Organic LETTERS

Letter

pubs.acs.org/OrgLett

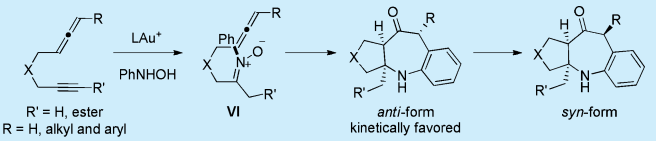
Gold-Catalyzed *N,O*-Functionalizations of 6-Allenyl-1-ynes with *N*-Hydroxyanilines To Construct Benzo[*b*]-azepin-4-one Cores

Antony Sekar Kulandai Raj,[†] Balaji S. Kale,[†] Bhanudas Dattatray Mokar, and Rai-Shung Liu*

Department of Chemistry, National Tsing-Hua University, Hsinchu, 30013, Taiwan, ROC

Supporting Information

ABSTRACT: Gold-catalyzed reactions of 6-allen-1-ynes with *N*-hydroxyanilines afford thermally stable benzoazepin-4-ones in *anti*-selectivity; these *anti*-configured products are easily isomerized to their *syn*-isomers on a silica column. The mechanism of reactions likely involve initial nitrone/allene cycloadditions, followed by skeletal rearrangement of resulting intermediates.

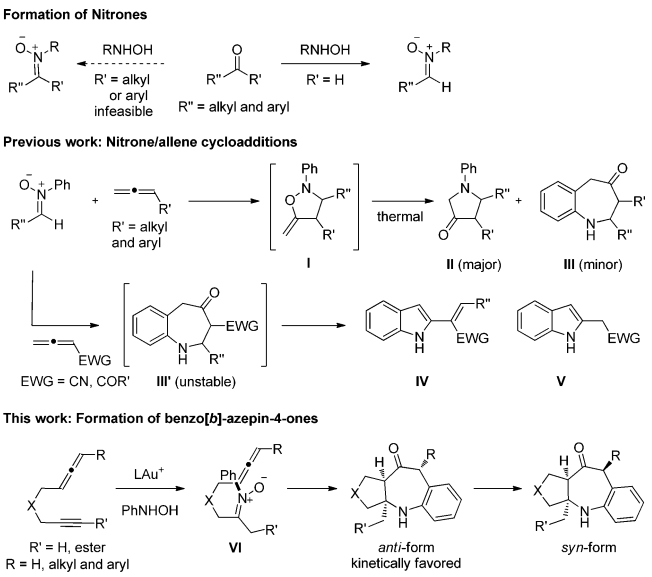


Nitrones are versatile building blocks to construct isoxazolidine frameworks through diastereo- or enantioselective [3 + 2]-cycloadditions with alkenes;[1] these species are commonly generated in situ from the reactions of *N*-hydroxyamines with aldehydes.[2] Ketone-derived nitrones (R, R′ = alkyl or aryl) are generally kinetically unstable[3a] unless R′ or R″ is an electron-withdrawing group.[3b−e] With aldehyde-derived nitrones, unactivated allenes generally deliver pyrrolidin-3-ones (**II**) from a rearrangement of 5-alkylideneisoxazolidines (**I**),[4] whereas electron-deficient allenes typically afford indole derivatives **IV** or **V** through a facile rearrangement of unstable benzoazepin-4-one intermediates **III′**.[5] [3 + 2]-Cycloadditions of ketone-derived nitrones (R′, R″ = alkyl or aryl) with unactivated allenes still remain undocumented.[6] In our recent findings, terminal alkynes react with *N*-hydroxyanilines to generate ketone-derived nitrones that enable [3 + 2]-cycloadditions with tethered alkenes.[7] We report here gold-catalyzed *N,O*-functionalizations of 6-allenyl-1-ynes with *N*-hydroxyanilines to initially generate these nitrones (**VI**), further affording benzoazepin-4-ones efficiently. Notably, the kinetic control of these new reactions is to form *anti*-configured products, which are subsequently isomerized to their *syn*-isomers on a silica column (Scheme 1).

The importance of this work is to provide a facile and stereoselective construction of valuable benzoazepin-4-one cores that are present in bioactive molecules **VII**−**XII**.[8] Homocryptolepione (**VII**) is a natural product isolated from the Ghanaian plant, gryptolepis sanquinolenta;[8a,b] oxcarbazepine (**VIII**) was used to treat epilepsy and bipolar disorder.[8c] Dehydrotolvaptan (**IX**)[8d] exhibited oxytocin and vasopressin antagonists whereas benzoazepin-4-ol (**X**)[8e] showed in vitro antiparasitic activity against trypanosome cruzi. Species **XI** and **XII** are mitochondrial benzodiazepine receptor (MBR) receptors (Figure 1).[8f]

Table 1 optimizes the reactions with common gold catalysts. Our initial tests employed IPrAuCl/AgX (5 mol %, X = NTf_2 and OTf) to catalyze the reactions of 6-allenyl-1-yne **1a** with *N*-hydroxyaniline **2a** in dichloromethane (DCM, 25 °C, 20 h), affording benzoazepin-4-one **3a** in 40% and 38% yields,

Scheme 1. Chemoselectivities between Allenes and Nitrones



respectively; unreacted 6-allenyl-1-yne **1a** was recovered in 27−31% (entries 1−2). A high loading (10 mol %) of IPrAuCl/$AgNTf_2$ led to a complete consumption of the initial **1a** to yield the desired **3a** in 71% (entry 3). Heating this mixture in DCE at 60 °C (2.5 h) further improved the yield of **3a** up to 85% (entry 4). With a small loading (1.2 equiv) of *N*-hydroxyaniline, the reaction still gave the desired **3a** in 87% yield. A switch of catalyst to P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgNTf_2$ (10 mol %) maintained the same efficiency in hot DCE (60 °C, 2 h, entry 6). The reactions became less efficient in other solvents such as THF, toluene and DMF, giving the desired **3a** in low yields (entries 7−9). The proposed structure of compound **3a** was

Received: August 24, 2017

DOI: 10.1021/acs.orglett.7b02629
Org. Lett. XXXX, XXX, XXX−XXX

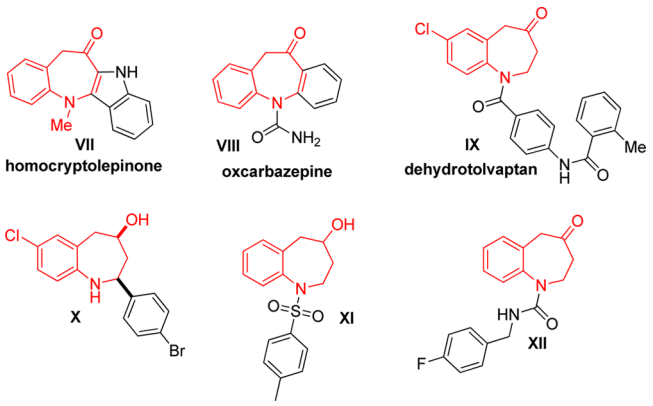
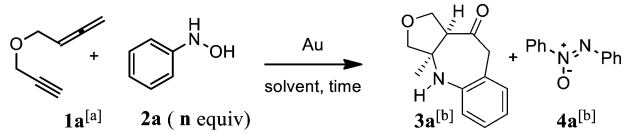


Figure 1. Representative bioactive molecules.

Table 1. Synthesis of Benzoazepin-4-ones with Various Catalysts[a]



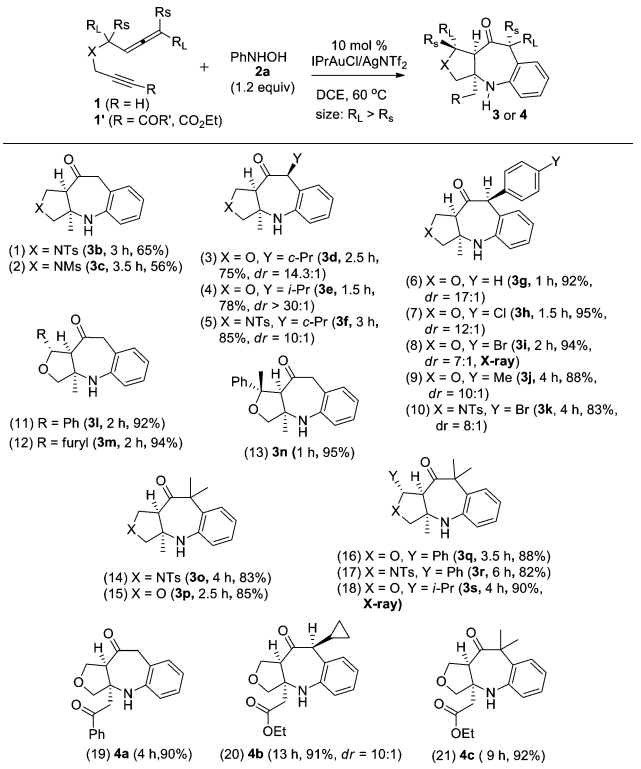
					yield (%)[b]	
entry	catalyst (mol %)	*n*	solvent	°C/h	3a	4a
1	IPrAuCl/AgNTf$_2$ (5)	2	DCM	25/20	40	42
2	IPrAuCl/AgOTf (5)	2	DCM	25/20	38	42
3	IPrAuCl/AgNTf$_2$ (10)	2	DCM	25/12	71	20
4	IPrAuCl/AgNTf$_2$ (10)	2	DCE	60/2.5	85	15
5	IPrAuCl/AgNTf$_2$ (10)	1.2	DCE	60/1.5	87	–
6	LAuCl/AgNTf$_2$ (10)	1.2	DCE	60/2	86	–
7	IPrAuCl/AgNTf$_2$ (10)	1.2	THF	60/24	35	20
8	IPrAuCl/AgNTf2 (10)	1.2	toluene	60/24	40	20
9	IPrAuCl/AgNTf2 (10)	1.2	DMF	60/5	–	–

[a][**1a**] = 0.3 M, 6-allenyl-1-yne **1a** was recovered in 27% and 31% in entries 1−2. [b]Product yields are obtained after purification from a silica column. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene, L = P(*t*-Bu)$_2$(*o*-biphenyl).

inferred from X-ray diffraction[9] of its relative **3i** (Table 2, entry 8).

Table 2 shows the scope of these catalytic reactions with 6-allenyl-1-ynes **1** bearing various substituents on alkynes, allenes and bridging units X. For NTs or NMs-bridged 6-allenyl-1-ynes **1b** and **1c**, their reactions with *N*-hydroxyaniline **2a** delivered benzoazepin-4-ones **3b** and **3c** in reasonable yields (56−65%, entries 1−2). We prepared *O*- and *N*-linked alkyl-substituted allenes **1d**−**1f**; their resulting benzoazepin-4-ones **3d**−**3f** were obtained with high yields and good diastereoselectivity (dr >10:1, entries 3−5); proton NOE confirms the *syn*-configuration of the major isomers. For aryl-substituted allenes **1g**−**1k**, their corresponding products **3g**−**3k** were produced efficiently and highly diastereoselectively (dr > 7:1 entries 6−10); the molecular structure of compound **3i** was confirmed by X-ray diffraction to confirm the *syn*-configuration.[9] We also prepared 6-allenyl-1-ynes **1l**−**1n** bearing one or two substituents at the C(5)-carbon, yielding desired benzoazepin-4-ones **3l**−**3n** as single diastereomers exclusively (entries 11−13); these C(5)-substituents significantly enhance the product yields (>90%) because of the Thorpe−Ingold effects.[10] We also examined the reactions on trisubstituted allene substrates **1o**-**1s**, affording desired benzo azepin-4-ones **3o**−**3s** in satisfactory

Table 2. Reactions with Various 6-Allenyl-1-ynes[a,b]

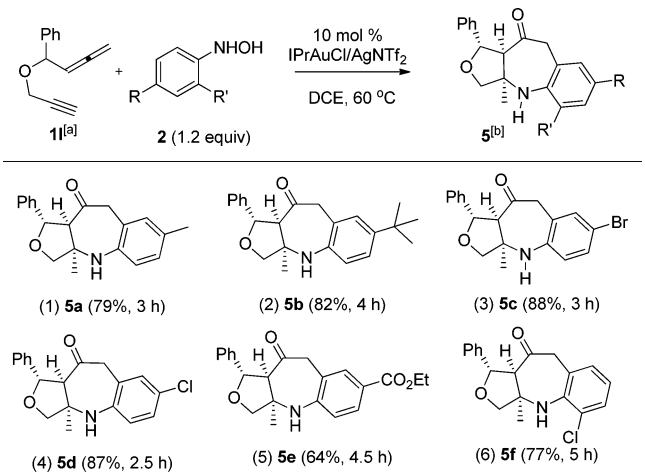


[a][**1a**] = 0.3 M. [b]Product yields are obtained after purification from a silica column. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

yields (82−90%, entries 14−18). 6-Allenyl-1-ynes (**1a′**−**1c′**) bearing alkynyl esters or ketones were also compatible with these reactions, yielding desired benzoazepin-4-ones **4a**−**4c** in high yields (90−92%, entries 19−21).

The scope of reactions is significantly expanded with their compatibility with various *N*-hydroxyanilines (Table 3). We prepared *N*-hydroxyanilines **2b**−**2c** bearing *p*-phenyl substituents including R = Me and *tert*-butyl to test the reactions, their resulting benzoazepin-4-ones **5a**−**5b** were obtained in satisfactorily yields (79−82%). Notably, *N*-hydroxyanilines **2d**−**2f** bearing R = Br, Cl and CO$_2$Et were also applicable substrates

Table 3. Reactions with Various *N*-Hydroxyanilines[a,b]



[a][**1l**] = 0.3 M. [b]Product yields are obtained after purification from a silica column. IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene.

DOI: 10.1021/acs.orglett.7b02629
Org. Lett. XXXX, XXX, XXX−XXX

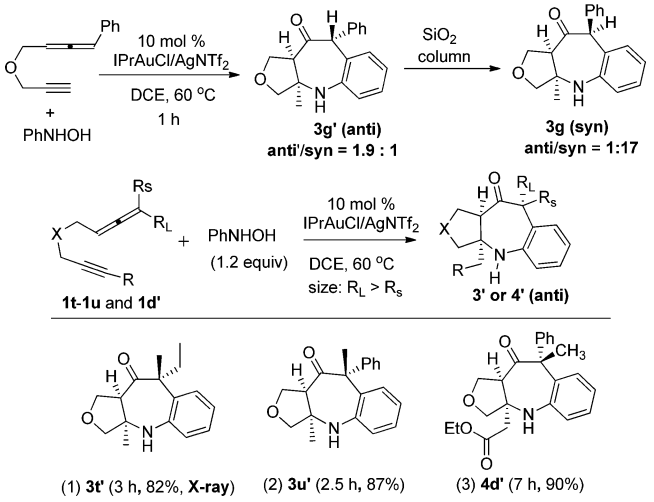
although the mechanisms involve anilinium carbocations. For 2-choro substituted derivative **2g**, its corresponding product **5f** was obtained in 77% yield.

Notably, ^{1}H NMR spectra of crude **3g** indicates that the *anti*-isomer **3g′** is the major species (*anti*/*syn* = 1.9:1); purification of this crude mixture on a silica column allowed a rapid epimerization, yielding *syn*-isomer **3g** (*syn*/*anti* = 17:1) predominantly. To ascertain this *anti*-selectivity, we prepared trisubstituted allene substrates **1t**−**1u** and **1d′**, affording desired products **3t′**−**3u′** and **4d′** as single isomeric products; the *anti*-configurations of compounds **3t′** and **4d′** were established by ^{1}H NOE spectra. The molecular structure of compound **3t′** was again confirmed by X-ray diffraction.[9]

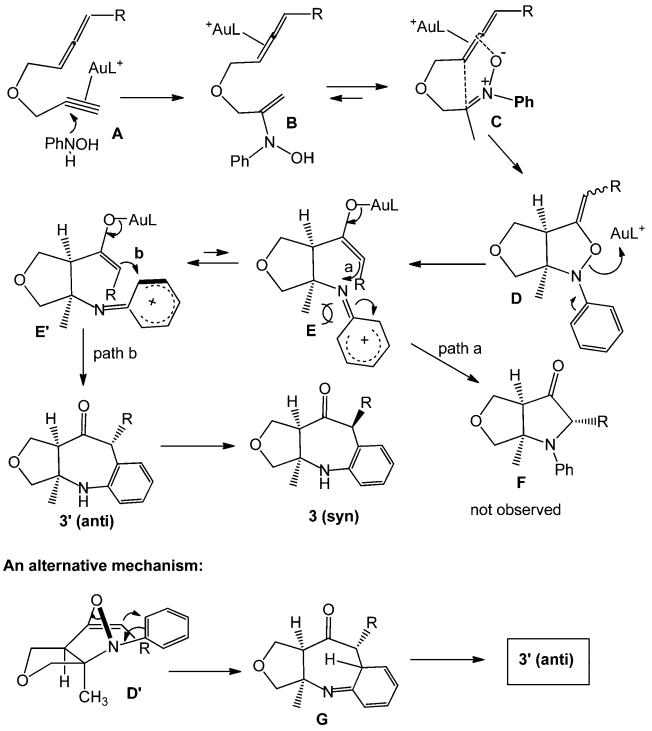
This work reports unprecedented nitrone/allene reactions,[4−6] affording kinetically stable benzoazepin-4-ones **3′** with *anti*-selectivity, which subsequently rearrange to their *syn*-isomers. Reported heterocycles such as pyrrolidin-3-ones (**II**) and indole derivatives **IV** or **V**, as depicted in Scheme 1, are completely absent.[4−6] In a postulated mechanism, as depicted in Scheme 3, gold-catalyzed attack of *N*-hydroxyaniline at alkynes **A** forms species **B**, and eventually nitrones **C**; this *N*-attack regioselectivity as represented by **B** is operable only in the presence of an alkene[7] or alllene in this system. A subsequent nitrone/allene cycloaddition yields 5-alkylideneisoxazolidine species **D**, followed by a gold-catalyzed *N*−*O* cleavage to yield a gold enolate **E** bearing an anilinium moiety. Two possible conformations, **E** or **E′**, are conceivable for this enolate intermediate to affect their reaction chemoselectivity toward pyrrolidin-3-ones **F** versus benzoazepin-4-ones **3′**. Herein, conformation **E** is difficult to form because of a steric hindrance between the methyl and anilinium groups. In our preferable conformation **E′**, methyl is larger than its adjacent hydrogen, rendering its anilinium ring lying above the enolate moiety; accordingly, this intramolecular cyclization is expected to yield benzoazepin-4- ones **3′** with *anti*-selectivity. We envisage that the amino group of species **3′** facilitates its *anti*/*syn* isomerization through a proton transfer.

Herein, we do not exclude an alternative process involving a 3,3-sigamatropic rearrangement of intermediate **D′** that has a *E*-configured alkene. This rearrangement will also provide *anti*-configured precursor **G** before a tautomerization to the final product **3′**.

Scheme 2. Data to Confirm the *anti*-Selectivity



Scheme 3. Postulated Mechanisms



Dipolar [3 + 2]-cycloadditions of ketone-derived nitrones with unactivated allenes remain unexplored in nitrone chemistry.[6] We report the feasibility of such reactions through gold-catalyzed *N*,*O*-functionalizations[11,12] of 6-alllenyl-1-ynes with *N*-hydroxyanilines to afford stable benzoazepin-4-ones in *anti*-selectivity. These *anti*-configured products are easily isomerized to their *syn*-isomers on a silica column. Such a chemoselectivity and antiselectivity is rationalized with a postulated gold-enolate intermediate bearing an anilinium moiety; its preferable conformation controls the chemoselectivity and stereoselection of benzoazepin-4-one products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02629.

Experimental details and spectral data of all compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: rsliu@mx.nthu.edu.tw.

ORCID

Rai-Shung Liu: 0000-0002-2011-8124

Author Contributions

†A.S.K.R. and B.S.K. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the financial support of this work from Ministry of Science and Technology, Taiwan.

DOI: 10.1021/acs.orglett.7b02629
Org. Lett. XXXX, XXX, XXX−XXX

REFERENCES

(1) Selected reviews: (a) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocyclic and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley: New York, 2002. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887−2092. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−910. (d) Cardona, F.; Goti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7832−7835.

(2) (a) Hames, J.; Macaluso, A. *Chem. Rev.* **1964**, *64*, 473−495. (b) Snider, B. B.; Lin, H.; Foxman, B. M. *J. Org. Chem.* **1998**, *63*, 6442−6443. (c) Torrente, S.; Noya, B.; Branchadell, V.; Alonso, R. *J. Org. Chem.* **2003**, *68*, 4772−4783. (d) Grigorev, I. A. *Oxides, Nitrones and Nitronates in Organic Synthesis*; Feuer, H., Ed.; Wiley: Hoboken, 2008; pp 129−434.

(3) (a) Pfeiffer, J. Y.; Beauchemin, A. M. *J. Org. Chem.* **2009**, *74*, 8381−8383. (b) Nguyen, T. B.; Martel, A.; Dhai, R.; Dujardin, G. *Org. Lett.* **2008**, *10*, 4493−4496. (c) Winterfeldt, E.; Krohn, W.; Stracke, H. *Chem. Ber.* **1969**, *102*, 2346−2361. (d) Pernet-Poil-Chevrier, A.; Cantagrel, F.; Le Jeune, K.; Philouze, C.; Chavant, P. Y. *Tetrahedron: Asymmetry* **2006**, *17*, 1969−1974. (e) Cantagrel, F.; Pinet, S.; Gimbert, Y.; Chavant, P. Y. *Eur. J. Org. Chem.* **2005**, *2005*, 2694−2701.

(4) (a) Padwa, A.; Kline, D. N.; Norman, B. H. *J. Org. Chem.* **1989**, *54*, 810−817. (b) Tufarriello, J. J.; Ali, S. A.; Klingele, H. O. *J. Org. Chem.* **1979**, *44*, 4213−4215.

(5) (a) Anderson, L. L.; Kroc, M. A.; Reidl, T. W.; Son, J. *J. Org. Chem.* **2016**, *81*, 9521−9529 (review). (b) Blechert, S. *Liebigs Ann. Chem.* **1985**, *1985*, 673−682. (c) Mo, D.-L.; Wink, D. J.; Anderson, L. L. *Chem. - Eur. J.* **2014**, *20*, 13217−13225. (d) Wilkens, J.; Kuhling, A.; Blechert, S. *Tetrahedron* **1987**, *43*, 3237−3246. (e) Singh, R. R.; Liu, R.-S. *Chem. Commun.* **2014**, *50*, 15864−15866.

(6) Cycloadditions of electron-deficient allenes with trisubstituted nitrones bearing two electron-withdrawing groups were recently reported, see: Garcia-Castro, M.; Kremer, L.; Reinkemeier, C. D.; Unkelbach, C.; Strohmann, C.; Ziegler, S.; Ostermann, C.; Kumar, K. *Nat. Commun.* **2015**, *6*, 6516−6528.

(7) (a) Huple, D. B.; Mokar, B. D.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2015**, *54*, 14924−14928. (b) Mokar, B. D.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2016**, *55*, 11892−11896.

(8) (a) Sharaf, M. H. M.; Schiff, P. L., Jr.; Tackie, A. N.; Phoebe, C. H., Jr.; Davis, A. O.; Andrews, C. W.; Crouch, R. C.; Martin, G. E. *J. Heterocycl. Chem.* **1995**, *32*, 1631−1636. (b) Waetjen, F.; Dahl, B. H.; Drejer, J.; Jensen, L. H.; (NeuroSearch A/S, Den). Application: US, 1995, 8 pp Cont-in-part of US 5,242,918. (c) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Tetrahedron* **2007**, *63*, 690−702. (d) Ogawa, H.; Kondo, K.; Yamashita, H.; Kan, K.; Tominaga, M.; Yabuuchi, Y. (Otsuka Pharmaceutical Co., Ltd., Japan). Application: WO, 1994, 159 pp. (e) Gómez-Ayala, S.; Castrillón, J. A.; Palma, A.; Leal, S. M.; Escobar, P.; Bahsas, A. *Bioorg. Med. Chem.* **2010**, *18*, 4721−4739. (f) Seko, T.; Katsumata, S.; Kato, M.; Manako, J.-i.; Ohmoto, K. (Ono Pharmaceutical Co., Ltd., Japan). Application: WO, 2003, 222 pp.

(9) Crystallographic data of compounds **3i**, **3s** and **3t′** were deposited at Cambridge Crystallographic Data Center: **3i** (CCDC 1567416), **3s** (CCDC 1567417) and **3t′** (CCDC 1568212).

(10) (a) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080−1106. (b) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735−1766. (c) Kaneti, J.; Kirby, A. J.; Koedjikov, A. H.; Pojarlieff, I. G. *Org. Biomol. Chem.* **2004**, *2*, 1098−1103. (d) Bachrach, S. M. *J. Org. Chem.* **2008**, *73*, 2466−2468.

(11) Recent review for gold-catalyzed *N*,*O*-functionalizations of alkynes, see: Huple, D. B.; Ghorpade, S.; Liu, R.-S. *Adv. Synth. Catal.* **2016**, *358*, 1348−1367.

(12) For gold-catalyzed intermolecular reactions of *N*-hydroxyamines with alkynes or allenes, see: (a) Wang, Y.; Ye, L.; Zhang, L. *Chem. Commun.* **2011**, *47*, 7815−7817. (b) Wang, Y.; Liu, L.; Zhang, L. *Chem. Sci.* **2013**, *4*, 739−746. (c) Kawade, R. K.; Huang, P.-H.; Karad, S. N.; Liu, R.-S. *Org. Biomol. Chem.* **2014**, *12*, 737−740. (d) Chen, J.-M.; Chang, C.-J.; Ke, Y.-J.; Liu, R.-S. *J. Org. Chem.* **2014**, *79*, 4306−4311.

DOI: 10.1021/acs.orglett.7b02629
Org. Lett. XXXX, XXX, XXX−XXX