Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

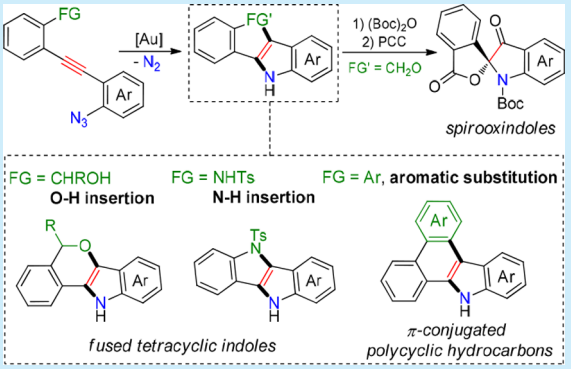
Gold-catalyzed Bicyclization of Diaryl Alkynes: Synthesis of Polycyclic Fused Indole and Spirooxindole Derivatives

Ju Cai,[†] Bing Wu,[†] Guangwei Rong,[†] Cheng Zhang,[†] Lihua Qiu,*[,†] and Xinfang Xu*[,†,‡]

[†]College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China
[‡]School of Pharmaceutical Sciences, Sun Yat-Sen University, Guangzhou 510006, China

Supporting Information

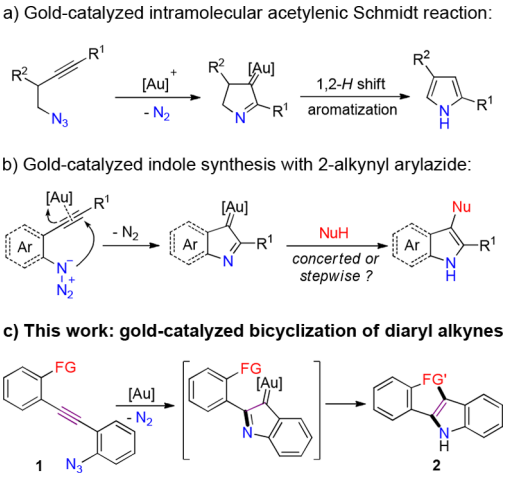
ABSTRACT: An unprecedented gold-catalyzed bicyclization reaction of diaryl alkynes has been developed for the synthesis of indoles in good to high yields. Mechanistically, this alkyne bifunctionalization transformation was terminated by a stepwise formal X−H insertion reaction to furnish the corresponding polycyclic-frameworks with structural diversity, and the key intermediate 3*H*-indole was isolated and characterized for the first time. In addition, further transformation of these generated tetracyclic-indoles with PCC as the oxidant provided straightforward access to the spirooxindoles in high yields.



The indole nucleus is a very important element of many natural and synthetic useful molecules with significant biological activities.[1] Thus, the synthesis of indole has been drawing considerable attention since its first discovery by Baeyer in 1866.[2] Classic approaches have been extensively studied and proven to be extremely useful, such as Fischer indole synthesis,[3] Bartoli indole synthesis,[4] and Leimgruber−Batcho indole synthesis.[5] Recently, catalytic aromatic ring modifications have shown broad applications for the diversity synthesis of multifunctionalized indoles.[6] However, examples for the synthesis of indoles with polycyclic fused rings[7] or spiro structures,[8] which are the key structural motifs in many pharmacologically important compounds, are quite limited with these classical approaches.[9] Thus, the development of efficient methods for the synthesis of structural appealing indole molecules is highly desired.

In recent decades, the gold-catalyzed alkyne transformations have shown broad applications in synthetic organic chemistry for the construction of carbon−carbon and carbon−heteroatom bonds.[10] Since the pioneering example reported by Teles,[11] numerous exciting research works have been disclosed based on the electrophilic activation of the π-systems via homogeneous gold catalysis.[12] It is noteworthy that Toste realized the first gold-catalyzed intramolecular Schmidt reaction of an alkyne with a tethered azide moiety, affording multisubstituted pyrroles under mild conditions (Scheme 1a).[13] This strategy was further investigated by Zhang,[14] Gagosz,[15] Ohno,[16] and Ye[17] through the interception of corresponding intermediates with various nucleophiles to build indole skeletons in the presence of a gold catalyst (Scheme 1b). Although an α-imino carbenoid intermediate was proposed and recognized as the key intermediate in these transformations, the mechanism for the subsequent carbenoid reaction step, whether concerted or stepwise, was not disclosed. In addition, anthranils,[18] indazoles,[19] isoxazoles,[20] nitrosobenzenes,[21] amines,[22] nitriles,[23] isocyanoacetates,[24] imines,[25] and others[26] have also been used as nitrogen sources for the annulation with alkynes to offer the corresponding *N*-heterocycles with structural diversity. Inspired by those advances and as the continuation of our interest in alkyne bifunctionalization for the synthesis of heterocycles,[27] we envisioned that a general approach for the construction of polycyclic frameworks could be realized via intramolecular

Scheme 1. Gold-catalyzed Alkyne Cyclization with Azide



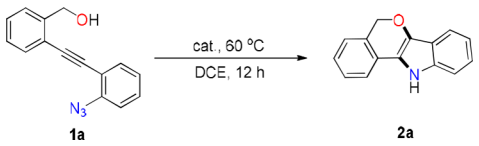
Received: March 22, 2018

DOI: 10.1021/acs.orglett.8b00939
Org. Lett. XXXX, XXX, XXX−XXX

interception of an *in situ* formed carbenoid intermediate. Herein, we present our recent results in this context; a gold-catalyzed intramolecular bicyclization of diaryl alkynes **1** in which the α-imino carbenoid intermediate was terminated with O−H/N−H insertion, and electrophilic aromatic substitution to yield to the corresponding polycyclic *N*-heterocycles with structural diversity (Scheme 1c). Moreover, a stepwise *H*-shift mechanism for the final carbenoid reaction step was proposed and verified for the first time in this work.

Initially, we employed the diaryl alkyne **1a**, easily synthesized from corresponding *ortho*-alkyl aniline and aryl halide via coupling reaction followed azidation as the model substrate (Table 1). Various transition metal catalysts were screened, such

Table 1. Optimization of the Reaction Conditions[a]



1a **2a**

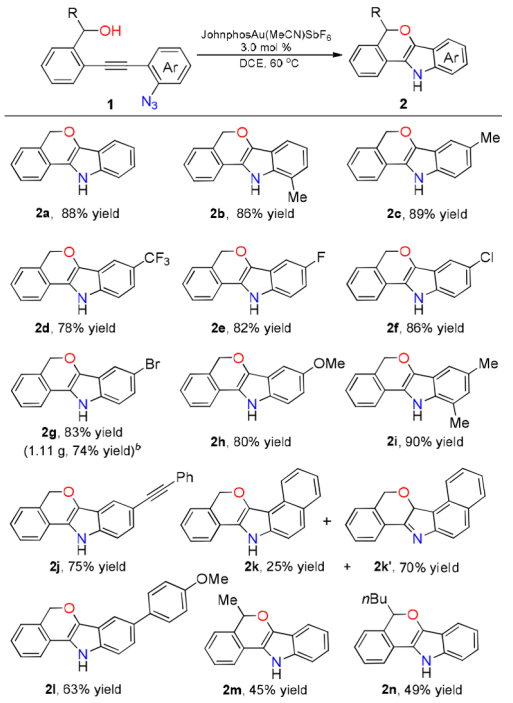
entry	cat. (mol %)	yield (%)[b]
1	$Cu(hfacac)_2$ (2.0)	ND[c]
2	$AgSbF_6$ (20)	<5%[d]
3	$Pd(dba)_3$ (5.0)	ND[c]
4	$Rh_2(OAc)_4$ (1.0)	ND[c]
5	PPh_3AuNTf_2 (5.0)	57
6	JohnphosAuCl (5)/$AgSbF_6$ (5.0)	36
7	JohnphosAu(CH_3CN)SbF_6 (5.0)	84
8	JohnphosAu(CH_3CN)SbF_6 (3.0)	88
9[e]	JohnphosAu(CH_3CN)SbF_6 (3.0)	85
10[f]	JohnphosAu(CH_3CN)SbF_6 (3.0)	46

[a]Reactions were carried out on a 0.2 mmol scale in 4.0 mL of solvent with corresponding catalyst at 60 °C under argon atmosphere for 12 h. [b]Isolated yields. [c]Low conversion (<10%) was observed, and most of the material **1a** was recovered. [d]60% conversions. [e]The reaction was carried out in dichloromethane under reflux. [f]The reaction was carried out in toluene.

as copper-, silver-, palladium-, and rhodium-complexes, which have been reported for the activation of alkynes (entries 1−4). However, no reaction occurred in most of these cases, and **1a** was decomposed into a complex mixture slowly in the presence of $AgSbF_6$ (entry 2). To our delight, the desired *tetra*-cyclic product **2a** was obtained in moderate to high yields when the reaction was catalyzed by gold-catalysts (entries 5−7). Although the combination of JohnphosAuCl and $AgSbF_6$ turned out to be less efficient, affording **2a** in only 36% yield (entry 6), the use of commercially available JohnphosAu(CH_3CN)SbF_6 showed much better results (entry 7, 84% yield), and the catalyst loading could be reduced to 3.0 mol % without decreasing the high yield (entry 8). In addition, both dichloromethane (DCM) and toluene were found to be compatible with this reaction, and the product **2a** was formed in high and moderate yields under these conditions, respectively (entries 9 and 10). The molecular structure of **2a** was inferred from X-ray diffraction analysis of its analogue **2d**.

With the optimal reaction conditions established, the substrate scope with respect to the various substitutions on the diaryl alkynes was investigated. As shown in Scheme 2, both electron-donating and electron-withdrawing groups were well tolerated with good to excellent yields (**2a**−**2l**). It was found that the reaction showed no obvious effect to the steric demand of the

Scheme 2. Substrate Scope[a]

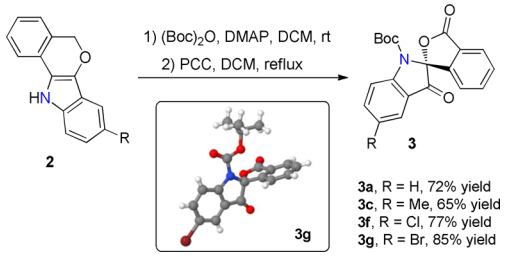


[a]Reactions were carried out on a 0.2 mmol scale with JohnphosAu(CH_3CN)SbF_6 (4.6 mg, 3.0 mol %) in DCE (4.0 mL) at 60 °C under argon atmosphere for 12 h. [b]The reaction was carried out on a 5.0 mmol scale with 2.0 mol % gold catalyst.

arenes (**2b** and **2i**). Functional groups, such as alkynyl (**2j**) and naphthyl (**2k**), were well tolerated. Two isomers were obtained in the case of reaction with **1k**, which may be due to the inherent thermostability of these products, and slow conversion of 3*H*-isomer **2k′** to the 1*H*-product **2k** was observed with proton NMR by monitoring the reaction mixture at different periods of reaction time in CD_2Cl_2 (see Figure S1).[28] In addition, the secondary alcohols were also viable and led to the tetracyclic products **2m** and **2n** in synthetically useful yields. It is noteworthy that the high yield was retained, and even the reaction was carried out on gram scale (**2g**, 74% yield, note b).

To demonstrate the practicality and synthetic utility of the current method, a further transformation with these fused indole products was conducted (Scheme 3). Although the direct

Scheme 3. Synthesis of Spirooxindole 3

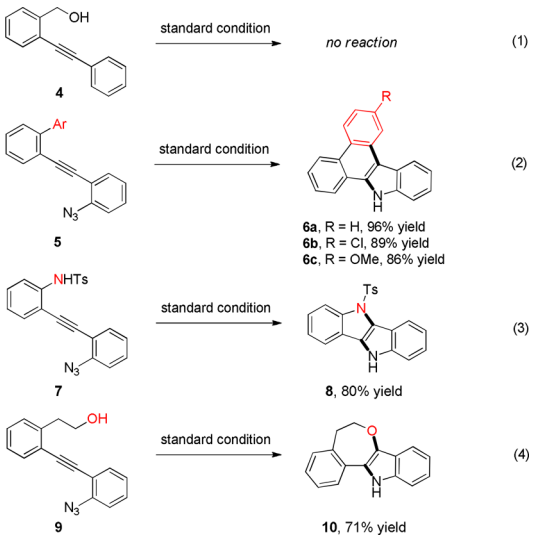


oxidation of the methylene part to the carbonyl group had failed, the spirooxindoles **3** were obtained in good to high yields from the Boc-protected substrates with PCC as the oxidant.[29] The molecular structure of **3g** was confirmed by X-ray diffraction. It is worth noting that polycyclic spirooxindoles are important scaffolds in natural products and pharmaceutical molecules,

DOI: 10.1021/acs.orglett.8b00939
Org. Lett. XXXX, XXX, XXX−XXX

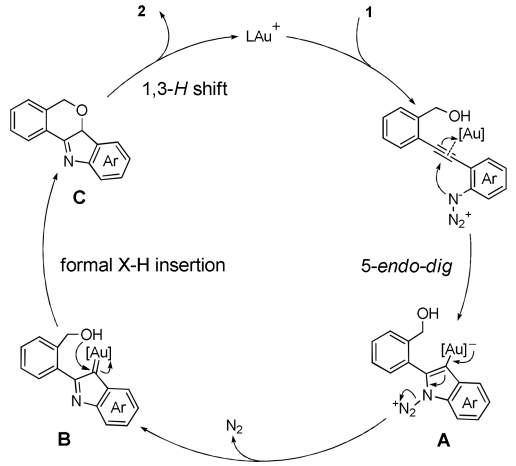
which have shown potential anticancer and cytotoxic activities.[30] This protocol provided straightforward access to these motifs from readily available materials under mild conditions.

Control experiments were conducted to explore the mechanism of this reaction. In order to rule out the possibility of the initial hydroxyl group addition with the activated alkyne moiety, substrate **4** without the azide group was prepared and applied to the reaction conditions. It turned out that no reaction occurred under the standard conditions with most of the starting material recovered (eq 1). Evidence for the existence of an α-imino carbenoid intermediate could be anticipated by the formation of products **6** and **8** from corresponding materials through electrophilic aromatic substitution and N−H insertion reaction as terminating reactions, respectively (eqs 2 and 3). In addition, this protocol could also be used for the preparation of seven-membered heterocycle **10** in 71% yield (eq 4). All these results not only well rationalized the reaction mechanism, but also underlined the synthetic advantages of our method in diversity oriented synthesis.



Based on these results and the reported literature,[13−17] a tentative mechanism was proposed for the generation of polycyclic indoles, which is shown in Scheme 4. Initial 5-*endo*-*dig* nucleophilic cyclization of the gold(I) activated alkyne moiety with tethered azide formed intermediate **A**, which further led to α-imino gold carbenoid species **B** after extrusion of N_2. Subsequently, the gold carbenoid intermediate was captured by the nucleophilic hydroxyl group through a stepwise formal O−H insertion reaction to generate the corresponding polycyclic product **2** via **C** after 1,3-*H*. It is worth noting that the 1,3-*H* shift transformation to thermodynamically more stable 1*H*-indole was observed by the proton NMR for the first time and that one of the key intermediates, 3*H*-isomer **2k′**, was isolated and characterized (see Figure S1 for details).[28]

Scheme 4. Proposed Reaction Mechanism



In summary, we have developed an atom-economical approach to the fused indoles in good to high yields under mild reaction conditions. The reaction was initiated via a gold-catalyzed 5-*endo*-*dig* cyclization to form the α-imino carbenoid, followed by O−H/N−H insertion, and electrophilic aromatic substitution to yield the corresponding polycyclic *N*-heterocycles with structural diversity, including fused tetracyclic indoles and π-conjugated polycyclic hydrocabons (CPHs). Moreover, these tetracyclic-indole products could be further transformed into spirooxindoles with PCC as oxidant in high yields, which are privileged motifs in bioactive molecules, pharmaceuticals, and natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00939.

Experimental procedure and spectroscopic data for all compounds (PDF)

Accession Codes

CCDC 1587682 and 1832661 contain 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

*E-mail: qiulihua@suda.edu.cn.
*E-mail: xinfangxu@suda.edu.cn.

ORCID

Xinfang Xu: 0000-0002-8706-5151

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Support for this research from the National Natural Science Foundation of China and the NSFC of Jiangsu (NSFC21602148 and BK20150315) is gratefully acknowledged.

■ REFERENCES

(1) For reviews: (a) Sunil, D.; Kamath, P. R. *Mini-Rev. Med. Chem.* **2016**, *16*, 1470. (b) Zhang, M.; Chen, Q.; Yang, G. *Eur. J. Med. Chem.* **2015**, *89*, 421. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (d) Stempel, E.; Gaich, T. *Acc. Chem. Res.* **2016**, *49*, 2390.

(2) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608.

(3) (a) Robinson, B. *Chem. Rev.* **1969**, *69*, 227. (b) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29.

(4) Bartoli, G.; Dalpozzo, R.; Nardi, M. *Chem. Soc. Rev.* **2014**, *43*, 4728.

DOI: 10.1021/acs.orglett.8b00939
Org. Lett. XXXX, XXX, XXX−XXX

(5) Gribble, G. W. Leimgruber-Batcho Indole Synthesis. In *Indole Ring Synthesis: From Natural Products to Drug Discovery*; Gribble, G. W., Ed.; John Wiley & Sons: Chichester, 2016.
(6) For reviews: (a) Della Ca, N.; Fontana, M.; Motti, E.; Catellani, M. *Acc. Chem. Res.* **2016**, *49*, 1389. (b) Dalpozzo, R. *Chem. Soc. Rev.* **2015**, *44*, 742. (c) Zhang, B.; Studer, A. *Chem. Soc. Rev.* **2015**, *44*, 3505. (d) Song, J.; Chen, D.; Gong, L. *Natl. Sci. Rev.* **2017**, *4*, 381.
(7) (a) Singh, A. K.; Raj, V.; Saha, S. *Eur. J. Med. Chem.* **2017**, *142*, 244. (b) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2015**, *32*, 1389. (c) Zi, W.; Zuo, Z.; Ma, D. *Acc. Chem. Res.* **2015**, *48*, 702. (d) Wang, Y.; Lu, H.; Xu, P. *Acc. Chem. Res.* **2015**, *48*, 1832.
(8) (a) Yu, B.; Yu, D.; Liu, H. *Eur. J. Med. Chem.* **2015**, *97*, 673. (b) Ye, N.; Chen, H.; Wold, E. A.; Shi, P.; Zhou, J. *ACS Infect. Dis.* **2016**, *2*, 382. (c) Pavlovska, T. L.; Redkin, R. G.; Lipson, V. V.; Atamanuk, D. V. *Mol. Diversity* **2016**, *20*, 299. (d) Santos, M. M. M. *Tetrahedron* **2014**, *70*, 9735.
(9) (a) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (b) Xia, M.; Ma, R. *J. Heterocyclic Chem.* **2014**, *51*, 539. (c) Narayan, R.; Potowski, M.; Jia, Z.; Antonchick, A. P.; Waldmann, H. *Acc. Chem. Res.* **2014**, *47*, 1296. (d) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *2009*, 3003.
(10) For reviews: (a) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877. (d) Abu Sohel, S. M.; Liu, R. *Chem. Soc. Rev.* **2009**, *38*, 2269. (e) Wang, Y.; Muratore, M.; Echavarren, A. M. *Chem. - Eur. J.* **2015**, *21*, 7332. (f) Harris, R. J.; Widenhoefer, R. A. *Chem. Soc. Rev.* **2016**, *45*, 4533.
(11) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415.
(12) For reviews: (a) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. (b) Luo, Y.; Pan, X.; Yu, X.; Wu, J. *Chem. Soc. Rev.* **2014**, *43*, 834. (c) Zheng, Z.; Wang, Z.; Wang, Y.; Zhang, L. *Chem. Soc. Rev.* **2016**, *45*, 4448. (d) Yoshida, H. *ACS Catal.* **2016**, *6*, 1799. (e) Fürstner, A. *Angew. Chem., Int. Ed.* **2018**, *56*, 2.
(13) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.
(14) (a) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8358. (b) Yan, Z.; Xiao, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8624.
(15) (a) Wetzel, A.; Gagosz, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354. (b) Gronnier, C.; Boissonnat, G.; Gagosz, F. *Org. Lett.* **2013**, *15*, 4234. (c) Lonca, G. H.; Tejo, C.; Chan, H. L.; Chiba, S.; Gagosz, F. *Chem. Commun.* **2017**, *53*, 736.
(16) (a) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2014**, *16*, 3138. (b) Matsuoka, J.; Matsuda, Y.; Kawada, Y.; Oishi, S.; Ohno, H. *Angew. Chem., Int. Ed.* **2017**, *56*, 7444.
(17) Shen, W.; Sun, Q.; Li, L.; Liu, X.; Zhou, B.; Yan, J.; Lu, X.; Ye, L. *Nat. Commun.* **2017**, *8*, 1748.
(18) Jin, H.; Tian, B.; Song, X.; Xie, J.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2016**, *55*, 12688.
(19) Yu, Y.; Chen, G.; Zhu, L.; Liao, Y.; Wu, Y.; Huang, X. *J. Org. Chem.* **2016**, *81*, 8142.
(20) (a) Sahani, R. L.; Liu, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 1026. (b) Shen, W.; Xiao, X.; Sun, Q.; Zhou, B.; Zhu, X.; Yan, J.; Lu, X.; Ye, L. *Angew. Chem., Int. Ed.* **2017**, *56*, 605. (c) Sahani, R. L.; Liu, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 12736.
(21) Pagar, V. V.; Jadhav, A. M.; Liu, R. *J. Am. Chem. Soc.* **2011**, *133*, 20728.
(22) (a) Yu, Y.; Shu, C.; Tan, T.; Li, L.; Rafique, S.; Ye, L. *Org. Lett.* **2016**, *18*, 5178. (b) Yu, Y.; Shu, C.; Zhou, B.; Li, J.; Zhou, J.; Ye, L. *Chem. Commun.* **2015**, *51*, 2126. (c) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7168.
(23) Zhang, J.; Zhang, Q.; Xia, B.; Wu, J.; Wang, X.; Chang, J. *Org. Lett.* **2016**, *18*, 3390.
(24) Zheng, D.; Li, S.; Wu, J. *Org. Lett.* **2012**, *14*, 2655.
(25) Chen, G.; Zhang, X.; Wei, Y.; Tang, X.; Shi, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 8492.
(26) (a) Li, S.; Luo, Y.; Wu, J. *Org. Lett.* **2011**, *13*, 4312. (b) Xiao, Q.; Ye, S.; Wu, J. *Org. Lett.* **2012**, *14*, 3430. (c) Hsu, Y.; Hsieh, S.; Li, P.; Liu, R. *Chem. Commun.* **2018**, *54*, 2114. (d) Zhu, L.; Mao, Z.; Huang, X. *Org. Lett.* **2015**, *17*, 30. (e) Prechter, A.; Henrion, G.; Faudot dit Bel, P.; Gagosz, F. *Angew. Chem., Int. Ed.* **2014**, *53*, 4959.
(27) (a) Zheng, Y.; Mao, J.; Weng, Y.; Zhang, X.; Xu, X. *Org. Lett.* **2015**, *17*, 5638. (b) Zhang, C.; Chang, S.; Qiu, L.; Xu, X. *Chem. Commun.* **2016**, *52*, 12470. (c) Yao, R.; Rong, G.; Yan, B.; Qiu, L.; Xu, X. *ACS Catal.* **2016**, *6*, 1024.
(28) See Supporting Information for details.
(29) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, *4*, 245.
(30) For reviews: (a) Yu, B.; Yu, D.; Liu, H. *Eur. J. Med. Chem.* **2015**, *97*, 673. (b) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (c) Zhou, F.; Liu, Y.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381.

DOI: 10.1021/acs.orglett.8b00939
Org. Lett. XXXX, XXX, XXX−XXX