Communication

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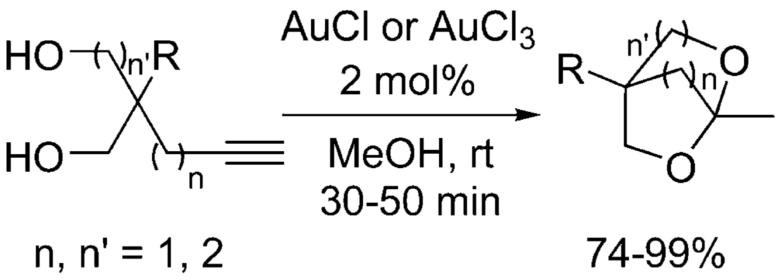

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Highly Efficient Access to Strained Bicyclic Ketals via Gold-Catalyzed Cycloisomerization of Bis-homopropargylic Diols

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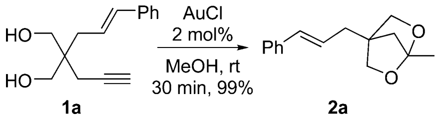
Recent years have witnessed tremendous growth in the number of gold-catalyzed reactions for carbon−carbon and carbon−heteroatom bond formations.[1] Cyclizations of α-hydroxyallenes[2a] and hydroxyl-functionalized 1,5-enynes,[2b] cycloisomerization of enynes,[3] and novel enyne rearrangements[4] allowed ideal and selective reactions in the presence of Au^{III} and Au^{I} catalysts. In pursuit of the investigation on atom-economical metal-catalyzed cycloisomerization reactions,[5] we envisaged that bis-homopropargylic diols might undergo clean Au-catalyzed cyclization under extremely mild conditions. Bis-homopropargylic alcohols are indeed simple starting materials that have shown interesting cyclization behaviors in the presence of Pd,[6] W, Ru, and Rh catalysts.[7] The cycloisomerization of bis-homopropargylic diols has though been scarcely studied on very specific substrates in the presence of Pd catalysts.[8] Having no precedent for such gold performance, we wish therefore to describe herein our preliminary results concerning a general room temperature Au^{I}- and Au^{III}-catalyzed cycloisomerization of bis-homopropargylic diols leading to strained dioxabicyclo[2.2.1], -[2.2.2], or -[3.2.1] ketals.

Initial experiments were performed using bis-homopropargylic alcohol **1a** as a model substrate, easily prepared by malonic addition of the corresponding halides and reduction of the diester. The cyclization was attempted in the presence of 2 mol % of commercially available AuCl catalyst in various solvents and was found to occur very smoothly in MeOH at room temperature, in a very short time (eq 1).[9] After an easy work up that consisted of a filtration of the reaction mixture on a Celite pad, the corresponding functionalized ketal **2a** was isolated in high purity and in 99% yield. It is noteworthy to mention that no addition of methanol[10] on the alkyne was observed.

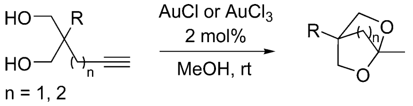


(1)

1a **2a**

Having in mind that the AuCl catalyst presumably interacts with the alkyne motif through its Lewis acidic character,[1,9] we also conducted the reaction without metal in the presence of Amberlyst 15[2a,11] at room temperature to highlight the catalyst efficiency, and no traces of **2a** were detected after 30 min reaction time. Further investigations on the generality of the cyclization process were then pursued. The structural motif of strained 2,6-dioxabicyclo[2.2.1] ketal **2a** was particularly intriguing as it is present in natural products, such as frontalin, brevicomin, and other polycyclic ethers.[12] Such a process would offer an easy and general access to these derivatives and some analogues. To extend the scope of the method, we prepared functionalized diols **1b**−**i** via malonic addition and reduction of diester functions and studied their cyclization in the presence of 2 mol % of AuCl in MeOH. As illustrated in Table 1, the reaction conditions were compatible with various side chains, such as benzyl (entry 1), phenyl (entry 2), or *n*-butyl (entry 3) groups. The corresponding bicyclic ketals **2b**−**d** were obtained in excellent 80−99% yield and very short reaction time.[13]

Table 1. AuCl- and $AuCl_3$-Catalyzed Cycloisomerization of Bis-homopropargylic Diols in Methanol at Room Temperature



1b-i **2a-i**

entry	diol	R	catalyst		time (min)	yield (%)[a]
1	**1b**	Bn	AuCl	**2b**	30	99
2	**1c**	Ph	AuCl	**2c**	30	99
3	**1d**	*n*-Bu	AuCl	**2d**	30	80
4	**1e**	cinnamyl $n = 2$	AuCl	**2e**	30	82
5	**1f**	allyl $n = 2$	AuCl	**2f**	30	91
6	**1a**	cinnamyl $n = 1$	$AuCl_3$	**2a**	45	82
7	**1b**	Bn	$AuCl_3$	**2b**	30	99
8	**1c**	Ph	$AuCl_3$	**2c**	30	99
9	**1g**	allyl	$AuCl_3$	**2g**	50	74
10	**1h**	cyclohex-2-enyl	$AuCl_3$	**2h**	30	94
11	**1i**	3-methylbut-2-enyl	$AuCl_3$	**2i**	30	77

[a] Isolated yield.

The cycloisomerization process was not limited to the synthesis of functionalized 2,6-dioxabicyclo[2.2.1] ketals, as the reaction of diols **1e** and **1f** afforded cleanly the [2.2.2] bicyclic ketals **2e** and **2f** in 82 and 91% yield (entries 4 and 5), respectively. Anticipating that other gold catalysts may also be efficient for this process, we envisaged to test the catalytic properties of a higher valent gold precursor, such as $AuCl_3$ (Table 1).[14] Excellent results were indeed observed for cinnamyl (entry 6), benzyl (entry 7), and phenyl (entry 8) functionalized diols as the strained ketals were obtained in 82−99% yields.

Other allylic substituted diols, such as **1g**−**i**, were also attractive precursors, and their cyclizations led to original structures that may be further functionalized on the remaining allylic side chain. The allylic ketals **2g**−**i** were obtained in good to excellent yields (74−94%, entries 9−11). It has to be noted that such substrates underwent a different and highly specific reactivity compared to that of their diester-functionalized analogues, which are usually cyclized under another mode via C−C and C−O bond formations, leading to methoxycyclopentyl derivatives.[3] Interestingly, under our reaction conditions, no addition of the alcohol moieties was observed on the alkene, as recently described by the Kozmin's group,[2b] and no reactivity of the allylic side chain was detected.[1h,15] To examine the formation of unsymmetrical strained bicyclic ketals, we envisaged to prepare triol **1j** starting from commercially available 2-acetyl succinic acid dimethyl ester **3** (Scheme 1). The regioselective alkylation of diester **3** followed by reduction of the esters and ketone moieties afforded triol **1j** in good overall yield. The cyclization reaction occurred very smoothly and chemoselec-

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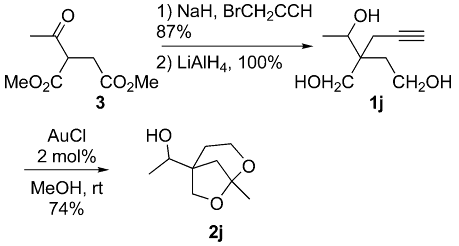
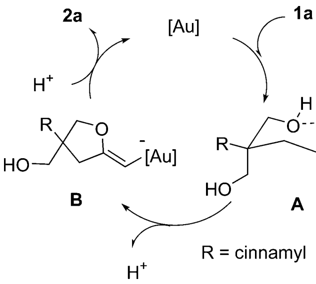
Scheme 1



Scheme 2



tively as both primary alcohols reacted with the alkyne moiety. The dioxabicyclo[3.2.1] ketal was isolated in 74% yield.

A plausible mechanism of the Au$^{\text{I}}$- or Au$^{\text{III}}$-catalyzed cycloisomerization of bis-homopropargylic diols is shown in Scheme 2. The reaction may be initiated by the formation of the π-alkynyl complex **A** through the complexation of the unsaturated triple bond to the Au catalyst. The coordination of the triple bond, therefore, enhances the electrophilicity of the alkyne as usually advocated for metal-catalyzed reactions of alkynes.[6] The addition of one alcohol may be favored by an intramolecular complexation of the OH group to the gold catalyst, as already envisaged by Teles and co-workers[10] for the addition of methanol to alkynes. The enol vinylgold intermediate **B** may then be protonolyzed leading to an enol ether, which then undergoes another intramolecular addition of the remaining alcohol leading to the cyclic ketal **2a**. This latter step may also be catalyzed by gold, considering the proposed mechanism for the Au(I)-catalyzed cyclization of α-hydroxyallenes.[2a]

In conclusion, we have found that either Au$^{\text{I}}$ or Au$^{\text{III}}$ catalysts promote a highly efficient cycloisomerization of bis-homopropargylic diols under very mild conditions and in very short time. This process, starting from easily accessible materials, was shown to be general and atom-economical, leading to functionalized strained bicyclic ketals. The reaction conditions were compatible with various functional groups and allowed the formation of dioxabicyclo[2.2.1], -[2.2.2], and [3.2.1] ketals. The mechanism was proposed and presumably involves a Lewis acid-type activation, followed by two intramolecular cyclizations. The high catalyst activity of gold catalysts associated with very mild reaction conditions would allow further applications toward the synthesis of natural products and other structurally original polycyclic heterocycles.

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Supporting Information Available: Experimental procedure and full analyses of ketals **2a**−**j**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For representative examples and seminal references, see: (a) Hashmi, A. S. K. *Gold Bull.* **2004**, *37*, 51−65. (b) Arcadi, A.; Di Giuseppe, S. *Curr. Org. Chem.* **2004**, *8*, 795−812. (c) Hashmi, A. S. K.; Schwarz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285−2288. (d) Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2005**, *127*, 6966−6967. (e) Alfonsi, M.; Arcadi, A.; Aschi, M.; Bianchi, G.; Marinelli, F. *J. Org. Chem.* **2005**, *70*, 2265−2273. (f) Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 15978−15979. (g) Dyker, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4237−4239. (h) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807.

(2) (a) Hoffman-Roder, A.; Krause, N. *Org. Lett.* **2001**, *3*, 2537−2538. (b) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962−6963.

(3) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; Bunuel, E.; Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2402−2406. (b) Nevado, C.; Cardenas, D. J.; Echavarren, A. M. *Chem.*−*Eur. J.* **2003**, *9*, 2627−2635. For recent reviews, see: (c) Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. (d) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts*−*Org. Chem.* **2003**, *16*, 397−425.

(4) Mamane, V.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655.

(5) (a) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, in press. (b) Charruault, L.; Michelet, V.; Taras, R.; Gladiali, S.; Genêt, J.-P. *Chem. Commun.* **2004**, 850−851. (c) Nevado, C.; Charruault, L.; Michelet, V.; Nieto-Oberhuber, C.; Muñoz, M. P.; Méndez, M.; Rager, M.-P.; Genêt, J.-P.; Echavarren, A. M. *Eur. J. Org. Chem.* **2003**, 706−713.

(6) For recent reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079−3160. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398.

(7) For selected studies with W catalyst, see: (a) Alcazar, E.; Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 3877−3880. (b) McDonald, F. E. *Chem.*−*Eur. J.* **1999**, *5*, 3103−3106. For recent studies with Rh and Ru catalysts, see: (c) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763−4776. (d) Trost, B. M.; Rhee, Y. H. *Org. Lett.* **2004**, *6*, 4311−4313. (e) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482−7483. (f) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2002**, *124*, 2528−2533.

(8) (a) Hosokawa, T.; Makabe, Y.; Shinohara, T.; Murahashi, S.-I. *Chem. Lett.* **1985**, 1529−1530. (b) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845−1852.

(9) No reaction was observed in the absence of gold catalyst.

(10) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415−1418.

(11) For the Amberlyst-15-catalyzed oxaspirocyclization, see: Young, J.-J.; Jung, L.-J.; Chen, K.-M. *Tetrahedron Lett.* **2000**, *41*, 3411−3413.

(12) (a) Kumar, D. N.; Rao, B. V.; Ramanjaneyulu, G. S. *Tetrahedron: Asymmetry* **2005**, *16*, 1611−1614. (b) Suga, H.; Inoue, K.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47−56 and references therein. (c) Strunz, G. M.; Yu, C.-M.; Ya, L.; White, P. S.; Dixon, E. A. *Can. J. Chem.* **1990**, *68*, 782−786. (d) Ibrahim, N.; Eggimann, T.; Dixon, E. A.; Wieser, H. *Tetrahedron* **1990**, *46*, 1503−1514.

(13) Standard procedure: a mixture of bis-homopropargylic diol, AuCl (2 mol %) in degassed methanol (0.5 mol L^{-1}) was stirred under argon atmosphere at room temperature. After completion of the reaction, the mixture was filtered through a short pad of Celite (EtOAc), and the solvents were evaporated under reduced pressure to give the corresponding ketal.

(14) For Au(III)-catalyzed addition of oxygen nucleophiles to alkynes, see: (a) Gasparrini, F.; Giovannoli, M.; Misiti, D.; Natile, G.; Palmieri, G.; Maresca, L. *J. Am. Chem. Soc.* **1993**, *115*, 4401−4402. (b) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729−3731.

(15) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858−10859.

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