Synthesis M. Md M. Hassan et al. Special Topic

Iridium-Catalyzed Site-Selective Borylation of 8-Arylquinolines

Mirja Md Mahamudul Hassan[a]
Md Emdadul Hoque[a]
Sayan Dey[a]
Saikat Guria[a]
Brindaban Roy[b]
Buddhadeb Chattopadhyay*[a]

[a] Center of Bio-Medical Research, Division of Molecular Synthesis & Drug Discovery, SGPGIMS Campus, Raebareli Road, Lucknow 226014, Uttar Pradesh, India
buddhadeb.c@cbmr.res.in
buddhachem12@gmail.com
[b] University of Kalyani, Chemistry Department, Kalyani, Nadia, 741235, West Bengal, India

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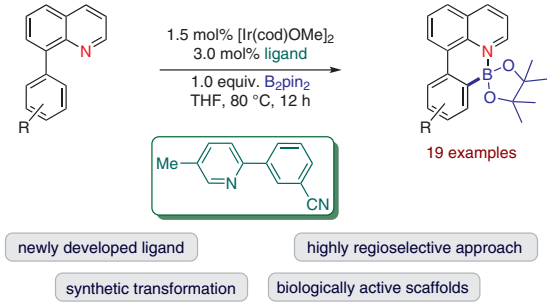

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Abstract We report a convenient method for the highly site-selective borylation of 8-arylquinoline. The reaction proceeds smoothly in the presence of a catalytic amount of $[Ir(OMe)(cod)]_2$ and 2-phenylpyridine derived ligand using bis(pinacolato)diborane as the borylating agent. The reactions occur with high selectivity with many functional groups, providing a series of borylated 8-aryl quinolines with good to excellent yield and excellent selectivity. The borylated compounds formed in this method can be transformed into various important synthons by using known transformations.

Key words borylation, C–H activation, ligand design, 8-arylquinoline, synthetic transformations

The quinoline heterocycle is an important structural motifs in many drugs and biologically active compounds as well as in many fields of chemistry, including molecular electronics and dyes.[1–3] Given the various applications, it is often necessary to synthesize diversely functionalized quinoline heterocycles.[4] Classically, the parent quinoline ring is synthesized from the corresponding anilines.[5] The classical methods offer a variety of substituted quinolines but they suffer from multistep process, harsh reaction conditions and low overall yield of the functionalized products.[6] In order to develop milder reaction conditions, transition-metal-catalyzed site-selective C–H functionalization[7] can be a suitable alternative. In recent years, several methods using Rh,[8] Pd,[9] Cu,[10] Ni,[11] and Ag[12] catalysts have been developed for the regioselective C–H functionalization of quinoline derivatives, which are mainly functionalized at the C2 position. Some metal-free approaches have also been developed for the C2-H functionalization.[13] On the other hand, regioselective C–H bond activation and functionalization of 8-arylquinoline heterocycles are less explored.[14] Moreover, there is only one report of quinoline-directed *ortho*-olefination[15] of 8-aryl quinolines, despite being a very important scaffold in many biologically active compounds, as well as in the aza BINOL atroposelective family (Figure 1).[16]

Thus, it would be intriguing to develop an alternative method that would solve some of the aforementioned issues.

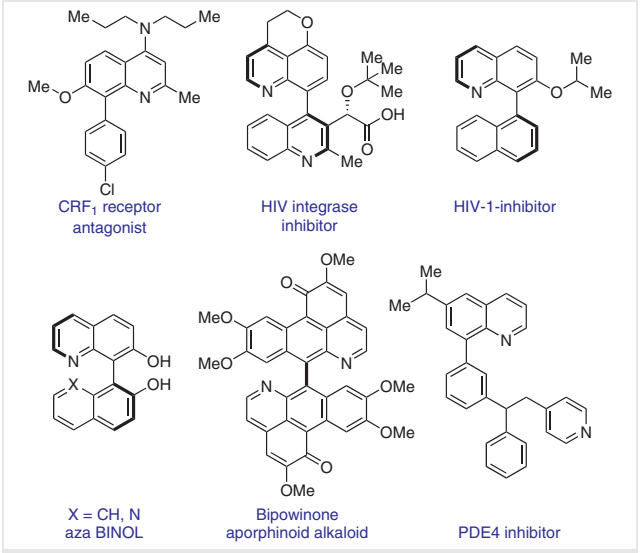
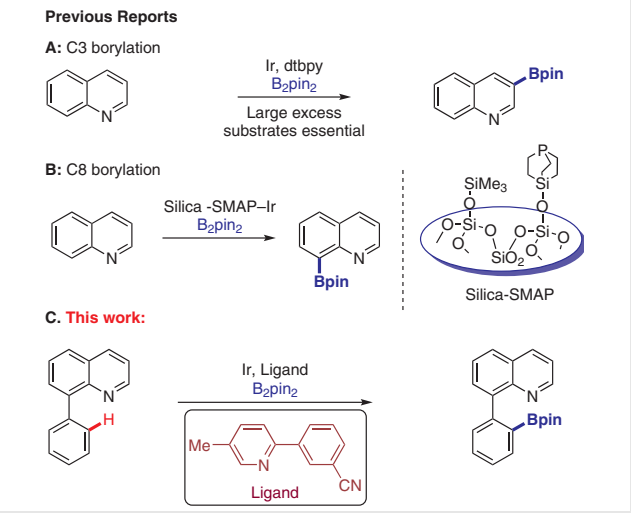


Figure 1 Biologically active compounds

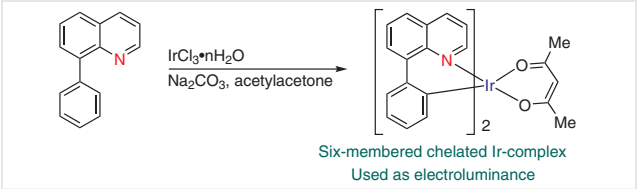
Among various C–H functionalization reactions, iridium-catalyzed C–H borylation[17] has evolved as a potential arene/heteroarene functionalization method considering its mild reaction conditions, compatibility with various functional groups and versatile synthetic transformation of the C–B bonds.[18] However, the main drawback of the C–H borylation of arenes is the site-selectivity, which is largely controlled by steric effects.[17] During last two decades, several research groups have developed many powerful strate-

gies for the directed site-selective *ortho*-borylation of functionalized arenes and heteroarenes. A wide range of directing groups have been implemented for the directed borylation of arenes and heteroarenes, including carbonyls,[19] various nitrogen-containing directing groups,[20] silanes,[21] thianes,[22] and ethers.[23] Simultaneously, borylation of unsubstituted and diversely substituted quinolines was also well studied. In 2002, Ishiyama, Miyaura, Hartwig, and others reported[24] iridium-catalyzed C3-selective borylation of quinoline (Scheme 1A) in the presence of bidentate 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbpy) ligand with a large excess of substrate (10 equivalent). After that, Marder and Steel reported[25] guidelines for achieving site-selective C2, C4, C6 and C7 borylation of disubstituted quinolines. Later, Sawamura and Marder reported C8-selective borylation of quinoline by using their developed[26,27] Silica-SMAP ligand (Scheme 1B). Surprisingly, borylation of 8-aryl quinolones has not yet been developed. Herein, we report a method for the directed *ortho*-selective C–H activation and borylation of 8-arylquinolines using $[Ir(OMe)(cod)]_2$ and a new type of 2-phenylpyridine ligand framework containing a nitrile group. It has been demonstrated that the developed catalytic system is highly effective for the borylation of a wide range of quinolines and the borylated products can be isolated with high isolated yields (Scheme 1C).



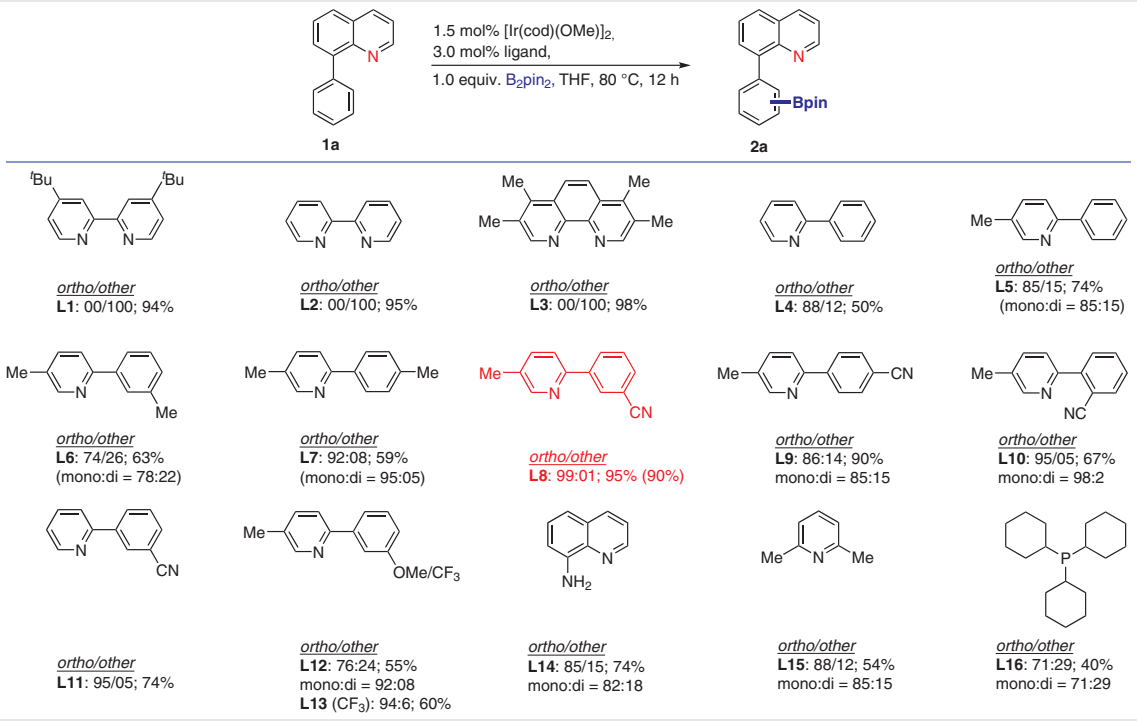
Scheme 1 Previous reports and present development

In 2005, the Liu group reported[28] an interesting work related to 8-phenylquinoline in which they studied the photophysical properties of six-membered chelated iridium complexes (Scheme 2). Inspired by this work, we hypothesized that in the presence of a suitable ligand system, iridium-metal can activate the *ortho*-C–H bond of (8-quinoryl)arenes via directed coordination. So with this hypothesis, we can develop a C–H activated species of (8-quinoryl)arenes for borylation that can be utilized for site-selective C–H functionalization of 8-arylqunoline derivatives.



Scheme 2 Previous report of six-membered iridium chelated complex

We first tested the borylation of 8-arylquinolones with different ligand scaffolds to optimize the reaction conditions (Scheme 3). We started our initial investigation with substrate **1a** with conventional 4,4′-di-*tert*-butyl bipyridine (**L1**) ligand[29] at 80 °C, which gave non-selective borylation with B_2pin_2 (1.0 equiv). Diborylation at the C3- and C5-positions dominated, with other unidentified borylated products being formed. Other similar types of ligands such as **L2** and **L3** also resulted in similar outcomes. The lack of selectivity with these ligands may be attributed to the strong coordinating ability of these ligands, with the iridium tris boryl complex generated in situ unable to give selective borylation as it resulted in sterically directed borylation to the sterically less hindered C–H bond of the compound.[25,30] In contrast, employment of 2-phenylpyridine (**L4**) as a ligand gave a very encouraging outcome as it resulted in 88% *ortho*-selective borylation with 50% conversion of **1a**. With these interesting results, we started screening a range of 2-phenylpyridine derivatives and found that ligand **L5** gave better conversion with the same type of selectivity with varying amounts of diborylated product. We thought that changing the electronics of the 2-phenyl pyridine ligand systems may result in better outcomes. Towards this end, screening **L7**, containing a methyl group at the 4-position of the phenyl group, gave better selectivity, but the conversion was compromised. Remarkably, when the reaction was performed with a newly designed ligand **L8**, we observed that the borylation proceeded smoothly, affording 95% product conversion and 99% *ortho*-selectivity. However, the use of other ligand frameworks such as **L9** and **L10**, gave less conversion than with **L8** and moderate *ortho*-selectivity. To study the electronic effects of the 5-methyl group, ligand **L11** was employed and it was found to be less effective towards *ortho*-borylation of 8-phenylquinoline. An electron-donating group (-OMe) (**L12**) at the 3-position of the phenyl ring gave lower selectivity, while ligand **L13**, containing an electron-withdrawing $-CF_3$ group, gave higher selectivity. It is assumed that the electronics of the nitrile group of the ligand may have influenced the selectivity, but the precise role of the nitrile group of the ligand is not yet clear. Next, to see the effect of hemilabile ligand, 8-aminoquinoline (**L14**) was tested in the borylation reaction; however, this ligand system was not as suitable as the **L8** system. Moreover, use of monodentate ligands such as **L15** and **L16** also failed to give improved outcomes.



Scheme 3 Ligand screening and reaction optimization. All reactions were conducted on 0.2 mmol scale, GC/MS ratios and conversion are given. Isolated yields are given in parentheses. The ratio of *ortho*/other = *ortho*/(quinoline ring borylation). [a] Without ligand conversion 40% and *ortho*/other 99:1. [b] Reaction with HBpin (conversion 59% and *ortho*/others 99:1)

For further optimization, it was found that among the iridium pre-catalysts, $[Ir(cod)OMe]_2$ was effective towards *ortho* borylation of 8-arylquinoline, while $[Ir(coe)_2Cl]_2$ failed to give the product and $[Ir(cod)Cl]_2$ gave less conversion (see the Supporting Information for details).

Thus, encouraged by the development of new ligand systems based on the 2-phenylpyridine framework containing a nitrile group (**L8**), we tested a range of substituted 8-arylquinolines under the optimized reaction conditions (Scheme 4). It has been noticed that 2-substituted substrates containing fluoro compounds (**1b**)[31] gave good isolated yields without giving other isomers but other substrates (e.g., 2-phenyl) failed to give the product under identical conditions. When we explored the use of substrates bearing a 3-substituted group on the aryl ring, such as methyl (**1c**), trifluoromethyl (**1d**), nitrile (**1e**), and chloro (**1f**), we found that in all cases a single isomer was isolated with good yield. Although there are possibilities for the formation of another *ortho*-isomers, steric hindrance suppressed their formation.

We also observed that 4-substituted 8-arylquinolines were excellent substrates for the borylation reactions, providing the corresponding borylated products in good yields. Substrates containing methyl (**1g**), trifluoromethyl (**1h**), cyano (**1i**), chloro (**1j**), fluoro (**1k**), and phenyl (**1l**) gave almost exclusively a single *ortho*-isomer without any diborylated products. The disubstituted substrates containing 2,4-difluoro (**1m**), 3,4-difluoro (**1n**), and 3-fluoro-4-phenyl (**1p**) afforded *ortho*-borylation without loss of selectivity. The developed reaction conditions tolerated substrates containing ester functionality (**1q**) and gave one regioisomer with respect to the quinoline moiety.

In this context, it deserves mentioning that all the borylated products exhibited strong B–N interactions, with ^{11}B NMR signals ranging from 7–10 ppm compared to the ^{11}B NMR shift of ~31 ppm for borylated substrates without any boron heteroatom coordination (Figure 2). Whereas the borylated 2-phenylpyridine showed an NMR shift of ~13.7 ppm,[32] indicating the B–N coordination, but, compound **2a** showed relatively high B–N coordination, which may be due to the rigid conformation.

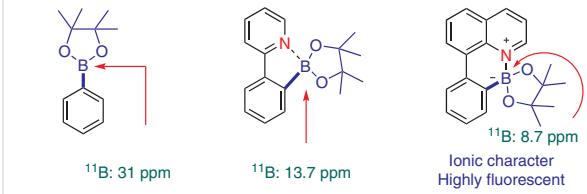
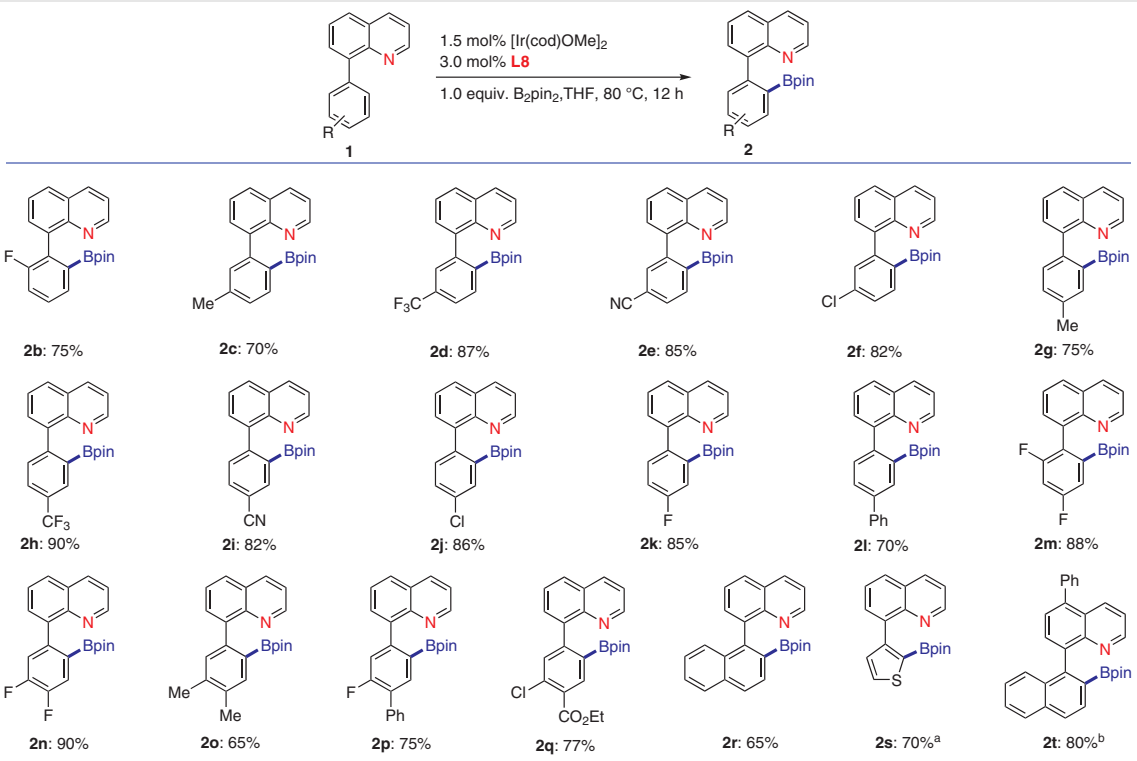


Figure 2 Characteristic B–N coordination

With this strong B–N coordination, the borylated 8-arylquinoline product behaved like an ionic compound and showed fluorescent behavior.[33] The naphthalene-contain-



Scheme 4 Selective *ortho*-borylation of substituted 8-arylquinolines. All reactions were conducted at 0.3 mmol scale. Isolated yields are reported. [a] 10% *ortho*,*ortho*-diborylated product. [b] NMR conversion reported.

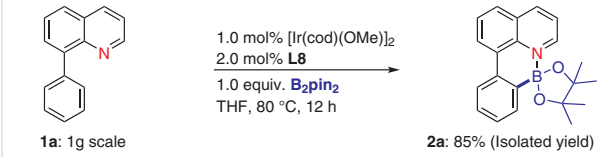
ing compound **2r** showed a boron NMR shift of ~31 ppm, which indicates that the compound does not involve B–N coordination. The lack of B–N coordination may be attributed to a rotational barrier between the naphthalene and quinoline moieties, with a sterically crowded and stable conformation that disallowed B–N coordination. Another interesting example is substrate **1s**, containing a thiophene ring, which gave excellent site-selective borylation at the C2-position of the thiophene ring, with a minor amount of *ortho,ortho* diborylated product. Substrate **1t**, with phenyl groups at both the C8- and C5-positions of the quinolone ring also afforded 80% conversion through directed borylation at the C-8 ring (Scheme 4).

To show the practical utility of the developed reaction conditions, a gram-scale reaction was performed with substrate **1a**, using lower catalyst loading, which gave the corresponding borylated product **2a** in 85% isolated yield (Scheme 5).

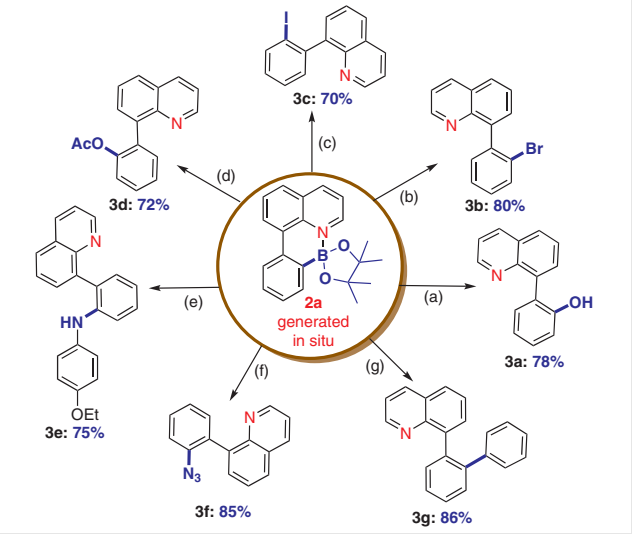
Further synthetic utility of our borylated methodology was demonstrated by transforming *ortho*-borylated 8-phenylquinoline **2a** into a wide array of other important functionalities. Such transformations may produce new chemical entities and expand the scope of drug discovery.

To showcase the utility of the approach, we transformed the borylated product generated in situ into a range of other important functionalities. Thus, **2a** was converted into 2-(quinolin-8-yl)phenol **3a** in 78% isolated yield by treatment with $NaBO_3$. We then showed that Cu-catalyzed bromination (**3b**) and iodination (**3c**) could also be performed. By using one equivalent of $Cu(OAc)_2$, acetylation reaction afforded 72% yield of the corresponding product **3d**. The Cu-catalyzed Chan–Lam coupling of compound **2a**, generated in situ, with 4-ethoxyaniline gave the aminated quinoline scaffold (**3e**) that is known to be a family of active drugs. Moreover, a Cu-catalyzed azidation reaction has also been demonstrated that gave 85% isolated yield of **3f**. Furthermore, the synthetic utility of the developed reaction conditions has been demonstrated by a Suzuki–Miyura cross-coupling reaction that afforded the corresponding compound (**3g**) with good isolated yield (Scheme 6).

The standard iridium-catalyzed borylation reaction mechanism with strong bidentate ligand has been known[30] for a long time. We believed that our reaction might either also follow the same catalytic cycle or proceed via a bis-



Scheme 5 Large-scale synthesis



Scheme 6 Further transformations. *Reagents and conditions*: (a) $NaBO_3·4H_2O$ (3.0 equiv), THF/H_2O (1:1), r.t., 3 h; (b) $CuBr_2$ (3.0 equiv), $MeOH/H_2O$ (1:1), 80 °C, 12 h; (c) ICl (1.5 equiv), CH_2Cl_2, r.t., 2 h; (d) $Cu(OAc)_2$ (1.0 equiv), MeCN/EtOH (20:1), 80 °C, 6 h; (e) $Cu(OAc)_2$ (1.0 equiv), Et_3N (2.0 equiv), 4-ethoxyaniline (2.0 equiv), MeCN/EtOH (20:1), 80 °C, 24 h; (f) NaN_3 (1.5 equiv), $Cu(OAc)_2$, MeOH, 55 °C, 12 h; (g) bromobenzene (1.0 equiv), $pd(pph_3)_4$ (2.0 mol%), K_2CO_3 (2.0 equiv), DME/H_2O (2:1), 100 °C, 12 h.

borylated Ir(III) complex intermediate.[19f] Further mechanistic investigations to elucidate the exact mechanism are in progress.

In summary, we have developed a general method for the directed *ortho*-borylation of 8-arylquinoline catalyzed by $[Ir(OMe)(cod)]_2$ and 2-phenyl derived ligand containing nitrile group at the C3 position of the phenyl ring. The developed method offers a new strategy for the synthesis of a diverse range of *ortho*-borylated 8-aryl quinoline with high functional group tolerance. The developed ligand can be synthesized in a single, scalable step and the reaction shows excellent reactivity and selectivity for 8-aryl quinoline. The synthetic utility of this strategy was further extended by applying the borylated materials in a one-pot transformation to various valuable synthons through hydroxylation, azidation, amination and other reactions. We anticipate that the developed method will find wide application in C–H functionalization chemistry and allied fields of research.

All commercially available chemicals were used as received unless otherwise indicated. Pinacolborane (HBpin) and bis(pinacolato)diboron (B_2pin_2) were procured from A. K. Scientific. Bis(1,5-cyclooctadiene)di-μ-methoxy-diiridium(I)($[Ir(OMe)(cod)]_2$) was procured from Sigma–Aldrich. Tetrahydrofuran (THF) was heated at reflux over sodium/benzophenone ketyl, distilled and degassed twice before reaction. Dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) was distilled over CaH_2. Column chromatography was performed on flash silica gel (ACME) and basic alumina. Thin-layer chromatography was performed on 0.25 mm thick aluminum-backed silica gel plates purchased from Merck and visualized with ultraviolet light (λ = 254 nm). ^1H, ^{13}C and ^{11}B NMR spectra were recorded with a Bruker 400 MHz NMR spectrometer.

All coupling constants (*J*) are apparent, *J* values were measured at the indicated field strengths in Hertz (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, bs = broad singlet, dt = doublet of triplet, td = triplet of doublet, ddd = doublet of doublets of doublets). High-resolution mass spectra (HRMS) were obtained at the Centre of Biomedical Research Mass Spectrometry Service Center with a Waters GCT Premier instrument run on electron ionization (EI) direct probe or a Waters QTOF Ultima instrument run on electrospray ionization (ESI). GC/MS (Agilent Technology) was obtained from the Centre of Biomedical Research Institute and for the analysis RAM temperature was used at 50 °C for each sample.

The preparation of starting materials **1a–s**, ligands and reaction optimizations are described in the Supporting Information.

Typical Procedure

In an argon-filled glove box, a 5.0 mL Wheaton microreactor was charged with $[Ir(cod)OMe]_2$ (3.0 mg, 1.5 mol%), ligand (1.74 mg, 3.0 mol%), B_2pin_2 (76.2 mg, 1.0 equiv), and anhydrous THF (1.0 mL) sequentially. The mixture was stirred for 5 minutes at r.t., then 8-arylquinoline **1a–s** (0.3 mmol) was added. The microreactor was capped with a Teflon pressure cap and placed into a preheated aluminum block at 80 °C. The reaction mixture was stirred for 12 h. After completion (monitored by GC-MS), THF was removed under reduced pressure and chromatographic separation with silica gel (EtOAc) gave borylated compounds **2a–t**.

8-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2a)

Yield: 89.4 mg (90%); light-yellow solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 4.8 Hz, 1 H), 8.49 (d, *J* = 8.0 Hz, 1 H), 8.43 (d, *J* = 7.2 Hz, 1 H), 7.94–7.96 (m, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.73–7.78 (m, 2 H), 7.66 (dd, *J* = 7.6, 5.2 Hz, 1 H), 7.34–7.39 (m, 2 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4, 141.8, 139.8, 135.9, 133.1, 131.4, 129.4, 128.7, 127.9, 127.6, 127.2, 126.8, 124.9, 120.0, 80.6, 26.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{23}BNO_2$: 332.1816; found: 332.1818.

8-(2-Fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2b)

Yield: 78.6 mg (75%); white solid.

^1H NMR (400 MHz, $CDCl_3$): δ = 9.50 (d, *J* = 4.4 Hz, 1 H), 8.61 (d, *J* = 7.6 Hz, 1 H), 8.48 (d, *J* = 7.6 Hz, 1 H), 7.87 (d, *J* = 8.0 Hz, 1 H), 7.75 (q, *J* = 7.6 Hz, 2 H), 7.65 (dd, *J* = 8.4, 5.2 Hz, 1 H), 7.38–7.33 (m, 1 H), 7.06 (q, *J* = 8.0 Hz, 1 H), 1.15 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.45 (d, *J* = 252.5 Hz), 145.7, 141.5, 140.3, 132.8 (d, *J* = 17.2 Hz), 129.9 (d, *J* = 8.5 Hz), 129.3 (d, *J* = 3.6 Hz), 129.2, 128.5, 127.3 (d, *J* = 3.2 Hz), 127.2, 124.1 (d, *J* = 5.1 Hz), 120.1, 115.4 (d, *J* = 24.4 Hz), 81.1, 26.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 10.6.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{22}BFNO_2$: 350.1728; found: 350.1726.

8-(5-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2c)

Yield: 72.5 mg (70%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.56 (d, *J* = 4.4 Hz, 1 H), 8.45 (d, *J* = 8.4 Hz, 1 H), 8.40 (d, *J* = 7.2 Hz, 1 H), 7.83 (dd, *J* = 11.6, 8.4 Hz, 2 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.63 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.59 (s, 1 H), 7.20 (d, *J* = 7.2 Hz, 1 H), 2.40 (s, 3 H), 1.20 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 141.7, 140.3, 136.7, 136.3, 133.6, 131.7, 129.5, 128.9, 128.7, 127.7, 126.8, 125.9, 120.1, 80.7, 26.7, 21.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 9.8

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}BNO_2$: 346.1978; found: 346.1982.

8-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(trifluoromethyl)phenyl)quinoline (2d)

Yield: 104.2 mg (87%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (d, *J* = 4.4 Hz, 1 H), 8.57 (d, *J* = 7.6 Hz, 1 H), 8.52 (d, *J* = 7.6 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 8.02 (s, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 7.84 (t, *J* = 8.0 Hz, 1 H), 7.75 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.60 (d, *J* = 7.6 Hz, 1 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8, 142.5, 139.7, 136.2, 132.0, 131.7, 129.6 (q, *J* = 32.1 Hz), 129.6, 129.1, 128.2, 127.9, 124.9 (q, *J* = 268.2 Hz), 124.3 (q, *J* = 3.7 Hz), 121.5 (q, *J* = 4.1 Hz), 120.5, 81.0, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}BF_3NO_2$: 400.1696; found: 400.1693.

3-(Quinolin-8-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (2e)

Yield: 90.8 mg (85%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 4.8 Hz, 1 H), 8.59 (d, *J* = 8.0 Hz, 1 H), 8.45 (d, *J* = 7.6 Hz, 1 H), 8.05–8.03 (m, 2 H), 7.97 (d, *J* = 8.4 Hz, 1 H), 7.83 (t, *J* = 8.0 Hz, 1 H), 7.77 (dd, *J* = 7.6, 5.2 Hz, 1 H), 7.62 (d, *J* = 7.6 Hz, 1 H), 1.21 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 142.7, 139.4, 136.7, 132.2, 130.8, 130.7, 129.6, 129.1, 128.4, 128.3, 128.3, 120.7, 119.9, 111.0, 81.1, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 7.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}BN_2O_2$: 357.1774; found: 357.1782.

8-(5-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2f)

Yield: 89.9 mg (82%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, *J* = 4.4 Hz, 1 H), 8.52 (d, *J* = 8.0 Hz, 1 H), 8.38 (d, *J* = 7.2 Hz, 1 H), 7.88 (dd, *J* = 7.6, 2.4 Hz, 2 H), 7.78–7.75 (m, 2 H), 7.70 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 1.20 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 142.2, 139.8, 137.7, 133.4, 133.1, 131.8, 129.5, 128.9, 128.1, 127.9, 127.7, 124.8, 120.4, 80.8, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}BClNO_2$: 366.1432; found: 366.1435.

8-(4-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2g)

Yield: 77.7 mg (75%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.59 (d, *J* = 4.8 Hz, 1 H), 8.49 (d, *J* = 8.4 Hz, 1 H), 8.39 (d, *J* = 7.2 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.76–7.72 (m, 2 H), 7.70–7.65 (m, 2 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 2.41 (s, 3 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5, 141.9, 139.9, 137.6, 133.4, 133.3, 132.3, 129.6, 128.9, 128.3, 127.4, 126.5, 125.2, 123.4, 120.1, 80.7, 26.9, 21.7.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{25}BNO_2$: 346.1978; found: 346.1975.

8-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-4-(trifluoromethyl)phenyl)quinoline (2h)

Yield: 107.8 mg (90%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 4.4 Hz, 1 H), 8.55 (d, *J* = 8.0 Hz, 1 H), 8.47 (d, *J* = 7.2 Hz, 1 H), 8.22 (s, 1 H), 7.93 (d, *J* = 8.4 Hz, 1 H), 7.86 (d, *J* = 8.0 Hz, 1 H), 7.79 (t, *J* = 8.0 Hz, 1 H), 7.73 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.58 (d, *J* = 8.0 Hz, 1 H), 1.23 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.9, 142.4, 139.7, 139.1, 131.6, 129.6, 129.6, 129.0, 128.6, 128.4 (q, *J* = 3.9 Hz), 128.2, 127.8 (q, *J* = 270.6 Hz), 125.0, 124.0 (q, *J* = 3.8 Hz), 120.5, 81.0, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}BF_3NO_2$: 400.1696; found: 400.1693.

4-(Quinolin-8-yl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (2i)

Yield: 87.6 mg (82%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.63 (d, *J* = 4.8 Hz, 1 H), 8.59 (d, *J* = 8.4 Hz, 1 H), 8.48 (d, *J* = 7.2 Hz, 1 H), 8.21 (s, 1 H), 7.98 (d, *J* = 8.0 Hz, 1 H), 7.83 (t, *J* = 8.8 Hz, 2 H), 7.77 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.61 (d, *J* = 8.0 Hz, 1 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.7, 142.7, 139.8, 139.5, 135.5, 130.9, 130.7, 129.6, 129.0, 129.0, 128.8, 125.1, 120.7, 120.2, 111.2, 81.1, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 7.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{22}BN_2O_2$: 357.1774; found: 357.1777.

8-(4-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2j)

Yield: 94.3 mg (86%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 4.8 Hz, 1 H), 8.53 (d, *J* = 8.0 Hz, 1 H), 8.39 (d, *J* = 7.2 Hz, 1 H), 7.87 (d, *J* = 8.4 Hz, 2 H), 7.78–7.68 (m, 3 H), 7.30 (dd, *J* = 8.4, 2.0 Hz, 1 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 142.4, 139.5, 134.7, 134.1, 131.9, 131.4, 129.6, 129.0, 127.8, 127.4, 127.3, 126.6, 120.3, 80.9, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}BClNO_2$: 366.1432; found: 366.1446.

8-(4-Fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2k)

Yield: 89.0 mg (85%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (d, *J* = 4.8 Hz, 1 H), 8.50 (d, *J* = 8.0 Hz, 1 H), 8.35 (d, *J* = 7.2 Hz, 1 H), 7.82 (d, *J* = 8.0 Hz, 1 H), 7.76–7.66 (m, 3 H), 7.62 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.01 (td, *J* = 8.4, 2.4 Hz, 1 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3 (d, *J* = 248.1 Hz), 145.5, 142.4, 139.3, 132.0, 131.7 (d, *J* = 2.6 Hz), 129.6, 128.9, 127.5, 127.1 (d, *J* = 7.6 Hz), 126.9, 120.2, 117.5 (d, *J* = 18.4 Hz), 114.3 (d, *J* = 22.4 Hz), 80.8, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{22}BFNO_2$: 350.1728; found: 350.1730.

8-(3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1′-biphenyl]-4-yl)quinoline (2l)

Yield: 85.5 mg (70%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.65 (d, *J* = 4.8 Hz, 1 H), 8.52 (d, *J* = 8.4 Hz, 1 H), 8.48 (d, *J* = 7.2 Hz, 1 H), 8.21 (s, 1 H), 7.87 (d, *J* = 8.0 Hz, 2 H), 7.79 (t, *J* = 8.0 Hz, 1 H), 7.74–7.69 (m, 3 H), 7.61 (d, *J* = 6.4 Hz, 1 H), 7.45 (t, *J* = 76 Hz, 2 H), 7.35 (d, *J* = 7.2 Hz, 1 H), 1.24 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 142.1, 141.9, 140.3, 139.9, 135.1, 132.8, 130.2, 129.6, 129.0, 128.8, 127.8, 127.2, 127.1, 127.0, 126.2, 125.5, 120.2, 80.8, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 9.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{26}BNO_2$: 408.2135; found: 408.2132.

8-(2,4-Difluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2m)

Yield: 96.9 mg (88%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 4.8 Hz, 1 H), 8.61 (d, *J* = 7.6 Hz, 1 H), 8.51 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 8.0 Hz, 1 H), 7.68 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.47 (dd, *J* = 8.0, 2.4 Hz, 1 H), 6.81–6.75 (m, 1 H), 1.17 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.93 (dd, *J* = 250.1, 11.0 Hz), 160.6 (dd, *J* = 258.5, 11.8 Hz), 145.3, 142.4, 139.6, 132.3 (d, *J* = 18.8 Hz), 129.3, 128.8, 127.7 (d, *J* = 4.5 Hz), 127.1, 120.1, 119.3 (d, *J* = 3.9 Hz), 113.4 (dd, *J* = 18.1, 3.2 Hz), 103.2 (dd, *J* = 28.3, 25.8 Hz), 81.0, 26.6.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}BF_2NO_2$: 368.1633; found: 368.1633.

8-(4,5-Difluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2n)

Yield: 99.1 mg (90%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.53 (dd, *J* = 5.2, 1.6 Hz, 1 H), 8.60 (d, *J* = 7.6 Hz, 1 H), 8.49 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.83 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.73 (t, *J* = 8.0 Hz, 1 H), 7.67 (dd, *J* = 8.4, 5.2 Hz, 1 H), 7.47 (dd, *J* = 8.4, 2.8 Hz, 1 H), 6.77 (ddd, *J* = 12.8, 8.4, 2.4 Hz, 1 H), 1.16 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.7 (dd, *J* = 252.2, 11.3 Hz), 160.4 (dd, *J* = 258.6, 11.7 Hz), 145.1, 142.2, 139.4, 132.1 (d, *J* = 18.6 Hz), 129.1, 128.6, 127.5 (d, *J* = 4.5 Hz), 126.9, 120.0, 119.2 (t, *J* = 3.8 Hz), 113.2 (dd, *J* = 18.1, 3.2 Hz), 103.0 (dd, *J* = 28.3, 25.8 Hz), 80.3, 26.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{21}BF_2NO_2$: 368.1633; found: 368.1631.

8-(4,5-Dimethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2o)

Yield: 70.0 mg (65%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.54 (d, *J* = 4.8 Hz, 1 H), 8.44 (d, *J* = 8.0 Hz, 1 H), 8.36 (d, *J* = 7.2 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.72 (d, *J* = 7.6 Hz, 1 H), 7.68 (s, 1 H), 7.62 (dd, *J* = 8.0, 4.8 Hz, 1 H), 7.53 (s, 1 H), 2.34 (s, 3 H), 2.31 (s, 3 H), 1.20 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6, 141.5, 140.5, 136.4, 135.5, 134.3, 133.9, 133.2, 129.5, 128.7, 127.3, 126.7, 126.4, 120.0, 80.7, 26.7, 20.1, 19.8.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 10.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{27}BNO_2$: 360.2135; found: 360.214.

8-(2-Fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,1′-biphenyl]-4-yl)quinoline (2p)

Yield: 95.7 mg (75%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.64 (d, *J* = 5.2 Hz, 1 H), 8.54 (d, *J* = 8.4 Hz, 1 H), 8.39 (d, *J* = 7.2 Hz, 1 H), 8.01 (d, *J* = 9.2 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.79 (t, *J* = 7.6 Hz, 1 H), 7.73 (dd, *J* = 8.0, 5.2 Hz, 1 H), 7.68 (d, *J* = 7.6 Hz, 2 H), 7.56 (d, *J* = 13.2 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.37 (t, *J* = 7.2 Hz, 1 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1 (d, *J* = 244.8 Hz), 145.8, 142.3, 139.8, 136.9 (d, *J* = 7.4 Hz), 136.6, 134.1 (d, *J* = 3.3 Hz), 131.7 (d, *J* = 2.6 Hz), 129.6, 129.2 (d, *J* = 2.9 Hz), 129.0, 128.5, 128.1, 127.6, 127.4, 120.4, 112.3 (d, *J* = 23.3 Hz), 80.9, 26.9.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{26}BFNO_2$: 426.2041; found: 426.2053.

Ethyl 2-Chloro-4-(quinolin-8-yl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (2q)

Yield: 101.1 mg (77%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.60 (dd, *J* = 5.2, 1.6 Hz, 1 H), 8.56 (dd, *J* = 8.0, 1.2 Hz, 1 H), 8.49 (d, *J* = 8.0 Hz, 1 H), 8.27 (s, 1 H), 7.97 (s, 1 H), 7.92 (d, *J* = 7.2 Hz, 1 H), 7.81 (t, *J* = 8.0 Hz, 1 H), 7.74 (dd, *J* = 8.4, 5.2 Hz, 1 H), 4.42 (q, *J* = 7.2 Hz, 2 H), 1.42 (t, *J* = 7.2 Hz, 3 H), 1.22 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 145.7, 142.7, 139.5, 134.3, 134.1, 133.7, 130.9, 129.6, 129.1, 128.8, 128.2, 128.2, 127.9, 120.5, 81.1, 61.5, 26.9, 14.4.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 7.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{24}H_{26}BClNO_4$: 438.1643; found: 438.1646.

8-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)naphthalen-1-yl)quinoline (2r)

Yield: 74.3 mg (65%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 2.8 Hz, 1 H), 8.19 (d, *J* = 8.0 Hz, 1 H), 7.94–7.85 (m, 4 H), 7.64–7.57 (m, 2 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.31 (dd, *J* = 8.4, 4.0 Hz, 1 H), 7.26–7.22 (m, 1 H), 0.83 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.9, 148.5, 144.8, 140.8, 136.0, 134.9, 132.8, 131.6, 130.5, 128.7, 128.1, 127.3, 127.3, 126.8, 126.3, 125.8, 125.6, 120.7, 100.1, 82.9, 24.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 31.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{25}BNO_2$: 382.1978; found: 382.1998.

8-(2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)thiophen-3-yl)quinoline (2s)

Yield: 70.8 mg (70%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.70 (d, *J* = 5.2 Hz, 1 H), 8.53 (d, *J* = 8.0 Hz, 1 H), 8.17 (d, *J* = 7.2 Hz, 1 H), 7.77–7.68 (m, 3 H), 7.55 (d, *J* = 4.8 Hz, 1 H), 7.44 (d, *J* = 4.8 Hz, 1 H), 1.36 (s, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 143.0, 138.7, 137.3, 130.0, 129.7, 128.9, 127.5, 127.4, 125.7, 124.5, 120.6, 81.1, 27.5.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 7.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}BNO_2S$: 338.1386; found: 338.1386.

5-Phenyl-8-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)quinoline (2t)

Crude NMR data is reported (see SI for details).

Conversion: 80%

^{1}H NMR (400 MHz, $CDCl_3$): see the Supporting Information.

^{11}B NMR (128 MHz, $CDCl_3$): δ = 8.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{27}BNO_2$: 408.2135; found: 408.2130.

Further Transformations

2-(Quinolin-8-yl)phenol (3a)

A 25 mL round-bottom flask was charged with borylated product (**2a**; 0.3 mmol) generated in situ in THF/H_2O (1:1) and the solution was cooled to 0 °C and stirred for 5 minutes. A solution of $NaBO_3{\cdot}4H_2O$ (138.5 mg, 3.0 equiv) was then added to the reaction mixture and stirred at r.t. for 3 h. The reaction was quenched with water and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification with silica gel (20% EtOAc in hexane) gave the product **3a**.

Yield: 51.8 mg (78%); light-yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.84 (s, 1 H), 8.93 (d, *J* = 4.1 Hz, 1 H), 8.35 (d, *J* = 8.3 Hz, 1 H), 7.90 (t, *J* = 6.8 Hz, 2 H), 7.71 (t, *J* = 7.7 Hz, 1 H), 7.54 (dd, *J* = 8.2, 4.0 Hz, 1 H), 7.42 (dd, *J* = 17.5, 8.1 Hz, 2 H), 7.19 (d, *J* = 8.0 Hz, 1 H), 7.08 (t, *J* = 7.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.2, 149.4, 145.4, 139.0, 138.7, 133.5, 132.8, 130.1, 128.7, 128.4, 127.9, 127.7, 121.2, 121.1, 119.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{12}NO$: 222.0919; found: 222.0912.

8-(2-Bromophenyl)quinoline (3b)

A 5.0 mL Wheaton microreactor was charged with borylated product (**2a**; 0.3 mmol) generated in situ, $CuBr_2$ (201.0 mg, 3.0 equiv), MeOH (2.0 mL), and water (2.0 mL). The microreactor was capped with a Teflon pressure cap and the reaction mixture was stirred at 80 °C for 12 h. After 12 h, the reaction mixture was cooled to r.t., diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification of the crude mass with silica gel (5% EtOAc in hexane) gave the product **3b**.

Yield: 68.2 mg (80%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 4.1 Hz, 1 H), 8.22 (d, *J* = 8.3 Hz, 1 H), 7.90 (d, *J* = 7.4 Hz, 1 H), 7.74 (d, *J* = 8.1 Hz, 1 H), 7.64 (t, *J* = 7.2 Hz, 2 H), 7.44–7.40 (m, 3 H), 7.32–7.28 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 146.3, 141.0, 140.5, 136.3, 132.7, 131.9, 130.7, 129.2, 128.4, 128.34, 127.1, 126.01, 124.41, 121.21.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}BrN$: 284.0075; found: 284.0074.

8-(2-Iodophenyl)quinoline (3c)

An oven-dried 5.0 mL Wheaton microreactor was charged with borylated product (**2a**; 0.3 mmol) generated in situ, and CH_2Cl_2 (2.0 mL). ICl (73.0 mg, 1.5 equiv in 1.0 mL CH_2Cl_2) was added dropwise to the reaction mixture. The reaction mixture was then stirred at r.t. for 8 h. After completion (monitored by GC-MS), the reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (2 × 10 mL). The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification of the crude mass with silica gel (5% EtOAc in hexane) gave the product **3c**.

Yield: 69.3 mg (70%); solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.93 (d, *J* = 3.5 Hz, 1 H), 8.22 (d, *J* = 8.2 Hz, 1 H), 8.01 (d, *J* = 7.9 Hz, 1 H), 7.91 (d, *J* = 7.6 Hz, 1 H), 7.62 (q, *J* = 7.3 Hz, 2 H), 7.48 (t, *J* = 7.4 Hz, 1 H), 7.41 (dd, *J* = 11.2, 6.1 Hz, 2 H), 7.13 (t, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 146.1, 145.2, 143.5, 139.1, 136.3, 130.9, 130.7, 129.1, 128.6, 128.3, 127.9, 126.0, 121.2, 100.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}IN$: 331.9936; found: 331.9929.

2-(Quinolin-8-yl)phenyl Acetate (3d)

An oven-dried 5.0 mL Wheaton microreactor was charged with borylated product (**2a**; 0.3 mmol) generated in situ, $Cu(OAc)_2$ (54.5 mg, 1.0 equiv), acetonitrile (2.0 mL), and EtOH (0.2 mL). The reaction mixture was then stirred at 80 °C for 6 h. After 6 h, the reaction mixture was cooled to r.t., diluted with water (15 mL) and extracted with EtOAc (3 × 10 mL). The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification of the crude mass with silica gel (30% EtOAc in hexane) gave the product **3d**.

Yield: 56.9 mg (72%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.81 (d, *J* = 4.0 Hz, 1 H), 8.11 (d, *J* = 8.2 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.56 (d, *J* = 7.0 Hz, 1 H), 7.49 (d, *J* = 7.7 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.33–7.28 (m, 2 H), 7.16 (t, *J* = 4.0 Hz, 1 H), 1.63 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.4, 150.5, 148.7, 146.4, 137.2, 136.3, 132.8, 132.1, 130.9, 128.9, 128.4, 128.2, 126.2, 125.9, 122.8, 121.2, 20.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{14}NO_2$: 264.1025; found: 264.1017.

***N*-(4-Ethoxyphenyl)-2-(quinolin-8-yl)aniline (3e)**

An oven-dried 5.0 mL Wheaton microreactor was charged with borylated product (**2a**; 0.3 mmol) generated in situ, $Cu(OAc)_2$ (54.5 mg, 1.0 equiv), 4-ethoxy aniline (82.0 mg, 2.0 equiv), Et_3N (100 µL, 2.0 equiv), powered molecular sieves (100.0 mg), acetonitrile (2.0 mL), and EtOH (0.2 mL). The reaction mixture was then stirred at 80 °C for 24 h. After 24 h, the reaction mixture was cooled to r.t., diluted with water (15 mL) and extracted with EtOAc (3 × 10 mL). The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification of the crude mass with silica gel (20% EtOAc in hexane) gave the product **3e**.

Yield: 76.6 mg (75%); yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (d, *J* = 4.1 Hz, 1 H), 8.26 (d, *J* = 8.3 Hz, 1 H), 7.88 (d, *J* = 8.1 Hz, 1 H), 7.78 (d, *J* = 7.1 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.46 (dd, *J* = 8.3, 4.1 Hz, 1 H), 7.30 (d, *J* = 7.6 Hz, 1 H), 7.28–7.24 (t, *J* = 7.0 Hz, 2 H), 7.00 (t, *J* = 7.2 Hz, 1 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 6.76 (d, *J* = 8.7 Hz, 2 H), 6.12 (s, 1 H), 3.96 (q, *J* = 7.0 Hz, 2 H), 1.37 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 150.7, 146.5, 143.9, 139.6, 137.1, 136.7, 132.2, 132.1, 129.4, 128.8, 128.6, 128.2, 127.0, 122.1, 121.3, 120.1, 115.8, 115.2, 63.9, 15.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{21}N_2O$: 341.1654; found: 341.1648.

8-(2-Azidophenyl)quinoline (3f)

A 5.0 mL Wheaton microreactor was charged with borylated product (**2a**; 0.3 mmol) generated in situ, NaN_3 (58.5 mg, 1.5 equiv), $Cu(OAc)_2$ (5.5 mg, 10 mol%), and MeOH (2.0 mL). The microreactor was capped with a Teflon pressure cap and the reaction mixture was stirred at 55 °C for 12 h. After 12 h, the reaction mixture was cooled to r.t., diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of the crude mass with silica gel (5% EtOAc in hexane) gave the product **3f**.

Yield: 62.8 mg (85%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.91–8.90 (m, 1 H), 8.20 (d, *J* = 8.4 Hz, 1 H), 7.87 (dd, *J* = 7.2, 2.0 Hz, 1 H), 7.63–7.57 (m, 2 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.41–7.38 (m, 2 H), 7.31–7.24 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 146.5, 138.6, 137.8, 136.4, 132.3, 132.0, 131.0, 129.2, 128.5, 128.4, 126.1, 124.7, 121.2, 118.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{11}N_4$: 247.0984; found: 247.0977.

8-([1,1′-Biphenyl]-2-yl)quinoline (3g)

A 5.0 mL Wheaton microreactor was charged with borylated product (**2a**; 0.3 mmol) generated in situ, bromobenzene (47.1 mg, 1.0 equiv), $Pd(PPh_3)_4$ (7.0 mg, 2.0 mol%), K_2CO_3 (82.9 mg, 2.0 equiv), DME (1.0 mL), and water (0.5 mL), sequentially. The microreactor was degassed well with nitrogen and capped with a Teflon pressure cap and the reaction mixture was stirred at 100 °C for 12 h. After 12 h, the reaction mixture was cooled to r.t., diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combine organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Chromatographic purification of the crude mass with silica gel (5% EtOAc in hexane) gave 8-([1,1′-biphenyl]-2-yl)quinoline (**3g**).

Yield: 72.6 mg (86%); white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (d, *J* = 4.0 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.71 (dd, *J* = 7.2, 2.4 Hz, 1 H), 7.55–7.46 (m, 4 H), 7.41–7.36 (m, 2 H), 7.32 (dd, *J* = 8.2, 4.1 Hz, 1 H), 7.10–7.06 (m, 2 H), 7.02–7.01 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.2, 146.8, 142.1, 142.0, 141.0, 138.4, 136.1, 131.9, 131.8, 130.2, 129.4, 128.4, 128.0, 127.5, 127.3, 126.9, 126.2, 125.9, 120.8.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{16}N$: 282.1283; found: 282.1281.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/-a-1506-3884.

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