Organic LETTERS

Letter

pubs.acs.org/OrgLett

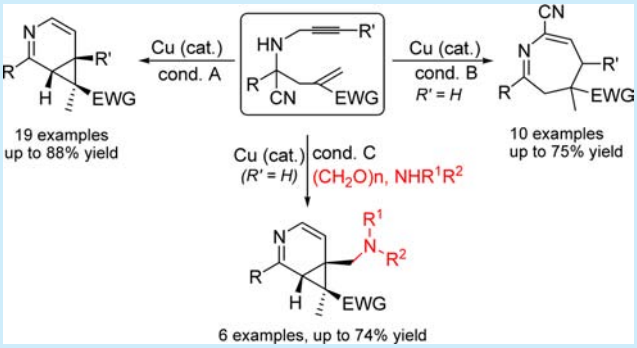
Copper-Promoted Cyclization of α-Amino Nitrile-Tethered Enynes: Controllable Synthesis of 3-Azabicyclo[4.1.0]hepta-2,4-dienes and 4,5-Dihydro-3*H*-azepines

Qiu-Qin Xu,[†,§] Qi-Lan Hou,[‡,§] Wei Liu,[†] Hai-Jing Wang,[†] and Wei-Wei Liao*[,†]

[†]College of Chemistry and [‡]College of Life Science, Jilin University, 2699 Qianjin Street, Changchun 130012, China

Supporting Information

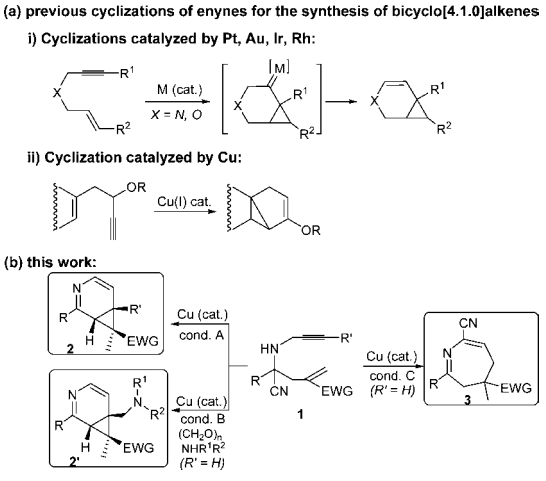
ABSTRACT: The first example of Cu-promoted cyclization of α-amino nitrile-tethered enynes incorporating an electron-deficient alkene component is described. A wide range of functionalized 3-azabicyclo[4.1.0]hepta-2,4-dienes and 4,5-dihydro-3*H*-azepines were prepared efficiently in a controllable manner. Moreover, the diverse cascade process enables efficient incorporation of tertiary amine moieties under mild reaction conditions. A possible reaction pathway is proposed on the basis of a series of control experiments.



Rapid and efficient construction of structural complexity from readily available starting materials represents an appealing and significant challenge in organic synthesis. The transition-metal-catalyzed cyclization of enynes offers an attractive pathway for the conversion of relatively simple acyclic substrates to a variety of valuable cyclic compounds which have been difficult to prepare by conventional methods.[1] Recently, the versatile cyclization chemistry of enynes has made possible the construction of valuable functional bicyclo[4.1.0]alkene frameworks by means of transition-metal catalysts.[1d,i,2,3] Typically, the presence of electron rich C−C double bond component is to be pivotal to the accomplishment of this electrophilic activation-involved transformation in which the N, O, or C atom bridged the C−C triple bond and double bond units (Scheme 1a), while the cyclization of enynes incorporating an electronically deficient C−C double bond proved to be challenging and has been never reported. On the other hand, this type of catalytic cyclization was dominated by Pt, Au, Ir, and Rh catalysts,[2] while other lower cost metal catalyzed cyclizations are rare. Fehr et al. disclosed an elegant copper-catalyzed cyclization of enyne including a propargylic alcohol moiety to construct a bicyclo[3.1.0]hexene framework, but with a limited substrate scope (Scheme 1a).[4] Moreover, the development of an efficient cyclization of enynes, which enables facile assembly of extra heteroatom units and subsequently functionalizes bicyclo[4.1.0]alkene frameworks, is unexploited. It is therefore of great significance to develop an alternative, less expensive metal-catalyzed cyclization of enynes containing an electron-deficient C−C double bond to furnish the structurally diverse cyclic compounds.

α-Amino nitriles are versatile intermediates in synthetic chemistry and have been widely used in the generation of multiple polyfunctional structures.[5] In the course of our efforts toward the development of efficient catalytic synthetic approaches to prepare nitrogen-containing heterocycles via functionalized α-amino nitriles,[6] we became interested in an alternative cyclization of α-amino nitrile-tethered enynes incoporating an electron-deficient alkene component to construct valuable aza-heterocycles. Herein, we report a controllable Cu-promoted cyclization of α-amino nitrile-tethered enynes to deliver various 3-azabicyclo[4.1.0]-hepta-2,4-dienes and 4,5-dihydro-3*H*-azepines with the novel feature that tertiary amine units are readily incorporated (Scheme

Scheme 1. Cyclization of Enynes



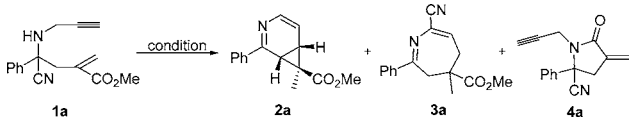
Received: June 27, 2016
Published: July 27, 2016

DOI: 10.1021/acs.orglett.6b01864
Org. Lett. 2016, 18, 3854−3857

1b),[7] which are challenging targets for current metal-mediated methods.

Our study began with the cyclization of α-amino nitrile tethered enyne **1a**. Initially, the lactamization was expected to occur to provide compound **4a** in the presence of Lewis acid. However, when enyne **1a** was treated with 10 mol % of $Ti(OEt)_4$, azabicyclo[4.1.0]hepta-2,4-diene **2a** was isolated in 67% yield, along with the small amount of 4,5-dihydro-3*H*-azepine **3a** and lactam **4a** (Table 1, entry 1). Lewis acids such as $Fe(acac)_3$ gave

Table 1. Selected Optimization of Reaction Conditions[a]



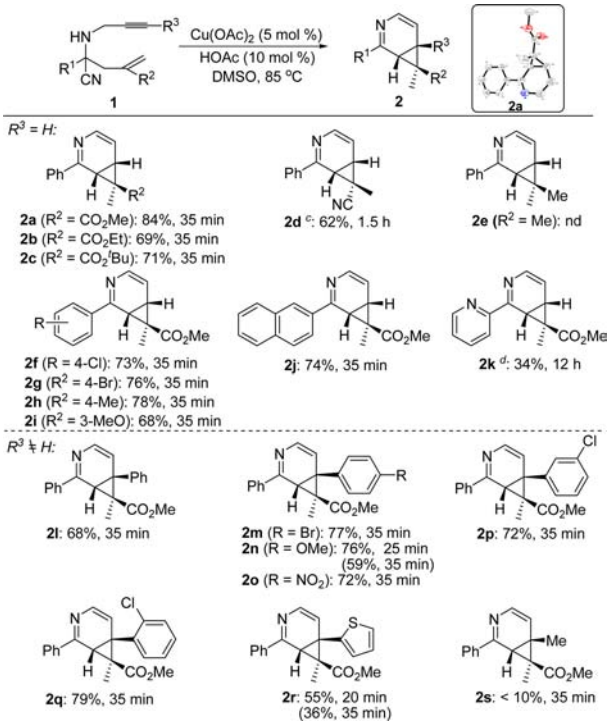
entry	conditions	time (h)	yield[b] (%) 2a	3a
1	$Ti(OEt)_4$, CH_3CN, reflux	24	67	6
2	$Fe(acac)_3$, CH_3CN, reflux	17	73	<1
3	$Cu(OAc)_2$, CH_3CN, reflux	3.5	63	9
4[c]	$Cu(OAc)_2$, HOAc, CH_3CN, reflux	3.5	68	17
5[c]	$Cu(OAc)_2$, HOAc, DMSO, 85 °C	0.58	74	14
6[d,e]	$Cu(OAc)_2$, HOAc, DMSO, 85 °C	0.58	88	7
7	DMSO, 85 °C	3	5	nd
8[c]	HOAc, DMSO, 85 °C	0.58	42	nd
9[d,e]	$Cu(OAc)_2$, HOAc, DMSO, 85 °C	22	22	63
10[d,f]	$Cu(OAc)_2$, HOAc, 85–110 °C	0.58/3.5	8	75
11	$PtCl_2$, toluene, 80 °C	21	23	nd

[a]Reactions were performed with **1a** (0.2 mmol) and catalyst (10 mol %) in solvent (2 mL). [b]Isolated yield. [c]HOAc (30 mol %) was added. [d]HOAc (10 mol %) was added. [e]Catalyst (5 mol %) in DMSO (4 mL). [f]Catalyst (5 mol %) in DMSO (2 mL).

similar results (Table 1, entry 2). Further investigation revealed that this novel cyclization of α-amino nitrile-tethered enyne **1a** can be accelerated dramatically in the presence of 10 mol % of $Cu(OAc)_2$, which gave products **2a** and **3a** in 63% and 9% yields, respectively, after 3.5 h (Table 1, entry 3). Other copper catalysts gave inferior results.[8] The catalytic amount of HOAc had a positive effect on this process with regard to the outcome of compound **2a** and **3a** (Table 1, entry 4). DMSO proved to be optimal solvent in which efficient cyclization can be achieved with improved yield of **2a** within 35 min (Table 1, entry 5). The performance of this reaction with a reduced amount of $Cu(OAc)_2$ (5 mol %) and HOAc (10 mol %) in diluted DMSO furnished the desired product **2a** in high yield as a single isomer (Table 1, entry 6). The traces of **2a** were observed without $Cu(OAc)_2$ and HOAc, while a 42% yield of **2a** was obtained within 35 min in the presence of 30 mol % of HOAc (Table 1, entries 7 and 8). During the course of optimizing the reaction conditions for the production of **2a**, 4,5-dihydro-3*H*-azepine **3a** was observed in most of the cases, which may have stemmed from the ring-opening of compound **2a** by the attack of the cyanide anion generated in situ. This result enabled us to develop a novel cascade sequence to access 4,5-dihydro-3*H*-azepine derivatives in an atom-economical fashion. Pleasingly, the production of **3a** can be improved markedly by the prolongation of reaction times, which further confirmed the synthetic relationship between **2a** and **3a** (Table 1, entry 9). Further manipulation of this cascade sequence with phased temperature elevation gave the desired product **3a** in 75% yield (Table 1, entry 10). Finally, treatment of **1a** with $PtCl_2$ (10 mol %), which has been proven to be a superior catalyst for electrophilic activation-involved cycloisomerization of enynes,[2a−f] provided 3-azabicyclo[4.1.0]-hepta-2,4-diene **2a** in very low yield (Table 1, entry 11).

Using the $Cu(OAc)_2$ (5 mol %) and HOAc (10 mol %) system, we examined the generality of the cyclization of α-amino nitrile tethered enynes for azabicyclo[4.1.0]hepta-2,4-dienes **2** (Scheme 2).[9,10] A series of electron-withdrawing groups (R^2) on the vinyl

Scheme 2. Substrate Scope[a,b]



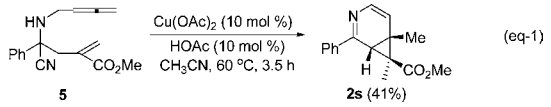
[a]Reaction conditions: **1** (0.2 mmol), $Cu(OAc)_2$ (5 mol %) and HOAc (10 mol %) in DMSO (4 mL) at 85 °C unless otherwise noted. [b]Isolated yield. Single isomer was observed. [c]Confirmed by X-ray crystal analysis. [d]Run at $Cu(OAc)_2$ (10 mol %) in CH_3CN (2 mL) at reflux.

moiety of enynes **1** were evaluated. Ethyl ester and *tert*-butyl ester analogues gave results similar to those for substrate **1a** (**2b** and **2c**), while the substrate with a cyano moiety as an EWG group (R^2) also provided the desired product **2d** in slightly decreased yield with prolonged reaction times. Notably, methyl-substituted enyne did not give the desired product **2e** at all. Varying the aromatic substituents (R^1) of enyne **1** showed that aromatic ring systems bearing either an electron-donating group (Me in **2h** and MeO in **2i**) or an electron-withdrawing group (Cl in **2f** and Br in **2g**) were tolerated and that the C−Br bond remained intact when a bromine substituent (**2g**) was introduced. The substituent patterm of arene had a few effects on this cyclization (**2i**). A naphthyl-substituted enyne can also serve as a good substrate and provided the desired product **2j** in 74% yield. However, treatment of pyridyl substituted enyne resulted in a sluggish reaction that gave **2k** bearing pyridyl in low yield, which indicates that basic group may not be tolerated well in this cyclization. In fact, the addition of extra bases had an obvious inhibition on this cyclization.[8]

Next, we investigated the scope of the Cu-promoted cyclization with regard to the substituents on the alkyne moieties of enynes **1** (Scheme 2). A range of enynes including various internal alkyne moieties were evaluated. Electron-neutral (**2l**), electron-donating

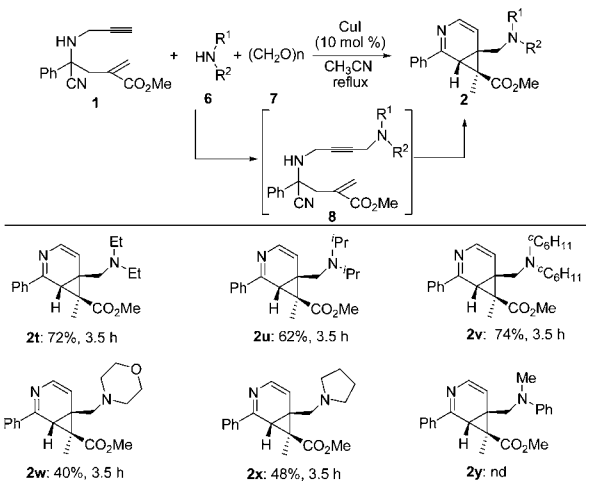
DOI: 10.1021/acs.orglett.6b01864
Org. Lett. 2016, 18, 3854−3857

(MeO in **2n**), and electron-withdrawing groups (Br in **2m**) on the benzene ring of alkyne moiety were well tolerated. Substrates bearing electron-withdrawing groups underwent efficient cyclization to give good isolated yields of the desired products (**2m**, **2o** and **2p**) and product **2q** with sterically demanding substituent on the cyclopropyl ring, while the electron-donating analogue delivered the desired product **2n** in slightly decreased yield. Pleasingly, the completion of this cyclization within shortened reaction times led to an improved yield of product **2n**, suggesting that (1) the desired product may not be stable enough to stand for longer reaction times under standard reaction conditions and (2) a substrate bearing an electron-donating group may react faster than its electron-withdrawing analogue. Indeed, prolonged reaction times resulted in the sharp decrease in yields of both electron-donating and electron-withdrawing substituted products, while the cyclization of a mixture of **1n** and **1o** (**1n**/**1o** = 1/1) provided the desired products **2n** and **2o** with the proportion of 1.3/1 in 15 min under optimal reaction conditions (for details, see Scheme S2).[11] A thienyl group could be introduced as R^3 and furnished a good yield of **2r**, while alkyl group substituted enyne gave the desired product **2s** in very low yield. Notably, allene analogue **5** can deliver the desired methyl-substituted product **2s** in 41% yield under modified reaction conditions (eq 1).



During the study of the generality and scope of the reaction, we became interested in the extension of this cyclization to enynes bearing internal heteroatom-embedded alkyne units (Scheme 3).

Scheme 3. Substrate Scope of Cascade Three-Component Process[a,b]

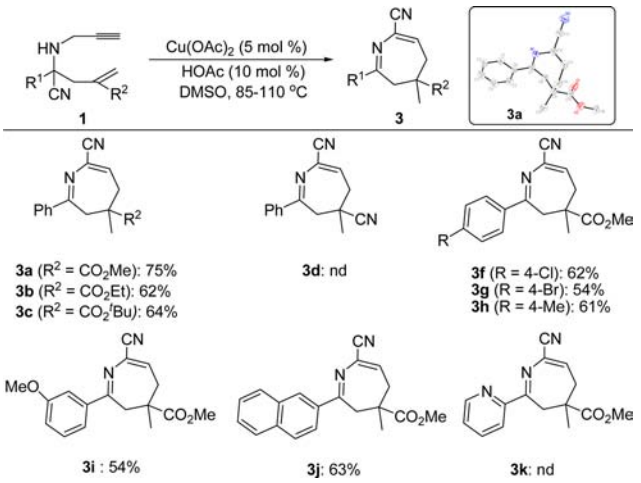


[a]Reaction conditions: **1** (0.2 mmol), CuI (10 mol %), amine **4** (0.28 mmol), and $(CH_2O)_n$ **5** (0.6 mmol) in CH_3CN (1 mL) at reflux. [b]Isolated yield. Single isomer was observed.

Propargylamines are important synthetic intermediates, which can be readily prepared from a three-component procedure between terminal alkynes, aldehydes, and amines in the presence of copper catalysts.[12] However, our initial attempt to obtain clean coupling product **8** from enyne **1a**, formaldehyde, and secondary amine failed. To our delight, the desired cyclized product **2** can be obtained directly through a cascade three-component process under modified reaction conditions. Treatment of **1a**, formaldehyde, and diethylamine with CuI (10 mol %) furnished the desired product **2t** in 72% yield. Highly hindered diisopropylamine gave product **2u** in moderate yield, while dicyclohexylamine delivered the desired product **2v** in good yield. Other cyclic secondary amines such as morpholine and piperidine showed lower reactivity, leading to the desired products in 40% (**2w**) and 48% yields (**2x**), respectively. However, *N*-methylaniline was unreactive (**2y**). Nevertheless, this novel cascade coupling–cyclization sequence of α-amino nitrile-tethered enynes provided a facile route to access 3-azabicyclo[4.1.0]hepta-2,4-dienes bearing tertiary amine moieties, which are difficult to access using current metal-mediated cyclization procedures, thus illustrating the potential of the process for the functionalization of 3-azabicyclo[4.1.0]alkene frameworks.

Subsequently, having the optimized reaction conditions for the catalytic $Cu(OAc)_2$/HOAc and phased temperature-elevation system in hand (Table 1, entry 10), the scope of the cascade sequence of enynes **1** to access 4, 5-dihydro-3*H*-azepine derivatives **3** was investigated (Scheme 4). The electron-

Scheme 4. Substrate Scope of Cycloisomerization of 1[a,b]



[a]Reactions were performed with **1** (0.2 mmol), $Cu(OAc)_2$ (5 mol %), and HOAc (10 mol %) in DMSO (2 mL) at 85 °C for 35 min and then stirred at 110 °C for 3.5 h. [b]Isolated yield.

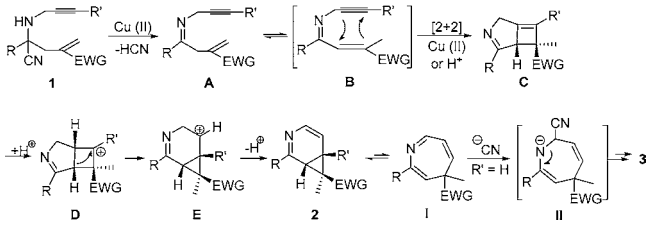
withdrawing groups (R^2) on the vinyl moiety of enynes **1** had considerable effects on this cyclization/ring-opening cascade sequence. Ethyl ester and *tert*-butyl ester gave the desired products **3b** and **3c** in moderate yields, while substrate with a cyano moiety as an EWG group (R^2) did not give the desired product **3d**, even with prolonged reaction times. Substituents with different electronic natures on the aromatic ring, such as halogen and methyl, were tolerated (**3f–h**), and both substituent pattern and electronic nature (R^3) on the aromatic ring had few effects on the chemical outcome of this cascade transformation (**3f–i**). Naphthyl- substituted 4,5-dihydro-3*H*-azepine (**3j**) can also be achieved in 63% yield. Although pyridyl-substituted enyne gave cyclopropane **2k** in low yield, no desired ring-opening product (**3k**) was observed under the phased temperature-elevation reaction conditions. In addition, treatment of enynes bearing in terminal alkyne moieties with the catalytic $Cu(OAc)_2$/HOAc and phased temperature-elevation system did not give the desired products, regardless of the type of internal alkyne moiety.

The unprecedented formation of 3-azabicyclo[4.1.0]hepta-2,4-dienes **2** and 4,5-dihydro-3*H*-azepines **3** drove us to gain some

DOI: 10.1021/acs.orglett.6b01864
Org. Lett. 2016, 18, 3854–3857

preliminary mechanistic understanding of this transformation. On the basis of the control experiments (for details, see the SI), a possible Lewis acid catalyzed polarized [2 + 2] cycloaddition triggered mechanism was proposed even though that a clear outline remained unknown (Scheme 5).[13] Imine intermediate **A**,

Scheme 5. Plausible Mechanism



generated from possible $Cu(OAc)_2$-promoted decyanation of enyne **1**, followed C=C bond isomerization, undergoes a polarized [2 + 2] cycloaddition to give cyclobutene **C** with the aid of $Cu(OAc)_2$.[14] Compound **C** may undergo a carbocation involved-rearrangement process to form intermediates **D** and **E**, which followed a hydrogen elimination to give products **2**.[15] Subsequent 6-π electrocyclic ring opening of product **2** would lead to 7-membered aza triene **II**, which may be trapped by cyanide and provide product **3**.

In conclusion, we developed a novel Cu-promoted cyclization of α-amino nitrile tethered enynes incorporating electron-deficient alkene components. Under a controllable and distinct cascade process, a wide range of functionalized 3-azabicyclo[4.1.0]hepta-2,4-dienes and 4,5-dihydro-3*H*-azepines were prepared efficiently. In addition, the diverse cascade coupling−cyclization sequences enabled tertiary amine units to be incorporated into targeted molecules with high efficiency. Further studies on the mechanism and synthetic application of this reaction are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01864.

Experimental procedures and analytical data for all new compounds (PDF)

NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wliao@jlu.edu.cn.

Author Contributions

§Q.-Q.X and Q.-L.H. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the NSFC (No. 21372096) and the Open Project of State Key Laboratory for Supramolecular Structure and Materials (sklssm2016013) for financial support.

■ REFERENCES

(1) The transition-metal-catalyzed cycloisomerization of enynes, selected reviews: (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.-Y.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (d) Bruneau, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 2328. (e) Zhang, L.-M.; Sun, J.-W.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (f) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (g) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (h) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (i) Dorel, R.; Echavarren, A. M. *J. Org. Chem.* **2015**, *80*, 7321.

(2) For examples with Pt catalysts: (a) Blum, J.; Beer-Kraft, H.; Badrieh, Y. *J. Org. Chem.* **1995**, *60*, 5567. (b) Fürstner, A.; Szillat, H.; Stelzer, F. *J. Am. Chem. Soc.* **2000**, *122*, 6785. (c) Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* **2001**, *123*, 11863. (d) Soriano, E.; Ballesteros, P.; Marco-Contelles, J. *J. Org. Chem.* **2004**, *69*, 8018. (e) Xia, J. B.; Liu, W.-B.; Wang, T.-M.; You, S.-L. *Chem. - Eur. J.* **2010**, *16*, 6442. With Au catalyst: (f) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654. (g) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (h) Zhang, D.-H.; Wei, Y.; Shi, M. *Chem. - Eur. J.* **2012**, *18*, 7026. With Ir: (i) Dieckmann, M.; Jang, Y.-S.; Cramer, N. *Angew. Chem., Int. Ed.* **2015**, *54*, 12149. (j) Sim, S. H.; Lee, S. I.; Park, J. H.; Chung, Y. K. *Adv. Synth. Catal.* **2010**, *352*, 317. With Rh catalysts: (k) Nishimura, T.; Maeda, Y.; Hayashi, T. *Org. Lett.* **2011**, *13*, 3674. With Pd catalysts: (l) Oh, H. M.; Park, J. E.; Kim, J.; Kim, J. H.; Kang, Y. K.; Chung, Y. K. *Chem. - Eur. J.* **2014**, *20*, 9024.

(3) For a review on bicyclo[*n*.1.0]alkenes, see: Billups, W. E.; Haley, M. M.; Lee, G. *Chem. Rev.* **1989**, *89*, 1147.

(4) Cu-catalyzed cyclopropanation of propargylic carboxylates: (a) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2901. (b) Fehr, C.; Farris, I.; Sommer, H. *Org. Lett.* **2006**, *8*, 1839. Cu-mediated cyclopropanation of *N*-allyl enamine carboxylates, see: (c) Toh, K. K.; Wang, Y.-F.; Ng, E. P. J.; Chiba, S. *J. Am. Chem. Soc.* **2011**, *133*, 13942. (d) Toh, K. K.; Biswas, A.; Wang, Y.-F.; Tan, Y.-Y.; Chiba, S. *J. Am. Chem. Soc.* **2014**, *136*, 6011.

(5) For selected reviews, see: (a) Albright, J. D. *Tetrahedron* **1983**, *39*, 3207. (b) Enders, D.; Shilvock, J. P. *Chem. Soc. Rev.* **2000**, *29*, 359. (c) Opatz, T. *Synthesis* **2009**, *2009*, 1941.

(6) (a) Chen, J.-M.; Xu, Q.-Q.; Liao, W.-W. *Chem. - Eur. J.* **2014**, *20*, 13876. (b) Zhuang, Z.; Hu, Z.-P.; Liao, W.-W. *Org. Lett.* **2014**, *16*, 3380. (c) En, D.; Zou, G.-F.; Guo, Y.; Liao, W.-W. *J. Org. Chem.* **2014**, *79*, 4456.

(7) For recent examples of the synthesis of azepine derivatives, see: (a) Schultz, E. E.; Lindsay, V. N. G.; Sarpong, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 9904. (b) Tian, Y.; Wang, Y.; Shang, H.; Xu, X.; Tang, Y. *Org. Biomol. Chem.* **2015**, *13*, 612. (c) Feng, J.-J.; Lin, T.-Y.; Zhu, C.-Z.; Wang, H.-m.; Wu, H.-H.; Zhang, J.-L. *J. Am. Chem. Soc.* **2016**, *138*, 2178.

(8) For the details of optimizing reaction conditions, see the SI.

(9) **CAUTION**: HCN (highly toxic) is generated during this reaction, and all appropriate precautions must be taken to avoid exposure. See the SI for full details.

(10) The relative configurations of **2a**, **2d**, and **3a** were determined on the basis of X-ray crystal structural analyses (see the SI for details). The relative configurations of compounds **2l** and **2t** were confirmed by NOE experiments. The configurations of other products were assigned by analogy.

(11) Under optimal reaction conditions, the traces of **2m** and **2a** were obtained after 16 h.

(12) For a selected review, see: (a) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. V. D. *Chem. Soc. Rev.* **2012**, *41*, 3790. For a Cu-catalyzed example, see: (b) Bieber, L. W.; da Silva, M. F. *Tetrahedron Lett.* **2004**, *45*, 8281.

(13) Selected reviews for catalytic [2 + 2] cycloadditions for accessing cyclobutanes and cyclobutenes: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783. (b) Xu, Y.; Conner, M. L.; Brown, M. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 11918. Synthetic applications of cyclobutanes and cyclobutenes: (c) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485. (d) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449.

(14) The possibility that HOAc may promote the polarized [2 + 2] cycloaddition cannot be ruled out.

(15) The exceptionally small size of the C≡N group may explain the different relative configurations between **2a** and **2d**.

DOI: 10.1021/acs.orglett.6b01864
Org. Lett. 2016, 18, 3854−3857