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Gold-Catalyzed Synthesis of Benzil Derivatives and α-Keto Imides via Oxidation of Alkynes

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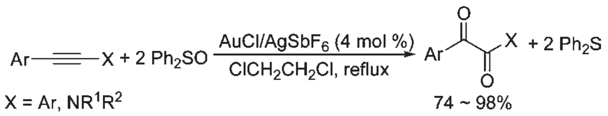
ABSTRACT



An efficient process based on the gold-catalyzed redox reaction has been developed to oxidize 1,2-diarylacetylene or ynamide to 1,2-diaryldiketone or α-keto imide respectively. This process can tolerate a variety of functional groups and affords 1,2-dicarbonyl compounds in excellent yields under mild reaction conditions.

1,2-Dicarbonyl functionalities are found in numerous bioactive natural products.[1] Moreover, they are versatile building blocks in a string of chemical transformations.[2] Several synthetic strategies have been reported to obtain this useful structure, such as oxidation of carbon substituted alkynes[3] or heteroatom substituted alkynes,[4] oxidation of α-hydroxyketones,[5] substitution of oxalyl chloride or α-keto acid chloride,[6] and some other transformations.[7] However, several drawbacks such as low chemoselectivity, high toxicity, and low functionality tolerance are still issues in this area. Consequently, the development of general and convenient methods for construction of 1,2-dicarbonyl derivatives are of great importance.

In the past decade, gold-catalyzed transformations have attracted considerable attention due to their strong π acidity for the activation of unsaturated carbon carbon bonds toward nucleophilic attack.[8] The stability of gold catalysts to air and moisture renders gold catalysis a straightforward protocol in modern synthesis. Recently, gold-catalyzed redox procedures using sulfoxide and amine-*N*-oxide as the oxidant have been reported.[9] In the reactions, alkynes are employed as a precursor of α-carbonyl gold-carbenoids, which bypasses the use of potentially explosive diazo compounds (Scheme 1a). We envisioned that the hypothetic α-carbonyl gold-carbenoids **C** could be oxidized

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[†] Zhejiang Sci-Tech University.

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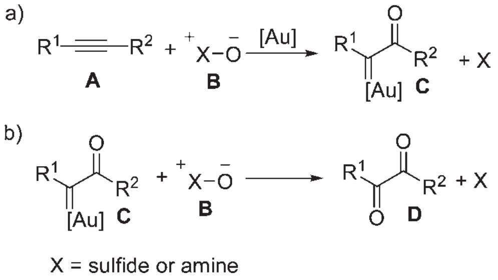
(1) For selected examples, see: (a) Rozwadowska, M. D.; Chrzanowska, M. *Tetrahedron* **1985**, *41*, 2885. (b) Angelstro, M. R.; Mehdi, S.; Burkhart, J. P.; Peet, N. P.; Bey, P. *J. Med. Chem.* **1990**, *33*, 11. (c) Maurya, R.; Singh, R.; Deepak, M.; Handa, S. S.; Yadav, P. P.; Mishra, P. K. *Phytochemistry* **2004**, *65*, 915. (d) Mahabusarakam, W.; Deachathai, S.; Phongpaichit, S.; Jansakul, C.; Taylor, W. C. *Phytochemistry* **2004**, *65*, 1185. (e) Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613. (f) Wadkins, R. M.; Hyatt, J. L.; Wei, X.; Yoon, K. J. P.; Wierdl, M.; Edwards, C. C.; Morton, C. L.; Obenauer, J. C.; Damodaran, K.; Beroza, P.; Danks, M. K.; Potter, P. M. *J. Med. Chem.* **2005**, *48*, 2906.

(2) For recent examples, see: (a) Wolkenberg, S. E.; Wisnoski, D. D.; Leister, W. H.; Wang, Y.; Zhao, Z.; Lindsley, C. W. *Org. Lett.* **2004**, *6*, 1453. (b) Shipe, W. D.; Yang, F.; Zhao, Z.; Wolkenberg, S. E.; Nolt, M. B.; Lindsley, C. W. *Heterocycles* **2006**, *70*, 655. (c) Deng, X.; Mani, N. *Org. Lett.* **2006**, *8*, 269. (d) Held, I.; Xu, S. J.; Zipse, H. *Synthesis* **2007**, 1185. (e) Rong, F.; Chow, S.; Yan, S.; Larson, G.; Hong, Z.; Wu, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1663. (f) Herrera, A. J.; Rondón, M.; Suárez, E. *J. Org. Chem.* **2008**, *73*, 3384. (g) Boyce, G. R.; Johnson, J. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 8930.

(3) For recent examples on synthesis of 1,2-diketones, see: (a) Katriszky, A. R.; Zhang, D.; Kirichenko, K. *J. Org. Chem.* **2005**, *70*, 3271. (b) Giraud, A.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron* **2006**, *62*, 7667. (c) Wan, Z.; Jones, C. D.; Mitchell, D.; Pu, J. Y.; Zhang, T. Y. *J. Org. Chem.* **2006**, *71*, 826. (d) Mousset, C.; Provot, O.; Hamze, A.; Bignon, J.; Brion, J.-D.; Alami, M. *Tetrahedron* **2008**, *64*, 4287. (e) Niu, M.; Fu, H.; Jiang, Y.; Zhao, Y. *Synthesis* **2008**, 2879. (f) Tan, K. J.; Wille, U. *Chem. Commun.* **2008**, 6239. (g) Chu, J.-H.; Chen, Y.-J.; Wu, M.-J. *Synthesis* **2009**, 2155. (h) Ren, W.; Xia, Y.; Ji, S.-J.; Zhang, Y.; Wan, X.; Zhao, J. *Org. Lett.* **2009**, *11*, 1841. (i) Ren, W.; Liu, J.; Chen, L.; Wan, X. *Adv. Synth. Catal.* **2010**, *352*, 1424. (j) Mori, S.; Takubo, M.; Yanase, T.; Maegawa, T.; Monguchi, Y.; Sajiki, H. *Adv. Synth. Catal.* **2010**, *352*, 1630.

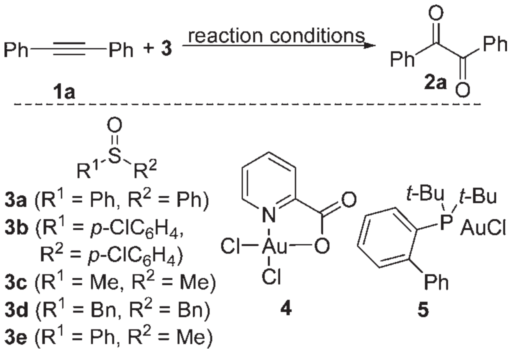
10.1021/ol200270t

Scheme 1. Initial Hypothesis



by the same oxidant **B** (Scheme 1b, sulfoxide or amine-*N*-oxide). Thus, 1,2-dicarbonyl compounds **D** can be synthesized from alkynes and very mild oxidants, which offers a new method to access useful 1,2-dicarbonyl compounds.[10]

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst (4 mol %)	sulfoxide (equiv)	solvent	temp (°C)	yield[b] (%)
1	**4**	**3a** (3.0)	CH_2Cl_2	rt	0
2	$Ph_3PAuCl/AgSbF_6$	**3a** (3.0)	CH_2Cl_2	rt	19
3	**5**/$AgSbF_6$	**3a** (3.0)	CH_2Cl_2	rt	3
4	$AuCl_3/AgSbF_6$	**3a** (3.0)	CH_2Cl_2	rt	11
5	$AuCl/AgSbF_6$	**3a** (3.0)	CH_2Cl_2	rt	63
6	$AuCl/AgSbF_6$	**3a** (3.0)	DCE	rt	73
7	$AuCl/AgSbF_6$	**3a** (3.0)	DCE	60	81
8	$AuCl/AgSbF_6$	**3a** (3.0)	DCE	85	93
9	$AuCl/AgSbF_6$	**3b** (3.0)	DCE	85	68
10	$AuCl/AgSbF_6$	**3c** (3.0)	DCE	85	0
11	$AuCl/AgSbF_6$	**3d** (3.0)	DCE	85	9
12	$AuCl/AgSbF_6$	**3e** (3.0)	DCE	85	17
13	$AuCl/AgSbF_6$	**3a** (2.0)	DCE	85	67
14	$AuCl/AgSbF_6$	**3a** (4.0)	DCE	85	91
15	$AuCl/AgSbF_6$[c]	**3a** (3.0)	DCE	85	69
16	$AuCl/AgSbF_6$[d]	**3a** (3.0)	DCE	85	96
17	AuCl	**3a** (3.0)	DCE	85	7
18	$AgSbF_6$	**3a** (3.0)	DCE	85	0
19[e]	$AuCl/AgSbF_6$	**3a** (3.0)	DCE	85	94
20[e,f]	$AuCl/AgSbF_6$	**3a** (3.0)	DCE	85	95

[a] All reactions were carried out under an atmosphere of nitrogen in 2 mL of dry solvent. The flask was covered by aluminum foil. 0.2 mmol scale. [b] Isolated yield. [c] 2 mol % of catalysts. [d] 6 mol % of catalysts. [e] No aluminum foil covered. [f] The reaction was conducted in the air with solvent of technical grade.

To test the feasibility of this idea, 1,2-diphenylacetylene **1a** and 3 equiv of diphenylsulfoxide **3a** were treated with various gold and silver catalyst systems in CH_2Cl_2 at room temperature (Table 1, entries 1−5). When 4 mol % of $AuCl/AgSbF_6$ was used, the benzil could be obtained in 63% yield (entry 5). Solvent also has a great impact on the reaction yield;[11] $ClCH_2CH_2Cl$ was the optimal solvent under our screened conditions (entry 6). The yield was further improved to 93% by raising the reaction temperature to 85 °C (entry 8). Among the sulfoxides we examined, the diphenylsulfoxide was the best one (entries 8−12). The effect of the loading of catalyst and sulfoxide was also investigated; 4 mol % of catalyst and 3 equiv of diphenylsulfoxide gave the highest yield (entries 13−16). Control experiments indicated that both AuCl and $AgSbF_6$ were

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(4) For recent reviews on synthesis and reaction of ynamides, see: (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem., Int. Ed.* **2010**, *49*, 2840. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064. For a recent example on synthesis of α-keto imides, see: (c) Al-Rashid, Z. F.; Johnson, W. L.; Hsung, R. P.; Wei, Y.; Yao, P.-Y.; Liu, R.; Zhao, K. *J. Org. Chem.* **2008**, *73*, 8780. For a related example on synthesis of α-keto amides, see: (d) Zhang, C.; Jiao, N. *J. Am. Chem. Soc.* **2010**, *132*, 28.

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(7) For recent examples, see: (a) Allais, C.; Constantieux, T.; Rodriguez, J. *Synthesis* **2009**, 2523. (b) Tada, N.; Shomura, M.; Nakayama, H.; Miura, T.; Itoh, A. *Synlett* **2010**, 1979. (c) Bouma, M.; Masson, G.; Zhu, J. *J. Org. Chem.* **2010**, *75*, 2748. (d) Mossetti, R.; Pirali, T.; Tron, G. C.; Zhu, J. *Org. Lett.* **2010**, *12*, 820.

(8) 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) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (d) Skouta, R.; Li, C.-J. *Tetrahedron* **2008**, *64*, 4917. (e) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (f) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (g) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (h) Jiménez- Núnez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (i) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (j) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (k) Michelet, V.; Toullec, P. Y.; Genêt, J. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (l) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.

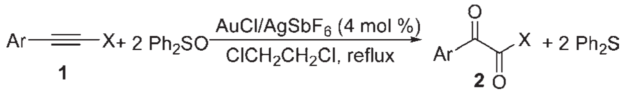
(9) For intramolecular reaction, see: (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (c) Li, G.; Zhang, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5156. (d) Yeom, H.-S.; Lee, J.-E.; Shin, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7040. (e) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394. (f) Davies, P. W.; Albrecht, S. J.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 8372. (g) Cui, L.; Zhang, G.; Peng, Y.; Zhang, L. *Org. Lett.* **2009**, *11*, 1225. (h) 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. For intermolecular reaction, see: (i) Cuenca, A. B.; Montserrat, S.; Hossain, K. M.; Mancha, G.; Lledos, A.; Medio-Simon, M.; Ujaque, G.; Asensio, G. *Org. Lett.* **2009**, *11*, 4906. (j) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (k) Ye, L.; He, W.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 8550. (l) Lu, B.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 14070. (m) Li, C.-W.; Pati, K.; Lin, G.-Y.; Sohel, S. M. A.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891. For other recent reports on synthesis of α-keto carbenoids from alkynes, see: (n) Couty, S.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2819. (o) Al-Rashid, Z. F.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 661.

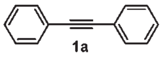
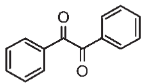
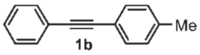
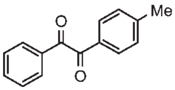
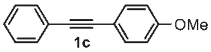
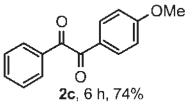
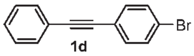
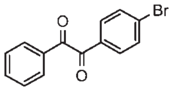
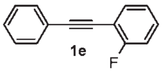
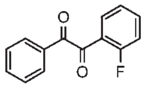
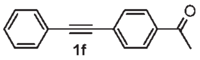
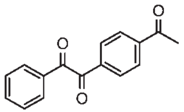
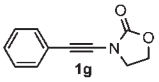
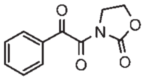
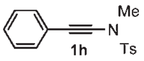
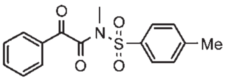
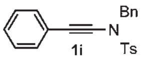
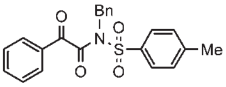
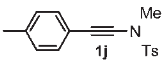
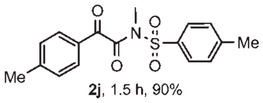
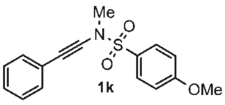
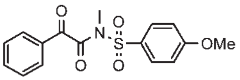
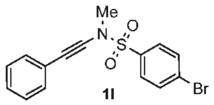
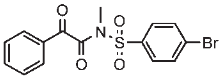
(10) 1,2-Diketones have been observed as byproducts in the reports by the Zhang and Liu groups; for references, see ref 9l and 9m.

(11) A 24% yield was observed when the reaction was performed in toluene. No benzil was obtained when the reaction was conducted in THF or CH_3CN.

necessary for the high yield (entries 17 and 18). It is noteworthy that the reaction can be conducted in air with solvent of technical grade (entry 20).

Table 2. Oxidation of Various 1,2-Diarylalkynes or Ynamides to 1,2-Dicarbonyl Compounds[a]

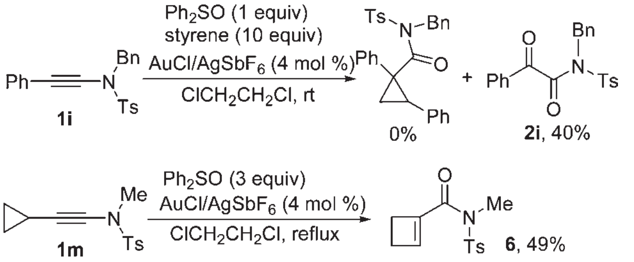


entry	substrate	product[b]
1	 **1a**	 **2a**, 12 h, 95%
2	 **1b**	 **2b**, 3 h, 98%
3	 **1c**	 **2c**, 6 h, 74%
4	 **1d**	 **2d**, 8 h, 93%
5	 **1e**	 **2e**, 8 h, 75%
6	 **1f**	 **2f**, 6 h, 80%
7	 **1g**	 **2g**, 8.5 h, 94%
8	 **1h**	 **2h**, 2 h, 96%
9	 **1i**	 **2i**, 5 h, 90%
10	 **1j**	 **2j**, 1.5 h, 90%
11	 **1k**	 **2k**, 1.5 h, 80%
12	 **1l**	 **2l**, 1.5 h, 97%

[a] The reaction was conducted in the air with solvent of technical grade. 0.2 mmol substrate and 0.6 mmol diphenylsulfoxide in 2.0 mL of $ClCH_2CH_2Cl$. [b] Isolated yield.

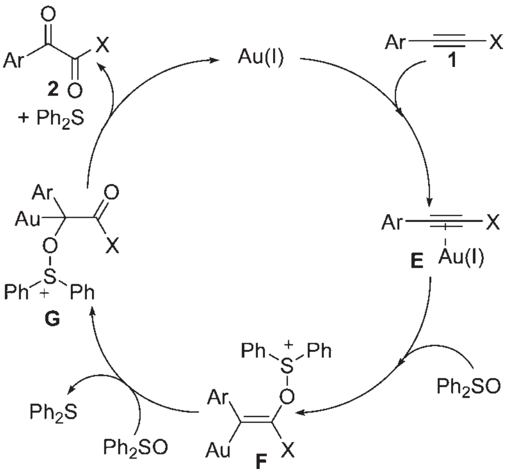
With the optimal conditions in hand, the substrate scope was then examined. As shown in Table 2, high yield can be observed when oxidizing the diarylalkynes and ynamides to 1,2-diaryldiketones and α-keto imides respectively. Functional groups such as methyl ether, bromide, fluoride, and ketone are well tolerated. 1,2-Dicarbonyl compounds bearing a bromide on the phenyl ring were obtained in more than 90% yield (entries 4 and 12), which can be further functionalized by a cross coupling reaction. The reaction proceeded smoothly when the aryl group was substituted with a methoxy group, but a slightly low yield compared to other substrates was achieved (entries 3 and 11).

Scheme 2. Preliminary Study on Mechanism



To clarify the reaction mechanism, 10 equiv of styrene were used to trap the hypothetic gold carbenoid (Scheme 2). Only 40% of the 1,2-dicarbonyl compound **2i** could be obtained without any cyclopropane product, which may suggest that no free gold carbenoid was formed. In the gold-catalyzed redox reactions, Toste[9b] and Zhang[9c] have previously proposed a gold carbenoid intermediate in the intramolecular reactions. However, in the crossover experiments performed by Ujaque, Asensio,[9i] and Liu group,[9m] no products which incorporate the external sulfides were detected, thus excluding the formation of an α-carbonyl gold-carbenoid. We synthesized the substrate **1m** and subjected it to the optimal reaction conditions, and

Scheme 3. Proposed Catalytic Cycle



cyclobutene derivative **6**, the same product that resulted for the Liu group,[9m] was obtained in 49% yield (Scheme 2), which means our oxidation procedure should have a similar mechanism as that reported by Liu. Furthermore, O_2 should not be the oxidizing species since similar results were achieved when the reaction proceeded either in the air or in the N_2 atmosphere (Table 1, entry 8 vs 20).

Based on the above facts, we envision that coordination of the cationic Au(I) to the alkyne facilitates the attack of sulfoxide, which results in the formation of vinyl gold species **F** (Scheme 3). The nucleophilic addition of another molecule of sulfoxide to **F**[12] followed by the loss of diphenyl sulfide would afford intermediate **G**. Subsequently, Au(I)-assisted sulfide release produces the 1,2-dicarbonyl compound **2** and regenerates the catalyst.

In summary, we have developed an efficient process for oxidizing alkynes to the 1,2-dicarbonyl compounds based on the gold-catalyzed redox reaction. Various 1,2-diaryldiketones or α-keto imides bearing sensitive functional groups can be obtained in high to excellent yields under mild reaction conditions. Furthermore, due to easy access to a variety of substrates by Sonogashira coupling[13] or copper mediated amidation of bromoalkynes or terminal acetylenes,[14] this work provides a very straightforward method to achieve useful 1,2-dicarbonyl functionality from simple materials. Further investigation on details of the mechanism is ongoing in our laboratory.

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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.

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(12) For a related report on nucleophilic attack on vinyl gold species, see 9m.

(13) (a) Takahashi, S.; Kuroyama, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1980**, *8*, 627. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834. (c) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

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