OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

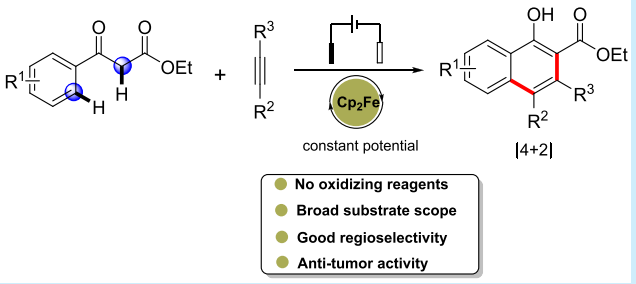
Electrochemical Synthesis of 1-Naphthols by Intermolecular Annulation of Alkynes with 1,3-Dicarbonyl Compounds

Mu-Xue He, Zu-Yu Mo, Zi-Qiang Wang, Shi-Yan Cheng, Ren-Ren Xie, Hai-Tao Tang,* and Ying-Ming Pan*

State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University, Guilin 541004, People's Republic of China

Supporting Information

ABSTRACT: C-centered radical cyclization under electrochemical conditions is a feasible strategy for constructing cyclic structures. Reported herein is the electrochemical synthesis of highly functionalized 1-naphthols using alkynes and 1,3-dicarbonyl compounds by (4 + 2) annulation of C-centered radical. Electrolysis was conducted with Cp_2Fe as redox catalyst, thereby eliminating the use of oxidants and transition-metal catalysts. The synthesized 1-naphthol compounds showed good antitumor activity in vitro, and further studies indicated that compound **3bl** induced tumor cell apoptosis.



The development of new, efficient, and environmentally friendly synthetic methods to construct polysubstituted naphthalene compounds have been a topic of great research interest because these backbone motifs are ubiquitous in natural products and bioactive compounds.[1] Highly substituted 1-naphthols have a broad spectrum of biological activities, such as V-ATPase inhibition[2] and anticancer,[3] anti-inflammatory,[4] antiviral,[5] antimalarial,[6] antiplatelet,[7] and antibacterial[8] properties (Figure 1). Although many methods to synthesize 1-

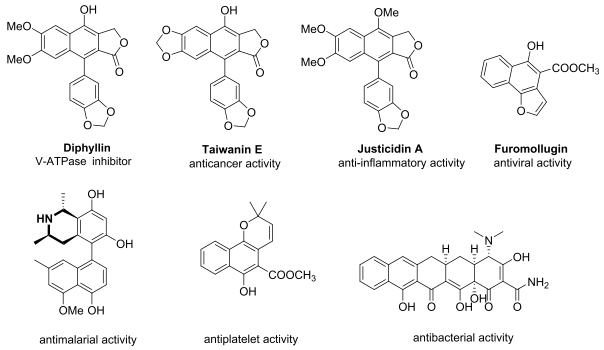
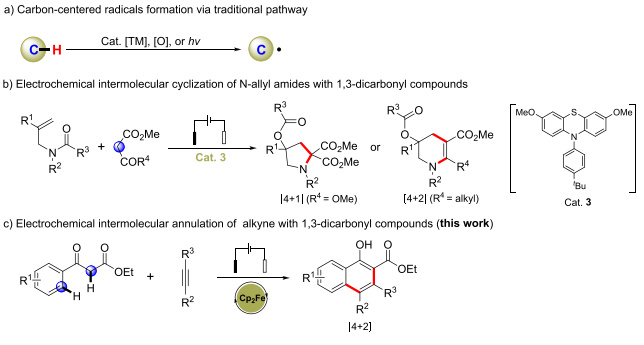


Figure 1. Biological activity of 1-naphthol derivatives.

naphthol compounds have been reported, the strategies often have several defects, including complex synthesis steps,[9] restricted reaction substrates,[10] and use of transition-metal catalysts such as Se,[11] Pd,[12] and Rh.[13] Catalytic activation of C−H bonds to form carbon radicals and synthesize 1-naphthol compounds was developed by Yu,[14] Narender,[15] and Wang.[16] In these reports, however, the use of expensive noble metals, stoichiometric oxidants, and transition-metal catalysts was indicated as a common shortcoming. Therefore, developing an inexpensive and environmentally friendly synthesis method is an important endeavor.

Carbon-centered radicals, which have numerous properties and high reactivity, are attractive reaction intermediates in organic synthesis. The efficient construction of C−C bond cyclization reactions via the C-radical pathway has been studied.[17] Electron transfer produces a C-centered radical from transition-metal catalysts, such as Pd(II) and Co(III). Addition of stoichiometric oxidants [Ag(I), Cu(II), and X_2] or photocatalysts to the reaction can play a similar role (Scheme 1a).[14−16,18] C-radical intermediates are more electrophilic than neutral substrates. Subsequent nucleophilic attack and further oxidation of these C-radicals lead to bioactive compounds. Organic electrosynthesis is a convenient and environmentally friendly synthetic tool that can employ electrons as reagents

Scheme 1. Different Methods To Generate and Cyclize C-Radicals



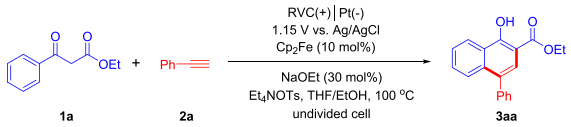
Received: December 18, 2019

DOI: 10.1021/acs.orglett.9b04549
Org. Lett. XXXX, XXX, XXX−XXX

and generate radical intermediates.[19] Xu's group recently reported the selective and efficient electrochemical intermolecular C-radical reactions of 1,3-dicarbonyl compounds via a phenothiazine-based redox catalyst using N-allyl amides as four-atom donors reacted with dimethylmalonate to form pyrrolidines via (4 + 1) annulation or with ketoesters to give tetrahydropyridine derivatives via (4 + 2) annulation (Scheme 1b).[20] Intermolecular cyclization of 1,3-dicarbonyl compounds under electrochemical conditions is rarely reported. Inspired by previous works on C-radical reactions, we report herein the electrochemical synthesis of highly functionalized 1-naphthols using alkynes and 1,3-dicarbonyl compounds by (4 + 2) annulation (Scheme 1c). The proposed reaction uses inexpensive Cp_2Fe as a redox catalyst to produce H_2 as the only theoretical byproduct.

Cyclization of ethyl benzoylacetate **1a** and phenylacetylene **2a** was used as a model reaction to optimize the electrolysis conditions (Table 1 and Table S1). The results of electrolysis

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

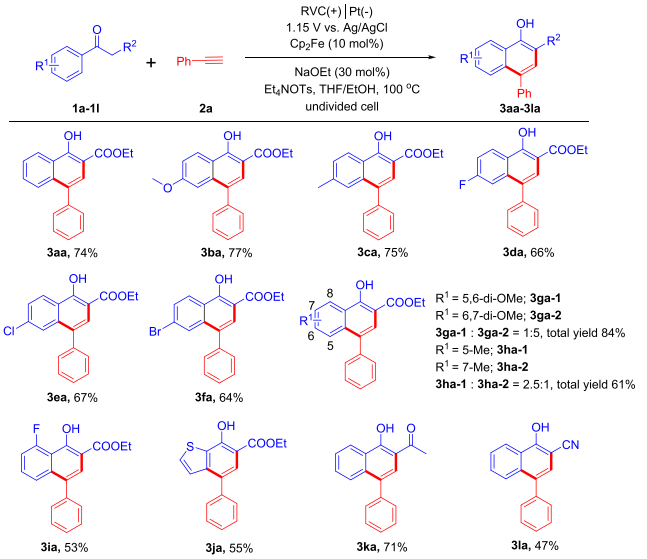
entry	variation from standard conditions	yield[b] (%)
1	none	74
2	no electricity	NR
3	no Cp_2Fe	22
4	no NaOEt	36
5	reaction at rt	trace
6	reaction at 80 °C	40
7[c]	constant current: 10 mA	48
8	NH_4I (30 mol %) as base	trace
9	Na_2CO_3 (30 mol %) as base	trace
10	NaOEt (50 mol %) as base	32
11	EtOH as solvent	27
12	CH_3CN as solvent	trace
13	constant potential: 1.2 V vs Ag/AgCl	61
14	constant potential: 1.0 V vs Ag/AgCl	55

[a]Reaction conditions: reticulated vitreous carbon (RVC) anode (100 PPI, 1 cm × 1 cm × 1.2 cm), Pt plate cathode (1 cm × 1 cm), undivided cell, constant potential = 1.15 V vs Ag/AgCl, **1a** (0.5 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv), catalyst (10 mol %), base (30 mol %), electrolyte (2.0 equiv), THF/EtOH = 1:1 (10 mL), 100 °C, 2 h (5.3−1.2 F mol^{-1}). [b]Isolated yields. [c]1.5 F mol^{-1}. NR = no reaction.

were optimal when the reaction was conducted in an undivided cell in the presence of Cp_2Fe as a catalyst in THF/EtOH mixed solvent at a constant potential of 1.15 V vs Ag/AgCl with NaOEt (30 mol %) as a base (entry 1). Under these conditions, the current and charge consumption decreased from 35 to 8 mA (Figure S2) and from 5.3 to 1.2 F mol^{-1}, respectively. A series of control experiments validated the necessity of each reaction condition. The desired product **3aa** was not obtained without electricity (entry 2), whereas reduced yield was obtained in the absence of Cp_2Fe (entry 3) and NaOEt (entry 4). Reaction at rt (entry 5) or 80 °C (entry 6) led to a dramatic decrease in yield. When **1a** and **2a** were reacted at a constant current of 10 mA (1.5 F mol^{-1}), the yield decreased (entry 7). Other bases, such as NH_4I (entry 8) and Na_2CO_3 (entry 9), were less effective than NaOEt. The reaction time was shortened to 1 h after addition of 50 mol % NaOEt, but more byproducts were formed and the desired yield decreased (entry 10). The change in solvent had a negative effect on product yield (entries 11−12). We also tested the yield variation under different constant potential conditions, and results showed that increases (entry 13) or decreases (entry 14) in potential slightly reduced yield.

Under optimal conditions (Table 1, entry 1), acetyl benzene and alkyne substrates were expanded and explored, respectively. The scope of the electrochemical synthesis of 1-naphthols was first explored by changing the substituents of acetyl benzene substrate (Scheme 2). In the absence of

Scheme 2. Substrate Scope of Acetyl Benzene[a]



[a]Reaction conditions: reticulated vitreous carbon (RVC) anode (100 PPI, 1 cm × 1 cm × 1.2 cm), Pt plate cathode (1 cm × 1 cm), undivided cell, constant potential = 1.15 V vs Ag/AgCl, **1a** (0.5 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv), Cp_2Fe (10 mol %), NaOEt (30 mol %), Et_4NOTs (2.0 equiv), THF/EtOH = 1:1 (10 mL), 100 °C, 2 h. Isolated yields.

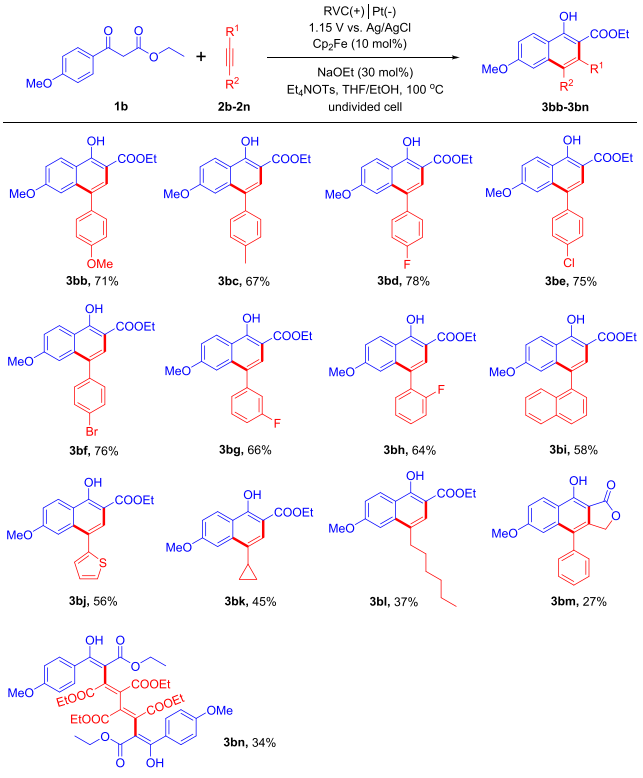
substitution, ethyl benzoylacetate **1a** reacted with phenylacetylene **2a** gave a yield of 74%. Electron-donating (**3ba**−**3ca**) or electron-withdrawing (**3da**−**3fa**) substituents at the para position of the benzene ring were studied, and all groups provided good yields. However, in general, electron-donating groups had higher yields than electron-withdrawing groups due to the stronger electron-donating ability of the former. Monosubstitution of the phenyl ring at the ortho (**3ia**) position produced the desired product in moderate yields. Two easily separated isomers could be obtained from the methoxy groups of disubstituted phenyl rings at a **3ga-1**/**3ga-2** ratio of 1:5. Moreover, compounds with low steric resistance (**3ga-2**) produced higher yields, thereby showing that the reaction has good regioselectivity. The meta-substituted compound **3ha** (2.5:1) could also give two isomers. The target product of cyclization (**3ja**) was obtained by connecting other heterocyclic rings to the benzene ring. We applied the proposed method to the cyclization of benzoylacetone and benzoylacetonitrile with phenylacetylene and obtained products with yields of 71% (**3ka**) and 47% (**3la**), respectively.

In the above work, the *p*-methoxy-substituted ethyl benzoylacetate reacted with an alkyne gave the best yield.

DOI: 10.1021/acs.orglett.9b04549
Org. Lett. XXXX, XXX, XXX−XXX

Therefore, this compound was reacted with various substituted alkynes as a substrate to obtain highly substituted 1-naphthol compounds (Scheme 3). First, para-, meta-, and ortho-

Scheme 3. Substrate Scope of Alkynes[a]

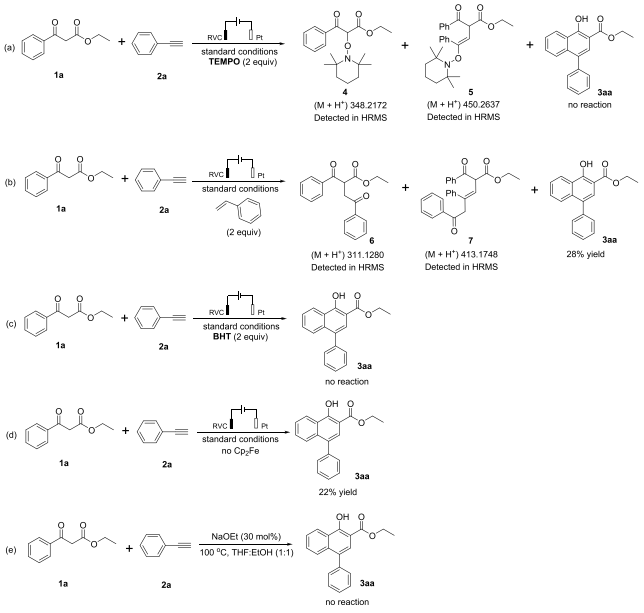


[a]Reaction conditions: reticulated vitreous carbon (RVC) anode (100 PPI, 1 cm × 1 cm × 1.2 cm), Pt plate cathode (1 cm × 1 cm), undivided cell, constant potential = 1.15 V vs Ag/AgCl, **1a** (0.5 mmol, 1.0 equiv), **2a** (0.75 mmol, 1.5 equiv), Cp_2Fe (10 mol %), NaOEt (30 mol %), Et_4NOTs (2.0 equiv), THF/EtOH = 1:1 (10 mL), 100 °C, 2 h. Isolated yields.

substitutions of phenylacetylene with electron-withdrawing and electron-donating groups (**3bb**−**3bh**) resulted in a series of target products with good yield (64−78%). We found that electron-withdrawing groups were generally more productive than electron-donating groups. 1-Acetylene naphthalene could be used as a suitable substrate to react with 1,3-dicarbonyl compounds to obtain moderate yields (**3bi**, 58%). Heterocyclic substituted alkynes, such as 2-acetylene thiophene, could also be reacted to generate the desired product (**3bj**). However, chain and cyclic alkane-substituted alkynes gave low yields (**3bk**, **3bl**). Phenylpropionic acid and 1, 3-dicarbonyl compound generated lactone compound (**3bm**) under electrochemical conditions, and the yield of compound **3bm** dropped sharply to 27%.[21] Moreover, symmetrical ester-substituted alkynes did not produce naphthol compound, but an uncyclized dimer was synthesized (**3bn**).[21]

Having established the scope of the method, control experiments were performed to study the reaction mechanism (Scheme 4). Adding 2 equiv of TEMPO or BHT to the optimal reaction system resulted in nondetection of 1-naphthol compound **3aa** (Scheme 4, eqs a and c), but products **4** and **5** were detected under TEMPO by using HRMS (Scheme 4, eq a). Addition of 2 equiv of styrene allowed the synthesis of small amounts of **3aa** as well as products **6** and **7** (Scheme 4, eq b).

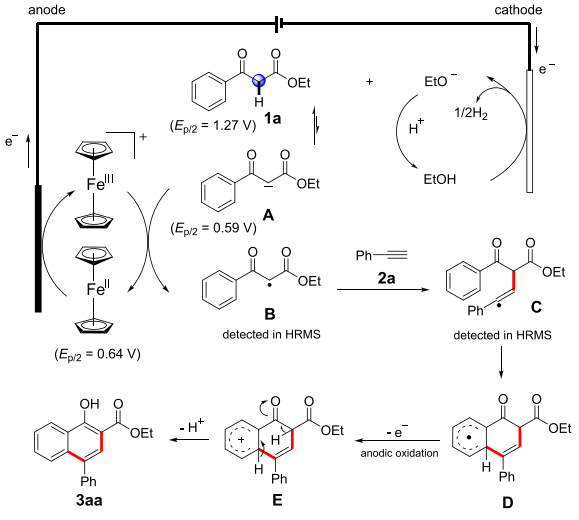
Scheme 4. Control Experiments



The above experimental results indicate that radical intermediates are involved in the electrochemical reaction process. When Cp_2Fe was removed from the reaction, the desired product **3aa** could be obtained but with reduced yield (Scheme 4, eq d). In other words, direct electrolysis results in lower yields than those produced by indirect electrolysis. Thus, under the conditions of no catalyst, current and electrolyte, **3aa** was not detected in the reaction (Scheme 4, eq e). The above reaction results indicate that 1,3-dicarbonyl compounds do not undergo intermolecular cyclization with alkynes as a carbon anion but reacts with alkynes after oxidation to form a carbon radical intermediate.

Based on the above experiments and cyclic voltammetry experiments (Figure S3), a possible mechanism of electrochemical intermolecular cyclization with **1a** and **2a** as substrates is proposed (Scheme 5). Under electrochemical conditions, ethanol undergoes a reduction reaction at the cathode to produce an ethoxylated anion and H_2. Although the oxidation potential between Cp_2Fe and substrate **1a** shows a

Scheme 5. Proposed Mechanism



DOI: 10.1021/acs.orglett.9b04549
Org. Lett. XXXX, XXX, XXX−XXX

wide gap and the reagents are difficult to react ($E_{p/2}$ = 1.27 and 0.64 V vs Ag/AgCl for **1a** and Cp_2Fe, respectively), the oxidation potential of the conjugate base **A** of substrate **1a** is slightly lower than that of Cp_2Fe ($E_{p/2}$ = 0.59 V vs Ag/AgCl for **A**). Therefore, Cp_2Fe could oxidize intermediate **A** to conduct a single-electron transfer (SET). In other words, the ethoxylated anion reacts with the 1,3-dicarbonyl compound **1a** to form the carbanion intermediate **A**. Note that the ethoxylated anion in this reaction is derived from the cathodic reduction of ethanol and addition of NaOEt to the system. Meanwhile, at the anode, Cp_2Fe is oxidized to Cp_2Fe^+, which can be oxidized to intermediate **A**, generating a C-radical intermediate **B**. Radical intermediate **B** reacts with alkyne **2a** to give intermediate **C**, which then undergoes intermolecular cyclization to give intermediate **D**. According to the control experiment results, the adducts of radical intermediates **B** (or **C**) and TEMPO could be detected by HRMS, which proves that intermediates **B** and **C** are produced in the reaction process. Finally, intermediate **E** is obtained by oxidation, and 1-naphthol compound **3aa** is obtained by removal of the proton. The removed proton can combine with the ethoxylated anion to complete the reaction cycle.

As described above, 1-naphthol compounds have antiviral, antibacterial, antitumor, and other biological activities. Here, the in vitro cytotoxicities of compounds **3aa**-**3la** and **3bb**-**3bn** against four cancer cell lines, namely Hela, T-24, HepG-2, and MGC-803, and one human normal cell line, namely WI-38, were screened by using MTT assay with 5-FU as the positive control. As shown in Table S8, compound **3bl** shows a favorable antitumor activity against the T-24 cell line with an IC_{50} value of 9 ± 1 μM. Moreover, the IC_{50} value of compound **3bn** on the Hela cell line was 9 ± 2 μM, which indicates a significant inhibitory effect on tumor cells. On the basis of these experimental results, the mechanism of the antitumor activity of **3bl** on the T-24 cell line was further studied. The detailed experimental results are described in the Supporting Information.

In summary, we have developed a method to synthesis 1-naphthol compounds by intermolecular (4 + 2) cyclization under electrochemical conditions. Through our electrochemical method, 1,3-dicarbonyl compounds generate a C-centered radical and promote intermolecular cyclization. Our method uses inexpensive Cp_2Fe as a redox catalyst with the release of H_2, thereby eliminating the need for noble metal catalysts and external oxidants. In vitro cytotoxicity screening of five cell lines was performed by using MTT assay, and **3bl** and **3bn** revealed significant antitumor activity toward different tumor cell lines. Compound **3bl** inhibited the cancer cell migration and treated the cancer cell have displayed nuclear apoptotic characteristics such as nuclear fragmentation and shrunken nuclei.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04549.

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1946107 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Authors

*Email: httang@gxnu.edu.cn.
*Email: panym@mailbox.gxnu.edu.cn.

ORCID

Hai-Tao Tang: 0000-0001-7531-0458
Ying-Ming Pan: 0000-0002-3625-7647

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21861006), Guangxi Natural Science Foundation of China (2016GXNSFEA380001, 2018GXNSFBA281151), Guangxi Key R&D Program (No. AB18221005), Science and Technology Major Project of Guangxi (AA17204058-21), Guangxi science and technology base and special talents (guike AD19110027), College Students Innovation and Entrepreneurship Training Program (201910602131), and State Key Laboratory for Chemistry and Molecular Engineering of Medicinal Resources (CMEMR2019-A03) for financial support.

■ REFERENCES

(1) (a) Makar, S.; Saha, T.; Singh, S. K. *Eur. J. Med. Chem.* **2019**, *161*, 252−276. (b) Al Kobaisi, M.; Bhosale, S. V.; Latham, K.; Raynor, A. M.; Bhosale, S. V. *Chem. Rev.* **2016**, *116*, 11685−11796. (c) Suraru, S. L.; Wuerthner, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 7428−7448.

(2) Zhang, Z. T.; Ma, J. L.; Zhu, L.; Zhao, Y. *Eur. J. Med. Chem.* **2014**, *82*, 466−471.

(3) Hsu, H. H.; Kuo, W. W.; Day, C. H.; Shibu, M. A.; Li, S. Y.; Chang, S. H.; Shih, H. N.; Chen, R. J.; Viswanadha, V. P.; Kuo, Y. H.; Huang, C. Y. *Environ. Toxicol.* **2017**, *32*, 2021−2031.

(4) Youm, J.; Lee, H.; Choi, Y.; Yoon, J. *J. Cell. Mol. Med.* **2018**, *22*, 2680−2691.

(5) Ho, L. K.; Don, M. J.; Chen, H. C.; Yeh, S. F.; Chen, J. M. *J. Nat. Prod.* **1996**, *59*, 330−333.

(6) Hallock, Y. F.; Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H.; Schaeffer, M.; Gulden, K. P.; Bringmann, G.; Lee, A. Y.; Clardy, J.; Frangois, G.; Boyd, M. R. *J. Org. Chem.* **1994**, *59*, 6349−6355.

(7) Chung, M. I.; Jou, S. J.; Cheng, T. H.; Lin, C. N.; Ko, F. N.; Teng, C. M. *J. Nat. Prod.* **1994**, *57*, 313−316.

(8) Sun, C.; Hunt, D. K.; Clark, R. B.; Lofland, D.; O'Brien, W. J.; Plamondon, L.; Xiao, X. Y. *J. Med. Chem.* **2011**, *54*, 3704−3731.

(9) Yang, T. F.; Wang, K. Y.; Li, H. W.; Tseng, Y. C.; Lien, T. C. *Tetrahedron Lett.* **2012**, *53*, 585−588.

(10) (a) Giedyk, M.; Turkowska, J.; Lepak, S.; Marculewicz, M.; ó Proinsias, K.; Gryko, D. *Org. Lett.* **2017**, *19*, 2670−2673. (b) Cui, L. Q.; Dong, Z. L.; Liu, K.; Zhang, C. *Org. Lett.* **2011**, *13*, 6488−6491.

(11) Shahzad, S. A.; Vivant, C.; Wirth, T. *Org. Lett.* **2010**, *12*, 1364−1367.

(12) (a) Mao, Y. J.; Liu, Y.; Hu, Y. W.; Wang, L.; Zhang, S. L.; Wang, W. *ACS Catal.* **2018**, *8*, 3016−3020. (b) Youn, S. W.; Kim, B. S.; Jagdale, A. R. *J. Am. Chem. Soc.* **2012**, *134*, 11308−11311. (c) Peng, S.; Wang, L.; Wang, J. *Chem. - Eur. J.* **2013**, *19*, 13322−13327.

(13) Hojo, D.; Tanaka, K. *Org. Lett.* **2012**, *14*, 1492−1495.

(14) Jiang, H.; Cheng, Y. Z.; Zhang, Y.; Yu, S. Y. *Org. Lett.* **2013**, *15*, 4884−4887.

DOI: 10.1021/acs.orglett.9b04549
Org. Lett. XXXX, XXX, XXX−XXX

(15) Naresh, G.; Kant, R.; Narender, T. *Org. Lett.* **2015**, *17*, 3446−3449.
(16) Lu, T.; Jiang, Y. T.; Ma, F. P.; Tang, Z. J.; Kuang, L.; Wang, Y. X.; Wang, B. *Org. Lett.* **2017**, *19*, 6344−6347.
(17) Yi, H.; Zhang, G. T.; Wang, H. M.; Huang, Z. Y.; Wang, J.; Singh, A. K.; Lei, A. W. *Chem. Rev.* **2017**, *117*, 9016−9085.
(18) (a) Sivaguru, P.; Wang, Z.; Zanoni, G.; Bi, X. *Chem. Soc. Rev.* **2019**, *48*, 2615−2656. (b) Demarteau, J.; Debuigne, A.; Detrembleur, C. *Chem. Rev.* **2019**, *119*, 6906−6955. (c) Chu, X. Q.; Ge, D.; Shen, Z. L.; Loh, T. P. *ACS Catal.* **2018**, *8*, 258−271. (d) Nagode, S. B.; Kant, R.; Rastogi, N. *Org. Lett.* **2019**, *21*, 6249−6254. (e) Kaga, A.; Chiba, S. *ACS Catal.* **2017**, *7*, 4697−4706. (f) Ouyang, X. H.; Song, R. J.; Hu, M.; Yang, Y.; Li, J. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 3187−3191.
(19) (a) Wang, H. M.; Gao, X. L.; Lv, Z. C.; Abdelilah, T.; Lei, A. W. *Chem. Rev.* **2019**, *119*, 6769−6787. (b) Jiang, Y. Y.; Xu, K.; Zeng, C. C. *Chem. Rev.* **2018**, *118*, 4485−4540. (c) Waldvogel, S. R.; Lips, S.; Selt, M.; Riehl, B.; Kampf, C. J. *Chem. Rev.* **2018**, *118*, 6706−6765. (d) Kärkäs, M. D. *Chem. Soc. Rev.* **2018**, *47*, 5786−5865. (e) Möhle, S.; Zirbes, M.; Rodrigo, E.; Gieshoff, T.; Wiebe, A.; Waldvogel, S. R. *Angew. Chem., Int. Ed.* **2018**, *57*, 6018−6041. (f) Francke, R.; Little, R. D. *Chem. Soc. Rev.* **2014**, *43*, 2492−2521.
(20) Wu, Z. J.; Li, S. R.; Xu, H. C. *Angew. Chem., Int. Ed.* **2018**, *57*, 14070−14074.
(21) For the reaction substrates and reaction conditions of compounds **3bm** and **3bn** see Scheme S1.

DOI: 10.1021/acs.orglett.9b04549
Org. Lett. XXXX, XXX, XXX−XXX