2-Aryl-4-chloro-3-iodoquinolines as substrates for the synthesis of 2,3-diaryl-4-methoxyquinolines

Malose J. Mphahlele* and Vathiswa Mtshemla

Department of Chemistry, College of Science, Engineering and Technology, University of South Africa, PO Box 392, Pretoria 0003, South Africa

Sequential functionalisation of 2-aryl-4-chloro-3-iodoquinolines *via* palladium–catalysed cross-coupling with phenylboronic acid followed by displacement of the 4-chloro atom from the resulting 2,3-diaryl-4-chloroquinolines with methoxide ion yielded 2,3-diaryl-4-methoxyquinolines. The latter were also prepared *via* Suzuki–Miyaura cross-coupling of 2-aryl-3-iodo-4-methoxyquinolines with phenylboronic acid. Demethylation of the methoxy compounds (BBr_3) gave the 2,3-diaryl-4(1*H*)-quinolinones.

Keywords: 3-iodoquinolines, Suzuki–Miyaura cross coupling, arylation, quinolin-4-ones

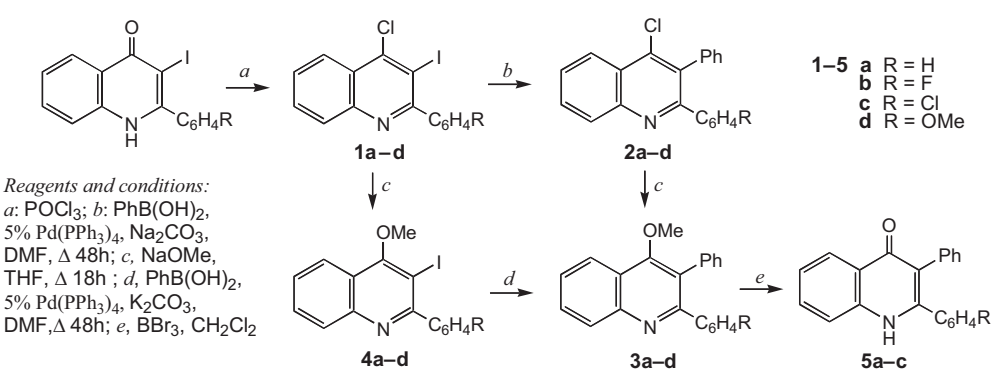
Quinoline moiety is widely distributed in biologically active compounds such as antimalarial, anti-inflammatory, antibacterial, and antihypertensive agents.[1-4] Aryl substituted quinolines have been reported to serve as potent inhibitors of tyrosine kinase PDGF-RTK.[5] The naturally occurring 4-methoxy-2-phenylquinoline and its 2-(methylenedioxyphenyl) analogue have recently been found to show inhibitory activity against *Mycobacterium tuberculosis* $H_{37}Rv$.[6] In the course of our ongoing quinolin-4(1*H*)-one studies, we prepared a series of 2-aryl-3-bromo-4-chloroquinolines and their 1-methyl-4-oxo derivatives for further studies of chemical transformation and biological activity.[7] In pursuance of our research on the development of derivatives with potential antimalarial or antibacterial activity, we became interested in the synthesis of 2,3-diarylquinolines bearing a methoxy group at the 4-position. These systems are not easily accessible through the well-known methods for the synthesis of polysubstituted quinolines such as the Skraup, Döbner–Miller, Friedländer and Combes reactions.[8]

A literature search revealed only one paper describing the synthesis of 3-aryl-2-(ethyl/phenyl)-4-phenoxyquinolines as quinoline-based estrogen receptor modulators, which involves initial C-2 coupling of 3-aryl-2,4-dichloroquinolines with alkyl- or aryl-zinc reagents (R_2Zn; R = Et, Ph) followed by displacement of the 4-chlorine atom with bromophenol derivative.[9] In this investigation, we opted for the use of indirect methods that involve 2-aryl-4-chloro-3-iodoquinolines as key intermediates for generating 4-substituted 2,3-diarylquinolines *via* palladium–catalysed cross coupling with phenylboronic acid. Our approach takes advantage of the known ease of displacement of a 4-chlorine atom by nucleophiles and the potential for iodine to facilitate metal-catalysed carbon–carbon bond formation. We herein describe the outcome of palladium–catalysed cross-coupling of 2-aryl-4-chloro-3-iodoquinolines with phenylboronic acid and further chemical transformations of the resulting products.

Results and discussion

The Suzuki reaction is one of the versatile procedures for the synthesis of unsymmetrical biaryl derivatives and is known to proceed best with aryl or heteroaryl iodides or bromides, and either poorly or not at all with the corresponding chlorides.[10-12] Activated heteroaryl chlorides such as 4-chloropyridine derivatives with arylboronic acids are, however, also known to undergo $Pd(PPh_3)_4$–catalysed coupling with ease.[13,14] This literature observation made it difficult for us easily to predict how different the reactivity of the two C*sp*^{2}–halogen bonds in 2-aryl-4-chloro-3-iodoquinolines would be during Suzuki–Miyaura cross-coupling. We nevertheless took advantage of the known order of reactivity in transition metal–mediated cross-coupling of aryl halides (I > Br >> Cl)[15,16] which can allow selective coupling with bromides or iodides in the presence of chlorides. With this consideration in mind we converted the known 2-aryl-3-iodoquinolin-4(1*H*)-ones[7] into the corresponding previously undescribed 2-aryl-4-chloro-3-iodoquinolines **1** using phosphoryl chloride under reflux.

Substrates **1** were then subjected to $Pd(PPh_3)_4$-catalysed coupling reaction with phenylboronic acid in DMF in the presence of 2M sodium carbonate and the corresponding 2,3-diaryl-4-chloroquinolines **2** were isolated in only moderate yields, conversion being incomplete even after 48 hours (Scheme 1). Change of base to K_2CO_3 or solvent to DME led to reduced yields due to poor conversion of the substrate. Characteristic features in the ^{1}H NMR and ^{13}C NMR spectra that distinguished products **2** from the corresponding



Scheme 1 Preparation of 2,3-diarylquinolines and quinolinones.

* Correspondent. E-mail: mphahmj@unisa.ac.za

substrates are the increased number of signals in the aromatic region. We took advantage of the known ease of displacement of a halogen atom at the γ-position of the quinoline nucleus by nucleophiles, and subjected compounds **2** to sodium methoxide in methanol–THF mixture under reflux. However, we isolated the starting material unchanged, presumably because of poor solubility of the substrate in this solvent mixture. The 2,3-diaryl-4-methoxyquinolines **3** were prepared in reasonable yields when systems **2** were subjected to sodium methoxide in refluxing methanol–DMF mixture (Scheme 1). These products were easily distinguished from the corresponding precursors by the presence of an intense methoxy peak at δ *ca* 3.54 ppm in the ^{1}H NMR spectra of products **3**, which also served as retrospective confirmation of the regioselective displacement of iodine from **1** by phenylboronic acid.

The observed moderate overall yields of **3** from **1** due to incomplete conversion of substrates prompted us to explore an alternative route incorporating the 4-methoxy group into the 2-aryl-3-iodoquinoline moiety prior to coupling with phenylboronic acid. Consequently, we subjected substrates **1** to sodium methoxide in methanol–THF mixture under reflux, to afford the corresponding, hitherto unknown, 2-aryl-3-iodo-4-methoxyquinolines **4** (Scheme 2). We initially examined the use of $Pd(PPh_3)_4$ as catalysts and 2M Na_2CO_3 as base in DMF and observed 60% conversion into the required 2,3-diaryl-4-methoxyquinolines. The rate of Suzuki coupling and the yields are known to be increased by stronger bases and larger cation size, which are better solvated, resulting in a more basic anion.[17] We therefore resorted to the use of $Pd(PPh_3)_4$ and 2M K_2CO_3 in DMF and isolated by column chromatography the 2,3-diaryl-4-methoxyquinolines **3** in reasonable yields.

Prompted by the scant attention paid in the literature to the synthesis of 2,3-diaryquinolin-4(1*H*)-ones, in the last part of this investigation we subjected systems **3** to demethylation using boron tribromide in dichloromethane at room temperature. Compounds **3a-c** afforded the corresponding 2,3-diarylquinolin-4(1*H*)-ones **5a–c** in reasonable yields without any need for column chromatographic separation. On the other hand, **3d** afforded a complex mixture of products lacking the methoxy signals in the ^{1}H NMR spectrum. Several attempts to synthesise systems **5** *via* palladium–catalysed Suzuki cross-coupling of the corresponding 2-aryl-3-iodoquinolin-4(1*H*)-ones with phenylboronic acid always led to complex mixtures of products that were difficult to separate by conventional column chromatography. Thus, demethylation of systems **3** represents a convenient synthetic strategy for the construction of 2,3-diarylquinolin-4(1*H*)-ones of potential biological interest that can be obtainable only with difficulty otherwise.

Overall, the results described in this investigation present another example showing the potential of 2-aryl-4-chloroquinolines in the synthesis of 2,3,4-trisubstituted quinolines which are themselves suitable candidates for further studies of chemical transformation and biological activity. Moreover, polysubstituted quinoline derivatives are known to undergo self-assembly into a variety of nano and meso structures with enhanced electronic and photonic properties.[18]

Experimental

Melting points were recorded on a Thermocouple digital melting point apparatus. IR spectra were recorded as powders using 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 $CDCl_3$ or DMSO-d_6 solutions using a Varian Mercury 300 MHz NMR spectrometer and the chemical shifts are measured relative to the solvent peaks. Low and high-resolution mass spectra were recorded at an ionisation potential of 70eV using a Micromass Autospec-TOF (double focusing high resolution) instrument. Elemental analysis was performed at the Department of Chemistry of the University of Cape Town.

Typical procedure for the synthesis of the 4-chloro-3-iodoquinolines **1**

4-Chloro-3-iodo-2-phenylquinoline (**1a**): 3-Iodo-2-phenylquinolin-4-(1*H*)-one[7] (2.00 g, 5.8 mmol) and phosphoryl chloride (20 ml) were heated under reflux for 3 hours. The cooled solution was transferred to a conical flask and quenched slowly with ice-cold water. After 30 minutes the mixture was neutralised with 25% aqueous ammonia and stirred vigorously at room temperature. The resulting precipitate was filtered and recrystallised (EtOAc) to afford **1a** as a white solid (1.16 g, 55%), m.p. 150–153 °C. IR: ν_{max} 1555, 1339, 1088 1026, 845, 762 cm^{-1}. NMR (DMSO-d_6): δ_H 7.47–7.58 (5H, m), 7.77 (1H, dt, J = 1.5 and 7.8 Hz), 7.91 (1H, dt, J = 1.2 and 7.8 Hz), 8.07 (1H, d, J = 8.4 Hz), 8.26 (1H, dd, J = 0.9 and 8.4 Hz); δ_C 99.2, 124.7, 125.0, 127.8, 128.7, 129.0, 129.1, 129.4, 131.3, 143.2, 146.5, 146.6, 162.5. MS (EI): *m/z* 367 (28) 365 (M$^+$, 83), 238 (100), 220 (69), 203 (58); HRMS (EI): calcd for $C_{15}H_9{}^{35}ClIN$: 364.9466, found: 364.9468. Anal. calcd for $C_{15}H_9ClIN$: C, 49.28; H, 2.49; N, 3.84; found: C, 49.08; H, 2.48; N, 3.47%.

4-Chloro-2-(4'-fluorophenyl)-3-iodoquinoline (**1b**): 2-(4'-Fluorophenyl)-3-iodoquinolin-4(1*H*)-one (1.98 g, 5.4 mmol) in phosphoryl chloride (20 ml) was treated as described for **1a** to afford **1b** as a white solid (1.28 g, 62%) m.p. 176–178 °C (EtOAc). IR: ν_{max} 1597, 1508, 1343, 1219, 828, 758 cm^{-1}. NMR (DMSO-d_6): δ_H 7.35 (d, 2H, J = 9.0 Hz), 7.64 (2H, dd, J = 5.7 and 9.0 Hz), 7.78 (1H, dt, J = 1.2 and 7.8 Hz), 7.92 (1H, dt, J = 1.5 and 7.8 Hz), 8.08 (1H, d, J = 9.0 Hz), 8.27 (1H, dd, J = 0.6 and 8.7 Hz); δ_C 99.3, 114.7 (d, $^2J_{CF}$ = 21.6 Hz); δ_C 1293, 124.7, 125.0, 129.1, 131.3, 131.4 (d, $^3J_{CF}$ = 8.3 Hz), 139.6 (d, $^4J_{CF}$ = 3.6 Hz), 146.6, 146.7, 161.5, 162.2 (d, $^1J_{CF}$ = 244.8 Hz). MS (EI): *m/z* 385 (32), 383 (M$^+$, 94), 256 (100), 221 (73); HRMS (EI): calcd for $C_{15}H_8{}^{35}ClFIN$: 382.9374, found 382.9368. Anal. calcd for $C_{15}H_8ClFIN$: C, 46.97; H, 2.11; N, 3.67; found: C, 47.15; H, 2.05; N, 3.65%.

4-Chloro-2-(4'-chlorophenyl)-3-iodoquinoline (**1c**): 2-(4'-Chlorophenyl)-3-iodoquinolin-4(1*H*)-one (2.0 g, 5.2 mmol) in phosphoryl chloride (25 ml) was treated as described for **1a** to afford **1c** as a white solid (1.35 g, 65%) m.p. 218–220 °C (EtOAc). IR: ν_{max} 1605 1473 1342, 1247, 1092, 822, 756 cm^{-1}. NMR (DMSO-d_6): δ_H 7.59 (2H, d, J = 8.4 Hz), 7.70 (2H, d, J = 8.4 Hz), 7.83 (1H, dt, J = 1.5 and 7.5 Hz), 7.94 (1H, dt, J = 1.2 and 7.5 Hz), 8.11 (1H, d, J = 8.4 Hz), 8.26 (1H, dd, J = 0.9 and 8.4 Hz); δ_C 99.2, 124.7, 125.0, 127.9, 129.2, 129.4, 131.1, 131.4, 133.5, 142.0, 146.5, 146.8, 161.3. MS (EI): *m/z* 403 (8), 401(42), 399 (M$^+$, 62), 273 (100), 238 (70), 220 (54). HRMS (EI): calcd for $C_{15}H_8{}^{35}Cl_2IN$: 398.9079. Found: 398.9078. Anal. calcd for $C_{15}H_8Cl_2IN$: C, 45.04; H, 2.02; N, 3.51; found: C, 44.83; H, 2.02; N, 3.44%.

4-Chloro-3-iodo-2-(4'-methoxyphenyl)quinoline (**1d**): 2-(4'-Methoxyphenyl)-3-iodoquinolin-4(1*H*)-one (2.0 g, 5.3 mmol) in phosphoryl chloride (20 ml) was treated as described for **1a** to afford **1d** as a white solid (1.18 g, 56%), m.p. 185–187 °C (EtOAc). IR: ν_{max} 1606, 1511, 1246, 1177, 1030, 824, 760 cm^{-1}. NMR (DMSO-d_6): δ_H 3.84 (3H, s), 7.05 (2H, d, J = 9.0 Hz), 7.54 (2H, d, J = 9.0 Hz), 7.75 (1H, tt, J = 1.5 and 8.0 Hz), 7.89 (1H, tt, J = 1.5 and 7.5 Hz), 8.05 (1H, d, J = 7.8 Hz), 8.24 (1H, d, J = 8.3 Hz); δ_C 55.4, 98.2, 113.3, 125.1, 125.7, 128.2, 129.7, 130.6, 130.9, 136.0, 147.3, 147.7, 160.1, 162.2. MS (EI): *m/z* 395 (M$^+$, 6), 269 (100), 254 (69), 191 (24), 162 (27), 127 (32). HRMS (EI): calcd for $C_{16}H_{11}{}^{35}ClINO$: 394.9568, found: 394.9574. Anal. calcd for $C_{16}H_{11}ClINO$: C, 48.42; H, 2.81; N, 3.55; found: C, 48.41; H, 2.69; N, 3.40%.

$Pd(PPh_3)_4$ catalysed cross-coupling reactions of **1** *with $PhB(OH)_2$: typical procedure*

4-Chloro-2,3-diphenylquinoline (**2a**): A mixture of **1a** (0.65 g, 1.78 mmol), phenylboronic acid (0.26 g, 2.14 mmol) and $Pd(PPh_3)_4$ (0.10 g, 0.09 mmol) was taken in DMF (10 ml) in a two-necked flask equipped with a stirrer bar, rubber septum and condenser. After degassing with argon for 10 minutes aqueous Na_2CO_3 (2M, 3.6 ml) was introduced through a syringe and degassed further with argon for 10 minutes. The mixture was refluxed at 80–90 °C under argon atmosphere for 48 hours and then allowed to cool to room temperature. The cooled mixture was quenched with ice-cold water and the product was extracted into chloroform. The combined organic phases were washed with brine, dried over anhydrous Mg_2SO_4 and then evaporated under reduced pressure. The residue was purified by column chromatography (10 : 1 hexane–EtOAc, v/v) to afford **2a** as a solid (0.34 g, 60%) m.p. 116–118 °C (EtOH) (Lit.[19] 121 °C). IR: ν_{max} 1549; 1474, 1333, 1028, 848, 757, 751, 700 cm^{-1}. NMR (DMSO-d_6): δ_H 7.17–7.24 (5H, m), 7.29–7.34 (5H, m), 7.67 (1H, dt, J = 1.2 and 7.8 Hz), 7.80 (1H, dt, J = 1.2 and 7.8 Hz), 8.21 (1H, dd, J = 0.6 and 8.4 Hz), 8.33 (1H, dd, J = 0.9 and 8.4 Hz); δ_C 124.7, 125.5, 127.6, 127.7, 128.0, 127.9, 128.0, 129.7, 129.9, 130.3, 130.7, 133.0, 137.1, 140.3, 141.9, 147.6, 159.2.

MS (EI): *m/z* 315 (M^+, 11), 313 (100). Anal. calcd for $C_{21}H_{14}ClN$: C, 79.87; H, 4.47; N, 4.44; found: C, 79.65; H, 4.46; N, 4.45%.

4-Chloro-2-(4'-fluorophenyl)-3-phenylquinoline (**2b**): Compound **1b** (0.65 g, 1.69 mmol), phenylboronic acid (0.25 g, 2.03 mmol), $Pd(PPh_3)_4$ (0.10 g, 0.08 mmol) and Na_2CO_3 (2M, 3.4 ml) in DMF (10 ml) were treated as described above. Workup and column chromatography (10 : 1 hexane–EtOAc, v/v) afforded **2b** as a solid (0.31 g, 55%) m.p. 120–122 °C (EtOH). IR: ν_{max} 1597, 1555, 1537, 1506, 1470, 1342, 1219, 1157, 1085, 983, 876, 826, 756, 727 cm^{-1}. NMR (DMSO-d_6): δ_H 6.90 (2H, d, J = 8.7 Hz), 7.19 (2H, m), 7.28–7.35 (5H, m), 7.68 (1H, dt, J = 1.2 and 7.8 Hz), 7.80 (1H, dt, J = 1.2 and 7.8 Hz), 8.19 (1H, d, J = 8.4 Hz), 8.32 (1H, d, J = 7.8 Hz); δ_C 114.8 (d, $^2J_{CF}$ = 21.4 Hz), 124.7, 125.5, 127.7, 127.8, 128.2, 129.9, 130.4, 130.7, 131.7 (d, $^3J_{CF}$ = 8.3 Hz), 132.8, 136.3 (d, $^4J_{CF}$ = 2.9 Hz), 136.9, 142.1, 147.6, 158.0, 162.5 (d, $^1J_{CF}$ = 246.8 Hz). MS (EI) *m/z* 333 (M^+, 2), 314 (100); HRMS (EI) calcd for $C_{21}H_{13}{}^{35}ClFN$: 333.0721, found: 333.0694. Anal. calcd for $C_{21}H_{13}ClFN$: C, 75.57; H, 3.92; N, 4.00; found: C, 75.55; H, 3.77; N, 3.95%.

4-Chloro-2-(4'-chlorophenyl)-3-phenylquinoline (**2c**): Compound **1c** (0.65 g, 1.63 mmol), phenylboronic acid (0.24 g, 1.96 mmol), $Pd(PPh_3)_4$ (0.10 g, 0.08 mmol) and Na_2CO_3 (2M, 3.4 ml) in DMF (10 ml) were treated as described for **2a**. Workup and column chromatography (10 : 1 hexane–EtOAc, v/v) afforded **2c** as solid (0.28 g, 50%) m.p. 145–148 °C (EtOH). IR (neat): ν_{max}/cm^{-1} 1550, 1476, 1398, 1339, 1086, 1013, 826, 754, 700 cm^{-1}. NMR ($CDCl_3$): δ_H 7.16–7.21 (4H, m), 7.26–7.29 (2H, m), 7.31–7.37 (3H, m), 7.68 (1H, dt, J = 1.2 and 7.8 Hz), 7.80 (1H, dt, J = 1.5 and 7.8 Hz), 8.19 (1H, dd, J = 0.9 and 8.7 Hz), 8.32 (1H, dd, J = 1.2 and 8.4 Hz); δ_C 124.7, 125.5, 127.9, 128.0, 128.0, 128.3, 129.9, 130.5, 130.7, 131.1, 132.8, 134.2, 136.8, 138.7, 142.2, 147.6, 157.8. MS (EI) *m/z* 353 (7), 351 (39), 349 (M^+, 75), 348 (100); HRMS (EI) calcd for $C_{21}H_{13}{}^{35}Cl_2N$: 349.0425, found: 349.0426. Anal. calcd for $C_{21}H_{13}Cl_2N$: C, 72.02; H, 3.74; N, 4.00; found: C, 72.08; H, 3.85; N, 3.98%.

4-Chloro-2-(4'-methoxyphenyl)-3-phenylquinoline (**2d**): **1d** (0.65 g, 1.65 mmol), phenylboronic acid (0.24 g, 1.98 mmol), $Pd(PPh_3)_4$ (0.10 g, 0.08 mmol) and Na_2CO_3 (2M, 3.3 ml) in DMF (10 ml) was treated as described above. Workup and column chromatography (10 : 1 hexane–EtOAc, v/v) afforded **2d** as a solid (0.30 g, 53%) m.p. 110–112 °C (EtOH). IR: ν_{max} 1605, 1567, 1513, 1470, 1338, 1242, 1179, 1027, 833, 770, 746 cm^{-1}. NMR ($CDCl_3$): δ_H 3.76 (3H, s), 6.73 (2H, d, J = 9.0 Hz), 7.19–7.23 (2H, m), 7.26–7.34 (5H, m), 7.64 (1H, dt, J = 1.2 and 7.8 Hz), 7.78 (1H, dt, J = 1.2 and 7.8 Hz), 8.19 (1H, dd, J = 0.6 and 8.7 Hz), 8.30 (1H, dd, J = 0.6 and 8.4 Hz); δ_C 55.2, 113.2, 124.6, 125.3, 127.4, 127.6, 128.1, 129.7, 130.2, 130.7, 131.2, 132.7, 132.8, 137.6, 141.8, 147.7, 158.7, 159.4. MS (EI): *m/z* 347 (25), 346 (48), 345 (M^+, 72), 344 (100). Anal. calcd for $C_{22}H_{16}ClNO$: C, 76.41; H, 4.66; N, 4.05; found: C, 76.42; H, 4.70; N, 3.89%.

Methoxydechlorination of the 4-chloroquinolines **2** *with sodium methoxide in DMF: typical procedure*

4-Methoxy-2,3-diphenylquinoline (**3a**): A stirred mixture of **2a** (0.50 g, 1.58 mmol) and sodium methoxide (0.5M in MeOH, 2.38 mmol, 4.8 ml) in DMF (10 ml) was heated under reflux for 18 hours. The mixture was allowed to cool and quenched with ice-cold water. The product was extracted into chloroform and the combined organic phases were dried (Mg_2SO_4), filtered and evaporated. The residue was purified by column chromatography (3 : 2 EtOAc–hexane, v/v) to afford **3a** as a solid (0.27 g, 55%) m.p. 132–134 °C (EtOH). IR: ν_{max} 1615, 1555, 1483, 1360, 1136, 1105, 1065, 984, 760 cm^{-1}. NMR ($CDCl_3$): δ_H 3.54 (3H, s), 7.20–7.35 (10H, m), 7.57 (1H, tt, J = 1.5 and 7.5 Hz), 7.74 (1H, tt, J = 1.5 and 7.8 Hz), 8.17–8.22 (2H, m); δ_C 61.3, 122.3, 122.8, 125.3, 126.6, 126.4, 127.9. 128.2, 129.6, 130.1, 131.0, 131.2, 133.9, 135.1, 139.1, 148.8, 159.2, 161.5. Anal. calcd for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50; found: C, 84.70; H, 5.65; N, 4.23%.

2-(4'-Fluorophenyl)-4-methoxy-3-phenylquinoline (**3b**): A mixture of **2b** (0.45 g, 1.36 mmol) and sodium methoxide (0.5M in MeOH, 2.04 mmol, 4.1 ml) in DMF (10 ml) was treated as described above. Workup and column chromatography (3 : 2 EtOAc–hexane, v/v) afforded **3b** as a solid (0.26 g, 58%) m.p. 123–125 °C (EtOH). IR: ν_{max} 1594. 1503, 1474, 1333, 1223, 1157, 835, 765 cm^{-1}. NMR ($CDCl_3$): δ_H 3.54 (3H, s), 6.90 (2H, t, J = 8.7 Hz), 7.19–7.23 (2H, m), 7.27–7.36 (5H, m), 7.58 (1H, tt, J = 1.2 and 7.7 Hz), 7.75 (1H, tt, J = 1.2 and 7.8 Hz), 8.17 (1H, d, J = 8.4 Hz), 8.19 (1H, dd, J = 1.2 and 8.3 Hz); δ_C 61.4, 114.7 (d, $^2J_{CF}$ = 21.3 Hz), 122.4, 122.8, 125.2, 126.6, 127.4, 128.2, 129.2, 130.2, 131.0, 131.0, 131.7 (d, $^3J_{CF}$ = 8.1 Hz), 135.1 (d, $^4J_{CF}$ = 2.9 Hz), 148.2, 159.3, 161.7, 162.5 (d, $^1J_{CF}$ = 246.7 Hz). Anal. calcd for $C_{22}H_{16}FNO$: C, 80.23; H, 4.90; N, 4.25; found: C, 80.37; H, 4.77; N, 4.34%.

2-(4-Chlorophenyl)-4-methoxy-3-phenylquinoline (**3c**): Compound **2c** (0.5 g, 1.42 mmol) and sodium methoxide (0.5M in MeOH, 2.14 mmol, 4.3 ml) in DMF (10 ml) was treated as described for **3a**. Workup and column chromatography (3 : 2 EtOAc–hexane, v/v) afforded **3c** as a solid (0.29 g, 60%) m.p. 133–136 °C (EtOH). IR: ν_{max} 1563, 1486, 1360, 1090, 986, 806, 758 cm^{-1}. NMR ($CDCl_3$): δ_H 3.54, (3H, s), 7.16–7.34 (9H, m), 7.58 (1H, tt, J = 1.2 and 7.8 Hz), 7.74 (1H, tt, J = 1.5 and 7.8 Hz), 8.16 (1H, dd, J = 0.9 and 8.2 Hz), 8.18 (1H, J = 0.9 and 8.4 Hz); δ_C 61.3, 122.3, 122.8, 125.3, 126.6, 127.4, 127.9, 128.3, 129.5, 130.1, 131.0, 131.2, 133.9, 135.1, 139.0, 148.7, 159.2, 161.5. MS (EI): *m/z* 346 (M^+, 50), 345 (72), 344 (100); HRMS (EI): calcd for $C_{22}H_{16}NO^{35}Cl$, 345.9955; found: 346.0004. Anal. calcd for $C_{22}H_{16}{}^{35}ClNO$: C, 76.41; H, 4.66; N, 4.05; found: C, 76.32; H, 4.56; N, 4.01%.

4-Methoxy-2-(4'-methoxyphenyl)-3-phenylquinoline (**3d**): Compound **2d** (0.45 g, 1.30 mmol) and sodium methoxide (0.5M in MeOH, 1.95 mmol, 3.9 ml) in DMF (10 ml) was treated as described for **3a**. Workup and column chromatography (3 : 2 EtOAc–hexane, v/v) afforded **3d** as a solid (0.29 g, 65%) m.p. 135–137 °C (EtOH). IR: ν_{max} 1607, 1580, 1515, 1485, 1360, 1244, 1108, 1069, 1032, 986, 833, 758 cm^{-1}. NMR ($CDCl_3$): δ_H 3.52 (3H, s), 3.77 (3H, s), 6.73 (2H, d, J = 9.0 Hz), 7.21–7.33 (7H, m), 7.54 (1H, dt, J = 1.5 and 7.8 Hz), 7.72 (1H, dt, J = 1.5 and 7.8 Hz), 8.13-8.16 (2H, m); δ_C 55.2, 61.2, 113.1, 122.3, 122.6, 125.5, 126.1, 127.1, 128.1, 129.5, 129.8, 131.0, 131.3, 133.1, 135.7, 148.9, 159.3, 160.1, 161.3. MS (EI): *m/z* 341 (M^+, 86), 340 (100), 325 (28), 69 (42), 28 (52). HRMS (EI): calcd for $C_{23}H_{19}NO_2$ 340.1338, found 340.1341. Anal. calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10; found: C, 81.01; H, 5.80; N, 3.97%.

Synthesis of 2-aryl-3-iodo-4-methoxyquinolines **4a–d** *from* **1**: *typical procedure*

3-Iodo-4-methoxy-2-phenylquinoline (**4a**): A stirred mixture of **1a** (0.50 g, 1.37 mmol) and sodium methoxide (0.5M in MeOH, 3.01 mmol, 6.0 ml) in THF (10 ml) was refluxed for 18 hours. The mixture was allowed to cool to room temperature and then poured into ice-cold water. The product was extracted into chloroform and the combined chloroform extracts were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by column chromatography (1 : 4 EtOAc–hexane, v/v) to afford **4a** as a white solid (0.30 g, 60%), m.p. 153–155 °C (EtOH). IR: ν_{max} 1566, 1485, 1361, 1072, 980, 894, 763 cm^{-1}. NMR ($CDCl_3$): δ_H 4.10 (3H, s), 7.44–7.52 (3H, m), 7.56–7.63 (3H, m), 7.75 (1H, tt, J = 1.5 and 7.7 Hz), 8.10 (1H, t, J = 9.0 Hz); δ_C 62.0, 88.0, 121.9, 127.1, 127.9, 128.7, 129.2, 129.6, 130.6, 142.7, 149.0, 163.1, 164.8. MS (EI) *m/z* 361 (M^+, 100), 331 (30), 204 (35); HRMS (EI) calcd for $C_{16}H_{12}INO$: 360.9964, found: 360.9964. Anal. calcd for $C_{16}H_{12}INO$: C, 53.23; H, 3.35; N, 3.88; found: C, 53.07; H, 3.29; N, 3.68%.

2-(4'-Fluorophenyl)-3-iodo-4-methoxyquinoline (**4b**): A mixture of **1b** (0.50 g, 1.30 mmol) and sodium methoxide (0.5M in MeOH, 2.87 mmol, 5.7 ml) in THF (10 ml) was treated as described in the preparation of **4a**. Workup and column chromatography (1 : 4 EtOAc–hexane, v/v) afforded **4b** as a white solid (0.34 g, 70%) m.p. 140–142 °C (EtOH). IR: ν_{max} 1590, 1570, 1509, 1487, 1364, 1218, 1075, 982, 831, 768 cm^{-1}. NMR ($CDCl_3$): δ_H 4.10 (3H, s), 7.17 (2H, t, J = 8.9 Hz), 7.55–7.65 (3H, m), 7.76 (1H, dt, J = 1.2, and 7.8 Hz), 8.10 (1H, td, J = 0.9 and 5.6 Hz), 8.13 (1H, td, J = 0.9 and 5.6 Hz); δ_C 62.0, 87.9, 122.3, (d, $^2J_{CF}$ = 21.6 Hz), 121.9, 122.7, 127.2, 129.5, 130.7, 131.3 (d, $^3J_{CF}$ = 8.6 Hz), 138.7 (d, $^4J_{CF}$ = 3.5 Hz), 149.0, 162.0, 163.0 (d, $^1J_{CF}$ = 246.8 Hz), 164.9; MS (EI): *m/z* 379 (M^+, 100), 349 (26), 222 (31); HRMS (EI): calcd for $C_{16}H_{11}FINO$: 378.9866, found 378.9869. Anal. calcd for $C_{16}H_{11}FINO$: C, 50.71; H, 2.92; N, 3.69; found: C, 50.53; H, 2.79; N, 3.57%.

2-(4'-Chlorophenyl)-3-iodo-4-methoxyquinoline (**4c**): Compound **1c** (0.50 g, 1.25 mmol) and sodium methoxide (0.5M in MeOH, 2.75 mmol, 5.5 ml) in THF (10 ml) were treated as described for **4a**. Workup and column chromatography (1 : 4 EtOAc–hexane, v/v) afforded **4c** as a white solid (0.38 g, 77%) m.p. 178–180 °C (EtOH). IR: ν_{max} 1557, 1534, 1341, 1090, 824, 757 cm^{-1}. NMR ($CDCl_3$): δ_H 4.10 (3H, s), 7.46 (2H, d, J = 7.8 Hz), 7.58 (2H, d, J = 7.8 Hz), 7.60–7.65 (1H, m), 7.76 (1H, dt, J = 1.2 and 7.8 Hz), 8.09–8.10 (1H, m), 8.11–8.13 (1H, m); δ_C 62.0, 87.5, 122.0, 122.8, 127.3, 128.2, 129.6, 130.7, 130.8, 134.8, 141.0, 149.1, 161.8, 165.0. MS (EI) *m/z* 395 (M^+, 45), 379 (100), 349 (29), 222 (37). HRMS (EI): calcd for $C_{16}H_{11}{}^{35}ClINO$ 394.9596, found 394.9574. Anal. calcd for $C_{16}H_{11}ClINO$: C, 48.66; H, 2.81; N, 3.55; found: C, 48.70; H, 2.79; N, 3.61%.

3-Iodo-4-methoxy-2-(4'-methoxyphenyl)quinoline (**4d**): A mixture of **1d** (0.50 g, 1.26 mmol) and sodium methoxide (0.5M in MeOH, 2.78 mmol, 5.6 ml) in THF (10 ml) was treated as described for **4a**.

Workup and column chromatography (1:4 EtOAc–hexane, v/v) afforded **4d** as white solid (0.37 g, 75%) m.p. 167–170 °C (EtOH). IR: ν_{max} 1607, 1569, 1510, 1362, 1242, 828, 768 cm^{-1}. NMR ($CDCl_3$): δ_H 3.88 (3H, s), 4.09 (3H, s), 7.00 (2H, d, J = 8.7 Hz), 7.53–7.62 (3H, m), 7.74 (1H, dt, J = 1.2 and 7.5 Hz), 8.07–8.14 (2H, m); δ_C 55.3, 61.9, 88.3, 113.3, 121.9, 122.6, 126.9, 129.5, 130.5, 130.8, 135.2, 149.1, 160.0, 162.7, 164.7. MS (EI): *m/z* 391 (M^+, 100), 361 (25); HRMS (EI): calcd for $C_{17}H_{14}INO_2$: 391.0069, found: 391.0086. Anal. calcd for $C_{17}H_{14}INO_2$: C, 52.22; H, 3.61; N, 3.58; found: C, 51.74; H, 3.45; N, 3.39%.

General procedure for $Pd(PPh_3)_4$ catalysed cross-coupling of **4** *with $PhB(OH)_2$*

Compound **4** (1 equiv.), phenylboronic acid (1.2 equiv.) and $Pd(PPh_3)_4$ (5% of **4**) in DMF (5 ml per mmol of **4**) in a two-necked flask equipped with a stirrer bar, rubber septum and a condenser was flushed with argon for 10 min. Aqueous K_2CO_3 (2M, 2 ml per mmol of **4**) was introduced through a syringe, and the apparatus was purged with argon for a further 10 min. The mixture was heated at 80–90 °C for 48 h and then allowed to cool to room temperature. The cooled mixture was poured into ice-cold water and the product was extracted into chloroform. The combined organic phases were washed with brine, dried (Mg_2SO_4), filtered and then evaporated under reduced pressure. The residue was purified by column chromatography to afford the 2,3-diaryl-4-methoxyquinoline derivative **3**.

4-Methoxy-2,3-diphenylquinoline (**3a**): from **4a** (0.50 g, 1.39 mmol), phenylboronic acid (0.20 g, 1.67 mmol), $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) and 2M K_2CO_3 (2.8 ml) in DMF (10 ml); workup and column chromatography (15:1 hexane–EtOAc, v/v) afforded **3a** (0.36 g, 85%).

2-(4'-Fluorophenyl)-4-methoxy-3-phenylquinoline (**3b**): from **4b** (0.50 g, 1.32 mmol), phenylboronic acid (0.19 g, 1.58 mmol), $Pd(PPh_3)_4$ (0.08 g, 0.07 mmol) and 2M K_2CO_3 (2.6 ml) in DMF (10 ml) was treated as described above. Workup and column chromatography (15:1 hexane–EtOAc, v/v) afforded **3b** (0.34 g, 79%).

2-(4'-Chlorophenyl)-4-methoxy-3-phenylquinoline (**3c**)**.** A mixture of **4c** (0.50 g, 1.26 mmol), phenylboronic acid (0.18 g, 1.51 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) and 2M K_2CO_3 (2.5 ml) in DMF (10 ml) was treated as described above. Workup and column chromatography (15:1 hexane–EtOAc, v/v) afforded **3c** (0.35 g, 80%).

4-Methoxy-2-(4'-methoxyphenyl)-3-phenylquinoline **3d.** A mixture of **4d** (0.50 g, 1.28 mmol), phenylboronic acid (0.19 g, 1.54 mmol), $Pd(PPh_3)_4$ (0.07 g, 0.06 mmol) and 2M K_2CO_3 (2.6 ml) in DMF (10 ml) was treated as described above. Workup and column chromatography (15:1 hexane–EtOAc, v/v) afforded **3d** (0.36 g, 83%).

Demethylation of 4-methoxyquinolines (**4**) *with BBr_3 in dichloromethane: typical procedure*

2,3-Diphenylquinolin-4(1H)-one (**5a**): BBr_3 (0.24 g, 0.96 mmol) was added dropwise to a stirred solution of **4a** (0.20 g, 0.64 mmol) in dichloromethane (5 ml) at –10 °C. The mixture was allowed to warm to room temperature. Stirring was continued for 24 hours; then the mixture was cooled to 0 °C and diluted with dichloromethane. The mixture was quenched very slowly with ice-cold water and the organic layer was separated, dried ($MgSO_4$), filtered and then evaporated under reduced pressure. The crude product was recrystallised from ethanol to afford **5a** (0.12 g, 60%) m.p. 342–344 °C (EtOH). IR: ν_{max} 3064, 1622, 1608, 1553, 1515, 1351, 1288, 756 cm^{-1}. NMR (DMSO-d_6): δ_H 7.03–7.18 (5H, m), 7.29–7.36 (6H, m), 7.62–7.71 (2H, m), 8.15 (1H, d, J = 8.1 Hz), 11.79 (1H, br s); δ_C 118.4, 120.4, 123.1, 124.6, 125.3, 125.9, 127.2, 128.0, 128.9, 129.5, 131.7, 131.7, 135.2, 135.7, 139.6, 148.4, 175.4. MS (EI): *m/z* 297 (M^+, 46), 296 (100), 69 (37); HRMS (EI), calcd for $C_{21}H_{15}NO$: 297.1075, found: 297.1052. Anal. calcd for $C_{21}H_{15}NO$: C, 84.82; H, 5.08; N, 4.71; found: C, 84.92; H, 5.18; N, 4.51%.

2-(4'-Fluorophenyl)-3-phenylquinolin-4(1H)-one (**5b**): From **4b** (0.20 g, 0.61 mmol) and BBr_3 (0.23 g, 0.91 mmol) as described for **4a**, affording **5b** as a solid (0.13 g, 67%) m.p. 385–387 °C (EtOH). IR: ν_{max} 3074, 1625, 1606, 1552, 1510, 1352, 1217, 1155, 835, 760 cm^{-1}. NMR (DMSO-d_6): δ_H 7.05 (2H, d, J = 7.8 Hz), 7.06–7.20 (5H, m), 7.34–7.39 (3H, m), 7.67 (2H, d, J = 5.0 Hz), 8.13 (1H, d, J = 8.1 Hz), 11.80 (1H, br s); δ_C 115.1 (d, $^2J_{CF}$ = 21.7 Hz), 118.4, 120.6, 123.2, 124.7, 125.3, 126.1, 127.3, 131.7 (2 merged carbon signals), 131.8, 131.9 (d, $^3J_{CF}$ = 8.6 Hz), 135.6, 139.6 (d, $^4J_{CF}$ = 3.6 Hz), 147.5, 162.2 (d, $^1J_{CF}$ = 245.3 Hz), 175.3. MS (EI): *m/z* 315 (M^+, 70), 314 (100); HRMS (EI), calcd for $C_{21}H_{14}FNO$ 315.1059, found 315.1057. Anal. calcd for $C_{21}H_{14}FNO$: C, 79.99; H, 4.48; N, 4.44; found: C, 79.63; H, 4.48; N, 4.44%.

2-(4'-Chlorophenyl)-3-phenylquinolin-4(1H)-one (**5c**): From **4c** (0.20 g, 0.58 mmol) and BBr_3 (0.22 g, 0.87 mmol) in dichloromethane (5 ml) as described for **4a**, affording **5c** as a solid (0.13 g, 65%) m.p. 388–390 °C (EtOH). IR: ν_{max} 3064, 1622, 1605, 1552, 1515, 1485, 1353, 1090, 1018, 826, 756 cm^{-1}. NMR (DMSO-d_6): δ_H 7.04–7.20 (5H, m), 7.32–7.42 (5H, m), 7.67 (2H, s), 8.15 (1H, d, J = 7.5 Hz), 11.82 (1H, br s); δ_C 128.4, 130.6, 133.3, 134.7, 135.3, 136.2, 137.4, 138.1, 141.5, 141.7, 141.9, 143.8, 144.0, 145.5, 149.6, 157.3, 185.3. MS (EI): *m/z* 332 (40), 331 (M^+, 45), 330 (100), 69 (37). Anal. calcd for $C_{21}H_{14}ClNO$: C, 76.02; H, 4.25; N, 4.22; found: C, 75.96; H, 4.39; N, 4.09%.

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