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Carboxymethylpullulans Promoted Cu2O-Catalyzed Huisgen-Click Reaction

Weiwei Zhang, Baoqi Ren, Yuqin Jiang*, Zhiguo Hu*

Collaborative Innovation Center of Henan Province for Green Manufacturing of Fine Chemicals, Key Laboratory of Green Chemical Media and Reactions, Ministry of Education, School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, P. R. China.

E-mail: jiangyuqin@htu.cn; zghu@htu.cn.

A combination of carboxymethylpullulans (CMP) and Cu_2O has been developed as a highly efficient catalytic system for Huisgen-click reaction. Our results indicate that the acidic CMP could be used for 6 cycles without decreasing the activating efficiency for Cu_2O.

Introduction

By now click chemistry has emerged as a prominent organic transformation. The copper(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction is one of the most popular reactions within the click chemistry concept since discovered by the groups of Sharpless[1] and Meldal[2] independently. The CuAAC reaction has attracted much attention and been applied in the synthesis of pharmaceuticals, agrochemicals, dyes, corrosion inhibitors, biochemicals, polymers and functional materials due to its reliability, specificity and biocompatibility.[3]

A plethora of copper catalytic systems have been utilized for CuAAC reaction including Cu(I) species,[4] Cu(II) salts/reducing agents[2,5] and metallic copper.[6] Compared with other Cu(I) species, Cu_2O is the most readily available and practical catalyst. Efforts were made to enhance the catalytic efficiency of Cu_2O[7-11] because the directly used Cu_2O powder in the CuAAC reaction showed very poor catalytic efficiency.[12] To date, the catalytic capability of Cu_2O in CuAAC reactions has not been thoroughly exploited because of lacking appropriate reaction conditions. Very recently, inspired by the reported $PhCOOH/Cu_2O$ catalytic system by Hu et al.,[8] we have reported $Cu(OAc)_2 \cdot H_2O/NH_2NH_2 \cdot H_2O$ as a highly efficient catalytic system for the CuAAC reaction, which in situ generates Cu_2O-NPs and HOAc in water at room temperature.[13] Our results indicate that the in situ generated HOAc plays an important role in the CuAAC reaction. While not only the $PhCOOH/Cu_2O$ catalytic system, but also the $Cu(OAc)_2 \cdot H_2O/NH_2NH_2 \cdot H_2O$ catalytic system has drawbacks due to the unrecoverable and unreusable properties of the used small molecular organic acid in the processes, which both show better activating efficiency for Cu_2O.

Until now, polymers, as important supports, have been employed for immobilization of copper species

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for CuAAC reaction and resulted in easy removal, recovery and reusability of the copper catalyst.[14] To

solving the recyclability problem of small organic acid mentioned above, a water-soluble polymer linked

with such kind of small molecular organic acid could be considered, which usually should not dissolve in

common organic solvents, such as ethyl acetate, $CHCl_3$, CH_2Cl_2. Therefore, after the 1,2,3-triazoles

precipitated from the reaction mixture or extracted by water-insoluble organic solvents, the water-soluble

polymers could still remain in the water phase for reusing. Carboxymethylpullulan (CMP), which has been

widely studied in polymer chemistry,[15] is a water-soluble, nontoxic derivative of pullulan with carboxylic

acid groups linked to the main chain. The main aim of this work is to investigate the activated efficiency

and the recyclability ability of CMP in the Cu_2O-catalyzed CuAAC reaction. To the best of our knowledge,

there is still no report of CMP as the activator for Cu_2O on the CuAAC reaction. The work described in this

paper selected Cu_2O/CMP as a catalyst system for the CuAAC reaction in water and demonstrated that the

CMP showed better recyclability ability for Cu_2O than the reported PhCOOH and HOAc.
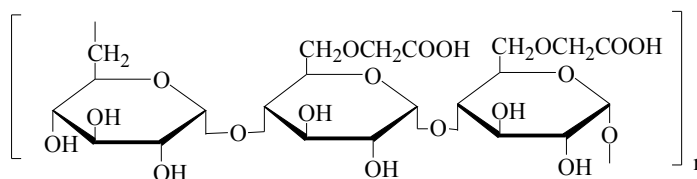
Scheme 1. Structure of carboxymethylpullulan (CMP)

Results and Discussion

CMP was prepared by reaction of alkali-pullulan with sodium chloroacetate in a 2:1 isopropanol-water

mixture according to the reported procedure.[15a] The Cu_2O was prepared according our previous literature.[13]

The reaction between propargyl phenyl ether and azide benzyl was selected as the model reaction (**Scheme

2**) to test the catalytic efficiency of the Cu_2O/CMP catalyst system. The reaction conditions were settled as

follows: propargyl phenyl ether (1.0 mmol), azide benzyl (1.0 mmol), Cu_2O (2 mol%), CMP (10 mol%),

and water (2 mL). The influence of the amount of CMP on the isolated yields of the model reaction was

investigated.
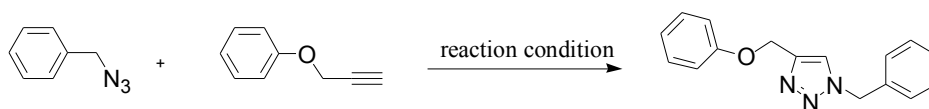
Scheme 2. Model reaction for screening the Cu_2O/CMP catalytic system

Initially, the pH values of different amount of CMP in 2 mL water were measured and the pH value of

the used water is 7.00. As shown in **Figure 1**, the pH value of the CMP solution greatly affected the isolated yield of the model reaction. When the amounts of the CMP (based on the alkyne) increased from 2 mol% to 20 mol%, the pH value decreased from 3.40 to 2.78 (line a), which is easy to understand that the more amount of acid the lower the pH value. The yields increased significantly over the concentration range of 2 mol% to 10 mol% (yield from 24.6% to 98.0%) and decreased over the concentration range of 10 mol% to 20 mol% (yield from 98.0% to 15.6%). The yield over the concentration range of 2 mol% to 10 mol% increased with the decreased of the pH values, which is consistent with our previous results that is the lower the pH value the faster the reaction rate.[13] As we all known that Cu_2O is almost insoluble in water, while in acidic water it becomes soluble and the Cu(I) ions are released, which is ready to disproportionate or be oxidized to copper (II). The lower the pH values, the faster the release rate. The CMP has two important roles in the Huisgen-click reaction. One is providing the needed protons, which promote the release of Cu(I) ions. The other role of CMP is acting as a stabling agent to prevent the disproportionation or oxidization of the released of Cu(I) ions. The *in situ* released Cu(I) in the reaction mixture catalyzed the Huisgen-click reaction between the added organic alkynes and azides. The more Cu(I) ions, the faster the reaction rate. While the contrary results obtained from the yields over the concentration range of 10 mol% to 20 mol%, which decreased from 98.0% to 15.6%. One reason is ascribed to the higher viscosity of the aqueous CMP solutions at the high concentration. Another reason is ascribed to the strong copper chelation ability of CMP. For proving this, special experiments were designed and carried out. To the round bottom flask, Cu_2O (2 mol%), CMP (10 mol%), and water (2 mL) were added. After stirred for 6 mins, propargyl phenyl ether (1.0 mmol) and azide benzyl (1.0 mmol) were added and stirred for another 20 mins. After working up, only 40% isolated yield was obtained. It is worthy to be mentioned that when Cu_2O (2 mol%), CMP (20 mol%), and water (2 mL) were put together and stirred for 6 mins, coagulation was observed. The same experimental result was obtained when it was carried out under a nitrogen atmosphere. The above experimental results confirmed the copper(I) chelation ability of CMP. Therefore the optimized reaction was settled as follows: Cu_2O (2 mol%), CMP (10 mol%), and water (2 mL) and the Cu_2O (2 mol%) should be the last one to be added.
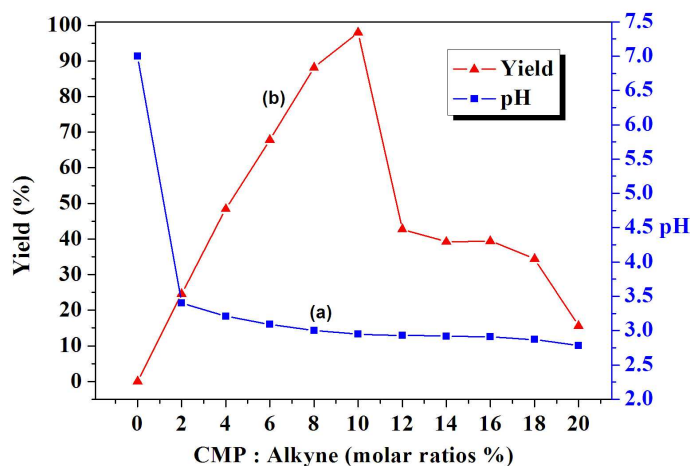
Figure 1. Effects of the amount of CMP to alkyne on yields and pH values

Secondly, the affection of the Cu_2O-loading on the model reaction was investigated. The model reaction was carried out in water at room temperature in 20 mins in presence of 10 mol% CMP. As shown in **Table 1**, it could be seen that the larger the catalyst loading, the faster the reaction rate (**entry 1** to **6**). The model reaction could be finished in 20 mins by increasing the catalyst loading above 2 mol%. When decreasing the catalyst loading to 1 mol%, it would take 2 h to complete the reaction. Further reducing the catalyst loading to 0.5 mol% and 0.1 mol%, it would take 10 h and 17 h to finish the model reaction respectively. Unfortunately, when the catalyst loading was reduced to 0.05 mol%, very poor yield (8%) was obtained even after reacting for 24 h. For improving the reaction rate of the model reaction at lower catalyst loading, heating is considered as a simple and direct way.[16] Very encouraged, the model reaction could complete in 20 mins when catalyzed by 0.5 mol% Cu_2O at 80 ºC (**entry 9**). At the same condition mentioned above, the reaction could complete smoothly in 20 mins even the amount of CMP reducing to 5 mol%. It is worth to mention that only 15% yield is obtained when catalyzed by 10 mol% Cu_2O in absence of CMP (**entry 8**), which indicated the importance of the CMP. The results above encouraged us to study the effect of the reaction temperature on the model reaction with the relatively lower loading of Cu_2O and CMP.

Table 1. The screening of the catalyst loading on the model reaction

Entry	Cu_2O (mol%)	Times (min) [a]	Yield(%) [b]
1	10	20	98/15 [c]
2	5	20	98
3	2	20	98
4	1	20	24
5	0.5	20	16
6	0.1	20	5
7	0.05	24 h	8

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8	0.05 [d]	24 h	15
9	0.5 [d]	20	98
10	0.5 [e]	20	98

[a] Reaction conditions: propargyl phenyl ether (1 mmol), azide benzyl (1 mmol), CMP (10 mol%), H_2O (2 mL), rt; [b] Isolated yields; [c] In absence of CMP; [d] Reaction temperature is at 80 ºC; [e] CMP (5 mol%), H_2O (2 mL), reaction temperature is at 80 ºC.

For investigating the effect of reaction temperature on the model reaction, the reaction conditions were settled as follows: propargyl phenyl ether (1.0 mmol), azide benzyl (1.0 mmol), Cu_2O (0.5 mol%), CMP (5 mol%), and water (2 mL). The model reaction was carried out in 20 mins at different temperature among the temperature range from 30 ºC to 100 ºC. As shown in **Figure 2**, the higher the reaction temperature, the faster the reaction rate from 30 ºC to 60 ºC. When the temperature is above 60 ºC, the yield obtained in 20 mins is almost the same. So the optimized reaction condition is as follows: propargyl phenyl ether (1.0 mmol), azide benzyl (1.0 mmol), Cu_2O (0.5 mol%), CMP (5 mol%) and water (2 mL) at 60 ºC.
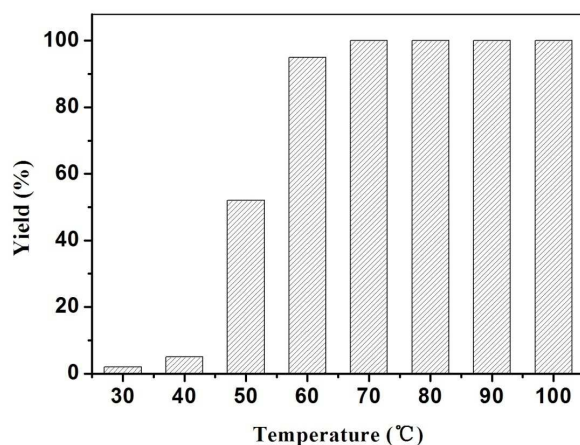

Figure 2. Effects of the reaction temperature on the model reaction
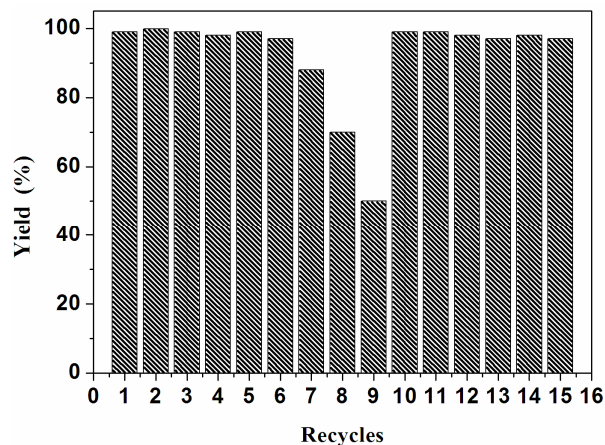

Figure 3. Recyclability of CMP for the model reaction

There is an interesting thing happened during working up the model reaction. When the reaction was

extracted by ethyl acetate, a yellow organic phase and an almost colorless water phase were obtained (**Figure 4**). It could be imaged that the *in situ* formed copper(I) ion might be coordinated with the obtained triazoles.[17] The bright yellow organic phase could maintain for several weeks without changes. When the propargyl phenyl ether was replaced by phenylacetylene, the extracting phenomenon was the same, even using CH_2Cl_2 or chloroform as the extracting solvents. It was very interesting that when the pure obtained triazoles from the model reaction were stirred with CMP and Cu_2O for 20 mins and the mixture were extracted by ethyl acetate, the organic phase was colorless. This indicated that chelation of triazoles with copper(I) happened in the Huisgen-click reaction cycles, which should be responsible for the leaching of Cu(I) from the catalytic system. When the yellow organic phase was washed by aqueous ammonia, it became colorless and the water phase became blue. The results mentioned above proving that the copper almost transferred to the organic phase, thus the catalysis copper could not be recycled. Therefore the recyclability of the CMP was investigated. The model reactions were carried out at 60 ºC in a relatively large scale: propargyl phenyl ether (10 mmol), azide benzyl (10 mmol), Cu_2O (0.5 mol%), CMP (5 mol%), and water (20 mL). After the reaction mixture extracting by ethyl acetate, the remaining water phase was added the same amount of starting alkyne, azide and Cu_2O. As shown in **Figure 3**, after the model reaction carried out for 6 cycles, the yield showed slowly decreasing. In the ninth cycle, the yield decreased sharply to 50 % and the pH values of the remaining water phase is 4.36. It could be imaged that the hydrogen ions were slowly consumed by Cu_2O. When the Cu_2O was replaced by CuOH (1 mol%), the same trend of pH and catalytic efficiency changes could be obtained. It was very interesting that after the remaining water phase was acidified by HCl to 2.82, the catalytic efficiency of CMP was recovered. The remaining water phase could be reused for another 6 times without notable yields changes. It is worth to mention that when the pure water in the absence of CMP was acidified by HCl to 2.82, the obtained yield is only 25.6% even if the reaction temperature is at 60 ºC. It should attribute to the stable ability of CMP for copper(I) ion and the importance of CMP for Cu_2O-AAC reaction.
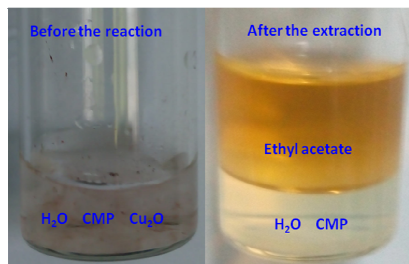

Figure 4. The picture of before the reaction (left) and after the reaction (right)

A wide range of diversely substituted terminal alkynes and azides were carried out under the optimized conditions in water at 60 ºC. As shown in **Table 2**, the reactions work well not only with alkyl azides, but also with aryl azides. All reactions were highly regioselective towards the 1,4-disubstituted triazoles within 20 mins.

Table 2. Synthesis of triazoles using CMP/Cu_2O system
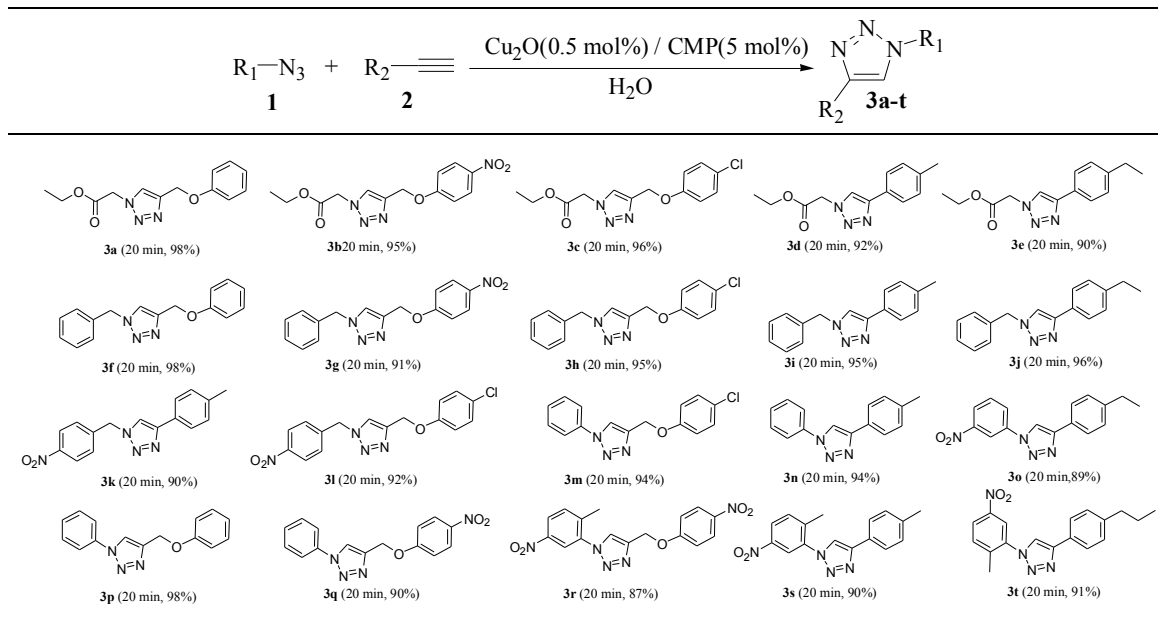
The proposed mechanism (**Scheme 3**) for the reaction will be the same as established mechanism shown in earlier report.[18] The CMP played important roles in the reaction:[8, 19-21] (a) CMP breaks the crystal structure of Cu_2O to allow the formation of copper(I) species-highly efficient catalysts for CuAAC reaction assisted by the its acidity; (b) CMP⁻ as a ligand coordinated Cu(I) of monomer to promote the formation of alkynyl-copper(I) intermediate (3) (**step 2**); (c) it had active effect on cycloaddition (**step 3**) and protonation of C-Cu bond (**step 4**); (d) the CMP comes into another cycle.
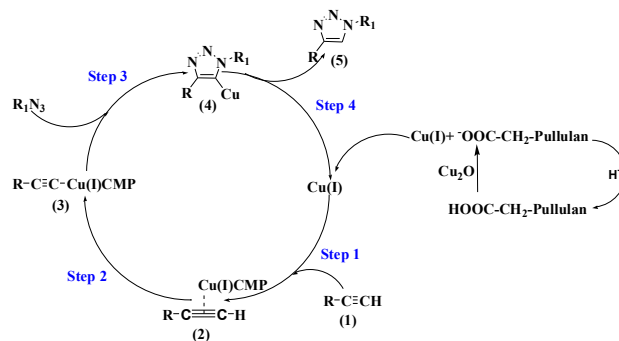
Scheme 3. Proposed mechanism for the CuAAC reaction

Conclusions

In summary, we presented a novel and high yield Cu_2O/CMP catalyst system in water with a relatively short reaction time. Such a method will be interesting as the remaining water phase containing CMP could be reused for several runs and could be recovered by simply acidified by hydrochloride acid.

Acknowledgements

Notes and references

1   V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596.

2   C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057.

3   (a) M. Whiting, J. Muldoon, Y.-C. Lin, S. M. Silverman, W. Lindstrom, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharpless, J. H. Elder and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 1435; (b) H. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128; (c) M. J. Giffin, H. Heaslet, A. Brik, Y. C. Lin, G. Cauvi, C.-H. Wong, D. E. McRee, J. H. Elder, C. D. Stout and B. E. Torbett, *J. Med. Chem.*, 2008, **51**, 6263; (d) H. Rajaram, M. K. Palanivelu, T. V. Arumugam, V. M. Rao, P. Nicholas Shaw, R. P. McGeary and B. P. Ross, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 4523; (e) H. Nandivada, X. W. Jiang and J. Lahann, *Adv. Mater.*, 2007, **19**, 2197; (f) C. F. Ye, G. L. Gard, R. W. Winter, R. G. Syvret, B. Twamley and J. M. Shreeve, *Org. Lett.*, 2007, **9**, 3841; (g) P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Frechet, K. B. Sharpless and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2004, **43**, 3928; (h) E.-H. Ryu and Y. Zhao, *Org. Lett.*, 2005, **7**, 1035; (i) G. K. Such, J. F. Quinn, A. Quinn, E. Tjipto and F. Caruso, *J. Am. Chem. Soc.*, 2006, **128**, 9318; (j) C. H. Wong, S. C. Zimmerman, *Chem. Commun.*, 2013, **49**, 1679; (k) W. P. Zhu, M. J. Zhong, W. W. Li, H.C. Dong and K. Matyjaszewski, *Macromolecules*, 2011, **44**, 1920; (l) Z. J. Zheng, F. Ye, L. S. Zheng, K. F. Yang, G. Q. Lai and L. W. Xu, *Chem. Eur. J.*, 2012, **18**, 14094; (m) X. B. Yao, Y. Gong, R. Mamuti, W. W. Xing, H. Zheng, X. Y. Tang and Y. Wang, *RSC Adv.*, 2014, **4**, 30492; (n) J. L. Huang, C. J. Li and D. G. Gray, *RSC Adv.*, 2014, **4**, 6965.

4   (a) S. Díez-González and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2008, **47**, 8881; (b) S. Díez-González, E. D. Stevens and S. P. Nolan, *Chem. Commun.*, 2008, **39**, 4747; (c) B. W. T. Gruijters, M. A. C.

Broeren, F. L. Delft, R. P. Sijbesma, P. H. H. Hermkens and F. P. J. T. Rutjes, *Org. Lett.*, 2006, **8**, 3163; (d) S. Özçubukçu, E. Ozkal, C. Jimeno and M. A. Pericàs, *Org. Lett.*, 2009, **11**, 4680; (e) J. García-Álvarez, J. Díez and J. Gimeno, *Green Chem.*, 2010, **12**, 2127; (f) L. Li, P. S. Lopes, V. Rosa, C. A. Figueira, M. A. Lemos, M. T. Duarte, T. Aviles and P. T. Gomes, *Dalton Trans.*, 2012, **41**, 5144; (g) S. Lal, J. McNally, A. J. P. White and S. Díez-González, *Organometallics*, 2011, **30**, 6225.

5   (a) K. B. Sharpless, V. V. Fokin, L. G. Green and V. V. Rostovtsev, *Angew. Chem., Int. Ed.*, 2002, **114**, 2708; (b) F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210.

6   (a) L. D. Pachón, J. H. Maarseveen and G. Rothenberg, *Adv. Synth. Catal.*, 2005, **347**, 811; (b) G. Molteni, C. L. Bianchi, G. Marinoni, N. Santo and A. Ponti, *New J. Chem.*, 2006, **30**, 1137; (c) I. S. Park, M. S. Kwon, Y. Kim, J. S. Lee and J. Park, *Org. Lett.*, 2008, **10**, 497.

7   Z. Zhang, C. Dong, C. Yang, D. Hu, J. Long, L. Wang, H. Li, Y. Chen and D. Kong, *Adv. Synth. Catal.*, 2010, **352**, 1600.

8   C. Shao, R. Zhu, S. Luo, Q. Zhang, X. Wang and Y. Hu, *Tetrahedron Lett.*, 2011, **52**, 3782.

9   H. López-Ruiz, J. E. D. L. Cerda-Pedro, S. Rojas-Lima, I. Pérez-Pérez, B. V. Rodríguez-Sánchez, R. Santillan and O. Coreño, *Arkivoc*, 2013, 139.

10   M. N. S. Rad, S. Behrouz, A. Movahedian, M. M. Doroodmand, Y. Ghasemi, S. Rasoul-Amini, A.-R. A. Gandomani and R. Rezaie, *Helv. Chim. Acta.*, 2013, **96**, 688.

11   K. Wang, X. Bi, S. Xing, P. Liao, Z. Fang, X. Meng, Q. Zhang, Q. Liu and Y. Ji, *Green Chem.*, 2011, **13**, 562.

12   (a) F. Alonso, Y. Moglie, G. Radivoy and M. Yus, *Eur. J. Org. Chem.*, 2010, **2010**, 1875; (b) Please see Supporting Information of the following report: E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1730; (c) D. Wang, N. Li, M. Zhao, W. Shi, C. Ma and B. Chen, *Green Chem.*, 2010, **12**, 2120.

13   Y. Q. Jiang, D. Y. Kong, J. L. Zhao, Q. H. Qi, W. Li and G. Q. Xu, *RSC Adv.*, 2014, **4**, 1010.

14   (a) C. Girard, E. Önen, M. Aufort, S. Beauvière, E. Samson, and J. Herscovici, *Org. Lett.*, 2006, **8**, 1689; (b) A. Sarkar, T. Mukherjee and S. Kapoor, *J. Phys. Chem. C*, 2008, **112**, 3334; (c) S. Roy, T. Chatterjee and Sk. M. Islarm, *Green Chem.*, 2013, **15**, 2532; (d) R. B. Nasir Baig and R. S. Varma, *Green Chem.*, 2013, **15**, 1839; (d) T. R. Chan and V. V. Fokin, *QSAR Comb. Sci.*, 2007, **11-12**, 1274; (e) M. Chtchigrovsky, A. Primo, P. Gonzalez, K. Molvinger, M. Robitzer, F. Quignard and F. Taran,

Angew. Chem., Int. Ed., 2009, **48**, 5916; (f) M. N. Tahir, R. Qamar, A. Adnan, E. Cho and S. Jung, *Tetrahedron Lett*., 2013, **54**, 3268; (g) L. Bonami, W. van Camp, D. van Rijckegen and F. E. Du Prez, *Macromol. Rapid Commun*., 2009, **30**, 34; (h) K. R. Reddy, K. Rajgopal and M. L. Kantam, *Catal. Lett*., 2007, **114**, 36; (i) U. Sirion, Y. J. Bae, B. S. Lee and D. Y. Chi, *Synlett*., 2008, 2326.

15 (a) I. Bataille, J. Huguet, G. Muller, G. Mocanu and A. Carpov, *Int. J. Biol. Macromol*., 1997, **20**,179; (b) G. Ali, C. Rihouey, D. Le Cerf, and L. Picton, *Carbohyd. Polym*., 2013, **93**, 109; (c) G. Mocanu, Z. Souguir, L. Picton and D. Le Cerf, *Carbohyd. Polym*., 2012, **89**, 578; (d) M. Legros, P. Cardinael, V. Dulong, L.Picton, D.Le Cerf, *Polym. J*., 2008, **40**, 1132; (e) K. Horie, M.Sakagami, K. Masuda, M. Notoya, H. Hamana, T. Yoshikawa and K. Hirano, *Biol. Pharm. Bull*., 2004, **27**, 1275.

16 Y. Q. Jiang, D. Y. Kong, J. L. Zhao, W. W. Zhang, W. J. Xu, W. Li and G. Q. Xu, *Tetrahedron Lett.*, 2014, **55**, 2410.

17 (a) D. Mendoza-Espinosa, G. E. Negrón-Silva, D. Ángeles-Beltrán, A. Álvarez-Hernández, O. R. Suárez-Castillo and R. Santillán, *Dalton Trans*., 2014, **43**, 7069; (b) D. Schweinfurth, K. I. Hardcastle and Uwe H. F. Bunz, *Chem. Commun*., 2008, 2203; (c) C. Deraedt, N. Pinaud and D. Astruc, *J. Am. Chem. Soc*., 2014, **136**,12092.

18 F. Himo, T. Lovell, R. Hilgraf, V. V. Rostovtsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210.

19 N. Balcioglu, I. Uraz (Unalan), C. Bozkurt and F. Sevin, *Polyhedron*, 1997, **16**, 327.

20 C. Shao, X. Wang, J. Xu, J. Zhao, Q. Zhang and Y. Hu, *J. Org. Chem.*, 2010, **75**, 7002.

21 C. Shao, G. Cheng, D. Su, J. Xu, X. Wang and Y. Hu, *Adv. Synth. Catal.*, 2010, **352**, 1587.

Graphical abstract
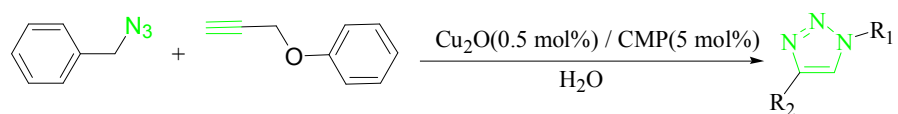
Cu$_2$O/CMP has been developed as a highly efficient catalytic system for Huisgen-click reaction in water at 60 ºC.