ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 12722

Received 30th May 2014,
Accepted 25th August 2014

DOI: 10.1039/c4cc04153d

www.rsc.org/chemcomm

Aerobic oxygenative cleavage of electron deficient C–C triple bonds in the gold-catalyzed cyclization of 1,6-enynes†

Dilip V. Patil, Hyun-Sub Park, Jaeyoung Koo, Jin Wook Han* and Seunghoon Shin*

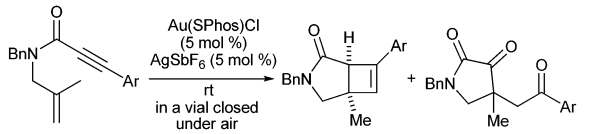
Gold-catalyzed aerobic oxygenative cleavage of triple bonds that occurs under the ambient pressure of air and at room temperature is reported; radical inhibition tests suggest that oxygenation occurs *via* a gold-bound metalloradical intermediate.

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

In oxidative transformations catalyzed by homogeneous gold complexes,[3–6] there has been an 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] A 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 the unique simultaneous cleavage of a single and a triple bond of propargyl ethers with the evolution of CO and CO_2 as C1 byproducts.[7d] We report herein that 1,6-enynes derived from propiolamides deliver tricarbonyl products **3** through a novel triple bond cleavage process.[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 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 a 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 the ligand, the ratio of **3a** *vs.* **2a** was highly dependent on the solvents: in accordance with Chung's report, the formation of bicyclo[3.2.0]hept-6-enes was favored in chlorinated solvents (entries 1–4), whereas a 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 an excellent isolated yield of **3b** (86%) 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]

Table 1 Examination of reaction conditions[a]



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

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

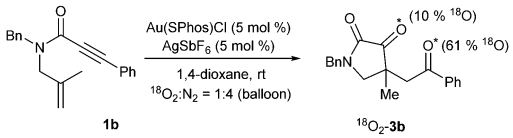
Entry	Substrate	Solvent	Time (h)	**2**[b] (%)	**3**[b] (%)
1	**1a**	CH_2Cl_2[c]	4	87	11
2	**1a**	CH_2Cl_2	4	86	
3	**1a**	$CHCl_3$	4	74	—
4	**1a**	1,2-DCE	4	66	—
5	**1a**	Toluene	4	25	45
6	**1a**	THF	4	—	54
7	**1a**	Et_2O	4	7	63
8	**1a**	1,4-Dioxane	4	—	75
9	**1b**	1,4-Dioxane	12	—	(73)[d]
10	**1b**	C_6H_5F	2	—	(82)[d]
11	**1b**	CF_3CH_2OH	1.5	—	(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.

Department of Chemistry and Institute for Natural Sciences, Hanyang University, Seoul 133-791, Korea. E-mail: jwhan@hanyang.ac.kr, sshin@hanyang.ac.kr; Fax: +82-2-2299-0762; Tel: +82-2-2220-0948

† Electronic supplementary information (ESI) available: Optimization study, experimental procedures and characterization data for new compounds. CCDC 933766. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc04153d

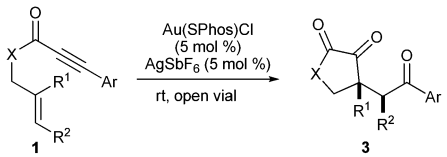
To investigate the source of carbonyl O atoms, we performed the reaction in the presence of a $H_2{}^{18}O$ or $^{18}O_2$ environment, employing **1b** as a substrate.[13] In the presence of $H_2{}^{18}O$ (15 equiv.) in 1,4-dioxane in an open flask, no ^{18}O atom was incorporated into **3b**.[12] However,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



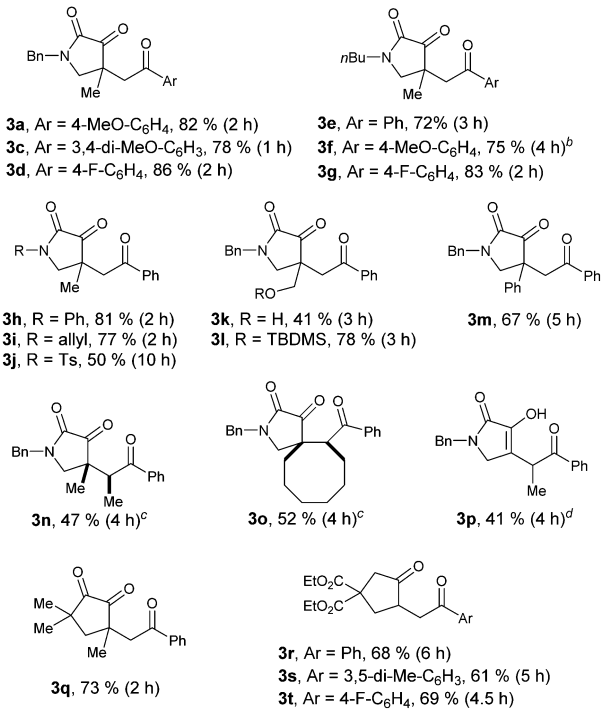
1b $^{18}O_2$-**3b** (1)

The scope of the present method was next probed for 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 catalysts in CF_3CH_2OH. Variations 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 moieties (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 were less effective, suggesting a developing strain in the transition state (**3n–p**). Those without R^1 substitution (**1p**) also afforded tricarbonyl **3p** as a major product. Notably, the carbocyclic analogue **3q–t** was formed smoothly without any event. Unfortunately, however, homoallyl amide substrates or ester-tethered substrates were unreactive. The net result of this triple bond cleavage is that the two Csp atoms of the alkyne are added to alkenes, forming synthetically useful 1,4-dicarbonyl compounds. For example, the product **3r** could be converted into a fused pyrrole **4r** *via* the Paal–Knorr synthesis (eqn (2)).

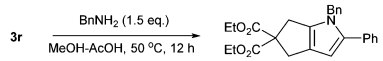
Table 2 Investigation of the reaction scope[a]



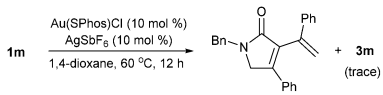
1 **3**



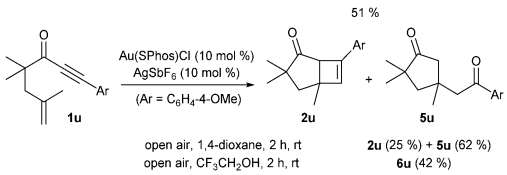
[a] CF_3CH_2OH (0.1 M) as a solvent unless otherwise noted; isolated yield after chromatography; reaction time in parentheses. [b] 1,4-Dioxane as a solvent. [c] The product was obtained as a single diastereomer. [d] **1p** as a mixture of *E*/*Z* (3 : 1) isomers was used.



(2)



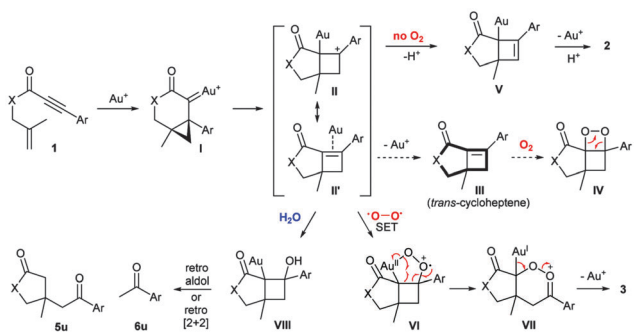
(3)



(4)

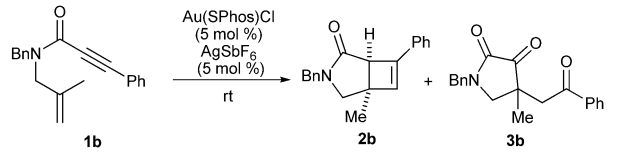
It is noteworthy that the reaction of **1m** at a higher temperature (60 °C) gave a predominantly metathesis type of product (51%, eqn (3)) that could arise *via* σ-bond reorganization of **II** (Scheme 1). Surprisingly, the reaction of **1u** unexpectedly provided dicarbonyl **5u** as a major product in 1,4-dioxane along with a small amount of **2u** (25%). In CF_3CH_2OH, the 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 the starting **1**, unless the cationic Au^+ is decomposed by the radical inhibitors. In contrast, if the oxygenation by O_2 occurs at the Au-bound stage (such as **II**/**II′**), the catalyst may be deactivated by the



Scheme 1 Proposed mechanism for the triple bond cleavage.

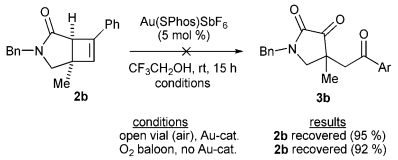
Table 3 Effect of radical inhibitors[a]



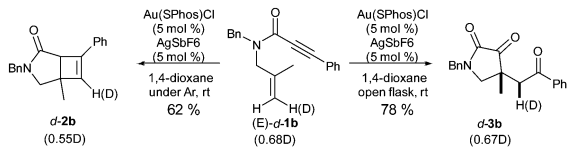
Entry	Conditions	Solvent	Time (h)	Product 1b (%)	Product 2b (%)	Product 3b (%)
1	Open vial, no additive	1,4-Dioxane	12	—	—	73
2	Open vial, BHT (10%)	1,4-Dioxane	15	94	—	—
3	Under Ar, no additive	CH_2Cl_2	6	—	85	—
4	Under Ar, BHT (10%)	CH_2Cl_2	6	—	84	—

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

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 amounts 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 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]



(5)



(6)

Exposure of **2b** in CF_3CH_2OH to air or O_2 (1 atm) in the presence or absence of the Au-catalyst resulted only in a near quantitative recovery of the starting **2b** (eqn (5)), suggesting that **2b** is not a precursor of **3b**. In a *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 an atmosphere of air, *d*-**3b** was obtained with no loss of D-atoms (eqn (6)).[15] This indicates that the oxygenation does not occur *via* allylic H-abstraction by peroxy radicals from ether solvents[7c] or *via* an ene-reaction with singlet O_2.[16]

From these experiments, we propose that the reaction of **1** most likely diverges 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** and 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, the liberated Au(I) should continue to consume **1**. To explain the catalyst deactivation (entry 2, Table 3), an alternative mechanism has been proposed that involves the reaction of **II**/**II**′ with a triplet oxygen to form a metalloradical **VI** through a single electron transfer from Au(I) to O_2.[5d,e,20] Catalyst poisoning by BHT most likely occurs at this stage. The following radical fragmentation *via* **VII** can lead to **3**. The observation of **5u** and **6u** may be explained by the addition of trace amount of extraneous 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.

In summary, we have reported herein the cyclization of 1,6-enynes with the cleavage of C–C triple bonds into 1,4-diketones. The cleavage of an 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 the atmospheric pressure of air (0.2 atm of O_2). Experiments indicated that the oxygenation product formed *via* the Au-bound intermediate, and not through metal-free autoxidation.

This work was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean Government (2014-011165, 2012-015662 and 2012M3A7B4049653).

Notes and references

1 (*a*) T. Punniyamurthy, S. Velusamy and J. Iqbal, *Chem. Rev.*, 2005, **105**, 2329; (*b*) S. S. Stahl, *Angew. Chem., Int. Ed.*, 2004, **43**, 3400; (*c*) K. M. Gligorich and M. S. Sigman, *Chem. Commun.*, 2009, 3854; (*d*) A. E. Wendlandt, A. M. Suess and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2011, **50**, 11062; (*e*) C. Zhang, C. Tang and N. Jiao, *Chem. Soc. Rev.*, 2012, **41**, 3464.

2 H. Itatani and H. Yoshimoto, *Chem. Ind.*, 1971, 674.

3 (*a*) M. C. B. James and A. S. K. Hashmi, in *Modern Gold Catalyzed Synthesis*, ed. A. S. K. Hashmi and F. D. Toste, Wiley-VCH, Weinheim, Germany, 2012, pp. 273–296; (*b*) C. Nevade and T. de Haro, in *New Strategies in Chemical Synthesis and Catalysis*, ed. B. Pignataro, Wiley-VCH, Weinheim, Germany, 2012, pp. 247–272For cycloisomerization of enynes in gold catalysis: (*c*) E. Jiménez-Núnez and A. M. Echavarren, *Chem. Rev.*, 2008, **108**, 3326.

4 Outer sphere oxidation of alkynes (reviews): (*a*) H. S. Yeom and S. Shin, *Acc. Chem. Res.*, 2014, **47**, 966; (*b*) L. Zhang, *Acc. Chem. Res.*, 2014, **47**, 877; (selected examples): (*c*) V. K. Pagar, A. M. Jadhav and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 20728; (*d*) A. M. Jadav, S. Bhunia, H.-Y. Liao and R.-S. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1769.

5 Inner sphere oxidation of Au(I): (*a*) H. A. Wegner, S. Ahles and M. Neuburger, *Chem. – Eur. J.*, 2008, **14**, 11310; (*b*) G. Zhang, Y. Peng, L. Cui and L. Zhang, *Angew. Chem., Int. Ed.*, 2009, **48**, 3112; (*c*) N. P. Mankad and F. D. Toste, *J. Am. Chem. Soc.*, 2010, **132**, 12859; (*d*) B. Sahoo, M. N. Hopkinson and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 5505; (*e*) X.-Z. Shu, M. Zhang, Y. He, H. Frei and F. D. Toste, *J. Am. Chem. Soc.*, 2014, **136**, 5844.

6 Hypervalent iodine-mediated oxidations: (*a*) A. Kar, N. Mangu, H. M. Kaiser, M. Beller and M. K. Tse, *Chem. Commun.*, 2008, 386; (*b*) J. P. Brand, J. Charpentier and J. Waser, *Angew. Chem., Int. Ed.*, 2009, **48**, 9346; (*c*) T. de Haro and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 1512.

7 For aerobic oxidations (excluding alcohols oxidation into carbonyl compounds): (*a*) Y. Liu, F. Song and S. Guo, *J. Am. Chem. Soc.*, 2006, **128**, 11332; (*b*) F. Song and Y. Liu, *J. Organomet. Chem.*, 2009,

694, 502; (*c*) A. S. K. Hashmi, M. C. B. Jaimes, A. M. Schuster and F. Rominger, *J. Org. Chem.*, 2012, **77**, 6394; (*d*) A. Das, R. Chaudhuri and R.-S. Liu, *Chem. Commun.*, 2009, 4046; (*e*) B.-L. Lu and M. Shi, *Chem. – Eur. J.*, 2011, **17**, 9070Use of TBHP as an oxidant; (*f*) D. Xing, B. Guan, G. Cai, Z. Fang, L. Yang and Z. Shi, *Org. Lett.*, 2006, **8**, 693.

8 For metal-catalyzed triple bond cleavage: (*a*) C.-H. Jun, C.-H. Lee, C.-W. Moon and H.-S. Hong, *J. Am. Chem. Soc.*, 2001, **123**, 8600; (*b*) T. Shimada and Y. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 6646.

9 (*a*) Y. T. Lee, Y. K. Kang and Y. K. Chung, *J. Org. Chem.*, 2009, **74**, 7922; (*b*) A. Escribano-Cuesta, P. Pérez-Galán, E. Herrero-Gómez, M. Sekine, A. A. C. Braga, F. Maseras and A. M. Echavarren, *Org. Biomol. Chem.*, 2012, **10**, 6105.

10 The authors thank one of the reviewers for valuable suggestion of the use of fluorinated solvents. See also: A. M. A. Dias, R. P. Bonifácio, I. M. Marrucho, A. A. H. Pádua and M. F. Costa Gomes, *Phys. Chem. Chem. Phys.*, 2003, **5**, 543.

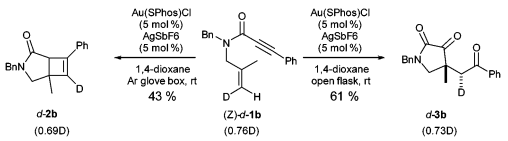
11 (**3a**) IR (neat): 1763, 1710, 1674 cm^{-1}; crystallographic data for compound **3e** (CCDC 933766).

12 ESI† for experimental details.

13 For oxidations involving H_2O producing H_2 gas as byproduct: (*a*) B. P. Taduri, S. M. A. Sohel, H.-M. Cheng, G.-Y. Lin and R.-S. Liu, *Chem. Commun.*, 2007, 2530; (*b*) S. Shin, A. K. Gupta, C. Y. Rhim and C. H. Oh, *Chem. Commun.*, 2005, 4429.

14 The lower amount of ^{18}O incorporation at the α-keto carbonyl is presumably due to a facile O-exchange with extraneous water.

15 Likewise, (Z)-d-**1b** provided similar results under both aerobic and anaerobic conditions.



16 L. B. Harding and W. A. Goddard III, *J. Am. Chem. Soc.*, 1980, **102**, 439.

17 Solution structure of a Au(I)-η^2-bound bicyclo[3.2.0]hept-1(7)ene (similar to **III**) was recently studied by NMR: R. E. M. Brooner, T. J. Brown and R. A. Widenhoefer, *Angew. Chem., Int. Ed.*, 2013, **52**, 6259; in the presence of polarizing C2-carbonyl, η^1-complex **II** is expected to be the more contributing resonance form.

18 For a single example in the $PtCl_4$-catalyzed cyclization of 1,7-enyne: J. Blum, H. Beer-Kraft and Y. Badrieh, *J. Org. Chem.*, 1995, **60**, 5567.

19 For the instability of the related fused cyclobutenes: (*a*) B. M. Trost, M. Yanai and K. Hoogsteen, *J. Am. Chem. Soc.*, 1993, **115**, 5294; (*b*) B. M. Trost, A. C. Guitierrez and E. M. Ferreira, *J. Am. Chem. Soc.*, 2010, **132**, 9206; (*c*) E. I. Negishi, S. J. Holmes, J. M. Tour and J. A. Miller, *J. Am. Chem. Soc.*, 1985, **107**, 2568; (*d*) Y. Odabachian and F. Gagosz, *Adv. Synth. Catal.*, 2009, **351**, 379; (*e*) S. Couty, C. Meyer and J. Cossy, *Angew. Chem., Int. Ed.*, 2006, **45**, 6726.

20 For a review on Au(II) complexes: A. Laguna and M. Laguna, *Coord. Chem. Rev.*, 1999, **193–195**, 837.