ORGANIC LETTERS

2012
Vol. 14, No. 18
4742–4745

Gold-Catalyzed Cyclizations of (*o*-Alkynyl)phenoxyacrylates with External Nucleophiles: Regio- and Stereoselective Synthesis of Functionalized Benzo[*b*]oxepines

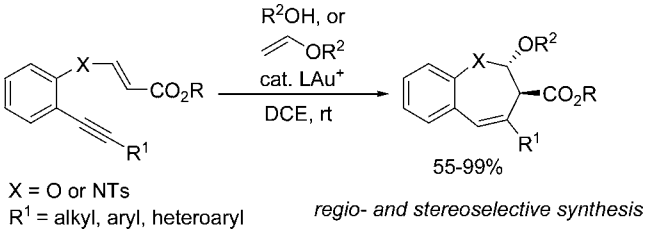
Jun Liu and Yuanhong Liu*

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, People's Republic of China

yhliu@mail.sioc.ac.cn

Received July 16, 2012

ABSTRACT



A catalytic approach to benzo[*b*]oxepines with high stereoselectivity by Au-catalyzed cyclization of (*o*-alkynyl)phenoxyacrylates with various nucleophiles under mild reaction conditions has been developed. Notably, the use of vinyl ether instead of alcohol could afford the same benzoxepines. The reaction may proceed by Au-catalyzed oligomerization of vinyl ether to release the alcohol, which then reacts with (*o*-alkynyl)phenoxyacrylates to furnish the benzoxepines.

The development of efficient methodologies for the construction of medium-sized rings remains a very important challenge in organic synthesis.[1] Benzo[*b*]oxepines are common seven-membered structural motifs found in many natural products,[2] biologically active substances,[3] and natural herbicides.[4] Therefore, considerable attention has been paid to the synthesis of functionalized benzo[*b*]-oxepines. Particularly, attractive strategies are based on transition-metal-catalyzed transformations, such as Rh-catalyzed intramolecular olefin hydroacylations,[5] Os-catalyzed hydroxylation of aromatic alkynols,[6] Pd-catalyzed [5 + 2] annulation of 2-acylmethoxyarylboronic acids[7] with allenoates[7a] or alkynes,[7b] Pd-catalyzed sequential alkylation–alkenylation reactions,[8] Au-catalyzed heterocyclization/Petasis–Ferrier rearrangement,[9] etc.

(1) For reviews on medium-sized rings in natural products, see: (a) Shiina, I. *Chem. Rev.* **2007**, *107*, 239. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963.

(2) For examples, see: (a) Bruder, M.; Haseler, P. L.; Muscarella, M.; Lewis, W.; Moody, C. J. *J. Org. Chem.* **2010**, *75*, 353. (b) Macias, F. A.; Molinillo, J. M. G.; Varela, R. M.; Torres, A.; Fronczek, F. R. *J. Org. Chem.* **1994**, *59*, 8261. (c) Engler, M.; Anke, T.; Sterner, O. J. *J. Antibiot.* **1997**, *50*, 330. (d) Engler, M.; Anke, T.; Sterner, O. J.; Brandt, U. J. *J. Antibiot.* **1997**, *50*, 325. (e) Asakawa, Y.; Hashimoto, T.; Takikawa, K.; Tori, M.; Ogawa, S. *Phytochemistry* **1991**, *30*, 235. (f) Kim, S.; Su, B.-N.; Riswan, S.; Kardono, L. B. S.; Afriastini, J. J.; Gallucci, J. C.; Chai, H.; Farnsworth, N. R.; Cordell, G. A.; Swanson, S. M.; Kinghorn, A. D. *Tetrahedron Lett.* **2005**, *46*, 9021. (g) Kashima, K.; Sano, K.; Yun, Y. S.; Ina, H.; Kunugi, A.; Inoue, H. *Chem. Pharm. Bull.* **2010**, *58*, 191.

(3) Wijnberg, J. B. P. A.; van Veldhuizen, A.; Swarts, H. J.; Frankland, J. C.; Field, J. A. *Tetrahedron Lett.* **1999**, *40*, 5767.

(4) Vyvyan, J. R.; Looper, R. E. *Tetrahedron Lett.* **2000**, *41*, 1151.

(5) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932.

(6) Varela-Fernández, A.; García-Yebra, C.; Varela, J. A.; Esteruelas, M. A.; Saá, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 4278.

(7) (a) Yu, X.; Lu, X. *J. Org. Chem.* **2011**, *76*, 6350. (b) Liu, G.; Lu, X. *Adv. Synth. Catal.* **2007**, *349*, 2247.

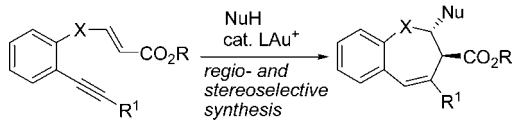
(8) Lautens, M.; Paquin, J. -F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972.

(9) Sze, E. M. L.; Rao, W.; Koh, M. J.; Chan., P. W. H. *Chem.—Eur. J.* **2011**, *17*, 1437.

10.1021/ol302252h
Published on Web 09/04/2012

Although much progress has been achieved, the reactions involving a stereoselective process is quite rare. Recently, we have developed several Au-catalyzed highly efficient methodologies for the construction of seven-membered carbo- or heterocycles such as Au-catalyzed Friedel–Crafts/hydroarylations[10] or tandem annulations leading to dihydrocyclohepta[*b*]indoles,[11] ring-opening cycloamination of aziridine-ynes leading to 3-benzo[*d*]azepines.[12] These results encouraged further exploration of the synthetic routes to benzo[*b*]oxepines. We hypothesized that the Au-catalyzed cyclization of (*o*-alkynyl)phenoxyacrylates with nucleophiles might offer an opportunity for the synthesis of benzoxepines. Here, we report our success in Au-catalyzed cyclization of (*o*-alkynyl)phenoxyacrylates assisted by external oxygen or nitrogen nucleophiles. The reaction provides a highly regio- and stereoselective route to benzo[*b*]oxepines and its analogues under mild reaction conditions (Scheme 1).

Scheme 1[a]



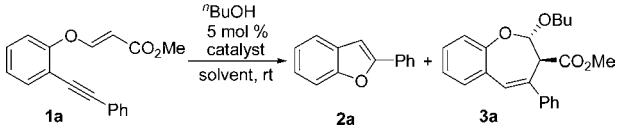
[a] X = O, NTs; NuH = ROH, $TMSN_3$.

The requisite substrates of (*E*)-2-alkynylphenoxyacrylates **1** could be easily synthesized through base-promoted addition reactions of the corresponding 2-alkynylphenols to methyl propiolate. To our delight, the reaction of (*E*)-methyl 3-(2-(phenylethynyl)phenoxy)acrylate **1a** with 2.0 equiv of *n*-BuOH catalyzed by 5 mol % of PPh_3AuNTf_2 cleanly delivered the desired 2,3-dihydrobenzo[*b*]oxepine **3a** in high yield (92%) (Table 1, entry 1). The result indicates that an *endo-dig* cyclization takes place preferentially rather than the *exo-dig* mode. High stereoselectivity is also noted, as only *trans*-**3a** was obtained. Increasing the amount of *n*-BuOH to 5.0 equiv, however, was found to result in the formation of 2-phenylbenzofuran **2a** in 43% yield. In this case, **3a** could be isolated in ca. 49% yield; however, it contained some byproducts, which could not be separated by column chromatography. One byproduct was assigned to be (*E*)-methyl 3-butoxyacrylate as compared with the NMR spectra of an authentic sample. Decreasing the amount of *n*-BuOH to 1.1 equiv afforded a lower yield (83%) (entry 3). Solvents such as DCM, THF, and toluene gave **3a** in lower yields (entries 4–6). Changing the counteranion of the Au catalyst to OTf^- or SbF_6^- led to **3a** in 66–72% yields (entries 7–8).

With the optimized reaction conditions in hand, we next examined the scope of differently substituted (*E*)-2-alkynylphenoxyacrylates. The results are summarized in Figure 1. The reactions accommodate a wide range of substituents on the alkyne terminus, since aryl, heteroaryl, and alkyl groups are all suitable for this cyclization reaction, and in all cases, benzo[*b*]oxepines **3** were obtained in high yields as a single diastereomer. The functionalities such as −MeO, −Cl, $-CF_3$, and *p*-CO_2Et on the terminal aryl rings were well tolerated during the reaction. Generally, substrates containing electron-withdrawing groups required longer reaction times (compare **3c**–**e** with **3b**). Alkyne **1f** with a sterically demanding 1-naphthyl group cyclized smoothly to generate **3f** in 78% yield. A thienyl group was also compatible, furnishing **3g** in 79% yield. *n*-Butyl or cyclopropyl substituted (*o*-alkynyl)phenoxyacrylate could be readily converted to **3h** and **3i** in 87–89% yields. Substitution with −Me or −Cl groups on the parent phenyl ring also worked efficiently to give **3j** and **3k** in 89% and 79% yields, respectively. A conformationally restricted (*E*)-methyl 3-(1-(alkynyl)naphthalen-2-yloxy)-acrylate **1l** provided **3l** in 79% yield. Interestingly, when a nitrogen-tethered acrylate was subjected to the reaction conditions, 2,3-dihydrobenzo[*b*]azepine **4** was obtained in 92% yield as a single diastereomer. Therefore the present reaction could be extended to the efficient synthesis of various aza-heterocycles by simply changing the heteroatom linkers. The structures of these benzoxepine derivatives were unambiguously confirmed by X-ray crystallographic analysis of **3d**, **3g**, and **4**.[13]

Next, we investigated the scope of nucleophiles (Table 2). It was found that, in addition to *n*-butanol, a variety of alcohols could be used as effective nucleophiles for this reaction. Treatment of **1a** with simple alcohols such as methanol or ethanol afforded the corresponding benzoxepine products **3m** and **3n** in 83–84% yields (Table 2,

Table 1. Optimization Studies for the Formation of Benzo[*b*]oxepine **3a**



entry	BuOH (equiv)	catalyst	solvent	time (h)	yield of **2a** (%)[a]	yield of **3a** (%)[a]
1	2	$Ph_3PAuNTf_2$	DCE	10	–	92
2	5	$Ph_3PAuNTf_2$	DCE	18	43	49[b]
3	1.1	$Ph_3PAuNTf_2$	DCE	8	–	83
4	2	$Ph_3PAuNTf_2$	DCM	25	–	79
5	2	$Ph_3PAuNTf_2$	THF	2	21	62[b,c]
6	2	$Ph_3PAuNTf_2$	toluene	7	–	42[d]
7	2	$Ph_3PAuOTf$	DCE	19	–	66[b]
8	2	$Ph_3PAuSbF_6$	DCE	19	–	72

[a] Isolated yield. [b] Containing some amounts of byproducts. [c] Reflux. [d] 80 °C, 38% of **1a** was recovered.

(10) Lu, Y.; Du, X.; Jia, X.; Liu, Y. *Adv. Synth. Catal.* **2009**, *351*, 1517.
(11) Xie, X.; Du, X.; Chen, Y.; Liu, Y. *J. Org. Chem.* **2011**, *76*, 9175.
(12) Du, X.; Yang, S.; Yang, J.; Liu, Y. *Chem.—Eur. J.* **2011**, *17*, 4981.

(13) See Supporting Information.

entries 1 and 2). A bulky alcohol such as *t*-BuOH afforded a moderate yield of **3o**, possible due to the strong steric effects (entry 3). Functional alcohols such as benzyl alcohol, allylic alcohol, or phenol underwent the cyclization reaction smoothly to generate the desired **3p**−**3r** in 82−89% yields (entries 4−6). In the case of **3r**, the use of JohnphosAuSbF$_6$(MeCN) (catalyst **A**) as the catalyst is required to achieve a better yield. Furthermore, a nitrogen nucleophile such as $TMSN_3$ could also be successfully employed for this cyclization, and the corresponding N_3-substituted benzoxepine **3s** was obtained in 85% yield (entry 7).

Electron-rich alkenes such as vinyl ethers are usually utilized as dipolarophiles in metal-catalyzed cycloaddition reactions.[14] Unexpectedly, here we found that when vinyl ethers were employed instead of alcohols, the same benzoxepines **3** could also be obtained. For example, treatment of **1a** with 5 mol % PPh_3AuNTf_2 and 5 equiv of *n*-butyl vinyl ether in DCE yielded *trans*-**3a** in 94% yield after 7 h at rt (Table 3, entry 1). As shown in Table 3, the reactions using vinyl ethers as components worked efficiently with a wide range of substrates, and good to excellent yields were obtained in most cases. To understand the mechanism, we treated *n*-butyl vinyl ether with 1 mol % PPh_3AuNTf_2 in DCE at rt. Vinyl ether was completely consumed after 1 h, and oligomerized products were formed, which was confirmed by NMR and ESI-MS examination.[15,16] Addition of phenoxyacrylate **1a** to the above reaction mixture also produced benzoxepine product **3a** in high yield. The result suggested that vinyl ether might not react with **1a** directly but served as a precursor. It is likely that *n*-BuOH was released during the oligomerization process, which then acts as a nucleophile to react with (*o*-alkynyl)phenoxyacrylates.[15] It is noted that there is no report for the oligomerization of vinyl ethers in Au- or Pt-catalyzed reactions employing vinyl ethers.[14a−l]

To understand the stereochemical course of this reaction, we also prepared *cis*-phenoxyacylate **5**. It was found

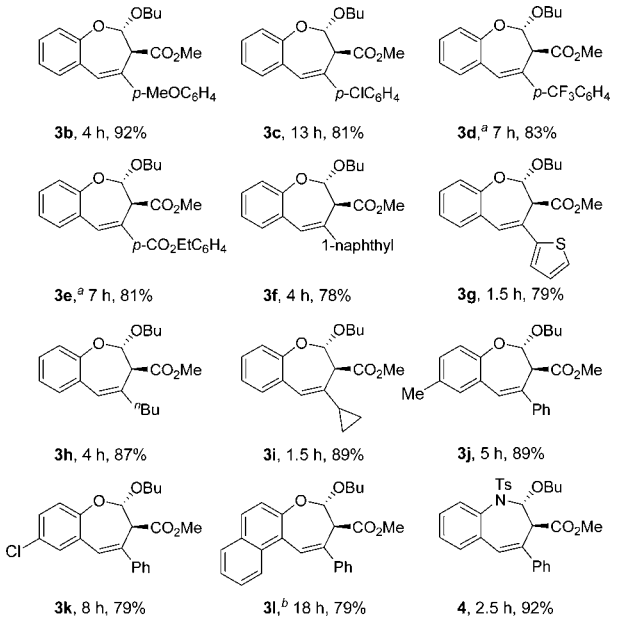
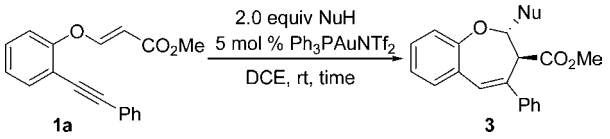


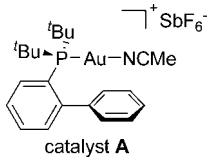
Figure 1. Au-catalyzed formation of benzo[*b*]oxepine or -[*b*]-azepine derivatives. All yields are isolated yields. Unless noted, all the reactions were carried out at rt using 2.0 equiv of *n*-BuOH and 5 mol % PPh_3AuNTf_2 in DCE. [a]50 °C, 10 mol % PPh_3AuNTf_2 was used. [b]1.1 equiv of *n*-BuOH was used.

Table 2. Gold-Catalyzed Cyclization of **1a** with Various Nucleophiles



entry	NuH	time (h)	product	yield[a]
1	MeOH	7	**3m**	84%
2		7	**3n**	83%
3		24	**3o**	55%
4		8	**3p**	82%
5		7	**3q**	89%
6	PhOH	3	**3r**	87%[b]
7	$TMSN_3$	3	**3s** (Nu = N_3)	85%[b]

[a]Isolated yield. [b]5 mol % of catalyst **A** was used instead of $Ph_3PAuNTf_2$.

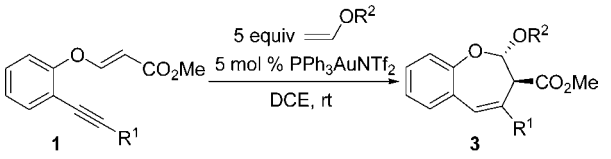


(14) For Au: (a) Melhado, A. D.; Luparia, M.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12638. (b) Li, G.; Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 6944. (c) Jadhav, A. M.; Bhunia, S.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 1769. (d) Teng, T.-M.; Das, A.; Huple, D. B.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 12565. (e) Teng, T.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 9298. (f) Garayalde, D.; Krüger, K.; Nevado, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 911. For Pt: (g) Kusama, H.; Ishida, K.; Funami, H.; Iwasawa., N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4903. (h) Kusama, H.; Funami, H.; Iwasawa, N. *Synthesis* **2007**, 2014. (i) Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2011**, *133*, 689. (j) Kusama, H.; Funami, H.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2004**, *6*, 605. (k) Kusama, H.; Miyashita, Y.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2006**, *8*, 289. (l) Ishida, K.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2010**, *132*, 8842. For W: (m) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226. (n) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814. (o) Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 2709. (p) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592.

(15) See: Kéki, S.; Nagy, M.; Deák, G.; Zsuga, M. *J. Phys. Chem. B* **2001**, *105*, 9896.

(16) For Au-catalyzed polymerization of styrenes, see: Urbano, J.; Hormigo, A. J.; de Frémont, P.; Nolan, S. P.; Díaz-Requejo, M. M.; Pérez, P. J. *Chem. Commun.* **2008**, 759. For Au-catalyzed polymerization of cyclopentadienes, see: Sanguramath, R. A.; Patra, S. K.; Green, M.; Russell, C. A. *Chem. Commun.* **2012**, 1060.

Table 3. Gold-Catalyzed Formation of Benzo[*b*]oxepines **3** via the Reactions with Vinyl Ethers



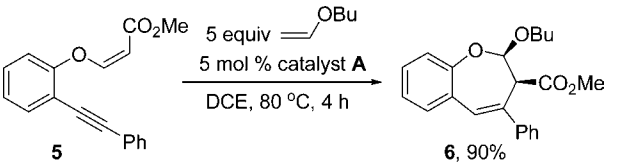
entry	R^1		R^2	time (h)	product	yield (%)[a]
1	Ph	**1a**	^{n}Bu	7	**3a**	94
2	*p*-MeOC$_6$H$_4$	**1b**	^{n}Bu	3.5	**3b**	93
3	*p*-ClC$_6$H$_4$	**1c**	^{n}Bu	22	**3c**	93
4[b]	*p*-CF$_3$C$_6$H$_4$	**1d**	^{n}Bu	20	**3d**	86
5[b]	*p*-CO$_2$EtC$_6$H$_4$	**1e**	^{n}Bu	6	**3e**	99
6	1-naphthyl	**1f**	^{n}Bu	7	**3f**	98
7	2-thienyl	**1g**	^{n}Bu	3	**3g**	82
8	^{n}Bu	**1h**	^{n}Bu	6	**3h**	77
9	cyclopropyl	**1i**	^{n}Bu	3	**3i**	87
10	Ph	**1a**	Et	7	**3n**	88
11	H	**1n**	^{n}Bu	8	–[c]	

[a] Isolated yields. [b] 50 °C. 10 mol % of PPh_3AuNTf_2 was used. [c] 44% of **1n** was recovered.

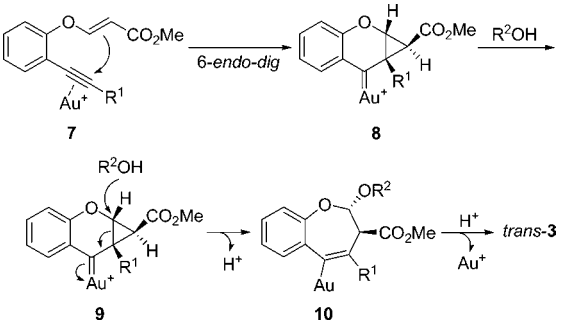
that the use of *n*-BuOH failed to produce the desired product. The major product was benzofuran **2a** in the presence of 5 mol % PPh_3AuNTf_2 in DCE, while the reaction became complicated when catalyst **A** was used as a catalyst. In contrast, **5** reacted with *n*-butyl vinyl ether smoothly in the presence of 5 mol % catalyst **A** at 80 °C to give **6** in 90% yield as a single *cis*-diastereomer (Scheme 2). The ^{1}H NMR of **6** shows the value of the coupling constant of the methine protons is as small as 1.6 Hz, while this value is 5.6 Hz in *trans*-**3a**. The above results indicated that the (*E*)- or (*Z*)-geometry of the starting acrylates reflects the stereochemistry of the benzoxepine products during the reaction.

A possible reaction mechanism for the present reactions with alcohols is shown in Scheme 3. Activation of the triple bond in enyne type substrate **1** by gold(I) triggers the intramolecular attack of the alkene and leads to the stereoselective formation of a cyclopropyl gold carbene intermediate **8**.[17] A subsequent regio- and stereoselective attack of the nucleophile on the cyclopropyl ring in **8** gives the vinyl gold species **10**,[18] which then undergoes protodemetalation to deliver the *trans*-benzoxepine **3**. In the presence of a large excess amount of alcohol, benzofuran **2** was observed as a byproduct. The formation of benzofuran

Scheme 2



Scheme 3



may be explained by competitive addition of ROH to the alkene moiety promoted by gold[19] followed by decomposition to give (*o*-alkynyl)phenol, which cyclizes in the presence of a gold catalyst to afford benzofuran **2**.[20]

In summary, we have developed a new catalytic approach to benzo[*b*]oxepines with high stereoselectivity through gold-catalyzed cyclization of (*o*-alkynyl)phenoxyacrylates with various nucleophiles under mild reaction conditions. Notably, vinyl ether could also be used to afford the same benzoxepines. The reaction may proceed by gold-catalyzed oligomerization of vinyl ether to release the alcohol, which then reacts with (*o*-alkynyl)phenoxyacrylates to furnish the benzoxepines. Clarification of the reaction mechanism and further application of this chemistry are in progress.

Acknowledgment. We thank the National Natural Science Foundation of China (Grant Nos. 21125210, 21121062), Chinese Academy of Science and the Major State Basic Research Development Program (Grant No. 2011CB808700) for financial support.

Note Added after ASAP Publication. Errors in Tables 1 and 3 were corrected September 5, 2012.

Supporting Information Available. Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of **3d**, **3g**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For reviews, see: (a) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (b) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (c) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271.

(18) For Au-catalyzed alkoxycyclization of enynes, see: (a) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141. (b) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633. (c) Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2003**, *9*, 2627. (d) Nieto-Oberhuber, C.; Muñoz, M. P.; Buñuel, E.; Nevado, C.; Cárdenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402. (e) Genin, E.; Leseurre, L.; Toullec, P. Y.; Genêt, J.-P.; Michelet, V. *Synlett* **2007**, 1780.

(19) For Au-catalyzed addition of alcohols to alkenes, see: (a) Hirai, T.; Hamasaki, A.; Nakamuru, A.; Tokunaga, M. *Org. Lett.* **2009**, *11*, 5510. (b) Zhang, X.; Corma, A. *Dalton Trans.* **2008**, 397. (c) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966.

(20) Zhang, Y.; Xin, Z.; Xue, J.; Li, Y. *Chin. J. Chem.* **2008**, *26*, 1461.

The authors declare no competing financial interest.