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Gold-Catalyzed Stereoselective Synthesis of  
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Formal [4 + 2] Cycloaddition on an *s-trans*-Heterodiene Framework

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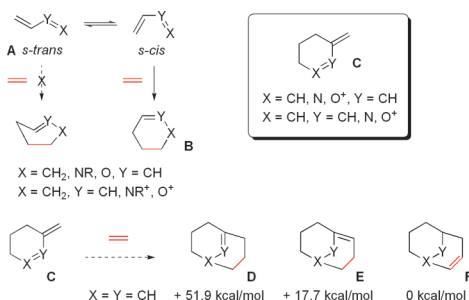
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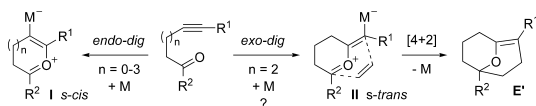
**Abstract:** We report a highly stereoselective Au-catalyzed synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes from diverse 1-oxo-4-oxy-5-ynes. Formation of these highly strained *anti*-Bredt oxacycles implies the workability of an unprecedented 1,4-dipole of *s-trans*-methylene(vinyl)oxonium. This work reveals the feasibility of a formal [4 + 2] cycloaddition on an *s-trans*-heterodiene framework.

[4 + 2] Cycloaddition reactions are powerful tools for constructing complex carbo- and heterocyclic frameworks.<sup>1</sup> Starting acyclic (hetero)dienes **A** are conformationally flexible and exhibit a rapid equilibrium between the *s-trans* and *s-cis* forms (Scheme 1), but only the *s-cis* conformer enables the cycloaddition.<sup>2</sup> This rule is invariable also with rigid *s-trans*-(hetero)dienes **C** that are also inactive toward the reactions. According to our energy estimate, the selection of bridgehead olefin **E** (X = Y = CH) as the primary cycloadduct should be a viable route, for which the energy is 34.2 kcal/mol less than that of the normal cycloadduct **D**.<sup>3</sup> Nevertheless, such an atypical formal cycloaddition (C + olefin → E) has been entirely ignored. This concept stimulated us to pursue its first realization for an *s-trans*-heterodiene framework, i.e., methylene(vinyl)oxonium **C** (X = CH, Y = O<sup>+</sup>), in this work.

## Scheme 1



## Scheme 2



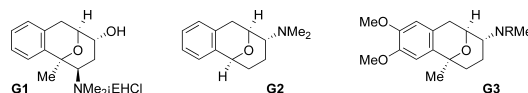
In the presence of Au and Pt catalysts, 1-oxo-*n*-ynes (*n* = 3–6) typically undergo *endo-dig* cyclizations to give *s-cis*-methylene(vinyl)oxoniums **I**, which serve as 1,3- or 1,4-dipoles to react with alkenes or alkynes.<sup>4–7</sup> In contrast, examples of *exo-dig* cyclizations are rare and have been restricted to 1-oxo-2-en-4-ynes that give furyl carbene intermediates.<sup>8</sup> We sought an unprecedented 6-*exo-dig* cyclization of 1-oxo-5-ynes, as depicted in Scheme 2, aiming

Table 1. Catalytic Activity over Various Metal Catalysts<sup>a</sup>

entry	substrate	catalyst (mol %)	condition	product <sup>b</sup>
1	<b>1a</b>	ClAuL (3)/AgSbF <sub>6</sub> (3)	DCM (25 °C, 2 h)	<b>2a</b> (18%) <sup>c</sup>
2	<b>1a</b>	ClAuL (3)/AgNTf <sub>2</sub> (3)	DCM (25 °C, 2 h)	<b>2a</b> (68%)
3	<b>1a</b>	ClAuL (3)	DCM (25 °C, 8 h)	<b>1a</b> (88%)
4	<b>1a</b>	AgNTf <sub>2</sub> (3)	DCM (25 °C, 8 h)	<b>1a</b> (91%)
5	<b>1a</b>	IPrAuCl (3)/AgNTf <sub>2</sub> (3)	DCM (25 °C, 1.5 h)	<b>1a</b> (21%), <b>2a</b> (35%)
6	<b>1a</b>	Ph <sub>3</sub> PAuCl (5)/AgNTf <sub>2</sub> (5)	DCM (25 °C, 2 h)	polymerization
7	<b>1a</b>	AuCl <sub>3</sub> (5)	DCM (25 °C, 2 h)	messy mixtures
8	<b>1a</b>	PtCl <sub>2</sub> /CO (5)	toluene (50 °C, 3 h)	polymerization
9	<b>1b</b>	ClAuL (3)/AgNTf <sub>2</sub> (3)	DCM (25 °C, 12 h)	<b>1b</b> (43%), <b>2b</b> (8%) <sup>c</sup>

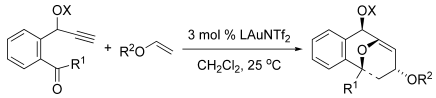
<sup>a</sup> L = P(*t*-Bu)<sub>2</sub>(*o*-biphenyl), [substrate] = 0.1 M. <sup>b</sup> Reported yields were determined after separation from a silica gel column. <sup>c</sup> Polymerization was observed for portion of **1a** and **1b** in entries 1 and 9.

## Scheme 3

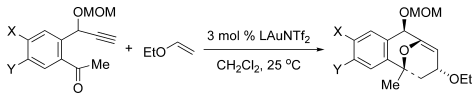


at the conformationally rigid *s-trans*-oxoniums **II**; their workability as 1,4-dipoles is the focus of this work.

We prepared 1-oxo-5-ynes **1a** and **1b** to test our working hypothesis using various catalysts (Table 1). Treatment of **1a** with ethoxyethene (3 equiv) and ClAuP(*t*-Bu)<sub>2</sub>(*o*-biphenyl)/AgSbF<sub>6</sub> (3 mol %) in dichloromethane (DCM) at 25 °C for 2 h resulted in complete consumption of the initial **1a**, giving **2a** in 18% yield together with a messy unknown mixture (entry 1). To our pleasure, the use of ClAuP(*t*-Bu)<sub>2</sub>(*o*-biphenyl)/AgNTf<sub>2</sub> (3 mol %) greatly improved the yield of the desired product **2a** to 68% (entry 2); control experiments showed no activity of either ClAuP(*t*-Bu)<sub>2</sub>(*o*-biphenyl) or AgNTf<sub>2</sub> (entries 3 and 4). Decreased activity was found for IPrAuCl/AgNTf<sub>2</sub> [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene], which gave **2a** in 35% yield and unreacted **1a** with 21% recovery. Ph<sub>3</sub>PAuCl/AgNTf<sub>2</sub>, AuCl<sub>3</sub>, and PtCl<sub>2</sub>/CO, each at 5 mol %, were unsuitable for this catalysis because of a complete decomposition of initial **1a** to polymers or messy unknown mixtures. We also examined the reaction of substrate **1b** and ethoxyethene using ClAuP(*t*-Bu)<sub>2</sub>(*o*-biphenyl)/AgNTf<sub>2</sub> but obtained the desired product **2b** in only 8% yield together with unreacted **1b** (43% recovery). The acyloxy group of **1a** appears to be crucial to the success of this gold catalysis. The 9-oxabicyclo[3.3.1]nona-4,7-diene framework of **2a** was confirmed by an X-ray diffraction study

**Table 2.** Scope of Aromatic 1-Oxo-5-yne Substrates<sup>a</sup>


entry	oxoyne	enol ether	t [h]	products <sup>b</sup>
1	X = Ac, R <sup>1</sup> = H ( <b>1a</b> )	R <sup>2</sup> = <i>n</i> -Bu	1	<b>2a'</b> (62%)
2	X = Ac, R <sup>1</sup> = Me ( <b>1c</b> )	R <sup>2</sup> = Et	2.5	<b>2c</b> (76%)
3	<b>1c</b>	R <sup>2</sup> = <i>n</i> -Bu	2	<b>2c'</b> (67%)
4	X = MOM, R <sup>1</sup> = H ( <b>1d</b> )	R <sup>2</sup> = Et	1	<b>2d</b> (85%)
5	<b>1d</b>	R <sup>2</sup> = <i>n</i> -Bu	1	<b>2d'</b> (82%)
6	X = MOM, R <sup>1</sup> = Me ( <b>1e</b> )	R <sup>2</sup> = Et	1	<b>2e</b> (82%)
7	<b>1e</b>	R <sup>2</sup> = <i>n</i> -Bu	1	<b>2e'</b> (94%)
8	X = MOM, R <sup>1</sup> = <i>n</i> -Pr ( <b>1f</b> )	R <sup>2</sup> = Et	1	<b>2f</b> (74%)
9	X = Bn, R <sup>1</sup> = Me ( <b>1g</b> )	R <sup>2</sup> = Et	1.5	<b>2g</b> (57%)
10	X = <i>n</i> -Bu, R <sup>1</sup> = Me ( <b>1h</b> )	R <sup>2</sup> = Et	1.5	<b>2h</b> (42%)

<sup>a</sup> L = P(*t*-Bu)<sub>2</sub>(*o*-biphenyl), [oxoyne] = 0.1 M, enol ether (3 equiv).<sup>b</sup> Reported isolated yields were determined after purification on a silica gel column.**Table 3.** Phenyl Effect of 1-Oxo-5-yne Substrates<sup>a</sup>


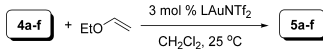
entry	oxoyne	t [h]	products <sup>b</sup>
1	X = OMe, Y = H ( <b>1i</b> )	1	<b>2i</b> (90%)
2	X = H, Y = OMe ( <b>1j</b> )	2.5	<b>2j</b> (86%)
3	X = Y = OMe ( <b>1k</b> )	2	<b>2k</b> (95%)
4	X = F, Y = H ( <b>1l</b> )	1	<b>2l</b> (83%)
5	X = H, Y = F ( <b>1m</b> )	1	<b>2m</b> (91%)
6	X = Cl, Y = H ( <b>1n</b> )	1	<b>2n</b> (78%)
7	X = H, Y = Cl ( <b>1o</b> )	1	<b>2o</b> (84%)

<sup>a</sup> L = P(*t*-Bu)<sub>2</sub>(*o*-biphenyl), [oxoyne] = 0.12 M, enol ether (3 equiv).<sup>b</sup> Reported isolated yields were determined after purification on a silica gel column.

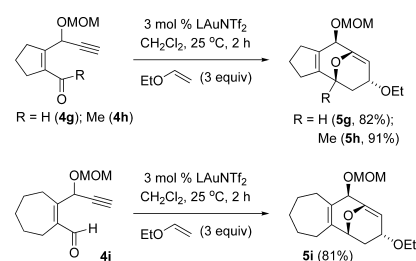
of its hydroxy derivative **3a** (X = OH);<sup>9</sup> this *anti*-Bredt structure confirms a [4 + 2] cycloaddition to *s-trans*-oxonium **II**. Notably, the route to the *anti*-Bredt [4 + 2] cycloadduct is not attainable with *s-cis*-oxonium **I** (*n* = 1, Scheme 2) and related benzopyrili-ums.<sup>5</sup> The utility of this synthesis is manifested by its facile access to bioactive molecules **G1–G3** (Scheme 3), which exhibit activity in the central nervous system and HIV-1 inhibitory effects.<sup>10</sup>

We prepared various aldehyde- and ketone-containing substrates **1a–h** bearing alterable 4-oxy groups to assess the scope of this catalysis (Table 2); each resulting product **2a'–h** was obtained as a single diastereomer despite its complicated molecular framework. Entries 1–3 show additional examples of the applicability of this new synthesis not only to ketone substrate **1c** but also to butoxyethene; the desired oxacycles **2a'–c'** were obtained in 62–76% yield. Particularly notable are the high yields (74–94%) of products **2d–f** produced from 1-oxo-5-yne **1d–f** bearing a methoxymethyl (MOM) ether group (entries 4–8). The effect of the 4-oxy group is also reflected by substrates **1g** and **1h** bearing benzyl and *n*-butyl ethers, respectively, which gave the corresponding products **2g** and **2h** in moderate yields (57 and 42%; entries 9 and 10).

We also prepared substrates **1i–o** to examine the effects of their phenyl substituents (Table 3); only one diastereomeric product was obtained in all cases. In entries 1–3, excellent product yields (86–95%) were obtained for oxacyclic compounds **2i–k** bearing a methoxy group at the phenyl C(4) or C(5) position. The workability with substrates **1l–o** bearing fluoro and chloro substituents, which produced the expected products **2l–o** in good yields (78–91%; entries 4–7), reflects the wide scope of this catalysis.

**Table 4.** Scope of Nonaromatic 1-Oxo-5-yne Substrates<sup>a</sup>


entry	oxoyne	t [h]	products <sup>b</sup>
1	R <sup>1</sup> = Y = H, X = Ac ( <b>4a</b> )	1	<b>5a</b> (63%)
2	R <sup>1</sup> = Me, Y = H, X = Ac ( <b>4b</b> )	2	<b>5b</b> (65%)
3	R <sup>1</sup> = H, Y = Me, X = Ac ( <b>4c</b> )	1	<b>5c</b> (73%)
4	R <sup>1</sup> = Y = H, X = MOM ( <b>4d</b> )	1	<b>5d</b> (78%)
5	( <b>4e</b> )	1.5	<b>5e</b> (76%)
6	( <b>4f</b> )	1	<b>5f</b> (63%)

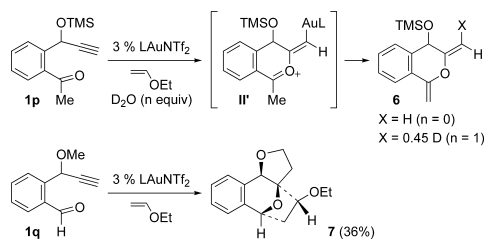
<sup>a</sup> L = P(*t*-Bu)<sub>2</sub>(*o*-biphenyl), [oxoyne] = 0.1 M, enol ether (3 equiv).<sup>b</sup> Reported isolated yields were determined after purification on a silica gel column.**Scheme 4**

The value of this catalysis is highlighted by its successful extension to nonaromatic 1-oxo-4-oxy-5-yne **4a–f**, which gave oxacyclic frameworks **5a–f** of various classes (Table 4). For substrates **4a–d** bearing tunable R<sup>1</sup> (R<sup>1</sup> = H, Me), OX (X = Ac, MOM), and Y (Y = H, Me) groups, the same gold catalysis delivered products **5a–d** in 63–78% yield (entries 1–4). For bicyclic oxoalkyne **4e**, gold catalysis gave the desired product **5e** in 76% yield; the stereochemistry of **5e** was confirmed with X-ray diffraction measurements.<sup>9</sup> We prepared acyclic oxoalkyne **4f**, which also gave the expected compound **5f** in 63% yield.

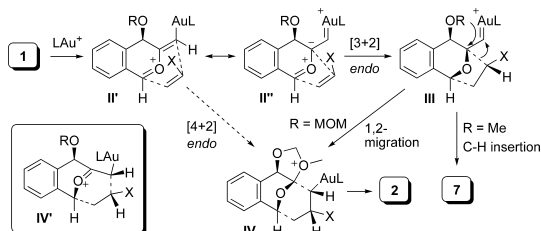
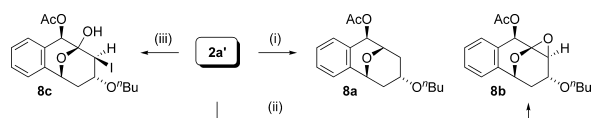
Shown in Scheme 4 are additional new frameworks that are readily available from this gold catalysis. We prepared aldehydes **4g/4i** and ketone **4h** bearing fused cyclopentenyl and cycloheptenyl rings, respectively, and their corresponding cycloadducts **5g/5i** and **5h** were obtained very efficiently (yields >81%) and stereoselectively.

As depicted in Scheme 5, we studied gold-catalyzed catalysis on substrate **1p** bearing a noncoordinating siloxy group, and its reaction with ethoxyethene gave compound **6** rather than the desired oxacyclic cycloadducts such as **2**. Compound **6** was formed with 45% deuterium (X = 0.45D) at the *trans*-vinyl hydrogen position in the presence of D<sub>2</sub>O (1 equiv); this information supports the intermediacy of gold-containing *s-trans*-oxonium **II'** through a 6-*exo-dig* mode. Accordingly, the oxy groups, including OMOM, OAc and OTMS, facilitate the 6-*exo-dig* cyclization via an electron-withdrawing effect on the alkyne rather than through metal coordination. We also prepared methoxy derivative **1q**, which gave complex oxacyclic species **7** in 36% yield;

Scheme 5



Scheme 6

Scheme 7<sup>a</sup>

<sup>a</sup> Reagents: (i) Pd–C/H<sub>2</sub> (1 atm), 1:1 1,4-dioxane/DCM, 25 °C, 16 h, 82% (ii) *m*-CPBA (1.5 equiv), NaHCO<sub>3</sub> (3 equiv), DCM, 1.5 h, 76% (iii) ICI (1.1 equiv), wet DCM, 1 h, 0 °C, 63%.

its formation may imply a gold-containing carbene intermediate **III**, as depicted in Scheme 6.

It is possible that compounds **2** are produced from either an initial [3 + 2] cycloaddition to  $\alpha$ -carbonyl ylide II''<sup>6</sup> or from a [4 + 2] cycloaddition on *s*-*trans*-oxonium II'.<sup>5</sup> We envisage that the [3 + 2] path would enable the oxy group to approach the enol ether closely, rendering great diastereocontrol of the cycloadducts. As shown in structure II'', the enol ether approaches the carbonyl ylide from the less-hindered *endo* face and away from the proximate oxy group (OR) to give gold carbenium **III**. The formation of compound **7** from 1-oxo-5-yne **1q** might imply intermediate **III**, whose carbene functionality would activate a methoxy C–H insertion.<sup>11</sup> An alternative stepwise [4 + 2] cycloaddition would make it difficult to rationalize the stereodirecting effect of the oxy group.

Importantly, this catalysis requires 1-oxo-5-yne **1** bearing an oxy group<sup>12,13</sup> to give the desired oxacycles **2**, with R = MOM or Ac being more efficient than R = TMS. We hypothesize that MOM assists a 1,2-alkyl migration to form stable oxonium species **IV**, which is subsequently convertible to the formal “[4 + 2] cycloadduct” **2**; we disfavor the bridgehead oxonium **IV'** because of its highly strained skeleton (see Scheme 1, species **D**). Verification of this hypothesis needs additional work in the future.

Scheme 7 shows the use of this catalysis for a stereoselective synthesis of highly oxygenated molecules. Stereoselective functionalization of **2a'** at the bridgehead olefin was readily achieved via (i) Pd/C hydrogenation and (ii) *m*-CPBA epoxidation from the open face, giving **8a** and **8b** in 82 and 76% yield, respectively. Treatment of **2a'** with ICI in wet CH<sub>2</sub>Cl<sub>2</sub> gave hemiketal **8c** (63%) as a single diastereomer.

In summary, we have reported a highly stereoselective Au-catalyzed synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes from diverse 1-oxo-5-yne bearing an indispensable 4-oxy group. Formation of these highly strained *anti*-Bredt oxacycles reveals the workability of an unpre-

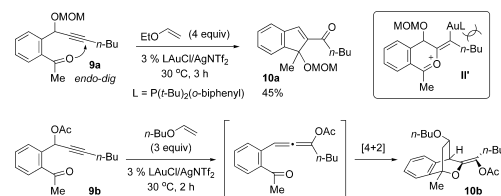
cedented 1,4-dipole of *s*-*trans*-methylene(vinyl)oxonium **II**. Nevertheless, in view of the highly diastereoselective outcome, the resulting cycloadducts arise from an initial [3 + 2] cycloaddition of  $\alpha$ -carbonyl ylide II'' followed by a ring expansion. The concept of a formal [4 + 2] cycloaddition on an *s*-*trans*-heterodiene should be helpful in the design of new synthetic methods.

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**Supporting Information Available:** Experimental procedures, characterization data for new compounds, and X-ray crystallographic data (CIF) for compounds **3a** and **5e**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) For reviews, see: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2002**, *41*, 1668. (b) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (c) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781. (d) Boger, D. L. *J. Heterocycl. Chem.* **1996**, *33*, 1519. (e) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869.
- (2) (a) Houk, K. N.; Lin, Y.-T.; Brown, F. K. *J. Am. Chem. Soc.* **1986**, *108*, 554. (b) Goldstein, E.; Beno, B.; Houk, K. N. *J. Am. Chem. Soc.* **1996**, *118*, 6036.
- (3) The calculations were performed using the B3LYP method with the LANL2DZ basis set (B3LYP/LANL2DZ).
- (4) For reviews, see: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Abu Sohail, S. Md.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269.
- (5) For *s*-cis-oxoniums **I**, their [4 + 2] cycloaddition intermediates **V** do not give *anti*-Bredt oxacycles **VI**; these hypothetical intermediates undergo facile rearrangement to dihydronaphthalenes<sup>5a,b</sup> or 8-oxabicyclo[3.2.1]octanes.<sup>6</sup> See: (a) Asao, N.; Kasahara, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 3504. (b) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458. (c) Hsu, Y.-C.; Ting, C.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2009**, *131*, 2090. (d) Shu, X.-Z.; Zhao, S.-C.; Ji, K.-G.; Zheng, Z.-J.; Liu, X.-Y.; Liang, Y.-M. *Eur. J. Org. Chem.* **2009**, 117.
- (6) For selected examples of [3 + 2] cycloadditions, see: (a) Kusama, H.; Ishida, K.; Funami, H.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4903. (b) Li, G.; Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 6944. (c) Oh, C. H.; Lee, J. H.; Lee, S. J.; Kim, J. I.; Hong, C. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7505. (d) Oh, C. H.; Lee, S. M.; Hong, C. S. *Org. Lett.* **2010**, *12*, 1308.
- (7) For other reactions of *s*-cis-oxonium **I**, see: (a) Liu, F.; Yu, Y.; Zhang, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 5505. (b) Jin, T.; Yamamoto, Y. *Org. Lett.* **2007**, *9*, 5259. (c) Jin, T.; Yamamoto, Y. *Org. Lett.* **2008**, *10*, 3137.
- (8) Miki, K.; Uemura, S.; Ohe, K. *Chem. Lett.* **2005**, *34*, 1068.
- (9) X-ray crystallographic data for compounds **3a** and **5e** are provided in the Supporting Information.
- (10) (a) Wünsch, B.; Zott, M.; Höfner, G. *Arch. Pharm.* **1992**, *325*, 733. (b) Wünsch, B.; Zott, M.; Höfner, G. *Arch. Pharm.* **1992**, *325*, 823. (c) Maurin, C.; Bailly, F.; Cortelle, P. *Curr. Med. Chem.* **2003**, *10*, 1795. (d) Dupont, R.; Jeanson, L.; Mouscadet, J.-F.; Cotellet, P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3175.
- (11) (a) Hashmi, A. S. K.; Schäfer, S.; Wölfl, M.; Gil, C. D.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6184. (b) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2809. (c) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (d) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488.
- (12) For internal alkyne **9a**, we observed a distinct 7-*endo-dig* cyclization to give indenyl ketone **10a** in 45% yield. The steric interaction between gold and *n*-butyl destabilizes intermediate II'. For the acetoxy derivative **9b**, we obtained **10b** stereoselectively from an initial 1,3-acetoxy shift followed by a [4 + 2] cycloaddition on benzopyrylium (see ref 13).



- (13) Teng, T.-M.; Liu, R.-S. *J. Am. Chem. Soc.* **2010**, *132*, 9298.

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