



**Copper(I)-triazole Dimer Formation and Rate Acceleration
in In-source Click Reaction**

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Copper(I)-triazole Dimer Formation and Rate Acceleration in In-source Click Reaction

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Abstract

Besides analytical applications, ambient mass spectrometry (MS) is also a special platform to do various chemical reactions. Chemistry in the laser desorption based ambient MS ion source can have its unique feature. Previously, the laser ablated copper(I) ions were used to catalyze in-source click reactions. Here, the advances of such in-source reaction is presented. First, the encounter and structure elucidation of a copper(I) triazole dimer is demonstrated. Then, based on the quick appearance of such dimer in the HALDI-MS spectrum, the rate acceleration effect is studied. Lastly, the crystalized dimer is used to catalyze in-flask click reaction, and confirmed the proposed “di-nuclear mechanism” of click reaction. This work is another example of how ambient in-source chemistry having unique features compared with traditional in-flask chemistry, and also shows some new insightful information can be got from the results studied from ambient in-source reactions.

Introduction

Ambient mass spectrometry¹ (MS), which is quick, sensitive and almost sample-preparation free, has been widely used in analytical and bio-analytical analyses. Besides detection and characterization of target molecules, many groups use ambient MS as a special platform to do in-source reactions. To further improve the selectivity and sensitivity of ambient MS, in-source derivatization of target analyte(s), both covalently and non-covalently, is a commonly used method. For example, betaine aldehyde was used in DESI-MS to covalently couple to hydroxyl groups in various biomolecules to enhance their MS responses.² To lower the detection limit of some small target molecules, β -cyclodextrin was used as the host molecule to induce the formation of host-guest complex.³ Moreover, due to the unique chemical and physical environment of ambient MS ion sources, several authors demonstrated the in-source reactions can be much different from the traditional in-flask reactions. Girod et al.⁴ first demonstrated the significant rate acceleration in both ESI and DESI ion sources, and evidenced the desolvation effect, the pH change, and the increment in concentration resulted from the shrinking of the charged microdroplets led to the unique phenomenon. Yan et al.⁵ also reported similar rate acceleration effect in paper spray ionization condition. Based on such rate acceleration, Muller et al.⁶ established a preparative ESI platform in which accelerated small scale organic synthesis could be done. Li et al.⁷ reported that under the trigger of high electric voltage, nitrogen atoms from air could be fixed in saturated hydrocarbons very quickly. Recently, several groups applied nano-ESI to fabricate new functional materials in ambient environment. For example, Badu-Tawiah et al.⁸ reported the peptide cross linking on ambient surfaces using nano-ESI assay. Li et al.⁹ reported that when metal wires were used in the nanoESI as electrodes, the corresponding metal-solvent complex could be seen in the mass spectra. If the metal-solvent complex containing charged droplets were deposited on a surface in ambient condition, metal nanoparticles could be synthesized and such nanoparticles were catalytically highly active. This technique could be used in the fabrication of various shape of nanostructured patterns by using proper masks.¹⁰ He et al.¹¹ demonstrated that biomolecules could be conjugated when sprayed from two adjacent nanoESI tips in ambient atmosphere, and the conjugated molecules could be

directly deposited on a surface which could then be functioned as a biosensor. These inspiring results show the ambient in-source chemistry has special features and also wide potential applications.

Laser based ambient ionization methods, of which typical examples are ELDI¹², LAESI¹³, MALDESI¹⁴, HALDI¹⁵ and LDSPI¹⁶, were developed by different groups for higher space resolution in MS imaging and better compatibility with water-rich biological samples. The understanding of the interactions of the substrate materials and the laser was basic and important. Brady et al.¹⁷ reported that the different substrate materials have influence on the MS responses of the target molecule. Zhang et al.¹⁸ reported that the pencil-written carbon material could be used as substrate to enhance the MS signals at different laser wavenumbers. Li et al.¹⁹ reported that when the pyroelectric material (LiNbO₃) was used as the substrate, the IR laser desorption ionization efficiency could be enhanced. Besides the signal enhancement, the interactions of laser and substrate material can also induce chemical reactions. For example, when analyzing proteins, Liu et al.²⁰ detected metal-protein complexes when the corresponding metal substrates were used in LDSPI-MS. Previously, Qiu et al.²¹ intentionally applied the laser ablated copper(I) ions to catalyze in-source click reactions by using HALDI-MS (Fig 1a) and the click reaction products (triazoles) were detected and verified by MS/MS. However, in the MS spectra, a previously unknown copper(I) triazole dimer was discovered (Fig 1b). In this work, the advances of the in-source click reaction catalyzed by the laser ablated copper(I) ions will be presented, including (1) the structure identification of the discovered copper(I) triazole dimer, (2) the significant rate acceleration indicated by the quick dimer formation in the in-source reaction, and (3) also the mechanistic information from the dimer catalyzed in-flask click reaction.

Experimental

The HALDI source has previously been described in detail¹⁵. The sample plate mounted to an XYZ translation stage was placed below the extended ion transfer tube, and a high voltage of typical 5.5 kV was applied to the sample target. IR irradiation from a pulsed Nd:YAG laser (Lai Yin Opto-Electronics Technology, Beijing, China) was focused onto the sample droplet by a set of

lens mounted on a linear translation stage for easy alignment. The incident angle of the laser beam onto the sample target was fixed at 45°. The laser was operated at a frequency of 20 Hz with a wavelength of 1064 nm. The typical laser energy was ca. 2.2 mJ/pulse with a pulse width of 10 ns. The horizontal distance (d) and vertical distance (l) between the mass spectrometer inlet and the illuminated spot were 3 mm and 10 mm, respectively. All the in-source reaction were performed by HALDI-MS. Typically, 200 μ L 5 mM phenylacetylene and 5 mM benzyl azide reaction solution (v/v, 1:1 MeOH/H₂O) was deposited on the substrate. Both the biased high voltage (typically of 5.5 kV) and IR-laser should be turned on to get the corresponding MS signal. Other experimental details, including in-flask click reactions, reaction monitoring, crystal growth and compound characterization data, could be found in the SI.

Results and Discussions

1 The Structure Identification Of The Copper(I) Triazole Dimer Detected In In-Source Click Reaction

The click reaction of phenylacetylene and benzyl azide was chosen as the example in this work (Fig 2a). Previously the formation of the triazole product was undoubtedly characterized via MS/MS. However, in the MS spectrum, a significant peak m/z 533 could be clearly seen and the peak of the triazole was compressed (Fig 2b). To know the chemical formula of this peak, we turned the in-source click reaction solution to high resolution MS analysis to get its accurate molecular weight and its isotopic distribution (insets in Fig 2b). The results indicated that the m/z 533 corresponded to copper(I) triazole dimer. From the extracted ion chromatograph (EIC) of m/z 533, it could be seen that the dimer formation was very quick. It only took about 30s to see its appearance. As the reaction time went on, the signal intensity of m/z 533 also increased, indicating that more and more copper(I) triazole dimer was generated.

The next question would be what the dimer's structure was. From literature, there were several similar copper(I) triazole complex. For example, Nolte et al.²² isolated a click intermediate, in which the copper(I) atom was bonded to the 3C position of the triazole ring (Fig 3a). Hohloch et

al.²³ synthesized a copper(I) triazole dimer, which was used as a catalyst for click reaction. In Hohloch's dimer, the copper(I) atom was bonded to the 3C position of the triazole ring (Fig 3b), too. Alvarez et al.²⁴ synthesized a multinuclear copper(I)-rhenium triazole complex, in which the copper(I) atom was bonded to the 4N position of the triazole ring (Fig 3c). Straub²⁵ calculated possible intermediates in click reaction process, and proposed copper bonded complex with open-ring triazole structure (Fig 3d). Since the peak of m/z 533 dimer was rather strong in MS spectra and its signal was steadily increasing with time, the open-ring structure, which was proposed as a transit intermediate, was less likely. The structures in Fig3 a-c indicated that the copper(I) atom could bond either to 3C or 4N position of the triazole ring. So merely based on MS data, the structure of m/z 533 could not be identified.

Luckily, the method to get the crystal of copper(I) triazole dimer detected in in-source click reaction was found. As shown in Fig 4a, 1-benzyl-4-phenyl-triazole and $\text{Cu}(\text{MeCN})_4\text{BF}_4$ were added into dichloromethane with the ratio 2:1. The solution was layered with hexane and after 48h in the room temperature, colorless and needle shaped crystals could be seen in the sample bottle. The crystal was put to XRD analysis and its structure was shown in Fig 4b. In this copper(I) triazole dimer, the copper(I) atom was bonded to the 4N position of the triazole ring, similar to that in Fig 3c. Since the copper(I) was not near to the 3C position, this dimer was not likely a click intermediate (for example, the structure in Fig 3a and 3d), but a previously unidentified product beyond commonly known click reaction. The results of the ESI-tandem-MS analysis of the crystal were shown in Fig 4c and Fig 4d, which were identical to that of the HALDI-tandem-MS analysis of the in-source generated dimer (Fig S1). So the structure of the cation m/z 533 discovered from in-source click reaction was characterized.

If a closer look was paid at the tandem MS data (Fig 4c-4d), an interesting gas phase chemistry could be found. Previous studies regarding the copper(I) triazole dimers shown in Fig 3 were not focused on their gas phase fragmentation in tandem MS. In the MS/MS spectrum in Fig 4c, fragments m/z 414 and m/z 316 were significant. In the MS^3 spectrum in Fig 4d, it was shown that the m/z 414 could transform to m/z 316 under collision induced dissociation (CID). Perera et

al.²⁶ reported that the attachment of residue water in ion trap MS was not uncommon for organometallic ions in the gas phase during CID. Here, one of the triazole ligands of the cation m/z 533 could be replaced by residue water in the ion trap, forming the m/z 316 fragment. However, the second fragmentation pattern, namely the retro [3+2] fragmentation was firstly experimentally encountered. The summary of the fragmentation route was shown in Fig 4e. Bozzelli et al.²⁷ used theoretical calculations to investigate retro [3+2] fragmentation in vacuum. The presented tandem MS data could intrigue future theoretical works into this field.

2 Rate Acceleration Indicated By The Dimer Formation

The quick appearance of m/z 533 in the HALDI-MS spectrum in the in-source click reaction indicated clear rate acceleration effect. As summarized in Fig 5a, in the in-source click reaction, the first step was the copper(I) catalyzed click reaction, as previously reported by Qiu et al.²¹; the second step was the copper(I) triazole dimer formation. If the two steps were combined, the overall reaction could be written as shown in Fig 5a. The reaction solution in the in-source reaction was shown in Fig 5b. In this figure, the laser spot and the bubbles could be seen. The formation of the bubbles indicated local reaction temperature could be very high. Sakka et al.²⁸ reported that under the similar laser irradiation conditions, the local temperature could be as high as 10^3 K. So the local high temperature was likely one of the reasons of rate acceleration. The other possible fact to rate accelerate may be the quick bonding formation of the *in situ* generated ligand-free copper(I) ions, because the break-ups of old chemical bonds were not needed.

To test the contributions of the two facts on rate acceleration, quantifying the in-source reaction should be done. First, the amount of the copper(I) catalyst in the in-source reaction was quantified. Neocuproine was a commonly used reagent to selectively bonded to copper(I) in aqueous solution and forming a yellow complex with a strong UV-vis absorbance.²⁹ After establishment of the calibration curve, the amount of the copper(I) atom in the in-source reaction after laser irradiation for 5 min was measured to be 0.04 mmol/L, or 0.8% equivalent (Fig 5c). The in-flask reactions (bulk conditions, denoted as condition C and D), which were designed as control experiments, were catalyzed by the same amount of catalysts. The in-source

reaction on copper substrate was denoted as condition A. Another in-source reaction (condition B), catalyzed by $\text{CuSO}_4/\text{Na ascorbate}$ (0.8% eq.) but on gold substrate was performed as well. This experiment was designed to test the contribution of laser heating. (Qiu et al.²¹ evidenced that the gold substrate was inert to the in-source click reaction.) The comparison of the amount of m/z 533, detected by high resolution MS, after 5 min in conditions A to D was shown in Fig 5d. From these results, it could be calculate that in-source reaction on copper substrate produce about 500 times more copper(I) triazole dimer (m/z 533) than that produced in in-flask conditions. In condition B, about 10 times more copper(I) triazole dimer was produced than that in in-flask conditions.

The total amounts of triazole generated could be detected by oxidizing the copper(I) atom by H_2O_2 ³⁰ and breaking the copper(I) triazole dimer. The detected signals of m/z 236 in conditions A to D were shown in Fig 5e. The triazole formed in condition A was slightly more than that formed in condition B, but much more than those formed in the control in-flask conditions. So the laser heating mainly accelerated the step 1 reaction in Fig 5a. If the Fig 5d was checked again, it could be found that while similar amounts of triazole were formed in conditions A and B, respectively, but the signal intensities of the copper(I) triazole dimer differed a lot. 50 times more dimer was generated in condition A compared with that in condition B. So the quicker bonding formation of the laser ablated ligand-free copper(I) may be ascribed to this acceleration effect.

To test whether the rate acceleration effect still existed after the laser irradiation off. Reaction solutions in conditions A and B, respectively, were transferred in flask, and denoted as conditions A' and B' later on. The four reaction solutions (A', B', C and D) were sampled at different time points to quantify the amount of m/z 533 by high resolution MS (Fig 5e). By differentiating the data in Fig 5e, the reaction rate after laser irradiation could be got (Fig S3). In condition B', C and D, the reaction rate increased with time and then became stable. These results were consistent with those reported by Rodionov et al.³⁰. But in condition A', the reaction rate decrease with time, indicating the copper(I) ions may be oxidized by air. So it could be concluded that the rate acceleration only existed during laser irradiation process.

In summary, the rate acceleration effect during laser irradiation has been studied. The laser heating contributed to the rate enhancement in step 1 in Fig 5a, while the quicker bonding formation of the laser ablated copper(I) ions with triazoles contributed to the rate enhancement in step 2 in Fig 5a. This rate acceleration effect has a different mechanism from former rate accelerations in spray based ionization sources^{4 and 6}, which may impel further focuses on in-source reactions on laser based ambient mass spectrometry.

3 Mechanistic Insight In The In-Flask Click Reaction Catalyzed By The Copper(I) Triazole Dimer

Reaction monitoring by MS could give useful information about the reaction mechanism.³¹ The discovered and structurally characterize copper(I) triazole dimer was tested to catalyze in-flask click reaction, and the reaction process was monitored by MS. The reaction of phenylacetylene and 4-chloro-benzyl azide was chosen as the example (Fig 6a). Fig 6b-6e were the mass spectra at different reaction time. In the beginning, only the “catalytic dimer” m/z 533 could be seen. As the time went on, two dimers, m/z 567 and m/z 601 was formed. The tandem MS analysis of the dimer analogs could be found in Fig S2. The dimer m/z 567 was formed by one initial triazole ligand, and the other ligand was the newly formed Cl-containing triazole. The dimer m/z 601 was formed by two Cl-containing triazole ligand. The increase and then decrease of m/z 567 and the steady increase of m/z 601 indicated the click reaction of phenylacetylene and 4-chloro-benzyl azide was going on, producing more and more triazole product. The formation of the copper(I) triazole analogs in this in-flask reaction indicated the copper(I) atom had a strong affinity to the 3N position of the triazole ring. This property has its merit in intermediates “fishing” by MS.

The reaction mechanism of click reaction has been studied over a decade. The di-nuclear mechanism was proposed and evidenced both theoretically²⁵ and experimentally³⁰. Worrell et al.³² used isotopically labeled copper(I) catalyst to catalyze click reaction and measured the isotopic distributions in the late stage copper containing intermediates. They provided direct support to the di-nuclear mechanism (Fig 7a). However, the direct observation of the proposed di-nuclear intermediate was not reported yet. In the in-flask click reaction catalyzed by CuL_2BF_4

(L=1-benzyl-4-phenyl triazole), because of the stability of the copper(I)-triazole bonding, the possible di-nuclear intermediate was proposed as shown in Fig 7b. Luckily, such di-nuclear intermediate was detected, and its isotopic distribution matched well with that got from theoretically calculation. This strong evidence again confirmed the di-nuclear mechanism of click reaction. Note that the signal intensity of such intermediate was low. In previous reaction systems, because various ligands could bond to the copper(I) atom, the MS signals corresponding to these di-nuclear intermediates may distributed along the m/z axis, making their detection more difficult (possibly below the detection limit). The strong binding of triazole ligand at 3N position of the triazole ring, however, could make the ligand not easy to change, and then make the MS signal of the di-nuclear intermediates concentrated in one (or limited numbers of) $m/z(s)$, which made the detection easier.

Conclusion

Besides analyses, ambient MS is a special platform for chemical reactions. Various unique phenomena as well as novel applications (e.g. material fabrications) shows the studies of in-source ambient chemistry are quite promising. In this paper, the advances in the in-source click reaction catalyzed by *in situ* generated copper(I) ions were reported. First, the discovery and the structure characterization of the copper(I) triazole dimer was presented. Then, the rate acceleration effect indicated by the formation of such dimer was studied. It was shown that the laser heating contributed to the rate enhancement of the click reaction, and the laser ablated copper(I) ions accelerated the dimer formation step. Lastly, the crystalized copper(I) triazole dimer was used as the catalyst to initiate in-flask click reaction, and from such reaction one of the proposed di-nuclear intermediate was detected. The results presented in this paper would inspire both analytical and organic chemists to use laser desorption based ambient MS to investigate chemical phenomena and reaction mechanisms. Future advances applying laser ablated metal ions to initiate other organometallic reactions may bring more intriguing results.

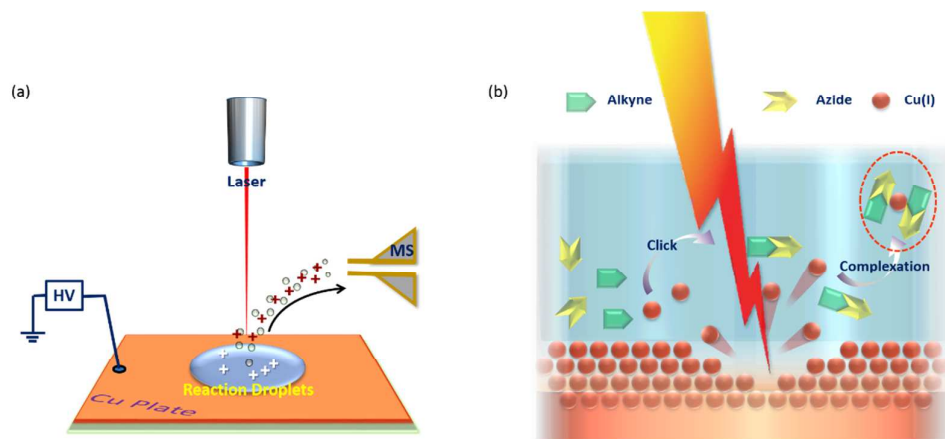


Fig 1 (a) Schematic demonstration of the instrument, and the in-source reaction. (b) Schematic demonstration of the click reaction and the copper(I) triazole dimer formation, which is induced by the laser-ablated copper(I) ions.

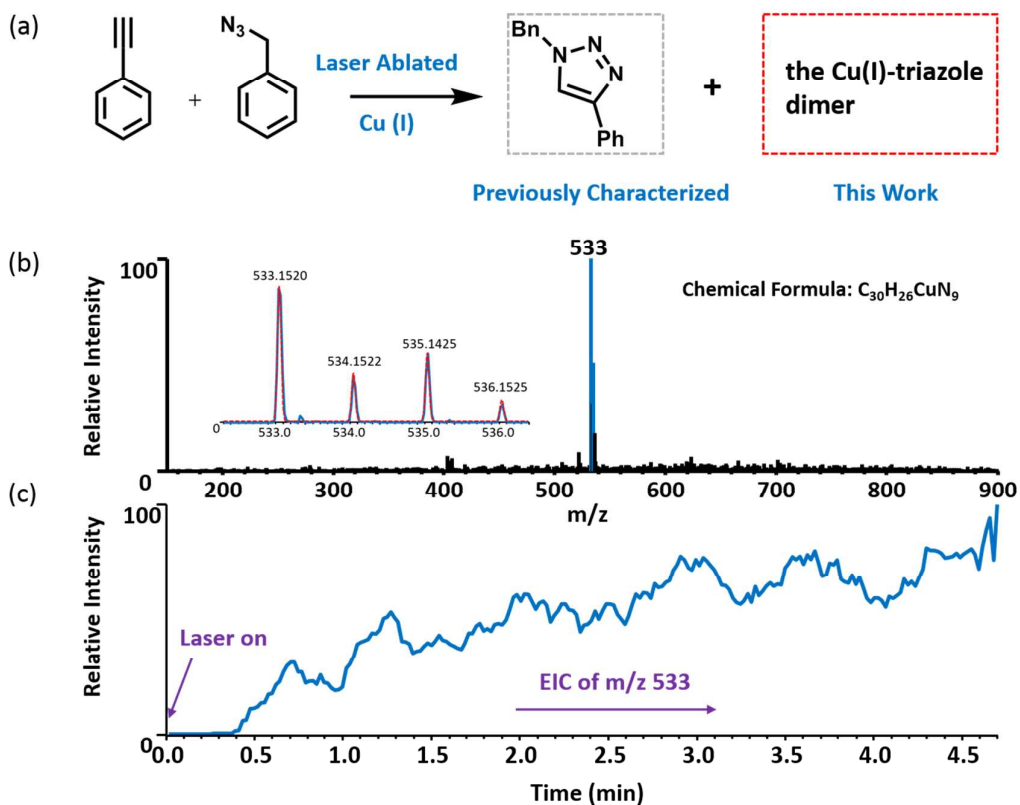


Fig 2 (a) The click reaction of phenylacetylene and benzyl azide was chosen as the example. (b) HALDI-MS spectrum of the in-source click reaction. Inset: high resolution MS detection of the accurate molecular weight and the isotopic distribution. (c) Extracted ion chromatogram (EIC) of the m/z 533 in the HALDI-MS reaction monitoring.

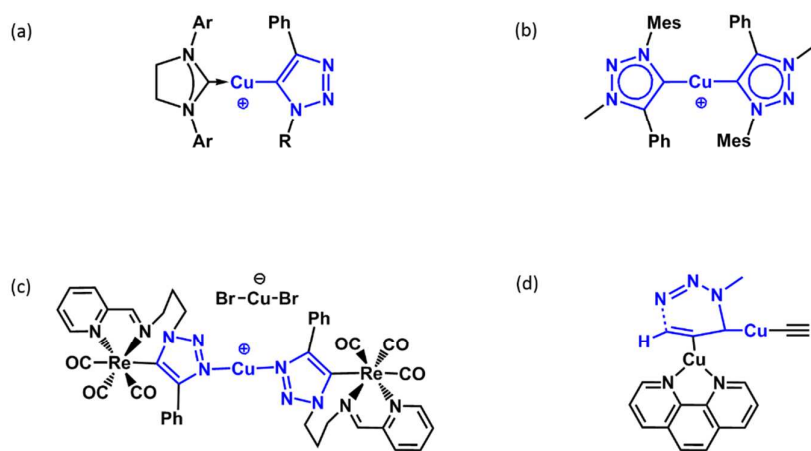


Fig 3 (a) The copper(I) carbene complex synthesized by Nolte *et al.*. (b) The copper(I) carbene complex synthesized by Hohloch *et al.*. (c) The copper(I)-rhenium triazole complex synthesized by Alvarez *et al.*. (d) The proposed intermediate in click reaction by Straub.

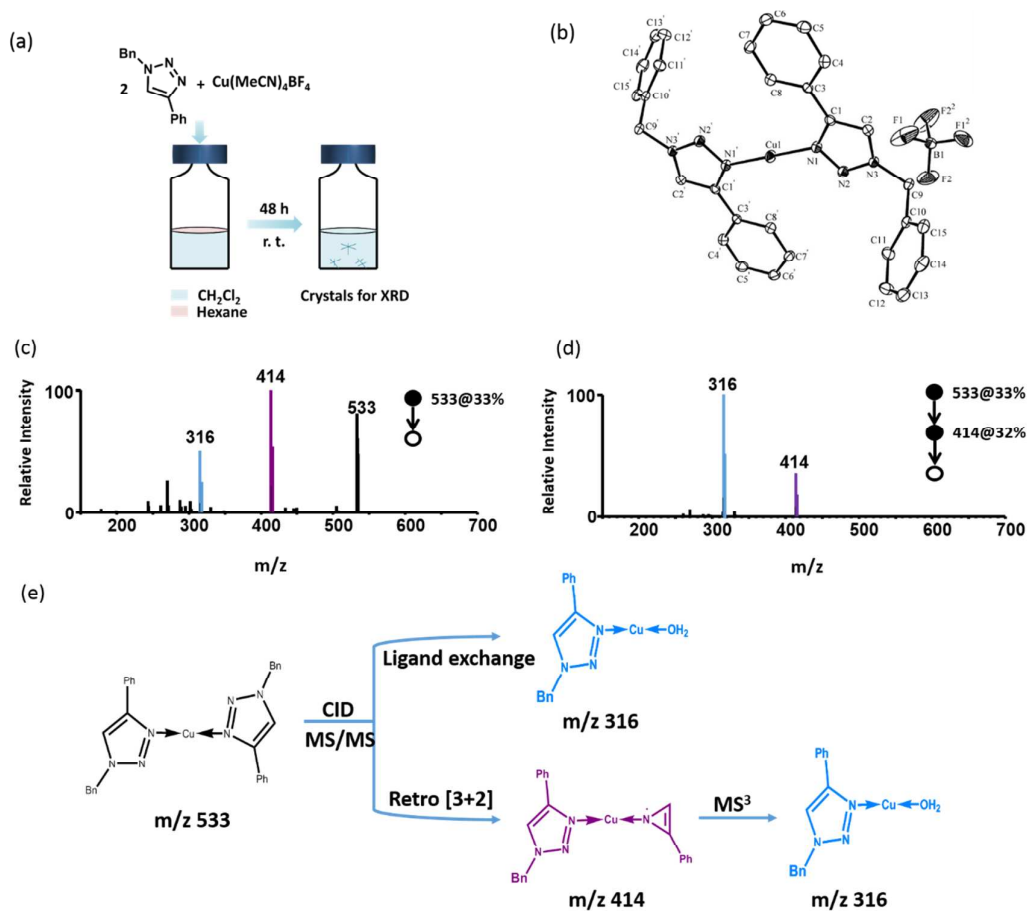


Fig 4 (a) Schematic illustration of the methods to get the copper(I) triazole dimer. (b) ORTEP drawing of dimer crystal with 30% thermal ellipsoids. Hydrogen atoms have been omitted for clarity. (c) ESI-MS/MS analysis of the dimer. (d) ESI-MS³ analysis of the dimer. (e) Proposed gas phase fragmentation pathway during collision induced dissociation (CID) of the dimer.

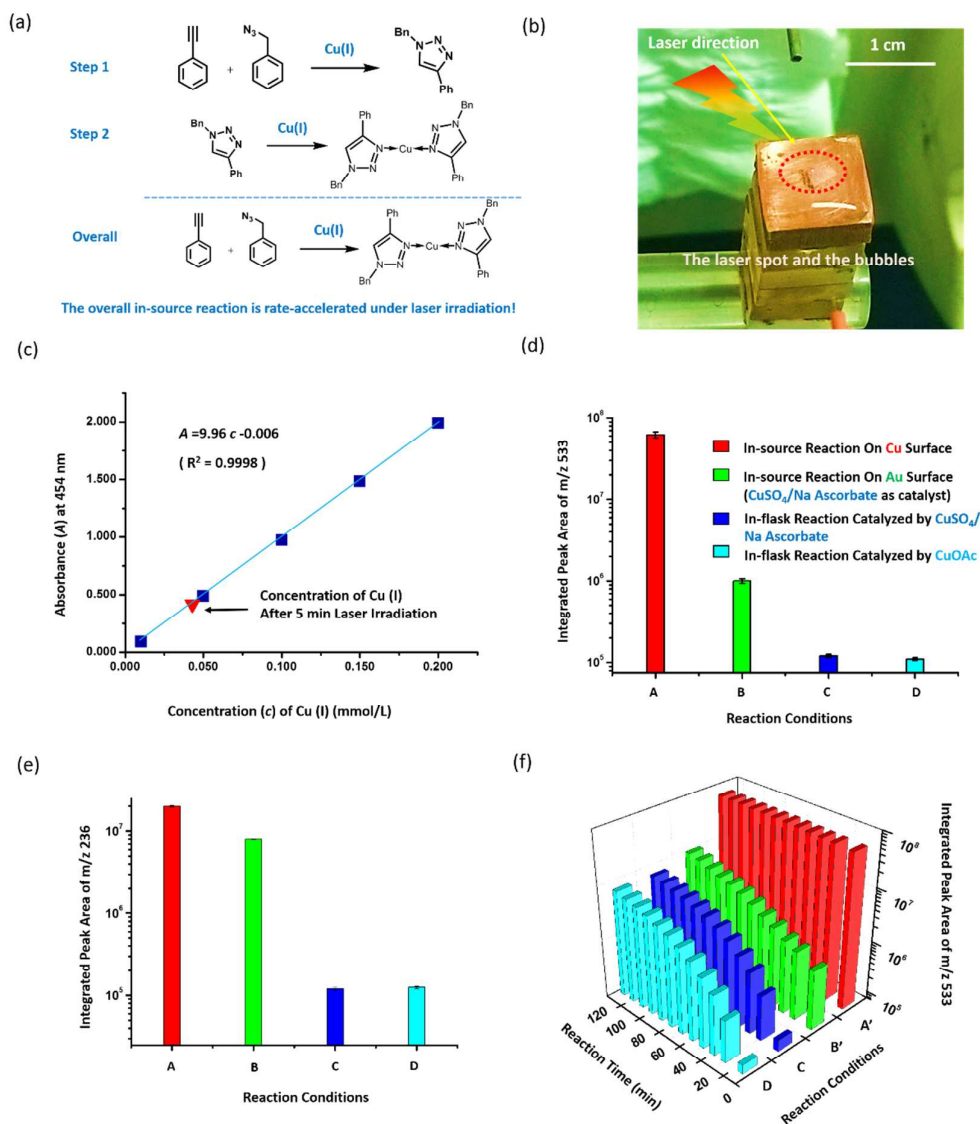


Fig 5 (a) In the in-source reaction, click reaction and the dimer formation steps coexisted. The overall reaction was accelerated. (b) The camera picture taken when the in-source reaction was going on. Laser spot and the bubbles could be seen. (c) Calibration curve established by using neocuproine method and measuring the copper(I) concentration in the in-source reaction after 5 min laser irradiation. (d) High resolution MS detection of the dimer product (m/z 533) at 5 min in different reaction conditions. (Condition A: in-source reaction on copper surface with laser irradiation for 5 min; Condition B: in-source reaction on gold surface with laser irradiation for 5 min, 0.8% *eq.* CuSO_4/Na ascorbate as the catalyst; Condition C: in-flask reaction catalyzed by 0.8% *eq.* CuSO_4/Na ascorbate; Condition D: in-flask reaction catalyzed by 0.8% *eq.* CuOAc .) (e) After H_2O_2 treatment, the copper(I) atoms were oxidized, and the total amounts of triazole (m/z 236) in conditions A to D could be detected by High resolution MS. (f) High resolution MS monitoring of the dimer product of in the reactions done in-flask. Conditions A' and B' means the in-source reaction solutions in conditions A and B, respectively, were transferred into flasks, and the reaction processes later on were monitored at different time points.

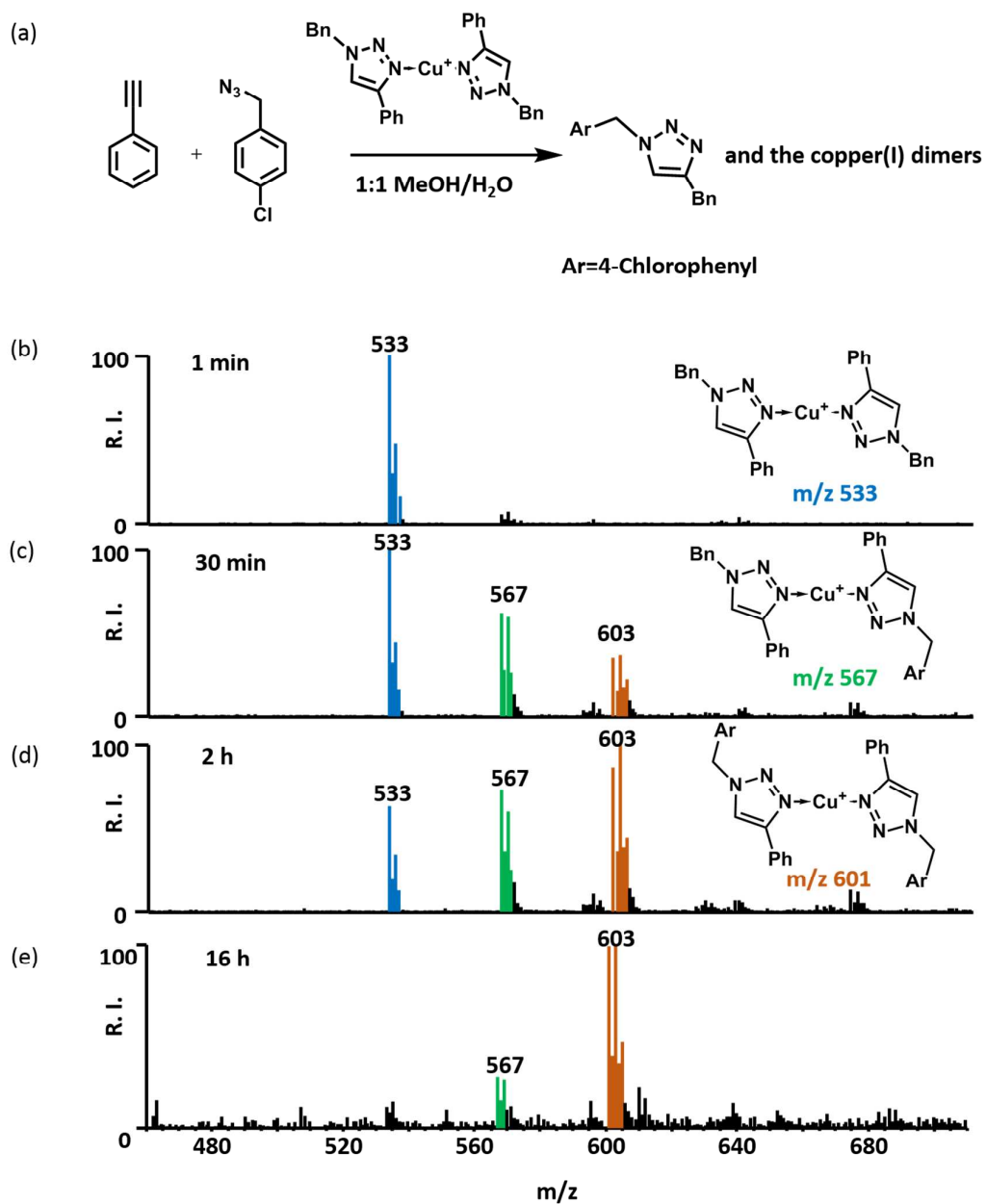


Fig 6 (a) In-flask click reaction catalyzed by the crystalized copper(I) triazole dimer. (b-e) Reaction monitoring of this in-flask click reaction. Dimer analogs were generated with reaction time increasing.

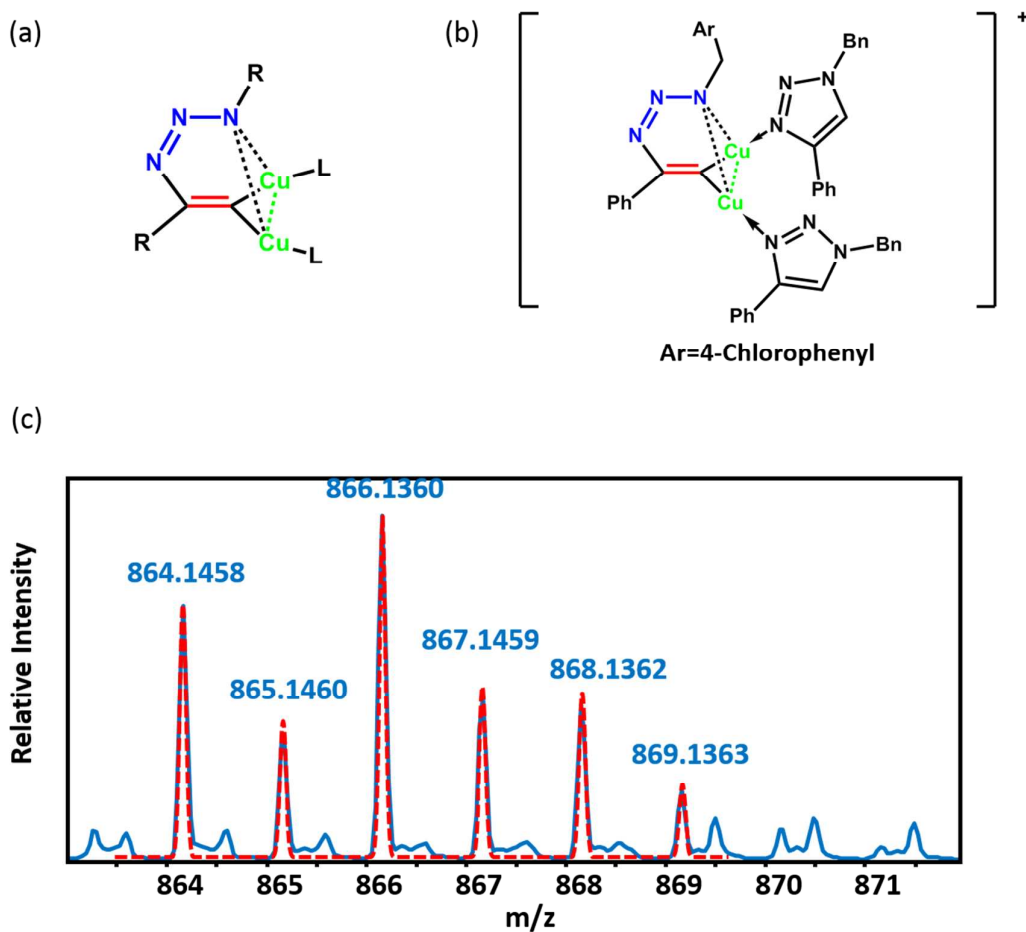


Fig 7 (a) Di-nuclear intermediate proposed by Worrell and coworkers. (b) Possible structure of the di-nuclear intermediate in the in-flask click reaction catalyzed by the crystallized copper(I) triazole dimer. (c) The high resolution MS spectrum of the di-nuclear intermediate. The red dashed line denoted the theoretical calculated isotopic distribution.

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