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A Free Radical Cascade Cyclization of Isocyanides with Simple Alkanes and Alcohols

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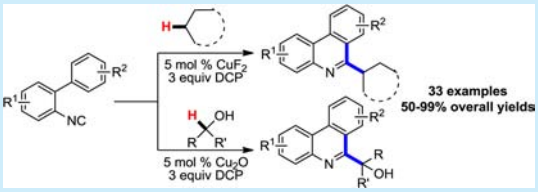
Supporting Information

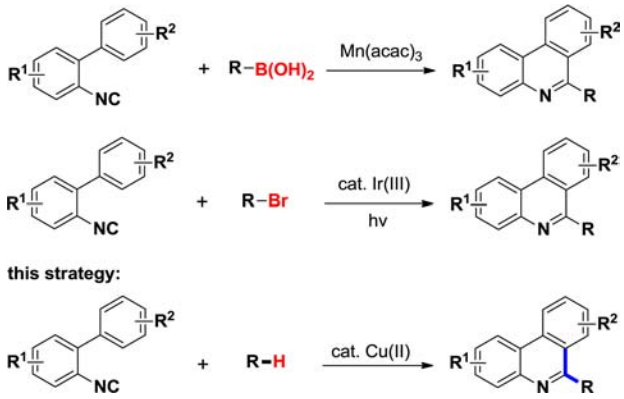
ABSTRACT: A copper-catalyzed free-radical cascade cyclization of isocyanides with simple alkanes and alcohols was developed, which allowed convenient access to various alkyl-substituted phenanthridines.



The strategy for C−C bond formation through C−H bond functionalization has drawn much attention in recent years.[1] Among them the free-radical-promoted (sp^3) C−H bond activation forming C−C bonds represents one of the most efficient methods.[2,3] In recent decades, Li and co-workers have explored a series of efficient methods for $C(sp^3)$−$C(sp^3)$ bond formation using simple alkanes through the cross-dehydrogenative-coupling (CDC) reactions.[4] Recently, a valuable $PhI(OCOCF_3)/NaN_3$-promoted oxidative cross-coupling reaction of heteroarenes with simple alkanes has been developed by Antonchick and Burgmann.[5] In addition, several protocols for $C(sp^3)$−$C(sp^2)$ bond construction with innate sp^3 C−H bonds via free-radical addition−elimination processes have been developed by us[6] and others.[7] Very recently, we have reported a free-radical addition/cyclization of *N*-arylacrylamides with simple alkanes, which allowed highly efficient access to alkylated oxindoles.[8] Although considerable advances in this field have been made, more efficient and versatile strategies for C−C bond formation by direct selective functionalization of unactived C−H bond would be highly desirable.

The skeleton of phenanthridines is widely found in pharmaceutical and bioactive compounds,[9] which draw much attention from synthetic chemists.[10] In 2012, Chatani and co-workers reported a Mn(III)-promoted oxidative cyclization of isocyanides with organoboron reagents, which provided an efficient strategy for preparation of aryl- and alkyl-substituted phenanthridines.[11] Very recently, a valuable approach to 6-alkylated phenanthridines using isocyanides and electron-deficient bromides by means of photoredox catalysis has been developed by Yu and co-workers.[12] Of particular interest in the C−C bond formation via direct selective C−H bond activation,[13] we began to reason that a free-radical-initiated cascade reaction[14] of isonitriles with simple alkanes would concisely synthesize various 6-alkylated phenanthridines using the strategy of C−H activation/C−C bond formation (Scheme 1) and the problems of regioselectivity would be solved by this strategy. To the best of our knowledge, the systhesis of 6-alkyl phenanthridines by using isonitriles with simple alkanes has never been reported. Herein, we report a Cu-catalyzed free radical cascade cyclization of isocyanides with alkanes and alcohols, which allows for convenient access to a series of 6-alkylated phenanthridine and its derivatives by selective functionalization of unactivated (sp^2)C−H and (sp^3)C−H bonds.

Scheme 1. Strategies for Preparation of Alkyl-Substituted Phenanthridines



To test the hypothesis, the reaction of 2-isocyano-5-methyl-1,1′-biphenyl (**1a**) with cyclohexane was carried out. It can be seen from Table 1 that the radical initiator is important to the reaction. Initiated by dicumyl peroxide (DCP), the desired product 6-cyclohexyl-2-methylphenanthridine (**2a**) was obtained in 53% yield without any catalyst (entry 1). It was found that the CuF_2 was better than other salts including CuBr, CuI, Cu_2O, CuO, $CuCl_2$, and copper powder (entries 2−8). Other radical initiators such as *tert*-butyl hydroperoxide (TBHP), di-*tert*-butyl peroxide (DTBP), and BPO proved to be less efficient than DCP (entries 9−11). The addition of 2 and 10 mL of cyclohexane as the solvent led to the isolation of the product **2a** in 58% and 41% yields, respectively (entries 12 and 13). Variation of the amount of the radical initiator and catalyst

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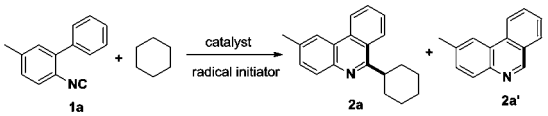
Table 1. Modification of the Typical Reaction Conditions[a]



entry	catalyst (mol %)	radical initiator (equiv)	solvent (mL)	yield (%)[b]
1	–	DCP (3)	5	53
2	CuBr (5)	DCP (3)	5	58
3	CuI (5)	DCP (3)	5	56
4	Cu (5)	DCP (3)	5	35
5	Cu_2O (5)	DCP (3)	5	55
6	CuO (5)	DCP (3)	5	60
7	$CuCl_2$ (5)	DCP (3)	5	57
8	**CuF_2 (5)**	**DCP (3)**	**5**	**68 (30)**
9	CuF_2 (5)	TBHP[c]	5	35
10	CuF_2 (5)	DTBP	5	25
11	CuF_2 (5)	BPO	5	13
12	CuF_2 (5)	DCP (3)	2	58
13	CuF_2 (5)	DCP (3)	10	41
14	CuF_2 (5)	DCP (2)	5	63
15	CuF_2 (5)	DCP (1)	5	58
16	CuF_2 (2)	DCP (3)	5	55
17	CuF_2 (10)	DCP (3)	5	65
18[d]	CuF_2 (5)	DCP (3)	5	60
19[e]	CuF_2 (5)	DCP (3)	5	–

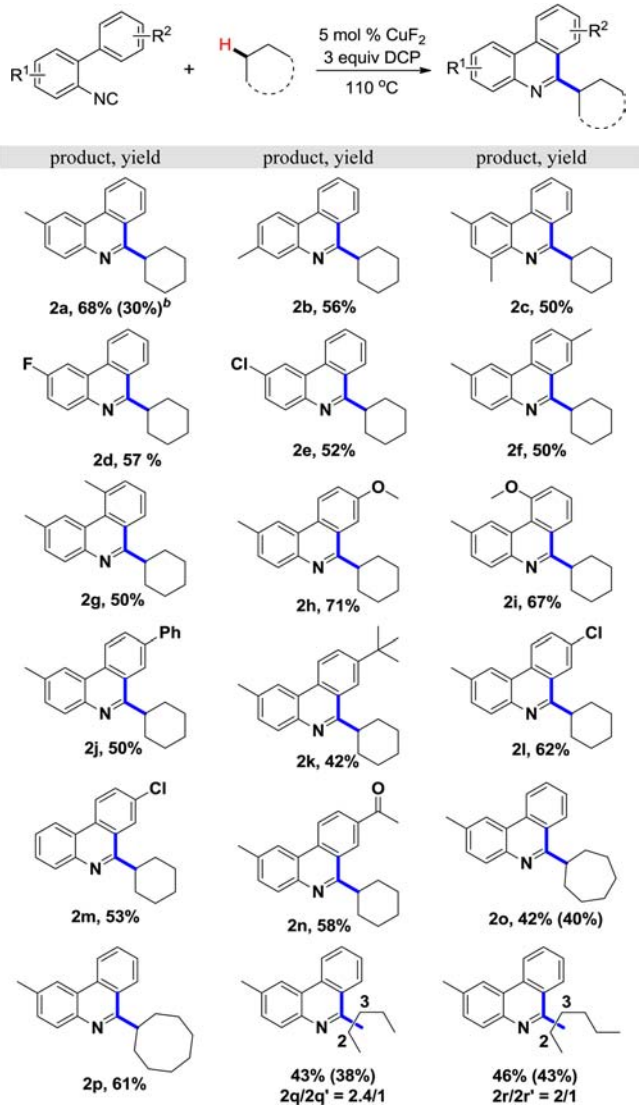
[a]Reaction conditions: isocyanide (1 equiv, 0.25 mmol), radical initiator (3 equiv, 0.75 mmol), cyclohexane as solvent, 110 °C (measured temperature of the oil bath), 7 h, unless otherwise noted. [b]Isolated yields. [c]TBHP (in decane). [d]120 °C. [e]80 °C.

resulted in a slightly lower yield of the product (entries 14−17). The yield of **2a** decreased with rising temperature (entry 18). However, no product was observed when the reaction was conducted at 80 °C (entry 19). Finally, the desired product **2a** along with a byproduct 2-methylphenanthridine (**2a′**) were isolated in 68% and 30% yields, respectively, under the typical reaction conditions: 1 equiv of isocyanide, 5 mol % CuF_2, 3 equiv of DCP, 5 mL of alkanes, 110 °C.

With the optimized conditions in hand, we next studied the scope of the reaction of isocyanides with alkanes (Table 2). It can be seen from Table 2 that the desired 6-alkylated phenanthridines are isolated in moderate to good yields through the radical cascade cyclization of various 2-isocyano-1,1′-biphenyls and derivatives with simple alkanes. Gratifyingly, the isocyanides bearing either electron-donating or -withdrawing groups in the biphenyl core all resulted in nearly quantitative overall yields of the 6-cyclohexyl substituted phenanthridines **2** and the 6-hydrogen substituted phenanthridines (**2a**−**2n**). Other cycloalkanes such as cycloheptane and cyclooctane also acted as effective substrates in this system (**2o** and **2p**). In the case of acyclic alkanes, high overall yields of the 6-alkyl-phenanthridines as well as the **2a′** were obtained (**2q** and **2r**). No alkylation occurred at the C1 position of the acyclic alkanes although the deviations of the bond dissociation energies (BDE) do not exceed 1.0 kcal mol^{-1}.[15]

As a continuation of our studies on the free-radical initiated α-hydroxy-sp^3 C−H bond activation of alcohols,[6,13a] we next turned our attention to the 6-alkylation of isocyanides with simple alcohols by using this strategy. As illustrated in Table 3, free-radical cascade cyclization of various 2-isocyano-1,1′-biphenyls and derivatives with ethanol and isopropanol gave

Table 2. Copper-Catalyzed Radical Cascade Reaction of Isocyanides with Simple Alkanes[a]



[a]Reaction conditions: isocyanide (0.25 mmol), DCP (0.75 mmol), CuF_2 (0.0125 mmol), 5 mL of alkane as solvent, 110 °C (measured temperature of the oil bath), 7 h, sealed tube. [b]Isolated yields of the desired products and **2a′** (in parentheses).

the desired products **3** and the byproducts **3′** in good to excellent overall yields under the typical conditions (Table 3, **3a**−**3l**). Notably, although relatively low yields of the desired products were isolated, other alcohols such as 2-butanol, cyclopropanol, and cyclohexanol can also act as effective substrates in this system (**3m**−**3o**). The conservation of the hydroxyl group allows versatile synthesis of complex products.

We then studied the possible mechanism for this reaction. When TEMPO was added into the system, the reaction was completely inhibited and no desired product was observed. Additionally, we also studied the initial intermolecular competing kinetic isotope effect (KIE) of this reaction. It was found that the rate-determining step would be the sp^3 C−H bond cleavage since a significant initial KIE (20% conversion) was observed with k_H/k_D = 6.7 (Scheme 2).

A plausible mechanism for this reaction is proposed (Scheme 3). The cumyloxyl radical would be formed through homolysis of the O−O bond in DCP with the assistance of Cu^n. Hydrogen

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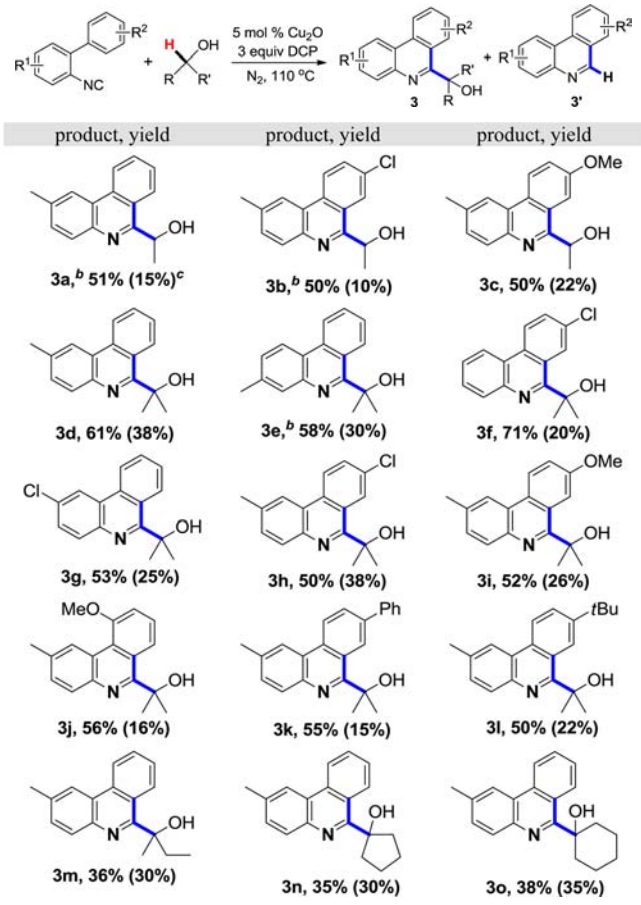
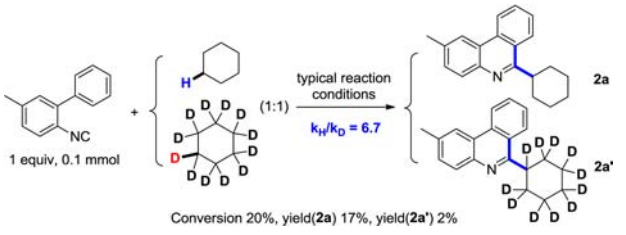
Table 3. Copper-Catalyzed Radical Cascade Reaction of Isocyanides with Simple Alcohols[a]

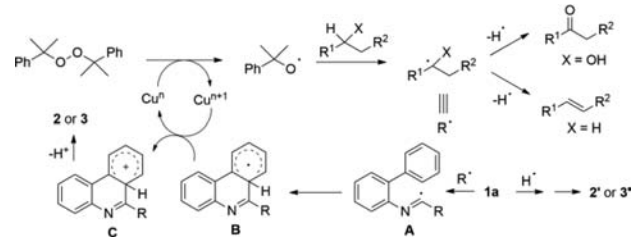


[a]Reaction conditions: isocyanide (0.20 mmol), DCP (0.6 mmol), Cu_2O (0.01 mmol), 4.95 mL of alcohol, and 0.05 mL of H_2O as the mixture solvent, unless otherwise noted, N_2, 110 °C (measured temperature of the oil bath), 11 h, sealed tube. [b]5 mL of alcohol as solvent. [c]Isolated yields of the desired products and **3′** (in parentheses).

Scheme 2. KIE Studies



Scheme 3. Possible Mechanism



abstraction of an alkane or α-hydroxy-C−H of the alcohol by the cumyloxyl radical forms an alkyl radical and acetophenone.[8,16] Further hydrogen-atom transfer from the alkyl radical and α-hydroxy-carbon-centered radical would generate the corresponding alkene and ketone, respectively. Addition of the alkyl radical to the biphenyl isocyanide **1** leads to the imidoyl radical intermediate **A**. Subsequently cyclization of **A** to the benzene unit would form radical **B**, which is oxidized by the Cu^{n+1} species to afford the phenanthridine and regenerates the Cu^n species. Alternatively, a carbocation would be formed via oxidation of the radical **A** by Cu^{n+1} species, followed by intramolecular electrophilic aromatic substitution (S_EAr) generating the product, which is also another possible pathway. The byproducts **2a′** and **3′** would be formed through a free radical addition/cyclization cascade of the H-atom with the isocyanides.

In summary, an efficient Cu-catalyzed free-radical addition/cyclization of isocyanides with simple alkanes and alcohols has been developed. It provides a convenient method for preparation of 6-alkyl-substituted phenanthridine and its derivatives via selective functionalization of unactivated (sp^3)C−H and (sp^2)C−H bonds. Further studies on C−C bond formation through selective sp^3 C−H bond functionalization of simple alkanes and alcohols are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected recent reviews on sp^3 C−H activation, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Bergman, R. G. *Nature* **2007**, *446*, 391. (c) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780. (d) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (e) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (f) Zhang, S.-Y.; Zhang, F.-M.; Tu, Y.-Q. *Chem. Soc. Rev.* **2011**, *40*, 1937. (g) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (h) Roizen, J. L.; Harvey, M. E.; Du Bois, J. *Acc. Chem. Res.* **2012**, *45*, 911. (i) White, M. C. *Science* **2012**, *335*, 807. (j) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726.

(2) For selected recent examples of C−C bond formation via sp^3 C−H bond activation: (a) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075. (b) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (c) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Zhang, F.-M.; Shi, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 8761. (d) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (e) Yoo, E. J.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 17378. (f) Qian, B.; Guo, S.; Shao, J.; Zhu, Q.; Yang, L.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2010**, *132*, 3650. (g) Qian, B.; Xie, P.; Xie, Y.; Huang, H. *Org. Lett.* **2011**, *13*, 2580. (h) Liu, W.; Liu, J.; Ogawa, D.; Nishihara, Y.; Guo, X.; Li, Z. *Org. Lett.* **2011**, *13*, 6272. (i) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am.*

Chem. Soc. **2011**, *133*, 6541. (j) Xie, P.; Xie, Y. J.; Qian, B.; Zhou, H.; Xia, C. G.; Huang, H. M. *J. Am. Chem. Soc.* **2012**, *134*, 9902. (k) Xie, P.; Xia, C.; Huang, H. *Org. Lett.* **2013**, *15*, 3370. (l) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (m) Zhu, Y.; Wei, Y. *Chem. Sci.* **2014**, *5*, 2379. (n) Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Org. Lett.* **2014**, *16*, 2530.

(3) For selected recent examples of sp^3 C−X (X = O, N) bond formation via sp^3C-H bond activation, see: (a) Kamata, K.; Yonehara, K.; Nakagawa, Y.; Uehara, K.; Mizuno, N. *Nat. Chem.* **2010**, *2*, 478. (b) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566. (c) Harvey, M. E.; Musaev, D. G.; Du Bois, J. *J. Am. Chem. Soc.* **2011**, *133*, 17207. (d) Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036. (e) Ni, Z. K.; Zhang, Q.; Xiong, T.; Zheng, Y. Y.; Li, Y.; Zhang, H. W.; Zhang, J. P.; Liu, Q. *Angew. Chem., Int. Ed.* **2012**, *51*, 1244. (f) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (g) Michaudel, Q.; Thevenet, D.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 2547. (h) Zhang, S. Y.; He, G.; Zhao, Y. S.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (i) Simmons, E. M.; Hartwig, J. F. *Nature* **2012**, *483*, 70. (j) McNeill, E.; Du Bois, J. *Chem. Sci.* **2012**, *3*, 1810. (k) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 591. (l) Gormisky, P. E.; White, M. C. *J. Am. Chem. Soc.* **2013**, *135*, 14052.

(4) For selected recent reviews on CDC reactions, see: (a) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. For C−C bond formation via activation of the sp^3 C−H bond of simple alkanes, see: (a) Zhang, Y.; Li, C.-J. *Eur. J. Org. Chem.* **2007**, 4654. (b) Deng, G.; Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278. (c) Deng, G.; Ueda, K.; Yanagisawa, S.; Itami, K.; Li, C.-J. *Chem.—Eur. J.* **2009**, *15*, 333. (d) Deng, G.; Li, C.-J. *Org. Lett.* **2009**, *11*, 1171. (e) Guo, X. Y.; Li, C. J. *Org. Lett.* **2011**, *13*, 4977.

(5) (a) Antonchick, A. P.; Burgmann, L. *Angew. Chem., Int. Ed.* **2013**, *52*, 3267. (b) Narayan, R.; Antonchick, A. P. *Chem.—Eur. J.* **2014**, *20*, 4568.

(6) Cui, Z. L.; Shang, X. J.; Shao, X. F.; Liu, Z. Q. *Chem. Sci.* **2012**, *3*, 2853.

(7) (a) Gong, J.; Fuchs, P. L. *J. Am. Soc. Chem.* **1996**, *118*, 4486. (b) Xiang, J.; Jiang, W.; Gong, J.; Fuchs, P. L. *J. Am. Soc. Chem.* **1997**, *119*, 4123. (c) Jang, Y.-J.; Shih, Y.-K.; Liu, J.-Y.; Kuo, W.-Y; Yao, C.-F. *Chem.—Eur. J.* **2003**, *9*, 2123.

(8) Li, Z.; Zhang, Y.; Zhang, L.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 382.

(9) (a) Theobald, R. S.; Schofield, K. *Chem. Rev.* **1950**, *46*, 170. (b) Simeon, S.; Rios, J. L.; Villar, A. *Pharmazie* **1989**, *44*, 593. (c) Brewster, W. K.; Nichols, D. E.; Riggs, R. M.; Mottola, D. M.; Lovenberg, T. W.; Lewis, M. H.; Mailman, R. B. *J. Med. Chem.* **1990**, *33*, 1756. (d) Nakanishi, T.; Suzuki, M.; Saimoto, A.; Kabasawa, T. *J. Nat. Prod.* **1999**, *62*, 864. (e) Sripada, L.; Teske, J. A.; Deiters, A. *Org. Biomol. Chem.* **2008**, *6*, 263.

(10) For selected recent examples of preparation of phenanthridine and its derivatives, see: (a) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257. (b) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792. (c) Leifert, D.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2013**, *15*, 6286. (d) Wang, Q.; Dong, X.; Xiao, T.; Zhou, L. *Org. Lett.* **2013**, *15*, 4846. (e) Cheng, Y.; Jiang, H.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 5520. (f) Zhang, B.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2014**, *16*, 250. (g) Gu, L.; Jin, C.; Liu, J.; Ding, H.; Fan, B. *Chem. Commun.* **2014**, *50*, 4643. (h) Zhu, T.-H.; Wang, S.-Y.; Tao, Y.-Q.; Wei, T.-Q.; Ji, S.-J. *Org. Lett.* **2014**, *16*, 1260. (i) Wang, L.; Sha, W.; Dai, Q.; Feng, X.; Wu, W.; Peng, H.; Chen, B.; Cheng, J. *Org. Lett.* **2014**, *16*, 2088. (j) Cao, J.-J.; Zhu, T.-H.; Wang, S.-Y.; Gu, Z.-Y.; Wang, X.; Ji, S.-J. *Chem. Commun.* **2014**, *50*, 6439. (k) Xiao, T.; Li, L.; Lin, G.; Wang, Q.; Zhang, P.; Mao, Z.-W.; Zhou, L. *Green Chem.* **2014**, *16*, 2418. (l) Liu, J.; Fan, C.; Yin, H.; Qin, C.; Zhang, G.; Zhang, X.; Yi, H.; Lei, A. *Chem. Commun.* **2014**, *50*, 2145. (m) Xia, Z.; Huang, J.; He, Y.; Zhao, J.; Lei, J.; Zhu, Q. *Org. Lett.* **2014**, *16*, 2546.

(11) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11363.

(12) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 13289.

(13) For our recent contributions on C−C bond formation/C−H bond activation, see: (a) Liu, Z.-Q.; Sun, L.; Wang, J.; Han, J.; Zhao, Y.; Zhou, B. *Org. Lett.* **2009**, *11*, 1437. (b) Liu, Z.-Q.; Zhang, Y.; Zhao, L.; Li, Z.; Wang, J.; Li, H.; Wu, L.-M. *Org. Lett.* **2011**, *13*, 2208. (c) Li, Z.; Zhang, Y.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 74. (d) Zhang, Y.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 226. (e) Zhang, Y.; Cui, Z.; Li, Z.; Liu, Z.-Q. *Org. Lett.* **2012**, *14*, 1838. (f) Shang, X.; Liu, Z.-Q. *Chem. Soc. Rev.* **2013**, *42*, 3253.

(14) For an excellent review on the free-radical cascade process, see: McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224.

(15) Luo, Y.-R. *Handbook of Bond Dissociation Energies in Organic Compounds*; CRC Press: Boca Raton, 2002.

(16) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900.