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Gold-Catalyzed Oxidative Rearrangement of Homopropargylic Ether via Oxonium Ylide

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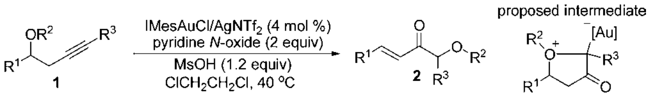
ABSTRACT



Synthetically useful α,β-unsaturated carbonyl compounds were obtained from gold-catalyzed oxidative rearrangement of homopropargylic ether under mild reaction conditions. Gold carbenoid and oxonium ylide are proposed as key intermediates.

Gold-catalyzed reactions have intensively been investigated in the past decade.[1] Numerous new transformations based on the π-acidity and electron-donor property of gold catalysts have been developed and applied in multistep syntheses. In 2007, Toste and co-workers[2a] and Zhang and co-workers[2b] independently reported that alkyne with a tethered sulfoxide could be used as precursor of α-oxo gold carbenoid. This method is promising because it offers a convenient and benign alternative to generate metal carbene, which is tranditionally obtained from the diazo compound.[2,3] Intermolecular oxidation of alkynes was subsequently realized by using pyridine *N*-oxide, and the metal carbenoid or gold-stabilized carbocation can be trapped

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(1) For selected reviews, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (d) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (e) Jiménez- Núnez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (f) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (g) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (h) Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (i) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (j) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232. (k) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (l) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.

(2) Selected examples of intramolecular redox reactions of alkynes: (a) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (b) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156. (c) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (d) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (e) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225. (f) Yeom, H.-S.; Lee, Y.; Jeong, J.; So, E.; Hwang, S.; Lee, J.-E.; Lee, S. S.; Shin, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1611. (g) Jadhav, A. M.; Bhunia, S.; Liao, H.-Y.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 1769. (h) Chen, D.; Song, G.; Jia, A.; Li, X. *J. Org. Chem.* **2011**, *76*, 8488. (i) Yeom, H.-S.; So, E.; Shin, S. *Chem.—Eur. J.* **2011**, *17*, 1764. (j) Patel, P.; Ramana, C. V. *Org. Biomol. Chem.* **2011**, *9*, 7327.

(3) Recent review for α-carbonyl gold carbenoids: (a) Xiao, J.; Li, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226. For examples using azide as nucleophiles, see: (b) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (c) Wetzel, A.; Gagosz, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 7354. (d) Lu, B.; Luo, Y.; Liu, L.; Ye, L.; Wang, Y.; Zhang, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8358. For similar reactions with different mechanism, see: (e) Cuenca, A. B.; Montserrat, S.; Hossain, K. M.; Mancha, G.; Lledos, A.; Medio-Simon, M.; Ujaque, G.; Asensio, G. *Org. Lett.* **2009**, *11*, 4906. (f) Li, C.-W.; Pati, K.; Lin, G.-Y.; Abu Sohel, S. M.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891. (g) Xu, C.-F.; Xu, M.; Jia, Y.-X.; Li, C.-Y. *Org. Lett.* **2011**, *13*, 1556. (h) Noey, E. L.; Luo, Y.; Zhang, L.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 1078. (i) Bhunia, S.; Ghorpade, S.; Huple, D. B.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2012**, *51*, 2939.

(4) Gold-catalyzed intramolecular reactions involving gold carbenes derived from intermolecular oxidation of alkynes: (a) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (b) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550. (c) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070. (d) Ye, L.; He, W.; Zhang., L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3236. (e) Vasu, D.; Hung, H.-H.; Bhunia, S.; Gawade, S. A.; Das, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2011**, *50*, 6911. (f) Davies, P. W.; Cremonesi, A.; Dumitrescu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8931. (g) Davies, P. W.; Cremonesi, A.; Martin, N. *Chem. Commun.* **2011**, *47*, 379. (h) Qian, D.; Zhang, J. *Chem. Commun.* **2011**, *47*, 11152. (i) Li, C.; Zhang, L. *Org. Lett.* **2011**, *13*, 1738. (j) Qian, D.; Zhang, J. *Chem. Commun.* **2012**, *48*, 7082. (k) Wang, Y.; Ji, K.; Lan, S.; Zhang, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1915. (l) Kramer, S.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 4681.

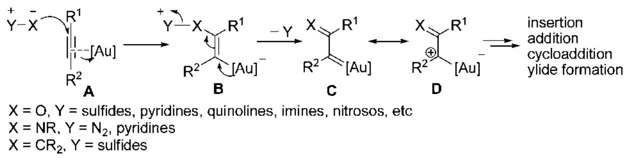
(5) Selected examples of intermolecular redox reactions of alkynes: (a) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (b) Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R.-S. *J. Am. Chem. Soc.* **2011**, *133*, 15372. (c) He, W.; Xie, L.; Xu, Y.; Xiang, J.; Zhang, L. *Org. Biomol. Chem.* **2012**, *10*, 3168.

(6) (a) *Metal Carbenes in Organc Synthesis*; Dorwald, F. Z., Ed.; Wiley-VCH: New York, 1999. (b) *Metal Carbenes in Organc Synthesis*; Dotz, K. H., Ed.; Springer-Verlag: Berlin, 2004. (c) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (e) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977. (f) Aggarwal, V. K.; Winn, C. L. *Acc. Chem. Res.* **2004**, *37*, 611.

10.1021/ol302238t

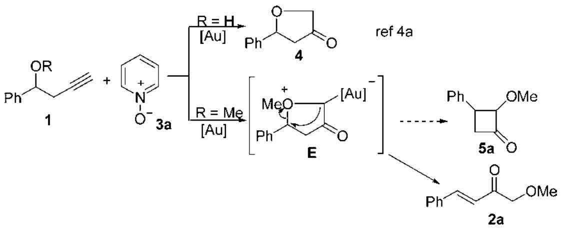
intramolecularly[4] or intermolecularly[5] (Scheme 1). Among all the trapping approaches of metal carbenoids, ylide formation and the subsequent reaction are attractive because chemical transformations of ylides have shown great versatility in the synthesis of natural products.[6] Surprisingly, little work has been done in this area.[7] Exploring new transformations based on ylide formation that evolve from alkynes and gold catalyst is of great significance.

Scheme 1. Gold-Catalyzed Oxidation of Alkynes



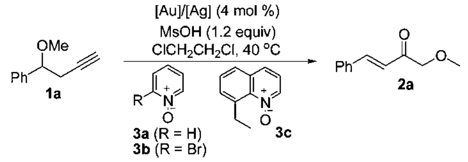
In 2010, Zhang and co-workers reported that in the presence of gold catalyst and pyridine *N*-oxide, homopropargylic alcohol could be converted into dihydrofuran-3-one **4** via α-oxo gold carbenoid and subsequent O−H insertion (Scheme 2).[4a] We envisioned that if the OH group was replaced by OMe group, instead of O−H insertion, an oxonium ylide may be formed and [1,2]-shift would lead to cyclobutanone **5**. To our surprise, when substrate **1a** was subjected to the gold-catalyzed redox reaction, instead of cyclobutanone, an α,*β*-unsaturated carbonyl compound **2a** was obtained in moderate yield. Herein, we report an unprecedented synthesis of α,*β*-unsaturated carbonyl compound from homopropargylic ether via oxonium ylide route.

Scheme 2. Design for the Trapping of α-Oxo Gold Carbenoid



Using **1a** as the model substrate, reaction conditions such as gold catalysts, silver catalysts, oxygen-delivering oxidants, acids, solvent and reaction temperature were screened, representative conditions are summarized in Table 1. The use of 4 mol % IMesAuCl/$AgNTf_2$ gave the best result, 68% of **2a** could be obtained (entry 5). Surprisingly, when 8-ethylquinoline *N*-oxide was used, the reaction completed in 2.5 h, but the products were complex and only trace **2a** could be isolated (entry 7). In the absence of MsOH, the reaction proceeded slowly; 34% of the substrate was recovered after 11 h, and **2a** could be obtained in 34% yield (entry 8). IMesAuCl, $AgNTf_2$ or $HNTf_2$ alone could not catalyze the reaction; the starting material was recovered unconsumed in each case after 24 h (entries 9, 10 and 11).

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (4 mol %)	*N*-oxide (2 equiv)	time (h)	yield (%)
1	$Ph_3PAuCl/AgSbF_6$	**3a**	3.5	40
2	$AuCl/AgSbF_6$	**3a**	6.5	31
3	$IMesAuCl/AgSbF_6$	**3a**	3.5	63
4	$IPrAuCl/AgSbF_6$	**3a**	7.0	48
5	$IMesAuCl/AgNTf_2$	**3a**	4.8	68
6	$IMesAuCl/AgNTf_2$	**3b**	8.0	46
7	$IMesAuCl/AgNTf_2$	**3c**	2.5	trace
8[b,c]	$IMesAuCl/AgNTf_2$	**3a**	11	34
9[b]	IMesAuCl	**3a**	24	0
10[b]	$AgNTf_2$	**3a**	24	0
11	$HNTf_2$	**3a**	24	0

[a] [**1a**] = 0.1 M; the reaction was conducted in 2 mL of 1,2-dichloroethane in open flask. [b] No MsOH was added. [c] 66% conversion.

The scope of this reaction was then examined (Scheme 3). Moderate to high yield could be obtained when methyl ethers with an electron-poor aromatic unit at the homopropargylic position were used (**2b**, **2c**, **2d**, **2e**, **2f** and **2g**). Halogen, trifluoromethyl, ester and cyano groups are well tolerated in this mild transformation. Aromatic ring at the homopropargylic position is necessary for high yield since **2h** could be obtained only in 28% yield. This method also worked well with phenyl ether and benzyl ether (**2i** and **2j**). Additionally, 2-methoxy substituted 1,3-diketone **2k** can be obtained in 52% yield from ynone **1k**; compound **6**, which is an sp^2 C−H insertion product, can also be isolated in 16% yield.[8] Interestingly, when substrates bearing electron-rich aryl ring were used, α,*β*-unsaturated carbonyl compound **2** and cyclobutanone **5** were obtained (**2l**, **2m**, **5l**, **5m** and **5n**). A general trend can be deduced here: the electron richer aryl ring the substrates bear, the higher ratio between **5** and **2** we can expect; this is in accordance with the relative stability of zwitterion (Scheme 4, intermediate **I**). We also tried other OH protecting group such as TBS and THP.

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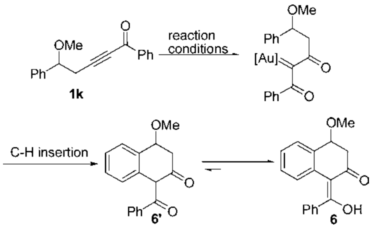
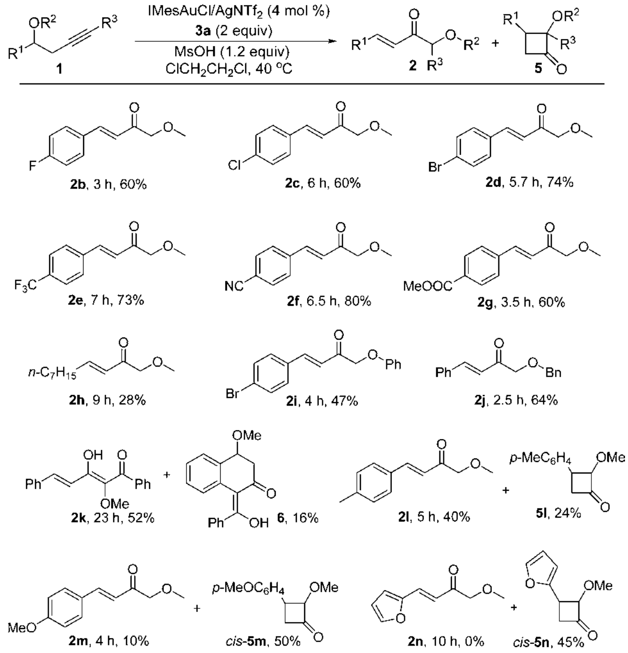
[7] (a) Davies, P. W.; Albrecht, S. J.-C. *Chem. Commun.* **2008**, 238. (b) Davies, P. W.; Albrecht, S. J.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8372. (c) Davies, P. W.; Albrecht, S. J.-C. *Synlett* **2012**, 70.

[8] The proposed mechanism for formation of compound **6**:



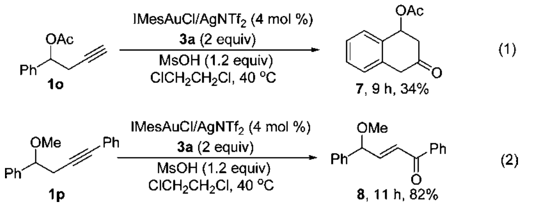
Scheme 3. Substrate Scope[a]



[a] [**1**] = 0.1 M; the reaction was conducted in 2 mL of 1,2-dichloroethane in open flask.

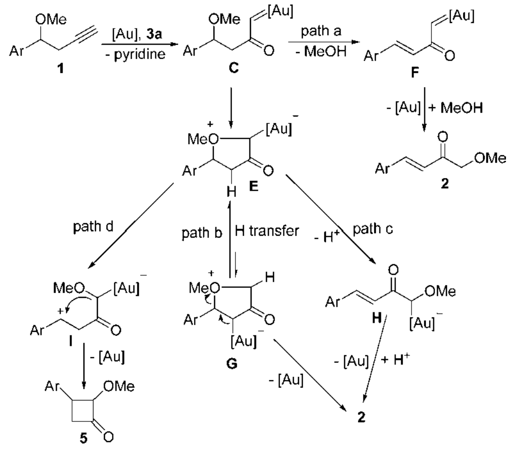
Since MsOH was used in the reaction, the OTBS or OTHP were hydrolyzed, only dihydrofuran-3-one was isolated. Remarkably, the *E*/*Z* selectivity of this reaction is perfect, all the enone products we obtained are (*E*)-isomers, and no (*Z*)-isomer could be detected from the crude NMR.

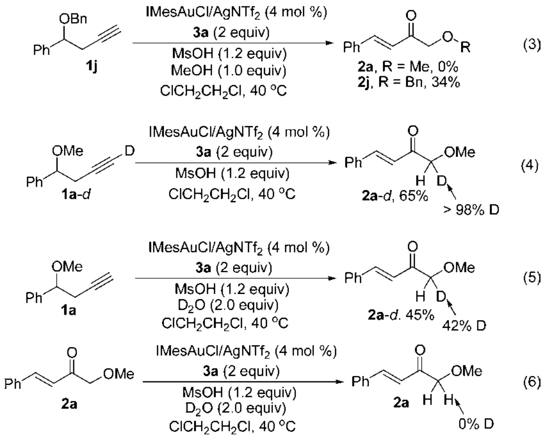
To shed light on the reaction mechanism, we synthesized homopropargylic ester **1o** and internal alkyne **1p**. Under the optimized reaction conditions, **1o** led to compound **7** (eq 1), which is an sp^2 C−H insertion product. When **1p** was employed, α,β-unsaturated carbonyl compound **8** could be obtained in 82% yield (eq 2). Compared with compound **2**, the regioselectivity here is different. On the basis of Zhang and co-workers' report,[4c] formation of α-oxo gold carbenoid and subsequent 1,2-C−H insertion led to final product **8**. These results, together with compound **6** in Scheme 3, indicate that α-oxo gold carbenoid plays a central role in this reaction.



As depicted in Scheme 4, several pathways could be possible. Nucleophilic attack of pyridine *N*-oxide to gold-activated alkyne **1** and subsequent expulsion of pyridine aided by gold catalyst affords carbenoid **C**. In path a, elimination of MeOH leads to intermediate **F**, which undergoes intermolecular O−H insertion to afford final product **2**. Alternatively, electrophilic carbene can be attacked by pendent oxygen atom, which results in oxonium ylide **E**. Intramolecular H transfer leads to intermediate **G** (path b), subsequent cleavage of C−Au and C−O bond affords **2** and regenerates gold catalyst. Instead of H transfer, proton at the α-position of carbonyl can be eliminated, followed by cleavage of C−O bond (path c); thus, intermediate **H** can be obtained. Compound **2** can be formed by subsequent protodeauration. When aryl ring at homopropargylic position is electron rich (Scheme 3, **1l**, **1m** and **1n**), relatively stable intermediate **I** can be obtained (path d), which undergoes intramolecular nucleophilic attack to afford cyclobutanone **5**.

Scheme 4. Proposed Mechanism





To gain more information about the mechanism, we did a crossover experiment (eq 3). When benzyl ether **1j** was used, 1 equiv of MeOH was added to trap the proposed intermediate **F** (Scheme 4); only **2j** could be isolated in 34% yield, which indicated that path a could not be the actual mechanism. We also prepared **1a**-*d*, which was deuterated 100% at alkyne terminus, and the gold-catalyzed reaction led to **2a**-*d* having a >98% deuterium content for the methylene position (eq 4). This result is in consistent with path b and path c. Furthermore, when **1a** was subjected to the optimized reaction conditions, 2 equiv of D_2O was added simultaneously (eq 5); 42% deuterated product could be obtained. To rule out the hydrogen exchange between **2a** and D_2O under the reaction conditions, **2a** was employed under the same conditions as eq 5; no deuterium labeled product could be obtained (eq 6). Thus, path c should be the most possible mechanism.

In summary, we have described a novel and convenient approach that converts homopropargylic ethers into α,β-unsaturated carbonyl compounds. The reaction tolerates various functional groups and generates a compound with excellent (*E*)-selectivity. Oxonium ylide is proposed as the key intermediate, which is generated from ether tethered alkynes and pyridine *N*-oxide for the first time. When substrates bearing an electron-rich aryl ring at the homopropargylic position were used, cyclobutanone could be obtained. We are working on this interesting reaction and trying to figure out the relationship between selectivity and structure of substrates and catalysts.

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Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.