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Visible Light-Promoted Phosphine-Catalyzed Difluoroalkylation of Arenes and Heterocycles

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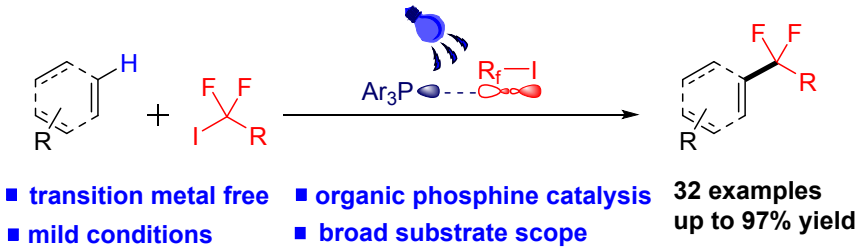
Supporting Information



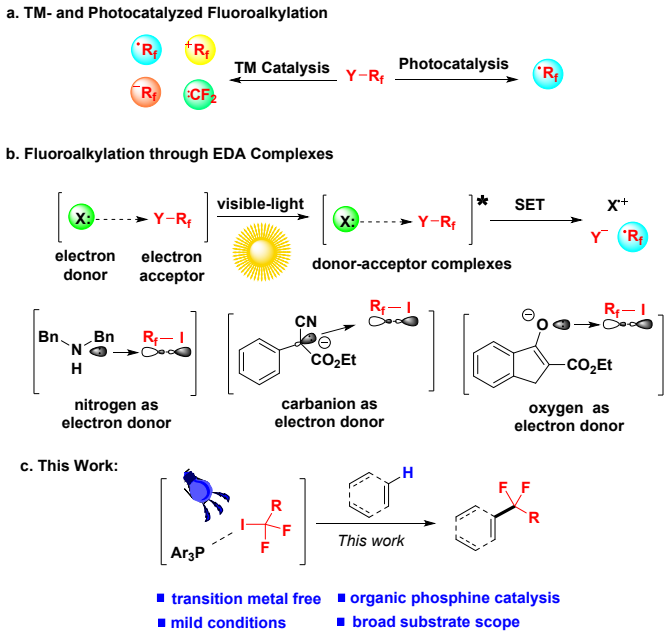
ABSTRACT: A visible light-promoted difluoroalkylation reaction of arenes or heterocycles using triaryl phosphine as the catalyst and difluoroalkyl iodide as the alkylating agent is presented. The strategy is highlighted by photocatalyst-free, mild reaction conditions, and broad substrate scope. Mechanistic experiments indicate that this reaction involves a radical-chain process that is initiated by an EDA complex formed from difluoroalkyl iodide and phosphine.

INTRODUCTION

Fluoroalkanes are highly valuable compounds possessing wide applications in pharmaceuticals industry, medicinal chemistry, and materials science.[1] More specifically, the *gem*-difluoromethyl group (CF_2) is chemically unique with physicochemical properties distinct from other monofluoro or trifluoro-containing congeners, and is being more and more commonly used as

bioisosteres of alcohols, amines or ketones with potentials to improve liver microsome stability and cellular permeability.[2] In the past decade, strategies for direct introduction of difluoroalkyl groups have received increasing attention.[3] Their transition metal-catalyzed difluoroalkylation of aromatic rings or alkenes has been well-established through a nucleophilic,[4] electrophilic,[5] radical,[6] or metal–difluorocarbene pathway (Scheme 1a).[7] Simultaneously, the visible-light-promoted difluoroalkylation reactions were regarded as a powerful addition for synthesis of difluoroalkylated skeletons.[8] Early in 2011, Stephenson's group[8a] reported a radical addition reaction of ethyl bromodifluoroacetate with olefins using a metal-photoredox catalyst. Later, organic photocatalysts such as eosin Y,[8f] perylene[8k] and [Mes-Acr]ClO_4[8l] were employed in the difluoroalkylation reactions. Recently, light- or thermo-sensitive electron donor-acceptor (EDA) complexes have been widely applied in organic synthesis due to the simplicity.[9] The formation of these EDA complexes generally depends on pseudo-electrostatic interactions between electron donor and acceptor substrates.[9a] Perfluoroalkyl iodides R_f–I, as a good electron acceptor, could form intermolecular electrostatic interactions between σ* antibonding orbital of the C–I bond and lone pairs of electron-rich atoms (carbanion, nitrogen or oxygen atoms).[9f] Accordingly, several applications have been reported for the visible light induced generation of perfluoroalkyl radicals through EDA complexes.[10] The Yu's[10e] and Chen's[10g] groups respectively reported a halogen bond induced radical addition reaction of iodoperfluoroalkylene with isocyanide or alkenes, which halogen bonds were caused from nitrogen or phosphorus atoms. He et al.[10l] has recently reported substrate-promoted perfluoroalkylation of uracils and cytosines without catalyst in visible-light irradiation. Further, the Melchiorre's group developed substrate-induced perfluoroalkylation reactions, which perfluoroalkyl radical (R_f•) was generated from EDA complexes formed from perfluoroalkyl iodide and α-cyano arylacetates[10a] or cyclic β-ketoester[10d] under blue light irradiation (Scheme 1b).

Scheme 1. Visible light-promoted fluoroalkylation

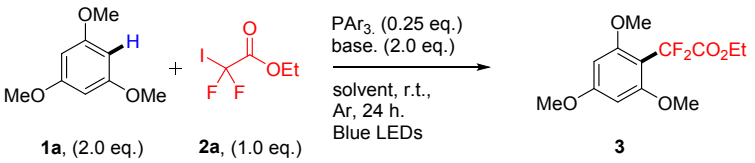


Meanwhile, organophosphines are widely used as ligands due to their electron-donating ability in transition metal catalyzed reactions. Recently, several groups reported the use of triaryl phosphines as single-electronic transfer (SET) medium in visible light-promoted transformations.[11] Sparkled by these pioneering works, we herein report on the application of triarylphosphine as electron donor of EDA complexes in a photocatalytic system to generate *gem*-difluoroalkyl radicals from the commonly used 2,2-difluoro-2-iodoacetate substrates. This protocol readily facilitated visible light-promoted *gem*-difluoroalkylation of inactivated arenes and heterocycles with broad substrate scope (Scheme 1c).

During the completion of our work, The Czekelius group[10o] reported a similar work for the photomediated radical addition reaction of alkenes with perfluoroalkyl iodides. Meanwhile, He's group[10n] reported a Heck-type difluoroalkylation or bisfunctionalization of alkenes with iododifluoroacetate. In their work, they used a phosphine/base (DPPM/DMPU) system through thermal initiation or phosohine (tri-tert-butylphosphine) system via photo initiation to realize fluoroalkylation of alkenes, which is similar to ours ($P(4\text{-}CF_3Ph)_3/K_2CO_3$) via visible light irradiation to realize difluoroalkylation of arene or heteroarenes.

RESULTS AND DISCUSSION

Table 1. Optimization of Conditions[a]



1a, (2.0 eq.) **2a**, (1.0 eq.) **3**

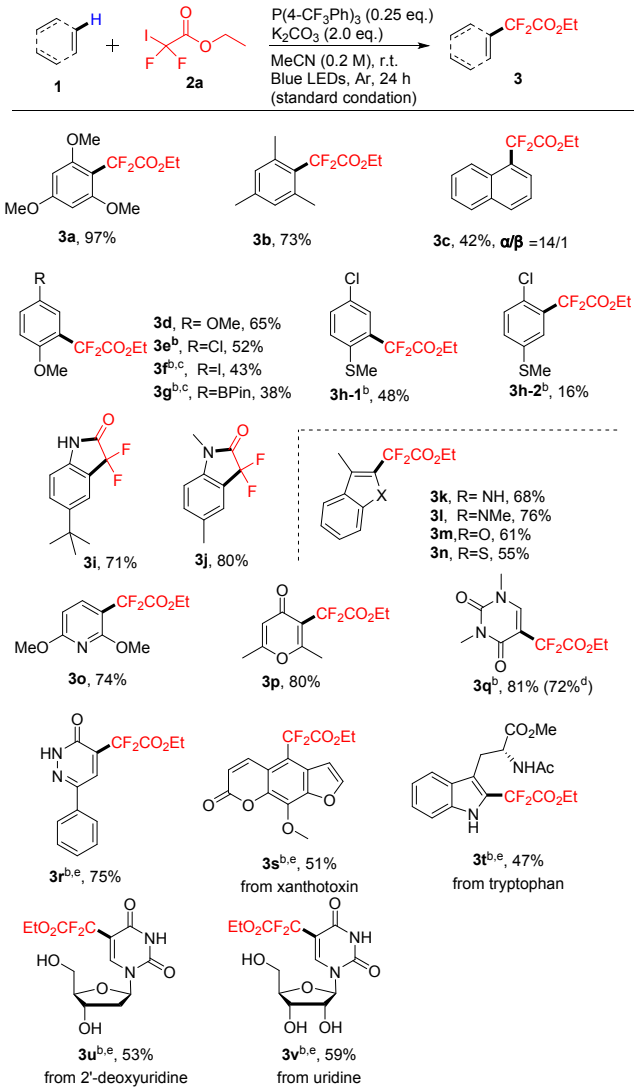
entry	catalyst	base	solvent	yield, %[b]
1	PPh_3	KOAc	DCM	48
2	PPh_3	KOAc	DMSO	54
3	PPh_3	KOAc	DMF	63
4	PPh_3	KOAc	MeCN	65
5	PPh_3	KOAc	MeOH	24
6	$P(C_6F_5)_3$	KOAc	MeCN	–
7	$P(4\text{-}OMePh)_3$	KOAc	MeCN	52
8	$P(4\text{-}CF_3Ph)_3$	KOAc	MeCN	85
9	$P(4\text{-}CF_3Ph)_3$	K_3PO_4	MeCN	76
10	$P(4\text{-}CF_3Ph)_3$	K_2CO_3	MeCN	90
11	$P(4\text{-}CF_3Ph)_3$	Cs_2CO_3	MeCN	65
12	$P(4\text{-}CF_3Ph)_3$	DABCO	MeCN	71
13[c]	$P(4\text{-}CF_3Ph)_3$	K_2CO_3	MeCN	88
14[d]	$P(4\text{-}CF_3Ph)_3$	K_2CO_3	MeCN	97
15[d]	–	K_2CO_3	MeCN	–
16[d]	$P(4\text{-}CF_3Ph)_3$	–	MeCN	–
17[d,e]	$P(4\text{-}CF_3Ph)_3$	K_2CO_3	MeCN	–
18[d,f]	$P(4\text{-}CF_3Ph)_3$	K_2CO_3	MeCN	–
19[d,g]	$P(4\text{-}CF_3Ph)_3$	K_2CO_3	MeCN	63

[a]Reaction condition: **1a** (0.2 mmol), **2a** (0.1 mmol), base (0.2 mmol), catalyst (0.025 mmol), solvent (1.0 mL), 24 h, Ar, 16W Blue LED. [b]Yields are determined by GC-MS using dodecane as internal standard. [c]N,N'-Dimethyl-N,N'-trimethyleneurea (DMPU, 0.01 mmol) as additive. [d]solvent (0.5 mL). [e]dark. [f]dark, 80 °C. [g]Reaction carried out under air.

To initiate the reaction, we chose 1,3,5-trimethoxybenzene (**1a**) and ethyl iododifluoroacetate (**2a**) to establish optimal conditions. As shown in Table 1, the reaction was performed using 25 mol% of PPh_3 as the catalyst and KOAc (2.0 equiv.) as the base in DCM under irradiation of 16W blue LED light strips, and the product **3a** was obtained in 48% yield (Table 1, entry 1). Then, several solvents were screened. To our delight, the yield of **3a** was increased to 65% by using acetonitrile as the solvent (Table 1, entry 4). The reaction was also conducted with different triarylphosphines (Table 1, entries 6-8), and the yield of 3a was improved to 85% when $P(4\text{-}CF_3Ph)_3$ was used as the catalyst (entry 8). Subsequently, we screened several inorganic bases (entries 9-12), and found K_2CO_3 to be the optimal giving product **3a** in 90% yield (entry 10).

Moreover, when N,N'-Dimethyl-N,N'-trimethyleneurea (DMPU) was used as the additive, the yield of **3a** had no changed. Further, we surveyed the concentration of the reaction, and found that the yield of **3a** was increased to 97% when 0.5 mL of MeCN (0.2 M) was used (Table 1, entry 14). Product **3a** was not detected in the absence of either phosphine (Table 1, entry 15), base (Table 1, entry 16) or light irradiation (Table 1, entry 17). In addition, the reaction did not proceed under traditional heating in oil bath (Table 1, entry 18), thus excluding the possibility of thermal initiation. Moreover, decreased yield was observed when the reaction was conducted in the air atmosphere (Table 1, entry 19). Collectively, the condition in entry 14 was selected as the optimal and standard reaction condition in this protocol.

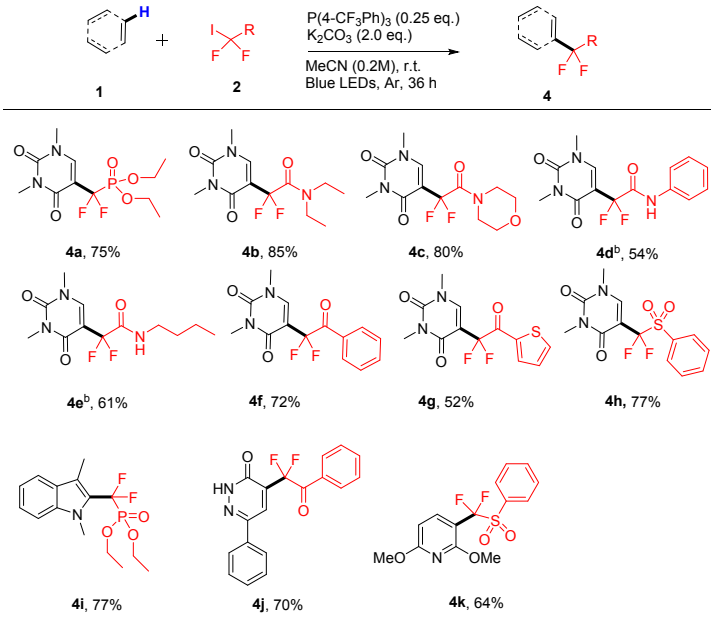
Scheme 2. Substrate Scope of *gem*-Difluoromethylation[a]



[a]Reaction condition: 1 (0.4 mmol), 2a (0.2 mmol), $P(4\text{-}CF_3Ph)_3$ (0.05 mmol), K_2CO_3 (0.4 mmol), in degassed MeCN (1 mL), were irradiated with 16 W blue LED at r. t. for 24 h. Yields of isolated product are given. [b]36 h. [c]1 (0.2 mmol), 2a (0.4 mmol). [d] Yields in 1.0 mmol scale. [e]DMF instead of MeCN.

To explore the scope of the *gem*-difluoromythylation reaction, various arenes were applied as the substrate and the results are summarized in Scheme 2. Substrates 1,3,5-trimethoxybenzene and mesitylene, bearing electron-rich substituents reacted with **2a** in a good to excellent yields. High positional selectivity was observed for naphthalene as the substrate delivering product **3c** with difluoroalkylation preferentially occurring at the α-position (α/β=14/1, determined by ^{19}F NMR). In addition, halogens, such as chloro and iodo, or borate substituted substrates were compatible as well, affording the corresponding products **3e-h** in moderate yields with potential for further functional transformation. Interestingly, lactamization products **3i** and **3j** were obtained in 71% and 80% yields, respectively from aniline substrates, thus providing an easy access for 3,3-difluoroindolin-2-ones. To expand the utility of this strategy, we turned our attention to diverse heterocycles as substrates (Scheme 2). Under the standard reaction conditions, 3-substituted benzoheterocycles such as indole, benzothiophene and benzofuran were readily transformed to the corresponding products **3k-n** in 55-76% yields. Meanwhile, pyridine, 4H-pyran-4-one, and pyrimidine-dione are also suitable substrates, leading to the corresponding products **3o-q** in 74-81% yields. In addition, 6-phenylpyridazin-3(2H)-one, the anti-inflammatory xanthotoxin, and the essential amino acid tryptophan all participated in the reaction as well, providing corresponding products **3r-t** in 47-75% yields with difluoroalkylation preferentially occurring at the electron-rich position. Appealingly, the more reactive 2-deoxyuridines, derived from antiviral drug trifluridine (TFT)[12] also well survived from the reaction conditions without additional protection, and the corresponding difluoroalkylated products **3u** and **3v** were generated in 53% and 59% yields, respectively. To test the synthetic scalability of our protocol, the reaction of 1,3-dimethyluracil **1q** with **2a** was conducted at 1 mmol scale, and the uracil difluoroacetate **3q** was obtained in 72% isolated yield. Unfortunately, simple and monosubstituted benzenes or non-substituted heterocyclic are not suitable for this method leading to low yields and poor regioselectivity.

Scheme 3. Reactions of Dimethyluracil with Diverse *gem*-Difluoroalkanes [a]



[a]Reaction condition: 1q (0.4 mmol), 2 (0.2 mmol), P(4-CF_3Ph)$_3$ (0.05 mmol), K_2CO_3 (0.4 mmol), MeCN (1 mL), 24h, Ar, Blue LEDs. Yields of isolated product are given. [b]0.2 mmol K_2CO_3.

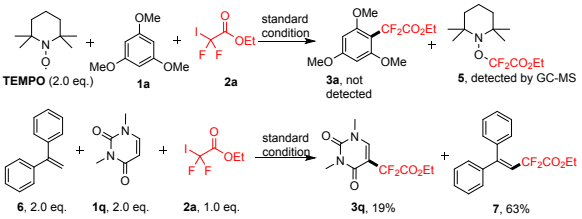
As shown in Scheme 3, with 1,3-dimethyluracil 1q as the substrate, a class of diverse iododifluoroalkanes were tested under the standard condition. Notably, difluoroiodomethylphosphonate and various difluoro-2-iodoacetamides reacted with 1q smoothly, providing corresponding products **4a-e** in 54-85% yields. Iododifluorophenylethanone, 2-(2,2-diofluoro-2-idio acetyl)thiophenen, as well as (difluoroiodomethyl)sulfonylbenzene are also suitable difluoromethylation reagents, affording corresponding products **4f-h** in 52-77% yields. In addition, we have also explored several iododifluoroalkanes reagents with other substrates, to our delight, three different heterocycles worked smoothly and gave the products **4i-k** in 64–77% yields. In a control reaction, the difluoroalkylation of 1,3-dimethyluracil **1q** in Scheme 3 did not occur without phosphine catalyst, indicating the necessity of P-catalyst in our protocol.

In the meantime, several mechanistic experiments were performed. First, two alkyl-radical trapping reagent (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and 1,1-diphenylethylene were used to catch electron-withdrawing gem-difluoroalkyl radical. The adduct TEMPO-CF_2CO_2Et was detected by gas chromatography-mass spectrometer (Scheme 4a). Meanwhile, difluoroacetate-trapped product of 1,1-diphenylethylene was separated and structurally

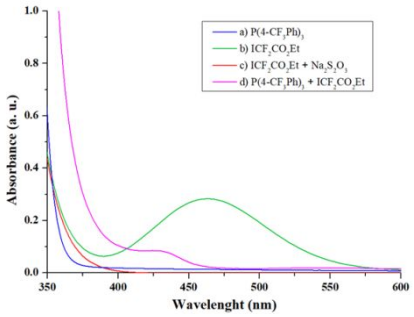
confirmed through NMR analysis (see SI Scheme S2). Further, in the UV/Vis absorption study, treatment of difluoroalkyl iodide **2a** with the $P(4\text{-}CF_3Ph)_3$ induced new absorption bands in the visible region (Scheme 4b), suggesting the possible formation of an EDA complex. In addition, the 1:1 molar ratio between **2a** and $P(4\text{-}CF_3Ph)_3$ in the EDA complex was established using Job's method[13a] with ^{19}F NMR spectroscopy, in which maximal chemical shift difference appeared at 50% molar fraction of difluoroalkyl iodide **2a** (Scheme 4c). Meanwhile, the equilibrium constant K_{EDA} (K_{EDA} = 9.22) was calculated using the Benesi–Hildebrand method (see SI Figure S4). [13b] These results suggest the formation of EDA complex between **2a** and $P(4\text{-}CF_3Ph)_3$. Finally, on the basis of Glorius's method,[13c] we calculated the quantum yield of the reaction (Φ = 2.4), indicating a chain propagation mechanism. Meanwhile, the reaction was found to continue to proceed when light was turned off, but with a slower rate, confirming the necessity of constant irradiation for completion of this reaction (Scheme 4d).[14]

Scheme 4. Mechanistic Investigation

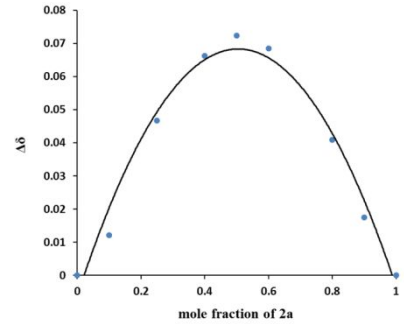
(a) Trapping experiment



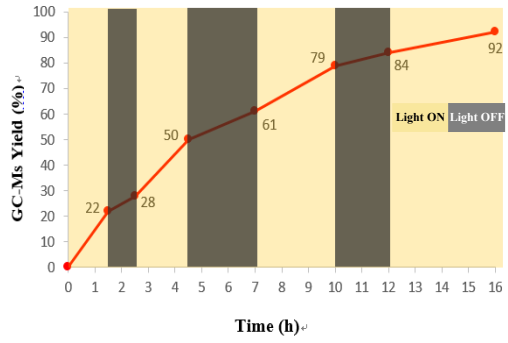
(b) Optical absorption spectra of reaction components.



(c) Job's plot between 2a and P(4-CF_3Ph)$_3$.



(d) Light/dark experiments for the model reaction



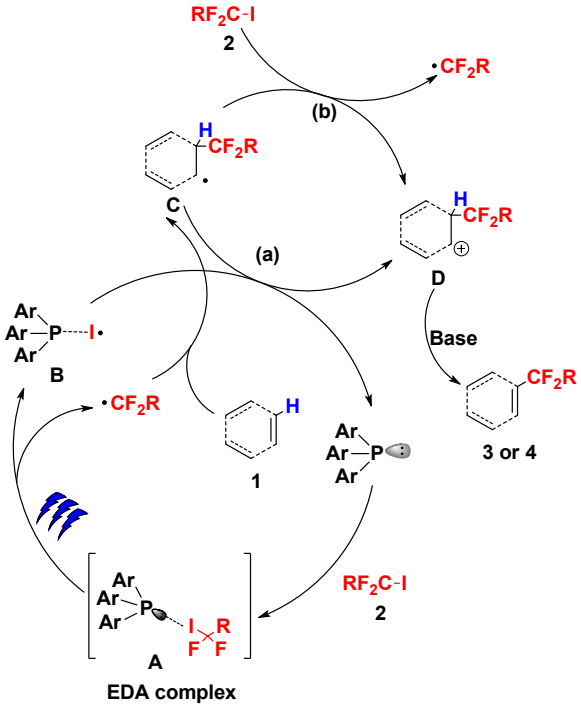
Based on the results above, a conceivable mechanism is proposed in Scheme 5. First, an EDA complex **A**, is assembled from iododifluoroacetate **2** and phosphine, which then undergoes visible light irradiation to generate difluoroalkyl radical (• CF_2R) and the intermediate **B**. Subsequently, the difluoroalkyl radical is captured by arenes or heteroarenes to afford aryl radical species **C**. Aryl cation **D** is then formed through two possible paths: (a) via a SET oxidation by intermediate **B** to recover phosphine catalyst; (b) via a radical exchange with RCF_2I

(2) to generate difluoromethyl radical, which then enters the radical chain process. The final products **3** or **4** are obtained by deprotonation with a base.

CONCLUSIONS

In summary, we describe a mild and efficacious strategy for direct *gem*-difluoromethylation of unactivated arenes and heterocycles with iododifluoroalkanes by a radical-chain mechanism through visible light-promoted phosphine catalysis. A broad range of substrates and diverse iododifluoroalkanes are well tolerant, facilitating a series of high value *gem*-difluoroalkanes, including several pharmaceutical agents.

Scheme 5. Proposed Reaction Mechanism



Experimental Section

All reactions performed in flame-dried glassware, including sealed tubes or Schlenck tubes. Liquids and solutions were transferred with syringes. All solvents and chemical reagents were obtained from commercial sources and used without further purifications. ^{1}H, and ^{13}C NMR spectra were recorded with tetramethylsilane as an internal reference. Low and high-resolution mass spectra were recorded on EI-TOF (electrospray ionization-time of flight). Flash column chromatography on silica gel (200 - 300 mesh) or RP-C18. The column output was monitored by TLC on silica gel (100 - 200 mesh) precoated on glass plates (15 x 50 mm), and spots were visualized by UV light at 254 nM. Commercially available chemicals were obtained from Acros

Organics, Strem Chemicals, Alfa Aesar, Adamas-beta, J&K. UV-Vis spectrum was measured by Shimadzu UV-2600 with pure MeCN as blank sample. The difluoroalkylation reagents **2**[15-19] were prepared according to corresponding literature procedures. All reactions were conducted under blue light bands (Blue sky lighting, 5050 types, 60 LEDs/m, 16W, wavelength range: 420 nm–500 nm). Unless otherwise stated all difluoroalkylation reactions were conducted inside 4 ml screw neck glass vials with a septa screw cap.

General procedures for synthesis of compounds 3 and 4. To a dried 4 mL of colorless glass bottle equipped with magnetic stirring bar, aromatic substrate (0.4 mmol, 2.0 equiv.), $P(4CF_3\text{-}Ph)_3$ (0.05 mmol, 22.3 mg, 0.25 equiv.) and K_2CO_3 (0.4 mmol, 55.2 mg, 2.0 equiv.) were added. The rubber septum was capped, evacuated briefly under high vacuum and charged with Ar balloon (5 times). Degassed MeCN (1.0 mL) or DMF (1.0 mL) and iododifluoroacetate (0.2mmol, 30 μL, 1.0 equiv.) were added by syringe. The bottle was placed at a distance of 1 cm from the 16W blue LEDs. After 24 h or 36 h, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified on a preparative TLC with petroleum ether/ethyl acetate as the eluent to afford products **3** or **4**.

For scale-up synthesis of 3q at 1 mmol: To a dried 25 mL of Schlenk tube was charged with magnetic stirring bar, 1, 3-dimethyluracil (2.0 mmol, 280.0 mg, 2.0 equiv.), $P(4CF_3\text{-}Ph)_3$ (0.25 mmol, 111.5 mg, 0.25 equiv.) and K_2CO_3 (2.0 mmol, 276.0 mg, 2.0 equiv.) were added. The rubber septum was capped, evacuated briefly under high vacuum and charged with Ar balloon (5 times). Then, degassed MeCN (5.0 mL) and ethyl iododifluoroacetate (1.0 mmol, 150 μL, 1.0 equiv.) were added by syringe. The bottle was placed at a distance of 1 cm from the 16W blue LEDs. After 36 h, the reaction mixture was filtered and the filtrate was concentrated. The residue was purified by a flash silica gel column chromatography to give product **3q** as a light yellow solid (189 mg, 72% yield).

*Ethyl 2,2-difluoro-2-(2,4,6-trimethoxyphenyl)acetate (**3a**)* The product (57.5 mg, 97% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 8:1) as colorless oil. Known compound.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.12 (s, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.82 (s, 3H), 3.79 (s, 6H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -96.3 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 164.8 (t, *J* = 33.4 Hz), 164.5, 163.2, 160.1 (t, *J* = 2.6 Hz), 113.3 (t, *J* =

248.0 Hz), 102.7 (t, *J* = 24.2 Hz), 91.3, 62.3, 56.1, 55.3, 14.0. EI-MS (m/z) 290 (M+); HRMS (EI): m/z [M+] calcd for $C_{13}H_{16}F_2O_5$, 290.0960. found, 290.0960.

*Ethyl 2,2-difluoro-2-mesitylacetate (**3b**)* The product (35.3 mg, 73% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 30:1) as colorless liquid. Known compound.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 2H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.43 (t, *J* = 4.3 Hz, 6H), 2.28 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -98.6 (q, *J* = 4.4 Hz). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 164.5 (t, *J* = 35.6 Hz), 139.9, 137.5 (t, *J* = 3.2 Hz), 131.0, 126.8 (t, *J* = 22.5 Hz), 116.2 (t, *J* = 253.3 Hz), 62.9, 21.5 (t, *J* = 20.9 Hz), 20.7, 13.8. EI-MS (m/z) 242 (M+); HRMS (EI): m/z [M+] calcd for $C_{13}H_{16}F_2O_2$, 242.1112 found, 242.1113.

*Ethyl 2,2-difluoro-2-(naphthalen-1-yl)acetate (**3c**)* The product (21.0 mg, 42% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 30:1) as white solid. Known compound.[19] mp 74-75 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.93 – 7.86 (m, 2H), 7.60 – 7.51 (m, 3H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -100.0 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 164.4 (t, *J* = 34.9 Hz), 133.8, 131.9, 129.3 (t, *J* = 2.3 Hz), 128.8, 128.4 (t, *J* = 23.1 Hz), 127.3, 126.3, 124.9 (t, *J* = 9.5 Hz), 124.5, 124.2 (t, *J* = 2.9 Hz), 114.3 (t, *J* = 251.2 Hz), 63.2, 13.8. EI-MS (m/z) 250 (M+); HRMS (EI): m/z [M+] calcd for $C_{14}H_{12}F_2O_2$, 250.0800. found, 250.0800.

*Ethyl 2-(2,5-dimethoxyphenyl)-2,2-difluoroacetate (**3d**)* The product (33.8 mg, 65% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 15:1) as colorless liquid. Known compound.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 3.0 Hz, 1H), 6.98 (dd, *J* = 9.0 Hz and 3.0 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 3.76 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -102.4 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 163.9 (t, *J* = 33.8 Hz), 153.5, 150.7 (t, *J* = 5.0 Hz), 122.7 (t, *J* = 24.1 Hz), 117.4, 112.8, 112.0 (t, *J* = 7.7 Hz), 111.8 (t, *J* = 249.4 Hz), 62.7, 56.3, 55.8, 13.9. EI-MS (m/z) 260 (M+); HRMS (EI): m/z [M+] calcd for $C_{12}H_{14}F_2O_4$, 260.0856. found, 260.0855.

*Ethyl 2-(5-chloro-2-methoxyphenyl)-2,2-difluoroacetate (**3e**)* The product (27.5 mg, 52% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 15:1) as colorless oil. Known compound.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 2.5 Hz, 1H), 7.41 (dd, *J* = 8.8 Hz and 2.5 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -103.1 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 163.4 (t, *J* = 33.7 Hz), 155.3 (t, *J* = 4.8 Hz), 132.0, 126.6 (t, *J* = 7.9 Hz), 125.8, 123.4 (t, *J* = 24.3 Hz), 112.7, 111.4 (t, *J*

= 249.7 Hz), 62.8, 56.0, 13.9. EI-MS (m/z) 264 (M+); HRMS (EI): m/z [M+] calcd for $C_{11}H_{11}ClF_2O_3$, 264.0363. found, 264.0359.

*Ethyl 2,2-difluoro-2-(5-iodo-2-methoxyphenyl)acetate (**3f**)* The product (30.5 mg, 43% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 15:1) as colorless oily liquid. Known compound.[19] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 2.1 Hz, 1H), 7.74 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -103.1 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 163.5 (t, *J* = 33.6 Hz), 156.6 (t, *J* = 4.8 Hz), 141.0, 135.0 (t, *J* = 6.5 Hz), 124.1 (t, *J* = 24.3 Hz), 113.6, 111.2 (t, *J* = 249.7 Hz), 82.3, 62.8, 55.9, 13.9. EI-MS (m/z) 356 (M+); HRMS (EI): m/z [M+] calcd for $C_{11}H_{11}F_2IO_3$, 355.9713. found, 355.9716.

*Ethyl 2,2-difluoro-2-(2-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (**3g**)* The product (27.0 mg, 38% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 10:1) as colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.83 (s, 3H), 1.34 (s, 12H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -102.7 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 164.1 (t, *J* = 33.9 Hz), 159.1 (t, *J* = 4.8 Hz), 139.3, 132.9 (t, *J* = 7.0 Hz), 121.4 (t, *J* = 24.2 Hz), 112.3 (t, *J* = 248.4 Hz), 110.5, 83.9, 62.6, 55.6, 24.8, 13.9. EI-MS (m/z) 356 (M+); HRMS (EI): m/z [M+] calcd for $C_{17}H_{23}BF_2O_5$, 356.1602. found, 356.1601.

*Ethyl 2-(2-chloro-5-(methylthio)phenyl)-2,2-difluoroacetate (**3h-1**)* The product (28.3 mg, 48% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 15:1) as colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.28 (d, *J* = 10.0 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.51 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -102.6 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 162.9 (t, *J* = 33.7 Hz), 138.4, 131.5 (t, *J* = 24.2 Hz), 130.8, 129.6, 128.1 (t, *J* = 4.1 Hz), 124.8 (t, *J* = 8.8 Hz), 112.0 (t, *J* = 251.5 Hz), 63.4, 15.7, 13.8. EI-MS (m/z) 280 (M+); HRMS (EI): m/z [M+] calcd for $C_{11}H_{11}ClF_2O_2S$, 280.0131. found, 280.0131.

*Ethyl 2-(5-chloro-2-(methylthio)phenyl)-2,2-difluoroacetate (**3h-2**)* The product (9.0 mg, 16% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 15:1) as colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.65 (m, 1H), 7.46 – 7.37 (m, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.40 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -102.6 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 163.3 (t, *J* = 33.7 Hz), 135.2 (t, *J* = 3.7 Hz), 134.9 (t, *J* = 23.5 Hz), 132.7, 132.3, 131.3, 126.6 (t, *J* = 9.3 Hz), 112.2 (t, *J* =251.5 Hz), 63.2, 18.6, 13.8. EI-MS (m/z) 280 (M+); HRMS (EI): m/z [M+] calcd for $C_{11}H_{11}ClF_2O_2S$, 280.0131. found, 280.0133.

5-(tert-Butyl)-3,3-difluoroindolin-2-one (3i) The product (32.0 mg, 71% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 5:1) as light yellow solid. mp 87-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 7.57 (s, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 6.98 – 6.89 (m, 1H), 1.32 (s, 9H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -111.6 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 167.7 (t, *J* = 30.4 Hz), 147.5, 138.6 (t, *J* = 7.3 Hz), 130.5, 121.9, 119.9 (t, *J* = 22.9 Hz), 111.1, 34.6, 31.3. EI-MS (m/z) 225 (M+); HRMS (EI): m/z [M+] calcd for $C_{12}H_{13}F_2NO$, 225.0965. found, 225.0971.

*3,3-Difluoro-1,5-dimethylindolin-2-one (**3j**)* The product (31.5 mg, 80% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 15:1) as light yellow liquid. Known compound.[20] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35(s, 1H), 7.31 – 7.27 (d, J = 7.6Hz, 1H), 6.78 (d, J = 7.6Hz, 1H), 3.19 (s, 3H), 2.36 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -112.2 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 165.3 (t, J = 30.4 Hz), 141.5 (t, J = 7.0 Hz), 133.8, 133.7, 125.2, 120.0 (t, J = 22.9 Hz), 111.1 (t, J = 249.8 Hz), 109.2, 26.3, 20.9. EI-MS (m/z) 197 (M+); HRMS (EI): m/z [M+] calcd for $C_{10}H_9F_2NO$, 197.0645. found, 197.0647.

*Ethyl 2,2-difluoro-2-(3-methyl-1H-indol-2-yl)acetate (**3k**)* The product (34.4 mg, 68% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 30:1) as yellow oil. Known compound.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 – 8.32 (m, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.38 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.30 (m, 1H), 7.18 (m, 1H), 4.35 (q, *J* = 7.1 Hz, 2H), 2.44 (t, *J* = 2.3 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.46 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) 163.45 (t, J =35.9 Hz), 135.51, 128.50, 124.21, 123.32 (t, J = 29.7 Hz), 120.03, 119.72, 113.81 (t, J = 3.6 Hz), 111.45, 111.39 (t, J = 251.4 Hz), 63.46, 13.88, 8.44. EI-MS (m/z) 253 (M+); HRMS (EI): m/z [M+] calcd for $C_{13}H_{13}F_2NO_2$, 253.0906. found, 253.0909.

*Ethyl 2-(1,3-dimethyl-1H-indol-2-yl)-2,2-difluoroacetate (**3l**)* The product (40.6mg, 76% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 5:1) as colorless oily liquid. Known compound.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.37 – 7.32 (m, 2H), 7.18 (dq, *J* = 7.9 Hz, 4.4 Hz and 3.8 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.85 (d, *J* = 1.4 Hz, 3H), 2.46 (t, *J* = 3.1 Hz, 3H), 1.34 (td, *J* = 7.2 Hz and 0.9 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -98.1 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 163.6 (t, *J* = 36.0 Hz), 138.0, 127.5, 124.7 (t, *J* = 28.6 Hz), 124.0, 119.8, 119.6, 114.2 (t, *J* = 3.8 Hz), 112.3 (t, *J* = 251.8 Hz), 109.5, 63.4, 31.4 (t, *J* = 4.3 Hz), 13.9, 8.9 (t, *J* = 2.7Hz). EI-MS (m/z) 267 (M+); HRMS (EI): m/z [M+] calcd for $C_{14}H_{15}F_2NO_2$, 267.1065. found, 267.1065.

*Ethyl 2,2-difluoro-2-(3-methylbenzofuran-2-yl)acetate (**3m**)* The product (31.0mg, 61% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 10:1) as

colorless oily liquid. Known compound.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.5 Hz and 1.1 Hz, 1H), 7.49 (dt, *J* = 8.3 Hz and 0.9 Hz, 1H), 7.39 (m, 1H), 7.31 (m, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 2.42 (t, *J* = 2.6 Hz, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -103.4 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 162.5 (t, *J* = 34.1 Hz), 154.2, 141.0 (t, *J* = 32.6 Hz), 128.9, 126.3, 123.1, 118.0, 112.3 (t, *J* = 250.1 Hz), 110.3, 108.4, 63.6, 13.9, 7.7. EI-MS (m/z) 254 (M+); HRMS (EI): m/z [M+] calcd for $C_{13}H_{12}F_2O_3$, 254.0746. found, 254.0749.

*Ethyl 2,2-difluoro-2-(3-methylbenzo[b]thiophen-2-yl)acetate (**3n**)* The product (29.7 mg, 55% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 10:1) as colorless oily liquid. Known compound.[21] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 1H), 7.80 – 7.74 (m, 1H), 7.47 – 7.41 (m, 2H), 4.34 (q, *J* = 7.2 Hz, 2H), 2.53 (t, *J* = 2.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -94.4 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 163.2 (t, *J* = 35.7 Hz), 140.1, 138.9, 133.9 (t, *J* = 4.8 Hz), 128.1 (t, *J* = 28.4 Hz), 126.0, 124.5, 122.7, 122.5, 112.6 (t, *J* = 252.7 Hz), 63.5, 13.9, 12.0. EI-MS (m/z) 270 (M+); HRMS (EI): m/z [M+] calcd for $C_{13}H_{12}F_2O_2S$, 270.0526. found, 270.0522.

*Ethyl 2-(2,6-dimethoxypyridin-3-yl)-2,2-difluoroacetate (**3o**)* The product (38.6mg, 74% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 5:1) as colorless oily liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.3 Hz, 1H), 6.37 (d, *J* = 8.4 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.6 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 164.8, 163.8 (t, *J* = 34.5 Hz), 159.7 (t, *J* = 5.2 Hz), 138.3 (t, *J* = 6.2 Hz), 112.2 (t, *J* = 248.4 Hz), 107.2 (t, *J* = 26.3 Hz), 101.3, 62.8, 53.8, 53.6, 13.9. EI-MS (m/z) 261 (M+); HRMS (EI): m/z [M+] calcd for $C_{11}H_{13}F_2NO_4$, 261.0812. found, 261.0807.

*Ethyl 2-(2,6-dimethyl-4-oxo-4H-pyran-3-yl)-2,2-difluoroacetate (**3p**)* The product (39.4 mg, 80% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 8:1) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.13 – 6.05 (m, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.51 (t, *J* = 3.4 Hz, 3H), 2.26 (d, *J* = 0.8 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -101.3 (q, *J* = 3.6 Hz). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 176.6 (t, *J* = 3.5 Hz), 167.3, 165.9, 162.9 (t, *J* = 31.9 Hz), 119.3 (t, *J* = 22.4 Hz), 113.6, 112.3 (t, *J* = 250.2 Hz), 62.9, 19.6, 18.8 (t, *J* = 4.9 Hz), 13.8. EI-MS (m/z) 246 (M+); HRMS (EI): m/z [M+] calcd for $C_{11}H_{12}F_2O_4$, 246.0693. found, 246.0698.

*Ethyl 2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetate (**3q**)* The product (35.3 mg, 73% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 4:1) as light yellow solid (42.4 mg, 81% yield). Known compound.[22] mp 80-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 3.47 (s, 3H), 3.29 (s, 3H),

1.32 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -104.8 (s). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 162.6 (t, *J* = 33.1 Hz), 160.3 (t, *J* = 4.0 Hz), 151.0, 142.7 (t, *J* = 8.1 Hz), 111.0 (t, *J* = 249.8 Hz), 106.8 (t, *J* = 25.3 Hz), 63.3, 37.6, 27.7, 13.7. EI-MS (m/z) 262 (M+); HRMS (EI): m/z [M+] calcd for $C_{10}H_{12}F_2N_2O_4$, 262.0765. found, 262.0760.

*Ethyl 2,2-difluoro-2-(3-oxo-6-phenyl-2,3-dihydropyridazin-4-yl)acetate (**3r**)* The product (44.1 mg, 75% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 2:1) as light yellow solid. mp 191-193 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.81 – 12.61 (s, 1H), 8.12 (d, *J* = 1.2 Hz, 1H), 7.88 – 7.77 (m, 2H), 7.53 – 7.45 (m, 3H), 4.43 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.2 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 161.9 (t, *J* = 32.1 Hz), 158.9 (t, *J* = 4.2 Hz), 145.6, 133.8, 133.7 (t, *J* = 25.1 Hz), 130.1, 129.1, 128.5 (t, *J* = 6.6 Hz), 126.0, 110.0 (t, *J* = 251.7 Hz), 63.7, 13.8. EI-MS (m/z) 294 (M+); HRMS (EI): m/z [M+] calcd for $C_{14}H_{12}F_2N_2O_3$, 294.0813. found, 294.0811.

*Ethyl 2,2-difluoro-2-(9-methoxy-7-oxo-7H-furo[3,2-g]chromen-4-yl)acetate (**3s**)* The product (34.5 mg, 51% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as white solid. mp 103-104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 10.2 Hz, 1H), 7.77 – 7.72 (m, 1H), 7.14 (q, *J* = 2.9 Hz, 1H), 6.47 (d, *J* = 10.1 Hz, 1H), 4.36 (s, 3H), 4.29 (q, *J* = 7.1 Hz, 2H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -95.8(s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 163.5 (t, *J* = 35.3 Hz), 159.1, 147.4 (t, *J* = 2.2 Hz), 146.5, 143.5, 140.8 (t, *J* = 2.5 Hz), 134.8, 125.3 (t, *J* = 3.9 Hz), 116.0, 114.4 (t, *J* = 3.1 Hz), 114.2, 113.8 (t, *J* = 26.7 Hz), 112.2 (t, *J* = 251.9 Hz), 107.2 (t, *J* = 7.1 Hz), 63.8, 61.3, 13.8. EI-MS (m/z) 338 (M+); HRMS (EI): m/z [M+] calcd for $C_{16}H_{12}F_2O_6$, 338.0590. found, 338.0596.

*Methyl (R)-2-acetamido-3-(2-(2-ethoxy-1,1-difluoro-2-oxoethyl)-1H-indol-3-yl)propanoate (**3t**)* The product (35.9 mg, 47% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 1:2) as yellow solid. mp 98-100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.80 (s, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.38 (d, *J* = 8.2 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.21 (d, *J* = 7.5 Hz, 1H), 4.91 (q, *J* = 7.2 Hz, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.68 (s, 3H), 3.38 (qd, *J* = 14.4, 6.5 Hz, 2H), 1.92 (s, 3H), 1.34 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ -99.5 (d, *J* = 267.1 Hz, 1F), -101.21 (d, *J* = 267.1 Hz, 1F). ^{13}C{1H} NMR (151 MHz, $CDCl_3$) δ 172.3, 170.0, 163.5 (t, *J* = 35.6 Hz), 135.7, 127.6, 124.6, 124.4 (t, *J* = 30.2 Hz), 120.7, 119.8, 112.3, 111.8, 111.2 (t, *J* = 251.8 Hz), 63.9, 52.8, 52.3, 26.8, 22.9, 13.8. EI-MS (m/z) 382 (M+); HRMS (EI): m/z [M+] calcd for $C_{18}H_{20}F_2N_2O_5$, 382.1334. found, 382.1335.

*Ethyl 2,2-difluoro-2-(1-((2R,4S,5R)-4-hydroxy-5-(hydroxymethyl) tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acetate (**3u**)* The product (37.1 mg, 53% yield) was obtained through silica gel chromatography (Dichloromethane / Methanol = 20:1) as white syrup solid. Known compound.[22] ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (s, 1H), 6.27 (t, *J* = 6.4 Hz, 1H), 4.42 (dt, *J* = 6.1 Hz and 3.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 3.97 (q, *J* = 3.0 Hz, 1H), 3.86 – 3.72 (m, 2H), 2.99 (s, 1H), 2.86 (s, 1H), 2.36 (m, 1H), 2.26 (dt, *J* = 13.5 Hz and 6.3 Hz, 1H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, CD_3OD) δ -104.9 (d, *J* = 274.4 Hz, 1F), -105.9 (d, *J* = 274.2 Hz, 1F). ^{13}C{1H} NMR (126 MHz, CD_3OD) δ 164.2 (t, *J* = 33.5 Hz), 162.6 (t, *J* = 4.2 Hz), 151.5, 142.3 (t, *J* = 8.1 Hz), 112.5 (t, *J* = 248.0 Hz), 108.8 (t, *J* = 25.5 Hz), 89.3, 87.4, 71.9, 64.3, 62.3, 42.0, 14.1. EI-MS (m/z) 351 (M+H); HRMS (EI): m/z [M+H] calcd for $C_{13}H_{16}F_2N_2O_7$, 351.0926. found, 351.0923.

*Ethyl 2-(1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetate (**3v**)* The product (43.2 mg, 59% yield) was obtained through silica gel chromatography (Dichloromethane/Methanol = 15:1) as white syrup solid. Known compound.[22] ^{1}H NMR (400 MHz, CD_3OD) δ 8.81 (s, 1H), 5.96 (d, *J* = 3.6 Hz, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.24 (p, *J* = 5.0 Hz, 2H), 4.09 (dt, *J* = 4.3 Hz and 2.1 Hz, 1H), 3.92 (dd, *J* = 12.1 Hz and 2.4 Hz, 1H), 3.78 (dd, *J* = 12.1 Hz and 2.1 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, CD_3OD) δ -105.0 (d, *J* = 274.5 Hz, 1F), -105.8 (d, *J* = 274.5 Hz, 1F). ^{13}C{1H} NMR (126 MHz, CD_3OD) δ 164.1 (t, *J* = 33.6 Hz), 162.5 (t, *J* = 3.5 Hz), 151.7, 142.4 (t, *J* = 8.0 Hz), 112.5 (t, *J* = 248.0 Hz), 109.0 (t, *J* = 25.3 Hz), 91.3, 86.5, 76.3, 70.9, 64.3, 61.5, 49.0, 14.1. EI-MS (m/z) 367 (M+H); HRMS (EI): m/z [M+H] calcd for $C_{13}H_{17}F_2N_2O_8$, 367.0954. found, 367.0957.

*Diethyl ((1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)difluoromethyl)phosphonate (**4a**)* The product (48.9mg, 75% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 4:1) as light yellow solid. Known compound.[22] mp 72-73 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 4.39 – 4.25 (m, 4H), 3.44 (s, 3H), 3.33 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 6H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.6(s, 1F), -106.9 (s, 1F). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 159.1, 151.0, 143.9 (td, *J* = 10.5 Hz and 3.4 Hz), 116.6 (td, *J* = 265.4 Hz and 223.0 Hz), 106.0 (td, *J* = 22.8 Hz and 15.2 Hz), 65.4, 65.3, 37.7, 27.9, 16.4, 16.3. EI-MS (m/z) 326 (M+); HRMS (EI): m/z [M+] calcd for $C_{11}H_{17}F_2N_2O_5P$, 326.0847. found, 326.0848.

*2-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-N,N-diethyl-2,2-difluoroacetamide (**4b**)* The product (49.1 mg, 85% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 4:1) as white solid. Known compound.[22] mp 68-69 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 3.59 (q, *J* = 7.1 Hz, 2H), 3.45 – 3.36 (m, 5H), 3.31 (s, 3H), 1.26 (t, *J*

= 7.1 Hz, 3H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -100.0 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 161.5 (t, *J* = 29.5 Hz), 160.1 (t, *J* = 3.6 Hz), 151.2, 141.5 (t, *J* = 9.5 Hz), 115.4 (t, *J* = 256.8 Hz), 108.6 (t, *J* = 25.3 Hz), 42.4, 42.2 (t, *J* = 6.4 Hz), 37.4, 27.7, 14.3, 12.1. EI-MS (m/z) 289 (M+); HRMS (EI): m/z [M+] calcd for $C_{12}H_{17}F_2N_3O_3$, 289.1236. found, 289.1232.

*5-(1,1-Difluoro-2-morpholino-2-oxoethyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**4c**)* The product (42.4 mg, 81% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as light yellow solid. mp 100-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 3.80 (d, *J* = 4.5 Hz, 2H), 3.72 – 3.68 (m, 4H), 3.63 (s, 2H), 3.41 (s, 3H), 3.28 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -98.9 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 160.7 (t, *J* = 29.8 Hz), 160.0 (t, *J* = 3.6 Hz), 151.0, 141.8 (t, *J* = 9.5 Hz), 115.3 (t, *J* = 256.4 Hz), 107.7 (t, *J* = 24.9 Hz), 66.5, 66.5, 46.5 (t, *J* = 6.6 Hz), 43.8, 37.4, 27.7. EI-MS (m/z) 303 (M+); HRMS (EI): m/z [M+] calcd for $C_{12}H_{15}F_2N_3O_4$, 303.1024. found, 303.1025.

*2-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoro-N-phenylacetamide (**4d**)* The product (33.4 mg, 54% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 2:1) as light yellow solid. mp 126-127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.00 (s, 1H), 7.75 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 3.43 (s, 3H), 3.29 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -105.4 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 160.8 (t, *J* = 26.1 Hz), 160.6 (t, *J* = 4.0 Hz), 150.8, 143.7 (t, *J* = 9.0 Hz), 136.3, 128.9, 125.3, 120.2, 112.6 (t, *J* = 254.5 Hz), 105.8 (t, *J* = 26.1 Hz), 37.6, 27.9. EI-MS (m/z) 309 (M+); HRMS (EI): m/z [M+] calcd for $C_{14}H_{13}F_2N_3O_3$, 309.0920. found, 309.0919.

*N-Butyl-2-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetamide (**4e**)* The product (35.2 mg, 61% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 6.95 (s, 1H), 3.43 (s, 3H), 3.34 – 3.26 (m, 5H), 1.54 (p, *J* = 7.4 Hz, 2H), 1.35 (dq, *J* = 14.6, 7.3 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.0 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 162.9 (t, *J* = 29.5 Hz), 160.2 (t, *J* = 3.7 Hz), 151.0, 143.3 (t, *J* = 9.1 Hz), 112.8 (t, *J* = 253.3 Hz), 106.2 (t, *J* = 25.9 Hz), 39.5, 37.5, 31.0, 27.8, 19.8, 13.6. EI-MS (m/z) 289 (M+); HRMS (EI): m/z [M+] calcd for $C_{12}H_{17}F_2N_3O_3$, 289.1236. found, 289.1236.

*5-(1,1-Difluoro-2-oxo-2-phenylethyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**4f**)* The product (42.3 mg, 72% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as light yellow solid. mp 121-122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.8 Hz, 2H), 7.69 (s, 1H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 3.51 (s, 3H), 3.31 (s,

3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -99.9 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 188.4 (t, *J* = 31.3 Hz), 160.3 (t, *J* = 3.9 Hz), 151.2, 142.5 (t, *J* = 8.6 Hz), 134.1, 132.5, 130.1 (t, *J* = 2.8 Hz), 128.6, 115.2 (t, *J* = 254.9 Hz), 107.9 (t, *J* = 24.9 Hz), 37.7, 27.9. EI-MS (m/z) 294 (M+); HRMS (EI): m/z [M+] calcd for $C_{14}H_{12}F_2N_2O_3$, 294.0816. found, 294.0813.

5-(1,1-Difluoro-2-oxo-2-(thiophen-2-yl)ethyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione ***(4g)*** The product (31.2 mg, 52% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as light yellow solid. mp 104-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.14 (m, 1H), 7.82 (dd, *J* = 4.9Hz and 1.0 Hz, 1H), 7.69 (s, 1H), 7.24 – 7.20 (m, 1H), 3.51 (s, 3H), 3.31 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -101.4 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 181.3 (t, *J* = 32.2 Hz), 160.3 (t, *J* = 3.9 Hz), 151.2, 142.8 (t, *J* = 8.6 Hz), 137.9 (t, *J* = 2.9 Hz), 136.6, 136.3 (t, *J* = 5.4 Hz), 128.7, 114.8 (t, *J* = 254.6 Hz), 107.4 (t, *J* = 25.1 Hz), 37.7, 27.9. EI-MS (m/z) 300 (M+); HRMS (EI): m/z [M+] calcd for $C_{12}H_{10}F_2N_2O_3S$, 300.0369. found, 300.0375.

5-(Difluoro(phenylsulfonyl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione ***(4h)*** The product (50.8 mg, 77%) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as light yellow solid. mp 174-175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.7 Hz, 2H), 7.78 (t, *J* = 7.5 Hz, 1H), 7.73 (s, 1H), 7.64 (t, *J* = 7.8 Hz, 2H), 3.52 (s, 3H), 3.35 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -99.5 (s). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 158.2, 150.8, 146.8 (t, *J* = 8.4 Hz), 135.4, 132.5, 130.9, 129.3, 120.5 (t, *J* = 289.9 Hz), 100.0 (t, *J* = 22.5 Hz), 38.0, 28.2. EI-MS (m/z) 330 (M+); HRMS (EI): m/z [M+] calcd for $C_{13}H_{12}F_2N_2O_4S$, 330.0484. found, 330.0486.

Diethyl ((1,3-dimethyl-1H-indol-2-yl)difluoromethyl)phosphonate ***(4i)*** The product (50.8 mg, 77% yield) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 4:1) as light yellow oil . ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 1H), 7.33 (d, *J* = 6.4 Hz, 2H), 7.15 (m, 1H), 4.32 – 4.07 (m, 4H), 3.89 (s, 3H), 2.46 (q, *J* = 3.2 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 6H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.5 (s, 1F), -106.7 (s, 1F). ^{13}C{1H} NMR (126 MHz, $CDCl_3$) δ 138.2, 127.6, 124.6 (td, *J* = 25.8 Hz and 13.5 Hz), 123.7, 119.6, 119.4, 117.3 (td, *J* = 264.4 Hz and 226.0 Hz), 114.6 (td, *J* = 7.7 Hz and 4.2 Hz), 109.5, 64.8, 64.7, 31.7, 16.4, 16.3, 9.2. EI-MS (m/z) 331 (M+); HRMS (EI): m/z [M+] calcd for $C_{15}H_{20}F_2NO_3P$, 331.1143. found, 331.1144.

4-(1,1-difluoro-2-oxo-2-phenylethyl)-6-phenylpyridazin-3(2H)-one ***(4j)*** The product (45.6 mg, 70%) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as white solid. mp 167-168 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.81 – 7.72 (m, 3H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.43 (m, 5H), 6.99 (d, *J* = 9.9 Hz, 1H). ^{19}F NMR (471 MHz,

$CDCl_3$) δ -89.8 (s). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$) δ182.11 (t, *J* = 29.2 Hz), 158.3, 145.6, 133.9, 133.4, 132.2, 132.12, 131.5, 130.5, 129.3, 129.1, 128.7, 126.3, 112.9 (t, *J* = 270.3 Hz). EI-MS (m/z) 326 (M+); HRMS (EI): m/z [M+] calcd for $C_{18}H_{12}F_2N_2O_2$, 326.0861. found, 326.0865.

*3-(Difluoro(phenylsulfonyl)methyl)-2,6-dimethoxypyridine (**4k**)* The product (42.4 mg, 64%) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 3:1) as white solid. mp 161-162 ^{0}C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 – 7.93 (m, 2H), 7.79 – 7.68 (m, 2H), 7.60 (t, *J* = 7.9 Hz, 2H), 6.39 (dt, *J* = 8.4, 1.0 Hz, 1H), 3.96 (s, 3H), 3.86 (s, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -98.4 (s). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$) δ 165.7, 161.5, 141.8 (t, *J* = 6.7 Hz), 134.9, 133.6, 130.8, 129.5, 122.1 (t, *J* = 298.5 Hz), 101.9, 100.1 (t, *J* = 23.4 Hz), 53.9, 53.8. EI-MS (m/z) 329 (M+); HRMS (EI): m/z [M+] calcd for $C_{14}H_{13}F_2NO_4S$, 329.0533. found, 329.0540.

*Ethyl 2,2-difluoro-4,4-diphenylbut-3-enoate (**7**)* The product (38.2 mg, 63%) was obtained through silica gel chromatography (Petroleum ether/Ethyl acetate = 15:1) as light yellow liquid. Known compound.[9s] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.20 (m, 10H), 6.28 (t, *J* = 11.7 Hz, 1H), 3.92 (q, *J* = 7.2 Hz, 2H), 1.18 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (471 MHz, $CDCl_3$) δ -90.97 (d, *J* = 11.8Hz). $^{13}C\{1H\}$ NMR (126 MHz, $CDCl_3$) δ 163.4 (t, *J* = 34.0 Hz), 150.9 (t, *J* = 11.2 Hz), 140.4, 137.0, 129.8 (t, *J* = 1.9 Hz), 129.0, 128.5, 128.3, 127.9, 127.8, 119.4 (t, *J* =28.4 Hz), 112.5 (t, *J* = 246.2 Hz), 62.7, 13.6. EI-MS (m/z) 302 (M+); HRMS (EI): m/z [M+] calcd for $C_{18}H_{16}F_2O_2$, 302.1114. found, 302.1113.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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