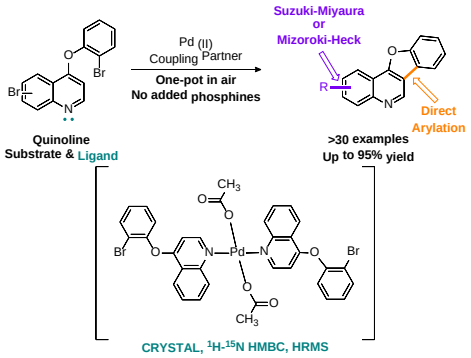
One-Pot Cross-Coupling/C-H Functionalisation Reactions: Quinoline as Substrate, and Ligand through N-Pd Interaction

Rachel M. Shanahan,[a†] Aobha Hickey,[a†] Lorraine Bateman,[a,b,c] Mark E. Light[d] and Gerard P. McGlacken*[a,b]

[a]School of Chemistry, Analytical and Biological Chemistry Research Facility, [b]Synthesis and Solid State Pharmaceutical Centre, [c]School of Pharmacy, University College Cork, Cork, T12 YN60, Ireland. [d]Department of Chemistry, University of Southampton, SO17 1BJ, United Kingdom.

*g.mcglacken@ucc.ie

[†]These two authors contributed equally.



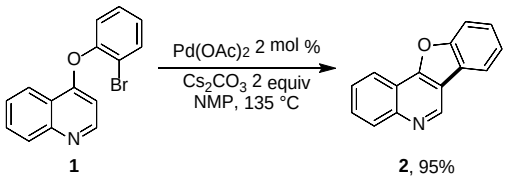
Abstract

Herein, we report a one-pot process which marries mechanistically distinct, traditional cross-coupling reactions with C-H functionalisation, using the same precatalyst. The reactions proceed in yields of up to 95%, in air, and require no extraneous ligand. The reactions are thought the be facilitated by harnessing the substrate quinoline as ligand and evidence of the palladium-quinoline interaction is provided by ^{1}H-^{15}N HMBC NMR spectroscopy as well as X-ray crystallographic structures. Application of the methodology is demonstrated by the quick formation of fluorescent, π-extended frameworks.

Introduction

The formation of multiple carbon-carbon bonds in a telescoped, one-pot procedure is an efficient and environmentally-friendly approach to the construction of new chemical entities.[1] However, carrying out two or more chemical reactions in a single vessel places significant demands on the methodologies involved, specifically in terms of reagent, catalyst and substrate compatibility.[2] Additionally, avoiding secondary manipulation during a reaction is highly preferable, if the procedures are to be applied industrially.

Pyridine, quinoline and furan moieties are prominent in synthetic and naturally occurring pharmacologically active compounds.[3] In drugs they represent the 2nd, 22nd and 25th most common ring systems respectively.[4] We recently reported a palladium-catalysed intramolecular direct arylation (DA) protocol which gives a variety of benzofuro[3,2-*c*]quinolines **2** from 4-(2-bromophenoxy)quinolines **1** in excellent yields (**Scheme 1**).[5]



1 **2**, 95%

Scheme 1 *Intramolecular direct arylation of* ***1****.*

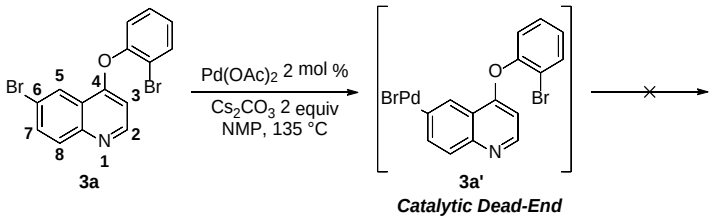
Chemoselectivity and regioselectivity proved very predictable in these mono-halogenated systems. Conversely, cross-coupling reactions involving substrates bearing more than one halogen are far less predictable.[6] The selective functionalisation of substrates with two different halogens usually relies upon the marked difference in the rates of oxidative addition (OA) at the C-X bonds. Using halogens of the same type is considerably more difficult, as significant rate differences in the oxidation step (I *vs* Br or Br *vs* Cl) are not easily harnessed.[7] A limited number of one-pot reactions combining C-H functionalisation with a Suzuki-Miyaura reaction have been reported.[8] However, we are aware of very few protocols which do not require perturbation of the reaction set-up by the addition of secondary reactants, reagents or catalysts, subsequent to reaction initiation.[9] In all cases, added phosphine

ligand is required. The use of phosphine ligands adds significantly to the cost of any catalytic process – in fact, they are often the most expensive component of a catalytic system.[10]

This report describes a selection of one-pot tandem Suzuki-Miyaura/Direct Arylation (SM/DA) and Mizoroki-Heck/Direct Arylation (MH/DA) reactions with di- and tri-bromoquinolines. Once the reaction is initiated, no further manipulation is required and no subsequent addition of solvents, reagents, reactants or catalysts is needed. Overall, the reaction proceeds using 2 mol% $Pd(OAc)_2$, in air, and without recourse to extraneous ligands. Through further development to a one-pot Heck-Mizoroki/Direct Arylation protocol, π-extended quinolines, with structural features of interest to medicinal[11] and materials[12] chemists, were prepared. These entities are challenging to synthesise by traditional, stepwise cross-coupling techniques.[13] We provide structural characterisation of initially-formed palladium-quinoline (Pd-Q) complexes using cystallography, mass spectrometry, and Heteronuclear Multiple Bond Correlation (HMBC) NMR spectroscopy.

Results and Discussion

Our initial aim was to test the chemoselectivity of **3a** and perhaps exploit entropic factors to carry out the intramolecular DA reaction, while leaving the bromide on the quinoline backbone untouched. Using the reaction conditions which had so efficiently furnished **2** from **1**, no DA was observed (**Scheme 2**). We doubted that the bromine on the quinoline ring would affect the electronics of the C-3 position to such an extent that C-H functionalisation would be prevented. Thus, we rationalised that OA at the quinoline-Br was favoured over the phenoxy-Br. In the absence of a suitable coupling partner, the OA product **3a'** was a catalytic dead-end, with the palladium trapped at a non-productive site.



Scheme 2 *Failed intramolecular DA of di-bromoquinoline* ***3a****.*

In an effort to liberate the palladium, phenyl boronic acid was introduced into the reaction mixture. Indeed, after optimisation, the Suzuki-Miyaura reaction occurred, along with the direct arylation, giving 2-phenyl-benzofuro[3,2-*c*]quinoline **4a** in 83% isolated yield (**Table 1**).

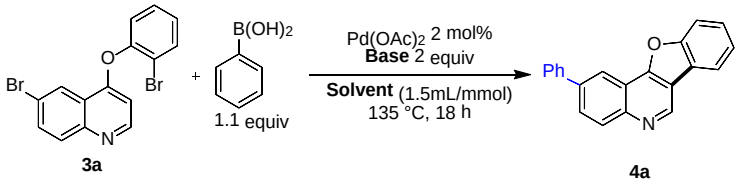


Table 1 *Solvent and base screen for tandem SM/DA reaction of* ***3a****.*

entry	base	solvent	conv. (%)	yield[a] (%)
1	Cs_2CO_3	NMP	100	73 (75)
2[b]	Cs_2CO_3	1,4-dioxane	90	68
3[c]	Cs_2CO_3	toluene	25	-
4[c]	Cs_2CO_3	xylene	16	-
5[c]	Cs_2CO_3	cyclohexanone	85	61
6[c]	Cs_2CO_3	*i*-PrOAc	25	-
7[c]	Cs_2CO_3	*n*-BuOAc	20	-
8	Na_2CO_3	NMP	100	80
9	K_2CO_3	NMP	100	86 (83)
10	KOH	NMP	30	20
11	NaOH	NMP	65	44
12	NaO*t*-Bu	NMP	0[d]	-

[a]Yields determined by [1]H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard, values in parentheses represent isolated yields. [b]Reaction carried out at 125 °C. [c]Reaction carried out at 110 °C. [d]Complete decomposition of ***3a*** *was observed.*

A broad range of substituted phenylboronic acids underwent one-pot tandem SM/DA coupling, allowing access to novel benzofuroquinolines in good to excellent yields. Both electron-releasing (**4b**, **4c**) and electron-withdrawing (**4d**–**4k**) groups were well tolerated. The chloride on **4f** and **4l** was

retained as a synthetic handle. Considering the prevalence of the pyridine moiety in biologically active compounds,[14] we also applied the SM/DA reaction conditions to this substrate and were pleased to furnish the benzofuropyridine **4m** in good yield. The Suzuki-Miyaura coupling was also conducive to positioning the bromine at C-7 (**4n**–**4r**) (**Figure 1**a).

We were then keen to expand the scope of our one-pot process to include Mizoroki-Heck transformations. Using either *tert*-butyl acrylate or styrene derivatives, the one-pot tandem MH/DA products were obtained in very good yields (**5a**–**5h**) (**Figure 1**b). Both transformations also worked efficiently when the second bromine was placed on the phenoxy ring (**6a**–**6c**) (**Figure 1**c). Given the apparent versatility of our methodology, a three-component tandem process was devised using tri-brominated substrates and two equivalents of either coupling partner (**7a**–**7c**) (**Figure 1**d). The structures of **4a**, **4n** and **5b** were confirmed by X-ray diffraction analysis of single crystals (**Figure 2**, see Supporting Information (SI) S3–S6).

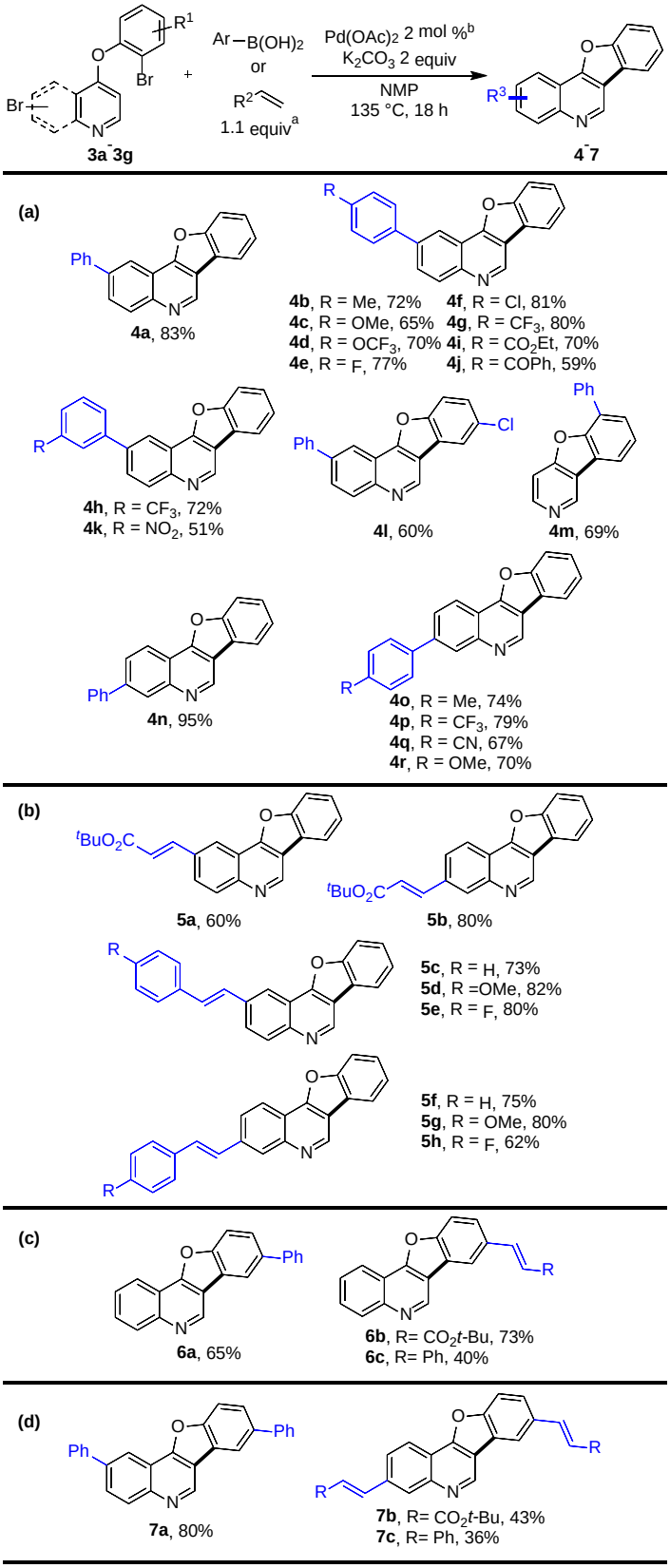


Figure 1 *One-pot tandem SM/DA and MH/DA substrate scope. All yields are isolated. [a]2.2 equiv. of coupling partner employed in the synthesis of* ***7a–7c****. [b]5 mol % Pd(OAc)₂ used for all styrene based derivatives.*

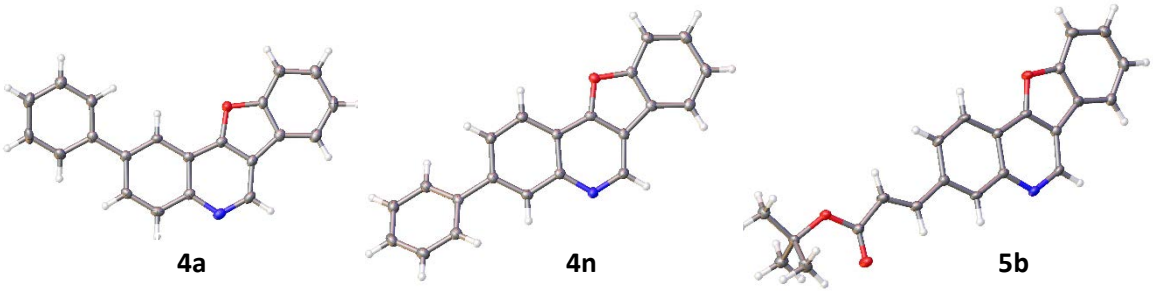
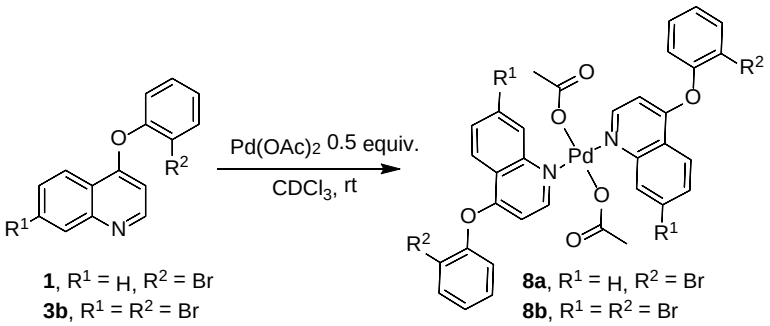


Figure 2 *Crystal structures of* ***4a****,* ***4n*** *and* ***5b*** *drawn at the 50% probability level. Second molecule in the asymmetric unit of* ***4a*** *omitted for clarity (see SI S4 for further information).*

Incorporating heteroatomic substrates in cross-coupling reactions usually necessitates the employment of added ligand and inert atmosphere[15] and in the reported C-H functionalisation of pyridines and quinolines,[16] ancillary ligands are also required. Considering that pyridines,[17] and indeed quinolines,[18] possess the propensity to act as ligands for palladium, we suspected that our methodology might be underpinned by Pd-Q coordination. In order to determine any Pd-Q interaction, we undertook ^{1}H-^{15}N HMBC NMR spectroscopy. Inherent in this powerful technique are gradient-enhanced pulse sequences, which allow for suppression of t_1 noise facilitating the observation of the relatively weak long-range ^{1}H-^{15}N correlations.[19] Overall, the low natural abundance and low gyromagnetic ratio are overcome. Using this technique, structures **8a** and **8b** were elucidated. Initially, 0.5 equiv. of $Pd(OAc)_2$ was added to **1** and to **3b** in $CDCl_3$ (**Scheme 3**) and the ^{1}H, ^{13}C and ^{1}H-^{15}N HMBC NMR spectra were recorded (see SI S14).



Scheme 3 *Precatalyst formation and structure.*

Complete consumption of both substrates was observed, accompanied by upfield shifts in the ^{1}H signals of the C-2, C-3 and C-8 protons and a dramatic upfield shift in the ^{15}N nucleus resonance (for example, from 291.7 ppm **1** to 196.7 ppm **8a**) in the respective ^{1}H-^{15}N HMBC spectra (**Figure 3**, SI S14–S25). The significant shielding of the nitrogen atom, and the considerable accompanying shift in both the C-2 and C-8 protons is indicative of direct Pd-N coordination.[20] Upon addition of $Pd(OAc)_2$ to **3h**, ^{1}H and ^{13}C NMR shifts analogous to those in **8a** and **8b** were observed. Similar downfield shifts were also discerned in the ^{1}H NMR spectra of **8a** in dioxane-d_8 and ACN-d_3 (SI S16, S20). Crystal structures for complexes **8a** and **8c** were obtained (**Figure 4**) and the compositions of **8a**–**8c** were also verified by HRMS data (SI S8–S13).

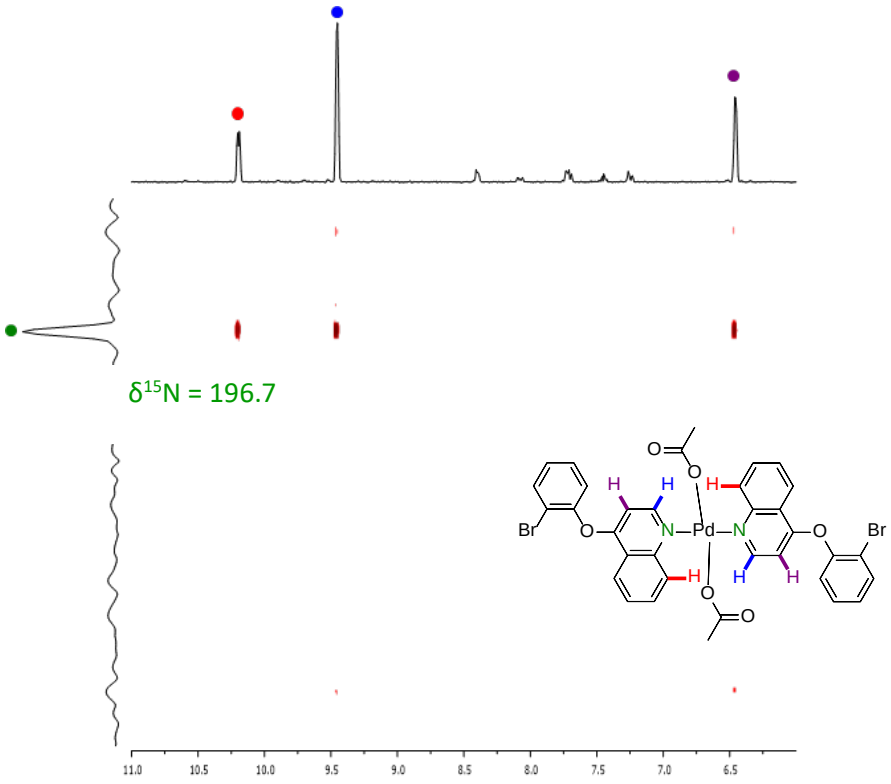


Figure 3 *^{1}H-^{15}N HMBC NMR spectrum of **8a** in $CDCl_3$ at 300 K as recorded at 600 MHz (^{1}H) and 60 MHz (^{15}N). All chemical shifts δ reported in ppm.*

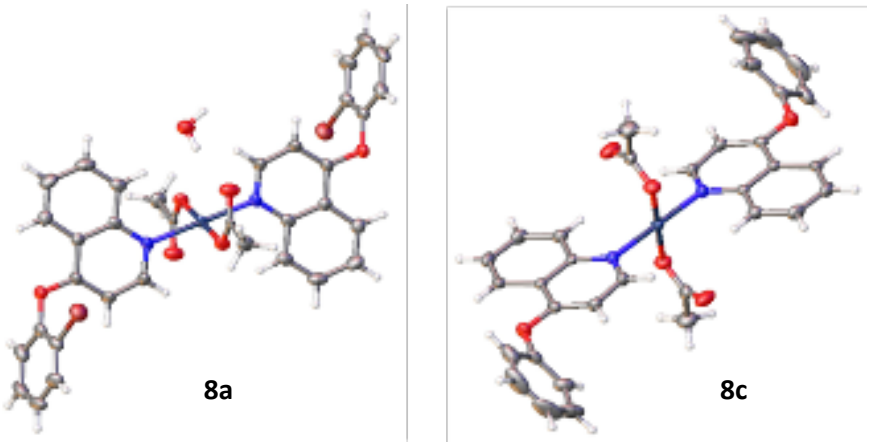
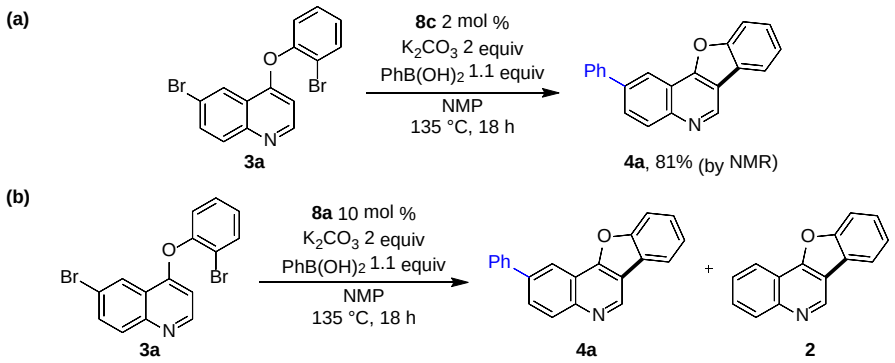


Figure 4 *Crystal structures of* ***8a*** *and* ***8c*** *drawn at the 50% probability level. Disordered solvent (methanol) treated using solvent masking techniques for structure* ***8c*** *(see SI S4–S7 for further information).*

We consider the Suzuki-Miyaura reaction to be the initial transformation in the sequence (SI Scheme S1 and Scheme S2), progressing *via* the typical Pd(II)/Pd(0) mechanistic cycle. For the DA step, we postulate two plausible mechanisms. Firstly, OA at C-Br followed by C-H activation *via*, for example, concerted metalation-deprotonation (CMD).[21] Secondly, a Pd(II)/Pd(IV) route is also plausible, as proposed by Yu and Morokuma.[16a,22]

Although undefined at this stage, we envisage these complexes playing an important role as precatalysts, with the quinoline aiding precatalyst-to-catalyst transformation, although it is difficult to rule out an additional role of the quinoline in preventing catalyst decomposition.[23] Importantly, **8c** was deemed a competent precatalyst for the SM/DA reaction (**Scheme 4**a). A further experiment using mono-bromo-Pd complex **8a** as the sole catalytic-source for the SM/DA reaction yielded both **2** and **4a**, proving the Pd-Q interaction is fluxional, and ruling out a spectator-only role for the quinoline ligands (analogous to phosphine ligands, for example) in the initially formed complexes **8a** and **8b** (**Scheme 4**b).[24]



Scheme 4 *Preformed **8c/8a** as competent precatalysts for the SM/DA reaction.*

Many small, conjugated organic molecules have the ability to emit fluorescent light and can be exploited for a variety of applications, such as in selective probes for ion detection,[12,25] optoelectronic devices[26] and as dyes or tags in bioimaging.[27] We were intrigued to investigate if our π-extended MH/DA products displayed any useful photophysical characteristics. Thus, UV-Visible absorption data for the styrene-functionalised compounds **2**, **5c**–**5h**, **6c** and **7c** was obtained and their fluorescent properties investigated. The standard benzofuro[3,2-*c*]quinoline framework **2** is given for comparison (**Table 2**).

Table 2 *UV-Vis data, fluorescence emission (em.) data and molar absorption coefficients (ε) for compounds **2**, **5c–5h**, **6c** and **7c** (See SI S125–S133 for more information).*

compd	abs. λ_{max} (nm)	em. λ_{em} (nm)	ε^a (dm^3 mol^{-1} cm^{-1})
2	257	353	63300
5c	301	389	45188
5d	259	416	38338
5e	300	388	42000
5f	337	387	38500
5g	260	421	31700
5h	336	386	43638
6c	258	382	36538
7c	342	346	51438

[a]ε calculated at 8 × 10^{-6} mol dm^{-3}.

All compounds exhibit their maximum absorption band (λ_{max}) in the UV or near-UV region and yield large molar absorption coefficients (ε) in the range of 10^4 dm^3 mol^{-1} cm^{-1}. The addition of further auxochromes to the substituted frameworks resulted in notable shifts in λ_{max}. For example, the

introduction of an electron releasing methoxy group (**5d**, **5g**) induced a hypsochromic shift relative to the parent styrene compounds **5c** and **5f.** In contrast, the more electronically poor quinoline frameworks (**5e**, **5h**) were blue shifted by a single nm. A significant bathochromic shift and increased intensity are displayed in the emission spectra for all compounds with respect to **2**. The addition of electron poor/rich groups to our molecular framework gives rise to tuneable differences in emission intensity and wavelength.

In summary, we report the occurrence of two mechanistically distinct reactions in one-pot, using the same precatalyst and without requisite for added ligand. The reactions work well in air, furnishing substituted benzofuroquinolines, which represent an interesting molecular framework for biological investigations. Direct evidence that the substrate quinoline forms a precatalytic species with palladium is provided, and excellent characterisation data is furnished. The π-extended products also display interesting and potentially useful florescence properties.

Experimental Section

Materials and 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 as thin films in DCM.

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 visualised under UV light.

High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier Tof LC-MS instrument in University College Cork. Samples were run in electrospray ionisation (ESI) mode using 50% acetonitrile-water containing 0.1% formic acid as eluent; samples were made up at a concentration of *ca*. 1 mg mL^{-1}. HRMS of metal-containing complexes were recorded on a Bruker compact TOF-MS in the University of York. Samples were run in electrospray ionisation (ESI) mode

using 50% MeOH-water as eluent; samples were made up at a concentration of *ca*. 1 mg mL^{-1}. Acquisitions were internally calibrated using sodium formate clusters.

Nuclear Magnetic Resonance (NMR) samples were run in deuterated chloroform ($CDCl_3$), deuterated dimethylsulfoxide ($(CD_3)_2SO$), deuterated dioxane ($C_4D_8O_2$) or deuterated acetonitrile (C_2D_3N) as specified. ^{1}H-NMR (600 MHz), ^{1}H-NMR (300 MHz) spectra were recorded on Bruker Avance III 600 and Bruker Avance III 300 NMR spectrometers, respectively, in proton coupled mode using tetramethysilane (TMS) as the internal standard. ^{13}C-NMR (150 MHz), ^{13}C-NMR (100 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on Bruker Avance III 600, Bruker Avance 400 and Bruker Avance III 300 NMR spectrometers, respectively, in proton decoupled mode at 300 K using TMS as the internal standard. ^{19}F-NMR (282 MHz) spectra were recorded on a Bruker Avance III 300 NMR spectrometer in proton decoupled mode at 300 K. ^{1}H-^{15}N HMBC spectra were recorded on a Bruker Avance III 600 NMR spectrometer [600 MHz (^{1}H), 60 MHz (^{15}N)], equipped with Bruker BBFO cryoprobe. All spectra recorded at 300 K and referenced externally to nitromethane at 380.2 ppm, the value of which was uncorrected. ^{1}H-^{15}N HMBC spectra were acquired using the Bruker HMBCqpndqf pulse program (2D H-1/X correlation *via* heteronuclear zero and double quantum coherence optimised on long range couplings), with 4 scans and spectral width of 600–650 ppm. 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).

Single-crystal X-ray analysis was performed on a Rigaku AFC12 FRE-HF diffractometer equipped with an Oxford Cryosystems low-temperature device. The crystals were kept at a steady T = 100(2) K during data collection. The structures were solved with the **ShelXT**[28] structure solution program using the Intrinsic Phasing solution method and by using **Olex2**[29] as the graphical interface. The models were refined with version 2016/6 of **ShelXL**[28] using Least Squares minimisation. Cell parameters were retrieved and refined using the **CrysAlisPro** (Rigaku, V1.171.40.37a, 2019). All non-hydrogen atoms

were refined anisotropically. Hydrogen atom positions were calculated geometrically and refined using the riding model. Further information available in the SI.

UV-Visible absorption was measured on a Thermo Scientific Evolution 60S UV-Visible Spectrophotometer. All solutions were made up in DCM and measurements were performed in high precision Quartz cells 10 mm in pathlength. A baseline in DCM was recorded by an internal reference detector. Molar absorption values were calculated using Beer's law at a concentration of 8×10^{-6} mol dm^{-3}. Fluorescence intensities were measured on PerkinElmer Fluorescence Spectrometer LS 55. All solutions were made up in DCM and measurements were performed in high precision Quartz cells 10 × 10 mm in pathlength. Spectra were recorded in the range 200–700 nm and compounds were excited at 257 nm.

General Procedure for Synthesis of 4-Phenoxyquinoline Substrates. A mixture of the 4-chloroquinoline substrate (1 equiv), the phenol (5 equiv) and NaOH (crushed pellets) (1.5 equiv) was stirred at 120 °C in an aluminium heating mantle until reaction was complete (2–6 h) as evident by TLC (Hex/EtOAc 8:2). The cooled reaction mixture was diluted with 10% aqueous NaOH (5 mL) and stirred at room temperature for 1 h. The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic layers were washed with 6 M NaOH (3 × 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 Hex/EtOAc (8:2) as eluent unless otherwise specified.

*6-Bromo-4-(2-bromophenoxy)quinoline (**3a**):* 6-Bromo-4-chloroquinoline (0.970 g, 4.0 mmol), 2-bromophenol (2.32 ml, 20 mmol) and NaOH (0.240 g, 6.0 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a pale yellow solid; yield: 1.406 g (93%); m.p. = 97–98 °C; IR (NaCl): ν 3399, 1590, 1491, 1350, 1221, 665 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.41 (d, *J* = 5.2 Hz, 1H), 7.19–7.28 (m, 2H), 7.39–7.47 (m, 1H), 7.73 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.84 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 8.67 (d, *J* = 5.2 Hz, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 104.2, 116.4, 120.3, 122.2, 123.3, 124.3, 127.6,

129.3, 130.9, 133.7, 134.4, 148.4, 150.8, 151.4, 159.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{10}Br_2NO$ 377.9129; found: 377.9132.

*7-Bromo-4-(2-bromophenoxy)quinoline (**3b**):* 7-Bromo-4-chloroquinoline (0.970 g, 4.0 mmol), 2-bromophenol (2.32 ml, 20.0 mmol) and NaOH (0.240 g, 6.0 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a pale yellow solid; yield: 1.397 g (92%); m.p. = 73–74 °C; IR (NaCl): ν 3064, 1561, 1468, 1301, 1220, 657 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.41 (d, *J* = 5.2 Hz, 1H), 7.19–7.30 (m, 2H), 7.39–7.48 (m, 1H), 7.66–7.76 (m, 2H), 8.25–8.33 (m, 2H), 8.66 (d, *J* = 5.2 Hz, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 103.9, 116.3, 119.7, 123.3, 123.5, 124.6, 127.6, 129.3, 129.8, 131.4, 134.4, 150.5, 150.8, 152.1, 160.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{10}Br_2NO$ 377.9129; found: 377.9119.

*6-Bromo-4-(2-bromo-4-chlorophenoxy)quinoline (**3c**)*: 6-Bromo-4-chloroquinoline (0.500 g, 2.06 mmol), 2-bromo-4-chlorophenol (2.140 g, 10.31 mmol) and NaOH (0.126 g, 3.14 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a pale pink solid; yield: 531 mg (77%); m.p. = 157–159 °C; IR (NaCl): ν 3392, 1590, 1467, 1349, 1256, 729, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.41 (d, *J* = 5.1 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.42 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.74 (d, *J* = 2.4 Hz, 1H), 7.84 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.98 (d, *J* = 9.0 Hz, 1H), 8.55 (d, *J* = 2.2 Hz, 1H), 8.68 (d, *J* = 5.1 Hz, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 104.1, 117.0, 120.5, 122.0, 124.0, 124.2, 129.4, 131.0, 132.4, 133.9, 134.0, 148.4, 149.6, 151.3, 159.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9Br_2ClNO$ 411.8739; found: 411.8730.

*4-(2,6-Dibromophenoxy)pyridine (**3d**)*: A neat mixture of 4-chloropyridine (0.250 g, 1.66 mmol) and 2,6-dibromophenol (0.630 g, 2.50 mmol) was stirred at 120 °C in an aluminium heating mantle until reaction was complete (16 h) as evident by TLC (Hex/EtOAc 8:2). The cooled reaction mixture was diluted with 10% aqueous NaOH (5 mL) and stirred at room temperature for 1 h. The aqueous phase was extracted with DCM (3 × 20 mL). The combined organic layers were washed with 6 M NaOH (3 × 10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was purified by recrystallisation from cyclohexane to give the title product as an off-

white solid; yield: 365 mg (66%); m.p. = 91–93 °C; IR (NaCl): ν 3393, 1590, 1434, 1261, 1200, 665 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.75 (d, *J* = 5.0 Hz, 2H), 7.07 (t, *J* = 8.1 Hz, 1H), 7.63 (dd, *J* = 8.1, 1.9 Hz, 2H), 8.49 (d, *J* = 5.2 Hz, 2H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 110.8, 118.3, 128.3, 133.1, 147.7, 151.5, 162.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{11}H_8Br_2NO$ 327.8973; found: 327.8961.

*4-(2,4-Dibromophenoxy)quinoline (**3e**)*: 4-Chloroquinoline (0.260 g, 1.60 mmol), 2,4-dibromophenol (2.00 g, 7.90 mmol) and NaOH (0.095 g, 2.40 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a pale yellow solid; yield: 517 mg (85%); m.p. = 125–126 °C; IR (NaCl): ν 3394, 1596, 1464, 1305, 1224, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.43 (d, *J* = 5.1 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.50–7.68 (m, 2H), 7.79 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 8.38 (dd, *J* = 8.4, 0.9 Hz, 1H), 8.70 (d, *J* = 5.1 Hz, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 103.8, 117.4, 119.3, 120.9, 121.8, 124.3, 126.5, 129.2, 130.4, 132.3, 136.6, 149.8, 150.5, 151.0, 160.3 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{10}Br_2NO$ 377.9129; found: 377.9114.

*6-Bromo-4-(2,4-dibromophenoxy)quinoline (**3f**)*: 6-Bromo-4-chloroquinoline (0.240 g, 0.99 mmol), 2,4-dibromophenol (1.247 g, 4.95 mmol) and NaOH (0.059 g, 1.5 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a pale yellow solid; yield: 268 mg (59%); m.p. = 162–163 °C; IR (NaCl): ν 3370, 1590, 1449, 1349, 1255, 665 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.42 (d, *J* = 5.1 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.56 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.80–7.91 (m, 2H), 7.98 (d, *J* = 9.0 Hz, 1H), 8.54 (d, *J* = 2.2 Hz, 1H), 8.68 (d, *J* = 5.1 Hz, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 104.2, 117.4, 119.7, 120.5, 122.0, 124.2, 124.4, 131.0, 132.4, 133.9, 136.7, 148.4, 150.1, 151.3, 159.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9Br_3NO$ 455.8234; found: 455.8233.

*7-Bromo-4-(2,4-dibromophenoxy)quinoline (**3g**)*: 7-Bromo-4-chloroquinoline (0.243 g, 1.0 mmol), 2,4-dibromophenol (1.26 g, 5.0 mmol) and NaOH (0.06 g, 1.5 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a white solid; yield: 398 mg (87%); m.p. = 140–142 °C; IR (NaCl) ν 3583, 1615, 1559, 1302, 1096, 666 cm^{-1}; ^{1}H-NMR

(300 MHz, $CDCl_3$) δ: 6.42 (d, *J* = 5.2 Hz, 1H), 7.13 (d, *J* = 8.6 Hz, 1H), 7.56 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.70 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.88 (d, *J* = 2.3 Hz, 1H), 8.18–8.36 (m, 2H), 8.68 (d, *J* = 5.2 Hz, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 103.9, 117.4, 119.6, 119.7, 123.3, 124.4, 124.7, 130.0, 131.5, 132.4, 136.7, 150.2, 150.5, 152.1, 160.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_9Br_3NO$ 455.8229; found: 455.8233.

*4-Phenoxyquinoline (**3h**)*:[30] 4-Chloroquinoline (0.164 g, 1.0 mmol), phenol (0.471 g, 5.0 mmol) and NaOH (0.06 g, 1.5 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a yellow oil; yield: 192 mg (87%); ^1H-NMR (300 MHz, $CDCl_3$) δ: 6.54 (d, *J* = 5.2 Hz, 1H), 7.13–7.22 (m, 2H), 7.23–7.33 (m, 1H), 7.39-7.50 (m, 2H), 7.56 (ddd, *J* = 8.2, 6.9, 1.1 Hz, 1H), 7.74 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 8.36 (dd, *J* = 8.4, 1.1 Hz, 1H), 8.66 (d, *J* = 5.1 Hz, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 104.4, 121.1, 121.5, 121.8, 125.6, 126.1, 129.1, 130.1, 130.3, 149.8, 151.1, 154.4, 161.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{12}NO$ 222.0913; found: 222.0913.

*6-Bromo-4-phenoxyquinoline (**3i**)*: 6-Bromo-4-chloroquinoline (0.500 g, 2.1 mmol), phenol (0.970 g, 10.31 mmol) and NaOH (0.126 g, 3.14 mmol) were reacted according to the general procedure for the synthesis of 4-phenoxyquinolines above to give the title product as a pale yellow solid; yield: 517 mg (83%); m.p. = 84–86 °C; IR (NaCl): v 3401, 1561, 1487, 1351, 1213, 667 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ: 6.54 (d, *J* = 5.2 Hz, 1H), 7.13–7.22 (m, 2H), 7.25–7.36 (m, 1H), 7.41–7.53 (m, 2H), 7.80 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.95 (d, *J* = 9.0 Hz, 1H), 8.53 (d, *J* = 2.2 Hz, 1H), 8.65 (d, *J* = 5.2 Hz, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 104.7, 120.2, 121.1, 122.6, 124.3, 125.9, 130.4, 130.9, 133.6, 148.3, 151.5, 154.0, 161.0 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{11}BrNO$ 300.0024; found: 300.0013.

General Procedure for Palladium-Catalysed One Pot Suzuki Miyaura and Intramolecular Direct Arylation Reactions. A mixture of the 4-(2-bromophenoxy)quinoline substrate (1 equiv), $PhB(OH)_2$ (1.1 equiv), $Pd(OAc)_2$ (2 mol %) and anhydrous K_2CO_3 (2 equiv) in anhydrous NMP (1.5 mL $mmol^{-1}$) was stirred at 135 °C in a sealed reaction tube in an aluminium multi-reaction heating mantle until the reaction was complete as evident by ^1H-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 unless otherwise specified.

*2-Phenylbenzofuro[3,2-c]quinoline (**4a**)*: A mixture of substrate **3a** (0.100 g, 0.26 mmol), phenyl boronic acid (0.035 g, 0.29 mmol), $Pd(OAc)_2$ (1.2 mg, 2 mol %) and anhydrous K_2CO_3 (0.073 g, 0.53 mmol) in anhydrous NMP (0.4 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; X-ray quality crystals were obtained *via* vapour diffusion from a saturated solution of toluene in hexane, the CCDC number is 1967876; yield: 63 mg (83%); m.p. = 169–171 °C; IR (NaCl): ν 3450, 1559, 1460, 1359, 1193 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.39–7.61 (m, 5H), 7.74–7.87 (m, 3H), 8.02–8.15 (m, 2H), 8.33 (d, *J* = 8.8 Hz, 1H), 8.62 (d, *J* = 1.7 Hz, 1H), 9.49 (s, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.6, 117.3, 118.4, 120.6, 122.7, 124.1, 127.3, 127.5, 127.9, 128.8, 129.0, 130.2, 139.7, 140.1, 144.2, 146.7, 156.0, 157.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{14}NO$ 296.1075; found: 296.1062.

*2-(p-Tolyl)benzofuro[3,2-c]quinoline (**4b**)* : A mixture of substrate **3a** (0.150 g, 0.396 mmol), o-tolylboronic acid (0.059 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a white solid; yield: 89 mg (72%); m.p. = 183–185 °C; IR (NaCl): ν 3583, 3401, 1505, 1460, 1358, 1190 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.45 (s, 3H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.44–7.62 (m, 2H), 7.69–7.82 (m, 3H), 8.02–8.16 (m, 2H), 8.33 (d, *J* = 8.8 Hz, 1H), 8.61 (d, *J* = 1.9 Hz, 1H), 9.49 (s, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 21.2, 112.1, 116.5, 117.4, 118.0, 120.7, 122.7, 124.1, 127.27, 127.34, 128.8, 129.8, 130.2, 137.2, 137.9, 139.6, 144.0, 146.6, 156.0, 157.6 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO$ 310.1232; found: 310.1222.

*2-(4-Methoxyphenyl)benzofuro[3,2-c]quinoline (**4c**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), 4-methoxyphenylboronic acid (0.066 g, 0.435 mmol), $Pd(OAc)_2$ (4.5 mg, 5 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a white solid; yield: 84 mg (65%); m.p. =

189–191 °C; IR (NaCl): ν 3320, 1505, 1460, 1359, 1246, 1190 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.90 (s, 3H), 7.01–7.12 (m, 2H), 7.43–7.60 (m, 2H), 7.71–7.81 (m, 3H), 8.01 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.10 (dd, *J* = 7.6, 0.9 Hz, 1H), 8.30 (d, *J* = 8.8 Hz, 1H), 8.55 (d, *J* = 1.9 Hz, 1H), 9.46 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 55.4, 112.1, 114.5, 116.5, 117.4, 117.5, 120.6, 122.7, 124.1, 127.2, 128.56, 128.61, 130.2, 132.6, 139.3, 143.9, 146.4, 156.0, 157.5, 159.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO_2$ 326.1181; found: 326.1185.

*2-(4-(Trifluoromethoxy)phenyl)benzofuro[3,2-c]quinoline (**4d**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), (4-(trifluoromethoxy)phenyl)boronic acid (0.090 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a yellow solid; yield: 105 mg (70%); m.p. = 148–150 °C; IR (NaCl): ν 3583, 1504, 1459, 1283, 1210, 1191, 1165 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37 (dd, *J* = 8.8, 0.9 Hz, 2H), 7.43–7.62 (m, 2H), 7.72–7.86 (m, 3H), 7.97 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.09 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.31 (d, *J* = 8.8 Hz, 1H), 8.54 (d, *J* = 2.0 Hz, 1H), 9.47 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.8, 117.4, 118.6, 120.5 (q, $^{1}J_{(C,F)}$ = 257 Hz), 120.7, 121.4, 122.6, 124.2, 127.4, 128.5, 128.9, 130.5, 138.3, 138.9, 144.5, 146.7, 149.2 (q, $^{3}J_{(C,F)}$ = 2 Hz), 156.0, 157.5 ppm; ^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$) δ: -58 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{13}F_3NO_2$ 380.0898; found: 380.0889.

*2-(4-Fluorophenyl)benzofuro[3,2-c]quinoline (**4e**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), 4-fluorophenylboronic acid (0.061 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; yield: 95 mg (77%); m.p. = 185–186 °C; IR (NaCl): ν 3391, 1561, 1460, 1334, 1192, 1123 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.16–7.29 (m, 2H), 7.46–7.62 (m, 2H), 7.72–7.83 (m, 3H), 8.00 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.13 (dd, *J* = 7.2, 1.3 Hz, 1H), 8.33 (d, *J* = 8.8 Hz, 1H), 8.57 (d, *J* = 2.0 Hz, 1H), 9.50 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.1, 115.9 (d, $^{2}J_{(C,F)}$ = 22 Hz), 116.7, 117.4, 118.2, 120.7, 122.7, 124.1, 127.3, 128.6, 129.1 (d, $^{3}J_{(C,F)}$ = 8 Hz), 130.4, 136.2, 138.7, 144.3, 146.6, 156.0, 157.5, 162.9 (d, $^{1}J_{(C,F)}$ = 247 Hz) ppm;

$^{19}F\{^{1}H\}$-NMR (282 MHz, $CDCl_3$) δ: -115 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{13}FNO$ 314.0981; found: 314.0971.

*2-(4-Chlorophenyl)benzofuro[3,2-c]quinoline (**4f**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), 4-chlorophenylboronic acid (0.068 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; yield: 106 mg (81%); m.p. = 191–192 °C; IR (NaCl): ν 3389, 1556, 1458, 1356, 1191, 821 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38–7.57 (m, 4H), 7.61–7.75 (m, 3H), 7.89 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.02 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 8.43 (d, *J* = 2.0 Hz, 1H), 9.39 (s, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.7, 117.3, 118.2, 120.7, 122.6, 124.1, 127.3, 128.3, 128.6, 129.1, 130.4, 134.1, 138.3, 138.5, 144.4, 146.7, 155.9, 157.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{13}ClNO$ 330.0680; found: 330.0676.

*2-(4-(Trifluoromethyl)phenyl)benzofuro[3,2-c]quinoline (**4g**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), (4-(trifluoromethyl)phenyl)boronic acid (0.083 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; yield: 114 mg (80%); m.p. = 194–195 °C; IR (NaCl): ν 3384, 1614, 1460, 1331, 1189, 1116 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.46–7.63 (m, 2H), 7.74–7.85 (m, 3H), 7.93 (d, *J* = 8.2 Hz, 2H), 8.04 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.13 (d, *J* = 7.4 Hz, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 8.65 (d, *J* = 1.9 Hz, 1H), 9.53 (s, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.8, 117.3, 119.0, 120.7, 122.6, 124.22, 124.23 (q, $^{1}J_{(C,F)}$ = 270 Hz), 125.9 (q, $^{3}J_{(C,F)}$ = 4 Hz), 127.5, 127.7, 128.4, 130.0 (q, $^{2}J_{(C,F)}$ = 33 Hz), 130.6, 138.1, 143.6, 144.8, 146.9, 156.0, 157.5 ppm; $^{19}F\{^{1}H\}$-NMR (282 MHz, $CDCl_3$) δ: -62 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{13}F_3NO$ 364.0949; found: 364.0938.

*2-(3-(Trifluoromethyl)phenyl)benzofuro[3,2-c]quinoline (**4h**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), (3-(trifluoromethyl)phenyl)boronic acid (0.083 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted

according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; yield: 104 mg (72%); m.p. = 171–173 °C; IR (NaCl): ν 3391, 1561, 1446, 1334, 1166, 1123 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45–7.73 (m, 4H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.95–8.09 (m, 3H), 8.13 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.37 (d, *J* = 8.8 Hz, 1H), 8.63 (d, *J* = 2.0 Hz, 1H), 9.52 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.8, 117.3, 118.7, 120.7, 122.6, 124.19, 124.20 (q, $^{1}J_{(C,F)}$ = 273 Hz), 124.3 (q, $^{3}J_{(C,F)}$ = 4 Hz), 124.6 (q, $^{3}J_{(C,F)}$ = 4 Hz), 127.5, 128.4, 129.5, 130.6, 130.7, 131.5 (q, $^{2}J_{(C,F)}$ = 32 Hz), 138.1, 140.9, 144.7, 146.8, 156.0, 157.5 ppm; ^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$) δ: -62 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{13}F_3NO$ 364.0944; found: 364.0947.

*Ethyl 4-(benzofuro[3,2-c]quinolin-2-yl)benzoate (**4i**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), 4-ethoxycarbonylphenylboronic acid (0.084 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a beige solid; yield: 105 mg (70%); m.p. = 160–161 °C; IR (NaCl): ν 2922, 1715, 1607, 1460, 1357, 1278, 1190 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.45 (t, *J* = 7.1 Hz, 3H), 4.44 (q, *J* = 7.1 Hz, 2H), 7.43–7.63 (m, 2H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.84–7.95 (m, 2H), 8.02–8.28 (m, 4H), 8.36 (d, *J* = 8.8 Hz, 1H), 8.67 (d, *J* = 1.7 Hz, 1H), 9.52 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 14.4, 61.1, 112.1, 116.7, 117.2, 118.8, 120.7, 122.5, 124.1, 127.3, 127.4, 128.8, 129.8, 130.2, 130.5, 138.3, 144.2, 144.6, 146.9, 155.9, 157.4, 166.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{18}NO_3$: 368.1281; found: 368.1282.

*(4-(Benzofuro[3,2-c]quinolin-2-yl)phenyl)(phenyl)methanone (**4j**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), (4-benzoylphenyl)boronic acid (0.098 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; yield: 94 mg (59%); m.p. = 184–187 °C; IR (NaCl): ν 3401, 1652, 1602, 1460, 1357, 1190 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.46–7.70 (m, 5H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.84–8.04 (m, 6H), 8.05–8.20 (m, 2H), 8.38 (d, *J* = 8.8 Hz, 1H), 8.71 (d, *J* = 1.9 Hz, 1H), 9.53 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.8, 117.4, 119.0, 120.7, 122.6, 124.2, 127.3, 127.5, 128.4, 128.5, 130.0, 130.6, 130.9,

132.5, 136.8, 137.6, 138.4, 144.0, 144.7, 146.9, 156.0, 157.5, 196.2 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{28}H_{18}NO_2$ 400.1332; found: 400.1331.

*2-(3-Nitrophenyl)benzofuro[3,2-c]quinoline (**4k**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), 3-nitrophenylboronic acid (0.072 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL mmol^{-1}) was reacted according to the general one pot SM/DA procedure above to give the title product as a yellow solid; yield: 69 mg (51%); m.p. = 227–228 °C; IR (NaCl): ν 3392, 1529, 1460, 1348, 1321, 1191 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.47–7.64 (m, 2H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 8.06 (dd, *J* = 8.8, 2.2 Hz, 1H), 8.10–8.19 (m, 2H), 8.30 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1H), 8.40 (d, *J* = 8.8 Hz, 1H), 8.65–8.73 (m, 2H), 9.55 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.2, 117.0, 117.4, 119.1, 120.8, 122.3, 122.5, 122.6, 124.3, 127.6, 128.2, 130.0, 131.0, 133.3, 137.1, 141.9, 145.1, 147.0, 148.9, 156.1, 157.5 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{21}H_{13}N_2O_3$: 341.0921; found: 341.0919.

*8-Chloro-2-phenylbenzofuro[3,2-c]quinoline (**4l**)*: A mixture of substrate **3c** (0.200 g, 0.60 mmol), phenylboronic acid (0.080 g, 0.658 mmol), $Pd(OAc)_2$ (2.7 mg, 2 mol %) and anhydrous K_2CO_3 (0.165 g, 1.20 mmol) in anhydrous NMP (0.9 mL, 1.5 mL mmol^{-1}) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; yield: 118 mg (60%); m.p. = 213–214 °C; IR (NaCl): ν 3583, 1461, 1359, 1192, 665 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.38–7.60 (m, 4H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.75–7.87 (m, 2H), 7.99–8.12 (m, 2H), 8.31 (d, *J* = 8.8 Hz, 1H), 8.55 (d, *J* = 1.8 Hz, 1H), 9.41 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 113.1, 115.8, 117.2, 118.4, 120.5, 124.2, 127.4, 127.5, 128.1, 129.1, 129.3, 129.9, 130.4, 140.0, 140.1, 144.0, 147.0, 154.3, 158.4 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{21}H_{13}ClNO$ 330.0681; found: 330.0684.

*6-Phenylbenzofuro[3,2-c]pyridine (**4m**)*: A mixture of substrate **3d** (0.150 g, 0.456 mmol), phenylboronic acid (0.061 g, 0.50 mmol), $Pd(OAc)_2$ (2.0 mg, 2 mol %) and anhydrous K_2CO_3 (0.126 g, 0.912 mmol) in anhydrous NMP (0.7 mL, 1.5 mL mmol^{-1}) was reacted according to the general one pot SM/DA procedure above and purified *via* column chromatography, using 100% Et_2O as eluent to give the title product as a pale yellow solid; yield: 77 mg (69%); m.p. = 66–68 °C; IR (NaCl): ν 3402, 3032,

1577, 1450, 1332, 1168 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.35–7.63 (m, 5H), 7.67 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.83–7.92 (m, 2H), 8.01 (dd, *J* = 7.7, 1.3 Hz, 1H), 8.67 (d, *J* = 5.7 Hz, 1H), 9.30 (s, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$) δ: 107.6, 120.1, 121.6, 122.4, 124.4, 126.4, 128.07, 128.13, 128.77, 128.80, 135.8, 143.7, 147.5, 153.1, 160.9 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{12}NO$ 246.0913; found: 246.0914. *Note*: Here, a second Suzuki-Miyaura reaction occurred in competition with the direct arylation. These products were separable by careful column chromatography.

*3-Phenylbenzofuro[3,2-c]quinoline (**4n**)*: A mixture of substrate **3b** (0.200 g, 0.528 mmol), phenylboronic acid (0.071 g, 0.58 mmol), $Pd(OAc)_2$ (2.4 mg, 2 mol %) and anhydrous K_2CO_3 (0.146 g, 1.06 mmol) in anhydrous NMP (0.8 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; X-ray quality crystals were obtained *via* vapour diffusion from a saturated solution of toluene in hexane, the CCDC number is 1967484; yield: 146 mg (95%); m.p. = 172–173 °C; IR (NaCl): v 3275, 1559, 1452, 1379, 1188 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37–7.64 (m, 5H), 7.72–7.88 (m, 3H), 7.98 (dd, *J* = 8.5, 1.7 Hz, 1H), 8.12 (dd, *J* = 7.5, 1.0 Hz, 1H), 8.42–8.59 (m, 2H), 9.54 (s, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.2, 116.1, 116.4, 120.6, 121.3, 122.8, 124.1, 126.6, 127.3, 127.5, 127.6, 128.0, 129.1, 140.2, 142.2, 144.9, 147.8, 156.1, 157.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{14}NO$ 296.1070; found: 296.1072.

*3-(p-Tolyl)benzofuro[3,2-c]quinoline (**4o**)*: A mixture of substrate **3b** (0.150 g, 0.396 mmol), o-tolylboronic acid (0.059 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a white solid; yield: 90 mg (74%); m.p. = 200–202 °C; IR (NaCl): v 3150, 1554, 1450, 1379, 1190 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.45 (s, 3H), 7.34 (d, *J* = 7.9 Hz, 2H), 7.44–7.60 (m, 2H), 7.66–7.81 (m, 3H), 7.97 (dd, *J* = 8.5, 1.5 Hz, 1H), 8.11 (dd, *J* = 7.6, 0.9 Hz, 1H), 8.42–8.52 (m, 2H), 9.51 (s, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$) δ: 21.2, 112.1, 115.9, 116.2, 120.5, 121.1, 122.7, 124.0, 126.4, 127.1, 127.2, 127.3, 129.8, 137.3, 137.9, 142.0, 144.7, 147.9, 156.0, 157.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO$ 310.1232; found: 310.1244.

*3-(4-(Trifluoromethyl)phenyl)benzofuro[3,2-c]quinoline (**4p**)*: A mixture of substrate **3b** (0.150 g, 0.396 mmol), (4-(trifluoromethyl)phenyl)boronic acid (0.083 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a yellow solid; yield: 114 mg (79%); m.p. = 205–208 °C; IR (NaCl): ν 3251, 1559, 1450, 1329, 1188, 1110 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.46–7.63 (m, 2H), 7.76–7.82 (m, 3H), 7.86–8.02 (m, 3H), 8.13 (dd, *J* = 7.6, 0.9 Hz, 1H), 8.49–8.57 (m, 2H), 9.55 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.2, 116.7, 120.7, 121.6, 122.6, 124.21, 124.22 (q, $^1J_{(C,F)}$ = 270 Hz), 126.0 (q, $^3J_{(C,F)}$ = 4 Hz), 126.2, 127.5, 127.7, 128.2, 129.9 (q, $^2J_{(C,F)}$ = 32 Hz), 140.4, 143.7, 145.1, 147.6, 156.1, 157.3 ppm; ^{19}F{^{1}H}-NMR (282 MHz, $CDCl_3$) δ: -62 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{13}F_3NO$ 364.0949; found: 364.0951. *Note:* ^{13}C-NMR shift at 116.7 ppm represents two individual carbon signals as confirmed by 2D NMR experiments.

*4-(Benzofuro[3,2-c]quinolin-3-yl)benzonitrile (**4q**)*: A mixture of substrate **3b** (0.150 g, 0.396 mmol), 4-cyanophenylboronic acid (0.065 g, 0.435 mmol), $Pd(OAc)_2$ (4.4 mg, 5 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a white solid; yield: 85 mg (67%); m.p. >250 °C; IR (NaCl): ν 3348, 2223, 1553, 1447, 1344, 1184 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.45–7.64 (m, 2H), 7.73–7.80 (m, 6H), 8.13 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.45–8.60 (m, 2H), 9.55 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 111.7, 112.3, 116.9, 117.0, 118.8, 120.8, 121.9, 122.6, 124.3, 126.0, 127.6, 128.1, 128.4, 132.9, 139.9, 144.7, 145.3, 147.5, 156.2, 157.2 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{13}N_2O$: 321.1028; found: 321.1033.

*3-(4-Methoxyphenyl)benzofuro[3,2-c]quinoline (**4r**)*: A mixture of substrate **3b** (0.150 g, 0.396 mmol), 4-methoxyphenylboronic acid (0.066 g, 0.435 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a white solid; yield: 88 mg (70%); m.p. = 157–158 °C; IR (NaCl): ν 3369, 2998, 1607, 1450, 1303, 1245, 1188 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.88 (s, 3H), 6.99–7.10 (m, 2H), 7.41–7.57 (m, 2H), 7.68–7.77 (m, 3H), 7.91 (dd, *J* = 8.6, 1.7 Hz, 1H),

8.07 (dd, *J* = 7.5, 1.5 Hz, 1H), 8.37–8.45 (m, 2H), 9.47 (s, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$) δ: 55.4, 112.1, 114.5, 115.7, 116.1, 120.5, 121.2, 122.8, 124.1, 126.3, 126.8, 127.1, 128.5, 132.7, 141.7, 144.8, 148.0, 156.0, 157.5, 159.8 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{16}NO_2$ 326.1176; found: 326.1173.

General Procedure for Palladium-Catalysed One Pot Mizoroki Heck and Intramolecular Direct Arylation Reactions. A mixture of the 4-(2-bromophenoxy)quinoline substrate (1 equiv), Heck coupling partner (1.1 equiv), $Pd(OAc)_2$ (2 mol % for *tert*-butyl acrylate or 5 mol % for styrene derivatives) and anhydrous K_2CO_3 (2 equiv) in anhydrous NMP (1.5 mL $mmol^{-1}$) was stirred at 135 °C in a sealed reaction tube in an aluminium multi-reaction heating mantle until the reaction was completed as evident by ^{1}H-NMR analysis (18–24 h). 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.

*tert-Butyl (E)-3-(benzofuro[3,2-c]quinolin-2-yl)acrylate (**5a**)* : A mixture of substrate **3a** (0.050 g, 0.132 mmol), *tert*-butyl acrylate (21 µL, 0.145 mmol), $Pd(OAc)_2$ (0.6 mg, 2 mol %) and anhydrous K_2CO_3 (0.036 g, 0.264 mmol) in anhydrous NMP (0.2 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a white solid; yield: 27 mg (60%); m.p. = 169–170 °C; IR (NaCl): ν 3393, 2976, 1701, 1560, 1460, 1366, 1238, 1151 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 9H), 6.60 (d, *J* = 16.0 Hz, 1H), 7.44–7.65 (m, 2H), 7.73–7.89 (m, 2H), 7.94 (dd, *J* = 8.9, 2.0 Hz, 1H), 8.11 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 8.51 (d, *J* = 1.9 Hz, 1H), 9.49 (s, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (100 MHz, $CDCl_3$) δ: 28.2, 80.9, 112.3, 117.0, 117.3, 120.8, 121.6, 122.0, 122.5, 124.3, 127.4, 127.6, 130.5, 133.4, 142.5, 145.1, 147.9, 156.1, 157.5, 166.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{20}NO_3$: 346.1438; found: 346.1434.

*tert-Butyl (E)-3-(benzofuro[3,2-c]quinolin-3-yl)acrylate (**5b**)*: A mixture of substrate **3b** (0.050 g, 0.132 mmol), *tert*-butyl acrylate (21 µL, 0.145 mmol), $Pd(OAc)_2$ (0.6 mg, 2 mol %) and anhydrous K_2CO_3 (0.036 g, 0.264 mmol) in anhydrous NMP (0.2 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a pale yellow solid; X-ray quality crystals were

obtained *via* vapour diffusion from a saturated solution of toluene in hexane, the CCDC number is 1967537; yield: 36 mg (80%); m.p. = 160–162 °C; IR (NaCl): ν 3393, 2976, 1703, 1560, 1452, 1366, 1285, 1149 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 9H), 6.59 (d, *J* = 16.0 Hz, 1H), 7.44–7.63 (m, 2H), 7.71–7.92 (m, 3H), 8.11 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.30–8.46 (m, 2H), 9.51 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 28.2, 80.8, 112.2, 117.1, 117.7, 120.8, 121.4, 122.0, 122.5, 124.3, 125.1, 127.6, 130.7, 135.6, 142.8, 145.2, 147.4, 156.2, 157.1, 166.0 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{20}NO_3$: 346.1438; found: 346.1432.

*(E)-2-Styrylbenzofuro[3,2-c]quinoline (**5c**)*: A mixture of substrate **3a** (0.114 g, 0.30 mmol), styrene (38 µL, 0.33 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol %) and anhydrous K_2CO_3 (0.083 g, 0.60 mmol) in anhydrous NMP (0.5 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a white solid; yield: 70 mg (73%); m.p. = 201–202 °C; IR (NaCl) ν 3379, 1662, 1561, 1377, 1188 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.22–7.66 (m, 9H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.98 (dd, *J* = 8.9, 2.0 Hz, 1H), 8.07 (dd, *J* = 7.6, 0.8 Hz, 1H), 8.22 (d, *J* = 8.9 Hz, 1H), 8.39 (d, *J* = 1.8 Hz, 1H), 9.41 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.7, 117.4, 118.6, 120.7, 122.7, 124.1, 126.8, 127.2, 127.3, 127.8, 128.1, 128.8, 130.1, 130.6, 136.1, 137.0, 143.9, 147.0, 156.0, 157.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{16}NO$ 322.1226; found: 322.1223.

*(E)-2-(4-Methoxystyryl)benzofuro[3,2-c]quinoline (**5d**)*: A mixture of substrate **3a** (0.114 g, 0.30 mmol), 4-methoxystyrene (44 µL, 0.33 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol %) and anhydrous K_2CO_3 (0.083 g, 0.60 mmol) in anhydrous NMP (0.5 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a white solid; yield: 86 mg (82%); m.p. = 190–192 °C; IR (NaCl) ν 3388, 1656, 1602, 1562, 1346, 1250, 1110 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.86 (s, 3H), 6.84–7.04 (m, 2H), 7.12–7.38 (m, 2H), 7.40–7.65 (m, 4H), 7.76 (d, *J* = 8.1 Hz, 1H), 7.97 (dd, *J* = 8.9, 1.8 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.21 (d, *J* = 8.9 Hz, 1H), 8.38 (d, *J* = 1.7 Hz, 1H), 9.41 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 55.4, 112.1, 114.3, 116.7, 117.5, 118.1, 120.7, 122.8, 124.1, 125.7, 127.2, 127.3, 128.0, 129.8, 130.1, 130.2, 136.5, 143.7, 146.9, 156.0, 157.4, 159.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{18}NO_2$ 352.1332; found: 352.1328.

*(E)-2-(4-Fluorostyryl)benzofuro[3,2-c]quinoline (**5e**)*: A mixture of substrate **3a** (0.114 g, 0.30 mmol), 4-fluorostyrene (39 µL, 0.33 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol %) and anhydrous K_2CO_3 (0.083 g, 0.60 mmol) in anhydrous NMP (0.5 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a yellow solid; yield: 82 mg (80%); m.p. = 189–191 °C; IR (NaCl) ν 3404, 1676, 1598, 1559, 1346, 1234, 1096 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.00–7.15 (m, 2H), 7.17–7.34 (m, 2H), 7.41–7.63 (m, 4H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.95 (dd, *J* = 8.9, 2.0 Hz, 1H), 8.07 (d, *J* = 7.5 Hz, 1H), 8.21 (d, *J* = 8.9 Hz, 1H), 8.37 (d, *J* = 1.8 Hz, 1H), 9.41 (s, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.1, 115.8 (d, $^2J_{(C,F)}$ = 22 Hz), 116.7, 117.4, 118.6, 120.7, 122.7, 124.1, 127.1, 127.3, 127.6 (d, $^6J_{(C,F)}$ = 2 Hz), 128.3 (d, $^3J_{(C,F)}$ = 8 Hz), 129.4, 130.2, 133.2 (d, $^4J_{(C,F)}$ = 3 Hz), 135.9, 144.0, 147.0, 156.0, 157.4, 162.6 (d, $^1J_{(C,F)}$ = 248 Hz) ppm; $^{19}F\{^1H\}$-NMR (282 MHz, $CDCl_3$) δ: -113 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{15}FNO$ 340.1132; found: 340.1135.

*(E)-3-Styrylbenzofuro[3,2-c]quinoline (**5f**)*: A mixture of substrate **3b** (0.114 g, 0.30 mmol), styrene (38 µL, 0.33 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol %) and anhydrous K_2CO_3 (0.083 g, 0.60 mmol) in anhydrous NMP (0.5 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a yellow solid; yield: 72 mg (75%); m.p. = 179–182 °C; IR (NaCl) ν 3583, 1656, 1632, 1561, 1348, 1190 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.20–7.65 (m, 9H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.91 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.07 (dd, *J* = 7.5, 0.9 Hz, 1H), 8.27 (d, *J* = 1.3 Hz, 1H), 8.36 (d, *J* = 8.6 Hz, 1H), 9.46 (s, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.1, 116.3, 120.6, 121.1, 122.7, 124.1, 124.9, 126.8, 127.2, 128.0, 128.1, 128.8, 130.7, 137.0, 138.5, 144.8, 147.9, 156.1, 157.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{16}NO$ 322.1226; found: 322.1227. *Note:* ^{13}C-NMR shifts at 116.3 and 128.1 ppm represents two individual carbon signals as confirmed by 2D NMR experiments.

*(E)-3-(4-Methoxystyryl)benzofuro[3,2-c]quinoline (**5g**)*: A mixture of substrate **3b** (0.114 g, 0.30 mmol), 4-methoxystyrene (44 µL, 0.33 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol %) and anhydrous K_2CO_3 (0.083 g, 0.60 mmol) in anhydrous NMP (0.5 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a yellow solid; yield: 84 mg (80%); m.p. = 168–170 °C; IR (NaCl) ν 3379, 1687, 1603, 1560, 1347, 1176, 1033 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.86

(s, 3H), 6.89–7.00 (m, 2H), 7.13–7.39 (m, 2H), 7.42–7.65 (m, 4H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.92 (dd, *J* = 8.6, 1.5 Hz, 1H), 8.09 (dd, *J* = 7.2, 1.3 Hz, 1H), 8.27 (d, *J* = 1.2 Hz, 1H), 8.38 (d, *J* = 8.6 Hz, 1H), 9.47 (s, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 55.4, 112.1, 114.3, 116.0, 116.2, 120.5, 121.0, 122.8, 124.1, 124.8, 126.0, 127.1, 127.5, 128.1, 129.8, 130.3, 138.9, 144.7, 148.0, 156.0, 157.4, 159.7 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{18}NO_2$ 352.1332; found: 352.1333.

*(E)-3-(4-Fluorostyryl)benzofuro[3,2-c]quinoline (**5h**)*: A mixture of substrate **3b** (0.114 g, 0.30 mmol), 4-fluorostyrene (39 µL, 0.33 mmol), $Pd(OAc)_2$ (3.4 mg, 5 mol %) and anhydrous K_2CO_3 (0.083 g, 0.60 mmol) in anhydrous NMP (0.5 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a yellow solid; yield: 63 mg (62%); m.p. = 209–211 °C; IR (NaCl) ν 3049, 1682, 1637, 1508, 1347, 1228, 1012 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ: 7.02–7.16 (m, 2H), 7.20–7.38 (m, 2H), 7.42–7.64 (m, 4H), 7.76 (dd, *J* = 7.6, 0.7 Hz, 1H), 7.91 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.04–8.15 (m, 1H), 8.28 (d, *J* = 1.4 Hz, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 9.48 (s, 1H), ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.1, 115.8 (d, $^2J_{(C,F)}$ = 22 Hz), 116.31, 116.34, 120.6, 121.1, 122.7, 124.1, 124.8, 127.3, 127.86, 127.89, 128.3 (d, $^3J_{(C,F)}$ = 8 Hz), 129.4, 133.2 (d, $^4J_{(C,F)}$ = 3 Hz), 138.3, 144.8, 147.9, 156.0, 157.4, 162.6 (d, $^1J_{(C,F)}$ = 248 Hz) ppm; $^{19}F\{^1H\}$-NMR (282 MHz, $CDCl_3$) δ: -113 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{15}FNO$ 340.1132; found: 340.1135.

General Procedure for Synthesis of Phenoxy-Substituted SM/DA and MH/DA Products. The same procedures and purification methods outlined for the SM/DA and MH/DA reactions were employed here using 4-(2,4-dibromphenoxy)quinoline **3e** (1 equiv) as the substrate.

*8-Phenylbenzofuro[3,2-c]quinoline (**6a**)*: A mixture of substrate **3e** (0.200 g, 0.528 mmol), phenylboronic acid (0.071 g, 0.58 mmol), $Pd(OAc)_2$ (2.4 mg, 2 mol %) and anhydrous K_2CO_3 (0.146 g, 1.06 mmol) in anhydrous NMP (0.8 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a yellow solid; yield: 103 mg (65%); m.p. = 153–155 °C; IR (NaCl): ν 2922, 1567, 1460, 1325, 1202 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ: 7.36–7.45 (m, 1H), 7.46–7.56 (m, 2H), 7.67–7.86 (m, 6H), 8.24–8.35 (m, 2H), 8.45 (dd, *J* = 8.1, 1.6 Hz, 1H), 9.55 (s, 1H) ppm; $^{13}C\{^1H\}$-NMR (75 MHz, $CDCl_3$) δ: 112.2, 116.4, 117.2, 119.1, 120.8, 123.3, 126.7, 127.1, 127.4,

127.5, 128.9, 129.4, 129.9, 137.9, 140.9, 144.4, 147.5, 155.5, 158.0 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{21}H_{14}NO$ 296.1070; found: 296.1072.

*tert-Butyl (E)-3-(benzofuro[3,2-c]quinolin-8-yl)acrylate (**6b**)*: A mixture of substrate **3e** (0.076 g, 0.20 mmol), *tert*-butyl acrylate (32 µL, 0.22 mmol), $Pd(OAc)_2$ (0.9 mg, 2 mol %) and anhydrous K_2CO_3 (0.055 g, 0.40 mmol) in anhydrous NMP (0.3 mL, 1.5 mL mmol^{-1}) was reacted according to the general one pot MH/DA procedure above to give the title product as a white solid; yield: 50 mg (73%); m.p. = 157–158 °C; IR (NaCl) ν 3434, 1703, 1638, 1594, 1566, 1367, 1203, 1151 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.58 (s, 9H), 6.47 (d, *J* = 15.9 Hz, 1H), 7.50–7.89 (m, 5H), 8.09–8.30 (m, 2H), 8.36 (dd, *J* = 8.1, 1.1 Hz, 1H), 9.45 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 28.3, 80.7, 112.5, 115.9, 117.1, 120.2, 120.4, 120.8, 123.5, 127.22, 127.24, 129.6, 130.0, 131.2, 143.0, 144.3, 147.7, 156.7, 158.2, 166.2 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ $C_{22}H_{20}NO_3$: 346.1438; found: 346.1430.

*(E)-8-Styrylbenzofuro[3,2-c]quinoline (**6c**)*: A mixture of substrate **3e** (0.076 g, 0.20 mmol), styrene (25 µL, 0.22 mmol), $Pd(OAc)_2$ (2.5 mg, 5 mol %) and anhydrous K_2CO_3 (0.055 g, 0.40 mmol) in anhydrous NMP (0.3 mL, 1.5 mL mmol^{-1}) was reacted according to the general one pot MH/DA procedure above to give the title product as a yellow solid; yield: 25 mg (40%); m.p. = 200–203 °C; IR (NaCl) ν 3583, 1650, 1598, 1567, 1324, 1195 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.11–7.47 (m, 5H), 7.55–7.61 (m, 2H), 7.63–7.87 (m, 4H), 8.11–8.32 (m, 2H), 8.39 (dd, *J* = 8.1, 1.3 Hz, 1H), 9.50 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.2, 116.2, 117.2, 118.2, 120.8, 123.3, 126.0, 126.5, 127.1, 127.8, 128.1, 128.8, 128.9, 129.4, 129.9, 133.9, 137.2, 144.4, 147.5, 155.6, 158.0 ppm; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for $C_{23}H_{16}NO$ 322.1226; found: 322.1223.

General Procedure for Synthesis of Three Component SM/DA and MH/DA Products. The same procedures and purification methods outlined for the SM/DA and MH/DA reactions were employed here using bromo-4-(2,4-dibromphenoxy)quinoline (1 equiv) as the substrate and double the equivalent of coupling partner (2.2 equiv).

*2,8-Diphenylbenzofuro[3,2-c]quinoline (**7a**)*: A mixture of substrate **3f** (0.200 g, 0.437 mmol), phenylboronic acid (0.117 g, 0.96 mmol), $Pd(OAc)_2$ (2.0 mg, 2 mol %) and anhydrous K_2CO_3 (0.121 g,

0.873 mmol) in anhydrous NMP (0.7 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot SM/DA procedure above to give the title product as a pale yellow solid; yield: 129 mg (80%); m.p. = 206–207 °C; IR (NaCl): ν 3054, 2920, 1682, 1560, 1460, 1358, 1200 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.37–7.60 (m, 6H), 7.68–7.88 (m, 6H), 8.07 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.28–8.40 (m, 2H), 8.64 (d, *J* = 1.7 Hz, 1H), 9.54 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 112.2, 116.6, 117.4, 118.4, 119.1, 123.3, 126.8, 127.4, 127.50, 127.54, 128.0, 128.9, 129.0, 130.3, 137.9, 139.8, 140.1, 140.9, 144.2, 146.8, 155.5, 158.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{27}H_{18}NO$ 372.1388; found: 372.1384. *Note:* ^{13}C-NMR shift at 128.9 ppm represents two individual carbon signals as confirmed by 2D NMR experiments.

*Di-tert-butyl 3,3'-(benzofuro[3,2-c]quinoline-3,8-diyl)(2E,2'E)-diacrylate (**7b**)*: A mixture of substrate **3g** (0.050 g, 0.11 mmol), *tert*-butyl acrylate (35 µL, 0.242 mmol), $Pd(OAc)_2$ (0.5 mg, 2 mol %) and anhydrous K_2CO_3 (0.030 g, 0.22 mmol) in anhydrous NMP (0.3 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a white solid; yield: 23 mg (43%); m.p. = 217–219 °C; IR (NaCl) ν 3402, 1703, 1638, 1559, 1512, 1368, 1201, 1148 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.50–1.61 (m, 18H), 6.40–6.67 (m, 2H), 7.66–7.94 (m, 5H), 8.23 (d, *J* = 0.8 Hz, 1H), 8.29–8.44 (m, 2H), 9.49 (s, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 28.22, 28.24, 80.7, 80.9, 112.6, 116.6, 117.6, 120.3, 120.5, 121.4, 122.3, 123.3, 125.3, 127.5, 130.7, 131.4, 136.0, 142.7, 142.8, 145.0, 147.7, 156.9, 157.8, 166.0, 166.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{29}H_{30}NO_5$: 472.2118; found: 472.2117.

*3,8-Di((E)-styryl)benzofuro[3,2-c]quinoline (**7c**)*: A mixture of substrate **3g** (0.115 g, 0.25 mmol), styrene (63 µL, 0.55 mmol), $Pd(OAc)_2$ (2.8 mg, 5 mol %) and anhydrous K_2CO_3 (0.069 g, 0.50 mmol) in anhydrous NMP (0.4 mL, 1.5 mL $mmol^{-1}$) was reacted according to the general one pot MH/DA procedure above to give the title product as a white solid; yield: 76 mg (36%); m.p. = >250 °C; IR (NaCl) ν 3387, 1691, 1594, 1560, 1326, 1044 cm^{-1}; ^{1}H-NMR (600 MHz, $(CD_3)_2SO$) δ: 7.20–7.54 (m, 9H), 7.59 (app. s, 2H), 7.63–7.75 (m, 4H), 7.87 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 8.17 (dd, *J* = 8.7, 1.4 Hz, 1H), 8.35 (d, *J* = 1.3 Hz, 1H), 8.41 (d, *J* = 8.5 Hz, 1H), 8.61 (d, *J* = 1.5 Hz, 1H), 9.69 (s, 1H) ppm;

$^{13}C\{^{1}H\}$-NMR (150 MHz, $(CD_3)_2SO$) δ: 112.8, 115.9, 116.4, 119.1, 121.4, 123.2, 127.0, 127.2, 127.3, 128.29, 128.33, 128.6, 129.0, 129.3, 131.2, 134.3, 137.3, 137.5, 139.0, 146.0, 148.1, 155.5, 157.4 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{31}H_{22}NO$ 424.1696; found: 424.1690. *Note:* This compound was highly insoluble, spectra were acquired on <3 mg of this compound after heating in $(CD_3)_2SO$ and it was difficult to directly assign. As with other compounds, some ^{13}C shifts from this spectrum represent more than one signal as confirmed by 2D NMR experiments.

Isolation of Suzuki-Miyaura Only Products. To further probe the hypothesis that the Suzuki-Miyaura reaction was occurring at the C-6 position before direct arylation at the C-3 position, substrate **3i** was synthesised. This substrate could only undergo the Suzuki-Miyaura reaction and proceeded as anticipated (SI Scheme S1).

*4-Phenoxy-6-phenylquinoline (**4s**)*: A mixture of substrate **3i** (0.200 g, 0.666 mmol, 1 equiv), phenylboronic acid (0.081 g, 0.666 mmol, 1 equiv), $Pd(OAc)_2$ (3.0 mg, 2 mol %) and anhydrous K_2CO_3 (0.184 g, 1.333 mmol, 2 equiv) in anhydrous NMP (1.0 mL, 1.5 mL $mmol^{-1}$) was stirred at 135 °C in a sealed reaction tube in an aluminium multi-reaction heating mantle until the reaction was completed as evident by ^{1}H-NMR analysis (4 h). 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 Hex/EtOAc (7:3–6:4) as eluent to give the title product as a pale yellow solid; yield: 168 mg (84%); m.p. = 78–80 °C; IR (NaCl): ν 3058, 1562, 1487, 1460, 1360, 1203 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.58 (d, *J* = 5.1 Hz, 1H), 7.16–7.57 (m, 8H), 7.72–7.74 (m, 2H), 8.03 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.17 (d, *J* = 8.8 Hz, 1H), 8.58 (d, *J* = 2.0 Hz, 1H), 8.67 (d, *J* = 4.9 Hz, 1H) ppm; $^{13}C\{^{1}H\}$-NMR (75 MHz, $CDCl_3$) δ: 104.6, 119.6, 121.2, 121.7, 125.7, 127.5, 127.7, 129.0, 129.6, 129.8, 130.3, 139.0, 140.5, 149.1, 151.1, 154.4, 162.1 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{16}NO$ 298.1226; found: 298.1228.

The tandem reaction was carried out on **3a** at a lower temperature to see if the Suzuki-Miyaura only product could be isolated and prove that it was happening prior to the direct arylation reaction. At

this temperature the major product was the uncyclised Suzuki-Miyaura product **4t**, although some of the tandem product **4a** and starting material **3a** were also isolated (SI Scheme S2).

*4-(2-Bromophenoxy)-6-phenylquinoline (**4t**)*: A mixture of substrate **3a** (0.150 g, 0.396 mmol), phenylboronic acid (0.048 g, 0.396 mmol), $Pd(OAc)_2$ (1.8 mg, 2 mol %) and anhydrous K_2CO_3 (0.109 g, 0.79 mmol) in anhydrous NMP (0.6 mL, 1.5 mL $mmol^{-1}$) was stirred at 100 °C in a sealed reaction tube in an aluminium multi-reaction heating mantle for 24 h. 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 Hex/EtOAc (8:2–7:3) as eluent to give the title product as a pale yellow solid; yield: 73 mg (49%); m.p. = 85–87 °C; IR (NaCl): ν 3059, 1564, 1460, 1361, 1222, 667 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.43 (d, *J* = 5.2 Hz, 1H), 7.16–7.32 (m, 2H), 7.34–7.57 (m, 4H), 7.70–7.84 (m, 3H), 8.05 (dd, *J* = 8.8, 2.1 Hz, 1H), 8.20 (d, *J* = 8.7 Hz, 1H), 8.62 (d, *J* = 2.0 Hz, 1H), 8.69 (d, *J* = 5.3 Hz, 1H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 103.9, 116.4, 119.6, 121.3, 123.3, 127.6, 127.9, 129.0, 129.3, 130.2, 134.4, 139.4, 140.3, 148.2, 150.5, 151.0, 161.5 ppm; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{15}BrNO$ 376.0332; found: 376.0331. *Note:* ^{13}C-NMR shifts at 127.6 and 129.0 ppm each represent two individual carbon signals as confirmed by 2D NMR experiments.

The Synthesis of Palladium-Quinoline Complexes.

*4-(2-Bromophenoxy)quinoline Palladium Diacetate Dimer (**8a**)*: To an NMR tube were added **1** (61.5 mg, 0.204 mmol, 1.0 equiv), $Pd(OAc)_2$ (22.9 mg, 0.102 mmol, 0.5 equiv) and $CDCl_3$ (0.6 mL); X-ray quality crystals were obtained *via* vapour diffusion from a saturated solution of toluene/methanol in hexane, the CCDC number is 1970630; decomposition >150°C; IR (NaCl) ν 3436, 1615, 1589, 1573, 1303, 1217, 1075, 695 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 6.47 (d, *J* = 6.2 Hz, 2H), 7.11–7.34 (m, 4H), 7.37–7.54 (m, 2H), 7.59–7.84 (m, 4H), 8.08 (ddd, *J* = 8.6, 7.0, 1.4 Hz, 2H), 8.41 (dd, *J* = 8.1, 0.9 Hz, 2H), 9.46 (d, *J* = 6.2 Hz, 2H), 10.20 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$) δ: 22.6, 103.9, 116.2, 121.3, 122.0, 123.4, 127.4, 128.1, 129.0, 129.4, 132.1, 134.5, 147.9, 150.2, 156.1, 162.6, 178.3 ppm; HRMS (ESI-TOF) *m/z*: $[M - OAc]^+$ calcd for $C_{32}H_{23}Br_2N_2O_4Pd$ 762.9054; found: 762.9081.

*7-Bromo-4-(2-bromophenoxy)quinoline Palladium Diacetate Dimer (**8b**)*: To an NMR tube were added **3b** (60.8 mg, 0.160 mmol, 1.0 equiv), $Pd(OAc)_2$ (18.0 mg, 0.080 mmol, 0.5 equiv) and $CDCl_3$ (0.6 mL). Decomposition >190°C; IR (NaCl) v 3419, 1623, 1590, 1511, 1306, 1219, 1063, 733, 693 cm^{-1}; ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.59 (s, 6H), 6.46 (d, *J* = 6.2 Hz, 2H), 7.16–7.37 (m, 4H), 7.41–7.57 (m, 2H), 7.66–7.93 (m, 4H), 8.29 (d, *J* = 8.8 Hz, 2H), 9.43 (d, *J* = 6.2 Hz, 2H), 10.36 (d, *J* = 1.7 Hz, 2H) ppm; ^{13}C{^{1}H}-NMR (150 MHz, $CDCl_3$) δ: 22.7, 104.2, 116.1, 120.1, 123.3, 123.5, 127.0, 128.4, 129.6, 131.2, 134.6, 148.4, 149.9, 157.4, 162.8, 178.4 ppm; HRMS (ESI-TOF) *m/z*: $[M - OAc]^+$ calcd for $C_{32}H_{21}Br_4N_2O_4Pd$ 918.7264; found: 918.7284. *Note:* ^{13}C-NMR shift at 131.2 ppm represents two individual carbon signals as confirmed by 2D NMR experiments.

*4-Phenoxyquinoline Palladium Diacetate Dimer (**8c**)*: To 25 mL RBF were added **3h** (55.0 mg, 0.249 mmol, 1.0 equiv), $Pd(OAc)_2$ (27.9 mg, 0.124 mmol, 0.5 equiv) and $CDCl_3$ (2 mL); X-ray quality crystals were obtained *via* vapour diffusion from a saturated solution of toluene/methanol in hexane, the CCDC number is 1970507; decomposition >150°C; IR (NaCl) v 3413, 1621, 1595, 1305, 1512, 1203, 1063 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.53 (s, 6H), 6.50 (d, *J* = 6.2 Hz, 2H), 7.03–7.21 (m, 4H), 7.23–7.51 (m, 6H), 7.61 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 2H), 7.99 (ddd, *J* = 8.6, 7.0, 1.4 Hz, 2H), 8.28 (dd, *J* = 8.4, 1.0 Hz, 2H), 9.34 (d, *J* = 6.2 Hz, 2H), 10.08 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$) δ: 22.7, 104.3, 121.4, 121.8, 122.0, 126.7, 127.3, 129.1, 130.7, 132.0, 148.0, 153.4, 156.1, 163.9, 178.3 ppm; HRMS (ESI-TOF) *m/z*: $[M - OAc]^+$ calcd for $C_{32}H_{25}N_2O_4Pd$ 607.0844; found: 607.0849.

Experiments to Prove Viability of Palladium-Quinoline Complexes.

1. A 0.062 M stock solution of **8c** in $CDCl_3$ was prepared and 0.1 mL (4.1 mg, 2 mol%) was transferred to a reaction tube and concentrated *in vacuo* to give a yellow residue. To the tube containing this residue were added substrate **3a** (0.118 g, 0.310 mmol, 1 equiv), phenylboronic acid (0.042 g, 0.341 mmol, 1.1 equiv), anhydrous K_2CO_3 (0.086 g, 0.62 mmol) and NMP (0.5 mL, 1.5 mL $mmol^{-1}$). The resulting mixture was stirred at 135 °C in the sealed reaction tube in an aluminium multi-reaction heating mantle until the reaction was complete as evident by ^{1}H-NMR analysis (20 h). The cooled reaction mixture was diluted with DCM, filtered through a short plug of Celite and concentrated *in*

vacuo. A yield of 81% **4a** was determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard (**Scheme 4**a).

2. A 0.062 M stock solution of **8c** in $CDCl_3$ was prepared and 0.1 mL (4.1 mg, 2 mol%) was transferred to a reaction tube and concentrated *in vacuo* to give a yellow residue. To the tube containing this residue were added substrate **1** (0.093 g, 0.310 mmol, 1 equiv), anhydrous K_2CO_3 (0.086 g, 0.62 mmol) and NMP (0.5 mL, 1.5 mL mmol^{-1}). The resulting mixture was stirred at 135 °C in the sealed reaction tube in an aluminium multi-reaction heating mantle until the reaction was complete as evident by ^{1}H-NMR analysis (20 h). The cooled reaction mixture was diluted with DCM, filtered through a short plug of Celite and concentrated *in vacuo*. A 99% yield of **2** was determined by ^{1}H-NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard (SI Scheme S3).

3. A 0.10 M stock solution of **8a** in $CHCl_3$ was prepared and 0.2 mL (16.5 mg, 10 mol%) was transferred to a reaction tube and concentrated *in vacuo* to give a yellow residue. To the tube containing this residue were added substrate **3a** (0.076 g, 0.20 mmol, 1 equiv), phenylboronic acid (0.027 g, 0.22 mmol, 1.1 equiv), anhydrous K_2CO_3 (0.055 g, 0.40 mmol) and NMP (0.3 mL, 1.5 mL mmol^{-1}). The resulting mixture was stirred at 135 °C in the sealed reaction tube in an aluminium multi-reaction heating mantle until the reaction was complete as evident by ^{1}H-NMR analysis (18 h). The cooled reaction mixture was diluted with DCM, filtered through a short plug of Celite and concentrated *in vacuo*. Upon analysis of the crude reaction mixture, no starting material remained and the peaks for both products **4a** and **2** were present. The signals for **4a** and **2** were too close to obtain accurate NMR yields and were non-separable by column chromatography (**Scheme 4**b).

Supporting Information

The Supporting Information is available; it includes copies of the ^{1}H, ^{13}C and ^{1}H -^{15}N HMBC NMR spectra, extraneous experiments, X-ray crystallography data, HRMS data for metal-containing complexes, fluorescence emission and UV-Vis absorption data (PDF).

Acknowledgements

The Authors would like to thank Dr Trevor Carey, Prof John Sodeau, Dr Peter Byrne and Dr Leticia Pardo for useful discussion. The Authors acknowledge the Irish Research Council (IRC) and Science Foundation Ireland (SFI) (grant number SFI/12/IP/1315) and the Synthesis and Solid State Pharmaceutical Centre (SSPC) (SFI/12/RC/2275). The Authors thank the European Cooperation in Science and Technology COST initiative for funding CA15106, C-H Activation in Organic Synthesis (CHAOS). This publication has emanated from research conducted with the financial support of SFI through a research infrastructure award for process flow spectroscopy (Prospect) under the grant number 15/RI/3221.

References

(1) (a) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.* **2016**, *7*, 866-880; (b) Vaxelaire, C.; Winter, P.; Christmann, M. One-Pot Reactions Accelerate the Synthesis of Active Pharmaceutical Ingredients. *Angew. Chem. Int. Ed.* **2011**, *50*, 3605-3607.

(2) Dobrounig, P.; Trobe, M.; Breinbauer, R. Sequential and iterative Pd-catalyzed cross-coupling reactions in organic synthesis. *Monatsh. Chem.* **2017**, *148*, 3-35.

(3) Majumdar, K. C.; Chattopadhyay, S. K. *Heterocycles in Natural Product Synthesis*; John Wiley & Sons: Weinheim, Germany, 2011.

(4) Taylor, R. D.; MacCoss, M.; Lawson, A. D. G. Rings in Drugs. *J. Med. Chem.* **2014**, *57*, 5845-5859.

(5) Shanahan, R. M.; Hickey, A.; Reen, F. J.; O'Gara, F.; McGlacken, G. P. Synthesis of Benzofuroquinolines via Phosphine-Free Direct Arylation of 4-Phenoxyquinolines in Air. *Eur. J. Org. Chem.* **2018**, *Special Issue*, 6140-6149.

(6) (a) Newman, S. G.; Lautens, M. The role of reversible oxidative addition in selective palladium (0)-catalyzed intramolecular cross-couplings of polyhalogenated substrates: synthesis of brominated indoles. *J. Am. Chem. Soc.* **2010**, *132*, 11416-11417; (b) Dobrounig, P.; Trobe, M.; Breinbauer, R. Sequential and iterative Pd-catalyzed cross-coupling reactions in organic synthesis. *Monatsh. Chem.* **2017**, *148*, 3-35.

(7) Wang, J.-R.; Manabe, K. Transition-Metal-Catalyzed Site-Selective Cross-Coupling of Di- and Polyhalogenated Compounds. *Synthesis* **2009**, *9*, 1405-1427.

(8) (a) Ma, X.; Gu, N.; Liu, Y.; Liu, P.; Xie, J.; Dai, B.; Liu, Z. One-pot synthesis of polyfluoroterphenyls via palladium-catalyzed Suzuki-Miyaura coupling of chlorobromobenzene and C-H bond functionalization of perfluoroarenes. *Appl. Organomet. Chem.* **2015**, *29*, 50-56; (b) Matsumura, K.; Yoshizaki, S.; Maitani, M. M.; Wada, Y.; Ogomi, Y.; Hayase, S.; Kaiho, T.; Fuse, S.; Tanaka, H.; Takahashi, T. Rapid Synthesis of Thiophene-Based, Organic Dyes for Dye-Sensitized Solar Cells (DSSCs) by a One-Pot, Four-Component Coupling Approach. *Chem. Eur. J.* **2015**, *21*, 9742-9747; (c) Ren, L.; Chu, W.; Guan, D.; Hou, Y.; Wang, M.; Yuan, X.; Sun, Z. Chemoselective one-pot synthesis of terphenyl derivatives by sequential directed C-H functionalization-Suzuki coupling. *Appl. Organomet. Chem.* **2014**, *28*, 673-677; (d) El Akkaoui, A.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. Direct Arylation of Imidazo[1,2-b]pyridazines: Microwave-Assisted One-Pot Suzuki Coupling/Pd-Catalysed Arylation. *Eur. J. Org. Chem.* **2010**, *2010*, 862-871; (e) Koubachi, J.; El Kazzouli, S.; Berteina-Raboin, S.; Mouaddib, A.; Guillaumet, G. Synthesis of polysubstituted imidazo[1,2-a]pyridines via microwave-

assisted one-pot cyclization/Suzuki coupling/palladium-catalysed heteroarylation. *J. Org. Chem.* **2007**, *72*, 7650-7655.

(9) (a) Geary, L. M.; Hultin, P. G. 2-Substituted Benzo[b]furans from (E)-1,2-Dichlorovinyl Ethers and Organoboron Reagents: Scope and Mechanistic Investigations into the One-Pot Suzuki Coupling/Direct Arylation. *Org. Lett.* **2009**, *11*, 5478-5481; (b) Wang, W.-Y.; Feng, X.; Hu, B.-L.; Deng, C.-L.; Zhang, X.-G. Synthesis of 6-(Trifluoromethyl) Phenanthridines via Palladium-Catalyzed Tandem Suzuki/C-H Arylation Reactions. *J. Org. Chem.* **2013**, *78*, 6025-6030; (c) Chai, D. I.; Lautens, M. Tandem Pd-Catalyzed Double C-C Bond Formation: Effect of Water. *J. Org. Chem.* **2009**, *74*, 3054-3061; (d) Nicolaus, N.; Franke, P. T.; Lautens, M. Modular Synthesis of Naphthothiophenes by Pd-Catalyzed Tandem Direct Arylation/Suzuki Coupling. *Org. Lett.* **2011**, *13*, 4236-4239; (e) Leclerc, J.-P.; André, M.; Fagnou, K. Heck, Direct Arylation, and Hydrogenation: Two or Three Sequential Reactions from a Single Catalyst. *J. Org. Chem.* **2006**, *71*, 1711-1714.

(10) Friedman, D.; Masiangioli, T.; Olson, S. *The Role of the Chemical Sciences in Finding Alternatives to Critical Resources: A Workshop Summary*; National Academies Press: Washington, DC, 2012.

(11) (a) Zhao, M.; Kamada, T.; Takeuchi, A.; Nishioka, H.; Kuroda, T.; Takeuchi, Y. Structure–activity relationship of indoloquinoline analogs anti-MRSA. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5551-5554; (b) Chen, Y.-L.; Chung, C.-H.; Chen, I. L.; Chen, P.-H.; Jeng, H.-Y. Synthesis and cytotoxic activity evaluation of indolo-, pyrrolo-, and benzofuro-quinolin-2(1H)-ones and 6-anilinoindoloquinoline derivatives. *Bioorg. Med. Chem.* **2002**, *10*, 2705-2712.

(12) Chang, Y.; Fu, J.; Yao, K.; Li, B.; Xu, K.; Pang, X. Novel fluorescent probes for sequential detection of Cu2+ and citrate anion and application in living cell imaging. *Dyes Pigm.* **2019**, *161*, 331-340.

(13) Although conventional EAS would not be useful here, it is worth noting that C-H borylation could be considered a viable route, as demonstrated in the following reports: (a) Mkhalid, I. A. I.; Coventry, D. N.; Albesa-Jove, D.; Batsanov, A. S.; Howard, J. A. K.; Perutz, R. N.; Marder, T. B. Ir-Catalyzed Borylation of C-H Bonds in N-Containing Heterocycles: Regioselectivity in the Synthesis of Heteroaryl Boronate Esters. *Angew. Chem. Int. Ed.* **2006**, *45*, 489-491. (b) Tajuddin, H.; Harrisson, P.; Bitterlich, B.; Collings, J. C.; Sim, N.; Batsanov, A. S.; Cheung, M. S.; Kawamorita, S.; Maxwell, A. C.; Shukla, L.; Morris, J.; Lin, Z.; Marder, T. B.; Steel, P. G. Iridium-catalyzed C-H borylation of quinolines and unsymmetrical 1,2-disubstituted benzenes: insights into steric and electronic effects on selectivity. *Chem. Sci.* **2012**, *3*, 3505-3515.

(14) Altaf, A. A.; Shahzad, A.; Gul, Z.; Rasool, N.; Badshah, A.; Lal, B.; Khan, E. A review on the medicinal importance of pyridine derivatives. *J. Drug Des. Med. Chem.* **2015**, *1*, 1-11.

(15) Yang, Y.; Lan, J.; You, J. Oxidative C-H/C-H Coupling Reactions between Two (Hetero)arenes. *Chem. Rev.* **2017**, *117*, 8787-8863.

(16) (a) Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. Ligand-Promoted C3-Selective Arylation of Pyridines with Pd Catalysts: Gram-Scale Synthesis of (±)-Preclamol. *J. Am. Chem. Soc.* **2011**, *133*, 19090-19093; (b) Iwai, T.; Sawamura, M. Transition-Metal-Catalyzed Site-Selective C-H Functionalization of Quinolines beyond C2 Selectivity. *ACS Catal.* **2015**, *5*, 5031-5040; (c) Hilton, M. C.; Dolewski, R. D.; McNally, A. Selective Functionalization of Pyridines via Heterocyclic Phosphonium Salts. *J. Am. Chem. Soc.* **2016**, *138*, 13806-13809; (d) Shota, K.; Soichiro, K.; Tomohiro, I.; G., S. P.; B., M. T.; Masaya, S. Site-Selective C-H Borylation of Quinolines at the C8 Position Catalyzed by a Silica-Supported Phosphane-Iridium System. *Chem. Asian J.* **2014**, *9*, 434-438.

(17) Park, H.; Chekshin, N.; Shen, P.-X.; Yu, J.-Q. Ligand-Enabled, Palladium-Catalyzed β-C(sp3)-H Arylation of Weinreb Amides. *ACS Catal.* **2018**, *8*, 9292-9297.

(18) (a) Wasa, M.; Chan, K. S. L.; Zhang, X.-G.; He, J.; Miura, M.; Yu, J.-Q. Ligand-Enabled Methylene C(sp3)-H Bond Activation with a Pd(II) Catalyst. *J. Am. Chem. Soc.* **2012**, *134*, 18570-18572; (b) He, Y.; Wu, Z.; Ma, C.; Zhou, X.; Liu, X.; Wang, X.; Huang, G. Palladium-Catalyzed Selective C-H Activation: A Simple Method to Synthesize C-3 Site Arylated Quinoline Derivatives. *Adv. Synth. Catal.* **2016**, *358*, 375-379.

(19) Martin, G. E.; Hadden, C. E. Long-Range 1H-15N Heteronuclear Shift Correlation at Natural Abundance. *J. Nat. Prod.* **2000**, *63*, 543-585.

(20) (a) Rosar, V.; Dedeic, D.; Nobile, T.; Fini, F.; Balducci, G.; Alessio, E.; Carfagna, C.; Milani, B. Palladium complexes with simple iminopyridines as catalysts for polyketone synthesis. *Dalton Trans.* **2016**, *45*, 14609-14619; (b) Pereira, M. T.; Antelo, J. M.; Adrio, L. A.; Martínez, J.; Ortigueira, J. M.; López-Torres, M.; Vila, J. M. Novel Bidentate [N,S] Palladacycle Metalloligands. 1H-15N HMBC as a Decisive NMR Technique for the Structural Characterization of Palladium-Rhodium and Palladium-Palladium Bimetallic Complexes. *Organometallics* **2014**, *33*, 3265-3274; (c) Villarreal, W.; Colina-Vegas, L.; Rodrigues de Oliveira, C.; Tenorio, J. C.; Ellena, J.; Gozzo, F. C.; Cominetti, M. R.; Ferreira, A. G.; Ferreira, M. A. B.; Navarro, M.; Batista, A. A. Chiral Platinum(II) Complexes Featuring Phosphine and Chloroquine Ligands as Cytotoxic and Monofunctional DNA-Binding Agents. *Inorg. Chem.* **2015**, *54*, 11709-11720.

(21) (a) García-Cuadrado, D.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. Proton Abstraction Mechanism for the Palladium-Catalyzed Intramolecular Arylation. *J. Am. Chem. Soc.* **2006**, *128*, 1066-1067; (b) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. Analysis of the Concerted Metalation-Deprotonation Mechanism in Palladium-Catalyzed Direct Arylation Across a Broad Range of Aromatic Substrates. *J. Am. Chem. Soc.* **2008**, *130*, 10848-10849; (c) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. Mechanisms of C-H bond activation: rich synergy between computation and experiment. *Dalton Trans.* **2009**, *2009*, 5820-5831.

(22) Jiang, J.; Yu, J.-Q.; Morokuma, K. Mechanism and Stereoselectivity of Directed C(sp3)-H Activation and Arylation Catalyzed by Pd(II) with Pyridine Ligand and Trifluoroacetate: A Computational Study. *ACS Catal.* **2015**, *5*, 3648-3661.

(23) Cabrera, P. J.; Lee, M.; Sanford, M. S. Second-Generation Palladium Catalyst System for Transannular C–H Functionalization of Azabicycloalkanes. *J. Am. Chem. Soc.* **2018**, *140*, 5599-5606.

(24) While it is difficult to rule out a role for NMP-stabilised Pd-nanoparticles, it is noted that these reactions work in dioxane. Also, the addition of quinoline ligands to the DA reaction of non-coordinationg substrates increases turnover significantly - these reactions will be published in due course.

(25) Zhao, X. J.; Huang, C. Z.; Huang, C. Z. Small organic molecules as fluorescent probes for nucleotides and their derivatives. *TrAC, Trends Anal. Chem.* **2010**, *29*, 354-367.

(26) Hou, L.; Zhang, X.; Cotella, G. F.; Carnicella, G.; Herder, M.; Schmidt, B. M.; Pätzel, M.; Hecht, S.; Cacialli, F.; Samorì, P. Optically switchable organic light-emitting transistors. *Nat. Nanotechnol.* **2019**, *14*, 347-353.

(27) Terai, T.; Nagano, T. Small-molecule fluorophores and fluorescent probes for bioimaging. *Pflugers Arch - Eur. J. Physiol.* **2013**, *465*, 347-359.

(28) Sheldrick, G. M. Crystal Structure Refinement with SHELXL. *Acta Crystallogr. Sect. C, Struct. Chem.* **2015**, *71*, 3-8.

(29) Dolomanov, O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. OLEX2: A Complete Structure Solution, Refinement and Analysis Program. *J. Appl. Crystallogr.* **2009**, *42*, 339-341.

(30) Mehra, M. K.; Tantak, M. P.; Arun, V.; Kumar, I.; Kumar, D. Metal-free regioselective formation of C-N and C-O bonds with the utilization of diaryliodonium salts in water: facile synthesis of N-arylquinolones and aryloxyquinolines. *Org. Biomol. Chem.* **2017**, *15*, 4956-4961.