JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja5097489 • Publication Date (Web): 10 Nov 2014

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Cu(II)/Cu(I)-Synergistic Cooperation to Lead the Alkyne C-H Activation

Ruopeng Bai,[†] Guanghui Zhang,[†,‡] Hong Yi,[†] Zhiliang Huang,[†,‡] Xiaotian Qi,[§] Chao Liu,[†] Jeffrey T. Miller,[‡] A. Jeremy Kropf,[‡] Emilio E. Bunel,[‡] Yu Lan,[*,§] and Aiwen Lei[*,†,‡]

[†]College of Chemistry and Molecular Sciences, Wuhan University, Wuhan 430072, P.R. China

[‡]Chemical Sciences and Engineering Division, Argonne National Laboratory, 9700 S. Cass Ave., Argonne, Illinois 60439, United States

[§]School of Chemistry and Chemical Engineering, Chongqing University, Chongqing 400030, P.R. China

Supporting Information Placeholder

ABSTRACT: An efficient alkyne C-H activation and homocoupling procedure has been studied which indicates that a Cu(II)/Cu(I) synergistic cooperation might be involved. *In situ* Raman spectroscopy was employed to study kinetic behavior, drawing the conclusion that Cu(I) rather than Cu(II) participates in the rate determining step. IR, EPR and X-ray absorption spectroscopy evidence were provided for structural information, indicating that Cu(I) has a stronger interaction with alkyne than Cu(II) in the C-H activation step. Kinetics study showed Cu(II) plays a role as oxidant in C-C bond construction step, which was a fast step in the reaction. X-band EPR spectroscopy showed that the coordination environment of $CuCl_2$(TMDEA) was affected by Cu(I). A putative mechanism with Cu(I)-Cu(II) synergistic cooperation procedure was proposed for the reaction.

Copper salts are well accepted as remarkable, important and promising catalysts,[1] which are widely used to synthesize a variety of compounds, such as natural products, medicine molecules, agrochemicals, and organic functional materials.[2] Among these, coupling reactions involving terminal alkynes is a significant branch, and have a history of over one century, and several named reactions were developed to build Csp-C single bonds, such as Glaser-Hay reaction[3] and Sonogashira reaction.[4] These processes have received extensive attention and been widely applied as simple and convenient methods to synthesize internal alkynes and diynes.[5] There have also been a number of studies that have investigated the reaction mechanism.[6]

However, the mechanistic research of these reactions still remains a challenge and attracted numerous attention. Usually, in most Cu-catalyzed coupling reactions with alkynes, it is generally proposed that the C-H activation of alkyne, to form Cu(I)-acetylide, is a smooth and facile step. It is generally accepted that Cu(I) acetylides are key intermediates for numerous Cu-catalyzed synthetic reaction,[7] however, sometimes without convincing evidences. As is well known, synthetic Cu-acetylide are polymers,[8] and are not kinetically active as catalytic intermediates in most reactions. As a result, different from other isolated intermediates, catalytic behavior of Cu-acetylide is not that active. Herein, we communicate an efficient autocatalytic alkyne C-H activation procedure via Cu(II)-Cu(I) synergistic cooperation.

Our initial effort focused on the kinetic behaviors of the homocoupling of terminal alkynes with Cu(II). Raman spectroscopy is a powerful method to monitor Raman-active C-C triple bonds. Herein, *in situ* FT-Raman spectroscopy was employed instead to detect the changes of alkyne substances (Figure 1). $CuCl_2$(TMEDA) (TMEDA = tetramethylethylenediamine) **2** could be reduced by phenylacetylene **1** promptly to form biphenylacetylene **3** at 37 °C (Figure 1a). In Figure 1b, a short induction period, less than 150s, was observed, together with an auto-acceleration curve. Similar kinetic behavior was observed when lowering the reaction to 0 °C, however, with a longer induction period and longer reaction time. Upon further cooling to -20 °C, the reaction was totally restrained unless rising the temperature.

As the kinetic behavior was so close to the autocatalytic reaction module, a similar autocatalytic procedure involving Cu(I) was proposed. To verify our hypothesis, a large concentration of Cu(I) was added to in the reaction at -20°C. The induction period disappeared and the reaction finished in about 10 min, and the reaction rate was evidently improved with 0.5 mmol $[CuCl(TMEDA)]_2$ (Figure 1c). Moreover, when decreasing the amount of $[CuCl(TMEDA)]_2$ to 0.1 mmol, the reaction was moderated and the induction period appeared again. These results indicated that Cu(I) was involved in the reaction, same as orthodox autocatalytic procedures.

To clear the roles Cu(I) and Cu(II) play in the reaction, we tried to investigate the interaction between Cu species and different substances. As Cu(II) is widely used to catalyze terminal alkynes coupling reactions,[6e, 7a, 7b] to elucidate the effect of Cu(II) specie in the reaction, detailed kinetic experiments of $CuCl_2$(TMEDA) and phenylacetylene were carried out for the observed initial rate constant of the reaction in the presence of same initial amount of $[CuCl(TMEDA)]_2$. As shown in Figure 2a, variation of the initial concentration of $CuCl_2$(TMEDA) displayed little influence upon the initial rate of the reaction, presenting a zero-order dependent on $CuCl_2(TMEDA)$. This indicated that it is more likely Cu(II) didn't participate in the rate determining step (RDS). Meanwhile, as shown in Figure 2b, a first-order kinetic plot was obtained on the initial concentration of phenylacetylene, suggesting that phenylacetylene was involved in the rate determining step.

$$\underset{1}{Ph-\equiv} + \underset{2}{CuCl_2(TMEDA)} \xrightarrow[DMF,\ N_2]{iPr_2NH} \underset{3}{Ph-\equiv-\equiv-Ph} + \underset{4}{[CuCl(TMEDA)]_2}$$

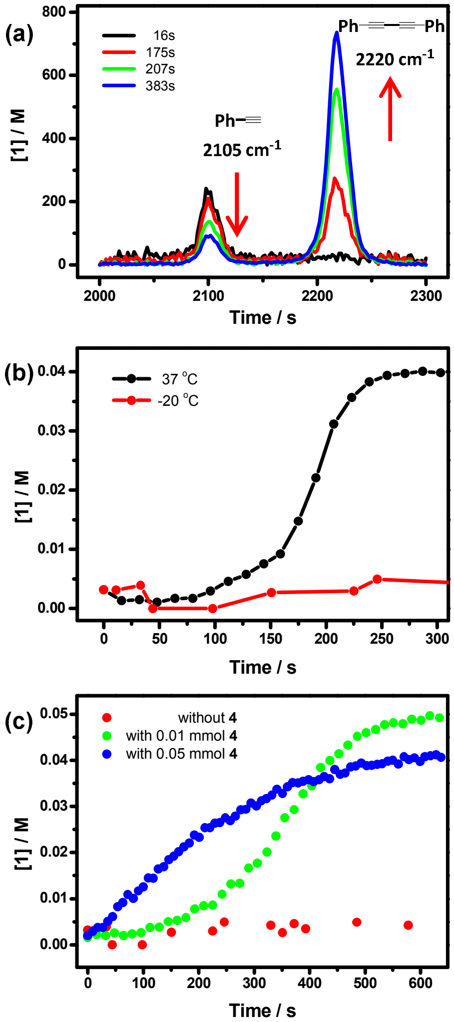


Figure 1. (a) Raman spectra change in the reduction process at 37 °C. (b) Kinetic profiles of the reduction process at 37 °C (black) and -20 °C (red). (c) Kinetic profiles with 0 mmol (red), 0.05 mmol (green), 0.5 mmol (blue) **4** at -20 °C. All of the reactions were carried out with **1** (2.0 mmol), **2** (1.0 mmol), iPr_2NH (2.0 mmol), in 10 mL DMF. See Supporting Information for details.

Moreover, for the purpose of investigating the reaction rate of C-C bond formation, stoichiometric reaction between $CuCl_2(TMEDA)$ and lithium phenylacetylide was carried out. On addition of $CuCl_2(TMEDA)$ solution into lithium phenylacetylide solution at -70 °C, the increase of diphenylacetylene was detected immediately, and the reaction was complete within 2 minutes monitored by *in situ* IR spectroscopy. Compared with the kinetic behavior above, this could be considered as direct evidence that Csp-Csp bond construction was a fast, non-rate-determining step in the reaction.

$$1 + 2 + iPr_2NH \xrightarrow[-20\ ^{\circ}C]{4,\ DMF,\ N_2} 3 + 4$$

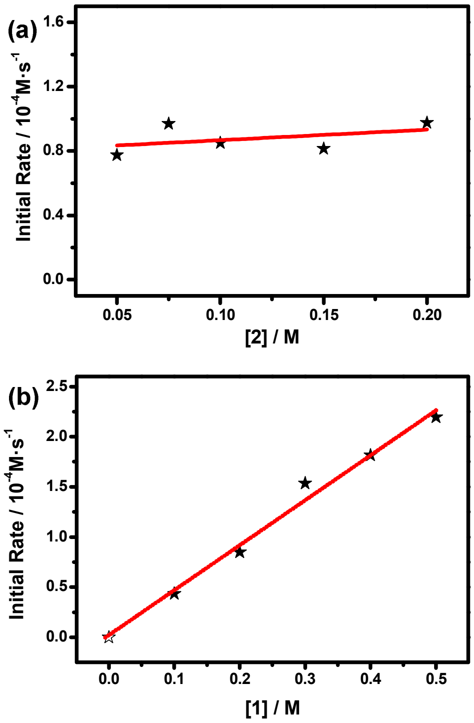


Figure 2. (a) Kinetic profiles with different concentration of $CuCl_2(TMEDA)$ at -20 °C. (b) Kinetic profiles and fitting curve of initial rate with different concentration of phenylacetylene at -20 °C, and the $K_{obv} = 4.485 \times 10^{-4}\ s^{-1}$. All of the reactions were carried out with **1** (2.0 mmol or as shown), $[CuCl(TMEDA)]_2$ (0.25 mmol), iPr_2NH (2.0 mmol), $CuCl_2(TMEDA)$ (2.0 mmol or as shown) in 10 mL DMF. See Supporting Information for details.

According to the kinetic behavior above, we put our efforts into discerning the catalytic intermediates in the catalytic process engaging various analytic methods. When phenylacetylene was introduced into the DMF solution of $[CuCl(TMEDA)]_2$, a weak Infrared (IR) shift of the peak of $[CuCl(TMEDA)]_2$ was detected from 796 cm^{-1} to 800 cm^{-1}. Similar effect was not observed by substitution $CuCl_2(TMEDA)$ for Cu(I). This phenomenon could be recurred by electron paramagnetic resonance (EPR): the addition of phenylacetylene didn't cause the peak shift of $CuCl_2(TMEDA)$. This phenomena can be explained by density functional theory (DFT) calculations: the coordination energy of phenylacetylene-Cu(II)-TMEDA adduct (+5.9 kcal/mol) is much higher than phenylacetylene-Cu(I)-TMEDA adduct (+1.2 kcal/mol),[9] ,which means that the coordination between phenylacetylene and Cu(II)-TMEDA adduct is more difficult than Cu(I)-TMEDA adduct.

In addition, we came to the same conclusion when investigating the interaction between Cu catalyst and phenylacetylene via X-ray absorption spectroscopy (XAS). As shown in Figure 3, in the R-space EXAFS spectra, a shorter average bond distance was observed once upon the addition of phenylacetylene, which suggested the coordination of phenylacetylene to Cu(I). Moreover, the shape of the XANES spectrum also changed, suggesting that phenylacetylene coordinated to Cu(I) center. On the contrary, when phenylacetylene was added into the $CuCl_2$/TMEDA solution, no obvious change was found in neither the XANES nor the EXAFS spectra. It can be concluded that Cu(I) has stronger interaction with phenylacetylene than Cu(II).

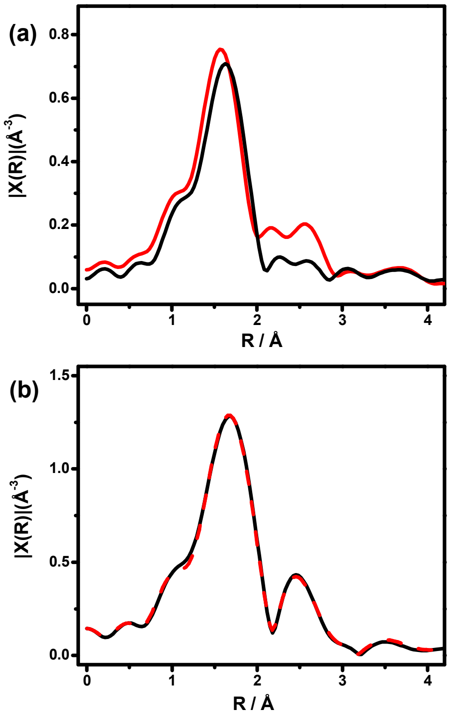


Figure 3. (a) k^2-weighted magnitude of the fourier transform (FT) of $[CuCl(TMEDA)]_2$ without (red) and with (black) phenylacetylene. (b) k^2-weighted magnitude of the fourier transform (FT) of $CuCl_2$(TMEDA) without (red) and with (black) phenylacetylene.

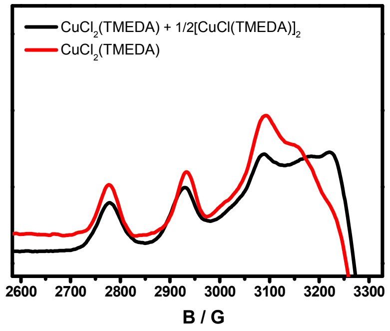
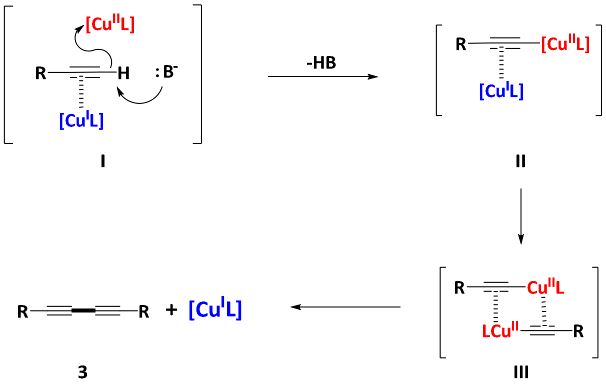


Figure 4. X-band EPR spectra of $CuCl_2$(TMEDA)-$[CuCl(TMEDA)]_2$ DMF solution (black, 0.01M $CuCl_2$(TMEDA) and 0.005M $[CuCl(TMEDA)]_2$), and $CuCl_2$(TMEDA) DMF solution (red, 0.01M).

Cu(I) could not only coordinate with the terminal alkynes, but affect the coordination environment of Cu(II). As shown in Figure 4, slight EPR spectra differences were observed by adding stoichiometric $[CuCl(TMEDA)]_2$ into $CuCl_2$(TMDEA) DMF solution. That indicates that the coordination environment of $CuCl_2$(TMDEA) was affected by added stoichiometric Cu(I). These results showed that the coordination environment of $CuCl_2$(TMDEA) could be affected by Cu(I), directing to a possibility of Cu(I)-Cu(II) intermediate structure.

Based on the investigations and clues above, putative mechanism was proposed (Scheme 1). First, Cu(I) coordinated with terminal alkyne reactants, to generate the coordination adduct intermediate **I**. By this step, inactive C-H bond could be activated for C-H activation. Subsequently, in the presence of base, **I** was deprotonated, and this step was considered as the rate determining step according to previous kinetic studies. Meanwhile, C-Cu(II) bond was constructed, to generate intermediate **II**. Next, **III** was generated from **II** by a dimerization step. Finally, **III** participated in the electron transfer and C-C bond formation step, to generate the final coupling product **3** and the reduced Cu(I) species.



Scheme 1. Key steps of the putative mechanism.

In conclusion, we have discovered an efficient terminal alkyne C-H activation and homocoupling procedure via Cu(I)-Cu(II) synergistic cooperation. By studying the kinetic behavior with *in situ* Raman spectroscopy, we came to the conclusion that Cu(I) participated in the rate determining step and accelerate the reduction procedure efficiently; and Cu(II) took part in the C-C bond formation step. IR, EPR, X-ray absorption spectroscopy experiments and DFT calculation were proceeded for observing the coordination between different Cu species and alkyne, giving a direct evidence that Cu(I) has a stronger coordination effect with terminal alkynes than Cu(II) to promote the C-H activation step. By kinetic studies, we made it clear that Cu(II) played a role as oxidant in C-C bond construction step, which was proved as a fast step in the reaction. Moreover, the difference of X-band EPR spectroscopy showed that the coordination environment of $CuCl_2$(TMDEA) was affected by Cu(I), drawing a possibility of Cu(I)-Cu(II) intermediate structure, which could be an efficient way to shorten the distance between Cu(II) oxidant and alkyne. All these clues described the catalytic circle: Cu(I) is more possible than Cu(II) to play a role as catalyst: coordinating with alkynes to promote C-H activation procedure, followed by a fast electron transfer step from Cu(II), to construct the homocoupling product. The overall reaction was proceeded with the assist of Cu(I)-Cu(II) synergistic cooperation. Further investigations will be carried out for detailed mechanisms and intermediate structures.

ASSOCIATED CONTENT

Supporting Information

The experimental procedure; detailed IR, EPR and XANES/EXAFS results; detailed information of DFT calculation. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

lanyu@cqu.edu.cn
aiwenlei@whu.edu.cn

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

This work was supported by the "973" Program from the MOST of China (2012CB725302), the National Natural Science Foundation of China (21390400, 21025206, 21272180 21302148 and 21372266), the Research Fund for the Doctoral Program of Higher Education of China (20120141130002) and the Program for Changjiang Scholars and Innovative Research Team in University (IRT1030).The Program of Introducing Talents of Discipline to Universities of China (111 Program) is also appreciated. Use of the Advanced Photon Source was supported by the U. S. Department of Energy, Office of Science, Office of Basic Energy Sciences, under Contract No. DE-AC02-06CH11357. MRCAT operations are supported by the Department of Energy and the MRCAT member institutions. Partial funding for J.T.M. was provided by the Chemical Sciences, Geosciences and Bioscience Division, U.S. Department of Energy, under contract no. DE-AC0-06CH11357. This work was also funded by the Chemical Sciences and Engineering Division at Argonne National Laboratory.

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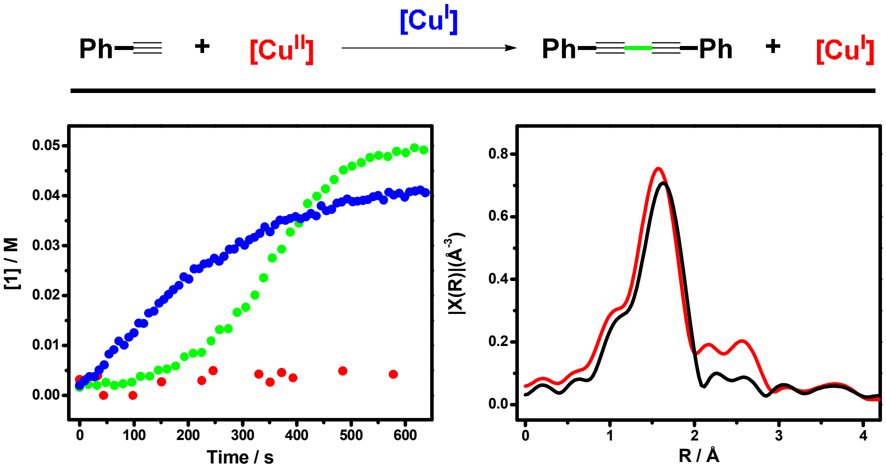
Ph
+
[Cu^{II}]
[Cu^{I}]
Ph
Ph
+
[Cu^{I}]
[1] / M
0.05
0.04
0.03
0.02
0.01
0.00
0
100
200
300
400
500
600
Time / s
|X(R)|(Å^{-3})
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
R / Å