Full Paper

Applied Organometallic Chemistry

Received: 26 March 2014 Revised: 14 April 2014 Accepted: 5 May 2014 Published online in Wiley Online Library: 17 June 2014

(wileyonlinelibrary.com) DOI 10.1002/aoc.3172

# Copper-catalyzed homo- and cross-coupling reactions of terminal alkynes in ethyl lactate

Jie-Ping Wan*, Shuo Cao and Yanfeng Jing

**The bio-based chemical ethyl lactate (EL) has been discovered to be an excellent medium for the Glaser-type homo- and cross-coupling reactions of terminal alkynes. Good to excellent yields of conjugate diynes have been obtained under ligand-free and mild heating conditions in the presence of CuI and molecular oxygen. Copyright © 2014 John Wiley & Sons, Ltd.**

*Additional supporting information may be found in the online version of this article at the publisher's web-site.*

**Keywords:** Glaser reaction; ligand-free, homo-coupling; cross-coupling; ethyl lactate

## Introduction

The oxidative coupling reaction between two terminal alkynes, also known as the Glaser reaction, is one of the most prevalently known methods for the construction of C–C bonds.[1,2] The conjugate 1,3-diyne products from the coupling reactions are highly useful compounds in organic synthesis such as natural products, antibacterial medicine[3–6] and organic conjugate diyne-based functional materials.[7–11] On the basis of the originally employed palladium/copper and other bicatalyst systems for oxidative couplings of terminal alkynes,[12–20] numerous efforts have been made to explore easy, low-cost and efficient new procedures to run these reactions. The employment of a single alternative transition metal catalyst such as palladium,[21,22] copper,[23–34] nickel[35] and cobalt[36,37] in the reactions has been found to be an improved protocol in terms of atom economics. In addition, discovering new oxidants[38–40] constitutes another frontier of the modern Glaser reaction.

Following daily increasing concerns on developing sustainable synthetic procedures and methods, special attention has been paid to the development of sustainable catalytic methods. In this regard, designing catalytic methods for the Glaser reaction in green media constitutes the major effort. During the past decade, a variety of different green media such as supercritical carbon dioxide,[41] water,[42] aqueous solvent,[43] ionic liquid,[44] polyethylene glycol[45,46] and 1,1,1,3,3-pentafluorobutane[47] have been successfully employed for the transformation. These methods provide elegant procedures for the synthesis of 1,3-diynes with cleaner operation. However, one or more disadvantages such as high cost of the media, intolerance to cross-coupling reactions and harsh reaction conditions have restricted the broad application of these methods. In this context, catalytic methods using an alternative low-cost green medium are still highly desirable, especially for those methods simultaneously allowing both homo- and cross-coupling reactions of terminal alkynes.[48–54]

Recently, our research interests in devising green organic synthesis in cheap, non-toxic and biodegradable bio-based media have disclosed that ethyl lactate (EL) is an efficient medium for different types of reactions such as ligand-free Suzuki coupling[55] and catalyst-free synthesis of disulfides.[56] In particular, during the investigation on disulfide formation from the oxidative coupling of thiols, we have observed that EL displayed an unique advantage as the medium by better dissolving oxygen.[56] Inspired by this property of EL as well as the significance of present research on bio-based solvent-mediated organic synthesis,[56–60] we present herein the EL-mediated,[61,62] copper-catalyzed Glaser reaction under ligand-free conditions, and both homo- and cross-coupling of terminal alkynes are covered.

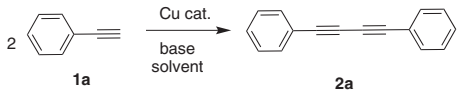
## Results and Discussion

First, based on the model coupling reaction between two molecules of phenylacetylene **1a**, different reaction conditions have been optimized. Initially, the reaction was performed in the presence of CuI and pyrrolidine in EL under aerobic and oxygen atmosphere, respectively. A comparison of the results suggested that the reaction under oxygen was evidently superior (Table 1, entries 1 and 2). Consequently, the experiments in aqueous EL media of different ratios showed that the presence of water was not favored (Table 1, entries 3–5). Different copper catalysts such as CuO, CuBr, $CuBr_2$, $Cu(OAc)_2$ and $CuCl_2$ were also screened, and the results revealed that CuI was the best copper catalyst (Table 1, entries 6–10). Subsequently, an amount of CuI of 10 mol% was found to be most appropriate according to corresponding experiments (Table 1, entries 2, 11 and12). Similarly, the amount of base additive was also varied, and 1.0 equiv. mol pyrrolidine was able to assist the reaction to give an equally good yield of **2a** as in the entries using larger amount of pyrrolidine (Table 1, entries 13 and 14). A parallel comparison of different bases including inorganic and organic ones, on the other hand, proved that pyrrolidine was the best base additive for this reaction (Table 1, entries 15–20). Finally, a slight increase in temperature (50°C)

* *Correspondence to: Jie-Ping Wan, Key Laboratory of Functional Small Organic Molecules, Ministry of Education, and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang 330022, P. R. China. E-mail: wanjieping@gmail.com*

*Key Laboratory of Functional Small Organic Molecules, Ministry of Education, and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, 330022, P. R. China*

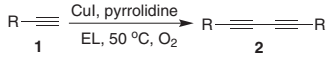
**Table 1.** Optimization of reaction conditions[a]




| Entry | Catalyst | Solvent | Base | Oxidant | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | CuI | EL | Pyrrolidine | air | 68 |
| 2 | CuI | EL | Pyrrolidine | $O_2$ | 84 |
| 3 | CuI | EL/$H_2O$ (1:1) | Pyrrolidine | $O_2$ | 35 |
| 4 | CuI | EL/$H_2O$ (3:1) | Pyrrolidine | $O_2$ | 17 |
| 5 | CuI | EL/$H_2O$ (1:3) | Pyrrolidine | $O_2$ | 14 |
| 6 | CuO | EL | Pyrrolidine | $O_2$ | Trace |
| 7 | $CuBr_2$ | EL | Pyrrolidine | $O_2$ | 48 |
| 8 | CuBr | EL | Pyrrolidine | $O_2$ | 24 |
| 9 | $Cu(AcO)_2.H_2O$ | EL | Pyrrolidine | $O_2$ | 32 |
| 10 | $CuCl_2.2H_2O$ | EL | Pyrrolidine | $O_2$ | 29 |
| 11[c] | CuI | EL | Pyrrolidine | $O_2$ | 83 |
| 12[d] | CuI | EL | Pyrrolidine | $O_2$ | 62 |
| 13[e] | CuI | EL | Pyrrolidine | $O_2$ | 84 |
| 14[f] | CuI | EL | Pyrrolidine | $O_2$ | 83 |
| 15[f] | CuI | EL | $Na_2CO_3$ | $O_2$ | Trace |
| 16[f] | CuI | EL | NaOH | $O_2$ | Trace |
| 17[f] | CuI | EL | $Et_3N$ | $O_2$ | Trace |
| 18[f] | CuI | EL | Morpholine | $O_2$ | 25 |
| 19[f] | CuI | EL | *t*-BuOK | $O_2$ | Trace |
| 20[f] | CuI | EL | DMAP | $O_2$ | 20 |
| 21[f,g] | CuI | EL | Pyrrolidine | $O_2$ | 90 |

[a]General conditions: phenylacetylene (0.6 mmol), copper catalyst (0.06 mmol) and base (1.2 mmol) in solvent (2 ml) under open air or oxygen balloon (for entries using $O_2$ as oxidant), stirred at room temperature for 16 h.
[b]Yield of isolated product.
[c]0.09 mmol CuI.
[d]0.03 mmol CuI.
[e]0.9 mmol pyrrolidine.
[f]0.6 mmol base.
[g]The temperature was 50°C.

**Table 2.** Homo-coupling reactions of terminal alkynes[a]




| Entry | R | Product | Yield (%)[b] |
|---|---|---|---|
| 1 | Ph | **2a** | 90 |
| 2 | 4-$MeC_6H_4$ | **2b** | 80 |
| 3 | 4-$MeOC_6H_4$ | **2c** | 42 |
| 4 | 4-$FC_6H_4$ | **2d** | 68 |
| 5 | 4-$ClC_6H_4$ | **2e** | 30 |
| 6 | 4-$BrC_6H_4$ | **2f** | 33 |
| 7 | 2-$ClC_6H_4$ | **2g** | 64 |
| 8 | 3-$BrC_6H_4$ | **2h** | 63 |
| 9 | *n*-butyl | **2i** | 62 |
| 10 | *n*-hexyl | **2j** | 77 |
| 11 | cyclopropyl | **2k** | 86 |
| 12 | *t*-butyl | **2l** | 48 |

[a]General conditions: alkyne **1** (0.6 mmol), CuI (0.06 mmol) and pyrrolidine (0.6 mmol) in EL (2 ml), stirred at 50°C for 16 h in an atmosphere of 1 atm $O_2$.
[b]Yield of isolated products.

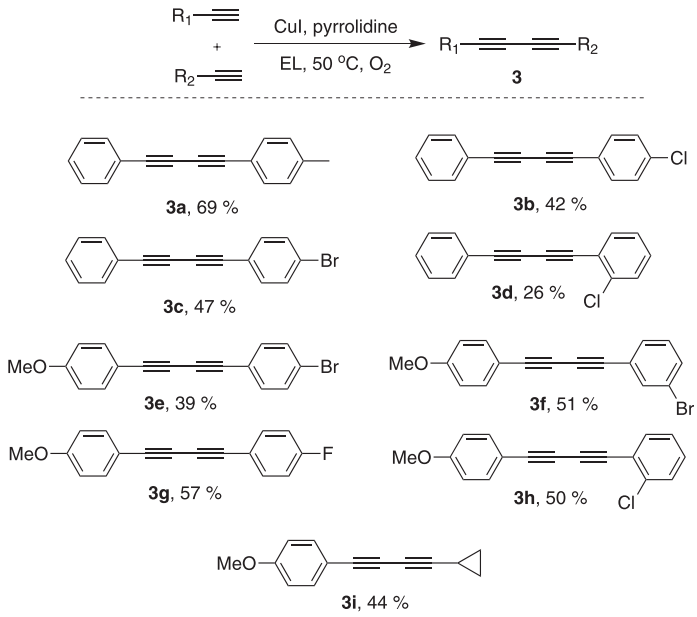
was able to promote the reaction to give the target 1,3-diyne **2a** in an excellent yield of 90% (Table 1, entry 21).

Following the experimental results from optimization, various terminal alkynes of different properties have been employed for corresponding homo-coupling reactions. The results from this section are presented in Table 2. It can be seen from these results that this EL-mediated protocol was generally applicable for alkyl alkynes and aryl alkynes bearing different functional groups. Corresponding diynes were obtained in moderate to excellent yields. It was notable that the present method enabled the coupling reaction of alkyl alkynes with equally good efficiency as aryl alkynes. In particular, alkyl alkynes such as cyclopropyl ethyne was able to dimerize to give the corresponding diyne product with excellent yield (Table 2, entry 11), while aryl alkynes *p*-chloro- and *p*-bromophenylacetylene provided corresponding products in only moderate yield probably because of loss of products during purification caused by their very low solubility (Table 1, entries 5 and 6).[48]

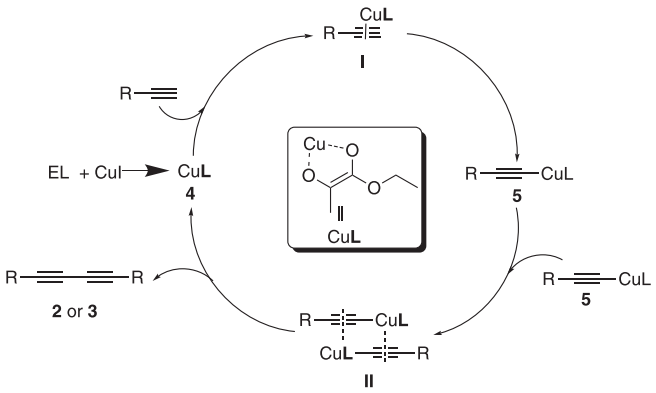
After examining homo-coupling reactions, we paid more attention to running cross-coupling reactions between two different terminal alkynes with this catalytic protocol. We were pleased to discover that this EL-mediated method also tolerated well the cross-coupling reactions of terminal alkynes containing different functional substructures. Results of the synthesis of 1,3-diynes of unsymmetrical structures are shown in Scheme 1. Satisfactory application scope was demonstrated by this section of experiment. For example, phenylacetylene reacted with phenylacetylene containing different functional groups such as alkyl, halides (**3a**, **3b**, **3c**, **3d**), and two phenylacetylenes containing different functional groups could also couple to give corresponding 1,3-diynes (**3e**, **3f**, **3g**, **3h**). Furthermore, cyclopropyl-functionalized terminal alkyne also successfully reacted with phenylacetylene to yield diyne **3i**. Owing to the presence of related homo-couplings as side reactions, experiments in this section gave generally moderate yields (26–69%).

According to the experimental results and analysis of the structure of EL itself, we assumed that EL acted not only as a medium in the reaction but also as a ligand of copper catalyst to promote the reactions. A mechanism of the reaction based on this assumption is shown in Scheme 2. The O,O-chelating sites in EL incorporated copper salt to generate the active Cu**L** catalyst **4**, which was able to activate the terminal alkyne substrate via transition state I to give intermediates **5**. The dimerization of **5** under oxidative conditions led to the final production of 1,3-diyne products **2** or **3** through another transition state II.

In conclusion, we have established a new and environmentally benign catalytic method for the Glaser reaction by employing EL as a green medium. The present method is effective for both homo-coupling of identical terminal alkyne and cross-coupling between two different terminal alkynes under ligand-free conditions, which consequently allowed the facile synthesis of both




**Scheme 1.** Cross-coupling reactions of terminal alkynes (the yield of isolated product was reported); general conditions: two different alkynes **1** (0.3 + 0.3 mmol), CuI (0.06 mmol) and pyrrolidine (0.6 mmol) in EL (2 ml), stirred at 50° C for 16 h in an atmosphere of 1 atm $O_2$.




**Scheme 2.** The proposed reaction mechanism.

structurally symmetrical and unsymmetrical 1,3-diynes. The present method could therefore serve as a complementary option in the field of 1,3-diyne synthesis.

## Experimental

### General Procedure for Homo- and Cross-Coupling of Terminal Alkynes

To a 10 ml round-bottom flask equipped with a stirring bar was added a terminal alkyne (0.6 mmol, for homo-coupling) or two different terminal alkynes (0.3 + 0.3 mmol, for cross-coupling), pyrrolidine (0.6 mmol, 1 equiv.), CuI (0.06 mmol, 0.1 equiv.) and EL (2 ml). The resulting mixture was stirred at 50°C under oxygen atmosphere (balloon) for 16 h (thin-layer chromatography, TLC). After cooling to room temperature, water (5 ml) was added and then extracted with ethyl acetate (3 × 10 ml).The combined organic solution was dried over anhydrous sodium sulfate and filtered. Subsequently, the solvent was removed under reduced pressure and the resulting residue was subjected to preparative TLC to provide pure product by using petroleum ether as eluent. All known compounds have been clearly identified by comparing their $^1$H NMR data with the corresponding literature, and new products have been characterized with abundant spectroscopic analysis (see supporting information).

### Acknowledgments

The work is financially supported by NSFC of China (No. 21102059), Department of Education of Jiangxi Province (GJJ13245), and a Sponsored Program for Cultivating Youths of Outstanding Ability in Jiangxi Normal University.

## References

[1] C. Glaser, *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422.
[2] C. Glaser, *Ann. Chem. Pharm.* **1870**, *154*, 137.
[3] L. K. Annabelle, S. Shun, R. Tykwinski, *Angew. Chem. Int. Ed.* **2006**, *45*, 1304.
[4] Y.-Z. Zhou, H.-Y. Ma, H. Chen, L. Qiao, Y. Yao, J.-Q. Cao, Y.-H. Pei, *Chem. Pharm. Bull.* **2006**, *54*, 1455.
[5] M. L. Lerch, M. K. Harper, D. J. Faulkner, *J. Nat. Prod.* **2003**, *66*, 667.
[6] S. Kanokmedhakul, K. Kanokmedhakul, I. Kantikeaw, N. Phonkerd, *J. Nat. Prod.* **2006**, *69*, 68.
[7] S. Eisler, A. D. Slepkov, E. Elliott, T. Luu, R. McDonald, F. A. Hegmann, R. R. Tykwinski, *J. Am. Chem. Soc.* **2005**, *127*, 2666.
[8] P. Sienmsen, R. C. Livingston, F. Diederich, *Angew. Chem. Int. Ed.* **2000**, *39*, 2632.
[9] X. Lv, J. Mao, Y. Liu, Y. Huang, Y. Ma, A. Yu, S. Yin, Y. Chen, *Macromolecules* **2008**, *41*, 501.
[10] S.-Y. Poon, W.-Y. Wong, K.-W. Cheah, J.-X. Shi, *Chem. Eur. J.* **2006**, *12*, 2550.
[11] J. D. Crowley, S. M. Goldup, A. L. Lee, D. A. Leigh, R. T. McBurney, *Chem. Soc. Rev.* **2009**, *38*, 1530.
[12] K. Sonogashira, Y. Tohda, N. Hagihara, *Tetrahedron Lett.* **1975**, *16*, 4467.
[13] A. Lei, M. Srivastava, X. Zhang, *J. Org. Chem.* **2002**, *67*, 1969.
[14] D. A. Alonso, C. Najera, M. Pacheco, *Adv. Synth. Catal.* **2003**, *345*, 1146.
[15] J.-H. Li, Y. Liang, Y.-X. Xie, *J. Org. Chem.* **2005**, *70*, 4393.
[16] J. Gil-Moltó, C. Najerá, *Eur. J. Org. Chem.* **2005**, 4073.
[17] C. Chen, Z. Ai, J. Lin, X. Hong, C. Xi, *Synlett* **2006**, 2454.
[18] J. D. Crowley, S. M. Goldup, N. D. Gowans, D. A. Leigh, V. E. Ronaldson, A. M. Z. Slawin, *J. Am. Chem. Soc.* **2010**, *132*, 6243.
[19] R. Roy, S. K. Das, F. Hernández-Mateo, F. Santoyo-González, Z. Gan, *Synthesis* **2001**, 1049.
[20] R. Rossi, A. Carpita, C. Bigelli, *Tetrahedron Lett.* **1985**, *26*, 523.
[21] S. Perrone, F. Bona, L. Troisi, *Tetrahedron* **2011**, *67*, 7386.
[22] S. Atobe, M. Sonoda, Y. Suzuki, T. Yamamoto, H. Masuno, H. Shinohara, A. Ogawa, *Res. Chem. Intermed.* **2013**, *39*, 359.
[23] A. S. Hay, *J. Org. Chem.* **1962**, *27*, 3320.
[24] P. Wasserscheid, W. Keim, *Angew. Chem. Int. Ed.* **2000**, *39*, 3772.
[25] K. Kamata, S. Yamaguchi, M. Kotani, K. Yamaguchi, N. Mizuno, *Angew. Chem. Int. Ed.* **2008**, *47*, 2407.
[26] D. Wang, J. Li, N. Li, T. Gao, S. Hou, B. Chen, *Green Chem.* **2010**, *42*, 15.
[27] K. Yin, C. Li, J. Li, X. Jia, *Green Chem.* **2011**, *13*, 591.
[28] X. Jia, K. Yin, C. Li, J. Li, H. Bian, *Green Chem.* **2011**, *13*, 2175.
[29] Y. He, C. Cai, *Catal. Sci. Technol.* **2012**, *2*, 1126.
[30] A. Kusuda, X.-H. Xu, X. Wang, E. Tokunaga, N. Shibata, *Green Chem.* **2011**, *13*, 843.
[31] Q. Zheng, R. Hua, Y. Wan, *Appl. Organometal. Chem.* **2010**, *24*, 314.
[32] H. Li, M. Yang, X. Zhang, L. Yan, J. Li, Y. Qi, *New. J. Chem.* **2013**, *37*, 1343.
[33] S. Adimurthy, C. C. Malakar, U. Beifuss, *J. Org. Chem.* **2009**, *74*, 5648.
[34] G. Cheng, H. Zhang, X. Cui, *RSC Adv.* **2014**, *4*, 1849.
[35] T.-P. Cheng, B.-S. Liao, Y.-H. Liu, S.-M. Peng, S.-T. Liu, *Dalton Trans.* **2012**, *41*, 3468.
[36] M. E. Krafft, C. Hirosawa, N. Dalal, C. Ramsey, A. Stiegman, *Tetrahedron Lett.* **2001**, *42*, 7733.
[37] G. Hilt, C. Hengst, M. Arndt, *Synthesis* **2009**, 395.
[38] Y. Zhu, Y. Shi, *Org. Biomol. Chem.* **2013**, *11*, 7451.

[39] X. Fan, N. Li, T. Shen, X.-M. Cui, H. Lv, H.-B. Zhu, Y.-H. Guan, *Tetrahedron* **2014**, *70*, 256.
[40] J.-X. Li, H.-R. Liang, Z.-Y. Wang, J.-H. Fu, *Monatsh. Chem.* **2011**, *142*, 507.
[41] J. Li, H. Jiang, *Chem. Commun.* **1999**, 2369.
[42] S.-N. Chen, W.-Y. Wu, F.-Y. Tsai, *Green Chem.* **2009**, *11*, 269.
[43] L. Zhou, H.-Y. Jiang, H.-L. Liu, H.-F. Jiang, *Chin. J. Chem.* **2007**, *25*, 1413.
[44] J. S. Yadav, B. V. S. Reddy, K. B. Reddy, K. U. Gayathri, A. R. Prasad, *Tetrahedron Lett.* **2003**, *44*, 6493.
[45] X.-L. Lu, Y.-H. Zhang, C.-C. Luo, Y.-G. Wang, *Synth. Commun.* **2006**, *36*, 2503.
[46] Y.-N. Li, J.-L. Wang, L.-N. He, *Tetrahedron Lett.* **2011**, *52*, 3485.
[47] A. Kusuda, X.-H. Xu, X. Wang, E. Tokunaga, N. Shibata, *Green Chem.* **2011**, *13*, 843.
[48] W. Yin, C. He, M. Chen, H. Zhang, A. Lei, *Org. Lett.* **2009**, *11*, 709.
[49] Y. Liu, C. Wang, X. Wang, J.-P. Wan, *Tetrahedron Lett.* **2013**, *54*, 3953.
[50] B. S. Navale, R. G. Bhat, *RSC Adv.* **2013**, *3*, 5220.
[51] I. J. S. Fairlamb, P. S. Bäuerlein, L. R. Marrison, J. M. Dickinson, *Chem. Commun.* **2003**, 632.
[52] R. Xiao, R. Yao, M. Cai, *Eur. J. Org. Chem.* **2012**, 4178.
[53] K. Balaraman, V. Kesavan, *Synthesis* **2010**, 3461.
[54] B. S. Navale, R. G. Bhat, *RSC Adv.* **2013**, *3*, 5220.
[55] J.-P. Wan, C. Wang, R. Zhou, Y. Liu, *RSC Adv.* **2012**, *2*, 8789.
[56] Y. Liu, H. Wang, C. Wang, J.-P. Wan, C. Wen, *RSC Adv.* **2013**, *3*, 21369.
[57] Y. Gu, F. Jérôme, *Chem. Soc. Rev.* **2013**, *42*, 9550.
[58] J. Yang, J.-N. Tang, Y. Gu, *Green Chem.* **2012**, *14*, 3304.
[59] J. S. Bennett, K. L. Charles, M. R. Miner, C. F. Heuberger, E. J. Spina, M. F. Bartels, T. Foreman, *Green Chem.* **2009**, *11*, 166.
[60] Y. Gu, F. Jérôme, *Green Chem.* **2010**, *12*, 1127.
[61] C. S. M. Pereira, V. M. T. M. Silva, R. E. Rodrigues, *Green Chem.* **2011**, *13*, 2658.
[62] S. Aparicio, R. Alcalde, *Green Chem.* **2009**, *11*, 65.

## Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.