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Synthesis of aryl-substituted quinolines and tetrahydroquinolines through Suzuki–Miyaura coupling reactions

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Abstract

The synthesis and characterization of substituted (trifluoromethoxy, thiomethyl, and methoxy) phenyl quinolines is described. Dichlorobis(triphenylphosphine)palladium(II)-catalyzed Suzuki–Miyaura cross-coupling of 6-bromo- and 6,8-dibromo-1,2,3,4-tetrahydroquinolines, 5-bromo-8-methoxyquinoline, and 5,7-dibromo-8-methoxyquinoline with substituted phenylboronic acids affords the corresponding 6-aryl- (**13a–d**), 6,8-diaryl- (**14a–c**), 5-aryl- (**15**), and 5,7-diaryl- (**16b**, **c**) tetrahydroquinolines and quinolines in high yields (68%–82%). The structures of all the products are characterized by ^{1}H NMR, ^{13}C NMR,^{19}F NMR, and Fourier transform infrared spectroscopy and by elemental analysis.

Keywords

aryl quinolines, nuclear magnetic resonance spectroscopy, quinolines, substituted phenyls, Suzuki–Miyaura cross-coupling, tetrahydroquinolines

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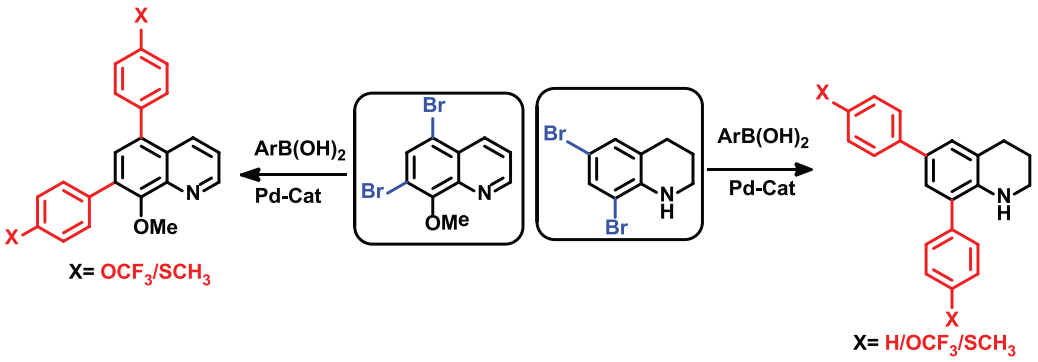

Introduction

Quinoline derivatives are found in many natural products[1] and synthetic drugs.[2] The quinoline scaffold has been used to develop compounds exhibiting a wide range of medicinal benefits,[3,4] such as anti-asthmatic, anti-inflammatory, antimalarial,[4] anticancer,[5] and antibiotic activity.[6]

Tetrahydroquinolines have an important position in synthetic organic chemistry due to the fact they possess high reactivity, a wide spectrum of chemical properties[7] and form the basis of many bioactive natural substances[8–12] and potential drugs.[13,14]

Halogenated tetrahydroquinoline derivatives are important initiators of progress in new methods for the development of medicinal chemistry. In the literature, the halogenation of 1,2,3,4-tetrahydroquinoline (**1**) is accomplished with halogens (bromine, chlorine, etc.), *N*-halosuccinimides, aqueous solutions of sodium chlorate and bromate, affording various halogen-substituted tetrahydroquinolines (Scheme 1) as key compounds and as precursors for numerous bioactive quinoline derivatives.[15]

Arylated quinolines were previously prepared by classic reactions, such as the Skraup, Doebner–Miller, Conrad–Limpach, Friedländer, and Pfitzinger syntheses.[16] Arylated quinolines are also prepared by cross-coupling reactions and other transition-metal-catalyzed transformations.[17–19] For example, arylated quinolines were prepared by

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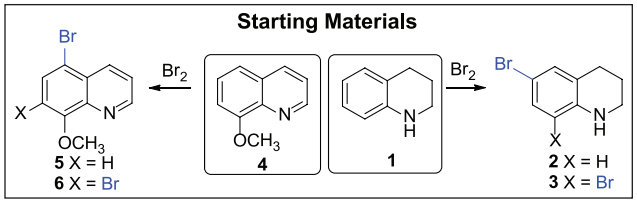
Suzuki–Miyaura coupling of arylboronic acids with haloaromatic compounds.[20] Although numerous studies on the transformation of haloquinolines into aryl quinolines are reported in the literature, there are fewer reports on the preparation of aryl tetrahydroquinolines. For example, Mphahlele et al. were interested in the palladium-catalyzed cross-coupling reactions of dihalogenoquinolines for the preparation of substituted tetrahydroquinolines and decided to investigate the synthesis of 2-aryl-6,8-dibromo-1,2,3,4-tetrahydroquinolines (**8**) (Scheme 2).[21–23] In other work, 5,7-diarylquinolines were prepared by Suzuki–Miyaura coupling of 5,7-dihalogenated quinolines.[24] Moreover, the synthesis of arylated quinolines was reported by Suzuki–Miyaura reactions of 5,7-dibromo-8-(trifluoromethylsulfonyloxy)quinoline (**11**) (Scheme 2).[25]

In the literature, many studies on the pharmacological features of aryl-substituted quinolines have been reported. The 6- or 8-aryl substituted 2,4-dimethoxyquinolines were found to exhibit high activity against the agriculturally important nematode, *Haemonchus contortus*.[26] Furthermore, 2-phenyl-quinoline-4-carboxylic acid derivatives were found to have significant effects on antibacterial activity.[27] In other work on phenyl quinolines, 2-(4-phenylquinolin-2-yl)phenol derivatives produced significant anti-inflammatory, analgesic and antipyretic activities and demonstrated efficient inhibition of the COX-2 enzyme.[28] A number of substituted 2-phenylquinolines displayed superior ERβ affinity in a cell-based transcriptional assay,[29] potent antiplatelet activities,[30] antimitotic activity,[31–33] and antiproliferative activity against the growth of certain cancer cells such as HCT-116 (colon cancer), MCF7 (breast cancer), and MDA-MB-435 (breast cancer) with low GI_{50} values.[34]



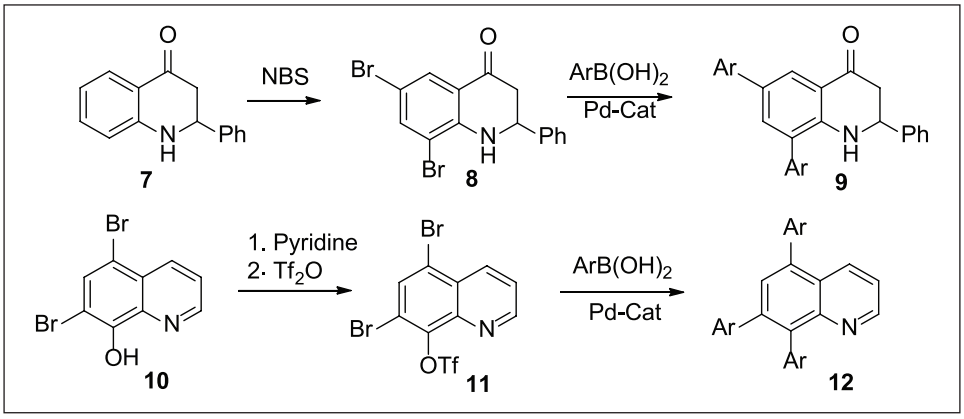
Scheme 1. Preparation of brominated tetrahydroquinolines (**2** and **3**) and quinolines (**5** and **6**).

Previously, we carried out the bromination of 1,2,3,4-tetrahydroquinoline (**1**)[15,35,36] with molecular bromine leading to the formation of polyfunctional quinoline derivatives, which was followed by transformation into their respective derivatives.[35,37–39] As an extension of the investigation of 1,2,3,4-tetrahydroquinoline (**1**) derivatives, we studied the regioselective bromination of methoxy-, cyano-, hydroxy-, and amino-substituted quinolines[38,40,41] with bromine under different conditions. The polyfunctional substituted quinolines were tested for their anticancer potentials and enzyme inhibition activities. It was found that substituted quinolines with different functional groups, especially 6,8-dibromo-1,2,3,4-tetrayhdroquinoline (**3**),[42] 5,7-dibromo-8-methoxyquinoline (**6**),[43] 5,7-dibromo-8-hydroxyquinoline,[43] and 6,8-diphenylquinoline[44] had anticancer activities against HeLa (human cervix carcinoma), HT29 (human colon carcinoma), C6 (rat glioblastoma), and MCF7 (human breast adenocarcinoma) cell lines, and monophenyl-substituted quinolines showed inhibitory effects on AChE (acetylcholinesterase), BChE (butyrylcholinesterase), and carbonic anhydrase isoenzymes I and II (hCA I and II).[20]

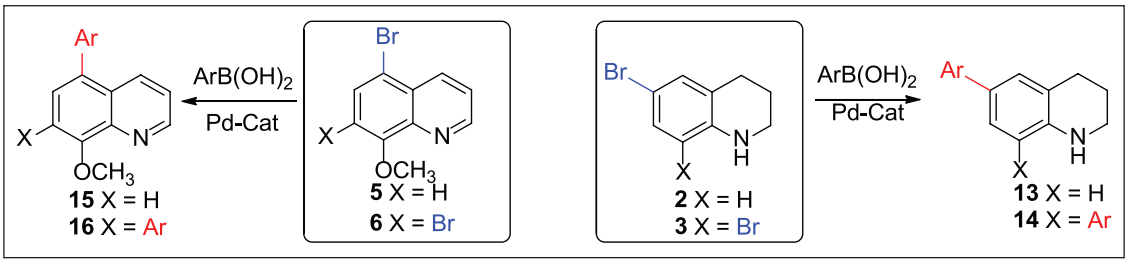
The promising anticancer activities of the analogous 6,8-dibromotetrahydroquinoline (**3**), 6,8-diphenylquinoline, and 5,7-dibromo-8-(hydroxy/methoxy)quinolines encouraged us to synthesize novel and potentially bioactive quinoline compounds. Based on our continued interest in the palladium-catalyzed cross-coupling reactions of bromoquinolines,[44] we herein describe the Suzuki–Miyaura cross-coupling reactions of 6-bromo- and 6,8-dibromo-1,2,3,4-tetrahydroquinolines (**2** and **3**), and 5-bromo- and 5,7-dibromo-8-methoxyquinolines (**5** and **6**) with substituted arylboronic acids to afford aryl-substituted tetrahydroquinoline and quinoline derivatives (Scheme 3).

Results and discussions

Attempted Suzuki–Miyaura cross-coupling of 6-bromo-1,2,3,4-tetrahydroquinoline (**2**) with a mixture of unsubstituted phenyl or 4-substituted (4-methoxy-, 4-trifluoromethoxy-, and 4-thiomethylphenyl) phenylboronic acids (1.0 equiv.) and 2 M K_2CO_3 in dimethylformamide in the presence of tetrakis(triphenylphosphine)

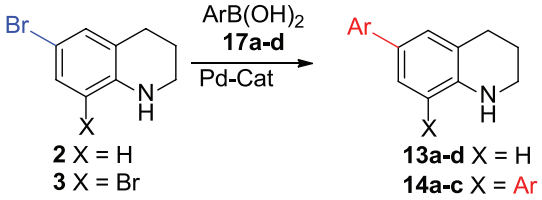


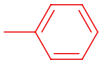
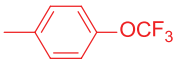
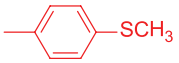
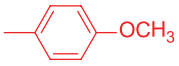
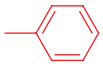
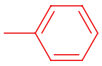
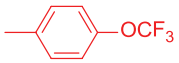
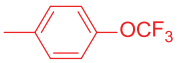
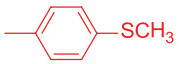
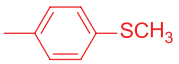
Scheme 2. Reported synthetic strategies toward arylated quinolines and tetrahydroquinolines.[21–23,25]



Scheme 3. Synthetic strategies toward arylated quinolines and tetrahydroquinolines in this study.

Table 1. The yields and melting points of **13a–d** and **14a–c**.



Product	X	Ar	Yield (%)	M.p. (°C)
13a	H		81	
13b	H		73	55–57
13c	H		68	71–73
13d	H		76	82–84
14a			80	100–101
14b			78	
14c			82	73–75

palladium(0) ($Pd(PPh_3)_4$) afforded 6-phenyl-, 6-(4-methylthio)phenyl-, 6-(4-trifluoromethoxy)phenyl-, and 6-(4-methoxy)phenyl-1,2,3,4-tetrahydroquinoline derivatives in high yields (68%–81%). 6-Phenyl-1,2,3,4-tetrahydroquinoline (**13a**)[45] and 6-(4-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroquinoline (**13b**)[46] were recently reported and the published spectral data confirmed the data obtained in this study. Moreover, 6,8-dibromo-1,2,3,4-tetrahydroquinoline (**3**) was treated with the same phenylboronic acids under identical reaction conditions to give 6,8-diphenyl-, 6,8-bis[4-(methylthio)phenyl)-, and 6,8-bis(4-(trifluo-romethoxy)phenyl]-1,2,3,4-tetrahydroquinolines in yields of 80%, 82%, and 78%, respectively (Table 1).

The structures of all substituted phenyl-containing compounds **13a–d** were confirmed by ^1H and ^{13}C NMR, Fourier transform infrared (FTIR), and elemental analysis. The ^1H NMR signals of coupled compounds **13a–d** are similar to starting material **2** except for the aromatic phenyl signals. The aliphatic triplets in the ^1H NMR spectra of compounds **13a–d** (3.39–3.35, ^3J=5.6 Hz and 2.88–2.83, ^3J=6.4 Hz; 3.37–3.33, ^3J=5.4 Hz and 2.86–2.81, ^3J=6.3 Hz; 3.36–3.32, ^3J=5.4 Hz and 2.85–2.81, ^3J=6.3 Hz; 3.35–3.31, ^3J=5.4 Hz and 2.85–2.81, ^3J=6.3 Hz, respectively) and aliphatic multiplet (2.02–1.94 ppm for all compounds **13a–d**) belong to the characteristic H-2, H-4, and H-3 protons in the nitrogen-containing rings of the tetrahydroquinolines (Figure 1). Multiplets for the aryl H signals of the quinoline and phenyl scaffolds of **13a–d** were observed in the range of 6.91–7.56 ppm. The H-7 protons of **13a–d** gave doublet signals at about 6.55 ppm (Figure 1). Moreover, the singlets in the ^1H NMR spectra of **13c** and **13d** at 2.52 and 3.84 ppm, respectively, verified the attachment of the 4-(methylthio)phenyl and 4-(methoxy)phenyl groups at C-6 of the quinoline ring (Figure 1). In the ^{13}C NMR spectra of compounds **13a–d**, three aliphatic carbon resonances (approx. 22.2, 27.1, 42.0 ppm) in the sp^3 region and ten aromatic carbon resonances are also in agreement with the suggested structures. Moreover, the signals at 122.5 (q, $^2J_{C,F}$=260 Hz, OCF_3), 16.5 (SCH_3), and 55.6 (OCH_3) ppm are consistent with proposed structures **13b**, **13c**, and **13d**, respectively. In the ^{19}F NMR spectrum of **13b**, a singlet at −58.2 ppm provided evidence for the 4-(trifluoromethoxy)phenyl at the C-6 position of the quinoline.

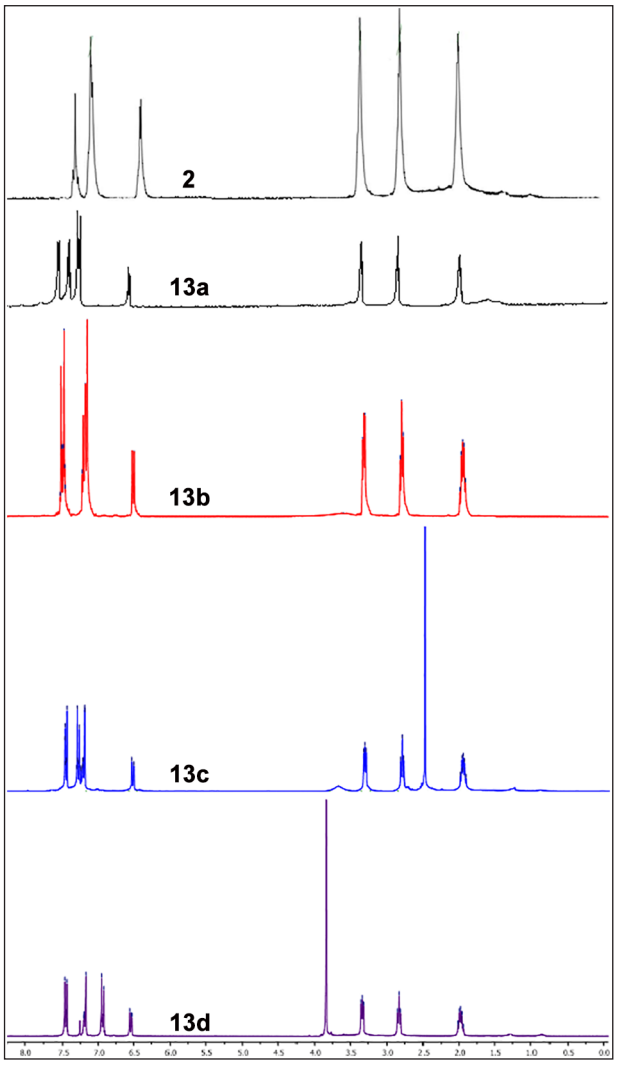


Figure 1. ^{1}H NMR spectra of 6-bromo-1,2,3,4-tetrahydroquinoline (**2**) (top; starting material) and the coupling derivatives **13a–d**.

The ^{1}H NMR spectra of **14a–c** showed the formation of diaryl (diphenyl, bis(4-trifluoromethoxy)phenyl, and bis(4-methylthio)phenyl) tetrahydroquinolines. The aliphatic triplets in the ^{1}H NMR spectra of compound **14a–c** (approx. 3.32 (^{3}J=5.4 Hz) and 2.92 (^{3}J=6.3 Hz) ppm) and aliphatic multiplets (approx. 2.00 ppm) belong to the characteristic H-2, H-4, and H-3 protons in the nitrogen-containing ring of the tetrahydroquinolines. The ^{1}H NMR spectrum of compound **14a** displayed multiplets for the aryl H signals of the quinoline and phenyl scaffolds in the range of 7.26–7.62 ppm while the aryl protons of **14c** gave multiplet signals at higher field (7.15–7.48 ppm) due to the electron-rich feature of the methylthio group. Moreover, the two singlets in the spectrum of **11c** at 2.50 and 2.53 ppm and the appearance of two singlets in the ^{19}F NMR spectrum of **14b** at −58.2 and −58.3 ppm indicated the attachment of the 4-(methylthio) phenyl and 4-(trifluoromethoxy)phenyl groups, respectively, at the C-6 and C-8 positions of the quinoline ring.

The high reactivities of **13a–d** and **14a–c** toward halogenation should enable them to act as valuable precursors for novel compounds used in a wide range of applications. Our recent publications showed that cyano-[38] and methoxy-substituted[41] tetrahydroquinolines underwent further bromination to give 3-brominated aromatic derivatives. 6-Aryl-8-bromotetrahydroquinoline and 6-aryl-3,8-dibromoquinoline derivatives can be obtained by bromination of 6-aryltetrahydroquinolines **13a–d** in two steps by our developed methods.[15,35,47] Also, these arylbromoquinolines can be transformed into substituted quinolines bearing different substituents by exchanging the bromine atom with different functional groups via metal-catalyzed substitution[35,48] or coupling reactions.[20] Therefore, substituted quinolines bearing three different groups at C-3, C-5, and C-8 can be synthesized.

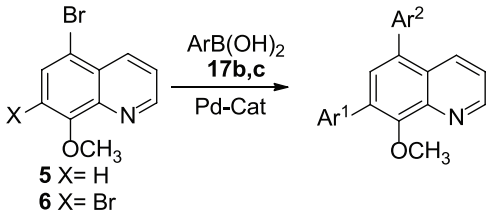
In our previous publication,[40] the direct bromination of 8-methoxyquinoline was reinvestigated and treatment of 8-methoxyquinoline with different equivalents of molecular bromine afforded 5-bromo-8-methoxyquinoline (**5**) and 5,7-dibromo-8-methoxyquinoline (**6**). In this study, compounds **5** and **6** were reacted with substituted phenylboronic acids via Suzuki–Miyaura cross-coupling reactions. These reactions furnished 8-methoxy-5-(4-(trifluoromethoxy)phenyl]quinoline (**15**), 8-methoxy-5,7-bis[4-(trifluoromethoxy) phenyl)quinoline (**16a**) and 8-methoxy-5,7-bis(4-(methylthio) phenyl) (**16b**) in good yields (70%–85%) (Table 2).

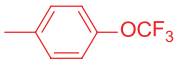
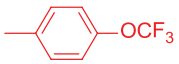
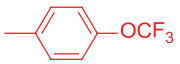
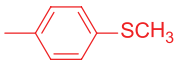
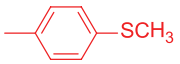
The ^{1}H and ^{13}C NMR, IR, and elemental analysis supported the assignment of compounds **15** and **16a,b** containing substituted phenyl groups. The ^{1}H NMR spectrum of **15** indicated the presence of an OCH_3 signal at 4.08 ppm, a characteristic doublet of doublets at 8.92 ppm (^{3}J=3.9 Hz, ^{4}J=1.8 Hz) corresponding to H-2, two doublets at 8.13 (^{3}J=8.4 Hz, H-4) and 7.06 (^{3}J=8.4 Hz, H-7) ppm, and six aromatic protons as a multiplet at 7.28–7.42 ppm. Moreover, in the ^{19}F NMR spectrum of **15**, the singlet appearing at −58.2 ppm was consistent with the proposed structure. These data led to the assignment of **15** as 8-methoxy-5-(4-(trifluoromethoxy)phenyl)quinoline. In the ^{1}H NMR spectrum of **16a**, a characteristic doublet of doublets at 9.00 ppm (^{3}J=4.2 Hz, ^{4}J=1.5 Hz) corresponding to H-2, a doublet at 8.23 ppm (^{3}J=8.4 Hz) belonging to H-4, another doublet of doublets at 7.45 ppm (^{3}J=8.4 Hz, ^{3}J=4.2 Hz, H-3), a singlet due to OCH_3 at 3.87 ppm and the aromatic signals at 7.32–7.39 (m, 4H), 7.52 (d, ^{3}J=9.6 Hz, 3H), and 7.77 (d, ^{3}J=8.7 Hz, 2H) ppm were consistent with the proposed structure. Similarly, the assignment of **16b** as 8-methoxy-5,7-bis(4-(methylthio)phenyl]quinoline was based on its ^{1}H NMR spectral data, which included two thiomethyl singlets at 2.54 and 2.56 ppm, a methoxy signal at 3.89 ppm and twelve aromatic proton signals.

Conclusion

In conclusion, we have demonstrated that the Suzuki–Miyaura cross-coupling of 6-bromo-1,2,3,4-tetrahydroquinoline, 6,8-dibromo-1,2,3,4-tetrahydroquinoline, 5-bromo-8-methoxyquinoline, and 5,7-dibromo-8-methoxyquinoline with substituted phenylboronic acids occurs without selectivity to afford the corresponding 6-aryl- (**13a–d**), 6,8-diaryl- (**14a–c**), 5-aryl (**15**), and 5,7-diaryl- (**16a,b**) tetrahydroquinolines and quinolines in a single-pot reaction. The aryl-substituted

Table 2. The yields and melting points of **15** and **16a,b**.



Product	Ar^1	Ar^2	Yield (%)	M.p. (°C)
15	H		73	80–82
16a			70	–
16b			85	172–174

tetrahydroquinolines **13a–d** and **14a–c** could be important starting materials for the synthesis of polyfunctionalized quinoline derivatives due to their high reactivity toward further bromination.[38,41] Studies are currently underway in our laboratory to investigate the reactivity and biological properties of the synthesized aryl-substituted quinolines.

Experimental

General

All the reagents and solvents were commercially available. Thin-layer chromatography was carried out on Merck silica F_{254} 0.255 mm plates, and spots were visualized by UV fluorescence at 254 nm. Classic column chromatography was performed using Merck 60 (70–230 mesh) silica gel. Melting points were determined on a Thomas–Hoover capillary melting point apparatus. Solvents were concentrated under reduced pressure. NMR spectra were recorded on an Oxford Instruments Varian at 300 MHz for ^{1}H NMR, at 75 MHz for ^{13}C NMR, and at 282 MHz for ^{19}F NMR. IR spectra were recorded on a Bruker Vertex 70v FTIR instrument. Elemental analyses were recorded on an ElementarVario MICRO Cube instrument. The NMR spectrums of all compounds are presented as Supplemental material.

One-pot Suzuki cross-coupling; general procedure. To a solution of bromotetrahydroquinoline or bromoquinoline **2**, **3**, **5** or **6** (1.0 equiv.) in 1,4-dioxane (30 mL) in a two-necked flask was added aq K_2CO_3 (3.0 M, 15 mL) and the mixture was stirred for 10 min at room temperature under an N_2 atmosphere. $Pd(PPh_3)_4$ (0.05 equiv.) and the unsubstituted or 4-substituted phenylboronic acid (1.3 equiv. for monobromides, 2.6 equiv. for dibromides) were added. The mixture was refluxed for 4 h at 90 °C. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with H_2O and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated under reduced pressure. The resulting residue was purified by column chromatography (silica gel, hexane/EtOAc) to afford the product.

*6-Phenyl-1,2,3,4-tetrahydroquinoline (**13a**)*: Yellow oil, yield 81% (0.40 g), R_f = 0.41 (6:1, hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.58 (br s, 1H, NH), 1.99–2.03 (m, 2H, H3), 2.86 (t, ^3J = 6.4 Hz, 2H, H4), 3.37 (t, ^3J = 5.6 Hz, 2H, H2), 6.57 (d, ^3J = 7.6 Hz, 1H, H7), 7.25–7.56 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.2, 27.1, 42.0, 114.4, 121.6, 125.5, 125.9, 126.3 (2C), 128.2, 128.6 (2C), 129.9, 141.5, 144.3. FTIR (cm^{-1}): 3432, 3023, 2945, 2921, 2832, 1597, 1483, 1434, 1359, 1331, 1287, 1201, 1185, 1128, 1100, 1073, 1025, 894, 861, 765, 699, 594, 575, 524, 498, 454. Anal. calcd for $C_{15}H_{15}N$ (209.12): C, 86.08; H, 7.22; N, 6.69; found: C, 86.24; H, 7.13; N, 6.62.

*6-(4-(Trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroquinoline (**13b**)*: Brown solid, yield 73% (0.26 g), m.p. 55–57 °C. R_f = 0.43 (6:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.95–2.02 (m, 2H, H3), 2.84 (t, 2H, ^3J = 6.3 Hz, H2), 3.35 (t, ^3J = 5.4 Hz, 2H, H4), 3.63 (s, 1H, NH), 6.55 (d, ^3J = 9.0 Hz, 1H, H7), 7.19–7.26 (m, 4H), 7.49–7.55 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3, 27.4, 42.2, 114.6, 119.1, 121.4 (2C), 121.8, 122.5 (q, $^2J_{C,F}$ = 260 Hz, OCF_3), 125.7, 127.6 (2C), 128.4, 128.6, 140.5, 144.9. ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.2. FTIR (cm^{-1}): 3450, 2953, 2836, 1610, 1526, 1493, 1443, 1402, 1358, 1214, 1133, 1009, 922, 897, 845, 804, 664, 610, 579, 523, 430. Anal. calcd for $C_{16}H_{14}F_3NO$ (293.10): C, 65.52; H, 4.81; N, 4.78; found: C, 65.54; H, 4.83; N, 4.82.

*6-(4-(Methylthio)phenyl]-1,2,3,4-tetrahydroquinoline (**13c**)*: Brown needles, yield 68% (0.20 g), m.p. 71–73 °C. R_f = 0.25 (8:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94–2.02 (m, 2H, H3), 2.52 (s, 3H, SCH_3), 2.83 (t, 2H, ^3J = 6.3 Hz, 2H, H2), 3.34 (t, ^3J = 5.4 Hz, 2H, H4), 3.70 (s, 1H, NH), 6.54 (d, ^3J = 9.3 Hz, 1H, H7), 7.20–7.32 (m, 4H), 7.45–7.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.5 (SCH_3), 22.4, 27.4, 42.2, 114.8, 121.9, 125.5, 126.9 (2C), 127.5 (2C), 128.1, 129.5, 135.8, 138.8, 144.3. FTIR (cm^{-1}): 3308, 3030, 2944, 2924, 2837, 1612, 1585, 1522, 1487, 1438, 1419, 1360, 1327, 1310, 1292, 1268, 1260, 1245, 1180, 1143, 1093, 1075, 1007, 952, 908, 827, 801, 724, 691, 603, 572, 505. Anal. calcd for $C_{16}H_{17}NS$ (255.11): C, 75.25; H, 6.71; N, 5.48; found: C, 75.34; H, 6.73; N, 5.52.

*6-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (**13d**)*: Yellow solid, yield 76% (0.40 g), m.p. 82–84 °C. R_f = 0.38 (8:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.94–2.02 (m, 2H, H3), 2.83 (t, 2H, ^3J = 6.3 Hz, 2H, H2), 3.33 (t, ^3J = 5.4 Hz, 2H, H4), 3.84 (s, 3H, OCH_3), 6.54 (d, ^3J = 8.7 Hz, 1H, H7), 6.91–6.96 (m, 2H), 7.17–7.20 (m, 2H), 7.43–7.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 27.4, 42.3, 55.6 (OCH_3), 114.3, 114.8, 121.9, 125.4, 127.5 (2C), 128.1, 130.0, 134.5, 144.0, 158.4. FTIR (cm^{-1}): 3337, 3300, 2943, 2928, 2834, 1608, 1494, 1463, 1297, 1272, 1238, 1179, 1040, 1021, 900, 822, 785, 725, 559, 525, 453. Anal. calcd for $C_{16}H_{17}NO$ (239.13): C, 80.30; H, 7.16; N, 5.85; found: C, 80.34; H, 7.13; N, 5.82.

*6,8-Diphenyl-1,2,3,4-tetrahydroquinoline (**14a**)*: White solid, yield 80% (1.25 g), m.p. 100–101 °C. R_f = 0.51 (6:1, hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02–2.06 (m, 2H, H3), 2.96 (t, ^3J = 6.0 Hz 2H, H2), 3.33 (t, ^3J = 6.0 Hz, 2H, H4), 4.14 (s, 1H, NH), 7.26–7.62 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 27.7, 42.1, 121.6, 126.0, 126.3 (2C), 126.8, 126.9, 127.2, 127.5, 128.6 (2C), 128.8, 128.9 (2C), 129.2, 129.4 (2C), 139.5, 141.3. FTIR (cm^{-1}): 3322, 3044, 2939, 2843, 2722, 1594, 1498, 1472, 1363, 1301, 1225, 1167, 1152, 1071, 1024, 1000, 886, 827, 810, 752, 691, 618, 594, 531, 508, 456. Anal. calcd for $C_{21}H_{19}N$ (285.15): C, 88.38; H, 6.71; N, 4.91; found: C, 88.34; H, 6.73; N, 4.87.

*6,8-Bis(4-(trifluoromethoxy)phenyl]-1,2,3,4-tetrahydroquinoline (**14b**)*: Light brown oil, yield 78% (0.53 g), R_f = 0.40 (9:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.97–2.01 (m, 2H, H3), 2.92 (t, ^3J = 6.3 Hz, 2H, H2), 3.32 (t, ^3J = 5.4 Hz, 2H, H4), 4.10 (br s, 1H, NH), 7.14–7.34 (m, 6H), 7.48–7.57 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 27.9, 42.8, 119.3 (q, $^2J_{C,F}$ = 264.8 Hz, OCF_3), 121.5 (2C), 121.8 (2C), 122.2, 122.7, 125.8, 127.0, 127.6 (2C), 128.1, 128.2, 129.1, 130.2 (2C), 138.4, 140.3, 141.8, 148.0, 148.8. ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.2, −58.3. FTIR (cm^{-1}): 3433, 2935, 2843, 1605, 1493, 1470, 1449 1339, 1247, 1203, 1158, 1104, 1018, 921, 844, 806, 679, 652, 543. Anal. calcd for $C_{23}H_{17}F_6NO_2$ (453.12): C, 60.93; H, 3.78; N, 3.09; found: C, 60.84; H, 3.73; N, 3.05.

*6,8-Bis(4-(methylthio)phenyl]-1,2,3,4-tetrahydroquinoline (**14c**)*: Yellow cubic, yield 82% (1.06 g), m.p. 73–75 °C. R_f = 0.45 (6:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.57 (br s, 1H, NH), 1.95–2.03 (m, 2H, H3), 2.50 (s, 3H, SCH_3), 2.53 (s, 3H, SCH_3), 2.90 (t, ^3J = 6.3 Hz, 2H, H2), 3.27 (t, ^3J = 5.4 Hz, 2H, H4), 7.15–7.48 (m, 10H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.0, 16.4, 22.1, 27.8, 42.3, 122.2, 126.7, 126.9 (2C), 127.1 (2C), 127.4 (2C), 127.5, 129.1, 130.1 (2C), 136.0, 136.1, 137.8, 138.4, 141.1. FTIR (cm^{-1}): 3415, 2950, 2921, 2810, 1599, 1512, 1486, 1433, 1331, 1291, 1252, 1186, 1086, 1012, 961, 886, 813, 750, 721, 532, 507, 474, 439. Anal. calcd for $C_{23}H_{23}NS_2$ (377.13): C, 73.17; H, 6.14; N, 3.71; found: C, 73.24; H, 6.10; N, 3.75.

*8-Methoxy-5-(4-(trifluoromethoxy)phenyl)quinoline (**15**)*: Brown solid, yield 73% (0.24 g), m.p. 80–82 °C. R_f = 0.41 (3:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.08 (s, 3H, OCH_3), 7.06 (d, ^3J = 8.4 Hz, 1H, H7), 7.28–7.42 (m, 6H), 8.13 (d, ^3J = 8.4 Hz, 1H, H4), 8.92 (dd, ^4J = 1.8 Hz, ^3J = 3.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.3, 107.2, 119.0, 121.2 122.0 122.4, 127.7, 130.8, 131.2 (2C), 134.2, 138.3, 140.3, 148.7, 149.4, 155.3. ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.2. FTIR (cm^{-1}): 3064, 2966, 2943, 2841, 1575, 1509, 1469, 1440, 1370, 1256, 1204, 1159, 1109, 1021, 996, 917, 859, 813, 782, 720, 669, 639, 595, 539, 491. Anal. calcd for $C_{17}H_{12}F_3NO_2$ (319.08): C, 63.95; H, 3.79; N, 4.39; found: C, 63.74; H, 3.90; N, 4.25.

*8-methoxy-5,7-bis(4-(trifluoromethoxy)phenyl]quinoline (**16a**)*: Yellow oil, yield 70% (0.21 g). R_f = 0.38 (3:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.87 (s, 3H, OCH_3), 7.32–7.39 (m, 4H), 7.45 (dd, ^3J = 8.4 Hz, ^3J = 4.2 Hz, 1H, H3), 7.52 (d, ^3J = 9.6 Hz, 3H), 7.77 (d, ^3J = 8.7 Hz, 2H), 8.23 (d, ^3J = 8.4 Hz, 1H, H4), 9.00 (dd, ^4J = 1.5 Hz, ^3J = 4.2 Hz, 1H, H2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 62.3, 116.6, 119.0 (q, $^2J_{C,F}$ = 256.5 Hz, OCF_3), 121.1 (2C), 121.4 (2C), 121.9, 122.4, 122.7, 127.7, 130.0, 131.2 (2C), 131.6 (2C), 132.2, 136.5, 137.7, 143.2, 149.0, 149.2, 150.2, 153.2. ^{19}F NMR (282 MHz, $CDCl_3$): δ −58.1, −58.2. FTIR (cm^{-1}): 2917, 2848, 1742, 1601, 1510, 1462, 1392, 1354, 1249, 1207, 1162, 1105, 1077, 1019, 990, 922, 881, 847, 797, 714, 678, 612, 591, 565, 530. Anal. calcd for $C_{24}H_{15}F_6NO_3$ (479.10): C, 60.13; H, 3.15; N, 2.92; found: C, 60.24; H, 3.10; N, 2.95.

*8-Methoxy-5,7-bis(4-(methylthio)phenyl)quinoline (**16b**)*: Yellow solid, yield 85% (0.14 g), m.p. 172–174 °C. R_f = 0.51 (6:1, hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.54 (s, 3H, SCH_3), 2.56 (s, 3H, SCH_3), 3.89 (s, 3H, OCH_3), 7.34–7.42 (m, 7H), 7.52 (s, 1H, H6) 7.68 (d, ^3J = 8.4 Hz, 2H), 8.24 (dd, ^3J = 8.7 Hz, ^4J = 1.5 Hz, 1H, H4), 9.00 (dd, ^4J = 1.5 Hz, ^3J = 3.9 Hz, 1H, H2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.9, 16.0, 62.2, 121.4, 126.4 (2C), 126.7 (2C), 127.5, 129.7, 130.1 (2C), 130.7 (2C), 132.7, 134.7, 134.8, 135.6, 136.0, 138.2, 138.4, 143.6, 150.1, 152.7. FTIR (cm^{-1}): 3023, 2920, 2835, 1904, 1596, 1492, 1454, 1427, 1380, 1340, 1267, 1222, 1189, 1077, 989, 960, 924, 823, 805, 727, 695, 509, 484, 437. Anal. calcd for $C_{24}H_{21}NOS_2$ (403.11): C, 71.43; H, 5.25; N, 3.47; found: C, 71.28; H, 5.20; N, 3.55.

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Supplemental material

Supplemental material for this article is available online.

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