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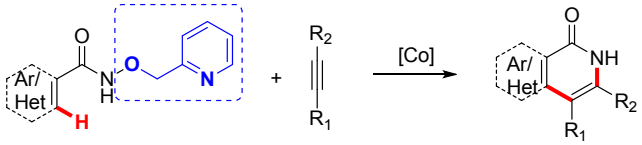
Graphic abstract



- new traceless directing group
- mild reaction conditions
- Cp*-free cobalt catalyzed
- 34 examples, up to 94% yield

ABSTRACT: A new traceless directing group, 2-(hydroxymethyl)pyridine, has been reported for the Cp*-free cobalt-catalyzed C–H activation/annulation reaction to synthesize isoquinolinones. The reaction exhibits good functional group tolerance, affording products in good to excellent isolated yields under mild conditions. Notably, the directing group can be removed directly *in situ* along the catalytic process.

INTRODUCTION

Research on efficient and convenient synthesis of heterocyclic compounds has increased significantly over the past decades. Among them, nitrogen-containing heterocyclic aromatic hydrocarbons, especially isoquinolinone and its derivatives, have aroused eager attention due to their remarkable pharmacological importance ranging from anticancer and antihypertensive.[1] Alternatively, transition-metal catalyzed C–H activation/annulations have emerged as an effective method for concise synthesis of heterocycles in recent years.[2]

In general, transition metal-catalyzed C–H activation relies mainly on precious metal (such as Ru[3], Rh[4], or Pd[5]) catalysts. In spite of their high catalytic activity, these metals are less abundant. So it would be advantageous if more-abundant first-row metal catalysts could emulate the reactivity of a noble-metal catalyst and enable comparable catalytic efficacy. To this, cobalt salts entered the focus of attention in C–H activation chemistry due to its low cost, low toxicity, unique reactivity, and abundant availability from the natural sources.[6] Recently, the groups of Daugulis,[7] Ackermann,[8] Song,[9] and others[10] have reported that air-stable commercially available Co^{II}/Co^{III} salts were applied to C(sp^2)–H activation/annulation assisted by a bidentate directing group.

On the other hand, the directing group was seen as the key to reaction acceleration control. It was also believed that bidentate auxiliaries could generate stable metallacycles and promote C–H activation. Nevertheless, the directing groups are generally difficult to remove after the catalytic procedure. For example, Daugulis

described that a methoxy group mounted on 8-aminoquinoline makes removal of the directing groups possible, while it is expensive and requires harsh reaction conditions.[7b] The multiple chemical steps involving removal of directing groups also mean low step economy and limit the application. Therefore, traceless directing groups, which can be removed directly *in situ* along the catalytic process, exhibit great potential in the bidentate directing group systems.[11] However, the functional groups that could be employed as the traceless directing groups remain relatively rare.[12] More recently, Cp*Co(III) catalyzed N-O or N-N bond cleavage type reactions had been well established for heterocycles synthesis.[13] It would be advantageous for the C−H activation/annulation using more cheaper and readily available Cp*-free cobalt salts based on a traceless directing group.

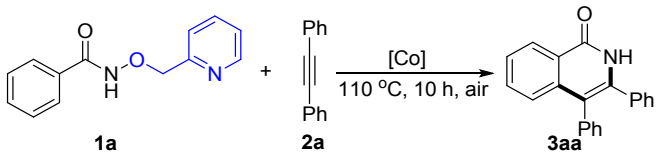
Guided by the aforementioned progress and our previous work,[14] we have attempted to develop novel protocols for concise synthesis of heterocycles using cheap and earth abundant cobalt catalyst. Herein, we report an efficient cobalt-catalyzed C(sp^2)–H bond activation/annulation based on a new traceless bidentate directing group to synthesize isoquinolinone derivatives. In this reaction, 2-(hydroxymethyl)pyridine was firstly used as a non-marking guide group, which could be removed directly *in situ* along the catalytic process.

RESULT AND DISCUSSION

We commenced our study by exploring reaction conditions with *N*-(pyridin-2-ylmethoxy)benzamide **1a** and diphenylacetylene **2a** (Table 1). Initially, the desired product **3aa** was observed in 22% isolated yield in the presence of

$Co(OAc)_2·4H_2O$, AgOAc in HFIP at 110 °C for 10 h (entry 1). Among the solvents examined, TFE exhibited the best transformation, giving the product **3aa** in 36% yield (entries 1-4). Encouraged by the solvent-change results, we then screened some bases or acids for the reaction. It was gratifying that, the yield rapidly increased to 64% when PivOH was added (entries 5-9). Meanwhile, the addition of KOAc also gave good yield of 62%, which indicated that reaction might require a large amount of acetate or pivalate for ligand exchange in the catalytic progress. Subsequent investigations indicated that a change of cobalt salts could not improve the reaction efficiency (entries 10-12).

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3aa**

Entry	Catalyst	Oxidant	Acid/Base	Solvent	Yields (%)
1	$Co(OAc)_2·4H_2O$	AgOAc		HFIP	22
2	$Co(OAc)_2·4H_2O$	AgOAc		TFE	36
3	$Co(OAc)_2·4H_2O$	AgOAc		EtOH	33
4	$Co(OAc)_2·4H_2O$	AgOAc		CH_3CN	29
5	$Co(OAc)_2·4H_2O$	AgOAc	KOAc	TFE	62
6	$Co(OAc)_2·4H_2O$	AgOAc	AcOH	TFE	53
7	$Co(OAc)_2·4H_2O$	AgOAc	PhCOOH	TFE	35
8	$Co(OAc)_2·4H_2O$	AgOAc	1-AdCOOH	TFE	55
9	$Co(OAc)_2·4H_2O$	AgOAc	PivOH	TFE	64
10	$CoCl_2·6H_2O$	AgOAc	PivOH	TFE	59
11	$CoC_2O_4·4H_2O$	AgOAc	PivOH	TFE	41
12	Cp*Co(CO)I_2	AgOAc	PivOH	TFE	40
13	$Co(OAc)_2·4H_2O$	Ag_2CO_3[b]	PivOH	TFE	43
14	$Co(OAc)_2·4H_2O$	AgOTf	PivOH	TFE	trace
15	$Co(OAc)_2·4H_2O$	AgTFA	PivOH	TFE	7
16[c,d]	$Co(OAc)_2·4H_2O$	AgOAc	PivOH	TFE	72
17[c,d,e]	$Co(OAc)_2·4H_2O$	AgOAc	PivOH	TFE	79
18[c,e,f]	$Co(OAc)_2·4H_2O$	AgOAc	PivOH	TFE	87

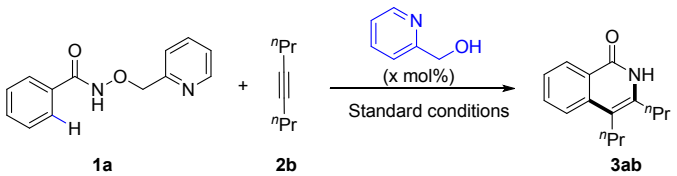
[a]Reaction conditions: substrate **1a** (0.2 mmol), **2** (0.3 mmol), $Co(OAc)_2·4H_2O$ (20 mol%), Oxidant

(2.0 equiv), Acid/Base (2.0 equiv), air atmosphere, solvent (1 mL), 10 h, isolated yields. [b]Ag_2CO_3 (1.0 eq). [c]$Co(OAc)_2{\cdot}4H_2O$ (40 mol%). [d]AgOAc (1.5 eq). [e]4-octyne instead of diphenylacetylene. [f]AgOAc (1.0 eq).

Changing the type of oxidant caused a decrease in yields (entries 13-15). The yield had no enhance after adding various additives (see SI). Therefore, we had to increase the amount of catalyst to 40 mol% and the yield rose to 72%. Considering the steric hindrance of diphenylacetylene which may inhibit the alkyne coordination to the metal center, 4-octyne **2b** was employed instead of diphenylacetylene **2a**. As a result, we obtained the target product **3ab** in 79% yield (entry 17). Reducing the amount of oxidant from 1.5 equiv to 1.0 equiv improved the reaction yield significantly (87%, entry 18).

According to previous studies,[15] we speculate that the high catalyst loading (40 mol%) required for this reaction is due to the coordination of metal with the 2-(hydroxymethyl)pyridine formed by the reaction which may reduce the catalytic activity of Co catalyst. In order to verify this speculation, we performed the reaction of **1a** and **2b** with additional 2-(hydroxymethyl)pyridine under the optimized reaction conditions. The yield of product **3ab** indeed decreased gradually with increasing the amount of 2-(hydroxymethyl)pyridine (Table 2).

Table 2. Effect of the Concentration of 2-(Hydroxymethyl)pyridine on the Yield of 3ab[a]



Entry	Additive (x mol%)	Yield (%)
1	20	72
2	40	45

3	60	31
4	80	25
5	100	25

[a]Reaction conditions: substrate **1a** (0.2 mmol), **2b** (0.3 mmol), $Co(OAc)_2 \cdot 4H_2O$ (40 mol%), TFE (1.0 mL), AgOAc (1.0 equiv), PivOH (2.0 equiv), additive (x mol%), air atmosphere, 10 h, isolated yields.

In addition, the influences of directing group for the reaction were discussed as follows (see Figure 1). The results indicated that substrate **1a** (as for **D**) exhibited a preferable reactivity for the reaction under identical conditions. No expected products were obtained when substrates **A**-**C**, **F** were used, and the substrate **E** gave **3ab** in relatively low yield.

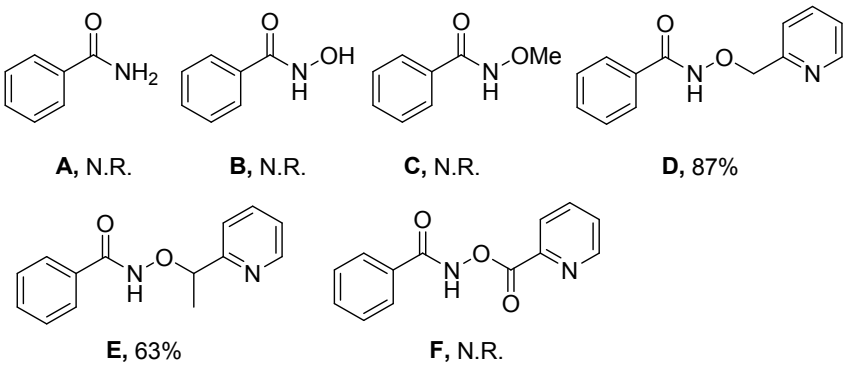
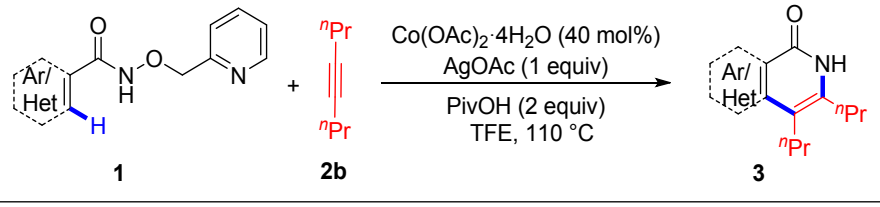


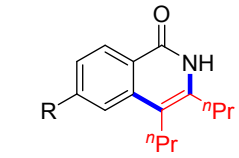
Figure 1. The influences of directing group for the reaction.

The optimized synthetic conditions allowed us to explore the substrate scope. Therefore, we first investigated the substrate scope of this reaction between various substrate **1** derivatives and 4-octyne **2b**. As shown in Table 3, a wide variety of functionalized *N*-(pyridin-2-ylmethoxy)benzamides were well tolarated by the cobalt catalyst to deliver the targeted products **3**. For example, benzamides with the electron-donating groups at the *para* position, such as methyl, ethyl, *tert*-butyl, and phenyl promoted this transformation smoothly. The desired products (**3bb**−**3db**, **3lb**) were obtained in excellent yields (79%−83%). *para*-Methoxy substituted benzamide

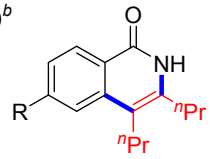
gives the desired product (**3eb**) in a relatively-low yield. In contrast, benzamides substituted with electron-withdrawing groups, such as -F, -Cl, -Br, -I, -CF_3, and -COOMe also reacted with **2b** smoothly, giving the corresponding products in 45-75% yields (**3fb**–**3kb**). When the -F substitution exists on the *meta* position, the reaction gave a regioisomeric mixture in good yields (**3ob**). With the steric hindrance of the

Table 3. Co(III)-Catalyzed Synthesis of Isoquinolinone Derivatives[a]

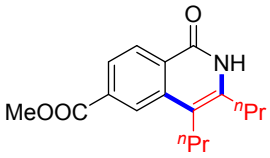




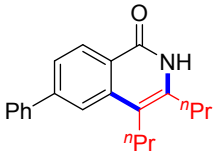
3ab: R = H, 87% (61%)[b]
3bb: R = Me, 82%
3cb: R = Et, 83%
3db: R = ^{t}Bu, 79%
3eb: R = OMe, 36%



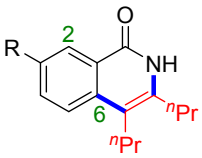
3fb: R = F, 71%
3gb: R = Cl, 75%
3hb: R = Br, 71%
3ib: R = I, 72%
3jb: R = CF_3, 45%



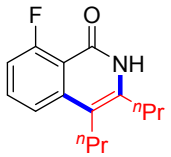
3kb, 60%



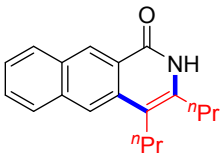
3lb, 83%



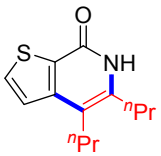
3mb: R = Me, 86%
3nb: R = OMe, 64%
3ob: R = F, 76% (2.4:1)[c]
3pb: R = Cl, 72%
3qb: R = CF_3, 37%



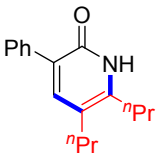
3rb, 46%[d]



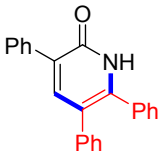
3sb, 46%



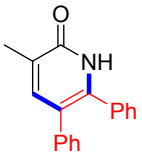
3tb, 56%



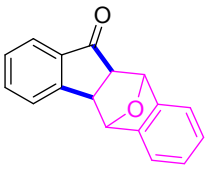
3ub, 67%



3ua, 67%[e]



3va, 64%[e]

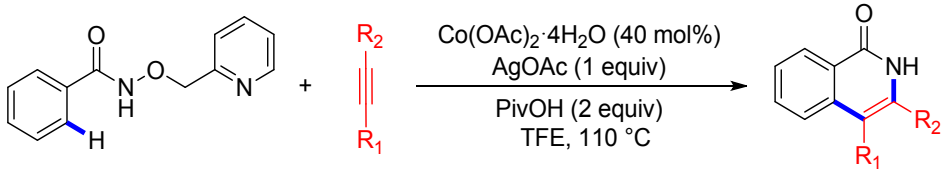


4, 23%[f]

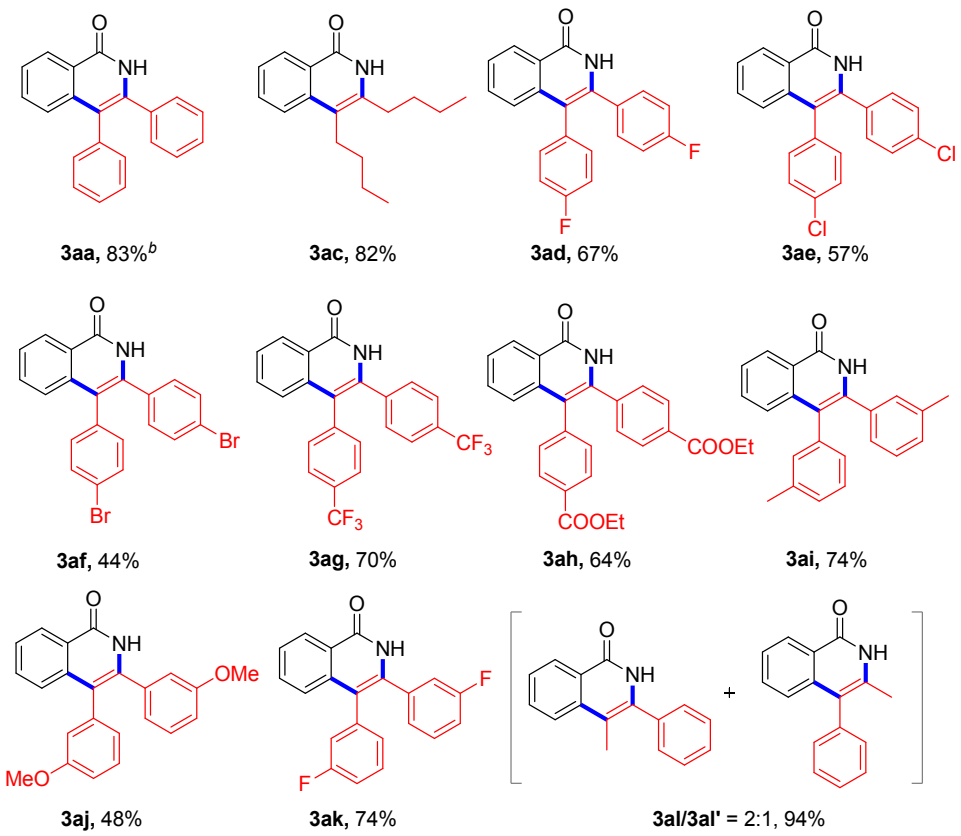
[a]Reaction conditions: substrate **1** (0.2 mmol), **2b** (0.3 mmol), $Co(OAc)_2·4H_2O$ (40 mol%), TFE (1.0 mL), AgOAc (1.0 equiv), PivOH (2.0 equiv), air atmosphere, 10 h, isolated yields. [b]Yield of 1.0 mmol scale. [c]The regioisomeric ratio was given in parentheses (C_6:C_2 = 2.4:1). [d]14 h. [e]Diphenylacetylene instead of **2b**. [f]7-Oxabenzonorbornadiene instead of **2b**.

meta-substituent increasing, the reaction occured only in the less obstructed position, exhibiting good regioselectivity (**3mb**, **3nb**, **3pb**, **3qb**). For instance, **3mb** was generated in an excellent yield of 86%. When a sterically hindered *ortho*-fluoro substituted *N*- (pyridin-2-ylmethoxy)benzamide was employed, the annulated product was given in moderate yield (**3rb**). This indicated that the steric hindrance of *ortho*-substitution had a significant effect on the efficiency of the reaction. In addition, the **1s** derived from a bicyclic system was smoothly converted to the corresponding benzo[*h*]-isoquinolinone **3sb**. It should be noted that the heteroarene and terminal olefins substrates were still compatible in this transformation (**3tb**, **3ub**, **3ua**, **3va**). To further reinforce the generality and practicality of the directing group, we targeted 7-oxabenzonorbornadiene with **1a** in the optimal conditions. Surprisingly, an unexpected five-membered [3+2] annulation product **4** was obtained in 23% yield.[15]

Table 4. Substrate Scope for Alkynes[a]



1a **2** **3**



3aa, 83%[b] **3ac**, 82% **3ad**, 67% **3ae**, 57%

3af, 44% **3ag**, 70% **3ah**, 64% **3ai**, 74%

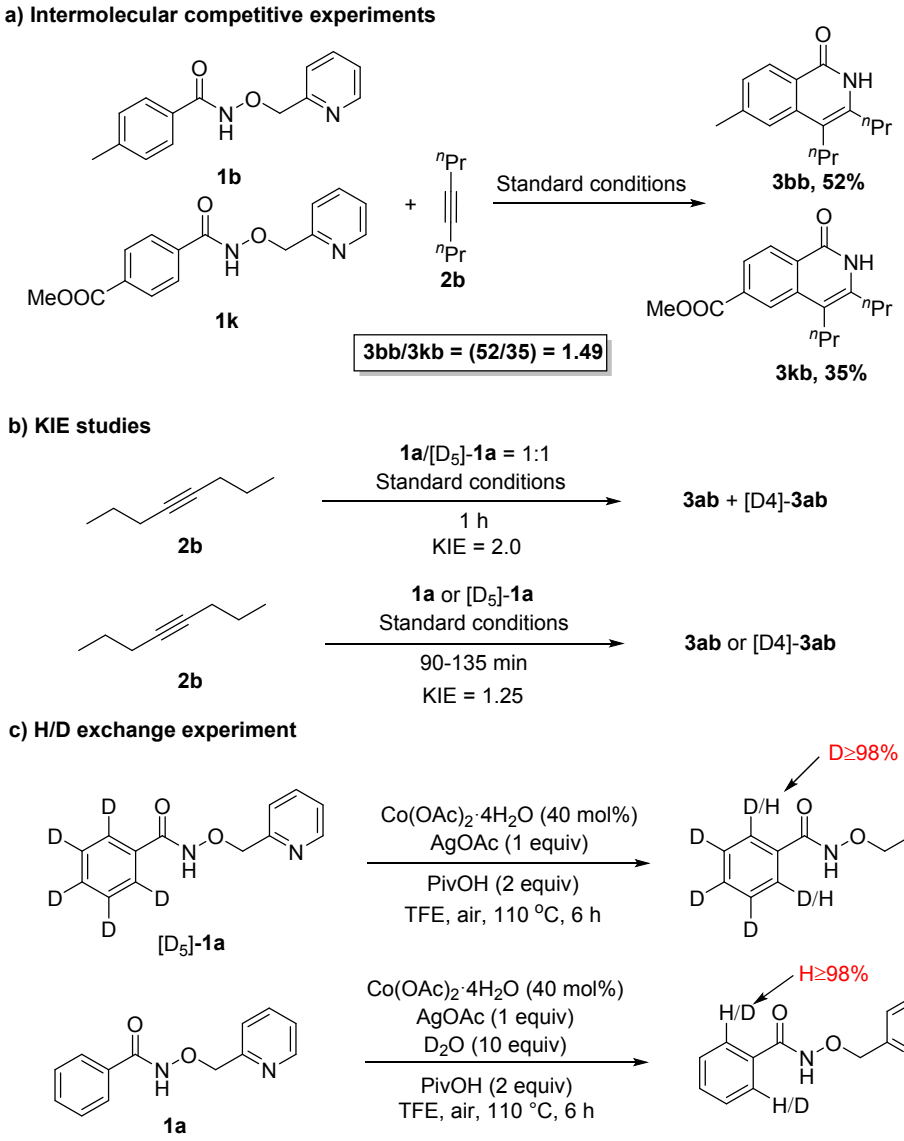
3aj, 48% **3ak**, 74% **3al/3al'** = 2:1, 94%

[a]Reaction conditions: substrate **1a** (0.2 mmol), **2** (0.3 mmol), $Co(OAc)_2{\cdot}4H_2O$ (40 mol%), TFE (1.0 mL), AgOAc (1.0 equiv), PivOH (2.0 equiv), air atmosphere, 10 h, isolated yields.

Subsequently, we investigated the scope of alkynes and experimental results are illustrated in Table 4. To our delight, we extended the length of the alkyl chain and the desirable target product was still obtained in 82% yield (**3ac**). The reaction gave product **3aa** in pleasant yield 83% under optimal conditions. Using 1.5 equiv of AgOAc as oxidant gave lower yield 72% (entry 16, Table 1). Phenylacetylenes with a para-substituent on the benzene ring such as -F (**3ad**), -Cl (**3ae**), -Br (**3af**), -CF_3 (**3ag**), and -COOEt (**3ah**) groups were also well tolerated, providing ample opportunities for further derivatization of the products. Furthermore, the desired products were obtained in good yields for *meta*-substituted tolanes, such as methyl (**3ai**, 74%), methoxy (**3aj**, 48%), and fluoro (**3ak**, 74%) groups. In addition, unsymmetrical

internal aryl alkyne, 1-phenylpropyne **2l**, was tested as substrate, giving a regioisomeric mixture (**3al**:**3al′** = 2:1) in 94% total yield. In addition, terminal alkynes (such as: 1-octyne or phenylacetylene) were employed under standard conditions, but no target product was detected.

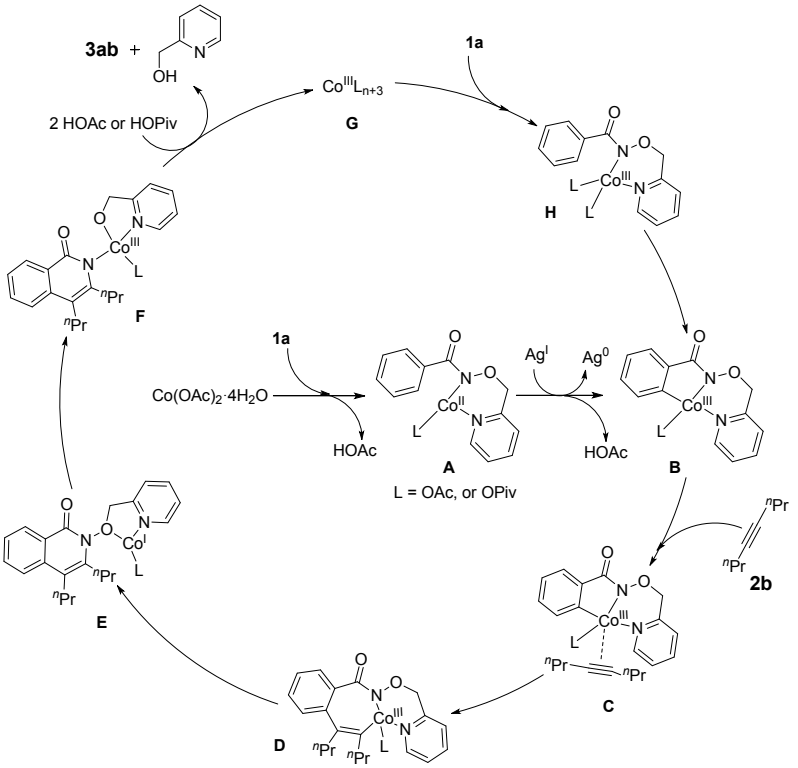
In order to gain further insight into the nature of the present reaction, the following experiments were performed to probe the reaction mechanism (Scheme 1). The competition experiment between **1b**/**1k** and **2b** was performed and revealed the preferred reaction for electron-rich **1b** (**3bb**/**3kb** = 1.49, Scheme 1a). An intermolecular kinetic isotope effect (KIE) experiment was carried out between benzamide **1a** and isotopically labelled substrate [D_5]-**1a** (Scheme 1b), resulting in a KIE value of approximately 2.0, suggesting that the formation of organometallic intermediates in the catalytic cycle might be affected by the H/D isotope. Then, a kinetic isotope effect (KIE) value of 1.25 was observed between **1a** or [D_5]-**1a** with **2b** in the parallel experiments. Furthermore, no H/D exchange could be detected in both the reaction of isotopically labeled substrates [D_5]-**1a** and **1a**/**D_2O** under standard reaction conditions without **2b**, indicating presumable irreversibility of the C–H cobaltation step (Scheme 1c).



Scheme 1. Mechanistic studies.

On the basis of the bove mechanistic studies and related reports,[7a, 8, 12b, 14a, 16] a plausible Co(III)/Co(I) catalytic cycle is illustrated in Scheme 2. Initially, $Co(OAc)_2 \cdot 4H_2O$ coordinates to the substrate **1a**, leading to the formation of intermediate **A** accompanied by release of one equivalent of acetic acid. Next, the Co(II) can be oxidized to Co(III) by the silver salt, and Co(III) can activate the aryl C-H bond through a CMD type process to generate intermediate **B**. Subsequently, the coordination of the Co(III) center of intermediate **B** with alkyne **2b** forms

intermediate **C**. Then, migratory insertion of alkyne into the C-Co bond of intermediate **C** gives the seven-membered cobaltacyclic intermediate **D**. After that, cross-redox cyclization of intermediate **D** affords intermediate **E**. The Co(I) insert to the N-O bond forming intermediate **F**. Demetallization of intermediate **F** delivers the desired product **3ab** and affords the putative cobalt(III) species **G**. The catalytically active cobalt(III) complex **G** coordinated with the benzylamide **1a** to give intermediate **H**. Finally, intermediate **H** generates intermediate **B** through a CMD type process for a new catalytic cycle.



Scheme 2. Proposed mechanistic pathway

CONCLUSION

In conclusion, an efficient cobalt-catalyzed C(sp^2)–H bond activation/annulation strategy using a new traceless bidentate directing group to synthesize isoquinolinones

has been developed. In the reaction, 2-(hydroxymethyl)pyridine was first used as a non-marking directing group and could be removed directly *in situ* along the catalytic process. The reaction exhibits a broad substrate scope, affording the products in good isolated yields. Moreover, mechanical investigation experiments provide a clearer experimental process. Further applications of the directing group strategy in other related types of C−H functionalization and detailed mechanistic studies are actively ongoing in our laboratory.

EXPERIMENTAL SECTION

General information. Unless otherwise mentioned, all materials were commercially obtained and used without further purification, and all the reactions were performed under the ambient air. Substrates **1a-1v** were synthesized from benzohydroxamate[17] according to the literature method.[18] ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on 400 MHz or 600 MHz, 101 MHz or 151 MHz, and 376 MHz or 565 MHz respectively on a Bruker DPX instrument[19]. High resolution mass spectra (HRMS) for new compounds were measured on a Waters Q-Tof Micro MS/MS System ESI spectrometer. Melting points were tested on a WC-1 instrument and uncorrected. Chemical shift multiplicities are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet).

General procedure for preparation of substrates 1. According to the literature method[18], a 250 mL round-bottom flask was charged with benzohydroxamate (13 mmol, 1.3 equiv), potassium hydroxide (13 mmol, 1.3 equiv) and methanol (50 mL).

The reaction mixture was heated to reflux and refluxing was continued for 30 min in an oil bath. After slowly cooling to room temperature, the sodium carbonate (15 mmol, 1.5 equiv) and water (50 mL) were added. Then 2-chloromethylpyridine (10 mmol, 1.0 equiv) was added dropwise at 0 °C and stirred at room temperature for 3 h. The reaction mixture was heated to 100 °C for 2 h in an oil bath. Excess methanol was removed under reduced pressure and the mixture extracted with dichloromethane, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography gave pure substrates.

General procedure for the synthesis of isoquinolinone derivatives 3. A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1** (0.2 mmol, 1.0 equiv), alkynes **2** (0.3 mmol, 1.5 equiv), $Co(OAc)_2{\cdot}4H_2O$ (40 mol%, 0.08 mmol), AgOAc (0.2 mmol, 1.0 equiv), PivOH (0.4 mmol, 2.0 equiv), and TFE (1.0 mL). The vessel was heated at 110 °C for 10 h in an oil bath, and cooled down to room temperature. Next, the reaction mixture was diluted with 25 mL of DCM, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was washed with DCM (3 x 10 mL). After that, the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Then product was purified by preparative TLC on silica gel using DCM/EA as eluent to afford **3**.

Procedure for the synthesis of product 4.

A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1a** (0.2 mmol, 1.0 equiv), 7-oxabenzonorbornadiene (0.3 mmol, 1.5 equiv), $Co(OAc)_2{\cdot}4H_2O$ (0.08 mmol, 0.4 equiv,), AgOAc (0.2 mmol, 1.0 equiv), PivOH (0.4

mmol, 2.0 equiv), and TFE (1.0 mL). The vessel was heated at 110 °C for 10 h in an oil bath, and cooled down to room temperature. Next, the reaction mixture was diluted with 25 mL of DCM, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was washed with DCM (3 x 10 mL). After that, the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. Then product was purified by preparative TLC on silica gel using DCM/EA as eluent to afford **4**.

Procedure for the synthesis of product 3aa on a 1 mmol scale. A 35 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1a** (1 mmol, 228.5 mg), alkynes **2b** (1.5 mmol, 220 µl, 1.5 equiv), $Co(OAc)_2{\cdot}4H_2O$ (0.4 mmol, 100 mg, 40 mol%), AgOAc (1 mmol, 167 mg, 1 equiv), PivOH (2 mmol, 235 µl, 2 equiv), and TFE (5.0 mL). The vessel was heated at 110 °C for 10 h in an oil bath, and cooled down to room temperature. After general treatment for the synthesis of isoquinolinone derivatives **3**, the product was purified by preparative TLC on silica gel (DCM/EA = 3:1) to yield **3ab** (181 mg, 61%) as a white solid.

Experiments for determination of electronic effect on the isoquinolinones synthesis. A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1b** (0.1 mmol, 24.2 mg), **1k** (0.1 mmol, 28.7 mg), alkynes **2b** (0.1 mmol, 11.4 mg), $Co(OAc)_2{\cdot}4H_2O$ (0.08 mmol, 20 mg), AgOAc (0.2 mmol, 33.4 mg), PivOH (0.4 mmol, 47 µl), and TFE (1.0 mL). The vessel was heated at 110 °C for 10 h in an oil bath, and cooled down to room temperature. After general treatment for the synthesis of isoquinolinone derivatives **3**, the residue was purified by

preparative TLC on silica gel with DCM/EA as the eluent to yield **3bb** (12.6 mg, 52%) and **3kb** (10 mg, 35%).

Experiments for independent initial rate comparison k_H/k_D. A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1a** (0.2 mmol, 45.7 mg), alkynes **2b** (0.3 mmol, 33.1 mg), $Co(OAc)_2{\cdot}4H_2O$ (0.08 mmol, 20 mg), AgOAc (0.2 mmol, 33.4 mg), PivOH (0.4 mmol, 47 μl) and TFE (1.0 mL). The vessel was heated at 110 °C for 90, 105, 120, 135 min in an oil bath, and immediately quenched separately with 2.0 mL EA. Next, the reaction mixture was diluted with 25 mL of EA, and filtered through a celite pad. The reaction solution was concentrated in vacum and ^{1}H NMR was taken using anisole (0.2 mmol, 21.6 mg) as the internal standard. The KIE was determined as $k_H/k_D = 0.0822/0.0657 \approx 1.25$.

Experiments for intermolecular kinetic isotope effects. A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1a** (0.1 mmol, 22.9 mg), [D_5]-**1a** (0.1 mmol, 23.4 mg), alkynes **2b** (0.3 mmol, 33.1 mg), $Co(OAc)_2{\cdot}4H_2O$ (0.08 mmol, 20 mg), AgOAc (0.2 mmol, 33.4 mg), PivOH (0.4 mmol, 47 μl) and TFE (1.0 mL). The vessel was heated at 110 °C for 1 h in an oil bath, and cooled down to room temperature. After general treatment for the synthesis of isoquinolinone derivatives **3**, the residue was purified by preparative TLC on silica gel (DCM/EA = 3/1) to afford the target products of **3ab** and [D_4]-**3ab** in 15% total yield. A mixture of **3ab** and [D_4]-**3ab** was determined on the basis of ^{1}H NMR analysis. Based on the integrations related to different hydrogen resonances, the kinetic isotope effect is calculated to be $k_H/k_D = 2.0$ ($k_H/k_D = 0.669/(1-0.669) = 2.0$).

Deuterium labeled experiments.

(a) A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate [D_5]-**1a** (0.2 mmol, 46.7 mg), $Co(OAc)_2{\cdot}4H_2O$ (0.08 mmol, 20 mg), AgOAc (0.2 mmol, 33.4 mg), PivOH (0.4 mmol, 47 μl), and TFE (1.0 mL). The vessel was heated at 110 °C for 6 h in an oil bath, and cooled down to room temperature. Next, the reaction mixture was diluted with 25 mL of DCM, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was washed with DCM (3 x 10 mL). After that, the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with DCM/EA as the eluent to afford substrate [D_5]-**1a**. The H/D exchange (D/H ≥ 98%) was calculated by ^{1}H NMR.

(b) A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1a** (0.2 mmol, 45.7 mg), $Co(OAc)_2{\cdot}4H_2O$ (40 mol%, 20 mg), AgOAc (0.2 mmol, 33.4 mg), D_2O(2.0 mmol, 36.2 μl), PivOH (0.4 mmol, 47 μl), and TFE (1.0 mL). The vessel was heated at 110 °C for 6 h in an oil bath, and cooled down to room temperature. Next, the reaction mixture was diluted with 25 mL of DCM, and the organic layer was washed with saturated aqueous $NaHCO_3$ solution (30 mL). The aqueous phase was washed with DCM (3 x 10 mL). After that, the combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC on silica gel with DCM/EA as the eluent to afford substrate **1a**.. The H/D exchange (H/D ≥ 98%) was calculated by ^{1}H NMR. No obvious deuterium incorporation was detected.

Reactions in the presence TEMPO, BHT or BQ. A 15 mL dry screw cap vial was equipped with a magnetic stir bar and charged with substrate **1a** (0.2 mmol, 45.7 mg), alkynes **2b** (0.3 mmol, 33.1 mg), $Co(OAc)_2 \cdot 4H_2O$ (0.08 mmol, 20 mg), AgOAc (0.2 mmol, 1.0 equiv), PivOH (0.4 mmol, 2.0 equiv), TEMPO (1 equiv, BHT 1 equiv or BQ 1 equiv) and TFE (1.0 mL). The vessel was heated at 110 °C for 10 h in an oil bath, and cooled down to room temperature. Next, the reaction mixture was diluted with 25 mL of EA, and filtered through a celite pad. The reaction solution was detected by TLC. The addition of a radical quencher, either TEMPO, BHT, or BQ, under standard reaction conditions, suppressed the formation of **3ab**, suggesting that the reaction likely proceeds through radical intermediates in some steps of the mechanism.[9d, 16a]

Characterizations of Substrates 1

N-(pyridin-2-ylmethoxy)benzamide **(1a):** white solid (1.18 g, 52% yield). R_f = 0.20 (PE:EA, 1:1). mp 69–70 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.57 (d, *J* = 4.3 Hz, 1H), 7.86 (s, 1H), 7.75 (d, *J* = 5.9 Hz, 2H), 7.64 (s, 1H), 7.55 (s, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.40–7.30 (m, 1H), 5.04 (d, *J* = 2.6 Hz, 2H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 164.5, 155.8, 149.0, 136.7, 132.2, 131.6, 128.4, 123.2, 122.8, 77.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}N_2O_2$ 229.0972; Found 229.0971.

4-methyl-N-(pyridin-2-ylmethoxy)benzamide **(1b):** white solid (1.40 g, 58% yield). R_f = 0.18 (PE:EA, 1:1). mp 107–108 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 8.54 (d, *J* = 4.4 Hz, 1H), 7.71 (td, *J* = 7.7, 1.7 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.46

(d, *J* = 7.8 Hz, 1H), 7.26–7.17 (m, 3H), 5.17 (s, 2H), 2.38 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 149.2, 137.0, 129.3, 127.1, 123.2, 122.7, 78.0, 21.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2O_2$ 243.1128; Found 243.1127.

4-ethyl-N-(pyridin-2-ylmethoxy)benzamide **(1c):** white solid (1.25 g, 49% yield). $\mathbf{R}_f$ = 0.18 (PE:EA, 1:1). mp 75–76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.52 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.82–7.57 (m, 3H), 7.49 (t, *J* = 14.7 Hz, 1H), 7.22 (d, *J* = 6.9 Hz, 3H), 5.16 (s, 2H), 2.67 (q, *J* = 7.5 Hz, 2H), 1.43–0.98 (m, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.4, 156.3, 149.2, 137.0, 128.1, 127.3, 123.2, 122.8, 78.0, 28.8, 15.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}N_2O_2$ 257.1285; Found 257.1284.

4-(tert-butyl)-N-(ptyridin-2-ylmehoxy)benzamide **(1d):** white solid (1.70 g, 60% yield). R_f = 0.21 (PE:EA, 1:1).mp 87–88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.23 (s, 1H), 8.51 (s, 1H), 7.73 (dd, *J* = 26.3, 8.4 Hz, 3H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.3 Hz, 2H), 7.25–7.20 (m, 1H), 5.17 (s, 2H), 1.31 (s, 9H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 155.5, 149.2, 149.1, 137.0, 129.0, 127.0, 125.6, 123.2, 122.8, 77.9, 34.9, 31.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{21}N_2O_2$ 285.1598; Found 285.1601.

4-methoxy-N-(pyridin-2-ylmethoxy)benzamide **(1e):** white solid (1.06 g, 41% yield). R_f = 0.18 (PE:EA, 1:1). mp 96–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.10 (s, 1H), 8.59–8.48 (m, 1H), 7.77–7.66 (m, 3H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.26–7.19 (m, 1H), 6.95–6.82 (m, 2H), 5.16 (s, 2H), 3.84 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.5, 156.3, 149.2, 136.9, 129.0, 123.2, 122.8, 113.9, 78.0, 55.4. HRMS (ESI-TOF)

m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2O_3$ 259.1077; Found 259.1078.

4-fluoro-N-(pyridin-2-ylmethoxy)benzamide **(1f):** white solid (1.11 g, 45% yield). R_f = 0.20 (PE:EA, 1:1). mp 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 8.47 (d, *J* = 3.1 Hz, 1H), 7.82–7.75 (m, 2H), 7.71 (td, *J* = 7.7, 1.6 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.26–7.19 (m, 1H), 7.10–6.99 (m, 2H), 5.15 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 164.9 (J_{C-F} = 257.4 Hz), 155.9, 149.0, 137.2, 129.6 (J_{C-F} = 8.5 Hz), 128.0, 123.4, 123.1, 115.7 (J_{C-F} = 21.9 Hz), 77.9. ^{19}F{^{1}H} NMR (376 MHz, CDCl3) δ -107.12. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}FN_2O_2$ 247.0877; Found 247.0876.

4-chloro-N-(pyridin-2-ylmethoxy)benzamide **(1g):** white solid (1.1 g, 42% yield). R_f = 0.23 (PE:EA, 1:1). mp 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.49 (dd, *J* = 21.3, 4.5 Hz, 1H), 7.79–7.64 (m, 3H), 7.39 (dt, *J* = 14.8, 7.9 Hz, 3H), 7.26–7.14 (m, 1H), 5.16 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.1, 149.1, 137.1, 128.9, 128.6, 123.3, 122.9, 77.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}ClN_2O_2$ 263.0582; Found 263.0583.

4-bromo-N-(pyridin-2-ylmethoxy)benzamide **(1h):** white solid (1.77 g, 58% yield). R_f = 0.19 (PE:EA, 1:1). mp 139–140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 8.58 (d, *J* = 4.9 Hz, 1H), 7.74 (td, *J* = 7.7, 1.7 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 2H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.31–7.26 (m, 1H), 5.17 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.3, 149.2, 137.1, 131.9, 128.7, 123.3, 122.7, 77.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}BrN_2O_2$ 307.0077; Found 307.0076.

4-iodo-N-(pyridin-2-ylmethoxy)benzamide **(1i):** white solid (1.95 g, 55% yield). R_f =

0.20 (PE:EA, 1:1). mp 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.52 (dd, *J* = 4.8, 0.6 Hz, 1H), 7.80–7.69 (m, 3H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.26–7.21 (m, 1H), 7.13–7.02 (m, 2H), 5.16 (s, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 166.2, 163.6, 156.1, 149.2, 137.1, 129.5, 123.3, 122.9, 115.8, 115.6, 77.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}IN_2O_2$ 354.9938; Found 354.9934.

N-(pyridin-2-ylmethoxy)-4-(trifluoromethyl)benzamide **(1j):** white solid (1.53 g, 53% yield). R_f = 0.20 (PE:EA, 1:1). mp 112–113 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.3 (s, 1H), 8.36 (s, 1H), 7.88 (s, 2H), 7.64 (d, *J* = 19.9 Hz, 3H), 7.46 (s, 1H), 7.12 (s, 1H), 5.16 (s, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 164.0, 155.8, 148.9, 137.2, 135.2, 133.2 ($J_{C\text{-}F}$ = 33.0 Hz), 127.7, 125.4, 123.6 ($J_{C\text{-}F}$ = 273.3 Hz), 123.4, 123.2, 77.8. ^{19}F{^{1}H} NMR (565 MHz, $CDCl_3$) δ -63.05. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}F_3N_2O_2$ 297.0845; Found 297.0846.

methyl 4-((pyridin-2-ylmethoxy)carbamoyl)benzoate **(1k):** white solid (1.72 g, 60% yield). R_f = 0.23 (PE:EA, 1:1). mp 86–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.53 (d, *J* = 4.1 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 2H), 7.82 (d, *J* = 8.1 Hz, 2H), 7.73 (td, *J* = 7.7, 1.6 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.25 (s, 1H), 5.19 (s, 2H), 3.93 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 156.2, 149.2, 137.1, 128.8, 128.6, 123.3, 122.8, 77.2, 52.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{15}N_2O_4$ 287.1026; Found 287.1027.

N-(pyridin-2-ylmethoxy)-[1,1'-biphenyl]-4-carboxamide **(1l):** white solid (1.49 g, 49% yield). R_f = 0.16 (PE:EA, 1:1). mp 104–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.73–7.65 (m, 3H), 7.61–7.53 (m, 4H), 7.51–

7.34 (m, 4H), 7.19 (m, 1H), 5.19 (s, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2, 156.2, 149.1, 144.7, 139.9, 137.0, 130.7, 128.9, 128.1, 127.8, 127.2, 123.3, 123.0, 78.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{17}N_2O_2$ 305.1285; Found 305.1286.

3-methyl-N-(pyridin-2-ylmethoxy)benzamide **(1m):** light yellow liquid (1.36 g, 56% yield). R_f = 0.22 (PE:EA, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.11 (s, 1H), 8.54 (s, 1H), 7.72 (t, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 7.49 (dd, *J* = 17.9, 7.3 Hz, 2H), 7.36–7.27 (m, 2H), 7.25 (d, *J* = 7.1 Hz, 1H), 5.17 (s, 2H), 2.36 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.2, 149.2, 138.5, 137.1, 132.7, 128.5, 128.2, 127.9, 124.4, 123.3, 122.9, 78.0, 21.3. HRMS (positive ESI) Calcd. For $C_{14}H_{14}N_2O_2$ $[M+H]^+$, 243.1128, Found: 243.1130. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2O_2$ 243.1128; Found 243.1128.

3-methoxy-N-(pyridin-2-ylmethoxy)benzamide **(1n):** white solid (1.08 g, 42% yield). R_f = 0.21 (PE:EA, 1:1). mp 50–51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1H), 8.54–8.43 (m, 1H), 7.70 (td, *J* = 7.7, 1.7 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.38–7.27 (m, 3H), 7.25–7.18 (m, 1H), 7.07–6.95 (m, 1H), 5.15 (s, 2H), 3.76 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 159.7, 155.8, 149.0, 137.2, 129.6, 123.4, 123.2, 119.2, 118.2, 112.3, 77.9, 55.4, 55.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{15}N_2O_3$ 259.1077; Found 259.1079.

3-fluoro-N-(pyridin-2-ylmethoxy)benzamide **(1o):** white solid (1.06 g, 43% yield). R_f = 0.25 (PE:EA, 1:1). mp 45-47 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.91 (s, 1H), 8.45 (t, *J* = 4.3 Hz, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.48 (t, *J* = 10.0

Hz, 2H), 7.37 (t, J = 7.9 Hz, 1H), 7.27–7.13 (m, 2H), 5.17 (s, 2H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 162.6 ($J_{C\text{-}F}$ = 252.3 Hz), 156.0, 149.1, 137.1, 134.2, 130.3, 130.2, 123.3, 123.0, 122.7, 118.8 ($J_{C\text{-}F}$ = 20.1 Hz),114.5 ($J_{C\text{-}F}$ = 21.7 Hz), 77.9. $^{19}F\{^1H\}$ NMR (565 MHz, CDCl3) δ -115.47. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}FN_2O_2$ 247.0877; Found 247.0876.

3-chloro-N-(pyridin-2-ylmethoxy)benzamide **(1p):** white solid (0.92 g, 35% yield). R_f = 0.16 (PE:EA, 1:1). mp 56–57 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.01 (s, 1H), 8.46 (t, J = 9.0 Hz, 1H), 7.76 (t, J = 1.7 Hz, 1H), 7.71 (td, J = 7.7, 1.7 Hz, 1H), 7.63 (t, J = 8.4 Hz, 1H), 7.47 (ddd, J = 10.3, 2.6, 1.2 Hz, 2H), 7.31 (t, J = 7.9 Hz, 1H), 7.26–7.17 (m, 1H), 5.15 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 155.8, 149.0, 137.2, 134.7, 133.6, 131.8, 129.9, 127.5, 125.3, 123.4, 123.2, 77.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}ClN_2O_2$ 263.0582; Found 263.0583.

N-(pyridin-2-ylmethoxy)-3-(trifluoromethyl)benzamide **(1q):** white solid (1.48 g, 50% yield). R_f = 0.19 (PE:EA, 1:1). mp 90–91 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.47 (d, J = 4.4 Hz, 1H), 8.05 (s, 1H), 7.96 (d, J = 7.8 Hz, 1H), 7.73 (td, J = 7.8, 1.7 Hz, 2H), 7.54 (t, J = 7.8 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.24 (dd, J = 7.1, 5.4 Hz, 1H), 5.18 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.0, 149.1, 137.2, 132.7, 131.3 ($J_{C\text{-}F}$ = 34.1 Hz), 130.4, 129.2, 128.3, 124.2, 123.6 ($J_{C\text{-}F}$ = 273.2 Hz), 123.4, 123.0, 77.7. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -62.83. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{14}H_{12}F_3N_2O_2$ 297.0845; Found 297.0846.

2-fluoro-N-(pyridin-2-ylmethoxy)benzamide **(1r):** white solid (1.06 g, 43% yield). R_f = 0.16 (PE:EA, 1:1). mp 109–110 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (s, 1H),

8.60 (s, 1H), 8.07 (s, 1H), 7.73 (t, J = 7.7 Hz, 1H), 7.54–7.40 (m, 2H), 7.27–7.24 (m, 2H), 7.17–6.98 (m, 1H), 5.19 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.2 ($J_{C\text{-}F}$ = 249.5 Hz), 155.8, 149.4, 137.0, 133.7 ($J_{C\text{-}F}$ = 8.7 Hz), 131.8, 125.0 ($J_{C\text{-}F}$ = 2.99 Hz), 123.2, 122.6, 119.0 ($J_{C\text{-}F}$ = 13.5 Hz), 116.0 ($J_{C\text{-}F}$ = 24.1 Hz), 78.3. $^{19}F\{^1H\}$ NMR (376 MHz, CDCl3) δ -110.43. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{12}FN_2O_2$ 247.0877; Found 247.0878.

N-(pyridin-2-ylmethoxy)-2-naphthamide **(1s)**: white solid (1.70 g, 61% yield). R_f = 0.22 (PE:EA, 1:1). mp 89–90 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.52 (dd, J = 10.7, 4.9 Hz, 1H), 8.28 (s, 1H), 7.91–7.76 (m, 4H), 7.71 (tdd, J = 7.3, 5.3, 1.7 Hz, 1H), 7.60–7.43 (m, 3H), 7.23 (dd, J = 11.8, 6.7 Hz, 1H), 5.23 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 149.2, 137.0, 134.9, 132.5, 128.9, 128.5, 127.8, 126.8, 123.5, 123.3, 122.9, 78.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{15}N_2O_2$ 279.1128; Found 279.1129.

N-(pyridin-2-ylmethoxy)thiophene-2-carboxamide **(1t):** white solid (1.38 g, 59% yield). R_f = 0.17 (PE:EA, 1:1). mp 83–84 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.83 (s, 1H), 8.47 (d, J = 4.5 Hz, 1H), 7.77–7.58 (m, 2H), 7.48 (t, J = 6.4 Hz, 2H), 7.24–7.18 (m, 1H), 7.04 (dd, J = 4.8, 3.9 Hz, 1H), 5.14 (s, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 161.7, 155.8, 149.1, 137.1, 135.0, 130.8, 127.6, 123.3, 123.0, 78.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{11}H_{11}N_2O_2S$ 235.0536; Found 235.0537.

2-phenyl-N-(pyridin-2-ylmethoxy)acrylamide **(1u):** white solid (1.42 g, 56% yield). R_f= 0.16 (PE:EA, 1:1). mp 91–92 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.51 (s, 1H), 8.45 (d, J = 4.2 Hz, 1H), 7.70 (td, J = 7.7, 1.7 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.33

(s, 5H), 7.25–7.17 (m, 1H), 6.04 (s, 1H), 5.66 (s, 1H), 5.09 (s, 2H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 155.9, 149.2, 142.3, 136.9, 136.0, 128.6, 127.8, 123.2, 122.8, 122.1, 78.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{15}N_2O_2$ 255.1128; Found 255.1130.

N-(pyridin-2-ylmethoxy)methacrylamide **(1v):** colorless liquid (0.77 g, 40% yield). R_f = 0.20 (PE: EA, 20:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 8.59 (dd, *J* = 12.5, 5.2 Hz, 1H), 7.72 (tt, *J* = 9.0, 4.5 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.1 Hz, 1H), 5.68 (s, 1H), 5.31 (d, *J* = 21.2 Hz, 1H), 5.10 (s, 2H), 1.94 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 156.3, 149.2, 137.0, 123.2, 122.7, 120.4, 77.7, 18.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{10}H_{13}N_2O_2$ 193.0972; Found 193.0971.

Characterizations of products.

3,4-dipropylisoquinolin-1(2H)-one **(3ab):** white solid (39.8 mg, 87%). R_f = 0.45 (DCM:EA, 3:1). mp 181–182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.50 (s, 1H), 8.46 (d, *J* = 8.0 Hz, 1H), 7.74–7.59 (m, 2H), 7.48–7.36 (m, 1H), 2.70 (td, *J* = 8.0, 1.6 Hz, 4H), 1.83–1.68 (m, 2H), 1.68–1.50 (m, 2H), 1.05 (dt, *J* = 9.2, 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 163.8, 138.5, 138.2, 132.3, 127.7, 125.3, 123.1, 113.1, 32.9, 28.6, 23.6, 22.8, 14.3, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{20}NO$ 230.1539; Found 230.1537.

6-methyl-3,4-dipropylisoquinolin-1(2H)-one **(3bb):** white solid (39.9 mg, 82%). R_f = 0.44 (DCM:EA, 3:1). mp 191–192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.87 (s, 1H), 8.33 (d, *J* = 8.1 Hz, 1H), 7.43 (s, 1H), 7.25 (dd, *J* = 6.4, 1.3 Hz, 1H), 2.66 (dd, *J* = 15.8, 7.9 Hz, 4H), 2.51 (s, 3H), 1.79–1.67 (m, 2H), 1.65–1.53 (m, 2H), 1.04 (t, *J* = 7.3

Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.6, 142.7, 138.6, 138.2, 127.7, 126.9, 122.9, 122.8, 112.7, 33.0, 28.5, 23.6, 22.7, 22.3, 14.3, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{22}NO$ 244.1696; Found 244.1694.

6-ethyl-3,4-dipropylisoquinolin-1(2H)-one **(3cb):** white solid (42.6 mg, 83%). R_f = 0.40 (DCM:EA, 3:1). mp 145–147 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.36 (d, *J* = 8.2 Hz, 1H), 7.45 (s, 1H), 7.29 (t, *J* = 6.8 Hz, 1H), 2.80 (q, *J* = 7.6 Hz, 2H), 2.74–2.59 (m, 4H), 1.80–1.67 (m, 2H), 1.67–1.53 (m, 2H), 1.32 (t, *J* = 7.6 Hz, 3H), 1.04 (td, *J* = 7.3, 1.6 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.4, 149.1, 138.7, 137.7, 128.1, 127.8, 127.6, 127.5, 126.0, 121.7, 121.5, 115.9, 113.2, 33.0, 29.6, 28.5, 23.6, 22.6, 15.5, 14.3, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{24}NO$ 258.1852; Found 258.1851.

6-(tert-butyl)-3,4-dipropylisoquinolin-1(2H)-one **(3db):** white solid (44.5 mg, 78%). R_f = 0.40 (DCM:EA, 3:1). mp 175–176 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 7.66 (dd, *J* = 8.2, 2.6 Hz, 1H), 7.51 (dd, *J* = 8.5, 1.7 Hz, 1H), 2.79–2.61 (m, 4H), 1.80–1.68 (m, 2H), 1.68–1.55 (m, 2H), 1.41 (s, 9H), 1.05 (td, *J* = 7.3, 1.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.6, 155.5, 138.3, 138.1, 127.4, 123.4, 122.8, 119.0, 113.1, 35.3, 33.0, 31.2, 28.6, 23.5, 22.8, 14.3, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{28}NO$ 286.2165; Found 286.2166.

6-methoxy-3,4-dipropylisoquinolin-1(2H)-one **(3eb):** white solid (18.7 mg, 36%). R_f = 0.48 (DCM:EA, 3:1). mp 184–185 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.40–8.34 (m, 1H), 7.03 (dd, *J* = 7.4, 2.3 Hz, 2H), 3.93 (s, 3H), 2.64 (dd, *J* = 16.0, 8.3 Hz, 4H), 1.71 (dt, *J* = 7.2, 6.0 Hz, 2H), 1.66–1.54 (m, 2H), 1.04 (td, *J* = 7.3, 1.5 Hz,

6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.1, 162.9, 140.5, 138.5, 129.8, 119.1, 113.8, 112.6, 105.3, 55.4, 33.1, 28.7, 23.3, 22.6, 14.3, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{22}NO_2$ 260.1645; Found 260.1644.

6-fluoro-3,4-dipropylisoquinolin-1(2H)-one **(3fb):** white solid (35.1 mg, 71%). R_f = 0.45 (DCM:EA, 3:1). mp 173–174 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.61 (s, 1H), 8.56–8.35 (m, 1H), 7.28 (dd, *J* = 10.5, 1.5 Hz, 1H), 7.14 (td, *J* = 8.4, 2.0 Hz, 1H), 2.77–2.58 (m, 4H), 1.83–1.70 (m, 2H), 1.66–1.51 (m, 2H), 1.06 (dd, *J* = 15.9, 7.4 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 165.6 ($J_{C\text{-}F}$ = 249.1 Hz), 163.3, 141.1 ($J_{C\text{-}F}$ = 9.2 Hz), 141.0 ($J_{C\text{-}F}$ = 8.6 Hz), 130.8 ($J_{C\text{-}F}$ = 10.2 Hz), 121.7, 113.9 ($J_{C\text{-}F}$ = 25.4 Hz), 112.7 ($J_{C\text{-}F}$ = 3.0 Hz), 108.4 ($J_{C\text{-}F}$ = 23.4 Hz), 33.0, 28.7, 23.4, 22.8 ($J_{C\text{-}F}$ = 2.54 Hz), 14.3, 14.0. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -106.13. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}FNO$ 248.1445; Found 248.1446.

6-chloro-3,4-dipropylisoquinolin-1(2H)-one **(3gb):** white solid (39.5 mg, 75%). R_f = 0.43 (DCM:EA, 3:1). mp 192–193 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.23 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.69 (d, *J* = 1.9 Hz, 1H), 7.45 (dd, *J* = 8.5, 1.9 Hz, 1H), 2.66–2.57 (m, 2H), 2.53 (dd, *J* = 6.7, 4.8 Hz, 2H), 1.66–1.53 (m, 2H), 1.53–1.41 (m, 2H), 0.96 (dt, *J* = 21.7, 7.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6) δ 161.6, 141.2, 139.9, 138.1, 129.8, 125.8, 124.1, 122.8, 110.7, 32.3, 28.0, 23.7, 22.9, 14.4, 14.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}ClNO$ 264.1150; Found 264.1149.

6-bromo-3,4-dipropylisoquinolin-1(2H)-one **(3hb):** white solid (43.6 mg, 71%). R_f = 0.43 (DCM:EA, 3:1). mp 183–185 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.15 (s,

1H), 8.13 (t, *J* = 19.1 Hz, 1H), 7.83 (d, *J* = 1.5 Hz, 1H), 7.58 (dd, *J* = 8.5, 1.6 Hz, 1H), 2.60 (dd, *J* = 16.4, 8.3 Hz, 2H), 2.57–2.51 (m, 2H), 1.59 (dq, *J* = 14.8, 7.3 Hz, 2H), 1.48 (dq, *J* = 14.7, 7.2 Hz, 2H), 0.96 (dt, *J* = 21.1, 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, DMSO-d_6) δ 161.5, 141.2, 140.1, 129.8, 128.6, 127.3, 125.8, 124.4, 110.6, 32.3, 27.9, 23.6, 22.9, 14.4, 14.1. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}BrNO$ 308.0645; Found 308.0647.

6-iodo-3,4-dipropylisoquinolin-1(2H)-one **(3ib):** white solid (51.1 mg, 72%). R_f = 0.43 (DCM:EA, 3:1). mp 177–179 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 8.02 (d, *J* = 1.3 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.75 (dd, *J* = 8.4, 1.4 Hz, 1H), 2.65–2.56 (m, 2H), 2.52 (dd, *J* = 7.3, 5.5 Hz, 2H), 1.66–1.53 (m, 2H), 1.53–1.40 (m, 2H), 0.96 (dt, *J* = 21.4, 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 161.4, 140.4, 139.4, 133.8, 131.5, 128.9, 124.1, 109.8, 101.2, 31.8, 27.4, 23.1, 22.4, 13.9, 13.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}INO$ 356.0506; Found 356.0507.

3,4-dipropyl-6-(trifluoromethyl)isoquinolin-1(2H)-one **(3jb):** white solid (26.7 mg, 45%). R_f = 0.43 (DCM:EA, 3:1). mp 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H), 8.56 (d, *J* = 8.3 Hz, 1H), 7.93 (s, 1H), 7.64 (dd, *J* = 8.4, 1.0 Hz, 1H), 2.81–2.64 (m, 4H), 1.84–1.69 (m, 2H), 1.69–1.52 (m, 2H), 1.07 (dt, *J* = 8.9, 7.4 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 163.2, 140.1, 138.6, 134.0 ($J_{C\text{-}F}$ = 32.2 Hz), 128.8, 127.1, 124.0 ($J_{C\text{-}F}$ = 272.1 Hz), 121.3 ($J_{C\text{-}F}$ = 3.16 Hz), 120.4 ($J_{C\text{-}F}$ = 4.21 Hz), 113.0, 33.0, 28.4, 23.6, 22.8, 14.2, 14.0. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -62.91. HRMS (positive ESI) Calcd. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}F_3NO$

298.1413; Found 298.1411.

1-oxo-3,4-dipropyl-1,2-dihydroisoquinolin-6-yl acetate **(3kb):** white solid (34.5 mg, 60%). R_f = 0.43 (DCM:EA, 3:1). mp 170–172 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.33 (s, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 8.24 (d, *J* = 1.1 Hz, 1H), 7.92 (dd, *J* = 8.3, 1.4 Hz, 1H), 3.93 (s, 3H), 2.77–2.62 (m, 2H), 2.60–2.53 (m, 2H), 1.62 (dt, *J* = 15.2, 7.4 Hz, 2H), 1.51 (dt, *J* = 14.8, 7.4 Hz, 2H), 0.98 (dt, *J* = 22.4, 7.3 Hz, 6H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 166.0, 161.1, 140.2, 137.6, 132.7, 127.9, 127.7, 124.6, 124.3, 110.8, 52.6, 31.8, 27.6, 23.2, 22.5, 14.0, 13.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{22}NO_3$ 288.1594; Found 288.1592.

6-phenyl-3,4-dipropylisoquinolin-1(2H)-one **(3lb):** white solid (50.6 mg, 83%). R_f = 0.45 (DCM:EA, 3:1). mp 189–191 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.51 (d, *J* = 8.2 Hz, 1H), 7.84 (s, 1H), 7.67 (t, *J* = 8.2 Hz, 3H), 7.58–7.47 (m, 2H), 7.41 (dd, *J* = 19.8, 12.4 Hz, 1H), 2.81–2.73 (m, 2H), 2.72–2.66 (m, 2H), 1.82–1.73 (m, 2H), 1.70–1.60 (m, 2H), 1.14–1.01 (m, 6H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 163.5, 145.2, 141.0, 138.9, 138.4, 129.0, 128.3, 128.0, 127.6, 124.8, 124.08, 121.6, 113.1, 33.1, 28.6, 23.6, 22.7, 14.3, 14.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{24}NO$ 306.1852; Found 306.1852.

7-methyl-3,4-dipropylisoquinolin-1(2H)-one **(3mb):** white solid (41.8 mg, 86%). R_f = 0.45 (DCM:EA, 3:1). mp 158–160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (s, 1H), 8.23 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 2.74–2.66 (m, 2H), 2.66–2.59 (m, 2H), 2.49 (s, 3H), 1.79–1.66 (m, 2H), 1.59 (dq, *J* = 15.0, 7.4 Hz, 2H), 1.09–0.98 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.4, 136.6, 136.2, 135.4,

134.0, 127.3, 124.9, 123.1, 113.2, 32.9, 28.6, 23.6, 22.6, 21.2, 14.3, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{22}NO$ 244.1696; Found 244.1694.

7-methoxy-3,4-dipropylisoquinolin-1(2H)-one **(3nb):** white solid (33.2 mg, 64%). R_f = 0.46 (DCM:EA, 3:1). mp 162–164 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.84 (d, *J* = 2.7 Hz, 1H), 7.58 (t, *J* = 19.5 Hz, 1H), 7.29 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.93 (s, 3H), 2.73–2.56 (m, 4H), 1.78–1.65 (m, 2H), 1.65–1.52 (m, 2H), 1.03 (td, *J* = 7.3, 3.8 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 162.9, 157.7, 135.1, 132.6, 126.2, 124.8, 122.9, 113.0, 107.4, 55.6, 32.8, 28.7, 23.7, 22.7, 14.3, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{22}NO_2$ 260.1645; Found 260.1643.

7-fluoro-3,4-dipropylisoquinolin-1(2H)-one **(3ob):** white solid (26.7 mg, 54%). R_f = 0.46 (DCM:EA, 3:1). mp 73-75 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 11.22 (s, 1H), 8.08 (dd, J = 9.2, 2.8 Hz, 1H), 7.67 (dd, J = 9.0, 5.0 Hz, 1H), 7.46 – 7.35 (m, 1H), 2.68 (dd, J = 16.1, 8.4 Hz, 4H), 1.79 – 1.71 (m, 2H), 1.63 – 1.54 (m, 2H), 1.05 (dt, J = 15.0, 7.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 163.0 ($J_{C\text{-}F}$ = 3.6 Hz), 160.1 ($J_{C\text{-}F}$ = 246.3 Hz), 137.4, 135.1 ($J_{C\text{-}F}$ = 1.7 Hz), 126.6 ($J_{C\text{-}F}$ = 7.9 Hz), 125.5 ($J_{C\text{-}F}$ = 7.5 Hz), 121.0 ($J_{C\text{-}F}$ = 23.5 Hz), 112.7, 112.5 ($J_{C\text{-}F}$ = 22.0 Hz), 32.8, 28.7, 23.6, 22.8, 14.3, 14.0. $^{19}F\{^1H\}$ NMR (565 MHz, $CDCl_3$) δ -115.78. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}FNO$ 248.1445; Found 248.1444.

5-fluoro-3,4-dipropylisoquinolin-1(2H)-one **(3ob'):** white solid (10.8 mg, 22%). R_f = 0.40 (DCM:EA, 3:1). mp 84-85 °C. ^1H NMR (600 MHz, $CDCl_3$) δ 10.88 (s, 1H), 8.32 – 8.21 (m, 1H), 7.35 (tdd, J = 13.6, 7.7, 5.8 Hz, 2H), 2.78 (td, J = 8.2, 3.2 Hz, 2H), 2.68 – 2.63 (m, 2H), 1.80 – 1.68 (m, 2H), 1.58 (dq, J = 14.8, 7.2 Hz, 2H), 1.05 (dt, J =

25.4, 7.3 Hz,6H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 162.5, 159.0 (J_{C-F} = 253.0 Hz), 138.7, 127.8 (J_{C-F} = 24.1 Hz), 127.7, 125.9 (J_{C-F} = 8.9 Hz), 123.8 (J_{C-F} = 3.7 Hz), 119.3 (J_{C-F} = 24.3 Hz), 113.2 (J_{C-F} = 4.9 Hz), 33.0, 30.6 (J_{C-F} = 11.8 Hz), 27.4 (J_{C-F} = 4.4 Hz), 22.8, 14.3, 14.0. $^{19}F\{^{1}H\}$ NMR (565 MHz, $CDCl_3$) δ -114.98. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}FNO$ 248.1445; Found 248.1448.

7-chloro-3,4-dipropylisoquinolin-1(2H)-one **(3pb):** white solid (37.9 mg, 72%). R_f = 0.42 (DCM:EA, 3:1). mp 166–167 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.28 (s, 1H), 8.12 (d, *J* = 1.2 Hz, 1H), 7.78–7.70 (m, 2H), 2.61 (dd, *J* = 18.6, 10.6 Hz, 2H), 2.57–2.52 (m, 2H), 1.59 (dq, *J* = 14.8, 7.3 Hz, 2H), 1.48 (dq, *J* = 14.8, 7.3 Hz, 2H), 0.96 (dt, *J* = 19.4, 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 160.6, 139.5, 136.5, 132.3, 129.8, 126.3, 125.9, 125.7, 110.7, 31.7, 27.8, 23.2, 22.5, 14.0, 13.6. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}ClNO$ 264.1150; Found 264.1149.

3,4-dipropyl-7-(trifluoromethyl)isoquinolin-1(2H)-one **(3qb):** white solid (22 mg, 37%). R_f = 0.46 (DCM:EA, 3:1). mp 152–153 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.61 (s, 1H), 8.71 (s, 1H), 7.95–7.81 (m, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 2.70 (dd, *J* = 16.0, 8.6 Hz, 4H), 1.84–1.69 (m, 2H), 1.66–1.53 (m, 2H), 1.06 (q, *J* = 7.3 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 163.3, 141.1, 141.0, 128.3 (J_{C-F} = 3.2 Hz), 127.2 (J_{C-F} = 33.2 Hz), 125.3 (J_{C-F} = 4.5 Hz), 124.7, 124.1 (J_{C-F} = 272.1 Hz), 124.0, 112.8, 33. 0, 28.5, 23.5, 22.8, 14.2, 13.9. $^{19}F\{^{1}H\}$ NMR (376 MHz, $CDCl_3$) δ -62.31. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{19}F_3NO$ 298.1413; Found 298.1415.

8-fluoro-3,4-dipropylisoquinolin-1(2H)-one **(3rb):** white solid (22.7 mg, 46%). R_f = 0.43 (DCM:EA, 3:1). mp 163–164°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H),

7.59 (td, J = 8.1, 5.2 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.04 (dt, J = 18.2, 9.0 Hz, 1H), 2.64 (dd, J = 15.8, 7.8 Hz, 4H), 1.82–1.70 (m, 2H), 1.64–1.51 (m, 2H), 1.05 (q, J = 7.5 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 163.1 ($J_{C\text{-}F}$ = 263.3 Hz), 161.3, 141.4, 139.5, 133.0 ($J_{C\text{-}F}$ = 9.7 Hz), 118.9 ($J_{C\text{-}F}$ = 4.5 Hz), 114.4 ($J_{C\text{-}F}$ = 5.7 Hz), 112.2 ($J_{C\text{-}F}$ = 3.6 Hz), 112.1 ($J_{C\text{-}F}$ = 23.1 Hz), 33.0, 29.0, 23.3, 22.6, 14.3, 13.9. $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -110.13. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{15}H_{19}FNO$ 248.1445; Found 248.1444.

3,4-dipropylbenzo[g]isoquinolin-1(2H)-one **(3sb):** yellow solid (25.7 mg, 46%). R_f = 0.45 (DCM:EA, 3:1). mp 192–193 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.82 (d, J = 55.9 Hz, 1H), 8.88 (s, 1H), 8.22 (s, 1H), 8.13 (q, J = 8.9 Hz, 2H), 7.62 (ddd, J = 8.2, 6.8, 1.2 Hz, 1H), 7.58–7.47 (m, 1H), 2.80–2.71 (m, 2H), 2.61–2.53 (m, 2H), 1.74–1.52 (m, 4H), 1.05 (t, J = 7.3 Hz, 3H), 0.96 (q, J = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6) δ 162.7, 138.0, 135.5, 134.5, 130.6, 129.4, 128.4, 128.4, 126.1, 124.7, 121.6, 110.9, 32.4, 28.5, 23.6, 22.8, 14.6, 14.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{22}NO$ 280.1696; Found 280.1695.

4,5-dipropylthieno[2,3-c]pyridin-7(6H)-one **(3tb):** white solid (26.3 mg, 56%). R_f = 0.45 (DCM:EA, 3:1). mp 152–153 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.35 (s, 1H), 7.70 (d, J = 5.2 Hz, 1H), 7.27 (d, J = 5.2 Hz, 1H), 2.73–2.60 (m, 4H), 1.78–1.66 (m, 2H), 1.66–1.48 (m, 2H), 1.02 (dt, J = 12.7, 7.3 Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 160.0, 148.3, 139.9, 133.0, 127.3, 123.1, 113.6, 32.1, 30.3, 23.9, 23.1, 14.2, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{13}H_{18}NOS$ 236.1104; Found 236.1102.

3-phenyl-5,6-dipropylpyridin-2(1H)-one **(3ub):** white solid (34.3 mg, 67%). R_f = 0.43 (DCM:EA, 3:1). mp 123-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.76 (s, 1H), 7.80 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.46 (s, 1H), 7.39 (dd, *J* = 10.3, 4.7 Hz, 2H), 7.34–7.27 (m, 1H), 2.62–2.54 (m, 2H), 2.46–2.36 (m, 2H), 1.80–1.69 (m, 2H), 1.62–1.51 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 163.07, 145.2, 144.1, 142.2, 136.8, 128.7, 128.4, 128.0, 127.2, 123.3, 117.5, 32.3, 32.0, 24.3, 22.9, 14.0, 13.8. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{22}NO$ 256.1696; Found 256.1695.

3,5,6-triphenylpyridin-2(1H)-one **(3ua):** white solid (20.6 mg, 32 %). mp 243–244 °C. R_f = 0.45 (DCM:EA, 3:1). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.04 (s, 1H), 7.83 (d, *J* = 7.2 Hz, 2H), 7.69 (s, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.37–7.28 (m, 4H), 7.25 (dd, *J* = 6.8, 5.0 Hz, 2H), 7.23–7.17 (m, 3H), 7.17–7.09 (m, 2H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 162.5, 142.9, 142.3, 137.9, 136.0, 133.6, 129.7, 129.5, 129.3, 128.6, 128.5, 128.4, 128.2, 127.8, 127.0, 119.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{18}NO$ 324.1383; Found 324.1382.

3-methyl-5,6-diphenylpyridin-2(1H)-one **(3va):** white solid (33.4 mg, 64%). R_f = 0.45 (DCM:EA, 3:1). mp 197–199 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.69 (s, 1H), 7.43 (d, *J* = 1.0 Hz, 1H), 7.34–7.23 (m, 3H), 7.23–7.11 (m, 5H), 7.05–6.99 (m, 2H), 2.07 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 162.7, 140.8, 138.4, 129.9, 129.6, 128.7, 128.3, 128.2, 126.5, 16.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{16}NO$ 262.1226; Found 262.1227.

3,4-diphenylisoquinolin-1(2H)-one **(3aa):** white solid (49.3 mg, 83%). R_f = 0.46

(DCM:EA, 3:1). mp 250–251 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.32 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.72–7.61 (m, 1H), 7.58–7.43 (m, 1H), 7.37–7.24 (m, 3H), 7.23–7.21 (m, 5H),7.20–7.09 (m, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.7, 138.6, 138.1, 135.8, 134.5, 132.5, 131.7, 129.8, 128.2, 128.2, 127.7, 127.0, 126.8, 126.2, 125.0, 124.9, 115.4. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{16}NO$ 298.1226; Found 298.1225.

3,4-dibutylisoquinolin-1(2H)-one **(3ac):** white solid (42.1 mg, 82%). R_f = 0.45 (DCM:EA, 3:1). mp 81–82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.75 (s, 1H), 8.44 (d, *J* = 8.0 Hz, 1H), 7.69 (t, *J* = 6.5 Hz, 2H), 7.52–7.33 (m, 1H), 2.75–2.64 (m, 4H), 1.76–1.64 (m, 2H), 1.62–1.38 (m, 6H), 1.03–0.92 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 138.5, 137.9, 132.4, 127.7, 125.4, 123.0, 113.2, 32.6 31.5, 30.8, 26.3, 23.0, 22.7, 14.0, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{24}NO$ 258.1852; Found 258.1853.

3,4-bis(4-fluorophenyl)isoquinolin-1(2H)-one **(3ad):** white solid (44.6 mg, 67%). R_f = 0.40 (DCM:EA, 3:1). mp 263–265 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.61 (s, 1H), 8.32 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.75–7.60 (m, 1H), 7.60–7.47 (m, 1H), 7.33–7.25 (m, 2H), 7.23–7.02 (m, 7H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.7 (J_{C-F} = 245.5 Hz), 161.6, 161.2 (J_{C-F} = 243.5 Hz), 138.0, 133.7 (J_{C-F} = 8.1 Hz), 132.6, 132.1 (J_{C-F} = 8.5 Hz), 132.0 (J_{C-F} = 3.2 Hz), 130.9 (J_{C-F} = 2.9 Hz), 126.8, 126.4, 125.0, 124.8, 115.2 (J_{C-F} = 21.1 Hz), 114.7 (J_{C-F} = 21.6 Hz). ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -115.02, 113.05. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}F_2NO$ 334.1038; Found 334.1037.

3,4-bis(4-chlorophenyl)isoquinolin-1(2H)-one **(3ae):** white solid (41.6 mg, 57%). R_f = 0.43 (DCM:EA, 3:1). mp 279–280 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.32 (d, *J* = 7.1 Hz, 1H), 7.72–7.62 (m, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.26 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 1H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.6, 137.7, 134.5, 133.5, 133.2, 133.1, 132.7, 132.0, 131.7, 128.4, 127.9, 126.9, 126.5, 125.1, 124.8, 114.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}Cl_2NO$ 366.0447; Found 366.0445.

3,4-bis(4-bromophenyl)isoquinolin-1(2H)-one **(3af):** white solid (39.8 mg, 44%). R_f = 0.45 (DCM:EA, 3:1). mp 285–287 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.64 (s, 1H), 8.32 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.71–7.62 (m, 1H), 7.58–7.50 (m, 3H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 161.6, 137.6, 137.6, 134.9, 133.9, 133.5, 132.7, 132.0, 131.3, 130.8, 126.8, 126.6, 125.1, 124.8, 121.9, 120.6, 114.5. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}Br_2NO$ 453.9437; Found 453.9436.

3,4-bis(4-(trifluoromethyl)phenyl)isoquinolin-1(2H)-one **(3ag):** white solid (60.6 mg, 70%). R_f = 0.45 (DCM:EA, 3:1). mp 245–247 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.36 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.74–7.67 (m, 3H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.61–7.55 (m, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 1H). ^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6) δ 162.1, 140.5, 138.7, 138.1, 137.8, 133.3, 133.1, 131.4, 129.3 (J_{C-F} = 31.6 Hz), 128.4 (J_{C-F} = 31.8 Hz), 127.4, 127.3, 125.7, 125.6 (J_{C-F} = 3.3 Hz), 125.2, 125.1 (J_{C-F} = 3.4 Hz), 124.6 (J_{C-F} = 272.1

Hz), 124.4 (J_{C-F} = 272.1 Hz), 115.2. $^{19}F\{^{1}H\}$ NMR (376 MHz, DMSO-d_6) δ -61.15, -60.95. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{14}F_6NO$ 434.0974; Found 434.0972.

diethyl 4,4'-(1-oxo-1,2-dihydroisoquinoline-3,4-diyl)dibenzoate **(3ah):** white solid (56.4 mg, 64%). R_f = 0.45 (DCM:EA, 3:1). mp 226–227 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.48 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.94 (d, *J* = 8.4 Hz, 2H), 7.71–7.59 (m, 1H), 7.55 (dd, *J* = 14.7, 7.7 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 3H), 7.27 (d, *J* = 7.2 Hz, 2H), 4.38 (dq, *J* = 10.4, 7.1 Hz, 4H), 1.40 (dd, *J* = 15.1, 7.2 Hz, 6H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 166.2, 165.8, 140.2, 138.8, 133.1, 131.9, 130.8, 129.8, 129.7, 129.4, 127.7, 127.3, 125.6, 61.3, 61.2, 14.3, 14.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{27}H_{24}NO_5$ 442.1649; Found 442.1647.

3,4-di-m-tolylisoquinolin-1(2H)-one **(3ai):** white solid (48.1 mg, 74%). R_f = 0.45 (DCM:EA, 3:1). mp 222–223 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.06 (s, 1H), 8.48 (d, *J* = 7.4 Hz, 1H), 7.64–7.56 (m, 1H), 7.53–7.46 (m, 1H), 7.36 (d, *J* = 8.1 Hz, 1H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.15–7.03 (m, 4H), 6.99 (dd, *J* = 14.1, 8.1 Hz, 3H), 2.30 (s, 3H), 2.26 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 138.1, 137.9, 135.6, 135.1, 132.6, 132.5, 129.7, 129.4, 128.9, 128.2, 128.2, 128.0, 127.4, 126.5, 126.4, 125.9, 21.4, 21.3. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}NO$ 326.1539; Found 326.1538.

3,4-bis(3-methoxyphenyl)isoquinolin-1(2H)-one **(3aj):** white solid (34.3 mg, 48%). R_f = 0.45 (DCM:EA, 3:1). mp 257–259 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 8.47 (d, *J* = 7.5 Hz, 1H), 7.63–7.55 (m, 1H), 7.49 (q, *J* = 7.2 Hz, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 8.6 Hz, 2H), 7.12–7.04 (m, 2H), 6.93–6.84 (m, 2H), 6.78 (d, *J* =

8.5 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 159.6, 158.7, 139.2, 136.8, 132.9, 132.7, 130.5, 127.9, 127.5, 127.4, 126.4, 125.7, 113.9, 113.9, 55.2, 55.2. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{23}H_{20}NO_3$ 358.1438; Found 358.1437.

3,4-bis(3-fluorophenyl)isoquinolin-1(2H)-one **(3ak):** white solid (49.3 mg, 74%). R_f = 0.45 (DCM:EA, 3:1). mp 215–217 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1H), 8.33 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.74–7.63 (m, 1H), 7.54 (dt, *J* = 17.6, 5.2 Hz, 1H), 7.42–7.33 (m, 1H), 7.33–7.24 (m, 1H), 7.20–7.08 (m, 5H), 7.07 (dd, *J* = 3.4, 1.8 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 167.1 (J_{C-F} = 243.2 Hz), 166.8, 166.5 (J_{C-F} = 243.2 Hz), 143.3 (J_{C-F} = 8.1 Hz), 142.8, 142.7 (J_{C-F} = 2.0 Hz), 141.7 (J_{C-F} = 8.1 Hz), 138.0, 135.5 (J_{C-F} = 8.7 Hz), 135.0 (J_{C-F} = 8.5 Hz), 133.2 (J_{C-F} = 2.7 Hz), 132.1, 131.8, 131.4 (J_{C-F} = 2.6 Hz), 130.4, 130.0, 123.7 (J_{C-F} = 21.3 Hz), 122.1 (J_{C-F} = 22.6 Hz), 120.5 (J_{C-F} = 20.6 Hz), 119.8, 119.4 (J_{C-F} = 20.8 Hz). $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6) δ -113.49, -113.27. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{21}H_{14}F_2NO$ 334.1038; Found 334.1037.

4-methyl-3-phenylisoquinolin-1(2H)-one **(3al):** white solid (29.6 mg, 63%). R_f = 0.45 (DCM:EA, 3:1). mp 201–202 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 7.79–7.68 (m, 2H), 7.58–7.41 (m, 6H), 2.26 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 162.6, 138.9, 136.8, 135.4, 132.7, 129.3, 129.1, 128.7, 127.8, 126.4, 125.4, 123.7, 109.2, 13.9. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}NO$ 236.1070; Found 236.1068.

3-methyl-4-phenylisoquinolin-1(2H)-one **(3al'):** white solid (14.6 mg, 31%). R_f = 0.35

(DCM:EA, 3:1). mp 243–246 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.98 (s, 1H), 8.46 (d, *J* = 7.6 Hz, 1H), 7.61–7.39 (m, 5H), 7.28 (t, *J* = 1.8 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 1H), 2.22 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.1, 136.2, 134.4, 133.4, 132.2, 132.2, 131.1, 128.8, 128.6, 127.6, 127.2, 125.8, 125.0, 117.4, 18.0. HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}NO$ 236.1070; Found 236.1068.

10,10a-dihydro-4bH-5,10-epoxybenzo[b]fluoren-11(5H)-one **(4):** yellow oil, (11.4 mg, 23%). R_f = 0.50 (PE:EA, 5:1). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 1H), 7.71–7.65 (m, 2H), 7.46–7.39 (m, 2H), 7.37 (m, 1H), 7.25–7.21 (m, 2H), 5.63 (s, 1H), 5.33 (s, 1H), 3.54 (d, *J* = 5.8 Hz, 1H), 2.89 (d, *J* = 5.8 Hz, 1H). The analytical data are in accordance with those reported in the literature.[15]

ASSOCIATED CONTENT

Supporting Information

Optimization of reaction conditions, mechanistic studies, and NMR spectra of compounds **1**, **3**, **4**. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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