# Microwave-Assisted One-Pot Synthesis of Isoquinolines, Furopyridines, and Thienopyridines by Palladium-Catalyzed Sequential Coupling−Imination−Annulation of 2-Bromoarylaldehydes with Terminal Acetylenes and Ammonium Acetate

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Ⓢ Supporting Information

ABSTRACT: A palladium-catalyzed microwave-assisted one-pot reaction for the synthesis of isoquinolines is developed. The reaction is carried out by sequential coupling−imination−annulation reactions of *ortho*-bromoarylaldehydes and terminal alkynes with ammonium acetate, and a variety of substituted isoquinolines, furopyridines, and thienopyridines is prepared in moderate to excellent yields (up to 86%).
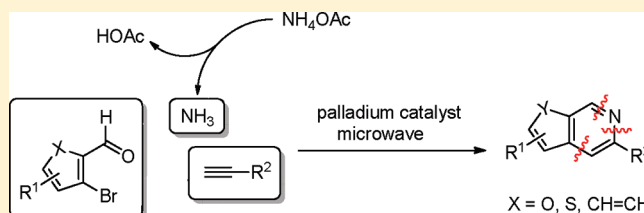
The synthesis of isoquinolines has attracted considerable attention from the organic synthetic community due to the wide range of biological activities exhibited by isoquinoline derivatives.[1] Of the numerous synthetic methods developed to construct the isoquinoline core structure, the late transition metal catalyzed isoquinoline synthesis plays a particularly significant role.[2] This is because these reactions usually require milder reaction conditions, compared to the classical synthetic methods, such as the Pictet−Spengler reaction, Pomeranz−Fritsch reaction, and Bischler−Napieralski reaction, which generally incorporate strong acidic conditions.[3] Among the late transition metal catalyzed syntheses of isoquinolines, the palladium catalyzed protocols have received the most attention due to the significant role palladium plays in carbon−carbon bond coupling[4] and annulation reactions of alkynes.[5] The reported palladium catalyzed isoquinoline synthesis generally starts from the *tert*-butyl imine of either 2-halo benzaldehyde or 2-alkynyl benzaldehyde, which are prepared from *tert*-butyl amine and the corresponding 2-halo benzaldehydes or 2-alkynyl benzaldehydes.[2a−c,l,n,o]

The concept of pot economy has been highlighted recently.[6] By combining a sequence of chemical transformations in a single reaction vessel, chemists are able to complete a multistep synthesis without the need for product isolation and purification between each successive synthetic step, thus avoiding a lengthy separation process of the intermediate chemical compounds and the generation of excess waste. However, the palladium-catalyzed one-pot synthesis of isoquinolines from commercially available starting materials still remains scarce. To the best of our knowledge, there are only two examples involving palladium-catalyzed one-pot synthesis of isoquinolines or 1,2-dihydroisoquinolines starting directly from commercially available 2-bromoarylaldehydes and

terminal acetylenes. A synthesis of 1,2-dihydroisoquinolin-1-ylphosphonates was reported by Wu via a tandem four-component reaction,[7] and a three-component cascade reaction for the synthesis of isoquinolines was reported by Abbiati in which aqueous ammonia was used as the reagent for the imination step.[8] In the latter case, only low to moderate chemical yields were obtained, with this methodology failing for linear aliphatic alkynes.
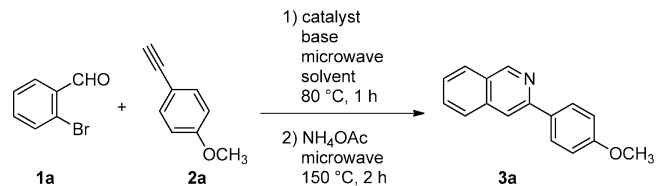
Ammonium acetate (NH$_4$OAc), a known ammonia source,[9] has only been employed once in the isoquinoline synthesis, specifically in its reaction with 2-(1,1-difluoroalkenyl)-benzaldehyde.[10] Only two isoquinoline derivatives were prepared by this method. Our interest in the late transition metal catalyzed annulation reaction has promoted our exploration of ammonium acetate as the ammonia source for the imination step in the palladium-catalyzed one-pot synthesis of isoquinolines.

The microwave enhanced one-pot reaction has been highlighted recently.[11] Microwave technology has been well-recognized to enhance chemical reactions and to generate clean and high-yielding chemical transformations. We hereby report a microwave-assisted one-pot reaction protocol to isoquinilones from commercially available 2-bromoarylaldehydes, terminal acetylenes, and ammonium acetate. No copper catalyst is involved in the current method, which is different from the previous palladium-catalyzed one-pot synthetic protocols for isoquinoline synthesis.[7,8]

Our initial study focused on the reaction of 2-bromobenzaldehyde, 4-methoxyphenyl acetylene, and ammonium acetate

Table 1. Optimization of Reaction Conditions for the One-Pot Isoquinoline Synthesis[a]

entry	catalyst	base	solvent	ammonium salt (equiv)	% yield[b]
1[c]	PdCl$_2$(PPh$_3$)$_2$ (2 mol %)/CuI (4 mol %)	Et$_3$N (1.0 mL)	DMF	NH$_4$OAc (5)	37
2	PdCl$_2$(PPh$_3$)$_2$ (2 mol %)/CuI (4 mol %)	Et$_3$N (1.0 mL)	DMF	NH$_4$OAc (5)	62
3	Pd(OAc)$_2$ (2 mol %) PPh$_3$ (4 mol %)/CuI (4 mol %)	Et$_3$N (1.0 mL)	DMF	NH$_4$OAc (5)	53
4	Pd(PPh$_3$)$_4$ (2 mol %)/CuI (4 mol %)	Et$_3$N (1.0 mL)	DMF	NH$_4$OAc (5)	66
5	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	Et$_3$N (1.0 mL)	DMF	NH$_4$OAc (5)	72
6	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	Et$_3$N (1.0 mL)	DMSO	NH$_4$OAc (5)	41
7	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	Et$_3$N (1.0 mL)	CH$_3$CN	NH$_4$OAc (5)	62
8	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	Et$_3$N (1.0 mL)	toluene	NH$_4$OAc (5)	36
9	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	K$_3$PO$_4$ (5 equiv)	DMF	NH$_4$OAc (5)	42
10	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	Cs$_2$CO$_3$ (5 equiv)	DMF	NH$_4$OAc (5)	49
11	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	DIPEA (5 equiv)	DMF	NH$_4$OAc (5)	60
12	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	KOAc (5 equiv)	DMF	NH$_4$OAc (5)	83
13	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	KOAc (2 equiv)	DMF	NH$_4$OAc (2)	82
14	Pd(OAc)$_2$ (1 mol %)/PPh$_3$ (2 mol %)	KOAc (2 equiv)	DMF	NH$_4$OAc (2)	67
15[d]	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	KOAc (2 equiv)	DMF	NH$_4$OAc (2)	79
16	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	KOAc (2 equiv)	DMF	(NH$_4$)$_2$CO$_3$ (2)	50
17	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	KOAc (2 equiv)	DMF	NH$_4$HCO$_3$ (2)	43
18	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	KOAc (2 equiv)	DMF	HCO$_2$NH$_4$ (2)	63
19[e]	Pd(OAc)$_2$ (2 mol %)/PPh$_3$ (4 mol %)	KOAc (2 equiv)	DMF	NH$_4$OAc (2)	60

[a]Representative procedure: 2-bromobenzaldehyde (**1a**, 1 equiv, 0.5 mmol), 4-methoxyphenyl acetylene (**2a**, 1.1 equiv, 0.55 mmol), catalyst, base, and solvent (2 mL) were mixed in a 5 mL microwave vial. The vial was flushed with nitrogen and sealed with an aluminum/Teflon crimp top. The reaction mixture was stirred at 80 °C under microwave (300 W) irradiation for 1 h. After cooling to room temperature, ammonium salt was added to the microwave vial, and the reaction mixture was stirred at 150 °C under microwave irradiation for 2 h. [b]Isolated yields after column chromatography. [c]2-Bromobenzaldehyde (**1a**, 1 equiv, 0.5 mmol), 4-methoxyphenyl acetylene (**2a**, 1.1 equiv, 0.55 mmol), PdCl$_2$(PPh$_3$)$_2$ (2 mol %), CuI (4 mol %), Et$_3$N (1.0 mL), NH$_4$OAc (5 equiv, 2.5 mmol), and DMF (2 mL) were mixed in a 5 mL microwave vial. The vial was flushed with nitrogen and sealed with an aluminum/Teflon crimp top. The reaction mixture was stirred at 150 °C under microwave (300 W) irradiation for 3 h. [d]The second step of the reaction was heated to 120 °C by microwave irradiation. [e]The reaction was carried out with an oil bath heating (step 1, 80 °C; step 2, 150 °C).

using the standard Sonogashira coupling condition. In the presence of 2 mol % of PdCl$_2$(PPh$_3$)$_2$ and 4 mol % of CuI, the one-pot reaction was completed in 3 h using DMF as the solvent and microwave irradiation as the heating source. By initially adding NH$_4$OAc to the reaction mixture, we effectively rendered the reaction a one-step process affording the desired product **3a** in a moderate 37% yield (Table 1, entry 1). After several trials, we found that by carrying out the one-pot reaction in two sequential steps, we were able to increase our yield of the desired product **3a** to 62% (Table 1, entry 2). Therefore, we added NH$_4$OAc to the reaction mixture after the palladium-catalyzed coupling was completed. As shown by TLC, there was no 2-bromobenzaldehyde remaining. After trying several palladium and copper catalyst systems (Table 1, entries 2−4), we found that in the absence of copper catalyst the combination of 2 mol % of Pd(OA$_C$)$_2$ and 4 mol % of PPh$_3$ gave the best yield (72%) (Table 1, entry 5). Other solvents such as DMSO, CH$_3$CN, and toluene were found to be inferior to DMF (Table 1, entries 6−8). Among the inorganic and organic bases investigated (Table 1, entries 9−11), KOAc showed superior effect, affording the desired product **3a** in an 83% yield (Table 1, entry 12). The loading of KOAc and NH$_4$OAc could be both reduced from 5 to 2 equiv with a similar chemical yield (Table 1, entry 13). Changing the conditions to a lower reaction temperature (120 °C) resulted in

a slightly lower chemical yield (79%) (Table 1, entry 15). Similarly, when the catalyst loading was reduced to 1 mol % of Pd(OAc)$_2$ and 2 mol % of PPh$_3$, the chemical yield decreased as well (Table 1, entry 14). Other ammonium salts were also investigated, including (NH$_4$)$_2$CO$_3$, NH$_4$HCO$_3$, and HCO$_2$NH$_4$ (Table 1, entries 16−18), all showing inferior results to NH$_4$OAc. When the reaction was carried out with oil bath heating (step 1, 80 °C; step 2, 150 °C), only a 60% yield of **3a** was obtained within the same reaction time parameters (Table 1, entry 19).

This one-pot reaction protocol has proved to be a very general route for an array of isoquinolines (Table 2). A wide variety of 2-bromobenzaldehydes has been studied in this reaction, in which both electron-donating substituents (Table 2, entries 3, 4, and 7) and electron-withdrawing substituents (Table 2, entry 5) are found to be compatible. Additionally, both the aryl and alkyl acetylenes are found to be compatible in this reaction as well. In particular, the linear alkyl acetylenes all gave good to excellent yields (Table 2, entries 2, 5, and 13). This is due to the development of a reaction pathway meant to circumvent the problem arising from the use of aqueous ammonia solution as the ammonia source, as had been done in previous studies.[8] A 75% yield is obtained when the sterically demanding 2-methoxyphenyl acetylene is used (Table 2, entry 8). However, only a moderate yield (38%) is obtained when the

Table 2. Preparation of Isoquinolines/Furopyridines/Thienopyridines by Microwave-Assisted One-Pot Reactions[a]

entry	3	% yield[b]	entry	3	% yield[b]
1)	3a	82	13)	3m	83
2)	3b	77	14)	3n	82
3)	3c	79	15)	3o	78
4)	3d	77	16)	3p	74
5)	3e	86	17)	3q	68
6)	3f	65	18)	3r	77
7)	3g	81	19)	3s	75
8)	3h	75	20)	3t	54
9)	3i	64	21)	3u	66
10)	3j	55	22)	3v	50
11)	3k	73	23)	3w	38
12)	3l	67	24)	3x	–

Table 2. continued

[a]Representative procedure: 2-bromoarylaldehyde (**1**, 1 equiv, 0.5 mmol), a terminal acetylene (**2**, 1.1 equiv, 0.55 mmol), Pd(OAc)$_2$ (2.25 mg, 2 mol %, 0.01 mmol), PPh$_3$ (5.25 mg, 4 mol %, 0.02 mmol), KOAc (98 mg, 2 equiv, 1 mmol), and DMF (2 mL) were mixed in a 5 mL microwave vial. The vial was flushed with nitrogen and sealed with an aluminum/Teflon crimp top. The reaction mixture was stirred at 80 °C under microwave (300 W) irradiation for 1 h. After cooling to room temperature, NH$_4$OAc (77 mg, 2 equiv, 1 mmol) was added to the microwave vial, and the reaction mixture was stirred at 150 °C under microwave irradiation for 2 h. [b]Isolated yields after column chromatography.

sterically more demanding 3,3-dimethylbut-1-yne is used (Table 2, entry 23). Besides 2-bromobenzaldehydes, 3-bromofuran-2-carbaldehydes and 3-bromothiophene-2-carbaldehydes have been successfully employed in the current synthetic protocol, leading to furopyridines (Table 2, entries 9 and 20) and thienopyridines (Table 2, entries 10−11 and 21−22), respectively. Trimethylsilyl acetylene fails in the current isoquinoline synthetic protocol, and no useful product is obtained from the reaction mixture (Table 2, entry 24).

Our effort to expand the current protocol from 2-bromoarylaldehydes to 2′-bromoarylketones has met very limited success. Under the optimal reaction conditions for 2-bromoarylaldehydes, no desired 1-substituted isoquinolines were obtained from 2′-bromoarylketones. Only very moderate chemical yields were obtained when 2′-iodoarylketones were employed instead of 2′-bromoarylketones. In the best case scenario, an 18% yield is obtained for compound **3y** (Table 3,

Table 3. Preparation of Isoquinolines by Microwave-Assisted One-Pot Reactions from 1-(2-Iodophenyl) Ethanone[a]

entry	**3**	% yield[b]
1)	**3y**	18
2)	**3z**	16

[a]Representative procedure: 1-(2-iodophenyl) ethanone (**1**, 1 equiv, 0.5 mmol), a terminal acetylene (**2**, 1.1 equiv, 0.55 mmol), Pd(OAc)$_2$ (2.25 mg, 2 mol %, 0.01 mmol), PPh$_3$ (5.25 mg, 4 mol %, 0.02 mmol), KOAc (98 mg, 2 equiv, 1 mmol), and DMF (2 mL) were mixed in a 5 mL microwave vial. The vial was flushed with nitrogen and sealed with an aluminum/Teflon crimp top. The reaction mixture was stirred at 80 °C under microwave (300 W) irradiation for 1 h. After cooling to room temperature, NH$_4$OAc (77 mg, 2 equiv, 1 mmol) was added to the microwave vial, and the reaction mixture was stirred at 150 °C under microwave irradiation for 2 h. [b]Isolated yields after column chromatography.

entry 1). This one-pot reaction presumably takes place by a Pd-catalyzed coupling reaction between a 2-bromoarylaldehyde and a terminal acetylene, followed by imination and intramolecular annulation reactions.

In conclusion, a palladium-catalyzed microwave assisted one-pot reaction for the synthesis of isoquinoline, furopyridine, and thienopyridine derivatives has been developed from commer-cially available 2-bromoarylaldehydes, terminal acetylenes, and NH$_4$OAc. Ammonium acetate is used as the imination reagent and gives superior results to its aqueous ammonia counterpart. No copper catalyst is necessary in the current reaction protocol. The preparation of an isoquinoline derivative library using the current protocol is underway in our laboratory.
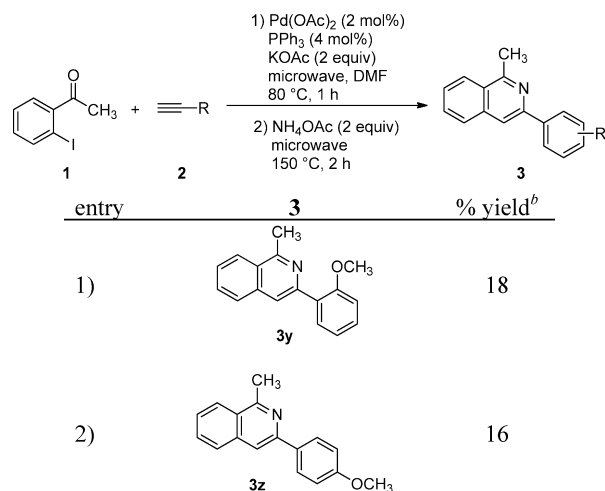
■ EXPERIMENTAL SECTION

General Information. All microwave irradiation reactions were carried out on a Biotage-EXP Microwave synthesis system, operating at a frequency of 2450 MHz with continuous irradiation power from 0 to 300 W. All reactions were carried out in 5 mL oven-dried Biotage microwave vials sealed with an aluminum/Teflon crimp top, which can be exposed to a maximum of 250 °C and 20 bar internal pressure. The reaction temperature was measured by an IR sensor on the outer surface of the process vial. All commercially available chemicals were used as received without further purification. All ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz respectively, using CDCl$_3$ or DMSO-d_6 as a solvent. The chemical shifts of all ^{1}H and ^{13}C NMR spectra are referenced to the residual signal of CDCl$_3$ (δ 7.26 ppm for the ^{1}H NMR spectra and δ 77.23 ppm for the ^{13}C NMR spectra) or DMSO-d_6 (δ 2.54 ppm for the ^{1}H NMR spectra and δ 40.45 ppm for the ^{13}C NMR spectra). The high resolution mass spectra were recorded on a double focusing magnetic sector mass spectrometer using electrospray ionization. The melting points are uncorrected.

General Procedure for the Preparation of Isoquinolines/Furopyridines/Thienopyridines. The 2-bromoarylaldehyde (**1**, 1 equiv, 0.5 mmol), a terminal acetylene (**2**, 1.1 equiv, 0.55 mmol), Pd(OAc)$_2$ (2.25 mg, 2 mol %, 0.01 mmol), PPh$_3$ (5.25 mg, 4 mol %, 0.02 mmol), KOAc (98 mg, 2 equiv, 1 mmol), and DMF (2 mL) were mixed in a 5 mL microwave vial. The vial was flushed with nitrogen and sealed with an aluminum/Teflon crimp top. The reaction mixture was stirred at 80 °C under microwave (300 W) irradiation for 1 h until the disappearance of the starting material as monitored by thin layer chromatography. After cooling to room temperature, NH$_4$OAc (77 mg, 2 equiv, 1 mmol) was added to the microwave vial, and the reaction mixture was stirred at 150 °C under microwave irradiation for 2 h until the disappearance of the starting material as monitored by thin layer chromatography. The reaction mixture was diluted with saturated brine (20 mL) and extracted with diethyl ether (3 × 10 mL). The organic layers were combined and washed with water (10 mL) to remove any remaining DMF and then dried over anhydrous MgSO$_4$. The solvent was removed under vacuum, and the residue was purified by flash column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the desired product **3**.

3-(4-Methoxyphenyl)isoquinoline (3a). The compound was obtained as a beige solid (96 mg, 82% yield): mp 102−103 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.33 (s, 1H), 7.80−8.20 (m, 2H), 7.78 (s, 1H), 7.57−7.69 (m, 4H), 7.06−7.40 (m, 2H), 3.90 (s, 3H). The ^{1}H NMR spectral data are in good agreement with the literature data.[8]

3-Tridecylisoquinoline (3b). The compound was obtained as a yellow oil (120 mg, 77% yield): ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.20 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.4 Hz, 1H), 7.45 (s, 1H), 2.92 (t, J = 7.6 Hz, 2H), 1.77−1.83 (m, 2H), 1.31−1.41 (m, 4H), 1.23−1.31 (m, 16H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 156.1, 152.2, 136.7, 130.3, 127.6, 127.2, 126.4, 126.2,118.1, 38.4,32.1, 30.2, 30.0, 29.9, 29.8, 29.7, 29.6, 29.5, 22.9, 14.3; IR (KBr) 2918, 2847, 1629, 1592, 1580, 1468, 965, 884, 759, 743, 719, 667 cm^{-1}; HRMS (EI) calcd for C$_{22}$H$_{33}$N 311.2613, found 311.2615.

3-(Cyclohex-1-en-1-yl)-7-methoxyisoquinoline (3c). The compound was obtained as a white solid (95 mg, 79% yield): mp 116–117 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.09 (s, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.53 (s, 1H), 7.28 (dd, J = 8.9, 2.6 Hz, 1H), 7.18 (d, J = 2.5 Hz, 1H), 6.93–6.94 (m, 1H), 3.93 (s, 3H), 2.54–2.58 (m, 2H), 2.29–2.33 (m, 2H), 1.82–1.87 (m, 2H), 1.68–1.73 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.0, 151.1, 150.3, 135.8, 132.3, 128.6, 128.5, 127.4, 123.5, 114.2, 104.9, 35.6, 26.3, 26.1, 23.1, 22.4; IR (KBr) 2932, 2857, 1651, 1578, 1559, 1540, 1508, 1489, 1456, 1225, 1159, 1026, 889, 856, 668 cm^{-1}; HRMS (EI) calcd for C$_{16}$H$_{17}$NO 239.1310, found 239.1311.

6,7-Dimethoxy-3-(thiophen-3-yl)isoquinoline (3d). The compound was obtained as a beige solid (104 mg, 77% yield): mp 134–136 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.01 (s, 1H), 7.93 (dd, J = 2.8, 0.9 Hz, 1H), 7.75 (s, 1H), 7.67 (dd, J = 5.0, 0.8 Hz, 1H), 7.39 (dd, J = 5.0, 3.1 Hz, 1H), 7.13 (s, 1H), 7.01 (s, 1H), 3.99 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.2, 150.1, 149.1, 146.6, 142.6, 133.3, 126.3, 126.1, 123.7, 122.4, 115.0, 105.4, 104.8, 56.2, 56.1; IR (KBr) 3106, 3092, 2989, 2962, 2938, 2829, 1622, 1593, 1577, 1499, 1459, 1423,1340, 1295, 1247, 1232, 1198, 1151, 1007, 895, 870, 843, 796, 760, 675 cm^{-1}; HRMS (EI) calcd for C$_{15}$H$_{13}$NO$_2$S 271.0667, found 271.0665.

4-(6-Fluoroisoquinolin-3-yl)butanenitrile (3e). The compound was obtained as a yellow oil (92 mg, 86% yield): ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.14 (s, 1H), 7.92–7.95 (m, 1H), 7.46 (s, 1H), 7.28–7.35 (m, 2H), 3.05 (t, J = 7.5 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.16–2.22 (m, 2H); ^{13}C NMR (100 MHz, CDCl$_3$) δ 163.5 (d, J_{C-F} = 251.6 Hz), 153.9, 152.3, 138.0 (d, J_{C-F} = 10.6 Hz), 130.7 (d, J_{C-F} = 9.8 Hz), 124.6, 119.7, 118.6 (d, J_{C-F} = 5.3 Hz), 117.6 (d, J_{C-F} = 25.7 Hz), 109.7 (d, J_{C-F} = 20.9 Hz), 36.4, 25.2, 16.7; IR (KBr) 3084, 3066, 2958, 2911, 2253, 2242, 1633, 1495, 1207, 895, 818, 711, 672 cm^{-1}; HRMS (EI) calcd for C$_{13}$H$_{11}$FN$_2$ 214.0906, found 214.0905.

6-Fluoro-3-(2-methoxyphenyl)isoquinoline (3f). The compound was obtained as a yellow oil (82 mg, 65% yield): ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.31 (s, 1H), 8.17 (s, 1H), 7.98 (dd, J = 9.0, 5.6 Hz, 1H), 7.92 (dd, J = 7.6, 1.8 Hz, 1H), 7.46 (dd, J = 9.5, 2.3 Hz, 1H), 7.38–7.41 (m, 1H), 7.33 (dt, J = 8.8, 2.4 Hz, 1H), 7.13 (dt, J = 7.5, 1.0 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 163.4 (d, J_{C-F} = 252.1 Hz), 157.2, 151.7, 150.2, 137.7 (d, J_{C-F} = 10.4 Hz), 131.6, 130.6 (d, J_{C-F} = 9.7 Hz), 129.9, 128.9, 124.7, 121.2, 120.8 (d, J_{C-F} = 5.3 Hz), 117.7 (d, J_{C-F} = 25.8 Hz), 111.6, 110.4 (d, J_{C-F} = 20.9 Hz), 55.8; IR (KBr) 3007, 2975, 1630, 1496, 1243, 1027, 887, 748 cm^{-1}; HRMS (EI) calcd for C$_{16}$H$_{12}$FNO 253.0903, found 253.0901.

7-(Thiophen-3-yl)-[1,3]dioxolo[4,5-g]isoquinoline (3g). The compound was obtained as a beige solid (103 mg, 81% yield): mp 146–147 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.97 (s, 1H), 7.93 (dd, J = 3.0, 1.3 Hz, 1H), 7.75 (s, 1H), 7.67 (dd, J = 5.0, 1.1 Hz, 1H), 7.40 (dd, J = 5.0, 3.1 Hz, 1H), 7.16 (s, 1H), 7.05 (s, 1H), 6.07 (s, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 151.3, 150.3, 148.3, 147.0, 142.4, 135.2, 126.4, 126.2, 125.0, 122.7, 116.0, 103.4, 102.8, 101.8; IR (KBr) 3106, 3091, 2910, 1598, 1479, 1455, 1231, 1031, 958, 934, 866, 854 cm^{-1}; HRMS (EI) calcd for C$_{14}$H$_9$NO$_2$S 255.0354, found 255.0354.

7-(2-Methoxyphenyl)-[1,3]dioxolo[4,5-g]isoquinoline (3h). The compound was obtained as a white solid (105 mg, 75% yield): mp 121–122 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.08 (s, 1H), 8.03 (s, 1H), 7.85 (dd, J = 7.6, 1.8 Hz, 1H), 7.35–7.38 (m, 1H), 7.20 (s, 1H), 7.08–7.12 (m, 2H), 7.03 (d, J = 8.3 Hz, 1H), 6.10 (s, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 157.1, 151.0, 150.0, 148.8, 148.4, 134.7, 131.5, 129.5, 129.4, 124.8, 121.2, 121.1, 111.5, 103.2, 103.1, 101.7, 55.9; IR (KBr) 3002, 2909, 1597, 1494, 1463, 1450, 1250, 1224, 1040, 1026, 959, 899, 839, 756, 668 cm^{-1}; HRMS (EI) calcd for C$_{17}$H$_{13}$NO$_3$ 279.0895, found 279.0896.

5-(4-Methoxyphenyl)furo[2,3-c]pyridine (3i). The compound was obtained as a yellow solid (72 mg, 64% yield): mp 128–130 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.91 (s, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.88 (s, 1H), 7.74 (t, J = 1.5 Hz, 1H), 7.01 (d, J = 8.8 Hz, 2H), 6.82 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 160.0, 151.5, 151.2, 148.6, 135.2, 133.3, 132.8, 128.4, 114.3, 112.2, 106.5, 55.5; IR (KBr) 3146, 3116, 2965, 2935, 2840, 1607, 1570, 1517, 1457, 1430,

1314, 1284, 1247, 1228, 1023, 878, 843, 818, 780 cm^{-1}; HRMS (EI) calcd for C$_{14}$H$_{11}$NO$_2$ 225.0790, found 225.0786.

5-(2-Methoxyphenyl)thieno[2,3-c]pyridine (3j). The compound was obtained as a yellow solid (66 mg, 55% yield): mp 95–97 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.25 (s, 1H), 8.22 (d, J = 0.9 Hz, 1H), 7.84 (dd, J = 7.6, 1.8 Hz, 1H), 7.69 (d, J = 5.4 Hz, 1H), 7.36–7.40 (m, 2H), 7.11 (dt, J = 7.4, 1.1 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 157.0, 149.9, 145.4, 144.2, 134.8, 132.2, 131.6, 129.6, 129.3, 123.5, 121.2, 119.1, 111.5, 55.8; IR (KBr) 3103, 3005, 2969, 2943, 2839, 1494, 1439, 1235, 1023, 900, 875, 822, 779 cm^{-1}; HRMS (EI) calcd for C$_{14}$H$_{11}$NOS 241.0561, found 241.0559.

5-(Thiophen-3-yl)thieno[2,3-c]pyridine (3k). The compound was obtained as a beige solid (79 mg, 73% yield): mp 120–122 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.14 (t, J = 0.7 Hz, 1H), 7.98 (d, J = 1.0 Hz, 1H), 7.94 (dd, J = 3.0, 1.3 Hz, 1H), 7.70 (dd, J = 5.0, 1.3 Hz, 1H), 7.67 (d, J = 5.4 Hz, 1H), 7.41 (dd, J = 5.0, 3.0 Hz, 1H), 7.35 (dd, J = 5.4, 0.7 Hz, 1H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 148.0, 146.0, 144.4, 142.4, 134.8, 132.6, 126.4, 126.3, 123.3, 122.9, 114.1; IR (KBr) 3095, 3041, 1587, 1446, 1294, 1182, 1031, 860, 798, 764, 665 cm^{-1}; HRMS (EI) calcd for C$_{11}$H$_7$NS$_2$ 217.0020, found 217.0020.

3-(4-Methoxyphenyl)isoquinolin-7-ol (3l). The compound was obtained as a light brown oil (84 mg, 67% yield): ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 (s, 1H), 9.23 (s, 1H), 8.25 (s, 1H), 7.90–7.95 (m, 2H), 7.38–7.43 (m, 2H), 7.34 (d, J = 2.3 Hz, 1H), 7.14 (d, J = 0.8 Hz, 1H), 7.11 (t, J = 0.8 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 157.7, 157.3, 151.0, 146.6, 131.7, 131.0, 130.2, 129.8, 129.6, 129.5, 124.4, 121.6, 121.5, 112.8, 108.7, 56.6; IR (KBr) 3423, 3065, 3003, 2957, 2934, 2834, 1574, 1559, 1540, 1504, 1489, 1457, 1241, 1158, 1025, 827, 752, 667 cm^{-1}; HRMS (EI) calcd for C$_{16}$H$_{13}$NO$_2$ 251.0946, found 251.0945.

4-(Isoquinolin-3-yl)butanenitrile (3m). The compound was obtained as a white solid (81 mg, 83% yield): mp 99–101 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.21 (s, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 8.3 Hz, 1H), 7.68 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.4 Hz, 1H), 7.53 (s, 1H), 3.09 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7.1 Hz, 2H), 2.19–2.25 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 152.7, 152.5, 136.4, 130.6, 127.6, 127.4, 126.9, 126.2, 119.7, 118.9, 36.3, 25.2, 16.6; IR (KBr) 2972, 2948, 2935, 2882, 2853, 2242, 1559, 1541, 1507, 1458, 892, 761, 666 cm^{-1}; HRMS (EI) calcd for C$_{13}$H$_{12}$N$_2$ 196.1000, found 196.1000.

7-Methoxy-3-(thiophen-3-yl)isoquinoline (3n). The compound was obtained as a beige solid (99 mg, 82% yield): mp 154–155 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.15 (s, 1H), 7.96 (dd, J = 3.1, 1.2 Hz, 1H), 7.84 (s, 1H), 7.71 (t, J = 1.3 Hz, 1H), 7.70 (d, J = 1.3 Hz, 1H), 7.41 (dd, J = 5.1, 3.1 Hz, 1H), 7.32 (dd, J = 9.0, 2.5 Hz, 1H), 7.19 (d, J = 2.5 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.4, 151.1, 146.1, 142.5, 132.3, 128.8, 128.4, 126.4, 126.1, 124.0, 122.5, 116.0, 104.9, 55.6; IR (KBr) 3119, 3101, 3007, 2967, 2937, 1587, 1490, 1236, 1208, 1155, 1025, 879, 824, 798, 697 cm^{-1}; HRMS (EI) calcd for C$_{14}$H$_{11}$NOS 241.0561, found 241.0557.

7-Methoxy-3-phenylisoquinoline (3o). The compound was obtained as a white solid (92 mg, 78% yield): mp 158–159 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 9.24 (s, 1H), 8.09–8.11 (m, 2H), 7.99 (s, 1H), 7.76 (d, J = 9.0 Hz, 1H), 7.49–7.52 (m, 2H), 7.38–7.42 (m, 1H), 7.34 (dd, J = 8.9, 2.5 Hz, 1H), 7.22 (d, J = 2.4 Hz, 1H), 3.95 (S, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 158.5, 151.1, 149.8, 139.9, 132.4, 129.0, 128.9, 128.6, 128.4, 126.9, 123.9, 116.6, 104.8, 55.6; IR (KBr) 3065, 3057, 2997, 1557, 1540, 1489, 1457, 1387, 1360, 1235, 1203, 1159, 1027, 880, 847, 760, 694 cm^{-1}; HRMS (EI) calcd for C$_{16}$H$_{13}$NO 235.0997, found 235.0992.

3-(Cyclohex-1-en-1-yl)-6,7-dimethoxyisoquinoline (3p). The compound was obtained as a yellow solid (100 mg, 74% yield): mp 143–145 °C; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.96 (s, 1H), 7.46 (s, 1H), 7.14 (s, 1H), 7.01 (s, 1H), 6.89–6.91 (m, 1H), 3.99 (s, 6H), 2.53–2.56 (m, 2H), 2.27–2.31 (m, 2H), 1.80–1.85 (m, 2H), 1.67–1.72 (m, 2H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 153.0, 151.7, 149.9, 149.2, 135.9, 133.3, 127.4, 123.5, 113.5, 105.5, 105.0, 56.2, 56.1, 26.3, 26.1, 23.1, 22.4; IR (KBr) 2993, 2929, 2862, 2823,1505, 1457, 1247, 1152, 1005 cm^{-1}; HRMS (EI) calcd for C$_{17}$H$_{19}$NO$_2$ 269.1416, found 269.1415.

6-Fluoro-3-tridecylisoquinoline (3q). The compound was obtained as a beige solid (112 mg, 68% yield): mp 60–61 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 9.16 (s, 1H), 7.92 (dd, J = 8.9, 5.6 Hz, 1H), 7.41 (s, 1H), 7.33 (dt, J = 9.6, 1.7 Hz, 1H), 7.27 (dt, J = 8.7, 2.2 Hz, 1H), 2.91 (t, J = 7.8 Hz, 2H), 1.77–1.81 (m, 2H), 1.32–1.40 (m, 4H), 1.25–1.31 (m, 16H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 163.5 (d, J_{C-F} = 251.5 Hz), 157.0, 151.9, 138.2 (d, J_{C-F} = 10.4 Hz), 130.7 (d, J_{C-F} = 10.0 Hz), 124.5, 117.8 (d, J_{C-F} = 5.3 Hz), 117.1 (d, J_{C-F} = 25.6 Hz), 109.6 (d, J_{C-F} = 20.8 Hz), 38.3, 32.1, 30.2, 29.89, 29.86, 29.8, 29.7, 29.63, 29.57, 22.9, 14.4; IR (KBr) 2955, 2919, 2849, 1637, 1494, 1471, 1465, 1209, 1143, 891, 820, 809 cm⁻¹; HRMS (EI) calcd for C₂₂H₃₂FN 329.2519, found 329.2519.

7-(Cyclohex-1-en-1-yl)-[1,3]dioxolo[4,5-g]isoquinoline (3r). The compound was obtained as a yellow solid (98 mg, 77% yield): mp 119–121 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 8.90 (s, 1H), 7.42 (s, 1H), 7.12 (s, 1H), 6.98 (s, 1H), 6.87–6.89 (m, 1H), 3.04 (s, 2H), 2.51–2.54 (m, 2H), 2.26–2.31 (m, 2H), 1.79–1.84 (m, 2H), 1.66–1.71 (m, 2H); ^{13}C NMR (125 MHz, CDCl₃) δ 152.0, 150.9, 149.5, 147.9, 135.8, 135.0, 127.6, 124.7, 114.3, 103.3, 102.8, 101.6, 26.3, 26.1, 23.1, 22.4; IR (KBr) 2931, 2923, 2863, 2818, 1591, 1476, 1452, 1223, 1039, 947, 858 cm⁻¹; HRMS (EI) calcd for C₁₆H₁₅NO₂ 253.1103, found 253.1101.

7-Phenyl-[1,3]dioxolo[4,5-g]isoquinoline (3s). The compound was obtained as a beige solid (93 mg, 75% yield): mp 112–114 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 9.02 (s, 1H), 8.03 (dd, J = 8.5, 1.4 Hz, 2H), 7.87 (s, 1H), 7.45 (t, J = 7.9 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 7.17 (s, 1H), 7.08 (s, 1H), 6.06 (s, 2H); ^{13}C NMR (125 MHz, CDCl₃) δ 151.2, 150.6, 150.2, 148.4, 139.7, 135.1, 128.8, 128.9, 126.9, 125.1, 116.5, 103.2, 102.9, 101.7; IR (KBr) 3057, 3035, 2900, 1483, 1459, 1233, 1047, 963, 885, 756, 691 cm⁻¹; HRMS (EI) calcd for C₁₆H₁₁NO₂ 249.0790, found 249.0789.

5-(Thiophen-3-yl)furo[2,3-c]pyridine (3t). The compound was obtained as a white solid (54 mg, 54% yield): mp 120–122 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 8.88 (s, 1H), 7.85–7.86 (m, 2H), 7.75 (d, J = 2.1 Hz, 1H), 7.67 (dd, J = 5.0, 1.1 Hz, 1H), 7.40 (dd, J = 5.0, 3.1 Hz, 1H), 6.82 (d, J = 1.9 Hz, 1H); ^{13}C NMR (125 MHz, CDCl₃) δ 151.5, 148.7, 147.5, 142.6, 135.1, 133.5, 126.5, 126.4, 122.6, 112.6, 106.4; IR (KBr) 3118, 3103, 1558, 1540, 1521, 1506, 1458, 1230, 1119, 1029, 874, 855, 794, 777, 677 cm⁻¹; HRMS (EI) calcd for C₁₁H₇NOS 201.0248, found 201.0248.

5-(4-Methoxyphenyl)thieno[2,3-c]pyridine (3u). The compound was obtained as a yellow solid (80 mg, 66% yield): mp 107–108 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 9.18 (s, 1H), 8.03 (d, J = 0.8 Hz, 1H), 7.99–8.02 (m, 2H), 7.67 (d, J = 5.4 Hz, 1H), 7.35 (d, J = 5.4 Hz, 1H), 7.00–7.03 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 160.2, 151.7, 146.2, 144.3, 134.6, 132.5, 128.3, 123.4, 114.3, 113.7, 55.5; IR (KBr) 3102, 3081, 3000, 2964, 2933, 2909, 2836, 1603, 1586, 1506, 1417, 1281, 1184, 1035, 1017, 837, 816, 769, 647 cm⁻¹; HRMS (EI) calcd for C₁₄H₁₁NOS 241.0561, found 241.0559.

5-Phenylthieno[2,3-c]pyridine (3v). The compound was obtained as a yellow solid (53 mg, 50% yield): mp 78–79 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 9.22 (s, 1H), 8.11 (s, 1H), 8.07 (dd, J = 8.4, 1.1 Hz, 2H), 7.70 (d, J = 5.4 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.42 (t, J = 7.2 Hz, 1H), 7.38 (d, J = 5.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl₃) δ 151.9, 146.1, 144.4, 139.9, 135.2, 132.6, 128.9, 128.6, 127.1, 123.4, 114.6; IR (KBr) 3082, 3053, 3023, 1542, 1532, 1475, 1438, 1393, 1298, 1236, 1188, 1065, 900, 870, 761, 691 cm⁻¹; HRMS (EI) calcd for C₁₃H₉NS 211.0456, found 211.0453.

3-(tert-Butyl)isoquinoline (3w). The compound was obtained as a colorless oil (35 mg, 38% yield): ^{1}H NMR (500 MHz, CDCl₃) δ 9.24 (s, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.63 (dt, J = 7.6, 0.9 Hz, 1H), 7.61 (s, 1H), 7.52 (dt, J = 7.5, 0.8 Hz, 1H), 1.47 (s, 9H). The ^{1}H NMR spectral data are in good agreement with the literature data.[12]

3-(2-Methoxyphenyl)-1-methylisoquinoline (3y). The compound was prepared using the general procedure except that 1-(2-iodophenyl) ethanone was used instead of 2-bromoarylaldehyde. The compound was obtained as a beige solid (22 mg, 18% yield): mp 90–91 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 8.13 (dd, J = 8.5, 0.4 Hz, 1H), 8.05 (s, 1H), 7.93 (dd, J = 7.6, 1.8 Hz, 1H), 7.84 (d, J = 8.2 Hz,

1H), 7.66 (dt, J = 7.0, 1.0 Hz, 1H), 7.57 (dt, J = 7.0, 1.2 Hz, 1H), 7.35–7.39 (m, 1H), 7.12 (dt, J = 7.5, 1.0 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 3.89 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 158.2, 157.3, 148.1, 136.4, 131.6, 130.0, 129.6, 129.5, 127.9, 126.9, 126.4, 125.9, 121.3, 120.1, 111.6, 55.9, 22.8; IR (KBr) 3007, 2935, 2836, 1557, 1539, 1490, 1458, 1435, 1267, 1238, 1025, 753, 668 cm⁻¹; HRMS (EI) calcd for C₁₇H₁₅NO 249.1154, found 249.1150.

3-(4-Methoxyphenyl)-1-methylisoquinoline (3z). The compound was prepared using the general procedure except that 1-(2-iodophenyl) ethanone was used instead of 2-bromoarylaldehyde. The compound was obtained as a beige solid (20 mg, 16% yield): mp 54–56 °C; ^{1}H NMR (500 MHz, CDCl₃) δ 8.08–8.12 (m, 3H), 7.84 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.63–7.66 (m, 1H), 7.52–7.55 (m, 1H), 7.02–7.04 (m, 2H), 3.88 (s, 3H), 3.03 (s, 3H); ^{13}C NMR (125 MHz, CDCl₃) δ 160.2, 158.6, 149.9, 137.1, 132.7, 130.2, 128.4, 127.7, 126.6, 126.4, 125.8, 114.33, 114.30, 55.6, 22.9; IR (KBr) 3073, 3057, 2994, 2959, 2917, 2836, 1607, 1514, 1250, 1176, 1028, 841, 668 cm⁻¹; HRMS (EI) calcd for C₁₇H₁₅NO 249.1154, found 249.1155.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

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