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Microwave-Assisted Synthesis of Phenanthridines by Radical Insertion/Cyclization of Biphenyl Isocyanides

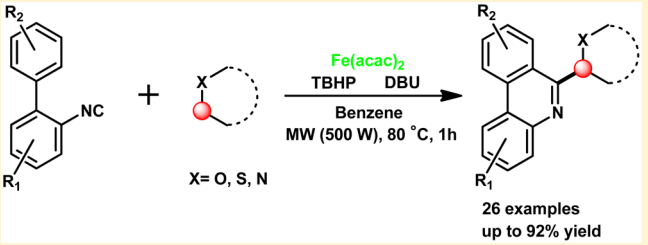
Yulong Xu,[†,⊥] Yiyi Chen,[†,⊥] Wei Li,[†] Qiong Xie,[†] and Liming Shao*[,†,‡]

[†]School of Pharmacy, Fudan University, 826 Zhangheng Road, Zhangjiang Hi-tech Park, Pudong, Shanghai 201203, China

[‡]Shanghai Center for Drug Discovery & Development, 826 Zhangheng Road, Zhangjiang Hi-tech Park, Pudong, Shanghai 201203, China

Supporting Information

ABSTRACT: A rapid microwave-assisted approach for the synthesis of phenanthridine derivatives from the radical insertion/cyclization reaction of biphenyl isocyanides with a C(sp^3)−H bond adjacent to a heteroatom has been developed. The protocol achieves wide substrate scope and good to excellent yields. The kinetic isotope effect (KIE) studies, radical inhibition studies, and Hammett plot analysis clearly disclose that the current reaction supports a radical mechanism.



INTRODUCTION

Over the past decades, extensive effort has been devoted to the development of novel and efficient methodologies on C−N bond formation for the synthesis of nitrogen-containing compounds.[1] Phenanthridines, which have attracted considerable attention, are an important class of nitrogen-containing compounds with a wide range of applications in material[2] and medicinal chemistry.[3] Drugs with this ubiquitous scaffold (Figure 1) present broad spectrum of bioactive properties ranging from antibacterial,[4] antituberculosis,[5] to antitumoral activity.[6] For instance, NK-109 (Figure 1), which contains a skeleton of phenanthridine, exhibits great antitumoral activities and has been proven to inhibit several human drug-resistant tumor cell lines.[7] Because of these wide applications, efficient and versatile methods for synthesis of phenanthridines have been extensively investigated. The Pictet−Hubert reaction is a classical method for synthesis of phenanthridines by using zinc chloride as dehydration agent for cyclization of *N*-acyl-2-biphenylamine at elevated temperatures.[8] Later, the Bischler−Napieralski cyclization involving P_4O_{10}, $POCl_3$, or PCl_5 at elevated temperature was widely used in synthesis of phenanthridines.[9] However, harsh conditions were required to facilitate the cyclization in these reactions. In recent years, much effort has been devoted to the development of mild and efficient synthetic routes to phenanthridines including transition metal-catalyzed approaches,[10] radical-promoted cyclization,[11] cycloaddition,[12] and insertion.[13]

In the past decade, free radical reactions have become powerful and efficient strategies in organic synthesis due to the avoidance of a prefunctionalization process.[14] Among widely various types of radical-based reactions, those taking advantage of the radical cascade reactions have proven to be highly valuable for the synthesis of complex polycyclic compounds.[15] Although there are various powerful methods to prepare phenanthridines, the radical cascade reaction of biphenyl isocyanides is always a simple and direct route with atom- and step-economical features. For example, Chatani's group reported the first example of the synthesis of phenanthridines by $Mn(acac)_3$-catalyzed oxidative cyclization of biphenyl isocyanides with organoboron reagents as radical precursors.[16] Subsequently, reactions using biphenyl isocyanides as radical acceptors to form phenanthridines have been frequently reported.[17] Despite the promising progress achieved in recent years, further exploration of convenient, efficient, and milder protocols with biphenyl isocyanides as radical acceptors is still needed. Herein we report a new oxidative radical insertion/cyclization of biphenyl isocyanides with a C(sp^3)−H bond adjacent to a heteroatom for the rapid microwave-assisted synthesis of multisubstituted phenanthridines. This oxidative cascade reaction is catalyzed by economical and environmentally benign iron[18] and involves the use of *tert*-butyl hydrogen peroxide (TBHP) as oxidant and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as ligand (Scheme 1).

RESULTS AND DISCUSSION

We initially studied the reaction of 2-isocyano-1,1′-biphenyl (**1a**, 0.3 mmol) with Et_2O (**2a**, 20 equiv), $FeCl_3$ (5 mol %) in benzene at 80 °C for 12 h under argon atmosphere and were able to isolate the desired phenanthridines **3a** in 15% yield (Table 1, entry 1). As we all know, the potential of microwaves to increase the rate, selectivity, and efficiency of chemical transformations has been well documented in the literature.[19] To our delight, for only 1 h, desired product **3a** was obtained in 18% yield at 80 °C under microwave-assisted conditions (Table 1, entry 2). We next tried to add 2 equiv of TBHP to the

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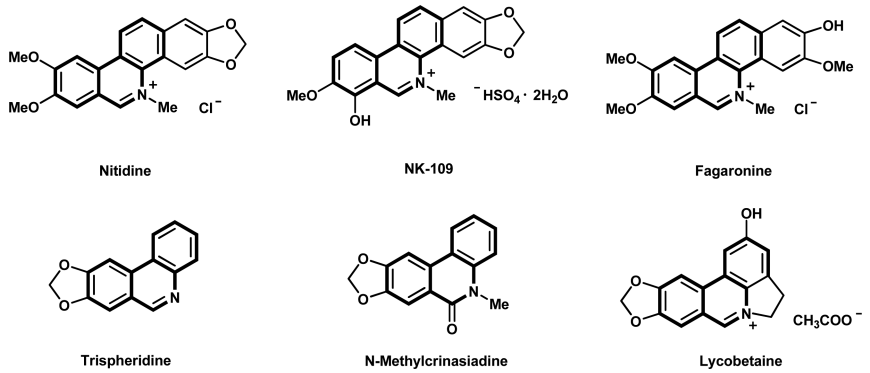


Figure 1. Biologically active phenanthridines.

Scheme 1. Fe-Catalyzed Oxidative Radical Insertion/Cyclization

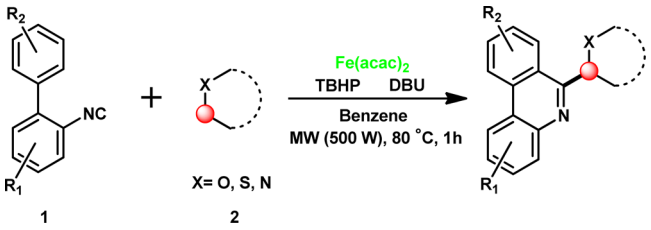
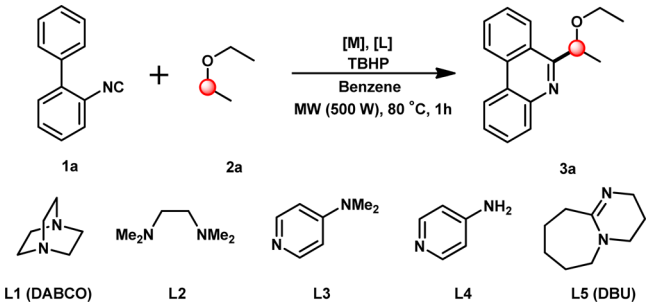


Table 1. Optimization of the Reaction Conditions[a]



entry	[M] (mol %)	[L] (mol %)	yield[b] (%)
1[c]	$FeCl_3$ (5)	–	15
2[d]	$FeCl_3$ (5)	–	18
3	$FeCl_3$ (5)	–	43
4	$FeCl_3$ (5)	**L1** (10)	60
5	$FeBr_3$ (5)	**L1** (10)	48
6	$FeCl_2$ (5)	**L1** (10)	57
7	$Fe(acac)_2$ (5)	**L1** (10)	75
8	–	**L1** (10)	0
9	$Fe(acac)_2$ (2)	**L1** (4)	36
10	$Fe(acac)_2$ (10)	**L1** (20)	61
11	$Fe(acac)_2$ (5)	**L2** (10)	59
12	$Fe(acac)_2$ (5)	**L3** (10)	32
13	$Fe(acac)_2$ (5)	**L4** (10)	36
14	$Fe(acac)_2$ (5)	**L5** (10)	89
15	$Fe(acac)_2$ (5)	**L5** (5)	58
16	$Fe(acac)_2$ (5)	**L5** (100)	83
17	$Fe(acac)_2$ (5)	**L5** (200)	87

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (20 equiv), catalyst [M], ligand [L], TBHP (anhydrous, 5 M in decane, 2 equiv), benzene (anhydrous, 0.5 mL), and Ar (argon) at 80 °C under microwave-assisted conditions (500 W) for 1 h. [b]Isolated yield of **3a**. [c]Without TBHP and microwave-assisted conditions for 12 h. [d]Without TBHP.

reaction system, and the yield of the target product significantly increased to 43% (Table 1, entry 3). As we know, certain iron ligands are thought to increase catalyst stability and to prevent aggregation of the metal. Gratifyingly, the yield increased to 60% when the ligand DABCO (**L1**) was used (Table 1, entry 4). Encouraged by these results, different iron catalysts (such as $FeBr_3$, $FeCl_2$, and $Fe(acac)_2$) were evaluated for the reaction between 2-isocyanobiphenyl (**1a**) and Et_2O (**2a**) under microwave-assisted conditions (Table 1, entries 5–7), among which $Fe(acac)_2$ provided the satisfactory yield (75%) (Table 1, entry 7). We noted that no desired product **3a** was observed in the absence of metal catalysts (Table 1, entry 8). With regard to the optimal amount of the catalyst, the reaction with 5 mol % of $Fe(acac)_2$ provided the best results (Table 1, entry 7 vs entries 9 and 10). Interestingly, the reaction was also sensitive to the ligand types. It was found that a dramatically improved yield (89%) of **3a** was obtained when DBU (**L5**) was used (Table 1, entries 7 and 11–13 vs entry 14). In addition, the yield decreased as the amount of DBU was reduced (Table 1, entry 15). However, increasing the amount of DBU gave a comparable yield to using 10 mol % of DBU (Table 1, entries 16 and 17), demonstrating that DBU acted as a ligand, not as a base. To further identify the roles of DBU, a UV–visible titration test was conducted. The absorption characteristic peaks of DBU and $Fe(acac)_2$ disappeared completely (Figure 2), which also confirmed that DBU acted as a ligand, not as a base. However, the possibility that the alkalinity of DBU promoted this transformation was not ruled out.

To demonstrate the substrate scope of this method, a variety of biphenyl isocyanides were examined (Table 2). Substitution on the isonitrile phenyl moiety indicated that the electron-deficient substrates slightly diminished the yields, with compounds **3f** being formed in moderate yield (69%). The substrates bearing electron-rich or electron-deficient groups on the non-isonitrile phenyl moiety all delivered the corresponding products in good to excellent yields (**3g–k**). The substituents at the different positions of the biphenyl isocyanides did not interfere with the reaction efficiency (**3l–n′**). When non-isonitrile phenyl moiety *m*-methyl-substituted substrate was used, two regioisomers **3n** and **3n′** were formed in a ratio of 1.5:1 (52% and 35%, respectively). Furthermore, this reaction was also versatile with respect to substitution and multi-substitution of the two phenyl rings (**3o–q′**). In the case of dioxy heterocyclic group-functionalized biphenyl isocyanide, a mixture of regioisomers was provided in a ratio of 2.3:1 (**3q** and **3q′**, 64% and 28%, respectively). Importantly, the obtained molecule **3q** contained a trisphaeridine framework (Figure 1),

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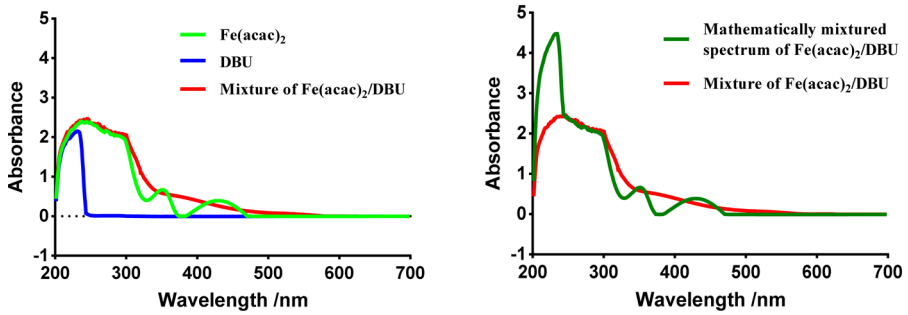
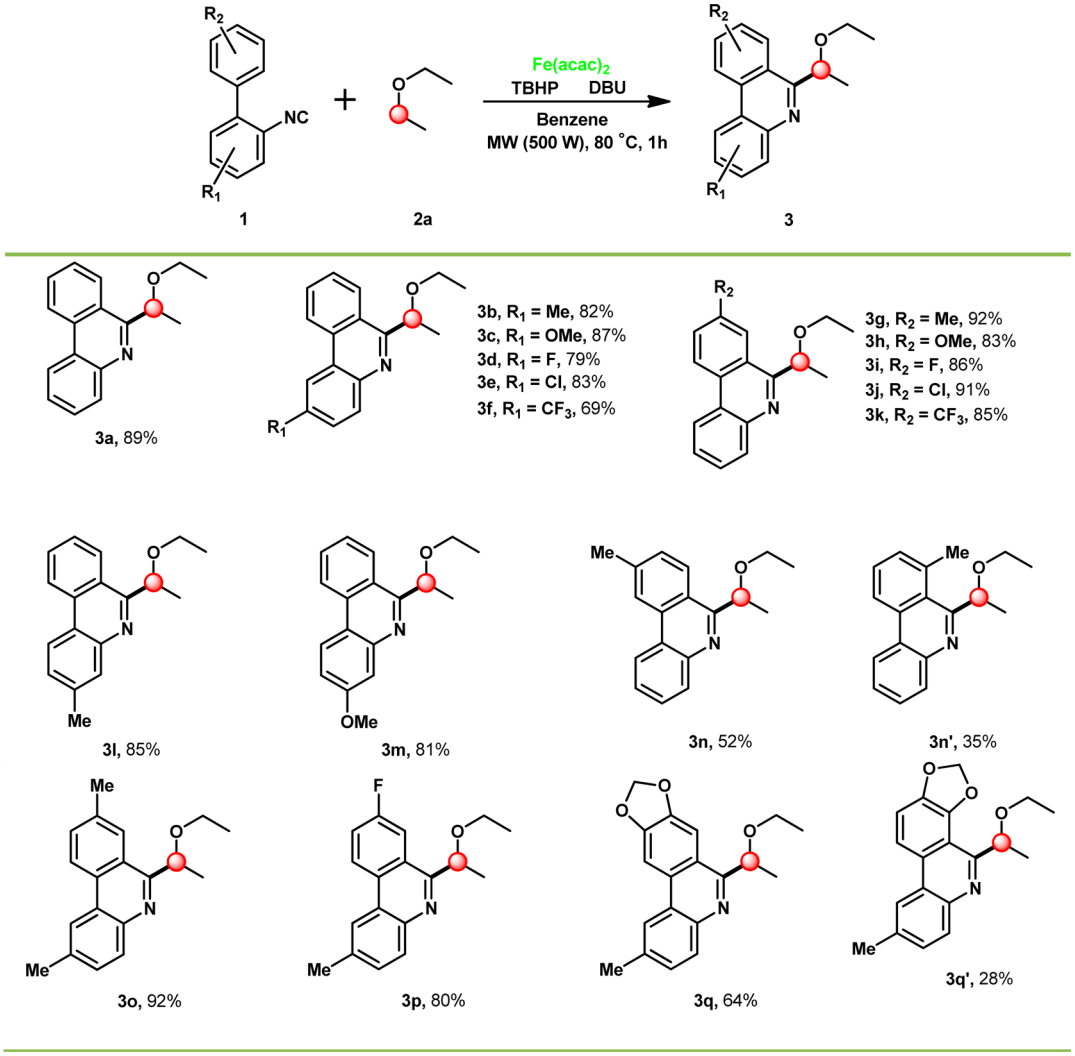


Figure 2. UV−visible titration analysis.

Table 2. Scope of Biphenyl Isocyanides[a]



[a]Reaction conditions: **1** (0.3 mmol), **2a** (20 equiv), $Fe(acac)_2$ (5 mol %), DBU (10 mol %), TBHP (anhydrous, 5 M in decane, 2 equiv), benzene (anhydrous, 0.5 mL), and Ar (argon) at 80 °C under microwave-assisted conditions (500 W) for 1 h. All reported yields were those of isolated products.

thus providing a good opportunity for potential applications in medicinal chemistry.

Then the reaction of **1a** with a $C(sp^3)$−H bond adjacent to a heteroatom was investigated (Table 3). A broad range of ethers was employed to react with **1a** under the optimized reaction conditions, giving rise to the corresponding phenanthridine derivatives in good yields (**4b**−**f**). For example, 1,2-dimethoxyethane (**2b**) was a good candidate, and under the present reaction conditions, we mainly obtained one isomer as the final product in an isolated yield of 71%. Moreover, the cascade sequence involving 2,3-dihydrobenzofuran (**2f**) was successful, as demonstrated by a modest yield of **4f** (65%). To our delight, a $C(sp^3)$−H bond adjacent to a sulfur atom was also suitable for the reaction. When we reacted **1a** and tetrahydro-2*H*-thiopyran (**2g**) under the optimized reaction conditions, the corresponding product **4g** was obtained in moderate yield

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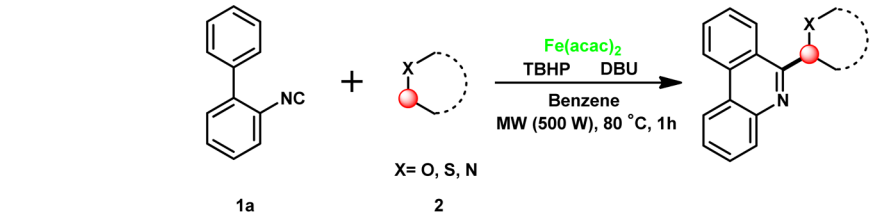
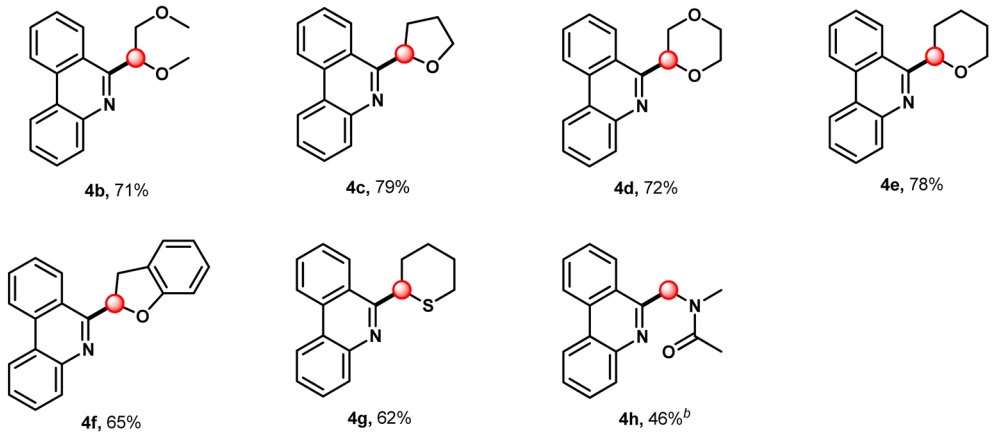
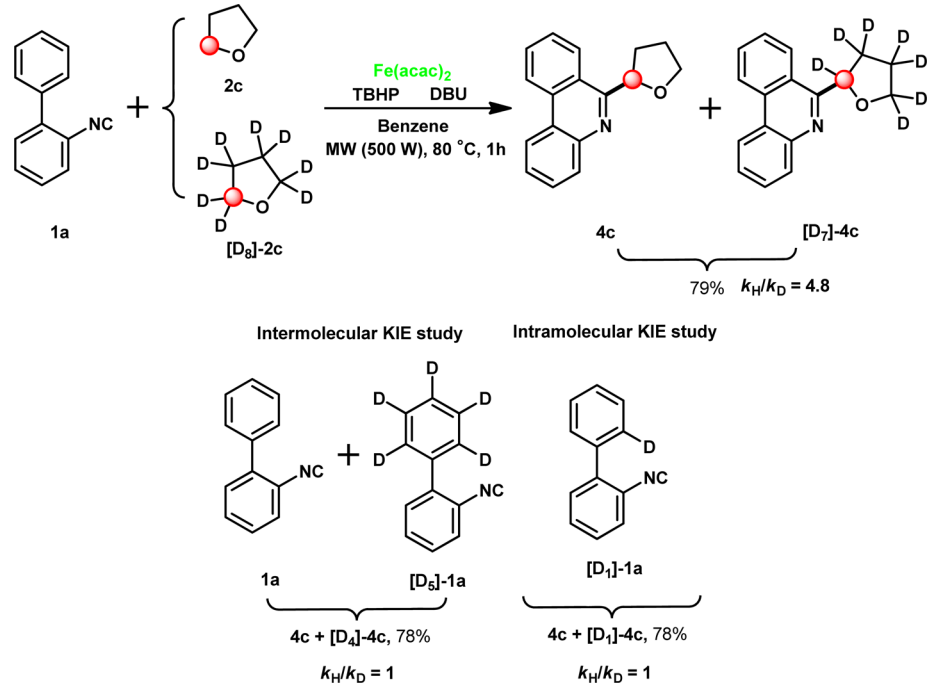
Table 3. Scope of Substrates 2 with a C(sp^3)−H Bond Adjacent to a Heteroatom[a]





[a]Reaction conditions: **1a** (0.3 mmol), **2** (20 equiv), $Fe(acac)_2$ (5 mol %), DBU (10 mol %), TBHP (anhydrous, 5 M in decane, 2 equiv), benzene (anhydrous, 0.5 mL), and Ar (argon) at 80 °C under microwave-assisted conditions (500 W) for 1 h. All reported yields were those of isolated products. [b]At 120 °C for 3 h.

Scheme 2. Kinetic Isotope Effect Studies



(62%). Interestingly, amide **2h** could also be used in this reaction, furnishing the desired product **4h** in 46% yield, thereby making this methodology more useful in organic synthesis.

To gain insight into the reaction mechanism, we set out to examine the kinetic isotope effect (KIE) of this reaction (Scheme 2). As a result, a significant KIE of 4.8 was observed in the experiment between THF and [d_8]-THF (the KIE was determined by ^{1}H NMR spectroscopy by analyzing the ratio of **4c** vs [d_7]-**4c**), indicating that C(sp^3)−H bond cleavage may be one of the rate-determining steps of this procedure. On the other hand, there was no kinetic isotope effect (k_H/k_D = 1) in either the intermolecular or intramolecular experiment (**4c** vs [d_4]-**4c** and **4c** vs [d_1]-**4c**, respectively). This result indicated

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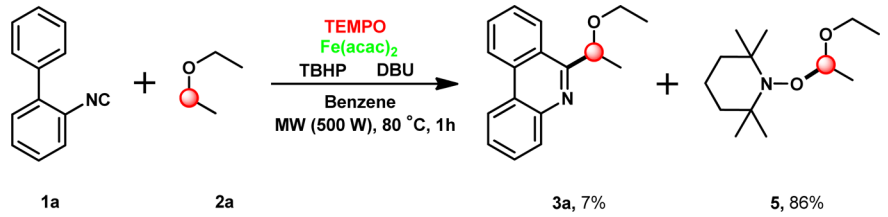
Scheme 3. Radical Inhibition Studies



that the mechanism of this oxidative cascade reaction was compatible with the S_EAr mechanism or the free-radical mechanism.[20] Then we conducted a radical inhibition experiment with addition of the known radical scavenger TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) under the standard reaction conditions (Scheme 3). Addition of radical scavenger significantly suppressed the reaction, which may support a radical mechanism being involved in this procedure.

Further support for a radical mechanism came from a Hammett plot analysis of the relative products formation (Table 2, **3a**, **3g**–**k**, **3n**+**3n′**) (Figure 3). With the use of

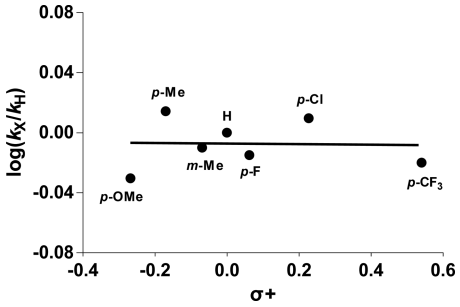


Figure 3. Hammett plot analysis.

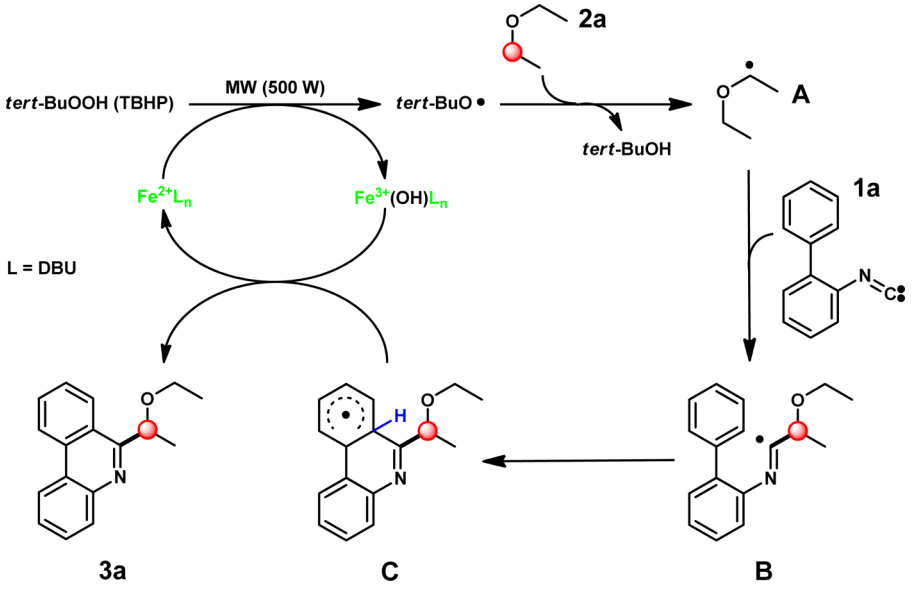
percent yield of the substituted phenanthridines as a measurement of the equilibrium constant for the reaction (k_X), a plot of the product formation ($\log k_X/k_H$) against σ^+ values showed a line with a slope that was close to zero, consistent with a neutral radical intermediate.[21] In addition, the oxidative cyclization pathway of biphenyl isocyanides with meta-substituted non-isonitrile phenyl rings showed an interesting regioselectivity (Table 2, **3n** vs **3n′** and **3q** vs **3q′**). We speculated that the observed regiochemistry was due to steric effects, and the regioisomer that gave the lowest energy conformation to create minimal steric hindrance effects was favored.

Taking into account the above results, we proposed a plausible mechanism for this insertion/cyclization reaction of biphenyl isocyanides with a C(sp^3)–H bond adjacent to a heteroatom (Scheme 4). Initially, TBHP was split by Fe^{2+} into a *tert*-butoxy radical and Fe^{3+}(OH) under microwave-assisted conditions. Then substrate **2a** was transformed into radical intermediate **A** in the presence of a *tert*-butoxy radical. Subsequently, addition of radical intermediate **A** to the 2-isocyanobiphenyl **1a** afforded the imidoyl radical **B**, which experienced a intramolecular hemolytic aromatic substitution to give the cyclized radical intermediate **C**. The product **3a** was finally created with the leaving of the H radical, which was abstracted by Fe^{3+}(OH).

CONCLUSION

We have successfully developed a general and practical protocol for the synthesis of phenanthridine derivatives by an insertion/cyclization reaction of biphenyl isocyanides with a C(sp^3)–H bond adjacent to a heteroatom under microwave-assisted conditions. The novel method presents the major advantages of 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.

Scheme 4. Plausible Mechanism



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EXPERIMENTAL SECTION

General Information. All reactions were carried out under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise stated. All of the microwave-assisted reactions were performed in an Initiator+ microwave system at the specified temperature using the standard mode of operation. The reactions were monitored by thin-layer chromatography (TLC) analysis. Silica gel (200−300 mesh) was used for column chromatography. High-resolution MS (HRMS) was analyzed by a TOF analyzer. The ion source is electrospray ionization (ESI). ^{1}H and ^{13}C spectra were recorded at 400 and 600 MHz, respectively. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of $CDCl_3$ (7.26 ppm). Data are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $CDCl_3$ (77.0 ppm) on the δ scale.

General Procedure for the Preparation of Biphenyl Isocyanides. Biphenyl isocyanides were prepared according to the known procedures.[16]

*2-Isocyano-1,1′-biphenyl (**1a**).*[17a] Green liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (m, 8H), 7.38 (m, 1H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.9, 138.2, 136.4, 130.0, 128.9, 128.4, 128.0, 127.8, 127.5, 127.2. MS (ESI) m/z 180.0 $[M + H]^+$.

*2-Isocyano-5-methyl-1,1′-biphenyl (**1b**).*[16] Green liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 6H), 7.23 (s, 1H), 7.17 (d, 1H, J = 8.1 Hz), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.1, 139.2, 138.0, 136.5, 130.5, 128.3, 128.1, 127.9, 127.6, 127.0, 121.5, 20.7. MS (ESI) m/z 194.1 $[M + H]^+$.

*2-Isocyano-5-methoxy-1,1′-biphenyl (**1c**).* Green liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 6H), 6.89 (m, 2H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 164.4, 159.2, 139.8, 136.5, 128.6, 128.3, 127.9, 127.8, 114.9, 113.0, 55.1. MS (ESI) m/z 210.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{14}H_{11}NO$, 210.0919; observed, 210.0915.

*5-Fluoro-2-isocyano-1,1′-biphenyl (**1d**).*[16] Green solid. Mp 51−53 °C (lit.[16] 50−52 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 6H), 7.14 (m, 1H), 7.07 (m, 1H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 166.0, 162.4, 160.7, 140.7, 140.6, 135.4, 129.2, 129.1, 128.3, 128.2, 128.1, 116.9, 116.8, 114.7, 114.6, 20.9, 14.9. MS (ESI) m/z 198.1 $[M + H]^+$.

*5-Chloro-2-isocyano-1,1′-biphenyl (**1e**).*[16] Green solid. Mp 72−75 °C (lit.[16] 71−73 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 7H), 7.35 (m, 1H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 167.2, 139.8, 135.1, 134.8, 130.0, 128.4, 128.3, 128.2, 128.1, 127.6, 122.5. MS (ESI) m/z 214.0 $[M + H]^+$.

*2-Isocyano-5-(trifluoromethyl)-1,1′-biphenyl (**1f**).*[17a] Green liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72 (s, 1H), 7.64 (q, 2H, J = 8.4 Hz), 7.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 168.8, 139.1, 135.0, 128.8, 128.5, 128.4, 128.3, 127.8, 127.6, 127.2, 127.0, 124.5, 120.9, 119.6. MS (ESI) m/z 248.0 $[M + H]^+$.

*2-Isocyano-4′-methyl-1,1′-biphenyl (**1g**).*[17a] Green liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (m, 5H), 7.35 (m, 1H), 7.30 (d, 2H, J = 7.9 Hz), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.7, 138.2, 137.7, 133.5, 129.9, 128.9, 128.7, 128.2, 127.3, 127.2, 124.0, 20.7. MS (ESI) m/z 194.1 $[M + H]^+$.

*2-Isocyano-4′-methoxy-1,1′-biphenyl (**1h**).*[17a] Green solid. Mp 59−60 °C (lit.[17a] 56−57 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (m, 5H), 7.34 (m, 1H), 7.02 (d, 2H, J = 8.7 Hz), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.6, 159.1, 137.9, 129.8, 129.6, 128.9, 128.7, 127.3, 127.1, 113.4, 54.7. MS (ESI) m/z 210.2 $[M + H]^+$.

*4′-Fluoro-2-isocyano-1,1′-biphenyl (**1i**).*[17c] Green liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 4H), 7.38 (m, 2H), 7.17 (t, 2H, J = 8.7 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 166.1, 163.0, 161.4, 137.2, 132.4, 130.2, 130.1, 129.9, 129.0, 127.7, 127.2, 124.1, 124.0, 115.1, 114.9. MS (ESI) m/z 198.1 $[M + H]^+$.

*4′-chloro-2-isocyano-1,1′-biphenyl (**1j**).*[17a] Pale yellow solid. Mp 95−97 °C (lit.[17a] 85−89 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 6H), 7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 166.3, 137.0, 134.8, 134.0, 129.8, 129.7, 129.1, 128.2, 127.9, 127.3. MS (ESI) m/z 214.0 $[M + H]^+$.

*2-Isocyano-4′-(trifluoromethyl)-1,1′-biphenyl (**1k**).*[17a] Pale green solid. Mp 75−77 °C (lit.[17a] 73−75 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.75 (d, 2H, J = 8.1 Hz), 7.64 (d, 2H, J = 8.1 Hz), 7.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 166.6, 139.9, 136.7, 129.8, 129.2, 128.8, 128.4, 127.4, 125.0, 124.9. MS (ESI) m/z 248.0 $[M + H]^+$.

*2-Isocyano-4-methyl-1,1′-biphenyl (**1l**).*[17b] Pale yellow solid. Mp 59−60 °C (lit.[17b] 60−62 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 5H), 7.29 (m, 3H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.4, 137.8, 136.4, 135.3, 129.8, 129.7, 128.4, 127.9, 127.6, 127.5, 20.2. MS (ESI) m/z 194.1 $[M + H]^+$.

*2-Isocyano-4-methoxy-1,1′-biphenyl (**1m**).* Green solid. Mp 60−62 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (m, 5H), 7.33 (d, 1H, J = 8.4 Hz), 7.01 (m, 2H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.6, 158.5, 136.2, 130.8, 130.7, 128.4, 127.9, 127.3, 115.5, 112.1, 55.1. MS (ESI) m/z 210.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{14}H_{11}NO$, 210.0919; observed, 210.0922.

*2-Isocyano-3′-methyl-1,1′-biphenyl (**1n**).*[17a] Green liquid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.38 (m, 7H), 7.23 (s, 1H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.9, 147.2, 137.9, 130.2, 129.9, 128.9, 127.3, 127.2, 122.3, 108.8, 107.8, 100.7. MS (ESI) m/z 194.1 $[M + H]^+$.

*2-Isocyano-4′,5-dimethyl-1,1′-biphenyl (**1o**).*[17b] Pale green solid. Mp 54−56 °C (lit.[17b] 50−52 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (m, 3H), 7.28 (m, 2H), 7.22 (s, 1H), 7.15 (d, 1H, J = 8.0 Hz), 2.42 (d, 6H, J = 5.3 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 164.9, 139.2, 138.0, 137.5, 133.6, 130.5, 128.6, 128.2, 127.9, 127.0, 20.7, 20.6. MS (ESI) m/z 208.1 $[M + H]^+$.

*4′-Fluoro-2-isocyano-5-methyl-1,1′-biphenyl (**1p**).*[16] Pale green solid. Mp 53−55 °C (lit.[16] 54−55 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (m, 2H), 7.34 (d, 1H, J = 8.0 Hz), 7.14 (m, 4H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.3, 163.0, 161.3, 139.4, 137.0, 132.5, 130.4, 130.1, 130.0, 128.3, 127.0, 121.5, 115.0, 114.9, 20.7. MS (ESI) m/z 212.1 $[M + H]^+$.

*5-(2-Isocyano-5-methylphenyl)benzo[d][1,3]dioxole (**1q**).*[17b] Yellow solid. Mp 72−74 °C (lit.[17b] 74−76 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35 (d, 1H, J = 8.0 Hz), 7.15 (m, 2H), 6.96 (m, 2H), 6.90 (d, 1H, J = 8.0 Hz), 6.02 (s, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 165.1, 147.1, 139.2, 137.6, 130.4, 130.3, 127.9, 127.0, 122.2, 108.8, 107.8, 100.7, 20.7. MS (ESI) m/z 238.1 $[M + H]^+$.

General Procedure for the Preparation of Phenanthridines. To a microwave reaction vial were added biphenyl isocyanides **1** (0.3 mmol), ethers/thioether/amide **2** (20 equiv), $Fe(acac)_2$ (5 mol %), DBU (**L5**, 10 mol %), TBHP (anhydrous, 5 M in decane, 2 equiv), and benzene (anhydrous, 0.5 mL). Then the vial was charged with argon and was stirred at the indicated temperature under microwave-assisted conditions (500 W) for the indicated time until complete consumption of starting material as monitored by TLC. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to afford the desired product.

*6-(1-Ethoxyethyl)phenanthridine (**3a**).* Yield: 67 mg, 89%; yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (d, 1H, J = 8.4 Hz), 8.65 (d, 1H, J = 8.3 Hz), 8.55 (m, 1H), 8.17 (m, 1H), 7.83 (m, 1H), 7.68 (m, 3H), 5.22 (q, 1H, J = 6.8 Hz), 3.58 (m, 1H), 3.46 (m, 1H), 1.78 (d, 3H, J = 6.8 Hz), 1.20 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.3, 142.6, 132.9, 129.8, 129.4, 128.0, 126.4, 126.3, 126.2, 123.4, 121.8, 121.3, 80.8, 64.0, 20.9, 14.9. MS (ESI) m/z 252.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{17}NO$, 252.1383; observed, 252.1385.

*6-(1-Ethoxyethyl)-2-methylphenanthridine (**3b**).* Yield: 65 mg, 82%; yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.88 (d, 1H, J = 8.3 Hz), 8.66 (d, 1H, J = 8.3 Hz), 8.35 (s, 1H), 8.07 (d, 1H, J = 8.3 Hz), 7.83 (t, 1H, J = 7.6 Hz), 7.67 (t, 1H, J = 7.6 Hz), 7.56 (d, 1H, J = 7.2 Hz), 5.21 (q, 1H, J = 6.7 Hz), 3.59 (m, 1H), 3.46 (m, 1H), 2.64 (s, 3H), 1.78 (d, 3H, J = 6.8 Hz), 1.22 (t, 3H, J = 7.0 Hz). ^{13}C NMR

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($CDCl_3$, 600 MHz) δ 160.2, 140.9, 137.4, 136.2, 132.7, 129.7, 129.6, 129.0, 126.2, 123.5, 123.3, 121.8, 120.9, 80.8, 64.0, 21.3, 20.9, 14.9. MS (ESI) m/z 266.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO$, 266.1539; observed, 266.1538.

6-(1-Ethoxyethyl)-2-methoxyphenanthridine (**3c**). Yield: 73 mg, 87%; yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.86 (d, 1H, J = 8.4 Hz), 8.58 (d, 1H, J = 8.4 Hz), 8.08 (d, 1H, J = 9.0 Hz), 7.89 (d, 1H, J = 2.5 Hz), 7.81 (t, 1H, J = 7.7 Hz), 7.67 (t, 1H, J = 7.7 Hz), 7.35 (m, 1H), 5.18 (q, 1H, J = 6.8 Hz), 4.01 (s, 3H), 3.57 (m, 1H), 3.44 (m, 1H), 1.77 (d, 3H, J = 6.8 Hz), 1.20 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 158.6, 157.8, 137.9, 132.4, 130.7, 129.4, 126.4, 126.2, 124.5, 123.6, 117.8, 102.3, 80.6, 63.9, 55.0, 20.8, 14.9. MS (ESI) m/z 282.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO_2$, 282.1489; observed, 282.1493.

6-(1-Ethoxyethyl)-2-fluorophenanthridine (**3d**). Yield: 64 mg, 79%; brown solid. Mp 73−75 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.89 (d, 1H, J = 8.4 Hz), 8.54 (d, 1H, J = 8.3 Hz), 8.16 (m, 2H), 7.87 (t, 1H, J = 7.6 Hz), 7.73 (t, 1H, J = 7.7 Hz), 7.47 (m, 1H), 5.21 (q, 1H, J = 6.8 Hz), 3.59 (m, 1H), 3.46 (m, 1H), 1.78 (d, 3H, J = 6.7 Hz), 1.22 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.5, 160.5, 159.9, 139.4, 131.6, 131.5, 129.9, 127.1, 126.3, 124.8, 124.7, 123.5, 122.0, 116.9, 116.8, 106.3, 106.2, 80.5, 64.0, 20.8, 14.9. MS (ESI) m/z 270.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{16}FNO$, 270.1289; observed, 270.1281.

2-Chloro-6-(1-ethoxyethyl)phenanthridine (**3e**). Yield: 71 mg, 83%; pale yellow solid. Mp 87−89 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.89 (d, 1H, J = 8.3 Hz), 8.59 (d, 1H, J = 8.3 Hz), 8.53 (d, 1H, J = 1.8 Hz), 8.10 (d, 1H, J = 8.7 Hz), 7.87 (t, 1H, J = 7.6 Hz), 7.70 (m, 2H), 5.21 (q, 1H, J = 6.8 Hz), 3.59 (m, 1H), 3.46 (m, 1H), 1.78 (d, 3H, J = 6.8 Hz), 1.22 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.6, 141.1, 132.2, 131.9, 130.9, 130.1, 128.5, 127.1, 126.3, 124.6, 123.6, 121.8, 121.0, 80.5, 64.1, 20.7, 14.9. MS (ESI) m/z 286.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{16}ClNO$, 286.0993; observed, 286.0982.

6-(1-Ethoxyethyl)-2-(trifluoromethyl)phenanthridine (**3f**). Yield: 66 mg, 69%; yellow solid. Mp 85−87 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.93 (d, 1H, J = 8.2 Hz), 8.85 (s, 1H), 8.71 (d, 1H, J = 8.3 Hz), 8.28 (d, 1H, J = 8.5 Hz), 7.93 (t, 2H, J = 7.5 Hz), 7.77 (t, 1H, J = 7.7 Hz), 5.25 (q, 1H, J = 6.8 Hz), 3.60 (m, 1H), 3.47 (m, 1H), 1.79 (d, 3H, J = 6.8 Hz), 1.23 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 163.8, 144.1, 132.5, 130.5, 130.3, 127.3, 126.5, 124.0, 123.7, 123.1, 121.8, 119.2, 119.1, 80.5, 64.2, 29.1, 20.8, 14.9. MS (ESI) m/z 320.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{16}F_3NO$, 320.1257; observed, 320.1245.

6-(1-Ethoxyethyl)-8-methylphenanthridine (**3g**). Yield: 73 mg, 92%; yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (s, 1H), 8.53 (m, 2H), 8.17 (d, 1H, J = 8.1 Hz), 7.66 (m, 3H), 5.23 (q, 1H, J = 6.8 Hz), 3.58 (m, 1H), 3.46 (m, 1H), 2.61 (s, 3H), 1.78 (d, 3H, J = 6.8 Hz), 1.22 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 160.9, 142.2, 136.4, 131.6, 130.7, 129.2, 127.6, 126.2, 125.5, 123.6, 123.5, 121.7, 121.1, 80.5, 64.0, 21.3, 20.9, 14.9. MS (ESI) m/z 266.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO$, 266.1539; observed, 266.1549.

6-(1-Ethoxyethyl)-8-methoxyphenanthridine (**3h**). Yield: 70 mg, 83%; yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.53 (d, 1H, J = 9.1 Hz), 8.45 (d, 1H, J = 7.6 Hz), 8.37 (d, 1H, J = 2.6 Hz), 8.14 (d, 1H, J = 8.1 Hz), 7.64 (m, 2H), 7.46 (m, 1H), 5.19 (q, 1H, J = 6.8 Hz), 3.98 (s, 3H), 3.59 (m, 1H), 3.46 (m, 1H), 1.78 (d, 3H, J = 6.8 Hz), 1.23 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 160.3, 157.7, 141.8, 129.2, 127.3, 127.0, 126.4, 124.7, 123.6, 123.3, 120.8, 120.7, 106.1, 81.4, 63.9, 54.9, 20.6, 15.0. MS (ESI) m/z 282.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO_2$, 282.1489; observed, 282.1487.

6-(1-Ethoxyethyl)-8-fluorophenanthridine (**3i**). Yield: 69 mg, 86%; yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.62 (m, 2H), 8.50 (d, 1H, J = 8.0 Hz), 8.15 (d, 1H, J = 8.1 Hz), 7.65 (m, 3H), 5.15 (q, 1H, J = 6.8 Hz), 3.59 (m, 1H), 3.44 (m, 1H), 1.76 (d, 3H, J = 6.8 Hz), 1.22 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.3, 160.5, 159.6, 142.3, 129.6, 129.5, 127.9, 126.7, 124.6, 124.5, 124.2, 124.1, 123.0, 121.1, 119.2, 119.0, 111.1, 110.9, 81.0, 64.1, 20.6, 14.9. MS (ESI) m/z 270.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{16}FNO$, 270.1289; observed, 270.1290.

8-Chloro-6-(1-ethoxyethyl)phenanthridine (**3j**). Yield: 78 mg, 91%; yellow solid. Mp 54−56 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.93 (d, 1H, J = 2.0 Hz), 8.60 (d, 1H, J = 8.9 Hz), 8.51 (d, 1H, J = 7.5 Hz), 8.17 (d, 1H, J = 8.0 Hz), 7.77 (m, 2H), 7.68 (m, 1H), 5.18 (q, 1H, J = 6.7 Hz), 3.60 (m, 1H), 3.45 (m, 1H), 1.77 (d, 3H, J = 6.8 Hz), 1.23 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 160.4, 142.4, 132.5, 131.3, 130.5, 129.4, 128.4, 126.8, 125.6, 124.2, 123.5, 122.9, 121.2, 80.7, 64.1, 20.8, 14.9. MS (ESI) m/z 286.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{16}ClNO$, 286.0993; observed, 286.0994.

6-(1-Ethoxyethyl)-8-(trifluoromethyl)phenanthridine (**3k**). Yield: 81 mg, 85%; yellow solid. Mp 53−54 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 9.30 (s, 1H), 8.73 (d, 1H, J = 8.7 Hz), 8.55 (d, 1H, J = 8.0 Hz), 8.18 (d, 1H, J = 8.2 Hz), 8.01 (m, 1H), 7.79 (t, 1H, J = 7.6 Hz), 7.69 (t, 1H, J = 7.6 Hz), 5.21 (q, 1H, J = 6.8 Hz), 3.62 (m, 1H), 3.43 (m, 1H), 1.78 (d, 3H, J = 6.8 Hz), 1.21 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.2, 143.3, 135.1, 129.6, 129.2, 128.3, 128.1, 126.9, 125.6, 124.0, 122.8, 122.5, 121.6, 80.9, 64.1, 20.8, 14.8. MS (ESI) m/z 320.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{16}F_3NO$, 320.1257; observed, 320.1256.

6-(1-Ethoxyethyl)-3-methylphenanthridine (**3l**). Yield: 68 mg, 85%; yellow solid. Mp 61−62 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.87 (d, 1H, J = 8.3 Hz), 8.58 (d, 1H, J = 8.3 Hz), 8.40 (d, 1H, J = 8.4 Hz), 7.98 (s, 1H), 7.78 (t, 1H, J = 7.6 Hz), 7.63 (t, 1H, J = 7.7 Hz), 7.45 (d, 1H, J = 8.3 Hz), 5.21 (q, 1H, J = 6.8 Hz), 3.58 (m, 1H), 3.45 (m, 1H), 2.57 (s, 3H), 1.78 (d, 3H, J = 6.8 Hz), 1.21 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.3, 142.8, 138.1, 133.0, 129.7, 129.0, 128.0, 126.2, 125.9, 123.1, 121.6, 121.1, 80.9, 64.0, 20.9, 14.9. MS (ESI) m/z 266.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO$, 266.1539; observed, 266.1549.

6-(1-Ethoxyethyl)-3-methoxyphenanthridine (**3m**). Yield: 68 mg, 81%; yellow solid. Mp 62−64 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.83 (d, 1H, J = 8.4 Hz), 8.54 (d, 1H, J = 8.4 Hz), 8.43 (d, 1H, J = 9.0 Hz), 7.79 (t, 1H, J = 7.7 Hz), 7.59 (m, 2H), 7.28 (m, 1H), 5.20 (q, 1H, J = 6.8 Hz), 3.97 (s, 3H), 3.58 (m, 1H), 3.46 (m, 1H), 1.77 (d, 3H, J = 6.8 Hz), 1.21 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.9, 159.5, 144.3, 133.1, 129.9, 126.2, 125.3, 122.5, 121.3, 117.5, 109.1, 80.6, 64.1, 55.0, 21.0, 14.9. MS (ESI) m/z 282.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO_2$, 282.1489; observed, 282.1487.

6-(1-Ethoxyethyl)-9-methylphenanthridine (**3n**). Yield: 41 mg, 52%; off-white solid. Mp 55−57 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.79 (d, 1H, J = 8.5 Hz), 8.54 (d, 1H, J = 8.2 Hz), 8.44 (s, 1H), 8.16 (d, 1H, J = 8.1 Hz), 7.71 (t, 1H, J = 7.5 Hz), 7.63 (t, 1H, J = 7.6 Hz), 7.50 (d, 1H, J = 8.5 Hz), 5.20 (q, 1H, J = 6.8 Hz), 3.58 (m, 1H), 3.45 (m, 1H), 2.64 (s, 3H), 1.78 (d, 3H, J = 6.8 Hz), 1.21 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.2, 142.7, 140.2, 133.1, 129.2, 128.2, 127.9, 126.1, 123.3, 121.5, 121.4, 121.3, 80.9, 64.0, 21.7, 21.0, 14.9. MS (ESI) m/z 266.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO$, 266.1539; observed, 266.1541.

6-(1-Ethoxyethyl)-7-methylphenanthridine (**3n′**). Yield: 28 mg, 35%; off-white solid. Mp 58−60 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.56 (m, 2H), 8.24 (d, 1H, J = 8.1 Hz), 7.66 (m, 3H), 7.52 (d, 1H, J = 7.1 Hz), 5.69 (q, 1H, J = 6.2 Hz), 3.49 (q, 2H, J = 6.9 Hz), 3.03 (s, 3H), 1.72 (d, 3H, J = 6.2 Hz), 1.21 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 160.4, 142.1, 135.1, 134.2, 131.3, 129.4, 128.9, 127.8, 126.2, 124.8, 123.4, 121.5, 120.3, 75.1, 62.8, 24.9, 19.7, 14.9. MS (ESI) m/z 266.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{19}NO$, 266.1539; observed, 266.1545.

6-(1-Ethoxyethyl)-2,8-dimethylphenanthridine (**3o**). Yield: 77 mg, 92%; yellow solid. Mp 52−54 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.63 (s, 1H), 8.53 (d, 1H, J = 8.5 Hz), 8.30 (s, 1H), 8.04 (d, 1H, J = 8.3 Hz), 7.64 (d, 1H, J = 7.7 Hz), 7.51 (m, 1H), 5.20 (q, 1H, J = 6.8 Hz), 3.57 (m, 1H), 3.45 (m, 1H), 2.60 (d, 6H, J = 2.7 Hz), 1.77 (d, 3H, J = 6.8 Hz), 1.22 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 159.8, 140.7, 136.1, 136.0, 131.3, 130.5, 129.2, 129.0, 125.4, 123.7, 123.3, 121.6, 120.7, 80.6, 63.9, 21.3, 21.2, 20.9, 14.9. MS (ESI) m/z

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280.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + Na]^+$ $C_{19}H_{21}NO$, 302.1515; observed, 302.1512.

*6-(1-Ethoxyethyl)-8-fluoro-2-methylphenanthridine (**3p**).* Yield: 68 mg, 80%; off-white solid. Mp 78−80 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.60 (m, 2H), 8.27 (s, 1H), 8.04 (d, 1H, J = 8.3 Hz), 7.56 (m, 2H), 5.14 (q, 1H, J = 6.7 Hz), 3.58 (m, 1H), 3.44 (m, 1H), 2.61 (s, 3H), 1.75 (d, 3H, J = 6.8 Hz), (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 161.2, 159.5, 159.4, 140.6, 136.7, 129.6, 129.4, 129.2, 124.6, 124.5, 124.2, 124.1, 122.9, 120.7, 118.9, 118.8, 111.0, 110.8, 81.0, 64.0, 21.3, 20.6, 20.9, 14.9. MS (ESI) m/z 284.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{18}FNO$, 284.1445; observed, 284.1448.

*6-(1-Ethoxyethyl)-2-methyl-[1,3]dioxolo[4,5-j]phenanthridine (**3q**).* Yield: 59 mg, 64%; yellow solid. Mp 105−107 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.18 (d, 2H, J = 8.2 Hz), 8.10 (d, 1H, J = 8.3 Hz), 7.46 (d, 1H, J = 8.2 Hz), 7.39 (d, 1H, J = 8.7 Hz), 6.22 (s, 2H), 5.58 (q, 1H, J = 6.3 Hz), 3.66 (m, 1H), 3.53 (m, 1H), 2.58 (s, 3H), 1.63 (d, 3H, J = 6.4 Hz), 1.28 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 157.5, 145.4, 142.4, 140.4, 136.4, 129.6, 128.9, 127.9, 122.7, 120.7, 115.7, 112.1, 110.8, 100.9, 63.9, 21.4, 20.4, 14.9. MS (ESI) m/z 310.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{19}H_{19}NO_3$, 310.1438; observed, 310.1440.

*4-(1-Ethoxyethyl)-8-methyl-[1,3]dioxolo[4,5-i]phenanthridine (**3q′**).* Yield: 26 mg, 28%; yellow solid. Mp 160−162 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.29 (s, 1H), 8.12 (s, 1H), 7.99 (d, 1H, J = 8.3 Hz), 7.93 (s, 1H), 7.49 (d, 1H, J = 8.3 Hz), 6.15 (s, 2H), 5.10 (q, 1H, J = 6.7 Hz), 3.56 (m, 1H), 3.42 (m, 1H), 2.59 (s, 3H), 1.73 (d, 3H, J = 6.8 Hz), 1.21 (t, 3H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 158.8, 150.0, 147.0, 140.6, 135.8, 130.5, 129.1, 128.9, 123.4, 120.6, 119.9, 103.6, 101.2, 99.6, 81.5, 63.9, 21.3, 20.7, 14.9. MS (ESI) m/z 310.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{19}H_{19}NO_3$, 310.1438; observed, 310.1440.

*6-(1,2-Dimethoxyethyl)phenanthridine (**4b**).* Yield: 57 mg, 71%; yellow solid. Mp 66−68 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.73 (d, 1H, J = 8.3 Hz), 8.63 (d, 1H, J = 8.3 Hz), 8.54 (d, 1H, J = 8.1 Hz), 8.22 (d, 1H, J = 8.1 Hz), 7.82 (t, 1H, J = 7.4 Hz), 7.69 (m, 3H), 5.33 (m, 1H), 4.14 (m, 1H), 3.82 (m, 1H), 3.44 (s, 6H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 157.3, 142.7, 132.7, 130.0, 129.6, 128.1, 126.7, 126.6, 125.8, 124.2, 123.4, 121.8, 121.3, 84.1, 74.6, 58.7, 56.7. MS (ESI) m/z 268.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{17}NO_2$, 268.1332; observed, 268.1332.

*6-(Tetrahydrofuran-2-yl)phenanthridine (**4c**).* Yield: 59 mg, 79%; yellow solid. Mp 93−95 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.65 (d, 1H, J = 8.3 Hz), 8.55 (d, 1H, J = 8.1 Hz), 8.45 (d, 1H, J = 8.3 Hz), 8.20 (d, 1H, J = 8.1 Hz), 7.83 (t, 1H, J = 7.7 Hz), 7.68 (m, 3H), 5.78 (t, 1H, J = 6.9 Hz), 4.22 (m, 1H), 4.08 (m, 1H), 2.74 (m, 1H), 2.43 (m, 1H), 2.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 158.7, 142.6, 132.7, 129.8, 129.7, 127.9, 126.6, 126.3, 125.9, 124.2, 123.5, 121.7, 121.2, 79.0, 68.4, 29.4, 25.4. MS (ESI) m/z 250.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{15}NO$, 250.1226; observed, 250.1219.

*6-(1,4-Dioxan-2-yl)phenanthridine (**4d**).* Yield: 57 mg, 72%; yellow solid. Mp 143−145 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.67 (d, 1H, J = 8.4 Hz), 8.57 (d, 1H, J = 8.0 Hz), 8.44 (d, 1H, J = 8.3 Hz), 8.22 (d, 1H, J = 7.9 Hz), 7.86 (t, 1H, J = 7.6 Hz), 7.71 (m, 3H), 5.50 (t, 1H, J = 6.1 Hz), 4.31 (d, 2H, J = 6.5 Hz), 4.12 (m, 2H), 3.92 (m, 2H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 155.5, 142.5, 132.6, 129.9, 129.9, 128.0, 126.8, 126.7, 125.5, 123.9, 123.4, 121.8, 121.3, 75.6, 69.4, 67.1, 66.0. MS (ESI) m/z 266.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{15}NO_2$, 266.1176; observed, 266.1165.

*6-(Tetrahydro-2H-pyran-2-yl)phenanthridine (**4e**).* Yield: 62 mg, 78%; yellow solid. Mp 100−102 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.55 (m, 3H), 8.24 (d, 1H, J = 8.1 Hz), 7.70 (m, 4H), 5.21 (d, 1H, J = 11.1 Hz), 4.30 (d, 1H, J = 12.6 Hz), 3.81 (t, 1H, J = 11.6 Hz), 2.28 (m, 1H), 2.08 (t, 2H, J = 12.3 Hz), 1.87 (m, 2H), 1.69 (d, 1H, J = 12.3 Hz). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 158.9, 142.7, 132.8, 129.8, 129.6, 127.8, 126.4, 126.3, 126.1, 123.8, 123.4, 121.7, 121.2, 79.9, 68.9, 29.9, 25.4, 23.2. MS (ESI) m/z 264.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{17}NO$, 264.1383; observed, 264.1384.

*6-(2,3-Dihydrobenzofuran-2-yl)phenanthridine (**4f**).* Yield: 58 mg, 65%; yellow solid. Mp 108−110 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.68 (d, 1H, J = 8.3 Hz), 8.57 (d, 1H, J = 7.9 Hz), 8.45 (d, 1H, J = 8.3 Hz), 8.18 (d, 1H, J = 7.9 Hz), 7.86 (t, 1H, J = 7.4 Hz), 7.71 (m, 3H), 7.33 (d, 1H, J = 7.3 Hz), 7.18 (t, 1H, J = 7.5 Hz), 6.94 (t, 1H, J = 7.4 Hz), 6.79 (m, 1H), 6.55 (t, 1H, J = 9.3 Hz), 4.38 (m, 1H), 3.64 (m, 1H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 158.5, 156.0, 142.4, 133.0, 130.0, 129.9, 128.1, 127.5, 126.9, 126.8, 126.4, 125.9, 124.4, 124.2, 123.7, 121.9, 121.3, 120.2, 109.1, 83.3, 32.6. MS (ESI) m/z 298.0 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{21}H_{15}NO$, 298.1226; observed, 298.1225.

*6-(Tetrahydro-2H-thiopyran-2-yl)phenanthridine (**4g**).* Yield: 52 mg, 62%; yellow solid. Mp 122−124 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.64 (d, 1H, J = 8.2 Hz), 8.53 (d, 1H, J = 8.0 Hz), 8.43 (d, 1H, J = 8.3 Hz), 8.21 (d, 1H, J = 7.8 Hz), 7.82 (t, 1H, J = 7.6 Hz), 7.68 (m, 3H), 4.88 (m, 1H), 3.03 (m, 1H), 2.83 (d, 1H, J = 13.4 Hz), 2.46 (m, 2H), 2.15 (m, 2H), 1.88 (m, 1H), 1.69 (m, 1H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 159.6, 143.0, 132.6, 129.7, 129.7, 127.9, 126.5, 126.2, 125.3, 123.6, 123.1, 122.0, 121.2, 45.3, 32.3, 30.1, 26.5, 26.2. MS (ESI) m/z 280.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{18}H_{17}NS$, 280.1154; observed, 280.1156.

*N-Methyl-N-(phenanthridin-6-ylmethyl)acetamide (**4h**).* Yield: 36 mg, 46%; pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.64 (d, 1H, J = 8.3 Hz), 8.56 (d, 1H, J = 8.2 Hz), 8.43 (d, 1H, J = 8.2 Hz), 8.15 (d, 1H, J = 8.0 Hz), 7.85 (t, 1H, J = 7.6 Hz), 7.71 (m, 3H), 5.31 (s, 2H), 3.00 (s, 3H), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 171.7, 170.1, 156.1, 153.2, 142.7, 132.4, 130.2, 130.1, 129.9, 129.4, 128.2, 128.0, 127.2, 127.0, 126.5, 125.8, 124.1, 123.6, 121.7, 121.4, 53.4, 50.5, 34.8, 34.4, 21.4, 21.0. MS (ESI) m/z 265.1 $[M + H]^+$. HRMS (ESI): calculated for $[M + H]^+$ $C_{17}H_{16}N_2O$, 265.1335; observed, 265.1341.

Experimental Procedure for UV−Visible Titration Analysis. All absorbance measurements were carried out on a UV-2550 spectrophotometer equipped with 1.0 mL quartz cells. The concentrations of $Fe(acac)_2$ and DBU are 0.0015 and 0.003 mg/mL, respectively. The UV−vis titration results imply that DBU acts as a ligand, not a base.

*Experimental Procedure for the Kinetic Isotope Effect Study between **2c** and [d_8]-**2c**.* To a microwave reaction vial were added **1a** (0.3 mmol), **2c** (10 equiv), [d_8]-**2c** (10 equiv), $Fe(acac)_2$ (5 mol %), DBU (**L5**, 10 mol %), TBHP (anhydrous, 5 M in decane, 2 equiv), and benzene (anhydrous, 0.5 mL). Then the vial was charged with argon and was stirred at 80 °C under microwave-assisted conditions (500 W) for 1 h. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to afford the mixture of **4c** and [d_7]-**4c**.

*The Mixture of **4c** and [d_7]-**4c**.* Yield: 60 mg, 79%; yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (d, 1H, J = 8.4 Hz), 8.56 (d, 1H, J = 8.1 Hz), 8.45 (d, 1H, J = 8.3 Hz), 8.20 (d, 1H, J = 7.8 Hz), 7.84 (t, 1H, J = 8.2 Hz), 7.68 (m, 3H), 5.79 (t, 0.83H, J = 6.9 Hz), 4.22 (m, 0.84H), 4.08 (m, 0.84H), 2.73 (m, 0.81H), 2.44 (m, 0.84H), 2.18 (m, 1.68H).

Experimental Procedure for the Intermolecular Kinetic Isotope Effect Study. To a microwave reaction vial were added **1a** (0.15 mmol), [d_5]-**1a** (0.15 mmol), **2c** (20 equiv), $Fe(acac)_2$ (5 mol %), DBU (**L5**, 10 mol %), TBHP (anhydrous, 5 M in decane, 2 equiv) and benzene (anhydrous, 0.5 mL). Then the vial was charged with argon, and was stirred at 80 °C under microwave-assisted conditions (500 W) for 1 h. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to afford the mixture of **4c** and [d_4]-**4c**.

*The Mixture of **4c** and [d_4]-**4c**.* Yield: 58 mg, 78%; yellow solid. ^1H NMR ($CDCl_3$, 400 MHz) δ 8.66 (d, 0.5H, J = 8.3 Hz), 8.56 (d, 1H, J = 8.1 Hz), 8.46 (d, 0.5H, J = 8.3 Hz), 8.23 (d, 1H, J = 7.8 Hz), 7.85 (t,

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0.5H, J = 7.6 Hz), 7.69 (m, 2.5H), 5.80 (t, 1H, J = 7.0 Hz), 4.23 (m, 1H), 4.08 (m, 1H), 2.73 (m, 1H), 2.45 (m, 1H), 2.18 (m, 2H).

Experimental Procedure for the Intramolecular Kinetic Isotope Effect Study. To a microwave reaction vial were added [d_1]-**1a** (0.3 mmol), **2c** (20 equiv), $Fe(acac)_2$ (5 mol %), DBU (**L5**, 10 mol %), TBHP (anhydrous, 5 M in decane, 2 equiv), and benzene (anhydrous, 0.5 mL). Then the vial was charged with argon and was stirred at 80 °C under microwave-assisted conditions (500 W) for 1 h. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 20:1) to afford the mixture of **4c** and [d_1]-**4c**.

*The Mixture of **4c** and [d_1]-**4c**.* Yield: 58 mg, 78%; yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (d, 1H, J = 8.3 Hz), 8.56 (d, 1H, J = 8.2 Hz), 8.46 (d, 0.5H, J = 8.2 Hz), 8.25 (d, 1H, J = 7.9 Hz), 7.85 (t, 1H, J = 7.2 Hz), 7.70 (m, 3H), 5.80 (t, 1H, J = 6.9 Hz), 4.24 (m, 1H), 4.08 (m, 1H), 2.71 (m, 1H), 2.45 (m, 1H), 2.17 (m, 2H).

Experimental Procedure for the Radical Inhibition Study. To a microwave reaction vial were added **1a** (0.3 mmol), **2a** (20 equiv), $Fe(acac)_2$ (5 mol %), DBU (**L5**, 10 mol %), TBHP (anhydrous, 5 M in decane, 2 equiv), TEMPO (2 equiv), and benzene (anhydrous, 0.5 mL). Then the vial was charged with argon, and was stirred at 80 °C under microwave-assisted conditions (500 W) for 1 h. After the reaction was finished, the reaction mixture was washed with brine. The aqueous phase was re-extracted with ethyl acetate. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuum, and the resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 50:1 to 20:1) to afford **5** in 86% yield and **3a** in 7% yield.

*1-(1-Ethoxyethoxy)-2,2,6,6-tetramethylpiperidine (**5**).* Yield: 118 mg, 86%; colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.86 (q, 1H, J = 5.5 Hz), 3.75 (m, 1H), 3.55 (m, 1H), 1.45 (m, 6H), 1.28 (d, 3H, J = 5.5 Hz), 1.22 (s, 3H), 1.15 (t, 3H, J = 7.1 Hz), 1.08 (m, 9H). ^{13}C NMR ($CDCl_3$, 600 MHz) δ 104.3, 62.2, 59.8, 58.5, 39.8, 39.4, 33.1, 33.0, 19.9, 19.3, 18.6, 16.6, 14.6. MS (ESI) m/z 230.2 $[M + H]^+$. HRMS (ESI): calculated for $[M + Na]^+$ $C_{13}H_{27}NO_2$, 252.1934; observed, 252.1936.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01589.

Kinetic isotope effect studies, radical inhibition studies, and ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*Tel: +86 152 2183 3166; fax: +86 021 5198 0201; e-mail: limingshao@fudan.edu.cn.

Author Contributions

⊥Y.X. and Y.C. contributed equally.

Notes

The authors declare no competing financial interest.

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