

Quick XAFS study on Pd/Cu catalyzed organic name reaction

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Abstract: Although copper acetylides have been widely used as nucleophiles, especially in transition-metal-catalyzed C-C bond formation, do not take it for granted that copper acetylide can be easily formed in the copper-catalyzed transformation of terminal alkynes. Herein, we disclosed that the typical σ -bonded copper acetylide is not the active intermediate in the Pd/Cu synergistically catalyzed Sonogashira coupling reaction. Copper acetylide is not observed in the stoichiometric reactions between copper(I) salt with terminal alkyne in the presence of Et₃N or *i*Pr₂NH monitored by in situ XAS and NMR spectroscopy. Density functional theory study indicates that the Pd/Cu synergy leads the transmetalation of terminal alkyne, and the palladium acetylide complex is formed directly instead of the formation of σ -bonded copper acetylide complex.

Do not take it for granted that copper acetylide can be easily formed in the copper-catalyzed transformation of terminal alkynes. Since copper has been employed as “mediator” in synthetic chemistry for more than a century, there are numerous useful and practical methods for C-C and C-heteroatom bond formation using copper catalysts¹⁻⁷. Especially, the copper-catalyzed functionalization of terminal alkynes has emerged as a powerful and attractive tool in the synthesis of pharmaceuticals, agrochemicals, and materials etc^{5,8-13}. For example, Glaser-Hay coupling reaction has become the most useful and convenient method to construct di- and oligo- acetylenes¹⁴⁻¹⁷. Palladium and copper synergistically catalyzed Sonogashira coupling reaction has also been the most powerful method to achieve the formation of Csp²-Csp bonds^{18,19}. Another well-known example is the copper-catalyzed alkyne-azide “click” reaction²⁰⁻²⁴. In these transformations, copper acetylides are usually considered as the key intermediates (**Fig. 1**). However, few examples provided evidence regarding the formation or transformation of copper acetylides under catalytic conditions. The structural details are still unclear due to their poor solubility and diverse structures. Several crystal structures of copper acetylides have been reported^{13,25-31}; however, crystal structures do not necessarily reflect the structures of the catalytically active species. Herein, we report detailed investigations into the “live” Pd/Cu synergistically catalyzed Sonogashira coupling reaction. Kinetic studies and stoichiometric experiments monitored by operando IR, in situ X-ray absorption (XAS)³²⁻³⁶ and NMR spectroscopy reveal that under catalytic conditions, copper acetylide does not form as the active intermediate. Computational result indicates that the transmetalation of terminal alkyne is assisted synergistically by both palladium and copper species without the formation of σ -bonded copper acetylide. The understanding of the active copper species under catalytic conditions should provide valuable assistance in the comprehension and design of copper-catalyzed transformation of terminal alkynes on similar systems.

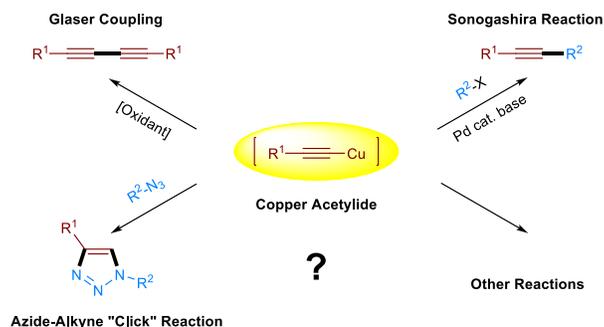


Fig. 1 Copper acetylides are usually considered as the intermediates in copper-catalyzed functionalization of terminal alkynes.

Results

At the outset of our studies, we selected a standard condition to proceed the catalytic Sonogashira coupling reaction. Catalyzed by 1 mol% PdCl₂(PPh₃)₂ and 2 mol% CuI, phenylacetylene **1** reacted with iodobenzene **2** smoothly to afford the coupling product **3** in good yield in the presence of normal organic base such as Et₃N or *i*Pr₂NH (**Fig. 2a**). As copper acetylide is often considered as the key intermediate in this transformation, we next synthesized the typical copper acetylide species (complex A) using NH₄OH as the base according to the general procedure³⁷, whose structure is also known as a polymer²⁵. To our surprise, treatment of the prepared copper acetylide species (complex A) with iodobenzene **2** only produced a yield of less than 5% cross-coupling product even in the presence of palladium catalyst (**Fig. 2b**). This result let us reconsider whether copper acetylide is the active intermediate of the Pd/Cu synergistically catalyzed Sonogashira coupling reaction.

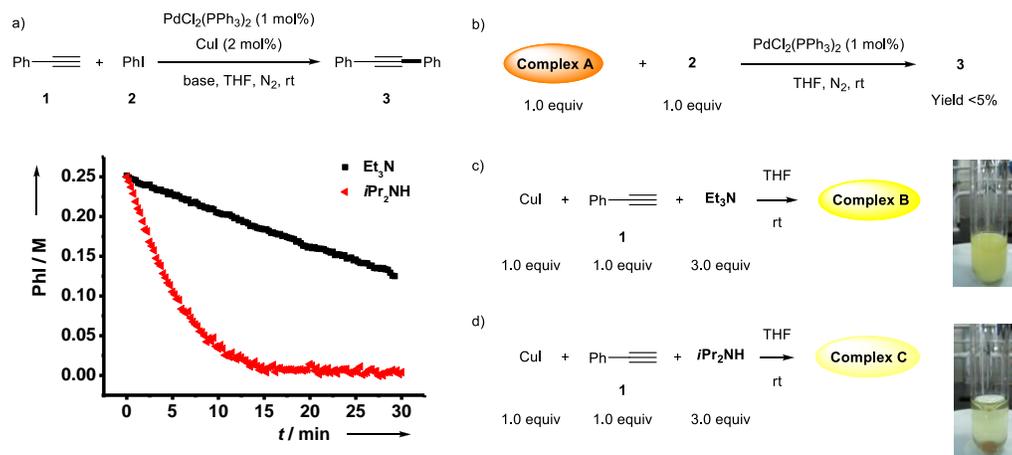


Fig. 2 Kinetic study of the catalytic Sonogashira coupling reaction and stoichiometric reactions investigation. **a)** Kinetic profiles of the consumption of **2** in the Sonogashira reaction monitored by operando IR spectroscopy. The ConClRT spectrum of **2** with peak at 1575 wave number cm^{-1} was used for the generation of the kinetic profiles which is assigned as the aromatic ring stretch frequency. Reaction conditions: **1** (1.1 mmol), **2** (1.0 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (1 mol%), CuI (2 mol%), and base (3.0 equiv) in 4 mL of THF under N_2 atmosphere at rt. Using Et_3N as the base for 30 min, 50% yield; for 4 h, 98% yield. Using $i\text{Pr}_2\text{NH}$ as the base for 15 min, 99% yield. Yields were determined by GC with naphthalene as the internal standard. **b)** The reaction of prepared copper acetylide complex **A** with **2** in the presence of $\text{PdCl}_2(\text{PPh}_3)_2$ (1 mol%). **c)** Stoichiometric reaction of **1** with CuI in the presence of Et_3N . **d)** Stoichiometric reaction of **1** with CuI in the presence of $i\text{Pr}_2\text{NH}$.

To gain more information, stoichiometric reactions of phenylacetylene **1** with copper salts were investigated in the presence of Et_3N or $i\text{Pr}_2\text{NH}$ under the similar conditions of catalytic reaction. As shown in (**Fig. 2c**), when 3.0 equiv of Et_3N were added into the mixture of CuI and phenylacetylene **1** in THF, a pale yellow suspension (complex **B**) was immediately formed. While, when 3.0 equiv of $i\text{Pr}_2\text{NH}$ were added into the mixture of CuI and phenylacetylene **1** in THF, a light yellow clear solution was generated (complex **C**) (**Fig. 2d**). Both complexes **B** and **C** were completely different from the typical copious bright yellow precipitate copper acetylide (complex **A**) with very poor solubility.

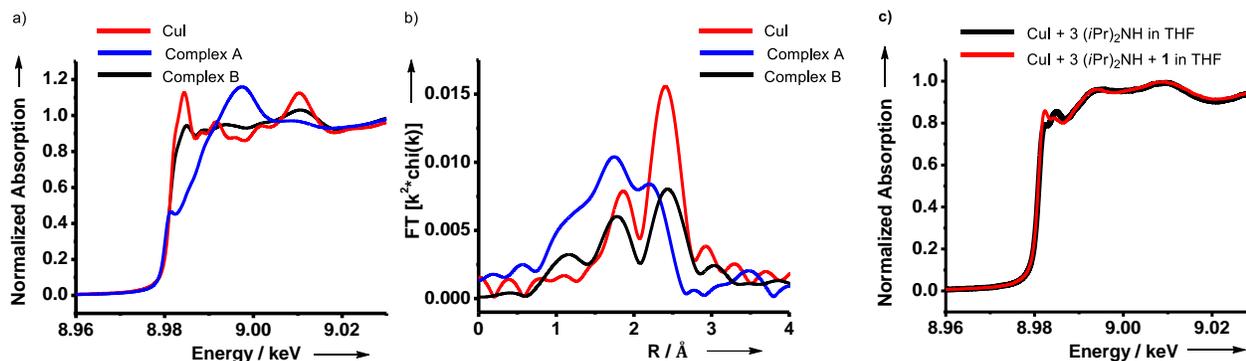


Fig. 3 X-ray absorption spectroscopy experiments. **a)** Cu XANES spectra of CuI , complexes **A** and **B**. **b)** k^2 -weighted magnitude of the Fourier transform. Complex **A** ($2.56 < k < 11.27$), complex **B** ($2.58 < k < 10.09$) and CuI ($2.56 < k < 10.96$). **c)** Cu XANES spectra of $\text{CuI}/i\text{Pr}_2\text{NH}$ and complex **C**.

The Cu K-edge XANES (X-Ray Absorption Near Edge Structure) spectra and the k^2 -weighted magnitude of the Fourier transform of complex **A**, **B** and CuI are shown in **Fig. 3a** and **3b**. Compared with CuI , the prepared copper acetylide complex **A** has a distinct coordination environment, and no Cu-I bond was observed. As shown in **Fig. 3b**, the Cu-I bond peaks still dominated the R-space EXAFS (Extended X-ray Absorption Fine Structure) spectrum indicating that most of the CuI remained unreacted in complex **B**. Meanwhile, the ^1H NMR spectra also showed that most of the terminal alkyne **1** still remained in the solution. Although complex **B** was a pale yellow suspension mixture, less than 20% conversion of **1** indicated that the typical σ -bonded copper acetylide species might not form under this condition.

The reactions of CuI , $i\text{Pr}_2\text{NH}$ with/without phenylacetylene **1** in THF were also investigated by XAS and NMR spectroscopy. Herein, $i\text{Pr}_2\text{NH}$ could directly react with CuI in THF to form a colorless clear solution. As shown in **Fig. 3c**, the XANES spectra of the two solutions were slightly different, which suggested the coordination environment only changed a little after the addition of phenylacetylene **1**, which is also consistent with the EXAFS data. The ^1H NMR spectra also revealed that $i\text{Pr}_2\text{NH}$ coordinated to the copper species. Interestingly, similar results have also been found by Vasella et al. when they used ^1H NMR to investigate the mixture of terminal alkynes, CuI and amine³⁸. The EXAFS data of $[\text{Cu}(\text{TMEDA})]_2$ (TMEDA: N',N',N'',N'' -tetramethylethane-1,2-diamine) was also collected and used as a model for the data analysis. In this case, it is reasonable to speculate that $i\text{Pr}_2\text{NH}$ functions as not only the base, but also a tunable N -ligand, which could coordinate to the CuI and enhanced the solubility of the copper catalyst. In addition, $i\text{Pr}_2\text{NH}$ might have accessible coordination/dissociation equilibrium allowing acetylene to react with copper sites. Thus, the above investigations

further confirmed that the typical σ -bonded copper acetylide did not form in the “live” catalytic Pd/Cu synergistically catalyzed Sonogashira coupling reactions.

References

- 1 Krause, N. *Modern organocopper chemistry*. (Wiley-VCH, 2002).
- 2 Meijere, A. d. & Diederich, F. *Metal-catalyzed cross-coupling reactions*. 2nd, completely rev. and enl. edn, (Wiley-VCH, 2004).
- 3 Hassan, J., Sevignon, M., Gozzi, C., Schulz, E. & Lemaire, M. Aryl-aryl bond formation one century after the discovery of the Ullmann reaction. *Chem. Rev.* **102**, 1359-1469 (2002).
- 4 Ley, S. V. & Thomas, A. W. Modern synthetic methods for copper-mediated C(aryl)-O, C(aryl)-N, and C(aryl)-S bond formation. *Angew. Chem., Int. Ed.* **42**, 5400-5449 (2003).
- 5 Beletskaya, I. P. & Cheprakov, A. V. Copper in cross-coupling reactions. *Coord. Chem. Rev.* **248**, 2337-2364 (2004).
- 6 Evano, G., Blanchard, N. & Toumi, M. Copper-Mediated Coupling Reactions and Their Applications in Natural Products and Designed Biomolecules Synthesis. *Chem. Rev.* **108**, 3054-3131 (2008).
- 7 Monnier, F. & Taillefer, M. Catalytic C-C, C-N, and C-O Ullmann-Type Coupling Reactions. *Angew. Chem., Int. Ed.* **48**, 6954-6971 (2009).
- 8 Siemsen, P., Livingston, R. C. & Diederich, F. Acetylenic coupling: a powerful tool in molecular construction. *Angew. Chem., Int. Ed.* **39**, 2632-2657 (2000).
- 9 Chinchilla, R. & Najera, C. The Sonogashira reaction: a booming methodology in synthetic organic chemistry. *Chem. Rev.* **107**, 874-922 (2007).
- 10 Chinchilla, R. & Najera, C. Recent advances in Sonogashira reactions. *Chem. Soc. Rev.* **40**, 5084-5121 (2011).
- 11 Fokin, V. V. in *Catal. Carbon-Heteroat. Bond Form.* pp. 199-225 (Wiley-VCH Verlag GmbH & Co. KGaA, 2010).
- 12 Shun, A. L. K. S. & Tykwinski, R. R. Synthesis of naturally occurring polyynes. *Angew. Chem., Int. Ed.* **45**, 1034-1057 (2006).
- 13 Lang, H., Jakob, A. & Milde, B. Copper(I) Alkyne and Alkynide Complexes. *Organometallics* **31**, 7661-7693, (2012).
- 14 Glaser, C. *Ber. Dtsch. Chem. Ges.* **2**, 422-424 (1869).
- 15 Hay, A. S. Oxidative Coupling of Acetylenes. III. *J. Org. Chem.* **27**, 3320-3321, (1962).
- 16 Fairlamb, I. J. S., Baeuerlein, P. S., Marrison, L. R. & Dickinson, J. M. Pd-catalyzed cross coupling of terminal alkynes to diynes in the absence of a stoichiometric additive. *Chem. Commun.*, 632-633 (2003).
- 17 Batsanov, A. S. *et al.* Requirement for an Oxidant in Pd/Cu Co-Catalyzed Terminal Alkyne Homocoupling To Give Symmetrical 1,4-Disubstituted 1,3-Diynes. *J. Org. Chem.* **70**, 703-706 (2005).
- 18 Sonogashira, K., Tohda, Y. & Hagihara, N. Convenient synthesis of acetylenes. Catalytic substitutions of acetylenic hydrogen with bromo alkenes, iodo arenes, and bromopyridines. *Tetrahedron Lett.*, 4467-4470 (1975).
- 19 Sonogashira, K. Development of Pd-Cu catalyzed cross-coupling of terminal acetylenes with sp_2 -carbon halides. *J. Organomet. Chem.* **653**, 46-49 (2002).
- 20 Rostovtsev, V. V., Green, L. G., Fokin, V. V. & Sharpless, K. B. A stepwise Huisgen cycloaddition process: copper(I)-catalyzed regioselective "ligation" of azides and terminal alkynes. *Angew. Chem., Int. Ed.* **41**, 2596-2599 (2002).
- 21 Tornøe, C. W., Christensen, C. & Meldal, M. Peptidotriazoles on Solid Phase: [1,2,3]-Triazoles by Regiospecific Copper(I)-Catalyzed 1,3-Dipolar Cycloadditions of Terminal Alkynes to Azides. *J. Org. Chem.* **67**, 3057-3064, (2002).
- 22 Hein, J. E. & Fokin, V. V. Copper-catalyzed azide-alkyne cycloaddition (CuAAC) and beyond: new reactivity of copper(I) acetylides. *Chem. Soc. Rev.* **39**, 1302-1315 (2010).
- 23 Meldal, M. & Tornøe, C. W. Cu-Catalyzed Azide-Alkyne Cycloaddition. *Chem. Rev.* **108**, 2952-3015, (2008).
- 24 Buckley, B. R. & Heaney, H. Mechanistic investigations of copper(I)-catalysed alkyne-azide cycloaddition reactions. *Top. Heterocycl. Chem.* **28**, 1-29, (2012).
- 25 Chui, S. S. Y., Ng, M. F. Y. & Che, C.-M. Structure determination of homoleptic AuI, AgI, and CuI aryl/alkylethynyl coordination polymers by X-ray powder diffraction. *Chem.-Eur. J.* **11**, 1739-1749 (2005).
- 26 Baxter, C. W. *et al.* Copper(I) alkynyl clusters, $[Cu_{x+y}(hfac)_x(C\equiv CR)_y]$, with Cu_{10} - Cu_{12} cores. *Chem.-Eur. J.* **12**, 6166-6174 (2006).
- 27 Yam, V. W.-W., Lo, K. K.-W., Fung, W. K.-M. & Wang, C.-R. Design of luminescent polynuclear copper(I) and silver(I) complexes with chalcogenides and acetylides as the bridging ligands. *Coord. Chem. Rev.* **171**, 17-41 (1998).
- 28 Abu-Salah, O. M. Perspectives in syntheses, structures and bonding of acetylide-containing clusters of Group 11 metals. *J. Organomet. Chem.* **565**, 211-216 (1998).
- 29 Olbrich, F., Behrens, U. & Weiss, E. Metalorganic compounds of copper. VII. Synthesis and Structure of Alkyne-Alkynyl-Copper(I)-complexes (Alkyne = 3,3,6,6-tetramethyl-1-thia-4-cycloheptyne; Alkynyl = $C\equiv CPh$, $C\equiv CMe_3$). *J. Organomet. Chem.* **472**, 365-370 (1994).
- 30 Diez, J., Gamasa, M. P., Gimeno, J., Aguirre, A. & Garcia-Granda, S. $[Cu_3(\mu_3-\eta^1-C\equiv CPh)_2(\mu-Ph_2PCH_2PPh_2)_3][BF_4]$, a triangulo copper(I) complex with an unprecedented bicapping system of two asymmetric $\mu_3-\eta^1$ -acetylide ligands. *Organometallics* **10**, 380-382 (1991).

- 31 Yam, V. W.-W., Fung, W. K.-M. & Cheung, K.-K. Synthesis, Luminescence, and Electrochemistry of Mix-Capped Trinuclear Copper(I) Acetylide Complexes. X-ray Crystal Structures of $[\text{Cu}_3(\mu\text{-dppm})_3(\mu_3\text{-}\eta^1\text{-C}\equiv\text{CC}_6\text{H}_4\text{OMe-}p)(\mu_3\text{-}\eta^1\text{-C}\equiv\text{CC}_6\text{H}_4\text{OEt-}p)]\text{PF}_6$ and $[\text{Cu}_3(\mu\text{-dppm})_3(\mu_3\text{-}\eta^1\text{-C}\equiv\text{CC}_6\text{H}_4\text{OMe-}p)(\mu_2\text{-}\eta^1\text{-C}\equiv\text{CC}_6\text{H}_4\text{NO}_2\text{-}p)]\text{PF}_6$. *Organometallics* **17**, 3293-3298 (1998).
- 32 Nelson, R. C. & Miller, J. T. An introduction to X-ray absorption spectroscopy and its in situ application to organometallic compounds and homogeneous catalysts. *Cataly. Sci. Technol.* **2**, 461-470, (2012).
- 33 Bañares, M. A. Operando methodology: combination of in situ spectroscopy and simultaneous activity measurements under catalytic reaction conditions. *Catal. Today* **100**, 71-77 (2005).
- 34 Ellis, P. J., Fairlamb, I. J. S., Hackett, S. F. J., Wilson, K. & Lee, A. F. Evidence for the Surface-Catalyzed Suzuki-Miyaura Reaction over Palladium Nanoparticles: An Operando XAS Study. *Angew. Chem., Int. Ed.* **49**, 1820-1824, (2010).
- 35 Lee, A. F., Ellis, P. J., Fairlamb, I. J. S. & Wilson, K. Surface catalysed Suzuki-Miyaura cross-coupling by Pd nanoparticles: an operando XAS study. *Dalton Trans.* **39**, 10473-10482 (2010).
- 36 Reimann, S. *et al.* Identification of the Active Species Generated from Supported Pd Catalysts in Heck Reactions: An in situ Quick Scanning EXAFS Investigation. *J. Am. Chem. Soc.* **133**, 3921-3930, (2011).
- 37 Owsley, D. C. & Castro, C. E. Substitution of aryl halides with copper(I) acetylides. 2-Phenylfuro[3,2-*b*]pyridine. *Org. Synth.* **52**, 128-131 (1972).
- 38 Cai, C. & Vasella, A. Oligosaccharide analogs of polysaccharides. Part 5. Studies on the cross-coupling of alkynes and haloalkynes. *Helv. Chim. Acta* **78**, 2053-2064, (1995).