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tolerate well with mild conditions.

# Electrochemical synthesis of 1,2-diketones from alkynes under transition-metal-catalyst-free conditions<sup>†</sup>

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We report an electrochemical protocol for the direct oxidation of internal alkynes with air to provide 1,2-diketones. A variety of functional groups as well as heterocycle-containing substrates can

1,2-Diketones are important structural motifs prevalent in a variety of bioactive molecules<sup>1</sup> and natural products, as well as versatile intermediates for many valuable transformations. Classical stoichiometric oxidation of internal alkynes usually require the use of strong oxidants such as KMnO<sub>4</sub>,<sup>2</sup> OsO<sub>4</sub>,<sup>3</sup> H<sub>3</sub>PO<sub>5</sub>,<sup>4</sup> dioxiranes,<sup>5</sup> organic peracids.<sup>6</sup> In the past decades, the direct catalytic oxidation of internal alkynes using oxygen as the mild oxidant has emerged as an efficient method for the rapid synthesis of such diketones. Among them, transition-metalcatalyzed (e.g., Pd,<sup>7</sup> Cu,<sup>8</sup> Au,<sup>9</sup> Ru<sup>10</sup>) methods offer an important alternative route to the production of 1,2-diketones (Scheme 1A). However, the above protocols uniformly suffer from relatively harsh reaction conditions and limited functional group tolerance. To overcome these limitations, recent attention has been paid to the photocatalytic methods (Scheme 1B).<sup>11</sup> For instance, Wang and Li reported a thiyl radical catalyzed oxidation of diarylalkynes under visible-light irradiation.<sup>11a</sup> Separately, Sun et al. demonstrated an aerobic photooxidation of alkynes using eosin Y catalysis.<sup>11b</sup> In 2017, Liu and co-workers also reported aerobic oxidation of alkynes to 1,2-diketones enabled by organic photoredox catalysis.<sup>11c</sup> However, despite these significant achievements, the development of practical and broadly applicable synthetic methods for 1,2-diketones under green and sustainable conditions is still highly desirable.<sup>12</sup>



Scheme 1 Approaches to 1,2-diketones via oxidation of internal alkynes.

Electrochemistry has been established as a powerful and environmentally friendly tool for the radical-based organic transformations at mild reaction conditions.13 In this context, we reasoned that the electrochemical protocol would expand the capacity of internal alkynes-oxidation-based strategies to the synthesis of 1,2-diketones under transition-metal-catalystfree conditions (Scheme 1C). Moreover, the present electrochemical synthesis is a complementary and alternative method to the previous transition-metal-catalyzed and photocatalysis approaches. Remarkably. heterocyclecontaining substrates can tolerate well with mild electrochemical conditions.

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Our studies commenced with the electrochemical transformation of 1,2-diphenylethyne (1) with graphite and platinum as anode and cathode, respectively. The optimized conditions were shown in Table 1.14,15 The 1,2-diketone product 2 was obtained in 87% isolated yield with 20 mA constant current, 1.0 equiv NaBF<sub>4</sub> in a mixture of DMF and H<sub>2</sub>O at room temperature (r.t.) for 8 h under air atmosphere (Table 1, entry 1). When other supporting electrolytes such as nBu<sub>4</sub>NPF<sub>6</sub> and LiClO<sub>4</sub> were used, similar yields can be obtained (Table 1, entries 2 and 3). The yield was significantly reduced with the use of MeOH, MeCN and DMSO as the solvents (Table 1, entries 4-6). The yield was reduced to 23% in the absence of HCOOH (Table 1, entry 7), and 24% and 62% yields was observed when HCOOH was replaced with HOAC and CF<sub>3</sub>COOH, respectively (Table 1, entries 8 and 9). Interestingly, the reaction proceeded less effectively under O2 atmosphere (Table 1, entry 10). This result can be ascribed to the further oxidation of the 1,2-diketone. Indeed, a certain amount of benzoic acid can be detected by GC-MS analysis. It was found that the reaction was shut down under  $N_2$  atmosphere (Table 1, entry 11). Other constant current (i.e., 10 mA and 30 mA) can also cause the reaction, but the yields were significantly diminished (Table 1, entries 12 and 13). The nature of the electrode materials exerted great effect on the reaction.<sup>16</sup> Using RVC and platinum as the anode, the

Table 1	Optimization of the reaction conditions <sup>a</sup>	
1 "standard conditions"		
Entry	Variation from the standard conditions	Yield (%) <sup>b</sup>
1	None	87
2	<sup>n</sup> Bu <sub>4</sub> NPF <sub>6</sub> instead of NaBF <sub>4</sub>	83
3	LiClO <sub>4</sub> instead of NaBF <sub>4</sub>	70
4	MeOH instead of DMF	16
5	MeCN instead of DMF	50
6	DMSO instead of DMF	43
7	Without HCOOH	23
8	HOAc instead of HCOOH	24
9	CF <sub>3</sub> COOH instead of HCOOH	62
10	O <sub>2</sub> atmosphere	77
11	N <sub>2</sub> atmosphere	trace
12	10 mA instead of 20 mA, 16 h	61
13	30 mA instead of 20 mA, 5 h	40
14	RVC instead of graphite as anode	60
15	platinum instead of graphite as anode	10
16	graphite instead of platinum as cathode	80
17	No electric current	0

<sup>o</sup>Standard conditions: graphite plate anode: (10 mm × 15 mm), **1** (0.3 mmol), NaBF<sub>4</sub> (1.0 mmol), DMF (9.0 mL), H<sub>2</sub>O (1.0 mL), platinum plate cathode: (10 mm × 10 mm), NaBF<sub>4</sub> (1.0 mmol), H<sub>2</sub>O (9.0 mL), HCOOH (1.0 mL) in H-type divided cell with an anion exchange membrane, constant current = 20.0 mA ( $j_{anode}$  = 13.3 mA cm<sup>-2</sup>), r.t., 8 h (20.0 F mol<sup>-1</sup>). <sup>b</sup>Isolated yield.



**Scheme 2** Substrate scope. The values in the parentheses were the coulombic efficiency.  ${}^{o}I = 10.0 \text{ mA}$ , the reaction time was 5 h (6.0 F mol<sup>-1</sup>).  ${}^{o}I = 30.0 \text{ mA}$ , the reaction time was 10 h (37.0 F mol<sup>-1</sup>).  ${}^{c}I = 10.0 \text{ mA}$ , CH<sub>3</sub>CN instead of DMF, LiClO<sub>4</sub> instead of NaBF<sub>4</sub>, the reaction time was 4 h (5.0 F mol<sup>-1</sup>).

yields decreased to 60% and 10%, respectively (Table 1, entries 14 and 15). However, 80% yield was obtained when platinum

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was replaced by graphite as the cathode (Table 1, entry 16). Finally, a control experiment demonstrated that electric current is necessary for reactivity (Table 1, entry 17). the cathodic reaction,  $H_2$  (65 mL, 2.9 mmol) could be obtained after 8 h.

With the optimized conditions in hand we began to evaluate the scope of the electrochemical oxidation of a variety of alkynes and the results were outlined in Scheme 2. It was found that various alkyne substrates, bearing either electron-donating or electron-withdrawing groups, could be smoothly converted into the corresponding 1,2-diketones in moderate to good yields (42-89%) under very mild conditions (Scheme 2A). Fluoro (3, 19, 24, 25), chlorine (4, 17) and bromine (5) groups were well compatible with the reaction, thus providing opportunities for further conversions with cross-coupling reactions. Additionally, the use of methyl-substituted (6, 16, 21, 23) or tert-butylsubstituted (7) alkynes gave the desired product in good yields. Furthermore, alkyne derivatives possessing cyano (8), methoxy (9, 20, 23), phenyl (10), ketone (11), trifluoromethyl (12, 23), trifluoromethoxy (13), nitro (14), ester (15, 20) and naphthyl (18) are well tolerated. It was further demonstrated that olefin group (26) can also survive well under current reaction conditions. Notably, the present reaction could be scaled up to 20 mmol (3.56 g), and the desired product 2 was smoothly furnished in 85% yield (3.57 g). Finally, the alkyl arylacetylenes substrates, which were not effectively transformed under previous photocatalytic conditions,<sup>11</sup> were also examined to evaluate compatibility of the present electrochemical protocol, and the corresponding 1,2-diketones (27-29) were successfully obtained in moderate yields.

The next investigation of the substrate scope was focused on heterocycle-containing substrates (Scheme 2B). It was demonstrated that triazole (**30**, **35**), pyridine (**31**, **36**) and thiophene (**32-36**) derivatives gave the desired products in 38-53% yields. In addition, the procaine and tyrosine-containing alkyne derivatives are successfully transformed to the corresponding 1,2-diketones (**37**, **38**), thus highlighting the



Scheme 3 Chemoselectivity in the presence of multiple triple bonds.



**Fig. 1** A) Competitive reaction between electron-rich alkyne (**46**) and electrondeficient alkyne (**47**). B) Cyclic voltammograms studies: a) solutions of **46** (red line), b) solutions of **47** (blue line) and c) the blank (black line); The cyclic voltammograms were recorded at a scan rate of 100 mV s<sup>-1</sup> at rt with two platinum electrodes.

applicability of this method for the late-stage modification of complex molecules (Scheme 2C).

This reaction displays an interesting chemselectivity profile. As shown in Scheme 3A, two triple bonds-containing internal alkynes **39** can easily be converted to the corresponding 1,2diketone **40** under the standard reaction conditions. Interestingly, **41** can be smoothly converted to 1,2-diketone **42** without the terminal alkyne group be oxidized (Scheme 3B). Moreover, when 1,4-diphenylbuta-1,3-diyne (**43**) was subject into the reaction a 1,4-diketone (**45**) was obtained as a major product with a new triple bond formation (Scheme 3C).

We next conducted a competitive reaction between electronrich methoxy-derived alkyne (**46**) and electron-deficient trifluoromethyl-derived alkyne (**47**) under standard conditions. In this case, the major product was **9** (51% yield), arising from reaction of the more electron-rich alkyne (Figure 1A). This result was matched with the cyclic voltammetric (CV) studies. As shown in Figure 1B, the oxidation potentials of **46** (electron-rich) and **47** (electron-deficient) are 1.44 and 2.00 V vs. SCE, respectively.

To understand the mechanism of the electrochemical reaction, we conducted free-radical trapping experiments. The formation of 1,2-diketone **2** was completely halted by using radical scavengers such as TEMPO (tetramethylpiperidinoxyl), BHT (2,6-di-*tert*-butyl-4-methylphenol) as well as PBN (*N*-*tert*-butyl- $\alpha$ -phenylnitrone). Unfortunately, no radical-adduct could be isolated at the current stage. These observations indicated that the reaction should proceed with the intermediacy of radical species.

To summarize, we have developed a green and efficient electrochemical method for the conversion of internal alkynes

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to 1,2-diketones under catalyst free conditions. This reaction features mild reaction conditions, inexpensive reagents and broad substrate scopes. A wide range of aryl alkynes as well as hetero-containing alkynes are well tolerated, and the corresponding 1,2-diketones can be achieved in moderate to good yields. More studies on expanding the utility of electrochemically-based radical reactions are ongoing in our laboratory.

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#### **Conflicts of interest**

There are no conflicts to declare.

#### Notes and references

- (a) Q. Liu, S. Perreault and T. Rovis, J. Am. Chem. Soc., 2008, 130, 14066; (b) M. M. Sheha, N. M. Mahfouz, H. Y. Hassan, A. F. Youssef, T. Mimoto and Y. Kiso, Eur. J. Med. Chem. 2000, 35, 887; (c) D. H. Slee, K. L. Laslo, J. H. Elder and L. R. Ollmann, A. Gustchina, J. Kervinen, A. Zdanov, A. Wlodawer and C. H. Wong, J. Am. Chem. Soc., 1995, 117, 11867; (d) T. Cupido, J. Tulla-Puche and J. Spengler, Curr. Opin. Drug. Discov. Devel., 2007, 10, 768; (e) W. Mahabusarakam, S. Deachathai, S. Phongpaichit, C. Jansakul and W. C. Taylor, Phytochemistry, 2004, 65, 1185.
- 2 (a) D. G. Lee and V. S. Chang, J. Org. Chem., 1979, 44, 2726; (b)
   D. G. Lee, V. S. Chang and W. D. Chandler, J. Org. Chem., 1985, 50, 4306.
- 3 M. Schroder and W. P. Grifith, J. Chem. Soc. Dalton Trans., 1978, 11 1599.
- 4 Y. Ogata, Y. Sawaki and T. Ohno, J. Am. Chem. Soc., 1982, 104, 216.
- 5 (a) R. Curci, M. Fiorentino, C. Fusco, R. Mello, F. P. Ballistreri, S. Failla and G. A. Tomaselli, *Tetrahedron Lett.*, 1992, 33, 7929;
  (b) R. W. Murray and M. Singh, *J. Org. Chem.*, 1993, 58, 5076.
- For selected exemples, see: (a) R. N. McDonald and P.-A. Schwab, *J. Am. Chem. Soc.*, 1964, **86**, 4866; (b) J. K. Stille and D. D. Whitehurst, *J. Am. Chem. Soc.*, 1964, **86**, 4871; (c) J. Ciabattoni, R. A. Campbell, C. A. Renner and P. W. Concannon, *J. Am. Chem. Soc.*, 1970, **92**, 3826.
- For selected examples, see: (a) J.-W. Xue, M. Zeng, X. Hou, Z. Chen and G. Yin, *Asian J. Org. Chem.*, 2018, **7**, 212; (b) S. Mori, M. Takubo, T. Yanase, T. Maegawa, Y. Monguchi and H. Sajiki, *Adv. Synth. Catal.*, 2010, **352**, 1630; (c) Y. Sawama, M. Takubo, S. Mori, Y. Monguchi and H. Sajiki, *Eur. J. Org. Chem.*, 2011, 3361; (d) S. Byun, J. Chung, T. Lim, J. Kwon and B. M. Kim, *RSC Adv.*, 2014, **4**, 34084.
- 8 (a) X.-F. Xia, Z. Gu, W. Liu, N. Wang, H. Wang, Y. Xia, H. Gao and X. Liu, *Org. Biomol. Chem.*, 2014, **12**, 9909; (b) W. Zhang, J. Zhang, Y. Liu and Z. Xu, *Synlett*, 2013, **24**, 2709.
- 9 C.-F. Xu, M. Xu, Y.-X. Jia and C.-Y. Li, *Org. Lett.*, 2011, **13**, 1556.
- (a) W. Ren, J. Liu, L. Chen and X. Wan, *Adv. Synth. Catal.*, 2010,
   **352**, 1424; (b) Y. Miao, A. Dupé, C. Bruneau and C. Fischmeister, *Eur. J. Org. Chem.*, 2014, 5071.
- (a) X. Zhu, P. Li, Q. Shi and L. Wang, *Green Chem.*, 2016, 18, 6373; (b) X. Liu, T. Cong, P. Liu and P. Sun, *J. Org. Chem.*, 2016, 81, 7256; (c) H. T. Qin, X. Xu and F. Liu, *ChemCatChem*, 2017, 9, 1409; (d) T. Hering, T. Slanina, A. Hancock, U. Wille and B. König, *Chem. Commun.*, 2015, 51, 6568; (e) V. Štrukil and I. Sajko, *Chem. Commun.*, 2017, 53, 9101.

- 12 For earlier examples, see: (a) K. J. Tan and U. Wille Chem. Commun., 2008, 6239; (b) U. Wille and I. And Sport Australian Chem. 2007, **60**, 420.
- 13 For selected recent examples, see: (a) Y. Kawamata, M. Yan, Z. Liu, D.-H. Bao, J. Chen, J. T. Starr and P. S. Baran, J. Am. Chem. Soc., 2017, 139, 7448; (b) E. J. Horn, B. R. Rosen, Y. Chen, J. Tang, K. Chen, M. D. Eastgate and P. S. Baran, Nature, 2016, 533, 77; (c) N. Fu, G. S. Sauer, A. Saha, A. Loo and S. Lin, Science, 2017, 357, 575; (d) Q.-L. Yang, Y.-Q. Li, C. Ma, P. Fang, X.-J. Zhang and T.-S. Mei, J. Am. Chem. Soc. 2017, 139, 3293; (e) S. Tang, L. Zeng and A. Lei, J. Am. Chem. Soc., 2018, 140, 13128; (f) R. Mei, N. Sauermann, J. C. A. Oliveira and L. Ackermann, J. Am. Chem. Soc., 2018, 140, 7913; (g) X.-L. Gao, P. Wang, L. Zeng, S. Tang and A. Lei, J. Am. Chem. Soc., 2018, 140, 4195; (h) F. Xu, Y.-L. Li, C. Huang and H.-C. Xu, ACS Catal., 2018, 8, 3820; (i) M.-J. Luo, M. Hu, R.-J. Song, D.-L. He and J.-H. Li, Chem. Commun., 2019, 55, 1124; (j) X.-Z. Tao, J.-J. Dai, J. Zhou, J. Xu and H.-J. Xu, Chem. Eur. J. 2018, 24, 6932. (k) L.-L. Zhang, G.-T. Zhang, P. Wang, Y.-L. Li and A. Lei, Org. Lett., 2018, 20, 7396; (I) C. Ma, P. Fang and T.-S. Mei, ACS Catal., 2018, 8, 7179.
- 14 A 40% yield of **2** can be obtained using an undivided cell.
- 15 The cathodic reaction was the formation of hydrogen (H<sub>2</sub>), which was identified by GC analysis, please see ESI for more details.
- 16 Preparative Electrolysis on the Laboratory Scale, Organic Electrochemistry, Fifth Edition, (Eds. J. Jçrissen, B. Speiser) CRC Press 2015, pp. 263–330.

4 | J. Name., 2012, 00, 1-3