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Gold-Catalyzed Cycloisomerization of *o*-Alkynylbenzaldehydes with a Pendant Unsaturated Bond: [3 + 2] Cycloaddition of Gold-Bound 1,3-Dipolar Species with Dipolarophiles

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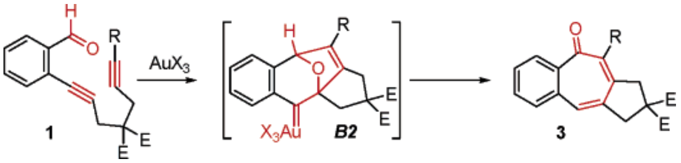
ABSTRACT



A new and novel Au-catalyzed cycloisomerization of ynals bearing a pendant unsaturated bond leading to synthetically valuable [6.7.*n*]-tricyclic compounds were developed. This study strongly supports the intermediacy of [3 + 2] cycloaddition proposed by DFT calculation and provides an easy access to key skeletons found in a variety of natural products.

Transition-metal-catalyzed cycloisomerizations of polyunsaturated systems are atom-economic and environmentally benign synthetic methods to provide efficient access to a variety of structural motifs in many natural products and useful building blocks in synthetic chemistry.[1] Due to the excellent alkynophilicity of gold,[2] particular attention has been paid to gold-based alkyne activation as an attractive strategy for developing new and efficient catalytic cyclizations. Recently, we reported that enynes bearing an aldehyde group underwent unprecedented Rh-catalyzed cyclizations, which could involve [3 + 2] cycloaddition of a Rh-carbenoid dipolar carbonyl ylide intermediate.[3] Yamamoto and coworkers recently reported a novel gold-catalyzed benzannulation of *o*-alkynylbenzaldehydes with alkynes involving a [4 + 2] cycloaddition of Au-pyrylium intermediates with dienophiles such as alkynes and enol ethers.[4] They also reported that ynals bearing a pendant alkyne group underwent [4 + 2] benzannulations intramolecularly.[5] In pursuit of our previous investigations, a closer look prompted us to look at cycloisomerizations involving Huisgen-type [3 + 2] cycloadditions of Au-pyrylium intermediates with dipolarophiles.[6] In this paper, we describe a novel discovery on the gold-catalyzed cycloisomerization of ynals bearing a pendant

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[1] For selected reviews, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (b) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813. (c) Echavarren, A. M.; Nevado, C. *Chem. Soc. Rev.* **2004**, *33*, 431.

[2] (a) For reviews of Au-catalyzed reactions, see: Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237. (b) Hashmi, A. S. K. *Gold Bull.* **2003**, *36*. 3. For selected examples for gold carbene species, see: (c) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806. (d) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6963. (e) Nieto-Oberhuber, C.; López, S.; Echavarren, A. M. *J. Am. Chem. Soc.* **2005**, *127*. 6178. (f) Furstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546.

[3] (a) Shin S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429. For recent benzannulation of enynals, see: (b) Ohe, K.; Miki, K.; Yokoi, T.: Nishino, F.; Uemura, S. *Organometallics* **2000**, *19*, 5525. (c) Ohe, K.; Yokoi, T.; Miki, K.; Nishino, F.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 526.

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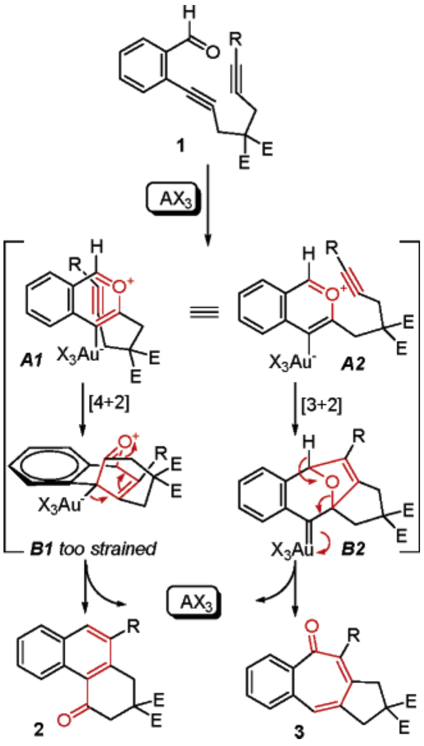
unsaturated bond to yield tricyclic compounds **3**, presumably via a [3 + 2] cycloaddition, as shown in Scheme 1.

Scheme 1

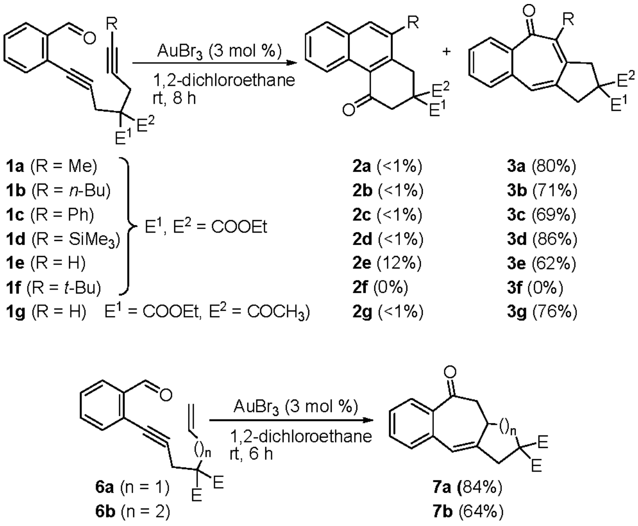


AuBr$_3$ complexation of *o*-alkynylbenzaldehyde **1** was expected to form the zwitterion **A1** as proposed by Yamamoto and co-workers. The intermediate **A1** is a conformer of **A2**, where the pendant alkyne unit is located right below/above the heterodiene unit. Although Yamamoto and co-workers succeeded in benzannulation to obtain the desired products at relatively high temperature, the intermediate **B1** seemed to be highly unstable due to the newly formed two bridged double bonds. In our experiments, we could isolate product **3** exclusively, similar to our Rh-catalyzed cyclization products. Like our proposed mechanism on the Rh-catalyzed reaction of enynals, the Au-catalyzed reaction of diynals might also occur via 1,3-dipolar cycloaddition to form the electron-deficient Au-carbene species **B2** which subsequently could undergo a sequential fragmentation to give product **3** and generate AuBr$_3$ for the next catalytic cycle. We carried out Au-catalyzed cycloisomerization using diynals bearing a *gem*-diester group in order to facilitate 1,3-dipolar cycloaddition. Recently, Straub reported DFT-calculated energies of the intermediates **4** and **5**, which are proposed intermediates in the Au-catalyzed reaction of ethynylbenzaldehyde and ethyne.[7] On the basis of on his calculation, the Gibbs free energy of a possible intermediate **4** (corresponding to **B1**) was slightly lower than that of the intermediate **5** (corresponding to **B2**) in 8.8 kcal/mol as shown in Figure 1, implying that both [4 + 2] intermediate **4** and [3 + 2] intermediate **5** could be formed.

Figure 1. Proposed intermediates of Au-catalyzed reaction of ethynylbenzaldehyde with ethylene.

In the case of intramolecular cycloisomerization (Scheme 1), the additional two highly strained double bonds in the **B1** intermediate might dramatically increase its energy, and hence, [3 + 2] cycloaddition to **B2** rather than [4 + 2] cycloaddition to **B1** could occur more easily at room temperature. To test such a chemoreversal concept, we focused on cycloisomerization of diynal **1a** in 1,2-dichloroethane with Au and Pt catalysts as shown in Scheme 2 and Table 1. AuCl$_3$ with/without combining AgOTf catalyzed [3 + 2] cycloaddition,[8] whereas a combination of AuCl$_3$ with PPh$_3$ did not catalyze any of these pathways (entries 1−3). Triphenylphosphine might react with AuCl$_3$ to destroy its catalytic activity or Lewis acidity. Au(+1) also catalyzed [3 + 2] cycloisomerization in competition with [4 + 2] cycloaddition in a 1:5 mixture of **2a** and **3a** (entry 4). Among the catalysts we examined, AuBr$_3$ was the best for 1,3-dipolar cycloaddition, where the bromide might play a key role in a certain stage in this transformation (entry 5). Note that the

Scheme 2



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(6) In fact, the Huisgen-type [3 + 2] cycloaddition transition states of carbonyl ylides and alkynes have been known for more than 30 years. (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 321. (b) Hamberger, H.; Huisgen, R. *J. Chem. Soc. D* **1971**, *19*, 119.

(7) Straub, B. F. *Chem. Commun.* **2004**, 1726.

(8) (a) Yao, T.,; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164. (b) Nguyen, R.-V.; Yao, X.-Q.; Bohle, D. S.; Li, C.-J. *Org. Lett.* **2005**, *7*, 673. (c) Yao, X.-Q.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 6884.

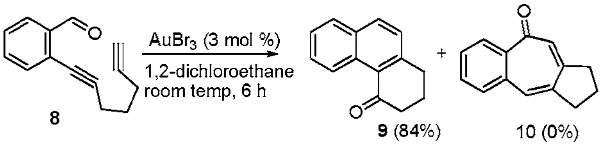
Table 1. Cycloisomerization of Ynal **1a** under Various Conditions

no.	catalyst	*T* (°C), time (h)	products	% yield
1	$AuCl_3$	25, 8	**3a**	40
2	$AuCl_3$/AgOTf	25, 8	**3a**	56
3	$AuCl_3$/PPh_3	80, 10		trace
4	AuCl	25, 8	**2a**/**3a** (1:5)	69
5	$AuBr_3$	25, 8	**3a**	80
6	$AuBr_3$	110, 8	**2a**/**3a** (1:1)	80
7	$PtCl_2$	80, 3	**2a**	40
8	$PtCl_4$	80, 3	**2a**	43

present cycloisomerization occurred readily at room temperature. Surprisingly, this reaction at higher temperature was found to give Yamamoto's product **2a** along with **3a** in roughly 1:1 ratio (entry 6). Pt(+4) and Pt(+2) are isoelectronic with Au(+3) and Au(+1), respectively.[9] Surprisingly, both Pt(+4) and Pt(+2) catalyzed this cycloisomerization to give the Yamamoto type **2a** as a major product along with decomposed products (entries 7 and 8).

Varying the R-group as *n*-butyl (**1b**), phenyl (**1c**), and TMS (**1d**) also worked well; these cycloisomerizations afforded the corresponding products **3b**, **3c**, and **3d** in 71%, 69%, and 86% yields, respectively. Diynal (**1e**, where R = H) underwent [3 + 2]-cycloisomerization as a major route to give **3e** in 62% yield but also gave rise to a small amount of the [4 + 2]-cycloisomerization product **2e** in 12% yield. Raising the temperature up to 80 °C in the **1e** reaction was found to shift the pathway from [3 + 2]- to [4 + 2]-cycloisomerization as a major route. Diynal **1f** bearing a sterically bulky *tert*-butyl substituent did not undergo cycloisomerization due to inaccessibility of the triple bond to the 1,3-dipolar component of the **A2** intermediate. Diynal **1g** bearing a keto functionality resulted in formation of the [3 + 2] product **3g** in 78% yield. Next, two enynals were tested toward these conditions. Both enynals **6a** and **6b** underwent cycloisomerization to afford the corresponding products **7a** and **7b** in 84% and 64% yields, respectively.

Searching for a determining factor governing chemoselectivity in Au-catalyzed cycloisomerization, we tested substrate **8** reported by the Yamamoto group (eq 1). The diynal **8** under Au catalysis underwent only [4 + 2]-benzannulation to **9** with no trace of **10** at *room temperature*, and no reaction took place at 0 °C. The only structural difference between **8** and **1e** is the absence of a *gem*-ester group, but chemoselective products were obtained from Au-catalyzed reactions, presumably due to Thorpe−Ingold effect favoring the formation of the five-membered ring products.



8

9 (84%)

10 (0%)

(1)

Since no experimental evidence for the formation of intermediate **B2** could be observed, a general structure of isolated products and Straub's quantum mechanical energy calculation of imaginary intermediates **4** and **5** could support our proposed mechanism that Au-catalyzed intramolecular reaction of diynals or enynals involves a [3 + 2]-cycloaddition at low temperature and [4 + 2]-cycloaddition at high temperature.

In conclusion, we discovered a new Au-catalyzed cycloisomerization of diynals and enynals bearing a *gem*-dialkyl group leading to synthetically valuable [6.7.*n*]-tricyclic compounds, key skeletons found in a variety of natural products including barbatusol, pisiferin, faveline, and xochitlolone.[10] Au-catalyzed syntheses of these tricyclic compounds could strongly support the intermediacy of the [3 + 2]-cycloaddition proposed from theoretical calculations.

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Supporting Information Available: Characterization of new compounds **3a**−**d**, **2e**, **3e**, **3g**, **7a**,**b**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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