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TMEDA-Assisted Effective Direct Ortho Arylation of Electron-Deficient *N*-Heteroarenes with Aromatic Grignard Reagents

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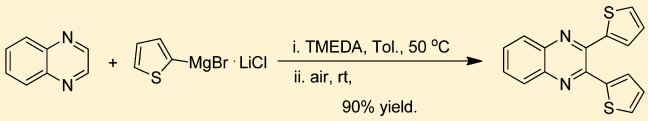
Supporting Information

ABSTRACT: In the addition of TMEDA in toluene, aryl Grignards could effectively and site-specifically ortho-arylate electron-deficient heteroarenes under mild conditions. This endeavor successfully changed the old low-yielding reaction, aryl Grignard addition to *N*-heteroarenes, into an efficient procedure for heterobiaryls. The combination of the inexpensive aryl Grignards, TMEDA, the cost-free air, no use of any transition-metal catalyst, the mild reaction conditions, and the high-yielding gram-scale results enables this new procedure to be cost-effective and potentially utilizable in industry.



INTRODUCTION

Currently, direct ortho arylations of electron-deficient *N*-heteroarenes, such as pyridines, quinolines, and isoquinolines, are attracting intensive research interest because the target heterobiaryls are central synthetic motifs of biologically active molecules[1] and useful materials.[2] Several different methods have been developed to prepare heterobiaryls from electron-deficient *N*-heteroarenes. Naturally, the successful cross-coupling methods of aryl halides with aryl metallics allowed access to these heterobiaryls, which comprised ortho-metalated pyridine or quinoline coupling with aryl halides[3] and ortho halo or tosyl heteroarenes with aryl metallics.[4] The common limitation of these methods is the indispensable preparation of ortho-halogenated or -tosylated heteroarenes prior to coupling. Ortho C−H functionalization with aryl halides[5a−d] or arylboronic acids[5e] catalyzed by transition metals was another disclosed protocol with moderate to good yields, in which a higher than 100 °C reaction temperature was generally needed. *N*-Oxides are effective surrogates of activated electron-deficient arenes; the cross-coupling of *N*-oxide-activated pyridines with haloarenes or tosylarenes was the most developed procedure in the catalysis of transition metals.[6] Other reported *N*-activations of pyridines comprised *N*-phenacyl and imino modes.[7] Furthermore, *N*-oxidized pyridine direct oxidative coupling with unactivated arenes was recently reported.[8] Activated *N*-heteroarenes with *N*-oxides considerably facilitated the direct ortho arylation of heteroarenes, but as the prior preparation of *N*-oxides and later elimination of the activating group was apparently unavoidable, this major limitation unavoidably increased the cost of the protocols and reduced their applicability. The additional transition-metal-catalyzed ortho arylation comprised the 1,2-addition/oxidation strategy of aryl metallics to heteroarenes at high reaction temperatures.[9]

All of these aforementioned protocols were chiefly based on transition-metal catalysis. To date the transition-metal-free procedures have mainly comprised direct ortho addition of aryl Grignards to *N*-oxide activated pyridines[10] and KO-*t*-Bu promoted direct coupling of pyrazine and pyridine with iodoarenes.[11] We are particularly interested in the transition-metal-free direct arylation of unactivated *N*-heteroarenes with aryl Grignards, because it has the advantages of no need for preparation of ortho halo or tosyl heteroarenes, no need for prior installation of activating groups and subsequent removal, and no need for the preparation of scarcely available and unstable heteroaryl metallics. Obviating the use of expensive and potentially toxic transition metals would further effectively eliminate the serious demand for their complete removal in the latter stages of the pharmaceutical synthesis. Additionally, inexpensive and readily available aryl Grignards and no need for very high reaction temperatures would undoubtedly reduce the cost and facilitate future industrial applications. It has long been known that aryl Grignards or lithiums can undergo 1,2-addition to unactivated *N*-heteroarenes and successive oxidation to furnish ortho arylation with oxidizing reagents; however, the low to moderate arylated yields render this procedure nearly impractical.[12] This situation stimulated the discovery of the aforementioned various methods for bypassing this procedure. Up to today, this procedure is basically undeveloped and remains a great challenge. On the basis of our recent research experience

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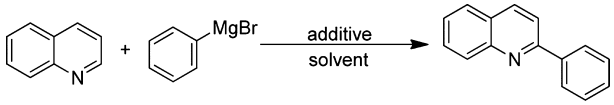
with Grignards,[13] we envisioned that some proper additive would probably enhance the arylation and upgrade the old procedure to be an efficient one. In this work we finally found that TMEDA could meet this serious requirement very well. This procedure is a good complement to the reported protocols for heterobiaryl preparation in a low-cost manner.

RESULTS AND DISCUSSION

We screened the solvents, and the results showed that toluene was optimal (THF was removed under vacuum and then toluene was introduced). Toluene gave a 76% isolated yield, much higher than that for THF (Table 1, entries 1−3). Then in toluene, a series of chelating additives were screened (entries 4−8). Only TMEDA and BDMAEE enhanced the yield, and TMEDA achieved the highest yield (up to 88%). TMEDA, as an easily available low-cost chelating additive, made this new procedure inexpensive. The load experiment of TMEDA showed that 1.0 equiv of TMEDA with respect to quinoline was optimal (entries 6 and 9−13). The amount of aryl Grignards used had a great influence on the yield (entries 14−18). The observation indicated that 3.0 equiv of PhMgBr was satisfactory (entry 6); lower amounts of Grignards led to decreased yield, but more than 3.0 equiv did not raise the yield any further. Finally, the reaction temperature was screened and 50 °C proved to be ideal (entries 6, 19, and 20). Normally, a small amount of 1,2-dihydroquinoline as an intermediate was included in the reaction mixture, but it was not necessary to add any additional oxidant. After the reaction was quenched, keeping the reaction mixture in the air for at most 12 h changes this small amount of impurity into oxidized quinoline and thus increases the yield. The cost-free air not only substantially caused the protocol to be environmentally friendly but also greatly decreased the expense of the procedure.

Table 1. Optimization of the Reaction Conditions[a]



entry	amt of PhMgBr (mmol)	additive (amt (mmol))[b]	solvent	temp (°C)	yield (%)[c]
1	0.9		THF	50	47
2	0.9		DCE[d]	50	62
3	0.9		toluene	50	76
4	0.9	NMM (0.3)	toluene	50	74
5	0.9	DMAP (0.3)	toluene	50	29
6	0.9	TMEDA (0.3)	toluene	50	88
7	0.9	BDMAEE (0.3)	toluene	50	80
8	0.9	HMTA (0.3)	toluene	50	51
9	0.9	TMEDA (0.18)	toluene	50	79
10	0.9	TMEDA (0.24)	toluene	50	84
11	0.9	TMEDA (0.36)	toluene	50	84
12	0.9	TMEDA (0.42)	toluene	50	83
13	0.9	TMEDA (0.48)	toluene	50	74
14	0.45	TMEDA (0.3)	toluene	50	73
15	0.6	TMEDA (0.3)	toluene	50	78
16	0.75	TMEDA (0.3)	toluene	50	82
17	1.05	TMEDA (0.3)	toluene	50	88
18	1.2	TMEDA (0.3)	toluene	50	89
19	0.9	TMEDA (0.3)	toluene	30	55
20	0.9	TMEDA (0.3)	toluene	70	84

[a]0.3 mmol of quinoline was used. [b]NMM is *N*-methylmorpholine, DMAP is 4-dimethylaminopryidine, TMEDA is tetramethylethylenediamine, BDMAEE is 2,2′-oxybis-(*N*,*N*-dimethylethanamine), and HMTA is hexamethylenetetramine(methenamine), respectively. [c]Isolated yield. [d]DCE is 1,2-dichloroethane.

With the optimized reaction conditions, the scope of aryl Grignards was first evaluated with quinoline (Table 2; **1**−**13**). As can be seen, normally aryl Grignards with electron-donating groups afforded excellent yields, while those with electron-withdrawing groups gave slightly lower yields. Heterobiaryls with two heteroarene units were mainly obtained with the activated deficient heteroarenes in transition-metal catalysis.[6c,d,7b,8b,10c] The transition-metal-catalyzed addition/oxidation procedures using orgnometallics did not report similar target products.[9] Herein the hard-to-prepare heteroaryl Grignards were synthesized using Knochel's method[4a,14] and heterobiaryls with two heteroarene units were thereby obtained in good to high yield (**11**−**13**). Then quinoline derivatives were investigated (**14**−**24**). 3-Bromoquinoline always gave high yields with various aryl Grignards, and the highest yield was 96% (**14**−**19**). Methyl-substituted quinolines gave good to high yields with different aryl Grignards (**20**−**24**).

Second, we evaluated the Grignard addition to isoquinolines (Table 3). The addition reaction was fully site-specific; it only gave isoquinolines with 1-arylation. For aryl Grignards, the highest yield was 64% with 4-MeC_6H_4MgBr (**26**). Bromo-substituted isoquinoline gave higher yields than isoquinoline itself, and 4-MeC_6H_4MgBr again gave the highest yield (**30**).

Unactivated pyridines are normally difficult substrates.[12] We next explored the direct ortho arylation of pyridines. Pyridine itself failed to give the ortho coupling product. Two 3-substituted pyridines were further investigated (Scheme 1). They both resulted in moderate yields with 6-addition, probably owing to the steric hindrance.

Quinoxaline is an interesting scaffold for many key materials and pharmacological compounds with the inclusion of two nitrogen atoms.[15] Recently, 2,3-diarylated quinoxalines were of particular interest for their proportionation of radical anions.[16] Our protocol could readily furnish these ortho-diarylated quinoxalines in excellent yield at 50 °C (Table 4). In contrast, the reaction temperature was much milder than that for the reported transition-metal catalytic version and diarylation was exclusively afforded in this work.[9b] It is notable that the transition-metal-catalyzed cross-coupling of halogenated quinoxaline with aryl Grignards[4a] and KO-*t*-Bu-promoted coupling of quinoxaline with iodobenzene[11] both only afforded monoarylated quinoxalines. Herein, even the heteroaryl Grignard resulted in high yield. To our knowledge, this is the first report about a heteroarene coupling with quinoxaline to obtain 2,3-diarylated heterotriaryls.

Finally, the easily handled, readily available, and inexpensive Grignard reagents and the mild reaction conditions spurred us to explore the gram-scale preparation of the heterobiaryls. To our gratification, 2.0 g of quinoline successfully afforded a high 83% yield (Scheme 2). This result renders this protocol highly potentially useful in industry.

CONCLUSION

In conclusion, we have demonstrated that TMEDA could efficiently enhance the direct ortho arylation of electron-deficient *N*-heteroarenes with aryl Grignards under mild reaction conditions, successfully upgrading the old low-yielding procedure to be a practical method in the preparation of ortho-arylated heterobiaryls as well as the interesting quinoxaline-derived heterotriaryls. The readily available and inexpensive aryl

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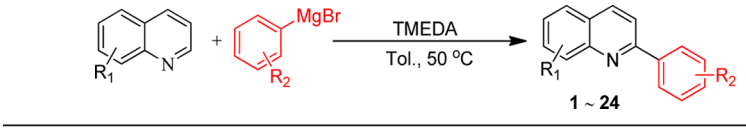
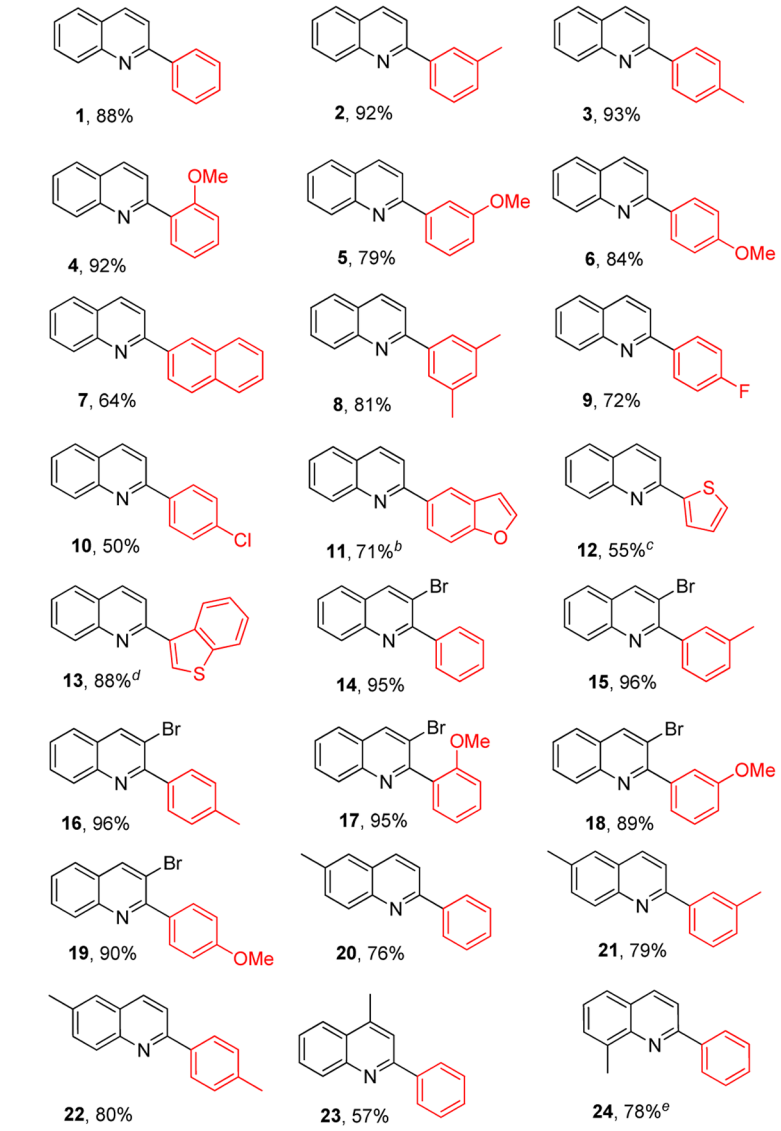
Table 2. Aryl Grignard Addition to Quinolines[a]





[a]ArMgBr/quinoline/TMEDA = 0.9/0.3/0.3 mmol. A 1.0 mL portion of toluene was used, and the reaction was carried out for 10 h at 50 °C. The crude product contained a small amount of 1,2-dihydroquinoline derivatives, which was oxidized to quinoline in air for 12 h at ambient temperature. The yield is the isolated yield. [b]The reaction time was 17 h. [c]ArMgBr/quinoline/TMEDA = 1.5/0.3/0.3, 36 h. [d]ArMgBr/quinoline/TMEDA = 1.5/0.3/0.3, 24 h. [e]The reaction time was 24 h at 70 °C.

Grignards and TMEDA, the cost-free air, the obviation of the need for a transition metal or prior installation and later elimination of any activating group, and the mild reaction conditions are prominent features of this report; these features make this protocol very cost-effective. Furthermore, the successful gram-scale experiment endows this protocol with potential utility in industry for pharmaceutical and material synthesis.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under an argon atmosphere, and solvents were dried according to the established procedures. Reactions were monitored by thin-layer chromatography (TLC); column chromatography purifications were carried out using silica gel. All reagents were purchased from commercial vendors unless otherwise stated. Grignard reagents were freshly prepared from magnesium powder with the corresponding bromides according to the established procedure[17] or Knochel's method, and their concentrations were determined by titration according to Love's method.[18] Melting points are uncorrected and were recorded on an X-4 melting point apparatus. HR-MS were measured by the ESI method with a Q-TOF mass spectrometer. ^{1}H NMR and ^{13}C NMR spectra were measured on 400 and 300 MHz spectrometers (NMR in $CDCl_3$ with TMS as an internal standard), and resonances are given in ppm.

General Procedure for the Arylation of the *N*-Heteroarenes. The aryl Grignard was prepared according to the established procedure,[17] and their concentrations were determined by titration according to Love's method.[18] The aryl Grignard (0.9 mmol) in THF

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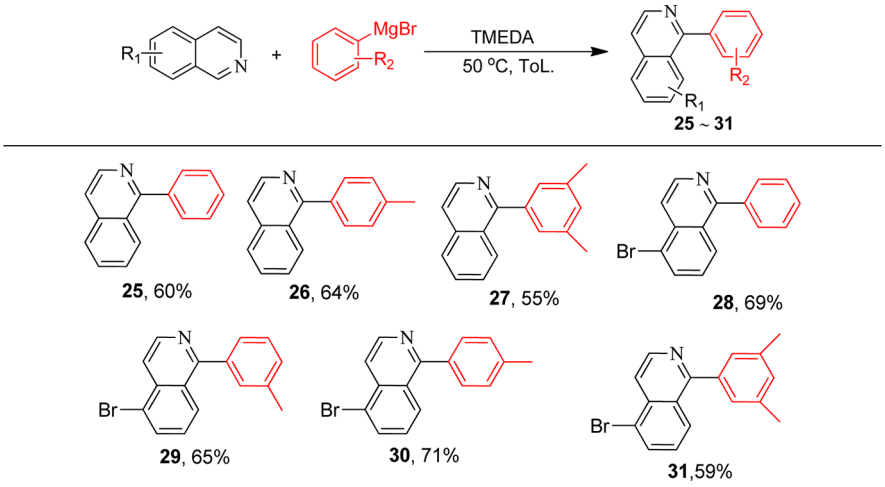
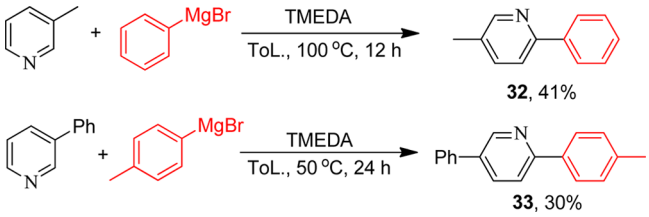
Table 3. Aryl Grignard Addition to Isoquinolines[a]

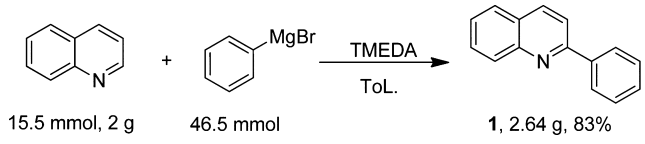


[a]ArMgBr/quinoline/TMEDA = 0.9/0.3/0.3 mmol. A 1.0 mL portion of toluene was used, and the reaction was carried out for 12 h at 70 °C for **25**–**27** and for 17 h at 50 °C for **28**–**31**. The crude product contained a small amount of 1,2-dihydroquinoline derivatives, which was able to be oxidized to quinoline in air for 12 h at ambient temperature. The yield is the isolated yield.

Scheme 1. Aryl Grignard Addition to Pyridines



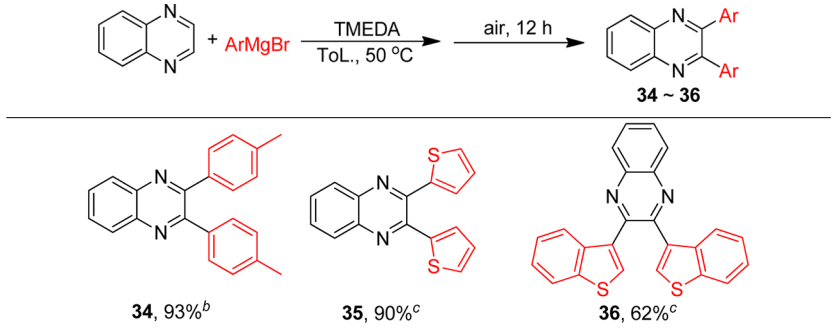
Scheme 2. Gram-Scale Ortho Arylation of Quinoline with the Grignard



was condensed to near-dryness under vacuum, and 1.0 mL of toluene was added to dissolve it under an argon atmosphere. Then TMEDA (0.3 mmol, 45.6 μL) was introduced into the Grignard reagent solution at room temperature. The mixture was stirred for 30 min, and the *N*-heteroarene (0.3 mmol) was successively introduced. The reaction mixture was stirred for 10 h at 50 °C. After the completion was checked with TLC, the reaction mixture was cooled to 0 °C and aqueous NH_4Cl was added dropwise to quench the reaction; then the mixture so obtained was stirred in the open air. After about 12 h the reaction mixture was checked with TLC, and then the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed successively with water and a small amount of brine, and dried with anhydrous Na_2SO_4. The combined filtrates were concentrated under vacuum to give the crude product. Finally purification by column chromatography afforded the target heterobiaryl.

General Procedure for the Arylation of the *N*-Heteroarene with the Heteroaryl Grignard Prepared with LiCl. The heteroaryl Grignards were prepared according to Knochel's method,[14] and their concentrations were determined by titration according to Love's method.[18] The heteroaryl aryl Grignard (1.5 mmol) in THF was condensed to near-dryness under vacuum, and 1.0 mL of toluene was added to dissolve it under an argon atmosphere. Then TMEDA (0.3 mmol, 45.6 μL) was introduced into the Grignard reagent solution at room temperature. The mixture was stirred for 30 min, and the *N*-heteroarene (0.3 mmol) was successively introduced. The reaction mixture was stirred for 36 h at 50 °C. After the completion was checked with TLC, the reaction mixture was cooled to 0 °C and aqueous NH_4Cl was added dropwise to quench the reaction; then the mixture so obtained was stirred in the open air. After about 12 h the reaction mixture was checked with TLC, and then the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, washed successively with water and a small amount of brine, and dried with anhydrous Na_2SO_4. The combined filtrates were concentrated under vacuum to give the crude product. Finally purification by column chromatography afforded the target heterobiaryls **12**, **13**, **35**, and **36**, respectively.

Table 4. Aryl Grignard Addition to Quinoxaline[a]



[a]ArMgBr/quinoxaline/TMEDA = 0.9/0.3/0.3 mmol. For **35** and **36**, 5.0 equiv Grignard was used. The yield is the isolated yield. [b]16 h. [c]36 h.

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*2-Phenylquinoline (**1**; Table 2):*[4d,5b] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); pale yellow solid; yield 88% (54.1 mg); mp 73 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43−7.56 (m, 4H), 7.73 (t, J = 5.9 Hz, 1H), 7.78−7.88 (m, 2H), 8.13−8.23 (m, 4H).

*2-(m-Tolyl)quinoline (**2**; Table 2):*[19] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 92% (60.5 mg); mp 36 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19−8.15 (m, 2H), 8.00 (s, 1H), 7.91 (d, J = 7.7 Hz, 1H), 7.85−7.77 (m, 2H), 7.75−7.67 (m, 1H), 7.52−7.47 (m, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.30−7.21 (m, 1H), 2.47 (s, 3H).

*2-(p-Tolyl)quinoline (**3**; Table 2):*[5b] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 93% (61.2 mg); mp 78 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18−8.13 (m, 2H), 8.06 (d, J = 8.0 Hz, 2H), 7.83−7.76 (m, 2H), 7.73−7.65 (m, 1H), 7.51−7.45 (m, 1H), 7.31 (d, J = 8.1 Hz, 2H), 2.41 (s, 3H).

*2-(2-Methoxyphenyl)quinoline (**4**; Table 2):*[20] column chromatography, silica gel (PE/EA, from 80/1 to 20/1); yellow solid; yield 92% (65.2 mg); mp 59 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23−8.17 (m, 2H), 7.88−7.78 (m, 3H), 7.77−7.71 (m, 2H), 7.55−7.50 (m, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.05−7.01 (m, 1H), 3.94 (s, 3H).

*2-(3-Methoxyphenyl)quinoline (**5**; Table 2):*[20] column chromatography, silica gel (PE/EA, from 80/1 to 20/1); pale yellow oil; yield 79% (55.7 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.13 (dd, J = 8.2, 1.0 Hz, 1H), 7.71 (m, 2H), 7.58−7.49 (m, 3H), 7.36 (m, 1H), 7.32−7.12 (m, 2H), 2.43 (s, 3H).

*2-(4-Methoxyphenyl)quinoline (**6**; Table 2):*[4d] column chromatography, silica gel (PE/EA, from 80/1 to 20/1); white solid; yield 84% (59.2 mg); mp 113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21−8.11 (m, 4H), 7.82 (t, J = 8.7 Hz, 2H), 7.74−7.67 (m, 1H), 7.53−7.46 (m, 1H), 7.08−7.02 (m, 2H), 3.88 (s, 3H).

*2-(Naphthalen-2-yl)quinoline (**7**; Table 2):*[5b,9a] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 64% (49.0 mg); mp 169 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (s, 2H), 7.99−7.86 (m, 7H), 7.53−7.50 (m, 4H).

*2-(3,5-Dimethylphenyl)quinoline (**8**; Table 2):*[5b] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); colorless oil; yield 81% (56.6 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23−8.11 (m, 2H), 7.87−7.66 (m, 5H), 7.51−7.47 (m, 1H), 7.09 (s, 1H), 2.43 (s, 6H).

*2-(4-Fluorophenyl)quinoline (**9**; Table 2):*[5b] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 72% (48.2 mg); mp 85 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25−8.09 (m, 4H), 7.83−7.75 (m, 2H), 7.75−7.67 (m, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.26−7.14 (m, 2H).

*2-(4-Chlorophenyl)quinoline (**10**; Table 2):*[4d,5b] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 50% (35.9 mg); mp 107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25−8.07 (m, 4H), 7.82 (d, J = 8.6 Hz, 2H), 7.76−7.70 (m, 1H), 7.57−7.45 (m, 3H).

*2-(Benzofuran-5-yl)quinoline (**11**; Table 2):* column chromatography, silica gel (PE/EA, from 80/1 to 20/1); white solid; yield 71% (52.2 mg); mp 70 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (d, J = 1.7 Hz, 1H), 8.25−8.10 (m, 3H), 7.90 (d, J = 8.6 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.77−7.68 (m, 1H), 7.67−7.61 (m, 2H), 7.51 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 155.7, 148.2, 145.7, 136.7, 134.8, 129.6, 129.5, 128.0, 127.4, 126.9, 126.1, 124.2, 120.6, 119.1, 111.6, 107.1; HR-MS calcd for $C_{17}H_{11}NO$ ($[M + H]^+$) 246.0913, found 246.0916.

*2-(Thiophen-2-yl)quinoline (**12**; Table 2):*[20] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 55% (34.8 mg); mp 131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.08 (m, 2H), 7.79−7.66 (m, 4H), 7.49−7.45 (m, 2H), 7.25−7.13 (m, 1H).

*2-(Benzo[b]thiophen-3-yl)quinoline (**13**; Table 2):*[21] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 88% (68.9 mg); mp 81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 1H), 8.24−8.17 (m, 2H), 7.94−7.71 (m, 5H), 7.55−7.32 (m, 3H).

*3-Bromo-2-phenylquinoline (**14**; Table 2):*[22] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); pale yellow solid; yield 95% (80.7 mg); mp 86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.77−7.71(m, 4H), 7.58−7.44 (m, 4H).

*3-Bromo-2-(m-tolyl)quinoline (**15**; Table 2):* column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 96% (85.5 mg); mp 87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.74−7.63 (m, 4H), 7.53 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 146.5, 139.8, 137.0, 129.9, 129.4, 129.3, 128.7, 128.1, 128.0, 127.2, 126.7, 126.4, 116.9, 21.4; HR-MS calcd for $C_{16}H_{12}BrN$ ($[M + H]^+$) 298.0253, found 298.0255.

*3-Bromo-2-(p-tolyl)quinoline (**16**; Table 2):*[22] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); paleyellow solid; yield 96% (85.5 mg); mp 92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.12 (d, J = 8.4 Hz, 1H), 7.75−7.64 (m, 4H), 7.52 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H).

*3-Bromo-2-(2-methoxyphenyl)quinoline (**17**; Table 2):* column chromatography, silica gel (PE/EA, from 80/1 to 20/1); white solid; yield 95% (89.2 mg); mp 143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.79−7.72 (m, 2H), 7.59−7.55 (m, 1H), 7.44−7.39 (m, 1H), 7.32−7.24 (m, 2H), 7.04−6.96 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.0, 146.4, 139.9, 130.0, 129.8, 129.5, 129.1, 128.2, 127.4, 126.4, 121.8, 114.8, 114.7, 55.3; HR-MS calcd for $C_{16}H_{12}BrNO$ ($[M - Br + H]^+$) 236.1070, found 236.1074.

*3-Bromo-2-(3-methoxyphenyl)quinoline (**18**; Table 2):* column chromatography, silica gel (PE/EA, from 80/1 to 20/1); white solid; yield 89% (83.6 mg); mp 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.79−7.72 (m, 2H), 7.60−7.55 (m, 1H), 7.44−7.39 (m, 1H), 7.32−7.25 (m, 2H), 7.04−7.00 (m, 1H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.0, 146.4, 141.0, 140.0, 130.1, 129.5, 129.1, 128.2, 127.5, 126.4, 121.8, 116.8, 114.8, 114.7, 55.3; HR-MS calcd for $C_{16}H_{12}BrNO$ ($[M - Br + H]^+$) 236.1070, found 236.1075.

*3-Bromo-2-(4-methoxyphenyl)quinoline (**19**; Table 2):* column chromatography, silica gel (PE/EA, from 80/1 to 20/1); white solid; yield 90% (84.5 mg); mp 122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.76−7.69 (m, 4H), 7.55−7.51 (t, J = 7.6 Hz, 1H), 7.20 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 157.6, 146.5, 139.9, 132.2, 130.9, 129.9, 129.3, 127.9, 127.1, 126.3, 117.0, 113.3, 55.3; HR-MS calcd for $C_{16}H_{12}BrNO$ ($[M - Br + H]^+$) 236.1070, found 236.1078.

*6-Methyl-2-phenylquinoline (**20**; Table 2):*[23] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 76% (50.1 mg); mp 66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15−8.05 (m, 4H), 7.78 (d, J = 8.8 Hz, 1H), 7.55−7.43 (m, 5H), 2.52 (s, 3H).

*6-Methyl-2-(m-tolyl)quinoline (**21**; Table 2):*[24] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 79% (55.3 mg); mp 76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−7.98 (m, 3H), 7.88 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.53 (s, 2H), 7.41−7.36 (m, 1H), 7.26−7.23 (m, 1H), 2.51 (s, 3H), 2.45 (s, 3H).

*6-Methyl-2-(p-tolyl)quinoline (**22**; Table 2):*[25] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 80% (56.0 mg); mp 133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.03 (m, 4H), 7.80 (d, J = 8.4 Hz, 1H), 7.56−7.52 (m, 2H), 7.31 (d, J = 7.6 Hz, 2H), 2.53 (s, 3H), 2.42 (s, 3H).

*4-Methyl-2-phenylquinoline (**23**; Table 2):*[9b] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 57% (37.5 mg); mp 49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19−8.12 (m, 3H), 7.95−7.92 (m, 1H), 7.71−7.66 (m, 2H), 7.52−7.40 (m, 4H), 2.70 (s, 3H).

*8-Methyl-2-phenylquinoline (**24**; Table 2):*[23] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow oil; yield 78% (51.3 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.17 (m, 3H), 7.91 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.58−7.39 (m, 5H), 2.91 (s, 3H).

*1-Phenylisoquinoline (**25**; Table 3):*[4d,7b] column chromatography, silica gel (PE/EA, from 40/1 to 15/1); white solid; yield 60% (36.9 mg); mp 79 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (d, J = 5.7 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.74−7.62 (m, 4H), 7.58−7.47 (m, 4H).

*1-(p-Tolyl)isoquinoline (**26**; Table 3):*[4d] column chromatography, silica gel (PE/EA, from 40/1 to 15/1); yellow oil; yield 64% (42.1 mg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (d, J = 5.8 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.74−7.50 (m, 5H), 7.36−7.28 (m, 2H), 2.45 (s, 3H).

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*1-(3,5-Dimethylphenyl)isoquinoline (**27**; Table 3):*[26] column chromatography, silica gel (PE/EA, from 40/1 to 15/1); yellow solid; yield 55% (38.5 mg); mp 26 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.58 (d, J = 5.7 Hz, 1H), 8.13 (d, J = 8.5 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.73−7.61 (m, 2H), 7.54 (dd, J = 11.3, 4.0 Hz, 1H), 7.30 (s, 2H), 7.13 (s, 1H), 2.40 (s, 6H).

*5-Bromo-1-phenylisoquinoline (**28**; Table 3):* column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 69% (58.8 mg); mp 65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (d, J = 5.9 Hz, 1H), 8.13−7.93 (m, 3H), 7.72−7.61 (m, 2H), 7.59−7.49 (m, 3H), 7.42−7.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1, 143.7, 143.3, 135.9, 133.8, 133.7, 129.9, 128.7, 128.3, 127.8, 127.3, 121.9, 118.8; HR-MS calcd for $C_{15}H_{10}BrN$ ($[M + H]^+$) 284.0069, found 284.0075.

*5-Bromo-1-(m-tolyl)isoquinoline (**29**; Table 3):* column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 65% (57.8 mg); mp 56 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.70 (d, J = 5.9 Hz, 1H), 8.12−7.94 (m, 3H), 7.52−7.29 (m, 5H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 143.6, 143.3, 139.0, 138.2, 135.9, 133.8, 130.5, 129.5, 128.1, 127.9, 127.6, 127.3, 127.0, 121.9, 118.7, 21.5; HR-MS calcd for $C_{16}H_{12}BrN$ ($[M + H]^+$) 298.0226, found 298.0232.

*5-Bromo-1-(p-tolyl)isoquinoline (**30**; Table 3):* column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 71% (63.5 mg); mp 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 5.9 Hz, 1H), 8.11−8.08 (m, 1H), 8.00−7.94 (m, 2H), 7.56 (d, J = 8.1 Hz, 2H), 7.39−7.30 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 143.4, 138.7, 136.2, 135.9, 133.6, 129.9, 129.0, 127.9, 127.6, 127.2, 121.9, 118.4, 21.3; HR-MS calcd for $C_{16}H_{12}BrN$ ($[M + H]^+$) 298.0226, found 298.0229.

*5-Bromo-1-(3,5-dimethylphenyl)isoquinoline (**31**; Table 3):* column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 59% (55.5 mg); mp 104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (d, J = 6.0 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 8.01−7.94 (m, 2H), 7.37 (dd, J = 8.4, 7.6 Hz, 1H), 7.26 (d, J = 0.6 Hz, 2H), 7.14 (s, 1H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 143.4, 139.0, 137.9, 135.8, 133.7, 130.4, 127.8, 127.2, 121.8, 118.6, 21.3; HR-MS calcd for $C_{17}H_{14}BrN$ ($[M + H]^+$) 312.0382, found 312.0385.

*2-Methyl-5-phenylpyridine (**32**; Scheme 1):*[7b] column chromatography, silica gel (PE/EA, from 40/1 to 10/1); yellow oil; yield 41% (20.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 4.4 Hz, 1H), 7.62−7.37 (m, 6H), 7.22−7.13 (m, 1H), 2.36 (s, 3H).

*5-Phenyl-2-(p-tolyl)pyridine (**33**; Scheme 1):*[27] column chromatography, silica gel (PE/EA, from 40/1 to 20/1); white solid; yield 30% (22.2 mg); mp 104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.96−7.92 (m, 3H), 7.77 (d, J = 8.4 Hz, 1H), 7.64−7.61 (m, 2H), 7.51−7.24 (m, 5H), 2.42 (s, 3H).

*2,3-Di-p-tolylquinoxaline (**34**; Table 4):*[28] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); white solid; yield 93% (86.4 mg); mp 132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89−6.82 (m, 8H), 6.53−6.43 (m, 4H), 2.16 (s, 6H).

*2,3-Bis(thiophen-2-yl)quinoxaline (**35**; Table 4):*[29] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 90% (79.4 mg); mp 129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H), 7.75−7.72 (m, 2H), 7.50 (d, J = 5.2 Hz, 2H), 7.27−7.24 (m, 2H), 7.03−7.06 (m, 2H).

*2,3-Bis(benzo[b]thiophen-5-yl)quinoxaline (**36**; Table 4):*[30] column chromatography, silica gel (PE/EA, from 80/1 to 40/1); yellow solid; yield 62% (73.4 mg); mp 172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25−8.22 (m, 2H), 8.03−8.00 (m, 2H), 7.85−7.81 (m, 4H), 7.37−7.24 (m, 6H).

■ ASSOCIATED CONTENT

Supporting Information

Figures giving NMR spectra of the 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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