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Cleavage of a Carbon−Carbon Triple Bond via Gold-Catalyzed Cascade Cyclization/Oxidative Cleavage Reactions of (*Z*)-Enynols with Molecular Oxygen

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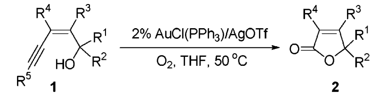
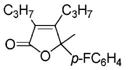
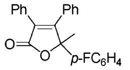
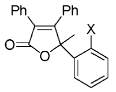
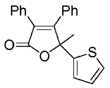
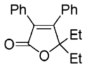
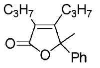
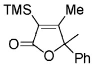
The cleavage of carbon−carbon triple bonds is one of the most challenging targets in organic chemistry.[1] Although much progress has been achieved in this area, most studies have focused on the stoichiometric organometallic reactions, such as alkyne−ligand scission on metal complexes[1b−d] or oxidative cleavage of alkynes to carboxylic acids.[1e,f] Except for metathesis of alkynes,[2] there have been very few examples for the metal-catalyzed alkyne cleavage reactions. Jun et al. reported rhodium-catalyzed hydroiminoacylation of alkynes followed by amine-assisted C−C double bond cleavage.[3] Yamamoto reported the cleavage of diynes via ruthenium-catalyzed hydroamination.[1g] Very recently, Liu et al. reported catalytic cleavage of ethynyl alcohol without organic promoters.[4] An ideal strategy for the design of such transformations is through cascade or domino reactions catalyzed by a single catalyst since multiple bonds are formed and/or cleaved in one sequence with high efficiency. In this communication, we present a new approach to the cleavage of triple bonds in (*Z*)-enynols involving gold-catalyzed cascade reactions of (*Z*)-enynols with molecular oxygen, in which gold was utilized as a single-pot catalyst to catalyze independent reactions in the same reaction vessel.

It has recently been shown that gold(III) salts and gold(I) complexes display considerable catalytic activity under moderate conditions.[5] We have reported an efficient synthetic approach to stereodefined dihydrofurans via gold-catalyzed cyclization of (*Z*)-2-en-4-yn-1-ols.[6] To determine the feasibility of the cyclization/oxidative cleavage process, we first examined the reaction of (*Z*)-enynol **1a** bearing a phenyl group on an alkyne moiety with molecular oxygen (eq 1). To our delight, the concept works nicely. When oxygen was gently bubbled through a THF solution of (*Z*)-enynol **1a** containing 2 mol % of cationic gold(I) complex $AuCl(PPh_3)$/AgOTf for 17 h at 50 °C, the triple bond in **1a** was smoothly cleaved and the butenolide **2a** was formed in 97% yield. It was expected that benzaldehyde should be isolated as a byproduct; however, the amount of the initial formed benzaldehyde (detected by GC) gradually decreased during the reaction, and instead, benzoic acid was obtained in 64% yield. A partial oxidation of THF was also observed.[7] When 1,4-dioxane was used as solvent, the desired product **2a** was formed in 46% yield after 3 days. The gold−oxo complex, $[(Ph_3PAu)_3O]BF_4$, also showed good catalytic activity in THF to afford 84% of **2a** (20 h). However, the use of $AuCl_3$ resulted only in the low yield of **2a** (17%). The structure of **2** was further confirmed by X-ray crystallographic analysis of product **2d** (R^1 = Me, R^2 = *o*-ClC_6H_4, R^3 = R^4 = Ph). This carbon−carbon triple bond cleavage reaction was investigated with a variety of (*Z*)-enynol substrates, as shown in Table 1. The alkyne moiety in enynol **1** bearing an aromatic ring as well as alkyl substituents reacted very well to produce butenolide products in 70−97% yields (except **2i**). It was observed that the intermediate of (*Z*)-5-ylidene-2,5-dihydrofurans **3**[6] (vide infra) was formed at the early stage of the reaction, which was further converted to butenolide by the reaction with dioxygen.

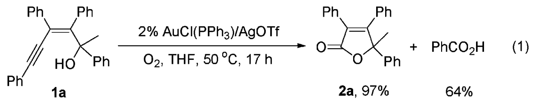
Table 1. Gold-Catalyzed Triple Bond Cleavage Reaction of (Z)-Enynols: Formation of Butenolides



1 **2**

entry	enynol	R^5	time^{a}	product	yield%^{b}
1	**1a**	Ph	17 h	(**2a**)	97^{c}
2	**1b**	*p*-$MeOC_6H_4$	4 h	(**2a**)	81
3	**1c**	*p*-ClC_6H_4	42 h	(**2a**)	90
4	**1d**	Ph	15 h	 (**2b**)	80
5	**1e**	Bu	3 h	 (**2c**)	96
6	**1f**	Bu	3 h	 (**2d**) X=Cl	82^{d}
7	**1g**	Bu	3 h	X=Br (**2e**)	81
8	**1h**	Bu	5 h	 (**2f**)	91
9	**1i**	Bu	2 h	 (**2g**)	92
10	**1j**	Bu	3 h	 (**2h**)	70
11	**1k**	Bu	1.5 h	 (**2i**)	41

[a] All the reactions were carried out at 50 °C (O_2 bubbling) using 2 mol % of $(PPh_3)AuCl$ and 2 mol % of AgOTf in THF. [b] Isolated yields. Unless specified, no attempt was made to isolate the byproduct of acids. [c] Benzoic acid was isolated in 64% yield. [d] Pentanoic acid was isolated in 21% yield.



1a **2a**, 97% 64%

The cyclization occurred much faster than subsequent cleavage reaction, thus the whole reaction time relied on the rate of the cleavage reaction. The effect of substitution on the phenyl ring was examined, and the electron-donating substituent (OMe) at the para-position of the phenyl ring made the reaction faster than the electron-withdrawing group (entries 2 and 3) due to the electronic activation of the exocyclic double bond in the intermediate of dihydrofuran. When an alkyl group was used as a terminal group of the alkyne moiety, the reaction proceeded much faster, furnishing the corresponding product **2c** in 96% yield within 3 h (entry 5).

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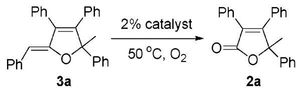
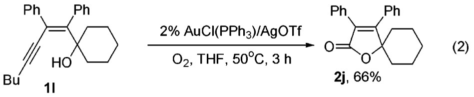
Scheme 1

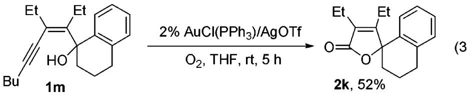


catalyst	*yield of* **2b**
$(PPh_3)AuOTf$, THF, 21 h	*90%*
$P(p\text{-}CF_3C_6H_4)_3AuOTf$, THF, 14 h	*92%*
$(PPh_3)AuOTf$, 1,4-dioxane, 20 h	*70%*
$(PPh_3)AuOTf$, CH_3CN, 4 days	*84%*
$(PPh_3)AuOTf$, $(ClCH_2)_2$, 5 days	*61%*
$(PPh_3)AuOTf$, air, THF, 36 h	*99%*
$AuCl_3$, $(ClCH_2)_2$, 24 h	*6%*

The effect of substitution on the α-carbon of an alcoholic group in **1** has also been examined: alkyl, aryl, and heteroaryl substitution at C-1 were all compatible with cyclization conditions, and high yields of the corresponding butenolides were obtained in each case (70−96%). However, when (*Z*)-enynol **1k** bearing a TMS substituent at C-3 was employed, the corresponding product **2i** was formed in a low yield of 41% (entry 11). Interestingly, this method can also be used to construct spirolactones which are frequently occurring motifs in biologically active molecules (eqs 2 and 3).[8]



(2)



(3)

To elucidate the reaction mechanism, we carried out the oxidative cleavage reaction from dihydrofurans **3** (Scheme 1). Oxidative cleavage of the C═C double bond to carbonyl compounds is an important functional group transformation, which is commonly achieved by ozonation or stoichiometric oxidation.[9] However, metal-catalyzed cleavage reactions using molecular oxygen have not yet been extensively developed.[10] To our knowledge, there is no report concerning gold-catalyzed cleavage reactions using molecular oxygen.[11,12] Treatment of **3a** with 2 mol % of $AuCl(PPh_3)/AgOTf$ in THF at 50 °C for 21 h in the atmosphere of O_2 (1 atm) afforded butenolide **2a** as anticipated in 90% yield. The byproduct of benzoic acid was isolated in 26% yield. No reaction was observed in the absence of Au(I). The results clearly indicated that Au(I) could catalyze the oxidative cleavage reaction efficiently. The gold(I) complex $AuClP(p\text{-}CF_3C_6H_4)_3/AgOTf$ also showed good catalytic activity in THF to afford 92% of **2a**. However, $AuCl_3$ was ineffective to this reaction. The use of solvent, such as 1,4-dioxane, CH_3CN, or 1,2-dichloroethane, resulted in a lower conversion or a prolonged reaction time. With optimized reaction conditions in hand, we investigated the reaction of a series of dihydrofurans with molecular oxygen, and in all cases, the desired products were formed in good yields (69−90%).[13] However, controlled experiments showed that the reaction was completely suppressed in the presence of a radical scavenger, such as 2,6-di-*tert*-butyl-*p*-cresol or 4-hydroxy-TEMPO, implying that a radical species is involved. Normal olefins, such as 1-decene or styrene, are inert to oxidative cleavage under the same reaction conditions, whereas an enol ether (for example, (2-butoxyvinyl)benzene) do react.[13] We were also interested in testing the stability of Au(I) complexes by ^{31}P NMR studies.[13] The ^{31}P NMR spectrum showed that there is no change of the chemical shift (33.8 ppm in THF) for $AuCl(PPh_3)$ after 24 h under O_2. This result indicated that $AuCl(PPh_3)$ is stable under the atmosphere of O_2. It was found that the cationic gold(I) complex ($AuCl(PPh_3)$ + AgOTf, 29.6 ppm in THF) is unstable and converted to a new phosphorus species (45.4 ppm in THF, 45.6 ppm in $CDCl_3$) after 48 h under O_2. The ^{31}P NMR spectra of the crude reaction mixture of **1f** showed three peaks at −19.3, 33.8, and 45.4 ppm. The species at 45.4 ppm was suggested to be $(PPh_3)_2Au^+$ due to the fact that the chemical shifts are consistent with those found in the literature (45.6 ppm in $CDCl_3$).[14]

The presented results clearly demonstrate that Au(I) acted as a single-pot catalyst to catalyze cyclization to dihydrofurans **3** followed by an oxidative cleavage reaction efficiently, which resulted in the cleavage of C−C triple bonds in (*Z*)-enynols and converting it to butenolides directly. It is also indicated that the cyclization was not interfered with under the atmosphere of dioxygen.

In conclusion, we have developed a highly efficient method for the cleavage of carbon−carbon triple bonds in (*Z*)-enynols under mild reaction conditions. This one-pot protocol is realized by a tandem reaction, which is composed of gold(I)-catalyzed cyclization and oxidative cleavage of a dihydrofuran intermediate into the resulting butenolides. Clarification of the reaction mechanism and further application of this chemistry are in progress.

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Supporting Information Available: Experimental details and spectroscopic characterization of compounds **1b**,**c**, **1j**−**m**, and **2a**−**k** and CIF file giving crystallographic data of **2d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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