View Article Online

ChemComm

Chemical Communications

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: K. Ni, L. Meng, H. Ruan and L. Wang, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC04090K.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the <u>Ethical guidelines</u> still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.



rsc.li/chemcomm



COMMUNICATION

Chemical Communications

Received 00th January 20xx, Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Controllable chemoselectivity in coupling of bromoalkynes with alcohols under visible-light irradiation without additives: Synthesis of propargyl alcohols and α-ketoesters

Ke Ni, Ling-Guo Meng,*,^a Hongjie Ruan, and Lei Wang*,^{a,b}

www.rsc.org/

Published on 21 June 2019. Downloaded by Nottingham Trent University on 6/21/2019 3:02:09 PM.

The chemoselectivity of visible-light-induced coupling reactions of bromoalkynes with alcohols can be controlled by simple changes to the reaction atmosphere (N₂ or O₂). A N₂ favours propargyl alcohols via a direct C-C coupling process, whereas an O₂ atmosphere results in the generation of α -ketoesters through the oxidation of the C=C/C-O coupling pathway.

Efficiently controlling chemoselectivity during the organic transformation is an important challenge in organic synthesis. In general, switching the formation of different chemical bonds from the same starting point is a shortcut for chemoselectivity. Most importantly, when studying the aspects of fundamental chemical bond formation, especially controlled divergent chemical bond formation, reactions that form C-C and C-O bonds can be regarded as an importan research focus. Alternative mainstream approaches rely on cross-coupling reactions using transition-metal catalysts.¹⁻³ In the past few decades, visible-light-initiated synthetic chemistry has shown significant improvements for the construction of complicated compounds via the promotion of different functional transformations, and these synthetic transformations have outstanding advantages (such as sustainability, utilization of a green energy, and simple operation),⁴ which offer significant convenience and environmental benefits compared to more traditionally employed transition-metal catalysis. However, most photochemical bond formation happens in the presence of photocatalysts.⁵ Some photoreactions occur without the addition of photocatalyst, but require the addition of oxidant, additives and biohazardous light.⁶ Accordingly, developing a simple and feasible methods for chemical bond formation under visible-light irradiation without the addition of metals, catalysts or other additives is a meaningful goal of organic synthesis. Recently, bromoacetylenes attracted our attention due to their photo-reactivity under visible-light irradiation.7 Finding alternative suitable substrates for coupling radical intermediated derived from bromoacetylenes might trigger a new reaction. Accordingly, we explored the possibility of a

Previous work:



Scheme 1 Synthetic routes to propargyl alcohols and α -ketoesters.

coupling reaction between bromoalkynes and alcohols. To our delight, propargyl alcohols and α -ketoesters were smoothly generated when the reaction was carried out under visible-light irradiation in the presence of N₂ and O₂ (Scheme 1g); the chemoselectivity of the photoreaction was easily regulated by changing the reaction atmosphere. In further comparisons with similar photo-driven cross-coupling reactions,⁸ we found that our synthetic strategy was more practical due to utilization of easily available starting materials lack of requirment of extra reagents (such as catalysts, oxidants and additives).

^{a.} Department of Chemistry, Huaibei Normal University, Huaibei, Anhui 235000, P.R. China.

E-mail: milig@126.com, leiwang@chnu.edu.cn

^{b.} State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, P. R. China.

⁺ Footnotes relating to the title and/or authors should appear here.

Electronic Supplementary Information (ESI) available: See DOI: 10.1039/x0xx00000x



Scheme 2 Visible-light-promoted oxidative esterification^{*a,b*}

^{*a*}Reaction conditions: **1** (0.20 mmol), **2** (2.0 mL), blue LED (420–470 nm), in O₂ for 12 h; [CH₃CN was used as solvent when bromoalkynes reacted with other alcohols (containing C atoms \geq 3, 2.0 mmol)]. ^{*b*}Isolated yield. ^{*c*}Reaction for 24 h ^{*d*}MeOH was used as solvent.

Until now, different synthetic platforms were used for the generation of propargyl alcohols and α -ketoesters.^{9,10} For example, both of these compounds can be routinely obtained by reacting expensive transition-metal catalysts or unstable organometallics (e.g., Grignard and organolithium reagents) with their corresponding synthetic precursors (Scheme 1a–c).¹¹ Other methods are available for the synthesis of α -ketoesters, but require unavailable or expensive starting materials, transitional-metal catalysts, toxic oxidants and assisted conditions (Scheme 1d–f).¹² Herein, we report a visible-light propelled coupling reaction of bromoalkynes and alcohols in the presence of N₂ and O₂ for the preparation of propargyl alcohols and α -ketoesters without additional catalysts and photosensitizers.

At the outset of this investigation, we blended phenylethynyl bromide (**1a**) into ethanol (**2a**), and the mixture was stirred under various conditions (see SI for details). The desired product, ethyl 2-oxo-2-phenylacetate (**3aa**), was generated as the major product in 57% isolated yield when the reaction was performed in the presence of air under blue LED (420–470 nm) irradiation for 12 h. Pleasingly, the yield of **3aa** was increased to 73% by changing the reaction was exposed to a blue LED light source (420–425 or 450–455 nm). As the light source was removed from the reaction, only a trace amount of **3aa** was detected. Oxidative esterification could be not be effectively triggered by red, yellow, blue, or green LED light

source. The chemoselectivity was switched toward the formation of 4-phenylbut-3-yn-2-ol (4aa) when the reaction was stirred under a nitrogen atmosphere, albeit with a lower yield. The yield of 4aa could be increased to 45% by varying the reaction time and the wavelength of blue LED light source. Under otherwise identical conditions, we further examined the effect of changing the concentration of 2a in ethanol, and found that 2a in 0.033 mol/L gave 63% yield of the product.

With the optimized reaction conditions, oxidative esterification of **1a** and **2a** proceeded to give the desired α -ketoesters irrespective of the substitution groups in bromoalkynes, and the results are summarized in Scheme 2. A variety of electron-rich and electronpoor groups at the para-position of the benzene rings were well tolerated, producing the anticipated α-ketoesters with good efficiency in most cases. For example, aromatic bromoalkynes with electron-donating groups (Me, Et, "Pr or "Bu), reacted with 2a to afford the corresponding products (3ba-3ea) in 70-76% yields, whereas the presence of a strong electron-donating group (CH₃O) in bromoalkyne 1 suppressed the reactivity of the substrate; only a trace amount of the desired product was detected, and most of the starting materials were recovered. Substrate 1 containing electronwithdrawing groups, such as F, Cl, Br and NO₂, also resulted in good yields (52-78%) of the corresponding products (3fa-3ia). When a substituent (Me, F, or Cl) was moved to the meta-position of the benzene rings, the desired products 3ja-3la were obtained with satisfactory yields (68-72%). Further investigation indicated that 2substituted phenyl bromoalkynes, including 1-(bromoethynyl)-2methylbenzene (1m) and 1-(bromoethynyl)-2-chlorobenzene (1n), were also suitable for the reactions, but had slight ortho-position effect (3ma vs 3ba; 3na vs 3ga). The efficiency of the reaction was decreased when the Br-atom present in 1a was changed to a Clatom or I-atom, probably owing to the inappropriate reactivities of phenylethynyl chloride and phenylethynyl iodide during the reaction. No obvious desired product was detected when benzylacetylene bromide was added to the reaction. To further extend the substrate scope of this oxidative coupling reaction, a variety of alcohols were examined. Straight chain alcohols with different lengths, such as methanol, propanol, butanol, amyl alcohol, hexanol, and octanol, could be smoothly reacted with 1a to generate the corresponding α -ketoesters (**3ab–3ag**) at moderate to good yields, implying that the efficiency of the reaction was not affected by increasing the length of the carbon chain. For an alcohol with a branched chain, such as isopropanol, a moderate yield of 3ah was afforded, indicating an obvious steric hindrance effect. In addition, the steric hindrance effect was weakened as the branched chain group was moved away from the reaction centre (3ai-3ak vs 3ah). When phenylmethanol and 4-bromophenylmethanol were subjected to the reaction, the corresponding products (3al and 3am) were produced at 60% and 59% yields, respectively. The generality of this method was also appropriate for ethylene glycol, and a 62% yield of 3an was obtained. Interestingly, 3an could be used as substrate and converted into the bi- α -ketoester **3ao**; however, the yield was low. Only a trace amount of 3ao was detected during the formation of **3an**. It should be noted that alcohols (2c-2n, and 3an) containing more than three carbon atoms with high boiling points were difficult to remove from the reaction system; therefore, after quickly screening the solvents (see SI for

Journal Name

Visible-light-promoted alkynylation of alcohols ^{<i>a,b</i>}

R ¹ Br bl	R ² CH ₂ OH (2) ue LED (420-425 nm) N ₂ , 48 h	R ¹ OH R ²
R ¹ -	R ¹ = H, 4aa , 63% R ¹ = Me, 4ba , 51% R ¹ = Et, 4ca , 50% R ¹ = ⁿ Pr, 4da , 53% R ¹ = ^t Bu, 4ea , 61%	R ¹ = OMe, 4fa , 30%° R ¹ = F, 4ga , 57% R ¹ = CI, 4ha , 61%° R ¹ = Br, 4ia , 60%°
P ¹ OH Me	R ¹ = Me, 4ja , 50% ^c R ¹ = F, 4ka , 62% ^c	R ¹ = Cl, 4la , 62% ^c R ¹ = Br, 4ma , 64% ^c
ОН	R ¹ = Cl, 4na , 62% ^c R ¹ = Br, 4oa , 64% ^c	
	R ² = H, 4ab ,40% ^{<i>c</i>} R ² = Et, 4ac , 51% ^{<i>c</i>} R ² = ^{<i>n</i>} Pr, 4ad , 36% ^{<i>c</i>}	R ² = ^{<i>n</i>} Bu, 4ae , 34% ^c R ² = (Me) ₂ , 4af , 31% ^c R ² = ^{<i>i</i>} Pr, 4ag , 35% ^c

^{*a*}Reaction conditions: **1** (0.20 mmol), **2** (2.0 mL), blue LED (420–425 nm), in N₂, for 48 h. ^{*b*}Isolated yield. ^{*c*}Reaction for 72 h.

details), we determined that these high boiling alcohols optimally reacted with 1a in CH₃CN under blue LED irradiation. Further, no reaction was found when phenol replaced ethanol as substrate.

Subsequently, we investigated the scope of visible lightpromoted alkylation of alcohols, and the results are shown in Scheme 3. Bromoalkynes with different groups on their phenyl rings, reacted with ethanol to produce the corresponding propargyl alcohols 4. There were no obvious electron effects on the yields whether the substrates contained electron-rich or -poor substituents (4aa-4ea, 4ja with electron-rich groups, 50-63% yields; 4ga-4ia, 4ka-4ma with electron-poor groups, 57-64% yields). However, a low yield of 4fa was afforded when 1-(bromoethynyl)-4-methoxybenzene was employed as the substrate. When the substituents (Cl and Br) were located at the ortho-position of the benzene rings, the desired products 4na and 4oa resulted with comparable yields and no observed steric hindrance. Next, different alcohols were used to investigate the scope of the alkynylation reaction. When methanol or propanol was reacted with 1a, the desired products 4ab and 4ac was isolated at 40% and 51% yield, respectively. Other alcohols including butanol, pentanol, isopropanol and iso-butanol with a larger steric hindrance afforded the corresponding products at 31–36% yields.

To gain insight into the reaction mechanism, several control experiments were conducted, as shown in Scheme 4. Oxidative esterification was completely inhibited when O2 was removed from the reaction system (Scheme 4a), indicating that the O-atom in the α -keto esters products was from O₂. Both esterification and alkynylation reactions were almost suppressed when the radical scavenger 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) was added to the reaction, which implied that the reaction was accomplished via a free radical process. Meanwhile ethoxy radicald (EtO*) or carbon radicals (MeCH•OH) may have been captured by HRMS analysis (Scheme 4b and 4c), but we could not be sure which one was formed to couple with TEMPO (one or both of them have). The reaction was complicated, and the same possible byproducts as described in our previous reports were observed by HRMS analysis when only 1a was irradiated under O2 (Scheme 4d).7 Further the self-coupling product (4,4-dibromobut-3-en-1-yne-1,3-



Scheme 4 Control experiments.

diyl)dibenzene could be isolated through an enrichment operation when the reaction was under N₂ (Scheme 4e).¹³ No reaction of alcohol **2a** occurred whether the reaction took place in N₂ or O₂ (Scheme 4f). In this in-depth study, we found that both self-coupling and cross-coupling products could be detected by GC-MS when a mixture of **1a** and **1g** was analysed under N₂ atmosphere (Scheme 4g). The above results (Scheme 4d–4g) imply that the initiation of the reaction might be started from the homolysis of bromoalkynes.

Based on our assays as well as previous reports, a plausible mechanism is proposed in Scheme 5. The results of the control experiment (Scheme 4) support homolytic cleavage of the C(sp)-Br bond in **1a** to deliver a radical intermediate **A** and bromide radical (Br[•]).¹⁴ When the reaction was in O₂, an alkynyl radical **A** coupled with O₂ to transform into intermediate **B** (electron spin resonance (ESR) experiments proved the nonexistence of ¹O₂ during the reaction; see SI for detail). With the assistance of Br[•], substrate **2a** was converted into the alkoxyl radical **C**, which reacted with intermediate **B** to form intermediate **D**. Finally, the desired product **3aa** was generated via a rearrangement process from intermediate **E** variations of intermediate **C**. Subsequently, intermediate **E** coupled with **A** to give the product **4aa**. We speculate that intermediate **C** might be more easily formed than **E** after comparing the reaction



Scheme 5 Proposed mechanism.

time for the the formation of α -ketoesters and propargyl alcohols. Furthermore, the obvious isotopic effect (k_H/k_D value of 6.14 determined by ¹H NMR, see SI for detail) was observed in the alkynylation of alcohols, implying that H-atom transfer is the rate-determining step during the formation of propargyl alcohols. On the other hand, although we cannot know whether the formation of product **F** is derived from the coupling of **A** and **C**, **F** failed to convert to **3aa** under optimized reaction conditions. Furthermore, we still do not understand the relationship between the wavelength of the blue LED light source and the homolysis of bromoalkynes.

Conclusions

In conclusion, we developed a catalyst and additive-free coupling reactions of bromoalkynes and alcohols for the synthesis of α -ketoesters and propargyl alcohols. This visible-light-promoted chemoselective transformation was controlled by changing the reaction atmosphere. N₂ favoured propargyl alcohols formations via a direct C–C coupling process, whereas an O₂ atmosphere resulted in the generation of α -ketoesters through oxidation of the C=C/C–C coupling pathway. The advantages of this chemoselective photopromoted-synthetic platform include the use of a simple procedure without the addition of catalysts or additives or the need for harsh conditions. Further studies on visible-light promoted reactions using bromoalkynes as precursors are underway in our laboratory.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21772062, 21572078 and 21402061), the Scientific Research Project of Anhui Provincial Education Department (KJ2015TD002) and the Natural Science Foundation of Anhui (1708085MB45) for financial support of this work.

Notes and references

- Selected reviews about transition-metal catalyzed C-C formation: (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174; (b) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624; (c) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215.
- 2 Selected examples about transition-metal catalyzed C–O formation: (a) S. Kundu, C. Greene, K. D. Williams, T. K. Salvador, J. A. Bertke, T. R. Cundari and T. H. Warren, J. Am. Chem. Soc., 2017, 139, 9112; (b) X.-F. Cheng, Y. Li, Y.-M. Su, F. Yin, J.-Y. Wang, J. Sheng, H. U. Vora, X.-S Wang and J.-Q. Yu, J. Am. Chem. Soc., 2013, 135, 1236; (c) K. Muto, J. Yamaguchi and K. Itami, J. Am. Chem. Soc., 2012, 134, 169.
- Selected examples about transition-metal catalyzed controllable chemical bond formation: (a) D. Zell, M. Bursch, V. Müller, S. Grimme and L. Ackermann, *Angew. Chem., Int. Ed.*, 2017, 56, 10378; (b) H. Kondo, N. Akiba, T. Kochi and F. Kakiuchi, *Angew. Chem., Int. Ed.*, 2015, 54, 9293; (c) M. T. Wentzel, V. J. Reddy, T. K. Hyster and C. J. Douglas, *Angew. Chem., Int. Ed.*, 2009, 48, 6121. (d) S. Wang, S. Tang and A. Lei, *Science Bulletin*, 2018, 63, 1006.

- For selected reviews, see: (a) I. Ghosh, L. Marzow, AtticDasmiRe Shaikh and B. König, Acc. Chem. Res., 2016, 49, 31566; (b) 99.4K. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, Acc. Chem. Res., 2016, 49, 1911; (c) D. C. Fabry and M. Rueping, Acc. Chem. Res., 2016, 49, 1969; (d) J. M. R. Narayanam and C. R. J. Stephenson, Chem. Soc. Rev., 2011, 40, 102; (e) J-R. Chen, X.-Q. Hu, L.-Q. Lu and W.-J. Xiao, Chem. Soc. Rev., 2016, 45, 2044. (f) Y. Xi, H. Yi and A. Lei, Org. Biomol. Chem., 2013, 11, 2387. (g) C. Bian, A. K. Singh, L. Niu, H. Yi and A. Lei, Asian J. Org. Chem., 2017, 6, 386, (h) Y. Chen, L.-Q, Lu, D.-G. Lu, C.-J. Zhu and W.-J. Xiao, Sci. China Chem., 2019, 62, 24.
- 5 (a) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (b) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075; (c) M. N. Hopkinson, A. Tlahuext-Aca and F. Glorius, *Acc. Chem. Res.*, 2016, **49**, 2261.
- For selected examples, see: (a) H. Tan, H. Li, W. Ji and L. Wang, Angew. Chem., Int. Ed., 2015, 54, 8374; (b) L. Li, X. Mu, W. Liu, Y. Wang, Z. Mi and C.-J. Li, J. Am. Chem. Soc., 2016, 138, 5809; (c) Y. Sato, S.-I. Kawaguchi, A. Nomoto and A. Ogawa, Angew. Chem., Int. Ed., 2016, 55, 9700; (d) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni and P. Melchiorre, Nature, 2016, 532, 218.
- 7 K. Ni, L.-G. Meng, K. Wang and L. Wang, Org. Lett., 2018, 20, 2245.
- 8 (a) J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel and G. A. Molander, *Acc. Chem. Res.*, 2016, **49**, 1429; (b) M. Fagnoni, D. Dondi, D. Ravelli and A. Albini, *Chem. Rev.*, 2007, **107**, 2725.
- 9 For selected examples about synthesis of propargyl alcohols: (*a*)
 S. L. Kundu, K. Mitra and A. Majee, *RSC Adv.*, 2015, 5, 13220; (*b*)
 B. M. Trost and A. Quintard, *Angew. Chem., Int. Ed.*, 2012, 51, 6704.
- 10 For selected examples about synthesis of α-ketoesters: (a) K. Furukawa, H. Inada, M. Shibuya and Y. Yamamoto, Org. Lett., 2016, **18**, 4230; (b) L. Liu, L. Du, D. Zhang-Negrerie, Y. Du and K. Zhao, Org. Lett., 2014, **16**, 5772; (c) C. Chen and C. David, J. Chem. Soc., Chem. Commun., 1991, **18**, 1289. (d) B, Eftekhari-Sis and M. Maryam, Chem. Rev., 2015, **115**, 151.
- (a) F. S. Y. Zi and I. Vilotijevic, *Chem. Commun.*, 2018, **54**, 3266;
 (b) X. Zhang, Z. Lu, C. Fu and S. Ma, *Org. Biomol. Chem.*, 2009, **7**, 3258;
 (c) K. Thai, S. M. Langdon, F. Bilodeau and M. Gravel, *Org. Lett.*, 2013, **15**, 2214;
 (d) R. K. Dieter, R. R. Shiarma, H. Yu and V. K. Gore, *Tetrahedron*, 2003, **59**, 1083.
- (a) K. Moriyama, M. Takemura and H. Togo, Org. Lett., 2012, 14, 2414; (b) Y. Zheng, R. Bian, X. Zhang, R. Yao, L. Qiu, X. Bao and X. Xu, Eur. J. Org. Chem., 2016, 3872; (c) S. B. Salunke, N. S. Babu and C.-T. Chen, Adv. Synth. Catal., 2011, 353, 1234; (d) P. C. B. Page and S. Rosenthal, Tetrahedron Lett., 1986, 27, 1947; (e) C. Zhang, P. Feng and N. Jiao, J. Am. Chem. Soc., 2013, 135, 15257; (f) A. Stergiou, A. Bariotaki, D. Kalaitzakis and I. Smonou, J. Org. Chem., 2013, 78, 7268. (g) Z. Zhang, J. Su, Z. Zha and Z. Wang, Chem. Eur. J., 2013, 19, 17711.
- 13 (a) P.-H. Liu, L. Li, J. A. Webb, Y. Zhang and N. S. Goroff, Org. Lett., 2004, 6, 2081; (b) V. K. Karapala, H.-P. Shih and C.-C. Han, Org. Lett., 2018, 20, 1550.
- 14 B. Martelli, P. Spagnolo and M. Tiecco, J. Chem. Soc (B)., 1970, 1413.



The chemoselectivity of visible-light-induced coupling reactions of bromoalkynes with alcohols can be controlled by simple changes to the reaction atmosphere.