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Studies of one-pot double couplings on dibromoquinolines

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ABSTRACT

In a series of studies, the regioselectivity of Suzuki couplings of dibromoquinolines has been investigated. In general, it is much harder to achieve high levels of regioselectivity in these systems compared to many of the other dibromoheteroaromatics that have been studied. Useful levels of selectivity could be achieved for both a 5,7-dibromoquinoline as well as 3,4-dibromoquinoline. Double Suzuki couplings could also be achieved on these two compounds.

1. Introduction

Highly substituted quinolines are valuable compounds, particularly in the pharmaceutical area. For example, both mefloquine (an antimalerial)[1] and talnetant (a potenial NK3 receptor antagonist)[2] feature substituted quinoline cores (Fig. 1). Their importance has certainly resulted in the development of a number of methods for the synthesis of substituted quinolines.[3] There are the classic condensation-type approaches, including the Skraup, Doebner–von Miller, Friedlander, and Combes reactions.[4] More recently, though, there has been tremendous growth in the application of cross-coupling chemistry to haloquinolines.[5]

Our interest has been the in the development of conditions for rendering cross-coupling approaches more convergent by employing one-pot, regioselective double couplings on dihaloheteroaromatics.[6,7] Given the importance of substituted quinolines, we were interested in applying this approach to them as well.

There have been several earlier reports of regioselectivity in the cross-couplings of polyhaloquinolines (Scheme 1). 4,7-Dichloroquinoline has been studied by two different groups, with both reporting good selectivity for coupling at the 4 position.[8] In one case, the initial Suzuki coupling at C4 was the followed by a second coupling reaction at C7 to afford product **1** in 69% yield over the two steps.[9]

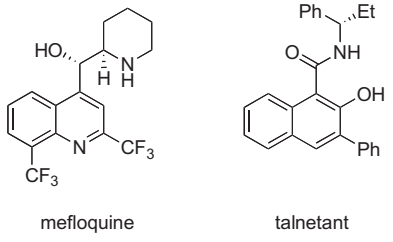
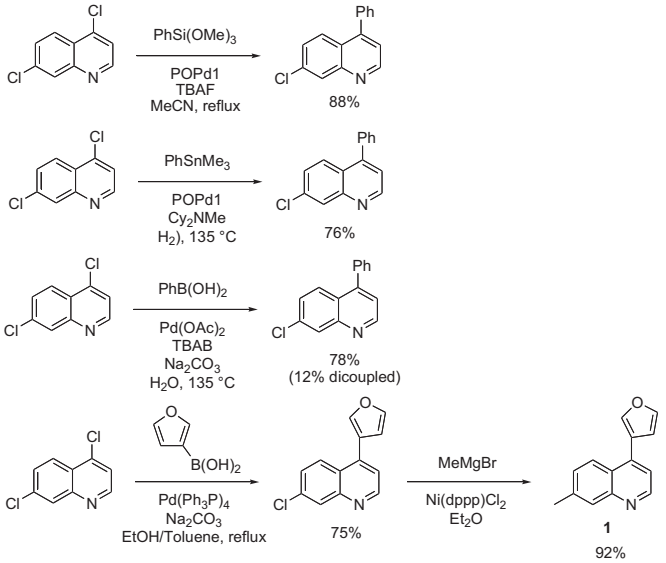


Fig. 1. Some biologically active quinolines.



Scheme 1. 4,6-Dichloroquinoline couplings.

In the two reports on couplings of 8-alkoxy-5,7-dibromoquinolines, the only one that studied regioselectivity reported good selectivity for coupling at the 5 position[10] (Scheme 2). The other reported a symmetrical double coupling of both bromides under standard Suzuki conditions.[11]

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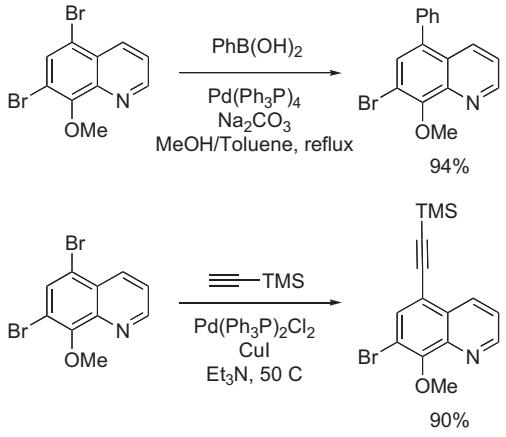
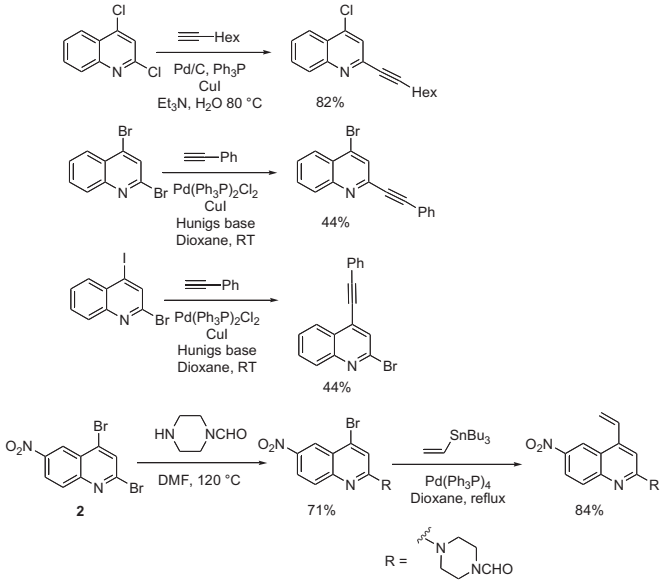


Scheme 2. 8-Alkoxy-5,7-dibromoquinoline couplings.

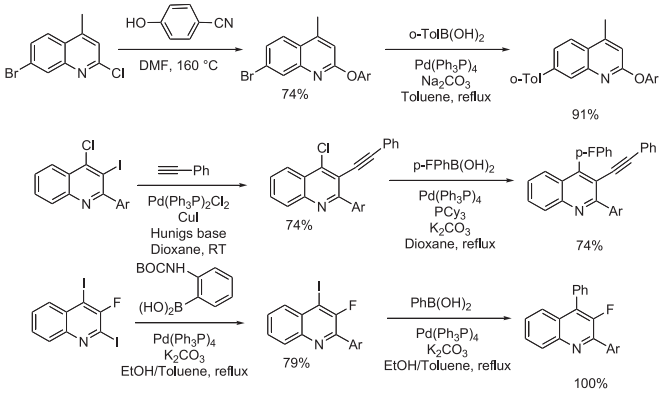
In the case of 2,4-dihaloquinones, there have been several studies (Scheme 3). The earliest had initially been reported to couple at the C4 position.[12] This regioselectivity was later corrected to be a Sonogashira coupling at C2.[13] Similar regioselectivity has also been reported for Stille, Heck, and Suzuki couplings of 2,4-dibromoquinoline.[14] Interestingly, by employing 2-bromo-4-iodoquinoline, the intrinsic regioselectivity of dihaloquinolines can be overcome and Sonogashira coupling of this compound affords the product of coupling at C4 with complete selectivity. Finally, a two-pot double coupling of dibromoquinoline **2** has also been reported. In this case, the first coupling is a simple S_NAr reaction with an amine, which occurs at C2, followed by a Stille coupling at the remaining bromide.[15]



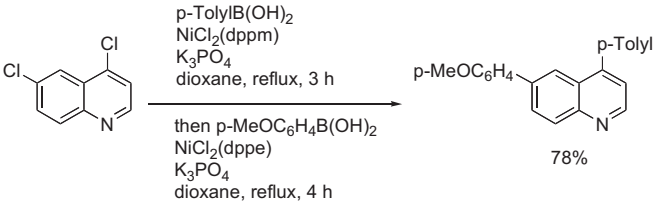
Scheme 3. 2,4-Dihaloquinoline couplings.

Other examples of regioselectivity as well as two-pot double couplings have been reported as well (Scheme 4). For the most part, these reactions feature a standard S_NAr reaction with either an amine or a phenol for the first 'coupling' and then a Suzuki coupling at the remaining halide.[16]

Finally, there have been reports of one-pot double couplings as well (Scheme 5). In a series of papers, Beletskaya has studied 4,6-dihaloquinolines.[17] Very good overall yields could be achieved for double Suzuki couplings as well as double Sonogashira couplings



Scheme 4. Double couplings of polyhaloquinolines.



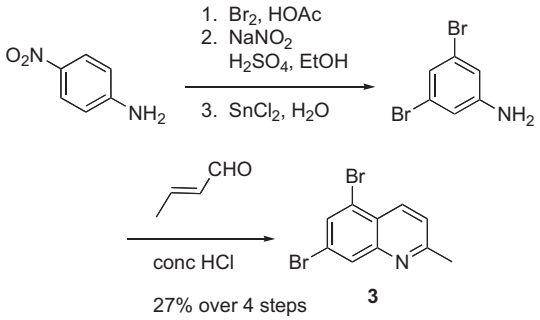
Scheme 5. 4,6-Dihaloquinoline double couplings.

and even mixed Suzuki/Sonogashira couplings and Suzuki/Buchwald–Hartwig aminations. Regioselectivity for the dichloride favored reaction at the 4 position, but this regioselectivity could be reversed by use of a more reactive halide (iodide or bromide) at the 6 position.

2. Results and discussion

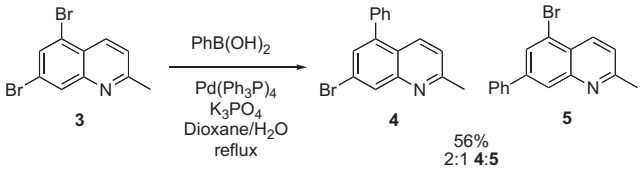
2.1. Studies on 5,7-dibromo-2-methylquinoline

Our studies in this area began with a 5,7-dibromoquinoline **3**. This substrate was selected since regiocontrol is difficult in the synthesis of 5 and/or 7 substituted quinolines when using most condensation approaches. The synthesis of the desired starting material is outlined in Scheme 6 and follows standard literature procedures. Thus, 3,5-dibromoaniline was prepared according to the procedure of Tour and was then condensed with crotonaldehyde in a conventional Dobner–von Miller synthesis to afford **3**.[18]



Scheme 6. Synthesis of 5,7-dibromoquinoline **3**.

Initial attempts at regioselectively coupling this material were not entirely satisfactory as a mixture of both isomers **4** and **5** was obtained (Scheme 7). Fortunately, **4** was the major isomer (2:1 ratio) and could be isolated by means of preparative TLC. Its identity

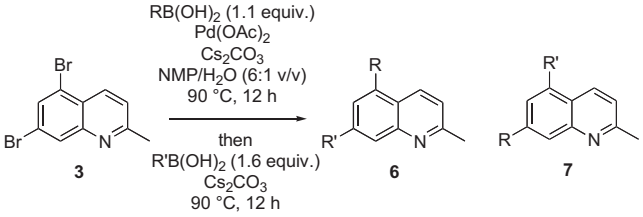


Scheme 7. Dibromoquinoline **3** regioselectivity.

was confirmed by dehalogenation of the remaining bromine atom under standard hydrogenation conditions. The resulting product exhibited the expected pattern of four doublets and one triplet in the aromatic region as opposed to the pattern of four doublets and one very narrow doublet for the regioisomer with coupling at C7. As a result, the ^{1}H NMR was consistent with coupling at the C5 bromine, rendering our results consistent with those reported by Trecourt.[10]

Several other sets of reaction conditions were explored, including variations in catalyst, base, and solvent, none of which significantly altered the isomeric ratio, but it was eventually noted that the conditions in Table 1 afforded the cleanest reaction mixture (as analyzed by TLC) and could successfully afford the dicoupled products as separable mixtures of isomers.

Table 1
Dibromoquinoline **3** double couplings



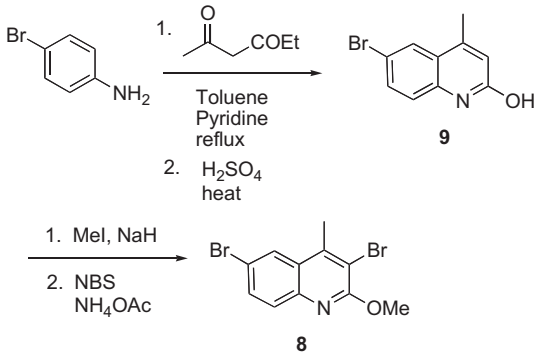
Entry	R	R′	Yield **6**	Yield **7**
1	*p*-MeOC$_6$H$_4$	Ph	37	17
2	Ph	*p*-MeOC$_6$H$_4$	53	18
3	*p*-FC$_6$H$_4$	Ph	96	0
4	Ph	*p*-FC$_6$H$_4$	43.6	25.5
5	*p*-MeOC$_6$H$_4$	*trans*-Heptenyl	30	23
6	*trans*-Heptenyl	*p*-MeOC$_6$H$_4$	35	17
7	Ph	3,4-diMeOC$_6$H$_3$	52	46
8	3,4-diMeOC$_6$H$_3$	Ph	51	47
9	3,4,5-triMeOC$_6$H$_2$	3,4-diMeOC$_6$H$_3$	55	28

Curiously, there was one set of coupling partners that did not afford a regioisomeric mixture—the coupling with *p*-fluorophenylboronic acid, followed by phenylboronic acid (Table 1, entry 3). The reason for this different behavior is not clear, but it was reproducible. All other coupling partners afforded roughly 2:1 regioisomeric mixtures in generally good yield. The regioisomers could be separated by careful column chromatography to afford pure products.

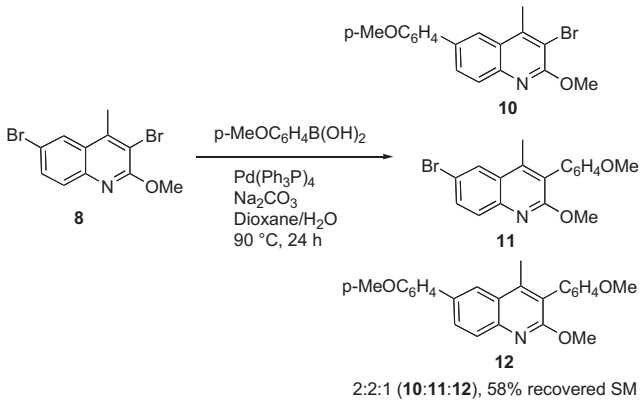
2.2. Studies on 3,6-dibromo-4-methyl-2-methoxyquinoline

Another quinoline that was explored was dibromoquinoline **8**. This compound was synthesized in fairly standard fashion using a Limpach–Knorr approach starting with *p*-bromoaniline (Scheme 8). Condensation with ethyl acetoacetate, followed by acid catalyzed cyclization afforded bromoquinoline **9**.[19] For ease of handling, the hydroxy group was methylated and was then brominated at C3 using NBS. Dibromoquinoline was thus formed in 31% yield over the four steps.

With the required dibromide in hand, regioselective couplings were undertaken. Using some standard conditions from earlier work on thiophenes, the test reaction in Scheme 9 was undertaken.



Scheme 8. Synthesis of dibromoquinoline **8**.



Scheme 9. Dibromoquinoline **8** regioselectivity.

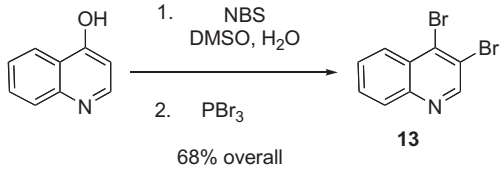
Unfortunately a highly complex and poorly separable mixture was produced, containing three products as well as considerable recovered starting material. Regioselectivity was effectively nonexistent, with both the products of coupling at C3 and C6 being formed in nearly equal amounts. The third product was eventually determined to be the product of dicoupling. Some attempts at optimization did lead to conditions that afforded better selectivity for coupling at C6 over C3, but larger amounts of dicoupling were formed and significant amounts of starting material still remained.

It was suspected that the introduction of a larger ether group at C2 might improve the selectivity of the coupling for steric reasons. Unfortunately, these larger ethers (such as isopropyl or benzyl) were resistant to bromination at C3. Further efforts in this series were discontinued at this point.

The identity of the coupling products was determined by careful separation of the three products. NMR spectroscopy clearly identified **10** and **11** as regioisomers, while **12** contained two sets of distinctive doublets for the *para* substituted aromatic substituents. The regioselectivity of compound **11** was assigned on the basis of an NOE experiment that clearly showed an interaction between the protons on the aryl substituent *ortho* to the biaryl linkage and the protons on the C4 methyl group on the quinoline. This same interaction was not present in regioisomer **10**.

2.3. Studies on 3,4-dibromoquinoline

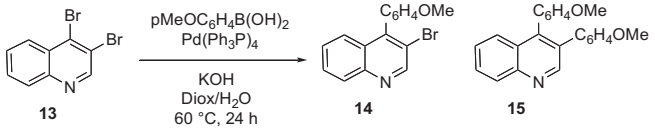
Another dibromoquinoline that was studied was 3,4-dibromoquinoline **13**. This compound was readily prepared in two steps (68% yield overall) from 4-hydroxyquinoline via bromination with NBS, followed by conversion of the hydroxyl into a bromide using PBr_3[20] (Scheme 10).



Scheme 10. Synthesis of 3,4-dibromoquinoline.

In general, excellent regioselectivity for coupling at C4 was obtained, regardless of reaction conditions (catalyst, base, and solvent). The most significant problem was discriminating between mono- and dicoupling. Considerable optimization of the catalyst, base, and solvent, eventually led to the combination of tetrakis(triphenylphosphine) palladium(0) with potassium hydroxide in a 6:1 (v/v) mixture of dioxane and water as the best option. Using these conditions, roughly 35% of the starting material remained, but dicoupling was kept to a minimum (Table 2, entry 1). The use of a greater excess of boronic acid did result in greater consumption of starting material, but only at the cost of the formation of greater amounts of dicoupled product **15**.

Table 2
Dibromoquinoline **13** monocouplings



Entry	Equivalents of boronic acid	Product ratio (**13**/**14**/**15**)[a]
1	1.2	35:52:3
2	1.4	17:63:14
3	1.6	15:70:10
4	1.8	12:55:32
5[b]	1.6	15:61:23
6[b]	1.8	10:61:23

[a] Ratio determined by ^{1}H NMR.
[b] Reaction at 90 °C.

The regioselectivity of this initial coupling was determined by means of extensive 2D NMR techniques. After assigning each proton and carbon signal in the NMR spectrum of **14**, HMBC was employed to determine connectivity between the aryl substituent and the quinoline ring. In particular, the observation of cross peaks in the HMBC spectrum of **14** between H2 and C3, H2 and C4, and H2′ and C4 were sufficient to rule out the product of coupling at C3 (Fig. 2). As it turns out this regioselectivity is also in agreement with that predicted using the ^{1}H NMR guidelines reported earlier by this group.[21] Thus, the chemical shift values for the 3 and 4 positions of quinoline are 7.26 and 8.00, respectively, thereby indicating that C4 should be the more reactive site for cross-couplings. It is also in agreement with the regioselectivity predicted by the bond dissociation energy calculations reported by Houk and co-workers for the corresponding chloroquinolines (96.2 kcal/mol for C4 and 97.5 kcal/mol for C3).[22]

Given the imperfect control over mono versus dicoupling, attempts to perform dicouplings on quinoline **13** were expected to afford highly complex mixtures of products. In an effort to simplify these mixtures, the initial coupling was conducted using an excess (1.6 equiv) of the boronic acid. This excess was expected to reduce the amount of starting material remaining and thereby simplify the product mixture after the second coupling to be largely one of dicoupling with the first boronic acid and regioselective mixed coupling with the two boronic acids. In practice, these mixtures could be separated with minimal difficulty using radial chromatography (Chromatotron) to afford good yields of the dicoupled products (Table 3).

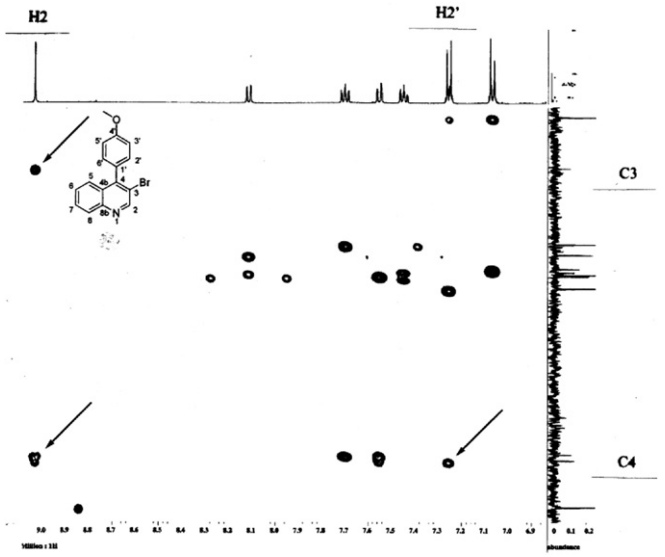
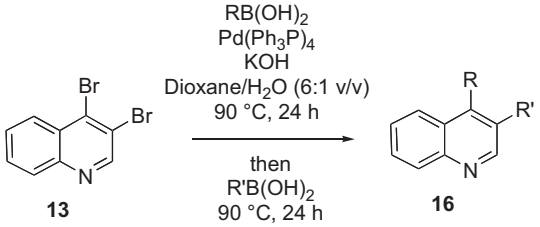


Fig. 2. Determination of regioselectivity on **14**.

Table 3
Dibromoquinoline **13** double couplings



Entry	R	R′	% Yield[a]
1	*p*-$MeOC_6H_4$	Ph	70
2	*p*-$MeOC_6H_4$	*m*-$NO_2C_6H_4$	68
3	*p*-$MeOC_6H_4$	2-Thiophenyl	68
4	*p*-$MeOC_6H_4$	*trans*-Heptenyl	0[b]
5	*m*-$NO_2C_6H_4$	*p*-$MeOC_6H_4$	52
6	2-Thiophenyl	*p*-$MeOC_6H_4$	33
7	*trans*-Heptenyl	*p*-$MeOC_6H_4$	68

[a] Isolated yields.
[b] Yield (72%) of the product of double coupling of dibromoquinoline **13** with the first boronic acid was the only product isolated.

Interestingly, numerous attempts to obtain the mixed coupling product with *p*-methoxyphenylboronic acid and *trans*-heptenylboronic acid failed completely and only afforded the dicoupling product with *p*-methoxyphenylboronic acid (Table 3, entry 4). The problem is clearly not the *p*-methoxyphenylboronic acid, as other couplings employing it proceeded normally. Similarly, the reversed order of addition worked well to afford the mixed product in good yield (Table 3, entry 7).

3. Conclusions

Given the importance of substituted quinolines, the ability to regioselectively coupling dihaloquinolines is of clear utility. The present research, in combination with prior studies clearly demonstrates that regioselectivity is often achievable. As 5,7-dibromoquinoline **3** shows, though, regioselectivity is not always complete. Further, both 3,6-dibromoquinoline **8** and 3,4-dibromoquinoline **13**

demonstrate that selectivity between mono- and dicoupling can be a more formidable challenge. Rather interestingly, using the ^{1}H NMR chemical shift method, the comparatively poor regioselectivity in the coupling of **3** relative to **13** can be appreciated as the chemical shift difference between C5 and C7 is only 0.07 ppm, compared to one of 0.74 ppm for C3 and C4.[23] Using Houk's model (for the corresponding chloroquinolines), a more significant difference of 1.3 kcal/mol for the bond dissociation energies at C3 and C4 versus only 0.6 kcal/mol for C5 versus C6 can be noted.[22] As a result, both models support the observed results.

With respect to halting the reaction at one coupling, although it might seem that a reduction in reaction temperature would be sufficient to enable control, that has not been the case in the present work and the reason for the difference in behavior of quinoline **3** and **13** is not yet clear. Hopefully, the present results will encourage the study of further dihaloquinoline isomers and lead to the establishment of reliable reaction conditions for the regioselective functionalization of these compounds as well.

4. Experimental

4.1. General

Melting points were measured on a Mel-Temp Capillary melting-point apparatus and are uncorrected. ^{1}H NMR spectra were recorded using a JEOL 500 MHz spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS. ^{13}C NMR spectra were recorded using a JEOL 500 MHz spectrometer, reported in δ (ppm) and referenced to the $CHCl_3$ signal. Infrared spectra were measure by a Varian 7000 FT-IR spectrometer with an SPECAC golden-gate ATR.

4.2. General conditions for the double coupling of quinoline

To a solution of 50.0 mg (0.167 mmol) of dibromoquinoline **3** in 2 mL of a 6:1 v/v mixture of NMP and water was added 1.9 mg (0.0084 mmol) of palladium acetate, 22.8 mg (0.187 mmol) of phenylboronic acid, and 108.3 mg (0.332 mmol) of cesium carbonate. The mixture was degassed by bubbling through argon for 5 min, then sealed and heated to 90 °C for 20 h. At this point, the reaction was cooled and 38.2 mg (0.273 mmol) of *p*-methoxyphenylboronic acid and 119.2 mg (0.366 mmol) of cesium carbonate were added. The reaction was once again heated to 90 °C for 24 h. The reaction was then cooled and partitioned between water and ether (20 mL of each). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to afford a crude mixture of products. These were separated on silica gel using flash column chromatography (20% ethyl acetate/hexanes as eluent) to afford 52.4 mg (53%) of 6-(4′-methoxyphenyl)-2-methyl-8-phenylquinoline and 18.1 mg (18%) of 8-(4′-methoxyphenyl)-2-methyl-6-phenylquinoline, both as light yellow oils.

4.2.1. 6-(4′-Methoxyphenyl)-2-methyl-8-phenylquinoline. Elution from silica using 25% ethyl acetate in hexanes afforded the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 2.77 (s, 3H), 3.91 (s, 3H), 7.06 (d, *J*=9 Hz, 2H), 7.23 (d, *J*=9 Hz, 2H), 7.53–7.37 (m, 6H), 7.71 (d, *J*=3 Hz, 1H), 7.79 (d, *J*=9 Hz, 1H), 8.15 (d, *J*=9 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 25.2, 55.8, 113.3, 114.8, 120.4, 122.0, 123.7, 127.6, 127.7, 127.9, 128.9, 129.3, 136.4, 135.6, 137.0, 143.6, 147.7, 158.8, 159.5; IR: 3110, 3070, 1650, 1540, 1420, 1410, 1380, 1160, 1120, 1080, 960, 810, 790 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{19}NO$: 325.1467; observed: 325.1466.

4.2.2. 8-(4′-Methoxyphenyl)-2-methyl-6-phenylquinoline. Elution from silica using 25% ethyl acetate in hexanes afforded the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 2.76 (s, 3H), 3.87 (s, 3H), 7.03 (d, *J*=8 Hz, 2H), 7.21 (d, *J*=8 Hz, 2H), 7.54–7.45 (m, 5H), 7.71 (d, *J*=3 Hz, 1H), 7.74 (d, *J*=9 Hz, 1H), 8.10 (d, *J*=9 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 25.3, 55.6, 113.1, 114.7, 120.4, 122.1, 123.5, 127.6, 127.8, 127.9, 128.9, 129.2, 136.3, 135.5, 137.0, 143.6, 147.6, 158.6, 159.4; IR: 3100, 3080, 1630, 1550, 1430, 1420, 1370, 1140, 1110, 1080, 960, 820, 780 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{19}NO$: 325.1467; observed: 325.1465.

4.2.3. 6-(4′-Fluorophenyl)-2-methyl-8-phenylquinoline. Elution from silica using 20% ethyl acetate in hexanes afforded the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 2.79 (s, 3H), 6.98 (s, 1H), 7.28–7.16 (m, 4H), 7.54–7.42 (m, 4H), 7.64 (d, *J*=3 Hz, 1H), 7.81–7.68 (m, 3H), 8.06 (d, *J*=9 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 25.2, 111.3, 120.4, 122.0, 123.7, 127.7, 127.9, 129.3, 116.0 (d, $J^{C,F}$=3 Hz), 129.5 (d, $J^{C,F}$=9 Hz), 132.0 (d, $J^{C,F}$=21 Hz), 136.4, 137.0, 143.6, 147.7, 158.8, 161.8 (d, $J^{C,F}$=240 Hz); IR: 3120, 3080, 1640, 1550, 1420, 1380, 1140, 1120, 1080, 940, 820, 770 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{16}FN$: 313.1267; observed: 313.1268.

4.2.4. 8-(4′-Fluorophenyl)-2-methyl-6-phenylquinoline. Elution from silica using 20% ethyl acetate in hexanes afforded the title compound as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 2.77 (s, 3H), 6.97 (s, 1H), 6.90 (t, *J*=7 Hz, 2H), 7.25 (d, *J*=7 Hz, 2H), 7.41 (d, *J*=9 Hz, 1H), 7.54–7.46 (m, 4H), 7.76 (dt, *J*=2, 7 Hz, 2H), 8.14 (d, *J*=9 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 25.2, 111.1, 116.0 (d, $J^{C,F}$=3 Hz), 120.3, 122.1, 123.7, 127.6, 127.9, 129.1, 129.2 (d, $J^{C,F}$=9 Hz), 132.0, 132.1 (d, $J^{C,F}$=22 Hz), 136.3, 137.1, 143.4, 147.8, 158.6, 161.4 (d, $J^{C,F}$=230 Hz); IR: 3110, 3070, 1630, 1540, 1430, 1410, 1380, 1150, 1120, 1080, 960, 810, 780 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{16}FN$: 313.1267; observed: 313.1266.

4.2.5. 6-(trans-Heptenyl)-8-(4′-methoxyphenyl)-2-methylquinoline. Elution from silica using 25% ethyl acetate in hexanes afforded the title compound as a light brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) 1.04 (t, *J*=7 Hz, 3H), 2.01 (quintet, *J*=7 Hz, 2H), 2.25 (quintet, *J*=7 Hz, 2H), 2.36 (t, *J*=7 Hz, 2H), 2.71 (s, 3H), 3.37 (t, *J*=7 Hz, 2H), 3.88 (s, 3H), 6.45 (dt, *J*=7, 15 Hz, 1H), 6.57 (d, *J*=15 Hz, 1H), 7.02 (d, *J*=8 Hz, 2H), 7.14 (d, *J*=9 Hz, 1H), 7.37 (d, *J*=8 Hz, 2H), 7.48 (d, *J*=3 Hz, 1H), 7.86 (s, 1H), 8.03 (d, *J*=9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 14.1, 22.8, 25.2, 29.6, 31.9, 33.3, 120.9, 121.3, 121.8, 125.7, 125.8, 127.7, 127.9, 129.0, 129.3, 135.2, 136.6, 138.4, 147.0, 159.0; IR: 3110, 3060, 1640, 1550, 1410, 1380, 1150, 1110, 1080, 950, 810, 790 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{27}NO$: 345.2093; observed: 345.2091.

4.2.6. 6-(trans-Heptenyl)-8-(4′-methoxyphenyl)-2-methylquinoline. Elution from silica using 25% ethyl acetate in hexanes afforded the title compound as a light brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) 1.04 (t, *J*=7 Hz, 3H), 2.01 (quintet, *J*=7 Hz, 2H), 2.25 (quintet, *J*=7 Hz, 2H), 2.36 (t, *J*=7 Hz, 2H), 3.87 (s, 3H), 6.39–6.28 (m, 2H), 7.02 (d, *J*=8 Hz, 2H), 7.27 (d, *J*=9 Hz, 1H), 7.69 (d, *J*=3 Hz, 1H), 7.75 (d, *J*=8 Hz, 2H), 8.09 (s, 1H), 8.32 (d, *J*=9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 14.0, 22.9, 25.2, 29.4, 31.9, 33.1, 120.8, 121.1, 121.6, 125.5, 125.8, 127.7, 129.6, 129.7, 135.1, 136.6, 138.1, 147.2, 159.1; IR: 3110, 3060, 1650, 1540, 1420, 1410, 1370, 1140, 1110, 1080, 960, 820, 780 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{27}NO$: 345.2093; observed: 345.2095.

4.2.7. 6-(2′,3′-Dimethoxyphenyl)-2-methyl-8-phenylquinoline. Elution from silica using 25% ethyl acetate in hexanes afforded the title compound as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) 2.76 (s, 3H), 3.95 (s, 3H), 3.98 (s, 3H), 6.99 (d, *J*=8 Hz, 1H), 7.21 (d, *J*=8 Hz, 1H), 7.34 (s, 1H), 7.53–7.46 (m, 6H), 7.71 (d, *J*=3 Hz, 1H), 8.09 (d, *J*=9 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR (125 MHz, $CDC1_3$) 25.2, 56.0, 56.1, 111.3, 112.2, 115.8, 120.4, 121.2, 123.7, 127.7, 127.9, 129.3, 129.7, 136.4, 137.0, 135.6, 143.6, 147.7, 148.7, 150.2, 150.3, 158.8; IR: 3100, 3080, 1640, 1540, 1430, 1420, 1380, 1150, 1120, 1080,

940, 810, 780 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{21}NO_2$: 355.1572; observed: 355.1570.

4.2.8. 8-(2′,3′-Dimethoxyphenyl)-2-methyl-6-phenylquinoline. Elution from silica using 25% ethyl acetate in hexanes afforded the title compound as a clear oil. ^1H NMR (500 MHz, $CDCl_3$) 2.78 (s, 3H), 3.91 (s, 3H), 3.98 (s, 3H), 7.06–7.00 (m, 2H), 7.42 (d, *J*=8 Hz, 1H), 7.50 (t, *J*=7 Hz, 2H), 7.74 (, *J*=3 Hz, 1H), 7.80 (d, *J*=3 Hz, 1H), 7.78 (s, 1h), 8.18 (d, *J*=9 Hz, 1H), 8.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 25.3, 56.1, 56.4, 111.3, 123.1, 115.6, 120.4, 121.1, 123.5, 127.7, 127.8, 129.2, 129.5, 135.4, 136.3, 127.0, 143.6, 147.8, 148.8, 150.1, 150.2, 158.6; IR: 3100, 3060, 1650, 1550, 1430, 1380, 1140, 1110, 1080, 950, 820, 790 cm^{-1}. HRMS (EI) calcd for $C_{24}H_{21}NO_2$: 355.1572; observed: 355.1575.

4.2.9. 2-Methyl-6-phenyl-8-(2′,3′,4′-trimethoxyphenyl)quinoline. Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) 2.75 (s, 3H), 3.89 (s, 6H), 3.91 (s, 3H), 3.93 (s, 3H), 3.95 (s, 3H), 6.70 (s, 2H), 6.97 (d, *J*=9 Hz, 1H), 7.02 (s, 1H), 7.25 (dd, *J*=9, 2 Hz, 1H), 7.34 (s, 1H), 7.72 (d, *J*=2 Hz, 1H), 8.15 (d, *J*=9 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 25.2, 56.0, 56.1, 56.2, 56.4, 104.9, 111.3, 112.6, 115.8, 120.4, 121.2, 122.0, 123.7, 130.7, 139.7, 135.6, 137.0, 138.1, 143.6, 147.7, 148.7, 150.3, 151.3, 158.8; IR: 3110, 3080, 1640, 1550, 1430, 1410, 1380, 1140, 1120, 1080, 960, 810, 790 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{27}NO_5$: 345.2064; observed: 345.2064.

4.2.10. 2-Methyl-8-phenyl-6-(2′,3′,4′-trimethoxyphenyl)quinoline. Elution from silica using 30% ethyl acetate in hexanes afforded the title compound as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$) 2.77 (s, 3H), 3.88 (s, 6H), 3.92 (s, 3H), 3.94 (s, 3H), 3.95 (s, 3H), 6.72 (s, 2H), 6.99 (d, *J*=9 Hz, 1H), 7.00 (s, 1H), 7.26 (dd, *J*=9, 2 Hz, 1H), 7.33 (s, 1H), 7.71 (d, *J*=2 Hz, 1H), 8.14 (d, *J*=9 Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCL_3$) 26.2, 56.3, 56.4, 56.6, 56.7, 103.9, 112.4, 112.7, 115.6, 120.3, 121.2, 122.1, 122.7, 130.6, 139.3, 135.7, 137.0, 137.8, 143.4, 147.6, 148.9, 150.0, 151.2, 158.6; IR: 3120, 3080, 1650, 1550, 1430, 1410, 1370, 1160, 1110, 1080, 940, 810, 780 cm^{-1}. HRMS (EI) calcd for $C_{27}H_{27}NO_5$: 345.2064; observed: 345.2062.

4.2.11. 4′-Bromoacetoacetanilide. Ethyl acetoacetate (1.7 g, 13 mmol) was added to a mixture of *p*-bromoaniline (2 g, 11.6 mmol), 25 mL of xylenes, and 0.1 mL of pyridine. This solution was heated to reflux for 3 h, after which 20 mL of xylenes was removed via rotary evaporation. Hexanes (25 mL) was added, and the mixture was chilled to 0 °C for 24 h. Filtration afforded 2.7 (92%) of the crude product as a purple solid.[19]

4.2.12. 6-Bromo-4-methyl-2-quinolone. A solution of 4′-bromoacetoacetanilide (2.8 g, 11 mmol) and 13 mL sulfuric acid was heated to 120 °C for 90 min, after which it was poured onto ice. Filtration afforded 1.8 g (70%) of the crude product as a white powder.[19]

4.2.13. 6-Bromo-4-methyl-2-methoxyquinoline. Sodium hydride (132 mg, 5.5 mmol) was added to a solution of 6-bromo-4-methyl-2-quinoline (1.18 g, 5 mmol) in 2.5 mL dimethyl formamide and allowed to react for 10 min. Iodomethane (705 mg, 5 mmol) was then added to the solution and allowed to react for 1 h, after which the reaction was monitored via TLC. Upon completion, the reaction was quenched with water and the product extracted with ethyl acetate. Concentration via rotary evaporation yielded the crude product, which was purified using silica gel flash chromatography (hexanes/ethyl acetate 10:1) to afford 0.8 g (66%) of the product as a yellow solid that was used directly in the next reaction.

4.2.14. 3,6-Dibromo-4-methyl-2-methoxyquinoline. N-Bromosuccinimide (222 mg, 1.25 mmol) was added to a solution of 6-bromo-4-methyl-2-methoxyquinoline (309 mg, 1.25 mmol) and 14 mg ammonium acetate in 20 mL acetonitrile. The reaction was allowed to proceed for 24 h, after which the acetonitrile was removed via rotary evaporation and the crude product was purified using silica gel flash chromatography (hexanes/ethyl acetate 10:1) to afford 295 mg (72%) of the product as a white solid. Mp: 170–172 °C; ^1H NMR (500 MHz, $CDCl_3$) 2.67 (s, 3H), 3.79 (s, 3H), 7.27 (d, *J*=9.1 Hz, 1H), 7.77 (d, *J*=9.1 Hz, 1H), 7.89 (s, 1H); ^{13}C NMR (125 MHz, $CDCL_3$) 19.3, 30.4, 115.0, 115.5, 120.7, 121.5, 127.5, 132.5, 136.5, 143.8, 157.1; IR: 3120, 3060, 1650, 1550, 1430, 1410, 1370, 1160, 1110, 1080, 960, 820, 790 cm^{-1}. HRMS (EI) calcd for $C_{11}H_9NOBr_2$: 328.9051; observed: 328.9054.

4.2.15. 3-Bromo-4-hydroxyquinoline. N-Bromosuccinimide (135 mg, 0.76 mmol) was added to a solution of 4-hydroxyquinoline (100 mg, 0.69 mmol) in 5 mL dimethylsulfoxide and 0.5 mL water. The reaction was allowed to continue for 24 h after which the DMSO was removed via rotary evaporation to afford 150 mg (97%) of the product as a yellow solid. Product was used without further purification.[20]

4.2.16. 3,4-Dibromoquinoline. Phosphorus tribromide (80.7 mg, 0.3 mmol) was added drop-wise to a solution of 3-bromo-4-hydroxyquinoline (67 mg, 0.3 mmol) in 2 mL dimethyl formamide. The reaction was allowed to proceed for 24 h, after which the mixture was poured onto ice. Filtration afforded 51 mg (60%) of the product as a white solid. Mp: 75–80 °C; ^1H NMR (500 MHz, $CDCl_3$) 7.67 (t, *J*=8.0 Hz, 1H), 7.78 (t, *J*=8.0 Hz, 1H), 8.09 (d, *J*=8.0 Hz, IH), 8.24 (d, *J*=8.0 Hz, 1H), 8.89 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 121.2, 127.4, 128.9, 129.1, 129.8, 130.3, 135.3, 146.6, 151.3; IR: 3060, 2920, 1560, 1480, 1330, 1100, 750 cm^{-1}. HRMS (EI) calcd for $C_9H_5NBr_2$: 284.8789; observed: 284.8791.

4.2.17. 3-Bromo-2-methoxy-6-(4′-methoxyphenyl)-4-methylquinoline. To a solution of 55.6 mg (0.168 mmol) of **8** in 2 mL of a 6:1 (v/v) mixture of dioxanes/water was added 9.7 mg (0.0084 mmol) of tetrakis(triphenylphosphine) palladium(0), 28.3 mg (0.202 mmol) of *para*-methoxyphenylboronic acid, and 18.8 mg (0.336 mmol) of potassium hydroxide. The solution was degassed by bubbling argon through it for 5 min and then heated to 90 °C for 24 h. The cooled reaction was then quenched with water (20 mL) and extracted with ethyl acetate (3×10 mL). Concentration in vacuo afforded a crude product that was purified using rotary chromatography (10% ethyl acetate in hexanes as eluent) to afford the title product as a white solid. Mp: 155–182 °C; ^1H NMR (500 MHz, $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) 20.07, 31.01, 55.48, 114.54, 115.06, 120.46, 121.15, 123.45, 128.20, 129.44, 132.48, 135.48, 137.30, 145.63, 158.02, 159.07. HRMS (EI) calcd for $C_{18}H_{16}NO_2Br$: 357.0364; observed: 357.0364.

4.2.18. 3-Bromo-4-(4′-methoxyphenyl)quinoline. To a solution of 48.5 mg (0.168 mmol) of **13** in 2 mL of a 6:1 (v/v) mixture of dioxanes/water was added 9.7 mg (0.0084 mmol) of tetrakis(triphenylphosphine) palladium(0), 28.3 mg (0.202 mmol) of *para*-methoxyphenylboronic acid, and 18.8 mg (0.336 mmol) of potassium hydroxide. The solution was degassed by bubbling argon through it for 5 min and then heated to 90 °C for 24 h. The cooled reaction was then quenched with water (20 mL) and extracted with ethyl acetate (3×10 mL). Concentration in vacuo afforded a crude product that was purified using rotary chromatography (15% ethyl acetate in hexanes as eluent) to afford the title product as a white solid. Mp: 88–105 °C; ^1H NMR (500 MHz, $CDCl_3$) 3.904 (s, 3H), 7.071 (d, *J*=8.6 Hz, 2H), 7.257 (d, *J*=8.59, 2H), 7.450 (t, *J*=7.9 Hz, 1H), 7.555 (d, *J*=7.4 Hz, 1H), 7.702 (t, *J*=7.4), 8.117 (d, *J*=8.6 Hz, 1H), 9.032 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 55.43, 114.04, 119.01, 126.51, 127.53, 128.91, 129.24, 129.49, 129.64, 130.80,

147.00, 147.56, 152.10, 159.85; IR: 3040, 2940, 1720, 1640, 1510, 1490, 1240, 1160, 1020, 810 cm^{-1}. HRMS (EI) calcd for $C_{16}H_{12}NOBr$: 313.0137; observed: 313.0135.

4.2.19. 2-Methoxy-3,6-bis(4′-methoxyphenyl)-4-methylquinoline. To a solution of 50.0 mg (0.167 mmol) of dibromoquinoline **8** in 2 mL of a 6:1 v/v mixture of dioxane and water was added 9.7 mg (0.0084 mmol) of tetrakis(triphenylphosphine) palladium(0), 61.4 mg (0.404 mmol) of *p*-methoxyphenylboronic acid, and 0.5 mL of 2-M aqueous sodium carbonate. The mixture was degassed by bubbling through argon for 5 min, then sealed and heated to 90 °C for 24 h. The reaction was then cooled and partitioned between water and ether (20 mL of each). The organic layer was dried over magnesium sulfate, filtered, and concentrated in vacuo to afford a crude mixture of products. Elution from silica using 20% ethyl acetate in hexanes afforded the title compound as a white solid. Mp: 160–185 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 2.396 (s, 3H), 3.788 (s, 3H), 3.851 (s, 3H), 3.867 (s, 3H), 6.985 (d, *J*=8.6 Hz, 2H), 7.018 (d, *J*=8.6 Hz, 2H), 7.221 (d, *J*=8.6 Hz, 2H), 7.442 (d, *J*=8.6 Hz, 1H), 7.575 (d, *J*=9.2, Hz, 2H), 7.759 (d, *J*=8.6 Hz, 1H), 7.924 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 16.11, 29.02, 54.36, 54.47, 112.75, 113.48, 113.73, 120.99, 122.47, 127.14, 127.73, 128.04, 130.38, 131.44, 131.93, 133.78, 137.03, 141.39, 157.97, 158.30, 160.88; IR: 3040, 3020, 2850, 1640, 1600, 1560, 1500, 1470, 1440, 1280, 1240, 1030, 800 cm^{-1}. HRMS (EI) calcd for $C_{25}H_{23}NO_3$: 385.1678; observed: 385.1675.

4.2.20. 3,4-Bis(4′-methoxyphenyl)quinoline. To a solution of 48.5 mg (0.168 mmol) of **13** in 2 mL of a 6:1 (v/v) mixture of dioxanes/water was added 9.7 mg (0.0084 mmol) of tetrakis(triphenylphosphine) palladium(0), 61.4 mg (0.404 mmol) of *p*-methoxyphenylboronic acid, and 37.6 mg (0.672 mmol) of potassium hydroxide. The solution was degassed by bubbling argon through it for 5 min and then heated to 90 °C for 24 h. After cooling, 0.336 mmol of the second boronic acid was added and the reaction mixture heated once again to 90 °C for 24 h. The cooled reaction was then quenched with water (20 mL) and extracted with ethyl acetate (3×10 mL). Concentration in vacuo afforded a crude product that was purified on silica using 20% ethyl acetate in hexanes as eluent afforded the title compound as a white solid. Mp: 100–111 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.79 (s, 3H), 3.847 (s, 3H), 6.80 (d, *J*=8.59 Hz, 2H), 6.90 (d, *J*=8.59 Hz, 2H), 7.10 (d, *J*=8.59 Hz, 2H), 7.12 (d, *J*=8.6 Hz, 2H), 7.73–7.68 (m, 2H), 8.16 (d, *J*=7.45 Hz, 2H), 8.97 (s, 1H); ^{13}C NMR (125 MHz, CDC_{l3}) 55.21, 56.03, 113.67, 113.74, 126.56, 126.72, 127.66, 128.61, 128.84, 129.52, 130.64, 131.30, 131.77, 132.89, 144.94, 147.48, 152.11, 158.60, 159.04; IR: 3080, 2920, 2840, 1720, 1620, 1590, 1500, 1470, 1280, 1240, 1160, 1050, 820, 760 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{19}NO_3$: 357.1365; observed: 357.1364.

4.3. General procedure for the double couplings of dibromoquinoline 13

To a solution of 48.5 mg (0.168 mmol) of **13** in 2 mL of a 6:1 (v/v) mixture of dioxanes/water was added 9.7 mg (0.0084 mmol) of tetrakis(triphenylphosphine) palladium(0), 0.202 mmol of boronic acid, and 18.8 mg (0.336 mmol) of potassium hydroxide. The solution was degassed by bubbling argon through it for 5 min and then heated to 90 °C for 24 h. After cooling, 0.336 mmol of the second boronic acid was added and the reaction mixture heated once again to 90 °C for 24 h. The cooled reaction was then quenched with water (20 mL) and extracted with ethyl acetate (3×10 mL). Concentration in vacuo afforded a crude product that was purified using rotary chromatography.

4.3.1. 3-(4′-Methoxyphenyl)-4-phenylquinoline. Elution from silica using 15% ethyl acetate in hexanes afforded the title compound as a white solid. Mp: 124–130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.813 (s, 3H), 6.873 (d, *J*=10.02 Hz, 2H), 7.108 (d, *J*=8.59 Hz, 2H), 7.181–7.161 (m, 2H), 7.269–7.201 (m, 3H), 7.468 (t, *J*=8.02 Hz, 1H), 7.701 (t, *J*=7.73 Hz, 1H), 7.743 (d, *J*=8.59 Hz, 1H), 8.171 (d, *J*=8.59 Hz, 1H), 8.982 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 55.23, 113.65, 126.63, 126.77, 126.96, 128.12, 128.36, 129.03, 129.53, 130.18, 131.28, 131.78, 133.27, 138.36, 145.25, 147.65, 151.89, 159.09; IR: 3050, 2920, 2840, 1730, 1610, 1520, 1480, 1380, 1240, 1170, 1040, 760 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{17}NO$: 311.1310; observed: 311.1308.

4.3.2. 3-(4′-Methoxyphenyl)-4-(trans-heptenyl)quinoline. Elution from silica using 15% ethyl acetate in hexanes afforded the title compound as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) 0.904 (t, *J*=6.8, 3H), 1.345–1.242 (m, 4H), 1.435 (quintet, 2H), 2.236 (quartet, 2H), 3.872 (s, 3H), 5.957 (m, 1H), 6.519 (d, *J*=17.7 Hz, 1H), 6.987 (d, *J*=8.6 Hz, 2H), 7.362 (d, *J*=8.6 Hz, 2H), 7.552 (t, *J*=7.45 Hz, 1H), 7.693 (t, *J*=7.45 Hz, 1H), 8.123 (d, *J*=7.45, 1H), 8.238 (d, *J*=7.45, 1H), 8.822 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 14.23, 22.71, 28.79, 31.57, 33.75, 55.49, 113.90, 124.57, 125.86, 126.69, 126.73, 128.92, 129.87, 131.00, 131.64, 132.07, 141.31, 141.85, 147.72, 152.02, 159.16; IR: 3080, 2930, 2860, 1610, 1520, 1290, 1250, 1170, 840 cm^{-1}. HRMS (EI) calcd for $C_{23}H_{25}NO$: 331.1936; observed: 331.1937.

4.3.3. 3-(4′-Methoxyphenyl)-4-(2′-thiophenyl)quinoline. Elution from silica using 15% ethyl acetate in hexanes afforded the title compound as a yellow solid. Mp: 108–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.807 (s, 3H), 6.846 (d, *J*=9.16 Hz, 2H), 7.032 (d, *J*=4.58 Hz, 1H), 7.092 (d, *J*=5.15 Hz, 1H), 7.186 (d, *J*=9.16 Hz, 2H), 7.410 (d, *J*=5.15 Hz, 1H), 7.535 (t, *J*=7.45, 1H), 7.726 (t, *J*=7.45, 1H), 7.936 (d, *J*=8.02, 1H), 8.182 (d, *J*=8.02, 1H), 8.973 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 55.18, 113.66, 114.78, 126.24, 126.92, 127.22, 127.28, 127.88, 128.41, 129.19, 129.28, 129.74, 130.23, 130.84, 134.20, 136.56, 147.06, 151.60, 158.96; IR: 3080, 2950, 2840, 1730, 1620, 1520, 1480, 1240, 1170, 1040, 830, 770 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{15}NOS$: 289.0874; observed: 289.0873.

4.3.4. 4-(4′-Methoxyphenyl)-3-(2′-thiophenyl)quinoline. Elution from silica using 15% ethyl acetate in hexanes afforded the title compound as a yellow solid. Mp: 109–118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.800 (s, 3H), 6.880–6.630 (m, 1H), 6.938–6.904 (m, 3H), 7.107 (d, *J*=8.59 Hz, 2H), 7.164 (d, *J*=5.73 Hz, 1H), 7.366 (t, *J*=8.02 Hz, 1H), 7.516 (d, *J*=8.59 Hz, 1H), 7.600 (t, *J*=7.92 Hz, 1H), 8.065 (d, *J*=8.02 Hz, 1H), 9.088 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 55.27, 114.08, 114.78, 126.46, 126.74, 126.91, 126.98, 127.20, 127.46, 127.91, 128.18, 129.18, 131.42, 139.88, 144.74, 147.01, 150.84, 159.71; IR: 3080, 3040, 2930, 2840, 1610, 1520, 1500, 1280, 1240, 1170, 1030, 830,760, 700 cm^{-1}. HRMS (EI) calcd for $C_{20}H_{15}NOS$: 289.0874; observed: 289.0872.

4.3.5. 3-(4′-Methoxyphenyl)-4-(3′-nitrophenyl)quinoline. Elution from silica using 20% ethyl acetate in hexanes afforded the title compound as a yellow solid. Mp: 120–132 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.779 (s, 3H), 6.797 (d, *J*=9.2 Hz, 2H), 7.060 (d, *J*=9.2 Hz, 2H), 7.577–7.052 (m, 4H), 7.755 (m, 1H), 8.143 (s, 1H), 8.232 (m, 2H), 9.022 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 55.25, 113.97, 122.83, 125.48, 126.51, 127.55, 129.36, 129.44, 129.92, 131.33, 131.68, 133.15, 136.67, 138.47, 142.32, 147.39, 148.13, 151.99, 159.01; IR: 3080, 2980, 2950, 2840, 1610, 1510, 1350, 1240, 1170, 1040, 830, 700 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{16}N_2O_3$: 356.1161; observed: 3556.1160.

4.3.6. 4-(4′-Methoxyphenyl)-3-(3′-nitrophenyl)quinoline. Elution from silica using 20% ethyl acetate in hexanes afforded the title compound as a yellow solid. Mp: 124–131 °C; ^{1}H NMR (500 MHz, $CDCl_3$) 3.834 (s, 3H), 6.907 (d, *J*=8.59 Hz, 2H), 7.114 (d, *J*=8.59 Hz, 2H), 7.549–7.422 (m, 3H), 7.789–7.744 (m, 2H), 8.119–8.081 (m, 2H), 8.212 (d, *J*=8.59, 1H), 8.977 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 55.27, 114.00, 122.00, 124.94, 126.68, 127.23, 127.31, 127.34, 129.09, 129.61, 129.76, 130.91, 131.63,

136.09, 140.17, 146.12, 148.00, 148.06, 150.70, 159.43; IR: 3100, 3040, 2960, 2840, 1620, 1530, 1500, 1350, 1250, 1170, 1030, 850, 770, 730 cm^{-1}. HRMS (EI) calcd for $C_{22}H_{16}N_2O_3$: 356.1161; observed: 356.1159.

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