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Copper-Catalyzed Oxidative Direct Cyclization of *N*-Methylanilines with Electron-Deficient Alkenes Using Molecular Oxygen

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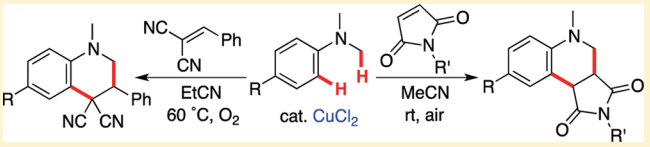
Supporting Information

ABSTRACT:

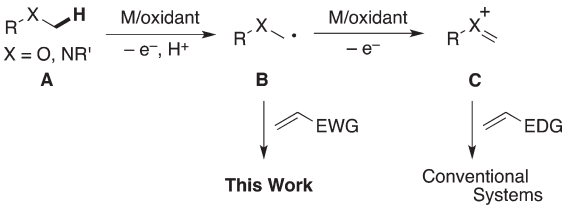


The oxidative direct cyclizaion of *N*-methylanilines with electron-deficient alkenes involving maleimides and benzylidene malononitriles through sp^3 and sp^2 C−H bond cleavage proceeds effectively under a $CuCl_2/O_2$ catalysis to provide the corresponding tetrahydroquinolines in good yields.

Metal-mediated dehydrogenative C−C bond formation through C−H bond cleavage has received significant attention in modern organic chemistry since it can skip the preactivation steps, such as halogenation and stoichiometric metalation, of the starting materials. In particular, the direct couplings at an sp^3 carbon center adjacent to heteroatoms involving nitrogen and oxygen have been widely explored.[1] This type of reaction is believed to proceed through the stepwise one-electron oxidation by the combination of transition metals and oxidants (Scheme 1). The electrophilic nature of the resultant iminium cations **C** allows some nucleophilic, electron-rich olefins including enols,[2] enamines,[3] and (hetero)arenes[4] to trap the species.[5] In this context, we may envisage that the appropriate control of the oxidation capacity of catalysts enables the preferable generation of radical intermediate **B**. If it were feasible, the reaction with electron-deficient olefins would be possible via SOMO/LUMO interaction, which provides the complementary reaction mode of the substrate **A**. During our study to develop such type coupling, a copper(II)/molecular oxygen catalyst system has been found to effectively work in the oxidative direct cyclization of *N*-methylanilines with maleimides and benzylidene malononitrile.[6] The reaction occurs under mild conditions to form the corresponding tetrahydroquinoline derivatives in good yields, showing the superiority of copper for the transformation.

We initially selected 4,*N*,*N*-trimethylaniline (**1a**) and *N*-phenylmaleimide (**2a**) as model substrates and investigated various combinations of transition metals and oxidants for capture of the radical intermediate corresponding to **B** in Scheme 1. Representative data are summarized in Table 1. Treatment of **1a** with **2a** in the presence of 20 mol % of $CuCl_2$ catalyst and a frequently used peroxide, *t*-BuOO*t*-Bu, in MeCN at room temperature afforded the tetrahydroquinoline skeleton **3aa** in 5% GC yield (entry 1). Apparently, the desired reaction mode was possible, albeit the yield was very low. Then, we

Scheme 1. Reaction Modes of sp^3 C−H Bond Adjacent to Heteroatom in Dehydrogenative Couplings[a]



[a] EWG = electron-withdrawing group, EDG = electron-donating group.

surveyed some oxidants. While *t*-BuOOH somewhat improved the reaction efficiency (entry 2), the ideal oxidant, molecular oxygen, proved to be optimal (entry 3). Moreover, the reaction under ambient conditions provided a better result, and **3aa** was isolated in 74% yield (entry 4). The coupling with a stoichiometric amount of $CuCl_2$ in the absence of O_2 was sluggish, indicating the pivotal role of O_2 in the catalytic cycle (entry 5). Other first transition elements such as nickel, iron, and manganese dropped the yield of **3aa** (entries 6−8).[6a] Addition of ligands such as 1,10-phenanthroline and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine and any changes of solvent system into toluene, DMF, or DMSO were detrimental (not shown).

With the conditions employed for entry 4 in Table 1, the cyclization of a variety of *N*-methylanilines **1** with **2a** was performed (Scheme 2). The methoxy and *tert*-butyl substituents at the 4-position were accommodated (**3ba** and **3ca**), while the nonsubstituted aniline decreased the yield (**3da**).[7] 3,4,*N*,*N*-Tetramethylaniline showed high reactivity to furnish a mixture of regioisomers **3ea** and **3ea**′ with 93% combined yield in favor of

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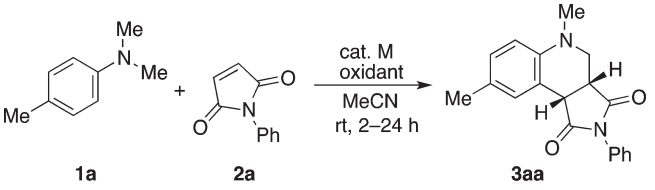
Table 1. Optimization Studies for Oxidative Direct Coupling of 4,*N*,*N*-Trimethylaniline (1a) with *N*-Phenylmaleimide (2a)[a]



1a 2a 3aa

entry	M (mol %)	oxidant	3aa, yield[b] (%)
1	$CuCl_2$ (20)	*t*-BuOO-*t*-Bu (1.0 equiv)	(5)
2	$CuCl_2$ (20)	*t*-BuOOH (1.0 equiv)	(40)
3	$CuCl_2$ (20)	O_2 (1 atm, balloon)[c]	58
4	$CuCl_2$ (20)	air	74
5	$CuCl_2$ (100)	none	(8)
6	$NiCl_2$ (20)	air	(9)
7	$FeCl_3$ (20)	air	trace
8	$MnCl_2$ (20)	air	(43)

[a] A mixture of **1a** (1.0 mmol), **2a** (0.50 mmol), M, and oxidant was stirred in MeCN (1.0 mL) for 2−24 h at room temperature under N_2. [b] Yield determined by GC method in parentheses. [c] Under O_2 (1 atm, balloon).

the formation of more congested **3ea**. In addition, a 2,4-disubstituted pattern was available for use (**3fa**). As the substitution on nitrogen, butyl and benzyl groups were compatible (**3ga and 3ha**) as well as methyl group. In these cases, the selective reaction at the Me position occurred, which would inform us about the reaction mechanism (vide infra). On the other hand, attempts to apply *N*,3,4-trimethylaniline (R^1 = 3,4-diMe, R^2 = H) and *N*,*N*-diethylaniline remained unsuccessful (data not shown).

Next, we investigated the scope of maleimides (Table 2). *N*-Arylmaleimides bearing electronically diverse functions such as methoxy, chloro, and trifluoromethyl underwent the direct coupling to give the corresponding tetracyclic frameworks **3ab**−**ad** in good yields (entries 1−3). Aliphatic systems **2e** and **2f** also were applicable to the reaction (entries 4 and 5).

We are tempted to assume the reaction mechanism as follows (Scheme 3). Initial single electron transfer from *N*-methylaniline **1** to the copper complex is followed by deprotonation to give the α-amino radical **4**. Subsequent electrophilic radical addition to maleimide **2** and cyclization onto the aromatic ring proceeds to generate the corresponding cyclohexadienyl radical **5**, which is then readily rearomatized by the second electron transfer/proton elimination leading to the product **3**.[6a,8] The trapping of **4** with **2** could take place much faster than the second one electron oxidation under the present $CuCl_2$/air system to suppress the overoxidation into the iminium cation **6**, en route to decomposition. The proposed mechanism also can account for the regioselectivity observed in the reaction with **1e** (Scheme 2, **3ea** + **3ea′**): the radical addition to methyl-substituted arenes preferably occurs at the *ortho*-position because of the stabilization through hyperconjugation.[9] We attribute the selective oxidation of **1** beyond the radical intermediate **4** to an association between **4** and the copper complex. The assumption is also consistent with the exclusive production of **3ga** and **3ha** (Scheme 2), in which the C−C bond formation predominantly occurs at the less congested Me position probably due to the steric factors in the copper association despite the fact that the corresponding

Scheme 2. Copper-Catalyzed Oxidative Direct Coupling of Various *N*-Methylanilines 1 with *N*-Phenylmaleimide (2a)

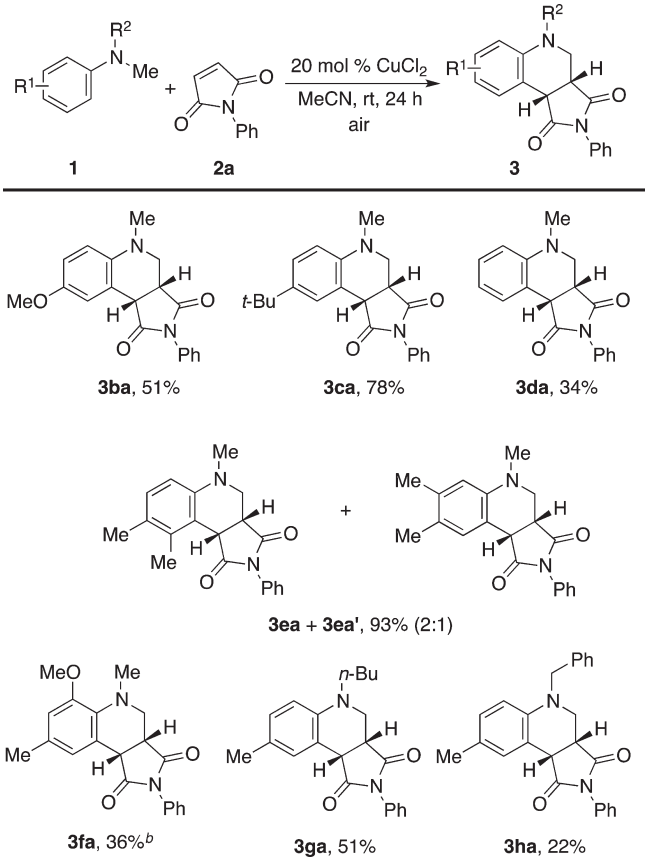
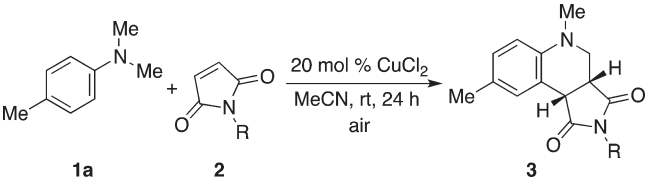


Table 2. Copper-Catalyzed Oxidative Direct Coupling of 4,*N*,*N*-Trimethylaniline (1a) with Various Maleimides 2[a]



entry	R **2**	**3**, yield (%)
1[b]	4-$MeOC_6H_4$ (**2b**)	**3ab**, 56
2	4-ClC_6H_4 (**2c**)	**3ac**, 75
3	4-$CF_3C_6H_4$ (**2d**)	**3ad**, 63
4	Me (**2e**)	**3ae**, 68
5	Bn (**2f**)	**3af**, 52

[a] A mixture of **1a** (1.0 mmol), **2** (0.50 mmol), and $CuCl_2$ (0.10 mmol) was stirred in MeCN (2.0 mL) for 24 h at room temperature under air. [b] Under O_2 (1 atm, balloon).

secondary and benzyl radicals are generally more stable than the methylene one. However, further efforts are essential for elucidation of the detailed mechanism.[10]

To demonstrate the synthetic utility of the process, we carried out the transformation of the product **3aa** (Scheme 4). The reduction upon treatment with Red-Al in heating toluene

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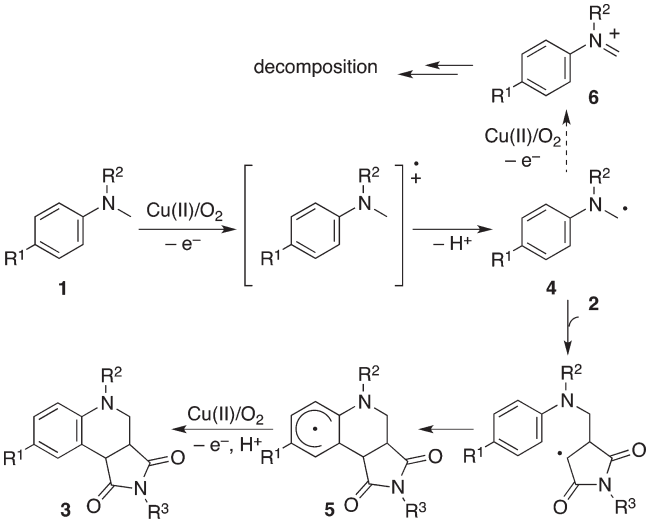
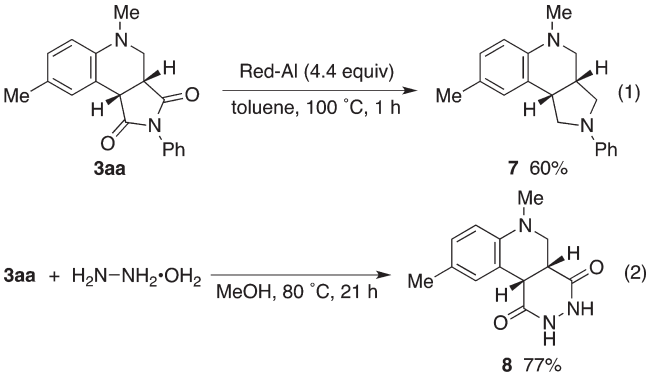
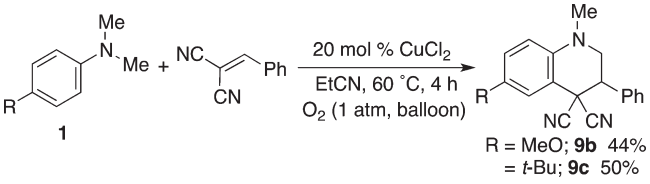
Scheme 3. Plausible Mechanism



Scheme 4



Scheme 5



afforded the corresponding pyrroloquinoline **7** in 60% yield with maintenance of the *cis*-configuration (eq 1).[11] Moreover, the reaction with hydrazine monohydrate resulted in the highly functionalized tetrahydropyridazinedione **8**, which could be a useful synthetic handle for further manipulation (eq 2).[12]

Finally, we evaluated some other electron-deficient alkenes, and to our delight, benzylidene malononitrile was found to be a suitable substrate class for the oxidative coupling with *N*-methylanilines **1** (Scheme 5).[13] The reaction proceeded regioselectively under somewhat modified conditions (EtCN, 60 °C, O_2) to produce the multiply substituted tetrahydroquinolines **9**. While preliminary, it shows the potential of the catalyst system for the radical-mediated process of *N*-methylaniline derivatives.

In conclusion, we have developed a simple copper/O_2 catalyst system for the oxidative cyclization of *N*-methylanilines with electron-deficient olefins. By an appropriate control of the catalyst oxidation capacity, the complementary reaction mode of *N*-methylanilines becomes effectively available. The catalysis provides a direct, dehydrogenative access to tetrahydroquionoline frameworks of importance in medicinal and pharmaceutical chemistry.

EXPERIMENTAL SECTION

Typical Procedure for Copper-Catalyzed Oxidative Cyclization of *N*-Methylanilines with 1. Synthesis of **3aa** (Table 1, entry 4) is representative. $CuCl_2$ (13 mg, 0.10 mmol), 4,*N*,*N*-trimethylaniline (**1a**, 135 mg, 1.0 mmol), *N*-phenylmaleimide (**2a**, 87 mg, 0.50 mmol), MeCN (2.0 mL), and dibenzyl (ca. 40 mg, internal standard) were placed in a 20 mL two-necked reaction flask equipped with a drying tube lined with calcium chloride. The solution was stirred at room temperature for 24 h under air. The formation of **3aa** was confirmed by GC analysis, and the resulting mixture was then quenched with water. The mixture was extracted with ethyl acetate, and the combined organic layer was dried over sodium sulfate. The mixture was then concentrated in vacuo and purified by silica gel column chromatography with *n*-hexane/ethyl acetate (5:1, v/v) to afford an analytically pure (3a*R**, 9b*S**)-5,8-dimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (**3aa**, 113 mg, 0.37 mmol) in 74% yield.

(3a*R,9b*S**)-2,5,8-Trimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3aa):** mp 195−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.80 (s, 3H), 3.05 (dd, J = 11.4, 4.4 Hz, 1H), 3.50 (ddd, J = 9.5, 4.4, 2.6 Hz, 1H), 3.58 (dd, J = 11.4, 2.6 Hz, 1H), 4.11 (d, J = 9.5 Hz, 1H), 6.65 (d, J = 8.4 Hz, 1H), 7.03 (dd, J = 8.4, 2.2 Hz, 1H), 7.25−7.28 (m, 2H), 7.34−7.37 (m, 2H), 7.40−7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 39.7, 42.3, 43.7, 51.1, 112.7, 118.7, 126.5, 128.6, 129.1, 129.4, 131.0, 132.2, 146.5, 176.0, 177.9 (one signal was overlapped by other one.); HRMS (EI) m/z (M^+) calcd for $C_{19}H_{18}N_2O_2$ 306.1368, found 306.1367.

(3a*R,9b*S**)-8-Methoxy-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ba):** oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78 (s, 3H), 3.01 (dd, J = 11.3, 4.4 Hz, 1H), 3.49 (ddd, J = 9.5, 4.4, 2.6 Hz, 1H), 3.55 (dd, J = 11.3, 2.6 Hz, 1H), 3.78 (s, 3H), 4.10 (d, J = 9.5 Hz, 1H), 6.67 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 8.8, 2.9 Hz, 1H), 7.12 (d, J = 2.9 Hz, 1H), 7.25−7.28 (m, 2H), 7.34−7.36 (m, 1H), 7.40−7.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.9, 42.6, 43.6, 51.4, 55.81, 113.6, 114.5, 115.8, 119.9, 126.5, 128.6, 129.1, 132.1, 142.9, 153.3, 175.7, 177.8; HRMS m/z (M^+) calcd for $C_{19}H_{18}N_2O_3$ 322.1317, found 322.1320.

(3a*R,9b*S**)-8-*tert*-Butyl-5-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ca):** mp 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 2.81 (s, 3H), 3.09 (dd, J = 11.4 4.6 Hz, 1H), 3.49 (ddd, J = 9.6, 4.6, 3.2 Hz, 1H), 3.56 (dd, J = 11.4, 3.2 Hz, 1H), 4.14 (d, J = 9.6 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 7.23−7.28 (m, 3H), 7.32−7.35 (m, 1H), 7.39−7.43 (m, 2H), 7.56 (d, J = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 34.1, 39.6, 42.3, 43.5, 50.8, 112.2, 118.1, 125.5, 126.5, 127.6, 128.6, 129.1, 132.1, 142.4, 146.2, 176.0, 177.9; HRMS m/z (M^+) calcd for $C_{22}H_{24}N_2O_2$ 348.1838, found 348.1836.

(3a*R,9b*S**)-5-Methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3da):** mp 184−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (s, 3H), 3.11 (dd, J = 11.5, 4.6 Hz, 1H), 3.52 (ddd, J = 9.6, 4.6, 2.8 Hz, 1H), 3.60 (dd, J = 11.5, 2.8 Hz, 1H), 4.15 (d, J = 9.6 Hz, 1H), 6.74 (d, J = 8.2 Hz, 1H), 6.90 (dd, J = 7.8, 7.3 Hz, 1H), 7.21−7.27 (m, 3H), 7.33−7.36 (m, 1H), 7.40−7.44 (m, 2H), 7.52 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.6, 42.2, 43.7, 50.76, 112.7, 118.7, 119.8, 126.5, 128.6, 128.8, 129.1, 130.4, 132.1, 148.6, 175.9, 177.8; HRMS m/z (M^+) calcd for $C_{18}H_{16}N_2O_2$ 292.1212, found 292.1208.

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Mixture of (3a*R,9b*S**)-5,8,9-trimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ea) and (3a*R**,9b*S**)-5,7,8-trimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ea′) (66:34):** oil; ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 2.20 (s, 0.34 × 3H, for **3ea′**), 2.22 (s, 0.34 × 3H, for **3ea′**), 2.25 (s, 0.66 × 3H, for **3ea**), 2.44 (s, 0.66 × 3H, for **3ea**),2.73 (s, 0.66 × 3H, for **3ea**), 2.77 (s, 0.34 × 3H, for **3ea′**), 2.86 (dd, *J* = 11.2, 4.7 Hz, 0.66 × 1H, for **3ea**), 2.99 (dd, *J* = 11.6, 4.4 Hz, 0.34 × 1H, for **3ea′**), 3.41−3.47 (m, 1H), 3.51−3.55 (m, 1H), 4.03 (d, *J* = 9.8 Hz, 0.34 × 1H, for **3ea′**), 4.57 (d, *J* = 9.8 Hz, 0.66 × 1H, for **3ea′**), 6.52−6.54 (m, 1H), 7.01 (d, *J* = 8.4 Hz, 0.66 × 1H, for **3ea**), 7.21−7.42 (m, 5.34H); ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 16.5, 18.8, 20.0, 20.4, 39.6, 39.7, 39.9, 41.8, 43.5, 44.7, 51.0, 52.6, 110.1, 114.1, 116.0, 120.0, 126.4, 126.5, 127.7, 128.5, 128.5, 128.9, 129.0, 129.0, 129.6, 131.3, 132.1, 132.2, 136.95, 136.97, 146.6, 148.3, 175.6, 176.1, 177.9, 178.7; HRMS for mixture *m*/*z* (M^+) calcd for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1524 and 320.1526.

(3a*R,9b*S**)-6-Methoxy-5,8-dimethyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3fa):** oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 2.85 (s, 3H), 3.38 (dd, *J* = 12.8, 6.2 Hz, 1H), 3.47−3.55 (m, 2H), 3.88 (s, 3H), 4.12 (d, *J* = 9.2 Hz, 1H), 6.65 (s, 1H), 7.12 (s, 1H), 7.26−7.28 (m, 2H), 7.36−7.39 (m, 1H), 7.43−7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 38.8, 41.5, 42.0, 51.5, 55.7, 111.3, 122.8, 123.1, 126.4, 128.7, 129.3, 132.1, 133.8, 134.5, 152.7, 175.7, 177.6; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{20}N_2O_3$ 336.1474, found 336.1478.

(3a*R,9b*S**)-5-Butyl-8-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ga):** oil; ^{1}H NMR (400 MHz, $CDCl_3$)δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.29−1.39 (m, 2H), 1.47−1.62 (m, 2H), 2.28 (s, 3H), 2.99−3.07 (m, 1H), 3.09 (dd, *J* = 11.6, 4.4 Hz, 1H), 3.20−3.27 (m, 1H), 3.47 (ddd, *J* = 9.5, 4.4, 2.6 Hz, 1H), 3.61 (dd, *J* = 11.6, 2.6 Hz, 1H), 4.06 (d, *J* = 9.5 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 7.00 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.23−7.33 (m, 2H), 7.33−7.36 (m, 2H), 7.39−7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.4, 20.5, 28.3, 42.5, 44.2, 48.6, 50.6, 112.6, 118.8, 126.4, 128.37, 128.5, 129.1, 129.2, 131.2, 132.2, 146.5, 176.0, 178.0; HRMS *m*/*z* (M^+) calcd for $C_{22}H_{24}N_2O_2$ 348.1838, found 348.1839.

(3a*R,9b*S**)-5-Benzyl-8-methyl-2-phenyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ha):** mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.20 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.52 (ddd, *J* = 9.5, 4.4, 2.6 Hz, 1H), 3.66 (dd, *J* = 11.7, 2.6 Hz, 1H), 4.14 (d, *J* = 9.5 Hz, 1H), 4.22 (d, *J* = 15.4 Hz, 1H), 4.44 (d, *J* = 15.4 Hz, 1H), 6.66 (d, *J* = 8.4 Hz, 1H), 6.94 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.22−7.31 (m, 7H), 7.35−7.40 (m, 2H), 7.43−7.48 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 42.6, 44.3, 49.5, 55.6, 113.6, 119.1, 126.5, 127.4, 127.6, 128.7, 129.18, 129.21, 129.24, 129.3, 131.1, 132.2, 138.0, 145.5, 176.0, 177.8; HRMS *m*/*z* (M^+) calcd for $C_{25}H_{22}N_2O_2$ 382.1681, found 382.1682.

(3a*R,9b*S**)-2-(4-Methoxyphenyl)-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ab):** mp 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.80 (s, 3H), 3.04 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.48 (ddd, *J* = 9.6, 4.6, 2.7 Hz, 1H), 3.57 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.80 (s, 3H), 4.08 (d, *J* = 9.6 Hz, 1H), 6.64 (d, *J* = 8.2 Hz, 1H), 6.91−6.95 (m, 2H), 7.04 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.16 −7.20 (m, 2H), 7.35 (d, *J* = 1.8, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 39.6, 42.2, 43.6, 51.0, 55.5, 112.6, 114.4, 118.7, 124.8, 127.7, 129.0, 129.3, 130.9, 146.5, 159.4, 176.2, 178.1; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{20}N_2O_3$ 336.1474, found 336.1471.

(3a*R,9b*S**)-2-(4-Chlorophenyl)-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ac):** mp 172−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.78 (s, 3H), 3.02 (dd, *J* = 11.4, 4.4 Hz, 1H), 3.48 (ddd, *J* = 9.5, 4.4, 2.6 Hz, 1H), 3.57 (dd, *J* = 11.4, 2.6 Hz, 1H), 4.09 (d, *J* = 9.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.21 −7.25 (m, 2H), 7.31 (d, *J* = 2.2, 1H), 7.36−7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 39.7, 42.3, 42.7, 51.0, 112.7, 118.5, 127.7, 129.2, 129.3, 129.5, 130.6, 130.9, 134.3, 146.5, 175.7, 177.7; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{17}ClN_2O_2$ 340.0979, found 340.0981.

(3a*R,9b*S**)-5,8-Dimethyl-2-[4-(trifluoromethyl)phenyl]-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ad):** oil; ^{1}H NMR (400 MHz, $CDCl_3$)δ 2.30 (s, 3H), 2.79 (s, 3H), 3.04 (dd, *J* = 11.4, 4.6 Hz, 1H), 3.52 (ddd, *J* = 9.6, 4.6, 2.8 Hz, 1H), 3.58 (dd, *J* = 11.4, 2.8 Hz, 1H), 4.12 (d, *J* = 9.6 Hz, 1H), 6.65 (d, *J* = 8.2 Hz, 1H), 7.04 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.32 (d, *J* = 1.8 Hz, 1H), 7.45 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 39.7, 42.3, 43.8, 51.0, 112.8, 118.3, 123.8 (q, *J* = 272.2 Hz), 126.2 (q, *J* = 3.9 Hz), 123.7, 129.3, 129.5, 130.4 (q, *J* = 32.6 Hz), 130.9, 135.2, 145.5, 175.6, 177.5; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{17}F_3N_2O_2$ 374.1242, found 374.1243.

(3a*R,9b*S**)-2,5,8-Trimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3ae):** mp 173−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 2.78 (s, 3H), 2.96 (dd, *J* = 11.7, 4.4 Hz, 1H), 2.98 (s, 3H), 3.34 (ddd, *J* = 9.5, 4.4, 2.6 Hz, 1H), 3.51 (dd, *J* = 11.7, 2.6 Hz, 1H), 3.95 (d, *J* = 9.5 Hz, 1H), 6.60 (d, *J* = 8.4 Hz, 1H), 7.01 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.29 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 25.4, 39.6, 42.2, 43.7, 50.9, 112.6, 118.8, 129.1, 129.3, 130.8, 146.4, 177.0, 179.0; HRMS *m*/*z* (M^+) calcd for $C_{14}H_{16}N_2O_2$ 244.1212, found 244.1206.

(3a*R,9b*S**)-2-Benzyl-5,8-dimethyl-3a,4,5,9b-tetrahydro-1*H*-pyrrolo[3,4-*c*]quinoline-1,3(2*H*)-dione (3af):** mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.75 (s, 3H), 2.96 (dd, *J* = 11.7, 4.4 Hz, 1H), 3.31 (ddd, *J* = 9.5, 4.4, 2.6 Hz, 1H), 3.45 (dd, *J* = 11.7, 2.6 Hz, 1H), 3.92 (d, *J* = 9.5 Hz, 1H), 4.60 (d, *J* = 14.3 Hz, 1H), 4.67 (d, *J* = 14.3 Hz, 1H), 6.61 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.22−7.31 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 39.5, 42.2, 42.9, 43.8, 51.2, 112.6, 118.9, 127.9, 128.5, 128.7, 129.1, 129.3, 130.8, 135.7, 146.4, 176.6, 178.6; HRMS *m*/*z* (M^+) calcd for $C_{20}H_{20}N_2O_2$ 320.1525, found 320.1522.

Typical Procedure for Copper-Catalyzed Oxidative Cyclization of *N*-Methylanilines with Benzylidene Malononitrile (Scheme 5). Synthesis of **9c** is representative. $CuCl_2$ (6.7 mg, 0.050 mmol) was placed in a 20-mL two-necked reaction flask, which was then filled with O_2 using the standard Schlenk technique. A solution of 4-*tert*-butyl-*N*,*N*-dimethylaniline (**1c**, 222 mg, 1.3 mmol), benzylidene malononitrile (39 mg, 0.25 mmol), and 1-methylnaphthalene (ca. 20 mg, internal standard) in EtCN (2.0 mL) was added, and the mixture was then heated at 60 °C. After being stirred for 4 h, the resulting solution was poured into water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate followed by evaporation and silica gel column purification (*n*-hexane/ethyl acetate =10:1, v/v) to furnish 6-*tert*-butyl-1-methyl-3-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarbonitrile (**9c**, 41 mg, 0.13 mmol) in 50% yield.

6-Methoxy-1-methyl-3-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarbonitrile (9b): mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 3H), 3.46 (dd, *J* = 12.0 Hz, 3.5 Hz, 1H), 3.63 (dd, *J* = 11.5 Hz, 3.5 Hz, 1H), 3.02 (s, 3H), 3.85 (dd, *J* = 12.0 Hz, 11.5 Hz, 1H), 6.73 (d, *J* = 9.1 Hz, 1H), 6.96 (dd, *J* = 9.1 Hz, 2.9 Hz, 1H), 7.07 (d, *J* = 2.9 Hz, 1H), 7.44−7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.4, 42.8, 46.1, 51.8, 56.1, 113.5, 113.5, 114.2, 114.5, 115.4, 118.9, 128.6, 129.3, 129.5, 135.0, 139.0, 152.0; HRMS *m*/*z* (M^+) calcd for $C_{19}H_{17}N_3O$ 303.1372, found 303.1369.

6-*tert*-Butyl-1-methyl-3-phenyl-2,3-dihydroquinoline-4,4(1*H*)-dicarbonitrile (9c): mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (s, 9H), 3.00 (s, 3H), 3.46 (dd, *J* = 12.4 Hz, 3.7 Hz, 1H), 3.60 (dd, *J* = 11.4 Hz, 3.7 Hz, 1H), 3.92 (dd, *J* = 12.4 Hz, 11.4 Hz, 1H), 6.70 (d, *J* = 8.7 Hz, 1H), 7.37 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 7.44−7.46 (m, 5H), 7.50 (d, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 34.2, 39.0, 42.8, 46.0, 51.6, 112.4, 112.7, 114.4, 115.5, 125.6, 128.6, 129.0, 129.3, 129.5, 135.1, 141.0, 142.1; HRMS *m*/*z* (M^+) calcd for $C_{22}H_{23}N_3$ 329.1892, found 329.1889.

Reduction of 3aa (Scheme 4, eq 1). The tetrahydroquinoline **3aa** (61 mg, 0.20 mmol) was placed in a 20-mL reaction flask, and the flask was flushed with nitrogen. Toluene (1.0 mL) and Red-Al (3.3 M

toluene solution, 0.27 mL, 0.88 mmol) were sequentially added dropwise. The mixture was heated at 100 °C for 1 h. After being allowed to cool to room temperature, the resulting solution was carefully quenched with a minimum amount of water. The suspension was then filtered through a short pad of neutral alumina and evaporated under reduced pressure. The obtained crude material was purified by column chromatography on silica gel with *n*-hexane/ethyl acetate (10:1, v/v) as eluent to provide (3a*R**, 9b*S**)-5,8-dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]quinoline (**7**, 33 mg, 0.12 mmol) in 60% yield.

(3a*R,9b*S**)-5,8-Dimethyl-2-phenyl-2,3,3a,4,5,9b-hexahydro-1*H*-pyrrolo[3,4-*c*]quinoline (7):** oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.74−2.82 (m, 1H), 2.87 (s, 3H), 2.92 (dd, J = 11.4, 11.4 Hz, 1H), 3.07 (dd, J = 11.4, 4.8 Hz, 1H), 3.17 (dd, J = 9.5, 2.2 Hz, 1H), 3.20 (dd, J = 9.1, 9.1 Hz, 1H), 3.48−3.54 (m, 1H), 3.70 (dd, J = 9.5, 6.6 Hz, 1H), 3.81 (dd, J = 9.1, 9.1 Hz, 1H), 6.55 (d, J = 8.0 Hz, 2H), 6.63 (d, J = 8.0 Hz, 2H), 6.67 (t, J = 7.3 Hz, 2H), 6.94−6.97 (m, 2H), 7.20−7.24 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4, 35.4, 39.6, 39.8, 52.1, 52.3, 55.1, 111.8, 112.2, 115.9, 123.8, 126.48, 128.3, 129.3, 130.3, 144.4, 147.8; HRMS m/z (M^+) calcd for $C_{19}H_{22}N_2$ 278.1783, found 278.1782.

Reaction of 3aa with Hydrazine (Scheme 4, eq 2). The tetrahydroquinoline **3aa** (306 mg, 1.0 mmol), hydrazine monohydrate (75 mg, 1.5 mmol), and MeOH (10 mL) were placed in a 20-mL reaction flask and then heated at 80 °C for 21 h under N_2. After the solvent and volatile materials were removed under reduced pressure, the residue was dissolved in dichloromethane and washed with 10% aq citric acid. Extraction with dichloroethane, evaporation, and silica gel column purification with *n*-hexane/ethyl acetate (1:4, v/v) produced (4a*R**, 10b*S**)-6,9-dimethyl-2,3,5,6-tetrahydropyridazino[4,5-*c*]quinoline-1,4-(4a*H*,10b*H*)-dione (**8**, 188 mg, 0.77 mmol) in 77% yield.

(4a*R,10b*S**)-6,9-Dimethyl-2,3,5,6-tetrahydropyridazino-[4,5-*c*]quinoline-1,4(4a*H*,10b*H*)-dione (8):** mp 220−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.75 (s, 3H), 2.96 (dd, J = 11.4 Hz, 4.4 Hz, 1H), 3.33 (ddd, J = 9.5 Hz, 4.4 Hz, 2.6 Hz, 1H), 3.52 (dd, J = 11.4 Hz, 2.6 Hz, 1H), 3.95 (d, J = 9.5 Hz, 1H), 4.26 (s, 2H), 6.60 (d, J = 8.4 Hz, 1H), 7.01 (dd, J = 8.4 Hz, 2.2 Hz, 1H), 7.23 (d, J = 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 39.6, 40.7, 42.3, 50.8, 112.7, 118.3, 129.3, 129.5, 130.8, 146.5, 174.2, 175.9; HRMS m/z (M^+) calcd for $C_{13}H_{15}N_3O_2$ 245.1164, found 245.1163.

■ ASSOCIATED CONTENT

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

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