

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

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S Supporting Information

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 CuCl₂(TMEDA) was affected by Cu(I). A putative mechanism with Cu(I)–Cu(II) synergistic cooperation procedure is proposed for the reaction.

Copper salts are well accepted as remarkable, important, and promising catalysts,¹ that 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 are a significant branch and have a history of over one century, and several named reactions were developed to build C_{sp}–C single bonds, such as Glaser–Hay³ and Sonogashira⁴ reactions. 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 has attracted extensive 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 reactions,⁷ however, sometimes without convincing evidence. As is well-known, synthetic Cu-acetylide are polymers⁸ 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). CuCl₂(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, <150 s, was observed, together with an autoacceleration 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 suppressed until the temperature was increased.

As the kinetic behavior was so close to the autocatalytic reaction model, 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, in the same manner as orthodox autocatalytic procedures.

To clearly identify the roles that 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,b} to elucidate the effect of Cu(II) specie in the reaction, detailed kinetic experiments of CuCl₂(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 CuCl₂(TMEDA) displayed little influence upon the initial rate of the reaction, presenting a zero-order dependence on CuCl₂(TMEDA). This indicated that it is likely Cu(II) did not participate in the rate-determining step (RDS). Meanwhile,

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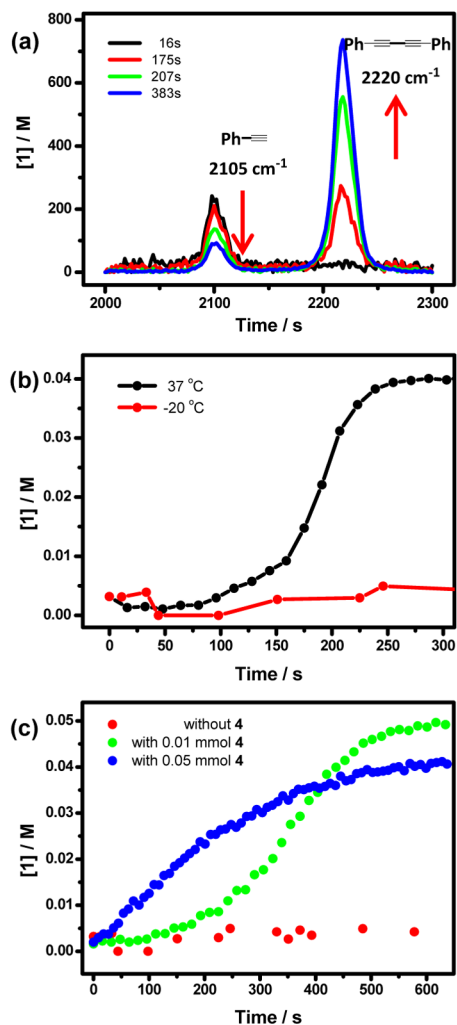
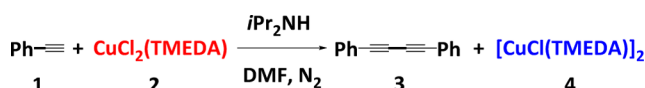


Figure 1. (a) Raman spectra change in the reduction process at 37 °C. (b) Kinetic profiles of the reduction process at 37 °C (black) and –20 °C (red). (c) Kinetic profiles with 0 (red), 0.05 (green), and 0.5 mmol (blue) **4** at –20 °C. All of the reactions were carried out with **1** (2.0 mmol), **2** (1.0 mmol), *i*Pr₂NH (2.0 mmol), in 10 mL DMF. See Supporting Information (SI) for details.

as shown in Figure 2b, a first-order kinetic plot was obtained based on the initial concentration of phenylacetylene, suggesting that phenylacetylene was involved in the RDS.

Moreover, for the purpose of investigating the reaction rate of C–C bond formation, stoichiometric reaction between CuCl₂(TMEDA) and lithium phenylacetylide was carried out. On addition of CuCl₂(TMEDA) solution into lithium phenylacetylide solution at –70 °C, the increase of diphenylacetylene was detected immediately, and the reaction was complete within 2 min as monitored by *in situ* IR spectroscopy. Compared with the kinetic behavior above, this could be considered as direct evidence that C_{sp}–C_{sp} bond formation was a fast, nonrate-determining step in the reaction.

According to the kinetic behavior above, we directed our efforts towards discerning the catalytic intermediates in the catalytic process using various analytical methods. When phenylacetylene was introduced into the DMF solution of

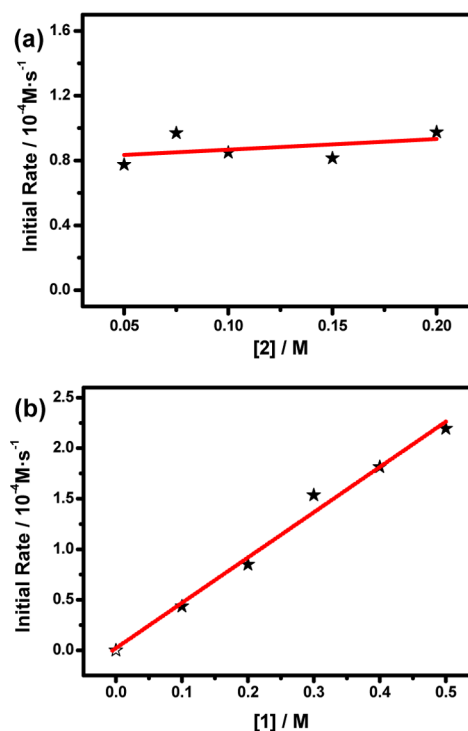
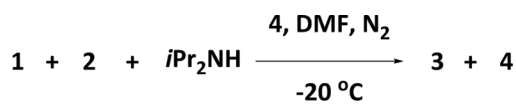


Figure 2. (a) Kinetic profiles with different concentration of CuCl₂(TMEDA) at –20 °C. (b) Kinetic profiles and fitting curve of initial rate with different concentration of phenylacetylene at –20 °C, and the $K_{\text{obv}} = 4.485 \times 10^{-4} \text{ s}^{-1}$. All of the reactions were carried out with **1** (2.0 mmol or as shown), [CuCl(TMEDA)]₂ (0.25 mmol), *i*Pr₂NH (2.0 mmol), and CuCl₂(TMEDA) (2.0 mmol or as shown) in 10 mL DMF. See SI for details.

[CuCl(TMEDA)]₂, a weak infrared (IR) shift of the peak of [CuCl(TMEDA)]₂ was detected from 796 to 800 cm^{–1}. Similar effect was not observed by substitution CuCl₂(TMEDA) for Cu(I). This phenomenon was also observed by electron paramagnetic resonance (EPR): the addition of phenylacetylene did not cause the peak shift of CuCl₂(TMEDA). These 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 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 the Cu(I) center. On the contrary, when phenylacetylene was added into the CuCl₂/TMEDA solution, no obvious change was found in either the XANES or the EXAFS spectra. It can be

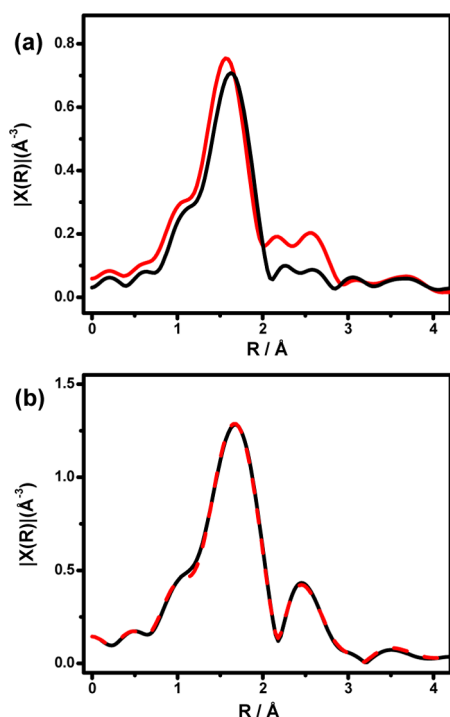


Figure 3. The k^2 -weighted magnitude of the Fourier transform (FT) (a) of $[\text{CuCl}(\text{TMEDA})]_2$ without (red) and with (black) phenylacetylene and (b) of $\text{CuCl}_2(\text{TMEDA})$ without (red) and with (black) phenylacetylene.

concluded that Cu(I) has a stronger interaction with phenylacetylene than Cu(II).

Cu(I) not only can coordinate with the terminal alkynes but also affect the coordination environment of Cu(II). As shown in Figure 4, slight EPR spectra differences were observed by

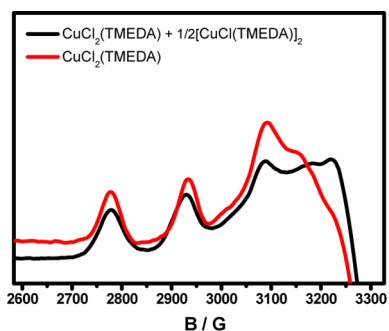
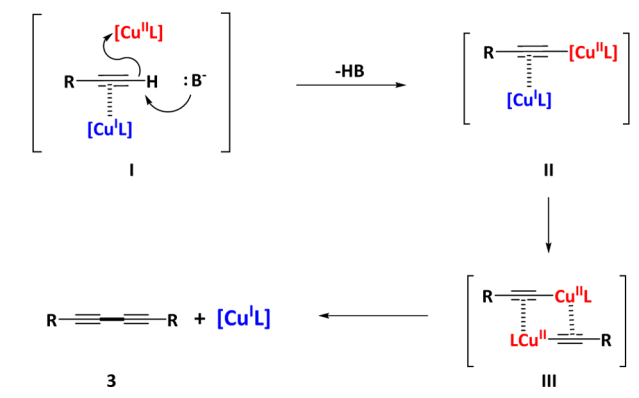


Figure 4. X-band EPR spectra of $\text{CuCl}_2(\text{TMEDA})$ - $[\text{CuCl}(\text{TMEDA})]_2$ DMF solution (black, 0.01 M $\text{CuCl}_2(\text{TMEDA})$ and 0.005 M $[\text{CuCl}(\text{TMEDA})]_2$) and $\text{CuCl}_2(\text{TMEDA})$ DMF solution (red, 0.01M).

adding stoichiometric $[\text{CuCl}(\text{TMEDA})]_2$ into $\text{CuCl}_2(\text{TMEDA})$ DMF solution. This indicated that the coordination environment of $\text{CuCl}_2(\text{TMEDA})$ was affected by added stoichiometric Cu(I). These results show that the coordination environment of $\text{CuCl}_2(\text{TMEDA})$ could be affected by Cu(I), suggesting the 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

Scheme 1. Key Steps of the Putative Mechanism



be activated for C-H activation. Subsequently, in the presence of base, I was deprotonated, and this step was considered as the RDS according to previous kinetic studies. Meanwhile, C-Cu(II) bond was formed generating 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.

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) participates in the RDS and accelerates the reduction procedure efficiently; and Cu(II) takes part in the C-C bond formation step. IR, EPR, XAS experiments and DFT calculations combined to elucidate the coordination between different Cu species and alkyne, giving direct evidence that Cu(I) has a stronger coordination effect with terminal alkynes than Cu(II) to promote the C-H activation step. From kinetic studies, it is clear that Cu(II) plays a role as an oxidant in C-C bond formation, which proved to be a fast step in the reaction. Moreover, the differences observed in X-band EPR spectroscopy showed that the coordination environment of $\text{CuCl}_2(\text{TMEDA})$ 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 of these clues described the catalytic cycle: 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 on DFT calculation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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