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Synthesis of Perfluorinated Isoquinolinediones through Visible-Light-Induced Cyclization of Alkenes

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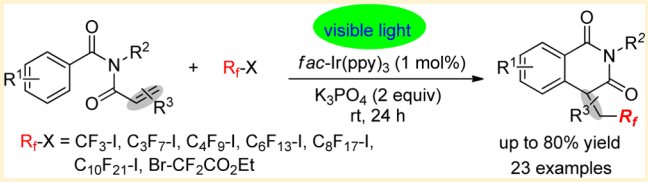
Supporting Information

ABSTRACT: A novel visible-light-induced carboperfluoroalkylation of alkenes using perfluoroalkyl iodides and bromides as R_f sources, leading to isoquinoline-1,3-diones, was developed. This method offers rapid entry to perfluorinated isoquinoline-1,3(2*H*,4*H*)-diones from *N*-alkyl-*N*-methacryloyl benzamides under mild reaction conditions, allowing for the incorporation of a wide variety of perfluorinated groups such as CF_3, C_3F_7, C_4F_9, C_6F_{13}, C_8F_{17}, $C_{10}F_{21}$, and CF_2CO_2Et.



Isoquinoline-1,3-diones are important structural motifs present in natural products and pharmaceutical compounds with certain biological properties.[1] Developing convenient methods for the synthesis of such molecules has attracted much attention from medicinal and synthetic chemists.[2] Chemical and physical properties of biologically active compounds are altered upon incorporation of the fluorinated groups. The higher solubility and lipophilicity imparted by the fluorinated groups lead to better cell membrane permeability and increased bioavailability.[3] Therefore, the introduction of fluorinated groups into potential pharmaceuticals has attracted increasing interest.[2] Recently, several examples of the incorporation of a trifluoromethyl group into an isoquinoline-1,3-dione skeleton via difunctionalization of alkenes have been disclosed (eq 1, Figure 1).[4] For example,

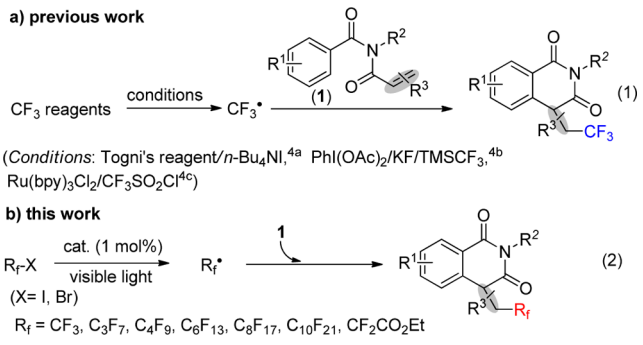


Figure 1. Synthesis of fluorinated isoquinoline-1,3-diones.

in 2013, Nevado and co-workers disclosed a pioneering aryltrifluoromethylation of alkenes, leading to trifluoromethylated isoquinoline-1,3-diones by using the combination of Togni's reagent/*n*-Bu_4NI.[4a] Very recently, Xia and co-workers reported an elegant approach to trifluoromethylated *N*-containing heterocycles by visible-light photoredox catalysis, albeit with only five examples leading to isoquinoline-1,3-diones.[4c] However, these successes have mainly been limited to the introduction of the CF_3 moiety. Therefore, developing complementary routes for the introduction of other fluorinated groups (e.g., perfluorinated groups) into the isoquinoline-1,3-dione scaffold are in high demand by synthetic chemists.

In the past few years, photoredox catalysis with visible light has aroused interest as a widely accepted method for the construction of functionalized organic molecules due to the advantages of mild conditions, high efficiency, and facile operation.[5,6] In this context, visible-light-mediated difunctionalization of alkenes to incorporate the fluorinated groups, acting as an attractive route to organofluorine compounds, has received considerable attention from synthetic chemists.[7] However, while significant progress has been made in these transformations involving various electrophilic or radical trifluoromethylating reagents (e.g., Umemoto's reagents,[7b,c,f,g,j] Togni's reagents,[7d,i] CF_3SO_2Na,[7a] and CF_3SO_2Cl[7h]), the visible-light-induced carboperfluoroalkylation of alkenes using perfluoroalkylating reagents such as perfluoroalkyl iodides or bromides is still quite rare. Usually, perfluoroalkyl iodides or bromides are commercially available reagents and, moreover, are much less expensive than other frequently encountered perfluoroalkylating reagents (e.g., R_fSO_2Cl and Togni's reagents) on a large scale.[8,9] In addition, photosensitized approaches to the generation of fluorinated radicals from inexpensive R_fI serves as a feasible and efficient method.[6,10] Thus, we hypothesized that the visible-light-induced radical carboperfluoroalkylation of methacryloyl benzamides toward perfluorinated isoquinoline-1,3-diones using R_f-I and/or R_f-Br as

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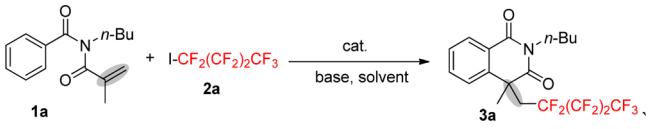
the R_f radical source is possible. With our ongoing studies on perfluoroalkylation of alkenes,[11a] we herein want to demonstrate a visible-light-induced carboperfluoroalkylation of methacryloyl benzamides using perfluoroalkyl iodides and bromides as the R_f radical precursors, thereby realizing the construction of functionalized isoquinoline-1,3-diones bearing various perfluorinated groups under benign reaction conditions (eq 2, Figure 1).

In our initial studies, the reaction between *N*-butyl-*N*-methacryloyl benzamide **1a** and perfluorobutyl iodide **2a** was applied as a model reaction to investigate the optimal conditions (Table 1). Encouragingly, a preliminary experiment

Table 1. Optimization of Reaction Conditions for 3a[a]



entry	catalyst	base	solvent	yield of **3a** (%)[b]
1	*fac*-Ir(ppy)$_3$	K_2CO_3	DMF	58
2	Ru(bpy)$_3$Cl$_2$	K_2CO_3	DMF	19
3	Ru(bpy)$_3$Cl$_2$·6H$_2$O	K_2CO_3	DMF	12
4	Eosin Y	K_2CO_3	DMF	0
5[c]	AIBN	K_2CO_3	DMF	26
6	*fac*-Ir(ppy)$_3$	K_3PO_4	DMF	80
7	*fac*-Ir(ppy)$_3$	Cs_2CO_3	DMF	40
8	*fac*-Ir(ppy)$_3$	Na_2CO_3	DMF	12
9	*fac*-Ir(ppy)$_3$	KOAc	DMF	31
10	*fac*-Ir(ppy)$_3$	K_3PO_4	dioxane	69
11	*fac*-Ir(ppy)$_3$	K_3PO_4	DMSO	15
12	*fac*-Ir(ppy)$_3$	K_3PO_4	CH_3CN	21
13	*fac*-Ir(ppy)$_3$	K_3PO_4	CH_2Cl_2	trace
14	none	K_3PO_4	dioxane	0
15[d]	*fac*-Ir(ppy)$_3$	K_3PO_4	dioxane	0

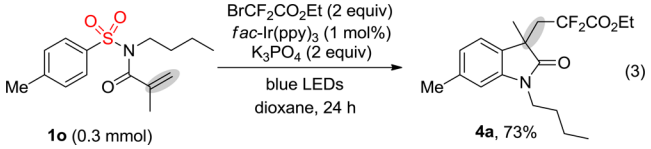
[a]Reaction conditions: **1a** (0.3 mmol), $CF_3(CF_2)_2CF_2I$ (2 equiv), photocatalyst (1 mol %), base (2 equiv), and solvent (2 mL), irradiation with a 5 W blue LED at room temperature for 24 h. DMSO = dimethyl sulfoxide. [b]Yield of the isolated product. [c]Using 2.0 equiv of AIBN at 100 °C. [d]Without visible light irradiation.

using 1 mol % *fac*-Ir(ppy)$_3$ as the photocatalyst,[6a−c] DMF (*N*,*N*-dimethylformamide) as the solvent, and K_2CO_3 as a base afforded the desired product **3a** in 58% yield under visible-light irradiation (Table 1, entry 1). Given that the catalyst usually has an important impact on photoredox catalysis, we next examined several typical photocatalysts such as Ru(bpy)$_3$Cl$_2$, Ru(bpy)$_3$Cl$_2$·6H$_2$O, and Eosin Y (entries 2−4). Nevertheless, no better results than *fac*-Ir(ppy)$_3$ were observed. In addition, we found that azodiisobutyronitrile (AIBN), an initiator generating R_f radical from perfluoroalkyl iodide R_fI in these previous reports,[11] could also promote the cyclization to form **3a**, albeit in a low yield of 26% (entry 5). Sequential screening found that the use of a base was essential for the cyclization, and K_3PO_4 proved to be the most efficient one, thereby increasing the yield to 80% (entry 6). Other inorganic bases such as Cs_2CO_3, Na_2CO_3, and KOAc led to lower yields (entries 7−9). Further screening of solvents showed that DMF remains as the best choice (entries 10−13). We also performed two control experiments and found that the cyclization reactions were completely inhibited with the removal of the Ir catalyst or light irradiation (entries 14 and 15).

With the optimized reaction conditions in hand, the substrate scope in the perfluorinated cyclization was investigated (Scheme 1). The *N*-substituents of methacryloyl benzamides proved to be important for the cyclization reaction. For example, the isopropyl, *n*-butyl, and benzyl groups on the N atom were of good reactivity under the optimal conditions, whereas a phenyl group on the N atom or unprotected methacryloyl benzamide (R^2 = H) was less efficient (Scheme 1, **3a−e**). Subsequently, we set out to investigate the effect of substituent on the benzamide moiety in the reaction. Irrespective of the electronic character of the substituted groups, a series of substituents (e.g., Me, MeO, Cl, F, and CF_3) at the 4-position of the aryl ring displayed good compatibility (**3f−j**). In addition, the cyclization of methacryloyl *m*-chlorobenzamide yielded a mixture of two regioselective products **3k** and **3k′** with moderate regioselectivity (2:1). In contrast to previously reported examples,[2h,4c] this reaction appears to be less sensitive to the steric effect of the substituent. For example, the *ortho*-methyl substituted methacryloyl benzamide **1l** was also compatible with the reaction conditions and afforded the desired **3l** in a yield of 67%. Unfortunately, sequential investigations demonstrated that the *β*-substituted olefin bearing a phenyl group was incompatible with the optimal conditions (**3m**). In addition, *mono*-substituted olefin (R^3 = H) is also a less efficient substrate for the perfluoroalkylation (**3n**). Next, we investigated the performance of other perfluoroalkyl iodides in the reaction. To our delight, a series of perfluoroalkyl iodides, such as C_3F_7I, $C_6F_{13}I$, $C_8F_{17}I$, etc., were observed to be well compatible with the perfluoroalkylation process, leading to the desired perfluorinated isoquinoline-1,3-diones in moderate to good yield (**3o−s**).

The difluoromethylene group (CF_2) serves as an intriguing structural motif that displays important functions in materials, pharmaceuticals, and agrochemical agents. Among these difluoromethylene groups, CF_2CO_2Et is very attractive due to easy modification into various CF_2-containing functional groups. Recently, the incorporation of a CF_2CO_2Et moiety into organic molecules using $BrCF_2CO_2Et$ as CF_2CO_2Et source by photoredox catalysis has attracted increasing interest.[12] With the background in mind, we sequentially examined the reactions of these *α*,*β*-unsaturated imide alkenes (**1a−b** and **1f−i**) with $BrCF_2CO_2Et$ under the aforementioned optimal conditions, thereby leading to the difluoroacetylated isoquinoline-1,3-diones. After brief screenings, the solvent switch from DMF to dioxane was observed to be more beneficial for the cyclization involving $BrCF_2CO_2Et$. To our delight, with this slight modification of reaction conditions, $BrCF_2CO_2Et$ underwent cascade radical addition/C-H cyclization to give the desired isoquinoline-1,3-diones bearing a CF_2CO_2Et moiety in moderate to good yields (Scheme 2, **3t−z**). Besides, the reaction of *meta*-substituted **1k** with $BrCF_2CO_2Et$ proceeded with excellent site control and afforded the product **3z** as the major regioisomer via the cyclization at the *para*-position of the chloro substituent.

Subsequently, we also investigated perfluorinating cyclization of conjugated tosyl amide **1o** with $BrCF_2CO_2Et$ under the above standard conditions (eq 3). Consistent with the previous findings,[3f,h,4a,b] the reaction underwent cascade perfluorobutylation/desulfonylation to give the corresponding oxindole **4a** in a yield of 73%.



To investigate the mechanism of the photoredox-catalyzed cyclization, a control experiment was performed by using the

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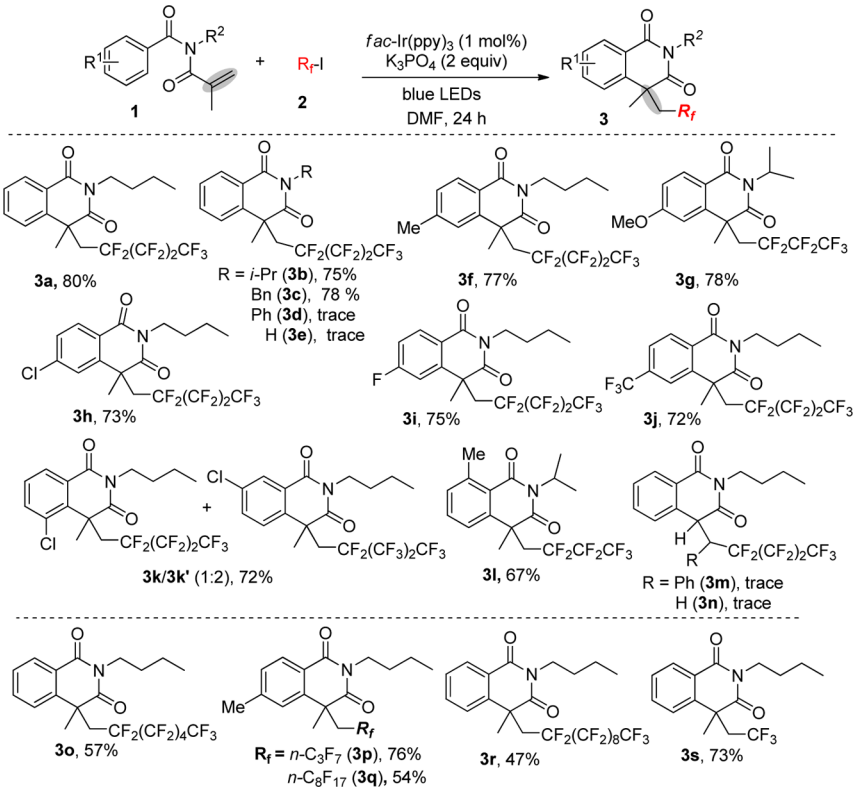
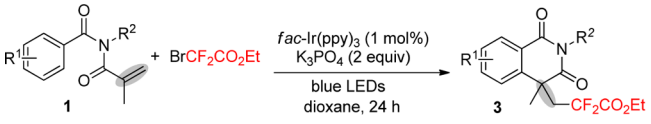
Scheme 1. Cyclization of Methacryloyl Benzamides with R_fI[a]



[a]Reaction conditions: **1** (0.3 mmol), R_fI (2 equiv), K_3PO_4 (2 equiv), *fac*-Ir(ppy)$_3$ (1 mol %), and DMF (2 mL), irradiation with a 5 W blue LED at room temperature for 24 h.

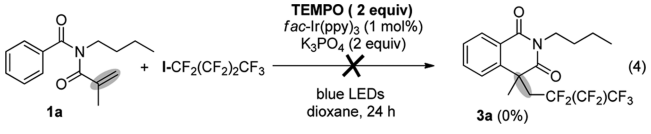
Scheme 2. Cyclization of Methacryloyl Benzamides with $BrCF_2CO_2Et$[a]



1a, R^1 = H, R^2 = *n*-Bu
1b, R^1 = H, R^2 = *i*-Pr
1f, R^1 = 4-Me, R^2 = *n*-Bu
1h, R^1 = 4-Cl, R^2 = *n*-Bu
3t, 75%
3u, 70%
3v, 67%
3w, 72%
1i, R^1 = 4-F, R^2 = *n*-Bu
1j, R^1 = 4-CF_3, R^2 = *n*-Bu
1k, R^1 = 3-Cl, R^2 = *n*-Bu
3x, 73%
3y, 69%
3z, 66%; **3z'**, <5%

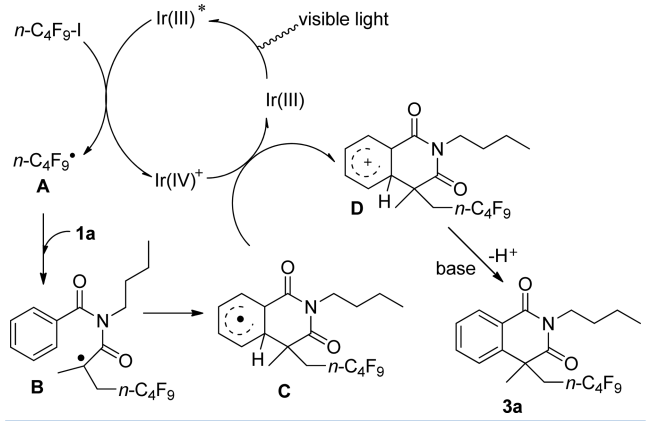
[a]Reaction conditions: **1** (0.3 mmol), $BrCF_2CO_2Et$ (2 equiv), K_3PO_4 (2 equiv), *fac*-Ir(ppy)$_3$ (1 mol %), and dioxane (2 mL), irradiation with a 5 W blue LED at room temperature for 24 h.

typical radical scavenge TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl). Under these conditions, the formation of the corresponding isoquinoline-1,3-dione **3a** was completely suppressed (eq 4), thus suggesting that the present reaction might involve a radical process.



A possible mechanism of the light-induced radical carboperfluororoalkylation was proposed as shown in Scheme 3.[4−12] First, the excited state [*fac*-Ir(III)(ppy)$_3$*] is formed under light irradiation, which is next oxidized by $CF_3(CF_2)_2CF_2$-I to generate a [*fac*-Ir(IV)(ppy)$_3$]$^+$ complex and a C_4F_9· radical species **A**. Subsequently, the C_4F_9· radical adds onto the C═C

Scheme 3. Proposed Mechanism for the Formation of 3a



bond of **1a** to form an alkyl radical **B**, followed by the cyclization on the aromatic ring of intermediate **B**, generating intermediate **C**. After the oxidation by [*fac*-Ir(IV)(ppy)$_3$]$^+$, the intermediate **C** is transformed into the cyclohexadienyl cation **D** with the concurrent regeneration of [*fac*-Ir(III)(ppy)$_3$]. Finally, the abstraction of an aryl hydrogen in intermediate **D** by base occurs, leading to the desired isoquinoline-1,3-dione **3a**.

In summary, we have developed a facile, mild, and efficient carboperfluoroalkylation reaction of alkenes, leading to isoquinoline-1,3-diones using perfluoroalkyl iodides or bromides as R_f source under light irradiation for the first time. The reaction conditions exhibit remarkable compatibility with various perfluoroalkyl halides, thereby realizing the incorporation of many perfluorinated groups such as CF_3, C_3F_7, C_4F_9, C_6F_{13}, C_8F_{17}, $C_{10}F_{21}$, and CF_2CO_2Et.

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EXPERIMENTAL SECTION

General. All manipulations of oxygen- and moisture-sensitive materials were conducted with a Schlenk technique under a nitrogen or argon atmosphere. Photoirradiation was carried out with a 5 W blue LED (light-emitting diode). Solvents were purified and dried in a standard manner. Flash column chromatography was performed using EM Silica gel 60 (300−400 mesh). Visualization was accomplished with UV light (254 nm) and/or an aqueous alkaline $KMnO_4$ solution, followed by heating. ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR spectra were recorded on a 400 or 500 MHz NMR spectrometer with trimethylsilane resonance as the internal standard. Unless otherwise noted, reagents were commercially available and were used without further purification. *N*-Alkyl-*N*-methacryloyl benzamides (**1**) were prepared according to literature procedures.[4]

General Procedure for the Synthesis of Perfluoroalkylated Isoquinoline-1,3-diones. To a mixture of methacryloyl benzamide **1** (0.3 mmol), *fac*-Ir(ppy)$_3$ (0.003 mmol, 1.0 mol %), and K_3PO_4 (0.6 mmol) in DMF (2.0 mL) was added perfluoroalkyl iodine (0.6 mmol) under a N_2 atmosphere, and then the resulting solution was stirred under 5 W blue LED irradiation at room temperature for 24 h. Then, the resulting mixture was diluted with Et_2O and washed with water and then brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 10:1 as the eluant) on silica gel to afford the corresponding perfluorinated isoquinoline-1,3-diones (products **3a**−**s**) in a yield listed in Scheme 1.

*2-Butyl-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)isoquinoline-1,3(2H,4H)-dione (**3a**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (111 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (d, J = 7.9 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.54−7.44 (m, 2H), 4.11−3.96 (m, 2H), 3.46 (dd, J = 33.6, 15.4 Hz, 1H), 2.87−2.69 (m, 1H), 1.69 (s, 3H), 1.65−1.57 (m, 2H), 1.45−1.35 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.3, 163.5, 140.7, 133.6, 129.4, 128.0, 125.7, 124.2, 120.9−103.1 (m), 43.3, 40.6, 40.4 (t, J = 20.2 Hz), 32.1, 29.6, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.1 (t, J = 9.9 Hz, 3F), −108.0 (d, $J_{F\text{-}F}$ = 273.4 Hz, 1F), −112.8 (d, $J_{F\text{-}F}$ = 274.2 Hz, 1F), −124.9 (br, 2F), −125.1 to −126.8 (m,2F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{19}F_9NO_2$ $[M + H]^+$ 464.1267, found: 464.1266.

*2-Isopropyl-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-isoquinoline-1,3(2H,4H)-dione (**3b**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (101 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (dd, J = 7.9, 1.2 Hz, 1H), 7.69−7.62 (m, 1H), 7.53−7.45 (m, 1H), 7.42 (d, J = 7.9 Hz, 1H), 5.24 (hept, J = 6.9 Hz, 1H), 3.51−3.34 (m, 1H), 2.83−2.65 (m, 1H), 1.68 (s, 3H), 1.50 (dd, J = 6.9, 2.7 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.4, 163.8, 140.6, 133.4, 129.4, 127.9, 125.6, 124.7, 118.7−105.4 (m), 45.7, 43.6, 40.5 (t, J = 20.2 Hz), 31.9, 19.3, 13.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −81.1 (t, J = 12.2 Hz, 3F), −107.7 (d, $J_{F\text{-}F}$ = 342.9 Hz, 1F), −112.8 (d, $J_{F\text{-}F}$ = 343.2 Hz, 1F), −124.9 (br, 2F), −125.0 to −126.9 (AB, $J_{F\text{-}F}$ = 419.3 Hz, 2F); HRMS m/z (ESI-TOF) calcd for $C_{18}H_{17}F_9NO_2$ $[M + H]^+$ 450.1111, found: 450.1109.

*2-Benzyl-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-isoquinoline-1,3(2H,4H)-dione (**3c**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (116 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (dd, J = 7.9, 1.2 Hz, 1H), 7.68 (td, J = 7.8, 1.4 Hz, 1H), 7.53−7.41 (m, 4H), 7.34−7.22 (m, 3H), 5.25 (q, J = 13.9 Hz, 2H), 3.49 (dd, J = 33.6, 15.4 Hz, 1H), 2.81 (ddd, J = 25.7, 15.4, 8.9 Hz, 1H), 1.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.4, 163.5, 140.6, 136.8, 133.8, 129.5, 128.7, 128.4, 128.1, 127.5, 125.8, 124.1, 119.1−115.1 (m), 77.4, 77.0, 76.7, 43.9, 43.6, 40.2(t, J = 19.7 Hz), 32.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.1 (t, J = 9.9 Hz, 3F), −107.4 (d, J = 273.3 Hz, 1F), −112.5 (d, J = 273.9 Hz, 1F), −124.9 to −127.2 (m, 2F); HRMS m/z (ESI-TOF) calcd for $C_{22}H_{17}F_9NO_2$ $[M + H]^+$ 498.1111, found: 498.1109.

*2-Butyl-4,6-dimethyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-isoquinoline-1,3(2H,4H)-dione (**3f**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (110 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 8.2 Hz, 1H), 7.17 (s, 1H), 4.05−3.91 (m, 2H), 3.39 (dd, J = 33.7, 15.1 Hz, 1H), 2.80−2.65 (m, 1H), 2.43 (s, 3H), 1.62 (s, 3H), 1.55 (dd, J = 15.3, 7.6 Hz, 2H), 1.35 (dq, J = 14.8, 7.4 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.4, 163.5, 144.5, 140.7, 129.3, 129.1, 126.0, 121.7, 118.5−105.8 (m), 43.3, 40.5 (t, J = 10.1 Hz), 32.1, 30.9, 29.6, 21.8, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.2 (t, J = 9.8 Hz, 3F), −108.0 (d, $J_{F\text{-}F}$ = 273.4 Hz, 1F), −112.8 (d, $J_{F\text{-}F}$ = 274.1 Hz, 1F), −124.9 (br, 2F), −125.1 to −126.9 (m,2F); HRMS m/z (ESI-TOF) calcd for $C_{20}H_{21}F_9NO_2$ $[M + H]^+$ 478.1424, found: 478.1427.

*4-(2,2,3,3,4,4,4-Heptafluorobutyl)-2-isopropyl-6-methoxy-4-methylisoquinoline-1,3(2H,4H)-dione (**3g**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (101 mg, 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.8 Hz, 1H), 7.00 (dd, J = 8.8, 2.4 Hz, 1H), 6.84 (d, J = 2.1 Hz, 1H), 5.22 (hept, J = 6.9 Hz, 1H), 3.91 (s, 3H), 3.49−3.31 (m, 1H), 2.76−2.60 (m, 1H), 1.66 (s, 3H), 1.48 (dd, J = 6.9, 2.0 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.5, 163.7, 142.8, 131.7, 119.5−109.8 (m), 117.7, 113.5, 111.0, 110.9, 55.6, 45.5, 43.7, 40.3 (t, J = 20.2 Hz), 32.0, 19.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −80.3 (t, J = 12.2 Hz, 3F), −108.5 (d, $J_{F\text{-}F}$ = 342.8 Hz, 1F), −113.6 (d, $J_{F\text{-}F}$ = 342.4 Hz, 1F), −127.2 to −129.1 (m, 2F); HRMS m/z (ESI-TOF) calcd for $C_{18}H_{19}F_7NO_3$ $[M + H]^+$ 430.1248, found: 430.1246.

*2-Butyl-6-chloro-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-isoquinoline-1,3(2H,4H)-dione (**3h**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (109 mg, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.25 (d, J = 8.5 Hz, 1H), 7.48 (d, J = 8.5 Hz, 1H), 7.43 (s, 1H), 4.08−3.95 (m, 2H), 3.47 (dd, J = 33.6, 15.4 Hz, 1H), 2.81−2.67 (m, 1H), 1.69 (s, 3H), 1.60 (q, J = 7.5 Hz, 2H), 1.44−1.34 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 173.6, 162.6, 142.3, 140.3, 131.0, 128.7, 125.9 (d, J = 2.4 Hz), 122.7, 118.3−105.5 (m), 43.3 (d, J = 2.6 Hz), 40.7, 40.5 (t, J = 19.7 Hz), 31.9, 29.5, 20.1, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.2 (t, J = 9.9 Hz, 3F), −108.0 (d, $J_{F\text{-}F}$ = 273.6 Hz, 1F), −112.8 (d, $J_{F\text{-}F}$ = 274.3 Hz, 1F), −124.9 (br, 2F), −125.1 to −126.9 (m, 2F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{18}ClF_9NO_2$ $[M + H]^+$ 498.0877, found: 498.0874.

*2-Butyl-6-fluoro-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-isoquinoline-1,3(2H,4H)-dione (**3i**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (108 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (dd, J = 8.8, 5.8 Hz, 1H), 7.16 (td, J = 8.7, 2.4 Hz, 1H), 7.10−7.05 (m, 1H), 4.05−3.91 (m, 2H), 3.42 (dd, J = 33.6, 15.3 Hz, 1H), 2.75−2.59 (m, 1H), 1.64 (s, 3H), 1.60−1.51 (m, 2H), 1.35 (dd, J = 15.2, 7.5 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.7, 166.0 (d, J = 205.6 Hz), 162.5, 143.7 (d, J = 10.1 Hz), 132.5 (d, J = 5.1 Hz), 130.8 (d, J = 5.1 Hz), 120.7, 116.1 (d, J = 5.1 Hz), 112.7 (d, J = 10.1 Hz), 118.2−105.7 (m), 43.5, 40.6 (t, J = 10.1 Hz), 32.0, 29.5, 20.1, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.2 (t, J = 9.4 Hz, 3F), −103.5 (s, 1F), −107.3 (d, $J_{F\text{-}F}$ = 273.2 Hz, 1F), −112.7 (d, $J_{F\text{-}F}$ = 273.7 Hz, 1F), −124.8 (br, 2F), −125.1 to −126.9 (m, 2F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{18}F_{10}NO_2$ $[M + H]^+$ 482.1173, found: 482.1175.

*2-Butyl-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-6-(trifluoromethyl)isoquinoline-1,3(2H,4H)-dione (**3j**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (115 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.3 Hz, 1H), 7.64 (s, 1H), 4.07−3.94 (m, 2H), 3.47 (dd, J = 33.2, 15.2 Hz, 1H), 2.85−2.68 (m, 1H), 1.68 (s, 3H), 1.56 (dd, J = 15.0, 7.3 Hz, 2H), 1.36 (td, J = 14.8, 7.2 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.5, 162.3, 141.4, 135.1 (q, J = 30.3 Hz), 130.3, 128.6, 127.1, 124.8 (q, J = 10.1 Hz), 122.9, 119.8−105.4 (m), 43.5, 40.9, 40.5 (t, J = 20.2 Hz), 31.9, 29.5, 20.1, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.4 (s, 3F), −81.2 (t, J = 9.8 Hz, 3F), −107.3 (d, $J_{F\text{-}F}$ = 273.3 Hz, 1F), −112.6 (d, $J_{F\text{-}F}$ = 273.0 Hz, 1F), −124.9 (br, 2F), −125.1 to −126.9 (m, 2F); HRMS m/z (ESI) calcd for $C_{20}H_{18}F_{12}NO_2$ $[M + H]^+$ 532.1141, found: 532.1144.

*2-Butyl-6-chloro-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-isoquinoline-1,3(2H,4H)-dione (**3k**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (36 mg, 24%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.32 (dd, J = 7.9, 1.3 Hz, 1H), 7.64 (dd, J = 7.9, 1.3 Hz, 1H), 7.42 (t, J = 7.9 Hz, 1H), 4.06−3.77 (m, 3H), 3.36 (dd, J = 35.4, 15.2 Hz, 1H), 1.86 (s, 3H), 1.61−1.52 (m, 2H), 1.41−1.30 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.5, 162.4, 137.0, 136.8, 132.8, 129.1, 127.1, 118.4−105.8 (m), 44.3, 41.4, 36.7 (t, J = 20.2 Hz),

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J. Org. Chem. 2015, 80, 12599−12605

29.4, 26.6, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.1 (t, J = 9.8 Hz, 3F), −111.6 (d, $J_{F\text{-}F}$ = 272.6 Hz, 1F), −113.6 (d, $J_{F\text{-}F}$ = 272.6 Hz, 1F), −125.0 (br, 2F), −125.2 to −126.9 (m, 2F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{18}ClF_9NO_2$ $[M + H]^+$ 498.0877, found: 498.0875.

*2-Butyl-6-chloro-4-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-isoquinoline-1,3(2H,4H)-dione (**3k′**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (72 mg, 48%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.24 (d, J = 2.3 Hz, 1H), 7.59 (dd, J = 8.5, 2.3 Hz, 1H), 7.35 (d, J = 8.4 Hz, 1H), 4.07−3.91 (m, 2H), 3.41 (dd, J = 33.7, 15.3 Hz, 1H), 2.79−2.62 (m, 1H), 1.63 (s, 3H), 1.55 (dd, J = 15.3, 7.6 Hz, 2H), 1.40−1.30 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.8, 162.3, 139.0, 134.4, 133.8, 129.1, 127.3, 125.8, 118.4−105.6 (m), 43.1, 40.8, 40.4 (t, J = 10.1 Hz), 32.0, 29.5, 20.1, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −81.2 (t, J = 9.8 Hz, 3F), −107.4 (d, $J_{F\text{-}F}$ = 272.5 Hz, 1F), −112.7 (d, $J_{F\text{-}F}$ = 272.6 Hz, 1F), −124.8 (br, 2F), −125.0 to −126.9 (m, 2F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{18}ClF_9NO_2$ $[M + H]^+$ 498.0877, found: 498.0879.

*4-(2,2,3,3,4,4,4-Heptafluorobutyl)-2-isopropyl-4,8-dimethyl-isoquinoline-1,3(2H,4H)-dione (**3l**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (83 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (t, J = 7.7 Hz, 1H), 7.28 (t, J = 6.6 Hz, 2H), 5.19 (hept, J = 6.9 Hz, 1H), 3.49−3.31 (m, 1H), 2.83−2.62 (m, 4H), 1.67 (s, 3H), 1.49 (dd, J = 6.9, 1.2 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.0, 164.4, 142.8, 141.8, 132.2, 132.0, 123.9, 123.2, 119.2−109.8 (m), 45.7, 43.6, 40.5 (t, J = 20.2 Hz), 32.2, 24.1, 19.4, 19.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −80.3 (t, J = 12.2 Hz, 3F), −108.6 (d, $J_{F\text{-}F}$ = 341.9 Hz, 1F), −113.5 (d, $J_{F\text{-}F}$ = 341.9 Hz, 1F), −126.6 to −129.0 (m, 2F); HRMS m/z (ESI) calcd for $C_{18}H_{19}F_7NO_2$ $[M + H]^+$ 414.1299, found: 414.1297.

*2-Butyl-4-methyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)-isoquinoline-1,3(2H,4H)-dione (**3o**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (96 mg, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (dd, J = 7.9, 1.3 Hz, 1H), 7.67 (td, J = 7.8, 1.4 Hz, 1H), 7.48 (ddd, J = 17.1, 12.1, 4.5 Hz, 2H), 4.11−3.97 (m, 2H), 3.46 (dd, J = 33.6, 15.3 Hz, 1H), 2.89−2.69 (m, 1H), 1.69 (s, 3H), 1.64−1.57 (m, 2H), 1.46−1.35 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.3, 163.5, 140.7, 133.6, 129.4, 128.0, 125.7, 124.2, 120.9−103.1 (m), 43.4, 40.6, 40.5 (t, J = 20.2 Hz), 32.1, 29.6, 20.2, 13.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −80.9 (t, J = 13.6 Hz, 3F), −107.6 (d, $J_{F\text{-}F}$ = 341.2 Hz, 1F), −112.4 (d, $J_{F\text{-}F}$ = 341.7 Hz, 1F), −121.8 (br, 2F), 122.9 (br, 2F), 123.9 (br, 2F), −125.2 to −127.0 (m, 2F); HRMS m/z (ESI) calcd for $C_{21}H_{19}F_{13}NO_2$ $[M + H]^+$ 564.1203, found: 564.1200.

*2-Butyl-4-(2,2,3,3,4,4,4-heptafluorobutyl)-4,6-dimethylisoquinoline-1,3(2H,4H)-dione (**3p**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (97 mg, 76%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.13 (d, J = 8.1 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.17 (s, 1H), 4.15−3.78 (m, 2H), 3.38 (dd, J = 33.4, 15.4 Hz, 1H), 2.86−2.57 (m, 1H), 2.43 (s, 3H), 1.62 (s, 3H), 1.60−1.51 (m, 2H), 1.35 (dq, J = 14.5, 7.1 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ: 174.4, 163.5, 144.5, 140.7, 129.3, 129.1, 126.0, 121.8, 118.7−108.1 (m), 43.3, 40.5, 40.2 (t, J = 19.8 Hz), 32.1, 29.6, 21.8, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.4 (t, J = 12.1 Hz, 3F), −108.6 (d, $J_{F\text{-}F}$ = 341.5 Hz, 1F), −113.5 (d, $J_{F\text{-}F}$ = 341.7 Hz, 1F), −126.6 to −129.1 (m, 2F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{21}F_7NO_2$ $[M + H]^+$ 428.1456, found: 428.1459.

*2-Butyl-4,6-dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,8-pentadecafluorooctyl)isoquinoline-1,3(2H,4H)-dione (**3q**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (110 mg, 54%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.14 (d, J = 8.1 Hz, 1H), 7.24 (s, 1H), 7.16 (d, J = 7.6 Hz, 1H), 4.05−3.91 (m, 2H), 3.40 (dd, J = 33.2, 15.2 Hz, 1H), 2.81−2.65 (m, 1H), 2.43 (s, 3H), 1.62 (s, 2H), 1.55 (dd, J = 15.3, 7.6 Hz, 2H), 1.35 (dq, J = 14.8, 7.4 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.4, 163.5, 144.5, 140.7, 129.3, 129.1, 126.0, 121.8, 117.2−91.6 (m), 43.3, 40.5, 40.3 (t, J = 28.9 Hz), 32.1, 29.6, 21.8, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −80.9 (t, J = 10.1 Hz, 3F), −107.6 (d, $J_{F\text{-}F}$ = 273.8 Hz, 1F), −112.4 (d, $J_{F\text{-}F}$ = 273.2 Hz, 1F), −120.7 to −122.4 (m, 6F), −122.5 (br, 2F), −123.9 (br, 2F), −126.2 (br, 2F); HRMS m/z (ESI-TOF) calcd for $C_{24}H_{21}F_{17}NO_2$ $[M + H]^+$ 678.1296, found: 678.1298.

*2-Butyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-henicosafluoroundecyl)-4-methylisoquinoline-1,3(2H,4H)-dione (**3r**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (108 mg, 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (dd, J = 7.9, 1.2 Hz, 1H), 7.67 (td, J = 7.8, 1.4 Hz, 1H), 7.53−7.38 (m, 2H), 4.10−3.97 (m, 2H), 3.46 (dd, J = 33.6, 15.3 Hz, 1H), 2.79 (ddd, J = 27.9, 15.3, 8.5 Hz, 1H), 1.69 (s, 3H), 1.64−1.56 (m, 2H), 1.48−1.34 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.3, 163.5, 133.6, 131.8, 129.4, 128.7, 128.4, 128.0, 122.1−102.7 (m), 46.4, 40.6 (t, J = 10.1 Hz), 32.1, 30.8, 29.6, 20.2, 13.7; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −80.8 (t, J = 12.7 Hz, 3F), −107.5 (d, $J_{F\text{-}F}$ = 341.0 Hz, 1F), −112.3 (d, $J_{F\text{-}F}$ = 341.5 Hz, 1F), −121.8 (br, 10F), −122.7 (br, 2F), −123.9 (br, 2F), −126.2 (br, 2F); HRMS m/z (ESI-TOF) calcd for $C_{25}H_{19}F_{21}NO_2$ $[M + H]^+$ 764.1075, found: 764.1077.

*2-Butyl-4-methyl-4-(2,2,2-trifluoroethyl)isoquinoline-1,3(2H,4H)-dione (**3s**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (69 mg, 73%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (dd, J = 7.9, 1.2 Hz, 1H), 7.68 (m, 1H), 7.50 (td, J = 8.0, 1.1 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 4.11−3.94 (m, 2H), 3.39 (dq, J = 15.1, 10.4 Hz, 1H), 2.82 (dq, J = 15.1, 9.8 Hz, 1H), 1.67 (s, 3H), 1.61(m, 2H), 1.41 (dq, J = 14.8, 7.4 Hz, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.3, 163.5, 140.4, 133.7, 129.3, 128.0, 125.6, 125.2 (q, J = 90.9 Hz), 124.4, 44.2 (q, J = 20.2 Hz), 43.5, 40.6, 31.4, 29.6, 20.2, 13.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −61.4 (t, J = 12.7 Hz, 3F); HRMS m/z (ESI-TOF) calcd for $C_{16}H_{19}F_3NO_2$ $[M + H]^+$ 314.1363, found: 314.1360.

General Procedure for the Synthesis of Difluoroacetylated Isoquinoline-1,3-diones. To a mixture of methacryloyl benzamide **1** (0.3 mmol), *fac*-Ir(ppy)$_3$ (0.003 mmol, 1.0 mol %), and K_3PO_4 (0.6 mmol) in dixoane (2.0 mL) was added $BrCF_2CO_2Et$ (0.6 mmol) under a N_2 atmosphere, and then the resulting solution was stirred under 5 W blue LED irradiation at room temperature for 24 h. The solvent was evaporated under reduced pressure, and the resulting mixture was filtered through a Florisil pad, diluted with Et_2O, and washed with water and then brine. The organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate 8:1 as the eluant) on silica gel to afford the corresponding perfluorinated isoquinoline-1,3-diones (products **3t**−**z**) in a yield listed in Scheme 2.

*Ethyl 3-(2-Butyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-difluoropropanoate (**3t**).* Eluent: Petroleum ether/ethyl acetate (8:1). Yellowish oil (83 mg, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.28 (dd, J = 7.9, 1.1 Hz, 1H), 7.63 (td, J = 7.8, 1.4 Hz, 1H), 7.50−7.44 (m, 1H), 7.42 (d, J = 7.9 Hz, 1H), 4.05−3.88 (m, 4H), 3.31 (ddd, J = 17.1, 15.2, 11.9 Hz, 1H), 2.91 (dt, J = 18.9, 14.8 Hz, 1H), 1.67−1.58 (m, 5H), 1.46−1.36 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 174.6, 163.5, 163.3 (t, J = 20.2 Hz), 140.7, 133.3, 129.2, 127.8, 126.0, 124.7, 114.5 (t, J = 222.2 Hz), 63.0, 44.6 (t, J = 20.2 Hz), 43.6, 40.6, 31.7, 29.6, 20.2, 13.8, 13.6; ^{19}F NMR (471 MHz, $CDCl_3$) δ: −99.4 (d, $J_{F\text{-}F}$ = 266.2 Hz, 1F), −104.3 (d, $J_{F\text{-}F}$ = 266.1 Hz, 1F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{24}F_2NO_4$ $[M + H]^+$ 368.1668, found: 368.1670.

*Ethyl 2,2-Difluoro-3-(2-isopropyl-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)propanoate (**3u**).* Eluent: Petroleum ether/ethyl acetate (8:1). Yellowish oil (74 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, J = 7.8 Hz, 1H), 7.57 (t, J = 7.6 Hz, 1H), 7.42 (t, J = 7.6 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 5.19 (dt, J = 13.9, 6.9 Hz, 1H), 4.04−3.83 (m, 2H), 3.31−3.19 (m, 1H), 2.84 (dt, J = 19.1, 14.8 Hz, 1H), 1.61 (s, 3H), 1.50−1.44 (m, 6H), 1.17 (d, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.8, 163.8, 163.3 (t, J = 30.3 Hz), 140.6, 133.2, 129.1, 127.8, 125.8, 125.3, 114.5 (t, J = 252.5 Hz), 63.0, 45.7, 44.7 (t, J = 30.3 Hz), 43.8, 31.6, 29.7, 19.4, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −99.3 (d, $J_{F\text{-}F}$ = 267.7 Hz, 1F), −104.3 (d, $J_{F\text{-}F}$ = 266.6 Hz, 1F); HRMS m/z (ESI-TOF) calcd for $C_{18}H_{22}F_2NO_4$ $[M + H]^+$ 354.1512, found: 354.1509.

*Ethyl 3-(2-Butyl-4,6-dimethyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-difluoropropanoate (**3v**).* Eluent: Petroleum ether/ethyl acetate (8:1). Yellowish oil (77 mg, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.12 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 9.9 Hz, 1H), 7.15 (s, 1H), 4.02−3.82 (m, 4H), 3.32−3.19 (m, 1H), 2.86 (dt, J = 19.4,

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J. Org. Chem. 2015, 80, 12599−12605

14.6 Hz, 1H), 2.42 (s, 3H), 1.61−1.53 (m, 5H), 1.36 (dd, J = 15.2, 7.6 Hz, 2H), 1.17 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.7, 163.6, 163.4 (t, J = 60.6 Hz), 144.2, 140.7, 129.2, 128.9, 126.4, 122.2, 114.5 (t, J = 353.5 Hz), 62.9, 44.6 (t, J = 30.3 Hz), 43.5, 40.5, 31.7, 29.6, 21.8, 20.2, 13.8, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −99.2 (d, $J_{F\text{-}F}$ = 266.5 Hz, 1F), −104.5 (d, $J_{F\text{-}F}$ = 266.6 Hz, 1F); HRMS m/z (ESI-TOF) calcd for $C_{20}H_{26}F_2NO_4$ $[M + H]^+$ 382.1825, found: 382.1822.

*Ethyl 3-(2-Butyl-6-chloro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-difluoropropanoate (**3w**).* Eluent: Petroleum ether/ethyl acetate (8:1). Yellowish oil (87 mg, 72%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.4, 2.3 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 4.10−3.92 (m, 5H), 3.27 (ddd, J = 18.7, 15.2, 11.3 Hz, 1H), 2.82 (dd, J = 32.3, 16.2 Hz, 1H), 1.60 (s, 3H), 1.58−1.53 (m, 2H), 1.36 (dq, J = 14.8, 7.4 Hz, 2H), 1.21 (t, J = 7.2 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.1, 163.2 (t, J = 30.3 Hz), 162.4, 139.1, 134.2, 133.5, 128.8, 127.7, 126.2, 114.4 (t, J = 252.5 Hz), 63.2, 44.5 (t, J = 20.2 Hz), 43.4, 40.8, 31.6, 30.9, 29.5, 20.2, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −100.8 (d, $J_{F\text{-}F}$ = 266.6 Hz, 1F), −103.6 (d, $J_{F\text{-}F}$ = 266.6 Hz, 1F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{23}ClF_2NO_4$ $[M + H]^+$ 402.1279, found: 402.1281.

*Ethyl 3-(2-Butyl-6-fluoro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-difluoropropanoate (**3x**).* Eluent: Petroleum ether/ethyl acetate (8:1). Yellowish oil (84 mg, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.31 (dd, J = 8.8, 5.9 Hz, 1H), 7.17 (ddd, J = 8.7, 8.0, 2.4 Hz, 1H), 7.10 (dd, J = 9.4, 2.4 Hz, 1H), 4.17−3.93 (m, 4H), 3.34 (ddd, J = 18.8, 15.2, 11.3 Hz, 1H), 2.83 (dd, J = 31.9, 16.5 Hz, 1H), 1.68−1.56 (m, 5H), 1.46−1.35 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 174.1, 165.9 (d, J = 255.4 Hz), 163.1 (t, J = 32.1 Hz), 162.6, 143.8, 132.3, 121.1, 115.8 (d, J = 21.1 Hz), 114.3 (t, J = 250.0), 112.8 (d, J = 23.2 Hz), 63.2, 44.5 (t, J = 20.7 Hz), 43.8, 40.6, 31.7, 29.5, 20.2, 13.8, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −100.3 (d, $J_{F\text{-}F}$ = 266.9 Hz, 1F), −103.5 (s, 1F), −103.6 (d, $J_{F\text{-}F}$ = 266.9 Hz, 1F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{23}F_3NO_4$ $[M + H]^+$ 386.1574, found: 386.1576.

*Ethyl 3-(2-Butyl-4-methyl-1,3-dioxo-6-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-difluoropropanoate (**3y**).* Eluent: Petroleum ether/ethyl acetate (8:1). Yellowish oil (90 mg, 69%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.38 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 4.07−3.95 (m, 4H), 3.34 (ddd, J = 19.2, 15.3, 11.2 Hz, 1H), 2.87 (q, J = 16.3 Hz, 1H), 1.65 (s, 3H), 1.58 (dd, J = 15.4, 7.9 Hz, 2H), 1.42−1.32 (m, 2H), 1.21 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 173.9, 163.0 (t, J = 30.3 Hz), 162.4, 141.6, 134.8 (q, J = 30.3 Hz), 130.1, 127.6, 124.6, 123.1, 114.3−111.7 (m), 63.2, 44.4 (t, J = 20.2 Hz), 43.7, 40.8, 31.6, 30.9, 29.5 (t, J = 20.2 Hz), 20.2, 13.7, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.2 (s, 3F), −100.4 (d, $J_{F\text{-}F}$ = 266.3 Hz, 1F), −103.1 (d, $J_{F\text{-}F}$ = 266.5 Hz, 1F); HRMS m/z (ESI-TOF) calcd for $C_{20}H_{23}F_5NO_4$ $[M + H]^+$ 436.1542, found: 436.1539.

*Ethyl 3-(2-Butyl-5-chloro-4-methyl-1,3-dioxo-1,2,3,4-tetrahydroisoquinolin-4-yl)-2,2-difluoropropanoate (**3z**).* Eluent: Petroleum ether/ethyl acetate (8:1). Yellowish oil (79 mg, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, J = 2.2 Hz, 1H), 7.55 (dd, J = 8.5, 2.3 Hz, 1H), 7.33 (d, J = 8.5 Hz, 1H), 4.16−3.78 (m, 5H), 3.27 (ddd, J = 18.8, 15.2, 11.3 Hz, 1H), 2.82 (dd, J = 32.3, 16.1 Hz, 1H), 1.60 (s, 3H), 1.58−1.53 (m, 2H), 1.36 (dd, J = 15.1, 7.5 Hz, 2H), 1.20 (d, J = 7.1 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 174.1, 163.3 (t, J = 10.1 Hz), 162.4, 139.1, 134.2, 133.5, 128.8, 127.7, 126.2, 114.5 (t, J = 272.7 Hz), 63.2, 44.5 (t, J = 20.2 Hz), 40.8, 31.6,, 29.7, 29.5, 20.2, 13.7, 13.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −100.3 (d, $J_{F\text{-}F}$ = 266.9 Hz, 1F), −103.6 (d, $J_{F\text{-}F}$ = 266.9 Hz, 1F); HRMS m/z (ESI) calcd for $C_{19}H_{23}ClF_2NO_4$ $[M + H]^+$ 402.1279, found: 402.1276.

*Ethyl 3-(1-Butyl-3-methyl-2-oxoindolin-3-yl)-2,2-difluoropropanoate (**4a**).* Eluent: Petroleum ether/ethyl acetate (10:1). Yellowish oil (77 mg, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.07 (d, J = 7.5 Hz, 1H), 6.85 (d, J = 7.5 Hz, 1H), 6.70 (s, 1H), 4.10−3.87 (m, 2H), 3.71 (ddt, J = 61.0, 14.5, 7.4 Hz, 2H), 2.90−2.67 (m, 2H), 2.40 (s, 3H), 1.73−1.60 (m, 2H), 1.48−1.33 (m, 5H), 1.20 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 179.0, 163.6 (t, J = 32.3 Hz), 143.0, 138.5, 128.0, 123.7, 122.4, 116.7, 114.7 (t, J = 252.6 Hz), 109.5, 62.8, 44.1 (d, J = 22.7 Hz), 39.9, 29.3, 25.8, 21.8, 20.1, 13.8, 13.6; ^{19}F NMR (376 MHz, $CDCl_3$) δ: −100.8 (d, $J_{F\text{-}F}$ = 266.5 Hz, 1F), −103.6 (d, $J_{F\text{-}F}$ = 266.6 Hz, 1F); HRMS m/z (ESI-TOF) calcd for $C_{19}H_{26}F_2NO_3$ $[M + H]^+$ 354.1876, found: 354.1877.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01803.

Characterization of products (^{1}H, ^{13}C, and ^{19}F NMR data) (PDF)

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Notes

The authors declare no competing financial interest.

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