Synthesis of 1,3-dioxo-substituted allenes via copper(I)-catalyzed coupling of α-oxo-alkynes and α-oxo-diazos by controlling the sequence of adding substrates

Chulong Liu, Yunxiang Weng, Xiaobao Zeng, Weiping Zheng, Xinyan Wang, Yuefei Hu

PII: S0040-4039(19)30026-7
DOI: https://doi.org/10.1016/j.tetlet.2019.01.015
Reference: TETL 50548

To appear in: *Tetrahedron Letters*

Received Date: 15 November 2018
Revised Date: 13 December 2018
Accepted Date: 8 January 2019

Please cite this article as: Liu, C., Weng, Y., Zeng, X., Zheng, W., Wang, X., Hu, Y., Synthesis of 1,3-dioxo-substituted allenes via copper(I)-catalyzed coupling of α-oxo-alkynes and α-oxo-diazos by controlling the sequence of adding substrates, *Tetrahedron Letters* (2019), doi: https://doi.org/10.1016/j.tetlet.2019.01.015

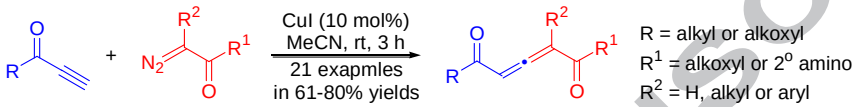
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Synthesis of 1,3-dioxo-substituted allenes via copper(I)-catalyzed coupling of α-oxo-alkynes and α-oxo-diazos by controlling the sequence of adding substrates

Leave this area blank for abstract info.

Chulong Liu,[a] Yunxiang Weng,[a] Xiaobao Zeng,[a] Weiping Zheng,[a] Xinyan Wang,[a]* Yuefei Hu[a]*



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of 1,3-dioxo-substituted allenes via copper(I)-catalyzed coupling of α-oxo-alkynes and α-oxo-diazos by controlling the sequence of adding substrates

Chulong Liu,[a] Yunxiang Weng,[a] Xiaobao Zeng,[a] Weiping Zheng,[a] Xinyan Wang,[a]* Yuefei Hu[a]*

[a] *Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
allenes
copper catalyst
cross-coupling
alkynes
diazo compounds

ABSTRACT

A novel direct synthesis of 1,3-dioxo-substituted allenes was developed by copper(I)-catalyzed coupling of α-oxo-alkynes and α-oxo-diazos. It was a sequence of adding substrates-controlled method and the desired products were synthesized chemoselectively by adding α-oxo-alkyne terminally.

Due to the unique scaffold of allene, numerous allenes showed biological activities and were widely used as building blocks in organic synthesis.[1] An allene substituted by electron-withdrawing-groups (EWGs) has at least two advantages: (a) the electrophilicity of the central carbon and the electron-deficiency of the double bonds can be enhanced significantly; (b) the functionalized products can be synthesized easily. As shown in Figure 1, 1-keto-3-allenecarboxylates **1** and 1,3-allenedicarboxylates **2** are two such typical allenes. Based on their electrophilic or nucleophilic additions and Diels-Alder reactions, many structurally novel natural products[2] and heterocycles[3] have been synthesized.

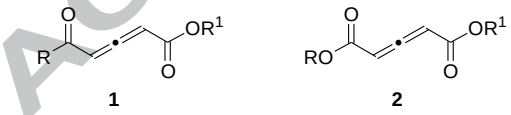
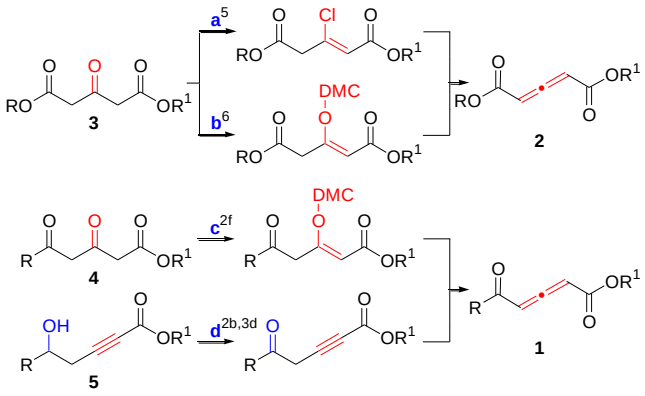


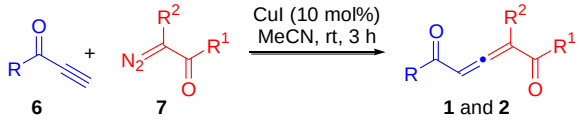
Figure 1. The structures of allenes **1** and **2**.

However, in the past decades, the synthetic methods for allenes **1** and **2** were underdeveloped compared to other allenes.[4] As shown in Scheme 1a-b, the conventional methods used today for the synthesis of allenes **2** by dehydration of 3-oxo-1,5-pentanedioates **3** were developed twenty years ago.[5,6] Although allenes **1** are very attractive synthons, their synthesis by dehydration of 3,5-dioxopentanoates **4** normally suffered from low efficiency due to the low chemoselectivity between two keto-carbonyls (Scheme 1c).[2f] The oxidation of 5-hydroxy-2-pentynoate **5** provided an alternative approach, in which the initially produced 5-oxo-2-pentynoates can be tautomerized to thermodynamically stable allenes **1** even in acidic conditions (Scheme 1d).[2b,3d] Since all these methods belong to the linear synthetic methods, the precursors **3**-**5** bearing the same carbon numbers as the target products **1**-**2** must be premade by multi-step syntheses.



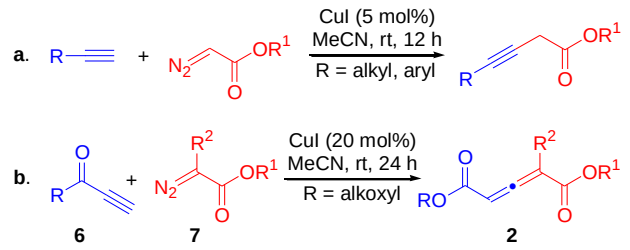
Scheme 1. Conventional methods for synthesis of **1** and **2**.

Herein, we report a direct method for synthesis of allenes **1** and **2** by a copper(I)-catalyzed cross-coupling between α-oxo-alkynes **6** and α-oxo-diazos **7** under mild conditions (Scheme 2). The efficiency and chemoselectivity of this method were simply controlled by adding α-oxo-alkynes **6** terminally.



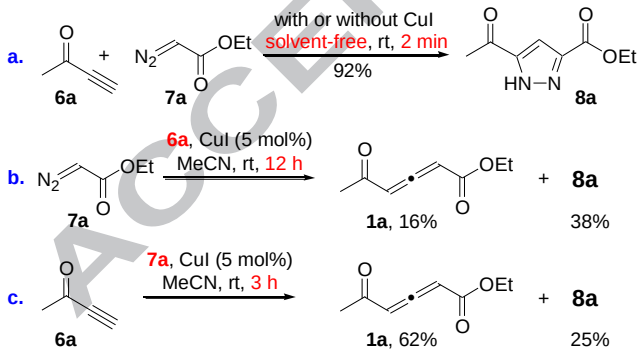
Scheme 2. Our new method.

In 2004, Fu[7] reported a copper(I)-catalyzed coupling of terminal alkynes and α-diazoacetates for the synthesis of 3-alkynyl butyrates under mild conditions (Scheme 3a). In 2013, Maruoka[8] employed Fu's method directly to synthesize a group of 1,3-allenedicarboxylates **2** (Scheme 3b). To our surprise, since then these two methods almost have not been used for the synthesis of the allenes **1** and **2** in literature.



Scheme 3. Fu's method and Maruoka's method.

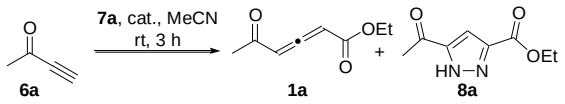
When we tried to use Fu's method to couple 3-butyn-2-one (**6a**) with ethyl diazoacetate (**7a**), the yield of product ethyl 5-oxo-2,3-hexadienoate (**1a**) varied widely (0-63%) from person to person. Thus, we assumed that the mechanisms for the methods in Scheme 3 may have not been clearly understood and solving this problem may lead to a general method for the synthesis of allenes **1** and **2** from easily accessible α-oxo-alkynes **6** and α-oxo-diazos **7**. Since the substrates and conditions used in these methods are very simple, we hypothesized that the problems may be caused by the sequence of adding substrates. Thus, three tests were made as shown in Scheme 4: (a) under the solvent-free conditions, a cycloadduct ethyl 5-acetylpyrazole-3-carboxylate (**8a**) was obtained in 92% yield within two minutes from **6a** and **7a** with or without CuI. This result is in agreement with the reference[9] that the cycloaddition of an electron-poor alkyne and an α-diazoacetate is an easy process; (b) by adding **7a** into the mixture of **6a** and CuI in CH_3CN, **1a** was obtained in 16% yield accompanied by **8a** in 38% yield; (c) by adding **6a** into the mixture of **7a** and CuI in CH_3CN, the coupling reaction was finished within 3 h to give **1a** and **8a** in 62% and 25% yields, respectively.



Scheme 4. Three conditional tests and results.

The above results strongly supported our hypothesis and also promoted us to optimize the reaction conditions further. As shown in Table 1, the tests for different Cu(I)-catalysts (entries 1-5) indicated that CuI was the only suitable catalyst for this coupling. The yield of **1a** was decreased and the yield of **8a** was increased by decreasing the amounts of CuI (entry 6). The best results were obtained when 10 mol% of CuI was used (entry 7). No **1a** was obtained in the absence of CuI (entry 9).

Table 1. Effects of catalysts on the yields of **1a** and **8a**.[a]



entry	Catalyst (mol%)	**1a** (%)[b]	**8a** (%)[b]
1	CuI (5)	62	25
2	CuBr (5)	5	31
3	CuCl (5)	trace	35
4	CuCN (5)	trace	38
5	CuOAc (5)	trace	45
6	CuI (3)	55	30
7	CuI (10)	65	21
8	CuI (15)	61	17
9	---	0	65

[a] To a solution of a catalyst and **7a** (1 mmol) in CH_3CN (2 mL) was added **6a** (1 mmol) and the mixture was stirred at room temperature for 3 h. [b] Isolated yields.

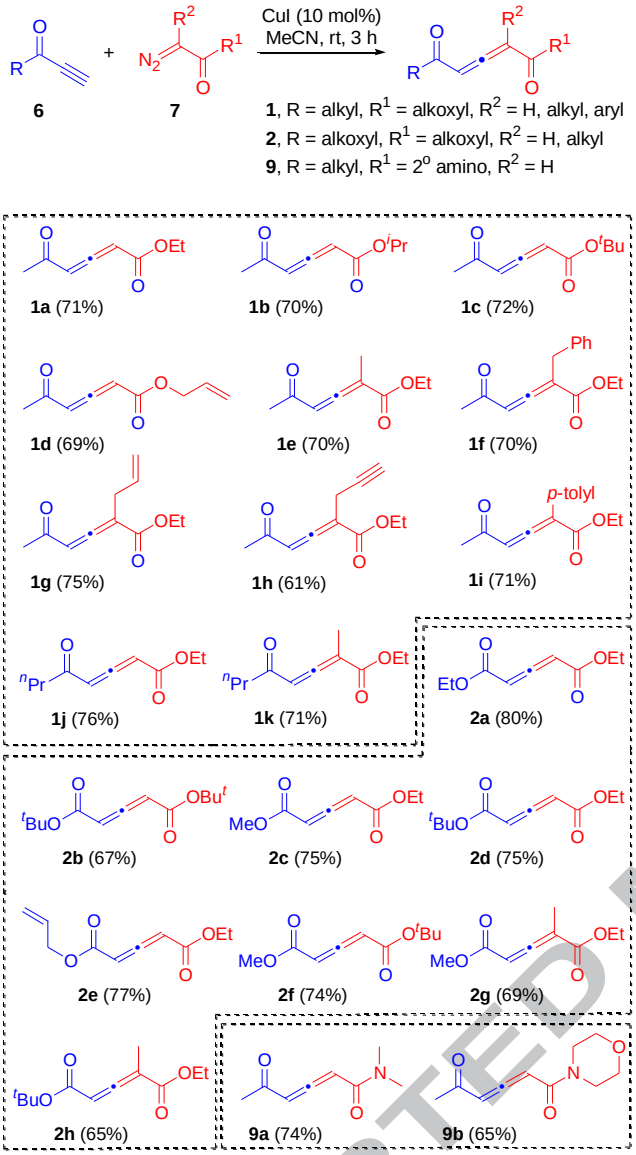
As shown in Table 2, CH_3CN proved to be the best solvent for this coupling among all tested coordinative solvents (entries 1-4). As was expected, the yield of **1a** was increased and the yield of **8a** was decreased by diluting the solutions (entries 5-7). The best results were obtained when 4 mL of CH_3CN were used (entry 6). No improvements were observed when the reaction ran at 0 °C (entry 8), but the yield of **1a** was decreased significantly when the reaction ran at 40 °C (entry 9).

Table 2. Effects of solvents on the yields of **1a** and **8a**.[a]

entry	Solvent (mL)	temp (°C)	time (h)	**1a** (%)[b]	**8a** (%)[b]
1	NMP (2)	25	3	22	42
2	DMF (2)	25	3	40	35
3	*n*-PrCN (2)	25	3	45	33
4	CH_3CN (2)	25	3	65	21
5	CH_3CN (3)	25	1	68	17
6	CH_3CN (4)	25	3	71	10
7	CH_3CN (5)	25	3	71	9
8	CH_3CN (4)	0	3	71	9
9	CH_3CN (4)	40	3	43	39

[a] To a solution of CuI (10 mol%) and **7a** (1 mmol) in CH_3CN was added **6a** (1 mmol) and the mixture was stirred for given temperature and time. [b] Isolated yields.

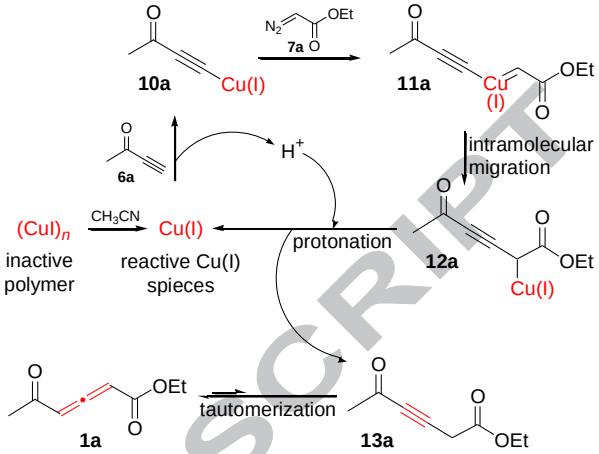
To generalize this method, the scope of substrates was tested under the standard conditions. As shown in Scheme 5, by fixing **6a**, the corresponding **1a-1i** were synthesized in moderate yields from **7a-7i**. Aryl substituted product **1i** was produced smoothly but with low stability (its decomposition was observed within 1 h). When hex-1-yn-3-one (**6b**) was used as a substrate, the corresponding **1j-1k** were synthesized. Similarly, 1,3-allene-dicarboxylates **2a-2h** were synthesized from the corresponding propargyl esters and α-diazoacetates, whether the two carboxylates are the same (**2a-2b**) or different (**2c-2h**). Trisubstituted allenes **1e-1i**, **1m** and **2g-2h** were easily synthesized by using α-substituted α-diazoacetates. Among them, the allyl and propargyl substituted products **1d**, **1g-1h** and **2e** are particularly significant to organic synthesis. As was expected, when **6a** reacted with α-diazoacetamides **7j** and **7k**, the products **9a** and **9b** were obtained, respectively. Under the standard conditions, **2a** was prepared in 66% yield on a 3 grams scale.



Scheme 5. The synthesis of the products **1a-1k**, **2a-2h** and **9a-9b**.

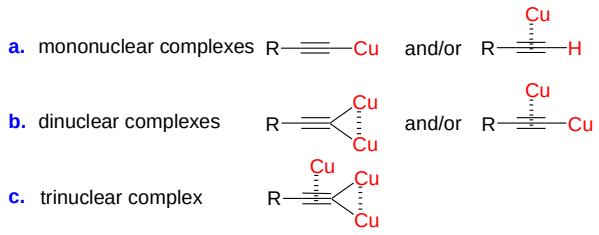
However, many substrates were seriously limited to this coupling method. For example, PhCOC≡CH mainly carried out a cycloaddition, possibly because it is a highly reactive dipolarophile. The diazos, such as CH_3COCHN_2, $CH_3COCHN_2COCH_3$, $PhCOCHN_2COPh$ and $EtO_2CHN_2CO_2Et$, were inert to the coupling and the last three were recovered in almost quantitative yields. These results may be caused by the fact that these diazos are too stable[10] to be decomposed by Cu(I)-catalyst. The fact that the propargyl group in **1h** stayed intact indicated that α-oxo-alkynes have much higher reactivity than normal alkynes. The most challenge question is why the alkene in **1g** stayed intact rather than carrying out a cyclopropanation? In fact, Fu has also reported[7] that no cyclopropanation of alkenes and O–H insertion of alcohols were detected in his work, but without any explanation.

Thus, a possible pathway for the formation of **1a** was proposed as shown in Scheme 6. Initially, a catalytically inactive polymer $(CuI)_n$ was dissociated by CH_3CN to generate a catalytically reactive $CuI{\cdot}CH_3CN$,[11] which was then coordinated by alkyne **6a** to form Cu(I)-acetylide **10a**. When **10a** was attacked by diazo **7a**, it was converted into Cu(I)-carbene **11a** with the loss of nitrogen. The initial cross-coupling product alkyne **13a** was formed by an intramolecular alkynyl migration of **11a** to give an intermediate **12a** followed by a protonation. Finally, **13a** was tautomerized to the thermodynamically stable allene **1a**.



Scheme 6. Proposed pathway for the formation of **1a**.

However, this pathway must be supplemented by three hypotheses in order to explain all experimental phenomena. First, Cu(I)-acetylide **10a** may be an *in situ* formed reactive mononuclear complex (Scheme 7a).[12] The differences by adding **6a** early or terminally may be resulted from the formation of dinuclear or mononuclear Cu(I)-acetylides, respectively.[13,14] By adding **6a** terminally, the *in situ* formed reactive mononuclear Cu(I)-acetylide was captured by **7a** rather than converting into a more stable dinuclear Cu(I)-acetylide (Scheme 7b). By adding **6a** early, parts of Cu(I)-species and **6a** were converted into inactive dinuclear Cu(I)-acetylide leading to a low efficient coupling. This hypothesis was also supported by two more facts: (a) the mononuclear Cu(I)-acetylide has been proposed as an intermediate for similar couplings by Wang based on DFT studies;[15] (b) our further tests showed that the yield of **1a** was further increased when **6a** was added through a syringe pump (71% in one portion; 78% for 30 min; and 79% for 60 min). Secondary, Cu(I)-acetylide **10a** may be the real catalyst for the decomposition of α-diazoacetate **7a**. Since the reactivity of Cu(I)-catalyst is significantly influenced by ligands, **10a** may not catalyze the decomposition of those stable diazos. Third, no other Cu(I)-carbene formed except Cu(I)-acetylide-carbene **11a** in this method. Thus, **11a** preferentially carried out an intramolecular alkynyl migration rather than an intermolecular cyclopropanation or O–H insertion.



Scheme 7. Proposed three different types of Cu(I)-acetylides.

In summary, a novel direct synthesis of 1,3-dioxo-substituted allenes was developed by copper(I)-catalyzed coupling of α-oxo-alkynes and α-oxo-diazos. Its chemoselectivity was controlled simply by the sequence of adding substrates. The mononuclear Cu(I)-acetylide was proposed as a key intermediate and a real Cu(I)-catalyst to well explain most of the results and phenomena.

Since this method was as simple as by adding α-oxo-alkynes terminally,[16] we may expect that it will have widespread applications in organic synthesis.

Acknowledgments

We gratefully acknowledge financial support from NNSFC (Nos. 2147210721372142 and 21372142).

References and notes

1. For selected reviews: (a) "*Progress in Allene Chemistry*," Guest editors: Alcaide, B. and Almendros, P., a themed issue of *Chem. Soc. Rev.* **2014**, *43*, 2879. (b) Lechel, T.; Pfrengle, F.; Reissig, H.-U.; Zimmer, R. *ChemCatChem* **2013**, *5*, 2100. (c) "*Modern Allene Chemistry*", ed. Krause, N. and Hashmi, A. S. K., Wiley-VCH, Weinheim, **2004**, vol. 1 and 2. (d) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196. (e) Taylor, D. R. *Chem. Rev.* **1967**, 317.
2. For selected recent references: (a) An, C.; Jurica, J. A.; Walsh, S. P.; Hoye, A. T.; Smith III, A. B. *J. Org. Chem.* **2013**, *78*, 4278. (b) Calter, M. A.; Li, N. *Org. Lett.* **2011**, *13*, 3686. (c) Wang, S.; Wu, F.; Rech, J. C.; Green, M. E.; Balachandran, R.; Horne, W. S.; Day, B. W.; Floreancig, P. E. *J. Am. Chem. Soc.* **2011**, *133*, 16668. (d) Crimmins, M. T.; Stevens, M. J.; Schaaf, G. M. *Org. Lett.* **2009**, *11*, 3990. (e) Smith III, A. B.; Jurica, J. A.; Walsh, S. P. *Org. Lett.* **2008**, *10*, 5625. (f) Yoshino, T.; Ng, F.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 14185. (g) Floreancig, P. E.; Rech, J. C. *Org. Lett.* **2005**, *7*, 5175. (h) Cox, C. D.; Siu, T.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5625.
3. For selected recent references: (a) Han, T.; Wang, Y.; Li, H.-L.; Luo, X.; Deng, W.-P. *J. Org. Chem.* **2018**, *83*, 1538. (b) Miura, H.; Sasaki, S.; Ogawa, R.; Shishido, T. *Eur. J. Org. Chem.* **2018**, 1858. (c) Bakshi, D.; Singh, A. *Org. Biomol. Chem.* **2017**, *15*, 3175. (d) Liu, F.; Wang, J.-Y.; Zhou, P.; Li, G.; Hao, W.-J.; Tu, S.-J.; Jiang, B. *Angew. Chem., Int. Ed.* **2017**, *56*, 15570. (e) Wang, Y.; Jiang, C.-M.; Li, H.-L.; He, F.-S.; Luo, X.; Deng, W.-P. *J. Org. Chem.* **2016**, *81*, 8653. (f) Li, H.-L.; Wang, Y.; Sun, P.-P.; Luo, X.; Shen, Z.; Deng, W.-P. *Chem. Eur. J.* **2016**, *22*, 9438.
4. For selected reviews: (a) Torres, Ò.; Pla-Quintana, A. *Tetrahedron Lett.* **2016**, *57* 3881. (b) Neff, R. K.; Frantz, D. E. *ACS Catal.* **2014**, *4*, 519. (c) Yu, S.; Ma, S. *Chem. Commun.* **2011**, *47*, 5384.
5. (a) Yoshida, M.; Hidaka, Y.; Nawata, Y.; Rudziński, J. M.; Ōsawa, E.; Kanematsu, K. *J. Am. Chem. Soc.* **1988**, *110*, 1232. (b) Bryson, T. A.; Dolak, T. M. *Org. Synth.* **1977**, *57*, 62. (c) Buchi, G.; Carlson, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 6470.
6. (a) Katoh, T.; Noguchi, C.; Kimura, H.; Fujiwara, T.; Ichihashi, S.; Nishide, K.; Kajimoto, T.; Node, M. *Tetrahedron: Asymmetry* **2006**, *17*, 2943. (b) Node, M.; Fujiwara, T.; Ichihashi, S.; Nishide, K. *Tetrahedron Lett.* **1998**, *39*, 6331.
7. Suárez, A.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3580.
8. Hashimoto, T.; Sakata, K.; Tamakuni, F.; Dutton, M. J.; Maruoka, K. *Nat. Chem.* **2013**, *5*, 240.
9. Vuluga, D.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *Green Chem.* **2009**, *11*, 156.
10. Mortén, M.; Hennum, M.; Bonge-Hansen, T. *Beilstein J. Org. Chem.* **2016**, *12*, 1590.
11. (a) Zhu, R.; Xing, L.; Wang, X.; Cheng, C.; Su, D.; Hu, Y. *Adv. Synth. Catal.* **2008**, *350*, 1253. (b) Healy, P. C.; Kildea, J. D.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1989**, *42*, 79. (c) Healy, P. C.; Kildea, J. D.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1988**, 1637.
12. In literature, Cu(I)-acetylides are commonly represented by a simple formula RC≡CCu, but in which each alkyne and Cu(I) are coordinated each other by one (mononuclear), two (dinuclear), or three C–Cu bonds (trinuclear). The order of stability for these complexes commonly is: mononuclear < dinuclear < trinuclear. For selected reviews: (a) Wang, X.; Wang, X.; Wang, X.; Zhang, J.; Liu, C.; Hu, Y. *Chem. Rec.* **2017**, *17*, 1231 (for the structures of Cu(I)-acetylides, see: pp 1232–1233). (b) Meldal, M.; Tornøe, C. W. *Chem. Rev.* **2008**, *108*, 2952 (for the structures of Cu(I)-acetylides, see: pp 2953–2956). (c) Lang, H.; Köhler, K.; Blau, S. *Coord. Chem. Rev.* **1995**, *143*, 113. (d) Nast, R. *Coord. Chem. Rev.* **1982**, *47*, 89.
13. Trinuclear Cu(I)-acetylide is excluded from this pathway because the premade trinuclear Cu(I)-acetylide **9a** was inert to couple with **7a**. A reference for similar results, see: Hassink, M.; Liu, X.; Fox, J. M. *Org. Lett.* **2011**, *13*, 2388.
14. Trinuclear Cu(I)-acetylide **9a** is an insoluble red solid and was synthesized by our early procedure: Chen, W.; Wang, B.; Liu, N.; Huang, D.; Wang, X.; Hu, Y. *Org. Lett.* **2014**, *16*, 6140.
15. (a) Wang, T.; Wang, M.; Fang, S.; Liu, J.-Y. *Organometallics* **2014**, *33*, 3941. (b) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 1114.
16. **A typical procedure for synthesis of ethyl 5-oxohexa-2,3-dienoate (1a).** To a stirred solution of CuI (19 mg, 0.1 mmol) and ethyl α-diazoacetate (**7a**, 114 mg, 1 mmol) in MeCN (3 mL) was added a solution of but-3-yn-2-one (**6a**, 68 mg, 1 mmol) in MeCN (1 mL). After the resultant mixture was stirred at room temperature for 3 h (monitored by TLC), the solvent was removed by vacuum and the residue was purified by flash chromatography (silica gel, 20% EtOAc in PE) to give 110 mg (71%) of the desired product **1a** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.15 (d, J = 6.0 Hz, 1H), 6.08 (d, J = 6.0 Hz, 1H), 4.26 (q, J = 7.3 Hz, 2H), 2.30 (s, 3H), 1.50 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 221.3, 195.3, 163.0, 100.4, 92.2, 61.6, 27.4, 14.0.

    The products **1b-1k**, **2a-2h** and **9a-9b** were prepared by the similar procedure.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at

Click here to remove instruction text...

Highlights

1. A new method for the synthesis of 1,3-dioxo-substituted allenes was developed.
2. It was achieved via CuI-catalyzed coupling of α-oxo-alkynes and α-oxo-diazos.
3. Its efficiency was controlled by adding α-oxo-alkyne terminally.
4. The mononuclear Cu(I)-acetylide was proposed as a real Cu(I)-catalyst.