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PAPER

One-pot synthesis of 2-aminoquinoline-based alkaloids from acetonitrile†

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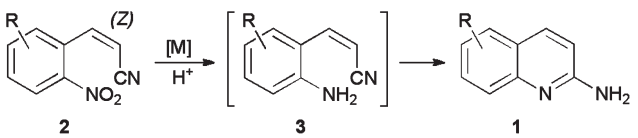
α-Diaminoboryl carbanions, readily prepared from acetonitrile, stereoselectively convert 2-nitrobenzaldehydes into nitrophenyl (*Z*)-acrylonitriles. Subsequent reductive cyclization leads to a series of 2-aminoquinoline derivatives. The entire procedure is practically operated in a single flask.

Introduction

2-Aminoquinoline[1] and related natural/unnatural congeners are pharmaceutically important alkaloids. Many of these exhibit various biological activities such as anthelmintic,[1] antiprotozoal,[2] antidepressant,[3] and antihypertensive[4] activities *etc.*[5] A recent study also revealed that 2-aminoquinolines possess subnanomolar potency for BACE1 (beta-site amyloid precursor protein cleaving enzyme 1) and may serve as a small BACE inhibitor for Alzheimer's disease therapeutics.[6] Therefore, these compounds continue to be an attractive study target and are anticipated as potent leads in the medicinal chemistry community.

Such a 2-aminoquinoline framework **1** (Scheme 1) is synthetically often prepared by means of a simple reductive cyclization of a nitrophenyl acrylonitrile **2**, through a presumed aminocyano olefin **3**, in the presence of an appropriate reducing metal (*e.g.*, [M] = Fe,[7] Zn,[7c] Sn,[8] Sm[9] and In,[7c] *etc.*[10]), typically under acidic conditions.[11] For mild and effective cyclization, the presence of a *Z*-acrylonitrile moiety in **2** is highly essential unless photochemical isomerization ($E \rightarrow Z$) is applied.[8] Even though the starting acrylonitrile **2** can be obtained from 2-nitrobenzaldehyde using Horner–Emmons reagents, the reported *Z*-selectivity is low ($E : Z = \sim 1 : 2$).[8,12]

Recently, we developed a facile stereoselective olefination for the synthesis of a series of β-monosubstituted acrylonitriles **5**[13] and α,β-disubstituted acrylonitriles **7**[14] with the assistance of a presumed α-diaminoboryl carbanion species **4** (Scheme 2). This



Scheme 1 Reductive cyclization of **2** into **1**.

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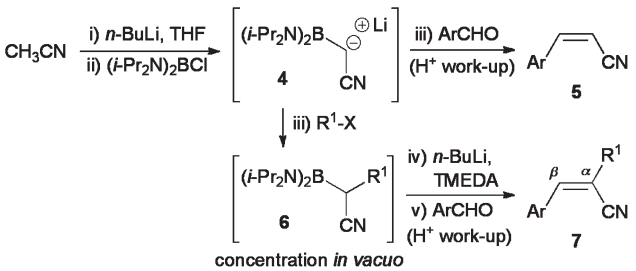


Scheme 2 *Z*-selective one-pot olefination.

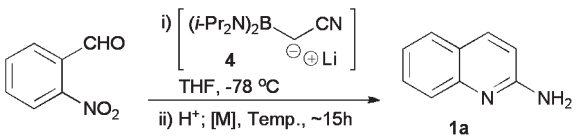
method is consistently *Z*-stereoselective ($E : Z = \sim 1 : 4$) for aromatic aldehydes and also the entire procedure, including reagent preparation as well as further modification, can be achieved in a single flask. Besides, since the olefination is normally worked up with an aqueous NH_4Cl solution, such an acidic quenched reaction mixture could be directly utilized for the next reductive cyclization by simply adding a proper reducing agent without isolation/purification of acrylonitrile **2**. Therefore, our protocol seemed to be highly advantageous for application to the synthesis of 2-aminoquinoline-based alkaloids.

Herein, we describe a one-pot, divergent approach leading to a series of 2-aminoquinoline derivatives from acetonitrile in a highly effective manner.

Results and discussion

Our preliminary study demonstrated that the carbanion **4** was well compatible with a nitro-group functionality and underwent *Z*-olefination with 2-nitrobenzaldehyde ($E : Z = 19 : 81$). Subsequent reductive cyclization conditions (*i.e.*, sources of acid and reducing agent, reaction temperature, *etc.*) were accordingly investigated (Table 1). To begin, following the olefination, the reaction mixture was quenched with a saturated NH_4Cl solution as usual and then directly exposed to zinc powder (entries 1 and 2). These initial attempts readily provided the desired 2-aminoquinoline **1a** in 65–68% yield. Even though NH_4Cl is a mild and convenient inorganic acid, the reaction in biphasic

Table 1 Condition optimization for one-pot reductive cyclization[a]



Entry	H^+ source (mL)	[M] (equiv.)	Temp.	**1a** (%)
1	sat. NH_4Cl (5)	Zn (5)	r.t.	68
2	sat. NH_4Cl (5)	Zn (5)	Reflux	65
3	sat. NH_4Cl (5)	Fe (5)	r.t.	38
4	AcOH (1)	Zn (5)	r.t.	76
5	AcOH (1)	Zn (5)	Reflux	76
6	AcOH (1)	Zn (3)	r.t.	37
7	AcOH (1)	Fe (5)	r.t.	16
8	MeOH (10)	Zn (5)	Reflux	28

[a] Reaction conditions: 2-nitrobenzaldehyde (1.0 mmol), **4** (1.1 mmol), THF (6.0 mL).

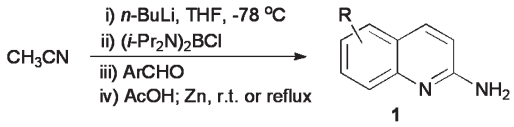
media (THF/aq·NH_4Cl) seemed to be slightly inefficient. Thus, a miscible organic acid, acetic acid, was alternatively employed (entries 4–6). The use of acetic acid successfully improved the overall yield of **1a** to 76%, which should be close enough to the theoretical yield based on the $E:Z$ ratio of the prior olefination. [Note: the *E*-isomer does not undergo cyclization under the conditions.] Another reducing metal, iron, was also tested; however, iron powder did not work well in this reaction system (entries 3 and 7). The use of methanol as a H^+ source also gave an inferior result (entry 8).

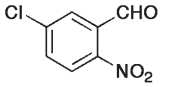
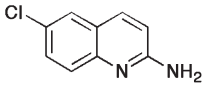
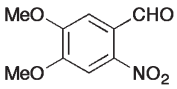
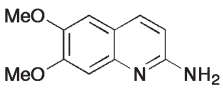
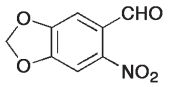
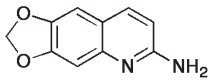
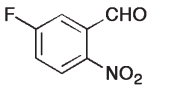
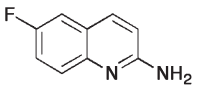
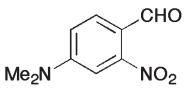
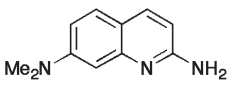
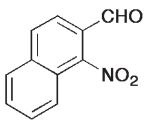
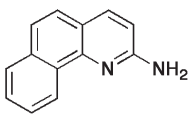
Table 2 illustrates various 2-nitrobenzaldehydes examined under the optimized conditions, *i.e.*, AcOH–Zn system. The expected functionalized 2-aminoquinolines **1b–1g** were smoothly obtained in 41–77% yield. Since the α-boryl carbanion protocol can also lead to α,β-disubstituted *Z*-acrylonitriles **7** *via* an intermediate **6** (see Scheme 2), one-pot synthesis of 3-substituted-2-aminoquinolines **8** was accordingly investigated (Table 3). After treating the carbanion **4** with an alkyl halide (R^1X), the obtained crude intermediate **6** was directly exposed to a base and then an aldehyde. Subsequent reductive cyclization at room temperature cleanly provided **8a–8i** in 55–73% yield.

To further test the generality of this one-pot protocol, 4-substituted-2-aminoquinoline synthesis was also attempted. 2′-Nitroacetophenone smoothly underwent olefination with the carbanion species **4** and provided desired (*Z*)-acrylonitrile with decent stereoselectivity ($Z:E$ = 83 : 17). Subsequent cyclization of the acrylonitrile was slow and not very effective; however, the expected product **9** was still obtained in 35% yield (Scheme 3). Elevation of the reaction temperature (*i.e.*, reflux conditions) did not help to improve the yield of **9**.[15]

Reductive *N*-alkylation of aminoarenes[16] as well as nitroarenes[17] with an aldehyde in the presence of Zn–AcOH reagents is well-demonstrated. Due to the similar reaction conditions, our one-pot protocol seemed further applicable to the preparation of *N*-alkylated 2-aminoquinoline derivatives directly from acetonitrile. Following reductive cyclization to **1a** and **8a** (Scheme 4), propanal (5 equiv.) was simply added into the reaction mixture without isolation of the aminoquinolines. The desired *N*-alkylation products, ***N*-1a** and ***N*-8a**, were successfully afforded in good yields (~60%).

Table 2 One-pot synthesis of 2-aminoquinolines **1b–1g**[a]



Entry	ArCHO	Product		**1** (%)
1			**1b**	67
2			**1c**	55
3[b]			**1d**	77
4[b]			**1e**	67
5[b]			**1f**	71
6[b]			**1g**	41

[a] 1.0 mmol reaction scale. [b] Reflux conditions.

Conclusions

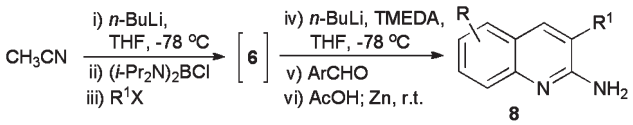
The use of a readily-accessible α-diaminoboryl carbanion species generated from acetonitrile enabled facile one-pot synthesis of a variety of substituted 2-aminoquinoline derivatives.

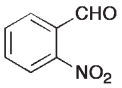
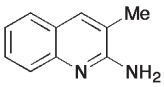
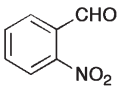
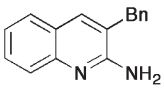
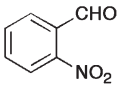
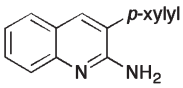
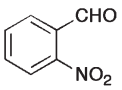
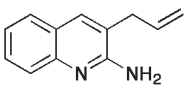
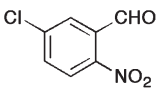
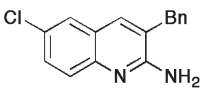
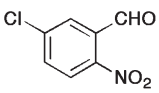
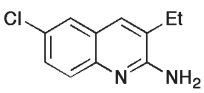
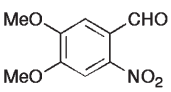
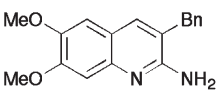
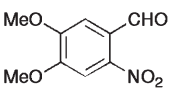
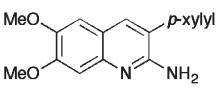
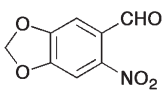
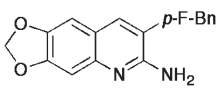
Experimental section

Materials and methods

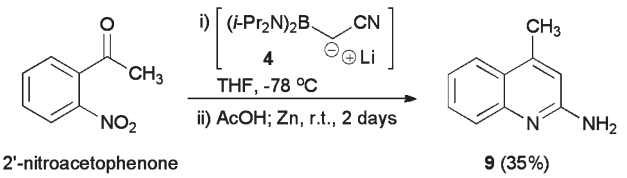
All experiments were performed in flame-dried glassware fitted with rubber septa under an argon atmosphere. Tetrahydrofuran (THF) was distilled over sodium/benzophenone ketyl. Tetramethylethylenediamine (TMEDA) was distilled over calcium hydride. Bis(diisopropylamino)chloroborane was prepared in accordance with a literature procedure.[18] Unless otherwise noted, all other reagents were obtained from commercial sources and used as received. ^1H Nuclear Magnetic Resonance (NMR) spectra were recorded at 300 or 500 MHz. Data are presented as follows: chemical shift (in ppm on the δ scale relative to δH 7.26 for the residual protons in $CDCl_3$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant (*J*/Hz), integration. Coupling constants were taken directly from the spectra and are uncorrected. ^{13}C NMR spectra were recorded at 75 or 125 MHz, and all chemical shift values are reported in ppm on the δ scale, with an internal reference of δC 77.0 for $CDCl_3$. Analytical TLC was performed on silica gel plates using UV light and/or potassium permanganate

Table 3 One-pot synthesis of 3-substituted-2-aminoquinolines **8a–8i**[a]

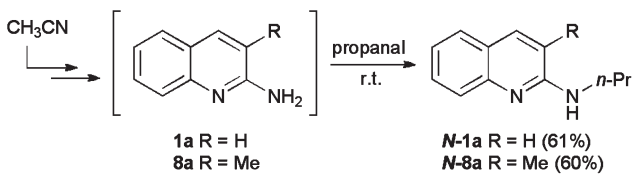


Entry	R^1X	ArCHO	Product		8 (%)
1	MeI			**8a**	66
2	BnBr			**8b**	73
3	*p*-Xylyl bromide			**8c**	72
4	Allyl bromide			**8d**	66
5	BnBr			**8e**	62
6	EtI			**8f**	59
7	BnBr			**8g**	64
8	*p*-Xylyl bromide			**8h**	55
9	*p*-F-BnBr			**8i**	64

[a] 1.0 mmol reaction scale.



Scheme 3 One-pot synthesis of 4-substituted-2-aminoquinoline.



Scheme 4 One-pot synthesis of *N*-alkylated-2-aminoquinolines.

stain followed by heating. Flash column chromatography was performed on silica gel 60A (32–63D).

Synthesis of 2-aminoquinolines 1 (1a–1g)

Into a solution of *n*BuLi (2.5 M in hexanes; 0.88 mL, 2.2 mmol) in THF (6 mL) at −78 °C was added acetonitrile (172 µL, 3.3 mmol) dropwise with stirring. After 20 min, $(i\text{-}Pr_2N)_2BCl$ (301 µL, 1.1 mmol) was added dropwise with stirring at −78 °C. After 1 h, an aldehyde (1.0 mmol) was added slowly with stirring at −78 °C and stirred for another hour. The reaction was then quenched with acetic acid (1.0 mL, 17.5 mmol) and allowed to warm up to room temperature. The reaction mixture was treated with zinc powder (0.33 g, 5.0 mmol) and stirred overnight at room temperature (for entries 1 and 2) or refluxed overnight (for entries 3–6). The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9–10. After stirring 30 min, the aqueous layer was extracted three times with EtOAc (5 mL each). The combined organic extracts were dried over $MgSO_4$, concentrated, and chromatographed ($CHCl_3$–MeOH eluent system) to give a 2-aminoquinoline derivative **1**.

2-Aminoquinoline (1a)

Column chromatography ($CHCl_3$–MeOH = 9 : 1) yielded **1a** (110 mg, 76%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.60–7.54 (m, 1H), 7.30–7.24 (m, 1H) 6.72 (d, J = 8.7 Hz, 1H), 4.73 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 147.4, 138.2, 129.8, 127.5, 125.8, 123.5, 122.7, 111.7; HRMS (TOF MS ES$^+$) calcd for $C_9H_9N_2$ 145.0766 $[M + H]^+$, found 145.0740. This product spectroscopically matched that of the known compound.[8]

6-Chloroquinolin-2-amine (1b)

Column chromatography ($CHCl_3$–MeOH = 9 : 1) yielded **1b** (120 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, J = 8.7 Hz, 1H), 7.68–7.42 (m, 3H), 6.72 (d, J = 8.7 Hz, 1H), 5.01 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 146.0, 137.1, 130.3, 127.8, 127.3, 126.2, 124.1, 112.6; HRMS (TOF MS ES$^+$) calcd for $C_9H_8ClN_2$ 179.0376 $[M + H]^+$, found 179.0383.

6,7-Dimethoxyquinolin-2-amine (1c)

Column chromatography ($CHCl_3$–MeOH = 9 : 1) yielded **1c** (112 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.7 Hz, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 6.57 (d, J = 8.7 Hz, 1H), 4.85 (brs, 2H), 3.94 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 152.4, 146.7, 143.3, 136.8, 117.7, 109.1, 106.0, 105.4, 55.9, 55.8; HRMS (TOF MS ES$^+$) calcd for $C_{11}H_{13}N_2O_2$ 205.0977 $[M + H]^+$, found 205.0976.

[1,3]dioxolo[4,5-*g*]quinolin-6-amine (1d)

Column chromatography ($CHCl_3$–MeOH = 9 : 1) yielded **1d** (145 mg, 77%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.7 Hz, 1H), 7.04 (s, 1H), 6.92 (s, 1H), 6.58 (d, J = 8.7 Hz, 1H), 6.02 (s, 2H), 4.67 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 150.7, 145.3, 144.9, 137.1, 119.1, 109.0, 103.7, 103.4, 101.3; HRMS (TOF MS ES$^+$) calcd for $C_{10}H_9N_2O_2$ 189.0664 $[M + H]^+$, found 189.0643.

6-Fluoroquinolin-2-amine (1e)

Column chromatography ($CHCl_3$–MeOH = 9 : 1) yielded **1e** (108 mg, 67%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.7 Hz, 1H), 7.67–7.57 (m, 1H), 7.36–7.20 (m, 2H), 6.73 (d, J = 8.7 Hz, 1H), 4.87 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2 (d, $^1J_{CF}$ = 240.9 Hz), 156.4, 144.3, 137.4 (d, $^4J_{CF}$ = 4.5 Hz), 127.7 (d, $^3J_{CF}$ = 8.5 Hz), 123.7 (d, $^3J_{CF}$ = 9.4 Hz), 119.1 (d, $^2J_{CF}$ = 24.8 Hz), 112.6, 110.9 (d, $^2J_{CF}$ = 21.5 Hz); HRMS (TOF MS ES$^+$) calcd for $C_9H_8FN_2$ 163.0672 $[M + H]^+$, found 163.0659.

N^7,N^7-dimethylquinoline-2,7-diamine (1f)

Column chromatography ($CHCl_3$–MeOH = 9 : 1) yielded **1f** (133 mg, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 8.4 Hz, 1H), 6.87–6.75 (m, 2H), 6.42 (d, J = 8.4 Hz, 1H), 5.17 (brs, 2H), 3.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 151.8, 148.1, 137.9, 128.1, 115.5, 111.6, 107.0, 103.9, 40.4; HRMS (TOF MS ES$^+$) calcd for $C_{11}H_{14}N_3$ 188.1159 $[M + H]^+$, found 188.1188.

Benzo[*h*]quinolin-2-amine (1g)

Column chromatography ($CHCl_3$–MeOH = 9.8 : 0.2) yielded **1g** (80 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18–9.10 (m, 1H), 7.95–7.81 (m, 2H), 7.69–7.51 (m, 4H), 6.77 (d, J = 8.4 Hz, 1H), 4.88 (brs, 2 h); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 145.6, 138.0, 134.1, 130.3, 127.59, 127.55, 126.0, 125.2, 124.2, 123.3, 120.3, 110.3; HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{11}N_2$ 195.0922 $[M + H]^+$, found 195.0917.

Synthesis of 3-substituted-2-aminoquinolines 8 (8a–8i)

Into a solution of *n*BuLi (2.5 M in hexanes; 0.88 mL, 2.2 mmol) in THF (6 mL) at −78 °C was added acetonitrile (172 μL, 3.3 mmol) dropwise with stirring. After 20 min, $(i\text{-}Pr_2N)_2BCl$ (301 μL, 1.1 mmol) was added dropwise with stirring at −78 °C. After 1 h, an alkylhalide (1.1 mmol) was added slowly with stirring at −78 °C and stirred for another hour. After the reaction mixture was allowed to warm up to room temperature, THF and acetonitrile were rotary evaporated. Another portion of THF (6.0 mL) was added to the reaction pot and cooled to −78 °C. TMEDA (165 μL, 1.1 mmol) and *n*-BuLi in hexanes (2.5 M; 0.44 mL, 1.1 mmol) were then added dropwise with stirring in this order at −78 °C. After 1 h, an aldehyde (1 mmol) was added slowly at −78 °C and stirred for another hour. The reaction was quenched with acetic acid (1 mL, 17.5 mmol) and allowed to warm up to room temperature. The reaction mixture was treated with a zinc powder (0.33 g, 5.0 mmol) and stirred overnight at room temperature. The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9–10. After stirring 30 min, the aqueous layer was extracted three times with EtOAc (5 mL each). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed to give a 3-substituted-2-aminoquinoline **8**.

3-Methylquinolin-2-amine (8a)

Column chromatography ($CHCl_3$–MeOH = 5 : 1) yielded **8a** (105 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69–7.45 (m, 4H), 7.22 (apparent t, J = 7.5 Hz, 1H), 5.28 (brs, 2H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 145.5, 136.9, 129.0, 126.8, 124.6, 124.1, 122.7, 119.6, 17.5; HRMS (TOF MS ES$^+$) calcd for $C_{10}H_{11}N_2$ 159.0922 $[M + H]^+$, found 159.0901. This product spectroscopically matched that of the known compound.[8]

3-Benzylquinolin-2-amine (8b)

Column chromatography (EtOAc–MeOH = 5 : 1) yielded **8b** (172 mg, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79–7.50 (m, 4H), 7.50–7.15 (m, 6H), 4.84 (brs, 2H), 4.00 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 146.7, 137.5, 137.4, 129.1, 128.9, 128.6, 127.1, 127.0, 125.5, 124.2, 122.7, 122.1, 37.9; HRMS

(TOF MS ES$^+$) calcd for $C_{16}H_{15}N_2$ 235.1235 $[M + H]^+$, found 235.1227.

3-(4-Methylbenzyl)quinolin-2-amine (8c)

Column chromatography (Benzene–Acetone = 1 : 1) yielded **8c** (178 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.64 (m, 2H), 7.64–7.49 (m, 2H), 7.26 (apparent t, J = 7.5 Hz, 1H), 7.18–7.06 (m, 4H), 4.85 (brs, 2H), 3.95 (s, 2H) 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 146.8, 137.3, 136.7, 134.4, 129.7, 129.1, 128.5, 127.1, 125.6, 124.4, 122.7, 122.3, 37.7, 21.0; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{17}N_2$ 249.1392 $[M + H]^+$, found 249.1383.

3-Allylquinolin-2-amine (8d)

Column chromatography (Benzene–Acetone = 1 : 1) yielded **8d** (122 mg, 66%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72–7.63 (m, 2H), 7.59 (d, J = 7.8 Hz, 1H), 7.52 (apparent t, J = 7.5 Hz, 1H), 7.25 (apparent t, J = 7.5 Hz, 1H), 6.03–5.91 (m, 1H), 5.28–5.06 (m, 4H), 3.38 (d, J = 6.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 146.4, 136.7, 134.5, 129.1, 127.0, 125.2, 124.2, 122.6, 121.2, 117.8, 36.0; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{13}N_2$ 185.1058 $[M + H]^+$, found 185.1079.

3-Benzyl-6-chloroquinolin-2-amine (8e)

Column chromatography ($CHCl_3$–MeOH = 5 : 1) yielded **8e** (166 mg, 62%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.51 (m, 3H), 7.43 (dd, J = 2.1 Hz, 9.0 Hz, 1H), 7.36–7.24 (m, 3H), 7.21–7.15 (m, 2H), 5.14 (brs, 2H), 3.94 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 144.6, 136.9, 136.4, 129.7, 129.0, 128.6, 127.8, 127.1, 126.5, 125.8, 124.6, 123.3, 37.7; HRMS (TOF MS ES$^+$) calcd for $C_{16}H_{14}ClN_2$ 269.0846 $[M + H]^+$, found 269.0832.

6-Chloro-3-ethylquinolin-2-amine (8f)

Column chromatography ($CHCl_3$–MeOH = 10 : 1) yielded **8f** (121 mg, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63–7.53 (m, 3H), 7.43 (dd, J = 2.4 Hz, 8.7 Hz, 1H), 5.04 (brs, 2H), 2.59 (q, J = 7.5 Hz, 2H), 1.36 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2, 144.4, 133.3, 129.3, 127.6, 126.7, 125.8, 125.7, 124.9, 23.7, 11.9; HRMS (TOF MS ES$^+$) calcd for $C_{11}H_{12}ClN_2$ 207.0689 $[M + H]^+$, found 207.0687.

3-Benzyl-6,7-dimethoxyquinolin-2-amine (8g)

Column chromatography ($CHCl_3$–MeOH = 5 : 1) yielded **8g** (188 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.39–7.15 (m, 6H), 6.95 (s, 1H), 5.97 (brs, 2H), 4.05 (s, 3H), 4.01 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 147.9, 146.3, 136.7, 134.6, 128.9, 128.6, 127.1, 126.9, 119.3, 117.0, 106.2, 98.0, 56.3, 56.0, 37.4; HRMS (TOF MS ES$^+$) calcd for $C_{18}H_{19}N_2O_2$ 295.1447 $[M + H]^+$, found 295.1467.

6,7-Dimethoxy-3-(4-methylbenzyl)quinolin-2-amine (8h)

Column chromatography ($CHCl_3$–MeOH = 5 : 1) yielded **8h** (170 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.28 (s, 1H), 7.14 (d, J = 7.5 Hz, 2H), 7.09 (d, J = 7.5 Hz, 2H), 7.00 (s, 1H), 5.89 (brs, 2H), 4.06 (s, 3H), 3.98 (s, 2H), 3.95 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 147.9, 146.3, 136.8, 134.7, 133.5, 129.7, 128.4, 126.7, 119.5, 117.1, 106.2, 98.1, 56.4, 56.0, 37.1, 21.0; HRMS (TOF MS ES$^+$) calcd for $C_{19}H_{21}N_2O_2$ 309.1603 $[M + H]^+$, found 309.1612.

7-(4-Fluorobenzyl)-[1,3]dioxolo[4,5-*g*]quinolin-6-amine (8i)

Column chromatography (Hex–EtOAc–MeOH = 5 : 5 : 1) yielded **8i** (190 mg, 64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.20–7.12 (m, 2H), 7.05–6.90 (m, 3H), 6.90 (s, 1H), 6.02 (s, 2H), 4.53 (brs, 2H), 3.91 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8 (d, $^1J_{CF}$ = 243.9 Hz), 155.0, 150.2, 145.0, 144.5, 136.6, 133.5 (d, $^4J_{CF}$ = 3.2 Hz), 130.0 (d, $^3J_{CF}$ = 7.9 Hz), 119.9, 119.3, 115.8 (d, $^2J_{CF}$ = 3.2 Hz), 103.5, 102.9, 101.2, 36.9; HRMS (TOF MS ES$^+$) calcd for $C_{17}H_{14}FN_2O_2$ 297.1039 $[M + H]^+$, found 297.1038.

Synthesis of 4-methylquinolin-2-amine (9)

Into a solution of *n*BuLi (2.5 M in hexanes; 0.88 mL, 2.2 mmol) in THF (6 mL) at −78 °C was added acetonitrile (172 μL, 3.3 mmol) dropwise with stirring. After 20 min, $(i\text{-}Pr_2N)_2BCl$ (301 μL, 1.1 mmol) was added dropwise with stirring at −78 °C. After 1 h, 2-nitroacetophenone (107 μL, 1.0 mmol) was added slowly with stirring at −78 °C and stirred for another hour. The reaction was then quenched with acetic acid (1 mL, 17.5 mmol) and allowed to warm up to room temperature. The reaction mixture was treated with zinc powder (0.33 g, 5.0 mmol) and stirred for 2 days at room temperature. The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9–10. After stirring 30 min, the aqueous layer was extracted three times with EtOAc (5 mL each). The combined organic extracts were dried ($MgSO_4$), rotary evaporated, and chromatographed (EtOAc–MeOH = 1 : 1) to give **9** (55 mg, 35%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, J = 8.1 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.55 (td, J = 8.4 Hz, 1.2 Hz, 1H), 7.33–7.24 (m, 1H), 6.57 (s, 1H), 5.00 (brs, 2H), 2.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 147.1, 146.2, 129.6, 126.0, 123.8, 123.6, 122.5, 111.9, 18.7; HRMS (TOF MS ES$^+$) calcd for $C_{10}H_{11}N_2$ 159.0922 $[M + H]^+$, found 159.0915.

Synthesis of *N*-alkylated-2-aminoquinolines (*N*-1a and *N*-8a)

The reaction mixture of **1a**/**8a** prepared as described in the general procedure above was quenched with acetic acid (1 mL, 17.5 mmol) and allowed to warm up to room temperature. The resulting mixture was then treated with zinc powder (0.523 g, 8.0 mmol) and stirred overnight at room temperature. Subsequently, propanal (364 μL, 5.0 mmol) was added and stirred for 4 days at room temperature. The mixture was basified with excess ammonium hydroxide (~15 mL) to pH 9–10. After stirring 30 min, the aqueous layer was extracted three times with

EtOAc (5 mL each). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and chromatographed to give the final products, ***N*-1a**/***N*-8a**.

N-Propylquinolin-2-amine (*N*-1a)

Column chromatography (Hex–EtOAc–MeOH = 5 : 5 : 1) yielded ***N*-1a** (114 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.60–7.47 (m, 2H), 7.19 (m, 1H), 6.63 (d, J = 9.0 Hz, 1H), 4.86 (brs, 1H), 3.48–3.40 (m, 2H), 1.68 (dq, J = 7.2, 7.2 Hz, 2H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 148.0, 137.3, 129.5, 127.4, 125.9, 123.3, 121.8, 110.9, 43.6, 22.9, 11.5; HRMS (TOF MS ES$^+$) calcd for $C_{12}H_{15}N_2$ 187.1235 $[M + H]^+$, found 187.1245.

3-Methyl-*N*-propylquinolin-2-amine (*N*-8a)

Column chromatography (EtOAc–MeOH = 95 : 5) yielded ***N*-8a** (120 mg, 60%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 8.4 Hz, 1H), 7.60 (s, 1H), 7.56–7.43 (m, 2H), 7.18 (td, J = 7.4 Hz, 0.9 Hz, 1H), 4.49 (brs, 1H), 3.60 (dt, J = 5.4, 7.2 Hz, 2H), 2.24 (s, 3H), 1.74 (tq, J = 7.2, 7.2 Hz, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 147.2, 135.3, 128.3, 126.6, 126.0, 123.6, 121.7, 119.5, 43.3, 22.9, 17.4, 11.7; HRMS (TOF MS ES$^+$) calcd for $C_{13}H_{17}N_2$ 201.1392 $[M + H]^+$, found 201.1390.

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