

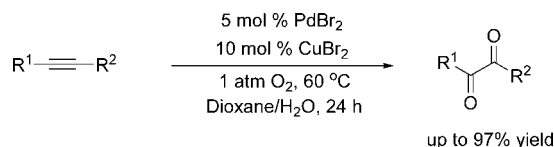
Wacker-Type Oxidation of Alkynes into
1,2-Diketones Using Molecular OxygenWei Ren,[†] Yuanzhi Xia,[†] Shun-Jun Ji,[†] Yong Zhang,[‡] Xiaobing Wan,^{*,†} and
Jing Zhao[§]

Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry,
Chemical Engineering and Materials Science, Soochow University,
Suzhou 215123, P. R. China, Testing and Analysis Center of Soochow University,
Suzhou 215123, P. R. China, and State Key Laboratory of Pharmaceutical
Biotechnology, School of Life Sciences, Nanjing University,
Nanjing 210093, P. R. China

wanxb@suda.edu.cn

Received February 16, 2009

ABSTRACT



An intriguing new Wacker-type oxidation of alkynes catalyzed by PdBr₂ and CuBr₂ is described, which opens an efficient access to 1,2-diketones using molecular oxygen. Under the optimized conditions, a variety of alkynes, including diarylalkynes, arylalkylalkynes, and dialkylalkynes, were compatible substrates in this transformation. The mechanism of this reaction was preliminarily investigated by control experiments.

Pd-catalyzed Wacker oxidation of alkenes consists of one of the most important industrial processes employing transition metal catalysts.¹ Owing to its high selectivity and excellent functional group tolerance, this transformation has found widespread application in synthetic chemistry.² Recent research in this field mainly focused on asymmetric versions,³ the use of molecular oxygen as the sole oxidant,⁴ and/or nucleophiles other than oxygen-based groups,^{5,6} which have led to remarkable progress in this field.

Compared with the impressive development of alkenes, Wacker-type oxidation of alkyne has not been explored thus far.⁷ We speculate this dichotomy in progress between alkenes and alkynes may be attributable to the differences in the assumed catalytic cycles. It seems to us that β -hydride elimination, the key step for Wacker oxidation of alkenes, might be difficult for similar reactions of alkynes. Thus,

[†] Soochow University.[‡] Testing and Analysis Center of Soochow University.[§] Nanjing University.

(1) For recent reviews, see: (a) Tsuji, J. *Pure Appl. Chem.* **1999**, *71*, 1539–1547. (b) Takacs, J. M.; Jiang, X. *Curr. Org. Chem.* **2003**, *7*, 369–396. (c) Cornell, C. N.; Sigman, M. S. *Inorg. Chem.* **2007**, *46*, 1903–1909. (d) Kotov, V.; Scarborough, C. C.; Stahl, S. S. *Inorg. Chem.* **2007**, *46*, 1910–1923.

(2) For representative examples, see: (a) Bäckvall, J.-E.; Åkermark, B.; Ljunggren, S. O. *J. Chem. Soc., Chem. Commun.* **1977**, 264–265. (b) Zaw, K.; Henry, P. M. *J. Org. Chem.* **1990**, *55*, 1842–1847. (c) Nelson, D. J.; Li, R.; Brammer, C. *J. Am. Chem. Soc.* **2001**, *123*, 1564–1568. (d) Keith, J. A.; Oxgaard, J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2006**, *128*, 3132–3233. (e) Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2007**, *129*, 12342–12343. (f) Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796–2797. (g) Hayashi, T.; Yamasaki, K.; Mimura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3036–3037.

(3) For representative examples, see: (a) Hosokawa, T.; Uno, T.; Inui, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1981**, *103*, 2318–2323. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063–5064. (c) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071–5075. (d) Uozumi, Y.; Kyota, H.; Kato, K.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **1999**, *64*, 1620–1625. (e) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907–2908. (f) Trend, R. M.; Ramtohl, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892–2895. (g) Trend, R. M.; Ramtohl, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788. (h) Wang, F.; Zhang, Y.; Yang, G.; Zhang, W. *Tetrahedron Lett.* **2007**, *48*, 4179–4182.

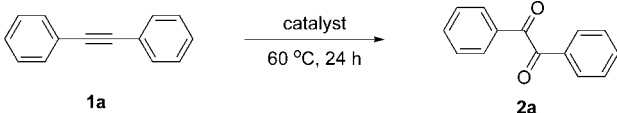
(4) (a) ten Brink, G.-J.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. *Chem. Commun.* **1998**, 2359–2360. (b) ten Brink, G.-J.; Arends, I. W. C. E.; Papadogianakis, G.; Sheldon, R. A. *Appl. Catal., A* **2000**, *194–195*, 435–442. (c) Muñoz, K. *Adv. Synth. Catal.* **2004**, *346*, 1425–1428. (d) Mitsudome, T.; Umetani, T.; Nosaka, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 481–485. (e) Cornell, C. N.; Sigman, M. S. *Org. Lett.* **2006**, *8*, 4117–4120. (f) Ref 3f. (g) Ref 3g.

development of a Wacker-type procedure for alkyne oxidation would not only expand the scope of the Wacker reaction but also pose an interesting mechanistic question. Furthermore, the 1,2-diketones, oxidation products of alkynes, are very important structural moieties in numerous biologically interesting compounds⁸ and are broadly utilized for construction of complex structures in organic synthesis.⁹ Although several methods have been reported for the oxidation of alkynes,¹⁰ these reactions are still suffering from drawbacks such as harsh conditions, narrow substrate scope, low yield, and/or chemoselectivity. Thus, developing a new and efficient protocol for clean catalytic oxidation of alkynes is still highly desirable. In this communication, we report the Wacker-type oxidation of alkynes, which affords 1,2-diketones using molecular oxygen as the stoichiometric oxidant under mild conditions.

We launched our efforts to develop the Wacker-type oxidation of alkynes under typical conditions employed for alkenes. Reaction of 1,2-diphenylethyne in DMF/H₂O in the presence of a catalytic amount of PdCl₂ and CuCl₂ afforded benzyl **2a** in 21% yield (Table 1, entry 1). Despite the modest yield obtained, the initial test result was quite encouraging since it attested the feasibility of Wacker-type oxidation of alkynes. An extensive screening of the reaction parameters indicated that the catalysts, cocatalysts, oxidants, and solvents all play critical roles on the reaction efficiency. The best result was obtained by treating 1,2-diphenylethyne with 5 mol % of PdBr₂ and 10 mol % of CuBr₂ in dioxane/H₂O under 1 atm of oxygen atmosphere, with a yield of 97% for **2a**. It should be noted that using air in place of oxygen could also give good yield of the product (Table 1, entry 16). Next, the practical utility of this oxidation process was evaluated, and up to 91% yield could be achieved on a scale of 60 mmol **1a** (Table 1, entry 22). Another feature of the reaction was that the use of molecular oxygen as the oxidant was essential for high conversion, as demonstrated by the fact that the yields decreased when other oxidants were employed (Table 1, entries 17–21).

With the optimized reaction conditions in hand, we began to examine the scope of this new Wacker-type oxidation of alkynes. As shown in Table 2, this transformation was highly efficient for a broad scope of substrates, wherein various

Table 1. Optimization of Reaction Conditions^a

					
entry	Pd(OAc) ₂	cocatalyst	oxidant	solvent	yield ^b
1	PdCl ₂	CuCl ₂	O ₂	DMF/H ₂ O	21%
2	Pd(OAc) ₂	Cu(OAc) ₂	O ₂	DMF/H ₂ O	0%
3	PdBr ₂	CuBr ₂	O ₂	DMF/H ₂ O	72%
4	PdBr₂	CuBr₂	O₂	Dioxane/H₂O	97%
5	—	CuBr ₂	O ₂	Dioxane/H ₂ O	0%
6	PdBr ₂	—	—	Dioxane/H ₂ O	0% ^c
7	PdBr ₂	CuBr ₂	—	Dioxane/H ₂ O	8%
8	PdBr ₂	CuBr ₂	O ₂	THF/H ₂ O	48%
9	PdBr ₂	CuBr ₂	O ₂	DMF/H ₂ O	72%
10	PdBr ₂	CuBr ₂	O ₂	DME/H ₂ O	52%
11	PdBr ₂	CuBr ₂	O ₂	EA/H ₂ O	15%
12	PdBr ₂	CuBr ₂	O ₂	ⁱ PrOH/H ₂ O	15%
13	PdBr ₂	CuBr ₂	O ₂	MeCN/H ₂ O	28%
14	PdBr ₂	CuBr ₂	O ₂	CH ₃ NO ₂ /H ₂ O	0%
15	PdBr ₂	CuBr ₂	O ₂	Acetone/H ₂ O	18%
16	PdBr ₂	CuBr ₂	air	Dioxane/H ₂ O	76%
17	PdBr ₂	CuBr ₂	benzoquinone	Dioxane/H ₂ O	89%
18	PdBr ₂	CuBr ₂	PhI(OAc) ₂	Dioxane/H ₂ O	30%
19	PdBr ₂	CuBr ₂	H ₂ O ₂	Dioxane/H ₂ O	12%
20 ^d	PdBr ₂	CuBr ₂	TBHP	Dioxane/H ₂ O	18%
21	PdBr ₂	CuBr ₂	DMSO	Dioxane/H ₂ O	14%
22 ^e	PdBr ₂	CuBr ₂	O ₂	Dioxane/H ₂ O	91%

^a 0.2 mmol **1a**, 5 mol % catalyst, 10 mol % cocatalyst. ^b Isolated yield.

^c Deoxybenzoin **3** was achieved in 30% yield. ^d TBHP: *tert*-butyl hydroperoxide. ^e 60 mmol **1a** was used.

functional groups, including halide, ketone, aldehyde, nitro, benzylic C–H bond, trifluoromethyl, ester, etc., could be tolerated. Apart from the diarylalkynes, alkynes bearing one or two aliphatic substituents were also suitable substrates under standard oxidation conditions, affording the corresponding diketone products in moderate to good yields (Table 2, entries 9–12). Although alkyne with a fused aromatic ring showed lower reactivity under the optimal conditions, product **2g** was isolated in high yield at elevated temperature (Table 2, entry 6).

It is remarkable that the aryl bromide was a compatible substrate in this transformation given its important synthetic application, as C–Br of the product could be further functionalized (Table 2, entry 2). It was also mechanistically interesting, as it is well-known that the C–Br bond is quite sensitive under a Pd(0)/(II) catalytic cycle. Furthermore, when alcohol and aldehyde, usually reactive under tradi-

(5) (a) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800–5807. (b) Hosokawa, T.; Takano, M.; Kuroki, Y.; Murahashi, S.-I. *Tetrahedron Lett.* **1992**, *33*, 6643–6646. (c) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584–3585. (d) Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974–980. (e) Bar, G. L. J.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2005**, *127*, 7308–7309. (f) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131. (g) Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett.* **2008**, *10*, 173–175.

(6) (a) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164–166. (b) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996–12997. (c) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868–2869. (d) Timokhin, V. I.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 17888–17893. (e) Rogers, M. M.; Kotov, V.; Chatwichten, J.; Stahl, S. S. *Org. Lett.* **2007**, *9*, 4331–4334. (f) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328–6335.

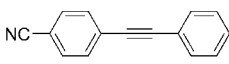
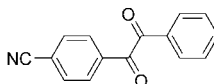
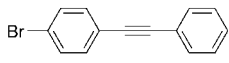
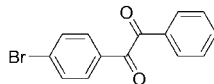
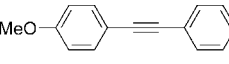
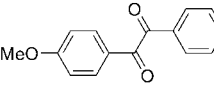
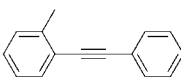
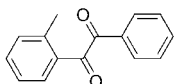
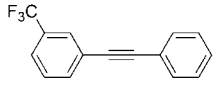
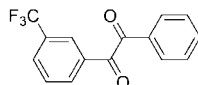
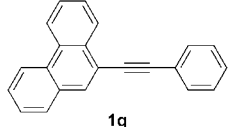
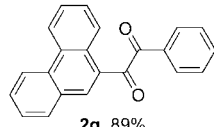
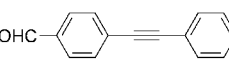
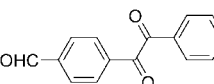
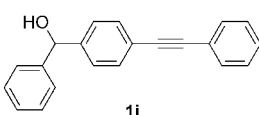
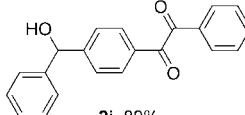
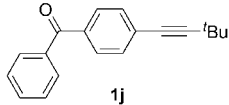
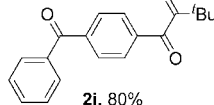
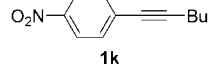
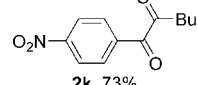
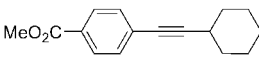
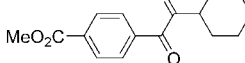
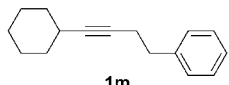
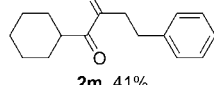
(7) For Pd-catalyzed cleavage reaction of alkynes, see: Wang, A.; Jiang, H. *J. Am. Chem. Soc.* **2008**, *130*, 5030–5031.

(8) Maurya, R.; Singh, R.; Deepak, M.; Handa, S. S.; Yadav, P. P.; Mishra, P. K. *Phytochemistry* **2004**, *65*, 915–920.

(9) Deng, X.; Mami, N. *Org. Lett.* **2006**, *8*, 269–272.

(10) For representative alkyne oxidation methods, see: (a) Zhu, Z.; Espenson, J. H. *J. Org. Chem.* **1995**, *60*, 7728–7732. (b) Dayan, S.; Ben-David, I.; Rozen, S. *J. Org. Chem.* **2000**, *65*, 8816–8818. (c) Murray, R. W.; Singh, M. *J. Org. Chem.* **1993**, *58*, 5076–5080. (d) Wolfe, S.; Ingold, C. F. *J. Am. Chem. Soc.* **1983**, *105*, 7755–7757. (e) Wan, Z.; Jones, C. D.; Mitchell, D.; Pu, J. Y.; Zhang, T. Y. *J. Org. Chem.* **2006**, *71*, 826–828. (f) Yusubov, M. S.; Zholobova, G. A.; Vasilevsky, S. F.; Tretyakov, E. V.; Knight, D. W. *Tetrahedron* **2002**, *58*, 1607–1610. (g) Giraud, A.; Provot, O.; Peyrat, J.-F.; Alami, M.; Brion, J.-D. *Tetrahedron* **2006**, *62*, 7667–7673. (h) Mousset, C.; Provot, O.; Hamze, A.; Bignon, J.; Brion, J.-D.; Alami, M. *Tetrahedron* **2008**, *64*, 4287–4294. (i) Yusubov, M. S.; Filimonov, V. D. *Synthesis* **1991**, 131–132. (j) Yusubov, M. S.; Krasnokutskaya, E. A.; Vasilyeva, V. P.; Filimonov, V. D.; Chi, K. W. *Bull. Korean Chem. Soc.* **1995**, *16*, 86–88. (k) Chi, K.-W.; Yusubov, M. S.; Filimonov, V. D. *Synth. Commun.* **1994**, *24*, 2119–2122. (l) Che, C.-M.; Yu, W.-Y.; Chan, P.-M.; Cheng, W.-C.; Peng, S.-M.; Lau, K.-C.; Li, W.-K. *J. Am. Chem. Soc.* **2000**, *122*, 11380–11392.

Table 2. Wacker-Type Oxidation of Alkynes

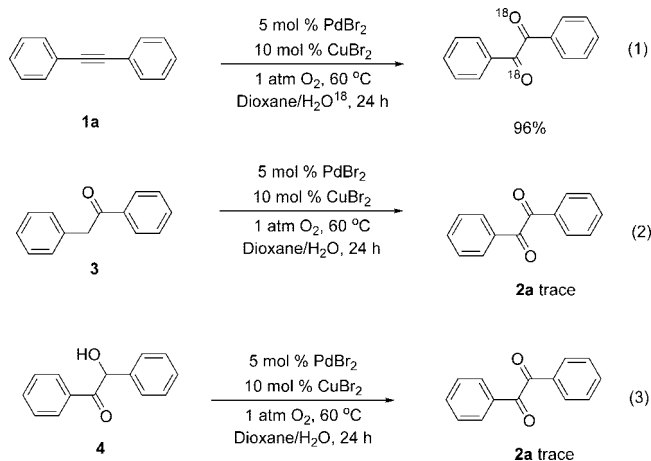
$\text{R}^1\text{—}\text{C}\equiv\text{C—R}^2 \xrightarrow[\text{Dioxane/H}_2\text{O, 24 h}]{\substack{5 \text{ mol } \% \text{ PdBr}_2 \\ 10 \text{ mol } \% \text{ CuBr}_2 \\ 1 \text{ atm O}_2, 60^\circ\text{C}}} \text{R}^1\text{—C(=O)—C(=O)—R}^2$		
entry	substrate	product/yield ^a
1		 2b , 89%
2		 2c , 97%
3		 2d , 90%
4		 2e , 77%
5		 2f , 93%
6 ^b		 2g , 89%
7		 2h , 90%
8		 2i , 89%
9 ^b		 2j , 80%
10		 2k , 73%
11		 2l , 67%
12		 2m , 41%

^a Isolated yield. ^b 80 °C for 24 h.

tional¹⁰ or Pd-catalyzed oxidation conditions,¹¹ were subjected to the Wacker-type oxidation conditions, only the triple bond oxidation products were isolated (Table 2, entries 7 and 8).

The current Wacker oxidation methodology shows several advantages compared with previously reported alkyne oxidation procedures,¹⁰ including: (1) the reaction is free of strong oxidant, (2) it works under mild and neutral reaction conditions, and (3) it affords clean conversion in high efficiency. Accordingly, this PdBr₂/CuBr₂ combination in dioxane/H₂O extends the Wacker oxidation to triple bonds and opens an efficient access to 1,2-diketones, which is an attractive alternative to traditional alkyne oxidation methods.

While the results in Table 2 show the potential applications of the transformation, understanding of the detailed reaction mechanism would be useful for further expansion. Experiments were carried out for mechanistic exploration, and the results revealed the following facts: (1) isotopic labeling experiments using H₂O¹⁸ revealed that both oxygen atoms of the 1,2-diketone product originated from water instead of molecular oxygen (Scheme 1, eq 1); (2) deoxybenzoin **3**

Scheme 1. Preliminary Study on Mechanism

and benzoin **4** seemed not to serve as intermediates in the reaction, as none of them were observed in the catalytic system and only a trace amount of product could be detected when these species were introduced to the optimal reaction conditions (Scheme 1, eq 2 and 3); (3) the presence of CuBr₂ is crucial for the formation of the 1,2-diketone product, while only about 30% yield of deoxybenzoin **3** was obtained in the absence of this cocatalyst (Table 1, entry 6); (4) addition of a radical trap, 2,2,6,6-tetramethyl-1-piperidinyloxy, to the reaction medium hardly influenced this oxidation, suggesting that the oxidation was not a radical process. Considering the controversy surrounding the Wacker process of alkenes,¹ further investigations on detailed mechanisms are underway in our laboratory.

In summary, a new Wacker-type reaction of alkynes under aerobic conditions has been developed. This transformation

(11) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420.

showed high efficiency and good functional group tolerance. Further investigations on mechanistic understanding, substrate scope expanding, and the use of molecular oxygen as the sole oxidant are ongoing.

Acknowledgment. This research was supported by the National Natural Science Foundation of China (2080-

2047) and the Bureau of Education, Jiangsu Province (08KJD150005).

Supporting Information Available: Experimental details and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL900344G