Gold(I)-Catalyzed and H$_2$O-Mediated Carbene Cascade Reaction of Propargyl Diazoacetates: Furan Synthesis and Mechanistic Insights

Ming Bao,[†,‡] Yu Qian,[†] Han Su,[‡] Bing Wu,[‡] Lihua Qiu,[‡] Wenhao Hu,*[,†][iD] and Xinfang Xu*[,†,‡][iD]

[†]School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China
[‡]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China
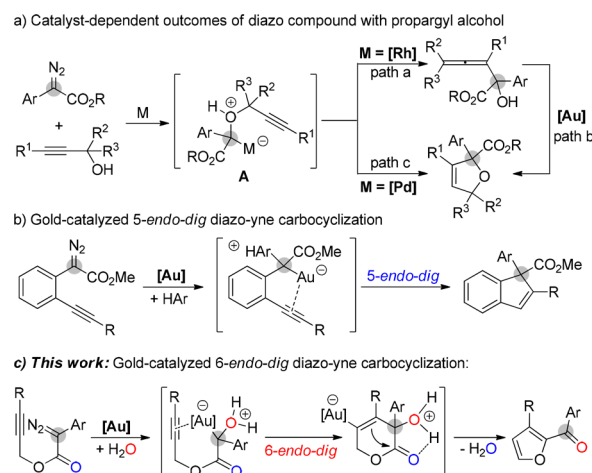
S *Supporting Information*

ABSTRACT: A novel gold-catalyzed water-mediated carbene cascade reaction of propargyl diazoacetates has been developed. Mechanistic investigation indicates that this reaction is initiated by gold-catalyzed gold–carbene formation followed by an unprecedented *6-endo-dig* carbocyclization with tethered alkyne through an oxonium ylide intermediate, terminated by a β-H elimination/protodeauration process to give the aromatized furan products in good to high yields with broad substrate generality. Notably, the proposed gold–carbene intermediates are verified by interception experiments.
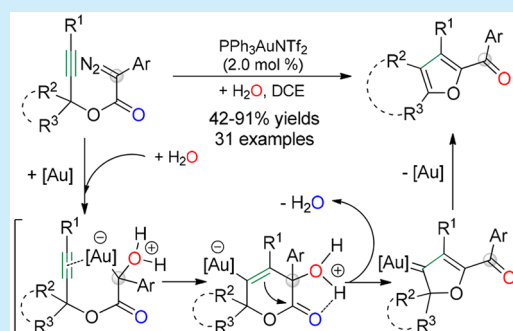
Transition-metal-catalyzed carbene reactions of diazo compounds represent a powerful tool in modern organic synthesis, allowing for the rapid assembly of valuable complex molecules which cannot be readily synthesized by other methods.[1] A variety of metal catalysts have been reported to mediate these transformations effectively, including rhodium,[2] copper,[3] palladium,[4] gold,[5] silver,[6] and others.[7] In particular, different metal–carbenes often exhibit distinct reactivity and selectivity, and the selection of metal catalysts is vital to the chemoselectivity in the carbene reactions.[8] For example, divergent outcomes have been disclosed in the catalytic reaction of diazoesters with propargylic alcohols,[9,10] although these transformations go through a common intermediate oxonium ylide **A** (Scheme 1a). Davies has reported that α-hydroxy allene was formed with excellent enantioselectivity through [2,3]-sigmatropic rearrangement (Scheme 1a, path a).[9] A stepwise formal [4 + 1] cycloaddition was then observed through a gold-catalyzed 5-*endo-dig* cyclization of in situ generated α-hydroxy allene (path b).[10a] Meanwhile, Hu developed a Pd-catalyzed direct [4 + 1] cycloaddition of diazoesters with propargylic alcohols to produce 2,5-dihydrofurans via corresponding oxonium ylide **A** (path c).[10b] Recently, Toste has disclosed a gold-catalyzed oxidative rearrangement of alkyne-tethered diazoketones via a gold-catalyzed 5-*exo-dig* carbocyclization.[11] Instead of using a diazo compound, Hashmi[12a] and Tang[12b] reported a catalytic oxidative 5-*exo-dig* cyclization of diynes in the presence of gold and rhodium catalysts, respectively. On the other hand, Zhang reported a gold-promoted 5-*endo-dig* carbocyclization of alkyne-tethered diazoacetates through a zwitterionic intermediate (Scheme 1b).[13] Inspired by these advances, and in continuation of our interest in carbene/alkyne metathesis (CAM) transformations,[14–16] we envisioned that the

Scheme 1. Catalytic Reaction of Diazo with Alkyne

a) Catalyst-dependent outcomes of diazo compound with propargyl alcohol

b) Gold-catalyzed 5-*endo-dig* diazo-yne carbocyclization

c) *This work:* Gold-catalyzed 6-*endo-dig* diazo-yne carbocyclization:
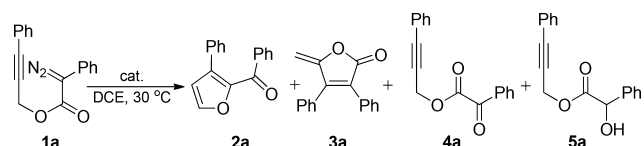
CAM process might be facilitated by the gold catalyst due to its soft Lewis acidity, which can activate the alkyne and bring this part close to the gold–carbene center for the metathesis process to occur preferentially. Herein, we report our recent results on this direction, a novel gold-catalyzed carbene cascade reaction of propargyl diazoacetates, which provides general access for the synthesis of multisubstituted furans in good to high yields with broad substrate generality under mild reaction conditions. In addition, the key step in this cascade transformation involving an unprecedented gold-catalyzed 6-*endo-dig* diazo-yne cyclization

(Scheme 1c) and the proposed gold–carbene intermediates are verified by interception experiments.

Initially, the propargyl diazoacetate **1a**, which was readily prepared with phenylacetic acid and propiolic alcohol via esterification followed by a diazo-transfer reaction,[17] was used as the model substrate (Table 1). To our delight, the furan product

Table 1. Condition Optimization[a]

entry	cat.	H₂O (equiv)	yield (%)[b] of 2a/3a/4a/5a
1[c]	PPh₃AuCl	0	
2	PPh₃AuNTf₂	0	57/12/<5/−
3[d]	AuCl₃	0	
4[d]	JohnphosAuSbF₆	0	−/<5/<5/−
5[e]	PPh₃AuNTf₂	0	−/<5/<5/−
6	PPh₃AuNTf₂	5.0	83/8/<5/<5
7[f]	PPh₃AuNTf₂	5.0	81/6/8/<5

[a]Unless indicated otherwise, the reaction of **1a** (55.2 mg, 0.2 mmol) was carried out at 30 °C in the presence of catalyst (2.0 mol %) in DCE (2.0 mL) with indicated equivalents of water for 8 h under argon atmosphere. [b]Isolated yields. [c]No reaction occurred, and most of the material **1a** was recovered. [d]All of the starting material was decomposed into a complex mixture. [e]100 mg of 4 Å MS was added, and the cross-coupling product of **1a** was obtained. [f]The reaction was carried out under open air.

2a was obtained in moderate yield combined with **3a** in 12% yield when the reaction was catalyzed by PPh₃AuNTf₂ (entry 2). It should be noted that only the cross-coupling product of diazo compound was generated when 4 Å MS was used as additive (entry 5), which indicates that water might be involved in the formation of furan product **2a**. NMR Analysis was conducted of the cationic gold catalyst in the presence of water, and no detectable variation was observed (see Figure S9 for details). After further optimizing the conditions by conducting the reaction in the presence of H₂O (5 equiv), the yield was improved significantly (83% yield, entry 6).[18] The other transition-metal catalysts, which have been reported to activate the diazo compound, were screened under these conditions, such as silver, rhodium, copper, and palladium salts (see Table S1).[17] Unfortunately, products **3**–**5** were isolated as the major products.[17] Notably, comparably high yield was obtained when the reaction was carried out under open air (entry 7). The structure of **2a** was inferred from X-ray diffraction analysis of its bromo analogue **2d**, and the generated 2-benzoylfuran motif is a core structure in many bioactive molecules,[20] such as the anti-inflammatory drug furprofen.[20a]

With the optimal reaction conditions established, the substrate scope with respect to the diazo compounds was investigated (Scheme 2). On the pendant alkyne, both electron-neutral and electron-rich aryl groups were all tolerated and gave the corresponding products in 67−87% yields (**2a**−**j**). Pleasingly, the sterically encumbered substrates had little impact on the efficiency of this transformation, and comparably high yields were obtained with both *ortho*- and *meta*-substituted diazo compounds (**2i,j**). In the case of alkyne with *o*-azido and *o*-alkenyl groups, the corresponding furan products **2k** and **2l** were also generated in 85% and 65% yields, respectively. The 1-

Scheme 2. Substrate Scope[a,b]
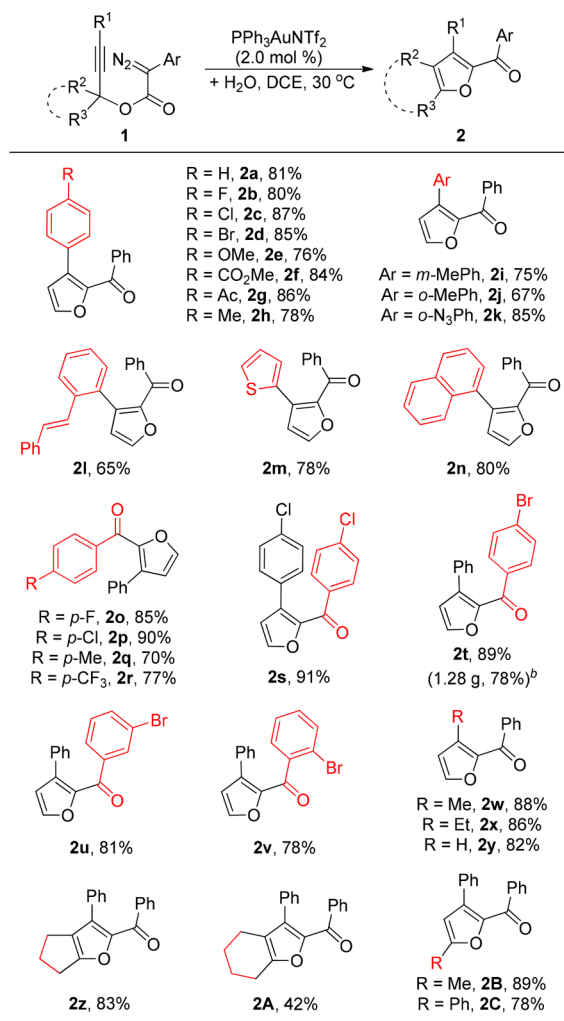
[a]Reactions were carried out on a 0.2 mmol scale with PPh₃AuNTf₂ (3.0 mg, 2.0 mol %) in DCE (2.0 mL) at 30 °C under open air for 8 h. [b]The reaction was carried out on a 5.0 mmol scale.

thienyl and 1-naphthyl group substituted diazo compounds also underwent the reaction smoothly, leading to the furan products in high yields (**2m** and **2n**). The effect of the aryl group adjacent to the diazo group was then evaluated; both electron-donating and electron-withdrawing group substituted aryl diazo compounds smoothly transformed to the corresponding products with fairly good yields (**2o**−**v**). Notably, the alkyl and terminal alkynes were well tolerated, and the desired products were isolated in high yields (**2w**−**y**). When the methylene part was exchanged with a cyclic species, the corresponding fused-cyclic products **2z** and **2A** were obtained in 83% and 42% yields. Moreover, with methyl- or phenyl-substituted methine as the linkage, substrates **1B** and **1C** performed well under these conditions to offer the H-migration products **2B** and **2C**[20e] in 81% and 78% yields, respectively. In addition, this reaction could be performed on a gram scale with slightly lower yields (**2t**, 78% yield, Scheme 2, note b).

To gain insight into the reaction mechanism, a series of control experiments were carried out. First, compounds **4a** and **5a** were isolated, and each was subjected to the standard reaction conditions. However, the furan product **2a** was not detected, which excluded the process of formation **2a** through **4a** or **5a**.[9,17]

No reaction occurred with corresponding substrate without the diazo group under the standard conditions,[17] which indicates that the reaction might initiate with the diazo group. Moreover, corresponding carbonylation and cyclopropanation products **4a** and **7** were isolated in high yields when the reactions were carried out under standard conditions in the presence of diphenyl sulfoxide and styrene, respectively (eq 1), which
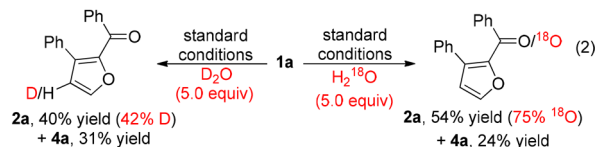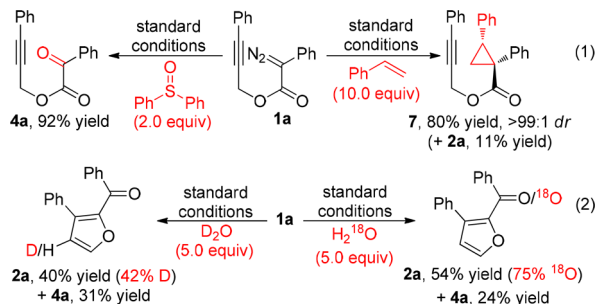
indicate that the reaction was initiated via the formation of gold carbene **A** (Scheme 3). Then isotope-labeled experiments were

Scheme 3. Proposed Reaction Mechanism
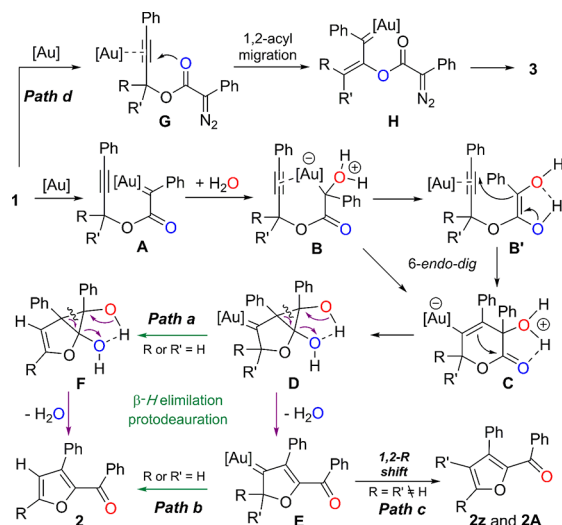
carried out under the standard conditions. The deuterated product **2a** was observed (eq 2, 42% D, see Figure S3 for details),[17] which suggests that a hydrogen elimination/protodeauration should be involved in this cascade process. In addition, the corresponding **2a-O**[18] product was formed when the reaction was performed in the presence of 5.0 equiv of H_2O^{18} (eq 2, 75% O,[18] see Figure S6 for details).[17] These results indicate that water must be involved in this cascade reaction, and the oxygen atom on the carbonyl group of the furan product comes from water. On the basis of the above results and previous reports,[11,21] a possible mechanism is described in Scheme 3. Initially, gold-catalyzed dinitrogen expulsion of diazoacetate **1** forms the gold carbene **A**, followed by 6-*endo-dig* carbocyclization with tethered alkyne through an oxonium ylide **B**, or via the corresponding enol form species **B′**, to give intermediate **C**. Ring contraction with simultaneous H-shift of **C** delivers the second carbene intermediate **D**, which converts to another carbene intermediate **E** through a pinacol rearrangement with the assistance of intramolecular *H*-bond activation and releasing a molecular of H_2O. Finally, the reaction is terminated by a β-H

elimination/protodeauration process to give the aromatized furan product **2a**.[22] An alternative reaction order, β-H elimination/protodeauration to form **F** followed by ring expansion and release of a molecule of H_2O, may also contribute to the formation of final furan product **2**. Direct 1,2-shift of **E** may also possible led to the formation of **2**, especially in the cases for the formation of **2z** and **2A** (path c). The carbonylation byproduct **4a** and O−H insertion byproduct **5a** are generated from intermediates **A** and **B**, respectively. The formation of **3a** might go through a 1,2-acyl migration to form gold carbene **H** via **G**[23] followed by a coupling reaction with the diazo part to form the 5-membered framework (path d).[24]

To verify the existence of the second gold carbenoid intermediate (either **D** or **E** in Scheme 3), interception experiments of materials with tethered carbene-philic species were carried out. Although only furan product **2E** was observed in high yield with material **1E** (eq 3), the Friedel−Crafts-type
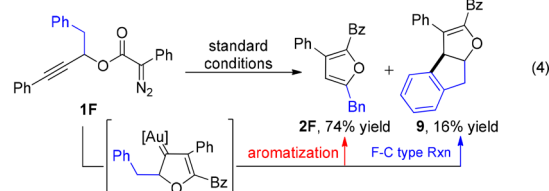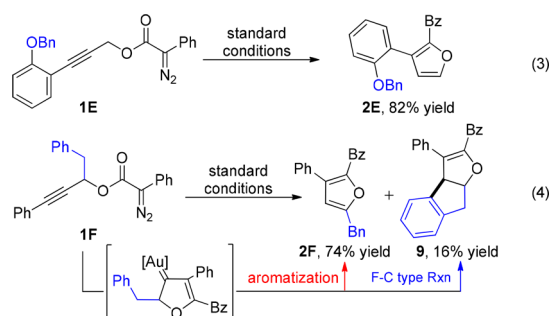
reaction product **9**, which might be generated via trapping of the corresponding gold carbenoid species **E** or another potential electrophilic intermediate (Scheme 3), was isolated and characterized from substrate **1F** under the standard conditions (eq 4).

To demonstrate the synthetic utility of the current method, further transformations with these furan products were conducted (Scheme 4). [4 + 2]-Cycloaddition of **2a** with

Scheme 4. Derivatization of 2
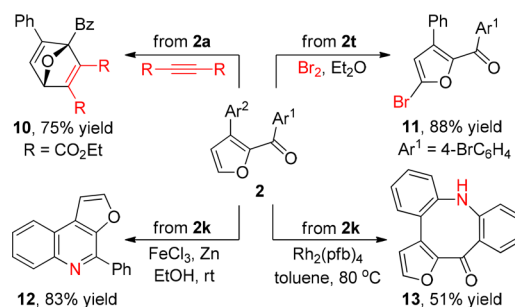
diethyl acetylenedicarboxylate occurred smoothly to form **10** in 75% yield. The furan product could be converted to 2-bromo derivative **11** in 88% yield when treated with bromine, which could be used for further modifications via coupling reactions.[17] Notably, the quinoline product **12** was obtained in 83% yield via an intramolecular catalytic reductive cyclization. In addition, the 8-membered heterocyclic product **13** could be generated in 51% yield from **2k** catalyzed by $Rh_2(pfb)_4$. These postsynthetic modifications of these generated 2-carboxyl furan products enhanced the potential value of this process.

In summary, we have developed a novel gold(I)-catalyzed carbene cascade reaction of propargyl diazoacetates that

provides straightforward access to the synthesis of multi-substituted furans in high to excellent yields. The salient features of this reaction include readily available starting materials, mild conditions, good functional group tolerance, and ease of further transformations. The mechanistic studies indicate that the assistance effect of water is essential in this unprecedented gold-catalyzed 6-endo-dig diazo-yne carbocyclization, and the proposed gold carbene intermediates are verified by interception experiments.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02251.

Experimental procedure and spectroscopic data for all compounds and crystallographic data for **2d** (PDF)

Accession Codes

CCDC 1827998 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
*E-mail: huwh9@mail.sysu.edu.cn.
*E-mail: xinfangxu@suda.edu.cn.

ORCID Ⓞ
Wenhao Hu: 0000-0002-1461-3671
Xinfang Xu: 0000-0002-8706-5151

Notes
The authors declare no competing financial interest.

■ REFERENCES

(1) For reviews, see: (a) Davies, H. M. L.; Hedley, S. J. *Chem. Soc. Rev.* **2007**, *36*, 1109. (b) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (c) Xia, Y.; Qiu, D.; Wang, J. *Chem. Rev.* **2017**, *117*, 13810. (d) Ford, A.; Miel, H.; Ring, A.; Slattery, C. N.; Maguire, A. R.; McKervey, M. A. *Chem. Rev.* **2015**, *115*, 9981.

(2) (a) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857. (b) Guo, X.; Hu, W. *Acc. Chem. Res.* **2013**, *46*, 2427. (c) Deng, Y.; Qiu, H.; Srinivas, H. D.; Doyle, M. P. *Curr. Org. Chem.* **2016**, *20*, 61.

(3) (a) Zhu, S.; Zhou, Q. *Acc. Chem. Res.* **2012**, *45*, 1365. (b) Zhao, X.; Zhang, Y.; Wang, J. *Chem. Commun.* **2012**, *48*, 10162.

(4) (a) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. (b) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586.

(5) For reviews, see: (a) Fructos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2016**, *52*, 7326. (b) Liu, L.; Zhang, J. *Chem. Soc. Rev.* **2016**, *45*, 506. Selected examples: (c) Briones, J. F.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 13314. (d) Yu, Z.; Ma, B.; Chen, M.; Wu, H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904. (e) Xi, Y.; Su, Y.; Yu, Z.; Dong, B.; McClain, E. J.; Lan, Y.; Shi, X. *Angew. Chem.,*

Int. Ed. **2014**, *53*, 9817. (f) Cao, Z.; Wang, X.; Tan, C.; Zhao, X.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197.

(6) (a) Hansen, J. H.; Davies, H. M. L. *Chem. Sci.* **2011**, *2*, 457. (b) Dias, R. H. V.; Browning, G. R.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 9270. (c) Thompson, J. L.; Davies, H. M. L. *J. Am. Chem. Soc.* **2007**, *129*, 6090.

(7) (a) Chan, W.; Yeung, S.; Zhou, Z.; Chan, A. S. C.; Yu, W. *Org. Lett.* **2010**, *12*, 604. (b) Cai, Y.; Zhu, S.; Wang, G.; Zhou, Q. *Adv. Synth. Catal.* **2011**, *353*, 2939. (c) Lo, V. K.; Guo, Z.; Choi, M. K.; Yu, W.; Huang, J.; Che, C. *J. Am. Chem. Soc.* **2012**, *134*, 7588.

(8) Xu, X.; Doyle, M. P. *Chin. Chem. Lett.* **2015**, *26*, 227.

(9) (a) Li, Z.; Boyarskikh, V.; Hansen, J. H.; Autschbach, J.; Musaev, D. G.; Davies, H. M. L. *J. Am. Chem. Soc.* **2012**, *134*, 15497. (b) Moniz, G. A.; Wood, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 5095.

(10) (a) Wang, J.; Yao, X.; Wang, T.; Han, J.; Zhang, J.; Zhang, X.; Wang, P.; Zhang, Z. *Org. Lett.* **2015**, *17*, 5124. (b) Shi, T.; Guo, X.; Teng, S.; Hu, W. *Chem. Commun.* **2015**, *51*, 15204.

(11) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838.

(12) (a) Nösel, P.; Comprido, L. N. S.; Lauterbach, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *J. Am. Chem. Soc.* **2013**, *135*, 15662. (b) Liu, R.; Winston-McPherson, G. N.; Yang, Z.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W. *J. Am. Chem. Soc.* **2013**, *135*, 8201.

(13) Ma, B.; Wu, Z.; Huang, B.; Liu, L.; Zhang, J. *Chem. Commun.* **2016**, *52*, 9351.

(14) (a) Padwa, A.; Xu, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5881. (b) Hoye, T. R.; Dinsmore, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4343. CAM reaction for the formation of furans: (c) Kinder, F. R.; Padwa, A. *Tetrahedron Lett.* **1990**, *31*, 6835. (d) Padwa, A.; Straub, C. S. *Org. Lett.* **2000**, *2*, 2093. (e) Padwa, A.; Straub, C. S. *J. Org. Chem.* **2003**, *68*, 227.

(15) Selected advances: (a) Le, P. Q.; May, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 12219. (b) González-Rodríguez, C.; Suárez, J. M.; Varela, J. A.; Saá, C. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 2724. (c) Qian, Y.; Shanahan, C. S.; Doyle, M. P. *Eur. J. Org. Chem.* **2013**, *2013*, 6032. (d) Torres, Ó.; Parella, T.; Solà, M.; Roglans, A.; Pla-Quintana, A. *Chem. - Eur. J.* **2015**, *21*, 16240. (e) Zhou, L.; Liu, Y.; Zhang, Y.; Wang, J. *Beilstein J. Org. Chem.* **2011**, *7*, 631.

(16) Our works: (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.

(17) See the Supporting Information for details.

(18) Li, L.; Shu, C.; Zhou, B.; Yu, Y.; Xiao, X.; Ye, L. *Chem. Sci.* **2014**, *5*, 4057.

(19) Wang, Y.; Wang, Z.; Li, Y.; Wu, G.; Cao, Z.; Zhang, L. *Nat. Commun.* **2014**, *5*, 3470.

(20) (a) D'Angelo, V.; Tessari, F.; Bellagamba, G.; De Luca, E.; Cifelli, R.; Celia, C.; Primavera, R.; Di Francesco, M.; Paolino, D.; Di Marzio, L.; Locatelli, M. *J. Enzyme Inhib. Med. Chem.* **2016**, *31*, 110. (b) Reichstein, A.; Vortherms, S.; Bannwitz, S.; Tentrop, J.; Prinz, H.; Müller, K. *J. Med. Chem.* **2012**, *55*, 7273. (c) Jana, R.; Paul, S.; Biswas, A.; Ray, J. K. *Tetrahedron Lett.* **2010**, *51*, 273. (d) Hosseyni, S.; Su, Y.; Shi, X. *Org. Lett.* **2015**, *17*, 6010. (e) Du, X.; Chen, H.; Liu, Y. *Chem. - Eur. J.* **2008**, *14*, 9495.

(21) For reviews on gold-catalyzed alkyne carbocyclization, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Zhang, L. *Acc. Chem. Res.* **2014**, *47*, 877. (c) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028. Selected recent examples: (d) Henrion, G.; Chavas, T. E. J.; Le Goff, X.; Gagosz, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6277. (e) Wang, Y.; Zheng, Z.; Zhang, L. *J. Am. Chem. Soc.* **2015**, *137*, 5316. (f) Sahani, R. L.; Liu, R. *Angew. Chem., Int. Ed.* **2017**, *56*, 1026.

(22) Cai, J.; Wu, B.; Rong, G.; Zhang, C.; Qiu, L.; Xu, X. *Org. Lett.* **2018**, *20*, 2733.

(23) (a) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 9244. (c) Rettenmeier, E.; Schuster, A. M.; Rudolph, M.; Rominger, F.; Gade, C. A.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 5880.

(24) Liu, P.; Sun, J. *Org. Lett.* **2017**, *19*, 3482.