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Synthesis of 8-Arylquinolines via One-Pot Pd-Catalyzed Borylation of Quinoline-8-yl Halides and Subsequent Suzuki−Miyaura Coupling

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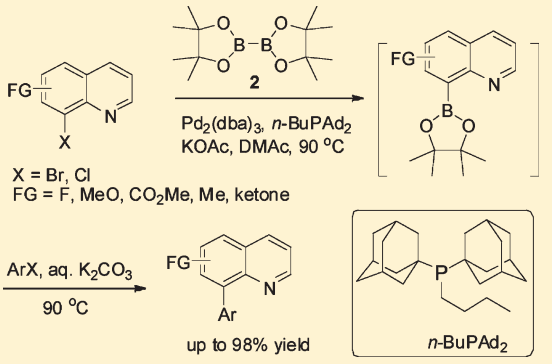
Supporting Information

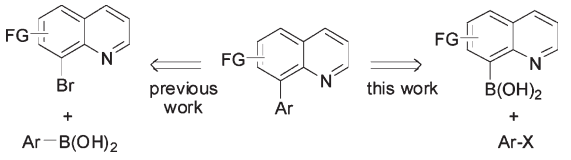
ABSTRACT: A one-pot process has been developed for the synthesis of 8-arylquinolines via Pd-catalyzed borylation of quinoline-8-yl halides and subsequent Suzuki−Miyaura coupling with aryl halides using *n*-BuPAd$_2$ as ligand. Yields of up to 98% were obtained.



8-Arylquinolines are pharmaceutically important scaffolds, broadly present in many molecules with a wide array of biological activity.[1] In addition, they have also been designed and synthesized as key structural elements in materials science.[2] Due to their structural rigidity with the nitrogen donor atom of quinolines, Song's group has recently developed a novel ligand incorporating 8-arylquinolines for activation of a C−Cl bond of $CHCl_3$ in the presence of Pt.[3]

Over the past four decades, transition-metal-catalyzed coupling reactions have evolved into an indispensable tool in academia and industry.[4] Among the many known reactions of this type, Suzuki−Miyaura couplings are particularly popular because of their significant benefits including reaction efficiency, mild conditions, high functional group tolerance, and the ease of handling and separating byproducts from reaction mixtures.[5] Usually, 8-arylquinolines are prepared via Pd-catalyzed Suzuki−Miyaura coupling of arylboronic acids instead of 8-quinolineboronic acids (Scheme 1).[6,7] This is partly due to the lack of efficient methods for synthesis of 8-quinolineboronic acids. Under conventional conditions, 8-quinolineboronic acid could be prepared in only moderate yields via Br/I exchange with alkyl lithium followed by quench with boronate.[8] Usually, cryogenic conditions were unavoidable and essential to maximize the yield of 8-quinolineboronic acids since the π-deficient quinoline could easily undergo nucleophilic addition at the 2-position.[9] In addition, this classic methodology suffers from low functional group tolerance. Our studies indicated that 8-quinolineboronic acids exhibit high stability under basic conditions, which makes them ideal coupling partners in the Suzuki−Miyaura coupling process. However, the lack of an efficient synthesis of 8-quinolineboronic acids prevents their wide application as coupling partners in the Pd-catalyzed coupling especially on large scale. On the other hand, 8-quinolineboronic acids possess unique biological activity and chemical reactivity.[10] Therefore, it is highly desirable to develop a milder and more efficient method for synthesis of 8-quinolineboronic acids.

Scheme 1. Synthesis of 8-Arylquinolines



The transition-metal-catalyzed cross-coupling reaction of aromatic substrates with (alkoxo)diborons has attracted considerable attention as a powerful tool for the synthesis of arylboron compounds. It is known that the iridium-catalyzed C−H coupling reaction of quinoline with bis(pinacolato)diboron **2** gave 3-borylated products.[11] Therefore, we focused on Pd-catalyzed borylation, which has found wide application for efficient synthesis of aryl boronates. Although Pd-catalyzed borylation of 8-quinoline halides has been reported in the literature, low yields were observed sometimes.[12] It has been also described that dimers could form as the major products during Pd-catalyzed borylation even in the presence of a weak base such as KOAc.[13] A general and efficient method for synthesis of 8-quinolineboronic acid via Pd-catalyzed borylation is still highly desired. Recently,

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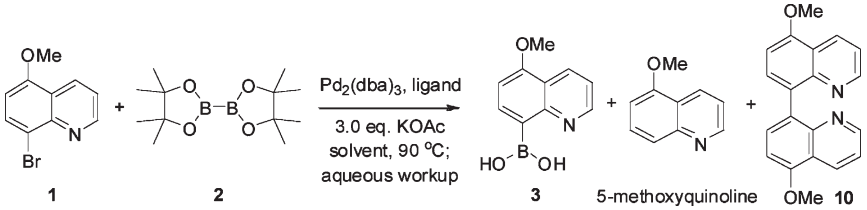
Table 1. Optimization of Reaction Conditions for Borylation of 8-Bromo-5-methoxy Quinoline with Bis(pinacolato)diboron 2[a]



entry	ligand	mol % Pd	Pd:L	solvent	time (h)	yield of **3**(%)[d]
1	dppf[b]	3		1,4-dioxane	12	68
2	dppf[b]	3		DMAc	5	33
3	$Pd(PPh_3)_4$	6		1,4-dioxane	20	72
4	S-Phos	2	1:4.0	1,4-dioxane	5	66
5	S-Phos	2	1:1.5	DMAc	6	70
6	X-Phos	2	1:1.5	DMAc	7	69
7	BI-DIME	2	1:1.5	DMAc	10	10
8	t-Bu_3P[c]	2		DMAc	1	60
9	Cy_3P	2	1:1.5	DMAc	2	77
10	n-$BuPAd_2$	2	1:1.5	1,4-dioxane	2	88
11	n-$BuPAd_2$	2	1:1.5	DMSO	2	88
12	n-$BuPAd_2$	2	1:1.5	DMF	1	90
13	n-$BuPAd_2$	2	1:1.5	DMAc	1	93 (88%)[e]
14	n-$BuPAd_2$	2	1:1.5	NMP	1	83

[a] Reaction conditions: 8-bromo-5-methoxy quinoline (0.2 g, 0.84 mmol), **2** (1.09 mmol), palladium catalyst (1−6 mol %), ligand, potassium acetate (2.52 mmol), solvent (1 mL), 90 °C, under N_2 atmosphere. Water was added to the reaction mixture after the reaction time indicated in the table. [b] $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ was used. [c] Di-μ-bromobis(tri-*tert*-butylphosphino)dipalladium(I) was used. [d] Yield determined by HPLC. [e] Number in parentheses refers to isolated yield.

we required access to 8-arylquinoline on large scale to support drug development. Herein, we report our efforts toward developing a general and efficient method for the synthesis of 8-arylquinolines via a one-pot Pd-catalyzed borylation of 8-quinoline halides and subsequent Suzuki−Miyaura coupling with aryl halides.

Our investigation commenced with optimization of Pd-catalyzed borylation of electron-rich 8-bromo-5-methoxyquinoline **1**. We first tried borylation with pinacol borane (PinB-H) under Buchwald's conditions [1.5 equiv PinB-H, 3 mol % $PdCl_2(CH_3CN)_2$, 12 mol % S-Phos, 3 equiv NEt_3, 1,4-dioxane (0.6 mL/mmol bromide)].[14] The reaction gave the debromo compound 5-methoxyquinoline as the only product. At this stage, we focused on borylation with bis(pinacolato)diboron **2**.[15] As observed on LC−MS, the borylation product was isolated as the boronic acid **3** instead of the pinacol boronate. We speculated hydrolysis of the pinacol boronate to corresponding boronic acid by water could be facilitated by an intramolecular N···HO hydrogen bond.[16] Our results are summarized in Table 1. Ligand screening indicated the application of commercially available $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ led to a slow reaction (entry 1). Even after 12 h, only 68% yield was obtained. Switching the solvent to DMAc gave lower conversion (entry 2). The borylation gave only 33% yield after 5 h. Even with 6 mol % of $Pd(PPh_3)_4$ as catalyst, the reaction was not complete and gave 72% yield after 20 h (entry 3). We speculated that the sluggish reaction might be caused by the formation of an inactive palladium complex derived from 8-diphenylphosphinoquinoline, which could form via aryl exchange.[17] Indeed, 8-diphenylphosphinoquinoline and its corresponding oxide were observed on LC−MS. The use of S-Phos and X-Phos gave moderate yield, and a significant amount of dimer 5,5′-methoxy-8,8′-bisquinoline **10** was observed (entries 4, 5, and 6).[18] The application of in-house ligand BI-DIME gave 10% yield after 10 h (entry 7). At the same time, 1.6:2.0:1.0 debromo product 5-methoxyquinoline, 8-quinolineboronic acid **2**, and 5,5′-methoxy-8,8′-bisquinoline **10** were observed on HPLC. To our delight, n-$BuPAd_2$ worked well for the borylation. The yield was 88% after 2 h when 1,4-dioxane was used as solvent (entry 10). The major byproduct observed on HPLC was 5,5′-methoxy-8,8′-bisquinoline **10**.[19] The application of other trialkylphosphines such as tri-*tert*-butyl phosphine and tricyclohexylphosphine gave inferior results due to the formation of debromo product 5-methoxyquinoline and 5,5′-methoxy-8,8′-bisquinoline **10** (entries 8 and 9). To the best of our knowledge, it was the first time that n-$BuPAd_2$ was identified as an active ligand for Pd-catalyzed borylation and exhibited high reactivity.[20] Switching the solvent to DMF or DMAc further reduced formation of dimer 5,5′-methoxy-8,8′-bisquinoline **10** and debromo product 5-methoxyquinoline and improved the yield up to 93% after 1 h (entry 13). However, the use of NMP generated more dimer **10** and gave the product 8-quinolineboronic acid **3** with 83% yield (entry 14). Considering the potential reduction capability of DMF,[21] DMAc was preferred as solvent for borylation of 8-quinoline halides.

The one-pot sequential borylation and Suzuki−Miyaura coupling protocol possesses many significant advantages.[22] It avoids the isolation and purification of boronic acids, improves the overall reaction yield, and reduces the process cost by fully utilizing expensive palladium catalyst. n-$BuPAd_2$ has been widely reported as an efficient ligand for Suzuki−Miyaura coupling in terms of productivity and activity.[23] We speculated that we could

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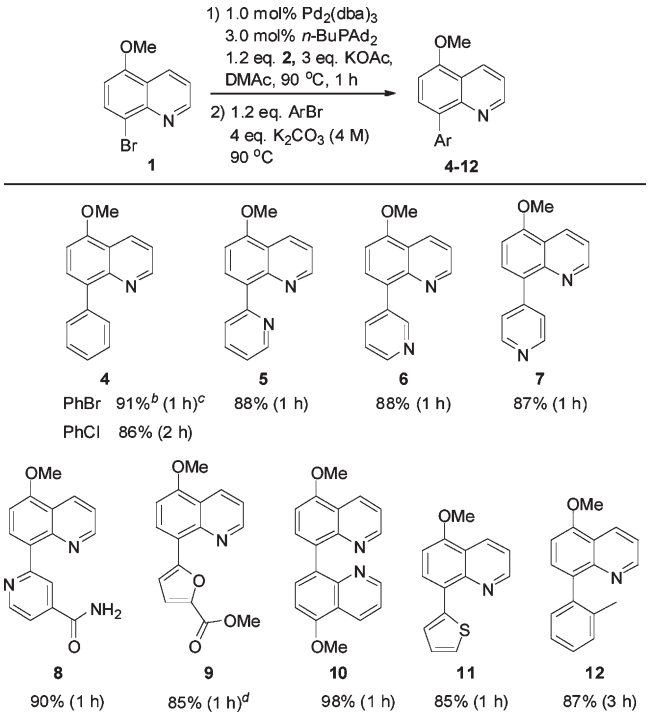
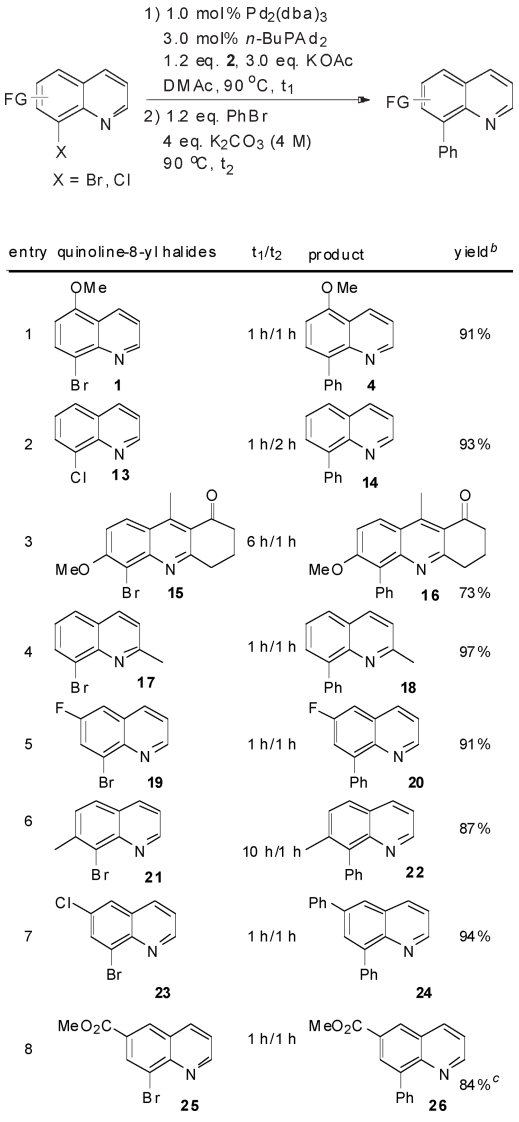
Scheme 2. Scope of One-Pot Sequential Palladium-Catalyzed Borylation and Suzuki−Miyaura Coupling Process for Synthesis of 8-Aryl-5-MeO Quinolines[a]



[a] Reaction conditions: 8-bromo-5-methoxy quinoline (0.2 g, 0.84 mmol), **2** (1.01 mmol), $Pd_2(dba)_3$ (1 mol %), *n*-BuPAd$_2$ (3 mol %), KOAc (2.52 mmol), DMAc (1 mL), 90 °C, 1 h; K_2CO_3 (4 M, 4 equiv), arylbromide or chloride (1.2 equiv), 90 °C, 1−2 h, under N_2 atmosphere. [b] Yield after chromatography on SiO_2. [c] Reaction time of Suzuki−Miyaura coupling. [d] Aqueous $NaHCO_3$ was used as base in Suzuki−Miyaura coupling.

apply the same catalyst system for subsequent Suzuki−Miyaura coupling for efficient synthesis of 8-arylquinolines. To this end, bromobenzene was subjected to Suzuki−Miyaura coupling after borylation under our optimized conditions. As shown in Scheme 2, the resulting 8-quinolineboronic acid **3** could smoothly couple with bromobenzene after introduction of aqueous potassium carbonate and gave 8-phenylquinoline **4** with 91% yield. Not surprisingly, the Suzuki−Miyaura coupling reaction also worked well for aryl chlorides considering the well-known high activity of the current catalyst system. To further delineate the scope and limitations of this protocol, more aryl and heteroaromatic halides were tested (Scheme 2). Due to the great activity of the catalyst system, the Suzuki−Miyaura coupling typically went to completion in less than 1 h. Meanwhile, thanks to the high stability of 8-quinolineboronic acid, the common protodeboronation was insignificant.[16,24] Under current conditions, the resulting 8-arylquinolines (**4**−**12**) could be isolated in good to excellent yields. In addition, this protocol avoided handling of labile boronic acids such as the notoriously unstable pyridinyl boronic acids for Suzuki−Miyaura coupling by direct use of the related halides.[25] For example, the use of 2, 3, or 4-bromopyridine gave the corresponding Suzuki−Miyaura coupling products **5**, **6**, and **7** in almost quantitative yields. Similarly, excellent yield of **8** was obtained with electron-deficient 6-bromonicotinamide. In the case of furan methyl ester, 50% yield of **9** was obtained due to ester hydrolysis in

Table 2. Scope of One-Pot Sequential Palladium-Catalyzed Borylation and Suzuki−Miyaura Coupling Process for Synthesis of 8-Arylquinolines[a]



[a] Reaction conditions: 8-bromo-5methoxy quinoline **1** (0.2 g, 0.84 mmol), **2** (1.01 mmol), $Pd_2(dba)_3$ (1 mol %), *n*-BuPAd$_2$ (3 mol %), KOAc (2.52 mmol), DMAc (1 mL), 90 °C, 1 h; K_2CO_3 (4 M, 4 equiv), aryl bromide or chloride (1.2 equiv), 90 °C, 1−2 h, under N_2 atmosphere. [b] Yield after chromatography on SiO_2. [c] Aqueous $KHCO_3$ was used as base in Suzuki−Miyaura coupling.

the presence of potassium carbonate. Switching to sodium bicarbonate improved the yield of **9** to 85%. The reaction with 2-bromothiophene also gave the desired coupling product **11** with 85% yield.[26] Of course, homocoupling product **10** could be isolated with quantitative yield under our conditions. With the sterically hindered *o*-bromotoluene, the coupling product **12** could be obtained with 87% yield after 3 h.

To define the scope and limitation of the current protocol for synthesis of 8-arylquinolines, a variety of 8-quinoline halides were subjected to our reaction conditions (Table 2). Typically, good to high yields of 8-arylquinolines could be obtained. Both electron-rich or electron-poor 8-quinoline bromides and chlorides

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worked well. Many functional groups including ketone, fluoride, and ester could be tolerated (entries 3, 5, and 8). With methoxy or methyl at the 7-position, the Suzuki−Miyaura coupling reaction took longer time, but good yields still were obtained (entries 3 and 6). With quinoline-8-yl chloride, both borylation and Suzuki−Miyaura coupling proceeded smoothly to provide 8-phenyl quinoline **14** in 93% yield (entry 2). When 6-chloro-8-bromoquinoline was used, no selectivity was observed in the presence of 1 equiv of **2**. With 2.2 equiv of **2**, the resulting 6,8-biphenylquinoline **24** could be isolated with 94% yield (entry 7).

In summary, the cross-coupling reaction of bis(pinacolato) diboron **2** and quinoline-8-yl halides in the presence of palladium/*n*-BuPAd$_2$ catalyst and potassium acetate in DMAc afforded 8-quinolineboronic acids with high yields. The utility of this method was amply demonstrated by the one-pot synthesis of 8-arylquinolines via the borylation and Suzuki−Miyaura coupling sequence. This protocol features high efficiency and simplicity for the synthesis of quinolines with an arene or heteroarene at the 8-position. Typically, good to excellent yields are obtained.

EXPERIMENTAL SECTION

General. All reactions were run in oven-dried flasks under nitrogen. Unless otherwise noted, reagents were commercially available and were used without purification. 8-Bromo-5-methoxyquinoline (**1**) and 5-bromo-6-methoxy-9-methyl-3,4-dihydroacridin-1(2*H*)-one (**15**)[27] and BIDIME[28] were synthesized following the literature procedure. HPLC conditions for reaction monitoring and quantitation: column Phenomenex Kinetex, C18, 3.0 mm × 100 mm, 2.6 μm particle size, column temperature at 35 °C, mobile phase A (0.2% H_3PO_4 in water), mobile phase B (80/20 acetonitrile/methanol), flow rate 1.0 mL min^{-1}, gradient program 3% B to 30% B in 7 min, to 85% B in 1 min, to 98% B in 0.5 min, hold at 98% B for 1.5 min, λ = 254 nm, flow rate 1.0 mL min^{-1}. The samples for HPLC were diluted with MeOH. Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR).

Experimental Procedure for Pd-Catalyzed Synthesis of 5-Methoxyquinolin-8-ylboronic Acid (3). To a dry and clean three-necked flask containing a magnetic stir bar were charged 8-bromo-5-methoxyquinoline (400 mg, 1.68 mmol), pinacol bis(pinacolato)diboron **2** (512 mg, 2.02 mmol), $Pd_2(dba)_3$ (15.4 mg, 16.8 μmol), *n*-BuPAd$_2$ (18.0 mg, 50.4 μmol), KOAc (494 mg, 5.04 mmol), and DMAc (1.5 mL) under nitrogen. Then the reaction mixture was heated at 90 °C. After 1 h, the reaction mixture was cooled to room temperature, and 40 mL of water was added slowly. The solid was collected by filtration and washed sequentially with 20 mL of water and 15 mL of toluene and then dried under vacuum to give the product **3** as a pale yellow solid (0.30 g, 88%). ^{1}H NMR (400 MHz, DMSO-d_6 and 1 drop of D_2O): δ 8.96 (dd, 1 H, J = 1.8, 4.3 Hz), 8.66 (dd, 1 H, J = 1.8, 8.4 Hz), 8.25 (d, 1 H, J = 7.8 Hz), 7.60 (dd, 1 H, J = 4.3, 8.5 Hz), 7.15 (d, 1 H, J = 8.0 Hz), 4.04 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6 and 1 drop of D_2O): δ 156.8, 152.3, 149.6, 138.7, 131.8, 120.3, 119.8, 105.2, 55.0. HRMS (ES pos): m/z calcd for $C_{10}H_{11}BNO_3^+$ (M + H$^+$) 204.0827, found 204.0838.

General Experimental Procedure for Pd-Catalyzed One-Pot Synthesis of 8-Arylquinolines. To a dry and clean three-necked flask containing a magnetic stir bar were charged quinoline-8-yl halides (0.84 mmol), pinacol bis(pinacolato)diboron (1.01 mmol, 1.2 equiv), $Pd_2(dba)_3$(1 mol %), *n*-BuPAd$_2$ (3 mol %), KOAc (2.52 mmol, 3 equiv), and DMAc (1 mL) under nitrogen. Then the reaction mixture was heated to 90 °C. After the reaction was determined to be complete by HPLC, degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol, 4 equiv) and aryl halide (1.0 mmol, 1.2 equiv) were charged. The resulting mixture was heated further for the time indicated in the text. After the reaction mixture was cooled to room temperature, water (15 mL) and EtOAc (15 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with water (15 mL) and brine (15 mL), dried over anhydrous sodium sulfate, and concentrated. Purification of the crude product by column chromatography on silica gel gave analytically pure product.

*5-Methoxy-8-phenylquinoline (**4**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), *n*-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and bromobenzene (160 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **4** as a solid (180 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (dd, 1 H, J = 1.8, 4.2 Hz), 8.67 (dd, 1 H, J = 1.8, 8.4 Hz), 7.72−7.67 (m, 3 H), 7.53−7.49 (m, 2 H), 7.44−7.41 (m, 2 H), 6.97 (d, J = 8.0 Hz, 1 H), 4.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.7, 150.4, 146.5, 139.7, 133.2, 131.0, 130.6, 130.2, 128.0, 127.0, 121.0, 120.1, 104.1, 55.8. HRMS (ES pos): m/z calcd for $C_{16}H_{14}NO^+$ (M + H$^+$) 236.1069, found 236.1076.

*5-Methoxy-8-(pyridin-2-yl)quinoline (**5**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), *n*-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and 2-bromopyridine (158 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product **5** as a solid (175 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1 H, J = 1.8,4.2 Hz), 8.75 (m, 1 H), 8.66 (dd, 1 H, J = 1.8, 8.4 Hz), 8.10 (m, 2 H), 7.78 (m, 1 H), 7.41 (m, 1 H), 7.26 (m, 1 H), 6.99 (d, 1 H, J = 8.2 Hz), 4.06 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 155.6, 150.5, 149.5, 146.5, 135.5, 131.5, 131.3, 131.1, 126.7, 121.6, 120.8, 120.1, 104.3, 55.9. HRMS (ES pos): m/z calcd for $C_{15}H_{13}N_2O^+$ (M + H$^+$) 237.1022, found 237.1032.

*5-Methoxy-8-(pyridin-3-yl)quinoline (**6**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), *n*-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and 3-bromopyridine (158 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product **6** as a solid (175 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.93 (m, 1 H), 8.89 (m, 1 H), 8.06 (dt, 1 H, J = 2.0, 7.9 Hz), 7.66 (d, 1 H, J = 8.0 Hz), 7.41 (m, 2 H), 6.95 (d, 1 H, J = 8.0 Hz), 4.05 (s, 3 H). ^{13}C NMR (100 MHz): δ 155.3, 151.0, 150.6, 148.0, 146.4, 138.1, 135.3, 131.0, 130.3, 129.4, 122.8, 121.1, 120.4, 104.2, 55.9. HRMS (ES pos): m/z calcd for $C_{15}H_{13}N_2O^+$ (M + H$^+$) 237.1022, found 237.1034.

*5-Methoxy-8-(pyridin-4-yl)quinoline (**7**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), *n*-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 1.05 mL, 4.2 mmol) and 4-bromopyridine hydrochloride (196 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product **7** as a solid (174 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (m, 1 H), 8.69 (m, 2 H), 8.66 (dd, 1 H, J = 1.8, 8.4 Hz) 7.68 (d, 1 H, J = 8 Hz), 7.65 (m, 2 H), 7.44 (dd, 1 H, J = 4.2, 8.5 Hz), 6.96 (d, 1 H,

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J = 8.0 Hz), 4.07 (s, 3 H). ^{13}C NMR (100 MHz): δ 155.8, 150.7, 149.5, 147.5, 146.2, 131.1, 130.5, 130.2, 125.4, 121.0, 120.5, 104.1, 55.9. HRMS (ES pos): m/z calcd for $C_{15}H_{13}N_2O^+$ (M + H$^+$) 237.1022, found 237.1031.

*2-(5-Methoxyquinolin-8-yl)isonicotinamide (**8**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and 2-bromoisonicotinamide (202 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 20% EtOAc/hexanes) afforded the product **8** as a pale yellow solid (213 mg, 90%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.98 (dd, 1 H, J = 1.8, 4.2 Hz), 8.81 (d, 1 H, J = 4.0 Hz), 8.65 (dd, 1 H, J = 1.6, 8.4 Hz), 8.50 (bs, 1 H), 8.23 (s, 1 H), 8.13 (d, 1 H, J = 8.2 Hz), 7.73 (dd, 1 H, J = 1.6, 6.7 Hz), 7.70 (bs, 1 H), 7.60 (dd, 1 H, J = 4.1, 8.5 Hz), 7.24 (d, 1 H, J = 8.4 Hz), 4.07 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.9, 157.1, 155.3, 150.7, 149.6, 145.6, 140.7, 131.6, 130.6, 130.0, 124.4, 120.7, 119.8, 119.2, 104.9, 56.1. HRMS (ES pos): m/z calcd for $C_{16}H_{14}N_3O_2^+$ (M + H$^+$) 280.1080, found 280.1085.

*Methyl 5-(5-Methoxy quinolin-8-yl)furan-2-carboxylate (**9**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with 9% degassed aqueous $NaHCO_3$ (3.14 g, 3.36 mmol) and methyl 5-bromo-2-fumorate (205 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **9** as a solid (213 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.05 (m, 1H), 8.62 (dd, 1 H, J = 1.8, 8.5 Hz), 8.23 (d, 1 H, J = 8.4 Hz), 7.76 (d, 1 H, J = 3.6 Hz), 7.63 (dd, 1 H, J = 4.2, 8.5 Hz), 7.46 (d, 1 H, J = 3.6 Hz), 7.23 (d, 1 H, J = 8.4 Hz), 4.06 (s, 3 H), 3.87 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.5, 155.4, 154.7, 151.0, 144.5, 141.7, 130.8, 127.9, 121.1, 120.5, 120.1, 119.1, 112.7, 105.1, 56.2, 51.7. HRMS (ES pos): m/z calcd for $C_{16}H_{14}NO_4^+$ (M + H$^+$) 284.0917, found 284.0932.

*5,5′-Dimethoxy-8,8′-biquinoline (**10**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol) and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and 8-bromo-5-methoxyquinoline (238 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 30% EtOAc/hexanes) afforded the product **10** as a solid (258 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.65 (d, 1 H, J = 2.3 Hz), 8.59 (d, 1 H, J = 8.5 Hz), 7.63 (d, 1 H, J = 7.9 Hz), 7.46 (m, 1H), 7.15 (d, 1H, J = 7.8 Hz), 4.1 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 154.0, 149.8, 147.5, 131.4, 131.1, 130.0, 120.2, 119.7, 104.3, 55.9. HRMS (ES pos): m/z calcd for $C_{20}H_{17}N_2O_2^+$ (M + H$^+$): 317.1284, found 317.1292.

*5-Methoxy-8-(thiophen-2-yl)quinoline (**11**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and 2-bromothiophene (163 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **11** as a solid (258 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.00 (dd 1 H, J = 1.8, 4.2 Hz), 8.61 (dd, 1 H, J = 1.8, 8.4 Hz), 7.94 (d, 1 H, J = 8.2 Hz), 7.65 (m, 1 H), 7.41 (m, 2 H), 7.17 (m, 1 H), 6.88 (d, 1 H, J = 1.3, 8.2 Hz), 4.01 (d, 3 H, J = 1.2 Hz). ^{13}C NMR (100 MHz): δ 154.6, 150.0, 145.4, 140.3, 131.0, 128.4, 126.5, 126.5, 125.7, 125.6, 120.9, 120.3, 104.3, 55.8. HRMS (ES pos): m/z calcd for $C_{14}H_{12}NOS^+$ (M + H$^+$) 242.0634, found 242.0642.

*5-Methoxy-8-o-tolylquinoline (**12**).* The general procedure above was followed, using 8-bromo-5-methoxyquinoline (200 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and 1-bromo-2-methylbenzene (171 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **12** as a solid (182 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (m 1 H), 8.61 (m, 1 H), 7.47 (d, 1 H, J = 7.8 Hz), 7.35−7.28 (m, 5 H), 6.89 (d, 1 H, J = 8.0 Hz), 4.0 (s, 3 H), 2.04 (s, 3 H). ^{13}C NMR (100 MHz): δ 154.7, 150.6, 147.2, 140.1, 137.4, 133.6, 130.8, 130.6, 130.2, 129.8, 127.5, 125.5, 120.8, 120.0, 103.9, 55.8, 20.6. HRMS (ES pos): m/z calcd for $C_{17}H_{16}NO^+$ (M + H$^+$) 250.1226, found 250.1230.

*8-Phenylquinoline (**14**).* The general procedure above was followed, using 8-chloroquinoline (200 mg, 1.22 mmol), pinacol bis(pinacolato)-diboron (373 mg, 1.47 mmol), $Pd_2(dba)_3$ (11.2 mg, 12.2 μmol), n-BuPAd$_2$ (13.1 mg, 36.7 μmol), KOAc (360 mg, 3.67 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and bromobenzene (230 mg, 1.47 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **14** as a pale yellow oil (233 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (dd, 1 H, J = 1.8, 4.2 Hz), 8.03 (dd, 1 H, J = 1.7, 8.3 Hz), 7.70−7.64 (m, 4 H), 7.49−7.43 (m, 3 H), 7.36 (m, 1H), 7.24 (m, 1 H). ^{13}C NMR (100 MHz): δ 150.4, 146.2, 141.0, 139.8, 136.4, 130.9, 130.5, 128.9, 128.2, 127.7, 127.6, 126.4, 121.1. HRMS (ES pos): m/z calcd for $C_{15}H_{12}N^+$ (M + H$^+$) 206.0964, found 206.0975.

*6-Methoxy-9-methyl-5-phenyl-3,4-dihydroacridin-1(2H)-one (**16**).* The general procedure above was followed, using 5-bromo-6-methoxy-9-methyl-3,4-dihydroacridin-1(2H)-one (269 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and bromobenzene (160 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **16** as a solid (258 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, 1 H, J = 9.44 Hz), 7.47−7.25 (m, 6 H), 3.91 (s, 3 H), 3.07−3.05 (m, 5H), 2.73 (t, 2 H, J = 8.0 Hz), 2.10 (t, 2 H, J = 8.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 162.6, 158.3, 149.5, 147.3, 135.0, 131.9, 127.3, 126.8, 126.5, 125.9, 123.4, 122.8, 113.2, 56.4, 41.2, 35.2, 21.4, 16.2. HRMS (ES pos): m/z calcd for $C_{21}H_{20}NO_2^+$ (M + H$^+$): 318.1488, found 318.1489.

*2-Methyl-8-phenylquinoline (**18**).* The general procedure above was followed, using 8-bromo-2-methylquinoline (187 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and bromobenzene (160 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **18** as a pale yellow oil (179 mg, 97%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.04 (d, 1 H, J = 8.4 Hz), 7.79−7.69 (m, 4 H), 7.52−7.45 (m, 3 H), 7.40−7.36 (m, 1 H), 7.26 (d, 1 H, J = 8.4 Hz), 2.67 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 158.7, 145.5, 139.9, 140.0, 136.2, 131.1, 130.3, 127.8,

127.3, 127.1, 127.0, 125.4, 121.8, 25.8. HRMS (ES pos): m/z calcd for $C_{16}H_{14}N^+$ (M + H$^+$): 220.1120, found 220.1132.

*6-Fluoro-8-phenylquinoline (**20**).* The general procedure above was followed, using 8-bromo-6-fluoroquinoline (190 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and bromobenzene (160 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **20** as a pale yellow oil (171 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.90 (dd, 1 H, J = 4.1, 4.1 Hz), 8.13 (dd, 1 H, J = 1.8, 8.3 Hz), 7.70−7.67 (m, 2 H), 7.53−7.47 (m, 3 H), 7.45−7.39 (m, 3 H). ^{13}C NMR (100 MHz): δ 161.1, 158.7, 149.5, 149.5, 143.8, 143.3, 138.4, 138.4, 135.7, 135.7, 130.6, 130.5, 129.7, 129.6, 128.2, 128.1, 128.1, 128.0, 121.7, 120.3, 120.1, 110.2, 110.0. HRMS (ES pos): m/z calcd for $C_{15}H_{11}FN^+$ (M + H$^+$) 224.0870, found 224.0880.

*7-Methyl-8-phenylquinoline (**22**).* The general procedure above was followed, using 8-bromo-7-methylquinoline (187 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (256 mg, 1.01 mmol), $Pd_2(dba)_3$ (7.7 mg, 8.4 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 0.84 mL, 3.36 mmol) and bromobenzene (160 mg, 1.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **22** as a solid (160 mg, 87%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.84 (dd, 1 H, J = 1.8, 4.2 Hz), 8.11 (dd, 1 H, J = 1.8, 8.2 Hz), 7.73 (d, 1 H, J = 8.4 Hz), 7.51−7.46 (m, 3 H), 7.42−7.38 (m, 1 H), 7.32−7.27 (m, 3 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 150.3, 147.3, 139.8, 139.1, 137.4, 135.7, 130.2, 129.4, 128.1, 127.0, 126.8, 126.7, 120.0, 21.2. HRMS (ES pos): m/z calcd for $C_{16}H_{14}N^+$ (M + H$^+$) 220.1120, found 220.1131.

*6,8-Diphenylquinoline (**24**).* The general procedure above was followed, using 8-bromo-6-chloroquinoline (212 mg, 0.84 mmol), pinacol bis(pinacolato)diboron (512 mg, 2.02 mmol), $Pd_2(dba)_3$ (15.4 mg, 16.8 μmol), n-BuPAd$_2$ (9.0 mg, 25.2 μmol), KOAc (247 mg, 2.52 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with degassed aqueous K_2CO_3 (4 M, 1.68 mL, 6.72 mmol) and bromobenzene (320 mg, 2.0 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **24** as a pale yellow oil (160 mg, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (dd, 1 H, J = 1.3, 4.1 Hz), 8.26 (dd, 1 H, J = 1.7, 8.3 Hz), 8.01 (bs, 2 H), 7.77−7.74 (m, 4 H), 7.54−7.49 (m, 4 H),7.45−7.39 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 145.5, 141.4, 140.3, 139.6, 139.0, 136.5, 130.7, 130.2, 129.1, 129.0, 128.1, 127.8, 127.6, 127.5, 125.1, 121.4. HRMS (ES pos): m/z calcd for $C_{21}H_{16}N^+$ (M + H$^+$) 282.1277, found 282.1279.

*Methyl 8-Phenylquinoline-6-carboxylate (**26**).* The general procedure above was followed, using methyl 8-bromoquinoline-6-carboxylate (266 mg, 1.0 mmol), pinacol bis(pinacolato)diboron (305 mg, 1.2 mmol), $Pd_2(dba)_3$ (9.2 mg, 10 μmol), n-BuPAd$_2$ (10.8 mg, 30 μmol), KOAc (294 mg, 3.0 mmol), and DMAc (1 mL). After the reaction was determined to be complete by HPLC, the reaction mixture was further treated with 25% degassed aqueous $KHCO_3$ (1.60 g, 4 mmol) and bromobenzene (188 mg, 1.2 mmol). Column chromatography on silica gel (eluting with 10% EtOAc/hexanes) afforded the product **26** as a solid (221 mg, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (dd, 1 H, J = 1.8, 4.2 Hz), 8.58 (d, 1 H, J = 1.9 Hz), 8.33 (d, 1 H, J = 2.0 Hz), 8.30 (dd, 1 H, J = 1.8, 8.3 Hz), 7.72−7.70 (m, 2 H), 7.53−7.43 (m, 4 H), 4.0 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.7, 152.3, 147.9, 141.4, 138.8, 137.6, 130.6, 130.4, 129.7, 128.1, 128.0, 127.8, 127.7, 52.5. HRMS (ES pos): m/z calcd for $C_{17}H_{14}NO_2^+$ (M + H$^+$) 264.1019, found 264.1027.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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