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Copper-Catalyzed Radical Cascade Difluoromethylation/Cyclization of 2-(3-Arylpropioloyl)benzaldehydes: A Route to Difluoromethylated Naphthoquinones

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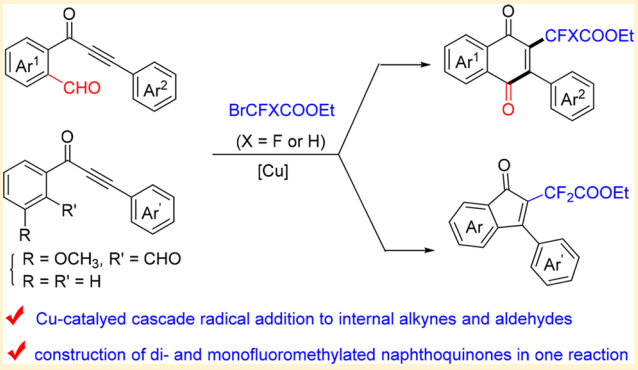
Supporting Information

ABSTRACT: A novel copper-catalyzed cascade difluoromethylation/cyclization of 2-(3-arylpropioloyl)benzaldehydes has been developed. This method affords an efficient and straightforward access to structurally diverse difluoromethylated naphthoquinones in one pot, starting from readily available starting materials. The reaction represents the first *trans*-acyldifluoromethylation of internal alkynes, which features aldehydes as acceptors for the addition of alkenyl radicals. Furthermore, this protocol can also access to monofluoromethylated naphthoquinone and difluoromethylated indanones in the same reaction condition.

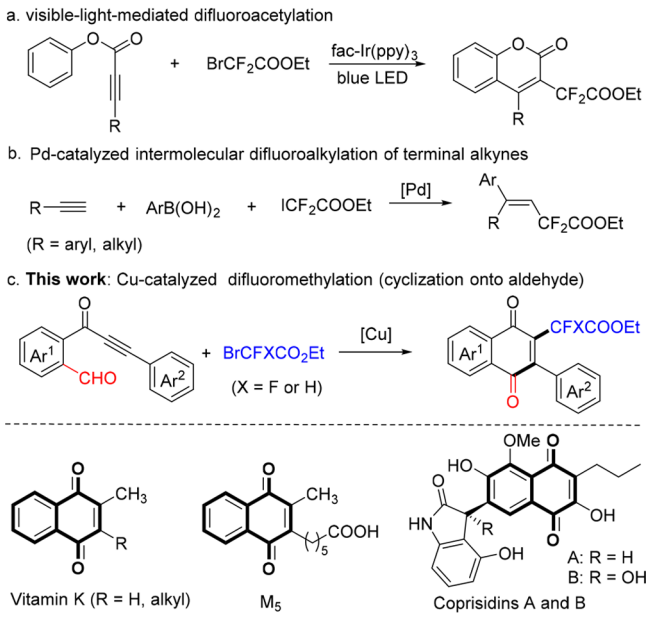


INTRODUCTION

The difluoromethylene group (CF_2) is a valuable and significant structural motif in medicinal chemistry,[1] which can function as bioisostere for an oxygen atom or a carbonyl group to improve the biological activity of small molecules.[2] Therefore, the development of new methods to introduce a CF_2 group into diverse organic structures has attracted considerable attention. The past several years we have witnessed rapid advances in copper or palladium-catalyzed fluoromethylation reactions for the construction of $C(sp^3)$-CF_2 bonds by difluoroalkyl radical addition to alkenes.[3,4] However, compared to difluoromethylation for the preparation of $C(sp^3)$-CF_2 bond containing organic substrates, strategies for incorporation of a CF_2 group onto alkenes have been less explored.

To date, the common strategies to construct $C(sp^2)$-CF_2 bonds are mostly limited to the transition-metal-mediated cross-coupling reactions and Heck-type reactions.[5,6] In contrast to those, the construction of $C(sp^2)$-CF_2 bonds by difluoroalkyl radical addition to alkynes is rare, presumably due to the decreased reactivity even it is definitely the most direct and atom economic means. Recently, Fu and Liang groups realized a $C(sp^2)$-CF_2 bond construction for the synthesis of 3-difluoroacetylated coumarins and indoloazepinone derivatives, which features a radical cyclization onto the aryl substituent (Scheme 1a).[7] More interestingly, Nevado and Liang groups independently reported a novel intermolecular three-component reaction involving terminal alkynes, boronic acids, and fluoroalkyl iodides to form trisubstituted difluoroalkenes (Scheme 1b).[8] Therefore, the continuing investigation of direct and efficient approaches toward $C(sp^2)$-CF_2 bond containing compounds is still important.

Scheme 1. Representative Methods for The Construction of $C(sp^2)$-CF_2 Bonds by Radical Addition to Alkynes



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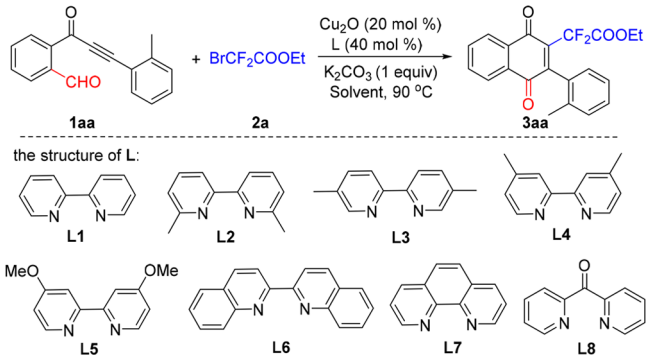
Naphthoquinone motifs are prevalent in a number of natural products and bioactive molecules. For examples, menadione and its derivative M5 have antimalarial property,[9] and coprisidins A and B were newly discovered natural naphthoquinone-oxindole alkaloids.[10] To the best of our knowledge, there is only one report by Davioud-Charvet for introducing CF_2 onto naphthoquinones.[11] However, it relies on the transformation of certain functional groups which inevitably requires additional steps for prefunctionalization. Driven by our interest in radical reactions and fluorine chemistry,[12] we explored the possibility of radical addition/cyclization of internal alkynes to form difluoromethylated naphthoquinones. Of note, the method described here is the first example of Cu-catalyzed radical difluoromethylation of disubstituted alkynes, in which aldehydes as acceptors for the addition of carbon-centered radicals (Scheme 1c).

RESULTS AND DISCUSSION

Initially, we utilized **1aa** and bromodifluoroacetate ($BrCF_2COOEt$) **2a** as the model substrates to optimize the reaction conditions, as $BrCF_2COOEt$ is commercially available, stable, and can be easily postfunctionalized. We believed that a single electron transfer (SET) between the Cu(I) catalyst and organohalide may produce the desired difluoromethyl radical. Although **3aa** was obtained with a poor yield in the presence of CuCN and 2,2′-bipyridine (**L1**) in MeCN at 90 °C (Table 1, entry 4), we were delighted to find that an improved yield was obtained by employing Cu_2O as a catalyst (Table 1, entry 6). However, other copper salts are not suitable catalysts (entries 1−3). We also find reactions nearly cannot be conducted in the absence of ligand, thus demonstrating the important role of the diamine ligand in the organocopper complex (Table 1, entry 7). The existence of K_2CO_3 also had a significant impact on the reaction efficiency, and a very low conversion was observed in the absence of K_2CO_3 (Table 1, entry 8). To further improve the reaction efficiency, a range of diamine ligands were investigated (Table 1, entries 9−15). Among the ligands tested, 5,5′-dimethyl-2,2′-bipyridine **L3** gave **3aa** in the best isolated yield of 68% (entry 10). Replacement of MeCN with EtOAc, CH_2ClCH_2Cl, or DMF led to inferior results (entries 17−19). The structure of difluoromethylated naphthoquinone **3aa** was unambiguously identified by the single-crystal X-ray analysis (Figure S2, see the Supporting Information).[13]

To ascertain the scope of this method, a variety of 2-(3-arylpropioloyl)benzaldehydes **1** were investigated, and the results are shown in Table 2. In general, the electronic effect of the substituents on Ar^2 does not obviously influence the reaction efficiency, and moderate to good yields of difluoromethylated naphthoquinones **3** were obtained (Table 2, **3aa**−**3pa**). It is noteworthy that important functional groups, such as ether, ester, chloride, bromide, are compatible with the reaction conditions (**3fa**−**3oa**), which may offer an opportunity for further derivatizations. What's more, the reaction of **1aa**, **1da**, and **1ha** afforded the corresponding product **3aa**, **3da**, and **3ha** in 68, 66, and 61% yield, respectively, indicating that the steric hindrance of Ar^2 has little impact on the reaction. Heteroaryl substituents were also compatible with the reaction, despite the expected products were provided in relatively lower yields (**3qa** and **3ra**). Then the Ar^1 group was varied. Substrates bearing either electron-withdrawing or donating groups will obviously effect the reactivity of aldehydes. In particular, electron-rich groups, such as Me, OMe, have a obvious negative effect on this transformation (**3xa**−**3ab**). In addition, We also tried to use

Table 1. Evaluation of The Reaction Conditions[a]



entry	[Cu]	ligand	solvent	yield[b] (%)
1	CuBr	**L1**	MeCN	0
2	CuOAc	**L1**	MeCN	0
3	$Cu(MeCN)_4PF_6$	-	MeCN	trace
4	CuCN	**L1**	MeCN	15
5	CuTc	**L1**	MeCN	50
6	Cu_2O	**L1**	MeCN	59
7	Cu_2O		MeCN	0
8[c]	Cu_2O	**L1**	MeCN	trace
9	Cu_2O	**L2**	MeCN	0
10	Cu_2O	**L3**	MeCN	68
11	Cu_2O	**L4**	MeCN	63
12	Cu_2O	**L5**	MeCN	51
13	Cu_2O	**L6**	MeCN	20
14	Cu_2O	**L7**	MeCN	0
15	Cu_2O	**L8**	MeCN	trace
16[d]	Cu_2O	**L8**	MeCN	64
17	Cu_2O	**L1**	EA	40
18	Cu_2O	**L1**	DCE	10
19	Cu_2O	**L1**	DMF	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), [Cu] (20 mol %), ligand (40 mol%), K_2CO_3 (0.2 mmol), MeCN (2.0 mL), 90 °C, 12 h. [b]Yields of the isolated products are given. [c]Without K_2CO_3. [d]0.4 mmol **2a** is used.

$BrCF_2PO(OEt)_2$, $BrCF_2CNEt_2$, and BrCFHCOOEt as the radical precursor, but they give no desired product or with low yield (**3ae**).

It is possible that the strong para-directing effect (+C) of methoxy, substrates **1ae** and **1af** could not convert to the naphthoquinone motifs. In contrast, it features a radical cyclization onto the aryl substituent to form indanones, whereas the formyl groups remain unchanged (**4a** and **4b**). These unpredicted results motivated us to think that substrates without aldehyde moiety will also produce difluoromethylated indanones in this standard reaction conditions. Then the substrate scope of this cyclization was explored (Table 3). However, four analogues were synthesized in comparatively low yields (**4c**−**4f**).

Finally, in order to study the possibility of a radical propagation mechanism, the reaction between **1aa** and **2** was repeated in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). As a result, **3aa** was not formed, and the TEMPO−CF_2COOEt adduct **6**[3d] was detected by the ^{19}F NMR analysis (8% yield) (eq 1). The radical clock reaction with α-cyclopropylstyrene (**1′**) as a radical trapping reagent provided the known product **7**[6a] in 16% yield, determined by ^{19}F NMR spectroscopy. Thus, a radical mechanism is depicted in Scheme 2 for this Cu-catalyzed difluoromethylation/cyclization reac-

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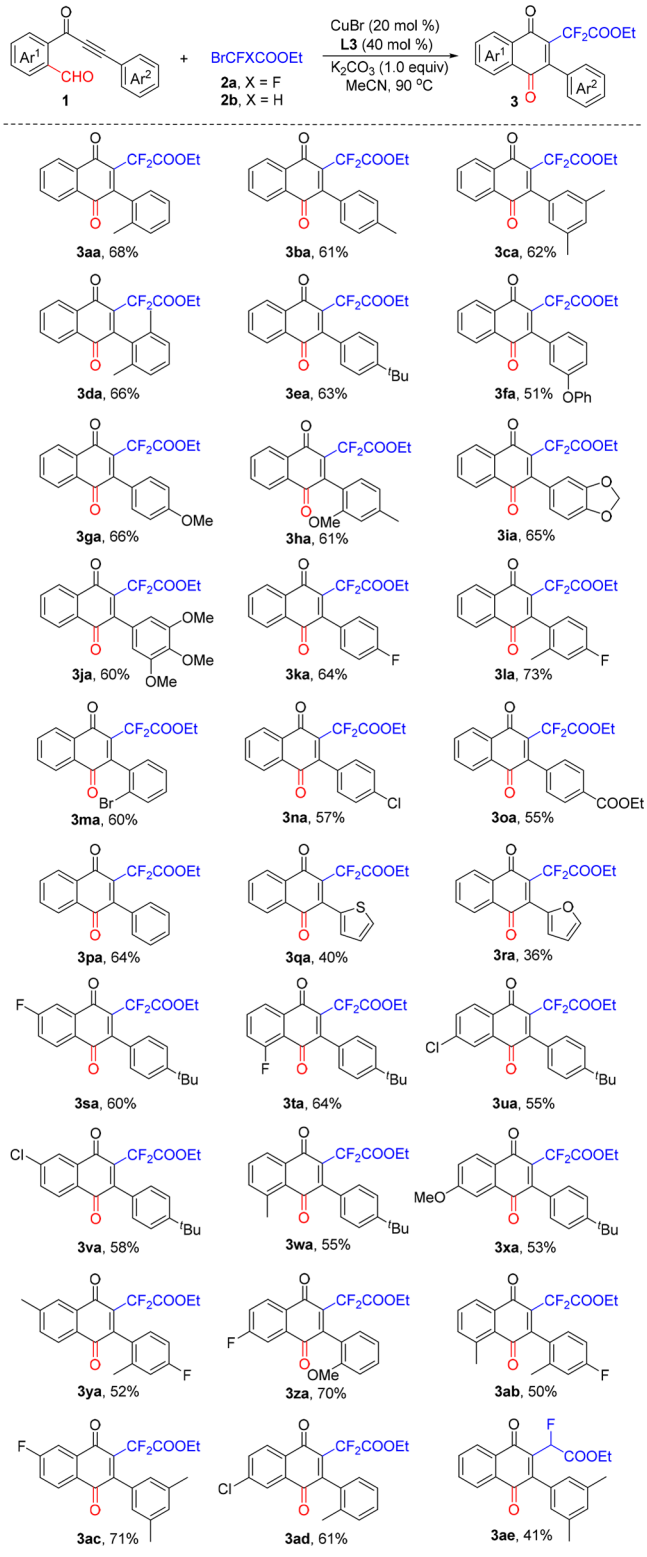
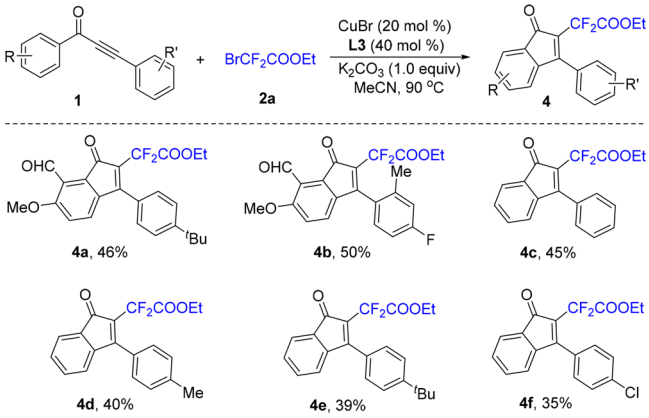
Table 2. Substrate Scope[a]



[a]Reaction conditions: **1aa** (0.2 mmol), **2** (0.6 mmol), Cu_2O (20 mol %), **L3** (40 mol%), K_2CO_3 (0.2 mmol), MeCN (2 mL), 90 °C, 12 h. Isolated yields.

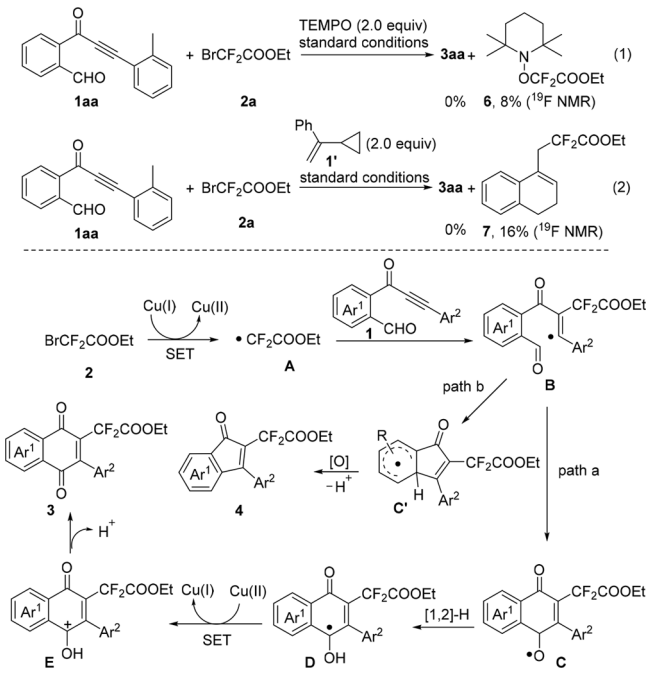
tion. First, the CF_2COOEt radical, generated by a single electron transfer (SET) from Cu(I) to BrCFXCOOEt **2**, adds to the C−C triple bond of **1** to deliver an alkenyl radical **B**. Theoretically, there are two possible ways for the radical transference of radical **B**. In path a, a subsequent cyclization of

Table 3. Cu-Catalyzed Radical Cyclization Toward Difluoromethylated Indanones[a]



[a]Reaction conditions: **1aa** (0.2 mmol), **2** (0.6 mmol), Cu_2O (20 mol %), **L3** (40 mol%), K_2CO_3 (0.2 mmol), MeCN (2 mL), 90 °C, 12 h. Isolated yields.

Scheme 2. Proposed Mechanism



the alkenyl radical to aldehyde provides an alkoxyl radical **C**, which could be converted into the carbon radical **D** via a 1,2-hydrogen atom transfer (HAT).[14] Subsequently, oxidation of **D** by Cu(II) species results in a cationic intermediate **E**, accompanied by the regeneration of Cu(I) catalyst. Finally, difluoromethylated naphthoquinones **3** are generated from **E** via the K_2CO_3-promoted deprotonation; and in path b, alkenyl radical **B** undergoes radical addition to generate cyclohexadienyl radical **C′**,[7,15] then oxidation and deprotonation yield the products **4**. Overall, there exists excellent regio- and chemoselectivity in this reaction.

CONCLUSION

In summary, compared with the enormous progress of trifluoromethylation research within of the past few years, methodology for the introduction of the CF_2 and CF groups into organic molecules through radical addition reactions is

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relatively rare. We disclose a novel Cu-catalyzed intramolecular difluoromethylation/cyclization of 2-(3-arylpropioloyl)-benzaldehydes, allowing the direct formation of a C(sp^2)-$CFXCO_2Et$ bond and the construction of a naphthoquinone ring in one reaction. This reaction features aldehydes as acceptors for the addition of carbon radicals, which represents the first trans-acyldifluoromethylation of internal alkynes, offering a novel approach to the direct synthesis of polysubstituted difluoromethylated alkenes.

EXPERIMENTAL SECTION

General Information. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded on 600 or 400 spectrometer using $CDCl_3$ as the solvent. Chemical shifts were referenced relative to residual solvent signal ($CDCl_3$: ^1H NMR: δ 7.26 ppm, ^{13}C NMR: δ 77.16 ppm). The following abbreviations are used to describe peak patterns where appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants (J) are reported in Hertz (Hz). HRMS were performed on AB Sciex LC 30A-Triple TOF 4600 apparatus (ESI). Melting points were measured with micro melting point apparatus.

General Experimental Procedure for the Synthesis of 2-(3-Arylpropioloyl)benzaldehyde 1. A 100 mL flask with a stir-bar was charged with *o*-bromobenzaldehyde (20 mmol) and *p*-TsOH (2 mmol). MeOH (40 mL) and trimethyl orthoformate (50 mmol) were added and the solution was heated to 70 °C for 3−8 h. Aqueous $NaHCO_3$ solution (3 mmol) was then added and most of the THF was evaporated. The solution was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated to afford the *o*-bromoacetal product (4.6 g, 100% yield), which was used in the next step without further purification.

To a 50 mL flask charged with *o*-bromoacetal (20 mmol) was added anhydrous THF (20 mL), and cooled to −78 °C. *n*-BuLi (24 mmol, 2.5 M in hexane) was then added over 30 min to the solution and the reaction was kept at −78 °C for another 1 h. Next, DMF (60 mmol) was added to the reaction solution over 20 min. The combined organic layer was then warmed to RT and kept for 1 h. The solution was then quenched with saturated aqueous NH_4Cl (20 mL), extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4. Then it was concentrated and the residue was subject to flash column chromatography on silica gel using ethyl acetate/petroleum ether (v/v, 1:10) as eluent to give the aldehyde product (2.9 g, 80% yield).

A 50 mL two-necked flask charged with phenylacetylene/phenylbromoacetylene (6 mmol) was evacuated and backfilled with Argon. Then anhydrous THF (20 mL) was added and cooled to −78 °C. *n*-BuLi (6 mmol, 2.5 M in hexane) was then added in 30 min to the solution and the reaction was kept at −78 °C for another 1 h. The above aldehyde (5 mmol) was added and the mixture was allowed to warmed to RT and kept for 1 h. The solution was then quenched with saturated aqueous NH_4Cl (20 mL), extracted with ethyl acetate (30 mL × 3). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4. Then it was concentrated and the residue was used in the next step without further purification.

To a 100 mL flask charged with the above secondary alcohol (4 mmol) was added anhydrous DCM (30 mL) and MnO_2 (40 mmol). The solution was kept vigorously stirring at room temperature for 10 h. Afterward, the solution was filtered by diatomite and the filtrate was concentrated. The residue was diluted with THF (20 mL) and aqueous HCl solution (20 mL, 2 N). Afterward, the solution was kept stirring at RT for 3 h. The residue was extracted with ethyl acetate (30 mL× 2), washed with saturated NaCl, dried over anhydrous Na_2SO_4. Then it was concentrated and the residue was subject to flash column chromatography on silica gel using ethyl acetate/petroleum ether (v/v, 1:10) as eluent to give product 2-(3-phenylpropioloyl)benzaldehyde **1** (0.73 g, 78% yield for the above two steps).

Selected Characterization of Substrates 1. *2-(3-(o-Tolyl)-propioloyl)benzaldehyde (**1aa**).* Yellow solid; mp 50−52 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.33 (dd, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H), 7.93 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.78−7.70 (m, 2H), 7.63 (d, J = 7.2 Hz, 1H), 7.40(dt, J_1 = 8.8 Hz, J_2 = 1.2 Hz, 1H), 7.30−7.22 (m, 2H), 2.56 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.1, 178.4, 142.6, 138.6, 137.5, 133.9, 133.4, 132.9, 131.9, 131.4, 130.0, 128.5, 126.1, 119.4; HRMS (ESI) (m/z): calcd for $C_{17}H_{12}O_2Na$ ($[M+Na]^+$), 271.0729; found 271.0722.

*2-(3-(2-Methoxy-4-methylphenyl)propioloyl)benzaldehyde (**1ha**).* Yellow solid; mp 104−105 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8. 50 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.76−7.70 (m, 2H), 7.42 (s, 1H), 7.28 (d, J = 6.6 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.5, 178.5, 160.3, 138.8, 137.6, 135.4, 134.0, 132.8, 132.8, 132.6, 130.3, 128.3, 110.9, 108.5, 92.6, 91.9, 56.1, 20.3; HRMS (ESI) (m/z): calcd for $C_{18}H_{14}O_3Na$ ($[M+Na]^+$), 301.0835; found 301.0837.

*2-(3-(3,4,5-Trimethoxyphenyl)propioloyl)benzaldehyde (**1ja**).* Yellow solid; mp 101−103 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.50(s, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.89 (d, J = 7.2 Hz, 1H), 7.74−7.67 (m, 2H), 6.88 (s, 2H), 3.88−3.86 (m, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.1, 178.3, 153.4, 141.6, 138.5, 137.4, 133.4, 132.9, 131.9, 128.5, 114.1, 110.7, 95.2, 87.3, 61.1, 56.4; HRMS (ESI) (m/z): calcd for $C_{19}H_{16}O_5$ Na ($[M+Na]^+$), 347.0890; found 347.0880.

*2-(3-(2-Bromophenyl)propioloyl)benzaldehyde (**1ma**).* White solid; mp 99−101 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.54 (d, J = 7.2 Hz, 1H), 7.96 (d, J = 7.2 Hz, 1H), 7.80−7.70 (m, 4H), 7.42−7.37 (m, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.2, 178.2, 138.1, 137.6, 135.5, 133.7, 133.0, 132.9, 132.4, 128.5, 127.6, 127.0, 122.2, 91.9, 90.7; HRMS (ESI) (m/z): calcd for $C_{16}H_9BrO_2Na$ ($[M+Na]^+$), 334.9678; found 334.9667.

*Ethyl 4-(3-(2-Formylphenyl)-3-oxoprop-1-yn-1-yl)benzoate (**1oa**).* White solid; mp 109−112 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8. 31 (d, J = 7.2 Hz, 1H), 8.09 (d, J = 7.8 Hz, 2H), 7.94 (d, J = 6.6 Hz, 1H), 7.77−7.73 (m, 4H), 4.40 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 6.6 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 191.9, 178.2, 165.5, 138.0, 137.5, 133.7, 133.0, 132.9, 132.5, 130.0, 129.7, 128.6, 123.8, 92.6, 89.0, 61.5, 14.3; HRMS (ESI) (m/z): calcd for $C_{19}H_{14}O_4Na$ ($[M+Na]^+$), 329.0784; found 329.0777.

*2-(3-(Furan-2-yl)propioloyl)benzaldehyde (**1ra**).* Brown solid; mp 82−83 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.25 (d, J = 7.8 Hz, 1H), 7.92 (d, J = 7.2 Hz, 1H), 7.75−7.70 (m, 2H), 7.60 (s, 1H), 7.08 (d, J = 3.0 Hz, 1H), 8.54 (d, J = 1.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.1, 177.7, 147.3, 137.9, 137.5, 134.6, 133.0, 132.0, 128.6, 122.8, 112.3, 93.5, 84.7; HRMS (ESI) (m/z): calcd for $C_{14}H_8O_3Na$ ($[M+Na]^+$), 247.0365; found 247.0361.

*2-(3-(4-(tert-Butyl)phenyl)propioloyl)-6-methoxybenzaldehyde (**1ae**).* White solid; mp 106−108 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.71 (s, 1H), 8. 38 (d, J = 7.2 Hz, 1H), 7.64 (d, J = 7.8 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 7.11 (d, J = 8.4 Hz, 1H), 4.04 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 188.8, 176.2, 165.7, 154.8, 136.4, 133.2, 131.6, 130.3, 125.9, 124.6, 116.9, 112.0, 94.5, 86.5, 56.5, 35.2, 31.2; HRMS (ESI) (m/z): calcd for $C_{21}H_{20}O_3Na$ ($[M+Na]^+$), 343.1304; found 343.1294.

General Experimental Procedure for Cu-Catalyzed Radical Cyclization of 1 and 2a. Under a N_2 atmosphere, to a 25 mL sealed tube containing **1** (0.2 mmol, 1.0 equiv), **2a** (121 mg, 0.6 mmol, 3.0 equiv), Cu_2O (5.8 mg, 0.04 mmol, 0.2 equiv), 5,5′-dimethyl-2,2′-bipyridine (14.7 mg, 0.08 mmol, 0.4 equiv), and K_2CO_3 (27.6 mg, 0.2 mmol, 1.0 equiv) were added dry MeCN (2 mL). After stirring at 90 °C for 12 h, the reaction mixture was cooled to room temperature and concentrated. Column purification on silica gel using ethyl acetate/petroleum ether (v/v = 1:10) as the eluent gave the desired product **3**.

*Ethyl 2-(1,4-Dioxo-3-(o-tolyl)-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate (**3aa**).* 50.3 mg, 68% yield; Yellow solid; mp 73−74 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.19−8.16 (m, 2H), 7.86−7.85 (m, 2H), 7.38 (dt, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.32−7.27 (m, 2H), 7.13 (d, J = 7.8 Hz, 1H), 4.39 (q, J = 7.2 Hz, 2H), 2.22 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.5, 183.4, 162.6 (t, J = 31.7 Hz), 149.7, 136.9 (t, J = 20.5 Hz), 135.2, 134.8, 134.6, 131.8, 131.7, 131.3, 129.7, 129.1, 127.6, 127.3, 126.6, 125.2, 111.5 (t, J = 254.3 Hz), 63.3, 20.0, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.7

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(d, J = 282.5 Hz, 1F), −103.7 (d, J = 288.2 Hz, 1F); HRMS (ESI) (m/z): calcd for $C_{21}H_{16}F_2O_4Na$ ([M+Na]$^+$), 393.0909; found 393.0917.

Ethyl 2-(1,4-Dioxo-3-(p-tolyl)-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ba)***. 45.1 mg, 61% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18−8.15 (m, 2H), 7.85−7.83 (m, 2H), 7.29 (d, J = 7.8 Hz, 2H), 7.23 (d, J = 7.8 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 2.43 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.1, 183.7, 162.9 (t, J = 31.7 Hz), 149.2, 139.7, 136.0 (t, J = 21.1 Hz), 131.8, 131.4, 129.1, 128.5, 128.3, 127.3, 126.5, 111.6 (t, J = 255.2 Hz), 63.3, 21.6, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.8; HRMS (ESI) (m/z): calcd for $C_{21}H_{16}F_2O_4Na$ ([M+Na]$^+$), 393.0909; found 393.0906.

Ethyl 2-(3-(3,5-Dimethylphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ca)***. 47.6 mg, 62% yield; Yellow solid; mp 132−134 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 7.10 (s, 1H), 6.92 (s, 2H), 4.36 (q, J = 7.2 Hz, 2H), 2.37 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.0, 183.6, 166.2, 162.8 (t, J = 31.7 Hz), 149.3, 137.1, 135.9 (t, J = 19.6 Hz), 134.8, 134.5, 131.7, 131.2, 131.11, 131.08, 127.2, 126.6, 126.4, 111.5 (t, J = 255.2 Hz), 63.2, 21.4, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.0; HRMS (ESI) (m/z): calcd for $C_{22}H_{18}F_2O_4Na$ ([M+Na]$^+$), 407.1065; found 407.1064.

Ethyl 2-(3-(2,6-Dimethylphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3da)***. 47.4 mg, 50.7% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18−8.15 (m, 2H), 7.85−7.83 (m, 2H), 7.23 (t, J = 7.8 Hz, 1H), 7.10 (d, J = 7.8 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 2.15 (s, 6H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.4, 183.1, 162.6 (t, J = 31.7 Hz), 149.5, 137.4 (t, J = 19.6 Hz), 134.9, 134.7, 134.6, 131.8, 131.7, 131.4, 128.6, 127.3, 127.1, 126.7, 111.6 (t, J = 255.2 Hz), 63.3, 20.2, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −104.5; HRMS (ESI) (m/z): calcd for $C_{22}H_{18}F_2O_4Na$ ([M+Na]$^+$), 407.1065; found 407.1064.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ea)***. 51.9 mg, 63% yield; Yellow solid; mp 134−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18−8.14 (m, 2H), 7.84−7.82 (m, 2H), 7.50−7.47 (m, 2H), 7.29−7.27 (m, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.39−1.34 (m, 12H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.1, 183.4, 163.0 (t, J = 30.2 Hz), 152.7, 149.2, 135.9 (t, J = 19.6 Hz), 134.8, 134.6, 131.8, 131.4, 129.0, 128.2, 127.3, 126.5, 124.7, 111.6 (t, J = 249.2 Hz), 63.3, 34.9, 31.4, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.8; HRMS (ESI) (m/z): calcd for $C_{24}H_{22}F_2O_4Na$ ([M+Na]$^+$), 435.1378; found 435.1376.

Ethyl 2-(1,4-Dioxo-3-(3-phenoxyphenyl)-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3fa)***. 45.7 mg, 51% yield; Yellow solid; mp 92−94 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 7.82−7.81 (m, 2H), 7.41 (t, J = 7.8 Hz, 1H), 7.34 (m, 2H), 7.11 (t, J = 7.2 Hz, 2H), 7.06−7.03 (m, 3H), 6.96 (s, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.7, 183.5, 162.7 (t, J = 31.7 Hz), 157.0, 156.7, 148.2, 127.3, 126.6, 123.8, 123.6, 119.8, 119.4, 110.2, 111.5 (t, J = 255.2 Hz), 63.4, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.2 (d, J = 28.2 Hz); HRMS (ESI) (m/z): calcd for $C_{26}H_{18}F_2O_5Na$ ([M+Na]$^+$), 471.1014; found 471.1010.

Ethyl 2,2-Difluoro-2-(3-(4-methoxyphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate ***(3ga)***. 51.0 mg, 66% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2H), 7.81−7.79 (m, 2H), 7.81−7.79 (m, 2H), 7.28 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 3.86 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.1, 183.7 (t, J = 3.0 Hz), 163.0 (t, J = 31.7 Hz), 160.9, 148.6, 135.5 (t, J = 19.6 Hz), 134.7, 134.5, 131.7, 131.3, 131.2, 127.3, 126.4, 123.2, 113.2, 111.7 (t, J = 253.7 Hz), 63.3, 55.4, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.5; HRMS (ESI) (m/z): calcd for $C_{21}H_{16}F_2O_5Na$ ([M+Na]$^+$), 409.0858; found 409.0854.

Ethyl 2,2-Difluoro-2-(3-(2-methoxy-4-methylphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate ***(3ha)***. 48.8 mg, 61% yield; Yellow solid; mp 92−93 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14−8.11 (m, 2H), 7.80−7.79 (m, 2H), 7.21 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 6.94 (d, J = 1.2 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 4.39−4.33 (m, 2H), 3.73 (s, 3H), 2.32 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.5, 183.2, 162.9 (t, J = 31.7 Hz), 154.6, 147.8, 136.8 (t, J = 21.1 Hz), 134.6, 134.3, 132.0, 131.4, 131.2, 129.9, 127.2, 126.5, 121.0, 111.6 (t, J = 255.2 Hz), 110.8, 63.2, 56.0, 20.6, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −100.8 (d, J = 282.5 Hz, 1F), −102.9 (d, J = 282.5 Hz, 1F); HRMS (ESI) (m/z): calcd for $C_{22}H_{18}F_2O_5Na$ ([M+Na]$^+$), 423.1014; found 423.1015.

Ethyl 2-(3-(Benzo[d][1,3]dioxol-5-yl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ia)***. 52 mg, 65% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13−8.09 (m, 2H), 7.81−7.79 (m, 2H), 6.88−6.86 (m, 1H), 6.81−6.79 (m, 2H), 6.02 (s, 2H), 4.35 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.9, 183.6, 162.9 (t, J = 31.7 Hz), 149.0, 148.5, 147.3, 136.0 (t, J = 21.1 Hz), 134.8, 134.6, 131.7, 131.3, 127.3, 126.5, 124.5, 123.8 (t, J = 3.0 Hz), 111.6 (t, J = 255.2 Hz), 110.0 (t, J = 1.5 Hz), 107.9, 101.6, 63.3, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −97.8; HRMS (ESI) (m/z): calcd for $C_{21}H_{14}ClF_2O_6Na$ ([M+Na]$^+$), 423.0650; found 423.0653.

Ethyl 2-(1,4-Dioxo-3-(3,4,5-trimethoxyphenyl)-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ja)***. 53.5 mg, 60% yield; Red solid; mp 161−162 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15−8.11 (m, 2H), 7.82−7.81 (m, 2H), 6.55 (s, 2H), 4.36 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.9, 183.6, 163.0 (t, J = 31.7 Hz), 152.7, 148.9, 139.2, 136.2 (t, J = 21.1 Hz), 134.9, 134.7, 131.7, 131.3, 127.3, 126.6, 126.4, 111.6 (t, J = 255.2 Hz), 106.9, 63.4, 61.1, 56.3, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.0; HRMS (ESI) (m/z): calcd for $C_{23}H_{20}F_2O_7Na$ ([M+Na]$^+$), 469.1069; found 469.1062.

Ethyl 2,2-Difluoro-2-(3-(4-fluorophenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate ***(3ka)***. 47.9 mg, 64% yield; Yellow solid; mp 50−52 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15−8.12 (m, 2H), 7.83−7.82 (m, 2H), 7.31−7.29 (m, 2H), 7.14 (t, J = 8.4 Hz, 2H), 4.36 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.9, 183.4, 163.6 (d, J = 249.2 Hz), 162.8 (t, J = 31.7 Hz), 148.0, 136.5 (t, J = 19.6 Hz), 134.9, 134.8, 131.7, 131.3, 131.2, 127.4, 126.6, 115.1, 115.0, 111.6 (t, J = 255.2 Hz), 63.5, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.3 (2F), −111.4 (1F); HRMS (ESI) (m/z): calcd for $C_{20}H_{13}F_3O_4Na$ ([M+Na]$^+$), 397.0658; found 397.0651.

Ethyl 2,2-Difluoro-2-(3-(4-fluoro-2-methylphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate ***(3la)***. 56.6 mg, 73% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15−8.13 (m, 2H), 7.84−7.83 (m, 2H), 7.07−7.04 (m, 1H), 6.99 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 1H), 6.95 (dt, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 4.36 (q, J = 7.2 Hz, 2H), 2.18 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.5, 183.2, 163.6 (d, J = 247.6 Hz), 162.6 (t, J = 31.7 Hz), 148.9, 138.1, 137.4 (t, J = 21.1 Hz), 134.9, 131.7, 131.4, 129.4, 127.4, 126.8, 116.9, 116.7, 112.5, 112.4, 111.5 (t, J = 255.2 Hz); ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.6 (d, J = 282.5 Hz, 1F), −103.5 (d, J = 288.2 Hz, 1F), −113.4 (1F); HRMS (ESI) (m/z): calcd for $C_{21}H_{15}F_3O_4Na$ ([M+Na]$^+$), 411.0814; found 411.0841.

*Ethyl 2-(3-(2-Bromophenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate****(3ma)***. 52.1 mg, 60% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, J = 3.0 Hz, 2H), 7.83 (m, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.40 (m, 1H), 7.32 (m, 1H), 7.22 (d, J = 7.2 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.3, 182.6, 162.5 (t, J = 31.7 Hz), 148.4, 136.9 (t, J = 21.1 Hz), 135.0, 134.7, 133.7, 132.3, 131.7, 131.4, 130.5, 129.4, 127.4, 127.0, 126.7, 121.9, 111.4 (t, J = 255.2 Hz), 63.5, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.9 (d, J = 288.2 Hz, 1F), −103.6 (d, J = 288.2 Hz, 1F); HRMS (ESI) (m/z): calcd for $C_{20}H_{13}BrF_2O_4Na$ ([M+Na]$^+$), 456.9857; found 456.9857.

Ethyl 2-(3-(4-Chlorophenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2- difluoroacetate ***(3na)***. 44.5 mg, 57% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14−8.12 (m, 2H), 7.83−7.82 (m, 2H), 7.43−7.42 (m, 2H), 7.25−7.24 (m, 2H), 4.37 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.7, 183.3, 162.7 (t, J = 31.7 Hz), 147.8, 136.5 (t, J = 21.1 Hz), 135.8, 135.0, 134.8, 131.6, 131.3, 130.5 (t, J = 3.0 Hz), 129.6, 128.1, 127.4, 126.6, 111.5 (t, J = 255.2 Hz), 63.5, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.8; HRMS (ESI) (m/z): calcd for $C_{20}H_{13}ClF_2O_4Na$ ([M+Na]$^+$), 413.0362; found 413.0351.

Ethyl 4-(3-(2-Ethoxy-1,1-difluoro-2-oxoethyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)benzoate ***(3oa)***. 47.1 mg, 55% yield; Yellow solid; mp 146−147 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16−8.14 (m,

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4H), 7.86−7.84 (m, 2H), 7.40 (m, 2H), 4.44−4.38 (m, 4H), 1.43 (t, J = 7.2 Hz, 3H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.5, 183.2, 166.2, 162.6 (t, J = 31.7 Hz), 148.1, 136.6 (t, J = 21.1 Hz), 135.9, 135.0, 134.8, 133.1, 131.6, 131.2, 128.9, 127.3, 126.7, 111.5 (t, J = 255.2 Hz), 63.5, 61.3, 14.4, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.0; HRMS (ESI) (m/z): calcd for $C_{23}H_{18}F_2O_6Na$ ([M+Na]$^+$), 451.0963; found 451.0959.

Ethyl 2-(1,4-Dioxo-3-phenyl-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3pa)***. 45.6 mg, 64% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15−8.13 (m, 2H), 7.83−7.81 (m, 2H), 7.47−7.44 (m, 3H), 7. 32−7.30 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.0, 183.6, 162.8 (t, J = 31.7 Hz), 149.0, 136.2 (t, J = 21.1 Hz), 134.9, 134.6, 131.7, 131.34, 131.26, 129.4, 129.0 (t, J = 3.0 Hz), 127.7, 127.3, 126.6, 111.6 (t, J = 255.2 Hz), 63.4, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.9; HRMS (ESI) (m/z): calcd for $C_{20}H_{14}F_2O_4Na$ ([M+Na]$^+$), 379.0752; found 379.0749.

Ethyl 2-(1,4-Dioxo-3-(thiophen-2-yl)-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3qa)***. Twenty-nine mg, 40% yield; Yellow solid; mp 103−107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17−8.10 (m, 2H), 7.82−7.80 (m, 2H), 7.76 (dd, J_1 = 5.2 Hz, J_2 = 0.8 Hz, 1H), 7.46−7.45 (m, 1H), 7.17−7.15 (m, 1H), 4.34 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.7, 183.2, 163.0 (t, J = 31.7 Hz), 143.0, 134.8, 133.9, 133.5, 131.3, 129.7, 128.3, 127.4, 126.8, 126.6, 123.5, 111.5 (t, J = 255.2 Hz), 63.2, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.2; HRMS (ESI) (m/z): calcd for $C_{18}H_{12}F_2O_4SNa$ ([M+Na]$^+$), 385.0316; found 385.0310.

Ethyl 2,2-Difluoro-2-(3-(furan-2-yl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate ***(3ra)***. 24.9 mg, 36% yield; Yellow solid; mp 82−83 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15−8.14 (m, 1H), 8.10−8.09 (m, 1H), 7.81−7.79 (m, 2H), 7.73 (d, J = 1.8 Hz, 1H), 7.31 (d, J = 3.6 Hz, 1H), 6.65 (q, J = 1.8 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.2, 182.6, 163.2 (t, J = 31.7 Hz), 146.9, 144.0, 136.0, 134.8, 134.7, 131.8, 131.3, 127.2, 126.5, 121.1, 113.2, 111.1 (t, J = 255.2 Hz), 102.5, 100.1, 63.2, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −101.8; HRMS (ESI) (m/z): calcd for $C_{18}H_{13}F_2O_5$ ([M+H]$^+$), 347.0724; found 347.0726.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-7-fluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3sa)***. 51.6 mg, 60% yield; Yellow solid; mp 151−152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.80 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 3H), 7.28 (d, J = 8.4 Hz, 2H), 4.38 (q, J = 7.2 Hz, 2H), 1.39 (s, 9H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.2, 182.4, 166.7 (t, J = 258.2 Hz), 162.8 (t, J = 31.7 Hz), 152.9, 149.3, 136.0 (t, J = 21.1 Hz), 134.4, 129.9, 129.0, 128.0, 127.8, 124.7, 122.0 (d, J = 24.2 Hz), 114.0 (d, J = 24.2 Hz), 111.5 (t, J = 255.2 Hz), 63.4, 34.9, 31.3, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.6 (2F), −99.9 (1F); HRMS (ESI) (m/z): calcd for $C_{24}H_{21}F_3O_4Na$ ([M+Na]$^+$), 453.1284; found 453.1273.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-5-fluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ta)***. 55 mg, 64% yield; Yellow solid; mp 143−144 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 7.80−7.76 (m, 1H), 7.52−7.48 (m, 1H), 7.47−7.45 (m, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.33 (q, J = 7.2 Hz, 2H), 1.35 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.8, 181.8, 162.8 (t, J = 31.7 Hz), 161.1 (d, J = 270.3 Hz), 152.9, 150.0, 136.0 (d, J = 8.4 Hz), 135.1(t, J = 21.1 Hz), 133.0, 129.1, 127.8, 124.7, 123.6 (d, J = 21.1 Hz), 122.9, 119.7 (d, J = 4.5 Hz), 111.4 (t, J = 255.2 Hz), 63.4, 34.9, 31.4, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.8 (2F), −110.8 (1F); HRMS (ESI) (m/z): calcd for $C_{24}H_{21}F_3O_4Na$ ([M+Na]$^+$), 453.1284; found 453.1273.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-6-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ua)***. 49.1 mg, 55% yield; Yellow solid; mp 83−85 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09−8.07 (m, 2H), 7.75 (dd, J_1 = 8.4 Hz, J_2 = 1.8 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 1.36 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.2, 182.7, 162.8 (t, J = 31.7 Hz), 153.0, 149.1, 141.9, 136.0 (t, J = 21.1 Hz), 134.7, 132.9, 129.6, 129.0, 128.3, 127.8, 127.2, 124.8, 111.5 (t, J = 255.2 Hz), 63.4, 35.0, 31.4, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.6; HRMS (ESI) (m/z): calcd for $C_{24}H_{21}ClF_2O_4Na$ ([M+Na]$^+$), 469.0988; found 469.0974.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-7-chloro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)- 2,2-difluoroacetate ***(3va)***. 51.7 mg, 58% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H), 7.75 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.46 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 4.34 (q, J = 7.2 Hz, 2H), 1.36 (s, 9H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.2, 182.7, 162.8 (t, J = 31.7 Hz), 153.0, 149.4, 141.7, 135.8, 134.8, 132.4, 130.0, 129.1, 127.9, 126.5, 124.7, 111.5 (t, J = 247.6 Hz), 63.4, 35.0, 31.4, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.6; HRMS (ESI) (m/z): calcd for $C_{24}H_{21}ClF_2O_4Na$ ([M+Na]$^+$), 469.0988; found 469.0979.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-5-methyl-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3wa)***. 46.9 mg, 55% yield; Yellow solid; mp 130−132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.07 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.64 (m, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 4.37 (q, J = 7.2 Hz, 2H), 2.78 (s, 3H), 1.39 (s, 9H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.8, 184.0, 162.9 (t, J = 31.7 Hz), 152.5, 150.2, 142.2, 138.7, 134.9 (t, J = 21.1 Hz), 133.7, 132.8, 129.6, 128.9, 128.7, 125.4, 124.6, 111.5 (t, J = 255.2 Hz), 34.9, 31.4, 23.0, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.1; HRMS (ESI) (m/z): calcd for $C_{25}H_{24}F_2O_4Na$ ([M+Na]$^+$), 449.1535; found 449.1519.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-6-methoxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3xa)***. 46.9 mg, 53% yield; Yellow solid; mp 162−164 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.08 (d, J = 9.0 Hz, 1H), 7.56 (d, J = 2.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.29−7.27 (m, 3H), 4.36 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 1.39 (s, 9H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 184.3, 182.5, 164.8, 163.0 (t, J = 31.7 Hz), 152.6, 148.8, 136.0 (t, J = 21.1 Hz), 133.8, 129.1, 129.0, 128.3, 125.5, 124.6, 121.1, 111.7 (t, J = 255.2 Hz), 110.5, 63.2, 56.1, 34.9, 31.4, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.6; HRMS (ESI) (m/z): calcd for $C_{25}H_{24}F_2O_5Na$ ([M+Na]$^+$), 465.1484; found 465.1472.

Ethyl 2,2-Difluoro-2-(3-(4-fluoro-2-methylphenyl)-7-methyl-1,4-dioxo-1,4-dihydronaphthalen −2-yl)acetate ***(3ya)***. 41.8 mg, 52% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (d, J = 7.8 Hz, 1H), 7.93 (m, 1H), 7.62−7.61 (m, 1H), 7.06−7.04 (m, 1H), 6.99−6.93 (m, 2H), 4.38−4.34 (m, 2H), 2.53 (s, 3H), 2.16 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.6, 183.3, 163.1 (d, J = 247.6 Hz), 162.7 (t, J = 31.7 Hz), 148.9, 146.2, 138.1, 137.3 (t, J = 21.1 Hz), 135.7, 131.3, 129.5, 129.4, 127.8, 127.6, 127.0, 116.8 (t, J = 22.6 Hz), 112.4 (t, J = 22.6 Hz), 111.5 (t, J = 255.2 Hz), 63.4, 22.1, 20.18, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.9 (d, J = 282.5 Hz, 1F), −99.9 (d, J = 282.5 Hz, 1F); HRMS (ESI) (m/z): calcd for $C_{22}H_{17}F_3O_4Na$ ([M+Na]$^+$), 425.0971; found 425.0964.

Ethyl 2,2-Difluoro-2-(6-fluoro-3-(2-methoxyphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)acetate ***(3za)***. 56.6 mg, 70% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (dd, J_1 = 8.4 Hz, J_2 = 4.8 Hz, 1H), 7.77 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.48−7.42 (m, 2H), 7.13 (dd, J_1 = 7.2 Hz, J_2 = 1.8 Hz, 1H), 7.03 (dt, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 4.35 (dq, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 2H), 3.76 (s, 3H), 1.34 (dt, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.2, 182.1, 166.6 (d, J = 259.7 Hz), 162.8 (t, J = 31.7 Hz), 156.6, 147.8, 137.1 (t, J = 19.6 Hz), 134.6 (d, J = 9.1 Hz), 131.0, 130.0 (d, J = 9.1 Hz), 129.5, 128.1, 121.7 (d, J = 22.6 Hz), 121.0, 120.2, 113.9 (d, J = 22.6 Hz), 111.5 (t, J = 255.2 Hz), 110.8, 63.3, 55.8, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −100. Eight (d, J = 288.2 Hz, 1F), −102.8 (d, J = 288.2 Hz, 1F), −100.3 (s, 1F); HRMS (ESI) (m/z): calcd for $C_{21}H_{15}F_3O_5Na$ ([M+Na]$^+$), 427.0764; found 427.0761.

Ethyl 2,2-Difluoro-2-(3-(4-fluoro-2-methylphenyl)-5-methyl-1,4-dioxo-1,4- dihydronaphthalen-2-yl)acetate ***(3ab)***. 40.2 mg, 50% yield; Oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.06 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.68 (t, J = 7.8 Hz, 1H), 7.63 (m, 1H), 7.08−7.05 (m, 1H), 7.01−6.94 (m, 2H), 4.36 (q, J = 7.2 Hz, 2H), 2.71 (s, 3H), 2.18 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 185.2, 183.6, 163.1 (d, J = 247.6 Hz), 162.6 (d, J = 31.7 Hz), 149.9, 142.4, 138.8, 138.1 (d, J = 7.6 Hz), 136.3 (t, J = 21.1 Hz), 133.9, 132.8, 129.5, 129.4 (d, J = 9.1 Hz), 128.1, 125.6, 116.7 (d, J = 21.1 Hz), 112.4 (d, J = 22.6 Hz), 111.4 (t, J = 255.2 Hz), 63.4, 20.2, 14.0; ^{19}F NMR

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(565 MHz, $CDCl_3$) δ −100.05 (d, J = 282.5 Hz, 1F), −100.3 (d, J = 104.0 Hz, 1F), −113.5 (s, 1F); HRMS (ESI) (m/z): calcd for $C_{22}H_{17}F_3O_4Na$ ($[M+Na]^+$), 425.0971; found 425.0963.

Ethyl 2-(3-(3,5-Dimethylphenyl)-7-fluoro-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ac)***. 57.1 mg, 71% yield; Yellow solid; mp 100−102 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.17 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.77 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.47 (dt, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.49 (d, J = 8.4 Hz, 3H), 7.28 (d, J = 8.4 Hz, 2H), 4.38 (q, J = 7.2 Hz), 7.10 (s, 1H), 6.90 (s, 2H), 4.36 (q, J = 7.2 Hz, 2H), 2.36 (s, 6H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.2, 182.4, 166.7 (d, J = 259.7 Hz), 162.8 (t, J = 31.7 Hz), 149.6, 137.3, 136.0 (t, J = 21.1 Hz), 134.4 (d, J = 9.1 Hz), 131.2, 130.8, 129.9 (d, J = 9.1 Hz), 127.9, 126.6, 122.0 (d, J = 24.2 Hz), 113.9 (d, J = 24.2 Hz), 111.5 (t, J = 255.2 Hz), 63.4, 21.4, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.9, −99.9; HRMS (ESI) (m/z): calcd for $C_{22}H_{17}F_3O_4Na$ ($[M+Na]^+$), 425.0971; found 425.0962.

Ethyl 2-(6-Chloro-1,4-dioxo-3-(o-tolyl)-1,4-dihydronaphthalen-2-yl)-2,2-difluoroacetate ***(3ad)***. 49.3 mg, 61% yield; Yellow solid; mp 110−112 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.14−8.12 (m, 2H), 7.80 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 7.38 (t, J = 7.2 Hz, 1H), 7.32−7.27 (m, 2H), 7.11 (d, J = 7.2 Hz, 1H), 4.38 (q, J = 7.2 Hz, 2H), 2.21 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.6, 182.4, 162.6 (t, J = 31.7 Hz), 149.7, 142.0, 137.1 (t, J = 19.6 Hz), 135.2, 134.7, 132.8, 131.5, 129.8, 129.6, 129.3, 128.4, 127.6, 127.2, 125.3, 111.4 (t, J = 256.7 Hz), 63.4, 20.0, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −99.6 (d, J = 284.0 Hz, 1F), −103.6 (d, J = 278.3 Hz, 1F); HRMS (ESI) (m/z): calcd for $C_{21}H_{15}ClF_2O_4Na$ ($[M+Na]^+$), 427.0519; found 427.0513.

Ethyl 2-(3-(3,5-Dimethylphenyl)-1,4-dioxo-1,4-dihydronaphthalen-2-yl)-2-fluoroacetate ***(3ae)***. Thirty mg, 41% yield; Yellow solid; mp 100−102 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17−8.14 (m, 2H), 7.81−7.79 (m, 2H), 7.13 (s, 1H), 6.97 (s, 2H), 5.58 (d, J = 46 Hz, 1H), 4.30 (m, 2H), 2.37 (s, 6H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 183.8 (d, J = 181.1 Hz), 168.0 (d, J = 24.1 Hz), 150.9, 138.2, 134.4, 132.3, 132.1, 131.8, 131.7, 130.9, 127.5, 127.1, 126.8, 84.0 (d, J = 187.1 Hz), 62.2, 21.5, 14.2; ^{19}F NMR (565 MHz, $CDCl_3$) δ −180.4; HRMS (ESI) (m/z): calcd for $C_{22}H_{19}FO_4Na$ ($[M+Na]^+$), 389.1159; found 389.1163.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-7-formyl-6-methoxy-1-oxo-1H-inden-2-yl)-2,2-difluoroacetate ***(4a)***. 40.7 mg, 46% yield; Yellow solid; mp 88−90 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 1.36 (s, 9H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.2, 189.7, 163.2, 162.6 (t, J = 33.2 Hz), 161.7, 153.6, 146.1, 129.8, 128.0 (t, J = 24.2 Hz), 127.4, 126.9, 125.8, 125.3, 122.7, 111.4, 110.9 (t, J = 250.7 Hz), 63.4, 56.8, 35.0, 31.3, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.8; HRMS (ESI) (m/z): calcd for $C_{25}H_{24}F_2O_5Na$ ($[M+Na]^+$), 465.1484; found 465.1474.

Ethyl 2,2-Difluoro-2-(3-(4-fluoro-2-methylphenyl)-7-formyl-6-methoxy-1-oxo-1H-inden-2-yl)acetate ***(4b)***. 41.8 mg, 50% yield; Oil; ^1H NMR (600 MHz, $CDCl_3$) δ 9.51 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.16−7.13 (m, 1H), 7.00−6.96 (m, 2H), 6.86 (d, J = 8.4 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 3.88 (s, 3H), 2.24 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 190.1, 189.4, 164.2, 163.5, 162.6, 162.4 (t, J = 31.7 Hz), 160.3, 145.0, 137.9 (t, J = 7.6 Hz), 129.5 (t, J = 22.6 Hz), 128.5, 127.7, 125.4, 122.3, 117.5 (d, J = 21.1 Hz), 113.4 (d, J = 21.1 Hz), 111.4, 110.8 (t, J = 250.7 Hz), 63.6, 56.8, 19.9, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −100. Two (d, J = 288.2 Hz, 1F), −102.4 (d, J = 288.2 Hz, 1F), −111.5 (s, 1F); HRMS (ESI) (m/z): calcd for $C_{22}H_{17}F_3O_5Na$ ($[M+Na]^+$), 441.0920; found 441.0909.

Ethyl 2,2-Difluoro-2-(1-oxo-3-phenyl-1H-inden-2-yl)acetate ***(4c)***. Thirty mg, 45% yield; Yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 6.6 Hz, 1H), 7.54−7.51 (m, 5H), 7.42−7.36 (m, 2H), 7.10 (d, J = 7.2 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.7, 162.9 (t, J = 33.2 Hz), 143.9, 134.0, 130.9, 130.8, 130.5, 130.1, 129.0 (t, J = 18.1 Hz), 128.5, 128.2, 124.4 (t, J = 24.1 Hz), 123.5, 123.4, 111.2 (t, J = 249.0 Hz), 63.4, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.1; HRMS (ESI) (m/z): calcd for $C_{19}H_{14}F_2O_3Na$ ($[M+Na]^+$), 351.0803; found 351.0805.

Ethyl 2,2-Difluoro-2-(1-oxo-3-(p-tolyl)-1H-inden-2-yl)acetate ***(4d)***. 27.4 mg, 40% yield; Yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 (d, J = 6.6 Hz, 1H), 7.44 (d, J = 7.8 Hz, 2H), 7.42−7.36 (m, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.14 (d, J = 7.2 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 2.45 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.9, 163.0 (t, J = 33.2 Hz), 144.0, 141.1, 133.8, 130.8, 130.3, 129.3, 128.4, 127.9, 124.0 (t, J = 24.1 Hz), 123.5, 123.4, 111.3 (t, J = 249.0 Hz), 63.4, 21.7, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.0; HRMS (ESI) (m/z): calcd for $C_{20}H_{16}F_2O_3Na$ ($[M+Na]^+$), 365.0960; found 365.0965.

Ethyl 2-(3-(4-(tert-Butyl)phenyl)-1-oxo-1H-inden-2-yl)-2,2-difluoroacetate ***(4e)***. Thirty mg, 39% yield; Yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, J_1 = 6.6 Hz, J_2 = 0.6 Hz, 1H), 7.54−7.53 (m, 2H), 7.50−7.48 (m, 2H), 7.43−7.40 (m, 1H), 7.39−7.36 (m, 1H), 7.17 (d, J = 7.2 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 1.38 (s, 9H), 1.29 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.9, 163.0 (t, J = 33.2 Hz), 154.2, 144.0, 133.8, 130.8, 130.3, 128.2, 127.9, 125.5, 124.0 (t, J = 24.1 Hz), 123.6, 123.4, 111.3 (t, J = 249.0 Hz), 63.3, 35.1, 31.3, 13.9; ^{19}F NMR (565 MHz, $CDCl_3$) δ −97.8; HRMS (ESI) (m/z): calcd for $C_{23}H_{22}F_2O_3Na$ ($[M+Na]^+$), 407.1429 ; found 407.1432.

Ethyl 2-(3-(4-Chlorophenyl)-1-oxo-1H-inden-2-yl)-2,2-difluoroacetate ***(4f)***. 25.4 mg, 35% yield; Yellow oil; ^1H NMR (600 MHz, $CDCl_3$) δ 7.57 (d, J = 6.6 Hz, 1H), 7.52−7.48 (m, 4H), 7.44−7.38 (m, 2H), 7.07 (d, J = 6.6 Hz, 1H), 4.32 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.5, 161.9, 143.7, 136.8, 134.1, 131.1, 130.0, 129.7, 129.2, 129.0, 124.9 (t, J = 24.1 Hz), 123.7, 123.2, 111.1(t, J = 250.5 Hz), 63.6, 14.0; ^{19}F NMR (565 MHz, $CDCl_3$) δ −98.3; HRMS (ESI) (m/z): calcd for $C_{19}H_{13}ClF_2O_3Na$ ($[M+Na]^+$), 385.0413; found 385.0414.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00964.

Spectroscopic data of products **3** and **4**, as well as X-ray data of **3aa** (PDF)

X-ray crystallographic data for compound **3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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