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Efficient Synthesis of γ-Lactones via Gold-Catalyzed Tandem Cycloisomerization/Oxidation

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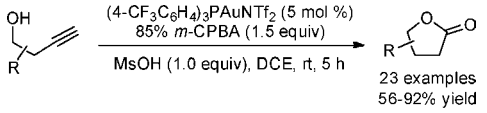
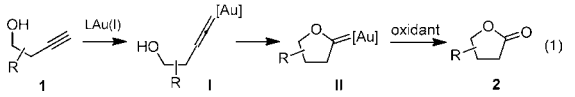
ABSTRACT



A novel Au-catalyzed tandem cycloisomerization/oxidation of homopropargyl alcohols was developed. Various γ-lactones can be accessed readily by utilizing this strategy. Notably, the mechanism of this reaction is distinctively different from the related Ru-catalyzed reactions where the ruthenium vinylidene intermediate was proposed.

Homogeneous gold catalysis is still undergoing rapid growth, and more fascinating facets of gold chemistry have been revealed.[1] It is surprising, however, that few examples have been reported about gold vinylidenes as reactive intermediates.[2] In 1999, Trost and co-workers demonstrated an elegant protocol for the Ru-catalyzed oxidative cyclization of homopropargyl alcohol,[3] and the ruthenium vinylidene intermediate was proposed in this catalytic cycle. This cyclization reaction provides a novel access to γ-lactone synthesis from readily available homopropargyl alcohol, but the reaction demands high temperature (95 °C) and the yields are generally moderate. Very recently, Zhang's group reported a gold-catalyzed cycloisomerization of benzene-1,2-diynes, where a gold vinylidene intermediate is most likely involved on the basis of both mechanistic studies and theoretical calculations.[4] This result inspired us to further explore gold vinylidene chemistry, which might serve as a complementary method for Trost's lactone synthesis. We envisioned that the gold vinylidene intermediate **I** might be generated by reacting homopropargyl alcohol **1** with a gold complex. Then, this highly reactive gold complex **I** could be trapped quickly by an intramolecular O−H insertion to form oxacarbene species **II**, which would be further oxidized to γ-lactone **2** (eq 1).



To implement this design, the critical issue is to find a suitable oxidant to minimize the side reaction caused by gold-catalyzed intermolecular oxidations of alkynes via an α-oxo gold carbene route.[5,6] We recently found that when simple *m*-CPBA was used as the oxidant,[7] gold could also catalyze such an oxidative cyclization reaction even at

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(4) (a) Ye, L.; Wang, Y.; Aue, D. H.; Zhang, L. *J. Am. Chem. Soc.* **2012**, *134*, 31. During the course of our study, three more recent examples about gold vinylidenes were reported by Hashmi: (b) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456. (c) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Nösel, P.; Jongbloed, L.; Rudolph, M.; Rominger, F. *Adv. Synth. Catal.* **2012**, *354*, 555. (d) Hashmi, A. S. K.; Braun, I.; Rudolph, M.; Rominger, F. *Organometallics* **2012**, *31*, 644.

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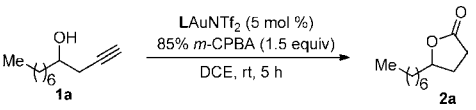
room temperature in good to excellent yields, providing a very efficient and practical method for the preparation of γ-lactone derivatives. However, mechanism studies revealed that this catalytic cyclization reaction did not proceed via the gold vinylidene intermediate according to our initial assumption. Instead, it occurred presumably through a tandem Au-catalyzed oxycyclization, followed by an acid-accelerated oxidation sequence, which behaved distinctively different from the related Ru-catalyzed reactions, where the intermediacy of ruthenium vinylidene was proposed.[3a] In this paper, we report these preliminary results.

Homopropargyl alcohol **1a** was chosen as the model substrate for our initial study. Considering that strong nucleophilic oxidants such as quinoline/pyridine *N*-oxides would lead to the formation of dihydrofuran-3-ones[5f] via an α-oxo gold carbene intermediate, we initially examined the reaction by using the oxidants which worked well in the Ru-catalyzed oxidative cyclization.[3a] However, all (maleimide, *N*-hydroxysuccinimide, and *N*-hydroxyphthalimide) failed to furnish the desired lactone. To our delight, it was found that the corresponding γ-lactone **2a** could be obtained in 50% yield by using *m*-CPBA as the oxidant (Table 1, entry 1). Among the different gold catalysts examined (entries 2−8), $(4\text{-}CF_3C_6H_4)_3PAuNTf_2$ gave a slightly improved yield (entry 7). We were pleased to find that the addition of acids substantially improved the reaction (entries 9−12), and an excellent yield (90%) could be achieved in the presence of 1.0 equiv of MsOH (entry 11). The use of other acids failed to improve the yield (entries 13 and 14). Of note, without using any gold catalyst, no γ-lactone **2a** was observed under the acidic reaction conditions, and $PtCl_2$ and $AgNTf_2$ were not effective in promoting this reaction (entries 15 and 16).

Under the optimal reaction conditions, various homopropargyl alcohols were tested to examine the generality of the current reaction. As shown in Table 2, this reaction proceeded smoothly with various substrates, and the yields ranged from 56% to 92%. A range of functional groups were tolerated, including bromo (entry 4), azido (entry 5), protected amino (entry 6), and hydroxy (entries 7 and 8). In addition, aromatic substrates also gave the corresponding γ-lactones in moderate to good yields, and substitutions on the aromatic ring at different positions

Table 1. Optimization of Reaction Conditions[a]



entry	gold catalyst	acid (equiv)	yield[b] (%)
1	$Ph_3PAuNTf_2$		50
2	Cy-JohnPhosAuNTf$_2$		26
3	XPhosAuNTf$_2$		27
4	BrettPhosAuNTf$_2$		8
5	$Et_3PAuNTf_2$		24
6	IPrAuNTf$_2$		8
7	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$		53
8	$(C_6F_5)_3PAuNTf_2$		25
9	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	MsOH (0.2)	61
10	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	MsOH (0.5)	72
11	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	MsOH (1.0)	90[c]
12	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	MsOH (1.3)	81
13	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	CF_3CO_2H (1.0)	77
14	$(4\text{-}CF_3C_6H_4)_3PAuNTf_2$	$HNTf_2$ (1.0)	16
15[d]	$PtCl_2$	MsOH (1.0)	16
16	$AgNTf_2$	MsOH (1.0)	<5[e]

[a] Reaction conditions: [**1a**] = 0.05 M; DCE: 1, 2-dichloroethane. [b] Estimated by ^{1}H NMR using diethyl phthalate as internal reference. [c] Yield of isolated **2a** was 86%. [d] Toluene, 80 °C. [e] Most **1a** remained unreacted.

were readily allowed (entries 9−13). Moreover, tertiary homopropargylic alcohols were suitable substrates for this reaction to furnish the corresponding γ-lactones (entries 14−18). Notably, substrates **1t** and **1u** could also undergo smooth tandem cycloisomerization to afford the strained 5,6-cis-fused **2t** and **2u**, highlighting the synthetic utility of this methodology (entries 19 and 20). To test the practicality of the current catalytic system, the reaction was carried out on a gram scale in the presence of 2.5 mol % of gold catalyst, and the desired product **2a** was afforded in 85% yield (entry 21). Finally, it should be pointed out that a number of the γ-lactones in Table 2 are of significant interest, including **2a**, a food additive;[8] **2g**, an intermediate as an antituberculosis agent;[9] **2o**, known for anticonvulsant activity;[10] **2p**, a commercial liqorice root extract;[11] and **2r**, a perfuming agent.[12]

The utility of this chemistry was further demonstrated in the concise and efficient synthesis of steroidal spiro-γ-lactone **2v** (Scheme 1), which showed efficient inhibitory activity for enzyme 17β-hydroxysteroid dehydrogenase (17β-HSD).[13] Starting from estrone, the formation of the spiro-γ-lactone **2v** was achieved in a respectable 58% yield.

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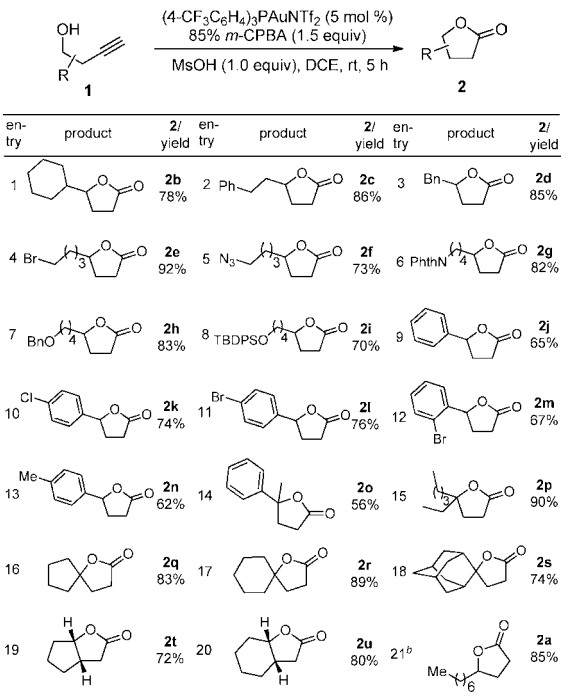
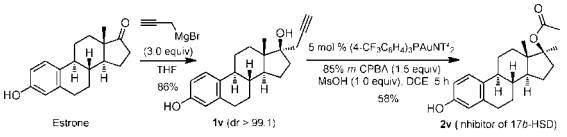
Table 2. Reaction Scope for the Formation of γ-Lactones[a]



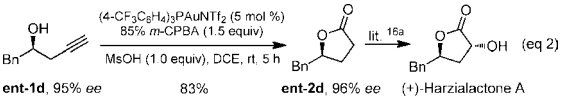
[a] Reactions run in vials; [**1**] = 0.05 M; isolated yields are reported. [b] 10 mmol scale, 2.5 mol % gold catalyst was used, 7 h.

It is noteworthy that, starting from the same estrone, compound **2v** typically demands rather lengthy synthesis, including the additional necessary protection and deprotection stages of the sequence.[13a]

Scheme 1. Synthesis of Spiro-γ-lactone **2v**



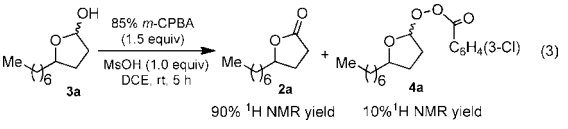
Since chiral homopropargyl alcohols were readily available,[14] this chemistry provided easy access to chiral γ-lactones, which are important classes of bioactive heterocycles that are difficult to construct.[15] For example, the enantiomerically enriched alcohol **ent-1d**, obtained easily from L-phenylalanine,[14f] was converted into corresponding γ-lactone **ent-2d** with the ee maintained during this gold catalysis (eq 2). Of note, chiral γ-lactone **ent-2d** could be further oxidized to (+)-harzialactone A,[16] an antitumor marine metabolite.

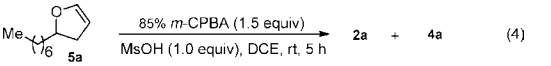


To probe the mechanism of this reaction, we first monitored the cyclization reaction of **1a** by ^{1}H NMR and detected two unknown intermediates **4a-1** and **4a-2**, which could be converted to the γ-lactone **2a** after 5 h (Figure 1, see the Supporting Information). However, trying to establish their structures by using ES-MS or isolate these active species failed.

To elucidate these structures, we then prepared hemiacetal substate **3a** and treated it with *m*-CPBA (eq 3). Gratifyingly, in the presence of 1.0 equiv of MsOH, γ-lactone **2a** was formed in 90% yield. Importantly, we indeed observed the same intermediates (10%) which were detected in the above ^{1}H NMR experiments, suggesting that the unknown intermediates **4a-1** and **4a-2** should be the peroxide **4a**. Without the additional MsOH, however, the conversion of this reaction was very low, and only 17% γ-lactone **2a** was obtained after 5 h. This study also explained well the role of acid in this reaction.

In addition, we also synthesized the dihydrofuran substrate **5a** to further investigate the reaction (eq 4). It was found that almost no lactone **2a** and peroxide intermediate **4a** were formed under the previously optimized reaction conditions. However, in the presence of 5 equiv of H_2O, the reaction did afford the desired lactone **2a**, and the intermediate **4a** was also observed from the ^{1}H NMR spectrum. Of note, neither lactone **2a** nor peroxide **4a** formation was observed without using the gold catalyst. We also performed the reaction by slow addition of dihydrofuran **5a** using the syringe pump to try to mimic the slow formation of the intermediate during gold catalysis. To our delight, the reaction proceeded very well to afford the desired lactone **2a** in 90% yield. It is noteworthy that in this case, lactone **2a** could be formed in similar efficiency in the absence of gold. These results strongly supported that the reaction presumably involves a 5-endo-dig cyclization of homopropargyl alcohol, followed by the acid-accelerated oxidation.





conditions	**2a** (^{1}H NMR yield)	**4a** (^{1}H NMR yield)
5 mol % (4-$CF_3C_6H_4$)$_3$PAuNTf$_2$, 5 equiv H_2O	33%	21%
no gold, 5 equiv H_2O	<5%	<5%
5 mol % (4-$CF_3C_6H_4$)$_3$PAuNTf$_2$[a]	90%	<5%
no gold[a]	87%	<5%

[a] Slow addition of **5a** with a syringe pump.

However, in treatment of the substrate **1a** with 5 mol % gold catalyst in the absence of *m*-CPBA, neither

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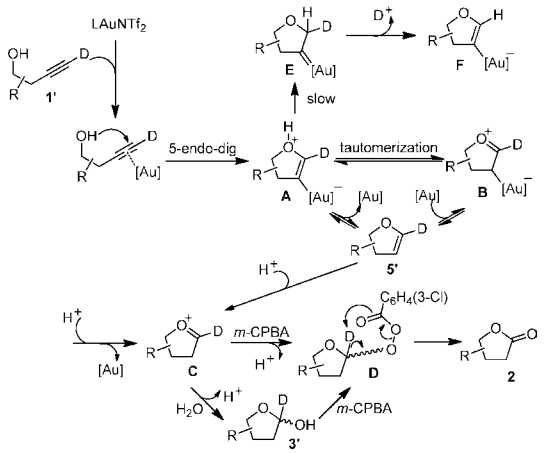
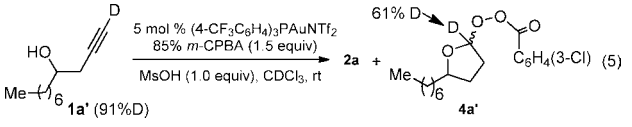
Scheme 2. Plausible Mechanism for This Catalytic Cyclization



dihydrofuran **5a** nor lactone **2a** was formed, with only the formation of trace hemiacetal compound **3a** (~3% ^{1}H NMR yield). These results suggested that the dihydrofuran **5a** was actually not fully generated in the reaction system. In another words, once generated, it should be protonated into oxocarbenium intermediate very quickly. This study also exhibits well the advantage of such a tandem cycloisomerization/oxidation sequence.

Finally, we performed deuterium labeling studies. It was found that when substrate **1a′** (91% D) was treated under the optimized reaction conditions, almost no deuterium incorporation into the lactone **2a** was observed (eq 5). Importantly, we detected 61% deuterium incorporation into peroxide **4a** by ^{1}H NMR, indicating that the gold vinylidene pathway was less likely.[17]



On the basis of these experimental observations, a plausible mechanism for this catalytic cyclization is proposed (Scheme 2). The reaction may initially involve the formation of π complex through coordination of the gold catalyst to the triple bond of homopropargyl alcohol **1′**. Next, 5-*endo-dig* cyclization formed vinyl gold intermediate **A**, which would be transformed into the oxocarbenium intermediate **C** in the presence of acid.[18] The intermediate dihydrofuran **5′**, once generated, should be rapidly protonated to intermediate **C** in order to avoid the epoxidation of its electron-rich C−C double bond by *m*-CPBA. Finally, the nucleophilic attack by the *m*-CPBA ought to liberate the product **2** via the formation of the peroxide intermediate **D**. In this process, the role of H_2O (from 85% *m*-CPBA) is likely to access the hemiacetal **3′** via hydration of dihydrofuran intermediate **5′**, which could finally undergo an acid-accelerated oxidation to deliver the final lactone **2**.[7c] The decrease of deuterium of the compound **4a′** from 91% to 61% was probably due to the fact that some of intermediate **A** was converted to intermediate **F** during the reaction.

In summary, we have developed a flexible and general solution for the synthesis of various γ-lactones via a tandem gold-catalyzed cycloisomerization and in situ regioselective *m*-CPBA oxidation sequence, which is distinctively different from the related ruthenium catalysis. Notably, with this newly established methodology, enantiospecific synthesis of γ-lactones could be easily achieved in a highly efficient and concise manner, and its application has further been demonstrated by a formal synthesis of harzialactone A. The use of readily available substrates, a simple procedure, and mild reaction conditions and, in particular, no need to exclude moisture or air ("open flask") render these methods potentially useful in organic synthesis.

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Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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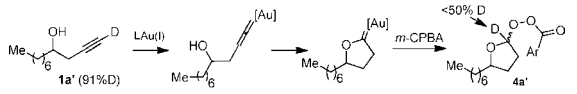
(17) If the D in **4a** is from *m*-CPBA via gold carbene insertion, the deuterium incorporation into intermediate **4a** should be much less than 50% (the active H/D in the reaction system was from OH, MsOH, D, *m*-CPBA).



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The authors declare no competing financial interest.