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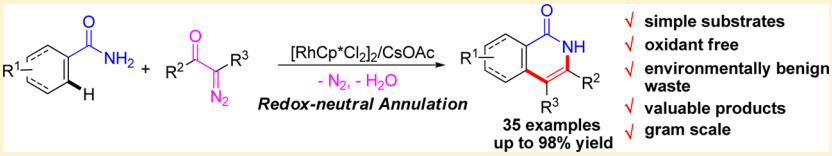
Rh(III)-Catalyzed Redox-Neutral Annulation of Primary Benzamides with Diazo Compounds: Approach to Isoquinolinones

Youzhi Wu,[†] Peng Sun,[†] Kaifan Zhang, Tie Yang, Hequan Yao,* and Aijun Lin*

State Key Laboratory of Natural Medicines and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing, 210009, P. R. China

Supporting Information



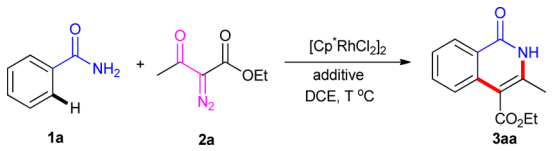
ABSTRACT: Reported herein is a Rh-catalyzed redox-neutral annulation of primary benzamides with diazo compounds, representing an efficient and economic protocol to isoquinolinones. The procedure exhibited good functional group tolerability, scalability, and regioselectivity, obviating the need for oxidants, and only environmentally benign N_2 and H_2O were released. Further utilization of the method provided an alternative route to functionalized isoquinolines.

The development of a new synthetic strategy to enhance the selectivity and step economy and reduce the generation of undesired waste is an important goal of chemists. During the past two decades, the direct C−H functionalization has been proved to be one powerful approach to satisfy this expectation due to its inherent advantages of avoiding prefunctionalization of substrates[1] and achieving highly regioselective functionalization of one C−H bond over the others employing directing group assisted transition-metal-mediated transformations.[2]

Recently, the readily available diazo compounds as carbene precursors have been widely employed in C−H activation for direct C−C bond formation, particularly in the heterocycles synthesis with N-protected benzamides[3a−c] or anlines,[3d,e] aryloximes,[3f,g] sulfoximines,[3h] and others.[3i] To the best of our knowledge, primary benzamides as substrate candidates involved in the transition-metal-mediated C−H activation processes[4] with diazo compounds has not been reported up to date. To further explore diazo compounds as participant in C−H activation and also in conjunction with our ongoing interest in diazo chemistry,[5] herein, we will report the first example of Rh-catalyzed annulation reaction between primary benzamides and diazo compounds, leading to the direct synthesis of isoquinolinones. Isoquinolinones are important heterocycles found in natural products[6] and pharmaceuticals,[7] and the syntheses have been achieved through transition-metal-mediated tandem C−H activation/annulation of benzamides with alkynes,[8] while either external or internal oxidants are necessary to ensure the catalytic cycles.[9] Moreover, the regioselectivity of internal alkynes could not be well controlled in some cases.[10] In our work, the primary benzamides could serve as good substrates and directing groups for direct C−H bond activation as well as predisposing the intermediates toward the intramolecular C−N bond formation. Moreover, no oxidants were needed and only environmentally benign N_2 and H_2O were released.

Initially, our investigations focused on the combination of benzamide **1a** and ethyl diazoacetoacetate **2a** to optimize the reaction conditions (Table 1). The desired product **3aa** was obtained in 17% yield in the presence of $[Cp^*RhCl_2]_2$ (2.5 mol %) and $AgSbF_6$ (10 mol %) in 1,2-dichloroethane (DCE) at 100 °C under an argon atmosphere (Table 1, entry 1). When

Table 1. Optimization of the Reaction Conditions[a]



entry	additives (mol %)	temperature (°C)	yield (%)[b]
1	$AgSbF_6$ (10)	100	17
2	NaOAc (10)	100	34
3	KOAc (10)	100	28
4	$Cu(OAc)_2$ (10)	100	35
5	CsOAc (10)	100	38
6	CsOAc (20)	100	66
7	CsOAc (50)	100	98(96)[c]
8	CsOAc (50)	80	78
9[d]	CsOAc (50)	100	70
10[e]	CsOAc (50)	100	N.R.

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), additives in DCE (2.0 mL) was stirred at 100 °C for 7 h under Ar. [b]Yield was determined by ^1H NMR using dibromomethane as the internal standard. [c]Isolated yield. [d]1.5 mol % of $[Cp^*RhCl_2]_2$. [e]Without $[Cp^*RhCl_2]_2$.

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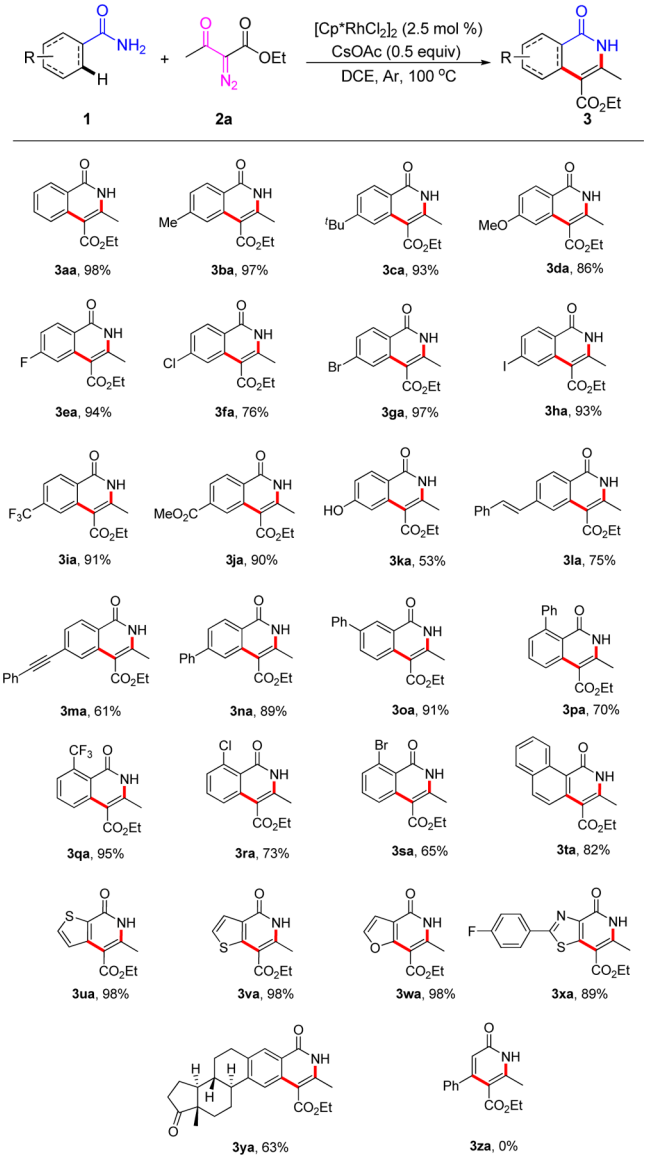
CsOAc (10 mol %) was employed as the additive, the yield of **3aa** was increased to 38% (Table 1, entry 5). Further increasing the amount of CsOAc to 50 mol %, the yield was significantly improved to 98% (Table 1, entry 7). An attempt to lower the reaction temperature resulted in decreased yield (Table 1, entry 8). When 1.5 mol % catalyst was used, the yield was decreased to 70% (Table 1, entry 9). Omission of $[Cp^*RhCl_2]_2$ completely shut down the reaction (Table 1, entry 10).

With the optimized conditions in hand, we investigated the substrate scope of benzamides to test the generality of this annulation reaction (Table 2). It was found that a variety of amides could successfully cyclize to give the desired products in good to excellent yields. An electron-donating group such as a methyl, a *tert*-butyl and a methoxy group at the *para*-position of the benzene ring offered **3ba**, **3ca**, and **3da** in 97%, 93%, and 86% yield, respectively. Halogen substituents offered **3ea**−**3ha** in 76−97% yields, which could be subjected to further synthetic transformations. An electron-withdrawing group such as a CF_3 and an ester group afforded **3ia** and **3ja** in 91% and 90% yields. **3la** and **3ma** with unsaturated C=C double bonds and C≡C triple bonds could be obtained in 75% and 61% yields. It was interesting to note that the reaction could also tolerate an unprotected OH group and the **3ka** was completed in 53% yield. Owing to the steric effect, *ortho*-phenyzl-substituted benzamide provided **3pa** in 70% yield, while *para*- and *meta*-phenyzl-substituted benzamides provided **3na** and **3oa** in 89% and 91% yields. **3qa** with a CF_3 group at the *ortho*-position could be furnished in 95% yield. 1-Naphthamide gave the desired product **3ta** with three continuous six-membered rings in 82% yield. In regard to the heteroaromatic amides such as thiophene, furane and thiazole delivered the desired products **3ua**−**3xa** in 89−98% yields. Both the thiophene-2-carboxamide and thiophene-3-carboxamide were compatible in our system. The reaction could also work well with the complex substrate, benzamide **1y**, derived from estrone, which reacted smoothly under the optimal conditions, affording the corresponding product **3ya** in 63% yield. An alkenyl amide, such as cinnamamide, could not offer the desired product **3za**. Moreover, the reaction could proceed smoothly on a gram scale (5 mmol), offering **3aa** in 1.13 g (98% yield).

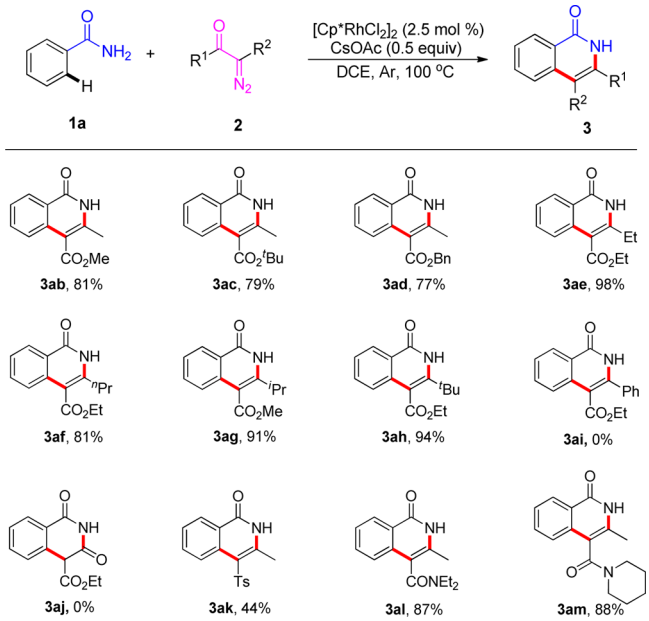
After the examination of benzamides, dizao compounds were also investigated, and the results are described in Table 3.

Table 2. Substrates of Primary Benzamides[a,b]



[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), and CsOAc (0.5 equiv) in DCE (2.0 mL) was stirred at 100 °C for 7 h under Ar. [b]Isolated yield.

Table 3. Scope of Diazo Compounds[a,b]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), $[Cp^*RhCl_2]_2$ (2.5 mol %), and CsOAc (0.5 equiv) in DCE (2.0 mL) was stirred at 100 °C for 7 h under Ar. [b]Isolated yield.

When the ester with a methyl, a *tert*-butyl, or a benzyl group was used, the **3ab**−**3ad** were given in 77−81% yields. R^1 with an ethyl or an *n*-propyl group afforded **3ae** and **3af** in 98% and 81% yields. When R^1 with branched alkyl groups such as an isopropyl and a *tert*-butyl group were used, the **3ag** and **3ah** were given in 91% and 94% yields. R^1 with a phenyl group could not give the desired product **3ai**. When diethyl 2-diazomalontae **2j** was used as the substrate, **3aj** was not observed. R^2 with a Ts group gave **3ak** in moderate yield. R^2

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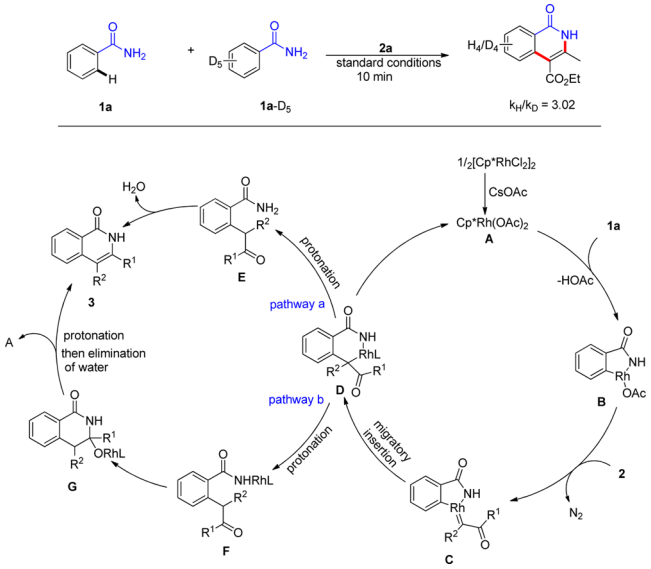
with amides (**2l**, **2m**) were also compatible and offered **3al** and **3am** in 87% and 88% yields.

To understand the reaction mechanism, we conducted an isotope-labeling experiment with deuterium-labeled benzamide. Significant primary kinetic isotope effects were observed (k_H/k_D = 3.02), which suggested that the C−H bond cleavage was likely to be involved in the rate-limiting step. On the basis of the above-mentioned observation and literature precedents,[3b,f,11] a plausible reaction mechanism is proposed in Scheme 1. After the anion exchange with CsOAc, the active

Scheme 1. Mechanism Study

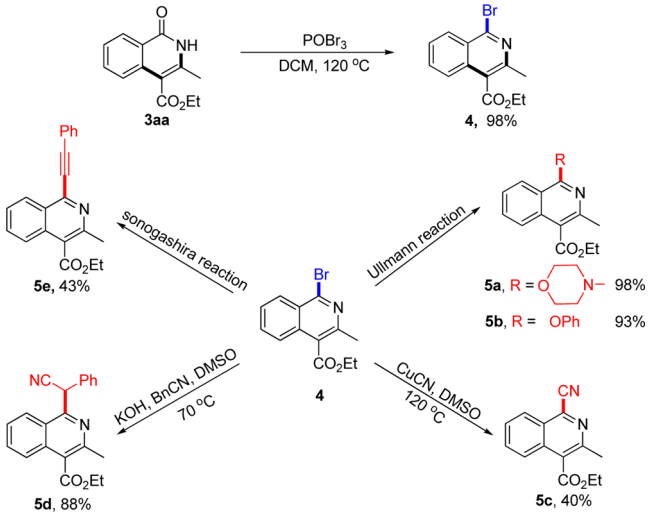


catalyst **A** was generated. Then, an arene rhodation occurred and afforded the intermediate **B**, which reacted with diazo compound **2** to give the intermediate **C** via the Rh carbene formation pathway.[3b,f] Migratory insertion of carbenoid gave a six-membered rhodacylic intermediate **D**. At this stage, two pathways were possible. In pathway "a", protonation of **D** delivered the alkylated intermediate **E** and regenerated **A** to the next reaction cycle. The final product **3** was formed via intramolecular nucleophilic addition of **E** with the elimination of water. In pathway "b",[11] protonation of **D** delivered the carbonyl intermediate **F**. The formed Rh−N bond could add across the carbonyl group, affording the cyclorhodated intermediate **G**, which then underwent protonolysis and elimination of H_2O to give the final product **3** and the recovered **A**.

To enlarge the application of our method, isoquinolinone **3aa** could be further transformed to isoquinolines (Scheme 2), which are also one of the most important structural motifs present in natural products[12] with wide range of biological activities.[13] First, treatment of **3aa** with $POBr_3$ in DCM gave bromination product **4**, which could be easily functionalized. **5a** and **5b** were obtained via Ullmann reaction of **4** in 98% and 93% yield, respectively. 1-Cyano substituted isoquinoline **5c** was obtained in 40% yield. Similarly, 1-alkyl-substituted isoquinoline **5d** could be obtained via nucleophilic substitution reaction in 88% yield. Alkynyl-substituted product **5e** was obtained in moderate yield through Sonogashira reaction.

In summary, we have developed the first example of Rh-catalyzed redox-neutral annulation of primary benzamides with diazo compounds. This tandem C−H activation/annulation

Scheme 2. Further Transformation of Generated Isoquinolinone

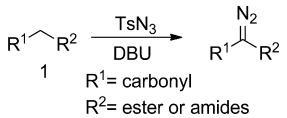


provided a facile method to the direct synthesis of isoquinolinones and exhibited good functional group tolerability, scalability, and regioselectivity, obviating the need for oxidants, and only environmentally benign N_2 and H_2O were released. Primary mechanistic insights revealed that the C−H bond cleavage of the benzene ring is the key rate-limiting step. Initial functionalization reactions illustrated the synthetic prospect of our method to isoquinolines.

EXPERIMENTAL SECTION

General Information. All chemicals and reagents were purchased from commercial suppliers and used without further purification. The products were purified by column chromatography on silica gel. Melting point (mp) was measured on a microscopic melting point apparatus. ^{1}H NMR spectra were recorded at a 300 MHz NMR spectrometer. ^{13}C NMR spectra were recorded at 75 and 125 MHz NMR spectrometers. NMR experiments were reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) or DMSO-d_6 (δ 2.50 or 40.5 ppm) as the internal standard. Infrared spectra (IR) were recorded on the FT-IR spectrometer. High-resolution mass measurement was performed with an electrospray ionization (ESI) method on a Q-TOF mass spectrometer operating in positive ion mode.

General Procedure for the Synthesis of Diazo Compounds. Diazo substrates were synthesized from the corresponding ketonic esters or ketonic amides.[5a,14]



To a solution of **1** (5 mmol) in CH_3CN was added 6 mmol of TsN_3. Then, the reaction mixture was cooled to 0 °C and a solution of DBU (6 mmol) in 10 mL of CH_3CN was added dropwise. Next, the reaction temperature was raised to room temperature. After stirring for 3 h, the residue was extracted with ethyl acetate for 3 times. The combined organic layers were washed with water and brine sequentially, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography on silica gel to afford the corresponding products in 70−90% yields.

General Procedure for the Synthesis of 1a−1x. Aryl carboxylic acid (10 mmol) in $SOCl_2$ (10 mL) was refluxed at 85 °C. After 30 min, the mixture turned clear. The reaction was stopped, and the reaction solution was concentrated to give the acyl chloride. A solution of acyl chloride prepared above in anhydrous dichloromethane (10

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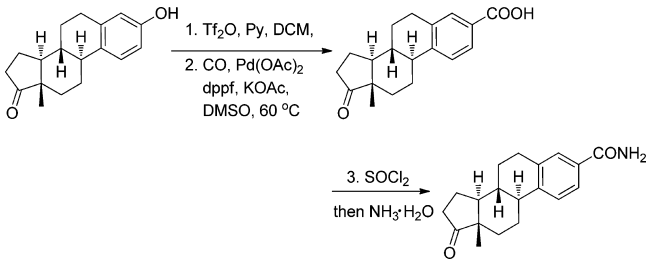
mL) was injected dropwise to an aqueous ammonia solution (con. 20 mL) in an ice bath. After stirring for 30 min, the precipitate was collected by suction filtration, washed with water and *n*-hexane, and dried under reduced pressure at 50 °C. Recrystallization from ethyl acetate afforded the desired compounds **1a−1x**.

General Procedure for the Synthesis of 1y.[15]



Step 1: Pyridine (10.0 mmol, 2.0 equiv) was added to a stirring solution of estrone (5.0 mmol, 1.0 equiv) in DCM (25 mL) under Ar. Then, triflic anhydride (6.0 mmol, 1.2 equiv) was added dropwise to the mixture in an ice bath. The mixture was warmed to room temperature and stirred for 5 h. Then, the reaction was quenched by the addition of water. The layers were separated, and the aqueous phase was extracted with DCM (30 mL × 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure to afford the corresponding crude trifluoromethane-sulfonate substituted compound. The crude compound was used without further purification.

Step 2: $Pd(OAc)_2$ (0.25 mmol, 5 mol %), 1,1′-bis(diphenylphosphino)ferrocene (1 mmol, 20 mol %), and potassium acetate (20 mmol, 4 equiv) were added to the crude compound in DMSO (50 mL). The reaction mixture was stirred at 60 °C under a balloon of CO overnight. The mixture was then cooled to room temperature, quenched with 1 M HCl (pH < 3), and extracted with EtOAc (50 mL × 3). The combined organic phase was washed with brine, dried over sodium sulfate, filtered, and evaporated under reduced pressure to afford the corresponding crude carboxylic acid. The crude carboxylic acid was purified by column chromatography on silica gel to obtain the corresponding acid.

Step 3: **1y** was obtained by the same way as that for **1a−1x**.

General Procedure for the Rhodium-Catalyzed Annulations. A sealed tube was charged with benzamide **1** (0.5 mmol), $[Cp^*RhCl_2]_2$ (0.0125 mmol, 2.5 mol %), CsOAc (0.25 mmol), and dry 1,2-dichloroethane (2.0 mL). After stirring the reaction mixture at room temperature for 5 min, diazo compound **2** (0.75 mmol) was added. Under an argon atmosphere, the reaction mixture was stirred at 100 °C for 7 h. Then, the mixture was cooled to room temperature and diluted with dichloromethane (10 mL), then filtered through a Celite pad, and washed with dichloromethane (20 mL × 3). The filtrate was concentrated, and the product was purified by column chromatography on silica gel with dichloromethane/MeOH as eluent to afford the corresponding product **3**.

*Ethyl 3-Methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3aa**).*[16,17] 113 mg, 98% yield; white solid, mp 191−193 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.26 (s, 1H), 8.42 (d, J = 7.3 Hz, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.74−7.59 (m, 1H), 7.48 (t, J = 7.5 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.0, 164.4, 141.4, 135.9, 133.1, 127.3, 126.3, 124.4, 124.0, 109.4, 61.2, 18.8, 14.3 ppm; IR (KBr) 3174, 3049, 2984, 1709, 1682, 1614, 1201, 868, 784 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{13}NO_3 + H]^+$ 232.0968, found 232.0967.

*Ethyl 3,6-Dimethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ba**).*[16] 119 mg, 97% yield; white solid, mp 206−207 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.55 (s, 1H), 8.10 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.31 (d, J = 8.1 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.35 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.0, 162.0, 143.4, 142.1, 135.6, 128.0, 127.3, 124.0, 122.2, 107.6, 61.2, 22.1, 18.4, 14.5 ppm; IR (KBr) 3174, 3056, 2975, 1708, 1683, 1619, 1288, 1176, 897, 792 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{15}NO_3 + H]^+$ 246.1125, found 246.1126.

*Ethyl 6-tert-Butyl-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ca**).* 134 mg, 93% yield; light yellow solid, mp 194−196 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.37 (s, 1H), 8.36 (d, J = 8.5 Hz, 1H), 7.96 (s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 4.48 (q, J = 6.9 Hz, 2H), 2.61 (s, 3H), 1.46 (t, J = 7.0 Hz, 3H), 1.39 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 164.3, 156.5, 141.6, 135.8, 127.0, 124.5, 121.6, 120.5, 109.5, 61.1, 35.5, 31.1, 18.8, 14.4 ppm; IR (KBr) 3174, 3044, 1701, 1655, 1617, 1460, 1291, 1177, 1108 cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{21}NO_3 + H]^+$ 288.1594, found 288.1593.

*Ethyl 6-Methoxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3da**).*[16] 112 mg, 86% yield; light yellow solid, mp 182−185 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.28 (s, 1H), 8.31 (d, J = 8.9 Hz, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 8.9, 2.1 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 2.60 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 163.9, 163.4, 142.9, 138.1, 129.2, 117.6, 115.9, 108.6, 105.6, 61.1, 55.4, 19.2, 14.4 ppm; IR (KBr) 3191, 2908, 1693, 1682, 1611, 1366, 1328, 1172, 1072, 840, 641 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{15}NO_4 + H]^+$ 262.1074, found 262.1076.

*Ethyl 6-Fluoro-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ea**).* 117 mg, 94% yield; light yellow solid, mp 233−234 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.26 (s, 1H), 7.63 (d, J = 11.0 Hz, 1H), 7.34 (s, 1H), 4.37 (d, J = 6.5 Hz, 2H), 2.41 (s, 3H), 1.35 (d, J = 6.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4, 165.2 (d, $^1J_{C\text{-}F}$ = 247.2 Hz), 161.3, 145.2, 138.1, 130.7 (d, $^3J_{C\text{-}F}$ = 10.5), 121.3, 114.9 (d, $^2J_{C\text{-}F}$ = 23.4), 109.8 (d, $^2J_{C\text{-}F}$ = 24.5), 106.7, 61.3, 18.9, 14.5 ppm; IR (KBr) 3174, 3038, 2991, 1720, 1682, 1617, 1330, 1283, 870, 777 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{12}FNO_3 + H]^+$ 250.0874, found 250.0876.

*Ethyl 6-Chloro-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3fa**).*[16] 101 mg, 76% yield; light yellow solid, mp 213−214 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.81 (s, 1H), 8.18 (d, J = 8.5 Hz, 1H), 7.91 (s, 1H), 7.51 (s, 1H), 4.36 (d, J = 7.1 Hz, 2H), 2.39 (s, 3H), 1.33 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 161.5, 145.2, 137.1, 129.4, 129.4, 127.7, 126.8, 123.2, 106.1, 61.3, 19.0, 14.5 ppm; IR (KBr) 3168, 2973, 2925, 1718, 1684, 1457, 1323, 1283, 874, 671 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{12}ClNO_3 + H]^+$ 266.0578, found 266.0576.

*Ethyl 6-Bromo-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ga**).* 150 mg, 97% yield; light yellow solid, mp 223−225 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.82 (s, 1H), 8.11−8.08 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H), 4.38 (q, J = 7.0 Hz, 2H), 2.41 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 161.5, 145.2, 137.1, 129.4, 129.4, 127.7, 126.8, 123.2, 106.1, 61.3, 19.0, 14.5 ppm; IR (KBr) 3168, 3032, 2981, 1719, 1685, 1621, 1285, 1198, 870, 771 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{12}BrNO_3 + H]^+$ 310.0073, found 310.0071.

*Ethyl 6-Iodo-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ha**).* 166 mg, 93% yield; light yellow solid, mp 239−240 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.76 (s, 1H), 8.28 (s, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.0 Hz, 1H), 4.61−4.13 (m, 2H), 2.40 (s, 3H), 1.36 (t, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.3, 161.8, 144.7, 136.9, 135.0, 133.0, 128.9, 123.5, 105.9, 102.2, 61.3, 19.0, 14.5 ppm; IR (KBr) 3174, 3032, 2970, 1697, 1648, 1596, 1286, 1245, 784, 634 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{12}INO_3 + H]^+$ 357.9935, found 357.9934.

*Ethyl 3-Methyl-1-oxo-6-(trifluoromethyl)-1,2-dihydroisoquinoline-4-carboxylate (**3ia**).* 136 mg, 91% yield; light yellow solid, mp 199−200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.67 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 4.46 (q, J = 7.0 Hz, 2H), 2.59 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 161.7, 142.8, 138.7, 131.8, 129.7 (q, $^2J_{C\text{-}F}$ = 32.4 Hz), 128.9, 126.1 (q, $^3J_{C\text{-}F}$ = 7.5 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 271.4 Hz), 120.9, 109.2, 61.4, 18.2, 14.2 ppm; IR (KBr) 3185, 3097, 2991, 1720, 1678, 1634, 1376, 1273, 824, 674 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{12}F_3NO_3 + H]^+$ 300.0842, found 300.0844.

*4-Ethyl 6-Methyl 3-Methyl-1-oxo-1,2-dihydroisoquinoline-4,6-dicarboxylate (**3ja**).* 130 mg, 90% yield; light yellow solid, mp 201−204 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.87 (s, 1H), 8.51 (s, 1H), 8.27 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 4.40 (q, J = 6.8 Hz, 2H), 3.92 (s, 3H), 2.41 (s, 3H), 1.38 (t, J = 6.8 Hz, 3H) ppm;

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^{13}C NMR (75 MHz, DMSO-d_6) δ 166.4, 166.1, 161.5, 144.5, 135.4, 133.5, 127.9, 127.1, 126.1, 126.0, 107.1, 61.3, 53.0, 18.8, 14.5 ppm; IR (KBr) 3191, 3056, 2985, 1737, 1723, 1678, 1623, 1279, 1245, 765 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{15}NO_5 + H]^+$ 290.1023, found 290.1021.

*Ethyl 6-Hydroxy-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ka**).* 65 mg, 53% yield; light yellow solid, mp 246−247 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.37 (s, 1H), 10.37 (s, 1H), 8.06 (d, J = 8.7 Hz, 1H), 7.15 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 4.35 (q, J = 6.9 Hz, 2H), 2.33 (s, 3H), 1.35 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.1, 161.9, 161.8, 142.6, 137.6, 129.6, 116.9, 116.3, 108.2, 107.2, 61.1, 18.5, 14.6 ppm; IR (KBr) 3303, 3144, 1652, 1599, 1360, 1243, 1173, 794, 647 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{13}NO_4 + H]^+$ 248.0917, found 248.0916.

*(E)-Ethyl 3-Methyl-1-oxo-6-styryl-1,2-dihydroisoquinoline-4-carboxylate (**3la**).* 125 mg, 75% yield; light yellow solid, mp 216−218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.62 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.69 (d, J = 7.4 Hz, 2H), 7.51−7.24(m, 5H), 4.43 (q, J = 7.1 Hz, 2H), 2.38 (s, 3H), 1.39 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9, 161.8, 142.8, 141.7, 137.0, 136.1, 131.8, 129.2, 128.7, 128.3, 127.7, 127.4, 123.8, 123.3, 123.0, 107.7, 61.3, 18.5, 14.6 ppm; IR (KBr) 3179, 3020, 2890, 1700, 1663, 1610, 1286, 1068, 688, 638 cm^{-1}; HRMS (ESI) calcd for $[C_{21}H_{19}NO_3 + H]^+$ 334.1438, found 334.1434.

*Ethyl 3-Methyl-1-oxo-6-(phenylethynyl)-1,2-dihydroisoquinoline-4-carboxylate (**3ma**).* 101 mg, 61% yield; light yellow solid, mp 175−177 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.75 (s, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.03 (s, 1H), 7.62 (t, J = 6.6 Hz, 3H), 7.50−7.43 (m, 3H), 4.40 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.6, 161.6, 144.1, 135.6, 132.1, 129.8, 129.3, 128.9, 127.8, 127.3, 127.1, 123.9, 122.2, 106.8, 92.2, 89.2, 61.4, 18.8, 14.5 ppm; IR (KBr) 3179, 3050, 2979, 1717, 1664, 1654, 1618, 1275, 1196, 751, 689 cm^{-1}; HRMS (ESI) calcd for $[C_{21}H_{17}NO_3 + H]^+$ 332.1281, found 332.1272.

*Ethyl 3-Methyl-1-oxo-6-phenyl-1,2-dihydroisoquinoline-4-carboxylate (**3na**).* 137 mg, 89% yield; light yellow solid, mp 232−234 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 8.29 (d, J = 8.3 Hz, 1H), 8.10 (s, 1H), 7.79−7.71 (m, 3H), 7.56−7.43 (m, 3H), 4.41 (q, J = 7.0 Hz, 2H), 2.42 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 161.9, 144.8, 143.4, 139.9, 136.0, 129.6, 128.8, 128.1, 127.5, 125.3, 123.4, 122.4, 107.6, 61.2, 18.7, 14.6 ppm; IR (KBr) 2997, 2902, 1714, 1683, 1620, 1289, 1187, 647 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{17}NO_3 + H]^+$ 308.1281, found 308.1279.

*Ethyl 3-Methyl-1-oxo-7-phenyl-1,2-dihydroisoquinoline-4-carboxylate (**3oa**).* 140 mg, 91% yield; light yellow solid, mp 241−243 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.45 (d, J = 1.8 Hz, 1H), 8.07 (dd, J = 8.6, 1.9 Hz, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.77 (d, J = 7.4 Hz, 2H), 7.54−7.49 (m, 2H), 7.42 (t, J = 7.2 Hz, 1H), 4.40 (q, J = 7.1 Hz, 2H), 2.40 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 162.1, 142.7, 139.3, 138.1, 134.7, 131.8, 129.6, 128.3, 127.1, 125.4, 124.8, 124.5, 107.4, 61.3, 18.6, 14.6 ppm; IR (KBr) 3168, 2914, 1705, 1658, 1612, 1339, 1211, 833, 694 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{17}NO_3 + H]^+$ 308.1281, found 308.1283.

*Ethyl 3-Methyl-1-oxo-8-phenyl-1,2-dihydroisoquinoline-4-carboxylate (**3pa**).* 107 mg, 70% yield; light yellow solid, mp 260−262 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.29 (s, 1H), 7.82−7.61 (m, 2H), 7.31−7.16(m, 6H), 4.38 (d, J = 6.7 Hz, 2H), 2.32 (s, 3H), 1.35 (t, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9, 160.8, 143.5, 142.9, 141.3, 136.5, 131.6, 129.5, 128.4, 127.0, 126.2, 123.4, 120.9, 107.6, 60.8, 17.6, 14.0 ppm; IR (KBr) 3091, 2395, 1715, 1662, 1620, 1472, 1262, 1230, 1131, 756, 697 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{17}NO_3 + H]^+$ 308.1281, found 308.1283.

*Ethyl 3-Methyl-1-oxo-8-(trifluoromethyl)-1,2-dihydroisoquinoline-4-carboxylate (**3qa**).* 142 mg, 95% yield; light yellow solid, mp 179−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.42 (s, 1H), 8.40 (d, J = 8.3 Hz, 1H), 8.25 (s, 1H), 7.59 (d, J = 8.3 Hz, 1H), 4.47 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 163.5, 143.7, 135.9, 134.6 (q, $^2J_{C\text{-}F}$ = 32.1), 128.3, 125.8, 123.7 (q, $^1J_{C\text{-}F}$ = 271.4), 122.3 (q, $^3J_{C\text{-}F}$ = 3.6), 108.9, 61.5, 19.3, 14.3 ppm; IR (KBr) 3191, 2997, 2809, 1676, 1655, 1317, 1304, 1190, 1176, 1120, 1085, 638 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{12}F_3NO_3 + H]^+$ 300.0842, found 300.0841.

*Ethyl 8-Chloro-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ra**).* 97 mg, 73% yield; light yellow solid, mp 195−197 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.65 (s, 1H), 7.78−7.59 (m, 2H), 7.49 (dd, J = 7.2, 1.6 Hz, 1H), 4.36 (q, J = 7.1 Hz, 2H), 2.31 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9, 160.3, 142.7, 138.7, 134.3, 133.4, 129.5, 123.6, 120.6, 107.8, 61.5, 18.1, 14.5 ppm; IR (KBr) 3174, 3079, 2991, 1725, 1672, 1619, 1254, 1139, 806, 641 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{12}ClNO_3 + H]^+$ 266.0578, found 266.0577.

*Ethyl 8-Bromo-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3sa**).* 100 mg, 65% yield; light yellow solid, mp 195−197 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.68 (s, 1H), 7.74 (s, 1H), 7.71 (s, 1H), 7.53 (t, J = 8.0 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.9, 160.3, 142.5, 138.6, 133.5, 133.3, 124.2, 122.1, 121.3, 107.9, 61.5, 18.1, 14.5 ppm; IR (KBr) 3174, 3067, 2991, 1714, 1677, 1620, 1369, 1275, 1201, 1140, 812, 641 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{12}BrNO_3 + H]^+$ 310.0073, found 310.0072.

*Ethyl 3-Methyl-1-oxo-1,2-dihydrobenzo[h]isoquinoline-4-carboxylate (**3ta**).* 115 mg, 82% yield; light yellow solid, mp 205−208 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.05 (s, 1H), 10.12 (d, J = 8.5 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 7.4 Hz, 1H), 7.79 (d, J = 9.1 Hz, 1H), 7.73 (dd, J = 8.5, 1.4 Hz, 1H), 7.68−7.63 (m, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.44 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.3, 162.8, 142.8, 137.4, 134.4, 131.6, 131.6, 128.7, 126.9, 126.8, 122.4, 117.1, 109.3, 61.6, 18.0, 14.5 ppm; IR (KBr) 3073, 3026, 1711, 1652, 1607, 1297, 1225, 1112, 1024, 828, 645 cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{15}NO_3 + H]^+$ 282.1125, found 282.1127.

*Ethyl 5-Methyl-7-oxo-6,7-dihydrothieno[2,3-c]pyridine-4-carboxylate (**3ua**).* 116 mg, 98% yield; light yellow solid, mp 180−182 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.98 (s, 1H), 8.08 (d, J = 5.3 Hz, 1H), 7.74 (d, J = 5.3 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.55 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.8, 158.5, 148.1, 144.7, 134.7, 127.6, 126.3, 105.3, 60.9, 19.2, 14.6 ppm; IR (KBr) 3085, 2867, 1698, 1646, 1590, 1276, 1121, 791, 615 cm^{-1}; HRMS (ESI) calcd for $[C_{11}H_{11}NO_3S + H]^+$ 238.0532, found 238.0533.

*Ethyl 6-Methyl-4-oxo-4,5-dihydrothieno[3,2-c]pyridine-7-carboxylate (**3va**).* 116 mg, 98% yield; light yellow solid, mp 262−263 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.92 (s, 1H), 7.59 (d, J = 5.5 Hz, 1H), 7.45 (d, J = 5.5 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.2, 158.9, 148.9, 148.0, 128.4, 127.5, 123.6, 103.7, 61.3, 19.8, 14.6 ppm; IR (KBr) 3079, 2973, 1701, 1647, 1593, 1304, 1274, 1227, 1104, 727, 628 cm^{-1}; HRMS (ESI) calcd for $[C_{11}H_{11}NO_3S + H]^+$ 238.0532, found 238.0531.

*Ethyl 6-Methyl-4-oxo-4,5-dihydrofuro[3,2-c]pyridine-7-carboxylate (**3wa**).* 108 mg, 98% yield; light yellow solid, mp 219−221 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.93 (s, 1H), 7.92 (d, J = 2.1 Hz, 1H), 6.94 (d, J = 2.1 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.57 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.8, 159.2, 158.3, 149.2, 144.7, 114.1, 106.8, 99.5, 60.8, 18.7, 14.7 ppm; IR (KBr) 2979, 2814, 1712, 1677, 1310, 1261, 1104, 644 cm^{-1}; HRMS (ESI) calcd for $[C_{11}H_{11}NO_4 + H]^+$ 222.0761, found 222.0760.

*Ethy 2-(4-Fluorophenyl)-6-methyl-4-oxo-4,5-dihydrothiazolo[4,5-c]pyridine-7-carboxylate (**3xa**).* 148 mg, 89% yield; light yellow solid, mp 296−298 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.27 (s, 1H), 8.02 (dd, J = 8.6, 5.4 Hz, 2H), 7.36 (t, J = 8.7 Hz, 2H), 4.30 (q, J = 7.0 Hz, 2H), 2.61 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 164.6, 164.0 (d, $^1J_{C\text{-}F}$ = 251.6), 157.4, 150.5, 144.8, 142.0, 129.7, 129.3 (d, $^3J_{C\text{-}F}$ = 8.7), 116.8 (d, $^2J_{C\text{-}F}$ = 22.1), 61.7, 19.8, 14.5 ppm; IR (KBr) 3061, 2997, 2902, 2867, 1664, 1479, 1345, 1230, 1103, 838, 645 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{13}FN_2O_3S + H]^+$ 333.0704, found 333.0703.

*(3aS,3bR,11bS,13aS)-Ethyl 9,13a-Dimethyl-1,7-dioxo-2,3,3a,3b,4,5,7,8,11b,12,13,13a-dodecahydro-1H-cyclopenta[5,6]-naphtho[1,2-g]isoquinoline-10-carboxylate (**3ya**).* 128 mg, 63%

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yield; light yellow solid, mp 218−220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.81 (s, 1H), 8.12 (s, 1H), 7.91 (s, 1H), 4.47 (dd, J = 13.7, 6.7 Hz, 2H), 3.07−3.02 (m, 2H), 2.64−2.32 (m, 6H), 2.20−1.94 (m, 4H), 1.67−1.43 (m, 9H), 0.92 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.6, 167.2, 163.9, 146.2, 140.5, 135.8, 133.6, 126.7, 121.9, 120.9, 109.1, 61.1, 50.7, 47.9, 44.8, 37.7, 35.8, 31.5, 28.9, 26.3, 25.5, 21.6, 19.0, 14.4, 13.8 ppm; IR (KBr) 3197, 2914, 1739, 1655, 1618, 1189 cm^{-1}; HRMS (ESI) calcd for $[C_{25}H_{29}NO_4 + H]^+$ 408.2169, found 408.2166.

Methyl 3-Methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ab**).[17] 88 mg, 81% yield; light yellow solid, mp 216−218 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.22 (d, J = 7.4 Hz, 1H), 7.81 (d, J = 8.1 Hz, 1H), 7.78−7.67 (m, 1H), 7.50 (t, J = 7.1 Hz, 1H), 3.90 (s, 3H), 2.37 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 167.4, 162.1, 142.6, 135.5, 133.4, 127.2, 126.6, 124.5, 124.3, 107.5, 52.4, 18.5 ppm; IR (KBr) 2932, 2360, 2336, 1715, 1618, 1297, 1208, 653 cm^{-1}; HRMS (ESI) calcd for $[C_{12}H_{11}NO_3 + H]^+$ 218.0812, found 218.0810.

tert-Butyl 3-Methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ac**).[16] 102 mg, 79% yield; light yellow solid, mp 208−210 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.20 (s, 1H), 8.42 (d, J = 7.6 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.76−7.61 (m, 1H), 7.46 (t, J = 7.3 Hz, 1H), 2.58 (s, 3H), 1.65 (s, 9H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.4, 164.3, 139.8, 136.0, 133.0, 127.3, 126.1, 124.1, 124.0, 111.1, 82.2, 28.4, 18.5 ppm; IR (KBr) 2908, 1713, 1687, 1635, 1474, 1295, 1151, 1122, 653 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{17}NO_3 + H]^+$ 260.1281, found 260.1280.

Benzyl 3-Methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ad**).[16] 113 mg, 77% yield; light yellow solid, mp 191−192 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.22 (dd, J = 8.0, 1.0 Hz, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.71 (ddd, J = 8.4, 7.1, 1.5 Hz, 1H), 7.54−7.46 (m, 3H), 7.46−7.33 (m, 3H), 5.41 (s, 2H), 2.36 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 166.8, 162.1, 142.7, 136.2, 135.5, 133.3, 129.0, 128.7, 127.3, 126.6, 124.4, 124.4, 107.4, 67.0, 18.6 ppm; IR (KBr) 3044, 2908, 2849, 1715, 1673, 1616, 1281, 1204, 727, 638 cm^{-1}; HRMS (ESI) calcd for $[C_{18}H_{15}NO_3 + H]^+$ 294.1125, found 294.1123.

Ethyl 3-Ethyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ae**). 120 mg, 98% yield; light yellow solid, mp 184−186 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.18 (s, 1H), 8.44 (d, J = 7.8 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.69 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 7.3 Hz, 1H), 4.46 (q, J = 6.9 Hz, 2H), 2.87 (q, J = 7.0 Hz, 2H), 1.44 (t, J = 6.8 Hz, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 164.6, 146.1, 135.8, 133.1, 127.3, 126.3, 124.4, 124.1, 109.0, 61.3, 26.1, 14.3, 14.0 ppm; IR (KBr) 3032, 2979, 1718, 1670, 1618, 1290, 1204, 786, 638 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{15}NO_3 + H]^+$ 246.1125, found 246.1124.

Ethyl 1-Oxo-3-propyl-1,2-dihydroisoquinoline-4-carboxylate (**3af**).[16] 105 mg, 81% yield; light yellow solid, mp 146−148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.11 (s, 1H), 8.42 (d, J = 7.4 Hz, 1H), 7.87 (d, J = 8.1 Hz, 1H), 7.75−7.61 (m, 1H), 7.51−7.46 (m, 1H), 4.46 (q, J = 7.1 Hz, 2H), 2.85−2.80 (m, 2H), 1.96−1.76 (m, 2H), 1.44 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.3 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 164.4, 144.7, 135.8, 133.1, 127.3, 126.4, 124.4, 124.1, 109.4, 61.3, 34.4, 23.0, 14.3, 14.0 ppm; IR (KBr) 3168, 2843, 1719, 1676, 1620, 1284, 1205, 682, 632 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{17}NO_3 + H]^+$ 260.1281, found 260.1283.

Methyl 3-Isopropyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ag**). 112 mg, 91% yield; light yellow solid, mp 188−190 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.23 (s, 1H), 8.43 (d, J = 8.0 Hz, 1H), 7.79−7.60 (m, 2H), 7.51−7.47 (m, 1H), 3.99 (s, 3H), 3.31−3.22 (m, 1H), 1.46 (s, 3H), 1.44 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 164.0, 147.8, 135.4, 133.1, 127.5, 126.5, 124.3, 124.2, 108.4, 52.4, 30.9, 20.8 ppm; IR (KBr) 2985, 1719, 1655, 1618, 1331, 1274, 1214, 1042, 654 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{15}NO_3 + Na]^+$ 268.0944, found 268.0939.

Ethyl 3-tert-Butyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate (**3ah**). 128 mg, 94% yield; white solid, mp 185−187 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.20 (s, 1H), 8.41 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.4 Hz, 1H), 7.37 (d, J = 8.2 Hz, 1H), 4.44 (q, J = 7.1 Hz, 2H), 1.51 (s, 9H), 1.43 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 163.0, 145.3, 135.9, 133.1, 127.3, 126.8, 124.1, 123.5, 109.6, 61.8, 36.7, 29.3, 14.0 ppm; IR (KBr) 3185, 1731, 1646, 1613, 1349, 1177, 1042, 779 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{19}NO_3 + Na]^+$ 296.1257, found 296.1244.

3-Methyl-4-tosylisoquinolin-1(2H)-one (**3ak**). 69 mg, 44% yield; light yellow solid, mp 143−145 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.97 (s, 1H), 8.21−8.14 (m, 2H), 7.79 (d, J = 8.1 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.43 (t, J = 7.3 Hz, 1H), 7.34−7.31 (m, 2H), 2.75 (s, 3H), 2.30 (s, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 165.9, 152.8, 148.1, 144.5, 137.5, 137.5, 134.3, 131.5, 131.0, 130.4, 128.6, 128.4, 115.0, 25.3, 24.1 ppm; IR (KBr) 2910, 2843, 1664, 1596, 1463, 1269, 1257, 1151, 764, 750 cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{15}NO_3S + H]^+$ 314.0845, found 314.0846.

N,N-Diethyl-3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxamide (**3al**). 112 mg, 87% yield; light yellow solid, mp 145−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.13 (s, 1H), 8.37 (d, J = 7.7 Hz, 1H), 7.66−7.54 (m, 1H), 7.41 (t, J = 7.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 3.62 (q, J = 7.0 Hz, 2H), 3.16 (q, J = 7.2 Hz, 2H), 2.34 (s, 3H), 1.29 (t, J = 7.1 Hz, 3H), 0.96 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 164.3, 135.7, 134.8, 133.2, 127.5, 126.4, 124.1, 123.2, 113.0, 43.2, 39.2, 17.1, 14.3, 12.9 ppm; IR (KBr) 2967, 2914, 1676, 1639, 1618, 1472, 1434, 1286, 609 cm^{-1}; HRMS (ESI) calcd for $[C_{15}H_{18}N_2O_2 + H]^+$ 259.1441, found 259.1443.

3-Methyl-4-(piperidine-1-carbonyl)isoquinolin-1(2H)-one (**3am**). 119 mg, 88% yield; light yellow solid, mp 214−216 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.01 (s, 1H), 8.43 (d, J = 7.6 Hz, 1H), 7.72−7.62 (m, 1H), 7.49 (d, J = 7.3 Hz, 1H), 7.43 (t, J = 5.1 Hz, 1H), 3.94−3.76 (m, 2H), 3.37−3.17 (m, 2H), 2.41 (s, 3H), 1.70 (d, J = 3.1 Hz, 4H), 1.46 (d, J = 3.5 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 164.3, 135.6, 135.0, 133.2, 127.5, 126.4, 124.1, 123.4, 112.6, 47.9, 42.6, 26.9, 25.9, 24.4, 17.2 ppm; IR (KBr) 2926, 2849, 1679, 1630, 1618, 1439, 1213, 614 cm^{-1}; HRMS (ESI) calcd for $[C_{16}H_{18}N_2O_2 + H]^+$ 271.1441, found 271.1440.

General Procedure for the Mechanism Study. Under an argon atmosphere, a mixture of **1a** (0.25 mmol) and **1a**-d_5 (0.25 mmol) was allowed to react with **2a** (0.75 mmol) in the presence of $[Cp^*RhCl_2]_2$ (7.7 mg, 2.5 mol %), CsOAc (0.5 equiv), and DCE (2 mL) at 100 °C for 10 min. The reaction was cooled down quickly in an ice bath. Then, the crude mixture was filtered through a Celite pad and washed with DCM (10 mL × 3). The filtrate was concentrated and determined by ^{1}H NMR analysis of the reaction mixture (see the Supporting Information for details).

Ethyl 1-Bromo-3-methylisoquinoline-4-carboxylate (**4**).[18] A sealed tube was charged with ethyl 3-methyl-1-oxo-1,2-dihydroisoquinoline-4-carboxylate **3aa** (0.5 mmol), $POBr_3$ (1.5 mmol), and DCM (4 mL). The reaction mixture was vigorously stirred at 150 °C for half an hour. The anisole was removed under reduced pressure, and the residue was diluted with DCM (15 mL), washed with saturated aqueous Na_2CO_3 (15 mL), and brine (15 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The product was purified by column chromatography on silica gel to give ethyl 1-bromo-3-methylisoquinoline-4-carboxylate **4**. 144 mg, 98% yield; white solid, mp 68−70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 8.4 Hz, 1H), 7.70 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 4.51 (q, J = 7.1 Hz, 2H), 2.67 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.7, 149.2, 145.8, 134.7, 132.0, 128.9, 128.2, 126.7, 124.2, 123.8, 61.9, 22.6, 14.3 ppm; IR (KBr) 2926, 2849, 1679, 1630, 1618, 1439, 1213, 614 cm^{-1}; HRMS (ESI) calcd for $[C_{13}H_{12}BrNO_2 + H]^+$ 294.0124, found 294.0123.

Ethyl 3-Methyl-1-morpholinoisoquinoline-4-carboxylate (**5a**). A sealed tube was charged with ethyl 1-bromo-3-methylisoquinoline-4-carboxylate **4** (0.5 mmol) and morpholine (5 mL). The reaction mixture was stirred at 150 °C for 5 h. The mixture was diluted with DCM and washed with water. The aqueous layer was washed twice with DCM, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel to give 3-methyl-1-morpholinoisoquinoline-4-carboxylate **5a**. 147 mg, 98% yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.1 Hz, 1H), 7.90 (d, J = 8.4 Hz, 1H), 7.61−7.56 (m, 1H), 7.48−7.35 (m, 1H), 4.48 (q, J = 7.1 Hz,

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2H), 3.96−3.84 (m, 4H), 3.51−3.37 (m, 4H), 2.61 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 161.0, 148.7, 136.0, 130.4, 125.4, 125.4, 124.4, 118.7, 117.7, 66.9, 61.2, 51.6, 23.3, 14.3 ppm; IR (KBr) 2932, 2849, 2377, 2336, 1711, 1275, 1257, 1234, 764, 750 cm^{-1}; HRMS (ESI) calcd for $[C_{17}H_{20}N_2O_3 + H]^+$ 301.1547, found 301.1549.

*Ethyl 3-Methyl-1-phenoxyisoquinoline-4-carboxylate (**5b**).*[19] A sealed tube with a magnetic stirring bar was charged with CuI (4.8 mg, 5 mol %), K_2CO_3 (0.6 mmol), **4** (0.5 mmol), phenol (0.6 mmol), and DMF (2 mL) under air. The reaction mixture was stirred for 30 min at room temperature and then transferred to a preheated oil bath at 110 °C. At the end of the reaction, the mixture was cooled to room temperature and diluted with EA, and the mixture was filtered through a Celite pad and washed with EA (10 mL × 3). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel to provide the desired product **5b**. 143 mg, 93% yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, J = 8.3 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H), 7.71−7.65 (m, 1H), 7.54−7.49 (m, 1H), 7.44−7.34 (m, 2H), 7.28−7.16 (m, 3H), 4.48 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 159.9, 153.8, 148.7, 136.4, 131.7, 129.4, 126.6, 124.8, 124.3, 123.8, 121.8, 119.1, 117.7, 61.4, 23.1, 14.4 ppm; IR (KBr) 2926, 1720, 1573, 1489, 1380, 1239, 1201, 763, 749 cm^{-1}; HRMS (ESI) calcd for $[C_{19}H_{17}NO_3 + H]^+$ 308.1281, found 308.1284.

*Ethyl 1-Cyano-3-methylisoquinoline-4-carboxylate (**5c**).*[20] A sealed tube was charged with ethyl 1-bromo-3-methylisoquinoline-4-carboxylate **4** (0.5 mmol), CuCN (1 mmol), and dimethylformamide (2 mL). The reaction mixture was refluxed at 140 °C for 3 h under nitrogen. At the end of the reaction, the mixture was poured into water (15 mL), the precipitate was filtered, and the residue was washed with EA (15 mL × 3). The water phase was washed with EA (10 mL × 3). The combined organic phase was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel to give the desired compound **5c**. 48 mg, 40% yield; white solid, mp 128−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37−8.28 (m, 1H), 7.94−7.91 (m, 1H), 7.86−7.81 (m, 1H), 7.78−7.73 (m, 1H), 4.59 (q, J = 7.1 Hz, 2H), 2.76 (s, 3H), 1.49 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 149.9, 135.0, 133.4, 132.6, 129.2, 127.3 127.0, 125.5, 124.4, 115.4, 62.4, 22.6, 14.3 ppm; IR (KBr) 2360, 2341, 1728, 1654, 1637, 1241, 1218, 765, 669 cm^{-1}; HRMS (ESI) calcd for $[C_{14}H_{12}N_2O_2 + H]^+$ 241.0972, found 241.0973.

*Ethyl 1-(Cyano(phenyl)methyl)-3-methylisoquinoline-4-carboxylate (**5d**).*[21] A sealed tube was charged with **4** (0.5 mmol), KOH (1.05 mmol), and 2-phenylacetonitrile (0.65 mmol), and the mixture was stirred in DMSO (2 mL) at 70 °C for 2 h. At the end of the reaction, the mixture was cooled to room temperature, diluted with EA (20 mL), and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The product was purified by column chromatography on silica gel to give the desired compound **5d**. 145 mg, 88% yield; white solid, mp 133−135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.72−7.60 (m, 1H), 7.55−7.40 (m, 3H), 7.36−7.23 (m, 3H), 6.02 (s, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.78 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 154.5, 148.5, 134.4, 134.2, 131.3, 129.2, 128.5, 127.6, 127.5, 124.8, 124.6, 124.2, 123.3, 118.7, 61.9, 43.8, 22.9, 14.3 ppm; IR (KBr) 2380, 2270, 1735, 1654, 1637, 1566, 1237, 1216, 1057, 702 cm^{-1}; HRMS (ESI) calcd for $[C_{21}H_{18}N_2O_2 + H]^+$ 331.1441, found 331.1439.

*Ethyl 3-Methyl-1-(phenylethynyl)isoquinoline-4-carboxylate (**5e**).*[22] An oven-dried Schlenk tube was charged with **4** (0.5 mmol), phenylacetylene (0.55 mmol), $PdCl_2(PPh_3)_2$ (3.51 mg, 1 mol %), CuI (2.86 mg, 3 mol %), and acetonitrile (2 mL). Then, Et_3N (75.91 mg, 1.5 equiv) was added, and the reaction mixture was heated to reflux for 16 h. Upon completion, the reaction was diluted with DCM (10 mL). The mixture was filtered through a Celite pad and washed with DCM (20 mL × 3). The filtrate was washed with H_2O and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel, and the desired product **5e** was obtained. 68 mg, 43% yield; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.77−7.67 (m, 3H), 7.67−7.56 (m, 1H), 7.45−7.33 (m, 3H), 4.54 (q, J = 7.1 Hz, 2H), 2.76 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3, 149.4, 145.1, 133.4, 132.3, 131.5, 129.5, 128.5, 127.4, 127.2, 124.0, 123.2, 121.9, 95.0, 86.6, 61.8, 23.1, 14.3 ppm; IR (KBr) 2922, 2353, 1721, 1693, 1649, 1351, 1261, 1061, 763 cm^{-1}; HRMS (ESI) calcd for $[C_{21}H_{17}NO_2 + H]^+$ 316.1332, found 316.1330.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02824.

Experimental procedures, and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ajlin@cpu.edu.cn (A.L.).
*E-mail: hyao@cpu.edu.cn (H.Y.).

Author Contributions

†Y. Wu and P. Sun contributed equally.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on the direct C−H functionalization, see: (a) Hartwig, J. F. *Nature* **2008**, *455*, 314−322. (b) Bruckl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826−839. (c) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10236−10254. (d) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068−5083. (e) Ashenhurst, J. A. *Chem. Soc. Rev.* **2010**, *39*, 540−548. (f) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918.

(2) For selected reviews on chelation-assisted C−H activation, see: (a) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007−1020. (b) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147−1169. (c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053−1064. (d) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281−295.

(3) For selected examples, see: (a) Hyster, T. K.; Ruhl, K. E.; Rovis, T. *J. Am. Chem. Soc.* **2013**, *135*, 5364−5367. (b) Cui, S.; Zhang, Y.; Wang, D.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3912−3916. (c) Chen, X.; Hu, X.; Bai, S.; Deng, Y.; Jiang, H.; Zeng, W. *Org. Lett.* **2016**, *18*, 192−195. (d) Tang, G.-D.; Pan, C.-L.; Li, X. *Org. Chem. Front.* **2016**, *3*, 87−90. (e) Mishra, N. K.; Choi, M.; Jo, H.; Oh, Y.; Sharma, S.; Han, S. H.; Jeong, T.; Han, S.; Lee, S.-Y.; Kim, I. S. *Chem. Commun.* **2015**, *51*, 17229−17232. (f) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204−12207. (g) Phatake, R. S.; Patel, P.; Ramana, C. V. *Org. Lett.* **2016**, *18*, 292−295. (h) Cheng, Y.; Bolm, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12349−12352. (i) Son, J.-Y.; Kim, S.; Jeon, W. H.; Lee, P. H. *Org. Lett.* **2015**, *17*, 2518−2521 and references cited therein.

(4) For selected examples, see: (a) Shin, K.; Park, S.-W.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 8584−8592. (b) Fabry, D. C.; Zoller, J.; Raja, S.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 10228−10231. (c) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908−6909. (d) Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem.,*

DOI: 10.1021/acs.joc.5b02824
J. Org. Chem. 2016, 81, 2166−2173

Int. Ed. **2013**, *52*, 4440−4444. (e) Arroniz, C.; Denis, J. G.; Ironmonger, A.; Rassias, G.; Larrosa, I. *Chem. Sci.* **2014**, *5*, 3509−3514.
(5) (a) Sun, P.; Wu, Y.; Yang, T.; Wu, X.; Xu, J.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2015**, *357*, 2469−2473. (b) Sun, P.; Wu, Y.; Huang, Y.; Wu, X.; Xu, J.; Yao, H.; Lin, A. *Org. Chem. Front.* **2016**, *3*, 91−95. (c) Jiang, H.; Gao, S.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Adv. Synth. Catal.* **2016**, *358*, 188.
(6) For selected examples, see: (a) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329−332. (b) Le, T. N.; Gang, S. G.; Cho, W.-J. *J. Org. Chem.* **2004**, *69*, 2768−2772. (c) Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T. A.; Pettit, G. R. *J. Org. Chem.* **2002**, *67*, 8726−8743.
(7) For selected examples, see: (a) Li, S. W.; Nair, M. G.; Edwards, D. M.; Kisliuk, R. L.; Gaumont, Y.; Dev, I. K.; Duch, D. S.; Humphreys, J.; Smith, G. K.; Ferone, R. *J. Med. Chem.* **1991**, *34*, 2746−2754. (b) Ruchelman, A. L.; Houghton, P. J.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **2005**, *48*, 792−804. (c) Nagarajan, M.; Morrell, A.; Fort, B. C.; Meckley, M. R.; Antony, S.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2004**, *47*, 5651−5661.
(8) For selected examples, see: (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449−6457. (b) Grigorjeva, l.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209−10212. (c) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952−14955. (d) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379−6382.
(9) Tang, Q.; Xia, D.; Jin, X.; Zhang, Q.; Sun, X.-Q.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 4628−4631.
(10) Yan, H.; Wang, H.; Li, X.; Xin, X.; Wang, C.; Wan, B. *Angew. Chem., Int. Ed.* **2015**, *54*, 10613−10617.
(11) (a) Shi, Z.; Grohmann, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 5393−5397. (b) Sharma, S.; Park, E.; Park, J.; Kim, I. S. *Org. Lett.* **2012**, *14*, 906−909.
(12) For selected examples, see: (a) Bergstrom, F. W. *Chem. Rev.* **1944**, *35*, 77−277. (b) Bringmann, G.; Dreyer, M.; Rischer, H.; Wolf, K.; Hadi, H. A.; Brun, R.; Meimberg, H.; Heubl, G. *J. Nat. Prod.* **2004**, *67*, 2058−2062. (c) Kashiwaba, N.; Morooka, S.; Kimura, M.; Ono, M.; Toda, J.; Suzuki, H.; Sano, T. *J. Nat. Prod.* **1996**, *59*, 803−805.
(13) For selected examples, see: (a) Trotter, B. W.; Nanda, K. K.; Kett, N. R.; Regan, C. P.; Lynch, J. J.; Stump, G. L.; Kiss, L.; Wang, J.; Spencer, R. H.; Kane, S. A.; White, R. B.; Zhang, R.; Anderson, K. D.; Liverton, N. J.; McIntyre, C. J.; Beshore, D. C.; Hartman, G. D.; Dinsmore, C. J. *J. Med. Chem.* **2006**, *49*, 6954−6957. (b) Song, Y.; Shao, Z.; Dexheimer, T. S.; Scher, E. S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2010**, *53*, 1979−1989.
(14) Rossbach, J.; Baumeister, J.; Harms, K.; Koert, U. *Eur. J. Org. Chem.* **2013**, *2013*, 662−665.
(15) Zhu, C.; Liang, Y.; Hong, X.; Sun, H.; Sun, W.-Y.; Houk, K. N.; Shi, Z. *J. Am. Chem. Soc.* **2015**, *137*, 7564−7567.
(16) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2009**, *11*, 2469−2472.
(17) Datta, D.; Tirodkar, R. B.; Usgaonkar, R. N. *Indian. J. Chem., Sect. B* **1980**, *19*, 641−643.
(18) Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627−5634.
(19) Sreedhar, B.; Arundhathi, R.; Reddy, P. L.; Kantam, M. L. *J. Org. Chem.* **2009**, *74*, 7951−7954.
(20) Trotter, B. B.; Nanda, K. K.; Kett, N. R.; Dinsmore, C. J.; Ponticello, G. S.; Claremon, D. A. Patent WO 2005030130, 2006.
(21) Chodkowski, A.; Wrobel, M. Z.; Turlo, J.; Kleps, J.; Siwek, A.; Nowak, G.; Belka, M.; Baczek, T.; Mazurek, A. P.; Herold, F. *Eur. J. Med. Chem.* **2015**, *90*, 21−32.
(22) Moulton, B. E.; Whitwood, A. C.; Duhme-Klair, A. K.; Lynam, J. M.; Fairlamb, I. J. S. *J. Org. Chem.* **2011**, *76*, 5320−5334.

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