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A Metal-Free Approach for Brønsted Acid Promoted C–H Alkylation of Heteroarenes with Alkyl Peroxides

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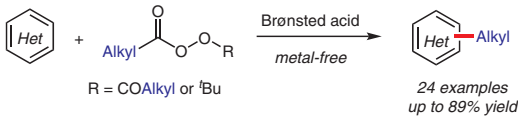

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Abstract A metal-free protocol for Minisci C–H alkylation of heteroarenes using alkyl peroxides as the alkylating reagents and internal oxidants simultaneously under promotion of Brønsted acid has been demonstrated. A series of alkyl substituted heteroarenes were readily prepared by the C–H alkylation in moderate to good yields. A possible pathway involving the addition of alkyl radical to heterocycle followed by rearomatization is described.

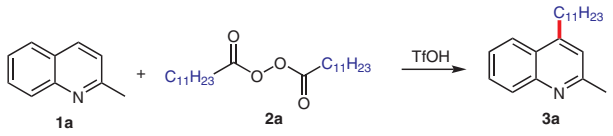
Key words metal-free conditions, Brønsted acid, C–H alkylation, heteroarenes, alkyl peroxides

Heteroarene moieties are significant structural motifs in natural products, pharmaceutical drugs, ligands, catalysts, and materials.[1] Among the numerous methods for constructing substituted heteroaromatics, direct C–H bond functionalization is the most prevailing strategy due to the high atom and step economy.[2] Moreover, C–H alkylation of heteroarenes has been well documented as an effective method, extremely enriching the diversity of C–H functionalization.[3] A pioneering and classical approach for the addition of alkyl radical to electron-deficient heteroarene followed by rearomatization is the Minisci reaction,[4] which uses alkyl carboxylic acids or halides as alkylating agents and Ag(I)/$S_2O_8^{2-}$ as oxidant. Motivated by Minisci reaction, the protocols involving radical pathway in C–H alkylation of heteroarenes have sprung up in recent years.[5] Metal-mediated Minisci-type strategy has been applied for C–H alkylation of heteroarenes, where alkyl acids, alkyl alcohols, alkyl organometallics, and olefins were used as alkyl reagents.[6] Recently, photocatalysis-mediated strategies further expanded the scope of Minisci alkylation of heteroaromatics under metal catalysis.[7] However, metal-free heteroaromatic alkylation has been less developed,[8] although it is more potential in the synthesis of drug molecules, avoiding the toxicity of the metal to the protein. The key challenges might be the appropriate coupling partner of heteroarenes and the matched oxidant under mild reaction conditions. To further broaden the metal-free method for Minisci C–H alkylation of heteroarenes and enhance the diversity of alkylating reagent, we herein employed alkyl peroxides as general alkyl groups and internal oxidants simultaneously to construct various alkyl-substituted heteroarenes via the promotion of a Brønsted acid.

Aiming at the exploration of C–H alkylation of heteroarenes, 2-methylquinoline (**1a**) and lauryl peroxide (LPO, **2a**) were used as the model substrates for the optimization of reaction conditions (Table 1). Initially, various Brønsted acids, such as TsOH·H_2O, TFA, MsOH, H_2SO_4, AcOH, and TfOH, were investigated under 80 °C for 12 hours. To our delight, 71% yield of alkylation product **3a** was obtained when using TfOH as the Brønsted acid (Table 1, entries 1–6). Screening of solvent indicated that MeCN was the optimal one (entries 7–10). Either increasing or decreasing the reaction temperature would lead to a lower yield of the product **3a** (entries 11–13). After testing for the amount of acid, one equivalent was found to be the most suitable for this transformation (entries 14–16). The control experiment suggested that Brønsted acid was essential for this alkylation (entry 17).

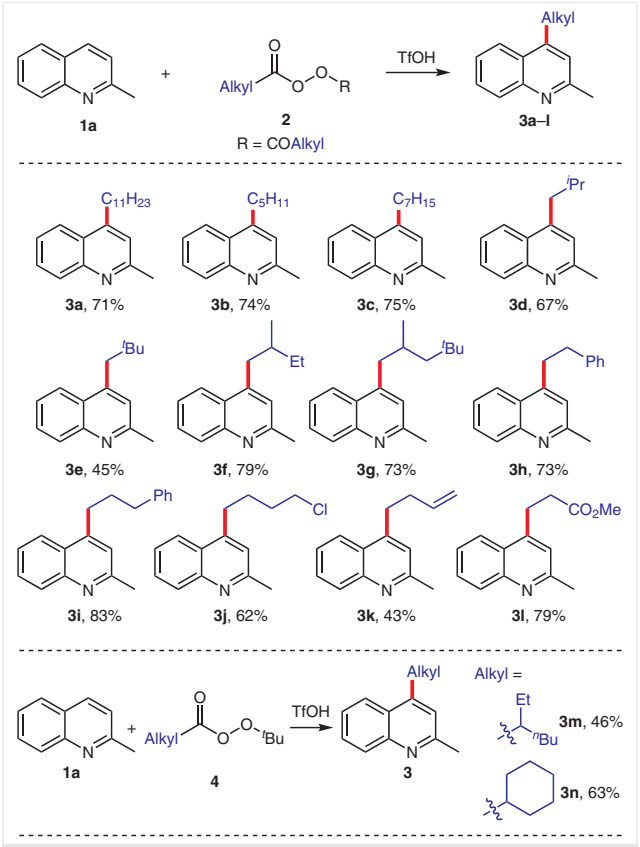
With the optimal reaction conditions in hand, the substrate scope of alkyl peroxides was next investigated (Scheme 1). Under the optimal conditions, the reaction of alkyl diacyl peroxides **2** with 2-methylquinoline (**1a**) afforded linear and branched chain alkylation products **3a–g** in moderate to good yields (45–79%). The alkyl diacyl peroxides possessing functional groups, such as phenyl, chloro, allyl, and ester, are smoothly transformed to the corresponding products **3h–l** in 43–83% yields. Except for the

Table 1 Optimization of the Reaction Conditions[a]



Entry	Acid (1 equiv)	Solvent	Temp (°C)	Yield (%)[b]
1	$TsOH·H_2O$	MeCN	80	40
2	TFA	MeCN	80	trace
3	MsOH	MeCN	80	2
4	H_2SO_4	MeCN	80	trace
5	AcOH	MeCN	80	trace
6	**TfOH**	**MeCN**	80	**76 (71)**[c]
7	TfOH	toluene	80	42
8	TfOH	1,4-dioxane	80	38
9	TfOH	THF	80	36
10	TfOH	DMF	80	18
11	TfOH	MeCN	100	42
12	TfOH	MeCN	60	40
13	TfOH	MeCN	40	trace
14[d]	TfOH	MeCN	80	50
15[e]	TfOH	MeCN	80	59
16[f]	TfOH	MeCN	80	38
17	–	MeCN	80	–

[a] Reaction conditions: **1a** (0.5 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv) in 2 mL of solvent for 12 h under N_2 atmosphere.
[b] Yields are determined by ^1H NMR analysis.
[c] Yield of the isolated product in parentheses.
[d] TfOH used: 1.5 equiv.
[e] TfOH used: 0.5 equiv.
[f] TfOH used: 0.25 equiv.



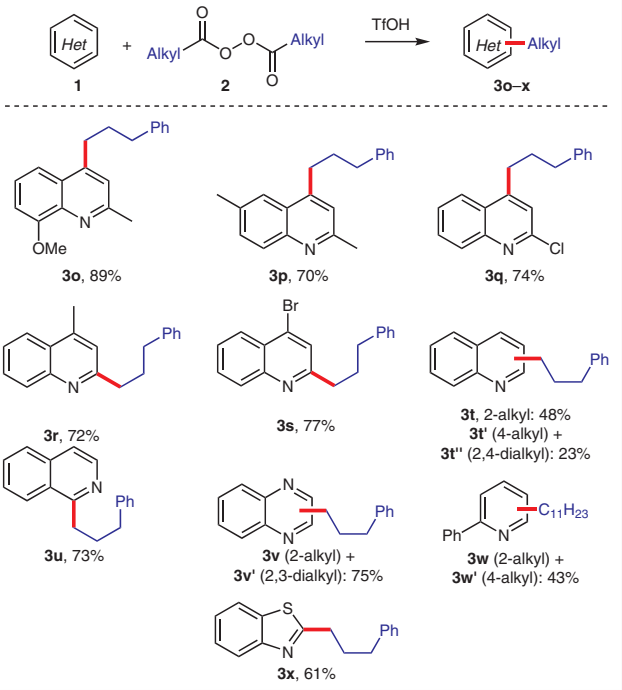
Scheme 1 Substrate scope of the alkyl peroxides

primary alkylation product, the secondary alkyl heteroarenes **3m** and **3n** also could be prepared from alkyl peresters **4** as the alkyl reagents (46% and 63% yield) because secondary alkyl peresters are relatively more stable and accessible than secondary alkyl diacyl peroxides (Scheme 1, bottom).

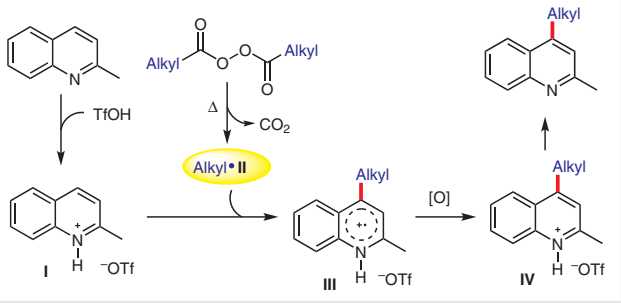
A variety of heteroarene compounds were next examined as shown in Scheme 2. 8-Methoxy-2-methylquinoline and 2,6-dimethylquinoline can both be converted to the desired products **3o** and **3p** in 89% and 70% yield, respectively. 2-Chloroquinoline gave the 4-alkyl-substituted product **3q** in 74% yield. 4-Substituted quinoline bearing methyl and bromo groups also react with alkyl diacyl peroxide to afford 2-alkylated products **3r** and **3s**. Selectivity for 2- and 4-position of quinoline leads to the generation of 2-, 4-, and 2,4-alkylation products **3t**, **3t′** and **3t″** (71%). Other heterocycles could be compatible in the alkylation. Isoquinoline is monoalkylated efficiently under the standard reaction conditions (**3u**, 73%). Quinoxaline and pyridine are transformed to the corresponding products **3v** and **3w** with regioselectivity. Benzothiazole is well tolerated in the alkylation reaction, providing the product **3x** in 61% yield.

In addition, based on our previous work on the decarboxylation of aliphatic acid,[9] we propose a possible pathway of the alkylation with 2-methylquinoline as an example (Scheme 3). Protonated 2-methylquinoline **I** is attacked by the alkyl radical **II** generated by the thermolysis of alkyl peroxide to produce the amino-radical cation **III**. The oxidation of intermediate **III** results in the rearomatization of protonated 4-alkylheteroarene **IV**, which would convert into the alkylated product following the workup.

In summary, we have developed a Brønsted acid promoted C–H alkylation of heterocycles under metal-free conditions. Alkyl peroxides are employed as general alkylating reagents and internal oxidants simultaneously, affording a series of alkyl heteroarenes in moderate to good yields. Besides, a plausible mechanism for the alkylation transformation is proposed, in which a radical process is involved.



Scheme 2 Substrate scope of the heteroarenes



Scheme 3 Proposed reaction mechanism

All reactions were carried out under an atmosphere of N_2 in a flame-dried glassware with magnetic stirring, unless otherwise indicated. Commercially obtained reagents were used directly as received. Solvents were dried by Innovative Technology Solvent Purification System. Liquids and solutions were transferred via syringe. All reactions were monitored by TLC. GC-MS data were recorded on Thermo ISQ QD. ^{1}H and ^{13}C NMR spectra were recorded on Bruker BioSpin Avance III HD spectrometer. Data for ^{1}H NMR spectra are reported relative to $CHCl_3$ as an internal standard (7.26 ppm) and are reported as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), and integration. Data for ^{13}C NMR spectra are reported relative to $CHCl_3$ as an internal standard (77.23 ppm) and are reported in terms of chemical shift (ppm). HRMS data were recorded on Waters Micromass GCT Premier or Thermo Fisher Scientific LTQ FT Ultra. Alkyl peroxides were prepared according to our previous work.[9]

Metal-Free Approach for Brønsted Acid Promoted C–H Alkylation of Heteroarenes; 2-Methyl-4-undecylquinoline (3a); Typical Procedure (Schemes 1 and 2)

To a flame-dried Schlenk tube, 2-methylquinoline (**1a**; 72 mg, 0.5 mmol, 1 equiv) and lauryl peroxide (**2a**; 299 mg, 0.75 mmol, 1.5 equiv) were added, followed by the addition of MeCN (2 mL) under N_2 atmosphere. Then TfOH (75 mg, 0.5 mmol, 1 equiv) was added sequentially. The reaction mixture was heated at 80 °C for 12 h, and then cooled to r.t. The solvent was removed by rotary evaporation, and then diluted with EtOAc, which washed with 10% aq NaOH (3 × 15 mL). The aqueous phase extracted with EtOAc (3 × 15 mL) and the combined organic phases were dried ($MgSO_4$). The solvent was removed by rotary evaporation under vacuum and the residue was chromatographed on silica gel (PE/EtOAc 20:1 → 10:1) to afford **3a** as a clear liquid; yield: 105 mg (0.35 mmol, 71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.3 Hz, 1 H), 7.97 (d, *J* = 8.2 Hz, 1 H), 7.69–7.59 (m, 1 H), 7.51–7.42 (m, 1 H), 7.11 (s, 1 H), 3.04–2.95 (t, *J* = 7.6 Hz, 2 H), 2.70 (s, 3 H), 1.78–1.67 (m, 2 H), 1.46–1.38 (m, 2 H), 1.33–1.22 (m, 14 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.77, 147.85, 147.23, 128.50, 128.09, 125.03, 124.48, 122.55, 120.73, 31.34, 31.09, 29.29, 28.93, 28.83, 28.80, 28.75, 28.65, 28.52, 24.48, 21.87, 13.30.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{21}H_{32}N]^+$: 298.2535; found: 298.2529.

2-Methyl-4-pentylquinoline (3b)[10]

Yellow oil; yield: 78.8 mg (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 1 H), 7.98 (d, *J* = 8.2 Hz, 1 H), 7.67–7.63 (m, 1 H), 7.52–7.46 (m, 1 H), 7.13 (s, 1 H), 3.05–2.98 (m, 2 H), 2.71 (s, 3 H), 1.80–1.71 (m, 2 H), 1.46–1.35 (m, 4 H), 0.92 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.63, 148.68, 148.07, 129.34, 128.92, 125.86, 125.31, 123.3, 121.58, 32.13, 31.91, 29.81, 25.32, 22.52, 14.01.

4-Heptyl-2-methylquinoline (3c)[11]

Yellow oil; yield: 90 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.2 Hz, 1 H), 7.96 (d, *J* = 8.3 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.11 (s, 1 H), 2.99 (t, *J* = 7.8 Hz, 2 H), 2.70 (s, 3 H), 1.73 (pent, *J* = 7.6 Hz, 2 H), 1.45–1.25 (m, 8 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.75, 148.91, 148.14, 129.41, 129.11, 126.02, 125.49, 123.54, 121.74, 32.32, 31.95, 30.28, 29.88, 29.30, 25.39, 22.82, 14.26.

4-Isobutyl-2-methylquinoline (3d)[12]

Yellow oil; yield: 67 mg (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 8.3 Hz, 1 H), 7.63 (t, *J* = 7.8 Hz, 1 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.04 (s, 1 H), 2.86–2.80 (m, 2 H), 2.70–2.67 (s, 3 H), 2.04 (m, 1 H), 0.96–0.91 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.49, 148.29, 147.66, 129.43, 129.06, 126.29, 125.39, 123.81, 122.80, 41.66, 29.43, 25.40, 22.92.

2-Methyl-4-neopentylquinoline (3e)

Yellow oil; yield: 79 mg (45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.1 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 7.68–7.59 (m, 1 H), 7.45 (m, 1 H), 7.08 (s, 1 H), 2.96 (s, 2 H), 2.72 (s, 3 H), 0.98 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.03, 148.45, 146.21, 129.44, 128.99, 127.31, 125.17, 124.87, 124.58, 44.49, 33.07, 30.33, 25.51.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{15}H_{20}N]^+$: 214.1596; found: 214.1590.

2-Methyl-4-(2-methylbutyl)quinoline (3f)

Yellow oil; yield: 84 mg (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 1 H), 7.96 (d, *J* = 8.3 Hz, 1 H), 7.64 (t, *J* = 7.1 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.08 (s, 1 H), 3.07 (dd, *J* = 8.4 Hz, 1 H), 2.70 (s, 3 H), 1.87–1.80 (m, 1 H), 1.52–1.41 (m, 1 H), 1.35–1.23 (m, 2 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 0.89 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.50, 148.36, 147.77, 129.50, 129.08, 126.3, 125.42, 123.84, 122.98, 39.78, 35.84, 29.99, 25.46, 19.47, 11.68.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{15}H_{20}N]^+$: 214.1596; found: 214.1590.

2-Methyl-4-(2,4,4-trimethylpentyl)quinoline (3g)

Yellow oil; yield: 93 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 1 H), 7.97 (d, *J* = 8.3 Hz, 1 H), 7.64 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.08 (s, 1 H), 3.04–2.94 (m, 1 H), 2.71 (s, 3 H), 2.05–1.94 (m, 1 H), 1.45–1.34 (m, 1 H), 1.23 (dd, *J* = 13.8, 6.5 Hz, 2 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.85 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.36, 148.22, 147.73, 129.41, 129.07, 126.35, 125.44, 123.77, 123.00, 51.52, 42.22, 31.18, 30.69, 30.12, 25.32, 22.84.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{18}H_{26}N]^+$: 256.2065; found: 256.2058.

2-Methyl-4-phenethylquinoline (3h)[12]

Yellow oil; yield: 84 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 8.4 Hz, 1 H), 8.01 (d, *J* = 8.3 Hz, 1 H), 7.68 (t, *J* = 7.6 Hz, 1 H), 7.50 (t, *J* = 7.5 Hz, 1 H), 7.32 (t, *J* = 7.3 Hz, 2 H), 7.23 (t, *J* = 6.1 Hz, 3 H), 7.08 (s, 1 H), 3.33 (t, *J* = 8.2 Hz, 2 H), 3.05 (t, *J* = 8.0 Hz, 2 H), 2.70 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.76, 148.16, 147.48, 141.22, 129.53, 129.19, 128.65, 128.48, 126.42, 125.78, 125.69, 123.26, 121.84, 36.33, 34.19, 25.37.

2-Methyl-4-(3-phenylpropyl)quinoline (3i)[13]

Yellow oil; yield: 108 mg (83%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.3 Hz, 1 H), 7.89 (d, *J* = 8.3 Hz, 1 H), 7.65 (t, *J* = 8.3 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.32 (d, *J* = 7.6 Hz, 2 H), 7.24–7.20 (m, 3 H), 7.12 (s, 1 H), 3.05–3.02 (t, *J* = 7.8 Hz, 2 H), 2.77 (t, *J* = 7.6 Hz, 2 H), 2.71 (s, 3 H), 2.15–2.06 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.79, 148.30, 148.22, 141.80, 129.51, 129.19, 128.63, 128.62, 126.21, 125.95, 125.60, 123.45, 121.79, 35.96, 31.70, 29.89, 25.46.

4-(4-Chlorobutyl)-2-methylquinoline (3j)

Yellow oil; yield: 72 mg (62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.4 Hz, 1 H), 7.93 (d, *J* = 8.3 Hz, 1 H), 7.64 (t, *J* = 8.1 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.10 (s, 1 H), 3.57 (t, *J* = 7.2 Hz, 2 H), 3.01 (t, *J* = 7.2 Hz, 2 H), 2.69 (s, 3 H), 1.92–1.85 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.67, 148.07, 147.72, 129.42, 129.16, 125.74, 125.61, 123.24, 121.65, 44.68, 32.40, 31.30, 27.20, 25.32.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{14}H_{17}ClN]^+$: 234.1050; found: 234.1043.

4-(But-3-en-1-yl)-2-methylquinoline (3k)

Brown liquid; yield: 43 mg (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 1 H), 7.97 (d, *J* = 8.3 Hz, 1 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.12 (s, 1 H), 5.96–5.84 (m, 1 H), 5.12–5.01 (m, 2 H), 3.11 (t, *J* = 7.8 Hz, 2 H), 2.70 (s, 3 H), 2.54–2.47 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.78, 148.21, 147.71, 137.49, 129.54, 129.19, 125.91, 125.63, 123.39, 121.82, 115.72, 34.07, 31.61, 25.46.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{14}H_{16}N]^+$: 198.1283; found: 198.1277.

Methyl 3-(2-Methylquinolin-4-yl)propanoate (3l)

Brown oil; yield: 90 mg (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.3 Hz, 1 H), 7.95 (d, *J* = 7.9 Hz, 1 H), 7.65 (t, *J* = 7.7 Hz, 1 H), 7.49 (t, *J* = 7.6 Hz, 1 H), 7.12 (s, 1 H), 3.68 (s, 3 H), 3.35 (t, *J* = 7.8 Hz, 2 H), 2.75 (t, *J* = 7.8 Hz, 2 H), 2.69 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.99, 158.88, 148.13, 146.33, 129.57, 129.37, 125.93, 125.56, 123.06, 121.64, 51.99, 34.11, 27.18, 25.40.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{14}H_{16}NO_2]^+$: 230.1181; found: 230.1173.

4-(Heptan-3-yl)-2-methylquinoline (3m)

Yellow oil; yield: 55 mg (46%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (t, *J* = 7.9 Hz, 2 H), 7.65 (t, *J* = 7.7 Hz, 1 H), 7.48 (t, *J* = 7.6 Hz, 1 H), 7.14 (s, 1 H), 3.40–3.32 (m, 1 H), 2.73 (s, 3 H), 1.87–1.68 (m, 4 H), 1.30–1.20 (m, 4 H), 0.80 (q, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.71, 152.82, 148.36, 129.61, 129.05, 126.75, 125.43, 123.2, 119.23, 35.61, 34.13, 29.90, 29.13, 25.66, 23.05, 14.15, 12.20.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{17}H_{24}N]^+$: 242.1909; found: 242.1904.

4-Cyclohexyl-2-methylquinoline (3n)[12]

Yellow oil; yield: 71 mg (63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.02 (d, *J* = 8.5 Hz, 2 H), 7.63 (t, *J* = 7.7 Hz, 1 H), 7.47 (t, *J* = 7.2 Hz, 1 H), 7.15 (s, 1 H), 3.32–3.23 (m, 1 H), 2.71 (s, 3 H), 2.04–1.81 (m, 5 H), 1.57–1.47 (m, 4 H), 1.38–1.23 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.95, 153.45, 148.31, 129.70, 128.92, 125.41, 125.32, 122.98, 118.46, 38.96, 33.74, 27.11, 26.50, 25.69.

8-Methoxy-2-methyl-4-(3-phenylpropyl)quinoline (3o)

Yellow solid; yield: 129.5 mg (89%); mp 96.3–96.8 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, *J* = 9.4 Hz, 1 H), 7.34 (t, *J* = 8.2 Hz, 1 H), 7.33–7.27 (m, 2 H), 7.23–7.18 (m, 3 H), 7.15 (s, 1 H), 7.01 (d, *J* = 7.1 Hz, 1 H), 4.06 (s, 3 H), 2.75 (t, *J* = 7.8 Hz, 2 H), 2.78–2.71 (m, 5 H), 2.13–2.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.82, 154.48, 147.19, 140.84, 139.11, 127.63, 127.60, 126.05, 125.18, 124.48, 121.42, 114.36, 106.39, 55.18, 34.97, 31.16, 30.65, 24.83.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{20}H_{22}NO]^+$: 292.1701; found: 292.1697.

2,6-Dimethyl-4-(3-phenylpropyl)quinoline (3p)

Yellow liquid; yield: 96 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.6 Hz, 1 H), 7.59 (s, 1 H), 7.48 (d, *J* = 10.4 Hz, 1 H), 7.36–7.30 (m, 2 H), 7.26–7.20 (m, 3 H), 7.08 (s, 1 H), 3.01 (t, *J* = 8.0 Hz, 2 H), 2.77 (t, *J* = 7.5 Hz, 2 H), 2.69 (s, 3 H), 2.50 (s, 3 H), 2.09 (pent, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.69, 147.55, 146.66, 141.83, 135.18, 131.28, 129.13, 128.65, 128.57, 126.16, 125.80, 122.43, 121.73, 35.86, 31.62, 31.50, 25.28, 21.94.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{20}H_{22}N]^+$: 276.1752; found: 276.1745.

2-Chloro-4-(3-phenylpropyl)quinoline (3q)

Yellow oil; yield: 104 mg (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (d, *J* = 8.4 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.67 (t, *J* = 7.7 Hz, 1 H), 7.50 (t, *J* = 8.2 Hz, 1 H), 7.30 (t, *J* = 7.3 Hz, 2 H), 7.24–7.17 (m, 4 H), 3.01 (t, *J* = 7.8 Hz, 2 H), 2.74 (t, *J* = 7.5 Hz, 2 H), 2.06 (pent, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.81, 150.73, 148.14, 141.35, 130.28, 129.45, 128.64, 128.57, 126.80, 126.31, 126.29, 123.65, 121.56, 35.75, 31.49, 31.33.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{18}H_{17}ClN]^+$: 282.1045; found: 282.1045.

4-Methyl-2-(3-phenylpropyl)quinoline (3r)[13]

Yellow oil; yield: 94 mg (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.4 Hz, 1 H), 7.91 (d, *J* = 7.5 Hz, 1 H), 7.65 (t, *J* = 7.0 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.30–7.24 (m, 2 H), 7.22–7.14 (m, 3 H), 7.09 (s, 1 H), 2.96 (t, *J* = 7.8 Hz, 2 H), 2.73 (t, *J* = 7.4 Hz, 2 H), 2.63 (s, 3 H), 2.14 (pent, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.30, 147.91, 144.36, 142.31, 129.51, 129.18, 128.64, 128.46, 126.95, 125.93, 125.60, 123.73, 122.19, 38.88, 35.92, 31.72, 18.80.

4-Bromo-2-(3-phenylpropyl)quinoline (3s)

Yellow oil; yield: 125 mg (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (d, *J* = 8.4 Hz, 1 H), 7.87 (d, *J* = 9.3 Hz, 1 H), 7.69 (t, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 7.0 Hz, 1 H), 7.36–7.30 (m, 3 H), 7.26–7.19 (m, 3 H), 3.03 (t, *J* = 7.6 Hz, 2 H), 2.77 (t, *J* = 7.5 Hz, 2 H), 2.09 (pent, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.33, 148.85, 142.20, 141.38, 130.30, 129.60, 128.69, 128.62, 126.95, 126.54, 126.34, 125.06, 123.82, 35.81, 31.44, 31.41.

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{18}H_{17}BrN]^+$: 326.0544; found: 326.0535.

2-(3-Phenylpropyl)quinoline (3t)[14]

Yellow oil; yield: 60 mg (48%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.06 (t, *J* = 7.2 Hz, 2 H), 7.78 (d, *J* = 8.0 Hz, 1 H), 7.69 (t, *J* = 7.7 Hz, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 7.35–7.27 (m, 3 H), 7.20–7.18 (m, 3 H), 3.07–3.00 (m, 2 H), 2.79–2.72 (m, 2 H), 2.17 (pent, *J* = 7.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.52, 147.96, 142.12, 136.25, 129.38, 128.86, 128.51, 128.34, 127.50, 126.75, 125.81, 125.72, 121.37, 38.84, 35.72, 31.59.

4-(3-Phenylpropyl)quinoline (3t′)[15] **and 2,4-Bis(3-phenylpropyl)quinoline (3t″)**

Yellow oil; **3t′** + **3t″** yield: 34 mg (23%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.82 (d, *J* = 4.5 Hz, 2.32 H), 8.15–8.13 (m, 2.4 H), 7.94–7.92 (m, 2.39 H), 7.70–7.67 (m, 2.37 H), 7.54–7.52 (m, 2.35 H), 7.38–7.26 (m, 6 H), 7.27–7.12 (m, 14.6 H), 3.15–3.02 (m, 4.88 H), 2.75–2.73 (m, 5.25 H), 2.72–2.70 (m, 1.81 H), 2.43–2.40 (m, 1.93 H), 2.13–2.07 (m, 5.17 H), 2.05–1.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.71, 148.89, 147.74, 141.51, 129.63, 129.30, 128.57, 128.49, 128.47, 128.37, 127.57, 126.49, 126.10, 125.89, 123.55, 120.83.

3t′

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{18}H_{18}N]^+$: 248.1439; found: 248.1433.

3t″

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{27}H_{28}N]^+$: 366.2222; found: 366.2215.

1-(3-Phenylpropyl)isoquinoline (3u)[16]

Yellow oil; yield: 90 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 5.7 Hz, 1 H), 8.01 (d, *J* = 8.4 Hz, 1 H), 7.76 (d, *J* = 8.2 Hz, 1 H), 7.61 (t, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 7.7 Hz, 1 H), 7.46 (d, *J* = 5.7 Hz, 1 H), 7.30–7.24 (m, 2 H), 7.23–7.15 (m, 3 H), 3.31 (t, *J* = 8 Hz, 2 H), 2.79 (t, *J* = 7.7 Hz, 2 H), 2.24–2.15 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.94, 142.19, 141.99, 136.37, 129.89, 128.65, 128.46, 127.50, 127.10, 127.03, 125.96, 125.33, 119.38, 36.06, 34.96, 31.25.

2-(3-Phenylpropyl)quinoxaline (3v) and 2,3-Bis(3-phenylpropyl)quinoxaline (3v′)

Brown solid; **3v** + **3v′** yield: 111 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 8.09–8.02 (m, 2 H), 8.02–7.99 (m, 1 H), 7.76–7.68 (m, 2 H), 7.67–7.64 (m, 1 H), 7.30–7.28 (m, 4 H), 7.22–7.15 (m, 5 H), 3.06–3.01 (m, 2 H), 2.96–2.90 (m, 1 H), 2.77–2.73 (m, 4 H), 2.25–2.15 (m, 2 H), 2.15–2.07 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.16, 156.09, 145.81, 142.23, 141.86, 141.60, 141.25, 140.97, 129.98, 129.20, 129.01, 128.89, 128.80, 128.55, 128.51, 128.44, 128.42, 126.01, 125.97, 35.82, 35.70, 35.54, 34.57, 30.84, 30.09, 29.74.

3v

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{17}H_{17}N_2]^+$: 249.1392; found: 249.1383.

3v′

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{26}H_{27}N_2]^+$: 367.2174; found: 367.2168.

2-Phenyl-6-undecylpyridine (3w) and 2-Phenyl-4-undecylpyridine (3w′)

Yellow oil; **3w** + **3w′** yield: 87 mg (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (m, 1 H), 8.57 (d, *J* = 5.0 Hz, 1 H), 8.02–7.97 (m, 4 H), 7.75–7.71 (m, 2 H), 7.54 (s, 1 H), 7.50–7.45 (m, 3.3 Hz, 4 H), 7.44–7.37 (m, 2 H), 7.23–7.21 (m, 1 H), 7.06–7.05 (m, 1 H), 2.70–2.61 (m, 2 H), 1.73–1.62 (m, 2 H), 1.43–1.22 (m, 25 H), 0.92–0.83 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.50, 157.4, 152.52, 149.67, 149.48, 139.68, 139.42, 136.71, 128.94, 128.76, 128.73, 128.66, 126.97, 126.92, 122.42, 122.07, 120.84, 120.54, 35.52, 31.92, 30.44, 29.65, 29.62, 29.54, 29.44, 29.34, 29.25, 22.69, 14.12.

3w and 3w′

HRMS (ESI): *m*/*z* [M + H$^+$] calcd for $[C_{22}H_{32}N]^+$: 310.2535; found: 310.2529.

2-(3-Phenylpropyl)benzo[*d*]thiazole (3x)[17]

Yellow oil; yield: 77 mg (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 7.8 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.47–7.42 (m, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.33–7.26 (m, 2 H), 7.21 (q, *J* = 9.0 Hz, 3 H), 3.13 (t, *J* = 7.8 Hz, 2 H), 2.76 (t, *J* = 7.8 Hz, 2 H), 2.21 (pent, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.78, 153.29, 141.32, 135.14, 128.54, 128.47, 126.07, 125.94, 124.72, 122.57, 121.52, 35.22, 33.74, 31.19.

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Supporting Information

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