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Direct One-Pot Synthesis of Primary 4-Amino-2,3-diaryl-quinolines *via* Suzuki-Miyaura Cross-Coupling of 2-Aryl-4-azido-3-iodoquinolines with Arylboronic Acids

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Abstract: Palladium-catalyzed Suzuki-Miyaura cross-coupling of 2-aryl-4-azido-3-iodo-quinolines with arylboronic acids afforded the corresponding primary 4-amino-2,3-diarylquinolines in a single-pot operation along with symmetrical biaryls and traces of the 2,3-diaryl-4-azidoquinolines. A plausible mechanism, which implicates palladium hydride species in the reduction of the incipient 2,3-diaryl-4-azidoquinolines to afford the 4-amino-2,3-diarylquinolines is proposed.

Keywords: 2-aryl-4-azido-3-iodoquinolines; Suzuki-Miyaura cross-coupling; symmetrical biaryls; 4-azido-2,3-diarylquinolines; 4-amino-2,3-diarylquinolines

1. Introduction

Our continued interest in the synthesis of primary 4-aminoquinoline derivatives stems from their importance as antimalarial, anti-inflammatory, antibacterial, and antihypertensive agents [1-4] as well as immunostimulants and non-nucleoside HIV-1 inhibitors [5,6]. Aryl substituted quinoline derivatives are also known to serve as potent inhibitors of tyrosine kinase PDGF-RTK [7]. Moreover, the 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 [8]. Although there are several methods described in the literature for the synthesis of primary 4-amino-2-arylquinolines [6,9-13], corresponding data for the

synthesis of 2,3-disubstituted 4-aminoquinoline derivatives is considerably less well documented [13,14]. These polysubstituted quinoline derivatives are not accessible *via* classical methods such as the Skraup, Doebner-von Miller, Friedlander and Combes syntheses [15]. Consequently, an indirect approach to efficiently functionalize the presynthesized halogenated quinoline derivatives via nucleophilic displacement and/or metal-catalyzed cross-coupling reactions leading to Csp^2–N and/or Csp^2–Csp^2 bond formation remains the method of choice. The 4-(2-methylphenylamino)-3-iodo-quinolines, for example, were previously subjected to palladium-catalyzed Heck reaction with terminal alkenes to afford the corresponding 3-vinylquinolines with gastric H^+/K^+-ATPase inhibitory activity [16]. On the other hand, the analogous 2-aryl-3-iodo-4-(phenylamino)quinolines were found to undergo one-pot palladium mediated C–I and C–H bond activation and subsequent Suzuki-Miyaura cross-coupling with arylboronic acids to afford mixtures of the 2,3-diaryl-4-(phenylamino)quinolines and 2-aryl-4-([(1,1'-biaryl)-2-yl]amino)quinoline derivatives [17]. Hitherto this investigation, the Staudinger reaction of 2-aryl-4-azido-3-halogenoquinolines (X = Br, I) with triphenylphosphine in refluxing tetrahydrofuran afforded the corresponding 2-aryl-3-halogeno-4-(triphenylphosphoran-ylideneamino)quinolines [18]. The latter were either hydrolyzed to the corresponding 4-amino-2-aryl-3-halogenoquinolines or subjected to palladium-catalyzed Suzuki-Miyaura cross-coupling with phenylboronic acid followed by acetic acid-promoted hydrolysis of the incipient 2,3-diaryl-phosphazenes to afford the 4-amino-2,3-diarylquinolines [18].

A literature search revealed two papers describing the outcome of tetrakis(triphenylphosphine)-palladium(0) [Pd(PPh₃)₄]-catalyzed Suzuki-Miyaura cross-couplings of 4-azido-3-bromopyridine with heteroarylboronic acids [19] and 1-azido-2-bromobenzene with a series of aryl- and heteroarylboronic acids [20]. In one case, involving the coupling of 1-azido-2-bromobenzene with 2-thiopheneboronic acid, the authors isolated 2-(2-azidophenyl)thiophene (40%), bromoaniline (2%) and 2-thiophenylaniline (3%) as products [20]. They attributed the formation of bromoaniline and 2-thiophenylaniline to hydrolysis of the corresponding incipient iminophosphorane resulting from the reaction between triphenylphosphine ligand and the azide function [20]. Prompted by this literature observation and the ability of iodine to facilitate metal-catalyzed carbon-carbon bond formation of the 2-aryl-3-iodo-4-(triphenylphosphoranylideneamino)quinolines [18] we decided to investigate the reactivity of the known 2-aryl-4-azido-3-iodoquinolines in palladium-catalyzed Suzuki-Miyaura cross-couplings. The main aim of this investigation was to assess the possibility of effecting direct one-pot synthesis of the primary 4-amino-2,3-diarylquinolines via Suzuki-Miyaura cross-coupling of the 2-aryl-4-azido-3-iodoquinolines with arylboronic acids.

2. Results and Discussion

The Suzuki-Miyaura reaction of aryl or heteroaryl halides with arylboronic acids is a well established procedure and its mechanism generally involves: (i) oxidative addition of an aryl halide to a Pd(0) active catalyst; (ii) transmetallation of Ar–Pd–X with $Ar'B(OH)_3^-M^+$; and (iii) reductive elimination to give a biaryl product [21,22]. The efficiency of a palladium catalyst, on the other hand, depends strongly on the ligand of palladium atom and the overall reactivity also depends on the nature of the palladium(0) complex precursor [23,24]. With this consideration in mind, we reacted the 4-azido-2-aryl-3-iodoquinolines **1a,b** with phenylboronic acid (1.2 equiv.) in refluxing DMF in the

presence of Pd(PPh₃)₄ and 2 M K₂CO₃ as a base as a reference starting point for exploration based on literature precedents. After 48 h we isolated by column chromatography on silica gel three products in sequence, which were identified using a combination of spectroscopic techniques as the symmetrical biphenyl **2a** (3%, 5%) 2,3-diaryl-4-azidoquinolines **3a** (6%), **b** (7%) and 4-amino-2,3-diarylquinolines **4a** (15%), **b** (35%), respectively. Under similar reaction conditions using palladium acetate as pre-catalyst, phenylboronic acid (1.5–2 equiv.) and 2 M K₂CO₃ as a base and DMF as solvent, we also isolated by column chromatography on silica gel after 48 h the biphenyl **2a** (21%, 26%), 4-azido-2,3-diarylquinolines **3c** (14%), **d** (14%) and 4-amino-2,3-diarylquinolines **4c** (30%), **d** (50%) in sequence. Analytical data for products **4** was found to compare favourably with those of the corresponding derivatives prepared as described in our previous communication [18]. The ¹H-NMR and ¹³C-NMR spectra of the azido derivatives **3**, on the other hand, revealed the presence of an increased number of signals in the aromatic region, which distinguished these products from the corresponding precursors. The presence of strong IR absorption band in the υ_{max} 2,110–2,119 cm⁻¹ (asymmetric) and υ_{max} 1,220–1,260 cm⁻¹ (symmetric) regions further distinguished systems **3** from the amino derivatives **4**. The analogous 4-phenyl-5-azidoquinolines on the other hand, previously afforded in refluxing xylene pyrido[2,3,4-*kl*]acridines via an intramolecular nitrene insertion reaction [25]. The 3-aryl-4-azido-7-methoxyquinolin-2(1*H*)-ones prepared from the reaction of 3-aryl-4-(chloro/tosyloxy)-7-methoxy-quinolin-2(1*H*)-ones with sodium azide in refluxing DMF were also found to undergo thermolytic ring closure to afford the 5-alkyl-3-methoxy-11*H*-indolo[3,2-*c*]quinolin-6(5*H*)-ones [26]. In the current investigation, no products resulting from thermolytic ring closure of **3** were isolated from the reaction mixtures.

Despite the outcome of the above reaction, we were concerned about the low yields and prolonged reaction times, presumably due to the slow oxidative addition step using Pd(PPh₃)₄ as precursor of the palladium(0) complex. This slow oxidative addition step is attributed to the inhibiting role of the extra PPh₃ generated in the second equilibrium {SPd(0)(PPh₃)₃ $\rightleftharpoons$ SPd(0)(PPh₃)₂ + PPh₃ (K_2/[PPh₃] << 1); S = solvent} to afford the low reactivity ligated 14-electron species (Pd(0)(PPh₃)₂) [24]. Conversely, the oxidative addition performed by the palladium(0) complex (Pd(0)(PPh₃)₂Cl⁻) generated by the reduction of dichlorobis(triphenylphosphine)palladium(II) (PdCl₂(PPh₃)₂) is reported to be more than 30 times faster than that performed from Pd(0)(PPh₃)₄ [24]. Likewise, alkylphosphine ligands are known to coordinate with palladium and increase its electron density more than arylphosphines and, in turn, accelerate the oxidative addition and reductive elimination steps in the catalytic cycle [27,28]. Consequently, we subjected substrates **1a–d** to 2 equiv. of phenylboronic acid in the presence of PdCl₂(PPh₃)₂-tricyclohexylphosphine (PCy₃) catalyst mixture and 2 M potassium carbonate in DMF under reflux (Scheme 1). The reaction in the presence of PdCl₂(PPh₃)₂-PCy₃ catalyst mixture was complete within 18 h. Analysis of the crude product mixtures by thin layer chromatography revealed in all cases three spots of different polarity and intensity with no traces of the spot corresponding to the starting material. The mixture was isolated by column chromatography on silica gel to afford the biphenyl **2a**, 4-azido-2,3-diarylquinolines **3a–d** (minor) and 4-amino-2,3-diarylquinolines **4a–d** (major) in sequence. The reaction conditions were also extended to include 4-fluorophenylboronic and 4-methoxyphenylboronic acids as coupling partners. Although in all cases, traces of the 4-azido-2,3-diarylquinolines **3** (2nd spot) were detected by thin layer chromatography in the crude product mixture,

careful column chromatographic separation on silica gel in most cases led to isolation of the self-coupled biaryl derivatives **2b,c** (minor) and the 4-amino-2,3-diarylquinolines **4a–l** as the major products.

Scheme 1. PdCl$_2$(PPh$_3$)$_2$-PCy$_3$ catalyzed Suzuki-Miyaura cross-coupling of **1** with ArB(OH)$_2$.

1a–d   **2a–c**   **3a–d,l**   **4a–l**
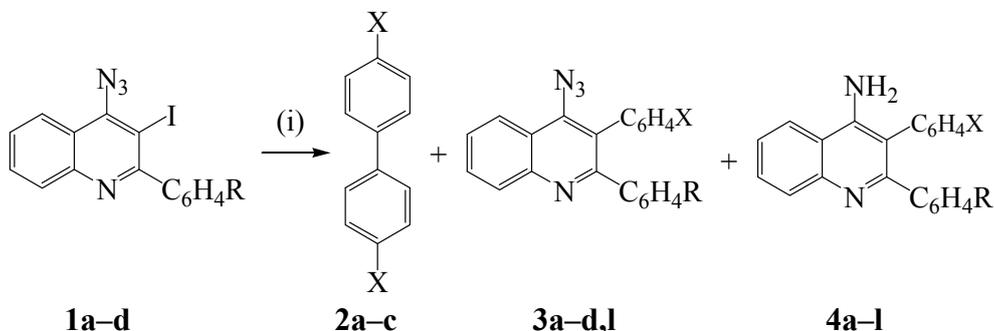
Reagents and conditions: (i) ArB(OH)$_2$ (2.0 equiv.), PdCl$_2$(PPh$_3$)$_2$, PCy$_3$, 2 M K$_2$CO$_3$, DMF, heat, 18 h.

3/4	4-R	4-X	% Yield 2	% Yield 3	% Yield 4
a	4-H	4-H	24 (**2a**)	12	57
b	4-F	4-H	10 (**2a**)	16	65
c	4-Cl	4-H	15 (**2a**)	10	54
d	4-OMe	4-H	26 (**2a**)	11	66
e	4-H	4-F	20 (**2b**)	-	65
f	4-F	4-F	12 (**2b**)	-	66
g	4-Cl	4-F	14 (**2b**)	-	56
h	4-OMe	4-F	21 (**2b**)	-	64
i	4-H	4-MeO	17 (**2c**)	-	63
j	4-F	4-MeO	18 (**2c**)	-	57
k	4-Cl	4-MeO	13 (**2c**)	-	60
l	4-OMe	4-MeO	28 (**2c**)	9	68

At first glance, we also thought products **4** are the result of the initial cross-coupling of **1** with arylboronic acids and subsequent *in situ* Staudinger reaction of the 2,3-diaryl-4-azidoquinolines **3** with PPh$_3$ released from the catalyst followed by hydrolysis of the incipient 2,3-diaryl-4-(triphenyl-phosphoranylideneamino)quinolones, in analogy with the previous literature observation [20]. However, this possibility was ruled out by the absence of triphenylphosphonium oxide in the reaction mixture or crude product (tlc monitoring or ^{31}P-NMR), which is the expected by-product of hydrolysis of phosphazene derivatives [18]. Recourse to literature, revealed a paper describing the results of palladium acetate (Pd(OAc)$_2$)-catalyzed Suzuki-Miyaura cross-coupling of nitroaryl halides with arylboronic acids in DMF/H$_2$O at 150 °C using K$_2$CO$_3$ as a base in the absence or presence of a ligand (PPh$_3$ or DABCO) [29]. The reaction afforded the corresponding biaryl derivatives with simultaneous reduction of nitro- to amino group and the authors attributed the reduction of the nitro group to molecular hydrogen based on literature precedent [30]. However, DMF-water mixture failed to reduce nitrobenzene to aniline at 150 °C [29]. Moreover, PdCl$_2$(PPh$_3$)$_2$-PCy$_3$ catalyzed cross-coupling of **1d** with PhB(OH)$_2$ using 2 M K$_2$CO$_3$ in dioxane also afforded **2a** (26%), **3d** (11%) and **4d** (62%) in sequence. We envisioned that molecular hydrogen generated from DMF-water medium in the presence of Pd(PPh$_3$)$_4$ or PdCl$_2$(PPh$_3$)$_2$ would also hydrogenolyze the azidoiodoquinolines **1** in analogy with

literature observation for the selective hydrogenolysis of azidoiodoarenes by H_2-Pd/C mixture to afford the azidoarenes [31].

The intriguing results observed in this investigation prompted us to propose a mechanism outlined in Scheme 2 to account for the one-pot palladium-catalyzed cross-coupling and subsequent reduction of the azido group to afford the primary 4-aminoquinolines **4**. The symmetrical biaryls **2** are the result of the self-coupling of aryl groups from arylboronic acid. Homo-coupling of arylboronic acids is a side reaction usually observed for the Suzuki-Miyaura cross-coupling reactions under both $Pd(PPh_3)_4$ and $Pd(OAc)_2$ catalysis especially when the cross-coupling is very slow [32,33]. The self-coupling step is known to be accompanied by the release of palladium hydride (PdH_2) along with metaboric acid (HOB=O) liberated in the form of borate under alkaline aqueous medium used in the Suzuki-Miyaura cross-coupling reactions [32]. The intermediate palladium hydride released during the catalytic cycle may either release hydrogen or serve as hydride source to reduce oxidants present in the reaction media and generate Pd(0) [32]. Although palladium hydride is implicated in the self-coupling mechanism [32], palladium hydrides L_2PdHCl [L = PCy_3 or $P(t\text{-}Bu)_3$], have been observed during the course of palladium-catalyzed Heck reaction [34].

Scheme 2. Proposed mechanism for the one-pot Suzuki-Miyaura cross-coupling and reduction of **1** incorporating self-coupling of $ArB(OH)_2$.
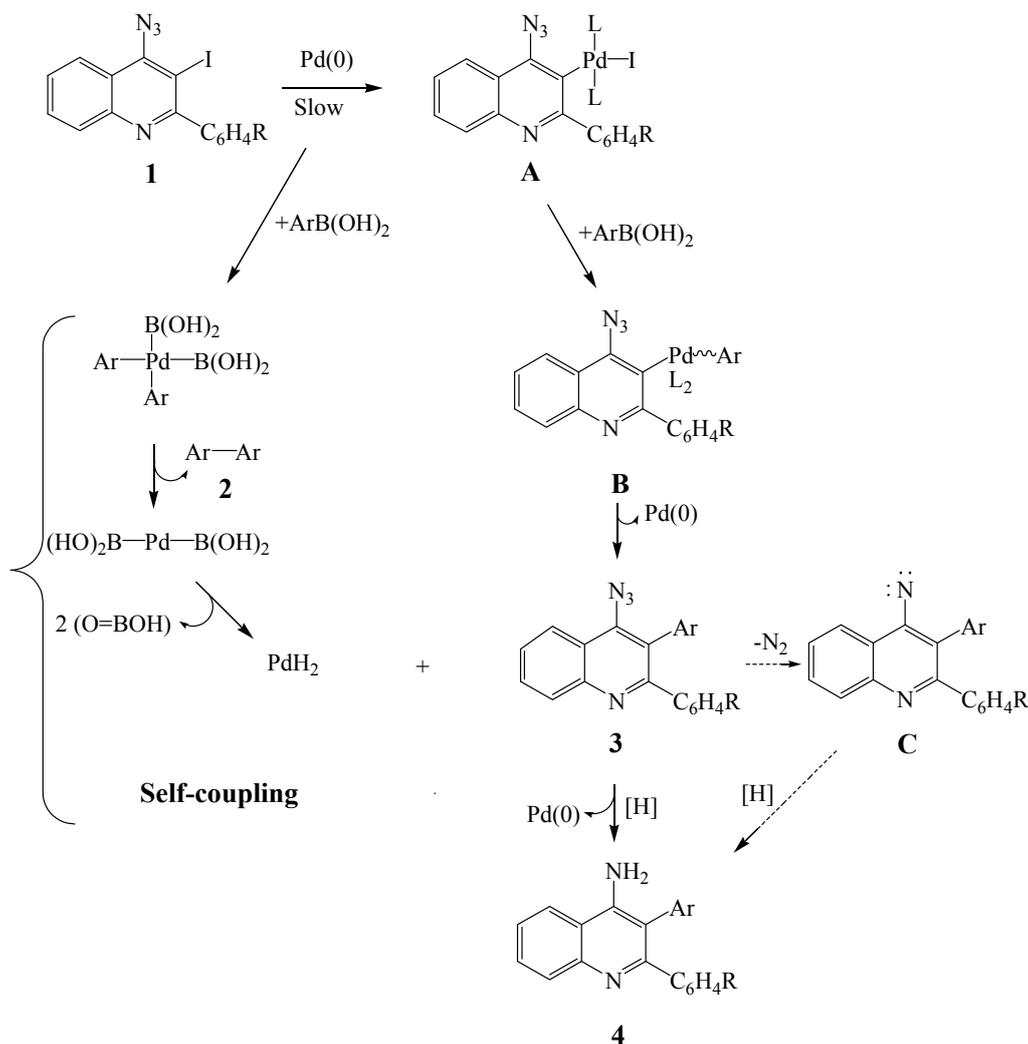
The envisioned self-coupling step is presumably accompanied by a slow oxidative addition of palladium(0) complex into **1** to form **A**, followed by transmetallation and reductive elimination from **B** to afford the corresponding 2,3-diaryl-4-azidoquinoline **3** (detected by tlc or isolated by column chromatography) as invoked in the classical Suzuki-Miyaura cross-coupling reaction mechanism. We envision that intermediate **3** is reduced by palladium hydride (PdH_2 or L_2PdHI) released from the self-coupling reaction to afford the 4-amino-2,3-diarylquinoline **4** in moderate yields. The possibility of formation of the latter via reduction of a nitrene intermediate **C** generated from **3** cannot be completely ruled out. Despite the fact that our proposed mechanism is necessarily speculative, it represents the best option consistent with the formation of the observed products in the presence or absence of PCy_3.

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 a 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 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 focusing high resolution) instrument. The synthesis and characterization of substrates **1** have been described elsewhere [18].

3.2. Typical Procedure for the PdCl₂(PPh₃)₂-PCy₃ Catalyzed Cross-Coupling Reactions of **1** with ArB(OH)₂

3.2.1. Biphenyl (**2a**), 4-Azido-2,3-diphenylquinoline (**3a**) and 4-Amino-2,3-diphenylquinoline (**4a**)

A mixture of **1a** (0.20 g, 0.54 mmol), phenylboronic acid (0.13 g, 1.08 mmol), 2M K_2CO_3 (1.2 mL), $PdCl_2(PPh_3)_2$ (0.02 g, 0.03 mmol) and PCy_3 (0.02 g, 0.05 mmol) in DMF (5 mL) in a two-necked flask equipped with a stirrer bar, rubber septum and a condenser was flushed for 30 min with argon gas. A balloon filled with argon gas was connected to the top of the condenser and 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 a ice-cold water and the product was taken-up into chloroform. The combined organic extracts were 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 (20% ethyl acetate-hexane) to afford **2a**, **3a** and **4a** in sequence.

Biphenyl (**2a**). Solid (19.5 mg, 24%), mp 69–71 °C (ethanol) (Lit. [35] 70–72 °C), R_F 0.94.

4-Azido-2,3-diphenylquinoline (**3a**). Solid (20 mg, 12%) mp 125–127 °C, R_F 0.63; v_{max} (neat) 764, 838, 1174, 1240, 1379, 2110 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.19–7.22 (m, 3H), 7.25–7.35 (m, 6H), 7.55–7.60 (m, 2H), 7.76 (dt, *J* 1.5 and 7.8 Hz, 1H), 8.15 (dd, *J* 0.6 and 8.7 Hz, 1H), 8.23 (d, *J* 8.7 Hz, 1H); δ_C (75 MHz, $CDCl_3$) 123.0, 126.5, 126.8, 127.7, 127.8, 128.3, 128.4, 129.0, 129.4, 129.6, 130.3, 131.5, 134.5,

140.1, 142.4, 147.8, 159.6; *m/z* 295 (100, MH$^+$-N$_2$), HRMS (ES): MH$^+$-N$_2$ found 295.1237. C$_{21}$H$_{15}$N$_2$$^+$ requires 295.1235.

4-Amino-2,3-diphenylquinoline (**4a**). Solid (90 mg, 57%), mp 238–240 °C (Lit. [18] 239–241 °C), R_F 0.15.

3.2.2. Biphenyl (**2a**), 4-Azido-2-(4-fluorophenyl)-3-phenylquinoline (**3b**) and
4-Amino-2-(4-fluoro-phenyl)-3-phenylquinoline (**4b**)

A mixture of **1b** (0.50 g, 1.28 mmol), phenylboronic acid (0.31 g, 2.56 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.04 g, 0.06 mmol), PCy$_3$ (0.04 g, 0.13 mmol), 2 M K$_2$CO$_3$ (2.6 mL) in DMF (10 mL) was treated as described above. Work-up and column chromatography on silica gel (20% ethyl acetate-hexane) afforded **2a** (19.6 mg, 10%), R_F 0.90; **3b** and **4b** in sequence.

4-Azido-2-(4-fluorophenyl)-3-phenylquinoline (**3b**). Solid (69.6 mg, 16%) mp 131–133 °C, R_F 0.63; ν_{max} (neat) 764, 838, 1159, 1221, 1364, 1480, 2110 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 6.90 (t, *J* 8.7 Hz, 2H), 7.24–7.30 (m, 4H), 7.35–7.38 (m, 3H), 7.59 (dt, *J* 1.2 and 7.5 Hz, 1H), 7.77 (dt, *J* 1.5 and 7.8 Hz, 1H), 8.13 (d, *J* 8.4 Hz, 1H), 8.23 (dd, *J* 1.2 and 8.4 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 114.7 (d, $^2J_{CF}$ 21.6 Hz), 121.5, 123.0, 126.3, 126.9, 128.5, 128.6, 129.4, 130.4, 131.4, 131.5 (d, $^3J_{CF}$ 8.3 Hz), 134.4, 136.2 (d, $^4J_{CF}$ 3.6 Hz), 142.6, 147.8, 158.5, 162.4 (d, $^1J_{CF}$ 246.2 Hz); *m/z* 313 (100, MH$^+$-N$_2$), HRMS (ES): MH$^+$-N$_2$ found 313.1146. C$_{21}$H$_{14}$FN$_2$$^+$ requires 313.1141.

4-Amino-2-(4-fluorophenyl)-3-phenylquinoline (**4b**). Solid (260 mg, 65%), mp 225–228 °C (Lit. [18] 215–217 °C), R_F 0.23.

3.2.3. Biphenyl (**2a**), 4-Azido-2-(4-chlorophenyl)-3-phenylquinoline (**3c**) and
4-Amino-2-(4-chloro-phenyl)-3-phenylquinoline (**4c**)

A mixture of **1c** (0.25 g, 0.62 mmol), phenylboronic acid (0.15 g, 1.23 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.02 g, 0.03 mmol), PCy$_3$ (0.20 g, 0.06 mmol), 2 M K$_2$CO$_3$ (1.2 mL) in DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (20% ethyl acetate-hexane) afforded **2a** (20.2 mg, 21%), R_F 0.90, **3c** and **4c** in sequence.

4-Azido-2-(4-chlorophenyl)-3-phenylquinoline (**3c**). Solid (19 mg, 10%), mp 140–141 °C (ethanol), R_F (20% ethyl acetate-hexane) 0.54; ν_{max} (neat) 838, 1159, 1221, 1364, 1504, 2110 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 7.16–7.20 (m, 2H), 7.22–7.28 (m, 4H), 7.33–7.38 (m, 3H), 7.58 (dt, *J* 1.2 and 8.1 Hz, 1H), 7.76 (dt, *J* 1.5 and 7.8 Hz, 1H), 8.12 (dd, *J* 1.5 and 8.4 Hz, 1H), 8.22 (dd, *J* 1.5 and 8.4 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 121.5, 123.0, 126.2, 127.0, 127.9, 128.5, 128.6, 129.4, 130.4, 131.0, 131.5, 134.0, 134.2, 138.6, 142.6, 147.8, 158.2; *m/z* 329 (100, MH$^+$-N$_2$), HRMS (ES): MH$^+$-N$_2$ found 329.0846. C$_{21}$H$_{14}$N$_2$^{35}Cl$^+$ requires 329.0845.

4-Amino-2-(4-chlorophenyl)-3-phenylquinoline (**4c**). Solid (130.7 mg, 64%), mp 228–231 °C (ethanol) (Lit. [18] 237–239 °C), R_F 0.09.

3.2.4. Biphenyl (**2a**), 4-Azido-2-(4-methoxyphenyl)-3-phenylquinoline (**3d**) and
4-Amino-2-(4-methoxyphenyl)-3-phenylquinoline (**4d**)

A mixture of **1d** (0.30 g, 0.76 mmol), phenylboronic acid (0.18 g, 1.49 mmol), $PdCl_2(PPh_3)_2$ (0.03 g, 0.04 mmol), PCy_3 (0.02 g, 0.07 mmol), 2 M K_2CO_3 (1.5 mL) in DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (20% ethyl acetate-hexane) afforded **2a** (0.02 g, 17%), R_F 0.87, **3d** and **4d** in sequence.

4-Azido-2-(4-methoxyphenyl)-3-phenylquinoline (**3d**). Solid (27.8 mg, 16%), mp 135–136 °C (ethanol), R_F 0.56; v_{max} (neat) 670, 743, 1030, 1247, 1504, 2110 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 3.76 (s, 3H), 6.73 (d, *J* 8.7 Hz, 2H), 7.19–7.22 (m, 2H), 7.27–7.35 (m, 5H), 7.64 (dt, *J* 1.5 and 8.1 Hz, 1H), 7.78 (dt, *J* 1.5 and 8.7 Hz, 1H), 8.19 (dd, *J* 0.9 and 8.1 Hz, 1H), 8.30 (dd, *J* 1.2 and 7.8 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 55.2, 113.2, 124.6, 125.3, 127.4, 127.6, 128.1, 129.7, 130.2, 130.7, 131.3, 132.7, 132.8, 137.4, 141.8, 147.7, 158.7, 159.4; *m/z* 353 (30, MH$^+$), 325.1346 (100, MH$^+$-N$_2$), HRMS (ES): MH$^+$ found 353.1414. $C_{22}H_{17}N_4O^+$ requires 353.1402.

4-Amino-2-(4-methoxyphenyl)-3-phenylquinoline (**4d**). Solid (160 mg, 66%), mp 166–169 °C (ethanol) (Lit. [18] 165–167 °C), R_F 0.10.

3.2.5. 4,4'-Difluoro-1,1'-biphenyl (**2b**) and 4-Amino-3-(4-fluorophenyl)-2-(phenyl)quinoline (**4e**)

A mixture of **1a** (0.20 g, 0.54 mmol), 4-fluorophenylboronic acid (0.15 g, 1.08 mmol), $PdCl_2(PPh_3)_2$ (0.02 g, 0.03 mmol), PCy_3 (0.02 g, 0.05 mmol), 2 M K_2CO_3 (1.2 mL) in DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (20% ethyl acetate-hexane) afforded **2b** and **4e** in sequence.

1-Fluoro-4-(4-fluorophenyl)benzene (**2b**). Solid (19.8 mg, 20%), mp 85–87 °C (ethanol) (Lit. [35] 87–88 °C), R_F 0.94.

*4-Amino-3-(4-fluorophenyl)-2-(phenyl)quinoli*ne (**4e**). Solid (110 mg, 65%), mp 243–245 °C (ethanol), R_F 0.15; v_{max} (neat) 692, 756, 1365, 1612, 3392 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 4.71 (br s, 2H), 7.03 (t, *J* 8.4 Hz, 2H), 7.14–7.21 (m, 5H), 7.27–7.31 (m, 2H), 7.49 (dt, *J* 1.5 and 8.7 Hz, 1H), 7.69 (dt, *J* 1.5 and 8.7 Hz, 1H), 7.78 (dd, *J* 0.6 and 8.7 Hz, 1H), 8.10 (dd, *J* 0.6 and 8.7 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 114.9, 116.1 (d, $^2J_{CF}$ 21.3 Hz), 117.4, 120.3, 125.2, 127.4, 127.9, 129.5, 129.6, 130.2, 132.2 (d, $^4J_{CF}$ 3.7 Hz), 132.8 (d, $^3J_{CF}$ 8.3 Hz), 141.1, 147.3, 147.6, 158.9, 162.0 (d, $^1J_{CF}$ 245.6 Hz); *m/z* 315 (100, MH$^+$), HRMS (ES): MH$^+$ found 315.1301. $C_{21}H_{16}FN_2$ requires 315.1293.

3.2.6. 1-Fluoro-4-(4-fluorophenyl)benzene (**2b**) and 4-Amino-2,3-bis(4-fluorophenyl)quinoline (**4f**)

A mixture of **1b** (0.50 g, 1.28 mmol), 4-fluorophenylboronic acid (0.36 g, 2.56 mmol), $PdCl_2(PPh_3)_2$ (0.04 g, 0.06 mmol), PCy_3 (0.04 g, 0.13 mmol), 2 M K_2CO_3 (2.6 mL) in DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (40% ethyl acetate-hexane) afforded **2b** (30 mg, 12%) R_F 0.90 and **4f** in sequence.

4-Amino-2,3-bis(4-fluorophenyl)quinoline (**4f**). Solid (280 mg, 66%), mp 247–249 °C (ethanol), R_F 0.23; ν_{max} (neat) 616, 797, 881, 1494, 1561, 1616, 3308, 3435 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 4.73 (br s, 2H), 6.88 (t, *J* 8.7 Hz, 2H), 7.05 (t, *J* 8.7 Hz, 2H), 7.16 (t, *J* 8.7 Hz, 2H), 7.27 (t, *J* 8.7 Hz, 2H), 7.49 (dt, *J* 1.2 and 8.4 Hz, 1H), 7.68 (dt, *J* 1.5 and 8.4 Hz, 1H), 7.78 (dd, *J* 1.2 and 8.4 Hz, 1H), 8.07 (d, *J* 8.1 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 114.6 (d, $^2J_{CF}$ 21.3 Hz), 114.7, 116.3 (d, $^2J_{CF}$ 21.4 Hz), 117.3, 120.3, 125.2, 129.7, 130.2, 131.4 (d, $^3J_{CF}$ 8.0 Hz), 132.2 (d, $^4J_{CF}$ 3.5 Hz), 132.8 (d, $^3J_{CF}$ 8.0 Hz), 137.2 (d, $^4J_{CF}$ 3.5 Hz), 147.4, 147.6, 157.8, 162.1 (d, $^1J_{CF}$ 246.2 Hz), 162.2 (d, $^1J_{CF}$ 245.6 Hz); *m/z* (100, MH$^+$), HRMS (ES): MH$^+$ found 333.1207. C$_{21}$H$_{15}$F$_2$N$_2^+$ requires 333.1203.

3.2.7. 1-Fluoro-4-(4-fluorophenyl)benzene (**2b**) and
4-Amino-2-(4-chlorophenyl)-3-(4-fluorophenyl)quinoline (**4g**)

A mixture of **1c** (0.25 g, 0.62 mmol), 4-fluorophenylboronic acid (0.17 g, 1.23 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.02 g, 0.03 mmol), PCy$_3$ (0.03 g, 0.06 mmol), 2 M K$_2$CO$_3$ (1.2 mL) in DMF (8 mL) was treated as described above. Work-up and column chromatography on silica gel (20% ethyl acetate-hexane) afforded **2b** (19.5 mg, 16%), R_F 0.88 and **4g** in sequence.

4-Amino-2-(4-chlorophenyl)-3-(4-fluorophenyl)quinoline (**4g**). Solid (141 mg, 65%), mp 246–248 °C (ethanol), R_F 0.10; ν_{max} (neat) 762, 833, 1224, 1431, 1490, 1616, 3191, 3310, 3428 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 4.73 (br s, 2H), 7.07 (t, *J* 8.7 Hz, 2H), 7.15–7.20 (m, 3H), 7.24–7.27 (m, 3H), 7.51 (dt, *J* 1.5 and 8.4 Hz, 1H), 7.71 (dt, *J* 1.5 and 8.1 Hz, 1H), 7.79 (dd, *J* 0.6 and 8.4 Hz, 1H), 8.08 (dd, *J* 0.6 and 8.7 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 114.7, 116.3 (d, $^2J_{CF}$ 21.3 Hz), 117.4, 120.3, 125.4, 127.9, 129.7, 130.2, 131.0, 132.1 (d, $^4J_{CF}$ 3.7 Hz), 132.8 (d, $^3J_{CF}$ 8.0 Hz), 133.6, 139.6, 147.4, 147.6, 157.6, 162.1 (d, $^1J_{CF}$ 246.5 Hz); *m/z* 349 (100, MH$^+$), HRMS (ES): MH$^+$ found 349.0912. C$_{21}$H$_{15}$FN$_2^{35}$Cl$^+$ requires 349.0908.

3.2.8. 1-Fluoro-4-(4-fluorophenyl)benzene (**2b**) and
4-Amino-3-(4-fluorophenyl)-2-(4-methoxyphenyl)quinoline (**4h**)

A mixture of **1d** (0.20 g, 0.50 mmol), 4-fluorophenylboronic acid (0.14 g, 0.99 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.02 g, 0.02 mmol), PCy$_3$ (0.02 g, 0.05 mmol), 2 M K$_2$CO$_3$ (1.0 mL) in DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (20% ethyl acetate-hexane) afforded **2b** (19.6 mg, 21%), R_F 0.93 and **4h** in sequence.

4-Amino-3-(4-fluorophenyl)-2-(4-methoxyphenyl)quinoline (**4h**). Solid (111 mg, 64%), mp 236–240 °C (ethanol), R_F 0.12; ν_{max} (neat) 609, 764, 834, 1211, 1245, 1591, 1608, 3412, 3477 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 3.75 (s, 3H), 4.73 (br s, 2H), 7.07 (t, *J* 8.7 Hz, 2H), 7.15–7.20 (m, 4H), 7.24–7.27 (m, 2H), 7.51 (t, *J* 8.4 Hz, 1H), 7.71 (t, *J* 8.4 Hz, 1H), 7.79 (dd, *J* 0.6 and 8.7 Hz, 1H), 8.08 (dd, *J* 0.6 and 8.7 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 55.2, 113.1, 114.8, 116.2 (d, $^2J_{CF}$ 21.3 Hz), 117.3, 120.3, 124.9, 129.5, 130.1, 131.0, 132.6 (d, $^4J_{CF}$ 3.2 Hz), 132.8 (d, $^3J_{CF}$ 8.0 Hz), 133.6, 147.2, 147.6, 158.4, 159.0, 162.0 (d, $^1J_{CF}$ 245.6 Hz); *m/z* 345 (100, MH$^+$), HRMS (ES): MH$^+$ found 345.1411. C$_{22}$H$_{18}$FN$_2$O$^+$ requires 345.1403.

3.2.9. 1-Methoxy-4-(4-methoxyphenyl)benzene (**2c**) and
4-Amino-3-(4-methoxyphenyl)-2-phenylquinoline (**4i**)

A mixture of **1a** (0.20 g, 0.54 mmol), 4-methoxyphenylboronic acid (0.16 g, 1.08 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.02 g, 0.03 mmol), PCy$_3$ (0.02 g, 0.05 mmol), 2 M K$_2$CO$_3$ (1.0 mL) in DMF (5 mL) was treated as described above. Work-up and column chromatography on silica gel (20% ethyl acetate-hexane) afforded **2c** and **4i** in sequence.

1-Methoxy-4-(4-methoxyphenyl)benzene (**2c**). Solid (30 mg, 16%), mp 179–181 °C (ethanol) (Lit. [35] 178–180 °C), R_F 0.63.

4-Amino-3-(4-methoxyphenyl)-2-phenylquinoline (**4i**). Solid (110 mg, 63%), mp 202–204 °C (ethanol), R_F 0.08; ν_{max} (neat) 704, 765, 1240, 1440, 1510, 1558, 1567, 1607, 3322, 3440 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 3.79 (s, 3H), 4.73 (br s, 2H), 6.87 (d, *J* 8.7 Hz, 2H), 7.11 (d, *J* 8.7 Hz, 2H), 7.16–7.20 (m, 3H), 7.17–7.35 (m, 2H), 7.48 (dt, *J* 0.9 and 7.8 Hz, 1H), 6.68 (t, *J* 0.9 and 8.4 Hz, 1H), 7.78 (dd, *J* 0.6 and 8.7 Hz, 1H), 8.10 (dd, *J* 0.6 and 8.4 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 55.2, 100.0, 114.4, 115.7, 117.5, 120.3, 125.0, 127.3, 127.6, 128.4, 129.3, 129.7, 130.1, 132.2, 141.4, 147.5, 158.7, 158.9; *m/z* 327. (100, MH$^+$), HRMS (ES): MH$^+$ found 327.1507. C$_{22}$H$_{19}$N$_2$O$^+$ requires 327.1497.

3.2.10. 1-Methoxy-4-(4-methoxyphenyl)benzene (**2c**) and
4-Amino-2-(4-fluorophenyl)-3-(4-methoxyphenyl)-quinoline (**4j**)

A mixture of **1b** (0.50 g, 1.28 mmol), 4-methoxyphenylboronic acid (0.39 g, 2.56 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.04 g, 0.06 mmol), PCy$_3$ (0.04 g, 0.13 mmol), 2 M K$_2$CO$_3$ (2.6 mL) and DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (40% ethyl acetate-hexane) afforded **2c** (50 mg, 18%), R_F 0.85 and **4j** in sequence.

4-Amino-2-(4-fluorophenyl)-3-(4-methoxyphenyl)quinoline (**4j**). Solid (250 mg, 57%), mp 190–192 °C (ethanol), R_F 0.10; ν_{max} (neat) 611, 763, 799, 1245, 1510, 1558, 1607, 3285, 3427 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 3.81 (s, 3H), 4.74 (br s, 2H), 6.87 (t, *J* 8.7 Hz, 2H), 6.88 (d, *J* 8.7 Hz, 2H), 7.09 (d, *J* 8.7 Hz, 2H), 7.31 (t, *J* 8.7 Hz, 2H), 7.47 (t, *J* 8.4 Hz, 1H), 7.67 (dt, *J* 1.2 and 8.4 Hz, 1H), 7.76 (d, *J* 8.4 Hz, 1H), 8.06 (dd, *J* 0.6 and 8.4 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 55.2, 114.5 (d, $^2J_{CF}$ 21.3 Hz), 114.6, 115.5, 117.4, 120.3, 125.0, 128.2, 129.4, 130.1, 131.5 (d, $^3J_{CF}$ 8.0 Hz), 132.1, 137.5 (d, $^4J_{CF}$ 3.5 Hz), 147.4, 147.6, 157.9, 158.8, 162.2 (d, $^1J_{CF}$ 245.3 Hz); *m/z* 345 (100, MH$^+$), HRMS (ES): MH$^+$ found 345.1403. C$_{22}$H$_{18}$FN$_2$O$^+$ requires 345.1411.

3.2.11. 1-Methoxy-4-(4-methoxyphenyl)benzene (**2c**) and
4-Amino-2-(4-chlorophenyl)-3-(4-methoxyphenyl)-quinoline (**4k**)

A mixture of **1b** (0.30 g, 0.74 mmol), 4-methoxyphenylboronic acid (0.22 g, 1.48 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.03 g, 0.04 mmol), PCy$_3$ (0.02 g, 0.07 mmol), 2 M K$_2$CO$_3$ (1.5 mL) in DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (40% ethyl acetate-hexane) afforded **2c** (29.7 mg, 19%), R_F 0.91 and **4k** in sequence.

4-Amino-2-(4-chlorophenyl)-3-(4-methoxyphenyl)quinoline (**4k**). Solid (160 mg, 60%), mp 223–225 °C (ethanol), R_F 0.26; ν_{max} (neat) 763, 826, 1246, 1511, 1559, 1609, 1633, 3291, 3432 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 3.82 (s, 3H), 4.74 (br s, 2H), 6.89 (d, *J* 8.4 Hz, 2H), 7.09 (d, *J* 8.4 Hz, 2H), 7.16 (d, *J* 8.4 Hz, 2H), 7.27 (d, *J* 8.4 Hz, 2H), 7.48 (t, *J* 7.5 Hz, 1H), 7.67 (t, *J* 7.5 Hz, 1H), 7.77 (d, *J* 8.4 Hz, 1H), 8.06 (d, *J* 8.4 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 55.2, 114.6, 115.5, 117.5, 120.3, 125.2, 127.8, 120.1, 129.4, 130.1, 131.1, 132.1, 133.4, 139.9, 147.5, 147.6, 157.7, 158.9; *m/z* (100, MH$^+$), HRMS (ES): MH$^+$ found 361.1111. C$_{22}$H$_{18}$N$_2$O^{35}Cl$^+$ requires 361.1103.

3.2.12. 1-Methoxy-4-(4-methoxyphenyl)benzene (**2c**), 4-Azido-2,3-bis(4-methoxyphenyl)quinoline (**3l**) and 4-Amino-2,3-bis(4-methoxyphenyl)quinoline (**4l**)

A mixture of **1d** (0.20 g, 0.50 mmol), 4-methoxyphenylboronic acid (0.15 g, 0.99 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.02 g, 0.02 mmol), PCy$_3$ (0.02 g, 0.05 mmol), 2 M K$_2$CO$_3$ (1 mL) in DMF (6 mL) was treated as described above. Work-up and column chromatography on silica gel (40% ethyl acetate-hexane) afforded **2c** (30 mg, 28%), R_F 0.88 and **4l** in sequence.

4-Azido-2,3-bis(4-methoxyphenyl)quinoline (**3l**). Solid (16.2 mg, 9%), mp 138–140 °C (ethanol), R_F 0.46; ν_{max} (neat) 715, 829, 1030, 1175, 1243, 1479, 1607, 2110 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 3.83 (s, 2x3H), 6.88 (d, *J* 8.7 Hz, 1H), 6.94 (d, *J* 8.7 Hz, 2H), 7.16 (d, *J* 8.7 Hz, 1H), 7.22 (d, *J* 8.7 Hz, 2H), 7.47 (d, *J* 8.7 Hz, 2H), 7.57 (dt, *J* 1.2 and 8.4 Hz, 1H), 7.75 (dt, *J* 1.2 and 8.4 Hz, 1H), 8.10 (dd, *J* 0.9 and 8.7 Hz, 1H), 8.21 (dd, *J* 0.9 and 8.7 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 55.2, 55.3, 113.9, 114.1, 123.0, 126.9, 127.7, 128.0, 129.4, 130.3, 131.0, 132.6, 133.4, 138.8, 143.1, 147.7, 158.5, 158.6, 159.7; *m/z* 355 (100, MH$^+$-N$_2$), HRMS (ES): MH$^+$-N$_2$ found 355.1449. C$_{23}$H$_{19}$N$_2$O$_2$$^+$ requires 355.1447.

4-Amino-2,3-bis(4-methoxyphenyl)quinoline (**4l**). Solid (120 mg, 68%), mp 202–204 °C (ethanol), R_F 0.25; ν_{max} (neat) 758, 1108, 1177, 1241, 1605, 3399, 3488 cm^{-1}; ^{1}H-NMR δ_H (300 MHz, CDCl$_3$) 3.75 (s, 3H), 3.81 (s, 3H), 4.70 (br s, 2H), 6.71 (d, *J* 8.7 Hz, 2H), 6.89 (d, *J* 8.7 Hz, 2H), 7.11 (d, *J* 8.7 Hz, 2H), 7.28 (d, *J* 9.0 Hz, 2H), 7.45 (dt, *J* 1.5 and 8.4 Hz, 1H), 7.65 (dt, *J* 1.5 and 8.4 Hz, 1H), 7.75 (d, *J* 8.7 Hz, 1H), 8.07 (dd, *J* 0.6 and 8.4 Hz, 1H); ^{13}C-NMR δ_C (75 MHz, CDCl$_3$) 55.1, 55.2, 113.0, 114.5, 115.6, 117.4, 120.3, 124.8, 128.7, 129.2, 130.0, 130.1, 132.2, 133.9, 147.4, 147.5, 158.5 (2xC), 158.7; MS (EI) *m/z* 357 (100, MH$^+$); HRMS (ES): MH$^+$ found 357.1611. C$_{23}$H$_{21}$N$_2$O$_2$$^+$ requires 357.1603.

3.3. Typical Procedure for the Pd(OAc)$_2$-Catalyzed Cross-Coupling Reactions of **1c,d** *with PhB(OH)$_2$*

3.3.1. Biphenyl (**2a**), 4-Azido-2-(4'-chlorophenyl)-3-phenylquinoline (**3c**) and 4-Amino-2-(4'-chloro-phenyl)quinoline (**4c**)

A mixture of **1c** (0.25 g, 0.62 mmol), phenylboronic acid (0.07 g, 1.23 mmol), Pd(OAc)$_2$ (0.01 g, 0.03 mmol) and 2 M K$_2$CO$_3$ (1.2 mL) in DMF (6 mL) in a two-necked flask equipped with a stirrer bar, rubber septum and a condenser was degassed with argon for 10 min. A balloon filled with argon was connected to the top of the condenser and the mixture was heated at 80–90 °C for 6 h. The mixture was cooled to room temperature and then poured into ice-cold water. The product was taken-up into chloroform and the organic solution was washed with brine, dried (anhydrous MgSO$_4$) and then

evaporated under reduced pressure. The residue was purified by column chromatography on silca gel (20% ethyl acetate-hexane) to afford three products **2a** (19 mg, 21%), R_F 0.94; **3c** (29.8 mg, 14%), R_F 0.50 and **4c** (60 mg, 30%), R_F 0.14 in sequence.

3.3.2. Biphenyl (**2a**), 4-Azido-2-(4'-methoxyphenyl)-3-phenylquinoline (**3d**) and
4-Amino-2-(4'-methoxyphenyl)quinoline (**4d**)

A mixture of **1d** (0.20 g, 0.50 mmol), phenylboronic acid (0.12 g, 0.10 mmol), Pd(OAc)$_2$ (0.01 g, 0.02 mmol) and 2 M K$_2$CO$_3$ (1.2 mL) in DMF (6 mL) was treated as described above. Workup and column chromatography on silica gel (20% ethyl acetate-hexane, v/v) yielded three products **2a** (20 mg, 26%), R_F 0.89; **3d** (30 mg, 14%), R_F 0.56 and **4d** (80 mg, 50%), R_F 0.11 in sequence.

4. Conclusions

In summary, the direct one-pot palladium-mediated coupling of 2-aryl-4-azido-3-iodoquinolines **1** with arylboronic acids and subsequent reduction of the azido group by the *in situ* generated palladium hydride represents a convenient synthetic strategy for the construction of primary 4-amino-2,3-diaryl-quinolines. The isolation of the symmetrical biaryl derivatives **2** and the observed *in situ* reduction of the azido to amino group using either Pd(OAc)$_2$, PdCl$_2$(PPh$_3$)$_2$ or Pd(PPh$_3$)$_4$ as the Pd(0) catalyst sources provide further support for the involvement of palladium hydride in the reductive elimination step of the catalytic cycle leading to self-coupling of arylboronic acids [32]. At least in our opinion, the results observed in this investigation rule out the possibility of an *in situ* reduction of the azido group via Staudinger reaction with PPh$_3$ generated from the catalyst [20] or possible hydrogenation using DMF/water mixture as previously proposed in the literature [29,30]. The versatility of this methodology can be extended to develop a streamlined approach to 2,3-disubstituted primary 4-amino-quinoline libraries and their annulated quinoline derivatives. Moreover, the biaryl scaffold represents a privileged structure for pharmaceutically important compounds [36-38].

Conflict of Interest

The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **1–4** are available from the authors.