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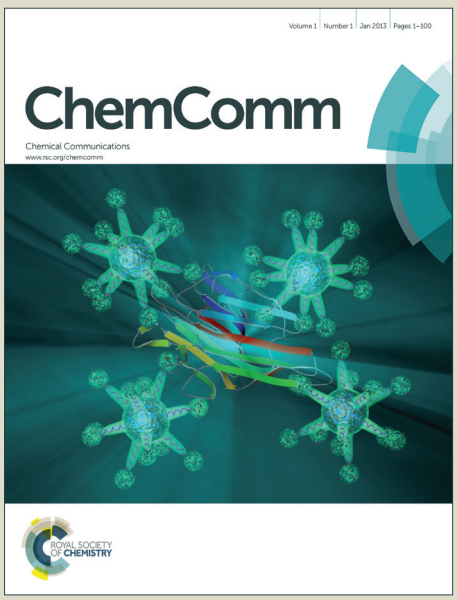

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COMMUNICATION

Aerobic Oxygenative Cleavage of Electron Deficient C-C Triple Bonds in the Gold-Catalyzed Cyclization of 1,6-Enynes

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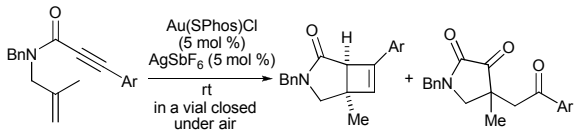
Gold-catalyzed aerobic oxygenative cleavage of triple bond that occurs under the ambient pressure of air and at room temperature is reported; Radical inhibition tests suggest that oxygenation occurs via a gold-bound metalloradical intermediate.

Dioxygen has recently received a great deal of attention as an ideal end-oxidant in transition metal-catalyzed oxidations and oxygenations, because it does not generate noxious by-products.[1] Selective oxidations occurring at ambient conditions (*ca.* 0.2 atm of O_2 and at RT) would be particularly appealing for larger-scale applications, considering operational hazard associated with pressurized oxygen gas (or even air) at elevated temperature.[2]

In oxidative transformations catalyzed by homogeneous gold complexes,[3-6] there have been increasing use of dioxygen as a reactant.[7] In 2006, Y. Liu and coworkers reported the oxidative cleavage of C-C triple bond of (Z)-enynols.[7a] This process involves Au(I)-catalyzed cyclization, followed by autoxidation of electron-rich enolethers.[7b] Similar type of autoxidation was observed by Hashmi and coworkers in the cyclization of propargyl amides into 2,5-disubstituted oxazoles having hydroperoxide functionality.[7c] Furthermore, R. –S. Liu and coworkers reported a unique simultaneous cleavage of a single and a triple bond of propargyl ethers with evolution of CO and CO_2 as C1 byproducts.[7d] We report herein 1,6-enynes derived from propiolamides deliver tricarbonyl products **3** through a novel triple bond cleavage.[8] Remarkably, this transformation cleaves electron-deficient triple bonds and proceeds efficiently under ambient oxygen pressure (*ca.* 0.2 atm) and at room temperature.

Recently, Chung and coworkers have reported cyclization of 1,6-enynes derived from propiolates or propiolamides into bicyclo[3.2.0]hept-6-enes, such as **2**, in the presence of cationic $Au(PPh_3)SbF_6$ in CH_2Cl_2 under nitrogen atmosphere.[9] Surprisingly, when the reaction was performed *without* rigorous exclusion of air (in a vial closed under ambient air), an unexpected tricarbonyl compound **3a** (11 %) was co-isolated along with **2a** (entry 1, Table 1). With SPhos as a ligand, the ratio of **3a** vs. **2a** was highly dependent on the solvents: In accord with Chung's report, the formation of bicyclo[3.2.0]hept-6-enes was favored in chlorinated solvents (entries 1-4), whereas predominant formation of tricarbonyl **3a** was obtained in toluene or ethereal solvents (entries 5-9). Furthermore, we were pleased to find that fluorinated solvents that are known to dissolve a larger amount of oxygen,[10] accelerated the reaction giving excellent isolated yield of **3b** (86 %)

Table 1 Examination of reaction conditions[a]



1a, Ar = C_6H_4(4-OMe)
1b, Ar = Ph

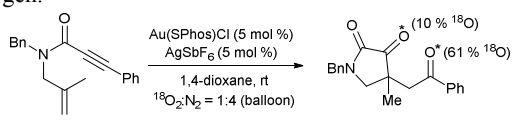
2a-b **3a-b**

entry	substrate	solvent	time	**2** (%)[b]	**3** (%)[b]
1	**1a**	CH_2Cl_2[c]	4 h	87	11
2	**1a**	CH_2Cl_2	4 h	86	
3	**1a**	$CHCl_3$	4 h	74	-
4	**1a**	1,2-DCE	4 h	66	-
5	**1a**	toluene	4 h	25	45
6	**1a**	THF	4 h	-	54
7	**1a**	Et_2O	4 h	7	63
8	**1a**	1,4-dioxane	4 h	-	75
9	**1b**	1,4-dioxane	12 h	-	(73)[d]
10	**1b**	C_6H_5F	2 h	-	(82)[d]
11	**1b**	CF_3CH_2OH	1.5 h	-	(86)[d]

[a] Reaction conditions: **1** (0.1 mmol, 0.1 M), Au(SPhos)Cl (5 mol %) and $AgSbF_6$ (5 mol %). [b] Yields based on crude NMR spectra (1,3,5-trimethoxybenzene) except noted otherwise. [c] $Au(PPh_3)Cl$ and $AgSbF_6$ was used. [d] Isolated yield after chromatography in parenthesis.

in 1.5 h at rt (entry 11). The structure of the tricarbonyl product was unambiguously confirmed by X-ray diffraction analysis of a related product **3e**.[11,12]

To investigate the source of carbonyl O atoms, we performed the reaction in the presence of $H_2{}^{18}O$ or $^{18}O_2$ environment, employing **1b** as a substrate.[13] In the presence of $H_2{}^{18}O$ (15 equiv.) in 1,4-dioxane in an open flask, no ^{18}O atom was incorporated into **3b**.[12] However, the reaction under $^{18}O_2$ balloon afforded 61 % and 10 % ^{18}O atom incorporation at the indicated positions (eqn (1)), confirming dioxygen is the source of carbonyl oxygen.[12,14]

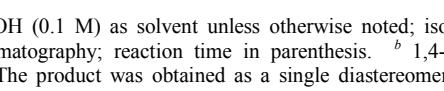


(1)

1b $^{18}O_2$-**3b**

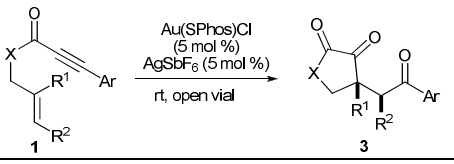
The scope of the present method was next probed with a range of substrates shown in Table 2. The reaction was conducted in an open vial, employing Au(SPhos)Cl and $AgSbF_6$ (5 mol % each) as catalyst in CF_3CH_2OH. Variation of electron-demand on the

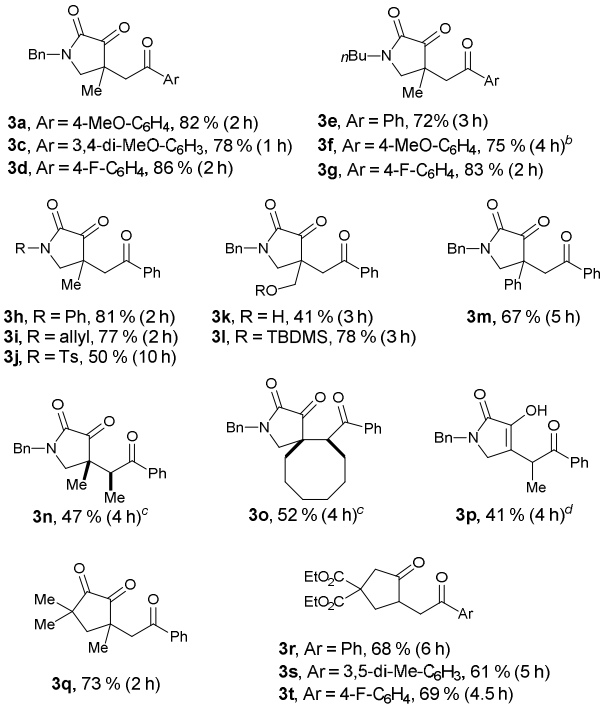
arylalkyne moiety were well-tolerated providing **3a-g** in good to excellent yields. Different *N*-substituents were also well-tolerated, including benzyl (**3b**), allyl (**3i**), alkyl (**3e**), phenyl (**3h**) and tosyl (**3j**) groups. Gratifyingly, different allyl moiety (R^1, R^2) could also be accommodated providing access to diverse substitution patterns in **3k-p**. Here, reactions of substrates with R^2 substitution was less effective, suggesting developing strain in the transition state (**3n-p**). Those without R^1 substitution (**1p**) also afforded tricarbonyl **3p** as a major product. Notably, carbocyclic analogue **3q-t** formed smoothly without event. Unfortunately, however, homoallyl amide substrates or ester-tethered substrates were unreactive. Net result of this triple bond cleavage is that the two C*sp* atoms of the alkyne are added to alkenes, forming synthetically useful 1,4-dicarbonyl compounds. For example, product **3r** could be converted into a fused pyrrole **4r** via Paal-Knorr synthesis (eqn (2)).



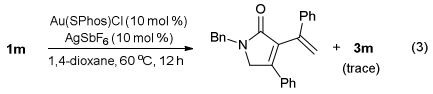
(2)

Table 2 Investigation of the reaction scope[a]

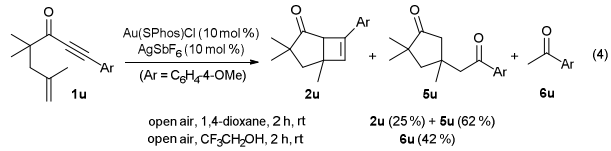




[a] CF_3CH_2OH (0.1 M) as solvent unless otherwise noted; isolated yield after chromatography; reaction time in parenthesis. [b] 1,4-dioxane as solvent. [c] The product was obtained as a single diastereomer. [d] **1p** as a mixture of E/Z (3:1) isomers were used.



(3)

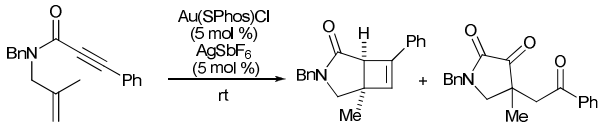


(4)

It is noteworthy that the reaction of **1m** at higher temperature (60 °C) gave predominantly metathesis type product (51 %, eqn (3)) that could arise via σ-bond reorganization of **II** (Scheme 1). Surprisingly, the reaction of **1u** provided unexpected dicarbonyl **5u** as a major product in 1,4-dioxane along with small amount of **2u** (25 %). In CF_3CH_2OH, acetophenone derivative **6u** was the only identifiable product (eqn (4)). At this point, the aberrant behavior of **1u** is not clearly understood, but seems to be related to the stability of the carbocationic **II** (Scheme 1).

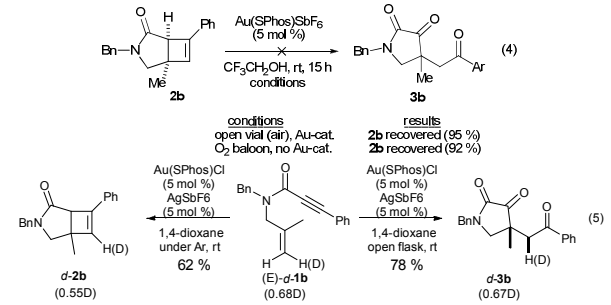
To deduce a possible mechanistic model, the following experiments were conducted. If the incorporation of triplet oxygen occurs after the Au turnover (*i.e.* at **III** in Scheme 1), radical inhibitors will not stop the conversion of starting **1**, unless the cationic Au^+ is decomposed by the radical inhibitors. On the contrary, if the oxygenation by O_2 occurs at the Au-bound stage (such as **II/II'**), the catalyst may be deactivated by the presence of radical inhibitors. The effect of BHT as a radical inhibitor for the formation of **2b** and **3b** from **1b** is summarized in Table 3. The formation of **3b** in 1,4-dioxane (under air) was completely blocked in the presence of catalytic amount of BHT and the starting **1b** was recovered (entries 2 vs. 1). In sharp contrast, the formation of **2b** in CH_2Cl_2 (under Ar) was not inhibited at all by the BHT (entries 4 vs. 3). These experiments suggest that the oxidation by O_2 occurs via *metallo-radical* intermediates, unlike previous metal-free autoxidation of electron-rich intermediates in the reactions of (Z)-enynols[7b] or propargyl amides.[7c]

Table 3 Effect of radical inhibitors[a]



entry	conditions	Solvent	time	1b	product 2b	product 3b
1	open vial, no additive	1,4-dioxane	12 h	-	-	73 %
2	open vial, BHT (10 %.)	1,4-dioxane	15 h	94 %	-	-
3	under Ar, no additive	CH_2Cl_2	6 h	-	85 %	-
4	under Ar, BHT (10 %.)	CH_2Cl_2	6 h	-	84 %	-

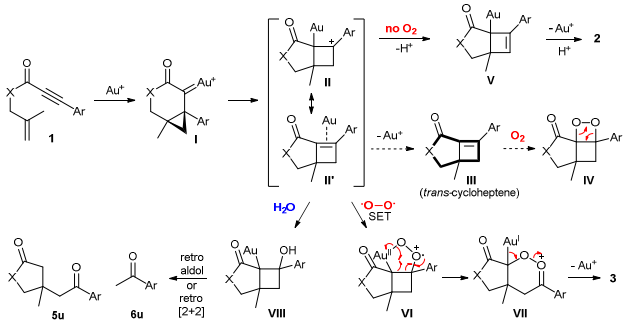
[a] NMR yield based on an internal standard; BHT: 2,6-di-*tert*-butylcresol.



(5)

Exposure of **2b** in CF_3CH_2OH to air or O_2 (1 atm) in the presence or absence of Au-catalyst resulted only in a near quantitative recovery of starting **2b** (eqn (4)), suggesting that **2b** is not a precursor of **3b**. In *d*-labelling study, the reaction of (*E*)-*d*-**1b** under anaerobic condition gave *d*-**2b** with a slight loss of deuterium at the methylene position of **1b**. In contrast, under the atmosphere of air, *d*-**3b** was obtained with no loss of D-atom (eqn (5)).[15] These indicated that the oxygenation do not occur via allylic H-abstraction by peroxy radicals from ether solvents[7c] or via ene-reaction with singlet O_2.[16]

From these experiments, we propose that the reaction of **1** most likely diverge from a Au-bound cationic bicyclo[3.2.0]heptane **II/II'** (Scheme 1).[9] The formation of **2** was computationally (DFT) studied by Kang and Chung[9a] and the proposed lowest-barrier *6-endo* path (**I**) is followed by ring expansion to generate the carbocationic **II**, stabilized by the flanking aryl group, in resonance with **II'**.[17] In the absence of O_2, deprotonation and deauration of **II** via **V** would lead to **2**. For the formation of **3**, a pathway involving Au(I) turnover from **II'** to form metal-free **III** then oxygenation to 1,2-dioxetane **IV**[18] was first considered. However, such a pathway should go through a highly strained *trans*-cycloheptenoid (**III**),[19] and furthermore, liberated Au(I) should continue to consume **1**. To explain the catalyst deactivation (entry 2, Table 3), an alternative mechanism is proposed that involves the reaction of **II/II'** with triplet oxygen to form a metalloradical **VI** through a single electron transfer from Au(I) to O_2.[5d,5e,20] Catalyst poisoning by BHT most likely occurs at this stage. The following radical fragmentation via **VII** can lead to **3**. Observation of **5u** and **6u** may be explained by the addition of water into cationic **II** stabilized by the electron-richer aryl groups. The following retro-aldol or [2+2] cyclo-reversion can generate **5u** and **6u**, respectively.



Scheme 1 Proposed mechanism for the triple bond cleavage.

In summary, we reported herein cyclization of 1,6-enynes with the cleavage of C-C triple bonds into 1,4-diketones. The cleavage of electron-deficient C-C triple bond is uncommon and the salient features of this reaction are that the reaction occurs efficiently at room temperature and under atmospheric pressure of air (0.2 atm of O_2). Experiments indicated that the oxygenation product formed from the Au-bound intermediate, not through a metal-free autoxidation.

Notes and references

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† Electronic Supplementary Information (ESI) available: Optimization study, experimental procedures and characterization data for new compounds.

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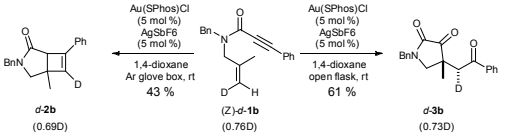

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