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Visible-Light-Induced Direct Difluoroalkylation of Uracils, Pyridinones, and Coumarins

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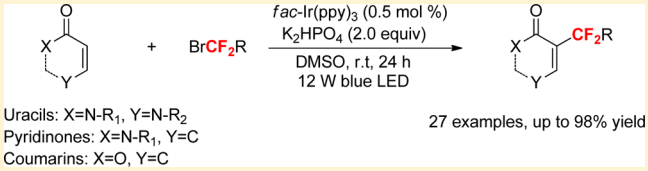
Supporting Information

ABSTRACT: An efficient and general method for the synthesis of difluoroalkylated uracils, pyridinones, and coumarins through visible-light-induced reaction with commercial materials is developed. The strategy proceeds with high efficiency under mild reaction conditions and shows excellent functional group compatibility, even toward bromide and hydroxyl group, thus demonstrates high potent application in a late-stage fluoroalkylation. Moreover, the difluoroalkylated products can be further transformed to a diverse variety of difluoroalkylated heterocycles, including molecules of potential biological activity.



INTRODUCTION

Uracils,[1] pyridinones,[2] and coumarins[3] are important scaffolds in pharmaceutical and life sciences. These scaffolds are useful building blocks and display various biological activities. For instance, 5-fluorouracil and its derivatives are popular antimetabolic drugs used in a clinical setting.[4] Trifluridine (TFT) is an anti-herpesvirus antiviral drug.[5] Substituted pyridinones and coumarins also play a valuable role in medicinal chemistry (Figure 1).[6]

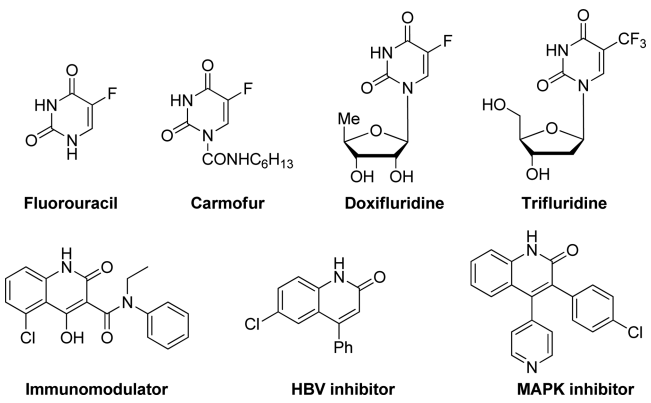


Figure 1. Examples of bioactive uracils and pyridinones.

Molecules containing fluorine atom(s) regularly exhibit beneficial effects in pharmaceutics.[7] Recently, the difluoromethylene (CF_2) group has attracted broad attention because it is considered a bioisostere of the oxygen atom and carbonyl groups and can modulate the pK_a value of neighboring functional groups such as amines.[8] To date, however, owing to a lack of general and efficient methods to access difluoroalkylated uracil, pyridinones, and coumarins, fewer studies have been made in the construction of such kinds of difluoroalkylated structures. Conceptually, the introduction of a difluoromethylene group (CF_2) onto uracils, pyridinones, and coumarins would open a good possibility toward discovering some interesting new biologically active molecules due to the unique properties of difluoromethylene. Even though a copper-catalyzed difluoroacetylation of enamides has been reported recently,[9a] the relatively high reaction temperature (80 °C) and requirement of protection of the hydroxyl and amide of this method restrict its wide application in life science. From the point of view of synthetic simplicity and convenience, the preparation of difluoroalkylated uracils, pyridinones, and coumarins under mild reaction conditions (room temperature) without additional protection and deprotection steps is an attractive alternative. As visible-light-induced photoredox-catalyzed reactions feature mild reaction conditions, high reaction efficiency, and broad substrate scope,[10] several important studies of visible-light-induced difluoroalkylation reactions were reported.[11] We envisioned the feasibility of direct difluoroalkylation of uracil, pyridinones, and coumarins and their structural variants through such a strategy.

Herein, we demonstrate a visible-light-induced difluoroalkylation of uracils, pyridinones, and coumarins. The significant advantages of this method are high efficiency, mild reaction conditions, and synthetic simplicity without protection and deprotection of hydroxyl and amine, thus providing a facile route for application in drug discovery and development.

RESULTS AND DISCUSSION

We initially probed the difluoromethylation of 1,3-dimethyluracil **1a** with ethyl bromodifluoroacetate ($BrCF_2CO_2Et$, **2a**) mediated by a variety of different photoredox catalysts. While most [Ru] sources provided no detectable difluoroalkylated product (Table 1, entries 1 and 2), *fac*-Ir(ppy)$_3$ promoted the desired reaction to afford a moderate yield of **3a** with K_2CO_3

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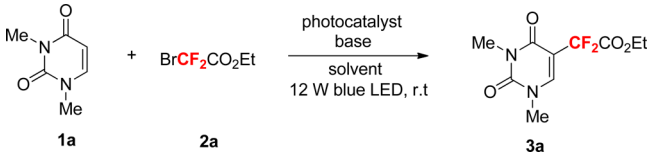
Table 1. Representative Results for Optimization of Visible-Light-Mediated Reaction of 1a and 2a[a,b]



entry	photocatalyst (mol %)	base (equiv)	solvent	3a, yield (%)
1	$Ru(bpy)_3Cl_2$ (1)	K_2CO_3 (2)	DCE	NR
2	$Ru(bpy)_3(PF_6)$ (1)	K_2CO_3 (2)	DCE	6
3	*fac*-Ir(ppy)$_3$ (1)	K_2CO_3 (2)	DCE	56
4	$Ir(ppy)_2(dtbbpy)(PF_6)$ (1)	K_2CO_3 (2)	DCE	NR
5	*fac*-Ir(ppy)$_3$ (1)	K_2CO_3 (2)	DMF	15
6	*fac*-Ir(ppy)$_3$ (1)	K_2CO_3 (2)	DMSO	80 (75)
7[c]	*fac*-Ir(ppy)$_3$ (1)	K_2CO_3 (2)	toluene	com
8	*fac*-Ir(ppy)$_3$ (1)	K_2CO_3 (2)	dioxane	50
9	*fac*-Ir(ppy)$_3$ (1)	K_2CO_3 (2)	diglyme	26
10	*fac*-Ir(ppy)$_3$ (1)	Na_2CO_3 (2)	DMSO	97
11	*fac*-Ir(ppy)$_3$ (1)	K_3PO_4 (2)	DMSO	81
12	*fac*-Ir(ppy)$_3$ (1)	Cs_2CO_3 (2)	DMSO	41
13	*fac*-Ir(ppy)$_3$ (1)	K_2HPO_4 (2)	DMSO	99 (98)
14[d]	*fac*-Ir(ppy)$_3$ (1)	K_2HPO_4 (2)	DMSO	89
15[d,e]	*fac*-Ir(ppy)$_3$ (1)	K_2HPO_4 (2)	DMSO	99
16[f]	*fac*-Ir(ppy)$_3$ (0.5)	K_2HPO_4 (2)	DMSO	99 (98)
17[f]	*fac*-Ir(ppy)$_3$ (0.5)	K_2HPO_4 (1)	DMSO	86
18[f]	*fac*-Ir(ppy)$_3$ (0.5)	none	DMSO	33
19[f]	none	K_2HPO_4 (2)	DMSO	NR
20[f,g]	*fac*-Ir(ppy)$_3$ (0.5)	K_2HPO_4 (2)	DMSO	NR

[a]Reaction conditions (unless otherwise specified): **1a** (0.2 mmol, 1.0 equiv), **2a** (0.6 mmol, 3.0 equiv), anhydrous solvent (1.5 mL), rt under Ar for 8 h. [b]Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard, and the number within parentheses represents the yield of the isolated product. [c]Com = complexity. [d]**1a** (0.2 mmol, 1.0 equiv), **2a** (0.4 mmol, 2.0 equiv). [e]Reaction time was 16 h. [f]**1a** (0.4 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), DMSO (3.0 mL), rt for 24 h. [g]Reaction performed without light.

(2.0 equiv) in DCE at room temperature under blue LED irradiation for 8 h (Table 1, entry 3). To improve the reaction efficiency, a series of reaction media were screened (Table 1, entries 5–9). DMF and dioxane were less efficient compared to DCE. The reaction was complicated when toluene and diglyme were used because reactions occurred between solvent and **2a** (Table 1, entries 7 and 9). A substantial improvement in the yield (i.e., isolated yield of 75%, entry 6) was observed when the solvent was switched to DMSO. Furthermore, a variety of different bases were screened for this reaction (Table 1, entries 10–13); stronger bases, such Cs_2CO_3, were found to be less effective. K_2HPO_4 was the best choice and afforded **3a** in 99% yield (Table 1, entry 13). The yield decreased to 89% when 2.0 equiv of **2a** was used (entry 14), and a quantitative yield was obtained when the reaction time was prolonged to 16 h (entry 15). To our delight, a comparable yield (98% isolated yield) was obtained by prolonging the reaction time to 24 h with the utilization of 0.5 mol % of Ir(ppy)$_3$ (entry 16). Only 86% yield was obtained when 1.0 equiv of K_2HPO_4 used (entry 17). As a control, only 33% yield of **3a** was obtained without the use of base, and no desired product was observed in the absence of *fac*-Ir(ppy)$_3$ or light, which indicates that a photoredox catalysis process was involved in the reaction (Table 1, entries 18–20).

With the optimum reaction conditions in hand, we investigated the scope of this visible-light-induced difluoroalkylation with diverse protected and unprotected uracils, and the results are summarized in Scheme 1. It was found that a variety of uracils can be successfully difluoroalkylated to the desired products in moderate to good yields. Uracil without protecting groups affords nearly the same yield as that of 1,3-dimethyluracil (**3b**), which indicates that the active amide group has no influence on the reaction efficiency. Various functional groups, such as methyl, ester, trifluoromethyl, and amino groups, were all well-tolerated and afforded the desired products in good to excellent yields (**3c–f**). Difluorobromoacetate amides can also react well in this reaction though are less reactive than **2a** (**3g**). Other electrophilic difluoroalkylation reagents such as $BrCF_2CF_2Br$ and 5-(bromodifluoromethyl)-3-phenyl-1,2,4-oxadiazole were less efficient, and only a moderate yield could be obtained (**3h**, **3i**). The yield of **3h** improved to 61% when CH_3CN was used as solvent. Uracil nucleosides and their structural variants play crucial roles in a variety of physiological and pathological processes. To date, most reported fluoroalkylation modifications to synthesize fluoroalkylated nucleosides have required the use of protecting groups on the carbohydrate component to deactivate the inherently reactive hydroxyl groups on the sugar ring. Given that carbon-free radicals are unreactive to hydroxyl and active hydrogen in lactam, we assume that this new site introduction of CF_2R moiety applied to unprotected uracil nucleosides could afford a straightforward and practical access to the unstudied difluoroalkylated nucleosides. To our delight, biologically active nucleosides, such as uridine and deoxyuridine, were successfully subjected to this simple protocol to access their difluoromethylated derivatives with high regioselectivity and yields without protection on sugar rings. We next evaluated the difluoromethylation of a diverse set of uridine and deoxyuridine and give the product in moderate to excellent yields (**3j–p**). Moreover, we conducted a large-scale reaction, and the results revealed that our strategy was effective on a gram scale (**3j**,**n**,**o**), which demonstrates the synthetic utility of the protocol.

Although 2-pyridinones and coumarins were important heterocyclic motifs found in numerous bioactive molecules, methods for introducing a difluoromethylene group to these structures are limited.[12] Therefore, the reaction of **2a** with 2-pyridinones and coumarins was also examined (Scheme 2). 2-Quinolinone with or without protecting groups furnished the corresponding product in good yield (**5a**,**b**). It should point out that bromo can also be tolerated in the reaction conditions. Therefore, a difluoromethylene analogue of fluorescent marker **5c** can be prepared in one step with high efficiency.[13] The extension of this method to 1-methyl-2-pyridone also led to the corresponding product in moderate yield. For 6-(trifluoromethyl)-2(1*H*)-pyridinone, the (dialkoxycarbonyl)difluoromethyl group was added to the substrate, and a yield of 34% was obtained. We next turned our attention to coumarins. Unsurprisingly, good to excellent yields (**5f–j**) can be obtained with excellent functional group compatibility even toward hydroxyl (**5i**). Butopyronoxyl was also a suitable reaction partner and afforded the corresponding product in 65% yields (**5k**). Moreover, a 4 mmol scale reaction was performed to demonstrate the synthetic utility, and a slightly improved yield (70%) was obtained (**5f**).

On the basis of previous reports,[11] a plausible reaction mechanism is shown in Scheme 3. First, irradiation with visible light excites Ir(ppy)$_3$ into a strong reductive species (i.e.,

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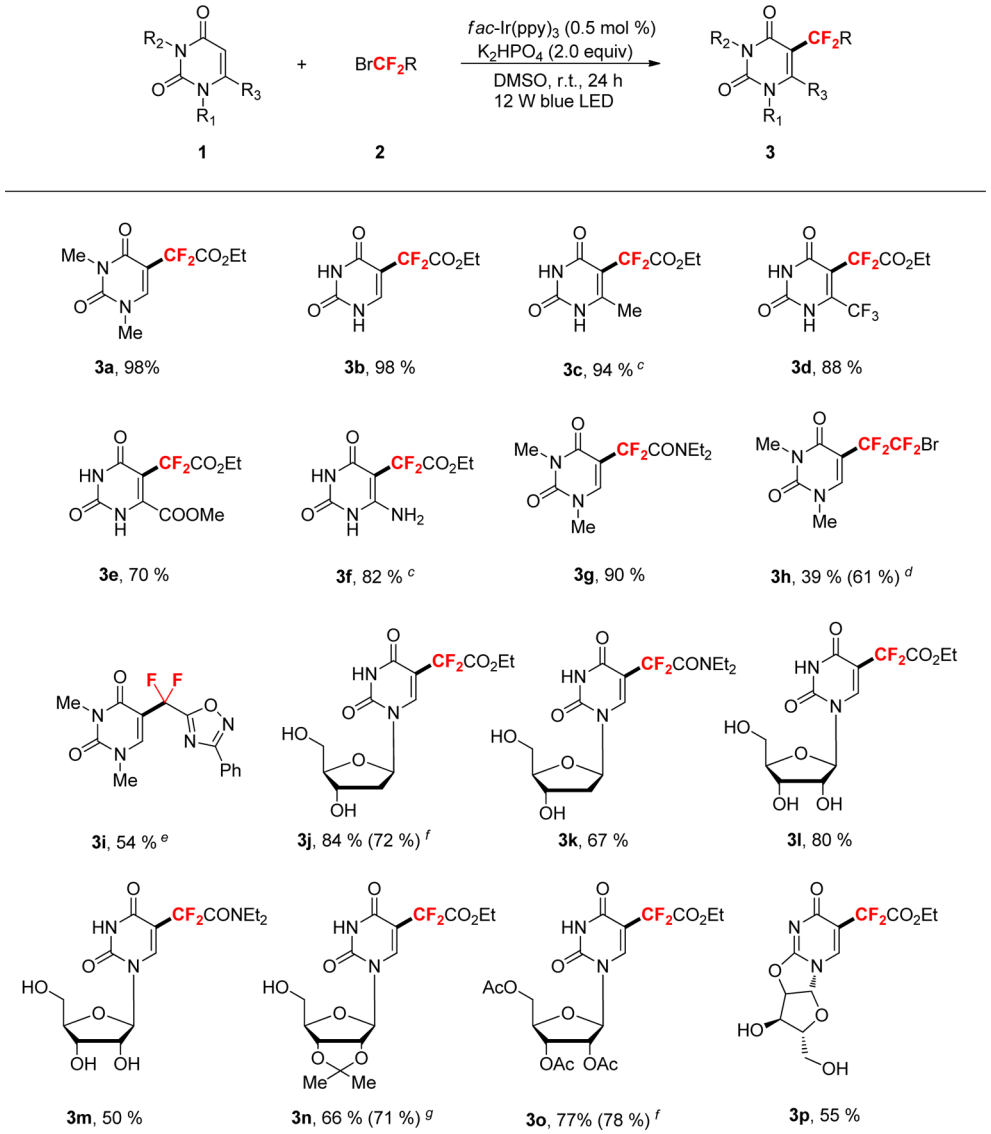
Scheme 1. Direct Difluoroalkylation of Uracils and Uracil Nucleosides[a,b]



[a]Reaction conditions (unless otherwise specified): **1** (0.4 mmol, 1.0 equiv), **2** (0.8 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.002 mmol, 0.5 mol %), K_2HPO_4 (0.8 mmol, 2.0 equiv) in anhydrous DMSO (3.0 mL), rt under Ar for 24 h. [b]Yield of isolated product. [c]1.5 equiv of K_2HPO_4 was used. [d]Reaction conditions: **1** (0.4 mmol, 1.0 equiv), **2c** (1.2 mmol, 3.0 equiv), *fac*-Ir(ppy)$_3$ (0.004 mmol, 1.0 mol %), K_2CO_3 (0.6 mmol, 1.5 equiv) in anhydrous CH_3CN (6.0 mL), rt for 24 h. [e]0.2 mmol scale, *fac*-Ir(ppy)$_3$ (0.0015 mmol, 0.75 mol %) was used. [f]2 mmol scale, 7.5 mL of DMSO, for 24 h. [g]1.2 mmol scale, 9 mL of DMSO, for 36 h.

*Ir(ppy)$_3$) that perform a single-electron-transfer (SET) process to generate $^{\bullet}CF_2R$ from $BrCF_2R$ (**2**). Subsequent regioselective addition of $^{\bullet}CF_2R$ to uracils (**1**) led to the carbon−radical intermediate (**A**), which are further oxidized to cation species (**B**) via a SET process with strong oxidant IVIr(ppy)$_3$. Finally, deprotonation of **B** with base could afford the corresponding difluoroalkylated product (**3**).

CONCLUSION

In summary, we have reported an efficient and general method for the synthesis of difluoroalkylation of uracils, pyridinones, and coumarins using a visible-light-induced reaction of difluoroalkyl bromides with uracils, pyridinones, and coumarins. The notable features of these reactions include their mild reaction conditions, synthetic simplicity, and excellent functional group compatibility. Further studies to uncover the biological activity of these compounds are currently underway in our laboratory.

EXPERIMENTAL SECTION

General Information. ^1H NMR and ^{13}C NMR spectra are reported relative to the chemical shift of tetramethylsilane (TMS). For ^{19}F NMR, $CFCl_3$ served as the outside standard and low field is positive. Chemical shifts (δ) are reported in ppm and coupling constants (J) in hertz (Hz). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. NMR yield was determined by ^{19}F NMR using fluorobenzene as an internal standard before the reaction was worked up. For HRMS (EI) measurements, the mass analyzer is TOF. For HRMS (ESI) measurements, the mass analyzer is FT-ICR.

Materials. All reagents were used as received from commercial sources. Blue LEDs (460−470 nm) were purchased from an online merchant. All reagents were weighed and handled in air and refilled under an inert atmosphere of Ar at room temperature. DMF and

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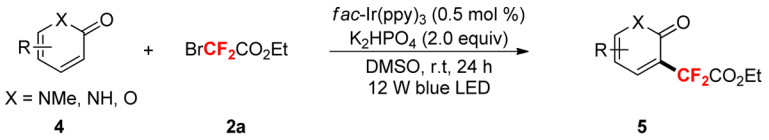
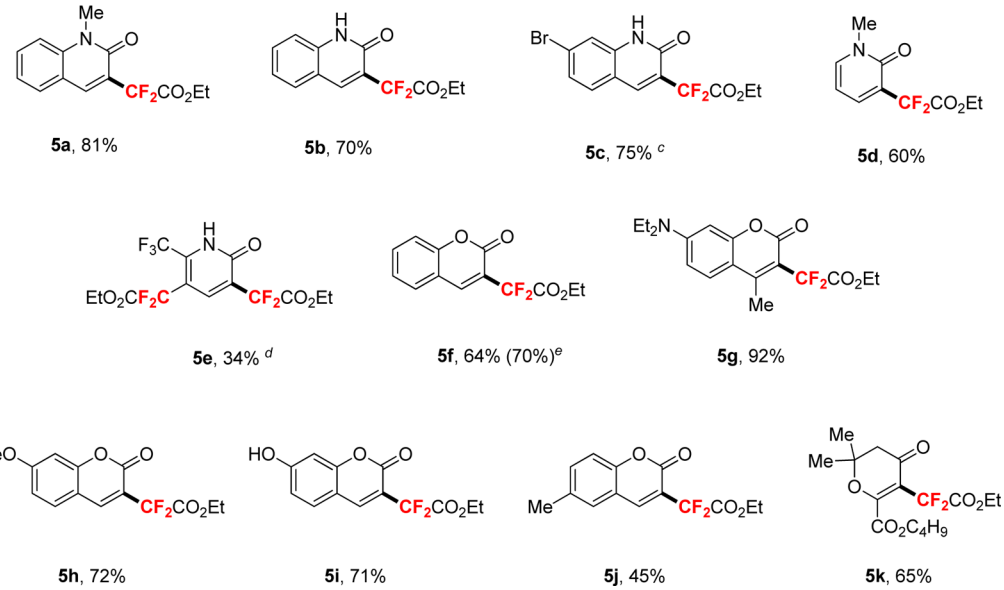
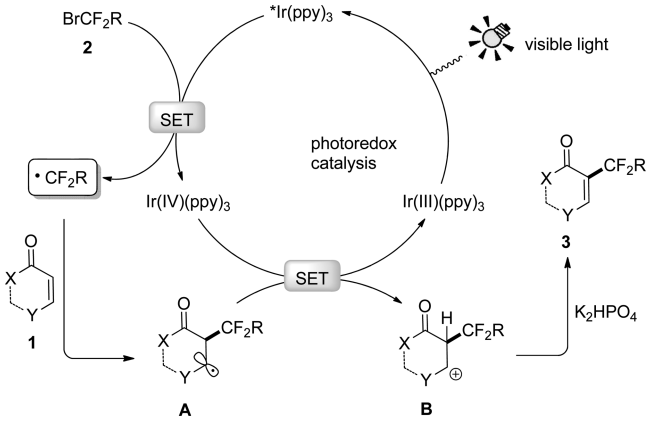
Scheme 2. Representative Results for Optimization of Visible-Light-Mediated Reaction of 4 and 2a[a]





[a]Reaction conditions (unless otherwise specified): **4** (0.40 mmol, 1.0 equiv), **2a** (0.8 mmol, 2.0 equiv), *fac*-Ir(ppy)$_3$ (0.5 mol %), K_2HPO_4 (0.80 mmol, 2.0 equiv) in anhydrous DMSO (3 mL), rt for 24 h. [b]Yield of isolated product. [c]0.2 mmol scale. [d]Ir(ppy)$_3$ (1 mol %) was used. [e]4 mmol scale, 20 mL of DMSO, for 48 h.

Scheme 3. Proposed Reaction Mechanism



DMSO were distilled under reduced pressure from CaH_2. Toluene and 1,4-dioxane was distilled from sodium and benzophenone immediately before use.

General Procedure for the Direct Difluoroalkylation of Uracils, Pyridinones, and Coumarins. To a 25 mL Schlenk tube equipped with a Teflon septum were added *fac*-Ir(PPy)$_3$ (1.3 mg, 0.5 mol %), K_2HPO_4 (140 mg, 2.0 equiv), and **1** or **4** (0.40 mmol, 1.0 equiv) under Ar, followed by DMSO (3 mL) with stirring. Compound **2** (0.80 mmol, 2.0 equiv) was subsequently added. The reaction was then irradiated with a 12 W blue LED (460 −470 nm). After being stirred for 24 h, the reaction mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography to provide pure product.

*Ethyl 2-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetate (**3a**).* The product (103 mg, 98% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:1) as a white solid: R_f = 0.65 (PE/EA = 1:1); mp 80.5−82.1 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 8.12 (s, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.52 (s, 3H), 3.22 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ 104.4 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (t, J = 33.0 Hz), 160.2 (t, J = 4.3 Hz), 151.0, 142.7 (dt, J = 8.2 Hz, 2.9 Hz), 111.0 (t, J = 248.2 Hz), 106.8 (tm, J = 25.0 Hz), 63.3, 37.6, 27.7, 13.7; MS (EI) m/z 262 (M^+), 189 (100), 132, 91; HRMS (EI) calcd for $C_{10}H_{12}N_2O_4F_2$ 262.0765, found 262.0763; IR (thin film) ν_{max} 3080, 1775, 1716, 1670, 1489 cm^{-1}.

*Ethyl 2-(2,4-Dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetate (**3b**).*[9b] The product (92 mg, 98% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:2) as a white solid: R_f = 0.21 (PE/EA = 1:1); mp 215.2−216.6 °C (lit.[9b] mp 211 °C); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.38 (s, 2H), 7.97 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ 104.7 (s, 2F); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.2 (t, J = 30.3 Hz), 162.0 (t, J = 4.3 Hz), 151.1, 142.5 (t, J = 8.0 Hz), 112.5 (t, J = 245.3 Hz), 107.6 (t, J = 25.0 Hz), 63.6, 14.1; MS (EI) m/z 234 (M^+), 161 (100), 118, 91; HRMS (EI) calcd for $C_8H_8N_2O_4F_2$ 234.0452, found 234.0445; IR (thin film) ν_{max} 3111, 3021, 1760, 1662, 1449 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(6-methyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acetate (**3c**).* K_2HPO_4 (1.5 equiv) was used. The product (93 mg, 94% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:1) as a white solid: R_f = 0.46 (PE/EA = 1:1); mp 239.0−240.1 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 4.28 (q, J = 7.2 Hz, 2H), 2.44 (t, J = 3.0 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, acetone-d_6) δ 97.2 (q, J = 3.2 Hz, 2F); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.5 (t, J = 33.0 Hz,), 161.6 (t, J = 5.2 Hz), 155.7, 149.4, 113.2 (t, J = 244.4 Hz), 103.6, 62.2, 16.6 (t, J = 5.1 Hz), 13.1; MS (EI) m/z 248 (M^+), 175 (100), 156, 132; HRMS

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(EI) calcd for $C_9H_{10}N_2F_2O_4$ 248.0609, found 248.0603; IR (thin film) ν_{max} 3243, 2955, 1755, 1732, 1659 cm^{-1}.

*Ethyl 2-(2,4-Dioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetate (**3d**).* The product (106 mg, 88% yield) was purified by silica chromatography (petroleum ether/ethyl acetate = 3:1) as a white solid: R_f = 0.24 (PE/EA = 1:1); mp 209.5−211.1 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.98 (s, 2H), 4.31 (q, J = 7.2 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ.-63.4 (t, J = 20.5 Hz, 3F), −101.6 (q, J = 20.5 Hz, 2F); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.5 (t, J = 32.1 Hz), 162.4 (t, J = 5.3 Hz), 149.1, 142.8 (q, J = 38.2 Hz), 120.0 (q, J = 276.0 Hz), 111.5 (t, J = 248.2 Hz), 107.8 (t, J = 23.6 Hz), 63.6, 13.9; MS (EI): m/z 302 (M^+), 257, 230 (100), 186; HRMS (EI): calcd for $C_9H_7N_2O_4F_5$ 302.0326, found 302.0328; IR (thin film) ν_{max} 3135, 3024, 1784, 1741, 1674 cm^{-1}.

*Methyl 5-(2-Ethoxy-1,1-difluoro-2-oxoethyl)-2,6-dioxo-1,2,3,6-tetrahydropyrimidine-4-carboxylate (**3e**).* The product (82 mg, 70% yield) was purified by silica chromatography (petroleum ether/ethyl acetate = 1:1) as a pale yellow solid: R_f = 0.49 (PE/EA = 2:3); mp 215.5−217.2 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.69 (s, 2H), 4.30 (q, J = 7.2 Hz, 2H), 3.93 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −101.9 (s, 2F); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.6, 162.2 (t, J = 4.8 Hz), 161.8, 149.9, 146.2 (t, J = 3.1 Hz), 112.1 (t, J = 246.6 Hz), 104.4 (t, J = 24.7 Hz), 63.7, 54.3, 14.0; MS (EI) m/z 292 (M^+), 233, 219 (100), 205, 185, 148; HRMS (EI) calcd for $C_{10}H_{10}N_2O_6F_2$ 292.0507, found 292.0510; IR (thin film) ν_{max} 3240, 1774, 1733, 1683 cm^{-1}.

*Ethyl 2-(6-Amino-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-2,2-difluoroacetate (**3f**).* The product (82 mg, 82%) was purified by silica gel chromatography (ethyl acetate (100%)) as a white solid: R_f = 0.33 (EA); mp > 300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 10.88 (s, 1H), 9.18 (s, 1H), 7.59 (s, 1H), 4.16 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ 94.7 (d, J = 17.7 Hz, 2F). ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 165.2, 162.6, 158.5, 149.0, 86.8, 60.6, 13.8; (ESI) m/z 250.1 (M^+ + 1); HRMS (ESI) calcd for $C_8H_{10}O_4N_3F_2$ 250.0634, found 250.0634; IR (thin film) ν_{max} 3419, 3006, 1750, 1731, 1683 cm^{-1}.

*2-(1,3-Dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-N,N-diethyl-2,2-difluoroacetamide (**3g**).* The product (104 mg, 90% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 2:1) as a white solid: R_f = 0.42 (PE/EA = 1:1); mp 67.5−69.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 3.59 (q, J = 7.1 Hz, 2H), 3.42 (s, 3H), 3.40 (q, J = 7.2 Hz, 2H), 3.30 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −100.1 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2 (t, J = 29.2 Hz), 160.1 (t, J = 3.5 Hz), 151.2, 141.5 (t, J = 9.4 Hz), 115.4 (t, J = 255.1 Hz), 108.5 (t, J = 24.9 Hz), 42.4, 42.2 (t, J = 6.4 Hz), 37.4, 27.7, 14.3, 12.1; MS (EI) m/z 289 (M^+), 189, 100 (100); HRMS (EI) calcd for $C_{12}H_{17}O_3N_3F_2$ 289.1238, found 289.1236; IR (thin film) ν_{max} 3099, 1720, 1667 cm^{-1}.

*5-(2-Bromo-1,1,2,2-tetrafluoroethyl)-1,3-dimethylpyrimidine-2,4-(1H,3H)-dione (**3h**).* Standard conditions, 39% yield. The reaction was performed with **1** (0.4 mmol, 1.0 equiv), $BrCF_2CF_2Br$ (1.2 mmol, 3.0 equiv), *fac*-Ir(ppy)$_3$ (0.004 mmol, 1.0 mol %), and K_2CO_3 (0.6 mmol, 1.5 equiv) in anhydrous CH_3CN (6.0 mL) for 24 h. The product (77 mg, 61% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 2:1) as a white solid: R_f = 0.60 (PE/EA = 2:1); mp 113.1−114.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 3.49 (s, 3H), 3.34 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −64.0 (t, J = 5.0 Hz), −107.0 (t, J = 5.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 150.8, 145.9 (t, J = 9.4 Hz), 120.6−110.0 (m), 101.6 (t, J = 24.4 Hz), 37.8, 28.1; MS (EI) m/z 320 (M^+), 318 (M^+), 189 (100); HRMS (EI) calcd for $C_8H_7O_2N_2F_4Br$ 317.9627, found 317.9619; IR (thin film) ν_{max} 3066, 1718, 1673 cm^{-1}.

*5-(Difluoro(3-phenyl-1,2,4-oxadiazol-5-yl)methyl)-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (**3i**).* The reaction was performed on a 0.2 mmol scale with 0.75 mol % catalyst loading, and the product (36 mg, 54% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 3:1) as a white solid: R_f = 0.41 (PE/EA = 2:1); mp 119.5−121.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 2H), 7.87 (s, 1H), 7.60−7.40 (m, 3H), 3.56 (s, 3H), 3.31 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −97.5 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (t, J = 35.1 Hz), 169.0, 159.9 (t, J = 3.7 Hz), 151.0, 143.2 (t, J = 8.0 Hz), 131.7, 128.9, 127.7, 125.8, 111.1 (t, J = 242.2 Hz), 106.2 (t, J = 25.1 Hz), 37.9, 27.9; MS (EI) m/z 334 (M^+ 100), 211, 188; HRMS (EI) calcd for $C_{15}H_{12}O_3N_4F_2$ 334.0877, found 334.0884; IR (thin film) ν_{max} 3071, 1720, 1674, 1602 cm^{-1}.

*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 (**3j**).* The product (118 mg, 84% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:3) as a pale yellow syrup-like solid in 72% yield when the reaction performed at a 2 mmol scale in 7.5 mL of DMSO: R_f = 0.50 (PE/EA = 1:4); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.51 (s, 1H), 8.74 (s, 1H), 6.31 (t, J = 6.4 Hz, 1H), 4.54 (m, 1H), 4.50 (d, J = 4.0 Hz, 1H), 4.44 (t, J = 4.2 Hz, 1H), 4.29 (q, J = 6.9 Hz, 2H), 4.02 (d, J = 2.4 Hz, 1H), 3.85 (m, 2H), 2.42−2.28 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ. −102.9 (d, J = 271.1 Hz, 1F), −105.1 (d, J = 272.6 Hz, 1F); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.8 (t, J = 33.2 Hz), 160.8 (t, J = 4.5 Hz), 150.2, 141.3 (t, J = 8.0 Hz), 112.0 (t, J = 246.1 Hz), 107.8 (t, J = 24.9 Hz), 88.5, 86.4, 71.4, 63.2, 61.8, 41.5, 13.7; MS (ESI) m/z 351.1 (M^+ + H); HRMS (ESI) calcd for $C_{13}H_{17}O_7N_2F_2$ 351.0998 (M^+ + H), found 351.0996; IR (thin film) ν_{max} 3502, 3220, 3071, 1698 cm^{-1}.

*N,N-Diethyl-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)acetamide (**3k**).* The product (101 mg, 67% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:2) as a yellow syrup-like solid: R_f = 0.54 (PE/EA = 1:3); ^{1}H NMR (400 MHz, methanol-d_4) δ 8.60 (s, 1H), 6.28 (t, J = 6.4 Hz, 1H), 4.42 (m, 1H), 3.96 (q, J = 3.3 Hz, 1H), 3.85−3.70 (m, 2H), 3.65−3.50 (m, 3H), 3.42 (q, J = 7.2 Hz, 2H), 2.40−2.20 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 1.16 (t, J = 6.8 Hz, 3H); ^{19}F NMR (376 MHz, methanol-d_4) δ −98.9 (d, J = 276.7 Hz, 1F), −100.1 (d, J = 276.7 Hz, 1F); ^{13}C NMR (100 MHz, methanol-d_4) δ 163.5 (t, J = 29.6 Hz), 162.2 (t, J = 3.6 Hz), 151.6, 141.6 (t, J = 8.9 Hz), 116.1 (t, J = 251.0 Hz), 110.1 (t, J = 25.2 Hz), 89.2, 87.4, 72.0, 62.4, 58.3, 43.5(t, J = 5.2 Hz), 43.4, 14.4, 12.4; MS (ESI) m/z 378.1 (M^+ + H); HRMS (ESI) calcd for $C_{15}H_{22}O_6N_3F_2$ 378.1471 (M^+ + H), found 378.1470; IR (thin film) ν_{max} 3408, 1690, 1653 cm^{-1}.

*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 (**3l**).* The product (117 mg, 80% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:3) as a pale yellow syrup-like solid: R_f = 0.33 (EA); ^{1}H NMR (500 MHz, acetone-d_6) δ 10.54 (br, 1H), 8.81 (s, 1H), 5.97 (d, J = 3.5 Hz, 1H), 4.75 (br, 1H), 4.54 (s, 1H), 4.35 (m, 2H), 4.30 (q, J = 7.0 Hz, 2H), 4.10 (m, 1H), 3.94 (d, J = 10.5 Hz, 1H), 3.84 (d, J = 11.0 Hz, 1H), 3.31 (s, 1H), 1.27 (t, J = 7.0 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.9 (d, J = 273.0 Hz, 1F), −105.1 (d, J = 273.0 Hz, 1F); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.3 (t, J = 33.5 Hz), 161.2 (t, J = 4.2 Hz), 150.9, 141.9 (t, J = 8.0 Hz), 112.5 (t, J = 245.6 Hz), 108.4 (t, J = 24.8 Hz), 90.9, 86.1, 76.1, 70.8, 63.7, 61.5, 14.2; MS (ESI) m/z 367 (M^+ + H), 235, 161 (100), 145; HRMS (ESI) calcd for $C_{13}H_{17}O_8N_2F_2$ (M^+ + H) 367.0947, found 367.0946; IR (thin film) ν_{max} 3552, 3496, 3295, 3084, 1759, 1698 cm^{-1}.

*2-(1-((2R,3R,4S,5R)-3,4-Dihydroxy-5-(hydroxymethyl)-tetrahydrofuran-2-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-N,N-diethyl-2,2-difluoroacetamide (**3m**).* The product (79 mg, 50% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:3) as a pale yellow solid: R_f = 0.41 (EA); mp 57.6−59.3 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.3 (br, 1H), 8.59 (s, 1H), 5.96 (d, J = 4.0 Hz, 1H), 4.77 (s, 1H), 4.49 (s, 1H), 4.31 (m, 2H), 4.06 (s, 1H), 3.89 (d, J = 11.6 Hz, 1H), 3.80 (d, J = 11.6 Hz, 1H), 3.52 (q, J = 6.8 Hz, 2H), 3.52 (q, J = 7.2 Hz, 2H), 3.29 (s, 1H), 1.17 (t, J = 6.8 Hz, 3H), 1.09 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ. −98.70 (s, 1F), −98.73 (s, 1F); ^{13}C NMR (100 MHz, acetone-d_6) δ 162.0 (t, J = 28.6 Hz), 160.5, 151.0, 140.7 (t, J = 9.0 Hz), 116.1 (t, J = 251.6 Hz), 110.3 (t, J = 25.0 Hz), 90.6, 86.2, 76.0, 71.1, 61.8, 42.7(t, J = 5.4 Hz), 42.5, 14.6, 12.6; MS (ESI) m/z 394.1 (M^+ +

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H); HRMS (ESI) calcd for $C_{15}H_{22}O_7N_3F_2$ 394.1420 (M^+ + H), found 394.1416; IR (thin film) ν_{max} 3400, 3064, 1695, 1653 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(1-((2R,3R,4S,5R)-6-(hydroxymethyl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)acetate (**3n**).* The product (107 mg, 66% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 2:1) as a yellow solid in 71% yield when the reaction was performed on a 1.2 mmol scale in 9.0 mL of DMSO for 36 h: R_f = 0.30 (PE/EA = 1:1); mp 76.1−78.0 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.61 (s, 1H), 8.57 (s, 1H), 6.02 (d, J = 2.0 Hz, 1H), 5.00 (dd, J = 6.0 Hz, 2.4 Hz, 1H), 4.92 (dd, J = 6.0 Hz, 3.2 Hz, 1H), 4.32 (m, 1H), 4.30 (q, J = 7.2 Hz, 2H), 3.86 (dd, J = 12.0 Hz, 3.2 Hz, 1H), 3.86 (dd, J = 11.6 Hz, 3.6 Hz, 1H), 1.53 (s, 3H), 1.33 (s, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −104.2 (d, J = 72.8 Hz, 1F), −105.1 (d, J = 78.4 Hz, 1F); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.0 (t, J = 33.2 Hz), 161.0 (t, J = 4.5 Hz), 150.45, 142.4 (t, J = 8.0 Hz), 114.0, 112.2 (t, J = 245.9 Hz), 108.2 (t, J = 24.8 Hz), 93.6, 88.2, 85.7, 81.4, 63.5, 62.5, 27.4, 25.3, 14.0; MS (ESI) m/z 407.1 (M^+ + H); HRMS (ESI) calcd for $C_{16}H_{21}O_8N_2F_2$ 407.1260, found 407.1251; IR (thin film) ν_{max} 3412, 3213, 3073, 1702 cm^{-1}.

*(2R,3R,4R,5R)-2-(Acetoxymethyl)-5-(5-(2-ethoxy-1,1-difluoro-2-oxoethyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-tetrahydrofuran-3,4-diyl Diacetate (**3o**).* The reaction was performed on a 2.0 mmol scale. The product (766 mg, 78% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 2:1) as a yellow syrup-like solid: R_f = 0.48 (PE/EA = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.87 (s, 1H), 7.96 (s, 1H), 6.06 (d, J = 5.2 Hz, 1H), 5.34 (t, J = 5.2 Hz, 1H), 5.30 (t, J = 4.8 Hz, 1H), 4.40−4.25 (m, 5H), 2.09 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.29 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ. −103.5 (d, J = 273.7 Hz, 1F), −105.2 (d, J = 273.7 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 169.6, 169.5, 162.0 (t, J = 35.4 Hz), 159.8 (t, J = 4.0 Hz), 149.6, 139.0 (t, J = 8.2 Hz), 110.6 (t, J = 248.4 Hz), 109.0 (t, J = 25.2 Hz), 87.5, 80.3, 73.1, 69.9, 63.4, 62.7, 20.3, 20.2, 13.6; MS (ESI) m/z 493.1 (M^+ + H); HRMS calcd for $C_{19}H_{23}O_{11}N_2F_2$ (ESI) 493.1264 (M^+ + H), found 493.1256; IR (thin film) ν_{max} 3001, 1748, 1698 cm^{-1}.

*Ethyl 2,2-Difluoro-2-((2R,3R,4R,5R)-3-hydroxy-2-(hydroxymethyl)-6-oxo-3,3a,6,9a-tetrahydro-2H-furo[2′,3′:4,5]oxazolo[3,2-a]pyrimidin-7-yl)acetate (**3p**).* The product (77 mg, 55% yield) as a yellow oil was purified by silica gel chromatography (ethyl acetate/acetone =10:1): R_f = 0.28 (EA); ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (s, 1H), 6.42 (d, J = 6.0 Hz, 1H), 5.30 (d, J = 6.0 Hz, 1H), 4.54 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 4.25 (m, 1H), 3.50 (dd, J = 2.4 Hz, 1.6 Hz, 2H), 1.25 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, CD_3OD) δ −106.7 (d, J = 275.2 Hz, 1F), −109.2 (d, J = 275.2 Hz, 1F); ^{13}C NMR (100 MHz, CD_3OD) δ 171.3 164.0 (t, J = 32.6 Hz), 162.8, 138.4 (t, J = 8.3 Hz), 115.9 (t, J = 24.3 Hz), 112.7 (t, J = 247.3 Hz), 92.6, 91.9, 91.8, 77.0, 64.3, 62.5, 14.1; MS (ESI) m/z 349.1 (M^+); HRMS (ESI) calcd for $C_{13}H_{15}O_7N_2F_2$ 349.0842 (M^+ + H), found 349.0836; IR (thin film) ν_{max} 3385, 1694 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(1-methyl-2-oxo-1,2-dihydroquinolin-3-yl)-acetate (**5a**).*[12] The product (91 mg, 81% yield) as a white solid was purified by silica gel chromatography (petroleum ether/ethyl acetate = 3:1): R_f = 0.44 (PE/EA = 1:1); mp 59.8−61.2 °C (lit.[12] colorless oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.64 (t, J = 7.2 Hz, 2H), 7.37 (d, J = 8.8 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 3.67 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.5 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1 (t, J = 32.6 Hz), 159.2 (t, J = 4.4 Hz), 140.2, 137.3 (t, J = 7.1 Hz), 132.3, 130.0, 124.7 (t, J = 24.1 Hz), 122.8, 118.7, 114.2, 111.2 (t, J = 247.6 Hz), 62.9, 29.2, 13.8; IR (thin film) ν_{max} 3038, 1782, 1740, 1672 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(2-oxo-1,2-dihydroquinolin-3-yl)acetate (**5b**).* The product (75 mg, 70% yield) as a white solid was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:1): R_f = 0.43 (PE/EA = 1:2); mp 191.1−192.8 °C;^{1}H NMR (400 MHz, acetone-d_6) δ 11.24 (s, 1H), 8.38 (s, 1H), 7.89 (s, J = 8.2 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.33 (t, J = 7.8 Hz, 1H), 4.31 (q, J = 7.2 Hz, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −106.4 (s, 2F); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.4 (t, J = 32.8 Hz), 160.2, 140.5, 139.2, 133.2, 130.3, 126.4 (t, J = 1.9 Hz), 123.7, 119.0, 116.3, 112.4 (t, J = 245.3 Hz), 63.4, 14.1; MS (EI) m/z 267 (M^+), 194 (100), 272 (95); HRMS (EI) calcd for $C_{13}H_{11}NO_3F_2$ 267.0707, found 267.0711; IR (thin film) ν_{max} 3165, 1754, 1667 cm^{-1}.

*Ethyl 2-(7-Bromo-2-oxo-1,2-dihydroquinolin-3-yl)-2,2-difluoroacetate (**5c**).* The reaction was performed on a 0.2 mmol scale and was carried out with $Ir(PPy)_3$ (0.5 mol %) and 3 mL of DMSO. The product (52 mg, 75% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:1) as a white solid: R_f = 0.81 (EA); mp 218.5−219.5 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 11.30 (s, 1H), 8.39 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 1.6 Hz, 1H), 7.47 (dd, J = 8.6 Hz, 1.8 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −106.0 (s, 2F); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.2 (t, J = 32.7 Hz), 160.0 (t, J = 4.3 Hz), 141.4, 138.9 (t, J = 7.2 Hz), 132.0, 126.88, 126.86, 126.7 (t, J = 23.7 Hz), 118.9, 118.0, 112.2 (t, J = 246.0 Hz), 63.5, 14.1; MS (EI) m/z 347 (M^+), 345 (M^+), 274 (100), 272 (95); HRMS (EI) calcd for $C_{13}H_{10}NO_3F_2Br$ 344.9812, found 344.9811; IR (thin film) ν_{max} 3080, 1756, 1660 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(1-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetate (**5d**).* The product (56 mg, 60% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 1:1) as yellow oil: R_f = 0.38 (PE/EA = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.2 Hz, 1H), 7.46 (d, J = 6.4 Hz, 1H), 6.28 (t, J = 6.8 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.53 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.7 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2 (t, J = 32.8 Hz), 159.9 (t, J = 5.0 Hz), 140.9, 137.5 (t, J = 6.8 Hz), 124.0 (t, J = 4.2 Hz), 111.4 (t, J = 247.4 Hz), 104.9, 62.9, 37.3, 13.8; MS (EI) m/z 231(M^+), 158 (100); HRMS (EI) calcd for $C_{10}H_{11}NO_3F_2$ 231.0707, found 231.0704; IR (thin film) ν_{max} 3082, 1769, 1648 cm^{-1}.

*Diethyl 2,2′-(2-Oxo-6-(trifluoromethyl)-1,2-dihydropyridine-3,5-diyl)bis(2,2-difluoroacetate) (**5e**).* The product (56 mg, 34% yield) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 4:1) as a yellow oil: R_f = 0.20 (PE/EA = 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 4.37 (m, 4H), 1.34 (m, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8 (t, J = 10.5 Hz, 3F), −98.2 (q, J = 10.5 Hz, 2F), −106.4 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.04 (t, J = 34.7 Hz), 162.0 (t, J = 32.1 Hz), 160.1, 138.9 (m), 137.5 (t, J = 7.5 Hz), 120.5, 117.7, 115−107 (m), 64.1, 63.6, 13.7; MS (EI) m/z 407 (M^+), 334, 261, 260 (100), 238; HRMS (EI) calcd for $C_{14}H_{12}NO_5F_7$ 407.0604, found 407.0609; IR (thin film) ν_{max} 3093, 1783, 1764, 1680 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(2-oxo-2H-chromen-3-yl)acetate (**5f**).*[12] The product (68 mg, 64%) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10:1) as a white solid: R_f = 0.32 (PE/EA = 8:1); 70% yield when the reaction performed at a 4.0 mmol scale in 20.0 mL of DMSO for 48 h; mp 72.2−73.8 °C (lit.[12] colorless oil); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1H), 7.68−7.60 (m, 2H), 7.42−7.34 (m, 2H), 4.38 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.2 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (t, J = 32.6 Hz), 157.9 (t, J = 4.1 Hz), 154.2, 141.9 (t, J = 7.0 Hz), 133.7, 129.2, 125.2, 121.1 (t, J = 25.4 Hz), 117.4, 117.0, 110.4 (t, J = 249.5 Hz), 63.6, 13.8; IR (thin film) ν_{max} 3028, 1777, 1731 cm^{-1}.

*Ethyl 2-(7-(Diethylamino)-4-methyl-2-oxo-2H-chromen-3-yl)-2,2-difluoroacetate (**5g**).* The product (130 mg, 92%) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 10:1) as a yellow solid: R_f = 0.35 (PE/EA = 3:1); mp 64.3−66.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 9.2 Hz, 1H), 6.63 (dd, J = 8.8 Hz, 2.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 3.42 (q, J = 7.0 Hz, 4H), 2.61 (t, J = 2.8 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.0 Hz, 6H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −95.4 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5 (t, J = 32.2 Hz), 159.9 (t, J = 7.9 Hz), 155.7, 155.5, 151.6, 126.8, 113.6 (t, J = 247.2 Hz), 111.0, 109.3, 108.8, 97.1, 62.9, 44.9, 14.9 (t, J = 5.8 Hz), 13.8, 12.4; MS (EI) m/z 353 (M^+), 338, 290 (100), 236; HRMS (EI) calcd for $C_{18}H_{21}NO_4F_2$ 353.1439, found 353.1432; IR (thin film) ν_{max} 1777, 1707, 1619 cm^{-1}.

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*Ethyl 2,2-Difluoro-2-(7-methoxy-2-oxo-2H-chromen-3-yl)acetate (**5h**).* The product (86 mg, 72%) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 8:1) as a white solid: R_f = 0.52 (PE/EA = 3:1); mp 114.5−115.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.50 (d, J = 8.8 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 6.84 (s, 1H), 4.37 (q, J = 6.6 Hz, 2H), 3.89 (s, 3H), 1.34 (t, J = 6.4 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −105.6 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 162.5 (t, J = 33.0 Hz), 158.3 (t, J = 4.8 Hz), 156.3, 141.9 (t, J = 6.8 Hz), 130.2, 117.3 (t, J = 25.6 Hz), 113.5, 111.1, 110.7 (t, J = 249.0 Hz), 100.8, 63.4, 55.9, 13.8; MS (EI) m/z 298 (M^+), 225 (100); HRMS (EI) calcd for $C_{14}H_{12}O_5F_2$ 298.0653, found 298.0650; IR (thin film) ν_{max} 1771, 1712, 1619 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(7-hydroxy-2-oxo-2H-chromen-3-yl)acetate (**5i**).* The product (81 mg, 71%) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 3:1) as a white solid: R_f = 0.48 (PE/EA = 2:1); mp 137.5−139.2 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.87 (s, 1H), 8.40 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 6.98 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 6.86 (d, J = 2.4 Hz, 1H), 4.36 (q, J = 7.0 Hz, 2H), 1.34 (t, J = 7.0 Hz, 3H); ^{19}F NMR (376 MHz, acetone-d_6) δ −105.6 (s, 2F); ^{13}C NMR (100 MHz, acetone-d_6) δ 163.9, 163.0 (t, J = 33.3 Hz), 158.9 (t, J = 4.8 Hz), 157.3, 143.3 (t, J = 6.8 Hz), 132.3, 117.1 (t, J = 23.0 Hz), 114.9, 112.1 (t, J = 246.6 Hz), 114.4, 103.4, 63.9, 14.1; MS (EI) m/z 284 (M^+), 211 (100); HRMS (EI) calcd for $C_{13}H_{10}O_5F_2$ 284.0496, found 284.0498; IR (thin film) ν_{max} 3335, 1760, 1731, 1608 cm^{-1}.

*Ethyl 2,2-Difluoro-2-(6-methyl-2-oxo-2H-chromen-3-yl)acetate (**5j**).* The product (51 mg, 45%) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 20:1) as a white solid: R_f = 0.35 (PE/EA = 8:1); mp 84.0−85.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.41(s, 1H), 7.27 (d, J = 8.2 Hz, 1H), 4,39 (q, J = 7.2 Hz, 2H), 2.44(s, 3H), 1.35 (t, J = 7.2 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −106.1 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (t, J = 32.6 Hz), 158.2 (t, J = 4.5 Hz), 152.3, 141.9 (t, J = 6.8 Hz), 135.0, 134.7, 128.9, 120.8 (t, J = 25.4 Hz), 117.2, 116.6, 110.5 (t, J = 249.2 Hz), 63.5, 20.7, 13.8; MS (EI) m/z 282 (M^+), 210, 209 (100); HRMS (EI) calcd for $C_{14}H_{12}O_4F_2$ 282.0704, found 282.0701; IR (thin film) ν_{max} 3074, 1780, 1736 cm^{-1}.

*Butyl 5-(2-Ethoxy-1, 1-difluoro-2-oxoethyl)-2,2-dimethyl-4-oxo-3,4-dihydro-2H-pyran-6-carboxylate (**5k**).* The product (90 mg, 65%) was purified by silica gel chromatography (petroleum ether/ethyl acetate = 6:1) as a colorless oil: R_f = 0.62 (PE/EA = 7:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4,30 (q, J = 7.2 Hz, 2H), 4,26 (t, J = 6.4 Hz, 2H), 2.60 (s, 2H), 1.68 (m, 2H), 1.52 (s, 6H), 1.39 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ −102.5 (s, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.4 (t, J = 3.2 Hz), 162.2 (t, J = 33.2 Hz), 161.7 (t, J = 4.0 Hz), 161.5, 111.1 (t, J = 249.8 Hz), 108.4 (t, J = 22.7 Hz), 84.9, 66.8, 63.0, 46.7, 30.0, 25.6, 18.8, 13.7, 13.5; MS (EI) m/z 348 (M^+), 247, 219 (100); HRMS (EI) calcd for $C_{16}H_{22}O_6F_2$ 348.1384, found 348.1389; IR (thin film) ν_{max} 1781, 1755, 1688, 1615 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02316.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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