Synthesis of Chromeno[3,4-*b*]quinolines: Electrophilic Aromatic Substitution under Heck Conditions

Andrew L. C. Morris, Yvette A. Jackson*

Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica, West Indies
Fax +1(876)9771835; E-mail: yvette.jackson@uwimona.edu.jm

Received 15 September 2010; revised 1 November 2010

Abstract: The palladium-mediated intramolecular coupling reaction of 2-[(3-substituted-phenoxy)methyl]quinolines for preparing chromeno[3,4-*b*]quinolines was explored. The results of the cyclizations gave convincing evidence for an electrophilic aromatic substitution mechanism under standard Heck conditions.

Key words: palladium catalysis, Heck reaction, electrophilic aromatic substitution, chromenoquinoline, aryl–heteroaryl coupling

Chromenoquinolines have been implicated in a wide range of biological activity including mimicry of anti-inflammatory agents such as cortisone and cortisol,[1] as well as inhibition of estrogens by binding to estrogen receptor beta (ERβ) sites.[2] Known to be mild carcinogens,[3] these compounds are also highly potent progestins[4] as well as inhibitors of passive cutaneous anaphylaxis.[5]

Reports of the synthesis of chromenoquinolines, particularly chromeno[3,4-*b*]quinolines, in the literature are sparse. We recently reported the first palladium-mediated preparation of a 6*H*-chromeno[3,4-*b*]quinoline **1** (R^1 = OMe, R^2 = H) (Figure 1).[6] During our efforts to synthesize heterocycles of type **1** (R^1 = OMe, R^2 = H), it was found that when compound **2** (R^1 = OMe, R^2 = H) was treated under standard Heck conditions the expected product was isolated in fair yields (45–58%) when carried out under both thermal and microwave conditions. When compound **3** was treated similarly, however, none of the desired product was isolated; the starting material was recovered unchanged. This led us to attempt elucidation of the mechanism of cyclization of these compounds.

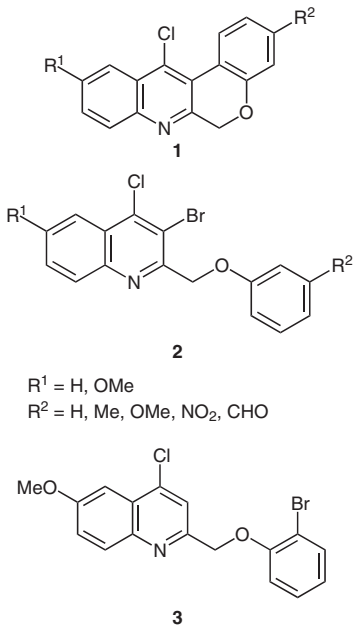
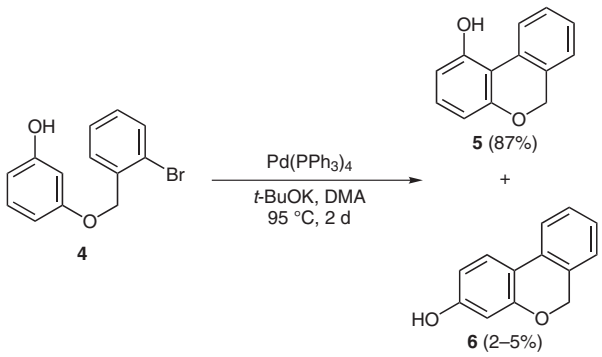


Figure 1

There have been conflicting suggestions in the literature as to how aryl–aryl as well as aryl–heteroaryl coupling reactions proceed when they are mediated by palladium.[7] Rawal et al.[8] reported the palladium-catalyzed intramolecular coupling of phenols with aryl halides to prepare 1-hydroxy-6*H*-benzo[*c*]chromene (**5**) (Scheme 1). It was found that when the phenoxy ring of compound **4** possessed a hydroxy group, under the basic conditions of the reaction, the phenoxide rendered the aryl ring more nucleophilic and, thus, more reactive in the coupling reaction. The 3-hydroxy derivative **6** was also isolated.

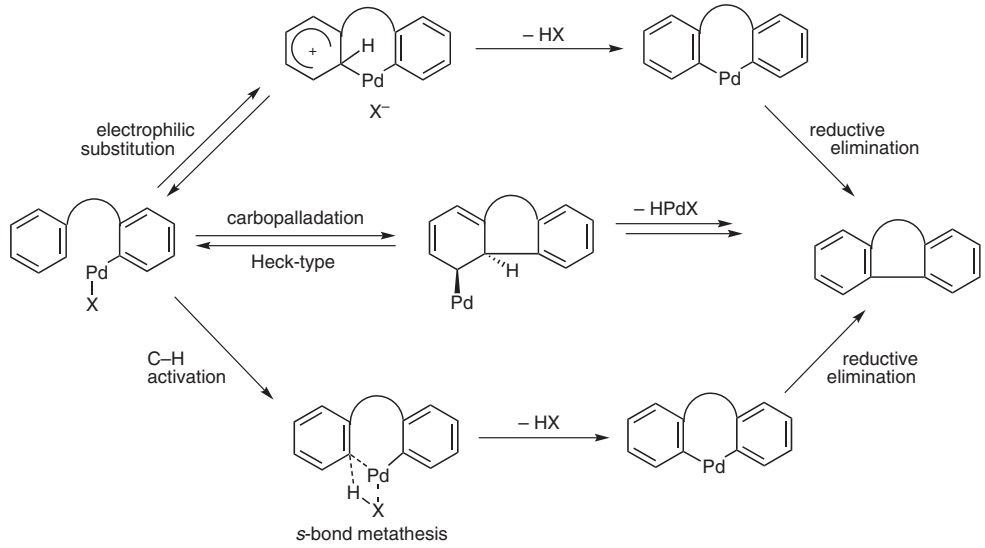


Scheme 1

In 2003 Buchwald and Hennessey[9] suggested three conceivable mechanisms, viz. (1) electrophilic substitution, (2) a Heck-type carbopalladation, and (3) C–H activation, for the formation of substituted oxindoles from α-chloroacetanilides.

Nishioka and co-workers[10] proposed analogous mechanisms for intramolecular aryl–aryl couplings. These are depicted in Scheme 2. While examining the palladium-assisted biaryl coupling involved in the preparation of phenanthridin-6(5*H*)-ones **8** from benzanilide precursors **7** (Scheme 3) formation of the biaryl bond was believed to

SYNTHESIS 2011, No. 2, pp 0229–0234
Advanced online publication: 26.11.2010
DOI: 10.1055/s-0030-1258344; Art ID: M06210SS



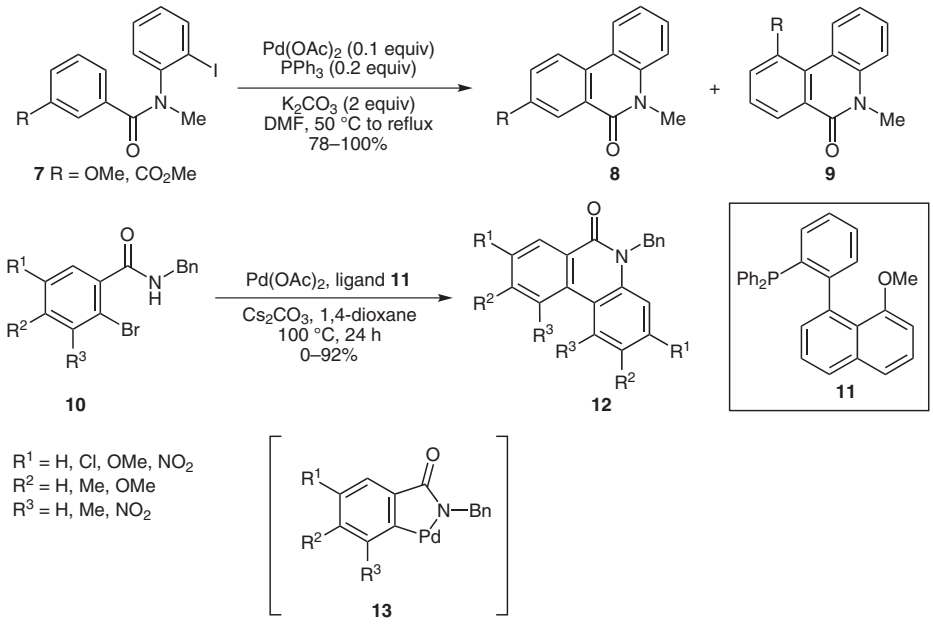
Scheme 2

have proceeded through a C–H activation process. They postulated that the substituents would have no effect on the outcome of the reaction other than that due to steric factors.

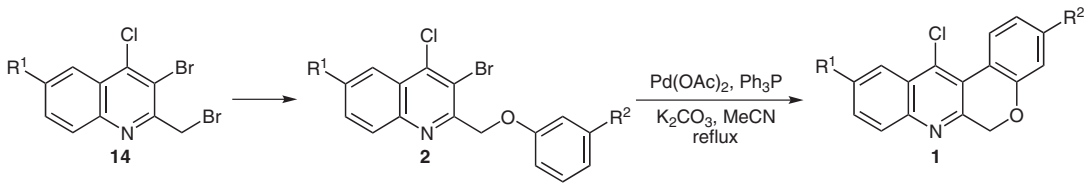
Later, during their synthesis of phenanthridinone derivatives **12** via a palladium-mediated coupling process, Kan et al.[11] found that the synthesis, which involved an aryl–aryl coupling, depended on the electronic properties of the ring (Scheme 3). The reaction proceeded through a domino process with associated C–C and C–N bond-forming reactions, via intermediate **13**. Those compounds with electron-withdrawing substituents proceeded in poor yields. In fact, those bearing a nitro group failed to give any of the desired products, while those bearing the weakly deactivating halogens gave the corresponding phenanthridinones in only 37–45% yield. When the rings bore electron-donating groups yields increased to 67–92%.

Many coupling reactions mediated by palladium have been referred to in the literature as 'Heck reactions'. When the coupling partners are two aryl (or heteroaryl) rings a different nomenclature may be required. The Heck-type reaction should usually proceed via *cis* addition and *syn* β-elimination. Thus, a route via carbopalladation would be less likely, although there has been suggestion of an alternative mechanism involving *anti* elimination or isomerization followed by *syn* elimination.[12]

In our efforts to elucidate the mechanism of the intramolecular coupling of 2-substituted 4-chloroquinolines, we prepared a series of ethers of type **2** from bromides **14**



Scheme 3



Scheme 4 Intramolecular palladium-mediated coupling of 2-substituted quinolines **2**

with a view to preparing chromeno[3,4-*b*]quinoline **1** (Scheme 4) according to a protocol previously reported.[6] The cyclizations were carried out under standard Heck conditions: palladium(II) acetate, triphenylphosphine, potassium carbonate, acetonitrile, reflux under an atmosphere of nitrogen. The results of the attempted cyclizations are presented in Table 1 and show that electronic factors dominate the course of the reaction under the prevailing conditions.

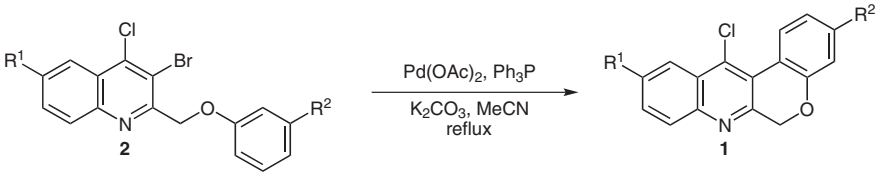
When the intramolecular coupling was carried out with compounds **2a**–**f** the reactions proceeded as expected in reasonable yields. Compounds **2g** and **2h**, which possessed strongly deactivating substituents, a formyl and a nitro group, respectively, on the phenoxy ring, did not give any product of cyclization after heating at reflux for 12 hours. From these reaction mixtures only starting material was recovered. The cyclizations are believed to proceed as shown in Scheme 5, similar to the mechanism proposed by Rawal.[8]

Compound **2a**, for example, oxidatively adds to palladium(0) resulting in σ-arylpalladium intermediate **15**. Although the phenyl ring is not as electron-rich as a phenolate anion the oxygen atom is able to render the benzene ring sufficiently nucleophilic to displace bromide from **15**. Abstraction of a proton by the base results in rearomatization and formation of palladium species **16**. Reductive elimination of palladium thus furnishes the observed tetracycle **1a**.

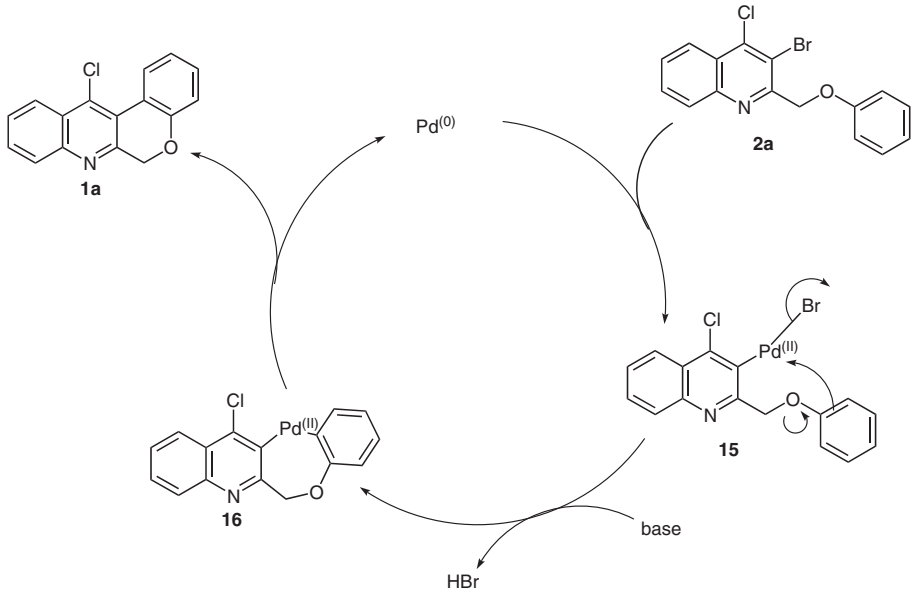
When the phenoxy ring possesses an electron-withdrawing group, such as a formyl or nitro group, its nucleophilic ability is significantly reduced. In our case, no reaction occurred. It is likely that the reduced electron density of the aromatic ring imparted by the presence of these groups does not allow for the formation of intermediate **16**, and hence, none of the tetracycle. It should also be noted that none of this intermediate or its precursor **15** was ever isolated.

Compound **3** was prepared from 6-methoxy-2-methyl-1*H*-quinolin-4-one (**17**)[6] as shown in Scheme 6. Heating a mixture of compound **17** and phosphorus pentachloride in the presence of pyridine-derived bases at reflux for two hours furnished 4-chloroquinoline **18** in 84% yield. Subsequent bromination in the presence of light afforded compound **19** in only 40% yield. Substitution of bromide **19** with 2-bromophenol provided ether **3** in 81% yield. When compound **3** was treated in similar manner to compounds **2a**–**h**, there was no reaction. With the bromine now on the phenoxy ring, following oxidative addition to palladium, formation of the tetracycle **1d** requires nucleophilic attack of palladium by a quinoline ring. The reduced electron density of this ring compared to, for example, benzene, prevents formation of intermediate **16** and, hence, no cyclized product is formed.

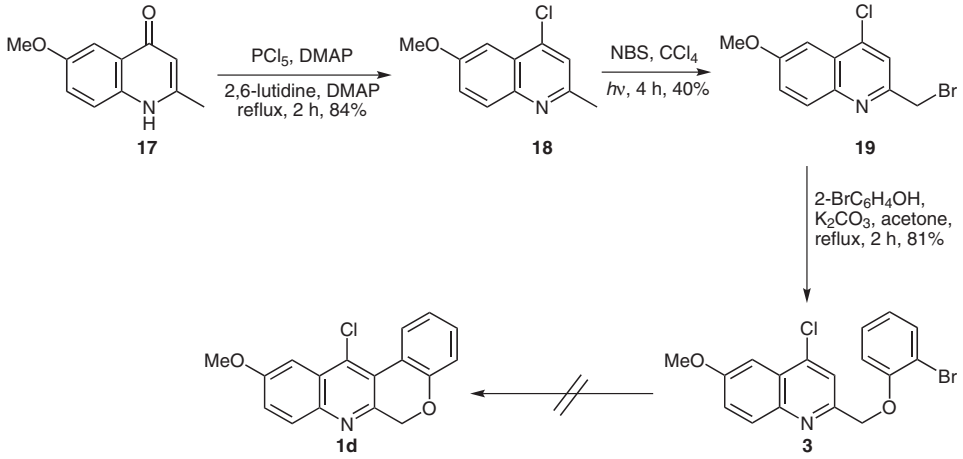
Table 1 Results of Cyclization of 3-Bromo-4-chloro-2-[(3-substituted phenoxy)methyl]quinoline **5** to Tetracycle **6**



Substrate	R^1	R^2	Time (h)	Product	Yield (%)
2a	H	H	9	**1a**	51
2b	H	Me	8	**1b**	40
2c	H	OMe	6	**1c**	58
2d	OMe	H	8	**1d**	58[6]
2e	OMe	Me	8	**1e**	49
2f	OMe	OMe	6	**1f**	52
2g	OMe	CHO	12		–
2h	OMe	NO_2	12		–



Scheme 5 Proposed mechanism for the formation of tetracycle **1a** from **2a**



Scheme 6 Synthesis of compound **3** and its attempted cyclization

In summary, the cyclization of 2-[(3-substituted phenoxy)methyl]quinolines to chromeno[3,4-*b*]quinolines under typical Heck conditions has been investigated. When subjected to these conditions the substrates demonstrate the role of electronic factors on the palladium-assisted reaction. Electron-donating groups increased the rate of the reaction, while electron-withdrawing groups retarded the cyclization. These findings give compelling evidence for an electrophilic aromatic substitution mechanism for the intramolecular direct aryl–aryl coupling mediated by palladium.

Melting points were determined in capillary tubes on a Thomas Hoover Melting Point apparatus and are uncorrected. IR spectra were recorded neat on a Bruker Vector 22 FTIR spectrophotometer and ^{1}H and ^{13}C NMR spectra in $CDCl_3$ on a Bruker Avance 200 MHz or 500 MHz spectrometer; TMS was used as an internal standard (δ = 0.0). Microanalyses were carried out at MEDAC Ltd., Chobham, Surrey, UK. Column chromatography was carried out on silica gel. All palladium-mediated reactions were performed under N_2 atmosphere. $Pd(OAc)_2$ was used as purchased from Aldrich.

2-(Bromomethyl)-4-chloro-6-methoxyquinoline (19)

Chloroquinoline **18** (200 mg, 0.96 mmol) was dissolved in CCl_4 (5 mL) and irradiated with a 150-W tungsten bulb. NBS (206 mg, 1.2 mmol) was added in small portions over 10 min. The mixture was then heated at reflux for 4 h while being irradiated. The mixture was then filtered and the filtrate concentrated, diluted with CH_2Cl_2 (15 mL), and washed with 30% $NaHSO_3$ soln (3 × 10 mL). The organic layer was dried (Na_2SO_4), concentrated, and recrystallized to give bromide **19** (110 mg, 40%) as orange plates; mp 78–80 °C (acetone).

IR: 1618, 1561, 1488 cm^{-1}.

^{1}H NMR: δ = 3.98 (s, 3 H, OCH_3), 4.65 (s, 2 H, CH_2Br), 7.42 (m, 2 H, H5, H7), 7.64 (s, 1 H, H3), 7.98 (d, *J* = 9.8 Hz, 1 H, H8).

^{13}C NMR: δ = 33.8, 55.8, 101.7, 101.8, 120.1, 121.5, 123.7, 126.8, 141.7, 144.3, 159.2.

Anal. Calcd for $C_{11}H_9BrClNO$: C, 46.11; H, 3.17; N, 4.89. Found: C, 46.04; H, 3.31; N, 4.64.

2-[(2-Bromophenoxy)methyl]-4-chloro-6-methoxyquinoline (3)
To a stirred suspension of 2-bromophenol (86 mg, 0.50 mmol) and K_2CO_3 (250 mg, 1.81 mmol) in acetone (5 mL) was added a soln of 2-(bromomethyl)-4-chloro-6-methoxyquinoline (**19**, 0.131 g, 0.45 mmol) in acetone (5 mL). The mixture was heated at reflux for 2 h and filtered; the filtrate was concentrated, diluted with EtOAc (20 mL), and washed with 1.5 M NaOH (3 × 10 mL). The organic layer was dried (Na_2SO_4) and then concentrated to give the crude product which was recrystallized to give compound **3** (138 mg, 81%) as light-brown needles; mp 133–135 °C (MeOH).

IR: 2996, 2040, 1477, 1453 cm^{-1}.

^1H NMR: δ = 3.98 (s, 3 H, OCH_3), 5.37 (s, 2 H, CH_2O), 6.88 (ddd, *J* = 8.2, 1.7, 0.5 Hz, 1 H, H4′), 6.99 (dd, *J* = 8.2, 1.0 Hz, 1 H, H6′), 7.25 (ddd, *J* = 8.1, 2.0, 0.5 Hz, 1 H, H5′), 7.42 (dd, *J* = 8.8, 2.5 Hz, 1 H, H7), 7.45 (s, 1 H, H5), 7.60 (dd, *J* = 7.9, 1.7 Hz, 1 H, H3′), 7.89 (s, 1 H, H3), 7.96 (dd, *J* = 9.7, 0.7 Hz, 1 H, H8).

^{13}C NMR: δ = 55.7, 71.4, 101.8, 112.3, 113.6, 119.5, 121.3, 122.5, 123.6, 128.6, 130.8, 133.5, 137.0, 142.1, 144.3, 154.6, 158.8.

Anal. Calcd for $C_{17}H_{13}BrClNO_2$: C, 53.92; H, 3.46; N, 3.70. Found: C, 54.17; H, 3.88; N, 3.51.

2-[(3-Substituted phenoxy)methyl]quinolines 2; General Procedure
A mixture of the appropriate 3-substituted phenol (1.2 equiv) and K_2CO_3 (5 equiv) was dissolved in acetone and the mixture stirred at r.t. for 15 min. (Bromomethyl)quinoline **14** was then added as a soln in acetone and the mixture heated at reflux for 2–3 h. The mixture was then filtered to remove inorganic material, concentrated, diluted with CH_2Cl_2 (20 mL) and washed with 2 M NaOH (2 × 5 mL). The organic layer was dried (Na_2SO_4) and concentrated to give **2**.

3-Bromo-4-chloro-6-methoxy-2-(phenoxymethyl)quinoline (**2d**)[6] is consistent with literature data.

3-Bromo-4-chloro-2-(phenoxymethyl)quinoline (2a)
Off-white needles, yield: 85%; mp 67–69 °C (EtOH).

IR: 3000, 2049, 1489, 1228 cm^{-1}.

^1H NMR: δ = 5.48 (s, 2 H, CH_2O), 6.99 (tt, *J* = 6.6, 0.7 Hz, 1 H, H4′), 7.08 (dd, *J* = 8.8, 0.6 Hz, 2 H, H2′, H6′), 7.31 (m, 2 H, H3′, H5′), 7.67 (ddd, *J* = 8.1, 6.4, 0.5 Hz, 1 H, H6), 7.79 (ddd, *J* = 8.1, 6.6, 1.5 Hz, 1 H, H7), 8.13 (ddd, *J* = 8.2, 1.2, 0.5 Hz, 1 H, H5), 8.24 (ddd, *J* = 8.1, 1.6, 0.5 Hz, 1 H, H8).

^{13}C NMR: δ = 72.1, 115.1, 118.4, 121.4, 124.5, 126.9, 128.7, 129.5, 130.0, 130.6, 142.7, 154.6, 156.7, 158.6.

Anal. Calcd for $C_{16}H_{11}BrClNO$: C, 55.12; H, 3.18; N, 4.02. Found: C, 55.58; H, 2.97; N, 4.22.

3-Bromo-4-chloro-2-[(3-methylphenoxy)methyl]quinoline (2b)
Cream-colored prisms; yield: 92%; mp 111–113 °C (EtOH).

IR: 2991, 2044, 1480, 1222 cm^{-1}.

^1H NMR: δ = 2.34 (s, 3 H, CH_3), 5.46 (s, 2 H, -OCH_2-), 6.79–6.91 (m, 3 H, H2′, H4′, H6′), 7.19 (t, *J* = 7.8 Hz, 1 H, H5′), 7.67 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1 H, H6), 7.79 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1 H, H7), 8.14 (ddd, *J* = 8.4, 1.4, 0.5 Hz, 1 H, H5), 8.23 (ddd, *J* = 8.4, 1.5, 0.5 Hz, 1 H, H8).

^{13}C NMR: δ = 21.5, 72.1, 111.9, 116.0, 118.4, 122.2, 124.5, 126.9, 128.7, 129.2, 130.0, 130.6, 139.5, 142.9, 146.4, 158.7, 163.1.

Anal. Calcd for $C_{17}H_{13}BrClNO$: C, 56.30; H, 3.61; N, 3.86. Found: C, 56.04; H, 3.56; N, 3.68.

3-Bromo-4-chloro-2-[(3-methoxyphenoxy)methyl]quinoline (2c)
White prisms; yield: 89% mp 91–93 °C (EtOH).

IR: 3001, 2050, 1489, 1229 cm^{-1}.

^1H NMR: δ = 3.79 (s, 3 H, OCH_3), 5.46 (s, 2 H, CH_2), 6.55 (ddd, *J* = 8.2, 2.3, 0.8 Hz, 1 H, H2′), 6.67 (m, 2 H, H6′, H4′), 7.20 (t, *J* = 8.6 Hz, 1 H, H5′), 7.66 (dd, *J* = 7.2, 1.4 Hz, 1 H, H6), 7.78 (dd, *J* = 7.2, 1.5 Hz, 1 H, H7), 8.13 (dd, *J* = 8.6, 1.0 Hz, 1 H, H5), 8.23 (dd, *J* = 8.2, 1.0 Hz, 1 H, H8).

^{13}C NMR: δ = 55.3, 72.1, 101.6, 107.1, 107.1, 118.4, 124.6, 126.9, 128.8, 129.9, 130.0, 130.7, 143.2, 146.4, 154.6, 159.9, 160.8.

Anal. Calcd for $C_{17}H_{13}BrClNO_2$: C, 53.92; H, 3.46; N, 3.70. Found: C, 53.63; H, 3.44; N, 3.74.

3-Bromo-4-chloro-6-methoxy-2-[(3-methylphenoxy)methyl]quinoline (2e)
Brown plates; yield: 89%; mp 105–107 °C (EtOH).

IR: 2990, 2047, 1477, 1225 cm^{-1}.

^1H NMR: δ = 2.34 (s, 3 H, CH_3), 3.98 (s, 3 H, OCH_3), 5.42 (s, 2 H, CH_2), 6.80 (d, *J* = 7.2 Hz, 1 H, H4′), 6.88 (m, 2 H, H2′, H6′), 7.18 (t, *J* = 7.6 Hz, 1 H, H5′), 7.40 (m, 2 H, H5, H7), 8.00 (dt, *J* = 9.7, 1.3 Hz, 1 H, H8).

^{13}C NMR: δ = 21.6, 55.8, 72.1, 102.3, 111.9, 116.0, 119.1, 122.1, 123.4, 129.2, 131.6, 133.9, 135.3, 135.9, 139.5, 151.9, 158.7, 159.6.

Anal. Calcd for $C_{18}H_{15}BrClNO_2$: C, 55.06; H, 3.85; N, 3.57. Found: C, 55.05; H, 3.80; N, 3.52.

3-Bromo-4-chloro-6-methoxy-2-[(3-methoxyphenoxy)methyl]quinoline (2f)
Peach-colored needles; yield: 91%; mp 118–119 °C (EtOH).

IR: 2990, 2051, 1470, 1222 cm^{-1}.

^1H NMR: δ = 3.79 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 5.43 (s, 2 H, CH_2), 6.54 (dd, *J* = 8.3, 2.5 Hz, 1 H, H2′), 6.70 (m, 2 H, H4′, H6′), 7.19 (t, *J* = 8.6 Hz, 1 H, H5′), 7.40 (m, 2 H, H5′, H7), 8.00 (dd, *J* = 8.6, 0.7 Hz, 1 H, H8).

^{13}C NMR: δ = 54.0, 54.8, 71.6, 100.4, 101.6, 106.1, 118.4, 122.9, 124.6, 127.5, 128.2, 129.2, 130.9, 140.0, 141.6, 151.3, 159.4, 160.4.

Anal. Calcd for $C_{18}H_{15}BrClNO_3$: C, 52.90; H, 3.70; N, 3.43. Found: C, 53.09; H, 3.74; N, 3.42.

3-[(3-Bromo-4-chloro-6-methoxyquinolin-2-yl)methoxy]benzaldehyde (2g)
Cream-colored prisms; yield: 73%; mp 147–149 °C (EtOH).

IR: 2999, 2780, 2044, 1692 cm^{-1}.

^1H NMR: δ = 4.00 (s, 3 H, OCH_3), 5.51 (s, 2 H, CH_2), 7.34 (dd, *J* = 7.9, 1.3 Hz, 1 H, H6), 7.47 (m, 4 H, H4, H5, H5′, H7′), 7.59 (br s, 1 H, H2), 8.00 (d, *J* = 9.1 Hz, 1 H, H8′), 9.99 (s, 1 H, CHO).

^{13}C NMR: δ = 55.8, 72.2, 102.3, 113.8, 119.0, 120.0, 122.3, 123.7, 123.8, 128.3, 130.2, 131.6, 137.8, 142.5, 151.1, 159.2, 159.8, 192.1.

Anal. Calcd for $C_{18}H_{13}BrClNO_3$: C, 53.16; H, 3.22; N, 3.44. Found: C, 53.03; H, 3.25; N, 3.13.

3-Bromo-4-chloro-6-methoxy-2-[(3-nitrophenoxy)methyl]quinoline (2h)
Pale-yellow prisms; yield: 83%; mp 177–179 °C (EtOH).

IR: 3001, 2041, 1531, 1343 cm^{-1}.

1H NMR: δ = 3.99 (s, 3 H, OCH_3), 5.55 (s, 2 H, CH_2), 7.41 (m, 2 H, H2′, H6′), 7.70 (dd, *J* = 8.1, 7.8 Hz, 1 H, H5′), 7.83 (m, 2 H, H5, H7), 8.11 (d, *J* = 8.3 Hz, 1 H, H8), 8.25 (d, *J* = 8.0 Hz, 1 H, H4′).

^{13}C NMR: δ = 55.8, 72.4, 102.3, 109.7, 116.3, 118.1, 122.0, 123.7, 124.6, 128.9, 130.0, 131.5, 146.3, 149.2, 150.6, 153.4, 159.9, 160.0.

Anal. Calcd for $C_{17}H_{12}BrClN_2O_4$: C, 48.20; H, 2.86; N, 6.61. Found: C, 48.56; H, 2.85; N, 6.84.

Substituted 12-Chloro-6*H*-chromeno[3,4-*b*]quinolines 1; General Procedure

A mixture of the appropriate quinoline **2**, $(Pd(OAc)_2$ (0.2 equiv), Ph_3P (0.4 equiv), and K_2CO_3 (20 equiv) in MeCN (6 mL) was stirred under a steady stream of N_2 at reflux until no starting material remained. The mixture was filtered and the filtrate concentrated. Without further purification the mixture was then subjected to flash chromatography (CH_2Cl_2–hexanes, 9:1) to give **1**.

12-Chloro-10-methoxy-6*H*-chromeno[3,4-*b*]quinoline (**1d**)[6] is consistent with literature data.

12-Chloro-6*H*-chromeno[3,4-*b*]quinoline (1a)

Pale-yellow liquid; yield: 51%.

IR: 2924, 1618, 1489 cm^{-1}.

^1H NMR: δ = 5.20 (s, 2 H, CH_2O), 7.15 (dd, *J* = 8.2, 0.5 Hz, 1 H, H9), 7.18 (dt, *J* = 7.8, 0.7 Hz, 1 H, H11), 7.38 (m, 2 H, H2, H3), 7.60 (d, *J* = 8.2 Hz, 1 H, H9), 7.78 (ddd, *J* = 8.2, 8.4, 1.5 Hz, 1 H, H10), 7.93 (d, *J* = 8.2 Hz, 1 H, H8), 8.58 (dd, *J* = 8.2, 0.5 Hz, 1 H, H1).

^{13}C NMR: δ = 72.1, 115.1, 118.4, 121.4, 124.2, 124.5, 125.7, 125.8, 126.9, 128.7, 129.5, 130.0, 130.6, 137.0, 146.4, 158.6.

Anal. Calcd for $C_{16}H_{10}ClNO$: C, 71.78; H, 3.77; N, 5.23. Found: C, 71.51; H, 3.40; N, 5.39.

12-Chloro-3-methyl-6*H*-chromeno[3,4-*b*]quinoline (1b)

Brown prisms; yield: 40%; mp 229–231 °C (EtOH).

IR: 2938, 1629, 1480 cm^{-1}.

^1H NMR: δ = 2.36 (s, 3 H, CH_3), 5.19 (s, 2 H, CH_2), 6.67 (d, *J* = 2.7 Hz, 1 H, H4), 6.95 (dd, *J* = 9.0, 2.7 Hz, 1 H, H2), 7.70 (m, 2 H, H9, H10), 8.02 (ddd, *J* = 8.4, 1.8, 0.9 Hz, 1 H, H11), 8.35 (ddd, *J* = 8.6, 1.6, 0.8 Hz, 1 H, H8), 8.52 (d, *J* = 8.8 Hz, 1 H, H).

^{13}C NMR: δ = 21.5, 72.3, 116.6, 120.6, 120.8, 124.5, 125.6, 127.9, 128.2, 129.8, 130.4, 132.1, 136.9, 138.3, 140.3, 144.2, 158.4.

Anal. Calcd for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.55; H, 4.02; N, 4.63.

12-Chloro-3-methoxy-6*H*-chromeno[3,4-*b*]quinoline (1c)

Pale-yellow prisms; yield: 58%; mp 102–104 °C (MeOH).

IR: 2931, 1620, 1479 cm^{-1}.

^1H NMR: δ = 3.87 (s, 3 H, OCH_3), 5.23 (s, 2 H, CH_2), 6.69 (d, *J* = 2.7 Hz, 1 H, H4), 6.76 (dd, *J* = 9.0, 2.7 Hz, 1 H, H2), 7.70 (m, 2 H, H9, H10), 8.02 (ddd, *J* = 8.4, 1.8, 0.9 Hz, 1 H, H11), 8.35 (ddd, *J* = 8.6, 1.6, 0.8 Hz, 1 H, H8), 8.53 (d, *J* = 8.8 Hz, 1 H, H1).

^{13}C NMR: δ = 55.5, 71.6, 108.9, 119.8, 124.6, 126.9, 127.6, 127.7, 128.2, 129.0, 129.7, 130.0, 135.1, 141.6, 146.9, 158.2, 161.6.

Anal. Calcd for $C_{17}H_{12}ClNO_2$: C, 68.58; H, 4.06; N, 4.70. Found: C, 68.35; H, 3.82; N, 4.46.

12-Chloro-10-methoxy-3-methyl-6*H*-chromeno[3,4-*b*]quinoline (1e)

Off-white prisms; yield: 49%; mp 176–178 °C (EtOH).

IR: 2999, 2925, 1629, 1479 cm^{-1}.

^1H NMR: δ = 2.40 (s, 3 H, CH_3), 3.99 (s, 3 H, OCH_3), 5.18 (s, 2 H, CH_2), 6.99 (m, 2 H, H2, H4), 7.36 (dd, *J* = 9.0, 2.5 Hz, 1 H, H9), 7.59 (d, *J* = 2.9 Hz, 1 H, H11), 7.91 (dd, *J* = 9.0, 0.4 Hz, 1 H, H8), 8.46 (dd, *J* = 8.0, 0.3 Hz, 1 H, H1).

^{13}C NMR: δ = 21.6, 55.6, 72.0, 102.8, 107.1, 113.5, 118.0, 120.5, 120.7, 122.0, 130.7, 132.9 137.7, 138.3, 139.5, 140.5, 156.7, 158.9.

Anal. Calcd for $C_{18}H_{14}ClNO_2$: C, 69.35; H, 4.53; N, 4.49. Found: C, 68.35; H, 3.82; N, 4.46.

12-Chloro-3,10-dimethoxy-6*H*-chromeno[3,4-*b*]quinoline (1f)

Pale-brown needles; yield: 52%; mp 157–159 °C (EtOH).

IR: 3002, 2923, 1620, 1485 cm^{-1}.

^1H NMR: δ = 3.87 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 5.19 (s, 2 H, CH_2), 6.68 (dd, *J* = 2.6, 0.4 Hz, 1 H, H4), 6.75 (dd, *J* = 9.1, 2.9 Hz, 1 H, H2), 7.36 (dd, *J* = 9.1, 2.8 Hz, 1 H, H9), 7.58 (dd, *J* = 2.8, 0.4 Hz, 1 H, H11), 7.91 (d, *J* = 9.2 Hz, 1 H, H8), 8.52 (d, *J* = 8.8, 0.5 Hz, 1 H, H1).

^{13}C NMR: δ = 55.5, 55.7, 72.1, 105.8, 108.1, 113.5, 118.0, 120.5, 120.7, 122.0, 125.6, 130.7, 137.7, 138.7, 139.0, 156.4, 158.6, 159.0.

Anal. Calcd for $C_{18}H_{14}ClNO_3$: C, 65.96; H, 4.31; N, 4.27. Found: C, 65.82; H, 4.71; N, 3.94.

References

(1) Coghlan, M. J.; Kym, P. R.; Elmore, S. W.; Wang, A. X.; Luly, J. R.; Wilcox, D.; Stashko, M.; Lin, C.-W.; Miner, J.; Tyree, C.; Nakane, M.; Jacobson, P.; Lane, B. C. *J. Med. Chem.* **2001**, *44*, 2879.

(2) Vu, A. T.; Campbell, A. N.; Harris, H. A.; Unwalla, A. J.; Manas, E. S.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4053.

(3) Bistochi, G. A.; De Me, G.; Ricci, A.; Croisy, A.; Jacquignon, P. *Heterocycles* **1978**, *9*, 247.

(4) Zhi, L.; Tegley, C. M.; Pio, B.; Edwards, J. P.; Motamedi, M.; Jones, T. K.; Marschke, K. B.; Mais, D. E.; Risek, B.; Shrader, W. T. *J. Med. Chem.* **2003**, *46*, 4104.

(5) Nohara, A.; Ishigura, T.; Kuyoshi, U. *J. Med. Chem.* **1985**, *28*, 559.

(6) Morris, A. L. C.; Jackson, Y. A. *Heterocycles* **2010**, *81*, 371.

(7) (a) Wiegand, S.; Schäfer, H. J. *Tetrahedron* **1995**, *51*, 5341. (b) Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.

(8) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.

(9) Hennessey, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

(10) Nishioka, H.; Nagura, C.; Abe, H.; Takeuchi, Y.; Harayama, T. *Heterocycles* **2006**, *70*, 549.

(11) Furuta, T.; Kitamura, Y.; Hashimoto, A.; Fujii, S.; Yanaka, K.; Kan, T. *Org. Lett.* **2007**, *9*, 183.

(12) Glover, B.; Harvey, K. A.; Liu, B.; Sharp, M. J.; Tymoschenko, M. F. *Org. Lett.* **2003**, *5*, 301.