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

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Supporting Information

**ABSTRACT:** 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 the employment of primary benzylamine as starting material as well as high selectivity in the 3- and 4- position of isoquinoline, generating 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,[2] Pictet−Spengler,[3] and Pomeranz−Fritsch[4] reactions are 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 group tolerance.

With the development of organometallic chemistry, much progress has recently been made toward accessing isoquinoline via chelation-assisted C−H functionalization. Generally, benzylamine derivatives, including imine,[5] amidine,[6] oxime,[7,8] and hydrazone,[9] served as four-atom components, and 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 a transformation was the most straightforward pathway leading to isoquinoline. However, a great challenge yet remained because not only was benzylamine sensitive to oxidant, the primary amino was also a poor directing group. Therefore, few examples were developed and were limited in the annulation of benzylamine with internal alkyne independently developed by Jun,[13] Satoh,[14] and Urriolabeitia,[15] where the selectivity in the 3- and 4-positions of isoquinoline was kept inherently unsolved. Herein, we wish to report the rhodium-catalyzed annulation of primary benzylamine with α-diazo ketone, allowing the construction of an 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 a 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 that 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

**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]At 80 °C. [d]At 120 °C.

other Rh catalysts and silver salts (Table 1, entries 5−8). Notably, acetate 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 (75%; Table 1, entry 10). Using the previously reported procedure,[10d] **3aa** was isolated in 50% yield (Table 1, entry 11).

The scope and limitations of this reaction were explored under the optimal conditions, as summarized in Figure 1. Various electron-donating groups (methyl, methoxy, and *tert*-butyl) as well as electron-withdrawing groups (fluoro, chloro,

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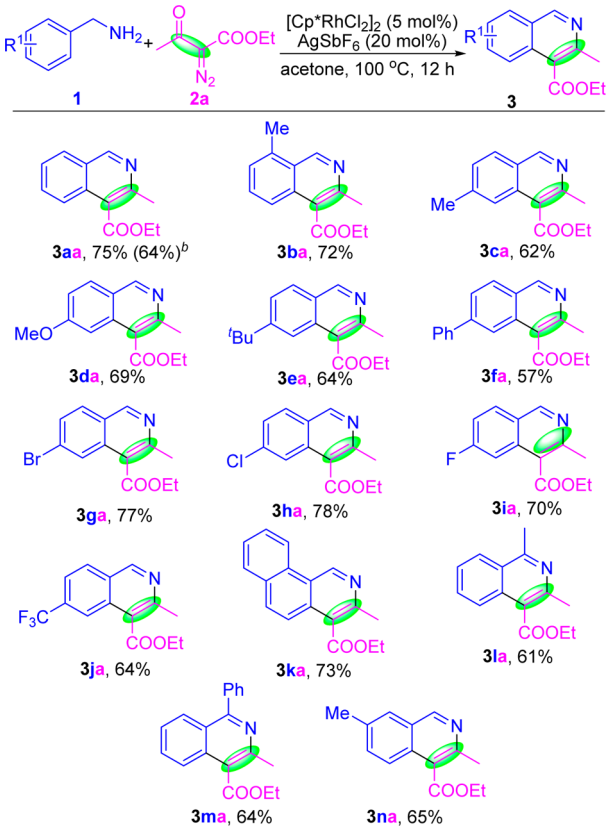



**Figure 1.** Substrate scope of benzylamines. [a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), in dry acetone (2 mL) for 12 h, 100 °C. [b]On a 0.5 mmol scale.

bromo, and trifluoromethyl) were tolerated well, providing the corresponding isoquinoline in moderate to good yields. The methyl installed in the frameworks may provide a 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, $\alpha$-substituted substrates, such as $\alpha$-methyl and phenyl benzylamines, ran smoothly, allowing facile access to 1,3,4-trisubstituted isoquinolines **3la** and **3ma** in moderate yields. Notably, 1-aminomethylnaphthalene (**1k**) was a good reaction partner toward benzo[*h*]isoquinoline **3ka** as a fused *N*-containing hetero aromatic framework in good yield (73%). Moreover, *meta*-methylbenzylamine provided **3na** as a sole product, and no regioisomer was observed by GC-MS or $^1$H NMR spectroscopy. For the practicability to be evaluated, the reaction was conducted on a 0.5 mmol scale, and desired product **3aa** was obtained in 64% yield.

Next, the scope of diazo ketones was studied (Figure 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.

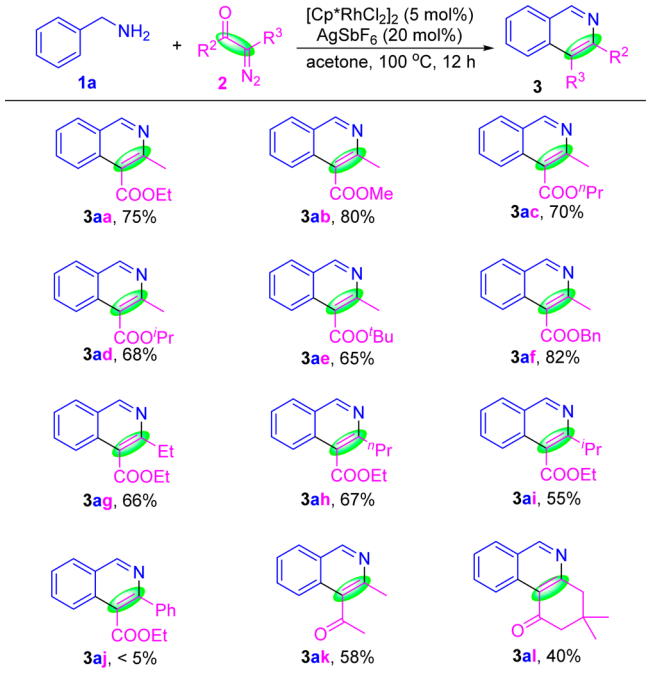
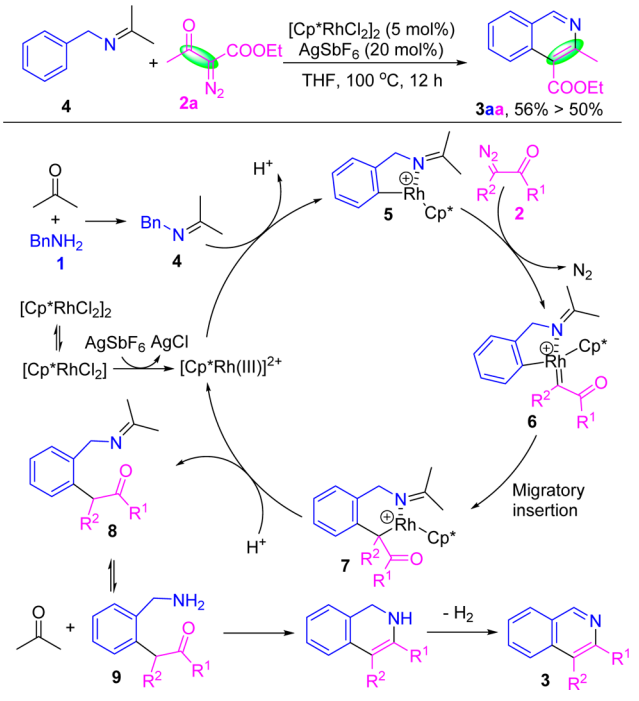



**Figure 2.** Substrate scope of $\alpha$-diazo ketones. [a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), in dry acetone (2 mL) for 12 h, 100 °C.

For the reaction mechanism to be explored, imine **4** was prepared and subjected to the procedure in THF, which gave a higher yield (56%) than that with benzylamine (50%; Table 1, entry 11). On the basis of the previously reported examples on the rhodium-catalyzed annulation with diazo compounds,[10d−f] a proposed mechanism is outlined in Scheme 1. First, 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

**Scheme 1. Mechanism Study**



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$[Cp^*RhCl_2]_2$ and $AgSbF_6$ generates $[Cp^*Rh(III)]^{2+}$ as an active cation Rh(III) species. Second, coordination of cationic rhodium species with imine **4** facilitates the ortho aromatic C−H bond cleavage to produce intermediate **5**. Then, the insertion of diazo **2** to the C−Rh bond of **5** takes place, leading to rhodium carbene intermediate **6** along with the loss of $N_2$. Afterward, the migratory insertion of rhodium carbene **7** provides intermediate **7**. Third, the protonation of **7** produces intermediate **8**, where the cation Rh(III) species is regenerated. Then, 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** to furnish 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 details, please see the 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**.

In conclusion, we have developed a rhodium-catalyzed annulation of benzylamine with diazo compounds, such as diazoacetoacetate esters and 2-diazoacetoacetone, leading to diverse 3,4-disubstituted isoquinolines 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 $\delta$ units, parts per million (ppm), and were referenced to $CDCl_3$ ($\delta$ 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 equiv), $[Cp^*RhCl_2]_2$ (6.2 mg, 5 mol %), $AgSbF_6$ (13.8 mg, 20 mol %), and acetone (2 mL). The tube was sealed with a Teflon-lined cap. The reaction mixture was stirred at 100 °C for 12 h in an oil bath. After 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 (1:3 ethyl acetate:petroleum ether) gave **3aa** (32.3 mg, 75% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ba** (32.8 mg, 72% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ca** (28.2 mg, 62% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3da** (33.8 mg, 69% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ea** (34.7 mg, 64% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3fa** (33.2 mg, 57% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ga** (45.3 mg, 77% yield) as yellow solid: mp 51−52 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ha** (38.8 mg, 78% yield) as yellow solid: mp 64−66 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ia** (31.7 mg, 68% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 168.0, 164.0 (d, $J_{C-F}$ = 252 Hz), 152.8, 151.0, 134.9 (d, $J_{C-F}$ = 11 Hz), 130.9 (d, $J_{C-F}$ = 10 Hz), 123.7, 122.6, 117.4 (d, $J_{C-F}$ = 7 Hz), 107.9 (d, $J_{C-F}$ = 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 (1:3 ethyl acetate:petroleum ether) gave **3ja** (36.2 mg, 64% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 167.6, 153.3, 151.5, 132.8 (d, $J_{C-F}$ = 33 Hz), 132.5, 129.1, 127.0, 125.0, 123.5, 122.6 (q, $J_{C-F}$ = 3.0 Hz), 121.7 (q, $J_{C-F}$ = 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.



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*Ethyl 3-Methylbenzo[h]isoquinoline-4-carboxylate (**3ka**).* Flash column chromatography on a silica gel (1:3 ethyl acetate:petroleum ether) gave **3ka** (39.3 mg, 73% yield) as yellow solid: mp 54−55 °C; $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3la** (27.9 mg, 61% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ma** (37.3 mg, 64% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3na** (32.8 mg, 65% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ab** (32.2 mg, 80% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ac** (32.1 mg, 70% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ad** (31.2 mg, 68% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ae** (31.5 mg, 65% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3af** (45.2 mg, 82% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ag** (30.1 mg, 66% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ah** (32.4 mg, 67% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ai** (26.8 mg, 55% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3ak** (21.5 mg, 58% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 (1:3 ethyl acetate:petroleum ether) gave **3al** (18.0 mg, 40% yield) as a yellow oil: $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 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) $\delta$ 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 on the ACS Publications website at DOI: 10.1021/acs.joc.6b01378.

Experimental details on the mechanism study along with copies of $^1$H and $^{13}$C NMR spectra of compounds **3aa**−**3ma** and **3ab**−**3al** (PDF)

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) For reviews, please see: (a) Khan, A. Y.; Kumar, G. S. *Biophys. Rev.* **2015**, *7*, 407. (b) Heravi, M. M.; Nazari, N. *Curr. Org. Chem.* **2015**, *19*, 2358. (c) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. *Phytomedicine* **2015**, *22*, 183. (d) Gualandi, A.; Mengozzi, L.; Manoni, E.; Cozzi, P. G. *Catal. Lett.* **2015**, *145*, 398. (e) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Tetrahedron Lett.* **2014**, *55*, 5705. (f) Iranshahy, M.; Quinn, R. J.; Iranshahi, M. *RSC Adv.* **2014**, *4*, 15900.

(2) Heravi, M. M.; Khaghaninejad, S.; Nazari, N. *Adv. Heterocycl. Chem.* **2014**, *112*, 183.

(3) For reviews, please see: (a) Stockigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538. (b) Lorenz, M.; van Linn, M. L.; Cook, J. M. *Curr. Org. Synth.* **2010**, *7*, 189.

(4) For reviews, please see: (a) Bobbitt, J. M.; Bourque, A. J. *Heterocycl.* **1987**, *25*, 601. (b) Rozwadowska, M. D. *Heterocycles* **1994**, *39*, 903.

(5) For reviews, please see: (a) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759. (b) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (c) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (d) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950. (e) Sun, Z.-M.; Chen, S.-P.; Zhao, P. *Chem. - Eur. J.* **2010**, *16*, 2619.

(6) Wei, X.; Zhao, M.; Du, Z.; Li, X. *Org. Lett.* **2011**, *13*, 4636.

(7) (a) Parthasarathy, K.; Cheng, C.-H. *J. Org. Chem.* **2009**, *74*, 9359. (b) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719. (c) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846. (d) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032. (e) Kornhaaß, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190. (f) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592.

(8) (a) Zheng, L.; Ju, J.; Bin, Y.; Hua, R. *J. Org. Chem.* **2012**, *77*, 5794. (b) Gerfaud, T.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 572. (c) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (d) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159. (e) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (f) Zhao, D.; Lied, F.; Glorius, F. *Chem. Sci.* **2014**, *5*, 2869.

(9) (a) Chuang, S.-C.; Gandeepan, P.; Cheng, C.-H. *Org. Lett.* **2013**, *15*, 5750. (b) Liu, W.; Hong, X.; Xu, B. *Synthesis* **2013**, *45*, 2137. (c) Huang, X.-C.; Yang, X.-H.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2014**, *79*, 1025.

(10) For reviews, please see: (a) Wu, Y.; Sun, P.; Zhang, K.; Yang, T.; Yao, H.; Lin, A. *J. Org. Chem.* **2016**, *81*, 2166. (b) Cheng, Y.; Bolm, C. *Angew. Chem., Int. Ed.* **2015**, *54*, 12349. (c) Liang, Y.; Yu, K.; Li, B.; Xu, S.; Song, H.; Wang, B. *Chem. Commun.* **2014**, *50*, 6130. (d) Shi, L.; Yu, K.; Wang, B. *Chem. Commun.* **2015**, *51*, 17277. (e) Wang, J.; Wang, M.; Chen, K.; Zha, S.; Song, C.; Zhu, J. *Org. Lett.* **2016**, *18*, 1178. (f) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204.

(11) For selected examples on the direct C−H functionalization towards isoquinolines with diazo compounds, please see: (a) Li, X. G.; Sun, M.; Jin, Q.; Liu, K.; Liu, P. N. *J. Org. Chem.* **2016**, *81*, 3901. (b) Li, J.; Tang, M.; Zang, L.; Zhang, X.; Zhang, Z.; Ackermann, L. *Org. Lett.* **2016**, *18*, 2742. (c) Wang, J.; Zha, S.; Chen, K.; Zhang, F.; Zhu, J. *Org. Biomol. Chem.* **2016**, *14*, 4848. (d) Yang, X.; Jie, J.; Li, H.; Piao, M. *RSC Adv.* **2016**, *6*, 57371.

(12) For reviews, please see: (a) Webb, N. J.; Marsden, S. P.; Raw, S. A. *Org. Lett.* **2014**, *16*, 4718. (b) Zhang, M.; Zhang, H.-J.; Han, T.; Ruan, W.; Wen, T.-B. *J. Org. Chem.* **2015**, *80*, 620. (c) Chu, H.; Sun, S.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 13327.

(13) Kim, D.-S.; Park, J.-W.; Jun, C.-H. *Adv. Synth. Catal.* **2013**, *355*, 2667.

(14) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 600.

(15) Villuendas, P.; Urriolabeitia, E. P. *J. Org. Chem.* **2013**, *78*, 5254.

(16) For selected examples on the functionalization of aromatic methyl, please see: (a) Guo, S.; Wan, G.; Sun, S.; Jiang, Y.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 5085. (b) Zhou, W.; Zhang, L.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7094. (c) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902. (d) Xue, Q.; Xie, J.; Li, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2013**, *49*, 3700. For reviews, see: (e) Dai, Q.; Jiang, Y.; Yu, J.-T.; Cheng, J. *Synthesis* **2016**, *48*, 329. (f) Schönherr, H.; Cernak, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 12256. (g) Barreiro, E. J.; Kümmerle, A. E.; Fraga, C. A. M. *Chem. Rev.* **2011**, *111*, 5215.

(17) Wang, B.; Lu, B.; Jiang, Y.; Zhang, Y.; Ma, D. *Org. Lett.* **2008**, *10*, 2761.

(18) Jiang, H.; Yang, J.; Tang, X.; Wu, W. *J. Org. Chem.* **2016**, *81*, 2053.

(19) Shi, L.; Ye, Z.-S.; Cao, L.-L.; Guo, R.-N.; Hu, Y.; Zhou, Y.-G. *Angew. Chem., Int. Ed.* **2012**, *51*, 8286.



DOI: 10.1021/acs.joc.6b01378
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