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Note

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Rhodium-Catalyzed Annulation of Primary Benzylamine with α-Diazo Ketone towards Isoquinoline

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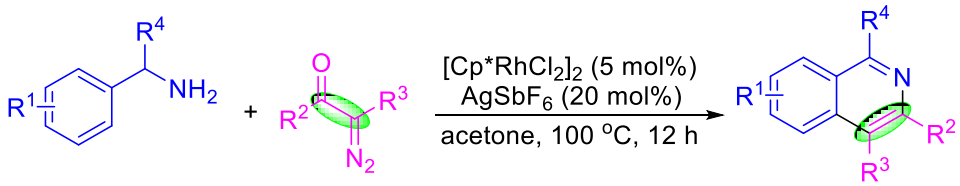
ABSTRACT



A rhodium-catalyzed annulation of commercially available primary benzylamine with α-diazo ketone was developed, leading to isoquinolines in moderate to good yields. This procedure features with the employment of primary benzylamine as starting material as well as the high selectivity in the 3- and 4- position of isoquinoline, rendering a key compliment to the previously developed annulation with internal alkyne.

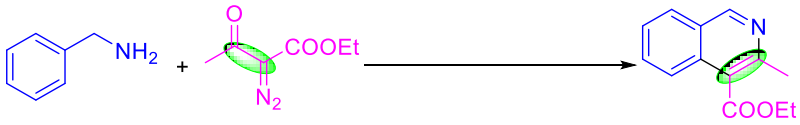
Isoquinolines are ubiquitous in numerous biologically active alkaloids, as well as phosphorescent materials, and fluorosensors.[1] Bischler-Napieralski reaction,[2] Pictet-Spengler reaction[3] and Pomeranz-Fritsch reaction[4] were traditional methods for the construction of such frameworks. However, in most cases, they suffered from harsh conditions, such as high temperature and strong acidic reaction media, resulting in low functional groups tolerance.

With the development of organometallic chemistry, recently, much progress has been made to access isoquinoline via chelation-assisted C-H functionalization. Generally, benzylamine derivatives, including imine,[5] amidine,[6] oxime[7,8] and hydrazone[9] served as a four-atom component; while alkynes,[5-9] *α*-diazo ketones[10,11] and geminal-substituted vinyl acetates[12] were C2 components. Undoubtedly, the employment of readily available primary benzylamine in such transformation was the most straightforward pathway leading to isoquinoline. However, great challenge remained yet because not only benzylamine was sensitive to oxidant, but also the primary amino was a poor directing group. Therefore,

few examples were developed and limited in the annulation of benzylamine with internal alkyne independently developed by Jun,[13] Satoh,[14] and Urriolabeitia,[15] where the selectivity in 3- and 4- positions of isoquinoline kept inherently unsolved. Herein, we wish to report the rhodium-catalyzed annulation of primary benzylamine with α-diazo ketone, allowing the construction of isoquinoline framework with diversity and high selectivity in the 3- and 4- positions.

Initially, the annulation between benzylamine (**1a**) and ethyl 2-diazoacetoacetate (**2a**) was selected as model reaction to screen the reaction conditions. To our delight, the target product, ethyl 3-methylisoquinoline-4-carboxylate (**3aa**) was obtained in 58% yield in the presence of $[Cp^*RhCl_2]_2$ (5 mol%) and $AgSbF_6$ (20 mol%) in 1,2-dichloroethane (DCE) at 100 °C for 12 h (Table 1, entry 1). The blank experiment confirmed both $[Cp^*RhCl_2]_2$ and $AgSbF_6$ were indispensable (Table 1, entries 2 and 3). The Rh(III) species $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ resulted in a comparable yield (Table 1, entry 4). After further optimization, we abnegated other Rh catalysts and silver salts (Table 1, entries 5-8). Notably, acetic ion, being an effective additive in numerous rhodium-catalyzed annulations via C-H functionalizations,[10a-c] inhibited the reaction (Table 1, entry 9). Among the solvents investigated, acetone gave the highest yield (Table 1, entry 10, 75%). Using the previously reported procedure,[10d] **3aa** was isolated in 50% yield (Table 1, entry 11).

Table 1. Screening the optimized reaction conditions [a]



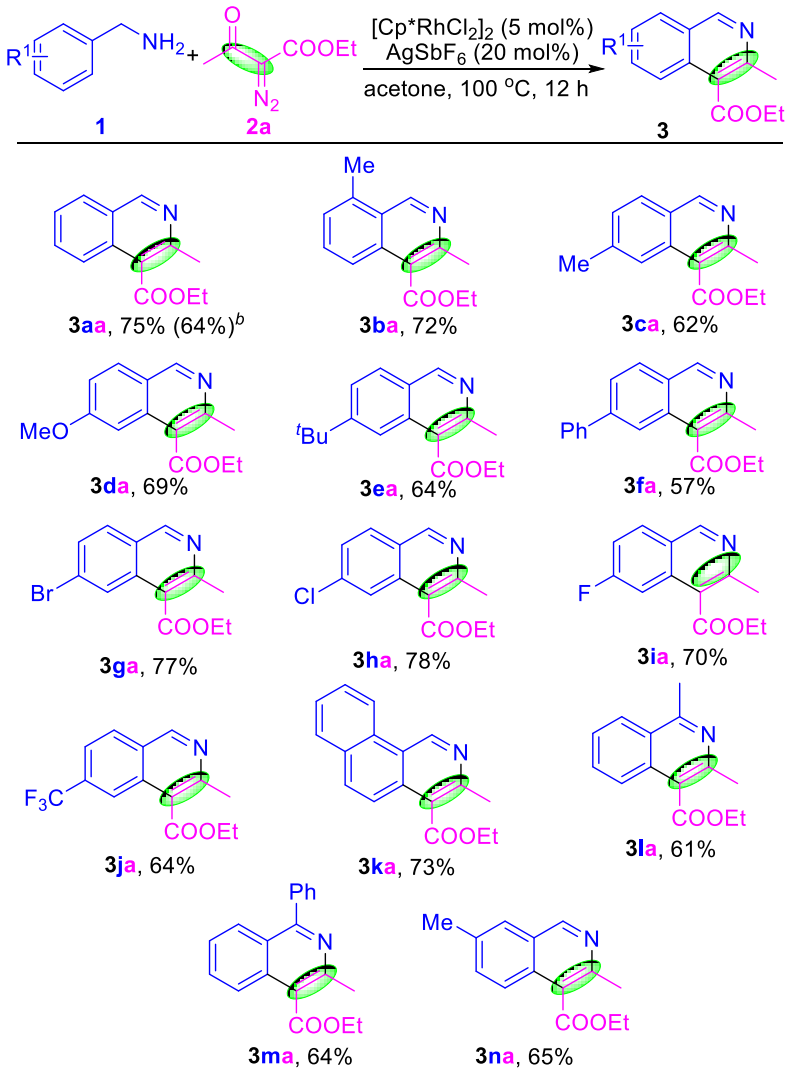
Entry	Catalyst	Additive	Solvent	Yield (%)[b]
1	$[Cp^*RhCl_2]_2$	$AgSbF_6$	DCE	58
2	$[Cp^*RhCl_2]_2$	-	DCE	<5
3	-	$AgSbF_6$	DCE	0
4	$[Cp^*Rh(MeCN)_3](SbF_6)_2$	-	DCE	52
5	$[Rh(cod)Cl]_2$	$AgSbF_6$	DCE	<5
6	$Rh(PPh_3)_3Cl$	$AgSbF_6$	DCE	<5
7	$[Cp^*RhCl_2]_2$	$AgBF_4$	DCE	<5
8	$[Cp^*RhCl_2]_2$	AgOAc	DCE	0
9	$[Cp^*RhCl_2]_2$	CsOAc	DCE	0
10	$[Cp^*RhCl_2]_2$	$AgSbF_6$	acetone	75(43)[c](70)[d]
11	$[Cp^*RhCl_2]_2$	$AgSbF_6$	THF	50
12	$[Cp^*RhCl_2]_2$	$AgSbF_6$	MeOH	<5
13	$[Cp^*RhCl_2]_2$	$AgSbF_6$	*n*-hexane	52
14	$[Cp^*RhCl_2]_2$	$AgSbF_6$	C_6HF_5	63

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), Rh catalyst (5 mol%), additive (20 mol%), solvent (2 mL), 100 °C, 12 h. [b] Isolated yield. [c] 80 °C. [d] 120 °C.

The scope and limitation of this reaction were explored under the optimal conditions, as summarized in Fig 1. Various electron-donating groups (methyl, methoxy and *tert*-butyl) as well as electron-withdrawing groups (fluoro, chloro, bromo and trifluoromethyl) were tolerated well, providing the corresponding isoquinoline in moderate to good

yields. The methyl installed in the frameworks may provide potential handle for further functionalization.[16] To our delight, the steric hindrance of *ortho*-substitution had almost no effect on the reaction efficiency, as 2-methylbenzylamine (**1b**) gave its corresponding annulation product (**3ba**) in 72% yield. Importantly, *α*-substituted substrates, such as *α*-methyl and phenyl benzylamines, ran smoothly, allowing to facile access 1,3,4-trisubstituted isoquinolines **3la** and **3ma** in moderate yields. Notably, 1-aminomethylnaphthalene (**1k**) was good reaction partner towards benzo[*h*]isoquinoline **3ka** as fused *N*-containing hetero aromatic framework in good yield (73%). Moreover, *meta*-methylbenzylamine provided **3na** as solely product and no regioisomer was observed by GC-MS and ^{1}H NMR spectroscopy. To evaluate the practicability, the reaction was conducted on a 0.5 mmol scale, and the desired product **3aa** was obtained in 64% yield.

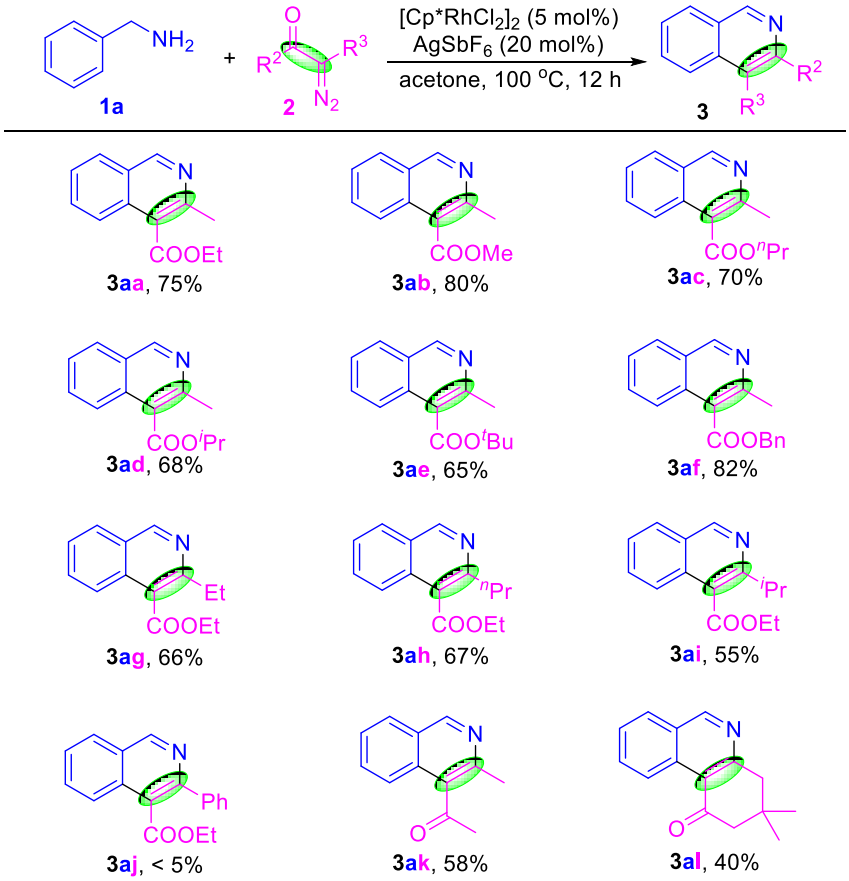
Figure 1. The substrate scope of benzylamines [a]



[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), in dry acetone (2 mL) for 12 h, 100 °C. [b] 0.5 mmol scale.

Next, the scope of diazo ketones was studied (Fig 2). A variety of diazoacetoacetate esters were tolerated well with yields ranging from 65 to 80% (**3ab**-**3af**). Importantly, the group installed on the 3- position of isoquinoline was not limited to methyl, as the 3-ethyl, *n*-propyl and *i*-propyl analogues were assembled in moderate yields (**3ag**-**3ai**). However, 2-diazobenzoylacetate failed to work under the procedure (**3aj**, < 5%). In particular, 2-diazoacetoacetone (**2k**) took part in the reaction to access 4-acetyl isoquinoline derivatives in moderate yield. Notably, 2-diazodimedone (**2l**) generated the fused cyclic products **3al** in 40% yield.

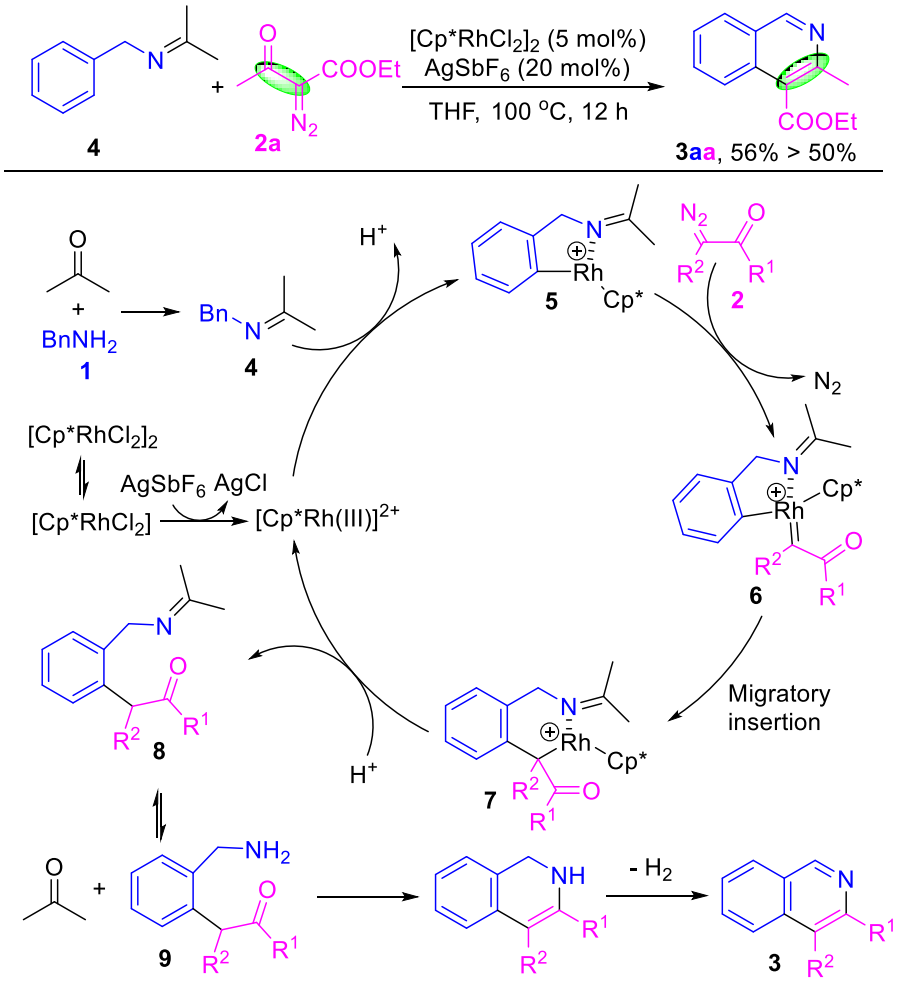
Figure 2. The substrate scope of α-diazo ketones [a]



[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol%), $AgSbF_6$ (20 mol%), in dry acetone (2 mL) for 12 h, 100 °C.

To explore the reaction mechanism, imine **4** was prepared and subjected to the procedure in THF, which gave a higher yield (56%) than benzylamine (Table 1, entry 11, 50%). Based on the previously reported examples on the rhodium-catalyzed annulation with diazo compounds,[10d-f] a proposed mechanism was outlined in Scheme 1. Firstly, in the case of ketone as solvent, imine **4** was formed by the reaction between benzylamine and acetone, by which, the coordination with catalyst is enhanced. Then, the reaction between $[Cp^*RhCl_2]_2$ and $AgSbF_6$ generates $[Cp^*Rh(III)]^{2+}$ as an active cation Rh(III) species. Secondly, coordination of cationic rhodium species with imine **4** facilitates the *ortho* ar-

omatic C-H bond cleavage to produce intermediate **5**. Then, the insertion of diazo **2** to C-Rh bond of **5** takes place leading to rhodium carbene intermediate **6**, along with the the loss of N_2. Afterwards, the migratory insertion of rhodium carbene **7** provides intermediate **7**. Thirdly, the protonation of **7** produces intermediate **8**, where the cation Rh(III) species is regenerated. Then, the intermediate **8** takes part in the proton-catalyzed equilibrium reactions with intermediate **9** and acetone, followed by the intra- molecular annulation of amino and carbonyl in **9** furnishes the ring closure leading to 1,2-dihydroisoquinoline. Finally, the aromatization of 1,2-dihydroisoquinoline provides the final product isoquinoline by the extrusion of H_2, as confirmed by $PdCl_2$ testing paper (For detail, please see Supporting Information). No ^{i}PrOH was determined by GC-MS. This step is believed to be the driving force in the equilibrium reactions between **8** and **9**.



Scheme 1. Mechanism Study

In conclusion, we have developed a rhodium-catalyzed annulation of benzylamine with diazo compounds, such as diazoacetoacetate esters and 2-diazoacetoacetone leading to a diverse of 3,4-disubstituted isoquinoline in moderate to

good yields with high regioselectivities. As such, it represents a key compliment to the previously developed annulation with internal alkyne.

EXPERIMENTAL SECTION

General Information: Unless otherwise noted, all chemicals were purchased from commercial suppliers and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature on a 400 MHz (100 MHz for ^{13}C) NMR spectrometer. NMR experiments are reported in δ units, parts per million (ppm), and were referenced to $CDCl_3$ (δ 7.26 or 77.0 ppm) as the internal standard. The coupling constants *J* are given in Hz. Column chromatography was performed using EM Silica gel 60 (300-400 mesh). High-resolution mass spectra (HRMS) were obtained using a Bruker micro TOF II focus spectrometer (ESI).

Experimental Procedure:

General Procedure for the Rhodium-Catalyzed Annulations.

Under air, a 20 mL Schlenk tube equipped with a stir bar was charged with **1** (0.2 mmol), diazo compound **2** (0.3 mmol, 1.5 eq.), $[Cp^*RhCl_2]_2$ (6.2 mg, 5 mol%), $AgSbF_6$ (13.8 mg, 20 mol%), acetone (2 mL). The tube was sealed with a Teflon lined cap. The reaction mixture was stirred at 100 ℃ for 12 h in oil bath. After the completion of the reaction, the solvent was concentrated in vacuum and the residue was purified by flash column chromatography on silica gel with petroleum ether-EtOAc as the eluent to give the desired product.

Ethyl 3-methylisoquinoline-4-carboxylate (3aa)[17]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3aa** (32.3 mg, 75% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 4.54 (q, *J* = 7.1 Hz, 2H), 2.74 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5, 153.3, 149.4, 133.1, 131.3, 127.8, 126.7, 126.4, 123.6, 123.2, 61.6, 22.9, 14.3.

Ethyl 3,8-dimethylisoquinoline-4-carboxylate (3ba):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ba** (32.8 mg, 72% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (s, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.0 Hz, 1H), 4.52 (q, *J* = 7.2 Hz, 2H), 2.75 (s, 3H), 2.72 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz)

δ 168.8, 150.0, 148.7, 135.6, 133.4, 131.1, 127.6, 125.4, 123.6, 121.7, 61.6, 22.7, 18.5, 14.3; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1175, found 230.1176.

Ethyl 3,6-dimethylisoquinoline-4-carboxylate (3ca):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ca** (28.2 mg, 62% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.12 (s, 1H), 7.83 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.38 (d, J = 7.9 Hz, 1H), 4.54 (q, J = 7.2 Hz, 2H), 2.71 (s, 3H), 2.52 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 152.8, 149.3, 142.0, 133.4, 129.0, 127.6, 124.9, 122.7, 122.4, 61.6, 22.9, 22.4, 14.3; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1175, found 230.1178.

Ethyl 6-methoxy-3-methylisoquinoline-4-carboxylate (3da):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3da** (33.8 mg, 69% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.02 (s, 1H), 7.81 (d, J = 8.7 Hz, 1H), 7.18-7.15 (m, 2H), 4.53 (q, J = 7.2 Hz, 2H), 3.90 (s, 3H), 2.70 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 161.8, 152.3, 150.4, 135.3, 129.6, 122.3, 122.1, 119.7, 101.6, 61.4, 55.4, 23.2, 14.3; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_3$ $(M + H)^+$ 246.1124, found 246.1129.

Ethyl 6-(*tert*-butyl)-3-methylisoquinoline-4-carboxylate (3ea):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ea** (34.7 mg, 64% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.13 (s, 1H), 7.88 (d, J = 8.7 Hz, 1H), 7.78 (s, 1H), 7.65 (dd, J = 8.7 Hz, 1H), 4.55 (q, J = 7.1 Hz, 2H), 2.72 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 154.6, 152.6, 149.4, 133.3, 127.4, 125.8, 124.8, 123.2, 118.5, 61.5, 35.5, 30.9, 22.9, 14.4; HRMS (ESI) m/z calcd for $C_{17}H_{22}NO_2$ $(M + H)^+$ 272.1645, found 272.1651.

Ethyl 3-methyl-6-phenylisoquinoline-4-carboxylate (3fa):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3fa** (33.2 mg, 57% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 8.05-8.00 (m, 2H), 7.81 (d, J = 8.5 Hz, 1H), 7.69-7.67 (m, 2H), 7.52-7.40 (m, 3H), 4.56 (q, J = 7.1 Hz, 2H), 2.76 (s, 3H), 1.48 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5, 153.0, 149.9, 144.1, 140.2, 133.5, 129.0, 128.4, 128.3, 127.6, 126.7, 125.5, 123.2, 121.5, 61.7, 23.0, 14.3; HRMS (ESI) m/z calcd for $C_{19}H_{18}NO_2$ $(M + H)^+$ 292.1332, found 292.1335.

Ethyl 6-bromo-3-methylisoquinoline-4-carboxylate (3ga):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ga** (45.3 mg, 77% yield) as yellow solid: mp 51-52 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.14 (s, 1H), 8.06 (s, 1H), 7.79 (d, J = 8.6 Hz, 1H), 7.63 (d, J = 8.6 Hz, 1H), 4.54 (q, J = 7.1 Hz, 2H), 2.73 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 153.1, 150.9, 134.2, 130.4, 129.3, 126.6, 126.2, 124.7, 122.0, 61.8, 23.2, 14.2; HRMS (ESI) m/z calcd for $C_{13}H_{13}BrNO_2$ $(M + H)^+$ 294.0124, found 294.0126.

Ethyl 6-chloro-3-methylisoquinoline-4-carboxylate (3ha)[17]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ha** (38.8 mg, 78% yield) as yellow solid: mp 64-66 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (s, 1H), 7.88-7.86 (m, 2H), 7.49 (dd, J = 8.7 Hz, 1H), 4.54 (q, J = 7.1 Hz, 2H), 2.73 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.9, 153.0, 151.0, 137.9, 133.9, 129.4, 127.9, 124.6, 122.9, 122.1, 61.8, 23.2, 14.2.

Ethyl 6-fluoro-3-methylisoquinoline-4-carboxylate (3ia):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ia** (31.7 mg, 68% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (s, 1H), 7.97-7.94 (m, 1H), 7.54 (dd, J = 10.5 Hz, 1H), 7.32 (td, J = 8.6 Hz, 1H), 4.53 (q, J = 7.1 Hz, 2H), 2.74 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 164.0 (d, $J_{C\text{-}F}$ = 252 Hz), 152.8, 151.0, 134.9 (d, $J_{C\text{-}F}$ = 11 Hz), 130.9 (d, $J_{C\text{-}F}$ = 10 Hz), 123.7, 122.6, 117.4 (d, $J_{C\text{-}F}$ = 7 Hz), 107.9 (d, $J_{C\text{-}F}$ = 23 Hz), 61.8, 23.2, 14.2; HRMS (ESI) m/z calcd for $C_{13}H_{13}FNO_2$ $(M + H)^+$ 234.0924, found 234.0922.

Ethyl 3-methyl-6-(trifluoromethyl)isoquinoline-4-carboxylate (3ja):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ja** (36.2 mg, 64% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.29 (s, 1H), 8.23 (s, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.74 (dd, J = 8.5 Hz, 1H), 4.57 (q, J = 7.2 Hz, 2H), 2.78 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6, 153.3, 151.5, 132.8 (d, $J_{C\text{-}F}$ = 33 Hz), 132.5, 129.1, 127.0, 125.0, 123.5, 122.6 (q, $J_{C\text{-}F}$ = 3.0 Hz), 121.7 (q, $J_{C\text{-}F}$ = 4.0 Hz), 62.0, 23.2, 14.2; HRMS (ESI) m/z calcd for $C_{14}H_{13}F_3NO_2$ $(M + H)^+$ 284.0892, found 284.0893.

Ethyl 3-methylbenzo[h]isoquinoline-4-carboxylate (3ka):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ka** (39.3 mg, 73% yield) as yellow solid: mp 54-55 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.95 (s, 1H), 8.72 (d, J = 8.2 Hz, 1H), 7.93-7.87 (m, 2H),

7.73-7.69 (m, 2H), 7.63 (d, *J* = 7.4 Hz, 1H), 4.57 (q, *J* = 7.1 Hz, 2H), 2.77 (s, 3H), 1.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.7, 150.9, 147.1, 133.2, 132.7, 131.4, 129.0, 128.8, 128.1, 127.4, 124.5, 122.6, 121.7, 121.5, 61.7, 22.9, 14.3; HRMS (ESI) m/z calcd for $C_{17}H_{16}NO_2$ $(M + H)^+$ 266.1175, found 266.1179.

Ethyl 1,3-dimethylisoquinoline-4-carboxylate (3la)[18]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3la** (27.9 mg, 61% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 4.52 (q, *J* = 7.2 Hz, 2H), 2.94 (s, 3H), 2.68 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9, 159.8, 148.0, 133.2, 130.8, 126.4, 125.7, 125.1, 124.1, 121.9, 61.5, 22.9, 22.6, 14.3.

Ethyl 3-methyl-1-phenylisoquinoline-4-carboxylate (3ma)[10f]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ma** (37.3 mg, 64% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.72-7.65 (m, 3H), 7.56-7.46 (m, 4H), 4.58 (q, *J* = 7.1 Hz, 2H), 2.80 (s, 3H), 1.49 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 161.7, 148.4, 139.1, 134.1, 130.9, 129.8, 128.8, 128.4, 127.8, 126.5, 124.5, 123.8, 122.5, 61.6, 23.1, 14.3.

Ethyl 3,7-dimethylisoquinoline-4-carboxylate (3na):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3na** (32.8 mg, 65% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.10 (s, 1H), 7.77 (d, *J* = 8.6 Hz, 1H), 7.69 (s, 1H), 7.52 (dd, *J* = 8.6 Hz, 1H), 4.52 (q, *J* = 7.1 Hz, 2H), 2.71 (s, 3H), 2.50 (s, 3H), 1.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.6, 152.6, 148.5, 136.7, 133.7, 131.4, 126.6, 126.6, 123.4, 123.0, 61.6, 22.8, 21.5, 14.3; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1175, found 230.1179.

Methyl 3-methylisoquinoline-4-carboxylate (3ab)[19]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ab** (32.2 mg, 80% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (s, 1H), 7.93 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.5 Hz, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.5 Hz, 1H), 4.04 (s, 3H), 2.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.0, 153.4, 149.6, 133.1, 131.4, 127.8, 126.8, 126.3, 123.6, 122.8, 52.4, 23.0.

n-Propyl 3-methylisoquinoline-4-carboxylate (3ac):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ac** (32.1 mg, 70% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.70 (t, J = 7.7 Hz, 1H), 7.55 (t, J = 7.5 Hz, 1H), 4.43 (t, J = 6.7 Hz, 2H), 2.74 (s, 3H), 1.84 (m, J = 6.7 Hz, 2H), 1.04 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 153.2, 149.4, 133.2, 131.3, 127.8, 126.7, 126.4, 123.6, 123.2, 67.3, 22.9, 22.0, 10.5; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1176, found 230.1175.

***i*-Propyl 3-methylisoquinoline-4-carboxylate (3ad):**

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ad** (31.2 mg, 68% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.70 (m, 1H), 7.55 (t, J = 7.4 Hz, 1H), 5.46 (m, J = 6.3 Hz, 1H), 2.73 (s, 3H), 1.46-1.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.0, 153.1, 149.0, 133.1, 131.3, 127.8, 126.7, 126.4, 123.5, 123.4, 69.4, 22.8, 21.9; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1176, found 230.1175.

tert-Butyl 3-methylisoquinoline-4-carboxylate (3ae)[19]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ae** (31.5 mg, 65% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.70 (m, 1H), 7.54 (t, J = 7.5 Hz, 1H), 2.74 (s, 3H), 1.68 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.8, 152.7, 148.4, 133.0, 131.2, 127.8, 126.6, 126.4, 124.5, 123.4, 82.8, 28.2, 22.6.

Benzyl 3-methylisoquinoline-4-carboxylate (3af)[19]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3af** (45.2 mg, 82% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.69-7.65 (m, 1H), 7.57-7.48 (m, 3H), 7.43-7.34 (m, 3H), 5.51 (s, 2H), 2.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.3, 153.4, 149.6, 135.2, 133.2, 131.4, 128.7, 128.6, 128.6, 127.8, 126.8, 126.3, 123.5, 122.8 , 67.4, 23.0.

Ethyl 3-ethylisoquinoline-4-carboxylate (3ag):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ag** (30.1 mg, 66% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.23 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.72-7.68 (m, 1H), 7.56 (t, J = 7.5 Hz, 1H), 4.53 (q, J = 7.1 Hz, 2H), 2.97 (q, J = 7.5 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.38 (t, J =

7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 154.2, 153.5, 133.1, 131.2, 127.8, 126.8, 126.4, 123.6, 122.8, 61.6, 29.8, 14.4, 14.3; HRMS (ESI) m/z calcd for $C_{14}H_{16}NO_2$ $(M + H)^+$ 230.1176, found 230.1177.

Ethyl 3-propylisoquinoline-4-carboxylate (3ah)[19]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ah** (32.4 mg, 67% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.22 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.71-7.67 (m, 1H), 7.55 (t, J = 7.5 Hz, 1H), 4.53 (q, J = 7.2 Hz, 2H), 2.92 (t, J = 7.7 Hz, 2H), 1.84 (m, J = 7.7 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.6, 153.4, 153.0, 133.1, 131.2, 127.8, 126.8, 126.4, 123.6, 123.2, 61.6, 38.4, 23.3, 14.3, 14.0.

Ethyl 3-isopropylisoquinoline-4-carboxylate (3ai):

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ai** (26.8 mg, 55% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.27 (s, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.71-7.67 (m, 1H), 7.57-7.54 (m, 1H), 4.53 (q, J = 7.1 Hz, 2H), 3.25 (hept, J = 6.7 Hz, 1H), 1.45 (t, J = 7.1 Hz, 3H), 1.39-1.38 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 157.0, 153.5, 132.9, 131.2, 127.8, 126.8, 126.5, 123.6, 122.3, 61.6, 33.6, 22.4, 14.3; HRMS (ESI) m/z calcd for $C_{15}H_{18}NO_2$ $(M + H)^+$ 244.1332, found 244.1333.

1-(3-Methylisoquinolin-4-yl)ethan-1-one (3ak)[17]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3ak** (21.5 mg, 58% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (s, 1H), 7.97 (d, J = 8.2 Hz, 1H), 7.72-7.68 (m, 1H), 7.62-7.55 (m, 2H), 2.66 (s, 3H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.0, 152.7, 145.8, 132.0, 131.3, 131.3, 128.1, 126.8, 126.5, 122.9, 32.7, 22.3.

3,3-Dimethyl-3,4-dihydrophenanthridin-1(2H)-one (3al)[17]:

Flash column chromatography on a silica gel (ethyl acetate: petroleum ether, 1: 3) give **3al** (18.0 mg, 40% yield) as yellow oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.39 (d, J = 8.7 Hz, 1H), 9.28 (s, 1H), 7.96 (d, J = 8.1 Hz, 1H), 7.83 (t, J = 7.8 Hz, 1H), 7.61 (t, J = 7.5 Hz, 1H), 3.23 (s, 2H), 2.66 (s, 2H), 1.16 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.1, 159.6, 157.3, 133.5, 133.2, 128.2, 127.7, 127.1, 125.7, 119.7, 54.1, 47.7, 32.8, 28.1.

ASSOCIATED CONTENT

Supporting Information:

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Experimental details on the mechanism study, along with copies of ^{1}H and ^{13}C NMR spectra of compounds **3aa**-**3ma** and **3ab**-**3al**.

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