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Insight into the Mechanism of the CuAAC Reaction by Capturing the Crucial $Au_4Cu_4 - \pi$ -Alkyne Intermediate

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ABSTRACT: The classic Fokin mechanism of the CuAAC reaction of terminal alkynes using a variety of Cu(I) catalysts is wellknown to include alkyne deprotonation involving a bimetallic $\sigma_i \pi$ -alkynyl intermediate. In this study, we have designed a CNTsupported atomically precise nanocluster Au₄Cu₄ (noted Au₄Cu₄/CNT) that heterogeneously catalyzes the CuAAC reaction of terminal alkynes without alkyne deprotonation to a $\sigma_i \pi$ -alkynyl intermediate. Therefore, three nanocluster- π -alkyne intermediates [Au₄Cu₄(π -CH=C-p-C₆H₄R)], R = H, Cl, and CH₃, have been captured and characterized by MALDI-MS. This Au₄Cu₄/CNT system efficiently catalyzed the CuAAC reaction of terminal alkynes, and internal alkynes also undergo this reaction. DFT results further confirmed that HC=CPh was activated by π -complexation with Au₄Cu₄, unlike the classic dehydrogenation mechanism involving the bimetallic $\sigma_i \pi$ -alkynyl intermediate. On the other hand, a Cu₁₁/CNT catalyst was shown to catalyze the reaction of terminal alkynes following the classic deprotonation mechanism, and both Au₁₁/CNT and Cu₁₁/CNT catalysts were inactive for the AAC reaction of internal alkynes under the same conditions, which shows the specificity of Au₄Cu₄ involving synergy between Cu and Au in this precise nanocluster. This will offer important guidance for subsequent catalyst design.

he metal-catalyzed azide–alkyne cycloaddition (MAAC) for click chemistry, especially solvated CuACC systems,¹⁻⁴ is of paramount importance for rapid assembly of functional molecules¹⁻³ and has been widely applied in the field of small-molecule syntheses,¹⁻⁵ polymeric materials,⁶ and biochemical systems.7 The well-recognized CuAAC mechanism using a variety of Cu(I) catalysts first involves a Cualkyne π -complex that converts into a Cu₂- σ , π -alkynyl intermediate species.⁸⁻¹⁰ Consistently, very few Cu catalysts have been found to catalyze the AAC reaction of internal alkynes,¹⁰ because the key intermediate is only obtained by deprotonation of terminal alkynes. Only strong σ -donor ligands on Cu such as N-heterocyclic carbenes avoid alkyne deprotonation and thus allow CuACC reaction of internal alkynes,^{11,12} common with many RuAAC catalysts that proceed with different regioselectivity and mechanism.^{13,14}

Under the guidance of "green chemistry", further research will focus on the design of durable heterogeneous nanocatalysts for large-scale industrial applications of AAC chemistry.^{11–13} So far, various supported CuAAC have been reported^{14–20} and reviewed,^{15,16} although the large majority of CuAAC catalysts are homogeneous.^{1–3} Therefore, acquisition of a molecular-level understanding of a homogeneous as well as heterogeneous CuAAC mechanism involving both terminal and internal alkynes will be the prerequisite to develop superior heterogeneous CuAAC catalytic systems.

Nanoclusters (NCs) offer the advantage of having a perfectly monodisperse and atomically precise nature, thereby providing superior precision and reproducibility to better decipher the structure/activity relationships at the molecular level.^{21–24} In this regard, Scott and co-workers confirmed that a supported Cu_{20} NC preserved the inherent characteristics and maintained structural integrity before and after catalysis.²⁵ Therefore, we selected a carbon-nanotube-(CNT)-supported atomically precise bimetallic NC, noted in short Au₄Cu₄/CNT, as the model catalyst. Interestingly, the capture of several terminal alkynes in π -complex intermediates was probed as well as the ability of Au₄Cu₄/CNT to serve as a heterogeneous CuAAC catalyst for terminal alkynes under mild conditions. Concomitantly, DFT studies have been conducted to examine the possibility of alkyne activation by π -complexation with Au₄Cu₄ rather than deprotonation. The CuAAC activity of monometallic Au₁₁/CNT and Cu₁₁/CNT nanocatalysts has also been compared to that of Au₄Cu₄/CNT in order to shed light on the catalytic synergy between Au and Cu in Au₄Cu₄.

In order to avoid pretreatment damaging the intact structure, $[Au_4Cu_4(dppm)_2(SAdm)_5]Br$ NC (denoted Au_4Cu_4) was chosen as the model catalyst, since all the Cu atoms in Au_4Cu_4 have been confirmed to be in the oxidation state I. The Au_4Cu_4 NC was synthesized and purified according to the literature²⁶ and characterized by UV–vis, MALDI-MS, and X-ray photoelectron spectroscopy (XPS) analyses as shown in Figure S1. Then, the corresponding Au_4Cu_4/CNT was prepared and characterized by FT-IR, XRD, TEM (including element mapping and EDS), and XPS analyses (Figures S2–S4). To sum up, all the tests indicated

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Communication

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Figure 1. (A) ¹H NMR spectrum of the *in situ* reaction; (B and C) XPS spectra of Au and Cu in Au_4Cu_4 NC, Au_4Cu_4 /CNT, and recycled Au_4Cu_4 /CNT.



Figure 2. (A) FT-IR and (B) ¹H NMR spectra of Au₄Cu₄ NC, PhC=CH, and the Au₄Cu₄ NC + PhC=CH mixture. (C) TLC of Au₄Cu₄ NC, Au₄Cu₄ NC mixed with PhC=CH (PA), and intermediate Au₄Cu₄*; MALDI-MS of the intermediate Au₄Cu₄* and simulation of the corresponding mass spectrum.

that the Au₄Cu₄ NC was successfully fixed on CNT, and its structure remained intact and evenly dispersed.

Table S1 shows that Au_4Cu_4/CNT exhibited excellent activity with a 96.4% conversion and 100% selectivity for the AAC reaction of PhCH₂N₃ with PhC=CH. Au_4Cu_4 NC was also loaded onto various supports such as SiO₂ or γ -Al₂O₃, and



Figure 3. Kohn–Sham MO analysis and qualitative valence-orbital energy level schemes of Au_4Cu_4 (CATA) based on SR-ZORA B3LYP/TZ2P calculations.



Figure 4. (A) Proposed reaction mechanism over the Au_4Cu_4 NC. (B) Potential energy diagrams of intermediates and transition states of reaction between PhC=CH and PhCH₂N₃ catalyzed by Au_4Cu_4 NC.

the yield of each of the catalysts was about 96%. The CNT, SiO_{2} , and γ -Al₂O₃ supports were all inert in the AAC reaction. Therefore, it was the intrinsic properties of the Au₄Cu₄ NC that were responsible for the catalytic activity. Table S2 shows that Au_4Cu_4/CNT was tolerant to various substrates in the AAC reaction, and various alkynes reacted smoothly to afford the corresponding products with 78.6-98.6% yield. From the in situ ¹H NMR spectrum (Figure 1A), no signal of the Sadm ligand was detected during the reaction, which confirmed that Au₄Cu₄ NC was not at all leaching, and even the signal of the product (1-benzyl-4-phenyl-1H-1,2,3-triazole) was detected at the later stage of the reaction. The yield of AAC did not decrease after three cycles (Table S1, entry 7), and the recycled Au₄Cu₄/CNT was characterized by XRD and XPS analysis. The XRD pattern revealed that there was no significant change before and after the reaction (Figure S2). The Au 4f_{7/2} band (Figure 1B) of recycled Au₄Cu₄/CNT (84.51 eV) remained unchanged compared to that of the fresh Au₄Cu₄/CNT (84.54 eV). However, the Cu $2P_{3/2}$ band (Figure 1C) in the recovered Au₄Cu₄/CNT (933.48 eV) exhibits a slight positive shift compared with the fresh Au₄Cu₄/CNT (932.98 eV), which was speculated to be due to PhC \equiv CH coordinated to a Cu atom of the Au₄Cu₄ NC to form a feedback π^* bond, resulting in charge transfer.²⁷

The uniform Au₄Cu₄ NC was used to study the mechanism, and it was found that the catalytic process was different from the dehydrogenation mechanism.^{8,9¹} First, the UV-vis spectra exhibited a blue shift (Figure S5) when PhC≡CH was added to Au₄Cu₄ NC, while the UV-vis spectra of the Au₄Cu₄ + PhCH₂N₃ mixture remained unchanged. A similar blue shift was detected when PhC=CH and PhCH2N3 were added together. Thus, the first step of the mechanism is activation of PhC \equiv CH by Au₄Cu₄. Then, the mixed solution (Au₄Cu₄ + PhC≡CH) was characterized. In the FT-IR spectra (Figure 2A), the characteristic absorption peak of 3293 cm^{-1} for H- $C \equiv CPh$ was observed, indicating that the H atom of PhC \equiv CH had not been removed during the activation process.²⁸ Meanwhile, the characteristic peak of the $C \equiv C$ bond was shifted from 2109 cm⁻¹ to 2104 cm⁻¹, which was probably due to feedback alkyne π^* bond coordination to Cu, so that the $C \equiv C$ bond becomes longer and its vibration frequency lower. Furthermore, the Cu 2P_{3/2} data in the recovered Au₄Cu₄/CNT also proved the existence of the feedback π^* bond. From the ¹H NMR spectrum (Figure 2B), the peak of H-C \equiv CPh (3.14) ppm) still existed in the Au₄Cu₄ + PhC≡CH mixture, accompanied by a certain displacement. In the meantime, the ratio of benzene-ring hydrogen (a) to alkynyl hydrogen (b) remained 2:1, indicating that PhC=CH does not lose its terminal hydrogen. We conjecture that PhC≡CH is first coordinated to Au₄Cu₄ NC with feedback π^* bond formation of a $[Au_4Cu_4-\pi-(CH\equiv CPh)]$ intermediate (referred to as $Au_4Cu_4^*$) rather than deprotonation of PhC=CH. The pure Au₄Cu₄* point appears below the Au₄Cu₄ point from the TCL board (Figure 2C). The MALDI-TOF data of the Au₄Cu₄* sample showed two ion peaks located at 2581.28 and 2647.33 Da, respectively. We speculate that the two peaks are the two fragment peaks due to instability of Au₄Cu₄* under the high energy of mass spectrometry ionization. For example, 2581.28 Da (calculation: $[Au_4Cu_4 + HC \equiv CPh - Sadm - H]^+$) was Au₄Cu₄* that lost one Sadm ligand and 2647.33 Da (calculation: $[Au_4Cu_4]^+$) was $Au_4Cu_4^*$ that lost PhC=CH. The other two alkynes (HC≡CPh-4-Cl and HC≡CPh-4-Me) were selected to coordinate Au₄Cu₄ in order to further verify the Au₄Cu₄* structure, respectively. Similar results were obtained by MALDI-TOF analysis. For CH≡CPh-4-Cl and CH≡CPh-4-Me, there are two ions peaks located at 2647.33 and 2615.36 Da (calculation: [Au₄Cu₄ + CH=CPh-4-Cl -Sadm - H]⁺) as well as 2647.33 Da and 2595.31 (calculation: $[Au_4Cu_4 + CH \equiv CPh-4-Me - Sadm - H]^+)$, respectively. All these data confirm that there is no dehydrogenation.

In order to obtain convincing evidence for the lack of alkyne deprotonation along the click reaction mechanism, we have designed related experiments to prove the π bond activation mechanism rather than deprotonation. First, we explored the click reaction in which the terminal acetylene was replaced by the inactive internal alkynes PhC=CPh and PhC=CCH₃, respectively, and the corresponding products were obtained successfully in high yields, which is a rarely observed click reaction over Cu catalysts (Figures S6 and S7). Next, we used PhC=CD instead of PhC=CH for a further controlled experiment. The ¹H NMR spectrum of the purified product

showed that there was no peak at 7.66 ppm (Figure S8), indicating that the D ending did not fall off during the whole reaction. All these results fully demonstrate that PhC≡CH is activated through π -complexation with Au₄Cu₄ rather than deprotonation. The known monometallic NCs $[Au_{11}(PPh_3)_8Cl_2]Cl$ (in short, Au_{11}) and $[Cu_{11}(TBBT)_9(PPh_3)_6](SbF_6)_2$ (in short, Cu_{11}) were synthesized for comparison, ^{29,30} and the corresponding supported catalysts Au₁₁/CNT and Cu₁₁/CNT were fabricated using similar methods (Figure S9). As expected, the catalytic performance of Au₄Cu₄/CNT is essentially different from that of Au₁₁/CNT and Cu₁₁/CNT. The details are as follows: the Cu₁₁/CNT exhibited a high activity for the AAC reaction of PhC=CH, comparable to that of Au₄Cu₄/CNT, while it had no activity for the internal alkynes. The Au₁₁/CNT was completely inactive for AAC reactions of both terminal and internal alkynes. Further, we explored the basic-reaction experiments $(Cu_{11} + PhC \equiv CH)$ and verified activation of the acidic hydrogen atom of terminal alkynes by Cu₁₁ through FT-IR and ¹H NMR spectra (Figures S10–S12). These results indicate that the exceptional properties of Au₄Cu₄/CNT are due to a specific synergistic effect between Au and Cu.

DFT calculations reveal that the coordination of PhC≡CH is plentiful at the side-coordination sites of Au₄Cu₄, where PhC≡CH prefers to bind to the Cu2 atoms with an adsorption energy of about -0.24 eV (Table S3), and the relative energies for each isomer of RE1 are shown in Table S4 (Figures S13 and S14). This side-coordination of PhC=CH on Cu promotes a π -d type interaction. As shown in Figure 3, there are two pairs of orbital interactions between Cu2 and PhC≡CH to stabilize the RE1 complex. The first one is the interaction between the virtual Cu 4p orbital and the π bonding of PhC \equiv CH, leading to ligand to metal π -donation. The second one is the interaction between occupied Cu2 orbitals and antibonding π^* orbitals of PhC \equiv CH, forming the metal-to-ligand π -back-donation. Thus, the net consequence is simply viewed as a charge-transfer model where the electron density transfer from PhC≡CH to Au₄Cu₄ leads to Cu2 retaining a +I oxidation state with a gain of negative charge from Au4 due to the difference in electronegativity. The charge on the PhC≡CH increased to +0.35 lel compared to 0.00 lel in pure PhC \equiv CH (Table S5), which promotes an unprecedented charge stabilization effect of Au atoms during the Cu2- π -PhC \equiv CH interaction. Activation of PhC \equiv CH itself through electron density donation is evidenced as shown by the elongation of the C \equiv C bond length from 1.226 Å in PhC≡CH to 1.268 Å in RE1 (Table S6). In addition, the bond length of both Cu2-Au3 and Cu2-Au4 extends upon the PhC≡CH side-coordinated on Cu2, implying that the coordination of PhC≡CH affects the charge distribution of the Cu2-Au3-Au4 domain.

The presence of charge transfer is crucial to the reaction channel between PhC=CH and PhCH₂N₃ because decentralization of charge prevents the formation of the C1–Cu2 bond or the destruction of the C1–H bond. The formation barrier for double C–N bonds is +0.96 eV (Table S3) with the Au4 atom migrating back to an adjacent Cu2 site. Afterward, Au3 plays a stabilization role via charge transfer from π -bonding to Au3 along with a change in Cu2–Au3 distance during the second PhC=CH coordination step at the Cu2 site. The calculated barrier for the step PhC=CH + IV \rightarrow RE1 + 1,4-disubstituted 1,2,3-triazoles is only +0.22 eV; thus, the formation of the C–N bond is the rate-determining step.

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Finally, the 1,4-disubstituted 1,2,3-triazoles is released and the RE1 is formed again. In the whole path, the flexibility in vibration of charge on Au support atoms makes the Cu2 retain an oxidation state of +I, providing ready access to a CuAAC mechanism.

In conclusion, we have designed a Au₄Cu₄/CNT catalyst to investigate the mechanism of the AAC reaction. Three nanocluster- π -alkyne intermediates [Au₄Cu₄(-CH \equiv C-4- C_6H_4R], R = H, Cl, and CH₃ were successfully captured for the first time, and their structure was shown by MALDI-MS. Moreover, the ¹H NMR, UV-vis, FT-IR, and DFT results further confirmed that the alkynes were activated by π complexation forming Au₄Cu₄* intermediates (real catalyst) and that the terminal H atom of HC=CPh is not stripped during catalysis. Interestingly, the Au₄Cu₄/CNT bimetallic system achieved CuAAC click reaction of internal alkynes. The corresponding Au₁₁/CNT and Cu₁₁/CNT nanocatalysts were not active for internal alkynes, showing that the specific properties of Au₄Cu₄ are due to Au-Cu synergistic effects. Therefore, this work provides an alternative proposal for the CuAAC mechanism involving the Au₄Cu₄ NC, which will provide great support for the design of further catalysts.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c12498.

Experimental procedures, computational details, TEM, UV–vis, ¹H NMR, ¹³C NMR XPS, XRD, IR, and absorption spectra (PDF)

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Notes

The authors declare no competing financial interest.

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