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Transition Metal-Free Oxidative Radical Decarboxylation/Cyclization for the Construction of 6-Alkyl/Aryl Phenanthridines

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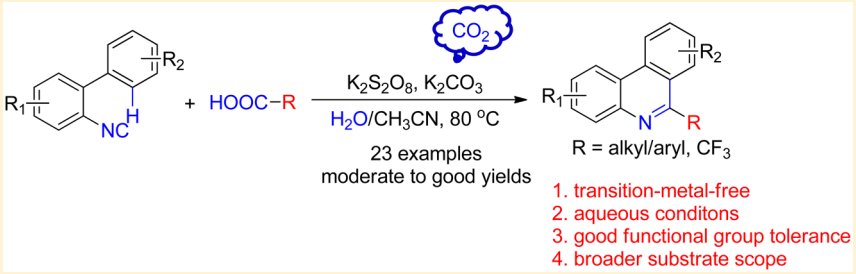
Supporting Information



ABSTRACT: A radical cascade decarboxylation/cyclization of 2-isocyanobiphenyls with aliphatic carboxylic acids as well as aromatic carboxylic acids under the transition metal-free conditions was reported. This process, which included formation of two new C−C bonds and cleavage of C−COOH bonds, afforded a novel and environmentally friendly approach to producing 6-alkyl/aryl phenanthridines with moderate to good yields.

Phenanthridine skeletons have attracted considerable attention because of their pharmaceutical and bioactive properties, including antiviral, antibacterial, antitumoral, cytotoxic, and DNA inhibitory properties.[1] Therefore, the development of new and efficient methods for the preparation of phenanthridines and their derivatives is very important. In recent years, the radical-driven oxidative coupling methodology has been established as a powerful strategy for preparing these compounds with atom- and step-economical features. In 2012, Chatani's group reported the first example of the synthesis of 6-alkyl/aryl phenanthridines by $Mn(acac)_3$-mediated oxidative cyclization of 2-isocyanobiphenyls with organoboron reagents as radical precursors.[2] Subsequently, several groups have successively reported their efforts for the construction of 6-alkyl or 6-aryl phenanthridines through the reaction of 2-isocyanobiphenyls with corresponding radical precursors, such as simple ethers,[3] alkanes,[4] alcohols,[4a] 2-bromide ethyl esters,[5] and 1,3-dicarbonyl compounds,[6] aryl sulfonyl chlorides,[7] and aryl amines,[8] and hydrazines[9] under radical conditions. Although these methods have their own specific applications, they still suffer from limited reaction scope, harsh reaction conditions, and the necessity of using transition metal catalysts. Very recently, Zhu et al. reported a metal-free approach to accessing 6-aryl/alkyl phenanthridines that utilizes acyl peroxides as a radical precursor,[10] which appears to be an environmentally friendly method. However, most of acyl peroxides are commercially unavailable. Thus, further developments for more practical and general alkylation/arylation methodologies are quite desired.

Carboxylic acids (or their salts) are readily available, stable, cheap, and structurally diverse substrates that are widely employed to form carbon−carbon and carbon−heteroatom bonds.[11] These reactions present potential advantages, such as high selectivity and atom economy, as well as the release of nontoxic CO_2. However, C−COOH bond cleavage usually requires a toxic transition metal catalytic system (e.g., palladium, copper, silver, etc.).[12] Thus, the decarboxylative cross-coupling of carboxylic acids under transition metal-free conditions remains a challenge.[13] In view of this, we disclose transition metal-free radical oxidative decarboxylation/cyclization in an aqueous solution, which provides a simple and general protocol for valuable 6-alkyl/aryl phenanthridines.

Initially, the model reaction of 2-isocyano-biphenyl **1a** and 2,2-dimethylbutanoic acid **2a** was employed to screen the reaction conditions, and the results are listed in Table 1. When **1a** (1.0 equiv) was treated with **2a** (2.0 equiv) in the presence of $AgNO_3$ (20 mol %) and $K_2S_2O_8$ (3.0 equiv) under an argon atmosphere in a CH_3CN/H_2O solvent (2 mL) [1/1 (v/v)] at 80 °C for 1 h, no desired product was observed (Table 1, entry

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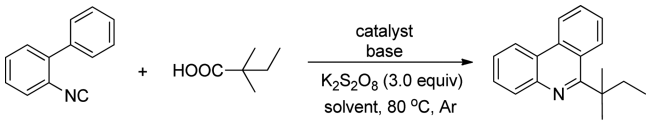
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	catalyst	solvent (v/v)	base (equiv)	yield[b] (%)
1	$AgNO_3$	CH_3CN/H_2O (1/1)	–	0
2	Ag_2O	CH_3CN/H_2O (1/1)	–	0
3	AgF	CH_3CN/H_2O (1/1)	–	0
4	Ag_2CO_3	CH_3CN/H_2O (1/1)	–	18
5	Ag_2CO_3	CH_3CN/H_2O (1/1)	K_2CO_3 (1.0)	54
6	Ag_2CO_3	CH_3CN/H_2O (1/1)	K_2CO_3 (1.5)	70
7	Ag_2CO_3	CH_3CN/H_2O (1/1)	K_2CO_3 (2.0)	32
8	–	**CH_3CN/H_2O (1/1)**	**K_2CO_3 (1.5)**	**74**
9[c]	–	CH_3CN/H_2O (1/1)	K_2CO_3 (1.5)	62
10[d]	–	CH_3CN/H_2O (1/1)	K_2CO_3 (1.5)	54
11	–	H_2O	K_2CO_3 (1.5)	0
12	–	CH_3CN	K_2CO_3 (1.5)	0
13	–	DMSO/H_2O (1/1)	K_2CO_3 (1.5)	18
14	–	DMF/H_2O (1/1)	K_2CO_3 (1.5)	<5
15	–	THF/H_2O (1/1)	K_2CO_3 (1.5)	0
16	–	acetone/H_2O (1/1)	K_2CO_3 (1.5)	0
17	–	dioxane/H_2O (1/1)	K_2CO_3 (1.5)	<5

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), catalyst (20 mol %), $K_2S_2O_8$ (0.6 mmol), K_2CO_3 (0.3 mmol), solvent (2.0 mL), 80 °C, under Ar for 1 h. [b]Isolated yield. [c]Under air. [d]At 60 °C.

1). Then, other silver catalysts (e.g., Ag_2O, AgF, and Ag_2CO_3) were tested (Table 1, entries 2−4, respectively). To our delight, desired product **3a** was obtained in 18% yield in the presence of Ag_2CO_3, although the majority of starting material **1a** was converted to a hydrolysis byproduct (Table 1, entry 4). We next tried to add 1.0 equiv of K_2CO_3 to the reaction system to improve the stability of **1a** (Table 1, entry 5), and the yield of the target product significantly increased to 54%. Different amounts of K_2CO_3 were employed, among which 1.5 equiv of K_2CO_3 provided the satisfactory yield (70%) (Table 1, entry 6). On the other hand, this reaction might be suppressed with an excess amount of K_2CO_3 (Table 1, entry 7). Surprisingly, the reaction can achieve a highest yield of 74% in the absence of Ag_2CO_3 (Table 1, entry 8). Both decreasing temperature and exposure to air negatively affected the reaction (Table 1, entries 9 and 10). In addition, we attempted to examine the effects of different solvent systems on the model reaction (Table 1, entries 11−17), but none of the other solvent systems were effective for this transformation. These results showed that the optimized conditions were 3.0 equiv of $K_2S_2O_8$ with 1.5 equiv of K_2CO_3 in a CH_3CN/H_2O solvent [1/1 (v/v)] at 80 °C under Ar for 1 h.

We next investigated the scope and generality of the reaction under optimized conditions. The results are summarized in Table 2. First, we evaluated the reactivity of 2-isocyanobiphenyl **1a** toward aliphatic carboxylic acids (Table 2, **3a**−**3k**). Notably, the transition metal-free system can be successfully applied to tertiary and secondary carboxylic acids (Table 2, **3a**−**3h**). It is worth noticing that aliphatic carboxylic acids that contain a cyclopropyl, ether, and Boc group provided the desired products in good yields, demonstrating the mild nature of the reaction conditions. To our delight, when primary alkyl carboxylic acids such as propanoic acid and phenylacetic acid were employed as reactants, the desired products could be achieved in moderate yields (Table 2, **3i** and **3j**). Comparatively, acetic acid, as a radical precursor, provided a trace amount of the corresponding products, which is possibly caused by the difficulty in generating methyl radical or capture methyl radical by **1a** (Table 2, **3k**). Furthermore, the oxidative cyclization of different 2-isocyanobiphenyls with **2a** was investigated (Table 2, **3l**−**3q**). Results showed that the method was successfully amenable to a wide range of 2-isocyanobiphenyls bearing different functional groups, such as F, OMe, COOMe, and Me (Table 2, **3l**−**3p**), and produced moderate to good yields. In addition, heterocyclic 2-isocyanobiphenyl was also favored in this system and afforded the corresponding product in 42% yield (Table 2, **3q**). We next attempted to apply the method to the reaction of 2-isocyanobiphenyl and aromatic carboxylic acids (Table 2, **3r**−**3v**). Previous studies proved that aromatic carboxylic acids had more difficulty in generating radicals for radical decarboxylation/coupling than aliphatic carboxylic acids. To our delight, aromatic carboxylic acids were also found to be suitable for the transformation and showed satisfactory tolerance with halogen groups, which provided useful components for further transformations through traditional cross-coupling reactions (Table 2, **3t** and **3u**).

The green system was further applied to 6-trifluoromethylphenanthridines (Scheme 1), which have recently caught the attention of chemists[14] because of thair significant effects on the chemical, physical, and biological properties of compounds after the introduction of a trifluoromethyl group.[15] In an initial experiment, CF_3COOH was subjected to the reaction system, but no desired products were observed. However, when CF_3SO_2Na (Langlois reagent) was used as the CF_3 radical source, the radical cyclization reaction proceeded smoothly in moderate yield under optimized reaction conditions. The present process with cheap CF_3 reagents and cost-effective oxidants provided a novel and practical approach for obtaining CF_3-containing phenanthridines.

To gain insights into reaction mechanism, TEMPO (2.0 equiv) as a radical scavenger was employed under standard reaction conditions (Scheme 2). As a result, the reaction was completely suppressed, which could indicate that this transformation involved radical intermediates.

A plausible reaction pathway is proposed in Scheme 3 on the basis of the observation described above and reported in the literature.[16] First, 2,2-dimethylbutanoic acid anion **I** is converted into radical **II** in the presence of sulfate anion radicals by homolytic cleavage of $K_2S_2O_8$. Subsequently, radical **II** is selectively added to isocyanide **1a**, which provides imidoyl radical **III** that can form intermediate **IV** through an intramolecular radical cyclization. Finally, further oxidation of **IV** by another sulfate radical produces the corresponding carbocation, which loses a proton under basic conditions to provide desired product **3a**.

In conclusion, we have successfully developed a general and practical protocol for the synthesis of phenanthridine derivatives by a transition metal-free radical cascade decarboxylation/cyclization reaction. The novel method presents the major advantages of a broad substrate scope, good functional group tolerance, and environmentally benign character. Further studies of the reaction mechanism and the extension of the substrate's scope are currently underway in our laboratory.

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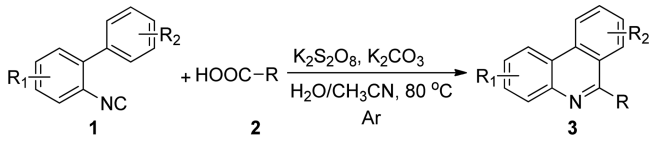
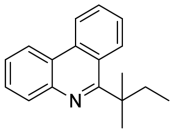
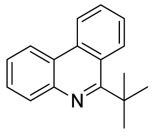
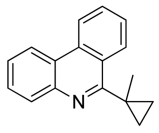
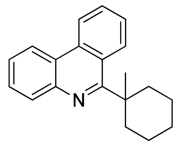
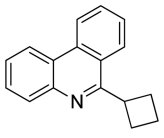
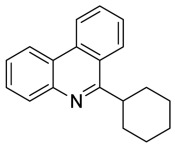
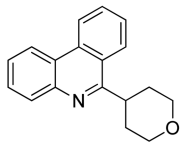
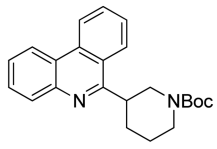
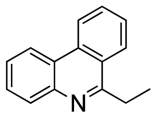
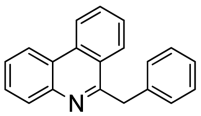
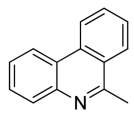
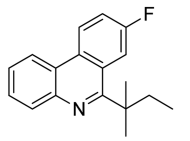
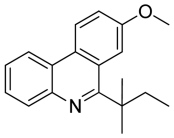
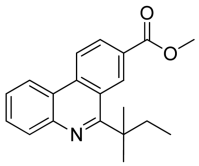
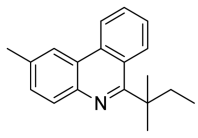
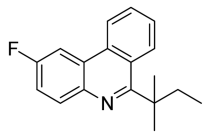
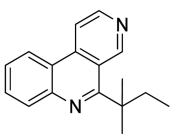
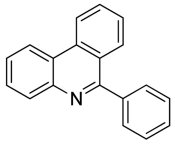
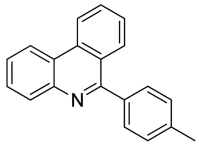
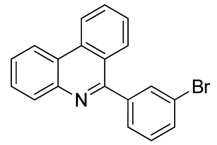
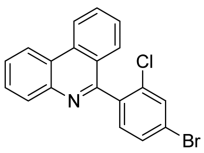
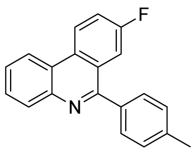
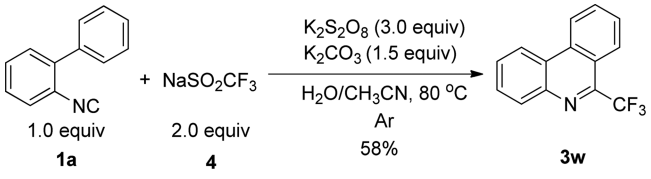
Table 2. Scope of the Oxidative Cyclization of Different Isocyanobiphenyls 1 and Carboxylic Acids 2[a,b]



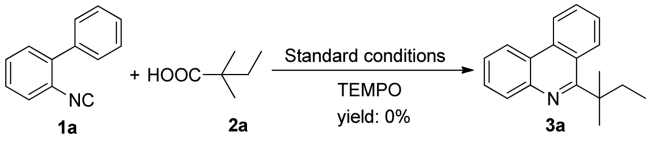
product, yield	product, yield	product, yield	product, yield
			
3a, 74%	**3b, 77%**	**3c, 55%**	**3d, 67%**
			
3e, 71%	**3f, 65%**	**3g, 66%**	**3h, 53%**
			
3i, 55%	**3j, 64%**	**3k, trace**	**3l, 68%**
			
3m, 77%	**3n, 65%**	**3o, 64%**	**3p, 73%**
			
3q, 42%	**3r, 48%**	**3s, 46%**	**3t, 37%**
			
3u, 35%	**3v, 43%**		

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.4 mmol), $K_2S_2O_8$ (0.6 mmol), K_2CO_3 (0.3 mmol), CH_3CN/H_2O [2 mL, 1/1 (v/v)], 80 °C, under Ar for 1 h. [b]Isolated yield.

Scheme 1. Further Applications



Scheme 2. Radical Trapping Experiment



EXPERIMENTAL SECTION

General Procedure for the Synthesis of 2-Isocyanobiphenyls. 2-Isocyanobiphenyls were prepared according to the reported method,[13b] including 2-isocyano-1,1′-biphenyl (**1a**),[13b] 4′-fluoro-2-

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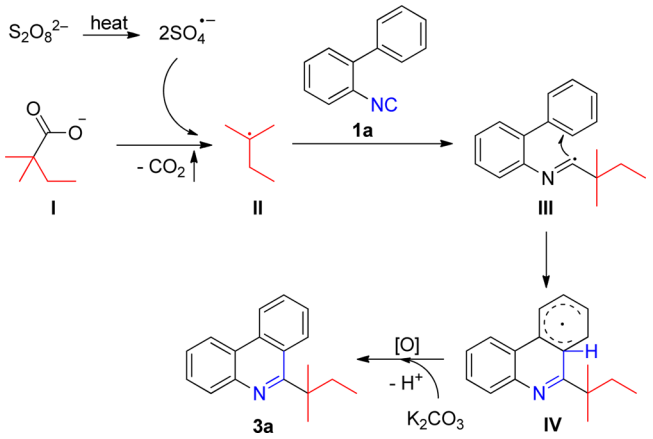
Scheme 3. Postulated Reaction Pathway



isocyano-1,1′-biphenyl (**1b**),[3b] 2-isocyano-4′-methoxy-1,1′-biphenyl (**1c**),[13b] methyl 2′-isocyano-[1,1′-biphenyl]-4-carboxylate (**1d**),[13b] 2-isocyano-5-methyl-1,1′-biphenyl (**1e**),[3b] 5-fluoro-2-isocyano-1,1′-biphenyl (**1f**),[17] and 4-(2-isocyanophenyl)pyridine (**1g**).

4-(2-Isocyanophenyl)pyridine (1g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76−8.73 (m, 2H), 7.55−7.42 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 144.9, 136.2, 130.4, 130.2, 129.8, 128.4, 123.9; HRMS (ESI-TOF) calcd for $C_{12}H_9N_2$ $[M + H]^+$ m/z 181.0766, found m/z 181.0769.

General Procedure for the Synthesis of 6-Alkyl/Aryl Phenanthridines. The mixture of 2-isocyanobiphenyl **1a** (0.20 mmol), carboxylic acid **2a** (0.40 mmol), and K_2CO_3 (0.30 mmol) in CH_3CN/H_2O [2.0 mL, 1/1 (v/v)] was treated with $K_2S_2O_8$ (0.60 mmol). The reaction mixture was allowed to stir at 80 °C for 1 h under an Ar atmosphere. Upon completion as shown by TLC, water (5 mL) was added to the reaction mixture. Then, the reaction mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel (eluent:petroleum ether/ethyl acetate, 200:1) to afford **3a** in 74% yield.

6-(*tert*-Pentyl)phenanthridine (3a). Colorless oil: 36.8 mg, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70−8.67 (m, 1H), 8.63 (d, J = 8.5 Hz, 1H), 8.52 (dd, J = 8.2, 1.1 Hz, 1H), 8.13 (d, J = 7.9 Hz, 1H), 7.81−7.75 (m, 1H), 7.72−7.67 (m, 1H), 7.66−7.58 (m, 2H), 2.21 (qd, J = 7.6, 0.4 Hz, 2H), 1.69 (d, J = 0.6 Hz, 6H), 0.73 (td, J = 7.5, 1.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 143.3, 134.1, 130.7, 129.6, 128.6, 128.0, 126.7, 126.4, 125.1, 123.6, 123.3, 121.9, 44.3, 35.8, 29.6, 9.9; HRMS (ESI-TOF) calcd for $C_{18}H_{20}N$ $[M + H]^+$ m/z 250.1590, found m/z 250.1588.

6-(*tert*-Butyl)phenanthridine (3b).[18] Colorless oil: 36.2 mg, 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 8.3 Hz, 1H), 8.61 (d, J = 8.5 Hz, 1H), 8.50 (d, J = 8.2 Hz, 1H), 8.12 (d, J = 8.0 Hz, 1H), 7.78−7.72 (m, 1H), 7.71−7.65 (m, 1H), 7.65−7.56 (m, 2H), 1.72 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 143.0, 134.1, 130.4, 129.4, 128.5, 128.4, 126.6, 126.1, 124.4, 123.5, 123.1, 121.7, 40.3, 31.3; HRMS (ESI-TOF) calcd for $C_{17}H_{18}N$ $[M + H]^+$ m/z 236.1434, found m/z 236.1430.

6-(1-Methylcyclopropyl)phenanthridine (3c). Colorless oil: 25.6 mg, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73−8.62 (m, 2H), 8.55 (dd, J = 8.1, 1.3 Hz, 1H), 8.20 (d, J = 6.4 Hz, 1H), 7.87−7.81 (m, 1H), 7.75−7.68 (m, 2H), 7.66−7.60 (m, 1H), 1.67 (s, 3H), 1.25 (t, J = 5.2 Hz, 2H), 1.05 (t, J = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 133.7, 130.6, 130.1, 128.9, 127.9, 127.3, 127.0, 125.4, 124.1, 122.8, 122.2, 30.1, 25.7, 14.1; HRMS (ESI-TOF) calcd for $C_{17}H_{16}N$ $[M + H]^+$ m/z 234.1277, found m/z 234.1273.

6-(1-Methylcyclohexyl)phenanthridine (3d). Colorless oil: 37.0 mg, 67% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69−8.61 (m, 2H), 8.51 (d, J = 8.1 Hz, 1H), 8.12 (d, J = 7.8 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.68 (t, J = 7.5 Hz, 1H), 7.59 (t, J = 7.6 Hz, 2H), 2.63−2.54 (m, 2H), 1.96−1.87 (m, 2H), 1.69 (s, 3H), 1.68−1.59 (m, 4H), 1.57−1.48 (m, 1H), 1.48−1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 143.3, 134.5, 130.5, 129.5, 128.7, 128.4, 126.7, 126.1, 124.8, 123.6, 123.4, 121.9, 43.9, 39.5, 27.6, 26.9, 23.4; HRMS (ESI-TOF) calcd for $C_{20}H_{22}N$ $[M + H]^+$ m/z 276.1747, found m/z 276.1741.

6-Cyclobutylphenanthridine (3e). Colorless oil: 33.1 mg, 71% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 8.3 Hz, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.18 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.2 Hz, 1H), 7.82−7.77 (m, 1H), 7.74−7.67 (m, 1H), 7.67−7.57 (m, 2H), 4.40 (p, J = 8.6 Hz, 1H), 2.83−2.69 (m, 2H), 2.59−2.47 (m, 2H), 2.27−2.16 (m, 1H), 2.03−1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 144.1, 133.2, 130.4, 130.2, 128.8, 127.4, 126.6, 126.4, 125.1, 123.9, 122.8, 122.2, 40.2, 27.6, 18.8; HRMS (ESI-TOF) calcd for $C_{17}H_{16}N$ $[M + H]^+$ m/z 234.1277, found m/z 234.1275.

6-Cyclohexylphenanthridine (3f).[4b] Colorless oil: 33.9 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.3 Hz, 1H), 8.52 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.72−7.65 (m, 2H), 7.62−7.57 (m, 1H), 3.65−3.57 (m, 1H), 2.12−2.04 (m, 2H), 2.01−1.80 (m, 5H), 1.63−1.52 (m, 2H), 1.50−1.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 144.2, 133.3, 130.2, 128.7, 127.4, 126.4, 125.9, 125.0, 123.6, 122.9, 122.1, 42.3, 32.6, 27.2, 26.6; HRMS (ESI-TOF) calcd for $C_{19}H_{20}N$ $[M + H]^+$ m/z 262.1590, found m/z 262.1587.

6-(Tetrahydro-2*H*-pyran-4-yl)phenanthridine (3g). Colorless oil: 34.7 mg, 66% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 8.2 Hz, 1H), 8.55 (d, J = 7.5 Hz, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.84 (t, J = 7.5 Hz, 1H), 7.71 (q, J = 6.5 Hz, 2H), 7.63 (t, J = 7.5 Hz, 1H), 4.20 (dd, J = 11.4, 2.6 Hz, 2H), 3.87 (t, J = 11.3 Hz, 1H), 3.74 (td, J = 12.1, 2.0 Hz, 2H), 2.42−2.27 (m, 2H), 2.00−1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 157.4, 144.1, 133.5, 130.4, 128.9, 127.6, 126.8, 125.5, 124.8, 123.7, 123.1, 122.2, 68.6, 39.5, 32.3; HRMS (ESI-TOF) calcd for $C_{18}H_{18}NO$ $[M + H]^+$ m/z 264.1383, found m/z 264.1377.

***tert*-Butyl 3-(Phenanthridin-6-yl)piperidine-1-carboxylate (3h).** Colorless oil: 38.4 mg, 53% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J = 8.2 Hz, 1H), 8.53 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 7.70 (t, J = 7.6 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 4.60−4.15 (m, 2H), 3.80−3.65 (m, 1H), 3.35−3.25 (m, 1H), 2.95−2.80 (m, 1H), 2.27−2.07 (m, 2H), 1.93−1.69 (m, 2H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 155.2, 143.9, 133.3, 130.5, 130.3, 128.8, 127.7, 126.8, 125.7, 124.9, 123.7, 123.0, 122.2, 79.8, 50.0, 44.5, 40.7, 30.8, 28.9, 25.9; HRMS (ESI-TOF) calcd for $C_{23}H_{27}O_2N_2$ $[M + H]^+$ m/z 363.2067, found m/z 363.2058.

6-Ethylphenanthridine (3i).[19] Yellow oil: 22.8 mg, 55% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.2 Hz, 1H), 8.53 (d, J = 8.2 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 8.13 (dd, J = 8.2, 1.1 Hz, 1H), 7.85−7.79 (m, 1H), 7.73−7.65 (m, 2H), 7.64−7.58 (m, 1H), 3.41 (q, J = 7.6 Hz, 2H), 1.51 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 143.7, 132.9, 130.3, 129.5, 128.6, 127.2, 126.2, 125.0, 123.6, 122.5, 121.9, 29.3, 13.5; HRMS (ESI-TOF) calcd for $C_{15}H_{14}N$ $[M + H]^+$ m/z 208.1126, found m/z 208.1129.

6-Benzylphenanthridine (3j).[19] Yellow solid: 34.4 mg, 64% yield; mp 101−103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 8.7 Hz, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.19 (t, J = 7.7 Hz, 2H), 7.78−7.71 (m, 2H), 7.67−7.61 (m, 1H), 7.59−7.53 (m, 1H), 7.31 (d, J = 7.6 Hz, 2H), 7.26−7.20 (m, 2H), 7.15 (t, J = 7.2 Hz, 1H), 4.76 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 143.6, 139.1, 133.2, 130.3, 129.8, 128.6, 128.5, 127.3, 127.0, 126.6, 126.3, 125.3, 123.9, 122.4, 121.9, 43.0; HRMS (ESI-TOF) calcd for $C_{20}H_{16}N$ $[M + H]^+$ m/z 270.1283, found m/z 270.1285.

8-Fluoro-6-(*tert*-pentyl)phenanthridine (3l). Colorless oil: 36.3 mg, 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69−8.63 (m, 1H), 8.46 (d, J = 8.1 Hz, 1H), 8.27−8.21 (m, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.6, 1H), 7.57−7.51 (m, 1H), 2.17 (qd, J = 7.4, 1.5 Hz, 2H), 1.67 (d, J = 1.7 Hz, 6H), 0.73 (td, J = 7.5, 1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (d, J = 3.6 Hz), 160.6 (d, J = 244.4 Hz), 142.9, 130.8, 128.6, 127.2, 126.1 (d, J = 7.6 Hz), 125.6 (d, J = 8.6 Hz), 123.2, 121.7, 118.8 (d, J = 23.5 Hz), 112.8 (d, J = 22.2 Hz), 44.3, 35.7, 29.4, 9.9; HRMS (ESI-TOF) calcd for $C_{18}H_{19}NF$ $[M + H]^+$ m/z 268.1496, found m/z 268.1491.

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8-Methoxy-6-(*tert*-pentyl)phenanthridine (3m). Colorless oil: 43.0 mg, 77% yield; ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (d, J = 9.1 Hz, 1H), 8.51 (d, J = 8.8 Hz, 1H), 8.05−8.02 (m, 1H), 8.01 (d, J = 2.4 Hz, 1H), 7.66−7.56 (m, 2H), 7.50−7.45 (m, 1H), 3.98 (s, 3H), 2.24 (q, J = 7.5 Hz, 2H), 1.69 (s, 6H), 0.71 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.6, 159.9, 144.3, 131.9, 130.1, 129.2, 128.6, 127.9, 126.6, 125.6, 123.2, 121.4, 110.7, 56.8, 45.8, 37.1, 30.5, 10.7; HRMS (ESI-TOF) calcd for $C_{19}H_{22}ON$ $[M + H]^+$ m/z 280.1696, found m/z 280.1692.

Methyl 6-(*tert*-Pentyl)phenanthridine-8-carboxylate (3n). Colorless oil: 40.0 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 8.72 (d, J = 8.7 Hz, 1H), 8.54 (d, J = 8.2 Hz, 1H), 8.38 (d, J = 8.6 Hz, 1H), 8.17 (d, J = 7.6 Hz, 1H), 7.78−7.73 (m, 1H), 7.64 (t, J = 7.6 Hz, 1H), 4.04 (s, 3H), 2.25 (q, J = 7.4 Hz, 2H), 1.72 (s, 6H), 0.73 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.6, 143.9, 137.3, 130.7, 130.4, 129.9, 129.5, 127.7, 127.2, 124.4, 123.6, 123.0, 122.5, 52.9, 44.5, 36.2, 29.8, 9.9; HRMS (ESI-TOF) calcd for $C_{20}H_{22}O_2N$ $[M + H]^+$ m/z 308.1645, found m/z 308.1641.

2-Methyl-6-(*tert*-pentyl)phenanthridine (3o). Colorless oil: 33.7 mg, 64% yield; ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (d, J = 8.3 Hz, 1H), 8.62 (d, J = 8.6 Hz, 1H), 8.37 (s, 1H), 7.94 (d, J = 8.3 Hz, 1H), 7.79−7.73 (m, 1H), 7.60−7.66 (m, 1H), 7.49 (d, J = 8.3 Hz, 1H), 2.57 (s, 3H), 2.24−2.15 (m, 2H), 1.65 (d, J = 1.1 Hz, 6H), 0.68 (td, J = 7.5, 1.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.7, 142.4, 137.5, 134.8, 131.0, 130.8, 130.5, 128.6, 127.1, 125.9, 124.4, 124.1, 122.4, 44.9, 36.4, 29.8, 21.9, 9.9; HRMS (ESI-TOF) calcd for $C_{19}H_{22}N$ $[M + H]^+$ m/z 264.1747, found m/z 264.1742.

2-Fluoro-6-(*tert*-pentyl)phenanthridine (3p). Colorless oil: 39.0 mg, 73% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 8.5 Hz, 1H), 8.54 (d, J = 8.3 Hz, 1H), 8.16−8.08 (m, 2H), 7.78 (t, J = 7.6 Hz, 1H), 7.69−7.63 (m, 1H), 7.45−7.38 (m, 1H), 2.20 (q, J = 7.4 Hz, 2H), 1.67 (s, 6H), 0.72 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 161.5 (d, J = 244.4 Hz), 140.0, 133.6 (d, J = 4.1 Hz), 132.7 (d, J = 8.9 Hz), 129.8, 128.1, 127.1, 125.1, 124.9 (d, J = 9 Hz) 123.5, 117.5 (d, J = 23.9 Hz), 106.9 (d, J = 23.1 Hz), 44.3, 35.8, 29.5, 9.9; HRMS (ESI-TOF) calcd for $C_{18}H_{19}NF$ $[M + H]^+$ m/z 268.1496, found m/z 268.1491.

5-(*tert*-Pentyl)benzo[*c*][2,7]naphthyridine (3q). Colorless oil: 21.0 mg, 42% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 8.88 (s, 1H), 8.51 (dd, J = 8.1, 0.7 Hz, 1H), 8.45 (d, J = 4.9 Hz, 1H), 8.22−8.11 (m, 1H), 7.84−7.77 (m, 1H), 7.72−7.63 (m, 1H), 2.23 (q, J = 7.5 Hz, 2H), 1.70 (s, 6H), 0.75 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 151.2, 147.2, 144.5, 139.3, 131.0, 130.9, 127.4, 122.4, 121.5, 120.4, 116.7, 44.4, 36.2, 29.6, 9.8; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2$ $[M + H]^+$ m/z 251.1543, found m/z 251.1538.

6-Phenylphenanthridine (3r).[8] Pale yellow solid: 24.5 mg, 48% yield; mp 68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (d, J = 8.4 Hz, 1H), 8.62 (d, J = 8.1 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 8.10 (d, J = 8.3 Hz, 1H), 7.88−7.83 (m, 1H), 7.79−7.72 (m, 3H), 7.71−7.66 (m, 1H), 7.64−7.50 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 144.0, 140.0, 133.8, 130.9, 130.6, 130.1, 129.3, 129.2, 129.1, 128.8, 127.5, 127.3, 125.6, 124.1, 122.5, 122.3; HRMS (ESI-TOF) calcd for $C_{19}H_{14}N$ $[M + H]^+$ m/z 256.1121, found m/z 256.1119.

6-(*p*-Tolyl)phenanthridine (3s).[18] Pale yellow solid: 24.7 mg, 46% yield; mp 106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 8.3 Hz, 1H), 8.61 (d, J = 8.1 Hz, 1H), 8.26 (d, J = 7.9 Hz, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.88−7.82 (m, 1H), 7.78−7.72 (m, 1H), 7.71−7.58 (m, 4H), 7.37 (d, J = 8.0 Hz, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 144.0, 139.0, 137.0, 133.9, 130.5, 130.0, 129.43, 129.37, 129.2 127.4, 127.2, 125.6, 124.0, 122.5, 122.3, 21.8; HRMS (ESI-TOF) calcd for $C_{20}H_{16}N$ $[M + H]^+$ m/z 270.1277, found m/z 270.1274.

6-(3-Bromophenyl)phenanthridine (3t). Pale yellow solid: 24.6 mg, 37% yield; mp 137−139 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, J = 8.3 Hz, 1H), 8.64 (dd, J = 8.0, 0.7 Hz, 1H), 8.27 (d, J = 7.0 Hz, 1H), 8.07 (d, J = 8.3 Hz, 1H), 7.93−7.86 (m, 2H), 7.79 (td, J = 8.0, 0.8 Hz, 1H), 7.72 (td, J = 8.0, 0.8 Hz, 1H), 7.69−7.63 (m, 3H), 7.44 (t, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 143.4, 133.7, 132.8, 132.0, 131.1, 130.2, 130.0, 129.2, 128.7, 128.6, 127.54, 127.48, 125.0, 124.0, 122.8, 122.5, 122.1; HRMS (ESI-TOF) calcd for $C_{19}H_{13}NBr$ $[M + H]^+$ m/z 334.0226, found m/z 334.0226.

6-(4-Bromo-2-chlorophenyl)phenanthridine (3u). Pale yellow solid: 25.6 mg, 35% yield; mp 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, J = 8.3 Hz, 1H), 8.64 (d, J = 8.1 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 7.82−7.66 (m, 4H), 7.66−7.58 (m, 2H), 7.43 (d, J = 8.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 143.7, 140.5, 134.2, 133.4, 132.8, 131.5, 131.4, 130.6, 129.4, 128.5, 128.0, 127.9, 125.3, 124.5, 122.6, 122.5, 121.2; HRMS (ESI-TOF) calcd for $C_{19}H_{12}NBrCl$ $[M + H]^+$ m/z 367.9836, found m/z 367.9837.

8-Fluoro-6-(*p*-tolyl)phenanthridine (3v). Pale yellow solid: 24.7 mg, 43% yield; mp 115−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 (dd, J = 9.1, 5.3 Hz, 1H), 8.56 (d, J = 8.1 Hz, 1H), 8.28 (s, 1H), 7.82−7.73 (m, 2H), 7.70 (t, J = 7.5 Hz, 1H), 7.66−7.58 (m, 3H), 7.39 (d, J = 7.9 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (d, J = 246 Hz), 160.5, 139.2, 130.4, 129.7, 129.5, 129.0, 127.5, 126.7 (d, J = 8.5 Hz), 125.0 (d, J = 8.3 Hz), 123.4, 121.9, 120.1, 113.6 (d, J = 20.9 Hz), 21.4; HRMS (ESI-TOF) calcd for $C_{20}H_{15}NF$ $[M + H]^+$ m/z 288.1183, found m/z 288.1179.

Experimental Procedure for the Synthesis of 6-Trifluoromethyl-phenanthridine (3w). Following the procedure for synthesis of 6-alkyl/aryl phenanthridines, **3w** was obtained by employing CF_3SO_2Na as a radical precursor instead of carboxylic acid **2a** in 58% yield.

6-(Trifluoromethyl)phenanthridine (3w).[13b] Pale yellow solid: 28.6 mg, 58% yield; mp 62 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (d, J = 8.4 Hz, 1H), 8.67−8.63 (m, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.19−8.14 (m, 1H), 7.93 (t, J = 7.8 Hz, 1H), 7.82−7.74 (m, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 147.3 (q, J = 32.4 Hz), 142.8, 135.3, 132.9, 131.6, 130.63, 130.58, 129.4, 126.6 (q, J = 3.3 Hz), 126.3, 124.0, 123.6, 123.3 (q, J = 274.6 Hz), 122.6; HRMS (ESI-TOF) calcd for $C_{14}H_9NF_3$ $[M + H]^+$ m/z 248.0682, found m/z 248.0678.

Experimental Procedure for Mechanistic Studies with TEMPO. To a mixture of 2-isocyanobiphenyl **1a** (0.20 mmol), carboxylic acid **2a** (0.40 mmol), K_2CO_3 (0.30 mmol), and TEMPO (0.40 mmol) in CH_3CN/H_2O [2.0 mL, 1/1 (v/v)] was added $K_2S_2O_8$ (0.60 mmol). The reaction mixture was allowed to stir at 80 °C for 1 h under an Ar atmosphere. After completion of the reaction, no desired product was detected by LC−MS.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01518.

^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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