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Gold-Catalyzed Stereoselective Synthesis of 9-Oxabicyclo[3.3.1]nona-4,7-dienes from Diverse 1-Oxo-4-oxy-5-ynes: A Viable Formal [4 + 2] Cycloaddition on an *s-trans*-Heterodiene Framework

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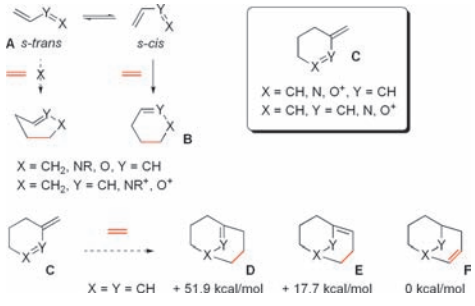
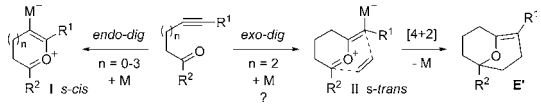
Abstract: We report a highly stereoselective Au-catalyzed synthesis of 9-oxabicyclo[3.3.1]nona-4,7-dienes from diverse 1-oxo-4-oxy-5-ynes. Formation of these highly strained *anti*-Bredt oxacycles implies the workability of an unprecedented 1,4-dipole of *s-trans*-methylene(vinyl)oxonium. This work reveals 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.[1] 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.[2] 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**.[3] 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^+), in this work.

Scheme 1

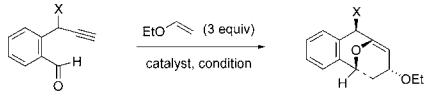


Scheme 2



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.[4−7] 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.[8] We sought an unprecedented 6-*exo-dig* cyclization of 1-oxo-5-ynes, as depicted in Scheme 2, aiming at the conformationally rigid *s-trans*-oxoniums **II**; their workability as 1,4-dipoles is the focus of this work.

Table 1. Catalytic Activity over Various Metal Catalysts[a]



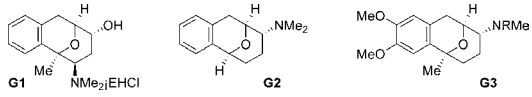
1a (X = OAc)
1b (X = H)

2a (X = OAc), **3a** (X = OH)
2b (X = H)

entry	substrate	catalyst (mol %)	condition	product[b]
1	**1a**	ClAuL (3)/$AgSbF_6$ (3)	DCM (25 °C, 2 h)	**2a** (18%)[c]
2	**1a**	ClAuL (3)/$AgNTf_2$ (3)	DCM (25 °C, 2 h)	**2a** (68%)
3	**1a**	ClAuL (3)	DCM (25 °C, 8 h)	**1a** (88%)
4	**1a**	$AgNTf_2$ (3)	DCM (25 °C, 8 h)	**1a** (91%)
5	**1a**	IPrAuCl (3)/$AgNTf_2$ (3)	DCM (25 °C, 1.5 h)	**1a** (21%), **2a** (35%)
6	**1a**	Ph_3PAuCl (5)/$AgNTf_2$ (5)	DCM (25 °C, 2 h)	polymerization
7	**1a**	$AuCl_3$ (5)	DCM (25 °C, 2 h)	messy mixtures
8	**1a**	$PtCl_2$/CO (5)	toluene (50 °C, 3 h)	polymerization
9	**1b**	ClAuL (3)/$AgNTf_2$ (3)	DCM (25 °C, 12 h)	**1b** (43%), **2b** (8%)[c]

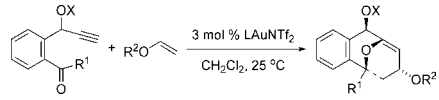
[a] L = P(*t*-Bu)$_2$(*o*-biphenyl), [substrate] = 0.1 M. [b] Reported yields were determined after separation from a silica gel column. [c] Polymerization was observed for portion of **1a** and **1b** in entries 1 and 9.

Scheme 3



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)$_2$(*o*-biphenyl)/$AgSbF_6$ (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)$_2$(*o*-biphenyl)/$AgNTf_2$ (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)$_2$(*o*-biphenyl) or $AgNTf_2$ (entries 3 and 4). Decreased activity was found for IPrAuCl/$AgNTf_2$ [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene], which gave **2a** in 35% yield and unreacted **1a** with 21% recovery. Ph_3PAuCl/$AgNTf_2$, $AuCl_3$, and $PtCl_2$/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)$_2$(*o*-biphenyl)/$AgNTf_2$ 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

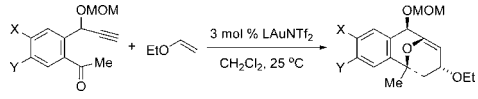
Table 2. Scope of Aromatic 1-Oxo-5-yne Substrates[a]



entry	oxoyne	enol ether	*t* [h]	products[b]
1	X = Ac, R^1 = H (**1a**)	R^2 = *n*-Bu	1	**2a′** (62%)
2	X = Ac, R^1 = Me (**1c**)	R^2 = Et	2.5	**2c** (76%)
3	**1c**	R^2 = *n*-Bu	2	**2c′** (67%)
4	X = MOM, R^1 = H (**1d**)	R^2 = Et	1	**2d** (85%)
5	**1d**	R^2 = *n*-Bu	1	**2d′** (82%)
6	X = MOM, R^1 = Me (**1e**)	R^2 = Et	1	**2e** (82%)
7	**1e**	R^2 = *n*-Bu	1	**2e′** (94%)
8	X = MOM, R^1 = *n*-Pr (**1f**)	R^2 = Et	1	**2f** (74%)
9	X = Bn, R^1 = Me (**1g**)	R^2 = Et	1.5	**2g** (57%)
10	X = *n*-Bu, R^1 = Me (**1h**)	R^2 = Et	1.5	**2h** (42%)

[a] L = P(*t*-Bu)$_2$(*o*-biphenyl), [oxoyne] = 0.1 M, enol ether (3 equiv). [b] Reported isolated yields were determined after purification on a silica gel column.

Table 3. Phenyl Effect of 1-Oxo-5-yne Substrates[a]



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

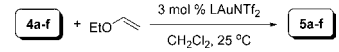
[a] L = P(*t*-Bu)$_2$(*o*-biphenyl), [oxoyne] = 0.12 M, enol ether (3 equiv). [b] Reported isolated yields were determined after purification on a silica gel column.

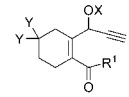
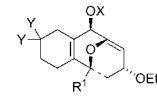
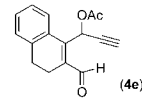
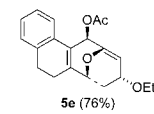
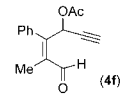
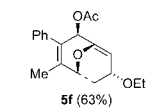
of its hydroxy derivative **3a** (X = OH);[9] this *anti*-Bredt structure confirms a [4 + 2] cycloaddition to *s-trans*-oxonium **II**. Notably, the route to the *anti*-Bredt [4 + 2] cycloadduct is not attainable with *s-cis*-oxonium **I** (*n* = 1, Scheme 2) and related benzopyryliums.[5] The utility 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.[10]

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-ynes **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.

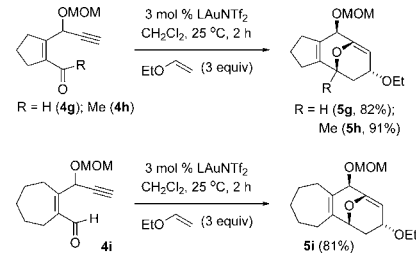
Table 4. Scope of Nonaromatic 1-Oxo-5-yne Substrates[a]



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

[a] L = P(*t*-Bu)$_2$(*o*-biphenyl), [oxoyne] = 0.1 M, enol ether (3 equiv). [b] Reported isolated yields were determined after purification on a silica gel column.

Scheme 4

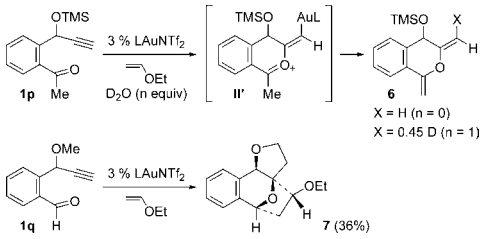


The value of this catalysis is highlighted by its successful extension to nonaromatic 1-oxo-4-oxy-5-ynes **4a**−**f**, which gave oxacyclic frameworks **5a**−**f** of various classes (Table 4). For substrates **4a**−**d** bearing tunable R^1 (R^1 = H, Me), OX (X = Ac, MOM), and Y (Y = H, Me) groups, 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.[9] We prepared acyclic oxoalkyne **4f**, which also gave the expected compound **5f** in 63% yield.

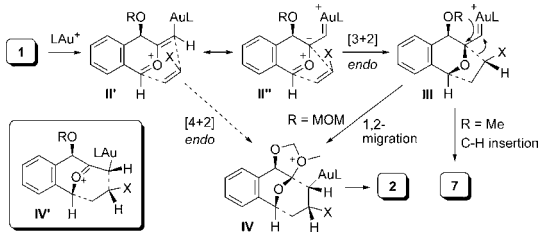
Shown in Scheme 4 are additional new frameworks that are readily available from this gold catalysis. We prepared aldehydes **4g**/**4i** and ketone **4h** bearing fused cyclopentenyl and cycloheptenyl rings, respectively, and their corresponding cycloadducts **5g**/**5i** and **5h** were obtained very 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_2O (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;

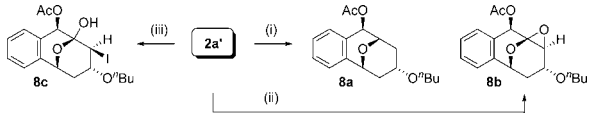
Scheme 5



Scheme 6



Scheme 7[a]



[a] Reagents: (i) Pd−C/H_2 (1 atm), 1:1 1,4-dioxane/DCM, 25 °C, 16 h, 82% (ii) *m*-CPBA (1.5 equiv), $NaHCO_3$ (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 α-carbonyl ylide **II″** [6] or from a [4 + 2] cycloaddition on *s-trans*-oxonium **II′**.[5] 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-oxy-5-yne **1q** might imply intermediate **III**, whose carbene functionality would activate a methoxy C−H insertion.[11] 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-ynes **1** bearing an oxy group[12,13] 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 disparage 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. Stereocontrolled 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 ICl in wet CH_2Cl_2 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-ynes bearing an indispensable 4-oxy group. Formation of these highly strained *anti*-Bredt oxacycles reveals the workability of an unprecedented 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 α-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.

Acknowledgment. The authors thank the National Science Council, Taiwan, for support of this work.

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.

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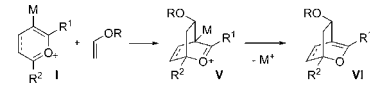
(4) For reviews, see: (a) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (b) Abu Sohel, S. Md.; Liu, R.-S. *Chem. Soc. Rev.* **2009**, *38*, 2269.

(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[5a,b] or 8-oxabicyclo[3.2.1]-octanes.[6] 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.

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(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.

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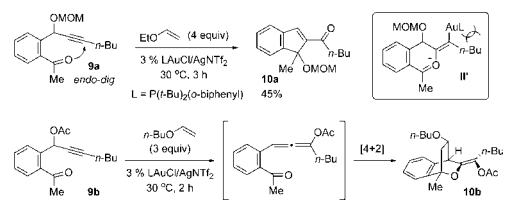
(12) For internal alkyne **9a**, we observed a distinct 7-*endo-dig* cyclization to give indenyl ketone **10a** in 45% yield. The steric interaction between gold and *n*-butyl destabilizes intermediate **II′**. For the acetoxy derivative **9b**, we obtained **10b** stereoselectively from an initial 1,3-acetoxy shift followed by a [4 + 2] cycloaddition on benzopyrilium (see ref 13).



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