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Gold-Catalyzed Oxidative Cyclization of 4-Allenyl-1-ynes with 8-Methylquinoline Oxide

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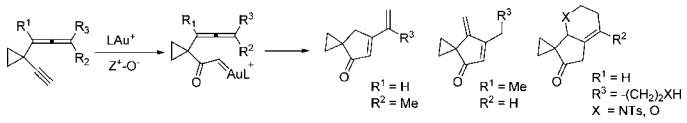
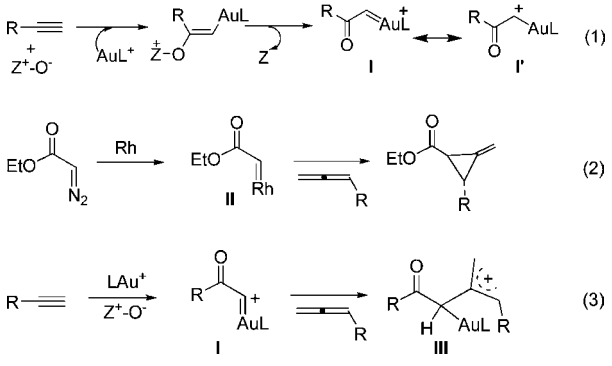
ABSTRACT



Gold-catalyzed oxidative cyclizations of 4-allenyl-1-ynes with 8-methylquinoline oxide are described; diverse products are produced depending on the allenyl substituents. This reaction comprises initial formation of α-oxo gold carbenes that are attacked by allene to form allyl cation intermediates.

The generation of α-oxo gold carbenes **I** via a regioselective oxidation of terminal alkynes with pyridine-based *N*-oxides represents the current utility of gold catalysis;[1−3] a general protocol is depicted in eq 1. Besides safe and easy operation, α-oxo gold carbenes **I** might exhibit chemoselectivity distinct from that of other metal carbenes generated from diazo precursors.[2d,4] One notable feature of gold carbenes **I** is the cationic character as represented by resonances **I′**,[2,5] synthetic equivalents as α-oxo carbocations are atypical in organic chemistry. For example, the reactions of rhodium carbene intermediates **II** with allenes were reported to undergo a typical cyclopropanation, giving methylenecyclopropane derivatives.[6]



We envisage that this reaction pattern can be varied with α-oxo gold carbene **I** as the intermediate. We report an altered chemoselectivity in the reactions of gold carbenes **I** with allenes to form allylic cations **III** that are subjected to

(1) Review: Xiao, J.; Li, X. *Angew. Chem.* **2011**, *123*, 7364. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226.

(2) For 8-methylquinoline oxides, see selected examples: (a) Li, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070. (b) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (c) Luo, Y.; Ji, K.; Li, Y.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 17412. (d) Ghorpade, S.; Su, M.-D.; Liu, R.-S. *Angew. Chem.* **2013**, *125*, 4323. *Angew. Chem., Int. Ed.* **2013**, *52*, 4229. (e) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. *Angew. Chem.* **2012**, *124*, 2993. *Angew. Chem., Int. Ed.* **2012**, *51*, 2939. (f) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angew. Chem.* **2011**, *123*, 7043. *Angew. Chem., Int. Ed.* **2011**, *50*, 6911. (g) Dateer, R. B.; Pati, K.; Liu, R.-S. *Chem. Commun.* **2012**, *48*, 7200. (h) Fu, J.; Shang, H.; Wang, Z.; Chang, L.; Shao, W.; Yang, Z.; Tang, Y. *Angew. Chem.* **2013**, *125*, 4292. *Angew. Chem., Int. Ed.* **2013**, *52*, 4198. (i) Pawar, S. K.; Wang, C.-D.; Bhunia, S.; Jadhav, A. M.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2013**, *52*, 7559.

(3) For other pyridine *N*-oxides, see selected examples: (a) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (b) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550. (c) Ye, L.; He, W.; Zhang, L. *Angew. Chem.* **2011**, *123*, 3294. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236. (d) Henrion, G.; Chavas, T. E. J.; Goff, X. L.; Gagosz, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 6277.

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(5) (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2008**, *47*, 6754. (b) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488. (c) Benitez, D.; Shapiro, N. D.; Tkatchouk, E.; Wang, Y.; Goddard, W. A., III; Toste, F. D. *Nat. Chem.* **2009**, *1*, 482. (d) Seidel, G.; Mynott, R.; Fürstner, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 2510. (e) Jiménez-Núñez, E.; Clavarie, C. K.; Bour, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 7892. (f) Li, C. W.; Lin, G. Y.; Liu, R.-S. *Chem.—Eur. J.* **2010**, *16*, 5803. (g) Miege, F.; Meyer, C.; Cossy, J. *Beilstein, J. Org. Chem.* **2011**, *7*, 717.

(6) See selected examples: (a) Linday, V. N. G.; Fiset, D.; Gritsch, P. J.; Azzi, S.; Charett, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 1463. (b) Huval, C. C.; Singleton, D. A. *J. Org. Chem.* **1994**, *59*, 2020. (c) Chen, J.; Lu, L.; Ma, S. *Tetrahedron* **2008**, *64*, 8899. (d) Yao, T.; Hong, A.; Sarpong, R. *Synthesis* **2006**, 3605. (e) Taherirastgar, F.; Brandsma, L. *Synth. Commun.* **1997**, *27*, 4035.

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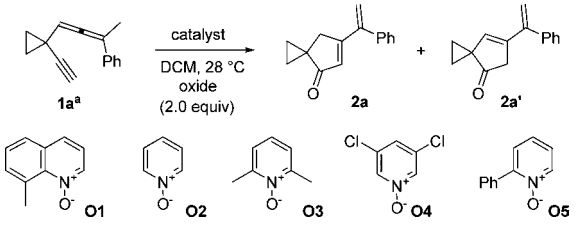
either deprotonation or nucleophilic addition, as depicted in eq 3. This new reaction pattern truly reflects the cationic character of the α-oxo gold carbene.[2,5]

We prepared 4-allenyl-1-yne **1a** bearing a cyclopropyl ring[7] and a trisubstituted allene to stabilize postulate allylic cation **III** (eq 3). We first tested 8-methylquinoline oxide because it did not need the assistance of Brønsted acids.[2] As shown in Table 1 (entry 1), the reaction of species **1a**, 8-methylquinoline oxide (**O1**, 2 equiv), and $Ph_3AuCl/AgSbF_6$ (8 mol %) in dichloromethane (DCM, 28 °C, 30 h) gave oxidatively cyclized product **2a** and its regioisomer **2a′**, each in 30−32% yields, with complete conversion. The yields of compounds **2a** and **2a′** were slightly increased to 34−35% with $Ph_3AuCl/AgNTf_2$ (entry 2). To our pleasure, the use of P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgX (X = SbF_6 and NTf_2) further enhanced the yields of each product to exceed 40% (entries 3−4). P(*t*-Bu)$_2$(*o*-biphenyl)-AuCl/$AgNTf_2$, at a 5 mol % loading, gave decreased yields (31−32%) of each product (entry 5). Less acidic IPrAuCl/$AgNTf_2$ appeared to be inefficient in giving desired **2a** and **2a′**, with their yields being <17% (entry 6). In control experiemnts, $AgNTf_2$ and $HNTf_2$ alone were catalytically inactive (entries 7−8). In the presence of the HOTf additive (30 mol %), only one regioisomer **2a** was obtained in 78% yield using P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgNTf_2$ (entry 9); the other regioisomer **2a′** was presumably converted to species **2a** with HOTf. We also tested the reaction on pyridine oxide (**O2**) and their subsituted derivatives **O3**−**O5** (entries 10−13); 2-phenylpyridine oxide gave compound **2a** with the best yield, ca. 46% (entry 13).

We tested the reactions on 4-allenyl-1-ynes **1b**−**1g** to expand the substrate scope; the data are shown in Scheme 1. In a typical reaction, substrates **1** were treated with 8-methylquinoline oxide (**O1**, 2 equiv), P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/$AgNTf_2$ (8 mol %), and HOTf (30 mol %) in DCM at 28 °C; these conditions assured the formation of one isomeric product **2**. This reaction was extensible to 4-allenylalk-1-ynes **1b**−**1e** bearing a fluoro, chloro, methyl, and methoxy substituent at the 4-phenyl carbon, giving 2,4-dien-1-ones **2b**−**2e** with yields exceeding 79%. The reactions were also compatible with substrates **1f**−**1g** bearing an aliphatic group R = *tert*-butyl and isopropyl; the corresponding 2,4-dien-1-ones **2f** and **2g** were obtained in 78−81% yields. The molecular structure of 2,4-dien-1-one **2c** was determined by X-ray diffraction.[8]

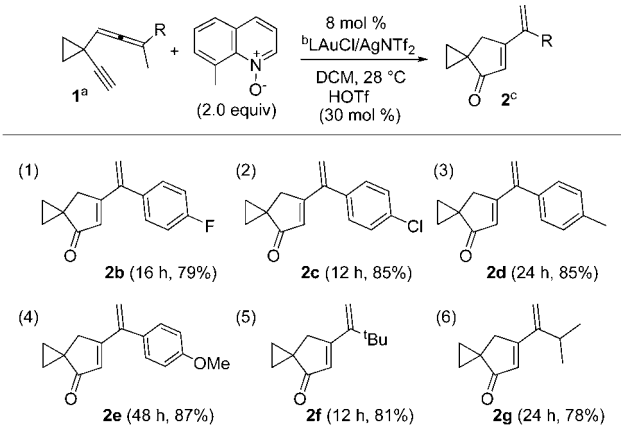
Table 1. Oxidation Cyclizations with Various Catalysts



entry	catalyst[b] (mol %)	oxide	additive (mol %)	time (h)	products (yields)[c] 1a	2a	2a′
1	PPh_3AuCl (8)/$AgSbF_6$ (8)	**O1**	—	23	—	30	32
2	PPh_3AuCl (8)/$AgNTf_2$ (8)	**O1**	—	24	—	34	35
3	LAuCl (8)/$AgSbF_6$ (8)	**O1**	—	24	—	41	40
4	LAuCl (8)/$AgNTf_2$ (8)	**O1**	—	24	—	41	43
5	LAuCl (5)/$AgNTf_2$ (5)	**O1**	—	36	—	32	31
6	IPrAuCl (8)/$AgNTf_2$ (8)	**O1**	—	36	8	17	16
7	$AgNTf_2$ (8)	**O1**	—	24	45	—	—
8	$HNTf_2$ (8)	**O1**	—	24	41	—	—
9	LAuCl (8)/$AgNTf_2$ (8)	**O1**	HOTf (30)	24	—	78	—
10	LAuCl (8)/$AgNTf_2$ (8)	**O2**	HOTf (30)	24	—	23	—
11	LAuCl (8)/$AgNTf_2$ (8)	**O3**	HOTf (30)	24	—	36	—
12	LAuCl (8)/$AgNTf_2$ (8)	**O4**	HOTf (30)	24	—	18	—
13	LAuCl (8)/$AgNTf_2$ (8)	**O5**	HOTf (30)	24	—	46	—

[a] [**1a**] = 0.025 M. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl). [c] Product yields are reported after purification from silica column.

Scheme 1. Substrate Scope for Oxidative Cyclization



[a] [**1**] = 0.025 M. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl). [c] Product yields are reported after purification from a silica column.

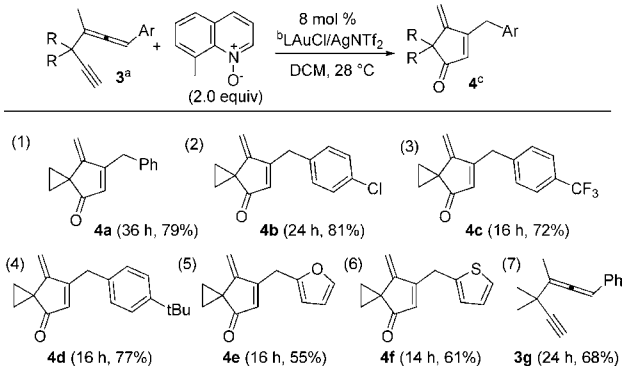
We examined this oxidative cyclization on additional substrates **3** bearing a varied trisubstituted allene; these species afforded distinct 2,4-dien-1-one products **4**, as depicted in Scheme 2. Notably, the catalytic reactions were performed without the HOTf additive because only one regioisomer was produced. Entry 1 shows the applicability of this catalysis to substrate **3a** bearing a phenyl group (Ar = Ph) to give desired **4a** in 79% yield. The same

(7) Cyclopropyl alkynes were frequently used in gold-catalytic reactions because their reactivities are greater than those of normal alkynes. See: (a) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (b) Shi, M.; Liu, L.-P.; Tang, J. *J. Am. Chem. Soc.* **2006**, *128*, 7430. (c) Li, C.-W.; Pati, K.; Lin, G.-Y.; Abu Sohel, S. M.; Hung, H.-H.; Liu, R.-S. *Angew. Chem.* **2010**, *122*, 10087. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891. (d) Liao, H. H.; Liu, R.-S. *Chem. Commun.* **2011**, *47*, 1339. (e) Yang, C.-Y.; Lin, M.-S.; Liao, H.-H.; Liu, R.-S. *Chem.—Eur. J.* **2010**, *16*, 2696. (f) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736. (g) Ye, S.; Yu, Z.-X. *Org. Lett.* **2010**, *12*, 804.

(8) The crystallographic data for compound **2c** was deposited at the Cambridge Crystallographic Deposit Center (CCDC 943248).

reactions worked well with substrates **3b**–**3d** bearing a chloro, trifluoromethyl, or *tert*-butyl group, giving desired 2,4-dien-1-ones **4b**–**4d** in satisfactory yields (72–81%, entries 2–4). Substrates **3e** and **3f** bearing 2-furanyl and 2-thienyl were also compatible with this reaction (entries 5–6); resulting products **4e** and **4f** were obtained in 55–61% yields. In entry 7, we prepared 4-allenyl-1-yne **3g** bearing a Me_2C connecting unit; its gold catalysis in DCM (24 h, 28 °C) led to its 68% recovery. This information indicates that a cyclopropane ring can activate the elctrophilic activation of alkyne because its σ-bond to alkynyl has a large amount of s-characater.

Scheme 2. Expanded Substrate Scope



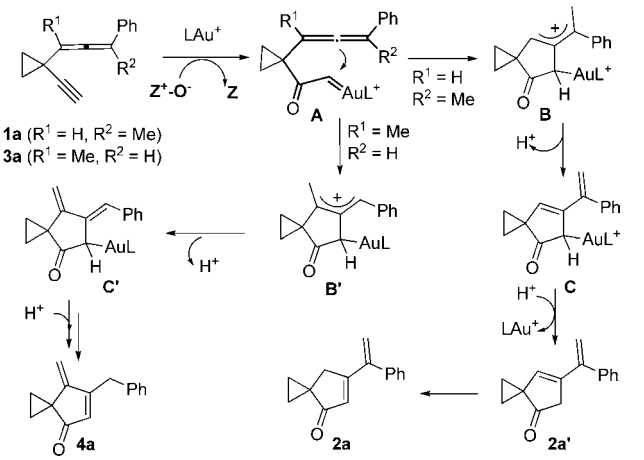
[a] [**3a**] = 0.025 M. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl). [c] Product yields are reported after purification from a silica column.

We postulate a mechanism to rationalize the formation of 2,4-dien-1-ones **2a** and **4a** from 4-allenyl-1-ynes **1a** and **3a** (Scheme 3). An initial oxidation of compounds **1a** and **3a** is expected to form α-oxo gold carbenes **A** that induces an attack of the tethered allene to give allylic cations **B** or **B′**. For starting **1a**, its corresponding cation **B** undergoes a loss of a proton to give gold-containing diene **C**, further producing observed product **2a′** upon hydrodeauration. The **2a′**→**2a** isomerization likely occurs under the reaction conditions involving P(*t*-Bu)$_2$(*o*-biphenyl)Au(H$_2$O)$^+$ as the Brønsted acid. In the case of starting **3a**, the corresponding cation **B′** forms gold-containing diene **C′** with a loss of a proton. Species **C′** ultimately forms observed 2,4-dien-1-one **4a** through hydrodeauration and a double bond shift. We hypothesize a *syn*-configuration for allyl cation **B** because it is less sterically hindered.

We prepared 4-allenyl-1-yne **5a** bearing a tethered alcohol to implement a three-component oxidative cyclization; its feasibility relies on an intramolecular alkoxylation on a postulated *anti*-configured allyl cation **D**. The treatment of species **5a** with 8-methylquinoline oxide (2 equiv) and P(*t*-Bu)$_2$(*o*-biphenyl)AuCl/AgNTf$_2$ (8 mol %) afforded desired 3-en-1-one **6a** in 78% yield (Scheme 4). This observation suggests the role of *anti*-configured allyl cation

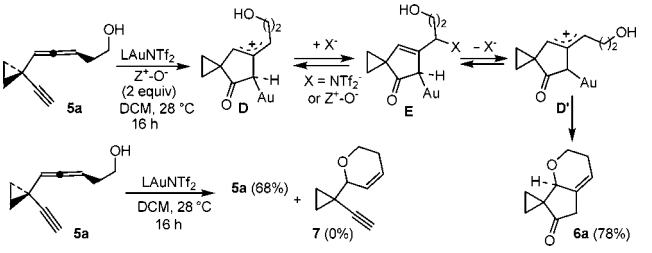
(9) The barriers are expected to be small in our systems because a cyclopropyl group and gold are present for allyl cations **D**/**D′**; see refs 5b, 5c, and: Bollinger, J. M.; Brinich, J. M.; Olah, G. A. *J. Am. Chem. Soc.* **1970**, *92*, 4025.

Scheme 3. Proposed Reaction Mechanism



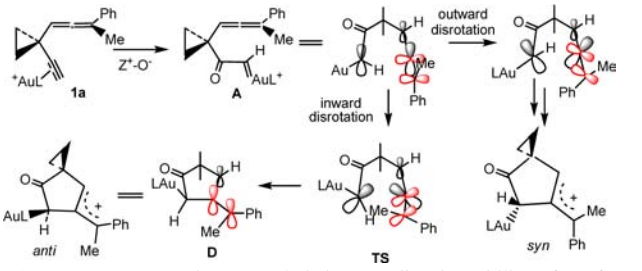
D that might coexist with its *syn*-isomer in an equilibrium state.[9] Our previous calculation on a related system predicts the occurrence of both *syn* and *anti* isomers for allyl cations **D**/**D′**.[10] The interconversion between *syn*- and *anti*-configured 1,2,3-trisubstituted allyl cations typically has a barrier of < 17 kcal/mol; this barrier is even smaller when an electron-donating group is present.[9]

Scheme 4. Gold-Catalyzed Reaction on 4-Allenyl-1-yne **5a**



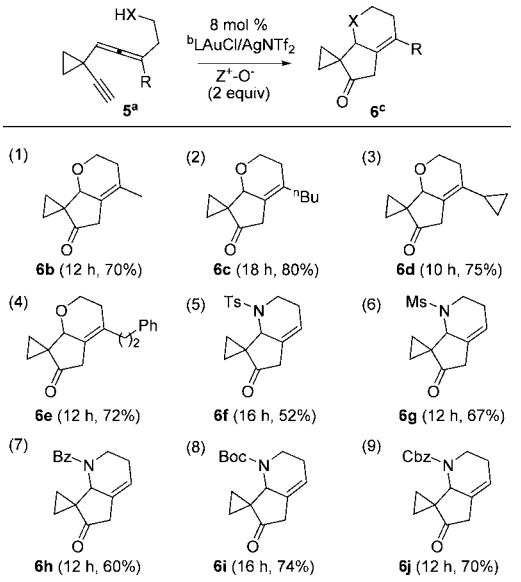
We envisage that NTf_2^- or 8-methylquinoline oxide might facilitate this *syn*/*anti* interconversion via a new intermediate **E** because they are weak coordinating ligands.[11] We performed a control experiment involving the treatment of the

(10) We postulate that the resulting α-oxo carbene **A** preferably undergoes a *dis*-rotation that has a smaller barrier than the *con*-rotation (see ref 2d). Since there are two possible rotation modes (inward versus outward) for starting **1a**, the resulting allyl cation **D** is expected to exist as a mixture of *syn*/*anti* forms, with its *syn*/*anti* ratio dependent upon the relative rates of the two rotations.



(11) Recent X-ray data revealed the coordinating ability of NTf_2^-; see ref 3d.

Scheme 5. Three-Component Oxidative Cyclizations

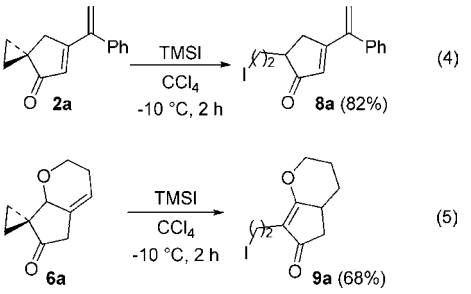


[a] [**5a**] = 0.033 M. [b] L = P(*t*-Bu)$_2$(*o*-biphenyl). [c] Product yields are reported after purification from a silica column.

same substrate with P(*t*-Bu)$_2$(*o*-biphenyl)AuNTf$_2$ (8 mol %) alone in DCM (28 °C, 16 h), but only starting **5a** was recovered in 68% yield (Scheme 4). This observation indicates that the alkyne group has a greater affinity than allene to coordinate with gold, thus impeding an allene alkoxylation. Accordingly the **5a**→**6a** transformation does not involve intermediate **7**, resulted from a prior allene alkoxylation.[12,13]

We assessed the substrate scope of this reaction on 4-allenyl-1-ynes **5b**–**5j** bearing a hydroxyl or an amine group; the results are presented in Scheme 5. As shown in entries 1–4, this three-component cyclization is applicable to trisubstituted allenes **5b**–**5e** bearing R = methyl, *n*-butyl, cyclopropyl, and 2-phenylethyl; the corresponding products **6b**–**6e** were obtained in satisfactory yields (70–80%). Entries 5–9 depict the workability with 4-allenyl-1-ynes **5f**–**5j** bearing various protected amines (X = NTs, NMs, NBz, NBoc, and NCbz), giving desired 3-en-1-ones **6f**–**6j** in moderate to good yields (52–74%).

The cyclopropane rings of resulting products **2a** and **6a** were readily cleaved by nucleophiles because their adjacent carbonyl groups can be activated by acid catalysts. For example, treatment of **2a** and **6a** with trimethylsilyl iodide (TMSI, 1.2 equiv) in CCl_4 (−10 °C, 2 h) afforded 5-iodoethyl derived products **8a** and **9a** in 82% and 68% yields respectively (eqs 4–5).



In summary, we report gold-catalyzed oxidative cyclizations of 4-allen-1-ynes[14,15] **1** and **3** to afford two distinct 2,4-dien-1-ones **2** and **4** efficiently. This process presumably involves an attack of allene at α-oxo gold carbenes to generate allyl cations, ending with a protodeauration. In the case of 4-allenyl-1-ynes **5** bearing a tethered alcohol or amine, their oxidative cyclizations afforded bicyclic 1,3-dienones **6** via an intramolecular cyclization of postulated allyl cation intermediates. These results manifested the carbocation character of α-oxo-gold carbenes.

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Supporting Information Available. Spectral data, NMR spectra, X-ray crystallographic data and spectral data of new compounds are provided in Supporting Information. This materials is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.