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FULL PAPER

Synthesis of benzofuroquinolines via phosphine-free direct arylation of 4-phenoxyquinolines in air.

Rachel M. Shanahan,[a] Aobha Hickey,[a] F. Jerry Reen,[b] Fergal O'Gara[c,d] and Gerard P. McGlacken*[a]

Abstract: A palladium-catalysed, phosphine-free, direct arylation of 4-phenoxyquinolines, in air is described. Using an intramolecular approach, the ring-closed products are formed in yields of up to 95%. This approach allows access to a range of benzofuroquinolines. An array of functional groups on both the quinoline and phenoxy rings are tolerated.

Introduction

The quinoline nucleus occurs in many natural and synthetic pharmacologically active compounds,[1] and is ranked 22nd in the top 100 most frequently used ring systems present in FDA approved drugs.[2] Thus, the quinoline motif is considered a privileged biological scaffold, utilised by synthetic chemists to build molecular complexity, and ultimately improve biological activity. As a versatile heterocycle, it displays reactivity similar to that of other aromatic (pyridine/benzene) analogues, and thus can undergo a wide range of synthetic transformations.[3-4]

One of the most important transformations in organic synthesis remains the linking of two (hetero)aryl groups via a new carbon-carbon bond.[5] Traditionally, the most reliable class of C-C bond forming reactions involves the palladium-catalysed coupling of an aryl or vinyl halide with an organometallic reagent.[6-9] Examples include the Suzuki-Miyaura coupling,[10] Stille coupling,[11] and Negishi coupling.[12] An alternative is the use of direct arylation protocols, which are less reliant on the installation of a reactive functionality prior to cross-coupling.[13-15]

Direct arylation of simple arenes has been increasingly utilised in organic synthesis to access complex polycyclic ring systems.[16-20] By comparison, similar reactions involving heterocycles tend to require specialised catalyst/ligand systems and are therefore less prevalent in the literature.[21] One of the earliest relevant examples of an intramolecular direct arylation of a heteroarene was reported in 1984 by Ames and Opalko.[22] As a recent example, Ha *et al.* reported a palladium-catalysed synthesis of benzofuropyridines in moderate to excellent yields.[23]

Herein we report a palladium-catalysed direct arylation of 4-phenoxyquinolines as a route to benzofuro[3,2-*c*]quinolines (Figure 1). Access to these products will aid exploration of their untapped biological potential, given that similar quinoline-based compounds exhibit anticancer,[24] antimalarial[25] and antibacterial[26] effects.

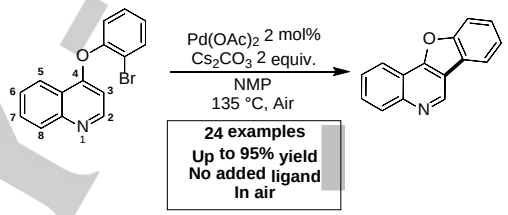

Figure 1. Intramolecular direct arylation of 4-phenoxyquinolines.

Previous syntheses of some of these substrates via direct arylation have relied upon positioning the activated carbon-halide on the C-3 position of the quinoline coupling partner[27-28] which limits the accessibility and versatility of products formed. The first example of non-directed direct arylation/C-H activation of the C-3 position of pyridines and quinolines was reported by Yu and co-workers (Figure 2(i)), using phenanthroline ligands under inert reaction conditions.[29] This method also relies upon the use of a large excess of the quinoline or pyridine substrate, which is only applicable to an intermolecular system. Herein we describe a system that requires no added ligand for arylation of the C-3 position of the quinoline ring, *via* intramolecular direct arylation, in air (Figure 2 (ii)).

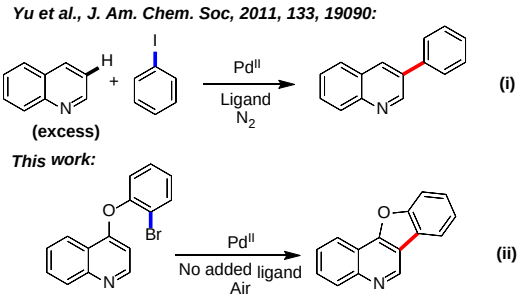

Figure 2. Palladium-catalysed direct arylation at the C-3 position of quinolines.

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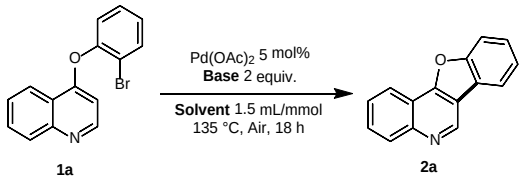
Results and Discussion

Initially, 4-(2-bromophenoxy)quinoline **1a** was chosen as a model substrate, which was readily accessible from reaction of 4-chloroquinoline and 2-bromophenol. Our initial coupling conditions allowed formation of the fused product **2a** in 57% isolated yield in air (Table 1 entry 1). Next, a variety of reaction parameters was accessed (Table 1). A solvent screen indicated that high-boiling point amide solvents were necessary for good conversion (entries 1-3). Other organic solvents gave little or no conversion to product (entries 4-8). Changing the base from Na_2CO_3 to K_2CO_3 or Cs_2CO_3 allowed the reaction to reach 100% conversion (entry 9 and 10), while use of a stronger butoxide base resulted in partial decomposition of the starting material (entry 11). A further reduction in catalyst loading to 2 mol% was also achieved (entry 12), at which point the desired product **2a** could be obtained in 95% isolated yield under the optimised conditions.

Table 1. Optimisation of reaction conditions.



1a **2a**

Entry[j]	Base	Solvent	Yield by NMR (%)[a]	Isolated Yield (%)
1	Na_2CO_3	DMA	-	57
2	Na_2CO_3	DMF	67	-
3	Na_2CO_3	NMP	70	72
4	Na_2CO_3	DMSO	0	-
5[b]	Na_2CO_3	1,4-Dioxane	0	-
6[b]	Na_2CO_3	EtOH	0	-
7[b]	Na_2CO_3	1,2-DCE	0	-
8[b]	Na_2CO_3	MeCN	0	-
9	K_2CO_3	NMP	72	-
10	Cs_2CO_3	NMP	83	-
11	NaO^{t}Bu	NMP	39[c]	-
12[d]	**Cs_2CO_3**	**NMP**	**99**	**95**
13[e]	Cs_2CO_3	NMP	33	-

[a] Yields determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. [b] Reaction carried out at the reflux temperature of solvent. [c] Decomposition of starting material observed. [d] 2 mol% $Pd(OAc)_2$ used. [e] 1 mol% $Pd(OAc)_2$ used.

With optimised conditions in hand, the substrate scope of the reaction was evaluated (Figure 3). Overall, it was observed that the reaction could tolerate a variety of functional groups on both the phenoxy and quinoline coupling partners. Substrates bearing weakly electron-withdrawing substituents (**2b-f**) on the phenoxy ring were well tolerated. Additionally, the chlorides in **2e** and **2f** were retained as a synthetic handle for further cross-coupling. The more strongly electron-withdrawing substituents on **2g** and **2h** led to cyclisation in excellent yields of 88% and 90%, respectively. Moderate yields were observed in the case of the nitro (**2i**) and ester (**2j**) analogues.

Longer reaction times were required in the case of electron-rich phenoxy substrates (**2k-m**). In the case of the naphthyl analogue **2n**, the desired product could only be obtained in 17% isolated yield, with the majority of the remaining material attributed to unreacted starting material. This may be due to the steric bulk of the naphthyl group hindering access to the coupling site. Pleasingly, compound **2o** bearing a pyridine moiety instead of an aryl was obtained in an excellent yield of 81%.

The scope of the reaction with respect to the quinoline was also examined. A methyl group at the C-2 position was well tolerated (**2p**). On the aryl backbone, both electron donating -OMe substituents (**2q** and **2r**) and electron withdrawing -CF_3, -F and -Cl substituents (**2s-v**) also led to very good yields of product. The reaction conditions were also applicable to a 4-phenoxy pyridine substrate.[30] A few quinoline analogues (*p*-pyridinyl, aldehydic, and those with an S-linker) failed to cyclise under these conditions.[31]

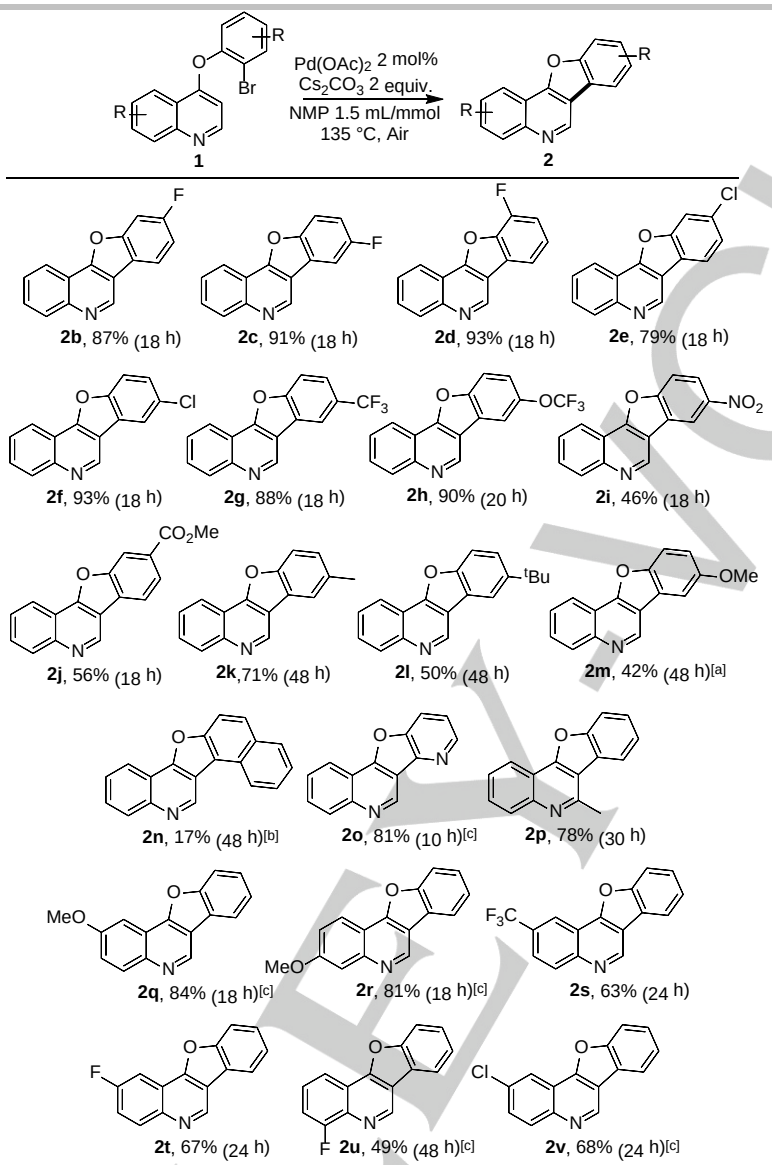
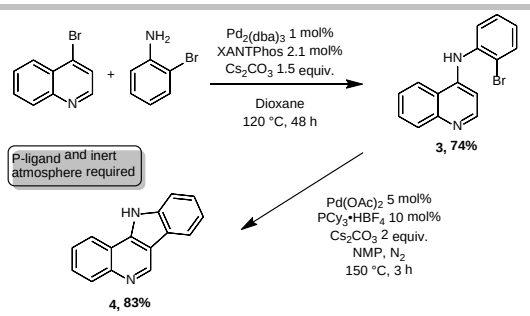


Figure 3. Substrate scope. All yields are isolated yields.[a] The yield of this product could be improved to 60% when using the following conditions: 5 mol% $Pd(OAc)_2$, 10 mol% $PCy_3.HBF_4$, 2 equiv. Cs_2CO_3 under N_2 at 135 °C for 18 h. [b] The yield of this product could be improved to 66% when using the same conditions described in [a]. [c] 5 mol% $Pd(OAc)_2$ used.

Compounds containing fused indolquinoline rings are known to possess antimalarial,[32] antiproliferative and anticancer activity.[33] Thus, we hoped to access similar compounds by including this functionality in our substrate scope. A Hartwig-Buchwald coupling gave the precursor **3** in 74% isolated yield (Scheme **1**). However, when this compound was subjected to the previously optimised direct arylation conditions given above, no product was observed. Even when using the protected (*N*-Boc) substrate, coupling could not be achieved under these conditions.[34] We reasoned at this point that inhibitive N-ligation to palladium could be avoided by the addition of competitive phosphine ligands.[35] Indeed, when a new catalytic system of 5 mol% $Pd(OAc)_2$ and 10 mol% $PCy_3.HBF_4$ was employed, the fused product could be obtained in 83% isolated yield after 3h. An inert atmosphere was required (Scheme **1**).[36]



Scheme 1. Synthesis and direct arylation of 4-anilinoquinoline substrate.

The mechanism probably proceeds via an initial oxidative addition followed by a rate-determing C-H activation via a concerted metalation deprotonation (CMD).[29,37-40] A CMD mechanism is often characterised by the acidity of the key C-H bond. To probe this, a number of competition experiments were carried out using a basic quinoline substrate **1a** and those substituted with an electron-withdrawing (**1s**) and an electron-donating (**1q**) group (Figure 4 and S.I.). In all cases the experiment revealed that the electron-poor substrate outpaced the electron-rich substrate.

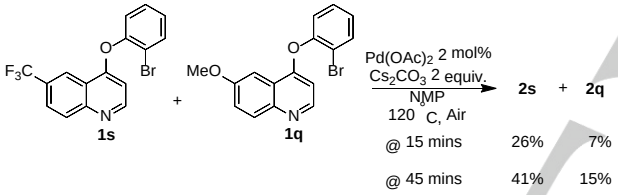


Figure 4. Competition experiment between **1s** and **1q**.

We then wished to apply the methodology to a more challenging quinoline of potential biological importance. Many species of bacteria use a sophisticated communication system termed 'quorum sensing' (QS).[41] This coordinated behaviour allows for the construction of protective biofilms and the production of virulence factors, ultimately for the benefit of the entire colony. In contrast to antibiotic treatment, disrupting QS, termed 'quorum quenching', is non-biocidal and thus as a strategy, is less likely to promote bacterial resistance by reducing the level of mutant dominance.[42] *Pseudomonas aeruginosa* uses quinolones such as 4-hydroxy-2-heptylquinoline (HHQ) and its 3-OH analogue Pseudomonas quinolone signal (PQS) to modulate quorum sensing (Figure 5). Thus analogues of these molecules could be used as competitive binders, disrupting numerous downstream processes.

Following on from our continuing investigation of quinolone and quinoline analogues of HHQ and PQS,[43-49] using molecules which are 'blocked' at the C-3 position, we chose to apply our intramolecular arylation methodology to a HHQ/PQS analogue (Figure 5). Substitution of C-3 is often crucial as it prevents hydroxylation of HHQ at this position by PqsH. Analogues with a hydroxyl group at C-3 can lead to unwanted agonistic behaviour.[50-51]

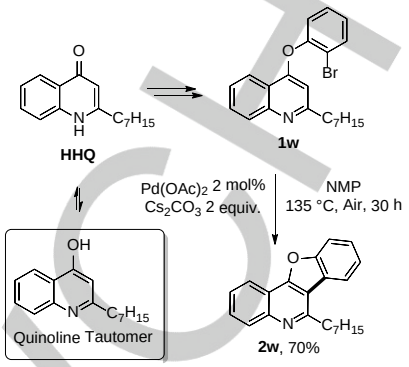


Figure 5. HHQ-like substrate blocked at C-3.

Thus HHQ was converted into the phenoxy procursor, which cyclised well, considering the steric encumbrance of the heptyl chain (the heptyl chain is critical for most biological activity). The impact of compound **2w** on quinolone signalling (more specifically PqsR signalling) was then investigated. HHQ (and PQS) are known to act as co-inducer signals of the PqsR LysR-type transcriptional regulator, leading to transcriptional activation of the *pqsA* promoter. Thus, the *pqsA* promoter itself acts as a proxy for activation of PqsR signalling. A *pqsA* fusion plasmid reporter (pLP0996) contains the *pqsA* promoter sequence upstream of the *lacZ* encoding gene and thus was ultimately used as indicator.[52] Wild-type *P. aeruginosa* produces endogenous HHQ, and thus any interference with activation of the plasmid encoded *pqsA*-promoter would likely infer antagonism of natural co-inducer binding. However, no such interference was observed and levels of *pqsA* transcriptional activation were comparable in carrier and cells treated with cyclised quinoline **2w** (Figure 6). Activation of the pLP0996 encoded *pqsA* promoter in a *pqsA* mutant lacking endogenous HHQ and PQS can only occur upon addition of exogenous signal. In this case, while HHQ activated promoter activity, addition of quinoline **2w** had no effect beyond baseline. Thus quinoline **2w** displayed neither agonist nor antagonist behaviour with respect to PqsR signalling. This was further evident from the lack of inhibition of pyocyanin production in a wild-type strain and the lack of pyocyanin restoration in the *pqsA* mutant.

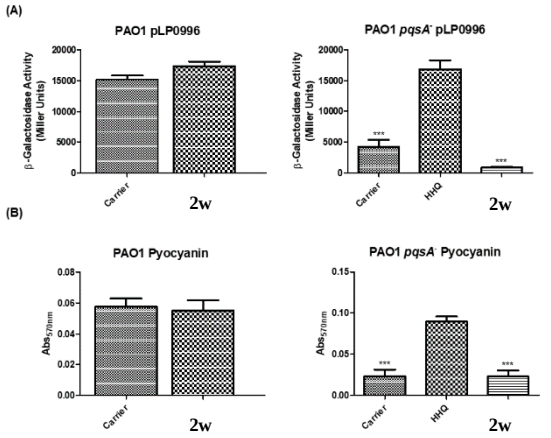


Figure 6. (A) Transcriptional activation of the *pqsA* promoter was unaffected in wild-type (PAO1 pMP0996) and mutant (PAO1 *pqsA*- pLP0996) cells upon addition of **2w.** This suggests that the compound is neither an antagonist nor an agonist of PqsR signalling under conditions tested. **(B)** Pyocyanin production followed a similar pattern, i.e. unaffected in the presence of **2w** in either the wild-type or mutant cells. All data presented is the mean (+/- SEM) of three independent biological replicates. Statistical analysis was performed by Students t-test and one way ANOVA with Bonferroni post-hoc testing (*** p<0.001).

The production of HHQ-like compounds which do not and cannot be hydroxylated in vivo at C-3[51] and thus do not exhibit any strong agonistic or antagonist behaviour, make for an excellent molecular framework for further modification and structure-activity studies. Further details of the biological activity will be published in due course.

Conclusions

In summary, the application of direct arylation methodology towards the synthesis of fused benzofuroquinoline products has been demonstrated. Placement of the halide on the phenoxy component of the coupling precursor allows for easy access to cyclised products. No added phosphine is required and the reactions can be carried out in air. Modification of the methodology allows for the inclusion of 4-anilinoquinoline substrates, without the requirement for *N*-protection. Finally, electron-poor quinolines appear to work best as evidenced by competition experiments. Application to a sterically hindered (C-2=*n*-heptyl) HHQ mimic proceeds well.

Experimental Section

General Methods: Solvents and reagents were used as obtained from commercial sources and without purification. Melting points were measured in a Thomas Hoover Capillary Melting Point apparatus. Infrared spectra were measured on a Perkin-Elmer FT-IR spectrometer. Nuclear Magnetic Resonance (NMR) samples were run in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d^6) as specified. ^{1}H NMR (600 MHz), ^{1}H NMR (500 MHz),^{1}H NMR (400 MHz),^{1}H NMR (300 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers, respectively, in proton coupled mode using tetramethysilane (TMS) as the internal standard. ^{13}C NMR (150 MHz), ^{13}C NMR (125 MHz), ^{13}C NMR (100 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Bruker Avance 600, Bruker Avance 500, Bruker Avance 400 and Bruker Avance 300 NMR spectrometers, respectively, in proton decoupled mode at 20 °C using tetramethysilane (TMS) as the internal standard. ^{19}F NMR (282 MHz) spectra were recorded on a Bruker Avance 300 NMR spectrometer in proton decoupled mode at 20 °C. All spectra were run at University College Cork. Chemical shifts (δ) are expressed as parts per million (ppm), positive shift being downfield from TMS; coupling constants (*J*) are expressed in hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as: s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), ddd (doublet of doublets of doublets), t (triplet), td (triplet of doublets), q (quartet), quin (quintet) and m (multiplet). High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument in electrospray ionisation (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up in acetonitrile at a concentration of *ca*. 1 mg/ml. Column chromatography was carried out using 60 Å (35-70 µm) silica. TLC was carried out on pre-coated silica gel plates (Merck 60 PF254). The developed plates were visualized under UV light.

Palladium-catalysed intramolecular direct arylation reactions were carried out in sealed reaction tubes which were placed in a solid multi-reaction heating plate.

General Procedures for Synthesis of 4-(2-bromophenoxy)quinoline Substrates 1a-1w:

Method (a): compounds 1a-1c, 1f, 1i, 1k, 1l, 1o-1w: A mixture of the 4-chloroquinoline substrate (1 equiv.), the substituted 2-bromophenol (5 equiv.) and sodium hydroxide (crushed pellets) (1.5 equiv.) was stirred at 120 °C until reaction was completed (2-6 h) as evident by thin layer chromatography (hexane/ethyl acetate 8:2). The cooled reaction mixture was diluted with 10% aq. NaOH (5 mL) and stirred at room temperature for 1 h. The aqueous phase was extracted with DCM (3 x 20 mL). The combined organic layers were washed with 6M NaOH (3 x 10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel using hexane/ethyl acetate (8:2) as eluent.

Method (b): compounds 1d, 1e, 1g, 1h, 1j, 1m, 1n: A mixture of 4-chloroquinoline (1 equiv.), the substituted 2-bromophenol (1.5 equiv.) and 4-dimethylaminopyridine (3 equiv.) in toluene (1.5 mL/mmol) was stirred at 130 °C until the reaction was completed as evident by thin layer chromatography (hexane/ethyl acetate 8:2). The cooled reaction mixture was diluted with 10% aq. NaOH (5 mL) and stirred at room temperature for 1 h. The aqueous phase was extracted with DCM (3 x 20 mL). The combined organic layers were washed with 3M NaOH (3 x 10 mL), 1M HCl (2 x 10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel using hexane/ethyl acetate (8:2) as eluent.

4-(2-Bromophenoxy)quinoline (1a): Method (a) - white solid (2.89 g, 78%); m.p. = 62-64 °C. IR (film) ν_{max} 3434, 1596, 1305, 1223, 659 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.41 (d, *J* = 5.1 Hz, 1H), 7.18-7.27 (m, 2H), 7.43 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 7.61 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.70-7.82 (m, 2H), 8.12 (d, *J* = 8.2 Hz, 1H), 8.42 (dd, *J* = 8.3, 0.9

Hz, 1H), 8.68 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 103.7, 116.4, 121.1, 121.9, 123.2, 126.3, 127.3, 129.1, 129.2, 130.2, 134.3, 149.8, 151.0, 151.2, 160.7 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{11}BrNO$: 300.0024; found: 300.0016.

4-(2-Bromo-5-fluorophenoxy)quinoline (1b): Method (a) - pale yellow solid (0.891 g, 91%); m.p. = 77-78 °C. IR (film) ν_{max} 3066, 1476, 1305, 1252, 1159, 601 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.49 (d, *J* = 5.1 Hz, 1H), 6.94-7.01 (m, 1H), 6.99 (d, *J* = 8.1 Hz, 1H), 7.57-7.74 (m, 2H), 7.80 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.37 (dd, *J* = 8.4, 1.0 Hz, 1H), 8.73 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.1, 110.7, 110.9 (d, $^2J_{(C,F)}$ = 25 Hz), 114.5 (d, $^2J_{(C,F)}$ = 22 Hz), 120.9, 121.7, 126.5, 129.2, 130.4, 134.7 (d, $^3J_{(C,F)}$ = 9 Hz), 149.9, 151.0, 152.0 (d, $^3J_{(C,F)}$ = 11 Hz), 160.1, 162.4 (d, $^1J_{(C,F)}$ = 250 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -111 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrFNO$: 317.9930; found: 317.9936.

4-(2-Bromo-4-fluorophenoxy)quinoline (1c): Method (a) - pale yellow solid (0.188 g, 38%); m.p. = 100-103 °C. IR (film) ν_{max} 3065, 1480, 1305, 1248, 1183, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.39 (d, *J* = 5.1 Hz, 1H), 7.10-7.29 (m, 2H), 7.48 (dd, *J* = 7.7, 2.8 Hz, 1H), 7.62 (ddd, *J* = 8.2, 5.5, 1.2 Hz, 1H), 7.79 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.40 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.69 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 103.4, 116.1 (d, $^2J_{(C,F)}$ = 23 Hz), 116.9 (d, $^3J_{(C,F)}$ = 10 Hz), 120.9, 121.3 (d, $^2J_{(C,F)}$ = 26 Hz), 121.8, 124.3 (d, $^3J_{(C,F)}$ = 9 Hz), 126.4, 129.2, 130.3, 147.4, 149.8, 151.0, 159.9 (d, $^1J_{(C,F)}$ = 250 Hz), 160.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -114 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrFNO$: 317.9930; found: 317.9935.

4-(2-Bromo-6-fluorophenoxy)quinoline (1d): Method (b) - pale yellow solid (0.318 g, 72%); m.p. = 118-119 °C. IR (film) ν_{max} 3064, 1502, 1471, 1305, 1271, 1042, 665 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.39 (d, *J* = 5.1 Hz, 1H), 7.15-7.30 (m, 2H), 7.47-7.54 (m, 1H), 7.63 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.79 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.46 (dd, *J* = 8.3, 1.1 Hz, 1H), 8.69 (d, *J* = 5.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 102.5, 116.5 (d, $^2J_{(C,F)}$ = 19 Hz), 118.3, 120.6, 121.9, 126.4, 127.7 (d, $^3J_{(C,F)}$ = 8 Hz), 129.10, 129.16, 130.2, 139.3 (d, $^2J_{(C,F)}$ = 14 Hz), 149.8, 150.9, 155.6 (d, $^1J_{(C,F)}$ = 255 Hz), 159.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -124 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrFNO$: 317.9930; found: 317.9921.

4-(2-Bromo-5-chlorophenoxy)quinoline (1e): Method (b) - white solid (0.290 g, 89%); m.p. = 79-81 °C. IR (film) ν_{max} 3370, 1562, 1464, 1305, 1252, 765, 665 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.48 (d, *J* = 5.1 Hz, 1H), 7.16-7.29 (m, 2H), 7.57-7.69 (m, 2H), 7.79 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 8.36 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.72 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.1, 114.4, 120.9, 121.7, 123.3, 126.5, 127.4, 129.2, 130.4, 134.5, 134.8, 149.9, 151.0, 151.9, 160.1 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrClNO$: 333.9634; found: 333.9622.

4-(2-Bromo-4-chlorophenoxy)quinoline (1f): Method (a) - off-white solid (1.97 g, 96%); m.p. = 112-115 °C. IR (film) ν_{max} 3403, 1596, 1465, 1392, 1257, 824, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.42 (d, *J* = 5.1 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.40 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.61 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.70-7.84 (m, 2H), 8.12 (d, *J* = 8.5 Hz, 1H), 8.38 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.70 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 103.7, 117.0, 120.9, 121.7, 123.8, 126.4, 129.2, 129.3, 130.3, 132.0, 133.9, 149.9, 150.0, 151.0, 160.4 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrClNO$: 333.9634; found: 333.9629.

4-(2-Bromo-4-(trifluoromethyl)phenoxy)quinoline (1g): Method (b) - sticky colourless oil (0.0731 g, 20%). IR (film) ν_{max} 1623, 1569, 1320, 1263, 1231, 1130, 588 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.50 (d, *J* = 5.1 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.54-7.70 (m, 2H), 7.79 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 8.00 (d, *J* = 1.7 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.34 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.73 (d, *J* = 4.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.7, 116.5, 121.0, 121.7, 122.6, 122.9 (q, $^1J_{(C,F)}$ = 272 Hz), 126.4 (q, $^3J_{(C,F)}$ = 4 Hz), 126.7, 129.2 (q, $^2J_{(C,F)}$ = 34 Hz), 129.3, 130.5, 131.7 (q, $^3J_{(C,F)}$ = 4 Hz), 150.0, 150.9, 154.4, 159.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -62 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{10}BrF_3NO$: 367.9898; found: 367.9886.

4-(2-Bromo-4-(trifluoromethoxy)phenoxy)quinoline (1h): Method (b) - pale yellow solid (0.3015 g, 78%); m.p. 50-52 °C. IR (film) ν_{max} 1640, 1597, 1306, 1253, 1218, 1187, 567 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.44 (d, *J* = 5.1 Hz, 1H), 7.22-7.35 (m, 2H), 7.55-7.69 (m, 2H), 7.79 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.38 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.71 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 103.8, 116.9, 120.4 (q, $^1J_{(C,F)}$ = 259 Hz), 120.9, 121.7, 121.8, 123.7, 126.5, 127.0, 129.2, 130.4, 146.6, 149.9, 150.0, 151.0, 160.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -58 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{10}BrF_3NO_2$: 383.9847; found: 383.9843.

4-(2-Bromo-4-nitrophenoxy)quinoline (1i): Method (a) - pale yellow solid (0.192 g, 80%); m.p. = 151-152 °C. IR (film) ν_{max} 3376, 1523, 1346, 1305, 1257, 665 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.65 (d, *J* = 5.0 Hz, 1H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.64 (ddd, *J* = 8.1, 7.1, 0.7 Hz, 1H), 7.83 (ddd, *J* = 8.4, 7.0, 1.3 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 8.25 (d, *J* = 8.8 Hz, 1H), 8.27 (dd, *J* = 8.9, 2.7 Hz, 1H), 8.65 (d, *J* = 2.6 Hz, 1H), 8.80 (d, *J* = 5.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 106.0, 115.9, 121.1, 121.2, 121.5, 124.6, 127.1, 129.5, 129.9, 130.7, 144.9, 150.2, 151.0, 157.2, 159.1 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrN_2O_3$: 344.9875; found: 344.9865.

Methyl 4-bromo-3-(quinolin-4-yloxy)benzoate (1j): Method (b) - off white solid (0.258 g, 62%); m.p. = 87-89 °C. IR (film) ν_{max} 3586, 2950, 1724, 1565, 1502, 1392, 1294, 1241, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.92 (s, 3H), 6.43 (d, *J* = 5.1 Hz, 1H), 7.63 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.76-7.90 (m, 4H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.40 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.70 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.6, 103.9, 121.0, 121.7, 122.0, 123.9, 126.5, 128.0, 129.2, 130.4, 131.6, 134.5, 149.9, 151.0, 151.4, 160.3, 165.4 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{13}BrNO_3$: 358.0079; found: 358.0089.

4-(2-Bromo-4-methylphenoxy)quinoline (1k): Method (a) - orange solid (0.242 g, 84%); m.p. = 122-125 °C. IR (film) ν_{max} 3064, 1568, 1485, 1392, 1255, 765 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.41 (s, 3H), 6.40 (d, *J* = 5.2 Hz, 1H), 7.13 (d, *J* = 8.2 Hz, 1H), 7.22 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.54 (d, *J* = 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.43 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.67 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 20.7, 103.5, 115.9, 121.1, 121.9, 122.9, 126.2, 129.1, 129.8, 130.1, 134.5, 137.5, 148.8, 149.8, 151.0, 161.0 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}Br$ NO: 314.0181; found: 314.0169.

4-(2-Bromo-4-(tert-butyl)phenoxy)quinoline (1l): Method (a) - pale yellow solid (0.073 g, 56%); m.p. = 68-70 °C. IR (film) ν_{max} 2963, 1568, 1488, 1391, 1306, 1263, 766 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (s, 9H), 6.43 (d, *J* = 5.1 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.60 (t, *J* = 7.6 Hz, 1H), 7.65-7.83 (m, 2H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.42 (d, *J* = 8.3 Hz, 1H), 8.67 (d, *J* = 5.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 31.3, 34.7, 103.6, 115.8, 121.1, 121.9,

122.6, 126.2, 126.3, 129.0, 130.2, 131.2, 148.5, 149.7, 150.9, 151.1, 160.9 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{19}BrNO$: 356.0650; found: 356.0642.

4-(2-Bromo-4-methoxyphenoxy)quinoline (1m): Method (b) - beige solid (0.304 g, 56%); m.p. = 184-185 °C. IR (film) ν_{max} 3062, 2835, 1595, 1487, 1392, 1212, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 6.38 (d, *J* = 5.2 Hz, 1H), 6.96 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 1H), 7.24 (d, *J* = 2.9 Hz, 1H), 7.60 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.77 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.43 (dd, *J* = 8.3, 0.9 Hz, 1H), 8.67 (d, *J* = 5.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.9, 103.3, 114.9, 116.7, 118.9, 121.0, 121.9, 123.7, 126.2, 129.0, 130.1, 144.5, 149.7, 151.0, 157.9, 161.3 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}BrNO_2$: 330.0130; found: 330.0125.

4-((1-Bromonaphthalen-2-yl)oxy)quinoline (1n): Method (a) - off-white solid (0.318 g, 61%); m.p. = 197-200 °C. IR (film) ν_{max} 3062, 1594, 1568, 1499, 1392, 1253, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.42 (d, *J* = 5.1 Hz, 1H), 7.36 (d, *J* = 8.8 Hz, 1H), 7.55-7.72 (m, 3H), 7.80 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 8.8 Hz, 1H), 8.14 (d, *J* = 8.5 Hz, 1H), 8.33 (d, *J* = 8.5 Hz, 1H), 8.51 (dd, *J* = 8.3, 1.0 Hz, 1H), 8.56 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 103.9, 115.2, 121.1, 121.3, 122.0, 126.3, 126.6, 127.1, 128.2, 128.4, 129.1, 129.8, 130.3, 132.4, 133.2, 149.0, 149.8, 151.1, 160.8 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{13}BrNO$: 350.0181; found: 350.0178.

4-((2-Bromopyridin-3-yl)oxy)quinoline (1o): Method (a) - pale pink solid (0.2378 g, 79%); m.p. 170-173 °C. IR (film) ν_{max} 1639, 1503, 1305, 1268, 666 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.45 (d, *J* = 5.1 Hz, 1H), 7.38 (dd, *J* = 8.0, 4.6 Hz, 1H), 7.47-7.70 (m, 2H), 7.79 (ddd, *J* = 8.4, 7.0, 1.4 Hz, 1H), 8.13 (d, *J* = 8.5 Hz, 1H), 8.28-8.47 (m, 2H), 8.72 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.1, 121.0, 121.7, 124.0, 126.7, 129.2, 130.5, 130.5, 136.6, 147.0, 148.7, 149.9, 150.8, 159.9 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_{10}BrN_2O$: 300.9976; found: 300.9986.

4-(2-Bromophenoxy)-2-methylquinoline (1p): Method (a) - pale pink solid (0.331 g, 93%); m.p. = 98-101 °C. IR (film) ν_{max} 2923, 1599, 1470, 1342, 1235, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.60 (s, 3H), 6.29 (s, 1H), 7.15-7.29 (m, 2H), 7.42 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.54 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.68-7.79 (m, 2H), 8.02 (d, *J* = 8.4 Hz, 1H), 8.35 (dd, *J* = 8.4, 1.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.8, 104.2, 116.3, 119.5, 121.7, 123.2, 125.4, 127.1, 128.3, 129.1, 130.2, 134.3, 149.4, 151.3, 159.9, 160.8 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}BrNO$: 314.0181; found: 314.0179.

4-(2-Bromophenoxy)-6-methoxyquinoline (1q): Method (a) - yellow sticky oil (0.599 g, 70%); IR (film) ν_{max} 3392, 1596, 1467, 1365, 1262, 1223, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.98 (s, 3H), 6.40 (d, *J* = 5.1 Hz, 1H), 7.16-7.29 (m, 2H), 7.37-7.47 (m, 2H), 7.64 (d, *J* = 2.8 Hz, 1H), 7.73 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 8.54 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.7, 99.4, 104.2, 116.4, 121.8, 122.9, 123.2, 127.2, 129.2, 130.7, 134.3, 145.9, 148.4, 151.3, 157.8, 159.7 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{13}BrNO_2$: 330.0130; found: 330.0130.

4-(2-Bromophenoxy)-7-methoxyquinoline (1r): Method (a) - pale yellow solid (0.380 g, 74%); m.p. = 99-100 °C. IR (film) ν_{max} 3388, 1622, 1428, 1315, 1227, 665 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.98 (s, 3H), 6.30 (d, *J* = 5.2 Hz, 1H), 7.15-7.29 (m, 3H), 7.36-7.47 (m, 2H), 7.72 (dd, *J* = 7.9, 1.5 Hz, 1H), 8.29 (d, *J* = 9.2 Hz, 1H), 8.59 (d, *J* = 5.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5, 102.4, 107.3, 115.8, 116.3, 119.2, 123.1, 123.2, 127.1, 129.1, 134.2, 151.2, 151.5, 151.8, 160.7, 161.3 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{12}BrNO_2$: 330.0130; found: 330.0128.

4-(2-Bromophenoxy)-6-(trifluoromethyl)quinoline (1s): Method (a) - off-white solid (0.254 g, 80%); m.p. = 67-69 °C. IR (film) ν_{max} 3069, 1570, 1467, 1316, 1224, 1126, 739 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.47 (d, *J* = 5.2 Hz, 1H), 7.21-7.32 (m, 2H), 7.46 (ddd, *J* = 8.1, 7.3, 1.6 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.95 (dd, *J* = 8.9, 2.1 Hz, 1H), 8.22 (d, *J* = 8.9 Hz, 1H), 8.76 (s, 1H), 8.77 (d, *J* = 5.2 Hz, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 104.4, 116.4, 120.2, 120.3 (q, $^3J_{(C,F)}$ = 5 Hz), 123.4, 124.1 (q, $^1J_{(C,F)}$ = 272 Hz), 126.0 (q, $^3J_{(C,F)}$ = 3 Hz), 127.8, 128.2 (q, $^2J_{(C,F)}$ = 33 Hz), 129.4, 130.3, 134.5, 150.6, 150.7, 153.2, 161.3 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -62 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{10}BrF_3NO$: 367.9898; found: 367.9894.

4-(2-Bromophenoxy)-6-fluoroquinoline (1t): Method (a) - pale yellow solid (0.344 g, 65%); m.p. = 75-79 °C. IR (film) ν_{max} 3422, 1630, 1262, 1222, 1177, 657 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.43 (d, *J* = 5.1 Hz, 1H), 7.19-7.24 (m, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.54 (td, *J* = 8.7, 2.8 Hz, 1H), 7.73 (d, *J* = 9.9 Hz, 1H), 8.02 (dd, *J* = 9.3, 2.8 Hz, 1H), 8.12 (dd, *J* = 9.2, 5.2 Hz, 1H), 8.64 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.0, 105.7 (d, $^2J_{(C,F)}$ = 24 Hz), 116.3, 120.4 (d, $^2J_{(C,F)}$ = 26 Hz), 121.7 (d, $^3J_{(C,F)}$ = 10 Hz), 123.3, 127.5, 129.3, 131.7 (d, $^3J_{(C,F)}$ = 10 Hz), 134.4, 146.9, 150.3 (d, $^6J_{(C,F)}$ = 3 Hz), 150.8, 160.3 (d, $^4J_{(C,F)}$ = 5 Hz), 160.4 (d, $^1J_{(C,F)}$ = 248 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -113 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrFNO$: 317.9930; found: 317.9917.

4-(2-Bromophenoxy)-8-fluoroquinoline (1u): Method (a) - pale yellow crystalline solid (0.2519 g, 53%); m.p. 87-90 °C. IR (film) ν_{max} 1631, 1597, 1264, 1224, 949, 612 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.45 (d, *J* = 5.1 Hz, 1H), 7.12-7.29 (m, 2H), 7.34-7.58 (m, 3H), 7.70 (dd, *J* = 8.0, 1.4 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.71 (d, *J* = 5.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.4, 114.3 (d, $^4J_{(C,F)}$ = 19 Hz), 116.2, 117.7 (d, $^4J_{(C,F)}$ = 5 Hz), 122.7 (d, $^3J_{(C,F)}$ = 3 Hz), 123.2, 126.0 (d, $^3J_{(C,F)}$ = 8 Hz), 127.55, 129.3, 134.3, 140.0 (d, $^2J_{(C,F)}$ = 13 Hz), 150.7, 151.2, 157.9 (d, $^1J_{(C,F)}$ = 256 Hz), 160.6 (d, $^4J_{(C,F)}$ = 4 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -125 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrFNO$: 317.9930; found: 317.9918.

4-(2-Bromophenoxy)-6-chloroquinoline (1v): Method (a) - off-white solid (0.4525 g, 90%); m.p. 89-90 °C. IR (film) ν_{max} 1642, 1563, 1262, 1222, 666, 643 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.41 (d, *J* = 5.2 Hz, 1H), 7.17-7.30 (m, 2H), 7.44 (ddd, *J* = 8.2, 7.3, 1.6 Hz, 1H), 7.65-7.69 (m, 2H), 8.04 (d, *J* = 9.0 Hz, 1H), 8.40 (d, *J* = 2.3 Hz, 1H), 8.66 (d, *J* = 5.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.2, 116.3, 121.0, 121.6, 123.2, 127.5, 129.3, 130.8, 131.1, 132.2, 134.3, 148.1, 150.7, 151.2, 160.0 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}BrClNO$: 333.9634; found: 333.9628.

4-(2-Bromophenoxy)-2-heptylquinoline (1w): Method (a) - off-white solid (0.205 g, 90%); m.p. = 75-77 °C. IR (film) ν_{max} 2926, 2855, 1600, 1470, 1359, 1234, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.85 (t, *J* = 6.7 Hz, 3H), 1.14-1.42 (m, 8H), 1.68 (m, 2H), 2.80 (t, *J* = 8.1 Hz, 2H), 6.30 (s, 1H), 7.17-7.25 (m, 2H), 7.42 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.53 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H), 7.63-7.81 (m, 2H), 8.05 (d, *J* = 8.4 Hz, 1H), 8.34 (dd, *J* = 8.3, 0.9 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 29.2, 29.4, 30.0, 31.8, 39.7, 103.8, 116.3, 119.7, 121.7, 123.1, 125.4, 127.1, 128.5, 129.2, 130.1, 134.3, 149.5, 151.4, 160.7, 164.2 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{25}BrNO$: 398.1120; found: 398.1135.

General Procedure for Palladium-Catalysed Intramolecular Direct Arylation Reactions for the Preparation of Compounds 2a-2w: A mixture of the 4-(2-bromophenoxy)quinoline substrate 1 (1 equiv.), $Pd(OAc)_2$ (2-5 mol%), and anhydrous caesium carbonate (2 equiv.) in anhydrous *N*-methylpyrrolidone (1.5 mL/mmol) was stirred at 135 °C in a sealed reaction tube until the reaction was completed as evident by ^{1}H NMR analysis. The cooled reaction mixture was diluted with DCM, filtered through a short plug of Celite and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel using DCM/EtOAc (99:1 – 95:5) as eluent.

Benzofuro[3,2-*c*]quinoline (2a):[27] White solid (0.068 g, 95%); m.p. = 132-135 °C (lit.[27] 135-138 °C). IR (film) ν_{max} 3369, 1566, 1510, 1399, 1190 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.44-7.58 (m, 2H), 7.65-7.83 (m, 3H), 8.12 (dd, *J* = 7.2, 0.9 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.44 (dd, *J* = 8.1, 1.0 Hz, 1H), 9.51 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.3, 117.2, 120.6, 120.8, 122.7, 124.1, 127.0, 127.2, 129.3, 129.9, 144.4, 147.4, 156.0, 157.5 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{10}NO$: 220.0762; found: 220.0755.

9-Fluorobenzofuro[3,2-*c*]quinoline (2b):[53] White solid (0.064 g, 88%); m.p. = 149-150 °C (lit.[53] 148-150 °C). IR (film) ν_{max} 3052, 1564, 1512, 1396, 1254, 1134 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.22 (ddd, *J* = 8.9, 6.9, 2.2 Hz, 1H), 7.45 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.63-7.85 (m, 2H), 8.00 (dd, *J* = 8.6, 5.3 Hz, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 8.36 (dd, *J* = 8.1, 1.1 Hz, 1H), 9.43 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 100.3 (d, $^2J_{(C,F)}$ = 27 Hz), 112.3 (d, $^2J_{(C,F)}$ = 24 Hz), 115.8, 117.0, 118.9 (d, $^4J_{(C,F)}$ = 2 Hz), 120.6, 121.2 (d, $^3J_{(C,F)}$ = 10 Hz), 127.2, 129.4, 129.8, 143.9, 147.1, 156.1 (d, $^3J_{(C,F)}$ = 14 Hz), 158.1 (d, $^5J_{(C,F)}$ = 3 Hz), 162.2 (d, $^1J_{(C,F)}$ = 247 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -112 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9FNO$: 238.0668; found: 238.0668.

8-Fluorobenzofuro[3,2-c]quinoline (2c):[27] White solid (0.087 g, 91%); m.p. = 163-164 °C (lit.[27] 162-163 °C). IR (film) ν_{max} 3368, 1565, 1479, 1319, 1247, 1146 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.21-7.33 (m, 1H), 7.65-7.87 (m, 4H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.41 (dd, *J* = 8.1, 1.0 Hz, 1H), 9.45 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 106.7 (d, $^2J_{(C,F)}$ = 26 Hz), 112.9 (d, $^3J_{(C,F)}$ = 9 Hz), 114.7 (d, $^2J_{(C,F)}$ = 26 Hz), 116.1 (d, $^4J_{(C,F)}$ = 4 Hz), 117.0, 120.8, 123.6 (d, $^3J_{(C,F)}$ = 11 Hz), 127.2, 129.6, 129.9, 144.2, 147.5, 151.9, 158.6, 159.7 (d, $^1J_{(C,F)}$ = 241 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -118 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9FNO$: 238.0668; found: 238.0659.

10-Fluorobenzofuro[3,2-c]quinoline (2d):[27] White solid (0.104 g, 93%); m.p. = 156-157 °C (lit.[27] 157-158 °C). IR (film) ν_{max} 3368, 1564, 1496, 1347, 1200, 1189 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27-7.35 (m, 1H), 7.42 (td, *J* = 8.0, 4.4 Hz, 1H), 7.73 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.79-7.92 (m, 2H), 8.29 (d, *J* = 8.2 Hz, 1H), 8.49 (dd, *J* = 8.1, 0.9 Hz, 1H), 9.50 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 113.7 (d, $^2J_{(C,F)}$ = 16 Hz), 116.0, 116.1 (d, $^4J_{(C,F)}$ = 4 Hz), 117.0, 120.8, 124.8 (d, $^3J_{(C,F)}$ = 6 Hz), 126.2 (d, $^3J_{(C,F)}$ = 3 Hz), 127.3, 129.7, 129.8, 142.7 (d, $^2J_{(C,F)}$ = 11 Hz), 144.3, 147.7, 148.3 (d, $^1J_{(C,F)}$ = 251 Hz), 157.8 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -135 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9FNO$: 238.0668; found: 238.0662.

9-Chlorobenzofuro[3,2-c]quinoline (2e): White solid (0.086 g, 79%); m.p. = 198-199 °C. IR (film) ν_{max} 3047, 1562, 1508, 1338, 1049, 755 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.66-7.87 (m, 3H), 8.00 (d, *J* = 8.3 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 9.46 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 112.8, 115.7, 117.0, 120.7, 121.1, 121.4, 124.8, 127.2, 129.6, 129.9, 132.9, 144.1, 147.5, 156.0, 157.8 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9ClNO$: 254.0373; found: 254.0363.

8-Chlorobenzofuro[3,2-c]quinoline (2f):[27] White solid (0.071 g, 93%); m.p. = 187-189 °C (lit.[27] 189-190 °C). IR (film) ν_{max} 2917, 1564, 1511, 1395, 1194, 871 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (dd, *J* = 8.8, 2.2 Hz, 1H), 7.69 (dd, *J* = 8.8, 0.4 Hz, 1H), 7.72 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 7.82 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 8.08 (dd, *J* = 2.2, 0.4 Hz, 1H), 8.28 (d, *J* = 8.2 Hz, 1H), 8.41 (dd, *J* = 8.2, 0.9 Hz, 1H), 9.46 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 113.1, 115.5, 117.0, 120.5, 120.8, 124.1, 127.28, 127.34, 129.75, 129.78, 130.0, 144.2, 147.6, 154.2, 158.2 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9ClNO$: 254.0373; found: 254.0370.

8-(Trifluoromethyl)benzofuro[3,2-c]quinoline (2g): White crystalline solid (0.0533 g, 88%); m.p. 170-173 °C. IR (film) ν_{max} 1627, 1567, 1333, 1310, 1151, 1110 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.65-7.91 (m, 4H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.35-8.48 (m, 2H), 9.52 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 112.5, 115.4, 116.8, 118.3 (q, $^3J_{(C,F)}$ = 4 Hz), 120.7, 123.0, 124.3 (q, $^3J_{(C,F)}$ = 4 Hz), 124.3 (q, $^1J_{(C,F)}$ = 272 Hz), 126.8 (q, $^2J_{(C,F)}$ = 33 Hz), 127.4, 129.9, 130.0, 144.1, 147.8, 157.2, 158.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -61 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_9F_3NO$: 288.0636; found: 288.0629.

8-(Trifluoromethoxy)benzofuro[3,2-c]quinoline (2h): White crystalline solid (0.1367 g, 90%); m.p. 124-126 °C. IR (film) ν_{max} 1641, 1512, 1280, 1247, 1206, 1141, 1156 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41 (ddd, *J* = 8.9, 2.4, 0.8 Hz, 1H), 7.64-7.88 (m, 3H), 7.95 (d, *J* = 1.1 Hz, 1H), 8.28 (d, *J* = 8.4 Hz, 1H), 8.41 (dd, *J* = 8.1, 1.0 Hz, 1H), 9.47 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 113.0, 113.6, 115.9, 117.0, 120.6 (q, $^1J_{(C,F)}$ = 257 Hz), 120.7, 120.8, 123.8, 127.4, 129.9, 130.0, 144.2, 145.8, 147.8, 153.9, 158.7 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -58 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_9F_3NO_2$: 304.0585; found: 304.0574.

8-Nitrobenzofuro[3,2-*c*]quinoline (2i): Orange solid (0.028 g, 46%); m.p. >250 °C. IR (film) ν_{max} 3030, 1528, 1397, 1344, 1200 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77 (ddd, *J* = 8.1, 7.2, 1.0 Hz, 1H), 7.84-7.91 (m, 2H), 8.32 (d, *J* = 8.5 Hz, 1H), 8.41-8.52 (m, 2H), 9.02 (d, *J* = 2.3 Hz, 1H), 9.56 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.6, 115.4, 116.8, 117.1, 120.8, 123.0, 123.6, 127.8, 130.1, 130.5, 144.1, 144.9, 148.1, 158.6, 159.3 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9N_2O_3$: 265.0613; found: 265.0611.

Methyl benzofuro[3,2-*c*]quinoline-9-carboxylate (2j): Beige solid (0.043 g, 56%); m.p. = 192-193 °C. IR (film) ν_{max} 3402, 1717, 1565, 1434, 1397, 1281, 1234 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.00 (s, 3H), 7.70 (m, 1H), 7.81 (ddd, *J* = 8.5, 7.0, 1.5 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.36-8.43 (m, 2H), 9.46 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 52.5, 113.6, 115.5, 116.9, 120.2, 121.0, 125.5, 126.8, 127.3, 129.0, 129.9, 130.0, 144.5, 147.8, 155.4, 159.0, 166.6 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{17}H_{12}NO_3$: 278.0817; found: 278.0811.

8-Methylbenzofuro[3,2-*c*]quinoline (2k):[27] White solid (0.062 g, 71%); m.p. = 145-148 °C (lit.[27] 149-150 °C). IR (film) ν_{max} 2917, 1564, 1510, 1321, 1192 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 7.35 (ddd, *J* = 8.5, 1.8, 0.5 Hz, 1H), 7.61-7.73 (m, 2H), 7.78 (ddd, *J* = 8.5, 6.9, 1.6 Hz, 1H), 7.89-7.92 (m, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 8.41 (dd, *J* = 8.1, 0.9 Hz, 1H), 9.47 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.4, 111.5, 116.2, 117.2, 120.5, 120.8, 122.6, 126.8, 128.3, 129.1, 129.8, 133.7, 144.3, 147.3, 154.3, 157.6 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{12}NO$: 234.0919; found: 234.0921.

8-(tert-Butyl)benzofuro[3,2-*c*]quinoline (2l):[27] Pale yellow solid (0.025 g, 50%); m.p. = 97-100 °C (lit.[27] 99-100 °C). IR (film) ν_{max} 2962, 1567, 1488, 1392, 1201 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 1.47 (s, 9H), 7.61 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.67-7.72 (m, 2H), 7.79 (ddd, *J* = 8.4, 6.9, 1.5 Hz, 1H), 8.10 (d, *J* = 1.7 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.42 (dd, *J* = 8.2, 1.0 Hz, 1H), 9.52 (s, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ: 31.9, 35.0, 111.4, 116.7, 116.9, 117.3, 120.8, 122.3, 125.1, 126.9, 129.2, 129.8, 144.4, 147.3, 147.4, 154.2, 157.8 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{18}NO$: 276.1388; found: 276.1377.

8-Methoxybenzofuro[3,2-*c*]quinoline (2m):[28] Off-white solid (0.032 g, 42%); m.p. = 165-167 °C (lit.[28] 160-162 °C). IR (film) ν_{max} 3350, 1570, 1486, 1330, 1186, 1164 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.96 (s, 3H), 7.13 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.54 (d, *J* = 2.6 Hz, 1H), 7.59-7.85 (m, 3H), 8.26 (d, *J* = 8.4 Hz, 1H), 8.40 (dd, *J* = 8.1, 1.0 Hz, 1H), 9.46 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.1, 103.3, 112.6, 115.5, 116.6, 117.3, 120.8, 123.3, 127.0, 129.3, 129.8, 144.4, 147.3, 150.7, 156.9, 158.1 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{12}NO_2$: 250.0868; found: 250.0858.

Naphtho[1',2':4,5]furo[3,2-*c*]quinoline (2n): Off-white solid (0.014 g, 17%); m.p. = 203-205 °C. IR (film) ν_{max} 2919, 1562, 1507, 1310, 1223 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ: 7.64 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.75 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.79-7.85 (m, 2H), 7.94 (d, *J* = 8.9 Hz, 1H), 8.02 (d, *J* = 8.9 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 8.33 (d, *J* = 8.4 Hz, 1H), 8.51 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.69 (d, *J* = 8.2 Hz, 1H), 9.97 (s, 1H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ: 112.7, 117.0, 117.3, 117.7, 120.7, 124.2, 125.3, 127.2, 127.7, 128.5, 128.8, 129.2, 129.4, 129.8, 131.0, 145.1, 146.4, 154.1, 157.0 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{19}H_{12}NO$: 270.0919; found: 270.0916.

Pyrido[2',3':4,5]furo[3,2-c]quinoline (2o): Pale yellow solid (0.0896 g, 81%); m.p. 174-175 °C. IR (film) ν_{max} 1637, 1570, 1306, 1264 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.42 (dd, *J* = 8.4, 4.8 Hz, 1H), 7.60-7.86 (m, 2H), 7.96 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.17-8.43 (m, 2H), 8.71 (dd, *J* = 4.8, 1.2 Hz, 1H), 9.66 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 115.3, 116.9, 119.0, 120.6, 121.3, 127.3, 130.0, 130.2, 142.8, 144.4, 146.6, 148.2, 149.2, 159.1 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{14}H_9N_2O$: 221.0715; found: 221.0710.

6-Methylbenzofuro[3,2-*c*]quinoline (2p):[27] Pale yellow solid (0.029 g, 78%); m.p. = 132-134 °C (lit.[27] 132-133 °C). IR (film) ν_{max} 3380, 1563, 1509, 1364, 1084 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.16 (s, 3H), 7.41-7.69 (m, 3H), 7.72-7.79 (m, 2H), 8.10 (dd, *J* = 7.6, 2.1 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.38 (dd, *J* = 8.1, 2.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 24.3, 112.1, 115.5, 116.2, 120.7, 121.8, 123.5, 124.0, 126.1, 126.7, 128.9, 129.4, 146.9, 154.8, 155.9, 157.5 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{12}NO$: 234.0919; found: 234.0915.

2-Methoxybenzofuro[3,2-c]quinoline (2q):[27] Off-white solid (0.095 g, 84%); m.p. = 150-152 °C (lit.[27] 150-153 °C). IR (film) ν_{max} 2954, 1350, 1514, 1468, 1228, 1191, 1031 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.96 (s, 3H), 7.28-7.53 (m, 4H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.97 (dd, *J* = 7.4, 0.8 Hz, 1H), 8.08 (d, *J* = 9.2 Hz, 1H), 9.23 (s, 1H) ppm ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.6, 98.5, 111.9, 116.4, 117.7, 120.6, 121.7, 122.8, 123.9, 127.1, 131.3, 141.5, 143.3, 155.8, 156.7, 158.2 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{12}NO_2$: 250.0868; found: 250.0858.

3-Methoxybenzofuro[3,2-c]quinoline (2r): Off-white solid (0.091 g, 81%); m.p. = 146-147 °C. IR (film) ν_{max} 3022, 1639, 1452, 1345, 1324, 1242, 1168 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 3.97 (s, 3H), 7.31 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.36-7.54 (m, 2H), 7.58 (d, *J* = 2.3 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 7.1 Hz, 1H), 8.25 (d, *J* = 9.0 Hz, 1H), 9.37 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 55.5, 108.4, 111.7, 112.0, 115.0, 119.7, 120.3, 121.9, 122.8, 123.9, 126.7, 144.6, 149.3, 155.8, 157.8, 160.7 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_{12}NO_2$: 250.0868; found: 250.0865.

2-(Trifluoromethyl)benzofuro[3,2-*c*]quinoline (2s): Yellow solid (0.049 g, 63%); m.p. = 141-143 °C. IR (film) ν_{max} 2917, 1567, 1443, 1348, 1167, 1111 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.43-7.67 (m, 2H), 7.80 (d, *J* = 8,2 Hz, 1H), 7.96 (dd, *J* = 9.0, 2.0 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 8.9 Hz, 1H), 8.75 (s, 1H), 9.60 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.3, 116.3, 117.3, 119.1 (q, $^3J_{(C,F)}$ = 5 Hz), 120.8, 122.1, 124.3 (q, $^1J_{(C,F)}$ = 270 Hz), 124.5, 124.9 (q, $^3J_{(C,F)}$ = 3 Hz), 127.9, 128.8 (q, $^2J_{(C,F)}$ = 33 Hz), 131.0, 146.4, 148.0, 156.1, 157.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -62 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{16}H_9F_3NO$: 288.0636; found: 288.0634.

2-Fluorobenzofuro[3,2-*c*]quinoline (2t):[53] White solid (0.025 g, 67%); m.p. = 146-148 °C (lit.[53] 148-149 °C). IR (film) ν_{max} 3399, 1515, 1462, 1364, 1195, 1175 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.45-7.61 (m, 3H), 7.76 (d, *J* = 8.1 Hz, 1H), 8.00 (dd, *J* = 8.6, 2.8 Hz, 1H), 8.10 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.26 (dd, *J* = 9.3, 5.2 Hz, 1H), 9.45 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 104.7 (d, $^2J_{(C,F)}$ = 24 Hz), 112.2, 116.8, 117.8 (d, $^3J_{(C,F)}$ = 11 Hz), 119.3 (d, $^2J_{(C,F)}$ = 26 Hz), 120.8, 122.5, 124.2, 127.6, 132.5 (d, $^3J_{(C,F)}$ = 9 Hz), 143.6 (d, $^6J_{(C,F)}$ = 3 Hz), 144.4, 156.1, 157.1 (d, $^4J_{(C,F)}$ = 5 Hz), 160.8 (d, $^1J_{(C,F)}$ = 249 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -111 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9FNO$: 238.0668; found: 238.0659.

4-Fluorobenzofuro[3,2-c]quinoline (2u): White crystalline solid (0.0405 g, 49%); m.p. 153-155 °C. IR (film) ν_{max} 1640, 1596, 1300, 1249, 949 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.68 (m, 4H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.99-8.27 (m, 2H), 9.53 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ: 112.2, 113.7 (d, $^2J_{(C,F)}$ = 19 Hz), 116.6 (d, $^2J_{(C,F)}$ = 19 Hz), 117.3, 118.9 (d, $^3J_{(C,F)}$ = 3 Hz), 120.9, 122.4, 124.3, 127.1 (d, $^3J_{(C,F)}$ = 8 Hz), 127.7, 137.3 (d, $^2J_{(C,F)}$ = 12 Hz), 144.6, 156.0, 157.0 (d, $^4J_{(C,F)}$ = 5 Hz), 158.6 (d, $^1J_{(C,F)}$ = 257 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$) δ: -122 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. For $C_{15}H_9FNO$: 238.0668; found: 238.0661.

2-Chlorobenzofuro[3,2-c]quinoline (2v):[53] White crystalline solid (0.0865 g, 68%); m.p. 141-142 °C (lit.[53] 139-141 °C). ^1H NMR (300 MHz, $CDCl_3$) δ: 7.38-7.58 (m, 2H), 7.59-7.76 (m, 2H), 8.02 (dd, *J* = 7.6, 0.6 Hz, 1H), 8.12 (d, *J* = 9.0 Hz, 1H), 8.27 (d, *J* = 2.3 Hz, 1H), 9.38 (s, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 112.2 116.9, 117.7, 119.8, 120.7, 122.3, 124.2, 127.6, 130.0, 131.4, 132.9, 144.4, 145.5, 156.0, 156.3 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_9ClNO$: 254.0373; found: 254.0368.

6-Heptylbenzofuro[3,2-*c*]quinoline (2w): White solid (0.056 g, 70%); m.p. = 90-92 °C. IR (film) ν_{max} 2917, 1559, 1445, 1363, 1202 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.88 (t, *J* = 6.7 Hz, 3H), 1.22-1.64 (m, 8H), 1.95 (dt, *J* = 15.7, 7.7 Hz, 2H), 3.40 (t, *J* = 8.0 Hz, 2H), 7.40-7.67 (m, 3H), 7.69-7.79 (m, 2H), 8.00 (d, *J* = 7.3 Hz, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 8.1 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 28.6, 29.2, 29.9, 31.8, 38.0, 112.1, 114.8, 116.2, 120.7, 121.8, 123.1, 124.0, 126.0, 126.6, 129.1, 129.3, 146.9, 155.9, 157.7, 159.0 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{22}H_{24}NO$: 318.1858; found: 318.1845.

Synthesis of *N*-(2-bromophenyl)quinolin-4-amine (3): To a degassed solution of $Pd_2(dba)_3$ (2 mol%) and XantPhos (4 mol%) in anhydrous 1,4-dioxane (4 mL/mmol) were added caesium carbonate (1.4 equiv.), 4-bromoquinoline (1 equiv.) and 2-bromoaniline (1.1 equiv.) under a nitrogen atmosphere. The reaction mixture was stirred at 120 °C under nitrogen for 24 h. The cooled reaction mixture was diluted with DCM, filtered through Celite and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel using DCM/EtOAc (3:1) as eluent to yield the product as a yellow solid (0.322 g, 74%); m.p. = 238-241 °C. IR (film) ν_{max} 3360, 3061, 1572, 1526, 1335, 747 cm^1. ^1H NMR (300 MHz, $CDCl_3$) δ: 6.88 (bs, 1H), 7.02 (td, *J* = 8.0, 1.5 Hz, 1H), 7.08 (d, *J* = 5.2 Hz, 1H), 7.31-7.38 (m, 1H), 7.51-7.61 (m, 2H), 7.65-7.78 (m, 2H), 8.01 (d, *J* = 8.3 Hz, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.66 (d, *J* = 5.2 Hz, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 103.4, 116.9, 120.0, 120.3, 122.2, 125.0, 125.8, 128.4, 129.6, 130.1, 133.5, 138.3, 146.2, 149.2, 150.8 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{12}BrN_2$: 299.0184; found: 299.0187.

Synthesis of 11H-indolo[3,2-c]quinoline (4)[54]: *N*-(2-bromophenyl)quinolin-4-amine **3** (1 equiv.), $Pd(OAc)_2$ (5 mol%), $PCy_3.HBF_4$ (10 mol%) and caesium carbonate (2 equiv.) were added to degassed *N*-methylpyrrolidone (1.5 mL/mmol) under Schlenk conditions under a nitrogen atmosphere. The reaction mixture was stirred at 150 °C (sand bath) for 3 h. The cooled reaction mixture was diluted with DCM and filtered through Celite. The mixture was washed with water (3 x 10 mL) and brine (15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by column chromatography over silica gel using DCM/EtOAc (7:3) as eluent to yield the product as an off-white solid (0.030 g, 83%); m.p. >250 °C (lit.[54] 340-341 °C). IR (film) ν_{max} 3355, 2916, 2849, 1567, 1512, 1459, 1236 cm^{-1}. ^1H NMR (300 MHz, DMSO-d^6) δ: 7.35 (t, *J* = 7.5 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.63-7.81 (m, 3H), 8.15 (dd, *J* = 8.2, 1.3 Hz, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 8.53 (dd, *J* = 8.0, 1.4 Hz, 1H), 9.60 (s, 1H), 12.72 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d^6) δ: 112.3, 114.8, 117.6, 120.6, 121.1, 122.4, 122.6, 126.0, 126.1, 128.5, 130.0, 139.3, 140.2, 145.3, 145.9 ppm. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd. for $C_{15}H_{11}N_2$: 219.0922; found: 219.0911.

Supporting Information (see footnote on the first page of this article): Additional competition experiments, as well as ^1H, ^{13}C and ^{19}F NMR spectra of all new compounds, key intermediates and final products.

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Keywords: quinoline • direct arylation • CH activation •

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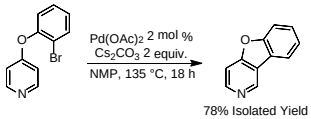
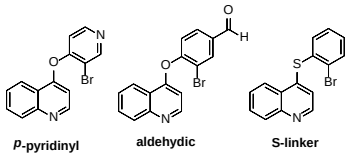
30. The authors wish to thank the reviewers for the suggestion to try the following reaction:



31. Substrates that failed to undergo clean coupling under the optimised conditions:



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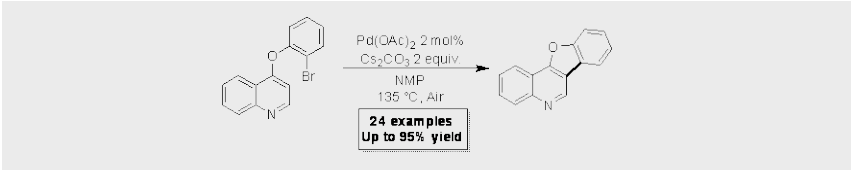

A palladium-catalysed, phosphine-free, direct arylation of 4-phenoxyquinolines in air is described. Using intramolecular direct arylation, the ring-closed products are formed in isolated yields of up to 95%. This approach allows access to a range of benzofuroquinolines, and an array of functional groups on both the quinoline and phenoxy rings is tolerated.

Direct Arylation

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Synthesis of benzofuroquinolines via phosphine-free direct arylation of 4-phenoxyquinolines in air .