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One-pot palladium-catalyzed C–I and C–H bond activation and subsequent Suzuki–Miyaura cross-coupling of 2-aryl-3-iodo-4-(phenylamino)quinolines with arylboronic acids

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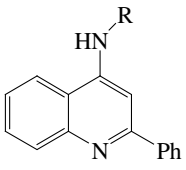
ABSTRACT

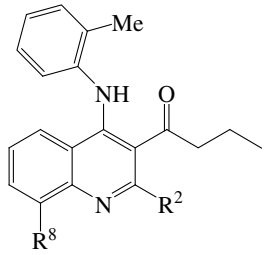
The 2-aryl-3-iodo-4-(phenylamino)quinolines undergo one-pot palladium-mediated C–I and C–H bond activation and subsequent Suzuki–Miyaura cross-coupling with arylboronic acids under anhydrous conditions to afford mixture of 2,3-diaryl-4-(phenylamino)quinolines (minor) and 2-aryl-4-([(1,1′-biaryl)-2-yl]amino)quinoline derivatives (major). The 2,3-diaryl-4-(phenylamino)quinolines were isolated as major products when 2 M K_2CO_3 was used as a base. A plausible mechanism, which implicates a six-membered palladacycle intermediate is proposed for the formation of the observed mixture of products. The prepared compounds were characterized using a combination of spectroscopic and X-ray crystallographic techniques.

1. Introduction

Continued interest in the synthesis of quinoline derivatives substituted with a primary amino group at the 4-position stems from their importance as antimalarial,[1] anti-inflammatory[2] and antihypertensive agents.[3] 4-Amino-2-arylquinolines have also been found to represent a novel class of NR1/2B subtype selective *N*-methyl-D-aspartate (NMDA) receptor antagonists.[4] Likewise the 2-aryl-4-(phenylamino)quinolines **I** represent an important class of compounds, which serve as potent immunostimulants,[5,6] non-nucleoside HIV-1 inhibitors[7] and reversible (H^+/K^+)ATPase inhibitors for the treatment of ulcers and related gastric disorders.[8] Literature reports indicate that the orientation of 4-(arylamino) substituent in quinolines **II**, which is controlled by the C-3 substituent is a very important factor in gastric H^+/K^+-ATPase inhibitory activity.[8a,b] Moreover, *ortho* substitution of the arylamino group was also found to impart small but significant improvements in biological activity by influencing the aryl ring to twist further out of the plane of the quinoline framework.[8b]



I



II R^2=H, R^8=OMe

R^2=H, R^8=OCH_2CH_2OH

Although there are several methods described in literature for the synthesis of 4-amino-2-arylquinolines, corresponding data for the preparation of 2,3-disubstituted quinoline derivatives bearing a primary *N*-substituted amino group is considerably less well-documented.[8–10] Such derivatives cannot be easily accessible via classical methods, such as the Skraup, Doebner–von Miller, Friedlander and Combes reactions.[11] Consequently, indirect approach to efficiently functionalize presynthesized halogenated quinoline derivatives via nucleophilic displacement and/or metal-catalyzed cross-coupling reactions to lead to Csp^2–N and/or Csp^2–Csp^2 bond formation remain the method of choice. Yum et al.[8c] subjected the 4-(2-methylphenylamino)-3-iodoquinolines to palladium-catalyzed Heck reaction with terminal alkenes to afford

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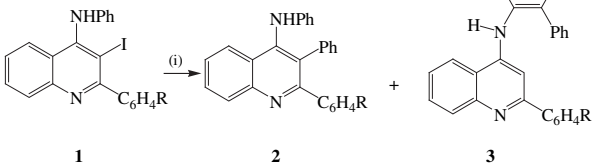
the corresponding 3-vinylquinolines with gastric H^+/K^+-ATPase inhibitory activity. Sonogashira cross-coupling of the analogous 2-aryl-3-iodo-4-(phenylamino)quinolines with terminal alkynes afforded the 1,2,4-triaryl-1*H*-pyrrolo[3,2-*c*]quinolines in one-pot operation.[12] The 2,3-diaryl-4-chloroquinolines derived from Suzuki cross-coupling of 2-aryl-4-chloro-3-iodoquinolines with 4-arylboronic acids were found to undergo dechloroamination with aniline to afford the 2,3-diaryl-4-(phenylamino)quinolines.[13] Our continued interest in the reactivity of 4-substituted 2-aryl-3-iodoquinolines prompted us to investigate the possibility of direct synthesis of 2,3-diaryl-4-(phenylamino)quinolines from the 2-aryl-3-iodo-4-(phenylamino)quinolines via Suzuki–Miyaura cross-coupling reaction using arylboronic acids.

2. Results and discussion

It is well known that the efficiency of a palladium catalyst strongly depends on the ligand of palladium atom and the overall reactivity also depends on the precursor of palladium(0) complex.[14] With this consideration in mind, we subjected the known 3-iodo-2-phenyl-4-(phenylamino)quinoline **1a**[12] to Suzuki–Miyaura cross-coupling with a mixture of phenylboronic acid and K_2CO_3 in anhydrous *N*,*N*-dimethyl formamide (DMF) in the presence of tetrakistriphenylphosphinepalladium(0) ($Pd(PPh_3)_4$) as a reference starting point based on literature precedence (Scheme 1).[15] We isolated by column chromatography on silica gel two products in sequence and in different ratio (entry 1). A similar product mixture was observed when dichlorobis(triphenylphosphine)palladium(II) ($PdCl_2(PPh_3)_2$) was used as the pre-catalyst (entry 2). The reaction was extended to palladium acetate ($Pd(OAc)_2$) to afford a similar mixture of products, albeit in very low yields (entry 3). This screening of palladium sources revealed $Pd(PPh_3)_4$ as the most efficient catalyst for this transformation while $PdCl_2(PPh_3)_2$ and $Pd(OAc)_2$ gave relatively lower yields (Scheme 1). In order to distinguish between the two products and to establish the mode of C–C bond formation, it was necessary to investigate their spectroscopic data. Spectroscopic data (NMR, IR and MS) for the minor product confirmed the structure to correspond to the expected **2a**, with 21 aromatic carbon-13 signals observed. The ^{13}C NMR spectrum of the major product accounted for 23 carbon resonances thus suggesting a different substitution pattern to that of the minor product. The ^1H NMR spectrum of the major product revealed the presence of an increased number of resonances in the aromatic region and the NH signal at δ ca. 6.54 ppm, which was also confirmed by the N–H IR absorption band at ν_{max} 3418 cm^{-1}.



1 **2** **3**

Entry	Catalyst	% Yield (**2a**)	% Yield (**3a**)
1	$Pd(PPh_3)_4$	34	57
2	$PdCl_2(PPh_3)_2$	5	18
3	$Pd(OAc)_2$	2	13

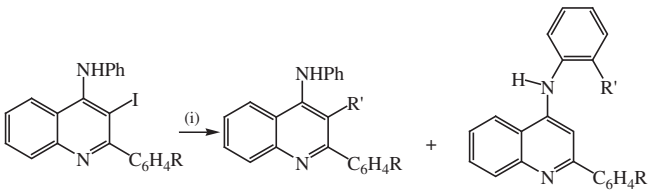
Reagents: (i) Pd catalyst, $PhB(OH)_2$, K_2CO_3, DMF, heat, 18h

Scheme 1. Suzuki–Miyaura cross-coupling of **1** with phenylboronic acid. Reagents: (i) Pd catalyst, $PhB(OH)_2$, K_2CO_3, DMF, heat, 18 h.

In addition to resonances corresponding to the 2-aryl and fused-benzo ring, we also observed the presence of an intense singlet at δ 7.58 ppm, which corresponds to 3-H. Moreover, the accurate calculated *m*/*z* value for this product represents closest fit consistent with the incorporation of the phenyl moiety. Based on spectroscopic data we ruled out the possibility of intramolecular aryl–aryl bond formation typical for appropriately substituted diarylamines to form carbazole moiety.[16,17] We tentatively assigned the structure of the major product to the 2-phenyl-4-([(1,1′-biphenyl)-2-yl]amino)quinoline derivative **3a**. We attributed the observed mixture of products as the consequence of a direct one-pot palladium-mediated C–I and C–H activation and subsequent Suzuki cross-coupling reaction with phenylboronic acid.

To establish the generality of this reaction, we extended the reaction conditions to other derivatives **1** using phenylboronic acid, 4-fluorophenylboronic acid and 2-phenylvinylboronic acid as coupling partners, respectively. Analysis of the crude product mixtures by thin layer chromatography on silica gel revealed in all cases only two spots of different polarity and intensity with no traces of the spot corresponding to the starting material. DMF was removed from the crude product mixture on a Büchii bulb-to-bulb distillation oven under reduced pressure and the relative proportion of the two products were also estimated using the difference in integral values of the NH signals in their ^1H NMR spectra. We isolated in all cases by column chromatography on silica gel products **2** (major spot) and **3** (minor spot) in sequence (Table 1). We also studied Suzuki–Miyaura cross-coupling of substrates **1a**–**d** with arylboronic acids in DMF using $Pd(PPh_3)_4$ as a Pd(0) catalyst source and 2 M K_2CO_3 as a base (Table 1). Interestingly, under these conditions we isolated systems **2** as the predominant products.

Table 1
Palladium-catalyzed cross-coupling of **1** to afford mixture of **2** and **3**



1 **2** **3**

	4-R	R′	% Yield **2**	% Yield **3**
a	H	$-C_6H_5$	34[a]	57[a]
			50[b]	14[b]
b	F	$-C_6H_5$	23[a]	54[a]
			65[b]	15[b]
c	Cl	$-C_6H_5$	11[a]	52[a]
			50[b]	12[b]
d	OMe	$-C_6H_5$	15[a]	52[a]
			62[b]	23[b]
e	F	*p*-FC_6H_4-	16[a]	54[a]
			50[b]	22[b]
f	OMe	*p*-FC_6H_4-	22[a]	54[a]
			56[b]	24[b]
g	F	$-CH{=}CHPh$	18[a]	56[a]
h	OMe	$-CH{=}CHPh$	21[a]	49[a]

[a] Reagents and conditions: (i) $ArB(OH)_2$ (1.2 equiv), 5% $Pd(PPh_3)_4$, 2 M K_2CO_3, DMF, 80 °C, 18 h.
[b] Reagents and conditions: (i) $ArB(OH)_2$ (1.2 equiv), $Pd(PPh_3)_4$, 2 M K_2CO_3 (aq), DMF, 80 °C, 18 h.

Crystals of quality suitable for X-ray diffraction studies were later obtained for products **2d** and **3h** and the molecular structures of **2** and **3** were also confirmed (Figs. 1 and 2).[18] Selected torsion angles for **2d** and **3h** are shown in Tables 2 and 3, respectively. The orientation adopted by the 4-arylamino group with respect to the

quinoline ring can be envisaged as being primarily due to a steric interaction between the phenyl ring and substituent at the 3- and 5-position of the quinoline framework. In the crystal lattice, compound **2** with an aryl group at the 3-position adopts the anticipated orientation with the 4-phenylamino group *syn* to the quinoline 5-position (*syn*-5) with C_{quin}–N and N–Ph torsion angles C(4A)–C(4)–N(15)–C(16)=−49.62° and C(17)–C(16)–N(15)–C(4)=−29.46°, respectively (Fig. 1 and Table 2).

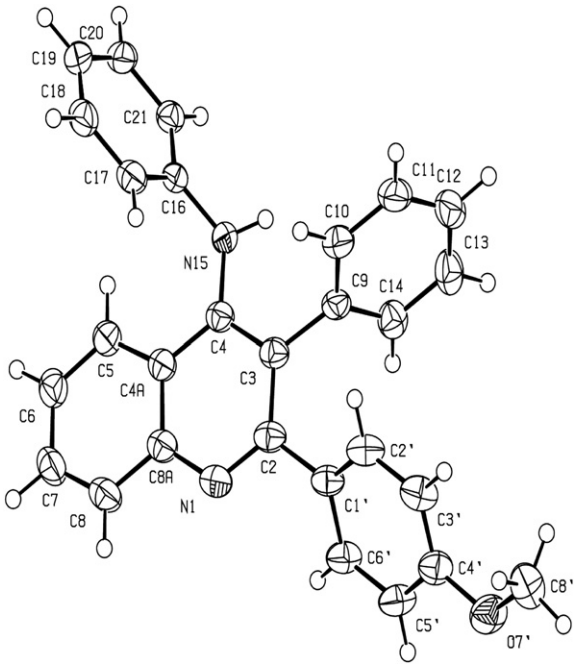


Fig. 1. ORTEP diagram (50% probability level) of 2-(4-methoxyphenyl)-3-phenyl-4-(phenylamino)quinoline **2d** showing crystallographic numbering.

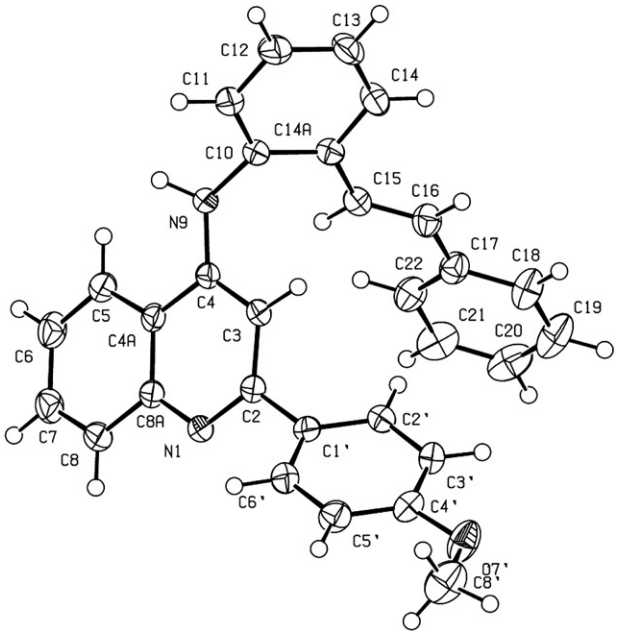


Fig. 2. ORTEP diagram (50% probability level) of 2-(4-methoxyphenyl)-4-(2′-[(2-phenylethenyl)phenyl-2-yl]amino)quinoline **3h**. For clarity, hydrogen atoms are not labelled.

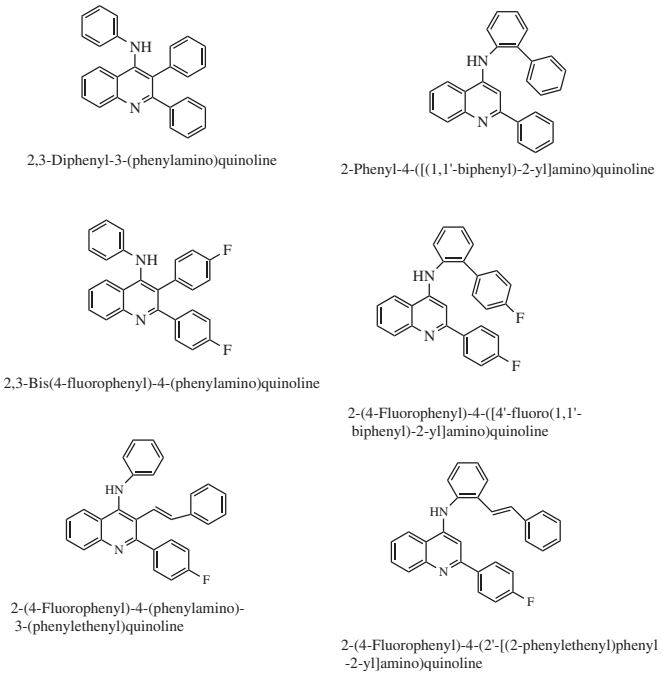


Fig. 3. Structures of representative examples of the 2,3-diaryl-4-(phenylamino) quinolines 2 and 2-aryl-4-([1,1′-biaryl)-2-yl]amino)quinolines **3**.

Table 2
Selected torsion angles (°) for **2d**. For atom labelling see Fig. 1

Compound **2d**	
C(6′)–C(1′)–C(2)–N(1)	−44.90°
C(2′)–C(1′)–C(2)–C(3)	−47.93°
C(2)–C(3)–C(9)–C(14)	−69.54°
C(4)–C(3)–C(9)–C(10)	−71.52°
C(4A)–C(4)–N(15)–C(16)	−49.62°
C(17)–C(16)–N(15)–C(4)	−29.46°

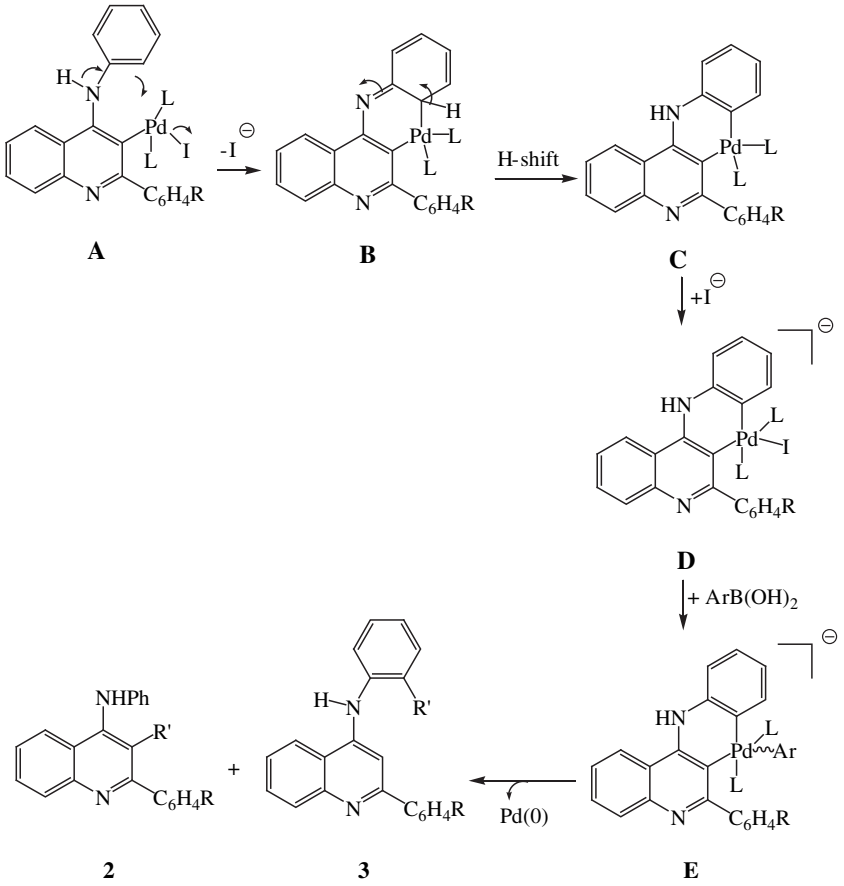
Table 3
Selected torsion angles (°) for **3h**. For atom labelling see Fig. 3

Compound **3h**	
C(6′)–C(1′)–C(2)–N(1)	−48.1°
C(2′)–C(1′)–C(2)–C(3)	−50.4°
C(14)–C(14A)–C(15)–C(16)	23.5°
C(15)–C(16)–C(17)–C(22)	5.7°
C(3)–C(4)–N(9)–C(10)	0.7°
C(14A)–C(10)–N(9)–C(4)	66.0°

With no substituent at the 3-position (R′=H), the orientation with a minimum steric strain, namely the phenyl group of phenylamino substituent *anti* to the quinoline 5-position (*anti*-5), is preferred (Fig. 2). The aryl ring of the phenylamino group is twisted further out of the plane of the quinoline framework with torsion angle C(14A)–C(10)–N(9)–C(4)=66° due to *ortho* substitution (Fig. 2 and Table 3). Moreover, the *anti* arrangement of the phenylamino group enables hydrogen bonding between the NH of one molecule and N-1 of another molecule [N(9)–H(9)·N(1)]: N(9)–H(9) 0.92(2) Å; H(9)·N(1) 1.99(2) Å; N(9)·N(1) 2.9045(19) Å; <N(9)H(9)N(1) 173°.

The mechanism of Suzuki cross-coupling reaction, which comprises three main steps: (a) oxidative addition, (b) transmetallation and (c) reductive elimination has been well-studied experimentally,[19–22] and certain aspects of the mechanism were also explored using computational techniques.[23] The intriguing results observed in this investigation prompted us to propose a mechanism

to account for the one-pot C–I and C–H activation and subsequent Suzuki cross-coupling reaction to afford a mixture of **2** and **3**. The first step in the above reaction involves oxidative addition of palladium(0) complex into **1** to form the solvated arylpalladium halide intermediate **A** (Scheme 2). Intramolecular C–H activation in organopalladium intermediates derived from *o*-halobiaryls to lead to 1,4-palladium migration is a well established process[24] and limited examples involving *o*-halobiaryls linked by a heteroatom have also been reported.[17a,25] Although a similar migration for the current systems cannot be completely ruled out, we envisage that deprotonation of nitrogen by the base occurs leading to its increased propensity for lone pair electron delocalization to the *ortho*-position of the anilino moiety. This strongly nucleophilic carbon presumably attacks Pd to form a more thermodynamically favoured six-membered palladacycle intermediate **B**, which in turn, undergoes hydride shift to afford the more stable palladacycle **C**. Palladacycles are implicated in various C–C bond formation reactions to form polycyclic derivatives,[17a,26] and they have also been isolated before and employed as catalysts.[27] Five-membered palladium(II) and palladium(IV) palladacycles have also been implicated in a mechanism involving palladium-mediated *ortho* alkylation of aromatic iodides with alkyl bromides followed by reaction with arylboronic acids to afford symmetrical and unsymmetrical 2,6-dialkyl-1,1′-biaryls.[26] Bedford and Welch, have shown that under stoichiometric conditions phosphinite-based palladacycles in the presence of arylboronic acid undergo a trasmetallation–reductive elimination process to generate Pd(0) species and the *ortho*-arylated ligand.[28] ^{19}F NMR and GC/MS were employed by Monteiro et al. to monitor the Suzuki cross-coupling of sulfur-containing palladacycles with phenylboronic acid under stoichiometric and catalytic conditions.[27] These authors observed the formation of zerovalent palladium species resulting from initial attack of the palladacycle by arylboronic acid to afford arylated palladacycle, which undergo reductive elimination to form the active Pd(0) species. Amatore et al.[21] recently observed the formation of a pentavalent Pd(II) anion, ArPd(OH)Ar′$(PPh_3)_2$, formed through coordination of the *trans*-ArPdAr′$(PPh_3)_2$ complex with hydroxide ion from the base used in Suzuki–Miyaura cross-coupling. The pentavalent Pd(II) anion, ArPd(OH)Ar′$(PPh_3)_2^-$, was found to undergo facile reductive elimination to generate ArAr′ and Pd(0) species. We envision coordination of **C** with the iodide ion released from **A** to form a pentavalent Pd(II) anion **D** (ArPd(I)Ar′$(PPh_3)_2^-$) capable of undergoing transmetallation with arylboronic acid. Based on the findings of Bedford and Monteiro we propose that the Pd(II) intermediate **D** undergoes transmetallation with arylboronic acid in a manner essentially identical to that invoked in a classical Suzuki mechanism to generate a pentacoordinated palladium(II) intermediate **E** or its anionic derivative, which in turn undergoes facile reductive elimination to afford products **2** and **3**. Although steric factors cannot be completely ruled out, we attribute the formation of products **3** under anhydrous conditions to be due to the increased nucleophilicity of the *ortho*-carbon of anilino moiety relative to the pyridine ring (C-3). In aqueous DMF, the formation of the envisioned six-membered palladacycle is presumably slowed down or reduced by possible protonation of the nucleophilic *ortho*-carbon by water. This would, in turn, favour transmetallation of intermediate **A** with arylboronic acid and subsequent reductive elimination to afford **2** as the major product.



Scheme 2. Proposed mechanism for the formation of mixture of **2** and **3**.

Six- or higher-membered palladacycles formed through remote C–H bond activation directed by heteroatom containing functional groups have been described in the literature.[29] Despite the fact that our proposed mechanism is necessarily speculative, it represents the most reasonable pathway to account for the observed mixture of products. The products prepared in this investigation represent suitable candidates for further studies of chemical transformation and biological activity. Systems **3**, for example, are analogues of tebuquine, a substituted biphenylaminoquinoline with greater antimalarial activity than amodiaquine in vivo[30,31] and in vitro.[32,33] Further investigations to extend the scope of this reaction to include other 4-arylheteroatom containing quinoline derivatives and various metal catalysts are currently underway in our laboratory.

3. Experimental

3.1. General

Melting points were recorded on a Thermocouple digital melting point apparatus and are uncorrected. IR spectra were recorded as powders using an FTS 7000 Series Digilab Win-IR Pro ATR (attenuated total reflectance) spectrometer. For column chromatography, Merck kieselgel 60 (0.063–0.200 mm) was used as a stationary phase. NMR spectra were obtained as $CDCl_3$ solutions using Varian Mercury 300 MHz NMR spectrometer and the chemical shifts are quoted relative to the solvent peaks. Low- and high-resolution mass spectra were recorded at an ionization potential of 70 eV using Micromass Autospec-TOF (double focussing high-resolution) instrument. The synthesis and characterization of substrates **1** have been described elsewhere.[12]

3.2. Suzuki cross-coupling of 1 with $ArB(OH)_2$ under anhydrous conditions. Typical procedure

*3.2.1. 2,3-Diphenyl-3-(phenylamino)quinoline **2a** and 2-phenyl-4-([(1,1′-biphenyl)-2-yl]amino)quinoline **3a**.* 3-Iodo-2-phenyl-4-(phenylamino)quinoline **1a** (0.30 g, 0.71 mmol), phenylboronic acid (0.10 g, 0.85 mmol), $Pd(PPh_3)_4$ (0.04 g, 0.04 mmol) and K_2CO_3 (0.20 g, 1.42 mmol) in DMF (20 mL) were added to a two-necked flask equipped with a stirrer bar, rubber septum and a condenser. The mixture was flushed for 20 min with argon gas, then a balloon filled with argon gas was connected to the top of the condenser. The mixture was heated with stirring at 80–90 °C under argon atmosphere for 18 h and then allowed to cool to room temperature. The cooled mixture was poured into ice-cold water and the product was taken-up into chloroform. The combined organic extracts were sequentially washed with brine, dried over anhydrous $MgSO_4$, filtered and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate/hexane mixture to afford products **2a** (minor) and **3a** (major) in sequence.

Compound **2a** white solid (0.09 g, 34%), mp 196–198 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.68; ν_{max} (neat) 1236, 1367, 1402, 1485, 1570, 3366 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.90 (s, 1H), 6.79 (d, *J* 7.5 Hz, 2H), 6.97 (t, *J* 7.5 Hz, 1H), 7.11–7.16 (m, 2H), 7.18–7.23 (m, 5H), 7.25–7.30 (m, 3H), 7.31–7.37 (m, 3H), 7.67 (dt, *J* 1.8 and 7.8 Hz, 1H), 7.77 (dd, *J* 0.9 and 8.4 Hz, 1H), 8.18 (dd, *J* 0.6 and 8.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 118.4, 121.6, 121.8, 125.3, 125.4, 125.6, 127.6, 127.7, 127.8, 128.9, 129.2, 129.4, 129.7, 130.1, 130.6, 135.9, 141.0, 144.9, 145.3, 148.5, 159.4; *m*/*z* (100, MH^+) 373; HRMS (ES): MH^+, found 373.1691. $C_{27}H_{21}N_{2+}$ requires 373.1688.

Compound **3a** white solid (0.15 g, 57%), mp 154–155 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.32; ν_{max} (neat) 1383, 1522, 1579, 3418 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.54 (s, 1H), 7.27 (t, *J* 7.8 Hz, 1H), 7.33–7.50 (m, 11H), 7.58 (s, 1H), 7.62 (d, *J* 7.5 Hz, 2H), 7.67 (d, *J* 6.0 Hz, 1H), 8.04 (d, *J* 6.0 Hz, 2H), 8.13 (d, *J* 9.3 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 100.3, 119.0, 119.3, 122.9, 124.6, 125.1, 127.5, 127.8, 128.5, 128.6, 128.9, 129.0, 129.1, 129.5, 130.3, 131.2, 135.2, 137.0, 138.2, 140.4, 147.9, 149.2, 158.3; *m*/*z* (100, MH^+) 373; HRMS (ES): MH^+, found 373.1721. $C_{27}H_{21}N_{2+}$ requires 373.1705.

*3.2.2. 2-(4-Fluorophenyl)-3-phenyl-4-(phenylamino)quinoline **2b** and 2-(4-fluorophenyl)-4-([(1,1′-biphenyl)-2-yl]amino)quinoline **3b**.* A mixture of **1b** (0.35 g, 0.79 mmol), phenylboronic acid (0.12 g, 0.95 mmol), $Pd(PPh_3)_4$ (0.05 g, 0.04 mmol) and K_2CO_3 (0.22 g, 1.59 mmol) in DMF (20 mL) was treated as described above. Workup and column chromatography on silica gel afforded **2b** and **3b** in sequence.

Compound **2b** white solid (0.07 g, 23%), mp 185–187 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.79; ν_{max} (neat) 844, 1224, 1401, 1485, 1571, 1599, 3368 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.90 (s, 1H), 6.77 (d, *J* 7.8 Hz, 2H), 6.89 (t, *J* 9.0 Hz, 2H), 6.97 (t, *J* 7.5 Hz, 1H), 7.10–7.14 (m, 2H), 7.20 (t, *J* 7.5 Hz, 2H), 7.27–7.36 (m, 6H), 7.67 (dt, *J* 1.2 and 7.8 Hz, 1H), (dd, *J* 0.6 and 8.4 Hz, 1H), 8.15 (dd, *J* 0.6 and 8.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 114.6 (d, $^2J_{CF}$ 21.3 Hz), 118.5, 121.6, 121.9, 125.2, 125.3, 125.4, 127.9, 129.0, 129.2, 129.6, 130.0, 130.6, 131.5 (d, $^3J_{CF}$ 8.3 Hz), 135.8, 137.1 (d, $^4J_{CF}$ 3.2 Hz), 145.0, 145.2, 148.4, 158.3, 162.3 (d, $^1J_{CF}$ 245.9 Hz); *m*/*z* (100, MH^+) 391; HRMS (ES): MH^+, found 391.1596. $C_{27}H_{20}FN_{2+}$ requires 391.1611.

Compound **3b** white solid (0.17 g, 54%), mp 161–163 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.52; ν_{max} (neat) 826, 1154, 1215, 1481, 1500, 1587, 3055, 3423 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.51 (s, 1H), 7.15 (d, *J* 9.0 Hz, 2H), 7.28 (t, *J* 9.3 Hz, 1H), 7.33–7.47 (m, 7H), 7.52 (s, 1H), 7.61 (t, *J* 9.3 Hz, 3H), 7.67 (d, *J* 7.53 Hz, 1H), 7.99–8.04 (m, 2H), 8.07 (d, *J* 7.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 99.9, 115.4 (d, $^2J_{CF}$ 21.4 Hz), 118.9, 119.3, 122.9, 124.7, 125.2, 127.9, 128.5, 128.9, 129.0, 129.3 (d, $^3J_{CF}$ 8.3 Hz), 129.7, 130.3, 131.3, 135.3, 136.5 (d, $^4J_{CF}$ 3.2 Hz), 137.0, 138.2, 148.0, 149.2, 157.2, 163.6 (d, $^1J_{CF}$ 246.7 Hz); *m*/*z* (100, MH^+) 391; HRMS (ES): MH^+, found 391.1595. $C_{27}H_{20}FN_{2+}$ requires 391.1611.

*3.2.3. 2-(4-Chlorophenyl)-3-phenyl-4-(phenylamino)quinoline **2c** and 2-(4-chlorophenyl)-4-([(1,1′-biphenyl)-2-yl]amino)quinoline **3c**.* A mixture of **1c** (0.30 g, 0.66 mmol), phenylboronic acid (0.10 g, 0.79 mmol), $Pd(PPh_3)_4$ (0.04 g, 0.03 mmol) and K_2CO_3 (0.18 g, 1.31 mmol) in DMF (5 mL) was treated as described above. Workup and column chromatography on silica gel afforded **2c** and **3c** in sequence.

Compound **2c** white solid (0.14 g, 52%), mp 169–171 °C; R_f (30% ethyl acetate/hexane) 0.82; ν_{max} (neat) 839, 1090, 1403, 1486, 1565, 3372 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.90 (s, 1H), 6.77 (d, *J* 8.1 Hz, 2H), 6.97 (t, *J* 7.5 Hz, 1H), 7.10–7.23 (m, 6H), 7.25–7.36 (m, 6H), 7.67 (dt, *J* 1.5 and 7.5 Hz, 1H), 7.75 (dd, *J* 1.2 and 8.7 Hz, 1H), 8.14 (d, *J* 8.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 118.6, 121.6, 122.0, 125.2, 125.3, 125.5, 127.9, 128.0, 129.1, 129.2, 129.4, 129.6, 130.0, 130.6, 131.1, 133.7, 135.6, 139.4, 145.1, 148.5, 158.0; *m*/*z* (100, MH^+) 407; HRMS (ES): MH^+, found, 407.1313. $C_{27}H_{20}N_2{}^{35}Cl^+$ requires 407.1315.

Compound **3c** white solid (0.04 g, 15%), mp 156–158 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.58; ν_{max} (neat) 822, 1090, 1425, 1480, 1589, 3059, 3422 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.51 (s, 1H), 7.28 (dt, *J* 1.5 and 8.5 Hz, 1H), 7.32–7.48 (m, 10H), 7.52 (s, 1H), 7.60 (t, *J* 7.5 Hz, 2H), 7.66 (dt, *J* 1.5 and 7.8 Hz, 1H), 7.98 (d, *J* 9.0 Hz, 2H), 8.08 (dd, *J* 0.9 and 8.5 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 99.8, 119.0, 119.3, 122.9, 124.8, 125.3, 127.9, 128.5, 128.7, 128.8, 128.9, 129.0, 129.7, 130.3, 131.3, 135.1, 135.3, 137.0, 138.2, 138.8, 148.1, 149.2, 156.9; *m*/*z* (100, MH^+) 407; HRMS (ES): MH^+, found 407.1296. $C_{27}H_{20}N_2{}^{35}Cl^+$ requires 407.1297.

*3.2.4. 2-(4-Methoxyphenyl)-3-phenyl-4-(phenylamino)quinoline **2d** and 2-(4-methoxyphenyl)-4-([(1,1′-biphenyl)-2-yl]amino)quinoline **3d**.* A mixture of **1d** (0.15 g, 0.33 mmol), phenylboronic acid (0.05 g, 0.40 mmol), $Pd(PPh_3)_4$ (0.02 g, 0.02 mmol) and K_2CO_3 (0.09 g, 0.66 mmol) in DMF (5 mL) was treated as described above. Workup

and column chromatography on silica gel afforded **2d** and **3d** in sequence.

Compound **2d** white solid (0.02 g, 15%), mp 160–162 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.63; ν_{max} (neat) 830, 1028, 1183, 1249, 1382, 1433, 1510, 1577, 3407 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.75 (s, 3H), 5.85 (s, 1H), 6.73 (d, *J* 9.0 Hz, 2H), 6.76 (d, *J* 9.3 Hz, 2H), 6.95 (t, *J* 7.8 Hz, 1H), 7.12–7.21 (m, 4H), 7.25–7.33 (m, 6H), 7.64 (t, *J* 7.8 Hz, 1H), 7.73 (d, *J* 7.5 Hz, 1H), 8.15 (d, *J* 9.0 Hz, 1H); δ_H (75 MHz, $CDCl_3$) 55.2, 113.1, 118.3, 121.6, 121.7, 125.2, 125.3, 125.6, 127.7, 128.9, 129.2, 129.4, 130.0, 130.6, 131.1, 133.5, 136.1, 144.8, 145.4, 148.5, 158.9, 159.1; *m*/*z* (100, MH^+) 403; HRMS (ES): MH^+, 403.1789. $C_{28}H_{22}N_2O^+$ requires 403.1810.

Compound **3d** white solid (0.07g, 52%), mp 185–187 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.23; ν_{max} (neat) 1026, 1177, 1249, 1365, 1440, 1604, 3052, 3420 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.86 (s, 3H), 6.46 (s, 1H), 6.99 (d, *J* 6.6 Hz, 2H), 7.23–7.45 (m, 8H), 7.55 (s, 1H), 7.60 (d, *J* 7.5 Hz, 2H), 7.65 (d, *J* 7.8 Hz, 2H), 8.00 (d, *J* 9.3 Hz, 2H), 8.07 (d, *J* 9.3 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 55.3, 99.9, 114.0, 118.9, 119.3, 122.7, 124.5, 124.8, 127.9, 128.5, 128.8, 128.9, 129.0, 129.5, 130.2, 131.2, 132.9, 135.1, 137.2, 138.2, 147.7, 149.3, 157.8, 160.5; *m*/*z* (100, MH^+) 403; HRMS (ES): MH^+, found 403.1801. $C_{28}H_{22}N_2O^+$ requires 403.1810.

*3.2.5. 2,3-Bis(4-Fluorophenyl)-4-(phenylamino)quinoline **2e** and 2-(4-fluorophenyl)-4-([4′-fluoro(1,1′-biphenyl)-2-yl]amino)quinoline **3e**.* A mixture of **1b** (0.20 g, 0.45 mmol), 4-fluorophenylboronic acid (0.08 g, 0.55 mmol), $Pd(PPh_3)_4$ (0.03 g, 0.02 mmol) and K_2CO_3 (0.13 g, 0.19 mmol) in DMF (5 mL) was treated as described above. Workup and column chromatography on silica gel afforded **2e** and **3e** in sequence.

Compound **2e** white solid (0.03 g, 16%), mp 152–153 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.82; ν_{max} (neat) 946, 1214, 1232, 1491, 1508, 1575, 1598, 3391 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.80 (s, 1H), 6.77 (d, *J* 7.8 Hz, 2H), 6.91 (t, *J* 8.7 Hz, 2H), 6.94–7.02 (m, 3H), 7.06–7.12 (m, 2H), 7.20 (t, *J* 7.8 Hz, 2H), 7.27–7.33 (m, 2H), 7.34 (dt, *J* 1.2 and 7.5 Hz, 1H), 7.67 (dt, *J* 1.5 and 7.4 Hz, 1H), 7.76 (dd, *J* 0.6 and 8.6 Hz, 1H), 8.14 (dd, *J* 0.6 and 8.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 114.8 (d, $^2J_{CF}$ 21.4 Hz), 116.2 (d, $^2J_{CF}$ 21.4 Hz), 118.3, 121.7, 122.0, 124.4, 125.2, 125.6, 129.3, 129.7, 130.0, 131.5 (d, $^3J_{CF}$ 8.0 Hz), 131.6 (d, $^4J_{CF}$ 3.7 Hz), 132.3 (d, $^3J_{CF}$ 8.0 Hz), 136.8 (d, $^4J_{CF}$ 3.2 Hz), 145.0, 145.2, 148.5, 158.3, 162.3 (d, $^1J_{CF}$ 247.0 Hz), 162.4 (d, $^1J_{CF}$ 246.2 Hz); *m*/*z* (100, MH^+) 409; HRMS (ES): MH^+, found 409.1500. $C_{27}H_{19}F_2N_{2+}$ requires 409.1516.

Compound **3e** white solid (0.10 g, 54%), mp 184–186 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.54; ν_{max} (neat) 826, 1154, 1215, 1481, 1500, 1587, 3055, 3423 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.40 (s, 1H), 7.06 (t, *J* 8.4 Hz, 2H), 7.14 (t, *J* 8.7 Hz, 2H), 7.29 (t, *J* 7.2 Hz, 1H), 7.36–7.44 (m, 5H), 7.45 (s, 1H), 7.60 (d, *J* 8.1 Hz, 2H), 7.67 (t, *J* 8.4 Hz, 1H), 8.01 (dd, *J* 5.4 and 8.6 Hz, 2H), 8.09 (d, *J* 8.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 99.8, 115.5 (d, $^2J_{CF}$ 21.4 Hz), 116.0 (d, $^2J_{CF}$ 21.4 Hz), 118.8, 119.2, 123.4, 125.0. 125.3, 128.7, 129.3 (d, $^3J_{CF}$ 8.6 Hz), 129.7, 130.4, 130.5 (d, $^3J_{CF}$ 8.3 Hz), 131.3, 134.1 (d, $^4J_{CF}$ 3.5 Hz), 134.6, 136.5 (d, $^4J_{CF}$ 3.4 Hz), 137.0, 148.0, 149.2, 157.1, 163.6 (d, $^1J_{CF}$ 247.1 Hz), 162.4 (d, $^1J_{CF}$ 246.2 Hz); *m*/*z* (100, MH^+) 409; HRMS (ES): MH^+, found 409.1501. $C_{27}H_{19}F_2N_{2+}$ requires 409.1516.

*3.2.6. 3-(4-Fluorophenyl)-2-(4-methoxyphenyl)-4-(phenylamino) quinoline **2f** and 4-([4′-fluoro(1,1′-biphenyl)-2-yl]amino)-2-(4-methoxyphenyl)quinoline **3f**.* A mixture of **1d** (0.10 g, 0.22 mmol), 4-fluorophenylboronic acid (0.04 g, 0.27 mmol), $Pd(PPh_3)_4$ (0.01 g, 0.01 mmol) and K_2CO_3 (0.06 g, 0.44 mmol) in DMF (5 mL) was treated as described above. Workup and column chromatography on silica gel afforded **2f** and **3f** in sequence.

Compound **2f** white solid (0.02 g, 22%), mp 160–162 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.50; ν_{max} (neat) 834, 1026, 1214, 1243, 1399, 1492, 1508, 1573, 3388 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.77 (s, 3H), 5.78 (s, 1H), 6.73–6.77 (m, 4H), 6.93–7.01 (m, 3H), 7.07–7.12 (m, 2H), 7.19 (t, *J* 7.8 Hz, 2H), 7.26 (d, *J* 8.7 Hz, 2H), 7.32 (dt, *J* 1.2 and 7.5 Hz, 1H), 7.65 (dt, *J* 1.5 and 7.4 Hz, 1H), 7.75 (dd, *J* 0.6 and 8.6 Hz, 1H), 8.14 (dd, *J* 0.6 and 8.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 55.2, 113.2, 116.1 (d, $^2J_{CF}$ 21.4 Hz), 118.1, 121.6, 121.7, 124.7, 125.2, 125.4, 129.2, 129.5, 130.0, 131.1, 132.0 (d, $^4J_{CF}$ 3.4 Hz), 132.3 (d, $^3J_{CF}$ 8.0 Hz), 133.3, 144.9, 145.2, 148.5, 159.0, 159.2, 162.2 (d, $^1J_{CF}$ 246.2 Hz); *m*/*z* (100, MH^+) 421; HRMS (ES): MH^+, found 421.1722. $C_{28}H_{22}N_2FO^+$ requires 421.1716.

Compound **3f** white solid (0.05 g, 54%), mp 185–187 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.20; ν_{max} (neat) 831, 1251, 1386, 1436, 1513, 1580, 3402 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (s, 3H), 6.39 (s, 1H), 6.99 (d, *J* 8.7 Hz, 2H), 7.05 (t, *J* 8.4 Hz, 2H), 7.27 (dt, *J* 1.2 and 7.4 Hz, 1H), 7.33–7.46 (m, 5H), 7.48 (s, 1H), 7.60 (d, *J* 8.4 Hz, 2H), 7.65 (dt, *J* 1.2 and 7.5 Hz, 1H), 7.99 (d, *J* 8.7 Hz, 2H), 8.08 (dd, *J* 0.6 and 8.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 55.3, 99.8, 114.0, 115.9 (d, $^2J_{CF}$ 21.3 Hz), 118.8, 119.2, 123.3, 124.8, 124.9, 128.7, 128.8, 129.5, 130.2, 130.6 (d, $^3J_{CF}$ 8.0 Hz), 131.2, 132.9, 134.2 (d, $^3J_{CF}$ 3.5 Hz), 134.4, 137.2, 147.8, 149.3, 157.7, 160.6, 162.4 (d, $^1J_{CF}$ 246.2 Hz); *m*/*z* (100, MH^+) 421; HRMS (ES): MH^+, 421.1698. $C_{28}H_{22}N_2FO^+$ requires 421.1716.

*3.2.7. 2-(4-Fluorophenyl)-4-(phenylamino)-3-(phenylethenyl)quinoline **2g** and 2-(4-fluorophenyl)-4-(2′-[(2-phenylethenyl)phenyl-2-yl] amino)quinoline **3g**.* A mixture of **1b** (0.30 g, 0.68 mmol), *trans*-2-vinylphenylboronic acid (0.12 g, 0.82 mmol), $Pd(PPh_3)_4$ (0.04 g, 0.03 mmol) and K_2CO_3 (0.19 g, 1.36 mmol) in DMF (5 mL) was treated as described above. Workup and column chromatography on silica gel afforded **2g** and **3g** in sequence.

Compound **2g** white solid (0.05 g, 18%), mp 166–169 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.74; ν_{max} (neat) 834, 1035, 1215, 1270, 1510, 1535, 1556, 3254 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.35 (s, 1H), 6.69 (d, *J* 16.8 Hz, 1H), 6.84 (d, *J* 8.1 Hz, 2H), 6.87 (d, *J* 8.4 Hz, 1H), 6.92 (d, *J* 16.8 Hz, 1H), 6.97 (t, *J* 7.5 Hz, 1H), 7.13 (t, *J* 8.4 Hz, 2H), 7.24–7.33 (m, 6H), 7.37 (t, *J* 7.7 Hz, 1H), 7.63–7.71 (d, *J* 7.5 Hz, 3H), 7.83 (d, *J* 8.4 Hz, 1H), 8.11 (d, *J* 8.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 115.1 (d, $^2J_{CF}$ 21.3 Hz), 117.7, 121.6, 121.8, 122.6, 123.7, 124.8, 125.8, 126.4, 128.3, 129.4, 129.6, 129.9, 131.7 (d, $^3J_{CF}$ 8.6 Hz), 135.3, 136.6, 137.1 (d, $^4J_{CF}$ 3.5 Hz), 134.4, 145.3, 147.9, 147.9, 158.5, 162.9 (d, $^1J_{CF}$ 246.4 Hz); *m*/*z* (100, MH^+) 417; HRMS (ES): MH^+, found 417.1747. $C_{29}H_{22}N_2F^+$ requires 417.1755.

Compound **3g** white solid (0.17 g, 56%), mp 117–121 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.54; ν_{max} (neat) 833, 962, 1045, 1156, 1222, 1270, 1510, 1532, 1556, 3244 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.60 (s, 1H), 7.03–7.13 (m, 3H), 7.17–7.32 (m, 5H), 7.30–7.44 (m, 5H), 7.51 (dt, *J* 1.2 and 7.5 Hz, 1H), 7.73 (dt, *J* 1.5 and 7.8 Hz, 1H), 7.80 (dd, *J* 1.8 and 7.1 Hz, 1H), 7.92 (d, *J* 7.8 Hz, 2H), 7.96 (d, *J* 8.1 Hz, 1H), 8.13 (d, *J* 8.1 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 100.1, 115.4 (d, $^2J_{CF}$ 21.3 Hz), 118.3, 119.4, 123.6, 125.2, 125.6, 126.3, 126.6, 127.1, 128.0, 128.7, 128.8, 129.3 (d, $^3J_{CF}$ 8.6 Hz), 129.7, 130.4, 131.6, 133.4, 136.5 (d, $^4J_{CF}$ 3.7 Hz), 136.9, 137.1, 148.7, 149.1, 157.2, 163.5 (d, $^1J_{CF}$ 247.1 Hz); *m*/*z* (100, MH^+) 417; HRMS (ES): MH^+, found 417.1755. $C_{29}H_{22}N_2F^+$ requires 417.1767.

*3.2.8. 2-(4-Methoxyphenyl)-4-(phenylamino)-3-(phenylethenyl) quinoline **2h** and 2-(4-methoxyphenyl)-4-(2-[(2-phenylethenyl)phenyl-2-yl]amino)quinoline **3h**.* A mixture of **1d** (0.15 g, 0.33 mmol), *trans*-2-vinylphenylboronic acid (0.06 g, 0.40 mmol), $Pd(PPh_3)_4$ (0.02 g, 0.02 mmol) and K_2CO_3 (0.09 g, 0.66 mmol) in DMF (5 mL) was treated as described above. Workup and column chromatography on silica gel afforded **2h** and **3h** in sequence.

Compound **2h** white solid (0.03 g, 21%), mp 159–161 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.54; ν_{max} (neat) 837, 1028, 1173, 1249, 1301, 1398, 1483, 1602, 3059, 3320 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.85 (s, 3H), 6.32 (s, 1H), 6.74 (d, *J* 16.8 Hz, 1H), 6.83 (d, *J* 8.4 Hz, 2H), 6.94–6.70 (m, 4H), 7.21–7.30 (m, 7H), 7.35 (dt, *J* 1.2 and 7.5 Hz, 1H), 7.65 (dt, *J* 1.5 and 8.7 Hz, 1H), 7.67 (d, *J* 7.5 Hz, 2H), 7.83

(d, *J* 8.4 Hz, 1H), 8.12 (d, *J* 8.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 55.4, 113.6, 117.5, 121.4, 122.0, 122.5, 124.3, 124.9, 125.5, 126.5, 128.1, 128.7, 129.4 (2× C), 129.9, 131.3, 133.5, 134.6, 136.8, 144.1, 145.6, 148.0, 159.2, 159.8; *m*/*z* (100, MH^+) 429; HRMS (ES): MH^+, found 429.1970. $C_{30}H_{25}N_2O^+$ requires 429.1967.

Compound **3h** white solid (0.07 g, 49%), mp 182–184 °C (ethanol); R_f (30% ethyl acetate/hexane) 0.24; ν_{max} (neat) 829, 965, 1247, 1392, 1477, 1513, 1584, 2834, 3029 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 3.82 (s, 3H), 6.53 (s, 1H), 6.93 (d, *J* 8.7 Hz, 2H), 7.08 (s, 1H), 7.14 (d, *J* 16.2 Hz, 1H), 7.20–7.45 (m, 9H), 7.48 (t, *J* 7.8 Hz, 1H), 7.71 (t, *J* 7.8 Hz, 1H), 7.88 (d, *J* 8.4 Hz, 1H), 7.91 (d, *J* 8.7 Hz, 2H), 7.94 (d, *J* 8.1 Hz, 1H), 8.13 (d, *J* 8.4 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 55.3, 100.1, 113.9, 118.3, 119.3, 123.6, 124.8, 125.3, 126.0, 126.6, 127.1, 128.0, 128.7, 128.8 (2× C), 129.5, 130.3, 131.6, 133.0, 133.2, 137.0, 137.4, 148.4, 149.2, 157.9, 160.5; *m*/*z* (100, MH^+) 429; HRMS (ES): MH^+, found 429.1968. $C_{30}H_{25}N_2O^+$ requires 429.1967.

3.3. $Pd(PPh_3)_4$ catalyzed cross-coupling reactions of 1 with $ArB(OH)_2$ in aqueous DMF. Typical procedure

2-Aryl-3-iodo-4-(phenylamino)quinoline **1** (1 equiv), arylboronic acid (1.2 equiv), $Pd(PPh_3)_4$ (5% of **1**), 2 M K_2CO_3 (2 equiv) and DMF (5 mL per mmol of **1**) were added to a two-necked flask equipped with a stirrer bar, rubber septum and a condenser. The mixture was flushed for 20 min with argon gas and a balloon filled with argon gas was connected to the top of the condenser. The mixture was heated with stirring at 80–90 °C under argon atmosphere for 18 h and then allowed to cool to room temperature. The cooled mixture was poured into ice-cold water and the product was taken-up into chloroform. The combined organic extracts were washed sequentially with brine, dried over anhydrous Mg_2SO_4, filtered and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate–hexane mixture to afford products **2a**–**f** (major) and **3a**–**f** (minor) in sequence (see Table 1).

3.4. Crystal structure solution and refinement

X-ray quality crystals of compounds **2d** and **3h** were obtained by slow crystallization from ethanol solutions. Intensity data were collected on a Bruker APEX II CCD area detector diffractometer with graphite monochromated Mo K_α radiation (50 kV, 30 mA) using the Bruker APEX 2[34] data collection software. The collection method involved ω-scans of width 0.5° and 512×512 bit data frames. Data reduction was carried out using the program Bruker SAINT+.[35] The crystal structure was solved by direct methods using Bruker SHELXTL.[36] Non-hydrogen atoms were first refined isotropically followed by anisotropic refinement by full matrix least-squares calculations based on F^2 using *SHELXTL*. Hydrogen atoms were first located in the difference map then positioned geometrically and allowed to ride on their respective parent atoms. Diagrams and publication material were generated using SHELXTL, PLATON[37] and ORTEP-3.[38]

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Supplementary data

Supplementary crystallographic data associated with this paper can be found in the online version at doi:10.1016/j.tet.2011.04.040.

References and notes

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