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

Catalyst-Controlled [3 + 2] and [4 + 2] Annulations of Oximes with Propargyl Alcohols: Divergent Access to Indenamines and Isoquinolines

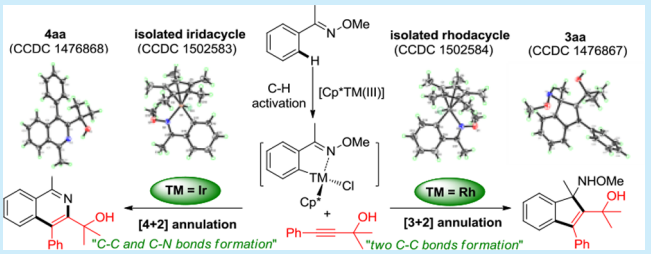
Wanchun Gong,[†,§,⊥] Zhi Zhou,[†,§] Jingjing Shi,[‡,§] Bo Wu,[†] Biyun Huang,[†] and Wei Yi*[,†]

[†]Key Laboratory of Molecular Clinical Pharmacology & Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong 511436, China

[‡]VARI/SIMM Center, Center for Structure and Function of Drug Targets, CAS-Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

Supporting Information

ABSTRACT: Rhodium(III)- and iridium(III)-catalyzed C−H activation of oximes and coupling with propargyl alcohols is discussed. Depending on the catalyst, the reaction pathway switched between [3 + 2] and [4 + 2] annulations, thus giving divergent access to indenamines and isoquinolines in a one-pot and atom-economical manner. The hydroxyl group in the tertiary propargyl alcohol substrate was found to be crucial in controlling chemoselectivity. Five-membered rhodacycle and iridacycle intermediates have also been identified for mechanism hypotheses.

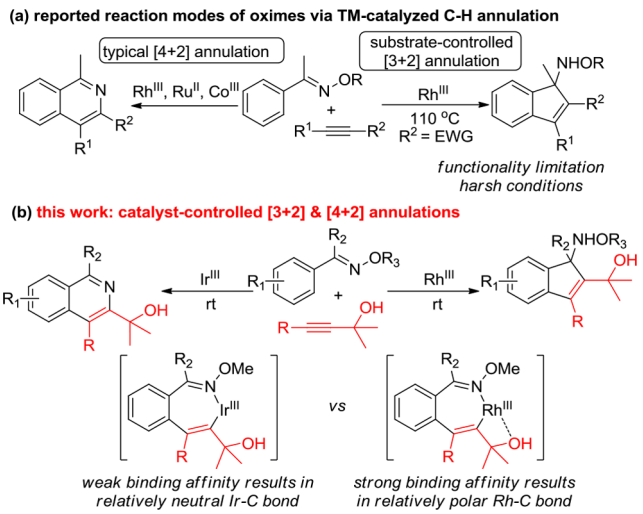


The construction of heterocyclic scaffolds via transition-metal (TM)-catalyzed C−H annulation represents a step- and atom-economical synthetic method owing to obviating the need for prefunctionalized substrates.[1] Over the past decades, a variety of heterocycles can be accessed through this protocol from less-functionalized substrates bearing nitrogen-, oxygen-, sulfur-, and phosphorus-containing directing groups (DGs).[2] Despite these notable advances, the development of classical DGs with novel diverse synthetic features is still in demand.

Among a broad range of DGs, oximes[3] are easily accessible and viewed as a class of efficient and installable DGs for the synthesis of nitrogen-containing heterocycles via rhodium(III)-, ruthenium(II)-, iridium(III)-, and cobalt(III)-catalyzed couplings of C−H bonds with alkynes,[4] alkenes,[5] diazo compounds,[6] and other coupling partners.[7] Typically, the TM-catalyzed coupling of oxime derivatives with alkynes follows a redox-neutral [4 + 2] annulation mode, leading to the synthesis of pyridines or isoquinolines (Scheme 1a, left). In 2015, by designing the proper alkynes to increase the polarity of the $Rh^{\delta+}$−$C^{\delta-}$ bond, Li and co-workers disclosed an alternative and attractive rhodium(III)-catalyzed [3 + 2] annulation mode of oximes with electron-deficient alkynes, such as trifluoromethanesulfonyl phenylacetylenes, for one-pot synthesis of indenamines (Scheme 1a, right).[8]

Inspired by these findings and taking into account the differences of various [Cp*TM(III)] in terms of Lewis acidity and steric effects, we envisaged that the reaction pathway between [3 + 2] and [4 + 2] annulation can be switched by tuning the TM catalyst species under similar reaction conditions, thus giving rise to completely different types of products from the same substrates. To the best of our knowledge, such a catalyst-controlled annulation mode remains an unexploited area.

Scheme 1. Diversified Reaction Modes of Oximes via TM-Catalyzed C−H Annulation



To validate our working hypothesis and in search for innovative transformation modes with oxime derivatives, we turned our attention to versatile and relatively electron-neutral propargyl alcohols as the model coupling partners, which have

Received: November 15, 2017

DOI: 10.1021/acs.orglett.7b03546
Org. Lett. XXXX, XXX, XXX−XXX

been used as one-, two-, or three-carbon synthons in TM-catalyzed C−H functionalization to deliver valuable structures.[9] Herein, we reveal the catalyst-controlled regioselective room-temperature C−H activation followed by [3 + 2] and [4 + 2] annulations of oximes with propargyl alcohols in rhodium(III) and iridium(III) catalysis, respectively (Scheme 1b). The hydroxyl group in the tertiary propargyl alcohol substrate is crucial for the chemoselectivity, probably due to its different binding affinities and modes with TM catalysts to induce the polarity of TM−C bonds at different levels, thus leading to efficient and chemoselective synthesis of indenamines and isoquinolines. Since both of the resulting products are privileged structural frameworks and present in many bioactive natural products and drug candidates,[10] the two atom-economical transformations should have broad synthetic utility.

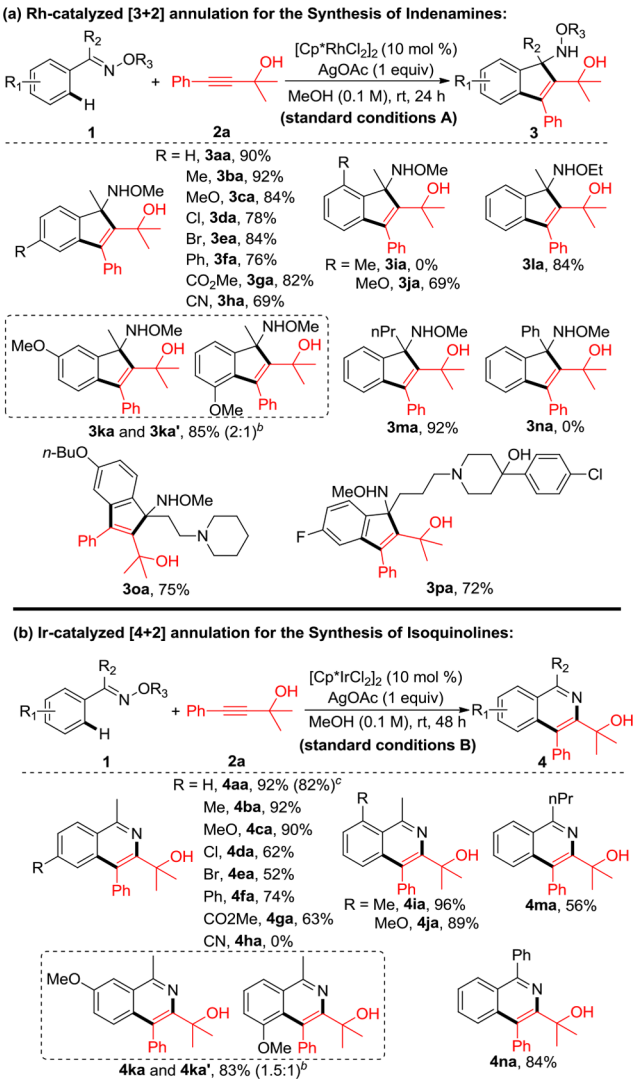
We commenced our investigation by examining the reaction of *O*-methyl oxime (**1a**) with 2-methyl-4-phenylbut-3-yn-2-ol (**2a**) under rhodium(III)-catalyzed conditions (see Supporting Information). In the presence of CsOAc (1 equiv), a trace of indenamine product **3aa** with specific regioselectivity could be obtained via a [3 + 2] annulation. As the rhodium(III)-catalyzed coupling between ketoximes and alkynes typically affords isoquinoline derivatives via a [4 + 2] annulation, the novel [3 + 2] selectivity prompted us to do further studies. A screening of additives indicated that AgOAc was an optimal base, affording the desired indenamine **3aa** in 90% yield, while other additives gave inferior results. Interestingly, an alternative [4 + 2] annulation could be achieved by simply switching $[Cp^*RhCl_2]_2$ to $[Cp^*IrCl_2]_2$ with the same substrates, leading to the efficient synthesis of isoquinoline product **4aa** with specific regioselectivity. The molecular structures of **3aa** and **4aa** were confirmed by single-crystal X-ray analysis (CCDC 1476867 and CCDC 1476868, respectively).

With the optimal conditions in hand, we next examined the reaction scope of oximes under rhodium(III)-catalyzed conditions for the synthesis of indenamine derivatives (Scheme 2a). Fortunately, various commonly encountered functional groups, including methyl (**3ba**), methoxyl (**3ca**), halogens (**3da** and **3ea**), phenyl (**3fa**), ester (**3ga**), and cyano (**3ha**), were well tolerated to furnish the corresponding products in moderate to good yields. With *ortho*-methoxyl-substituted *O*-methoxy oxime, the reaction proceeded smoothly to give the desired product in moderate yield (**3ja**), whereas *ortho*-methyl-substituted *O*-methoxyl oxime resulted in no reaction (**3ia**). When *meta*-methoxyl-substituted *O*-methoxyl oxime was used, the arene rhodation occurred at both sites, giving a mixture of regioisomers (**3ka** and **3ka′**). The reaction was also compatible with substrates bearing different substituents on the oxygen atom (**3la**) or α position of oxime (**3ma**), leading to the corresponding indenamine skeletons in good yields.

Encouraged by the above results, we were next intrigued to explore the feasibility of complex bioactive substrates for the late-stage C−H bond modifications. To our delight, the oxime derivatives of marketed drugs Dyclonine (**1o**) and Haloperidol (**1p**) underwent the coupling with **2a** smoothly to afford the desired indenamines, which not only provided an efficient and attractive strategy to generate new analogues of Haloperidol and Dyclonine for immediate drug screening but also further illustrated profound potential for late-stage C−H bond modifications in synthetic chemistry.

Subsequently, a variety of oximes were assessed for the synthesis of isoquinolines under optimized iridium(III)-catalyzed conditions (Scheme 2b). Good tolerance of *para*- or

Scheme 2. Scope of Oxime Substrates[a]



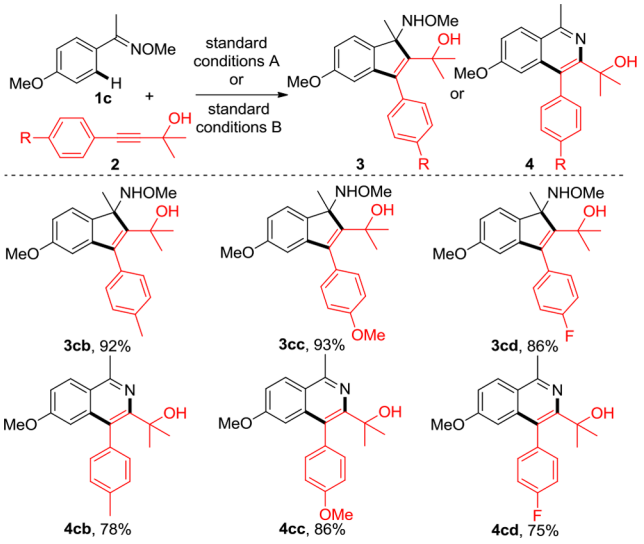
[a]All reactions were carried out in 0.2 mmol scale; isolated yield was reported. [b]Contained an inseparable mixture of isomers; the ratio was determined by ^1H NMR. [c]Yield of the product obtained with *O*-ethyl oxime **1l** is shown in the parentheses.

ortho-methyl-, methoxyl-, halogen-, phenyl-, and ester-substituted oximes was observed, furnishing the desired isoquinoline derivatives in moderate to good yields (**4aa**−**ga**, **4ia**, and **4ja**). In the case of *meta*-methoxy-substituted *O*-methoxy oxime, an inseparable mixture of regioisomers was obtained (**4ka** and **4ka′**). Moreover, α-propyl- and phenyl-substituted *O*-methoxy oximes also reacted smoothly, affording moderate yields of expected products (**4ma** and **4na**). It is necessary to note that other oximes bearing heterocyclic skeletons, such as furan and benzothiophene, as well as *O*-phenyl and *O*-*tert*-butyl oximes, were not tolerated for such rhodium(III)- or iridium(III)-catalyzed transformations (see the Supporting Information).

The scope of propargyl alcohols for the synthesis of indenamines and isoquinolines was then explored (Scheme 3). It is noteworthy that the tertiary alcohols are essential in controlling the chemo- and regioselectivity of these reactions. When **1c** was used as the model substrate, several propynol derivatives bearing different substituents on the phenyl ring were

DOI: 10.1021/acs.orglett.7b03546
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Scope of Propargyl Alcohols[a]



[a]All reactions were carried out in 0.2 mmol scale; isolated yield was reported.

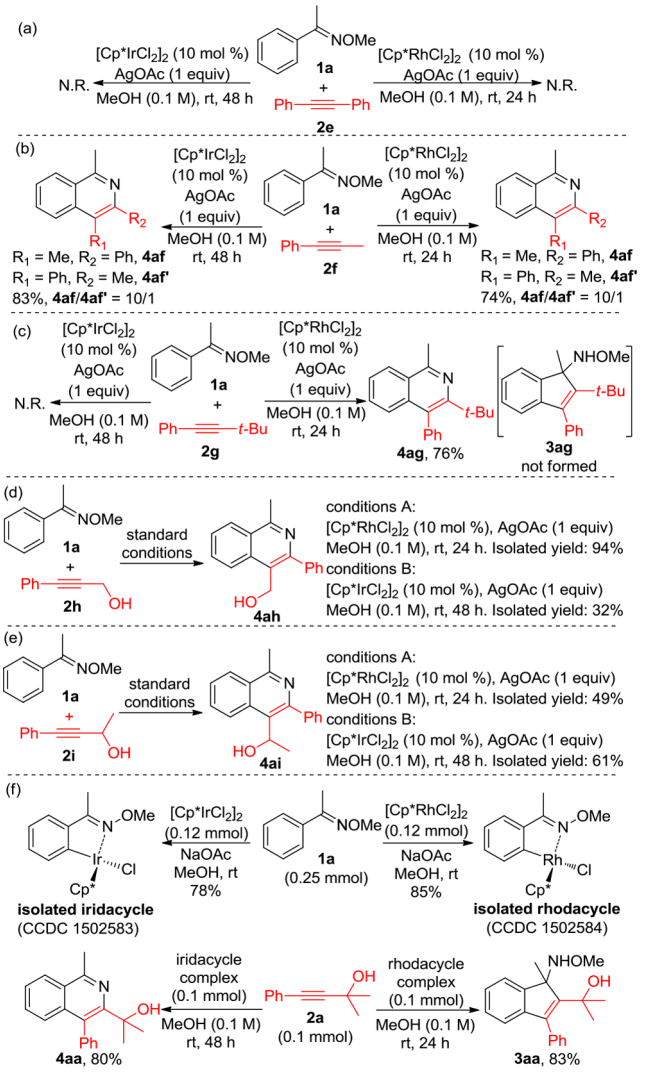
well tolerated to afford corresponding indenamine (**3cb**–**cd**) and isoquinoline (**4cb**–**cd**) derivatives in good yields.

To gain more insights into the effect of the tertiary alcohol group for these transformations, a series of experimental investigations were then carried out (Scheme 4). Diphenyl acetylene (**2e**) resulted in no reaction for both rhodium(III)- and iridium(III)-catalyzed conditions (Scheme 4a), whereas prop-1-yn-1-ylbenzene (**2f**) converted into a mixture of regioisomers of isoquinoline product under the standard conditions (Scheme 4b). When (3,3-dimethylbut-1-yn-1-yl)benzene (**2g**) was subjected to the reaction under rhodium(III)-catalyzed conditions, an exclusive regioselctive isoquinoline product (**4ag**) was obtained instead of an indenamine derivative (Scheme 4c). Moreover, both primary and secondary alcohols (**2h** and **2i**) resulted in contrary regioselectivity compared with tertiary alcohols, thus yielding only isoquinoline derivatives regardless of what catalyst was used (Scheme 4d,e). Summarizing these results, we can draw the following conclusions for these transformations: (1) the specific regioselectivity is probably due to the steric hindrance between *gem*-dimethyl and the C_3–H of the oxime substrate;[11] (2) the hydroxyl group in the tertiary propargyl alcohol substrate is essential for the [3 + 2] selectivity under rhodium(III)-catalyzed conditions.

Finally, stoichiometric amounts of $[Cp^*RhCl_2]_2$ as well as $[Cp^*IrCl_2]_2$ were treated with **1a** to capture the potential reactive intermediates (Scheme 4f). To our delight, both rhodacycle intermediate (CCDC 1502584) and iridacycle intermediate (CCDC 1502583) could be isolated successfully and characterized by X-ray crystallography. The following annulation of metallocycles with **2a** easily converted into the final indenamine and isoquinoline products, revealing that the reactions were initiated with the same arene metalation to afford the five-membered metallocycles as active intermediates, even though different KIE values were given in further isotope-labeling experiments (see the Supporting Information).

In summary, by employing tertiary propargyl alcohol derivatives as versatile coupling partners, we have developed efficient catalyst-controlled room-temperature C–H transformations of oximes for divergent synthesis of indenamine

Scheme 4. Experimental Investigation



and isoquinoline skeletons. Switchable [3 + 2] and [4 + 2] annulations can be achieved, respectively, under rhodium(III)- and iridium(III)-catalyzed conditions. The hydroxyl group in the tertiary propargyl alcohol substrate is crucial in controlling the chemoselectivity probably due to its distinctive coordination interaction with different TM catalysts depending on their Lewis acidities and steric effects. Considering the mild reaction conditions, good functional group tolerance, the valuable structure of the products, and the application potential for late-stage C–H functionalization, the present protocols should have further synthetic utility in constructing complex compounds and can also evoke more catalyst-controlled C–H activation reactions for divergent synthesis of other important structural motifs. More detailed investigations to understand the reaction mechanism and exploration for new transformation properties of propargyl alcohols in other TM catalysts, such as the recently popular cobalt(III) and manganese(I) species,[12] are in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03546.

DOI: 10.1021/acs.orglett.7b03546
Org. Lett. XXXX, XXX, XXX–XXX

Experimental procedures, characterization of products, and ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1476867−1476868 and 1502583−1502584 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 Author

*E-mail: yiwei@gzhmu.edu.cn.

ORCID

Wei Yi: 0000-0001-7936-9326

Present Address

[⊥]Central Research Institute of Shanghai Pharmaceuticals Holding Co., Ltd., Shanghai 201203, China.

Author Contributions

[§]W.G., Z.Z., and J.S. contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank NSFC (81502909), Guangdong Natural Science Funds for Distinguished Young Scholar (2017A030306031) for financial support on this study.

REFERENCES

(1) (a) Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003. For selected reviews, see: (b) Zhang, M. *Adv. Synth. Catal.* **2009**, *351*, 2243. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Gulías, M.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2016**, *55*, 11000.

(2) For selected reviews, see: (a) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (b) Colby, D. A.; Tsai, A. S.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2012**, *45*, 814. (c) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007. (d) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (e) Zhang, Y.; Zhang, Y.; Jie, X.; Zhao, H.; Li, G.; Su, W. *Org. Chem. Front.* **2014**, *1*, 843. (f) Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, *5*, 369. (g) Sun, H.; Guimond, N.; Huang, Y. *Org. Biomol. Chem.* **2016**, *14*, 8389. (h) Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900. (i) Agasti, S.; Dey, A.; Maiti, D. *Chem. Commun.* **2017**, *53*, 6544. (j) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864. (k) Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, *117*, 9247. (l) Rao, W.-H.; Shi, B.-F. *Org. Chem. Front.* **2016**, *3*, 1028.

(3) For selected recent reviews of C−H functionalization of oximes, see: (a) Huang, H.; Ji, X.; Wu, W.; Jiang, H. *Chem. Soc. Rev.* **2015**, *44*, 1155. (b) Huang, H.; Cai, J.; Deng, G.-J. *Org. Biomol. Chem.* **2016**, *14*, 1519. (c) Li, J.; Hu, Y.; Zhang, D.; Liu, Q.; Dong, Y.; Liu, H. *Adv. Synth. Catal.* **2017**, *359*, 710.

(4) For selected examples of transition-metal-catalyzed C−H annulation of oximes with alkynes, see: (a) Kornhaaß, C.; Li, J.; Ackermann, L. *J. Org. Chem.* **2012**, *77*, 9190. (b) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780. (c) Wang, H.; Koeller, J.; Liu, W.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 15525. (d) Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Angew. Chem., Int. Ed.* **2015**, *54*, 12968. (e) Muralirajan, K.; Kuppusamy, R.; Prakash, S.; Cheng, C.-H. *Adv. Synth. Catal.* **2016**, *358*, 774.

(5) For some recent examples of transition-metal-catalyzed C−H annulation of oximes with alkenes, see: (a) Chu, H.; Sun, S.; Yu, J.-T.; Cheng, J. *Chem. Commun.* **2015**, *51*, 13327. (b) Wen, J.; Wu, A.; Miao, Y.; Zhu, J. *Tetrahedron Lett.* **2015**, *56*, 5512. (c) Chen, R.; Qi, J.; Mao, Z.; Cui, S. *Org. Biomol. Chem.* **2016**, *14*, 6201. (d) Boerth, J. A.; Ellman, J. A. *Chem. Sci.* **2016**, *7*, 1474. (e) Zhang, Z.; Tang, M.; Han, S.; Ackermann, L.; Li, J. *J. Org. Chem.* **2017**, *82*, 664.

(6) (a) Shi, Z.; Koester, D. C.; Boultadakis-Arapinis, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 12204. (b) Iagafarova, I. E.; Vorobyeva, D. V.; Peregudov, A. S.; Osipov, S. N. *Eur. J. Org. Chem.* **2015**, *2015*, 4950. (c) Phatake, R. S.; Patel, P.; Ramana, C. V. *Org. Lett.* **2016**, *18*, 292.

(7) For selected examples, see: (a) Yu, S.; Li, X. *Org. Lett.* **2014**, *16*, 1220. (b) Zhou, X.; Yu, S.; Kong, L.; Li, X. *ACS Catal.* **2016**, *6*, 647. (c) Kim, H.; Chang, S. *Angew. Chem., Int. Ed.* **2017**, *56*, 3344.

(8) Zhou, X.; Yu, S.; Qi, Z.; Li, X. *Sci. China: Chem.* **2015**, *58*, 1297.

(9) For the lastest examples of transition-metal-catalyzed C−H annulation with propargyl alcohols, see: (a) Wu, X.; Wang, B.; Zhou, S.; Zhou, Y.; Liu, H. *ACS Catal.* **2017**, *7*, 2494. (b) Wu, X.; Wang, B.; Zhou, Y.; Liu, H. *Org. Lett.* **2017**, *19*, 1294. (c) Sen, M.; Dahiya, P.; Premkumar, J. R.; Sundararaju, B. *Org. Lett.* **2017**, *19*, 3699. (d) Lu, Q.; Greßies, S.; Klauck, F. J. R.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 6660. (e) Lu, Q.; Greßies, S.; Klauck, F. J. R.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 6660. (f) Hu, X.; Chen, X.; Zhu, Y.; Deng, Y.; Zeng, H.; Jiang, H.; Zeng, W. *Org. Lett.* **2017**, *19*, 3474. (g) Xu, Y.; Wang, F.; Yu, S.; Li, X. *Chin. J. Catal.* **2017**, *38*, 1390. (h) Lu, Q.; Greßies, S.; Cembellín, S.; Klauck, F. J. R.; Daniliuc, C. G.; Glorius, F. *Angew. Chem., Int. Ed.* **2017**, *56*, 12778.

(10) (a) Vieth, M.; Cummins, D. J. *J. Med. Chem.* **2000**, *43*, 3020. (b) Alajarín, R.; Burgos, C. In *Modern Heterocyclic Chemistry*; Alvarez-Builla, J., Vaquero, J. J., Barluenga, J., Eds.; Wiley-VCH: Weinheim, 2011; Vol. 3, p 1527.

(11) Liao, G.; Song, H.; Yin, X.-S.; Shi, B.-F. *Chem. Commun.* **2017**, *53*, 7824.

(12) For selected recent reviews, see: Wang, S.; Chen, S.-Y.; Yu, X.-Q. *Chem. Commun.* **2017**, *53*, 3165. (b) Yoshino, T.; Matsunaga, S. *Adv. Synth. Catal.* **2017**, *359*, 1245.

DOI: 10.1021/acs.orglett.7b03546
Org. Lett. XXXX, XXX, XXX−XXX