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Introduction of Quinolines and Isoquinolines onto Nonactivated α-C−H Bond of Tertiary Amides through a Radical Pathway

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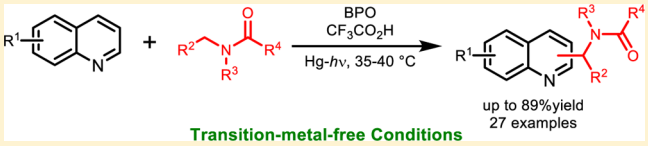
Supporting Information

ABSTRACT: Treatment of quinolines and isoquinolines with benzoyl peroxide in tertiary amides, such as *N*,*N*-dimethylacetamide, *N*,*N*-dimethylpropionamide, and *N*-acetylpyrrolidine, etc., under irradiation with a Hg lamp in the temperature range of 35 °C to 40 °C gave C−C-bonded quinolines and isoquinolines bearing amide groups with high regioselectivity in good to moderate yields, respectively, under transition-metal-free conditions.



INTRODUCTION

Synthetic studies of electron-deficient heteroaromatic bases, such as quinoline, isoquinoline, phenanthridine, etc., bearing amide functional groups are very attractive and important because most of the heteroaromatic bases possess biological activities; e.g., 5-chloro-2-hydroxy-*N*-(quinolin-8′-yl)benzamide **I** is a potent inhibitor of VEGFR-2 kinase,[1a] quinoline derivative **II** bearing an amide-*N*-methylene group at 8-position is a renin inhibitor for the treatment of hypertension,[1b] and 4-hydroxy-8-(methanesulfonylamino)quinoline-2-carboxamide **III** is an inhibitor of human plasma Lp-PLA2.[1c] The heteroaromatic bases also can be used as a luminescent probe, an example of which is phenanthridine derivative **IV** bearing an aza-crown-bonded amide-*N*-methylene group at the 6-position is a luminescent probe of adenosine nucleotides, as shown in Figure 1.[1d] Moreover, the amide groups can be easily transformed into amines by hydrolysis or reduction.

Today, there are many methods for the introduction of alkyl groups onto electron-deficient heteroaromatic bases, such as pyridine, quinoline, etc., through radical pathways,[2] typically, the decarboxylative alkylation of electron-deficient heteroaromatic bases with alkyl carboxylic acids, $AgNO_3$, and $K_2S_2O_8$ under heating conditions (the Minisci reaction),[3] the decarboxylative alkylation of electron-deficient heteroaromatic bases with *N*-acyloxy-2-thiopyridone prepared from alkyl carboxylic acids and *N*-hydroxy-2-thiopyridone, under tungsten-lamp irradiation (the Barton decarboxylation),[4] and the introduction of alkyl groups onto electron-deficient heteroaromatic bases with alkyl halides and tris(trimethylsilyl)silane or 1,1,2,2-tetraphenyldisilane in the presence of AIBN under warming conditions, or with alkyl halides and tetra(trimethylsilyl)silane under irradiation with a Hg lamp.[5] The introduction of crown ether onto an electron-deficient heteroaromatic base by using crown ether and *tert*-butyl hydrogen peroxide (TBHP) in the presence of $FeSO_4$ can be also carried out.[6] Those methods of introducing alkyl groups onto electron-deficient heteroaromatic bases through radical pathways are very attractive and useful because alkylated heteroaromatic bases that cannot be easily obtained by ionic electrophilic substitution (S_EAr) onto electron-deficient heteroaromatic bases using the Friedel−Crafts alkylation can be easily prepared. Recently, we reported a simple method for the introduction of ether, cyclic ether, and crown ether groups onto electron-deficient heteroaromatic bases with benzoyl peroxide (BPO) under heating and transition-metal-free conditions.[7] On the other hand, only a few studies of the introduction of a tertiary amide group onto electron-deficient heteroaromatic bases have been reported, i.e., the introduction of an amide group onto lepidine and quinoxaline with H_2SO_4 and hydroxylamine-*O*-sulfonic acid in the presence of $FeSO_4 \cdot 7H_2O$ in a mixture of formamide or DMF and water (10:1),[8a] the introduction of an amide group onto lepidine and quinoxaline with formamide or *N*,*N*-dimethylacetamide solvent in the presence of H_2SO_4, H_2O_2, and TiO_2 under sunlight irradiation,[8b] the preparation of 6-amidophenanthri-

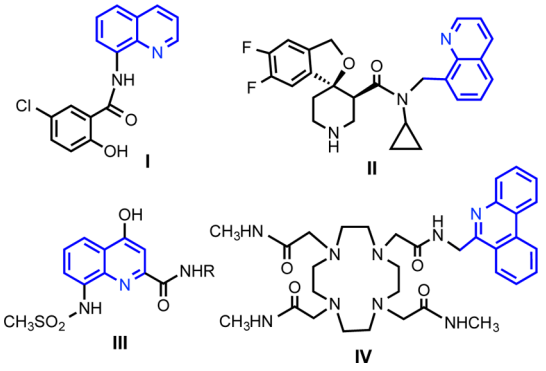


Figure 1. Quinolines and a phenanthridine bearing amide groups.

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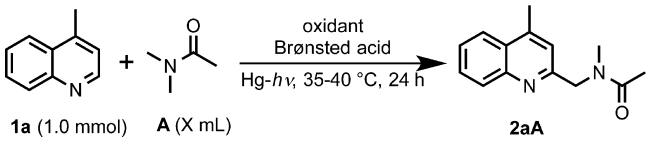
dine from 2-isocyanobiphenyl with amide and *tert*-butyl peroxybenzoate (TBPB) at 120 °C,[8c] and the introduction of an amide group at 2-position of benzothiazoles with potassium persulfate in *N*,*N*-dimethylacetamide at 70 °C.[8d] Additionally, there a few reports for amidation of arenes or heteroaromatic bases with formamides via formation of •$CONH_2$ (carbamoyl) radicals.[9] Here we would like to report the introduction of quinolines and isoquinolines onto the nonactivated α-C−H bond of tertiary amides with BPO under irradiation with a Hg lamp without using any transition metals.

RESULTS AND DISCUSSION

First, a solution of lepidine **1a** (1.0 mmol) and BPO (2.0 mmol) in the presence of trifluoroacetic acid (1.0 mmol) in *N*,*N*-dimethylacetamide **A** (5 mL) in a 30 mL screw-capped flask was irradiated with a Hg lamp (400 W high pressure) in the temperature range of 35 °C to 40 °C to give 2-(*N*-acetyl,*N*-methylamino)methyl-4-methylquinoline **2aA** in 82% yield, as shown in Table 1 (entry 1). When BPO was replaced with aq hydrogen peroxide (H_2O_2), *tert*-butyl hydrogen peroxide (TBHP), di-*tert*-butyl peroxide (DTBP), *tert*-butyl peroxybenzoate (TBPB), and potassium peroxodisulfate ($K_2S_2O_8$) under the same reaction conditions, the yield of compound **2aA** became low or moderate, and lepidine was recovered (entries 2−6, Table 1). When 3 equiv of $K_2S_2O_8$ was used under the same conditions as those in entry 6 in 5 and 8 mL of *N*,*N*-dimethylacetamide **A**, product **2aA** was obtained in moderate to low yields (entries 7 and 8, Table 1). This was because the solubility of $K_2S_2O_8$ in *N*,*N*-dimethylacetamide **A** was quite low under the present reaction conditions, and a homogeneous solution was not obtained during the irradiation with $K_2S_2O_8$. In contrast, a homogeneous solution was maintained during the irradiation with BPO. The addition of $FeSO_4$ as an electron transfer catalyst to a solution containing BPO (similar to the Fenton system) also reduced the yield of compound **2aA** (entry 9, Table 1). Moreover, when the acid was changed to a stronger acid than trifluoroacetic acid, such as toluenesulfonic acid, methanesulfonic acid, and trifluoromethanesulfonic acid, the yield of compound **2aA** almost did not change (entries 11−13, Table 1). When it was changed to a weaker acid than trifluoroacetic acid, such as acetic acid, compound **2aA** was not obtained at all (entry 14, Table 1). Thus, the complete protonation of lepidine to increase its reactivity toward nucleophilic radical species is required. Then the effect of the amounts of solvent (2.0 mL, 4.0 mL, and 8.0 mL) and BPO (1.5 equiv, 1.7 equiv, and 2.3 equiv) was studied, and it was found that treatment of lepidine **1a** (1.0 mmol) with BPO (1.7 mmol) in the presence of trifluoroacetic acid (1.0 mmol) in *N*,*N*-dimethylacetamide **A** (8.0 mL) under irradiation with a Hg lamp for 24 h in the temperature range of 35 °C to 40 °C was the best choice, giving compound **2aA** in 88% yield (entry 20 in entries 15−21, Table 1). The reason why the yield of **2aA** depends on the amount of *N*,*N*-dimethylacetamide **A** may be the smooth formation of a carbon-centered amide radical by the reaction of *N*,*N*-dimethylacetamide **A** with $PhCO_2$• and the suppression of the oxidation of the carbon-centered amide radical to carbo-cation by BPO under diluted conditions. In the absence of BPO under the same reaction conditions, the yield of compound **2aA** was 14% (entry 22, Table 1). In the absence of trifluoroacetic acid under the same reaction conditions, the yield of compound **2aA** was trace (entry 23, Table 1). When the present reaction was carried out under warming conditions at 100 °C for 24 h and under irradiation with a tungsten lamp (300 W) at 40 °C for 8 h, instead of irradiation with a Hg lamp, the yield of compound **2aA** was only 13% and 0%, respectively (entries 24 and 25, Table 1). Then a gram-scale experiment was performed with 8 mmol of lepidine in a 100 mL screw-capped flask under the same procedure and conditions as those in entry 20, Table 1, and compound **2aA** was obtained in 89% yield, as shown in Table 2. Thus, this method can be used for gram-scale preparation. On the basis of those results, various quinoline derivatives, such as 4,6-dimethylquinoline **1b**, 4,7-dichloroquinoline **1c**, 2-methylquinoline **1d**, 2,6-dimethylquinoline **1e**, 6-methoxy-2-methylquinoline **1f**, 6-fluoro-2-methylquinoline **1g**, 6-chloro-2-methylquinoline **1h**, 7-chloro-2-methylquinoline **1i**, and 6-bromo-2-methylquinoline **1j**, were treated with BPO in the presence of trifluoroacetic acid in *N*,*N*-dimethylacetamide **A** under the same reaction conditions as those in entry 20, Table 1, to provide the corresponding quinoline derivatives **2bA** to **2jA** bearing a tertiary amide group in good to moderate yields, respectively, as shown in Table 2. When quinoline derivatives **1k** and **1l** bearing an ester or an acetyl group were reacted with BPO in *N*,*N*-dimethylacetamide under the same reaction conditions, compounds **2kA** and **2lA** were produced in moderate yields, respectively. Similarly, treatment of isoquinoline **1m**, 4-bromoisoquinoline **1n**, and quinoxaline **1o** with BPO in *N*,*N*-dimethylacetamide **A** under the same reaction

Table 1. Introduction of Lepidine 1a onto *N*,*N*-Dimethylacetamide A To Form 2aA



1a (1.0 mmol) **A** (X mL) **2aA**

entry	X	oxidant (equiv)	Brønsted acid (equiv)	yield (%)
1	5.0	BPO (2.0)	CF_3CO_2H (1.0)	82
2	5.0	H_2O_2 (2.0)	CF_3CO_2H (1.0)	49
3	5.0	TBHP (2.0)	CF_3CO_2H (1.0)	10
4	5.0	DTBP (2.0)	CF_3CO_2H (1.0)	8
5	5.0	TBPB (2.0)	CF_3CO_2H (1.0)	14
6	5.0	$K_2S_2O_8$ (2.0)	CF_3CO_2H (1.0)	68
7	5.0	$K_2S_2O_8$ (3.0)	CF_3CO_2H (1.0)	56
8	8.0	$K_2S_2O_8$ (3.0)	CF_3CO_2H (1.0)	36
9[a]	5.0	BPO (2.0)	CF_3CO_2H (1.0)	21
10[a]	5.0	TBHP (2.0)	CF_3CO_2H (1.0)	36
11	5.0	BPO (2.0)	TsOH · H_2O (1.0)	80
12	5.0	BPO (2.0)	CH_3SO_3H (1.0)	81
13	5.0	BPO (2.0)	CF_3SO_3H (1.0)	78
14	5.0	BPO (2.0)	CH_3CO_2H (1.0)	trace
15	2.0	BPO (2.0)	CF_3CO_2H (1.0)	67
16	4.0	BPO (2.0)	CF_3CO_2H (1.0)	76
17	8.0	BPO (2.0)	CF_3CO_2H (1.0)	87
18	8.0	BPO (2.0)	CF_3CO_2H (1.3)	85
19	8.0	BPO (1.5)	CF_3CO_2H (1.0)	86
20	8.0	BPO (1.7)	CF_3CO_2H (1.0)	88
21	8.0	BPO (2.3)	CF_3CO_2H (1.0)	81
22	8.0	–	CF_3CO_2H (1.0)	14
23	8.0	BPO (1.7)	–	trace
24[b]	8.0	BPO (1.7)	CF_3CO_2H (1.0)	13
25[c]	8.0	BPO (1.7)	CF_3CO_2H (1.0)	0

[a]$FeSO_4 \cdot 7H_2O$ (0.3 equiv) was added. [b]Reaction was carried out at 100 °C for 24 h without irradiation with a Hg lamp. [c]Reaction was carried out at 40 °C for 8 h under irradiation with a tungsten lamp.

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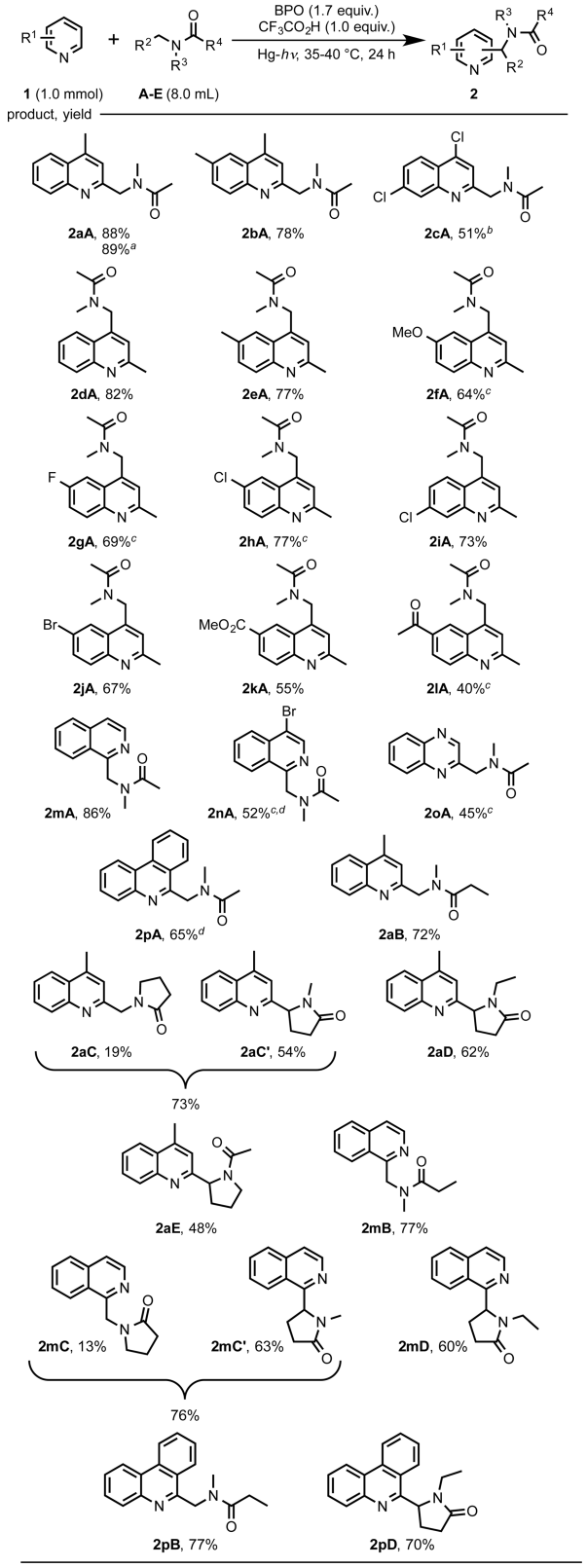
Table 2. Introduction of Quinoline, Isoquinoline, and Phenanthridine 1 onto Tertiary Amides A to E



[a]Reaction was carried out on a 8.0 mmol scale. [b]Solvent (10.0 mL) was used. [c]BPO (2.0 equiv) was used. [d]Reaction was carried out for 18 h.

conditions gave compounds **2mA**, **2nA**, and **2oA** in good to moderate yields, respectively. The same treatment of phenanthridine **1p**, a tricyclic heteroaromatic base, with BPO in *N*,*N*-dimethylacetamide **A** generated also the corresponding C−C bonded compound **2pA** in 65% yield. On the other hand, when lepidine was treated with BPO in *N*,*N*-dimethylpropionamide **B** and 1-methyl-2-pyrrolidone **C** instead of *N*,*N*-dimethylacetamide **A** under irradiation with a Hg lamp, 4-methyl-2-(*N*-methyl,*N*-propanoylamino)methylquinoline **2aB** and a mixture of 4-methylquinolines **2aC** and **2aC′** bearing a pyrrolidone group at 2-position were obtained in 72% and 73% yields (19% and 54%), respectively. Thus, 1-methyl-2-pyrrolidone has two reaction positions, i.e., the *N*-methyl group and the cyclic *N*-methylene group. These results are consistent with reported results, i.e., the smooth generation of carbon-centered amide radical by the hydrogen-atom abstraction of the *N*-methyl group in *N*,*N*-dimethylacetamide and two carbon-centered amide radicals by the hydrogen-atom abstraction of the *N*-methyl group and the *N*-methylene group in 1-methyl-2-pyrrolidone by a cumyloxy radical.[10] However, when 1-ethyl-2-pyrrolidone **D** instead of 1-methyl-2-pyrrolidone **C** was used as solvent with lepidine and BPO under the same irradiation conditions, single product **2aD** was obtained in 62% yield. This result may have been derived from the steric hindrance in the reaction of protonated lepidine salt with the carbon-centered amide radical formed by the hydrogen-atom abstraction of the *N*-ethyl group in 1-ethyl-2-pyrrolidone **D**, and the carbon-centered amide radical formed by the hydrogen-atom abstraction of the *N*-methylene group in 1-ethyl-2-pyrrolidone **D** reacted with protonated lepidine salt to give **2aD** alone. When *N*-acetylpyrrolidine **E** was used as solvent with lepidine and BPO under the same irradiation conditions, 1-acetyl-2-(4′-methylquinolin-2′-yl)pyrrolidine **2aE** was obtained in moderate yield. Similarly, when isoquinoline was treated with BPO in *N*,*N*-dimethylpropionamide **B**, 1-methyl-2-pyrrolidone **C**, and 1-ethyl-2-pyrrolidone **D** under irradiation with a Hg lamp, the corresponding C−C bonded products **2mB**, a mixture of **2mC** and **2mC′**, and **2mD** were obtained in 77%, 76% (13% and 63%), and 60% yields, respectively. When phenanthridine was treated with BPO in *N*,*N*-dimethylpropionamide **B** and 1-ethyl-2-pyrrolidone **D** under the same reaction conditions, the corresponding phenathridine derivatives **2pB** and **2pD** bearing an amide group at 6-position were obtained in 77% and 70% yields, respectively. When quinoline, which has two reactive positions toward nucleophilic radical species, was treated with BPO (1.0 equiv) in *N*,*N*-dimethylacetamide **A** under irradiation with a Hg lamp for 24 h, 2-(*N*-acetyl,*N*-methylamino)methylquinoline **2qA** (20%), 4-(*N*-acetyl,*N*-methylamino)methylquinoline **2qA′** (31%), and 2,4-bis[(*N*-acetyl,*N*-methylamino)methyl]quinoline **2qA″** (24%) were obtained in 75% yield, as shown in Scheme 1 (eq 1). On the other hand, when quinoline was treated with BPO (2.0 equiv) in *N*,*N*-dimethylacetamide under irradiation with a Hg lamp for 24 h, 2,4-bis[(*N*-acetyl,*N*-methylamino)-methyl]quinoline **2qA″** was obtained in 84% yield as a single product (eq 2). The structure of 1-ethyl-5-(4′-methylquinolin-2′-yl)pyrrolidin-2-one **2aD** was supported by X-ray crystallographic analysis (see Supporting Information).

Finally, the obtained C−C bonded compounds **2** are mainly mixtures of anti and syn forms with respect to the amide groups. Therefore, C−C bonded compounds **2** were converted into secondary amines **3** bearing a quinoline group and an

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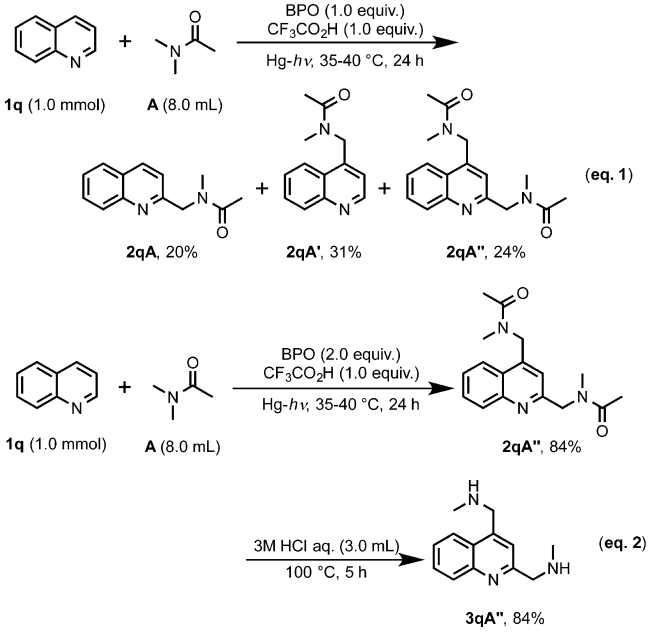
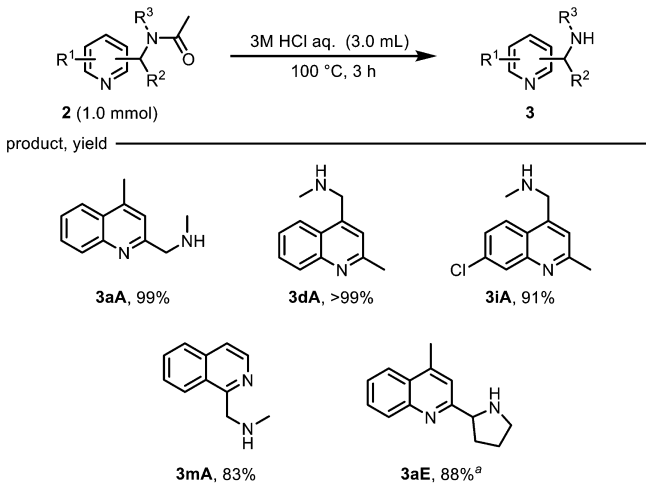
Scheme 1. Introduction of Quinoline 1q onto *N*,*N*-Dimethylacetamide A



isoquinoline group in good yields, respectively, by aq HCl hydrolysis for analysis, as shown in Table 3.

Table 3. Hydrolysis of Tertiary Amides 2 to Secondary Amines 3

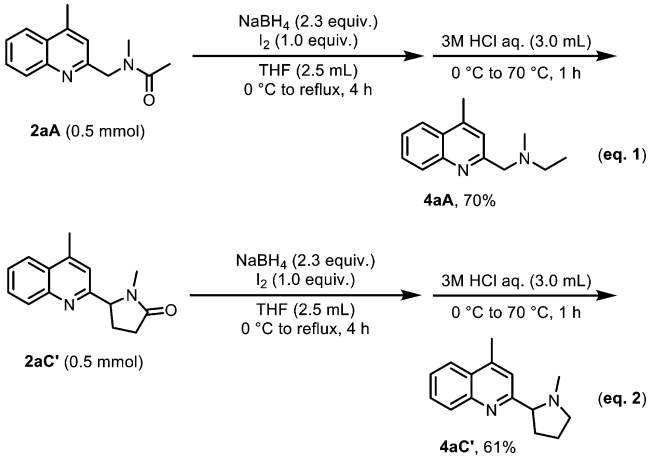


[a]Reaction was carried out on a 0.5 mmol scale.

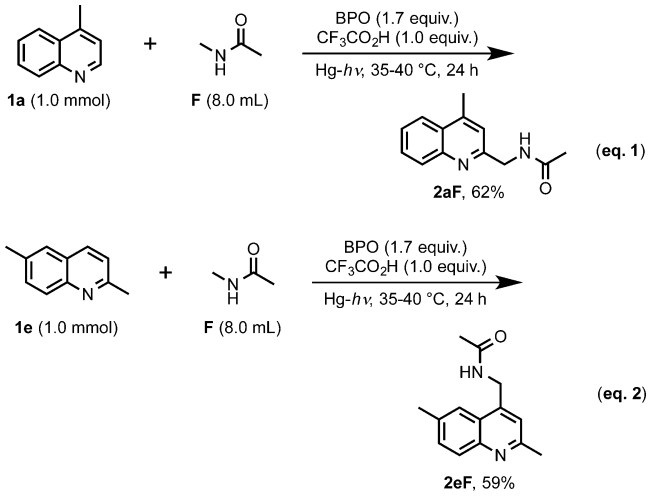
Then C−C bonded compounds **2aA** and **2aC′** were reduced to the corresponding tertiary amines **4aA** and **4aC′** bearing a quinoline group in 70% and 61% yields, respectively, by treatment with $NaBH_4$ (2.3 equiv) and I_2 (1.0 equiv) in THF for 4 h under refluxing conditions, as shown in Scheme 2 (eqs 1 and 2).

When *N*-methylacetamide **F** instead of *N*,*N*-dimethylacetamide **A** was treated with lepidine **1a** and 2,6-dimethylquinoline **1e** in the presence of BPO and trifluoroacetic acid under the same irradiation conditions with a Hg lamp, 2-(*N*-acetylamino)-methyl-4-methylquinoline **2aF** and 4-(*N*-acetylamino)methyl-2,6-dimethylquinoline **2eF** were obtained in 62% and 59% yields, respectively, as shown in Scheme 3.

Scheme 2. Reduction of Tertiary Amides 2 to Tertiary Amines 4 with $NaBH_4$ and I_2



Scheme 3. Introduction of Quinolines 1a and 1e onto *N*-Methylacetamide F



To support the present reaction mechanism, two experiments were carried out. When the reaction of lepidine with BPO (1.7 equiv) in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO, 3.0 equiv) and trifluoroacetic acid (1.0 equiv) in *N*,*N*-dimethylacetamide **A** was carried out under the same irradiation conditions, C−C bonded compound **2aA** was not obtained at all. Moreover, the reaction of lepidine with BPO (1.7 equiv) and trifluoroacetic acid (1.0 equiv) in *N*,*N*-dimethylacetamide **A** in the presence of *p*-cresol (3.0 equiv), which functions as a hydrogen atom donor to radical species, under the same irradiation conditions was also retarded to give compound **2aA** in only 14% yield. Thus, it is suggested that the present reaction proceeds via the radical pathway. The proposed reaction mechanism is shown in Scheme 4 with lepidine **1a** in *N*,*N*-dimethylacetamide **A**.

Benzoyloxyl radical formed by the homolytic bond cleavage of BPO under irradiation with a Hg lamp abstracts a hydrogen atom from the *N*-methyl group in *N*,*N*-dimethylacetamide **A** to form carbon-centered amide radical **IA** and benzoic acid (or abstraction of a hydrogen atom from the *N*-methyl group or the *N*-methylene group in 1-methyl-2-pyrrolidone **C** to form carbon-centered amide radicals **IC** and **IC′**). This nucleophilic carbon-centered amide radical **IA** reacts at the most electro-

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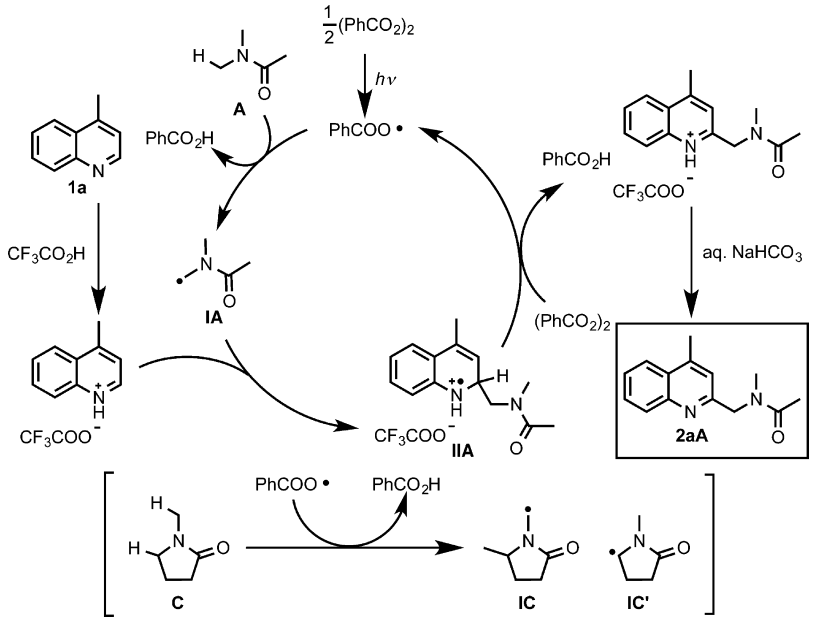
Scheme 4. Plausible Reaction Pathway



philic position of protonated lepidine, i.e., 2-position, to form C−C bonded intermediate **IIA**, which further reacts with BPO to give protonated C−C bonded quinoline derivative, together with the generation of benzoic acid and benzoyloxyl radical. Quinoline derivative **2aA** was obtained by neutralization with aq $NaHCO_3$ solution. Practically, the smooth generation of carbon-centered amide radical **IA** from *N*,*N*-dimethylacetamide **A** and two carbon-centered amide radicals adjoined to the nitrogen atom in 1-methyl-2-pyrrolidone **C** by a cumyloxy radical, i.e., an alkoxyl radical, has been reported by Bietti.[10]

CONCLUSION

The introduction of quinolines, isoquinolines, and phenanthridine onto the nonactivated α-C−H bond of tertiary amides was efficiently carried out by treatment with benzoyl peroxide under irradiation with a Hg lamp via the radical pathway. We believe that the present reaction would be useful because it would enable the preparation of unique quinolines, isoquinolines, and phenanthridines bearing tertiary amide groups.

EXPERIMENTAL SECTION

General Information. ^{1}H NMR spectra were measured on 400 MHz spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; quin = quintet; sext = sextet; m = multiplet; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on 100 MHz spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). High-resolution mass spectra (HRMS) were measured on orbitrap mass spectrometers. Characteristic peaks in the infrared (IR) spectra were recorded in wave numbers, cm^{-1}. Melting points were uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F-254). The products were purified by short column chromatography on neutral silica gel 60 (63−200 mesh).

Typical Experimental Procedure for Introduction of Lepidine to *N*,*N*-Dimethylacetamide with BPO under Irradiation with Hg-Lamp. To a solution of lepidine (**1a**; 1.0 mmol, 143.2 mg) and trifluoroacetic acid (1.0 mmol, 0.077 mL) in *N*,*N*-dimethylacetamide (**A**, 8.0 mL) in a 30 mL screw-capped flask was added benzoyl peroxide (wetted with ca. 25% water, 1.7 mmol, 549.1 mg) at room temperature, and the flask was flashed by Ar gas. Then the mixture was stirred for 24 h under irradiation with a high-pressure mercury lamp (Hg-lamp, 400W: AHH400S, 1.7 mW/cm^2) at the range of 35 °C to 40 °C. Then the reaction mixture was cooled to room temperature and quenched with sat. aq $NaHCO_3$ (10 mL). The mixture was extracted with AcOEt (20 mL × 5), and the organic layer was washed with brine (50 mL). The obtained organic layer was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was purified by short column chromatography on neutral silica gel (eluent: AcOEt/MeOH = 20/1) to give the product **2aA** (199.8 mg, 88% yield).

Typical Experimental Procedure for Hydrolysis of Tertiary Amides to Secondary Amines with Aqueous HCl. A solution of 2-(*N*-acetyl,*N*-methylamino)methyl-4-methylquinoline (**2aA**; 1.0 mmol, 228.3 mg) in aq 3 M HCl (3.0 mL) was stirred for 3 h at 100 °C. Then the reaction mixture was cooled to room temperature and quenched with sat. aq $NaHCO_3$ (20 mL). The mixture was extracted with $CHCl_3$ (20 mL × 5), and the obtained organic layer was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure to give the product **3aA** (184.0 mg, 99% yield).

Typical Experimental Procedure for Reduction of Tertiary Amides to Tertiary Amines with $NaBH_4$ and I_2. To a solution of 2-(*N*-acetyl,*N*-methylamino)methyl-4-methylquinoline (**2aA**; 0.5 mmol, 114.2 mg) and $NaBH_4$ (1.15 mmol, 43.5 mg) in THF (1.5 mL) was added dropwise a solution of I_2 (0.5 mmol, 126.9 mg) in THF (1.0 mL) under Ar atmosphere at 0 °C. Then the mixture was stirred for 4 h at 70 °C. Then the reaction mixture was cooled to 0 °C and added to aq 3 M HCl (3.0 mL) solution. The mixture was stirred for 1 h at 70 °C. The reaction mixture was cooled to room temperature and quenched with sat. aq $NaHCO_3$ (20 mL) solution. Then the mixture was extracted with $CHCl_3$ (20 mL × 5), and the obtained organic layer was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure, and the residue was purified by short column chromatography on neutral silica gel (AcOEt/MeOH = 2/1) to give the product **4aA** (74.9 mg, 70% yield).

For amide products **2aC**, **2aC′**, **2aD**, **2aF**, **2eF**, **2mC**, **2mC′**, **2mD**, and **2pD**, oil or solid, IR, ^{1}H NMR, ^{13}C NMR, and HRMS were shown in the following experimental section, due to the single isomer. However, other amide products **2** are a mixture of anti and syn in the amide group, and their ^{1}H NMR and ^{13}C NMR spectra are rather complicated. Therefore, for those amide products **2**, either oil or solid, IR and HRMS are shown in the following experimental section, and copies of ^{1}H NMR and ^{13}C NMR spectra are provided in Supporting

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Information. After acid hydrolysis of those amide products **2**, each single amine **3** was obtained, either oil or solid, and IR, ^{1}H NMR, ^{13}C NMR, and HRMS are shown in the following experimental section, and copies of those ^{1}H NMR and ^{13}C NMR spectra are provided in Supporting Information.

2-(*N*-Acetyl,*N*-methylamino)methyl-4-methylquinoline (2aA).[8a] (a mixture of anti and syn isomers) 199.8 mg, 88% yield; yellow solid; IR (neat) 2926, 1637, 1601, 1401, 756 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ 229.1335, found 229.1331.

2-(*N*-Acetyl,*N*-methylamino)methyl-4,6-dimethylquinoline (2bA). (a mixture of anti and syn isomers) 188.1 mg, 78% yield; yellow oil; IR (neat) 2921, 1644, 1600, 1398, 824 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O$ $[M + H]^+$ 243.1492, found 243.1489.

2-(*N*-Acetyl,*N*-methylamino)methyl-4,7-dichloroquinoline (2cA). (a mixture of anti and syn isomers) 143.3 mg, 51% yield; white solid; IR (neat) 2927, 1638, 1604, 1396, 819 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{13}Cl_2N_2O$ $[M + H]^+$ 283.0399, found 283.0398.

4-(*N*-Acetyl,*N*-methylamino)methyl-2-methylquinoline (2dA). (a mixture of anti and syn isomers) 188.0 mg, 82% yield; yellow oil; IR (neat) 2924, 1636, 1604, 1402, 755 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ 229.1335, found 229.1331.

4-(*N*-Acetyl,*N*-methylamino)methyl-2,6-dimethylquinoline (2eA). (a mixture of anti and syn isomers) 186.2 mg, 77% yield; yellow solid; IR (neat) 2920, 1645, 1603, 1400, 825 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O$ $[M + H]^+$ 243.1492, found 243.1489.

4-(*N*-Acetyl,*N*-methylamino)methyl-6-methoxy-2-methylquinoline (2fA). (a mixture of anti and syn isomers) 166.3 mg, 64% yield; yellow solid; IR (neat) 2933, 1621, 1404, 1232, 727 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O_2$ $[M + H]^+$ 259.1441, found 259.1438.

4-(*N*-Acetyl,*N*-methylamino)methyl-6-fluoro-2-methylquinoline (2gA). (a mixture of anti and syn isomers) 169.3 mg, 69% yield; yellow solid; IR (neat) 2924, 1637, 1609, 1405, 830 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}FN_2O$ $[M + H]^+$ 247.1241, found 247.1235.

4-(*N*-Acetyl,*N*-methylamino)methyl-6-chloro-2-methylquinoline (2hA). (a mixture of anti and syn isomers) 202.4 mg, 77% yield; yellow solid; IR (neat) 2924, 1637, 1605, 1401, 830 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}ClN_2O$ $[M + H]^+$ 263.0946, found 263.0939.

4-(*N*-Acetyl,*N*-methylamino)methyl-7-chloro-2-methylquinoline (2iA). (a mixture of anti and syn isomers) 191.1 mg, 73% yield; white solid; IR (neat) 2927, 1627, 1606, 1402, 890 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}ClN_2O$ $[M + H]^+$ 263.0946, found 263.0943.

4-(*N*-Acetyl,*N*-methylamino)methyl-6-bromo-2-methylquinoline (2jA). (a mixture of anti and syn isomers) 205.8 mg, 67% yield; yellow solid; IR (neat) 2924, 1640, 1607, 1401, 828 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}BrN_2O$ $[M + H]^+$ 307.0441, found 307.0434.

4-(*N*-Acetyl,*N*-methylamino)methyl-6-methoxycarbonyl-2-methylquinoline (2kA). (a mixture of anti and syn isomers) 158.7 mg, 55% yield; yellow solid; IR (neat) 2952, 1716, 1644, 1272, 751 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_3$ $[M + H]^+$ 287.1390, found 287.1386.

4-(*N*-Acetyl,*N*-methylamino)methyl-6-acetyl-2-methylquinoline (2lA). (a mixture of anti and syn isomers) 106.8 mg, 40% yield; yellow solid; IR (neat) 2924, 1671, 1642, 1402, 1263, 841 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}N_2O_2$ $[M + H]^+$ 271.1441, found 271.1437.

1-(*N*-Acetyl,*N*-methylamino)methylisoquinoline (2mA). (a mixture of anti and syn isomers) 183.5 mg, 86% yield; white solid; IR (neat) 2927, 1638, 1403, 826, 747 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}N_2O$ $[M + H]^+$ 215.1179, found 215.1175.

1-(*N*-Acetyl,*N*-methylamino)methyl-4-bromoisoquinoline (2nA). (a mixture of anti and syn isomers) 151.3 mg, 52% yield; yellow solid; IR (neat) 2927, 1631, 1410, 1255, 763 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{14}BrN_2O$ $[M + H]^+$ 293.0284, found 293.0279.

2-(*N*-Acetyl,*N*-methylamino)methylquinoxaline (2oA).[8b] (a mixture of anti and syn isomers) 97.6 mg, 45% yield; yellow oil; IR (neat) 2931, 1642, 1492, 1400, 756 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}N_3O$ $[M + H]^+$ 216.1131, found 216.1128.

6-(*N*-Acetyl,*N*-methylamino)methylphenanthridine (2pA).[8c] (a mixture of anti and syn isomers) 171.6 mg, 65% yield; yellow oil; IR (neat) 2926, 1643, 1486, 1402, 750 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ $[M + H]^+$ 265.1335, found 265.1332.

2-(*N*-Acetyl,*N*-methylamino)methylquinoline (2qA). (a mixture of anti and syn isomers) 42.2 mg, 20% yield; yellow oil; IR (neat) 2930, 1634, 1600, 1401, 776 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}N_2O$ $[M + H]^+$ 215.1179 found 215.1175

4-(*N*-Acetyl,*N*-methylamino)methylquinoline (2qA′). (a mixture of anti and syn isomers) 65.9 mg, 31% yield; yellow oil; IR (neat) 2930, 1643, 1596, 1401, 752 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}N_2O$ $[M + H]^+$ 215.1179 found 215.1177.

2,4-Bis[(*N*-methyl-*N*-acetylamino)methyl]quinoline (2qA″). (a mixture of anti and syn isomers) 71.3 mg, 24% yield; yellow oil; IR (neat) 2931, 1633, 1485, 1401, 754 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}N_3O_2$ $[M + H]^+$ 300.1707, found 300.1704.

2-(*N*-Methyl,*N*-propanoylamino)methyl-4-methylquinoline (2aB). (a mixture of anti and syn isomers) 174.3 mg, 72% yield; yellow oil; IR (neat) 2936, 1643, 1601, 1402, 756 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}N_2O$ $[M + H]^+$ 243.1492, found 243.1487.

1-[(4′-Methylquinolin-2′-yl)methyl]pyrrolidin-2-one (2aC). 44.6 mg, 19% yield; colorless oil; IR (neat) 2923, 1674, 1602, 1421, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (quin, J = 7.6 Hz, 2H), 2.50 (t, J = 7.6 Hz, 2H), 2.69 (s, 3H), 3.41 (t, J = 7.6 Hz, 2H), 4.73 (s, 2H), 7.22 (s, 1H), 7.56 (t, J = 8.4 Hz, 1H), 7.71 (t, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.8, 18.8, 30.8, 47.2, 49.2, 120.5, 123.7, 126.2, 127.4, 129.3, 129.5, 145.5, 147.3, 156.8, 175.3 ppm; HRMS (ESI) calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1335, found 241.1331.

1-Methyl-5-(4′-methylquinolin-2′-yl)pyrrolidin-2-one (2aC′). 129.6 mg, 54% yield; white solid, mp 145−146 °C; IR (neat) 2916, 1686, 1601, 1393, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98−2.09 (m, 1H), 2.47−2.71 (m, 3H), 2.73 (s, 3H), 2.78 (s, 3H), 4.82 (dd, J = 8.6, 5.2 Hz, 1H), 7.12 (s, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.74 (t, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 26.2, 28.6, 30.0, 66.5, 118.0, 123.7, 126.5, 127.5, 129.6 (2C), 146.1, 147.5, 160.6, 175.8 ppm; HRMS (ESI) calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1335, found 241.1334.

1-Ethyl-5-(4′-methylquinolin-2′-yl)pyrrolidin-2-one (2aD). 157.5 mg, 62% yield; white solid, mp 100−101 °C; IR (neat) 2935, 1685, 1600, 1419, 764 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, J = 7.2 Hz, 3H), 1.98−2.09 (m, 1H), 2.47−2.62 (m, 2H), 2.63−2.71 (m, 1H), 2.72 (s, 3H), 2.77 (dq, J = 14.5, 7.2 Hz, 1H), 3.80 (dq, J = 14.5, 7.2 Hz, 1H), 4.96 (dd, J = 8.5, 4.8 Hz, 1H), 7.13 (s, 1H), 7.59 (t, J = 8.4 Hz, 1H), 7.74 (t, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 18.9, 26.3, 30.3, 36.0, 63.8, 118.2, 123.7, 126.4, 127.5, 129.57, 129.64, 145.9, 147.5, 160.9, 175.4 ppm; HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1492, found 255.1489.

1-Acetyl-2-(4′-methylquinolin-2′-yl)pyrrolidine (2aE). (a mixture of anti and syn isomers) 122.8 mg, 48% yield; white solid; IR (neat) 2968, 1639, 1595, 1410, 758 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M + H]^+$ 255.1492, found 255.1490.

2-(*N*-Acetylamino)methyl-4-methylquinoline (2aF).[8a] 132.4 mg, 62% yield; white soild, mp 121−123 °C; IR (neat) 3293, 2920, 1634, 1549, 765 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H), 2.70 (s, 3H), 4.69 (d, J = 4.3 Hz, 2H), 7.17 (s, 1H), 7.57 (t, J = 8.4 Hz, 1H), 7.72 (t, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 23.2, 44.8, 120.5, 123.8, 126.1, 127.4, 129.1, 129.4, 145.1, 146.9, 155.7, 170.2 ppm; HRMS (ESI) calcd for $C_{13}H_{15}N_2O$ $[M + H]^+$ 215.1179, found 215.1175.

4-(*N*-Acetylamino)methyl-2,6-dimethylquinoline (2eF). 134.1 mg, 59% yield; yellow solid, mp 154−155 °C; IR (neat) 3253, 2916, 1628, 1560, 829 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.53 (s, 3H), 2.66 (s, 3H), 4.82 (d, J = 5.6 Hz, 2H), 7.12 (s, 1H), 7.51 (d, J = 8.5 Hz, 1H), 7.66 (s, 1H), 7.90 (d, J = 8.5 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 23.1, 25.0, 40.3, 120.7, 121.8, 124.5,

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128.8, 131.5, 135.9, 142.3, 146.3, 157.6, 170.1 ppm; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ 229.1335, found 229.1332.

1-(*N*-Acetyl,*N*-methylamino)methylisoquinoline (2mB). (a mixture of anti and syn isomers) 175.6 mg, 77% yield; yellow oil; IR (neat) 2936, 1638, 1481, 1404, 747 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ 229.1335, found 229.1334.

1-[(Isoquinolin-1′-yl)methyl]pyrrolidin-2-one (2mC). 30.5 mg, 13% yield; white solid, mp 97−99 °C; IR (neat) 2951, 1672, 1256, 834, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.94 (quin, J = 7.6 Hz, 2H), 2.45 (t, J = 7.6 Hz, 2H), 3.30 (t, J = 7.6 Hz, 2H), 5.09 (s, 2H), 7.61−7.67 (m, 2H), 7.71 (t, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.45 (d, J = 5.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 30.8, 46.9, 47.1, 121.0, 125.4, 126.7, 127.1, 127.9, 130.4, 136.3, 141.5, 155.8, 174.6 ppm; HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$ 227.1179, found 227.1176.

5-(Isoquinolin-1′-yl)-1-methylpyrrolidin-2-one (2mC′). 141.7 mg, 63% yield; yellow oil; IR (neat) 2925, 1673, 1395, 825, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.08−2.20 (m, 1H), 2.44−2.56 (m, 1H), 2.56−2.72 (m, 2H), 2.80 (s, 3H), 5.51 (dd, J = 7.9, 4.3 Hz, 1H), 7.61 (d, J = 5.8 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.73 (t, J = 7.9 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 8.13 (d, J = 7.9 Hz, 1H), 8.51 (d, J = 5.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0, 28.8, 29.9, 62.0, 120.5, 123.3, 125.9, 127.6, 127.8, 130.0, 136.6, 142.0, 158.0, 175.9 ppm; HRMS (ESI) calcd for $C_{14}H_{15}N_2O$ $[M + H]^+$ 227.1179, found 227.1176.

1-Ethyl-5-(isoquinolin-1′-yl)pyrrolidin-2-one (2mD). 144.3 mg, 60% yield; yellow oil; IR (neat) 2975, 1672, 1416, 1245, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, J = 7.3 Hz, 3H), 2.09−2.19 (m, 1H), 2.45−2.63 (m, 2H), 2.63−2.82 (m, 2H), 3.84 (dq, J = 14.7, 7.3 Hz, 1H), 5.64 (dd, J = 7.8, 4.4 Hz, 1H), 7.61 (d, J = 5.7 Hz, 1H), 7.65 (t, J = 7.9 Hz, 1H), 7.73 (t, J = 7.9 Hz, 1H), 7.90 (d, J = 7.9 Hz, 1H), 8.16 (d, J = 7.9 Hz, 1H), 8.51 (d, J = 5.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.4, 26.0, 30.2, 35.9, 59.0, 120.4, 123.1, 125.8, 127.5, 127.7, 130.0, 136.5, 141.9, 158.3, 175.4 ppm; HRMS (ESI) calcd for $C_{15}H_{17}N_2O$ $[M + H]^+$ 241.1335, found 241.1332.

6-(*N*-Methyl,*N*-propanoylamino)methylphenanthridine (2pB). (a mixture of anti and syn isomers) 213.1 mg, 77% yield; yellow solid; IR (neat) 2936, 1636, 1462, 1404, 752 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{19}N_2O$ $[M + H]^+$ 279.1492, found 279.1489.

1-Ethyl-5-(phenanthridin-6′-yl)pyrrolidin-2-one (2pD). 204.1 mg, 70% yield; white solid, mp 154−156 °C; IR (neat) 2974, 1669, 1443, 1272, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (t, J = 7.4 Hz, 3H), 2.12−2.25 (m, 1H), 2.44−2.58 (m, 1H), 2.60−2.74 (m, 2H), 2.90−3.03 (m, 1H), 3.92 (dq, J = 14.7, 7.4 Hz, 1H), 5.69 (dd, J = 8.2, 3.2 Hz, 1H), 7.64−7.77 (m, 3H), 7.89 (t, J = 8.2 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.2 Hz, 1H), 8.57 (d, J = 8.0 Hz, 1H), 8.72 (d, J = 8.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 25.8, 30.2, 36.3, 59.5, 121.8, 122.9, 123.6, 123.7, 124.2, 127.1, 127.5, 128.7, 130.3, 130.5, 133.4, 143.1, 157.8, 175.7 ppm; HRMS (ESI) calcd for $C_{19}H_{19}N_2O$ $[M + H]^+$ 291.1492, found 291.1490.

2-(*N*-Methylamino)methyl-4-methylquinoline (3aA). 184.0 mg, 99% yield; yellow oil; IR (neat) 3307, 2927, 1603, 1445, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.70 (s, 3H), 4.00 (s, 2H), 7.31 (s, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.69 (td, J = 8.4, 1.1 Hz, 1H), 7.97 (dd, J = 8.4, 1.1 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 36.4, 57.8, 121.2, 123.6, 125.8, 127.3, 129.1, 129.5, 144.5, 147.5, 159.8 ppm; HRMS (ESI) calcd for $C_{12}H_{15}N_2$ $[M + H]^+$ 187.1230, found 187.1225.

4,6-Dimethyl-2-(*N*-methylamino)methylquinoline (3bA). yellow oil; IR (neat) 3303, 2920, 1602, 1442, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.55 (s, 3H), 2.67 (s, 3H), 3.98 (s, 2H), 7.27 (d, J = 1.6 Hz, 1H), 7.52 (dd, J = 8.6, 1.6 Hz, 1H), 7.72 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 21.8, 36.4, 57.8, 121.2, 122.7, 127.2, 129.1, 131.2, 135.5, 143.8, 146.0, 158.8 ppm; HRMS (ESI) calcd for $C_{13}H_{17}N_2$ $[M + H]^+$ 201.1386, found 201.1382.

7-Chloro-4-hydroxy-2-(*N*-methylamino)methylquinoline (3cA). The 4-chloro group was converted into an OH group via aq HCl hydrolysis. White solid, mp 177 °C (decomp); IR (neat) 3285, 3069, 2939, 1494, 816 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48 (s, 3H), 3.81 (s, 2H), 6.14 (s, 1H), 7.28 (dd, J = 8.6, 1.8 Hz, 1H), 7.40 (d, J = 1.8 Hz, 1H), 8.27 (d, J = 8.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2, 51.7, 108.0, 117.0, 124.2, 124.3, 127.8, 138.0, 139.8, 150.5, 178.2 ppm; HRMS (ESI) calcd for $C_{11}H_{12}ClN_2O$ $[M + H]^+$ 223.0633, found 223.0633.

4-(*N*-Methylamino)methyl-2-methylquinoline (3dA). 187.3 mg, >99% yield; yellow oil; IR (neat) 3296, 2935, 1604, 1445, 726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.74 (s, 3H), 4.20 (s, 2H), 7.33 (s, 1H), 7.51 (t, J = 8.4 Hz, 1H), 7.68 (t, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 36.6, 52.1, 120.6, 122.9, 125.2, 125.6, 129.0, 129.3, 145.2, 147.9, 158.8 ppm; HRMS (ESI) calcd for $C_{12}H_{15}N_2$ $[M + H]^+$ 187.1230, found 187.1226.

2,6-Dimethyl-4-(*N*-methylamino)methylquinoline (3eA). yellow solid, mp 67−68 °C; IR (neat) 3302, 2919, 1603, 1442, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.54 (s, 3H), 2.59 (s, 3H), 2.71 (s, 3H), 4.17 (s, 2H), 7.29 (s, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.75 (s, 1H), 7.93 (d, J = 8.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 25.2, 36.6, 52.1, 120.6, 121.8, 125.1, 129.0, 131.2, 135.4, 144.5, 146.5, 157.8 ppm; HRMS (ESI) calcd for $C_{13}H_{17}N_2$ $[M + H]^+$ 201.1386, found 201.1387.

6-Methoxy-2-methyl-4-(*N*-methylamino)methylquinoline (3fA). yellow solid, mp 51−52 °C; IR (neat) 3315, 2924, 1603, 1229, 839 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 2.70 (s, 3H), 3.94 (s, 3H), 4.14 (s, 2H), 7.25 (d, J = 2.8 Hz, 1H), 7.30 (s, 1H), 7.34 (dd, J = 9.3, 2.8 Hz, 1H), 7.95 (d, J = 9.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.0, 36.6, 52.3, 55.5, 101.5, 120.7, 120.9, 126.0, 130.7, 143.86, 143.91, 156.1, 157.1 ppm; HRMS (ESI) calcd for $C_{13}H_{17}N_2O$ $[M + H]^+$ 217.1335, found 217.1332.

6-Fluoro-2-methyl-4-(*N*-methylamino)methylquinoline (3gA). yellow solid, mp 45−46 °C; IR (neat) 3307, 2792, 1515, 1222, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.72 (s, 3H), 4.12 (s, 2H), 7.35 (s, 1H), 7.44 (td, J = 9.3, 2.7 Hz, 1H), 7.64 (dd, J = 9.3, 2.7 Hz, 1H), 8.02 (dd, J = 9.3, 5.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.2, 36.6, 52.3, 106.8 (d, $J_{C,F}$ = 21.9 Hz), 119.0 (d, $J_{C,F}$ = 25.8 Hz), 121.3, 126.0 (d, $J_{C,F}$ = 9.5 Hz), 131.6 (d, $J_{C,F}$ = 9.5 Hz), 144.8 (d, $J_{C,F}$ = 5.7 Hz), 145.0, 158.1, 160.0 (d, $J_{C,F}$ = 246.1 Hz) ppm; HRMS (ESI) calcd for $C_{12}H_{14}FN_2$ $[M + H]^+$ 205.1136, found 205.1132.

6-Chloro-2-methyl-4-(*N*-methylamino)methylquinoline (3hA). yellow solid, mp 94−96 °C; IR (neat) 3319, 2784, 1603, 1444, 764 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 2.72 (s, 3H), 4.13 (s, 2H), 7.35 (s, 1H), 7.60 (dd, J = 8.9, 2.3 Hz, 1H), 7.96 (d, J = 8.9 Hz, 1H), 7.99 (d, J = 2.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 36.6, 52.1, 121.3, 122.2, 126.0, 129.8, 130.8, 131.4, 144.6, 146.3, 159.2 ppm; HRMS (ESI) calcd for $C_{12}H_{14}ClN_2$ $[M + H]^+$ 221.0840, found 221.0839.

7-Chloro-2-methyl-4-(*N*-methylamino)methylquinoline (3iA). 201.7 mg, 91% yield; yellow oil; IR (neat) 3292, 2791, 1604, 1445, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 3H), 2.72 (s, 3H), 4.16 (s, 2H), 7.33 (s, 1H), 7.45 (dd, J = 8.8, 2.0 Hz, 1H), 7.97 (d, J = 8.8 Hz, 1H), 8.03 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 36.6, 52.1, 120.8, 123.7, 124.5, 126.5, 128.2, 134.8, 145.4, 148.5, 160.1 ppm; HRMS (ESI) calcd for $C_{12}H_{14}ClN_2$ $[M + H]^+$ 221.0840, found 221.0839.

6-Bromo-2-methyl-4-(*N*-methylamino)methylquinoline (3jA). yellow soild, mp 123−124 °C; IR (neat) 3315, 2783, 1600, 1443, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 2.71 (s, 3H), 4.14 (s, 2H), 7.35 (s, 1H), 7.73 (dd, J = 8.8, 2.0 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 8.17 (d, J = 2.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 36.6, 52.0, 119.6, 121.3, 125.5, 126.5, 131.0, 132.4, 144.5, 146.6, 159.3 ppm; HRMS (ESI) calcd for $C_{12}H_{14}BrN_2$ $[M + H]^+$ 265.0335, found 265.0334.

2-Methyl-6-methoxycarbonyl-4-(*N*-methylamino)-methylquinoline (3kA). yellow solid, mp 57−59 °C; IR (neat) 3327, 2951, 1703, 1279, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 2.76 (s, 3H), 3.99 (s, 3H), 4.27 (s, 2H), 7.42 (s, 1H), 8.06 (d, J = 8.8 Hz, 1H), 8.26 (dd, J = 8.8, 1.7 Hz, 1H), 8.78 (d, J = 1.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 36.6, 51.9, 52.4, 121.2, 124.5, 126.2, 127.0, 128.7, 129.5, 146.8, 150.0, 161.5, 166.9 ppm;

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HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2$ $[M + H]^+$ 245.1285, found 245.1281.

6-Acetyl-2-methyl-4-(*N*-methylamino)methylquinoline (3lA). yellow solid, mp 79−80 °C; IR (neat) 3323, 2925, 1672, 1602, 1260 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 3H), 2.74 (s, 3H), 2.76 (s, 3H), 4.27 (s, 2H), 7.42 (s, 1H), 8.08 (d, J = 8.8 Hz, 1H), 8.21 (dd, J = 8.8, 1.8 Hz, 1H), 8.70 (d, J = 1.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 26.8, 36.7, 52.0, 121.4, 124.6, 125.0, 127.6, 129.7, 133.9, 147.1, 150.0, 161.6, 197.7 ppm; HRMS (ESI) calcd for $C_{14}H_{17}N_2O$ $[M + H]^+$ 229.1335, found 229.1331.

1-(*N*-Methylamino)methylisoquinoline (3mA). 142.7 mg, 83% yield; yellow oil; IR (neat) 3323, 2931, 1562, 822, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.60 (s, 3H), 4.38 (s, 2H), 7.56 (d, J = 5.8 Hz, 1H), 7.61 (t, J = 7.9 Hz, 1H), 7.68 (t, J = 7.9 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.46 (d, J = 5.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6, 54.2, 119.9, 124.5, 126.6, 127.2, 127.3, 129.9, 136.0, 141.6, 158.5 ppm; HRMS (ESI) calcd for $C_{11}H_{13}N_2$ $[M + H]^+$ 173.1073, found 173.1071.

4-Bromo-1-(*N*-methylamino)methylisoquinoline (3nA). yellow solid, mp 150 °C (decomp); IR (neat) 3327, 2844, 1255, 924, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 4.35 (s, 2H), 7.68 (t, J = 8.1 Hz, 1H), 7.80 (t, J = 8.1 Hz, 1H), 8.196 (d, J = 8.1 Hz, 1H), 8.198 (d, J = 8.1 Hz, 1H), 8.65 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6, 54.1, 118.7, 125.0, 126.7, 127.8, 128.2, 131.2, 134.7, 143.3, 158.2 ppm; HRMS (ESI) calcd for $C_{11}H_{12}BrN_2$ $[M + H]^+$ 251.0178, found 251.0181.

2-(*N*-Methylamino)methylquinoxaline (3oA).[11a] yellow oil; IR (neat) 3318, 2926, 1493, 1126, 758 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 4.14 (s, 2H), 7.72−7.81 (m, 2H), 8.05−8.14 (m, 2H), 8.90 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.2, 55.2, 129.0, 129.2, 129.4, 130.1, 141.8, 141.9, 145.2, 154.6 ppm; HRMS (ESI) calcd for $C_{10}H_{12}N_3$ $[M + H]^+$ 174.1026, found 174.1022.

6-(*N*-Methylamino)methylphenanthridine (3pA). yellow solid, mp 57−59 °C; IR (neat) 3323, 2930, 1586, 1446, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.67 (s, 3H), 4.46 (s, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.67−7.75 (m, 2H), 7.84 (t, J = 8.0 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.55 (d, J = 8.0 Hz, 1H), 8.64 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7, 54.7, 121.9, 122.4, 123.9, 124.8, 125.4, 126.6, 127.4, 128.6, 129.8, 130.4, 132.7, 143.3, 158.2 ppm; HRMS (ESI) calcd for $C_{15}H_{15}N_2$ $[M + H]^+$ 223.1230, found 223.1231.

2-(*N*-Methylamino)methylquinoline (3qA). yellow oil; IR (neat) 3303, 2930, 1600, 1504, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 4.09 (s, 2H), 7.45 (d, J = 8.4 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.4, 57.6, 120.5, 126.1, 127.3, 127.6, 128.8, 129.6, 136.7, 147.5, 160.0 ppm; HRMS (ESI) calcd for $C_{11}H_{13}N_2$ $[M + H]^+$ 173.1073, found 173.1073.

4-(*N*-Methylamino)methylquinoline (3qA′).[11b] yellow oil; IR (neat) 3291, 2931, 1593, 1508, 753 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 4.24 (s, 2H), 7.44 (d, J = 4.3 Hz, 1H), 7.58 (t, J = 8.4 Hz, 1H), 7.72 (t, J = 8.4 Hz, 1H), 8.09 (d, J = 8.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 8.88 (d, J = 4.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.5, 52.1, 119.7, 123.1, 126.5, 127.0, 129.0, 130.1, 145.3, 148.2, 150.3 ppm; HRMS (ESI) calcd for $C_{11}H_{13}N_2$ $[M + H]^+$ 173.1073, found 173.1071.

2,4-Bis(*N*-methylamino)methylquinoline (3qA″). 147.3 mg, 84% yield; brown oil; IR (neat) 3285, 2931, 1602, 1445, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.55 (s, 3H), 2.58 (s, 3H), 4.05 (s, 2H), 4.22 (s, 2H), 7.49 (s, 1H), 7.54 (t, J = 8.1 Hz, 1H), 7.69 (t, J = 8.1 Hz, 1H), 8.05 (d, J = 8.1 Hz, 1H), 8.09 (d, J = 8.1 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.4, 36.6, 52.3, 57.9, 119.2, 123.1, 126.0 (2C), 129.1, 129.7, 145.6, 147.9, 160.0 ppm; HRMS (ESI) calcd for $C_{13}H_{18}N_3$ $[M + H]^+$ 216.1495, found 216.1494.

4-Methyl-2-(pyrrolidin-2′-yl)quinoline (3aE). 93.4 mg, 88% yield; yellow oil; IR (neat) 3303, 2959, 1603, 1445, 756 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76−1.86 (m, 1H), 1.86−1.95 (m, 2H), 2.33 (sext, J = 6.5 Hz, 1H), 2.70 (s, 3H), 3.05−3.13 (m, 1H), 3.25−3.33 (m, 1H), 4.42 (t, J = 7.5 Hz, 1H), 7.31 (s, 1H), 7.52 (t, J = 8.3 Hz, 1H), 7.68 (t, J = 8.3 Hz, 1H), 7.96 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 8.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 26.1, 33.9, 47.4, 63.9, 120.2, 123.6, 125.7, 127.4, 129.0, 129.5, 144.6, 147.1, 163.4 ppm; HRMS (ESI) calcd for $C_{14}H_{17}N_2$ $[M + H]^+$ 213.1386, found 213.1382.

2-(*N*-Ethyl,*N*-methylamino)methyl-4-methylquinoline (4aA). 74.9 mg, 70% yield; yellow solid, mp 167 °C (decomp); IR (neat) 2969, 2790, 1603, 1446, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3H), 2.30 (s, 3H), 2.57 (q, J = 7.2 Hz, 2H), 2.70 (s, 3H), 3.78 (s, 2H), 7.48 (s, 1H), 7.53 (t, J = 8.3 Hz, 1H), 7.68 (t, J = 8.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 18.7, 42.1, 51.8, 64.2, 121.7, 123.6, 125.8, 127.4, 129.0, 129.5, 144.5, 147.4, 159.9 ppm; HRMS (ESI) calcd for $C_{14}H_{19}N_2$ $[M + H]^+$ 215.1543, found 215.1539.

4-Methyl-2-(1′-methylpyrrolidin-2′-yl)quinoline (4aC′). 68.9 mg, 61% yield, colorless oil; IR (neat) 2941, 2778, 1603, 1447, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.82−1.95 (m, 2H), 1.96−2.12 (m, 1H), 2.28 (s, 3H), 2.30−2.45 (m, 2H), 2.71 (s, 3H), 3.30 (t, J = 8.4 Hz, 1H), 3.44 (t, J = 8.4 Hz, 1H), 7.48 (s, 1H), 7.53 (t, J = 8.3 Hz, 1H), 7.68 (t, J = 8.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 23.1, 33.8, 40.8, 57.2, 73.4, 119.6, 123.6, 125.7, 127.6, 128.9, 129.6, 144.9, 147.3, 163.6 ppm; HRMS (ESI) calcd for $C_{15}H_{19}N_2$ $[M + H]^+$ 227.1543, found 227.1539.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02303.

^1H NMR and ^{13}C NMR spectra of all products **2**, **3**, and **4** and X-ray crystallograpic data for **2aD** (PDF)

CIF data for **2aD** (CIF)

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Notes

The authors declare no competing financial interest.

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