Organic LETTERS

Letter

pubs.acs.org/OrgLett

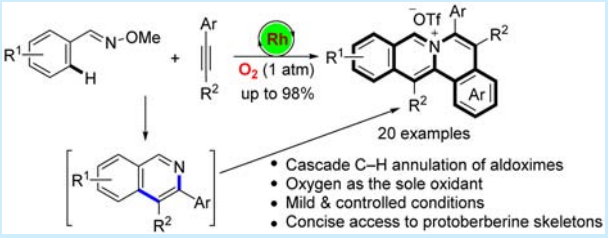
Cascade C−H Annulation of Aldoximes with Alkynes Using O_2 as the Sole Oxidant: One-Pot Access to Multisubstituted Protoberberine Skeletons

Junbin Tang, Shiqing Li, Zheng Liu, Yinsong Zhao, Zhijie She, Vilas D. Kadam, Ge Gao,* Jingbo Lan, and Jingsong You*

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P.R. China

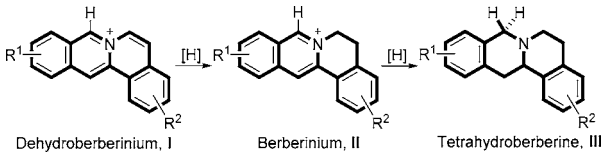
Supporting Information

ABSTRACT: A cascade double C−H annulation of aldoximes with alkynes to produce benz[*a*]acridizinium salts is developed by using a simple catalytic system of $[Cp^*Rh(OAc)_2]_2$ in the presence of $Zn(OTf)_2$ with oxygen as the sole oxidant. In addition, the challenging C−H annulation of aldoximes with alkynes, especially arylalkynes, to synthesize 1*H*-isoquinolines is also achieved under slightly modified conditions. This protocol provides an efficient one-pot access to multisubstituted dehydroberberinium skeletons from simple starting materials, which can be easily transformed into berberinium and tetrahydroberberine skeletons by controlled hydrogenation.



Protoberberine alkaloid is one of the largest families of all known alkaloids that exhibits extensive biological activities and has therapeutic applications.[1] The berberinium skeleton **II** is the basic skeleton of protoberberine alkaloids, and two structurally related skeletons are dehydroberberinium (**I**, also called benz[*a*]acridizinium salt) and tetrahydroberberine **III**. From the viewpoint of artifact synthesis, both **II** and **III** can be accessed from **I** through stepwise hydrogenation (Scheme 1).

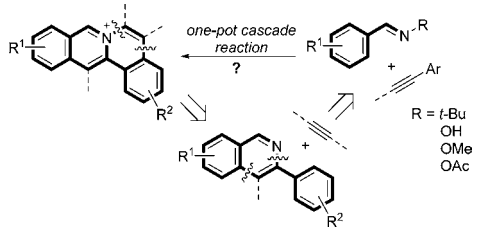
Scheme 1. Three Core Skeletons of Protoberberine Alkaloids



On the other hand, **I** belongs to a class of azonia aromatic heterocycles,[2] and is attractive core skeleton due to its potential as fluorescent probes[3] and DNA-binding agents.[4] Although the synthetic methodology of **I** by the quaternization of isoquinoline-1-carbaldehydes with benzyl bromides followed by the intramolecular cyclization has been established as early as in 1958,[5] the unavailability and lability of the starting materials make it unpractical and restricted to a very narrow substrate scope.

In recent years, transition-metal (TM)-catalyzed C−H activation and annulation reactions have emerged as a powerful strategy for the synthesis of *N*-heterocyclic compounds.[6] The avoidance of preparation of preactivated substrates and atom- and step-economy are especially advantageous for the construction of multifused heterocycles in natural products, pharmaceuticals, and functional materials. The retrosynthetic analysis of the benzo[*a*]acridizinium skeleton suggests that it could be accessed by a C−H annulation of 3-phenylisoquinoline with an alkyne, and 3-phenylisoquinoline could be prepared by a C−H annulation of an *N*-derivative of benzaldehyde with an alkyne (Scheme 2).

Scheme 2. Retrosynthetic Analysis of the Benz[*a*]acridizinium Skeleton



Previously, the TM-catalyzed C−H annulations have been established to synthesize pyridoisoquinolinium and quinolizinium salts from 2-phenylpyridines and 2-vinylpyridines[7] as well as isoquinolines from amines,[8] imines,[9] and oximes,[10] etc. Therefore, it is tempting to envisage a cascade C−H annulation of a certain *N*-derivative of benzaldehyde with alkynes to directly construct benz[*a*]acridizinium salts in one pot, which would be an extremely concise synthetic step for this tetracyclic skeleton.

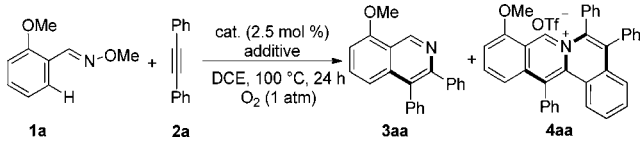
Received: December 19, 2016
Published: January 19, 2017

DOI: 10.1021/acs.orglett.6b03772
Org. Lett. 2017, 19, 604−607

However, this cascade strategy is still challenging in several aspects. First, the C−H annulation of aldoximes with alkynes to access 1*H*-isoquinolines is rare,[10c,11] although the annulation of ketoximes is well-established. Li et al. disclosed a sluggish annulation between benzaldehyde oxime and oct-4-yne yielding 3,4-dipropylisoquinoline in only 39% yield.[10c] A similar reaction in a sequential C−H bond activation reaction was reported by Cheng's group.[11] Second, the first annulation of this cascade reaction needs the alkynes having at least one aryl substituent to regioselectively assemble 3-arylisoquinolines, which is a structural prerequisite for the second annulation. Nevertheless, the known annulation of either aldoximes or benzaldimines is usually viable only for aliphatic alkynes.[9b,10c,11] Third, the subtle adjustment of the reaction conditions for double annulation is necessary. Urriolabeitia et al. previously reported a sequential annulation/alkenylation of amines with diphenylacetylene.[8c,d] Finally, the controlled stepwise annulations using different alkynes are also needed to enrich the substituent diversity. Due to our continuous interest in cationic organic functional materials, we herein report an effective synthesis of benz[*a*]-acridizinium salts by a Rh-catalyzed cascade annulation of aldoximes with alkynes using oxygen as the sole oxidant.[12]

We commenced our study by treating (*E*)-2-methoxybenzaldehyde *O*-methyl oxime **1a** (0.25 mmol) with diphenylacetylene **2a** (0.50 mmol) in the presence of $[(Cp^*RhCl_2)_2]$ (2.5 mol %) and $Cu(OAc)_2{\cdot}H_2O$ (2.0 equiv) in DCE at 100 °C in a nitrogen atmosphere for 24 h. Neither isoquinoline **3aa** nor the desired benz[*a*]acridizinium salt **4aa** was observed (Table 1, entry 1). Changing the additive to $Cu(OTf)_2$ afforded **3aa** and **4aa** in 18% and 37% yields, respectively (entry 2), which were characterized by the ^1H, ^{13}C, and ^{19}F NMR spectra as well as MS analysis. This result suggests that the OAc anion probably could not serve as the counteranion for the construction of the benz[*a*]acridizinium product.[7b] To our delight, the use of oxygen in combination with $Zn(OTf)_2$ exclusively delivered **4aa** in 57% yield, but **4aa** was not detected when LiOTf was used (entries 3 and 4). $Zn(OTf)_2$ may not only provide the OTf anion as the counteranion but also activate **2a** via coordination.[13] Replacing $[(Cp^*RhCl_2)_2]$ with $[Cp^*Rh(OAc)_2]_2$ gave **4aa** in 90% yield (entry 5). Considering the fact that acetic acid could enhance the oxidative ability of the molecular oxygen,[14] 1 equiv of acetic acid was added and resulted in almost quantitative yield (entry 6).[15] Even when the reaction temperature was lowered to 60 °C, **4aa** could be attained in 82% yield without any **3aa** detected (entry 7). When the reaction was conducted at room temperature, both **3aa** and **4aa** were obtained in very low yields (entry 8). These results suggested that the second annulation is much faster than the first one at higher temperature. It should be noted that in a nitrogen atmosphere most of **1a** was recovered and **3aa** was obtained in only 9% yield together with a trace amount of **4aa** (entry 9), showing the inferior activity of the aldoxime. The ruthenium catalyst[7c] gave very low yield, and the cobalt catalyst[7g,h] showed no activity at all (entries 10 and 11). To achieve the controlled synthesis of **3aa**, the conditions were further tuned at room temperature. By switching back to $Cu(OTf)_2$, the yields of both **3aa** and **4aa** increased, but **4aa** was still predominant (entry 12). When 1-AdCOOH was used in lieu of HOAc, **3aa** was obtained as the main product in 69% yield (entry 13), probably because the bulky Ad group sterically hinders **2a** approaching the rhodium center in the second catalytic cycle and therefore suppresses the second annulation. Finally, the $[(Cp^*RhCl_2)_2]$/AgOTf catalyst system gave the best yield of 77% for **3aa**, but **4aa** was still inevitably formed in 13% yield (entry 14). It needs to be pointed out that other *N*-derivatives including oxime, *O*-acetyl oxime, and *N*-*tert*-butylimine are also workable under the optimal conditions to directly afford **4aa** but in lower yields (see the Supporting Information).

Table 1. Optimization of the Reaction Conditions[a,b]



1a 2a 3aa 4aa

entry	catalyst	additive	3aa (%)	4aa (%)
1[c]	$[(Cp^*RhCl_2)_2]$	$Cu(OAc)_2{\cdot}H_2O$	nd	nd
2[c]	$[(Cp^*RhCl_2)_2]$	$Cu(OTf)_2$	18	37
3	$[(Cp^*RhCl_2)_2]$	$Zn(OTf)_2$	nd	57
4	$[(Cp^*RhCl_2)_2]$	LiOTf	nd	trace
5	$[Cp^*Rh(OAc)_2]_2$	$Zn(OTf)_2$	nd	90
6	**$[Cp^*Rh(OAc)_2]_2$**	**$Zn(OTf)_2$/HOAc**	**nd**	**95**
7[d]	$[Cp^*Rh(OAc)_2]_2$	$Zn(OTf)_2$/HOAc	nd	82
8[e]	$[Cp^*Rh(OAc)_2]_2$	$Zn(OTf)_2$/HOAc	6	7
9[f]	$[Cp^*Rh(OAc)_2]_2$	$Zn(OTf)_2$/HOAc	9	nd
10	$[(p\text{-cymene})RuCl_2]_2$	$Zn(OTf)_2$/HOAc	trace	12
11	$[Cp^*Co(CO)I_2]$	$Zn(OTf)_2$/HOAc	nd	nd
12[e,f]	$[Cp^*Rh(OAc)_2]_2$	$Cu(OTf)_2$/HOAc	14	30
13[e,f]	$[Cp^*Rh(OAc)_2]_2$	$Cu(OTf)_2$/1-AdCOOH	69	25
14[e,f]	**$[(Cp^*RhCl_2)_2]$/AgOTf**	**$Cu(OTf)_2$/1-AdCOOH**	**77**	**13**

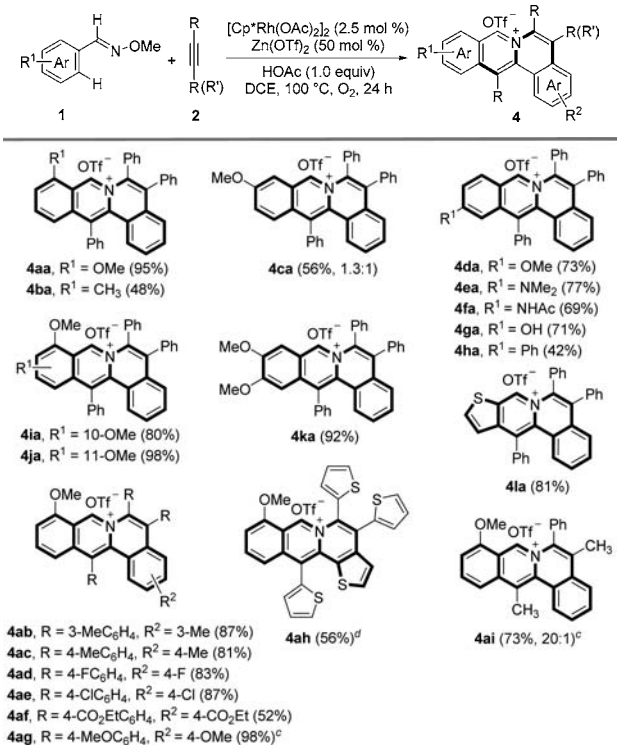
[a]Reaction conditions: (*E*)-2-methoxybenzaldehyde *O*-methyl oxime **1a** (0.25 mmol), 1,2-diphenylethyne **2a** (2.0 equiv), catalyst (2.5 mol %), M(II) $(OTf)_2$ (0.5 equiv) or M(I)OTf (1.0 equiv), acid (1.0 equiv), and DCE (1.0 mL) at 100 °C under an O_2 atmosphere for 24 h. nd = not detected. [b]Isolated yield. [c]Additive (2.0 equiv) under N_2 atmosphere. [d]At 60 °C. [e]At room temperature. [f]Under a N_2 atmosphere.

With the optimized reaction conditions in hand, we investigated the substrate scope of this cascade reaction (Table 2). For aldoximes, various functional groups on the phenyl ring were tolerable, and the corresponding products were isolated in moderate to excellent yields. Notably, the aldoxime **1g** with a free hydroxyl group could be successfully annulated to give **4ga** in 71% yield.[16] The lower yields of **4ba** and **4ha** showed the preference for electron-rich aldoximes, indicating that an electrophilic rhodation might be involved in the first catalytic cycle.[17] In the case of meta-substituted substrate **1c**, **4ca** was obtained as 1.3:1 mixed regioisomers in a 56% combined yield. However, 3,4-dimethoxy-substituted aldoxime **1k** afforded **4ka** as a single regioisomer in 92% yield. The heterocyclic aldoxime **1l** provided **4la** in 81% yield.

For alkynes, diarylalkynes containing both electron-rich and -deficient functional groups reacted smoothly to give the expected products in good yields. However, 1,2-di-*o*-tolylethyne only gave the corresponding isoquinoline in 34% yield without any salt formed. The product **4ai** was successfully obtained in 73% yield with a high regioselectivity of 20:1 in one pot, as determined by the NOESY analysis. For 1,2-di(thiophene-2-yl)ethyne, the $[(Cp^*RhCl_2)_2]$/AgOTf catalyst system was used to deliver **4ah** in a moderate yield of 56%.

DOI: 10.1021/acs.orglett.6b03772
Org. Lett. 2017, 19, 604−607

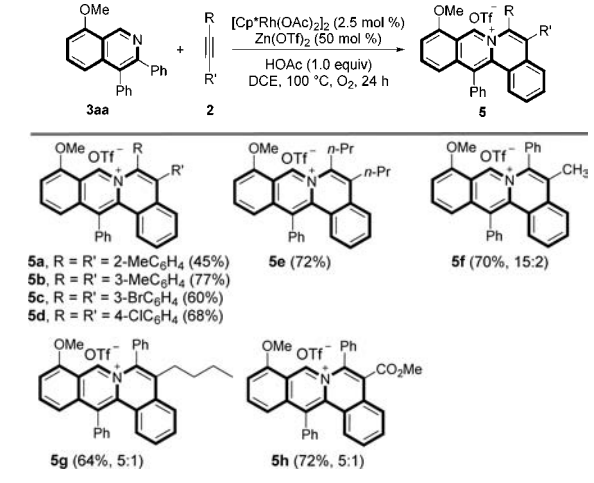
Table 2. Annulation of Aldoximes 1 with Alkynes 2[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2** (2.0 equiv), $[Cp^*Rh(OAc)_2]_2$ (2.5 mol %), $Zn(OTf)_2$ (50 mol %), HOAc (1.0 equiv), DCE (1.0 mL) under an O_2 atmosphere at 100 °C for 24 h. [b]Isolated yield. [c]$Cu(OTf)_2$ (50 mol %) instead of $Zn(OTf)_2$ was used at 60 °C. [d]$[(Cp^*RhCl_2)_2]$ (2.5 mol %) and AgOTf (10 mol %) instead of $[Cp^*Rh(OAc)_2]_2$ were used.

By applying the conditions in entry 14 of Table 1, **3aa** was isolated and subjected to further annulation under the optimal conditions to provide diversely substituted benz[*a*]acridizinium salts **5** (Table 3). Both diaryl- and dialkylalkynes delivered the desired salts in good yields. 1,2-Di-*o*-tolylethyne was compatible, giving **5a** in 45% yield. For unsymmetrical alkynes, the regioselective annulations mainly gave the products with the phenyl group installed proximal to the nitrogen atom, and the selectivities ranged from 5:1 to 15:2 as determined by the NOESY analysis. It needs to point out that **4aa** was only isolated in a low yield of 48% under the optimal conditions for the annulation of 2-phenylquinoline (see the Supporting Information),[7b] indicating that the present conditions are specific and highly efficient for the synthesis of benz[*a*]-acridizinium salts.

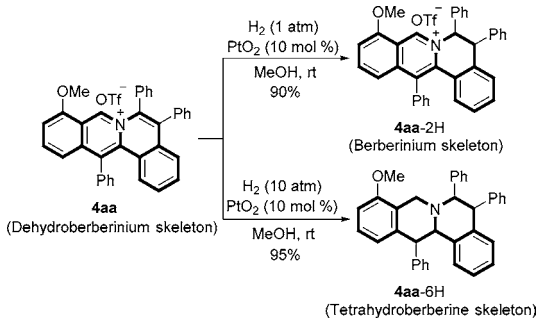
Table 3. Annulation of Isoquinoline 3aa with Alkynes 2[a,b]



[a]Reaction conditions: **3aa** (0.1 mmol), **2** (1.0 equiv), $[Cp^*Rh(OAc)_2]_2$ (2.5 mol %), $Zn(OTf)_2$ (50 mol %), HOAc (1.0 equiv), DCE (0.4 mL) under an O_2 atmosphere at 100 °C for 24 h. [b]Isolated yield.

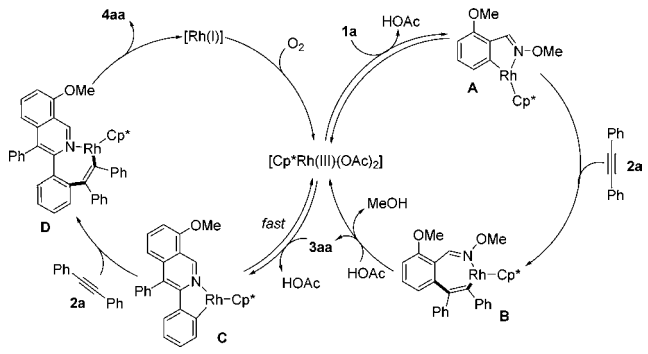
With benz[*a*]acridizinium salts (dehydroberberiniums) in hand, the corresponding berberinium and tertrahydroberberine skeletons could be easily accessed by hydrogenation.[5b,c] As exemplified here, the hydrogenation of **4aa** was conducted at room temperature utilizing 10 mol % of Adams catalyst under 1 and 10 atmospheric pressure, affording the corresponding **4aa**-2H[18] and **4aa**-6H[19] in 90% and 95% yields, respectively (Scheme 3).

Scheme 3. Access to Berberinium and Tetrahydroberberine Skeletons by the Hydrogenation of Dehydroberberinium



On the basis of the experimental results[20] and the known Rh-catalyzed C−H annulation processes,[7b,10c] a plausible catalytic pathway is proposed in Scheme 4. Aldoxime **1a** first coordinates

Scheme 4. Plausible Mechanism



with $Cp^*Rh(OAc)_2$ through an oxime-assisted reversible electrophilic C−H activation process to form a five-membered rhodacycle **A**. The alkyne insertion provides the intermediate **B**, which undergoes a redox neutral process to release isoquinoline **3aa** and the [Rh(III)] species. The subsequent coordination of **3aa** to the [Rh(III)] species is easy and fast through a pyridine-assisted reversible C−H activation process, generating a five-membered rhodacycle **C**. The routine alkyne insertion followed by reductive elimination gives the benz[*a*]acridizinium product **4aa** and releases the [Rh(I)] species. Finally, the [Rh(III)] catalyst is regenerated by the oxidation of oxygen for the next catalytic cycle.

DOI: 10.1021/acs.orglett.6b03772
Org. Lett. 2017, 19, 604−607

In summary, we develop a simple catalytic system containing $[Cp^*Rh(OAc)_2]_2$ and $Zn(OTf)_2$ with oxygen as the sole oxidant to produce benz[*a*]acridizinium salts via a cascade double C−H annulation of aldoximes with alkynes. It provides a one-pot protocol to access various multisubstituted dehydroberberinium skeletons from simple starting materials, which can be easily transformed into berberinium and tetrahydroberberine skeletons by the controlled hydrogenation. In addition, the challenging C−H annulation of aldoximes with alkynes, especially arylalkynes, to access 1*H*-isoquinolines is also achieved under slightly modified conditions. The current method demonstrates the high efficiency and potency of C−H annulation for the synthesis of multifused heterocyclic 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.6b03772.

Detailed experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of key intermediates and final products (PDF)

X-ray data for compound **4aa**-6H (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: gg2b@scu.edu.cn.

*E-mail: jsyou@scu.edu.cn.

ORCID

Ge Gao: 0000-0001-9980-7311

Jingsong You: 0000-0002-0493-2388

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for financial support from the National NSF of China (Nos 21472127 and 21432005) and the NCET-13-0384.

■ REFERENCES

(1) (a) Leitao da-Cunha, E. V.; Fechine, I. M.; Guedes, D. N.; Barbosa-Filho, J. M.; Sobral da Silva, M. *Alkaloids: Chem. Biol.* **2005**, *62*, 1−75. (b) Grycová, L.; Dostál, J.; Marek, R. *Phytochemistry* **2007**, *68*, 150. (c) Bhadra, K.; Kumar, G. S. *Med. Res. Rev.* **2011**, *31*, 821.

(2) (a) Gandeepan, P.; Cheng, C.-H. *Chem. - Asian J.* **2016**, *11*, 448. (b) Sucunza, D.; Cuadro, A. M.; Alvarez-Builla, J.; Vaquero, J. *J. Org. Chem.* **2016**, *81*, 10126.

(3) (a) Bortolozzi, R.; Ihmels, H.; Thomas, L.; Tian, M.; Viola, G. *Chem. - Eur. J.* **2013**, *19*, 8736. (b) Zhao, E.; Deng, H.; Chen, S.; Hong, Y.; Leung, C. W. T.; Lam, J. W. Y.; Tang, B. Z. *Chem. Commun.* **2014**, *50*, 14451.

(4) (a) Krey, A. K.; Hahn, F. E. *Science* **1969**, *166*, 755. (b) Ihmels, H.; Faulhaber, K.; Vedaldi, D.; Dall'Acqua, F.; Viola, G. *Photochem. Photobiol.* **2005**, *81*, 1107.

(5) Bradsher, C. K.; Jones, J. H. *J. Org. Chem.* **1958**, *23*, 430. (b) Bradsher, C. K.; Dutta, N. L. *J. Am. Chem. Soc.* **1960**, *82*, 1145. (c) Augstein, W.; Bradsher, C. K. *J. Org. Chem.* **1969**, *34*, 1349.

(6) For selected recent reviews, see: (a) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Tetrahedron Lett.* **2014**, *55*, 5705. (b) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (c) Gulías, M.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 11000. (d) Yang, Y.; Li, K.; Cheng, Y.; Wan, D.; Li, M.; You, J. *Chem. Commun.* **2016**, *52*, 2872.

(7) (a) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2008**, *130*, 12414. (b) Zhang, G.; Yang, L.; Wang, Y.; Xie, Y.; Huang, H. *J. Am. Chem. Soc.* **2013**, *135*, 8850. (c) Luo, C.-Z.; Gandeepan, P.; Cheng, C.-H. *Chem. Commun.* **2013**, *49*, 8528. (d) Luo, C.-Z.; Gandeepan, P.; Jayakumar, J.; Parthasarathy, K.; Chang, Y.-W.; Cheng, C.-H. *Chem. - Eur. J.* **2013**, *19*, 14181. (e) Luo, C.-Z.; Gandeepan, P.; Wu, Y.-C.; Tsai, C.-H.; Cheng, C.-H. *ACS Catal.* **2015**, *5*, 4837. (f) Davies, D. L.; Ellul, C. E.; Macgregor, S. A.; McMullin, C. L.; Singh, K. *J. Am. Chem. Soc.* **2015**, *137*, 9659. (g) Prakash, S.; Muralirajan, K.; Cheng, C.-H. *Angew. Chem., Int. Ed.* **2016**, *55*, 1844. (h) Lao, Y.-X.; Zhang, S.-S.; Liu, X.-G.; Jiang, C.-Y.; Wu, J.-Q.; Li, Q.; Huang, Z.-S.; Wang, H. *Adv. Synth. Catal.* **2016**, *358*, 2186.

(8) (a) Morimoto, K.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2011**, *40*, 600. (b) Kim, D.-S.; Park, J.-W.; Jun, C.-H. *Adv. Synth. Catal.* **2013**, *355*, 2667. (c) Villuendas, P.; Urriolabeitia, E. P. *J. Org. Chem.* **2013**, *78*, 5254. (d) Ruiz, S.; Villuendas, P.; Ortuño, M. A.; Lledós, A.; Urriolabeitia, E. P. *Chem. - Eur. J.* **2015**, *21*, 8626.

(9) (a) Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759. (b) Guimond, N.; Fagnou, K. *J. Am. Chem. Soc.* **2009**, *131*, 12050. (c) Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141. (d) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950. (e) Zhang, S.-S.; Liu, X.-G.; Chen, S.-Y.; Tan, D.-H.; Jiang, C.-Y.; Wu, J.-Q.; Li, Q.; Wang, H. *Adv. Synth. Catal.* **2016**, *358*, 1705. (f) He, K.-H.; Zhang, W.-D.; Yang, M.-Y.; Tang, K.-L.; Qu, M.; Ding, Y.-S.; Li, Y. *Org. Lett.* **2016**, *18*, 2840.

(10) For selected examples, see: (a) Parthasarathy, K.; Cheng, C.-H. *J. Org. Chem.* **2009**, *74*, 9359. (b) Too, P. C.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2010**, *12*, 5688. (c) Zhang, X.; Chen, D.; Zhao, M.; Zhao, J.; Jia, A.; Li, X. *Adv. Synth. Catal.* **2011**, *353*, 719. (d) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159. (e) Yoshida, Y.; Kurahashi, T.; Matsubara, S. *Chem. Lett.* **2011**, *40*, 1140. (f) Chinnagolla, R. K.; Pimparkar, S.; Jeganmohan, M. *Org. Lett.* **2012**, *14*, 3032. (g) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968.

(11) Yeh, C.-H.; Chen, W.-C.; Gandeepan, P.; Hong, Y.-C.; Shih, C.-H.; Cheng, C.-H. *Org. Biomol. Chem.* **2014**, *12*, 9105.

(12) (a) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. For recent examples of the alkyne annulation using oxygen as the sole oxidant, see: (b) Warratz, S.; Kornhaaß, C.; Cajaraville, A.; Niepötter, B.; Stalke, D.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 5513. (c) Mei, R.; Wang, H.; Warratz, S.; Macgregor, S. A.; Ackermann, L. *Chem. - Eur. J.* **2016**, *22*, 6759.

(13) Yang, X.; Hu, X.; Loh, T.-P. *Org. Lett.* **2015**, *17*, 1481.

(14) (a) Zhang, G.; Yu, H.; Qin, G.; Huang, H. *Chem. Commun.* **2014**, *50*, 4331. (b) Yang, L.; Zhang, G.; Huang, H. *Adv. Synth. Catal.* **2014**, *356*, 1509.

(15) Compound **4aa** was isolated in 90% yield when the reaction was conducted in air instead of oxygen.

(16) A mesoionic salt was obtained by using $Cu(OAc)_2{\cdot}H_2O$ as the oxidant, see: Zhang, W.; Wang, C.-Q.; Lin, H.; Dong, L.; Xu, Y.-J. *Chem. - Eur. J.* **2016**, *22*, 907.

(17) (a) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (b) Li, L.; Brennessel, W.; Jones, W. D. *Organometallics* **2009**, *28*, 3492.

(18) For recent syntheses of protoberberine alkaloids, see: (a) Gatland, A. E.; Pilgrim, B. S.; Procopiou, P. A.; Donohoe, T. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 14555. (b) Jayakumar, J.; Cheng, C.-H. *Chem. - Eur. J.* **2016**, *22*, 1800.

(19) CCDC 1516994 (**4aa**-6H) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/datarequest/cif.

(20) The deuterium-exchange experiments indicated that the cleavage of the *ortho*-C−H bonds of **1a** and **3aa** were both reversible processes; see the Supporting Information.

DOI: 10.1021/acs.orglett.6b03772
Org. Lett. 2017, 19, 604−607