Supporting Information

β -Arylation of Carboxamides via Iron-Catalyzed C(sp³)-H Bond Activation

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1. General

All the reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under a positive pressure of argon. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or teflon cannula. Analytical thin-layer chromatography was performed using glass plates pre-coated with 0.25-mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light (UV). Organic solutions were concentrated by rotary evaporation at *ca.* 15 Torr (evacuated with a diaphragm pump). Flash column chromatography was performed as described by Still et al. (*J. Org. Chem.* **1978**, 43, 2923–2924), employing Kanto Silica gel 60 (spherical, neutral, 140–325 mesh). Gas-liquid chromatographic (GLC) analysis was performed on a Shimadzu 14A or 14B machine equipped with glass capillary column HR-1 (0.25-mm i.d. × 25 m). Gel permeation column chromatography was performed on a Japan Analytical Industry LC-908 (eluent: toluene) with JAIGEL 1H and 2H polystyrene columns.

Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded with JEOL ECA-500 NMR spectrometers. Chemical data for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced internally to tetramethylsilane. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 125 MHz. Chemical data for carbons are reported in parts per million (ppm, δ scale) and are referenced to the carbon resonance of the solvent (CDCl_3 : $\delta = 77.0$). The data is presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiplet resonances, br = broad), coupling constant in Hertz (Hz), and integration. Mass spectra (GS MS) are taken at SHIMADZU Parvum 2 gas chromatograph mass spectrometer.

Commercial reagents were purchased from Tokyo Kasei Co., Aldrich Inc., and other commercial suppliers and were used after appropriate purification. Anhydrous ethereal solvents (stabilizer-free) were purchased from WAKO Pure Chemical and purified by a solvent purification system (GlassContour) equipped with columns of activated alumina and supported copper catalyst (Q-5) prior to use (*Organometallics* **1996**, 15, 1518-1520). The content of water in the solvents or the substrates were confirmed to be less than 30 ppm by Karl-Fischer moisture titrator. The Grignard

reagents were prepared from the corresponding bromide and magnesium turnings in anhydrous tetrahydrofuran (THF), and were titrated prior to use. Fe(acac)₃ (99.9+%) was purchased from Aldrich Inc. and used as received. Iron salts from other sources are mentioned in the text where appropriate. 1,2-bis(Diphenylphosphino)benzene (dppbz) was purchased from Aldrich Inc. and used as received. 1,2-Dichloroisobutane (DCIB) was purchased from Tokyo Kasei Co. and used as received. ZnBr₂•TMEDA was prepared according to the literature procedure (*Chem. Lett.* **1977**, 679-682).

The geometries of cycloalkanecarboxamides **5–8** were optimized using the Spartan '06 package (Wavefunction, Inc. Irvine, CA) using the Merck Molecular Force Field (MMFF) (Thomas A. Halgren, *J. Comp. Chem.*; **1996**; 490-519), where the reactive H, the beta-C, the alfa-C and the C(O)N of the directing group were fixed in the same plane.

Caution: we observed that contamination of the reaction mixture by atmospheric moisture significantly reduces the yield, and Grignard reagents stored for a long time gave lower yields than freshly prepared ones. We sometimes observed complete suppression of the reaction when using an old Grignard reagent or incompletely anhydrous conditions, and we ascribe this to the poisoning of the iron catalyst by hydroxide species. For best results, all the experiments described herein must be performed under rigorous anhydrous conditions with good quality (preferably freshly prepared) organometallic reagents.

2. Investigation of the Key Reaction Parameters

General procedure for the optimization study

A typical procedure for **Table S1**: A solution of PhMgBr in THF (1.02 mol/L, 0.7 mmol) was slowly added to a mixture of *N*-(quinolin-8-yl) aliphatic amide (0.1 mmol) and ZnBr₂•TMEDA (0.3 mmol) using a gas-tight syringe under argon. The resulted mixture was stirred at r.t. for 30 min, then a solution of Fe(acac)₃ (0.01 mmol) and 1,2-bis(diphenylphosphino)benzene (dppbz, 0.01 mmol) in 1.0 mL anhydrous THF was added. The resulted black mixture was stirred at r.t. for 10 min, and then 1,2-dichloroisobutane (0.2 mmol) was added. The mixture was stirred at 50 °C for 36 h. After cooling to r.t., tridecane (0.1 mmol) was added as an internal standard. Aqueous Rochelle's salt was then added, and the organic layer was extracted with diethyl ether and passed over a Florisil column. The mixture was analyzed by GC using tridecane as an internal standard.

Table S1. Optimization of the reaction conditions.

<p> 1 (0.1mmol, 8-Q = 8-quinolinyl) + $\left[\begin{array}{c} \text{Ph-MgBr} \\ (7 \text{ equiv}) \\ + \\ \text{ZnBr}_2 \cdot \text{TMEDA} \\ (3 \text{ equiv}) \end{array} \right] \xrightarrow[\text{THF, 50 } ^\circ\text{C, 36 h}]{\text{Fe(acac)}_3 (10 \text{ mol\%}), \text{dppbz} (10 \text{ mol\%}), \text{DCIB} (2 \text{ equiv})} \text{3}$ </p> <p>84% (nmr yield)</p>			<p>not formed</p>
modification from the optimal condition	yield of 3 ^a (%)	recovery of 1 ^a (%)	<p>not formed</p>
1. Optimal Condition	84	19 (15% Ph-Ph) ^b	
2. ZnCl ₂ instead of ZnBr ₂ ·TMEDA	32	66	<p>not formed</p>
3. ZnCl ₂ ·TMEDA instead of ZnBr ₂ ·TMEDA	75	23	
4. without Zinc Source	0	28	<p>not formed</p>
5. ZnCl ₂ ·TMEDA and PhMgCl instead	0	99	
6. PhMgCl instead	2	94	
7. dppe instead of dppbz	9	87	
8. dppp instead of dppbz	0	99	
9. dppf instead of dppbz	0	98	
10. <i>rac</i> -BINAP instead of dppbz	0	99	
11. Xant-Phos instead of dppbz	0	95	
12. Fe(acac) ₂ instead of Fe(acac) ₃	55	43	
13. FeF ₂ instead of Fe(acac) ₃	trace	97	
14. no Fe	0	99	
15. 5.0 eq of PhMgBr and 2.0 eq of ZnBr ₂ ·TMEDA	45	52	
16. added 1 μL water	34	65	

^a Based on **1**, estimated by GC using tridecane as an internal standard.

^b Based on PhMgBr

Reaction with 1.0 equiv of iron and ligand

A solution of PhMgBr in THF (1.02 mol/L, 1.1 mmol) was slowly added using a gastight syringe to a mixture of *N*-(quinolin-8-yl)pivalamide (0.1 mmol) and ZnBr₂•TMEDA (0.5 mmol) under argon. The resulted mixture was stirred at r.t. for 30 min, then a solution of Fe(acac)₃ (0.1 mmol) and dppbz (0.1 mmol) in 2.0 mL anhydrous THF was added. The resulted black mixture was stirred at r.t. for 10 min, and then 1,2-dichloroisobutane (0.4 mmol or 0 mmol) was added. The mixture was stirred at 50 °C for 24 h. After cooling to r.t., tridecane (0.1 mmol) was added as an internal standard. Aqueous Rochelle's salt was then added, and the organic layer was extracted with diethyl ether and passed over a Florisil column. The mixture was analyzed by GC using tridecane as an internal standard.

3. Preparation and Characterization of Aliphatic Carboxamide Substrates

General procedure:

Preparation of 8-aminoquinolinyl amides (compounds **sm1**-**sm15**, **sm19**)

*Preparation of 8-aminoquinoline amides from the acid halide (compounds **sm1** and **sm19**)*

In a 100-mL flask, 8-aminoquinoline (10 mmol) and NEt₃ (11 mmol) were dissolved in dichloromethane (20 mL), followed by slow dropwise addition of an acid chloride (12 mmol). The resulting mixture was stirred at r.t. for 6 h. The mixture was transferred to a separating funnel and washed with water (15 mL), sat. NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried over MgSO₄. After filtration and evaporation of volatiles, the obtained crude amide product was purified by silica gel chromatography (hexane: ethyl acetate = 10:1). (Reference: *J. Am. Chem. Soc.* **2005**, 127, 13155.)

*Synthesis of amides from the carboxylic acid (compounds **sm8**, **9**, **10**, **11**)*

In a 100-mL flask was placed a carboxylic acid (11 mmol). SOCl₂ (10 mL) was slowly added to the solution. The reaction mixture was refluxed for 3 h at 85 °C, then the excess SOCl₂ was removed under vacuo to give the crude acid chloride. The crude acid chloride was diluted with dry CH₂Cl₂ (20 mL). A solution of 8-aminoquinoline (10 mmol) and NEt₃ (11 mmol) in dichloromethane (20 mL) was added dropwise to the acid chloride solution at 0 °C. The resulting mixture was allowed warm to r.t., and then stirred overnight. The mixture was quenched with saturated NaHCO₃ solution and extracted with CH₂Cl₂ three times. These extracts were combined and dried over MgSO₄. After evaporation under vacuo, the crude amide product was purified by silica gel chromatography (hexane: ethyl acetate = 10:1). (Reference: *J. Am. Chem. Soc.* **2009**, 131, 6898–6899).

*Synthesis of amides from benzyl bromide and methyl isobutyrate (compounds **sm2**, **3**, **4**, **5**, **6**, **7**)*

A solution of LDA (30 mmol) in THF was prepared from diisopropylamine (32 mmol) and 1.6 M *n*-BuLi in hexane (19 mL). To this LDA solution, methyl isobutyrate (30 mmol) was added dropwise at –78 °C and the mixture was stirred at –78 °C for 1 h. Benzyl bromide (30 mmol) was added to the solution. The mixture was warmed to r.t. and stirred for 16 h before quenching at 0 °C with water. The mixture was extracted with Et₂O, and the combined organic layers were washed with brine. The organic layer was dried over MgSO₄, and then evaporated in vacuo to give the crude ester.

To this ester was added a solution of sodium hydroxide (20 mL, 2 mol/L) and methanol (30 mL), and the mixture was stirred at 60 °C overnight. The pH of the mixture was adjusted to 2 with HCl (3 mol/L), and then the product was extracted with Et₂O. The

aqueous layer was saturated with NaCl and extracted again with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under vacuum to give the crude carboxylic acid. This carboxylic acid was converted to the corresponding amide by the method described above. (Reference: *J. Am. Chem. Soc.* **2009**, *131*, 6898–6899).

*Synthesis of amides from methyl iodide and ethyl cyclic carboxylate (compounds **sm12**, **13**, **14**, **15**)*

A solution of LDA (30 mmol) in THF was prepared from diisopropylamine (32 mmol) and 1.6 M *n*-BuLi in hexane (19 mL). To this LDA solution, ethyl cyclic carboxylate (30 mmol) was added dropwise at –78 °C and the mixture was stirred at –78 °C for 1 h. Methyl iodide (40 mmol) was added to the solution. The mixture was warmed to r.t. and stirred for 10 h before quenching at 0 °C with water. The mixture was extracted with Et₂O, and the combined organic layers were washed with brine. The organic layer was dried over MgSO₄, and then evaporated in vacuo to give the crude ester.

To the ester was added a solution of sodium hydroxide (20 mL, 2 mol/L) and methanol (30 mL), and the mixture was stirred at 60 °C overnight. After removal of methanol in vacuo, the pH of the mixture was adjusted to 2 with HCl (3 mol/L). The product was extracted with Et₂O. The aqueous layer was saturated with NaCl and extracted again with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under vacuum to give the crude carboxylic acid, which was purified by silica gel chromatography (hexane: ethyl acetate = 5:1). The carboxylic acid gives the amide by the method shown above. (Reference: *J. Am. Chem. Soc.* **1981**, *103*, 436.)

Preparation of *N*-(2-methylquinolin-8-yl)pivalamide (compound **16)**

In a 100-mL flask, 2-methylquinolin-8-amine (10 mmol) and NEt₃ (11 mmol) were dissolved in dichloromethane (20 mL), followed by slow dropwise addition of pivaloyl chloride (12 mmol). The resulting mixture was stirred at r.t. for 6 h. The mixture was transferred to a separating funnel and washed with water (15 mL), sat. NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried over MgSO₄. After filtration and evaporation of volatiles, the crude amide product was purified by silica gel chromatography (hexane: ethyl acetate = 10:1).

Preparation of picolinamide starting materials (compound 17)

In a 100-mL flask, pyridin-2-ylmethanamine (10 mmol) and NEt₃ (11 mmol) were dissolved in dichloromethane (20 mL), followed by slow dropwise addition of pivaloyl chloride (12 mmol). The resulting mixture was stirred at r.t. for 6 h. The mixture was transferred to a separating funnel and washed with water (15 mL), sat. NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried over MgSO₄. After filtration and evaporation of volatiles, the crude amide product was purified by silica gel chromatography (hexane: ethyl acetate = 10:1). (Reference: *J. Am. Chem. Soc.* **2005**, *127*, 13155.)

Preparation of *N*-phenylpivalamide (compound 18)

Aniline (10 mmol) and NEt₃ (11 mmol) were dissolved in dichloromethane (20 mL), followed by slow dropwise addition of pivaloyl chloride (12 mmol). The resulting mixture was stirred at r.t. for 6 h. The mixture was transferred to a separating funnel and washed with water (15 mL), sat. NaHCO₃ (15 mL) and brine (15 mL). The organic layer was dried over MgSO₄. After filtration and evaporation of volatiles, the crude amide product was purified by silica gel chromatography (hexane: ethyl acetate = 20:1).

Characterization of Aliphatic Carboxamide Substrates

N-(Quinolin-8-yl)pivalamide (sm1)

This amide was obtained as a yellow oil. The compound data was in good agreement with the literature (Reference: *J. Am. Chem. Soc.* **2010**, *132*, 3965).

¹H NMR (500 MHz, CDCl₃) δ 10.28 (s, 1H), 8.84 – 8.78 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.53 (t, *J* = 7.9 Hz, 1H), 7.48 (dd, *J* = 8.3, 1.4 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.43 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 177.22, 148.18, 138.78, 136.27, 134.69, 127.89, 127.42, 121.49, 121.18, 116.16, 40.33, 27.72.

GC MS (EI) *m/z* (relative intensity): 228 (M⁺, 11), 171 (100), 144 (31), 116 (15).

2,2-Dimethyl-3-phenyl-*N*-(quinolin-8-yl)propanamide (sm2)

This amide was obtained as a pale yellow solid. Melting point: 61–63 °C (EtOAc/hexane).

¹H NMR (500 MHz, CDCl₃) δ 10.17 (s, 1H), 8.84 (dd, *J* = 7.6, 1.3 Hz, 1H), 8.74 (dd, *J*

= 4.2, 1.6 Hz, 1H), 8.13 (dd, J = 8.3, 1.6 Hz, 1H), 7.55 (t, J = 7.9 Hz, 1H), 7.49 (dd, J = 8.3, 1.3 Hz, 1H), 7.42 (dd, J = 8.2, 4.2 Hz, 1H), 7.23 – 7.09 (m, 5H), 3.05 (s, 2H), 1.41 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 176.02, 148.14, 138.76, 137.91, 136.20, 134.47, 130.25, 127.95, 127.86, 127.40, 126.32, 121.47, 121.31, 116.23, 46.83, 44.92, 25.22.

GC MS (EI) m/z (relative intensity): 304 (M^+ , 11), 171 (100), 144 (48), 117 (12), 91 (39).

3-(4-Chlorophenyl)-2,2-dimethyl-*N*-(quinolin-8-yl)propanamide (sm3)

This amide was obtained as a yellow solid. Melting point: 73–76 °C (EtOAc/hexane).

^1H NMR (500 MHz, CDCl_3) δ 10.13 (s, 1H), 8.83 – 8.78 (m, 1H), 8.73 (dd, J = 4.1, 1.6 Hz, 1H), 8.13 (dd, J = 8.1, 1.2 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.49 (dd, J = 8.2, 1.1 Hz, 1H), 7.41 (dd, J = 8.2, 4.2 Hz, 1H), 7.14 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.5 Hz, 2H), 2.99 (s, 2H), 1.41 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.55, 148.18, 138.67, 136.40, 136.20, 134.27, 132.21, 131.46, 128.07, 127.84, 127.32, 121.51, 121.45, 116.23, 46.17, 44.90, 25.23.

GC MS (EI) m/z (relative intensity): 338 (M^+ , 10), 171 (100), 144 (56), 125 (22).

3-(4-Bromophenyl)-2,2-dimethyl-*N*-(quinolin-8-yl)propanamide (sm4)

This amide was obtained as a yellow solid. Melting point: 92–94 °C (EtOAc/hexane).

^1H NMR (500 MHz, CDCl_3) δ 10.12 (s, 1H), 8.80 (dd, J = 7.5, 1.3 Hz, 1H), 8.73 (dd, J = 4.2, 1.7 Hz, 1H), 8.12 (dd, J = 8.3, 1.6 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 7.49 (dd, J = 8.3, 1.3 Hz, 1H), 7.41 (dd, J = 8.2, 4.2 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 2.98 (s, 2H), 1.40 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.50, 148.19, 138.66, 136.91, 136.19, 134.26, 131.86, 131.02, 127.83, 127.31, 121.52, 121.44, 120.36, 116.22, 46.22, 44.85, 25.24.

GC MS (EI) m/z (relative intensity): 383 (M^+ , 2), 382 (M^+ , 7), 214 (1), 213 (5), 172 (18), 171 (100), 145 (7), 144 (58), 117 (13), 116 (15).

3-(4-Fluorophenyl)-2,2-dimethyl-*N*-(quinolin-8-yl)propanamide (sm5)

This amide was obtained as a white solid. Melting point: 90–91 °C (EtOAc/hexane).

^1H NMR (500 MHz, CDCl_3) δ 10.13 (s, 1H), 8.81 (dd, J = 7.5, 1.3 Hz, 1H), 8.74 (dd, J = 4.2, 1.5 Hz, 1H), 8.13 (dd, J = 8.3, 1.5 Hz, 1H), 7.54 (t, J = 7.9 Hz, 1H), 7.49 (dd, J =

8.3, 1.3 Hz, 1H), 7.42 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.14 (dd, $J = 7.5, 5.4$ Hz, 2H), 6.86 (t, $J = 8.8$ Hz, 2H), 3.00 (s, 2H), 1.41 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.70, 161.64 (d, $J_{\text{F}} = 244.1$ Hz), 148.17, 138.70, 136.22, 134.33, 133.59 (d, $J_{\text{F}} = 3.4$ Hz), 131.54 (d, $J_{\text{F}} = 7.8$ Hz), 127.85, 127.36, 121.52, 121.41, 116.21, 114.74 (d, $J_{\text{F}} = 21.0$ Hz), 46.06, 44.95 (d, $J_{\text{F}} = 1.1$ Hz), 25.21.

GC MS (EI) m/z (relative intensity): 322 (M^+ , 18), 171 (100), 144 (68), 109 (48).

3-(3-Methoxyphenyl)-2,2-dimethyl-*N*-(quinolin-8-yl)propanamide (sm6)

This amide was obtained as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 10.16 (s, 1H), 8.84 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.72 (dd, $J = 4.2, 1.5$ Hz, 1H), 8.11 (dd, $J = 8.3, 1.4$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.47 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.40 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.10 (t, $J = 7.9$ Hz, 1H), 6.78 (d, $J = 7.5$ Hz, 1H), 6.73 (d, $J = 1.4$ Hz, 1H), 6.67 (dd, $J = 8.2, 2.6$ Hz, 1H), 3.58 (s, 3H), 3.02 (s, 2H), 1.42 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.97, 159.16, 148.12, 139.45, 138.69, 136.16, 134.42, 128.81, 127.81, 127.32, 122.66, 121.46, 121.32, 116.17, 115.35, 112.12, 54.87, 46.99, 44.93, 25.28.

GC MS (EI) m/z (relative intensity): 334 (M^+ , 18), 171 (100), 144 (67), 121 (22), 91 (9).

2,2-Dimethyl-3-(naphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (sm7)

This amide was obtained as a brown ropy oil.

^1H NMR (500 MHz, CDCl_3) δ 10.13 (s, 1H), 8.84 (d, $J = 8.0$ Hz, 1H), 8.60 (dd, $J = 4.0$ Hz, 1H), 8.11 (dd, $J = 8.0, 1.7$ Hz, 1H), 7.63-7.72 (m, 4H), 7.56 (t, $J = 8.0$, 1H), 7.49 (d, $J = 8.0$, 1H), 7.32-7.38 (m, 4H), 3.20 (s, 2H), 1.46 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 176.01, 148.05, 138.69, 136.10, 135.58, 134.44, 133.27, 132.18, 128.78, 128.74, 127.81, 127.53, 127.42, 127.39, 127.34, 125.67, 125.22, 121.42, 121.33, 116.27, 47.01, 45.14, 25.34.

GC MS (EI) m/z (relative intensity): 354 (M^+ , 19), 171 (100), 144 (87), 141 (35), 115 (13).

2,2-Dimethyl-*N*-(quinolin-8-yl)butanamide (sm8)

This amide was obtained as a brown oil. The compound data was in good agreement with the literature (Reference: *J. Am. Chem. Soc.* **2010**, 132, 3965).

^1H NMR (500 MHz, CDCl_3) δ 10.29 (d, $J = 44.2$ Hz, 1H), 8.96 – 8.69 (m, 2H), 8.14 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.48 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.44 (dd, $J = 8.3, 4.2$ Hz, 1H), 1.77 (q, $J = 7.5$ Hz, 2H), 1.40 (s, 6H), 0.96 (t, $J = 7.5$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 176.60, 148.17, 138.74, 136.24, 134.63, 127.88, 127.40, 121.47, 121.13, 116.10, 44.04, 34.09, 25.07, 9.29.

GC MS (EI) m/z (relative intensity): 242 (M^+ , 11), 171 (100), 144 (54), 116 (15), 71 (16).

2-Methyl-2-phenyl-*N*-(quinolin-8-yl)propanamide (sm9)

This amide was obtained as a white solid. Melting point: 106–108 °C (EtOAc/hexane).

^1H NMR (500 MHz, CDCl_3) δ 9.87 (s, 1H), 8.77 (d, $J = 7.7$ Hz, 1H), 8.59 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.06 (dd, $J = 8.3, 1.4$ Hz, 1H), 7.54 (d, $J = 7.5$ Hz, 2H), 7.50 (t, $J = 8.0$ Hz, 1H), 7.43 (d, $J = 8.2$ Hz, 1H), 7.40 (t, $J = 7.7$ Hz, 2H), 7.33 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.30 (t, $J = 7.3$ Hz, 1H), 1.78 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.76, 148.06, 144.84, 138.61, 136.03, 134.65, 128.73, 127.77, 127.27, 126.96, 126.31, 121.38, 121.20, 115.90, 48.34, 26.96.

GC MS (EI) m/z (relative intensity): 290 (M^+ , 3), 171 (100), 144 (9), 91 (17).

***N*-(Quinolin-8-yl)propionamide (sm10)**

This amide was obtained as a brown oil. The compound data was in good agreement with the literature (Reference: *J. Am. Chem. Soc.* **2010**, 132, 3965).

^1H NMR (500 MHz, CDCl_3) δ 9.81 (s, 1H), 8.83 – 8.75 (m, 2H), 8.12 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.51 (t, $J = 7.9$ Hz, 1H), 7.46 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.41 (dd, $J = 8.3, 4.2$ Hz, 1H), 2.59 (q, $J = 7.6$ Hz, 2H), 1.33 (t, $J = 7.6$ Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 172.37, 147.99, 138.22, 136.24, 134.46, 127.81, 127.31, 121.45, 121.21, 116.25, 31.13, 9.66.

GC MS (EI) m/z (relative intensity): 200 (M^+ , 17), 171 (50), 144 (100), 117 (19).

***N*-(Quinolin-8-yl)cyclohexanecarboxamide (sm11)**

This amide was obtained as a white solid. Melting point: 46–48 °C (EtOAc/hexane).

The compound data was in good agreement with the literature (Reference: *J. Am. Chem. Soc.* **2005**, 127, 13154).

^1H NMR (500 MHz, CDCl_3) δ 9.89 (s, 1H), 8.87 – 8.75 (m, 2H), 8.14 (dd, $J = 8.3, 1.6$

Hz, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 7.47 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.44 (dd, $J = 8.2, 4.2$ Hz, 1H), 2.48 (tt, $J = 11.7, 3.5$ Hz, 1H), 2.09 (dd, $J = 13.6, 1.8$ Hz, 2H), 1.93 – 1.82 (m, 2H), 1.77 – 1.70 (m, 1H), 1.64 (qd, $J = 12.4, 3.1$ Hz, 2H), 1.45 – 1.23 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.81, 148.04, 138.44, 136.30, 134.61, 127.88, 127.40, 121.48, 121.18, 116.34, 46.85, 29.71, 25.73, 25.71.

GC MS (EI) m/z (relative intensity): 254 (M^+ , 15), 171 (78), 144 (100).

1-Methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide (sm12)

This amide was obtained as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 10.30 (s, 1H), 8.86 – 8.79 (m, 2H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.48 (dd, $J = 8.3, 1.3$ Hz, 1H), 7.44 (dd, $J = 8.3, 4.2$ Hz, 1H), 2.26 – 2.16 (m, 2H), 1.70 – 1.46 (m, 7H), 1.46 – 1.37 (m, 1H), 1.36 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 176.72, 148.31, 138.91, 136.39, 134.91, 128.03, 127.56, 121.60, 121.19, 116.29, 44.47, 35.89, 25.96, 23.09.

GC MS (EI) m/z (relative intensity): 268 (M^+ , 13), 171 (100), 144 (80), 97 (14).

1-Methyl-*N*-(quinolin-8-yl)cyclopentanecarboxamide (sm13)

This amide was obtained as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 10.20 (s, 1H), 8.84 – 8.77 (m, 2H), 8.13 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 7.46 (dd, $J = 8.2, 1.3$ Hz, 1H), 7.43 (dd, $J = 8.2, 4.2$ Hz, 1H), 2.36 – 2.23 (m, 2H), 1.89 – 1.75 (m, 4H), 1.74 – 1.63 (m, 2H), 1.48 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 177.35, 148.12, 138.63, 136.21, 134.77, 127.84, 127.36, 121.44, 121.03, 116.03, 51.46, 37.88, 25.57, 24.90.

GC MS (EI) m/z (relative intensity): 254 (M^+ , 17), 171 (100), 144 (76), 83 (27).

1-Methyl-*N*-(quinolin-8-yl)cyclobutanecarboxamide (sm14)

This amide was obtained as a yellow oil.

^1H NMR (500 MHz, CDCl_3) δ 9.99 (s, 1H), 8.80 (dt, $J = 5.7, 1.4$ Hz, 2H), 8.15 (dd, $J = 8.2, 1.7$ Hz, 1H), 7.54 (t, $J = 7.9$ Hz, 1H), 7.49 (dd, $J = 8.3, 1.3$ Hz, 1H), 7.44 (dd, $J = 8.2, 4.2$ Hz, 1H), 2.71 – 2.61 (m, 2H), 2.12 – 1.97 (m, 3H), 1.96 – 1.85 (m, 1H), 1.64 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 177.06, 148.17, 138.61, 136.28, 134.61, 127.89, 127.40, 121.50, 121.17, 116.10, 45.62, 31.47, 25.14, 14.76.

GC MS (EI) m/z (relative intensity): 240 (M^+ , 12), 171 (100), 144 (31), 116 (11).

1-Methyl-*N*-(quinolin-8-yl)cyclopropanecarboxamide (sm15)

This amide was obtained as a yellow solid. Melting point: 96–98 °C (EtOAc/hexane).

^1H NMR (500 MHz, CDCl_3) δ 10.38 (s, 1H), 8.82 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.76 (dd, $J = 7.5, 1.5$ Hz, 1H), 8.15 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.52 (t, $J = 7.8$ Hz, 1H), 7.48 (dd, $J = 8.3, 1.5$ Hz, 1H), 7.45 (dd, $J = 8.2, 4.2$ Hz, 1H), 1.65 (s, 3H), 1.39 (q, $J = 3.9$ Hz, 2H), 0.75 (q, $J = 3.9$ Hz, 2H).

^{13}C NMR (126 MHz, CDCl_3) δ 173.71, 148.19, 138.61, 136.26, 134.67, 127.89, 127.41, 121.50, 121.15, 116.09, 20.59, 19.79, 16.76.

GC MS (EI) m/z (relative intensity): 226 (M^+ , 42), 197 (23), 182 (38), 171 (100), 157 (18), 143 (14), 129 (10), 116 (31), 101 (11), 89 (21), 83 (76).

***N*-(2-Methylquinolin-8-yl)pivalamide (sm16)**

This amide was obtained as a yellow solid. Melting point: 91–92 °C (EtOAc/hexane).

^1H NMR (500 MHz, CDCl_3) δ 10.37 (s, 1H), 8.75 (d, $J = 7.2$ Hz, 1H), 8.01 (d, $J = 8.4$ Hz, 1H), 7.52 – 7.36 (m, 2H), 7.30 (d, $J = 8.4$ Hz, 1H), 2.73 (s, 3H), 1.43 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 177.07, 156.92, 138.05, 136.34, 133.98, 126.34, 125.93, 122.20, 120.92, 116.04, 40.32, 27.66, 25.35.

GC MS (EI) m/z (relative intensity): 242 (M^+ , 10), 185 (100), 158 (19).

***N*-(Pyridin-2-ylmethyl)pivalamide (sm17)**

This amide was obtained as a yellow oil. The compound data was in good agreement with the literature (*J. Am. Chem. Soc.*, **2011**, 133, 8070).

***N*-Phenylpivalamide (sm18)**

This amide was obtained as a white crystal. The compound data was in good agreement with the literature (*Org. Lett.*, **2011**, 13, 3738).

***N*-Methyl-*N*-(quinolin-8-yl)pivalamide (sm19)**

This amide was obtained as a white crystal. Melting point: 146–147 °C ($\text{CDCl}_3/\text{MeOH}$).

^1H NMR (500 MHz, CDCl_3) δ 9.00 (d, $J = 4.0$ Hz, 1H), 8.20 (d, $J = 8.6$ Hz, 1H), 7.84 (d, $J = 8.0$ Hz, 1H), 7.61 (d, $J = 6.9$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.46 (q, $J = 4.0$ Hz,

1H), 3.36 (s, 3H), 0.94 (s, 9H).

¹³C NMR (126 MHz, CDCl₃) δ 179.11, 150.81, 145.02, 142.91, 136.15, 129.30, 129.26, 128.21, 126.06, 121.73, 40.84, 40.71, 29.16.

GC MS (EI) *m/z* (relative intensity): 185 (85), 157 (100), 130 (45), 129 (34).

4. Iron-Catalyzed Arylation of Aliphatic Carboxamide

Directed C–H arylation of 2,2-dimethyl-3-phenyl-*N*-(quinolin-8-yl)propanamide on gram scale (Figure 1a).

A freshly prepared solution of (4-methoxyphenyl)magnesium bromide in THF (0.5 mol/L, 28.0 mmol, 56 mL) was slowly added using a gastight syringe to a mixture of 2,2-dimethyl-3-phenyl-*N*-(quinolin-8-yl)propanamide (**1**, 4.0 mmol, 1.22 g) and ZnBr₂·TMEDA (12.0 mmol, 4.08 g) under argon. The resulted mixture was stirred at r.t. for 30 min, then a solution of Fe(acac)₃ (0.4 mmol, 140 mg) and dppbz (0.4 mmol, 184 mg) in anhydrous THF (5.0 mL) was added. The resulted black mixture was stirred at r.t. for 10 min, then 1,2-dichloroisobutane (8 mmol, 920 μL) was added via syringe. The mixture was stirred at 50 °C for 36 h. After cooling to r.t., aqueous Rochelle's salt was added (20 mL), and the organic layer was extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine, passed through a pad of Florisil, dried over MgSO₄, and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (hexane:ethyl acetate = 10:1) to afford 2-benzyl-3-(4-methoxyphenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide as a pale yellow oil (1.40 g, 85% yield).

2-Benzyl-3-(4-methoxyphenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide (Figure 1a,

compound 2)

^1H NMR (500 MHz, CDCl_3) δ 9.95 (s, 1H), 8.92 (d, J = 4.6 Hz, 1H), 8.66 – 8.54 (m, 1H), 8.05 (dd, J = 8.1, 2.4 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.46 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 8.2, 4.1 Hz, 1H), 7.25 (d, J = 7.1 Hz, 2H), 7.22 – 7.08 (m, 5H), 6.72 (d, J = 8.1 Hz, 2H), 3.66 (s, 3H), 3.49 (dd, J = 28.1, 13.2 Hz, 2H), 2.78 (dd, J = 19.0, 13.5 Hz, 2H), 1.35 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.55, 158.07, 147.93, 138.54, 137.63, 135.92, 134.14, 131.18, 130.26, 129.52, 127.90, 127.66, 127.20, 126.27, 121.29, 116.12, 113.31, 54.92, 49.96, 46.40, 45.74, 19.54 (two aromatic carbon signals are overlapping).

GC MS (EI) m/z (relative intensity): 410 (M^+ , 2), 319 (61), 175 (100), 171 (40), 144 (30), 121 (91), 91 (48), 77 (11).

General procedure for Table 1:

A freshly prepared solution of an arylmagnesium bromide in THF (7.0 equiv, 3.5 mmol, titrated before use) was slowly added using a gastight syringe to a mixture of the corresponding carboxamide (1.0 equiv, 0.50 mmol) and $\text{ZnBr}_2 \cdot \text{TMEDA}$ (3.0 equiv, 1.5 mmol, 510 mg) under argon. The resulted mixture was stirred at r.t. for 30 min, then a solution of $\text{Fe}(\text{acac})_3$ (10 mol %, 0.05 mmol, 17 mg) and dppbz (10 mol %, 0.05 mmol, 23 mg) in anhydrous THF (2.0 mL) was added. The resulted black mixture was stirred at r.t. for 10 min. Then 1,2-dichloroisobutane (1.00 mmol, 115 μL) was added via syringe and the mixture was stirred at 50 $^\circ\text{C}$ for 36 h. After cooling to r.t., aqueous Rochelle's salt was added (5 mL), and the organic layer was extracted with diethyl ether (15 mL x 3). The combined organic layers were washed with brine, passed through a pad of Florisil, dried over MgSO_4 , and concentrated under reduced pressure. The crude mixture was purified by column chromatography on silica gel (hexane:ethyl acetate = 20:1 - 10:1) to afford the corresponding arylated product.

2-Benzyl-3-(4-methoxyphenyl)-2-methyl-N-(quinolin-8-yl)propanamide (Table 1, entry 1): obtained in 79% yield as a white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.95 (s, 1H), 8.92 (d, $J = 4.6$ Hz, 1H), 8.66–8.54 (m, 1H), 8.05 (dd, $J = 8.1, 2.4$ Hz, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.46 (d, $J = 8.2$ Hz, 1H), 7.32 (dd, $J = 8.2, 4.1$ Hz, 1H), 7.25 (d, $J = 7.1$ Hz, 2H), 7.22–7.08 (m, 5H), 6.72 (d, $J = 8.1$ Hz, 2H), 3.66 (s, 3H), 3.49 (dd, $J = 28.1, 13.2$ Hz, 2H), 2.78 (dd, $J = 19.0, 13.5$ Hz, 2H), 1.35 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.55, 158.07, 147.93, 138.54, 137.63, 135.92, 134.14, 131.18, 130.26, 129.52, 127.90, 127.66, 127.20, 126.27, 121.29, 116.12, 113.31, 54.92, 49.96, 46.40, 45.74, 19.54 (two aromatic carbon signals are overlapping).

GC MS (EI) m/z (relative intensity): 410 (M^+ , 2), 319 (61), 175 (100), 171 (40), 144 (30), 121 (91), 91 (48), 77 (11).

2-(4-Fluorobenzyl)-3-(4-methoxyphenyl)-2-methyl-N-(quinolin-8-yl)propanamide (Table 1, entry 2): obtained in 74% yield as a white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.91 (s, 1H), 8.87 (dd, $J = 7.6, 1.3$ Hz, 1H), 8.61 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.08 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.47 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.34 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.16 (dd, $J = 8.5, 5.5$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 6.84 (t, $J = 8.7$ Hz, 2H), 6.71 (d, $J = 8.5$ Hz, 2H), 3.66 (s, 3H), 3.44 (dd, $J = 23.2, 13.4$ Hz, 2H), 2.72 (dd, $J = 13.7, 13.7$ Hz, 2H), 1.31 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.39, 161.57 (d, $J_{\text{F}} = 244.3$ Hz), 158.14, 148.03, 138.57, 136.02, 134.04, 133.34 (d, $J_{\text{F}} = 3.3$ Hz), 131.61 (d, $J_{\text{F}} = 7.8$ Hz), 131.21, 129.40,

127.73, 127.22, 121.46, 121.39, 116.19, 114.71 (d, $J_F = 21.0$ Hz), 113.37, 54.97, 50.00, 45.79, 45.53, 19.50.

GC MS (EI) m/z (relative intensity): 428 (M^+ , 2), 319 (56), 175 (100), 144 (29), 121 (83), 109 (38).

2-(4-Chlorobenzyl)-3-(4-methoxyphenyl)-2-methyl-N-(quinolin-8-yl)propanamide

(Table 1, entry 3): obtained in 71% yield as a white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.89 (s, 1H), 8.85 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.62 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.08 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.55 (t, $J = 7.9$ Hz, 1H), 7.48 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.36 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.15 – 7.09 (m, 6H), 6.70 (d, $J = 8.5$ Hz, 2H), 3.66 (s, 3H), 3.43 (dd, $J = 29.6, 13.4$ Hz, 2H), 2.71 (dd, $J = 24.0, 13.0$ Hz, 2H), 1.30 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.26, 158.16, 148.06, 138.57, 136.20, 136.03, 134.03, 132.16, 131.55, 131.22, 129.31, 128.07, 127.74, 127.22, 121.49, 121.42, 116.21, 113.38, 55.00, 49.95, 45.85, 45.61, 19.52.

GC MS (EI) m/z (relative intensity): 444 (M^+ , 1), 319 (56), 175 (100), 144 (127), 121 (75), 91 (8).

2-(4-Bromobenzyl)-3-(4-methoxyphenyl)-2-methyl-N-(quinolin-8-yl)propanamide

(Table 1, entry 4): obtained in 73% yield as a pale yellow viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.90 (s, 1H), 8.87 (dd, $J = 8.9, 7.9$ Hz, 1H), 8.61 (dd, $J =$

4.2, 1.6 Hz, 1H), 8.06 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.47 (d, $J = 8.2$ Hz, 1H), 7.34 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.6$ Hz, 2H), 7.07 (d, $J = 8.3$ Hz, 2H), 6.71 (d, $J = 8.7$ Hz, 2H), 3.65 (s, 3H), 3.43 (dd, $J = 22.7, 13.3$ Hz, 2H), 2.71 (dd, $J = 33.0, 13.3$ Hz, 2H), 1.31 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.19, 158.13, 148.03, 138.51, 136.68, 135.97, 133.97, 131.92, 131.18, 130.98, 129.24, 127.69, 127.16, 121.47, 121.38, 120.31, 116.17, 113.36, 54.95, 49.86, 45.82, 45.62, 19.49.

GC MS (EI) m/z (relative intensity): 489 (M^+ , 1), 488 (M^+ , 1), 320 (14), 319 (61), 175 (100), 144 (29), 121 (70), 191 (10).

2-(3-Methoxybenzyl)-3-(4-methoxyphenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide (Table 1, entry 5): obtained in 71% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.93 (s, 1H), 8.87 (dd, $J = 7.6, 1.1$ Hz, 1H), 8.62 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.09 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.54 (t, $J = 8.0$ Hz, 1H), 7.47 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.36 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.12 (d, $J = 8.6$ Hz, 2H), 7.07 (t, $J = 7.9$ Hz, 1H), 6.79 (d, $J = 7.3$ Hz, 1H), 6.75 (s, 1H), 6.70 (d, $J = 8.5$ Hz, 2H), 6.64 (dd, $J = 8.2, 2.5$ Hz, 1H), 3.67 (s, 3H), 3.55 (s, 3H), 3.44 (dd, $J = 21.2, 13.3$ Hz, 2H), 2.73 (dd, $J = 13.3, 6.6$ Hz, 2H), 1.31 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.75, 159.17, 158.11, 148.04, 139.22, 138.63, 136.03, 134.17, 131.25, 129.58, 128.83, 127.74, 127.25, 122.76, 121.42, 121.40, 116.23, 115.26, 113.37, 112.33, 55.02, 54.85, 50.03, 46.58, 45.82, 19.60.

GC MS (EI) m/z (relative intensity): 440 (M^+ , 2), 319 (58), 175 (100), 144 (28), 121 (98), 91 (19), 77 (12).

2-(4-Methoxybenzyl)-2-methyl-3-(naphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (Table 1, entry 6): obtained in 83% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.94 (s, 1H), 8.94 (dd, $J = 7.7, 1.2$ Hz, 1H), 8.47 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.02 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.72 – 7.65 (m, 3H), 7.63 (d, $J = 8.5$ Hz, 1H), 7.58 (t, $J = 8.0$ Hz, 1H), 7.47 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.39 – 7.35 (m, 3H), 7.26 (dd, $J = 8.0, 4.0$ Hz, 1H), 7.18 (d, $J = 8.5$ Hz, 2H), 6.74 (d, $J = 9.0$ Hz, 2H), 3.68 (s, 3H), 3.59 (dd, $J = 78.0, 13.4$ Hz, 2H), 2.90 (dd, $J = 64.9, 13.3$ Hz, 2H), 1.38 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.68, 158.11, 147.88, 138.52, 135.86, 135.33, 134.12, 133.20, 132.11, 131.26, 129.54, 128.87, 128.71, 127.65, 127.47, 127.39, 127.34, 127.18, 125.61, 125.17, 121.37, 121.27, 116.22, 113.35, 54.97, 50.12, 46.52, 45.77, 19.68.

GC MS (EI) m/z (relative intensity): 460 (M^+ , 2), 319 (67), 195 (36), 175 (100), 141 (47), 121 (80).

2,2-Dimethyl-3-phenyl-*N*-(quinolin-8-yl)propanamide (Table 1, entry 7) : the crude mixture was purified by gel permeation column chromatography (toluene) to afford the title compound in 33% yield as a white oil.

2-Benzyl-2-methyl-3-phenyl-*N*-(quinolin-8-yl)propanamide (Table 1, entry 7) : the crude mixture was purified by gel permeation column chromatography (toluene) to afford the titled compound in 31% yield as a pale white viscous liquid.

2,2-Dimethyl-3-phenyl-*N*-(quinolin-8-yl)propanamide

^1H NMR (500 MHz, CDCl_3) δ 10.17 (s, 1H), 8.84 (dd, $J = 7.6, 1.3$ Hz, 1H), 8.74 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.13 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.55 (t, $J = 7.9$ Hz, 1H), 7.49 (dd, $J = 8.3, 1.3$ Hz, 1H), 7.42 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.23–7.09 (m, 5H), 3.05 (s, 2H), 1.41 (s, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 176.02, 148.14, 138.76, 137.91, 136.20, 134.47, 130.25, 127.95, 127.86, 127.40, 126.32, 121.47, 121.31, 116.23, 46.83, 44.92, 25.22.

GC MS (EI) m/z (relative intensity): 304 (M^+ , 11), 171 (100), 144 (47), 117 (12), 91 (38).

2-Benzyl-2-methyl-3-phenyl-*N*-(quinolin-8-yl)propanamide

^1H NMR (500 MHz, CDCl_3) δ 9.93 (s, 1H), 8.90 (dd, J = 7.7, 1.2 Hz, 1H), 8.61 (dd, J = 4.2, 1.6 Hz, 1H), 8.08 (dd, J = 8.2, 1.5 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.48 (dd, J = 8.3, 1.2 Hz, 1H), 7.34 (dd, J = 8.2, 4.2 Hz, 1H), 7.22 (d, J = 8.0 Hz, 4H), 7.17 (dd, J = 8.1, 6.8 Hz, 4H), 7.12 (ddd, J = 8.3, 2.5, 1.2 Hz, 2H), 3.51 (d, J = 13.2 Hz, 2H), 2.80 (d, J = 13.2 Hz, 2H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.52, 148.00, 138.63, 137.59, 136.01, 134.17, 130.32, 127.96, 127.73, 127.29, 126.34, 121.36, 116.21, 49.91, 46.56, 19.59 (two aromatic carbon signals are overlapping).

GC MS (EI) m/z (relative intensity): 380 (M^+ , 4), 289 (87), 171 (100), 145 (73), 117 (27), 91 (94).

2-(4-Methoxybenzyl)-2-methyl-*N*-(quinolin-8-yl)butanamide (Table 1, entry 8): the crude mixture was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 15:1) to afford the titled compound in 53% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 10.12 (s, 1H), 8.85 (dd, J = 7.6, 1.1 Hz, 1H), 8.73 (dd, J = 4.2, 1.6 Hz, 1H), 8.12 (dd, J = 8.2, 1.3 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.48 (dd, J = 8.2, 1.1 Hz, 1H), 7.40 (dd, J = 8.3, 4.2 Hz, 1H), 7.10 (d, J = 8.5 Hz, 2H), 6.71 (d, J = 8.5 Hz, 2H), 3.68 (s, 3H), 3.19 (d, J = 13.5 Hz, 1H), 2.77 (d, J = 13.5 Hz, 1H), 2.04 (dq, J = 14.5, 7.4 Hz, 1H), 1.62 – 1.54 (m, 1H), 1.34 (s, 3H), 0.99 (t, J = 7.4 Hz, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.30, 158.04, 148.10, 138.68, 136.12, 134.38, 131.13,

129.81, 127.82, 127.35, 121.42, 121.20, 116.14, 113.29, 55.01, 49.02, 45.16, 32.63, 20.08, 9.13.

GC MS (EI) m/z (relative intensity): 348 (M^+ , 17), 171 (65), 144 (80), 121 (100), 77 (12).

1-(4-Methoxybenzyl)-*N*-(quinolin-8-yl)cyclohexanecarboxamide (Table 1, entry 9): the crude mixture was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 15:1) to afford the titled compound in 75% yield as a white liquid.

^1H NMR (500 MHz, CDCl_3) δ 10.02 (s, 1H), 8.82 (dd, J = 7.6, 1.3 Hz, 1H), 8.68 (dd, J = 4.2, 1.6 Hz, 1H), 8.10 (dd, J = 8.3, 1.6 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 7.46 (dd, J = 8.3, 1.2 Hz, 1H), 7.38 (dd, J = 8.2, 4.2 Hz, 1H), 7.01 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 8.5 Hz, 2H), 3.60 (s, 3H), 2.91 (s, 2H), 2.29–2.20 (m, 2H), 1.80–1.66 (m, 2H), 1.64–1.45 (m, 5H), 1.38–1.24 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.61, 158.04, 147.98, 138.63, 136.00, 134.41, 130.92, 129.04, 127.74, 127.30, 121.31, 121.04, 116.12, 113.15, 54.91, 49.55, 34.07, 25.86, 23.06 (two aliphatic carbon signals are overlapping).

GC MS (EI) m/z (relative intensity): 374 (M^+ , 14), 206 (17), 171 (59), 144 (83), 121 (100), 109 (10), 77 (10).

1-(4-Methoxybenzyl)-*N*-(quinolin-8-yl)cyclopentanecarboxamide (Table 1, entry 10): obtained in 69% yield as a white oil.

^1H NMR (500 MHz, CDCl_3) δ 9.98 (s, 1H), 8.78 (dd, J = 7.6, 1.3 Hz, 1H), 8.71 (dd, J = 4.2, 1.6 Hz, 1H), 8.12 (dd, J = 8.2, 1.6 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 7.47 (dd, J = 8.2, 1.3 Hz, 1H), 7.40 (dd, J = 8.2, 4.2 Hz, 1H), 7.07 (d, J = 8.6 Hz, 2H), 6.65 (d, J = 8.6 Hz, 2H), 3.64 (s, 3H), 3.05 (s, 2H), 2.29–2.18 (m, 2H), 1.89–1.75 (m, 6H).

^{13}C NMR (126 MHz, CDCl_3) δ 175.63, 158.09, 148.04, 138.62, 136.10, 134.54, 130.61, 130.38, 127.82, 127.37, 121.40, 121.08, 116.09, 113.42, 57.73, 55.00, 43.80, 35.23, 23.94.

GC MS (EI) m/z (relative intensity): 360 (M^+ , 14), 239 (18), 188 (23), 171 (51), 144 (100), 121 (95), 95 (11), 77 (12).

2-Benzyl-2-methyl-3-phenyl-*N*-(quinolin-8-yl)propanamide (Table 1, entry 11): the crude mixture was purified by gel permeation column chromatography (toluene) to afford the title compound in 80% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.93 (s, 1H), 8.90 (dd, J = 7.7, 1.2 Hz, 1H), 8.61 (dd, J = 4.2, 1.6 Hz, 1H), 8.08 (dd, J = 8.2, 1.5 Hz, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.48 (dd, J = 8.3, 1.2 Hz, 1H), 7.34 (dd, J = 8.2, 4.2 Hz, 1H), 7.22 (d, J = 8.0 Hz, 4H), 7.17 (dd, J = 8.1, 6.8 Hz, 4H), 7.12 (ddd, J = 8.3, 2.5, 1.2 Hz, 2H), 3.51 (d, J = 13.2 Hz, 2H), 2.80 (d, J = 13.2 Hz, 2H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.52, 148.00, 138.63, 137.59, 136.01, 134.17, 130.32, 127.96, 127.73, 127.29, 126.34, 121.36, 116.21, 49.91, 46.56, 19.59.

GC MS (EI) m/z (relative intensity): 380 (M^+ , 4), 289 (87), 171 (100), 145 (73), 117 (27), 91 (94).

2-Benzyl-2-methyl-*N*-(quinolin-8-yl)-3-(*p*-tolyl)propanamide (Table 1, entry 12): the crude mixture was purified by gel permeation column chromatography (toluene) to afford the title compound in 78% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.93 (s, 1H), 8.88 (dd, J = 7.6, 1.1 Hz, 1H), 8.62 (dd, J = 4.2, 1.3 Hz, 1H), 8.09 (dd, J = 8.2, 1.4 Hz, 1H), 7.56 (t, J = 7.9 Hz, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.36 (dd, J = 8.2, 4.2 Hz, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.16 (dd, J = 7.9, 7.1

Hz, 2H), 7.10 (t, $J = 7.3$ Hz, 3H), 6.97 (d, $J = 8.1$ Hz, 2H), 3.46 (dd, $J = 18.8, 13.3$ Hz, 2H), 2.77 (dd, $J = 13.3, 6.8$ Hz, 2H), 2.21 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.65, 147.99, 138.68, 137.69, 136.03, 135.80, 134.45, 134.26, 130.34, 130.21, 128.68, 127.95, 127.76, 127.33, 126.31, 121.35, 121.32, 116.25, 49.92, 46.49, 46.18, 20.92, 19.64.

GC MS (EI) m/z (relative intensity): 394 (M^+ , 3), 288 (21), 171 (100), 159 (82), 144 (52), 117 (24), 105 (92), 91 (72).

2-Benzyl-3-(4-(*tert*-butyl)phenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide (Table 1, entry 13): the crude mixture was purified by gel permeation column chromatography (toluene) to afford the title compound in 85% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.93 (s, 1H), 8.92 (dd, $J = 7.7, 1.1$ Hz, 1H), 8.60 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.06 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 1H), 7.47 (dd, $J = 8.3, 1.1$ Hz, 1H), 7.32 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.25 (d, $J = 7.1$ Hz, 2H), 7.22–7.15 (m, 6H), 7.15–7.10 (m, 1H), 3.54 (d, $J = 13.2$ Hz, 1H), 3.47 (d, $J = 13.3$ Hz, 1H), 2.81 (dd, $J = 13.3, 4.4$ Hz, 2H), 1.35 (s, 3H), 1.20 (s, 9H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.60, 149.01, 147.89, 138.57, 137.72, 135.95, 134.38, 134.22, 130.31, 129.96, 127.92, 127.68, 127.27, 126.28, 124.80, 121.29, 121.26, 116.17, 49.93, 46.38, 46.17, 34.17, 31.19, 19.66.

GC MS (EI) m/z (relative intensity): 436 (M^+ , 3), 345 (85), 289 (22), 201 (36), 171 (99), 145 (100), 117 (36), 91 (66).

2-Benzyl-2-methyl-*N*-(quinolin-8-yl)-3-(*m*-tolyl)propanamide (Table 1, entry 14): the crude mixture was purified by gel permeation column chromatography (toluene) to afford the titled compound in 78% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.88 (s, 1H), 8.86 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.61 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.10 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.55 (t, $J = 8.0$ Hz, 1H), 7.48 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.36 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.22–7.18 (m, 2H), 7.18–7.13 (m, 2H), 7.13–7.08 (m, 1H), 7.04 (t, $J = 7.8$ Hz, 1H), 6.99 (d, $J = 7.0$ Hz, 2H), 6.89 (d, $J = 7.3$ Hz, 1H), 3.45 (dd, $J = 36.8, 13.2$ Hz, 2H), 2.76 (dd, $J = 13.2, 10.9$ Hz, 2H), 2.10 (s, 3H), 1.29 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.69, 148.00, 138.70, 137.75, 137.46, 137.42, 136.04, 134.24, 131.16, 130.38, 127.98, 127.81, 127.77, 127.35, 127.33, 127.07, 126.33, 121.38, 121.35, 116.29, 49.91, 46.66, 46.40, 21.17, 19.64.

GC MS (EI) m/z (relative intensity): 394 (M^+ , 3), 303 (47), 289 (31), 207 (22), 171 (100), 144 (45), 105 (62), 91 (64).

2-Benzyl-3-(4-fluorophenyl)-2-methyl-N-(quinolin-8-yl)propanamide (Table 1, entry 16): the crude mixture was purified by gel permeation column chromatography (toluene) to afford the titled compound in 56% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.89 (s, 1H), 8.85 (dd, $J = 7.6, 1.2$ Hz, 1H), 8.61 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.09 (dd, $J = 8.2, 1.6$ Hz, 1H), 7.55 (t, $J = 7.9$ Hz, 1H), 7.48 (dd, $J = 8.3, 1.3$ Hz, 1H), 7.36 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.23–7.19 (m, 2H), 7.19–7.09 (m, 5H), 6.83 (t, $J = 8.8$ Hz, 2H), 3.47 (dd, $J = 13.3, 3.3$ Hz, 2H), 2.75 (dd, $J = 33.7, 13.3$ Hz, 2H), 1.30 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.31, 161.64 (d, $J_{\text{F}} = 244.2$ Hz), 148.08, 138.64, 137.47, 136.08, 134.08, 133.28 (d, $J_{\text{F}} = 3.2$ Hz), 131.66 (d, $J_{\text{F}} = 7.8$ Hz), 130.33, 128.02, 127.78, 127.29, 126.42, 121.50, 121.44, 116.25, 114.76 (d, $J_{\text{F}} = 21.0$ Hz), 49.94 (d, $J_{\text{F}} = 1.1$ Hz), 46.62, 45.69, 19.54.

GC MS (EI) m/z (relative intensity): 398 (M^+ , 3), 307 (34), 289 (34), 171 (100), 144 (37), 163 (27), 109 (55), 91 (51).

2-Benzyl-3-(3-fluorophenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide (Table 1, entry 17): the crude mixture was purified by gel permeation column chromatography (toluene) to afford the title compound in 51% yield as a pale white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.90 (s, 1H), 8.85 (dd, $J = 7.6, 1.1$ Hz, 1H), 8.62 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.10 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.55 (t, $J = 7.9$ Hz, 1H), 7.48 (dd, $J = 8.2, 1.0$ Hz, 1H), 7.36 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.20 (dd, $J = 8.1, 1.2$ Hz, 2H), 7.16 (t, $J = 7.4$ Hz, 2H), 7.13–7.06 (m, 2H), 6.97 (d, $J = 7.7$ Hz, 1H), 6.92 (d, $J = 10.1$ Hz, 1H), 6.82–6.75 (m, 1H), 3.48 (dd, $J = 18.1, 13.3$ Hz, 2H), 2.76 (dd, $J = 29.8, 13.2$ Hz, 2H), 1.32 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.21, 162.50 (d, $J_{\text{F}} = 245.2$ Hz), 148.07, 140.22 (d, $J_{\text{F}} = 7.3$ Hz), 138.69, 137.36, 136.09, 134.08, 130.35, 129.35 (d, $J_{\text{F}} = 8.3$ Hz), 128.03, 127.80, 127.34, 126.47, 126.00 (d, $J_{\text{F}} = 2.7$ Hz), 121.51, 121.43, 117.15 (d, $J_{\text{F}} = 21.0$ Hz), 116.34, 113.28 (d, $J_{\text{F}} = 20.9$ Hz), 49.91, 46.72, 46.14 (d, $J_{\text{F}} = 1.7$ Hz), 19.64.

GC MS (EI) m/z (relative intensity): 398 (M^+ , 2), 307 (22), 289 (38), 171 (100), 145 (35), 117 (16), 109 (29), 91 (51).

2-Benzyl-3-(3-(dimethylamino)phenyl)-2-methyl-*N*-(quinolin-8-yl)propanamide

(Table 1, entry 18): the crude mixture was purified by column chromatography on silica gel (n -hexane:EtOAc = 15:1) to afford the title compound in 80% yield as a yellow viscous liquid

^1H NMR (500 MHz, CDCl_3) δ 9.95 (s, 1H), 8.90 (dd, $J = 7.7, 1.3$ Hz, 1H), 8.62 (dd, $J =$

4.2, 1.7 Hz, 1H), 8.07 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.56 (t, $J = 8.0$ Hz, 1H), 7.47 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.34 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.24–7.20 (m, 2H), 7.19–7.14 (m, 2H), 7.14–7.07 (m, 3H), 6.56 (d, $J = 9.0$ Hz, 2H), 3.44 (dd, $J = 52.6, 13.4$ Hz, 2H), 2.82 (s, 6H), 2.77 (dd, $J = 13.3, 10.2$ Hz, 2H), 1.32 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.91, 149.19, 147.94, 138.65, 137.89, 135.95, 134.32, 130.95, 130.30, 127.89, 127.72, 127.29, 126.19, 125.45, 121.29, 121.20, 116.18, 112.38, 50.07, 46.26, 45.79, 40.57, 19.63.

GC MS (EI) m/z (relative intensity): 423 (M^+ , 4), 281 (20), 208 (15), 134 (100), 73 (46).

2-Benzyl-2-methyl-3-(naphthalen-2-yl)-*N*-(quinolin-8-yl)propanamide (Table 1, entry 19): the crude mixture was purified by gel permeation column chromatography (toluene) to afford the title compound in 69% yield as a white viscous liquid.

^1H NMR (500 MHz, CDCl_3) δ 9.91 (s, 1H), 8.91 (dd, $J = 7.6, 1.3$ Hz, 1H), 8.46 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.04 (dd, $J = 8.2, 1.4$ Hz, 1H), 7.73–7.63 (m, 3H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.57 (t, $J = 8.0$ Hz, 1H), 7.47 (d, $J = 8.3$ Hz, 1H), 7.38–7.32 (m, 3H), 7.28 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.26–7.22 (m, 2H), 7.22–7.16 (m, 2H), 7.15–7.11 (m, 1H), 3.61 (dd, $J = 51.3, 13.2$ Hz, 2H), 2.91 (dd, $J = 44.1, 13.2$ Hz, 2H), 1.37 (s, 3H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.60, 147.93, 138.60, 137.61, 135.92, 135.29, 134.17, 133.24, 132.17, 130.39, 128.94, 128.75, 128.00, 127.71, 127.52, 127.43, 127.38, 127.25, 126.38, 125.64, 125.21, 121.41, 121.32, 116.28, 50.07, 46.67, 46.60, 19.73.

GC MS (EI) m/z (relative intensity): 430 (M^+ , 6), 339 (96), 195 (100), 171 (97), 141 (90), 115 (35), 91 (75).

5. Deuterium-labeling and KIE Experiments

*Preparation of 1-methyl- d_3 -*N*-(quinolin-8-yl)cyclohexanecarboxamide*

A solution of LDA (30 mmol) in THF was prepared from diisopropylamine (32 mmol) and *n*-BuLi in hexane (1.6 M, 19 mL). To the LDA solution, ethyl cyclohexanecarboxylate (30 mmol) was added dropwise at -78 °C and the mixture was stirred at -78 °C for 1h. Iodomethane- d_3 (40 mmol) was then added to the solution. The

mixture was warmed to r.t. and stirred for 10 h before quenching at 0 °C with water. The mixture was extracted with Et₂O, and the combined organic layers were washed with brine. The organic layer was dried over MgSO₄, then evaporated in vacuo to give the crude ester.

To the ester was added a solution of sodium hydroxide (20 mL, 2 M) and methanol (30 mL). The mixture was stirred at 60 °C overnight. After removal of the methanol in vacuo, the pH of the mixture was adjusted to 2 with HCl (3 M). The product was extracted with Et₂O. The aqueous layer was saturated with NaCl and extracted again with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄ and concentrated under vacuum to give the crude carboxylic acid, which was purified by silica gel chromatography (hexane: ethyl acetate = 5:1). The carboxylic acid gave the amide by the method show in Part 3.

1-Methyl-*d*₃-*N*-(quinolin-8-yl)cyclohexanecarboxamide (Scheme 1): the amide was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 10:1) to afford the title compound as a yellow liquid. (Reference: *J. Am. Chem. Soc.* **1981**, *103*, 436.)

¹H NMR (500 MHz, CDCl₃) δ 10.28 (s, 1H), 8.82 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.78 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.43 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.38 (dd, *J* = 8.2, 4.2 Hz, 1H), 2.24–2.13 (m, 2H), 1.69–1.45 (m, 7H), 1.44–1.32 (m, 1H).

¹³C NMR (126 MHz, CDCl₃) δ 176.46, 148.06, 138.64, 136.11, 134.67, 127.77, 127.27, 121.36, 120.97, 116.03, 44.00, 35.56, 25.72, 22.84.

GC MS (EI) *m/z* (relative intensity): 271 (M⁺, 9), 171 (100), 144 (53), 116 (10).

Deuterium Labeling Experiment

A freshly prepared solution of (4-methoxyphenyl)magnesium bromide in THF (7.0 equiv, 3.5 mmol, 0.51M) was slowly added using a gastight syringe to a mixture of 1-methyl-*d*₃-*N*-(quinolin-8-yl)cyclohexanecarboxamide (1.0 equiv, 0.50 mmol) and ZnBr₂•TMEDA (3.0 equiv, 1.5 mmol, 0.51g) under argon. The resulted mixture was stirred at r.t. for 30 min, then a solution of Fe(acac)₃ (10 mol %, 0.05 mmol, 17 mg) and

dppbz (10 mol %, 0.05 mmol, 23 mg) in anhydrous THF (2.0 mL) was added. The resulted black mixture was stirred at r.t. for 10 min. Then 1,2-dichloroisobutane (1.0 mmol, 115 μ L) was added via syringe and the mixture was stirred at 50 $^{\circ}$ C for 22 h. After cooling to r.t., aqueous Rochelle's salt was added (5 mL), and the organic layer was extracted with diethyl ether (15 mL x 3). The combined organic layer was analyzed via GC and GC-MS, and then washed with brine, filtered through a pad of Florisil, dried over MgSO_4 , and concentrated under reduced pressure. The crude mixture was analyzed by NMR using 1,1,2,2-tetrachloroethane as an internal standard and then purified by column chromatography on silica gel (hexane:ethyl acetate = 20:1-10:1) to afford the corresponding arylated product and the recovered starting material. The deuterium incorporation in the isolated product and recovered starting material was estimated by ^1H NMR. Deuterium incorporation into the recovered anisole was observed by GC MS.

1-(2D-(4-methoxyphenyl)methyl)-N-(quinolin-8-yl)cyclohexanecarboxamide

(Scheme 1): the amide was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 10:1) to afford the titled compound as a white liquid.

^1H NMR (500 MHz, CDCl_3) δ 10.01 (s, 1H), 8.81 (dd, $J = 7.6, 1.3$ Hz, 1H), 8.69 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.12 (dd, $J = 8.3, 1.6$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.47 (dd, $J = 8.3, 1.3$ Hz, 1H), 7.40 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.01 (d, $J = 8.5$ Hz, 2H), 6.61 (d, $J = 9.0$ Hz, 2H), 3.61 (s, 3H), 2.27 – 2.18 (m, 2H), 1.78 – 1.67 (m, 2H), 1.63 – 1.45 (m, 5H), 1.38 – 1.27 (m, 1H).

^{13}C NMR (126 MHz, CDCl_3) δ 174.70, 158.08, 148.02, 138.70, 136.05, 134.46, 130.94, 129.04, 127.80, 127.37, 121.36, 121.07, 116.18, 113.19, 54.97, 49.44, 34.05, 25.91, 23.09.

GC MS (EI) m/z (relative intensity): 376 (M^+ , 16), 171 (57), 145 (64), 123 (100), 100 (14), 79 (10), 73 (10).

Intermolecular KIE experiment (Scheme 1)

A freshly prepared solution of (4-methoxyphenyl)magnesium bromide in THF (7.0 equiv, 3.5 mmol, 0.51M) was slowly added using a gastight syringe to a mixture of 1-methyl- d_3 -*N*-(quinolin-8-yl)cyclohexanecarboxamide (0.5 equiv, 0.25 mmol, 68 mg), 1-methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide (0.5 equiv, 0.25 mmol, 67 mg) and $\text{ZnBr}_2 \cdot \text{TMEDA}$ (3.0 equiv, 1.5 mmol, 0.51g) under argon. The resulted mixture was stirred at r.t. for 30 min, then a solution of $\text{Fe}(\text{acac})_3$ (10 mol %, 0.05 mmol, 17 mg) and dppbz (10 mol %, 0.05 mmol, 23 mg) in anhydrous THF (2.0 mL) was added. The resulted black mixture was stirred at r.t. for 10 min, then 1,2-dichloroisobutane (1.0 mmol, 115 μL) was added via syringe. The mixture was stirred at 50 $^\circ\text{C}$ for 1 h and then it was quenched by adding aqueous Rochelle's salt (5 mL). The organic layer was extracted with diethyl ether (15 mL x 3). The combined organic layer was analyzed via GC and GC-MS, and then washed with brine, passed through a pad of Florisil, dried over MgSO_4 , and concentrated under reduced pressure. The crude mixture was analyzed by NMR using 1,1,2,2-tetrachloroethane as an internal standard and then purified by column chromatography on silica gel (hexane:ethyl acetate = 20:1-10:1) to afford the corresponding arylated products. The isolated products were further analyzed by ^1H NMR to determine the ratio of **9** and **9-D**.

^1H -NMR spectrum of the mixture of **9** and **9-D**

^1H NMR (500 MHz, CDCl_3) δ **10.00 (s, 1H)**, 8.80 (dd, $J = 7.6, 1.0$ Hz, 1H), 8.69 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.12 (dd, $J = 8.2, 1.5$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.47 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.40 (dd, $J = 8.2, 4.2$ Hz, 1H), 7.00 (d, $J = 8.6$ Hz, 2H), 6.61 (d, $J = 8.6$ Hz, 2H), 3.61 (s, 3H), **2.90 (s, 1.60H)**, 2.33 – 2.18 (m, 2H), 1.83 – 1.66 (m, 2H), 1.62 – 1.45 (m, 5H), 1.38 – 1.25 (m, 1H).

KIE for two parallel reactions (Scheme 1)

A freshly prepared solution of (4-methoxyphenyl)magnesium bromide in THF (7.0 equiv, 3.5 mmol, 0.51M) was slowly added using a gastight syringe to a mixture of 1-methyl-*d*3-*N*-(quinolin-8-yl)cyclohexanecarboxamide (1.0 equiv, 0.50 mmol) and $\text{ZnBr}_2 \cdot \text{TMEDA}$ (3.0 equiv, 1.5 mmol, 0.51g) under argon. Another freshly prepared solution of (4-methoxyphenyl)magnesium bromide in THF (7.0 equiv, 3.5 mmol, 0.51M) was slowly added using a gastight syringe to a mixture of 1-methyl-*N*-(quinolin-8-yl)cyclohexanecarboxamide (1.0 equiv, 0.5 mmol), and $\text{ZnBr}_2 \cdot \text{TMEDA}$ (3.0 equiv, 1.5 mmol, 0.51g) under argon. Under otherwise identical reaction conditions, the two reaction mixtures were stirred at r.t. for 30 min, then a solution of $\text{Fe}(\text{acac})_3$ (10 mol %, 0.05 mmol, 17 mg) and dppbz (10 mol %, 0.05 mmol, 23 mg) in 2.0 mL anhydrous THF were added to each reaction. The resulted black mixtures were stirred at r.t. for 10 min, then 1,2-dichloroisobutane (1.0 mmol, 115 μL) and tridecane (0.5 mmol, 125 μL , as an internal standard) were added via syringe to each reaction. The mixtures were stirred at $50 \pm 1.5^\circ\text{C}$. The reactions were sampled every 10 minutes and analyzed by GC. The GC yield was calculated after calibrating the response of GC. The average ratio of the two target products (**9** and **9-D**) for the first 60 min reaction is reported as the KIE value.

¹H NMR spectrum (Table 1, entry 1)

¹³C NMR spectrum (Table 1, entry 1)

¹H NMR spectrum (Table 1, entry 2)

^{13}C NMR spectrum (Table 1, entry 2)

¹H NMR spectrum (Table 1, entry 3)

¹³C NMR spectrum (Table 1, entry 3)

¹H NMR spectrum (Table 1, entry 4)

¹³C NMR spectrum (Table 1, entry 4)

¹H NMR spectrum (Table 1, entry 5)

^{13}C NMR spectrum (Table 1, entry 5)

¹H NMR spectrum (Table 1, entry 6)

^{13}C NMR spectrum (Table 1, entry 6)

¹H NMR spectrum (Table 1, entry 7)

¹³C NMR spectrum (Table 1, entry 7)

¹H NMR spectrum (Table 1, entry 7)

¹³C NMR spectrum (Table 1, entry 7)

¹H NMR spectrum (Table 1, entry 8)

¹³C NMR spectrum (Table 1, entry 8)

[illegible]

^{13}C NMR spectrum (Table 1, entry 9)

¹H NMR spectrum (Table 1, entry 10)

^{13}C NMR spectrum (Table 1, entry 10)

¹H NMR spectrum (Table 1, entry 11)

¹³C NMR spectrum (Table 1, entry 11)

¹H NMR spectrum (Table 1, entry 12)

¹³C NMR spectrum (Table 1, entry 12)

¹H NMR spectrum (Table 1, entry 13)

^{13}C NMR spectrum (Table 1, entry 13)

¹H NMR spectrum (Table 1, entry 14)

^{13}C NMR spectrum (Table 1, entry 14)

¹H NMR spectrum (Table 1, entry 16)

^{13}C NMR spectrum (Table 1, entry 16)

¹H NMR spectrum (Table 1, entry 17)

¹³C NMR spectrum (Table 1, entry 17)

¹H NMR spectrum (Table 1, entry 18)

^{13}C NMR spectrum (Table 1, entry 18)

¹H NMR spectrum (Table 1, entry 19)

¹³C NMR spectrum (Table 1, entry 19)

¹H NMR spectrum (Scheme 1)

^{13}C NMR spectrum (Scheme 1)

¹H NMR spectrum (Scheme 1)

^{13}C NMR spectrum (Scheme 1)