3 Hz), 63.8, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −104.7 (s, 2F). **IR** (neat, cm^{-1}): 2988, 1777, 1288, 1113. **HRMS** (AP+): calcd for $[M + H]^+$ $C_{18}H_{15}F_2O_3$, 317.0989; found, 317.0994 (+1.6 ppm).

*Ethyl 2,2-Difluoro-2-(3-phenylbenzofuran-2-yl)acetate (**2d**).* Prepared following general procedure A from 3-phenylbenzofuran (**1d**). Compound **2d** was obtained as a colorless oil in 67% yield (51 mg) after flash chromatography (SiO_2, petroleum ether/ethyl acetate 19:1, R_f = 0.46). When the reaction was performed on 12.7 mmol (2.5 g) of **1d**, compound **2d** was obtained in 60% yield (2.4 g). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.50−7.33 (m, 8H), 7.22 (t, 1H, J = 7.6 Hz), 4.09 (q, 2H, J = 7.2 Hz), 1.13 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.1 (t, J_{CF} = 33.0 Hz), 154.1, 140.8 (t, J_{CF} = 30.8 Hz), 129.7 (2C), 129.5, 128.5 (3C), 128.0, 126.8, 123.7, 123.6 (t, J_{CF} = 3.3 Hz), 121.3, 111.9, 109.7 (t, J_{CF} = 249.2 Hz), 65.6, 13.7. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −99.9 (s, 2F). **IR** (neat, cm^{-1}): 2987, 1768, 1288, 1049. **HRMS** (AP+): calcd for $[M + H]^+$ $C_{18}H_{15}F_2O_3$, 317.0989; found, 317.0984 (−1.6 ppm).

*Ethyl 2,2-Difluoro-2-(3-(4-bromophenyl)benzofuran-2-yl)acetate (**2e**).* Prepared following general procedure A from 3-(4-bromophenyl)-benzofuran (**1e**). Compound **2e** was obtained as a colorless oil in 62% yield (59 mg) after flash chromatography (SiO_2, petroleum ether/ethyl acetate 19:1, R_f = 0.52). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.66−7.62 (m, 2H), 7.61−7.53 (m, 2H), 7.50−7.41 (m, 3H), 7.34 (t, 1H, J = 7.2 Hz), 4.27 (q, 2H, J = 7.2 Hz), 1.29 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.0 (t, J_{CF} = 33.0 Hz), 154.2 (t, J_{CF} = 1.1 Hz), 141.0 (t, J_{CF} = 31.4 Hz), 131.8 (2C), 131.3 (2C), 128.5, 127.7 (t, J_{CF} = 1.1 Hz), 126.9, 123.9, 122.8, 122.5 (t, J_{CF} = 2.8 Hz), 121.1, 112.0, 109.7 (t, J_{CF} = 250.3 Hz), 63.7, 13.8. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −101.0 (s, 2F). **IR** (neat, cm^{-1}): 2983, 1769, 1288, 1049. **HRMS** (AP+): calcd for $[M + H]^+$ $C_{18}H_{14}F_2O_3Br$, 395.0094; found, 395.0094 (0.0 ppm).

*Ethyl 2-(7-Phenylfuro[2,3-*f*]-1,3-benzodioxol-8-yl)-2,2-difluoroacetate (**2f**).* Prepared following general procedure A from 7-phenylfuro-[2,3-*f*]-1,3-benzodioxole (**1f**), except that the reaction mixture was heated at 80 °C for 8 h instead of 20 h. Compound **2f** was obtained as a yellow solid in 62% yield (53 mg) after flash chromatography (SiO_2, petroleum ether/ethyl acetate 9:1, R_f = 0.28). When the reaction was performed on 4.19 mmol (1.0 g) of **1f**, compound **2f** was obtained in 68% yield (1.0 g). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.49−7.43 (m, 5H), 7.04 (s, 1H), 6.87 (s, 1H), 6.02 (s, 2H), 4.15 (q, 2H, J = 7.2 Hz), 1.23 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.2 (t, J_{CF} = 33.0 Hz), 149.7 (t, J_{CF} = 1.1 Hz), 148.2, 145.6, 140.2 (t, J_{CF} = 31.4 Hz), 129.6, 129.5 (t, 2C, J_{CF} = 1.7 Hz), 128.5 (2C), 128.4, 124.2 (t, J_{CF} = 3.3 Hz), 121.4, 109.6 (t, J_{CF} = 249.2 Hz), 101.7, 99.1, 93.6, 63.5, 13.7. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −99.8 (s, 2F). **IR** (neat, cm^{-1}): 2983, 1767, 1461, 1304, 1030. **HRMS** (EI): calcd for [M] $C_{19}H_{14}F_2O_5$, 360.0809; found, 360.0815 (+1.7 ppm). Mp: 54−55 °C.

*Ethyl 2,2-Difluoro-2-(furan-2-yl)acetate (**2g**).* Prepared following general procedure A from furan (**1g**), except that the reaction mixture was heated at 60 °C for 25 h. Compound **2g** was obtained as a colorless oil in 52% yield (24 mg) after flash chromatography (SiO_2, pentane/diethyl ether 19:1, R_f = 0.55). (***Caution**: the product is highly volatile*). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.53−7.52 (m, 1H), 6.78−6.77 (m, 1H), 6.48−6.46 (m, 1H), 4.39 (q, 2H, J = 7.2 Hz), 1.37 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.4 (t, J_{CF} = 33.6 Hz), 144.9, 144.6 (t, J_{CF} = 34.1 Hz), 111.6 (t, J_{CF} = 3.3 Hz), 110.8−110.7 (m), 108.7 (t, J_{CF} = 248.1 Hz), 63.5, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −103.1 (s, 2F). **IR** (neat, cm^{-1}): 2990, 1767, 1260, 1010. **HRMS** (EI): calcd for [M] $C_8H_8F_2O_3$, 190.0442; found, 190.0444 (+1.3 ppm).

*Ethyl 2,2-Difluoro-2-(5-methylfuran-2-yl)acetate (**2h**).* Prepared following general procedure A from 2-methylfuran (**1h**), except that the reaction mixture was heated at 60 °C for 20 h. Compound **2h** was obtained as a colorless oil in 61% yield (30 mg) after flash chromatography (SiO_2, pentane/diethyl ether 19:1, R_f = 0.55). (***Caution**: the product is highly volatile*). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 6.65−6.62 (m, 1H), 6.06−6.04 (m, 1H), 4.39 (q, 2H, J = 7.2 Hz), 2.34 (s, 3H), 1.37 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.6 (t, J_{CF} = 34.1 Hz), 155.2 (t, J_{CF} = 2.2 Hz), 142.6 (t, J_{CF} = 33.6 Hz), 112.7−112.6 (m), 108.7 (t, J_{CF} = 247.6 Hz), 106.8 (d, J_{CF} = 3.9 Hz), 63.4, 13.9, 13.5. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −102.5 (s, 2F). **IR** (neat, cm^{-1}): 2990, 1767, 1280, 1050. **HRMS** (EI): calcd for [M] $C_9H_{10}F_2O_3$, 204.0598; found, 204.0608 (+4.9 ppm).

*Ethyl 2,2-Difluoro-2-(4,5-dimethylfuran-2-yl)acetate (**2i**).* Prepared following general procedure A from 2,3-dimethylfuran (**1i**), except that the reaction mixture was heated at 60 °C for 20 h. Compound **2i** was obtained as a colorless oil in 52% yield (27 mg) after flash chromatography (SiO_2, pentane/diethyl ether 49:1, R_f = 0.43). (***Caution**: the product is highly volatile*). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 6.52 (s, 1H), 4.38 (q, 2H, J = 7.2 Hz), 2.24 (s, 3H), 1.96 (s, 3H), 1.37 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.7 (t, J_{CF} = 34.1 Hz), 150.6 (t, J_{CF} = 2.2 Hz), 141.3 (t, J_{CF} = 33.0 Hz), 115.4 (t, J_{CF} = 1.1 Hz), 114.8−114.7 (m), 108.8 (t, J_{CF} = 247.0 Hz), 63.3, 13.9, 11.4, 9.7. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −102.6 (s, 2F). **IR** (neat, cm^{-1}): 2963, 1768, 1261, 1043. **HRMS** (EI): calcd for [M] $C_{10}H_{12}F_2O_3$, 218.0755; found, 218.0752 (−1.2 ppm).

*Ethyl 2,2-Difluoro-2-(5-(benzyloxymethyl)furan-2-yl)acetate (**2j**).* Prepared following general procedure A from 2-(benzyloxymethyl)-furan (**1j**), except that the reaction mixture was heated at 80 °C for 15 h instead of 20 h. Compound **2j** was obtained as a colorless oil in 64% yield (47 mg) after flash chromatography (SiO_2, pentane/diethyl ether 7:3, R_f = 0.46). When the reaction was performed on 10.6 mmol (2.0 g) of **1j**, compound **2j** was obtained in 70% yield (2.3 g). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.38−7.29 (m, 5H), 6.73 (ddd, 1H, J = 3.4, 1.7, 1.7 Hz), 6.40 (d, 1H, J = 3.4 Hz), 4.57 (s, 2H), 4.52 (s, 2H), 4.39 (q, 2H, J = 7.2 Hz), 1.36 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.3 (t, J_{CF} = 33.6 Hz), 154.7 (t, J_{CF} = 1.7 Hz), 144.3 (t, J_{CF} = 34.1 Hz), 137.5, 128.4 (2C), 127.9 (3C), 112.4 (t, J_{CF} = 3.9 Hz), 110.0, 108.5 (t, J_{CF} = 248.1 Hz), 72.3, 63.6, 63.5, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −103.0 (s, 2F). **IR** (neat, cm^{-1}): 2987, 1766, 1278, 1049. **HRMS** (EI): calcd for [M] $C_{16}H_{16}F_2O_4$, 310.1017; found, 310.1021 (+1.4 ppm).

*Ethyl 2,2-Difluoro-2-(5-((methoxymethoxy)methyl)furan-2-yl)-acetate (**2k**).* Prepared following general procedure A from 2-((methoxymethoxy)methyl)furan (**1k**), except that the reaction mixture was heated at 80 °C for 12 h instead of 20 h. Compound **2k** was obtained as a colorless oil in 65% yield (41 mg) after flash chromatography (SiO_2, pentane/diethyl ether 7:3, R_f = 0.43). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 6.71 (ddd, 1H, J = 3.4, 1.7, 1.7 Hz), 6.40 (d, 1H, J = 3.4 Hz), 4.67 (s, 2H), 4.55 (s, 2H), 4.38 (q, 2H, J = 7.2 Hz), 3.39 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.3 (t, J_{CF} = 33.6 Hz), 154.3 (t, J_{CF} = 1.7 Hz), 144.5 (t, J_{CF} = 33.6 Hz), 112.3 (t, J_{CF} = 3.9 Hz), 110.0, 108.5 (t, J_{CF} = 248.1 Hz), 95.5, 63.5, 60.6, 55.4, 13.8. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −103.0 (s, 2F). **IR** (neat, cm^{-1}): 2945, 1767, 1278, 1038. **HRMS** (EI): calcd for [M] $C_{11}H_{14}F_2O_5$, 264.0809; found, 264.0823 (+5.0 ppm).

*Ethyl 2,2-Difluoro-2-(5-(acetoxymethyl)furan-2-yl)acetate (**2l**).* Prepared following general procedure A from furfuryl acetate (**1l**), except that the reaction mixture was heated at 80 °C for 15 h instead of 20 h. Compound **2l** was obtained as a colorless oil in 63% yield (40 mg) after flash chromatography (SiO_2, pentane/diethyl ether 7:3, R_f = 0.47). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 6.72 (ddd, 1H, J = 3.4, 1.7, 1.7 Hz), 6.47 (d, 1H, J = 3.4 Hz), 5.05 (s, 2H), 4.39 (q, 2H, J = 7.2 Hz), 2.08 (s, 3H), 1.36 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 170.4, 162.1 (t, J_{CF} = 33.6 Hz), 152.1 (t, J_{CF} = 2.2 Hz), 144.8 (dd, J_{CF} = 34.1, 34.1 Hz), 112.5 (t, J_{CF} = 3.9 Hz), 111.3, 108.4 (t, J_{CF} = 248.1 Hz), 65.5, 57.5, 20.7, 13.8. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −103.1 (s, 2F). **IR** (neat, cm^{-1}): 2922, 1746, 1227, 1050. **HRMS** (E^+): calcd for $[M + Na]^+$ $C_{11}H_{12}F_2O_5Na$, 285.0550; found, 285.0545 (−1.8 ppm).

*Ethyl 2,2-Difluoro-2-(3-(benzyloxymethyl)furan-2-yl)acetate and Ethyl 2,2-Difluoro-2-(4-(benzyloxymethyl)furan-2-yl)acetate (**2m**).* Prepared following general procedure A from 3-(benzyloxymethyl)-furan (**1m**), except that the reaction mixture was heated at 60 °C for 24 h instead of 20 h. Compound **2m** was obtained as a 66:34 mixture of

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regioisomers as a colorless oil in 45% yield (66% based on recovered starting material) (33 mg) after flash chromatography [SiO_2, pentane/diethyl ether 19:1, R_f = 0.22 (major regioisomer), 0.18 (minor regioisomer)].

Ethyl 2,2-Difluoro-2-(3-(benzyloxymethyl)furan-2-yl)acetate (Major Regioisomer). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.47 (s, 1H), 7.37−7.29 (m, 5H), 6.60 (s, 1H), 4.60 (t, 2H, J = 1.9 Hz), 4.55 (s, 2H), 4.36 (q, 2H, J = 7.2 Hz), 1.34 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.3 (t, J_{CF} = 34.1 Hz), 144.0, 140.1 (t, J_{CF} = 34.7 Hz), 137.8, 128.4 (2C), 127.8 (2C), 127.7, 124.9 (t, J_{CF} = 1.7 Hz), 112.4, 109.7 (t, J_{CF} = 249.2 Hz), 72.3, 63.5, 62.3, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −102.7 (s, 2F). **IR** (neat, cm^{-1}): 2921, 1767, 1289, 1070. **HRMS** (E^+): calcd for $[M + H]^+$ $C_{16}H_{17}F_2O_4$, 311.1095; found, 311.1097 (+0.6 ppm).

Ethyl 2,2-Difluoro-2-(4-(benzyloxymethyl)furan-2-yl)acetate (Minor Regioisomer, Contaminated by the Major Regioisomer). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.50 (s, 1H), 7.37−7.32 (m, 5H), 6.81 (s, 1H), 4.56 (s, 2H), 4.42−4.35 (m, 4H), 1.37 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.3 (t, J_{CF} = 33.6 Hz), 145.1 (t, J_{CF} = 33.6 Hz), 142.7, 137.7, 128.5 (2C), 127.8 (3C), 123.6, 112.2 (t, J_{CF} = 3.3 Hz), 108.5 (t, J_{CF} = 248.1 Hz), 72.3, 63.5, 62.9, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −103.3 (s, 2F). **IR** (neat, cm^{-1}): 2922, 1768, 1290, 1091. **HRMS** (E^+): calcd for $[M + H]^+$ $C_{16}H_{17}F_2O_4$, 311.1095; found, 311.1104 (+2.9 ppm).

*Ethyl 2,2-Difluoro-2-(5-phenylfuran-2-yl)acetate (**2n**).* Prepared following general procedure A from 2-phenylfuran (**1n**), except that the reaction mixture was heated at 80 °C for 15 h instead of 20 h. Compound **2n** was obtained as a colorless oil in 58% yield (37 mg) after flash chromatography (SiO_2, pentane/diethyl ether 19:1, R_f = 0.44). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.72−7.68 (m, 2H), 7.45−7.40 (m, 2H), 7.34 (tt, 1H, J = 7.4, 1.3 Hz), 6.84 (ddd, 1H, J = 3.4, 1.7, 1.7 Hz), 6.70 (d, 1H, J = 3.4 Hz), 4.42 (q, 2H, J = 7.2 Hz), 1.39 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.4 (t, J_{CF} = 33.6 Hz), 156.3 (t, J_{CF} = 2.2 Hz), 143.5 (dd, J_{CF} = 33.6, 33.6 Hz), 129.5, 128.8 (2C), 128.5, 124.3 (2C), 113.6 (t, J_{CF} = 3.9 Hz), 108.7 (t, J_{CF} = 248.1 Hz), 105.6, 63.5, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −102.8 (s, 2F). **IR** (neat, cm^{-1}): 2988, 1765, 1273, 1042. **HRMS** (E^+): calcd for $[M + H]^+$ $C_{14}H_{13}F_2O_3$, 267.0833; found, 267.0841 (+3.0 ppm).

*Ethyl 2,2-Difluoro-2-(5-(4-methoxyphenyl)furan-2-yl)acetate (**2o**).* Prepared following general procedure A from 2-(4-methoxyphenyl)furan (**1o**), except that the reaction mixture was heated at 80 °C for 15 h instead of 20 h. Compound **2o** was obtained as a colorless oil in 59% yield (42 mg) after flash chromatography (SiO_2, pentane/diethyl ether 19:1, R_f = 0.26). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.65−7.62 (m, 2H), 6.96−6.93 (m, 2H), 6.81 (ddd, 1H, J = 3.4, 1.7, 1.7 Hz), 6.55 (d, 1H, J = 3.4 Hz), 4.41 (q, 2H, J = 7.2 Hz), 3.85 (s, 3H), 1.39 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.5 (t, J_{CF} = 33.6 Hz), 159.9, 156.5 (t, J_{CF} = 2.2 Hz), 142.8 (dd, J_{CF} = 34.1, 34.1 Hz), 125.9 (2C), 122.5, 114.2 (2C), 113.7 (t, J_{CF} = 3.9 Hz), 108.8 (t, J_{CF} = 247.6 Hz), 104.0, 63.4, 55.3, 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −102.5 (s, 2F). **IR** (neat, cm^{-1}): 2977, 1765, 1274, 1021. **HRMS** (EI): calcd for [M] $C_{15}H_{14}F_2O_4$, 296.0860; found, 296.0868 (+2.7 ppm).

*Ethyl 2,2-Difluoro-2-(5-(2-fluoro-4-methoxyphenyl)furan-2-yl)-acetate (**2p**).* Prepared following general procedure A from 2-(2-fluoro-4-methoxyphenyl)furan (**1p**), except that the reaction mixture was heated at 80 °C for 15 h instead of 20 h. Compound **2p** was obtained as a colorless oil in 61% yield (46 mg) after flash chromatography (SiO_2, pentane/diethyl ether 19:1, R_f = 0.21). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.74 (t, 1H, J = 8.9 Hz), 6.84 (ddd, 1H, J = 3.4, 1.7, 1.7 Hz), 6.79−6.67 (m, 3H), 4.42 (q, 2H, J = 7.2 Hz), 3.84 (s, 3H), 1.39 (t, 3H, J = 7.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 162.4 (t, J_{CF} = 34.1 Hz), 160.8 (d, J_{CF} = 11.0 Hz), 159.8 (d, J_{CF} = 251.4 Hz), 150.8−150.7 (m), 142.6 (dt, J_{CF} = 33.6, 1.1 Hz), 127.1 (d, J_{CF} = 5.0 Hz), 113.8 (dt, J_{CF} = 3.9, 1.7 Hz), 110.8 (d, J_{CF} = 12.7 Hz), 110.3 (d, J_{CF} = 3.3 Hz), 108.8 (t, J_{CF} = 248.1 Hz), 108.6 (d, J_{CF} = 11.6 Hz), 102.0 (d, J_{CF} = 25.3 Hz), 63.5, 55.6 (d, J_{CF} = 4.4 Hz), 13.9. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −102.7 (s, 2F), −111.9 (s, 1F). **IR** (neat, cm^{-1}): 2999, 1760, 1273, 1032. **HRMS** (EI): calcd for [M] $C_{15}H_{13}F_3O_4$, 314.0766; found, 314.0779 (+4.2 ppm).

General Procedure B: Saponification/Decarboxylation Sequence for the CF_2CO_2Et Moiety. Under a nitrogen atmosphere, the C-2-CF_2CO_2Et-substituted benzofuran or furan was dissolved in MeOH (0.3 M), and an aqueous solution of K_2CO_3 (3 equiv, 1 M) was added. After 30 min at room temperature, the reaction mixture was acidified to pH 1 by addition of a solution of HCl (2 N), and the solution was extracted with DCM (three times). The organic layer was washed with brine and dried over $MgSO_4$. The solvent was removed under vacuum to afford the corresponding C-2-CF_2CO_2H-substituted product in quantitative yield. This one was then added to a solution of CsF (5 equiv) in NMP (0.25 M) under a nitrogen atmosphere, and the tube was sealed. The resulting mixture was heated at 200 °C for 16 h. The solution was cooled and extracted with Et_2O (three times). The organic layer was washed with water (twice) and brine (twice) and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by flash chromatography (SiO_2, pentane/diethyl ether).

*2-(Difluoromethyl)benzofuran (**4a**).* Prepared following general procedure B from **2a** (0.24 mmol). Compound **4a** was obtained as a colorless oil in 65% yield (26 mg) after flash chromatography (SiO_2, pentane, R_f = 0.51). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.66 (d, 1H, J = 7.6 Hz), 7.56 (d, 1H, J = 8.1 Hz), 7.41 (t, 1H, J = 7.6 Hz), 7.31 (t, 1H, J = 8.1 Hz), 7.05 (s, 1H), 6.77 (t, 1H, J = 54.2 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 155.2 (t, J_{CF} = 1.1 Hz), 148.3 (t, J_{CF} = 28.6 Hz), 126.6 (t, J_{CF} = 1.1 Hz), 126.1, 123.6, 122.1, 111.9, 108.8 (t, J_{CF} = 236.6 Hz), 106.8 (t, J_{CF} = 5.0 Hz). **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −117.1 (dd, 2F, J = 54.2, 2.0 Hz). **IR** (neat, cm^{-1}): 1616, 1371, 1136. **HRMS** (EI): calcd for [M] $C_9H_6F_2O$, 168.0387; found, 168.0381 (−3.5 ppm).

*2-(Difluoromethyl)-3-phenylbenzofuran (**4b**).* Prepared following general procedure B from **2d** (0.67 mmol). Compound **4b** was obtained as a colorless oil in 85% yield (140 mg) after flash chromatography (SiO_2, pentane, R_f = 0.30). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.72 (d, 1H, J = 7.6 Hz), 7.65 (d, 1H, J = 8.3 Hz), 7.57−7.47 (m, 6H), 7.37 (t, 1H, J = 7.6 Hz), 6.78 (t, 1H, J = 52.1 Hz). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 154.5, 142.7 (t, J_{CF} = 23.7 Hz), 129.6 (t, J_{CF} = 1.7 Hz), 129.2 (2C), 129.1 (2C), 128.6, 127.0, 126.8, 123.9 (t, J_{CF} = 6.6 Hz), 123.6, 121.1, 112.1, 108.3 (t, J_{CF} = 234.4 Hz). **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −114.3 (d, 2F, J = 52.1 Hz). **IR** (neat, cm^{-1}): 1613, 1395, 1085, 1026. **HRMS** (EI): calcd for [M] $C_{15}H_{10}F_2O$, 244.0700; found, 244.0703 (+1.2 ppm).

*7-Phenyl-8-difluoromethylfuro[2,3-f]-1,3-benzodioxole (**4c**).* Prepared following general procedure B from **2f** (0.12 mmol), except that the reaction mixture was heated at 200 °C for 4 h instead of 16 h. Compound **4c** was obtained as a colorless oil in 64% yield (22 mg) after flash chromatography (SiO_2, pentane/diethyl ether 49:1, R_f = 0.35). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.56−7.47 (m, 5H), 7.07 (s, 1H), 6.99 (s, 1H), 6.65 (t, 1H, J = 52.1 Hz), 6.04 (s, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 150.1, 148.2, 145.5, 142.2 (t, J_{CF} = 23.7 Hz), 129.7, 129.1 (4C), 128.6, 124.5 (t, J_{CF} = 7.2 Hz), 120.3, 108.2 (t, J_{CF} = 234.4 Hz), 101.7, 99.0, 93.8. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −113.5 (d, 2F, J = 52.1 Hz). **IR** (neat, cm^{-1}): 1608, 1460, 1238, 1153, 1021. **HRMS** (EI): calcd for [M] $C_{16}H_{10}F_2O_3$, 288.0598; found, 288.0604 (+2.1 ppm).

*2-(Benzyloxymethyl)-5-(difluoromethyl)furan (**4d**).* Prepared following general procedure B from **2j** (0.24 mmol), except that the reaction mixture was heated at 200 °C for 4 h instead of 16 h. Compound **4d** was obtained as a colorless oil in 47% yield (27 mg) after flash chromatography (SiO_2, pentane/diethyl ether 19:1, R_f = 0.33). **^{1}H NMR** ($CDCl_3$, 300 MHz): δ 7.37−7.35 (m, 5H), 6.64 (s, 1H), 6.62 (t, 1H, J = 54.2 Hz), 6.39 (s, 1H), 4.59 (s, 2H), 4.52 (s, 2H). **^{13}C NMR** ($CDCl_3$, 75 MHz): δ 153.8 (t, J_{CF} = 2.2 Hz), 146.7 (t, J_{CF} = 29.7 Hz), 137.5, 128.5 (2C), 127.90 (2C), 127.85, 110.9 (t, J_{CF} = 4.4 Hz), 109.9, 108.4 (t, J_{CF} = 234.9 Hz), 72.3, 63.7. **^{19}F NMR** ($CDCl_3$, $CFCl_3$, 282 MHz): δ −115.3 (d, 2F, J = 54.2 Hz). **IR** (neat, cm^{-1}): 1359, 1071, 1017. **HRMS** (EI): calcd for [M] $C_{13}H_{12}F_2O_2$, 238.0805; found, 238.0815 (+4.2 ppm).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Böhm, H.-J.; Banner, D.; Bendels, S.; Kansy, M.; Kuhn, B.; Müller, K.; Obst-Sander, U.; Stahl, M. *ChemBioChem* **2004**, *5*, 637.

(2) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.

(3) (a) Landelle, G.; Panossian, A.; Pazenok, S.; Vors, J.-P.; Leroux, F. R. *Beilstein J. Org. Chem.* **2013**, *9*, 2476. (b) Liu, H.; Gu, Z.; Jiang, X. *Adv. Synth. Catal.* **2013**, *355*, 617. (c) Liang, T.; Neumann, C. N.; Ritter, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 8214. (d) Chen, P.; Liu, G. *Synthesis* **2013**, *45*, 2919. (e) Wang, X.; Truesdale, L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648. (f) Zhang, X.-G.; Dai, H.-X.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 11948. (g) Parsons, A. T.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 9120. (h) Ye, Y.; Lee, S. H.; Sanford, M. S. *Org. Lett.* **2011**, *13*, 5464. (i) Zeng, Y.; Zhang, L.; Zhao, Y.; Ni, C.; Zhao, J.; Hu, J. *J. Am. Chem. Soc.* **2013**, *135*, 2955.

(4) (a) *Comprehensive Heterocyclic Chemistry III*, 1st ed.; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008. (b) De Luca, L.; Nieddu, G.; Porcheddu, A.; Giacomelli, G. *Curr. Med. Chem.* **2009**, *16*, 1−20.

(5) (a) Lee, C. F.; Yang, L. M.; Hwu, T. Y.; Feng, A. S.; Tseng, J. C.; Luh, T. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4992. (b) Liu, C. Y.; Luh, T. Y. *Org. Lett.* **2002**, *4*, 4305.

(6) Hou, X. L.; Yang, S.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2007**, *18*, 187.

(7) (a) Katrizky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613. (b) Ando, K.; Kawamura, Y.; Akai, Y.; Kunitomo, J.; Yokomizo, T.; Yamashita, M.; Ohta, S.; Ohishi, T.; Ohishi, Y. *Org. Biomol. Chem.* **2008**, *6*, 296.

(8) (a) Fürstner, A.; Davies, P. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (b) Oppenheimer, J.; Johnson, W.; Tracey, M.; Hsung, R.; Yao, P. Y.; Liu, R.; Zhao, K. *Org. Lett.* **2007**, *9*, 2361.

(9) (a) Chiong, H. A.; Daugulis, O. *Org. Lett.* **2007**, *9*, 1449. (b) Do, H.-Q.; Khan, R. M. K.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185. (c) Yanagisawa, S.; Itami, K. *Tetrahedron* **2011**, *67*, 4425. (d) Carrër, A.; Rousselle, P.; Florent, J.-C.; Bertounesque, E. *Adv. Synth. Catal.* **2012**, *354*, 2751. (e) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137.

(10) (a) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6743. (b) Li, Y.; Waser, J. *Beilstein J. Org. Chem.* **2013**, *9*, 1763.

(11) (a) Mejía, E.; Togni, A. *ACS Catal.* **2012**, *2*, 521. (b) Iqbal, N.; Choi, S.; Ko, E.; Cho, E. J. *Tetrahedron Lett.* **2012**, *53*, 2005. (c) Kino, T.; Nagase, Y.; Ohtsuka, Y.; Yamamoto, K.; Uraguchi, D.; Tokuhisa, K.; Yamakawa, T. *J. Fluorine Chem.* **2010**, *131*, 98. (d) Seo, S.; Taylor, J. B.; Greaney, M. F. *Chem. Commun.* **2013**, *49*, 6385.

(12) (a) Ohtsuka, Y.; Yamakawa, T. *Tetrahedron* **2011**, *67*, 2323. (b) Lin, Q.; Chu, L.; Qing, F.-L. *Chin. J. Chem.* **2013**, *31*, 885. (c) Murakami, S.; Ishii, H.; Tajima, T.; Fuchigami, T. *Tetrahedron* **2006**, *62*, 3761. For an alternative strategy based on an oxidative coupling reaction with difluoroenol silyl ethers, see: (d) Uneyama, K.; Tanaka, H.; Kobayashi, S.; Shioyama, M.; Amii, H. *Org. Lett.* **2004**, *6*, 2733−2736.

(13) (a) Belhomme, M.-C.; Poisson, T.; Pannecoucke, X. *Org. Lett.* **2013**, *15*, 3428. (b) Lemonnier, G.; Hijfte, N. V.; Poisson, T.; Couve-Bonnaire, S.; Pannecoucke, X. *J. Org. Chem.* **2014**, *79*, 2916. (c) Poisson, T.; Belhomme, M.-C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277. (d) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 2270. (e) Milanole, G.; Couve-Bonnaire, S.; Bonfanti, J.-F.; Jubault, P.; Pannecoucke, X. *J. Org. Chem.* **2013**, *78*, 212. (f) Lemonnier, G.; Zoute, L.; Quirion, J.-C.; Jubault, P. *Org. Lett.* **2010**, *12*, 844.

(14) The active Cu(I) species can be generated through either reduction or disproportionation of Cu(II). For reduction, see: (a) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. For disproportion, see: (b) Ribas, X.; Calle, C.; Poater, A.; Casitas, A.; Gómez, L.; Xifra, R.; Parella, T.; Benet-Buchholz, J.; Schweiger, A.; Mitrikas, G.; Solà, M.; Llobet, A.; Stack, T. D. P. *J. Am. Chem. Soc.* **2010**, *132*, 12299 and references therein.

(15) See the Supporting Information for details.

(16) An alternative mechanism involving cupration of the benzofuran ring followed by an oxidative addition step with $BrCF_2CO_2Et$ cannot be precluded.

(17) We cannot rule out the possibility that the reductive elimination proceeds before the abstraction of the proton. On the other hand, cupration of the benzofuran ring followed by oxidative insertion into the C−Br bond of the $BrCF_2CO_2Et$ moiety might be considered as a plausible alternative pathway.

(18) For related process, see: (a) Fujikawa, K.; Fujioka, Y.; Kobayashi, A.; Amii, H. *Org. Lett.* **2011**, *13*, 5560. (b) Fujikawa, K.; Kobayashi, A.; Amii, H. *Synthesis* **2012**, *44*, 3015.

(19) (a) Meanwell, N. A. *J. Med. Chem.* **2011**, *54*, 2529. (b) Kirk, K. L. *Org. Process Res. Dev.* **2008**, *12*, 305. (c) Prakash, G. K. S.; Chacko, S. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 793. (d) Graton, J.; Wang, Z.; Brossard, A.-M.; Gonçalves Monteiro, D.; Le Questel, J.-Y.; Linclau, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 6176. (e) Giuffredi, G. T.; Gouverneur, V.; Bernet, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 10524.

(20) (a) Hu, J.; Zhang, W.; Wang, F. *Chem. Commun.* **2009**, 7465. For recent examples, see: (b) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, À. B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95. (c) Fier, P. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 5524. (d) Prakash, G. K. S.; Krishnamoorthy, S.; Ganesh, S. K.; Kulkarni, A.; Haiges, R.; Olah, G. A. *Org. Lett.* **2014**, *16*, 54. (e) Wang, X.; Liu, G.; Xu, X.-H.; Shibata, N.; Tokunaga, E.; Shibata, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 1827.

(21) (a) Casero, R. A., Jr.; Woster, P. M. *J. Med. Chem.* **2009**, *52*, 4551. (b) Takagi, H.; Tanaka, K.; Tsuda, H.; Kobayashi, H. *Int. J. Antimicrob. Agents* **2008**, *32*, 468. (c) Rewcastle, G. W.; Gamage, S. A.; Flanagan, J. U.; Frederick, R.; Denny, W. A.; Baguley, B. C.; Kestell, P.; Singh, R.; Kendall, J. D.; Marshall, E. S.; Lill, C. L.; Lee, W.-J.; Kolekar, S.; Buchanan, C. M.; Jamieson, S. M. F.; Shepherd, P. R. *J. Med. Chem.* **2011**, *54*, 7105.

(22) (a) Kim, Y. S. *J. Korean Chem. Soc.* **1963**, *7*, 189. (b) Battais, A.; Boutevin, B.; Pietrasanta, Y. *J. Fluorine Chem.* **1979**, *14*, 467.

(23) (a) Enthaler, S.; Spilker, B.; Erre, G.; Junge, K.; Tse, M.; Beller, M. *Tetrahedron* **2008**, *64*, 3867. (b) Kim, I.; Lee, S.-H.; Lee, S. *Tetrahedron Lett.* **2008**, *49*, 6579.

(24) Malamas, M. S.; Adebayo, F. O.; Dollings, P. J. U.S. Patent 6,221,902 B1, 2001.

(25) Kuhl, N.; Hopkinson, M.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 8230.

(26) Ikoma, M.; Oikawa, M.; Sasaki, M. *Tetrahedron* **2008**, *64*, 2740.

(27) Larsen, M. M.; Boydson, A. J. *J. Am. Chem. Soc.* **2013**, *135*, 8189.

(28) Haner, J.; Jack, K.; Nagireddy, J.; Racheem, M.; Durham, R.; Tam, W. *Synthesis* **2011**, 731.