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ARTICLE

Visible-light-induced radical cyclization of *N*-allylbenzamide with CF_3SO_2Na to trifluoromethylated dihydroisoquinolinones in water at room temperature

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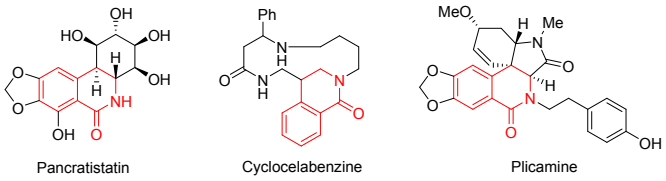
A green and efficient strategy for the preparation of trifluoromethylated dihydroisoquinolinones via a visible-light-induced radical cyclization of *N*-allylbenzamide with CF_3SO_2Na in water at room temperature was developed. This photoinduced reaction generated the desired products in good to excellent yields under simple and mild conditions.

Introduction

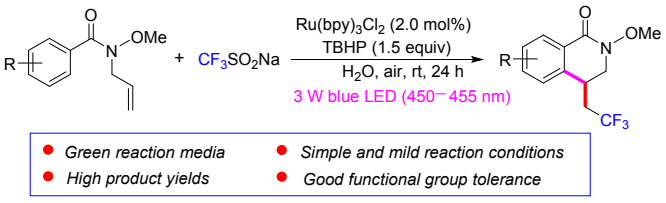
N-Containing heterocycles have been widely found in a variety of biologically and pharmacologically active compounds.[1] As one kind of them, 3,4-dihydroisoquinolone scaffold is frequently encountered in natural products and drug molecules, which exhibit important and extensive biological activities such as anti-tumor, anti-inflammatory, anti-allergic and estrogenic ones and their widespread applications in cancer diagnosis (Scheme 1).[2] Traditionally, the synthesis of 3,4-dihydroisoquinolone derivatives have relied primarily on the condensation of homophthalic anhydride with imines, which requires the prefunctionalization of starting materials.[3] Recently, by using the C–H activation strategy, Glorius, Guimond, Rovis, et al. developed Rh-catalyzed oxidative annulations of benzamides with olefins leading to 3,4-dihydrioisoquinolinones with the limitation of terminal and cyclic alkenes.[4] After that, Wang and Sun described a Rh-Mg co-catalyzed annulation of benzamides and alkynes to *cis*- and *trans*-3,4-dihydroisoquinolinones in high diastereoselectivities.[5]

N-Allylbenzamide represents an important and great valuable building block in organic synthesis.[6] In 1998, Zard and co-workers reported a pioneer work on the radical addition and cyclization of *N*-allylbenzamides to 3,4-dihydroisoquinolinones.[7] Most recently, the cascade radical addition and followed by an intramolecular cyclization of *N*-allylbenzamide to 3,4-dihydroisoquinolinone derivatives has attracted great attention of the synthetic community. For example, Han and Li reported DTBP-promoted radical cyclization of *N*-allylbenzamide with alcohols, alkanes and aldehydes for the synthesis of 4-substituted 3,4-dihydroisoquinolinones.[8] Meanwhile, Cui et al. developed a Cu-catalyzed trifluoromethylation/cyclization toward dihydroisoquinolinones in moderate yields using Togni's reagent because the incorporation of trifluoromethyl group (CF_3) into organic molecules can dramatically change the physical and biological properties, such as metabolic stability, binding selectivity and lipophilicity.[9]

In order to establish the novel and practical methodology under mild conditions and in continuation of our efforts on using CF_3SO_2Na as trifluoromethyl reagent[10] and photoredox catalysis[11] in the organic transformation of *N*-allylbenzamide,[12] herein, we wish to report a visible-light-induced synthesis of 4-trifluoromethylated dihydroisoquinolinones from *N*-allylbenzamides using CF_3SO_2Na (Langlois reagent) as a easily available and stable CF_3-source through a radical domino cyclization in one-pot. The reactions underwent smoothly to generate the desired products in good to excellent yields at room temperature under the irradiation of blue LED (450–455 nm) in water with a broad functional group tolerance (Scheme 2).



Scheme 1 Representative biologically active molecules containing 3,4-dihydroisoquinolinone skeleton.



Scheme 2 Visible-light-induced radical cyclization of *N*-allylbenzamide to 3,4-dihydroisoquinolinones.

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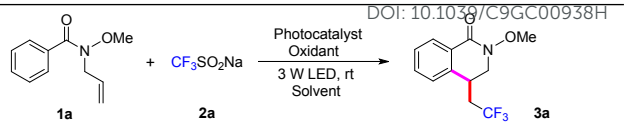
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Results and discussion

We initially chose *N*-allyl-*N*-methyloxybenzamide (**1a**) and sodium trifluoromethanesulfinate (CF_3SO_2Na, Langlois reagent) as the model substrates, *tert*-butyl hydroperoxide (TBHP, 70% solution in H_2O) as a radical initiator to explore the optimal reaction conditions through the variations of photocatalyst, oxidant, solvent and light source. Gratifyingly, the model reaction between **1a** and CF_3SO_2Na by using acridine red as photocatalyst and acetonitrile (CH_3CN) as solvent under the irradiation of 3 W blue LED (530–535 nm) in air for 24 h, afforded the desired product 2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**3a**) in 53% yield (Table 1, entry 1). Among the tested organic dyes and metal-complexes as photocatalysts, $Ru(bpy)_3Cl_2$ was superior to $Ru(phen)_3Cl_2$, Na_2-eosin Y, fluorescein, rhodamine B and rose bengal (Table 1, entries 2–7). In order to improve the efficiency of the model reaction, a variety of solvents were screened and the results were also presented in Table 1. It is pleased to find that water is the best solvent among the examined solvents (Table 1, entries 8–15). The solvents, DMSO and DMF gave the inferior product yields (68% of **3a** in DMSO and 64% of **3a** in DMF, respectively). However, no **3a** was observed when the model reaction was carried out in THF or DCM (dichloromethane). The mixed solvents, such as H_2O/CH_3CN (1:1), H_2O/DMSO (1:1) and H_2O/DMF (1:1) gave the 67–79% yields of **3a**. The screening of oxidant indicated that TBHP was the best of choice among the test oxidants including $K_2S_2O_8$, H_2O_2, TBPB and DTBP (Table 1, entries 16–19). Furthermore, the loading of $Ru(bpy)_3Cl_2$, the amount of TBHP, the ratio of **1a** to **2a**, and the reaction time were also optimized and found that 2.0 mol% of $Ru(bpy)_3Cl_2$, 1.5 equiv of TBHP, 2.0 equiv of CF_3SO_2Na, and the reaction for 24 h at room temperature were the best parameters (Table S1 in Supporting Information for detail). There is no difference between the model reaction was performed under nitrogen atmosphere and air atmosphere (Table S1, SI). It should be noted that no reaction was detected as the reaction was carried out in the absence of photocatalyst, oxidant, or light irradiation (Table S1, SI).

Under the optimized reaction conditions in hand, we then investigated the substrate scope and the generality of the reaction, as shown in Scheme 3. In general, *N*-allylbenzamides have a broad functional group tolerance and scope. It can be seen from Scheme 2, a range of *N*-allylbenzamides reacted with CF_3SO_2Na to afford the corresponding CF_3-incorporated products (**3a**–**3y**) in 61–94% yields. *N*-Allylbenzamides bearing both electron-rich and electron-deficient substituents on the aromatic rings exhibited the moderate to good reactivity to react with CF_3SO_2Na under the standard reaction conditions. *N*-Allylbenzamides possessing an electron-donating group (MeO, EtO, ^{t}Bu, Me or Et) on the *para*-position of benzene rings gave the corresponding products (**3b**–**3f**) in 85–94% yields. Meanwhile, *N*-allylbenzamides with an electron-withdrawing group (Ph, F, Cl, Br, I, CF_3, CO_2Me or CF_3O) on the *para*-position of phenyl rings generated the desired products (**3h**–**3n**) in 61–83% yields. It is obvious that the reactivity of substrates with electron-donating groups is superior to the substrates with electron-withdrawing groups. When the substituent was located on the *meta*-position of the aromatic ring in the substrates of *N*-allylbenzamides, the reaction delivered the mixture of regio-isomers in 1:2.2 and 1:1.4 ratio (**3o**/**3o'** and **3q**/**3q'**), respectively with good isolated yields

Table 1 Optimization of the reaction conditions[a]



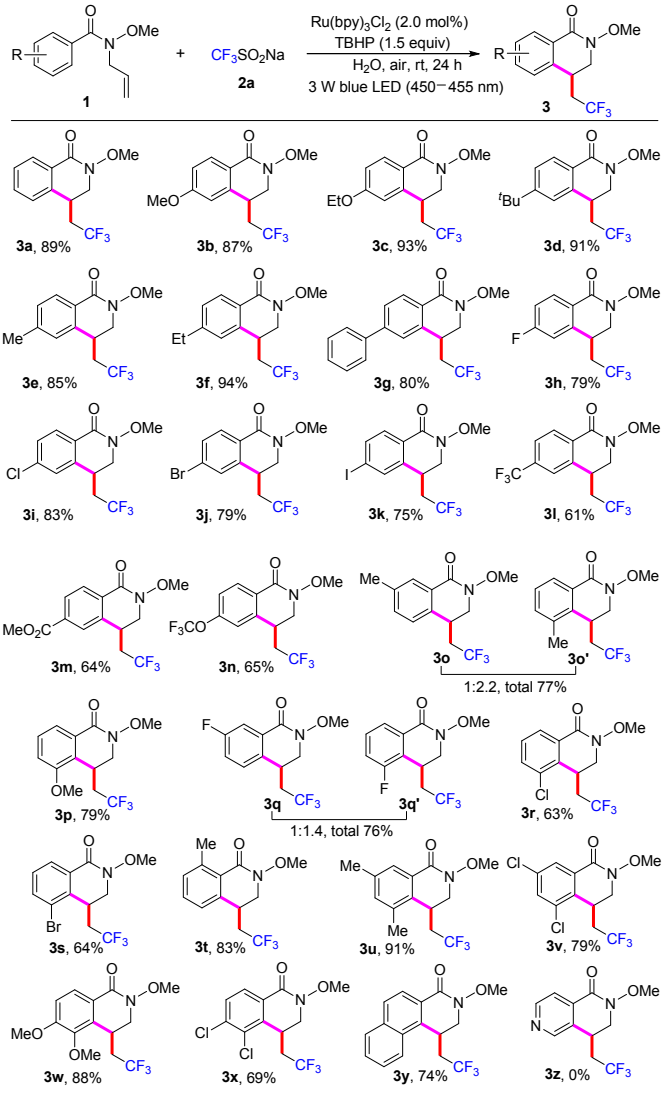
1a 2a 3a

Entry	Photocatalyst	Oxidant	LED (nm)	Solvent	Yield[b] (%)
1	Acridine red	TBHP	530–535	CH_3CN	53
2	$Ru(bpy)_3Cl_2$	TBHP	450–455	CH_3CN	65
3	$Ru(phen)_3Cl_2$	TBHP	420–425	CH_3CN	47
4	Na_2-Eosin Y	TBHP	530–535	CH_3CN	38
5	Fluorescein	TBHP	530–535	CH_3CN	53
6	Rhodamine B	TBHP	530–535	CH_3CN	Trace
7	Rose bengal	TBHP	530–535	CH_3CN	Trace
8	*$Ru(bpy)_3Cl_2$*	*TBHP*	*450–455*	*H_2O*	*89*
9	$Ru(bpy)_3Cl_2$	TBHP	450–455	DMSO	68
10	$Ru(bpy)_3Cl_2$	TBHP	450–455	DMF	64
11	$Ru(bpy)_3Cl_2$	TBHP	450–455	THF	NR
12	$Ru(bpy)_3Cl_2$	TBHP	450–455	DCM	NR
13	$Ru(bpy)_3Cl_2$	TBHP	450–455	H_2O/CH_3CN	73[c]
14	$Ru(bpy)_3Cl_2$	TBHP	450–455	H_2O/DMSO	79[d]
15	$Ru(bpy)_3Cl_2$	TBHP	450–455	H_2O/DMF	67[e]
16	$Ru(bpy)_3Cl_2$	$K_2S_2O_8$	450–455	H_2O	77
17	$Ru(bpy)_3Cl_2$	H_2O_2	450–455	H_2O	57
18	$Ru(bpy)_3Cl_2$	TBPB	450–455	H_2O	47
19	$Ru(bpy)_3Cl_2$	DTBP	450–455	H_2O	36

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.40 mmol), photocatalyst (2.0 mol%), oxidant (1.5 equiv), solvent (2.0 mL) at room temperature under LED irradiation (3 W) in air for 24 h and TBHP (70% solution in H_2O) was used in the reaction. [b] Isolated yield. [c] H_2O/CH_3CN in 1:1 ratio of V/V. [d] H_2O/DMSO in 1:1 ratio of V/V. [e] H_2O/DMF in 1:1 ratio of V/V. NR = no reaction.

(77% and 76%). Surprisingly, the reactions of substrates (**1p**, **1r**, and **1s**) also proceeded well and afforded the corresponding products (**3p**, **3r**, and **3s**) as sole ones in excellent regioselectivity with good yields (63–79%).

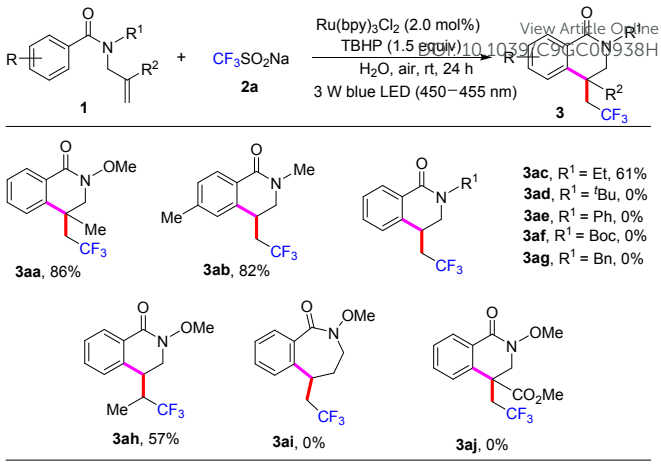
The structure of **3s** was further confirmed by single crystal X-ray diffraction analysis (Supporting Information for detail).[13] When the *ortho*-position substituted substrate **1t** was used in the reaction with **2a**, the anticipated product **3t** was isolated in 83% yield, indicating the negligibility of *ortho*-position effect. It should be noted that 3,5-disubstituted substrates (**1u** and **1v**) underwent the reaction with **2a** smoothly to generate the desired products (**3u**, and **3v**) in 91% and 79% yield, respectively. In addition, the reactions of 3,4-disubstituted substrates (**1w** and **1x**) provided **3w** and **3x** as sole products in high regioselectivity with good yields (88% and 69%, respectively). The reaction of *N*-allyl-*N*-methoxy-2-naphthamide



Scheme 3 The scope of *N*-allyl-*N*-methyloxybenzamides [reaction conditions: *N*-allyl-*N*-methyloxybenzamide (**1**, 0.20 mmol), **2a** (0.40 mmol), $Ru(bpy)_3Cl_2$ (2.0 mol%), TBHP (70% solution in water, 1.5 equiv), H_2O (2.0 mL), rt, 3 W blue LED (450–455 nm) irradiation for 24 h, isolated yield of the product after column chromatography purification].

(**1y**) also afforded the expected product **3y** in 74% yield. When *N*-allyl-*N*-methoxyisonicotinamide (**1z**) was used as one of the substrates, no desired product (**3z**) was observed under the present reaction conditions and the starting materials were recovery in almost quantitative yields.

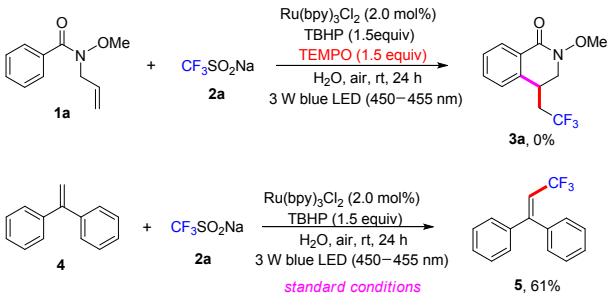
For further expand the scope of the substrate *N*-allylbenzamides, *N*-methoxy-*N*-(2-methylallyl)benzamide was used to react with CF_3SO_2Na under the optimized reaction conditions, providing the corresponding product **3aa** in 86% yield, shown in Scheme 4. Moreover, the reactions of *N*-allyl-*N*-methyl-(4-methyl)benzamide, *N*-allyl-*N*-ethylbenzamide and (*E*)-*N*-(but-2-en-1-yl)-*N*-methoxybenzamide with CF_3SO_2Na generated the desired products (**3ab**, **3ac** and **3ah**) in 57–82% yields. However, *N*-allyl-*N*-(*tert*-butyl)benzamide, *N*-allyl-*N*-phenylbenzamide, *tert*-butyl allyl(benzoyl)carbamate, *N*-allyl-*N*-benzylbenzamide, *N*-(but-3-en-1-yl)-*N*-methoxybenzamide, and methyl 2-((*N*-methoxybenzamido)-



Scheme 4 The extension of *N*-allyl-*N*-substituted benzamides [reaction conditions: *N*-allylbenzamide (**1**, 0.20 mmol), **2a** (0.40 mmol), $Ru(bpy)_3Cl_2$ (2.0 mol%), TBHP (70% solution in water, 1.5 equiv), H_2O (2.0 mL), rt, 3 W blue LED (450–455 nm) for 24 h, isolated yield of the product after column chromatography purification].

methyl)acrylate exhibited no reactivity to the reaction with **2a** under the standard reaction conditions, and no anticipated products (**3ad**–**3ag**, **3ai** and **3aj**) were obtained.

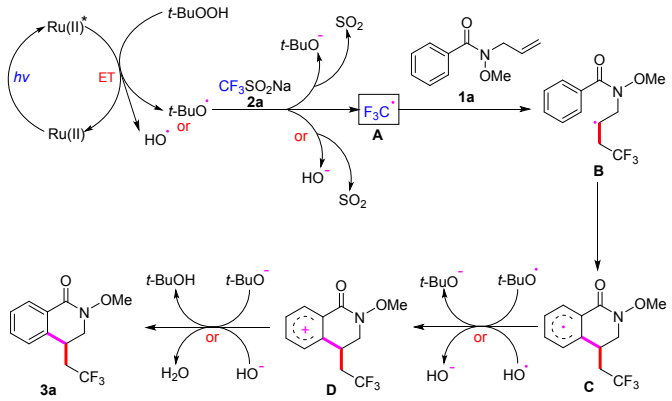
To further investigate the reaction mechanism of this transformation, some control experiments were performed, shown in Scheme 5. When a known radical scavenger, such as 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.5 equiv) was added into the reaction of *N*-allyl-*N*-methyloxybenzamide (**1a**) with CF_3SO_2Na (**2a**) under the standard conditions, the reaction was inhibited completely, suggesting that a CF_3 radical might be involved in the reaction. To capture the CF_3 free radical intermediate formed during the reaction, 1,1-diphenylethylene was added into the reaction system, and a radical coupling product **5** was isolated in 61% yield.



Scheme 5 The control experiments.

On the basis of the above results and related reports, a plausible mechanism is proposed in Scheme 6. Firstly, $[Ru(bpy)_3]^{2+}$ was activated to its excited state $[Ru(bpy)_3]^{2+*}$ under visible light irradiation. Next, TBHP procured energy from the excited $[Ru(bpy)_3]^{2+*}$ (energy transfer process) to generate the hydroxyl radical and *tert*-butoxy radical via homolytic cleavage of peroxide bond. Then the CF_3 free radical (**A**) was formed through the reaction of *tert*-butoxy radical or hydroxyl radical with CF_3SO_2Na. Subsequently, the obtained CF_3 radical (**A**) underwent an addition to the double bond of *N*-allylbenzamide (**1a**) to afford the radical

intermediate (**B**), followed by an intramolecular cyclization, providing a radical intermediate (**C**). The formed **C** was oxidized by *tert*-butoxyl radical or hydroxyl radical to generate a cationic intermediate (**D**) through a SET process. Finally, **D** lost a proton to produce the desired product **3a**, along with the formation of water or *tert*-butanol.



Scheme 6 The proposed mechanism.

Conclusions

In conclusion, we have developed a visible-light-induced radical cyclization strategy to access□CF_3-substituted dihydroisoquinolinones from *N*-allylbenzamides and readily available sodium trifluoromethanesulfinate (CF_3SO_2Na). The reactions generated the corresponding trifluoromethylated dihydroisoquinolinones in high yields with good functional-group tolerance under mild conditions. Further investigations on the detailed mechanism and the applications of this transformation are currently underway in our laboratory.

Experimental section

General remarks

The ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometer (400 MHz, 100 MHz or 376 MHz, respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectroscopy data of the product were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI). All the solvents and commercially available reagents were purchased from commercial suppliers. Products were purified by flash chromatography on 200–300 mesh silica gels, SiO_2.

Typical procedure for the preparation of trifluoromethylated dihydroisoquinolinones via a visible-light-induced radical cyclization in water at room temperature

A 5 mL oven-dried reaction vessel equipped with a magnetic stirrer bar was charged with *N*-allyl-*N*-methyloxybenzamide (**1a**, 0.20 mmol), CF_3SO_2Na (**2a**, 0.40 mmol), $Ru(bpy)_3Cl_2$ (2.0 mol%), TBHP (70% solution in water, 0.30 mmol), H_2O (2.0 mL). The reaction vessel was exposed to blue LED (450–455 nm, 3 W) irradiation at room temperature in air with stirring for 24 h. After completion of the reaction, the mixture was concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 9:1) to give the product **3a** (46.1 mg, 89% yield).

Characterization data for products

2-Methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3a). White solid. M. p. 70.9–71.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.16 (dd, J_1 = 7.8 Hz, J_2 = 1.0 Hz, 1H), 7.52 (td, J_1 = 15.0 Hz, J_2 = 1.3 Hz, 1H), 7.43 (td, J_1 = 15.2 Hz, J_2 = 0.9 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 4.05 (dd, J_1 = 12.2 Hz, J_2 = 4.2 Hz, 1H), 3.90 (s, 3H), 3.81 (dd, J_1 = 12.0 Hz, J_2 = 2.7 Hz, 1H), 3.48–3.43 (m, 1H), 2.75–2.66 (m, 1H), 2.44–2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.1, 139.0, 132.9, 128.8, 128.2, 127.5, 126.8, 126.1 (q, J = 275.9 Hz), 61.8, 51.2, 37.3 (q, J = 27.9 Hz), 33.7 (q, J = 2.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.71. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{13}F_3NO_2$: 260.0893, found: 260.0898.

2,6- Dimethoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3b). White solid. M. p. 84.1–85.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J = 8.7 Hz, 1H), 6.91 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 4.00 (dd, J_1 = 12.0 Hz, J_2 = 3.9 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.77 (dd, J_1 = 11.9 Hz, J_2 = 2.6 Hz, 1H), 3.41–3.36 (m, 1H), 2.76–2.67 (m, 1H), 2.42–2.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 163.1, 141.2, 131.0, 126.1 (q, J = 276.0 Hz), 120.4, 113.5, 111.9, 61.8, 55.5, 51.2, 37.1 (q, J = 27.9 Hz), 34.0 (q, J = 2.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.70. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO_3$: 290.0999, found: 290.0995.

6-Ethoxy-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3c). White solid. M. p. 87.5–89.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J = 8.7 Hz, 1H), 6.89 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.69 (d, J = 2.4 Hz, 1H), 4.09 (q, J = 7.0 Hz, 2H), 3.99 (dd, J_1 = 11.9 Hz, J_2 = 3.9 Hz, 1H), 3.87 (s, 3H), 3.76 (dd, J_1 = 11.9 Hz, J_2 = 2.7 Hz, 1H), 3.40–3.35 (m, 1H), 2.76–2.66 (m, 1H), 2.42–2.30 (m, 1H), 1.43 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 162.5, 141.2, 130.9, 126.1 (q, J = 275.9 Hz), 120.2, 113.9, 112.4, 63.8, 61.7, 51.3, 37.1 (q, J = 28.0 Hz), 33.9 (q, J = 2.7 Hz), 14.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.74. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{17}F_3NO_3$: 304.1155, found: 304.1159.

6-(*tert*-Butyl)-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3d). White solid. M. p. 116.3–118.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.08 (d, J = 8.3 Hz, 1H), 7.44 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 7.20 (d, J = 1.6 Hz, 1H), 4.04 (dd, J_1 = 12.0 Hz, J_2 = 3.9 Hz, 1H), 3.89 (s, 3H), 3.80 (dd, J_1 = 12.0 Hz, J_2 = 2.3 Hz, 1H), 3.44–3.41 (m, 1H), 2.75–2.66 (m, 1H), 2.40–2.32 (m, 1H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 156.8, 138.8, 128.7, 127.6 (q, J = 275.9 Hz), 125.4, 125.2, 123.7, 61.8, 51.39, 37.5 (q, J = 27.6 Hz), 35.1, 34.1 (q, J = 2.6 Hz), 31.0.

^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.59. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{16}H_{21}F_3NO_2$: 316.1519, found: 316.1521.

2-Methoxy-6-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3e). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.04 (s, 1H), 4.01 (dd, J_1 = 12.0 Hz, J_2 = 4.2 Hz, 1H), 3.88 (s, 1H), 3.79 (dd, J_1 = 12.0 Hz, J_2 = 2.5 Hz, 1H), 3.41–3.38 (m, 1H), 2.74–2.65 (m, 1H), 2.40 (s, 3H), 2.38–2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.4, 143.7, 139.1, 129.0, 128.8, 127.3, 126.1 (q, J = 27.7 Hz), 125.2, 61.8, 51.2, 37.2 (q, J = 27.7 Hz), 33.7 (q, J = 2.7 Hz), 21.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.75. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO_2$: 274.1049, found: 274.1056.

6-Ethyl-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3f). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.07 (d, J = 8.0 Hz, 1H), 7.25 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H), 7.05 (s, 1H), 4.02 (dd, J_1 = 12.0 Hz, J_2 = 3.9 Hz, 1H), 3.89 (s, 3H), 3.79 (dd, J_1 = 12.0 Hz, J_2 = 2.5 Hz, 1H), 3.43–3.38 (m, 1H), 2.73–2.66 (m, 3H), 2.39–2.32 (m, 1H), 1.25 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 149.9, 139.2, 129.0, 127.9, 126.2, 126.2 (q, J = 276.2 Hz), 125.5, 61.8, 51.3, 37.3 (q, J = 27.9 Hz), 33.8 (q, J = 2.7 Hz), 28.9, 15.1. ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.70. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{17}F_3NO_2$: 288.1206, found: 288.1211.

2-Methoxy-6-phenyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3g). White solid. M. p. 114.1–118.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (d, J = 2.0 Hz, 1H), 7.73 (dd, J_1 = 7.9 Hz, J_2 = 2.0 Hz, 1H), 7.63–7.61 (m, 2H), 7.46 (td, J_1 = 13.6 Hz, J_2 = 1.8 Hz, 2H), 7.40–7.36 (m, 1H), 7.31 (d, J = 7.9 Hz, 1H), 4.08 (dd, J_1 = 12.0 Hz, J_2 = 3.9 Hz, 1H), 3.91 (s, 3H), 3.83 (dd, J_1 = 12.0 Hz, J_2 = 3.0 Hz, 1H), 3.51–3.47 (m, 1H), 2.77–2.68 (m, 1H), 2.45–2.38 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.0, 141.4, 139.4, 137.8, 131.4, 128.9, 128.4, 127.9, 127.4, 127.2, 127.0, 126.2 (q, J = 276.0 Hz), 61.9, 51.4, 37.4 (q, J = 28.2 Hz), 33.5 (q, J = 2.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.64. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{18}H_{17}F_3NO_2$: 336.1206, found: 336.1203.

6-Fluoro-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3h). White solid. M. p. 78.9–82.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, J_1 = 8.7 Hz, J_2 = 5.8 Hz, 1H), 7.11 (td, J_1 = 17.0 Hz, J_2 = 2.5 Hz, 1H), 6.95 (dd, J_1 = 8.7 Hz, J_2 = 2.4 Hz, 1H), 4.05 (dd, J_1 = 12.0 Hz, J_2 = 3.9 Hz, 1H), 3.89 (s, 3H), 3.80 (dd, J_1 = 12.1 Hz, J_2 = 2.7 Hz, 1H), 3.46–3.41 (m, 1H), 2.75–2.67 (m, 1H), 2.44–2.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 163.2 (d, J = 152 Hz), 141.8 (d, J = 8.6 Hz), 131.8 (d, J = 9.5 Hz), 125.9 (q, J = 275.7 Hz), 124.2 (d, J = 2.7 Hz), 115.6 (d, J = 21.8 Hz), 113.8 (d, J = 22.2 Hz), 61.9, 51.2, 37.1 (q, J = 27.9 Hz), 33.7 (q, J = 2.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.69, –105.15. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{12}F_4NO_2$: 278.0799, found: 278.0801.

6-Chloro-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3i). White solid. M. p. 64.7–67.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, J = 8.4 Hz, 1H), 7.40 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 4.04 (dd, J_1 = 12.2 Hz, J_2 = 4.0 Hz, 1H), 3.89 (s, 3H), 3.80 (dd, J_1 = 12.1 Hz, J_2 = 2.7 Hz, 1H), 3.45–3.40 (m, 1H), 2.74–2.66 (m, 1H), 2.42–2.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 140.6, 139.1, 130.5, 128.7, 126.9, 126.5, 125.9 (q, J = 275.8 Hz), 61.9, 51.2, 37.1 (q, J = 28.1 Hz), 33.6 (q, J = 2.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.68. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{12}ClF_3NO_2$: 294.0503, found:294.0501.

6-Bromo-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3j). White solid. M. p. 74.7–76.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.93 (d, J = 8.4 Hz, 1H), 7.48 (dd, J_1 = 8.4 Hz, J_2 = 1.4 Hz, 1H), 7.34 (s, 1H), 3.96 (dd, J_1 = 12.2 Hz, J_2 = 3.8 Hz, 1H), 3.81 (s, 3H), 3.72 (d, J = 12.0 Hz, 1H), 3.37–3.33 (m, 1H), 2.69–2.55 (m, 1H), 2.37–2.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3, 140.7, 131.6, 130.5, 129.9, 127.6, 126.8, 125.9 (q, J = 275.9 Hz), 61.9, 51.1, 37.1 (q, J = 28.1 Hz), 33.4 (q, J = 2.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.66. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{12}BrF_3NO_2$: 337.9998, found: 337.9998.

6-Iodo-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3k). White solid, 76% yield. M. p. 68.6–72.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.85 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.62 (s ,1H), 4.02 (dd, J_1 = 12.2 Hz, J_2 = 4.0 Hz, 1H), 3.88 (s, 3H), 3.78 (dd, J_1 = 12.2 Hz, J_2 = 2.4 Hz, 1H), 3.41–3.37 (m, 1H), 2.73–2.64 (m, 1H), 2.40–2.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.6, 140.6, 137.7, 135.8, 130.4, 127.5, 125.9 (q, J = 275.3 Hz), 100.1, 61.9, 51.1, 37.2 (q, J = 28.0 Hz), 33.4 (q, J = 2.7 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.66. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{12}F_3INO_2$: 385.9859, found: 385.9862.

2-Methoxy-4-(2,2,2-trifluoroethyl)-6-(trifluoromethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3l). White solid, 64% yield. M. p. 91.7–93.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.29 (d, J = 8.2 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.51 (s, 1H), 4.09 (dd, J_1 = 12.2 Hz, J_2 = 4.0 Hz, 1H), 3.91 (s, 3H), 3.83 (dd, J_1 = 4.7 Hz, J_2 = 2.6 Hz, 1H), 3.55–3.52 (m, 1H), 2.77–2.68 (m, 1H), 2.45–2.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.5, 139.6, 134.6 (q, J = 130.2 Hz), 133.1, 131.1, 129.6, 125.1 (q, J = 3.7 Hz), 124.0 (q, J = 3.5 Hz), 123.2 (q, J = 254.0 Hz), 61.9, 51.0, 37.2 (q, J = 28.1 Hz), 32.5 (q, J = 2.4 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.11, –63.60. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{12}F_6NO_2$: 328.0767, found: 328.0769.

Methyl-2-methoxy-1-oxo-4-(2,2,2-trifluoroethyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylate (3m). White solid, 62% yield. M. p. 114.3–115.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.23 (d, J = 8.2 Hz, 1H), 8.06 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.92 (s, 1H), 4.07 (dd, J_1 = 12.2 Hz, J_2 = 4.0 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.85 (dd, J_1 = 12.2 Hz, J_2 = 2.8 Hz, 1H), 3.55–3.51 (m, 1H), 2.75–2.66 (m, 1H), 2.45–2.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8, 161.9, 139.1, 134.1, 131.7, 129.3, 129.2, 128.1, 127.3 (q, J = 275.7 Hz), 61.9, 52.6, 51.0, 37.2 (q, J = 28.3 Hz), 33.7 (q, J = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: –63.59. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{15}F_3NO_4$: 318.0948, found: 318.0952.

2-Methoxy-4-(2,2,2-trifluoroethyl)-6-(trifluoromethoxy)-3,4-dihydroisoquinolin-1(*2H*)-one (3n). Pale yellow oil, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, J = 8.6 Hz, 1H), 7.26 (dd, J_1 = 8.6 Hz, J_2 = 1.2 Hz, 1H), 7.08 (s, 1H), 4.07 (dd, J_1 = 12.0 Hz, J_2 = 4.0 Hz, 1H), 3.90 (s, 3H), 3.80 (dd, J_1 = 12.2 Hz, J_2 = 2.8 Hz, 1H), 3.47–3.44 (m, 1H), 2.75–2.66 (m, 1H), 2.42–2.37 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.0, 152.3, 141.2, 131.3, 126.4, 125.9 (q, J = 275.6 Hz), 121.5, 120.2, 118.7, 61.9, 51.3, 37.3 (q, J = 28.4 Hz), 33.8 (q, J = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −57.65, −63.62. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{12}F_6NO_3$: 344.0716, found: 344.0719.

2-Methoxy-7-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3o) and 2-Methoxy-5-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (1:2.2) (3o'). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (dd, J_1 = 7.4 Hz, J_2 = 0.56 Hz, 0.71H), 7.96 (d, J = 0.6 Hz, 0.29H), 7.37–7.29 (m, 1.74H), 7.12 (d, J = 7.8 Hz, 0.28H), 3.99 (td, J_1 = 26.9 Hz, J_2 = 4.1 Hz, 1H), 3.89 (m, 1.98 H), 3.88 (m, 1.06H), 3.80 (td, J_1 = 35.1 Hz, J_2 = 2.7 Hz, 1H), 3.55–3.53 (m, 0.77H), 3.49–3.38 (m, 0.34H), 2.79–2.64 (m, 1H), 2.38 (s, 0.93H), 2.36 (s, 2.09H), 2.34–2.03 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 163.1, 138.2, 137.4, 136.1, 134.8, 134.1, 133.6, 130.3, 129.1, 128.3, 128.0, 127.7, 127.6, 126.9, 126.7, 126.2 (q, J = 275.7 Hz), 124.8, 61.7, 61.7, 51.4, 50.3, 37.3 (q, J = 27.8 Hz), 34.8 (q, J = 27.8 Hz), 33.3 (q, J = 2.7 Hz), 30.6 (q, J = 2.4 Hz), 20.9, 18.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.70, −64.11. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO_2$: 274.1049; found: 274.1049.

2,5-Dimethoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3p). White solid. M. p. 91.3–92.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (dd, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.05 (dd, J_1 = 8.2 Hz, J_2 = 0.7 Hz, 1H), 3.94 (dd, J_1 = 12.3 Hz, J_2 = 4.0 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.85 (dd, J_1 = 12.1 Hz, J_2 = 1.2 Hz, 1H), 3.76 (d, J = 10.9 Hz, 1H), 2.62–2.53 (m, 1H), 2.32–2.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2, 155.0, 129.2, 128.9, 127.4, 126.4 (q, J = 275.8 Hz), 120.4, 114.1, 61.7, 55.8, 50.4, 34.6 (q, J = 27.8 Hz), 27.8 (q, J = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.80. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO_3$: 290.0999, found: 290.1001.

7-Fluoro-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3q) and 5-Fluoro-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (1:1.4) (3q'). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.96 (d, J = 7.7 Hz, 0.59H), 7.82 (dd, J_1 = 9.0 Hz, J_2 = 2.6 Hz, 0.41H), 7.45–7.39 (m, 0.65H), 7.29–7.19 (m, 1.44H), 4.05 (td, J_1 = 24.6 Hz, J_2 = 3.4 Hz, 1H), 3.90 (s, 3H), 3.86–3.71 (m, 1.51H), 3.48–3.43 (m, 0.52H), 2.77–2.62 (m, 1H), 2.44–2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6, 162.1 (d, J = 3.0 Hz), 161.8 (d, J = 2.2 Hz), 161.1, 159.6, 157.2, 134.7 (d, J = 3.4 Hz), 130.2, 130.1, 129.9 (d, J = 2.9 Hz), 129.6, 129.5, 128.9, 128.8, 127.2, 126.2, 126.0, 124.54 (q, J = 275.9 Hz), 124.48, 124.4 (d, J = 3.3 Hz), 120.0, 119.8, 119.6, 119.4, 115.4, 115.2, 61.8, 51.3, 50.5, 37.3 (q, J = 28.3 Hz), 35.5 (q, J = 28.2 Hz), 33.1 (q, J = 2.5 Hz), 27.3 (q, J = 2.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.67, −63.95, −112.45, −119.89. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{12}F_4NO_2$: 278.0799, found: 278.0801.

Chloro-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3r). White solid. M. p. 68.1–70.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.04 (dd, J_1 = 7.0 Hz, J_2 = 1.2 Hz, 1H), 7.50 (dd, J_1 = 6.9 Hz, J_2 = 1.2 Hz, 1H), 7.32 (t, J = 7.9 Hz, 1H), 3.93 (dd, J_1 = 8.8 Hz, J_2 = 3.8 Hz, 1H), 3.85 (d, J = 1.2 Hz, 1H), 3.83 (s, 3H), 3.75 (d, J = 11.2 Hz, 1H), 2.66–2.52 (m, 1H), 2.31–2.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.9, 136.6, 133.6, 132.1, 130.1, 129.3, 127.6, 126.0 (q, J = 276.2 Hz), 61.9, 49.8, 34.2 (q, J = 28.4 Hz), 31.4 (q, J = 2.6 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.69. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{12}ClF_3NO_2$: 294.0503, found: 294.0506.

5-Bromo-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3s). White solid. M. p. 70.1–72.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.31 (t, J = 7.9 Hz, 1H), 4.01 (dd, J_1 = 12.4 Hz, J_2 = 3.4Hz, 1H), 3.93 (s, 1H), 3.90 (s, 3H), 3.80 (d, J = 12.0 Hz, 1H), 2.69–2.60 (m, 1H), 2.37–2.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.7, 138.2, 137.0, 130.2, 129.6, 128.4, 126.0 (q, J = 276.3 Hz), 122.3, 61.9, 49.6, 34.4 (q, J = 28.2 Hz), 33.9 (q, J = 2.9 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.51. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{12}BrF_3NO_2$: 337.9998, found: 337.9998.

2-Methoxy-8-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3t). White solid. M. p. 59.1–59.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 6.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 3.98 (dd, J_1 = 12.2 Hz, J_2 = 3.5 Hz, 1H), 3.90 (s, 3H), 3.86 (d, J = 1.5 Hz, 1H), 3.55 (d, J = 11.0 Hz, 1H), 2.79–2.70 (m, 1H), 2.37 (s, 3H), 2.17–2.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.1, 137.4, 134.8, 134.1, 128.2, 128.0, 126.8, 126.2 (q, J = 276.1 Hz), 61.6, 50.2, 34.7 (q, J = 27.7 Hz), 30.5 (q, J = 2.4 Hz), 18.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −64.12. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO_2$: 274.1049, found: 274.1054.

2-Methoxy-5,7-dimethyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3u). White solid. M. p. 71.8–74.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.84 (s, 1H), 7.19 (s, 1H), 3.96 (dd, J_1 = 12.1 Hz, J_2 = 3.6 Hz, 1H), 3.89 (s, 3H), 3.85 (dd, J_1 = 12.1 Hz, J_2 = 1.6 Hz, 1H), 3.51 (d, J = 10.9 Hz, 1H), 2.77–2.68 (m, 1H), 2.34 (s, 3H), 2.33 (s, 3H), 2.14–2.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 137.8, 135.6, 134.5, 133.9, 128.0, 127.1, 126.2 (q, J = 276.0 Hz), 61.6, 50.3, 34.8 (q. J =27.5 Hz), 30.2 (q, J = 2.4 Hz), 20.7, 18.0. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −64.13. HRMS (ESI) ([M + H]$^+$) CalcdFor $C_{14}H_{17}F_3NO_2$: 288.1206, found: 288.1210.

5,7-Dichloro-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3v). White solid. M. p. 98.3–99.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.01 (d, J = 2.2 Hz, 1H), 7.50 (d, J = 2.2 Hz, 1H), 3.93 (dd, J_1 = 8.8 Hz, J_2 = 3.8 Hz, 1H), 3.85 (dd, J_1 = 6.8 Hz, J_2 = 1.5 Hz, 1H), 3.82 (s, 3H), 3.71 (d, J = 11.2 Hz, 1H), 2.64–2.50 (m, 1H), 2.27–2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.7, 135.2, 134.9, 133.1, 132.9, 131.0, 127.6, 125.9 (q, J = 276.2 Hz), 61.9, 49.6, 34.2 (q, J = 28.4 Hz), 31.0 (q, J = 2.6 Hz). ^{19}F

NMR (376 MHz, $CDCl_3$) δ: −63.70. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{11}Cl_2F_3NO_2$: 328.0113, found: 328.0115.

2,5,6-Trimethoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3w). White solid. M. p. 121.7–123.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (s, 1H), 6.64 (s, 1H), 4.01 (dd, J_1 = 11.9 Hz, J_2 = 4.0 Hz, 1H), 3.94 (d, J = 1.6 Hz, 6H), 3.88 (s, 3H), 3.77 (dd, J_1 = 11.9 Hz, J_2 = 2.4 Hz, 1H), 3.37–3.32 (m, 1H), 2.75–2.66 (m, 1H), 2.40–2.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.7, 152.8, 149.0, 132.9, 127.6 (q, J = 275.9 Hz), 120.5, 110.6, 109.0, 61.9, 56.2, 51.7, 37.3 (q, J = 27.8 Hz), 33.6 (q, J = 2.6 Hz), 29.64. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.63. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{14}H_{17}F_3NO_4$: 320.1104, found: 320.1109.

5,6-Dichloro-2-methoxy-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3x). White solid. M. p. 116.0–117.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.06 (d, J = 8.4 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 4.01 (dd, J_1 = 12.6 Hz, J_2 = 3.7 Hz, 1H), 3.93 (d, J = 1.5 Hz, 1H), 3.90 (s, 3H), 3.85 (d, J = 12.5 Hz, 1H), 2.71–2.62 (m, 1H), 2.35–2.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.4, 138.6, 138.2, 130.5, 130.2, 128.2, 128.0, 125.9 (q, J = 276.2 Hz), 61.9, 49.8, 34.0 (q, J = 28.5 Hz), 32.4 (q, J = 2.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.66. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{12}H_{11}Cl_2F_3NO_2$: 328.0113, found: 328.0116.

3-Methoxy-1-(2,2,2-trifluoroethyl)-2,3-dihydrobenzo[f]isoquinolin-4(*1H*)-one (3y). White solid. M. p. 96.3–98.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.22 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.94–7.88 (m, 2H), 7.69–7.62 (m, 2H), 4.16–4.08 (m, 2H), 4.03 (dd, J_1 = 12.0 Hz, J_2 = 1.3 Hz, 1H), 3.95 (s, 3H), 2.89–2.80 (m, 1H), 2.38–2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.8, 136.5, 135.7, 129.3, 128.8, 128.6, 128.1, 127.8, 126.3 (q, J = 276.1 Hz), 125.7, 124.0, 123.1, 62.0, 50.4, 34.9 (q, J = 27.7 Hz), 30.0 (q, J = 2.5 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.79. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{16}H_{15}F_3NO_2$: 310.1049, found: 310.1049.

2-Methoxy-4-methyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3aa). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.18 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H), 7.54 (td, J_1 = 15.2 Hz, J_2 = 1.5 Hz, 1H), 7.41 (td, J_1 = 15.2 Hz, J_2 = 1.0 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 3.91 (s, 3H), 3.79 (d, J = 12.0 Hz, 1H), 3.72 (d, J = 12.0 Hz, 1H), 2.67 –2.60 (m, 1H), 2.47–2.41 (m, 1H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.2, 143.6, 132.9, 129.0, 128.0, 127.3, 125.5 (q, J = 276.9 Hz), 124.3, 61.8, 57.2, 41.5 (q, J = 27.1 Hz), 37.1 (q, J = 1.2 Hz), 22.9. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −59.59. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO_2$: 274.1049, found: 274.1051.

2,6-Dimethyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3ab). White solid. M. p. 91.9–92.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J = 7.9 Hz, 1H), 7.19 (d, J = 7.9 Hz, 1H), 7.01 (s, 1H), 3.83 (dd, J_1 = 13.0 Hz, J_2 = 3.6 Hz, 1H), 3.45 (dd, J_1 = 13.0 Hz, J_2 = 2.6 Hz, 1H), 3.22–3.19 (m, 1H), 3.16 (s, 3H), 2.59–2.50 (m, 1H), 2.39 (s, 3H), 2.34–2.27 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.5, 142.8, 139.8, 128.8, 128.7, 126.9, 126.3 (q, J = 275.8 Hz), 126.0, 51.1, 36.9 (q, J = 27.8 Hz), 35.2 (q, J = 2.6 Hz), 32.5, 21.5. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −63.77. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO$: 258.1100, found: 258.1104.

(S)-2-Ethyl-4-(2,2,2-trifluoroethyl)-3,4-dihydroisoquinolin-1(*2H*)-one (3ac). White solid. M. p. 97.5–99.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.40 (m, 4H), 4.60 (s, 1H), 4.28–3.82 (m, 2H), 3.45–3.36 (m, 2H), 2.42–2.04 (m, 2H), 1.14 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.4, 135.8, 130.2, 129.9, 128.5, 128.2, 126.5, 126.0 (q, J = 275.2 Hz), 66.3, 51.8, 45.7, 39.6 (q, J = 27.2 Hz), 13.9. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{14}F_3NO$: 257.1027, found: 257.1031.

(S)-2-Methoxy-4-((S)-1,1,1-trifluoropropan-2-yl)-3,4-dihydroisoquinolin-1(*2H*)-one (3ah). White solid. M. p. 95.9–97.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, J = 7.2 Hz, 1H), 7.67 (s, 1H), 7.48 (d, J = 7.4 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 4.32–4.26 (m, 2H), 4.22–4.17 (m, 1H), 3.84–3.74 (m, 1H), 3.48 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 199.9, 170.3, 133.6, 133.0, 131.2, 130.1, 128.2 (q, J = 3.5 Hz), 127.1 (q, J = 279.2 Hz), 61.3, 53.6 (q, J = 25.3 Hz), 42.4, 30.8, 29.6. ^{19}F NMR (376 MHz, $CDCl_3$) δ: −66.21. HRMS (ESI) ([M + H]$^+$) Calcd For $C_{13}H_{15}F_3NO_2$: 274.1049, found: 274.1047.

(3,3,3-Trifluoroprop-1-ene-1,1-diyl)dibenzene (5). Colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (t, J = 3.0 Hz, 3H), 7.35–7.30 (m, 3H), 7.25–7.22 (m, 4H), 6.12 (q, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.5 (q, J = 5.3 Hz), 140.1, 137.3, 129.4, 129.11, 129.09, 128.5, 128.0, 127.9, 123.3 (q, J = 269.0 Hz), 115.5 (q, J = 33.6 Hz). HRMS (ESI) ([M + H]$^+$) Calcd For $C_{15}H_{12}F_3$: 249.0886, found: 249.0889.

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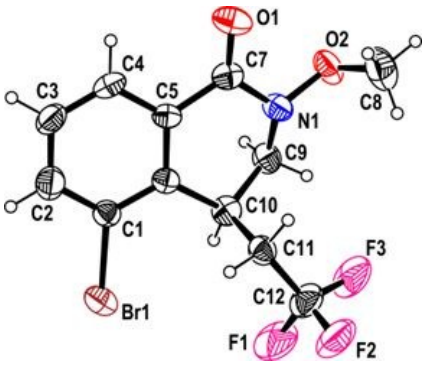
13 X-Ray single crystal structure of **3s** (CCDC: 1874460).



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Visible-light-induced radical cyclization of *N*-allylbenzamide with CF_3SO_2Na to trifluoromethylated dihydroisoquinolinones in water at room temperature

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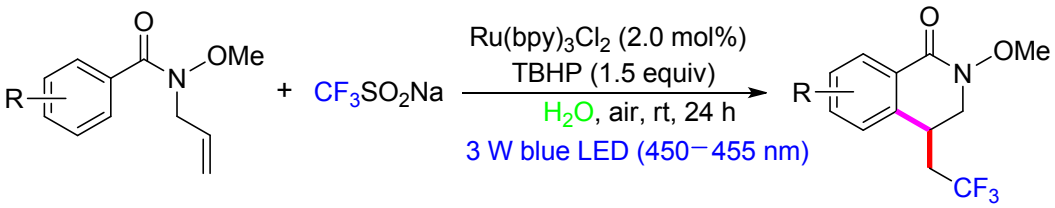
Abstract **:** An efficient strategy for the preparation of trifluoromethylated dihydroisoquinolinones *via* visible-light induced radical cyclization of *N*-allylbenzamide with CF_3SO_2Na was developed.



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