CHEMISTRY

Isolation of bis(copper) key intermediates in Cu-catalyzed azide-alkyne "click reaction"

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The copper-catalyzed 1,3-dipolar cycloaddition of an azide to a terminal alkyne (CuAAC) is one of the most popular chemical transformations, with applications ranging from material to life sciences. However, despite many mechanistic studies, direct observation of key components of the catalytic cycle is still missing. Initially, mononuclear species were thought to be the active catalysts, but later on, dinuclear complexes came to the front. We report the isolation of both a previously postulated π,σ-bis(copper) acetylide and a hitherto never-mentioned bis(metallated) triazole complex. We also demonstrate that although mono- and bis-copper complexes promote the CuAAC reaction, the dinuclear species are involved in the kinetically favored pathway.

The copper-catalyzed azide-alkyne cycloaddition (CuAAC) (*1*, *2*) is the flagship of the "click chemistry" arsenal (*3*, *4*). Because of the straightforward procedures, the high functional group tolerance, and the usually high yields, CuAAC has affected all fields of chemistry from material (*5*–*8*) to life sciences (*9*–*13*); however, the mechanism of the CuAAC is still under debate (*14*, *15*). The first postulated mechanism involved mono-copper complexes, although more recently, the participation of bis(copper) complexes has been suggested on the basis of kinetic experiments (*16*) and computational investigations (*17*–*19*). In 2013, Fokin and colleagues published a very elegant mechanistic study and stated that "monomeric copper-acetylide complexes $\mathbf{1_{Cu}}$ are not reactive towards organic azides unless an exogenous copper catalyst is added" (*20*). The marked difference with the previously accepted mechanism is the introduction of the cationic π,σ-bis(copper) acetylide complexes of type $\mathbf{1_{Cu2}}$ (Fig. 1) as the "catalytically active complex," instead of $\mathbf{1_{Cu}}$. However, such a dinuclear species was qualified as a "non-isolable and highly reactive intermediate." We have recently shown that the strong σ-donating and π-accepting properties of cyclic (alkyl)(amino) carbenes (CAACs) (*21*–*23*) allow for the isolation of electron-deficient (*24*), electron-rich (*25*), and even paramagnetic species (*26*). This prompted us to attempt using CAAC ligands to stabilize elusive species involved in the CuAAC catalytic cycle. Here, we report the isolation of a π,σ-bis(copper) complex of type $\mathbf{1_{Cu2}}$ and of an unprecedented catalytically active 3,5-bis(metallated) triazole $\mathbf{2_{Cu2}}$. Thanks to the unusual stability of these complexes, we compare the mono- and dinuclear-based mechanisms and bring unambiguous evidence that the latter is indeed kinetically favored.

We first prepared the monomeric (*27*, *28*) copper complex $\mathbf{1_{Cu}a}$ (figs. S7 and S8) by reacting lithium phenylacetylide with (CAAC)CuOAc (figs. S1 and S2) in tetrahydrofuran (THF) (Fig. 1A). We found that $\mathbf{1_{Cu}a}$ cleanly reacted with (CAAC)CuOTf (figs. S3 to S6) in methylene chloride, affording the desired cationic dinuclear complex $\mathbf{1_{Cu2}a}$ (figs. S9 and S10), which was isolated as a white solid in 95% yield. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra show only one set of signals for both CAAC ligands, even at temperatures as low as −80°C, which is indicative of a very fast exchange between the two "Cu(CAAC)" units. However, in the solid state, a single crystal x-ray diffraction study shows two different types of coordination, π and σ (Fig. 1C, left). The Cu-Cu distance [2.9387(4) Å] is slightly longer than those computationally predicted by Fokin and colleagues for model compounds (2.85 to 2.88 Å) (*19*). $\mathbf{1_{Cu2}a}$ proved to be air-stable and thermally robust [melting point (mp): 174°C].

Despite its thermodynamic stability, $\mathbf{1_{Cu2}a}$ reacts cleanly with benzyl azide in methylene chloride, affording $\mathbf{2_{Cu2}a}$ (figs. S11 and S12), which was isolated in 87% yield as an air- and moisture-stable, pale yellow solid. ^{1}H and ^{13}C NMR spectra show the presence of one benzyl and one phenyl group, as well as two magnetically nonequivalent CAAC moieties. X-ray diffraction studies of the corresponding tetrafluoroborate salt confirmed the 3,5-dimetallated-1,2,3-triazole structure $\mathbf{2_{Cu2}a}$ (Fig. 1C, center).

Because dinuclear complexes of type $\mathbf{2_{Cu2}a}$ had never been postulated in any CuAAC mechanism, the next question was whether it was involved in the catalytic cycle. Addition of a stoichiometric amount of phenyl acetylene to $\mathbf{2_{Cu2}a}$ led, after 5 hours, to the quantitative release of the 1-benzyl-4-phenyl-1,2,3-triazole **3** accompanied by the regeneration of the bis-copper complex $\mathbf{1_{Cu2}a}$. As an additional confirmation, the same reaction was repeated using $\mathbf{2_{Cu2}a}$ and a different alkyne ($Ph_2CHC{\equiv}CH$), which resulted in the isolation of **3** along with the corresponding π,σ-bis-copper complex $\mathbf{1_{Cu2}b}$ (Fig. 1C, right; figs. S13 and S14) in quantitative yields.

After having shown that the bis-copper complex $\mathbf{1_{Cu2}a}$ could be part of the catalytic cycle, we turned our attention to the corresponding mono-copper complex $\mathbf{1_{Cu}a}$. We found that a stoichiometric amount of benzyl azide slowly reacted with complex $\mathbf{1_{Cu}a}$, leading, after 16 hours, to the C-metallated heterocycle $\mathbf{2_{Cu}a}$ (figs. S15 and S16), which was isolated as a pale yellow solid in 61% yield (*29*). Addition of one equivalent of phenyl acetylene to $\mathbf{2_{Cu}a}$ led, after 5 hours, to the quantitative isolation of triazole **3** and regeneration of the mono-copper complex $\mathbf{1_{Cu}a}$.

These results as a whole suggest that both the mono- and bis-copper complexes could lead to the triazole **3**, at least under stoichiometric conditions. However, the kinetic profile of the reactions of $\mathbf{1_{Cu}a}$ and $\mathbf{1_{Cu2}a}$ with benzyl azide revealed critical rate acceleration when the bimetallic complex is used [k_{obs} ($\mathbf{1_{Cu2}a}$)/k_{obs} ($\mathbf{1_{Cu}a}$) > 94] (Fig. 1B and fig. S17) (*30*). In contrast, the protodemetallation of $\mathbf{2_{Cu2}a}$ and $\mathbf{2_{Cu}a}$ affording triazole **3** and regenerating $\mathbf{1_{Cu2}a}$ and $\mathbf{1_{Cu}a}$, respectively, proceeds at a similar rate (fig. S18). It should be noted that in both cases, the protodemetallation arises from the reaction with the terminal alkyne and, thus, does not necessitate an external Brønsted acid. These reactions lead back to the acetylide complexes $\mathbf{1_{Cu2}a}$ and $\mathbf{1_{Cu}a}$, which exclude the copper precatalyst (CAAC)CuOTf from the catalytic cycle.

The experiments discussed above reproduce parts of both postulated catalytic cycles under stoichiometric conditions. Each step proved to

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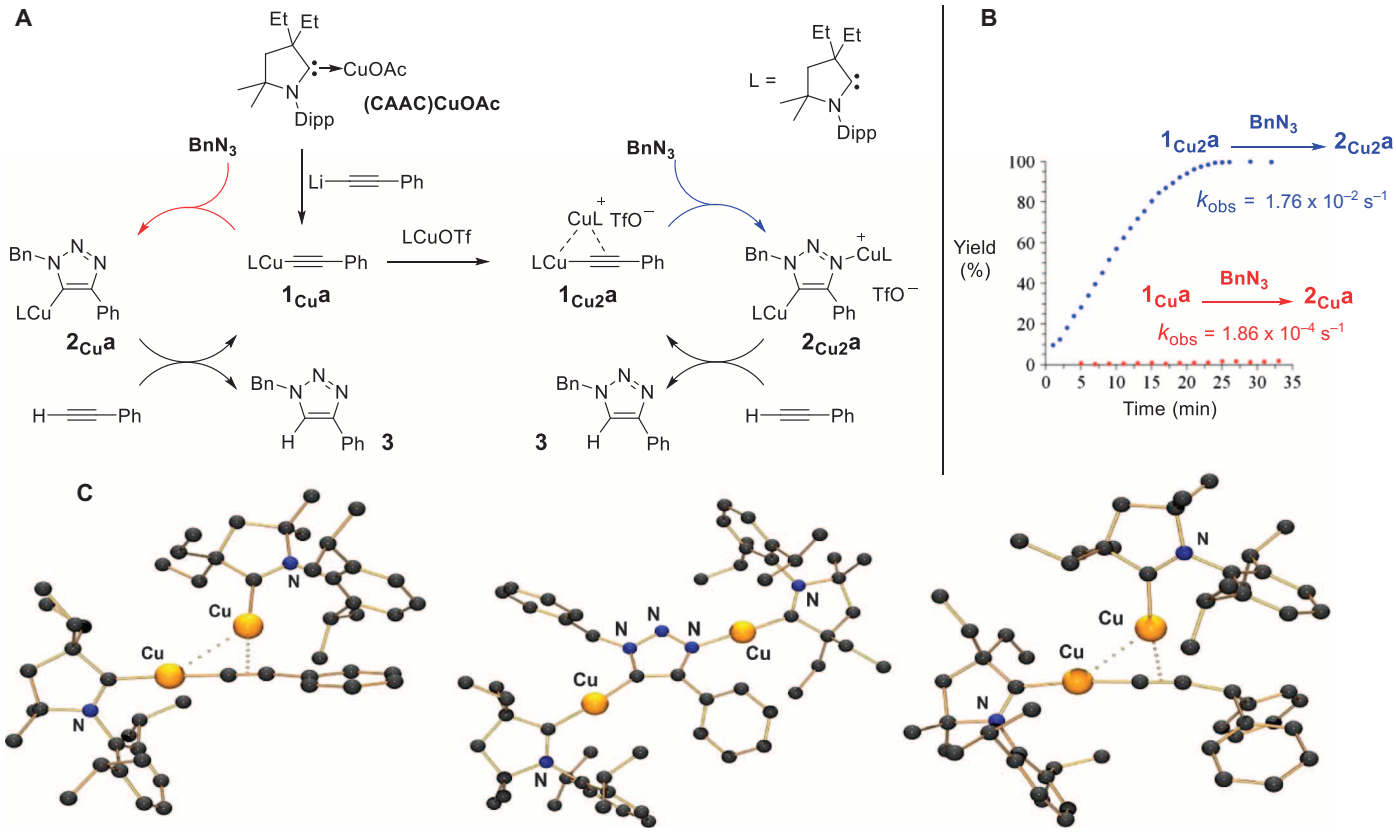

Fig. 1. Stepwise reproduction of the CuAAC reaction; isolation of mono- and bis(copper) intermediates involved in both catalytic pathways. (**A**) Stoichiometric reactions reproducing the different steps of the postulated CuAAC catalytic cycles, which allow for the isolation of a previously postulated π,σ-bis(copper) complex of type $\mathbf{1}_{Cu2}$ and of the never-mentioned bis(copper) triazole $\mathbf{2}_{Cu2}$. (**B**) Kinetic profiles of the stoichiometric reactions of $\mathbf{1}_{Cu}\mathbf{a}$ and $\mathbf{1}_{Cu2}\mathbf{a}$ with benzyl azide, which reveal the critical rate acceleration when the bimetallic complex $\mathbf{1}_{Cu2}\mathbf{a}$ is used. (**C**) Molecular view of complexes $\mathbf{1}_{Cu2}\mathbf{a}$ (left, table S1), $\mathbf{2}_{Cu2}\mathbf{a}$ (center, table S2), and $\mathbf{1}_{Cu2}\mathbf{b}$ (right, table S3) in the solid state (for clarity, H atoms and anions are omitted).

be extremely clean and high-yielding, and could be achieved either under strictly dry and anaerobic conditions or using nondried solvent under air. To confirm that the isolated complexes are active catalytic species, phenyl acetylene was reacted with benzyl azide at room temperature in methylene chloride using 10 mol % of $\mathbf{1}_{Cu}\mathbf{a}$ and $\mathbf{2}_{Cu}\mathbf{a}$, and only 5 mol % of $\mathbf{1}_{Cu2}\mathbf{a}$ and $\mathbf{2}_{Cu2}\mathbf{a}$. The kinetic profiles of the reactions reveal that the catalytic activity of the dinuclear complexes $\mathbf{1}_{Cu2}\mathbf{a}$ and $\mathbf{2}_{Cu2}\mathbf{a}$ is drastically higher (94 and 99% yields of **3** after 10 hours) than that of mononuclear complexes $\mathbf{1}_{Cu}\mathbf{a}$ and $\mathbf{2}_{Cu}\mathbf{a}$ (2 and 12% yields of **3** after 10 hours) (Fig. 2A and fig. S19). These results are in agreement with those obtained for the stoichiometric reactions. Note that although the reactions promoted by $\mathbf{1}_{Cu2}\mathbf{a}$ and $\mathbf{2}_{Cu2}\mathbf{a}$ proceed at the same rate, a short initiation period is observed with $\mathbf{1}_{Cu2}\mathbf{a}$, which is concomitant with the formation of $\mathbf{2}_{Cu2}\mathbf{a}$; after the initiation period, the concentration of $\mathbf{2}_{Cu2}\mathbf{a}$ remains constant over the course of the catalytic reaction (Fig. 2B). Similar observations can be made from the reactions catalyzed by complexes $\mathbf{1}_{Cu}\mathbf{a}$ and $\mathbf{2}_{Cu}\mathbf{a}$ (Fig. 2C), demonstrating that metallated triazoles $\mathbf{2}_{Cu}\mathbf{a}$ and $\mathbf{2}_{Cu2}\mathbf{a}$ are the resting states of their respective catalytic cycles.

The results described above demonstrate that the catalytic reaction operates efficiently once $\mathbf{1}_{Cu2}\mathbf{a}$ is formed. When phenyl acetylene was reacted with benzyl azide at room temperature, in the presence of 10 mol % (CAAC)CuOTf, we observed the near quantitative formation of triazole **3**, but only after 35 hours. The kinetic profile (Fig. 2A) shows a long initiation period, followed by drastic rate acceleration. Because the formation of the bis(nuclear) acetylide $\mathbf{1}_{Cu2}\mathbf{a}$ from $\mathbf{1}_{Cu}\mathbf{a}$ is a fast reaction (*vide supra*), we conclude that the formation of $\mathbf{1}_{Cu}\mathbf{a}$ is the limiting step of CuAAC reaction when (CAAC)CuOTf is the precatalyst. Indeed, when two equivalents of (CAAC)CuOTf were added to phenyl acetylene, in the absence of benzyl azide, no apparent reaction occurred after 8 hours at ambient temperature (Fig. 2D). The trifluoromethanesulfonate anion is too weakly basic to efficiently promote the metallation of the alkyne (*31*). Addition of one equivalent of triethylamine to the previous solution cleanly afforded $\mathbf{1}_{Cu2}\mathbf{a}$ along with $Et_3NH^+OTf^-$ within a few minutes. The effect of the presence of an additional base is also apparent on the kinetic profile of the catalytic reaction using 10 mol % (CAAC)CuOTf and 5 mol % triethylamine (Fig. 2E). As expected, a significant shortening of the initiation period is observed.

In conclusion, the isolation of the mono- and bis-copper acetylide complexes $\mathbf{1}_{Cu}\mathbf{a}$ and $\mathbf{1}_{Cu2}\mathbf{a}$ demonstrates that although both species are active in the catalytic cycle, the dinuclear complex is involved in the kinetically favored pathway (Fig. 3). The stability of $\mathbf{1}_{Cu2}\mathbf{a}$ seems to be in contradiction with previous reports (*21*). The peculiar electronic properties of the CAAC ligand possibly play a role (*32*), but the use of a weakly coordinating trifluoromethanesulfonate ligand is crucial. Indeed, when (CAAC)CuX complexes bear the more popular chloride or acetate X ligand, no bis(copper) complexes could be observed,

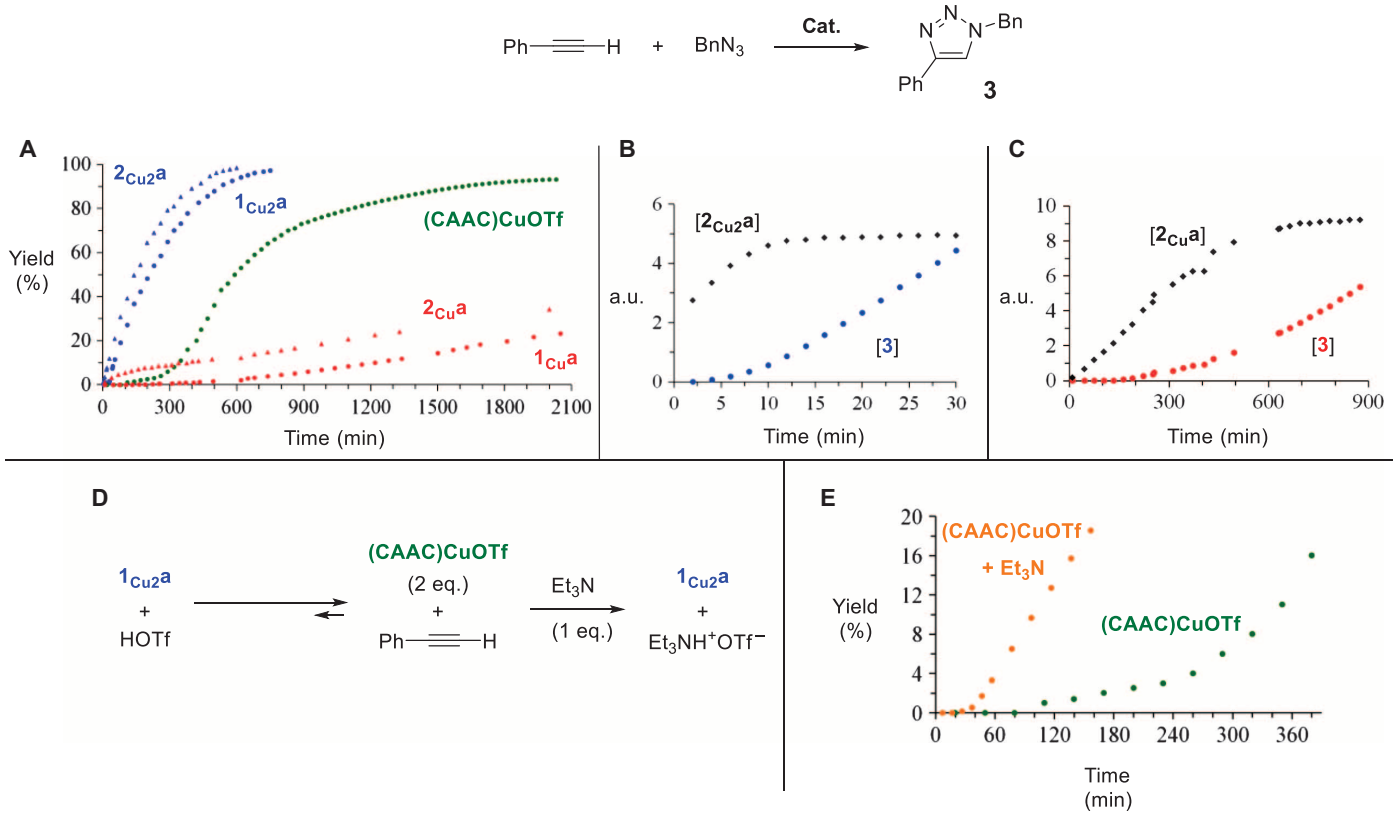

Fig. 2. Kinetic profiles of the CuAAC reaction of phenyl acetylene with benzyl azide using CAAC-supported mono- and bis(copper) catalysts. (**A**) The kinetic profiles of the catalytic reaction of phenyl acetylene with benzyl azide demonstrate the superior catalytic activity of the dinuclear complexes $\mathbf{1}_{Cu2}$**a** and $\mathbf{2}_{Cu2}$**a** over their mononuclear counterparts $\mathbf{1}_{Cu}$**a** and $\mathbf{2}_{Cu}$**a**, and show that the (CAAC)CuOTf complex adopts the dinuclear pathway after an initiation period. (**B**) Evolution of the amount of dimetallated triazole $\mathbf{2}_{Cu2}$**a** and free triazole **3** during the early period of the catalytic reaction using $\mathbf{1}_{Cu2}$**a** as catalyst, showing that $\mathbf{2}_{Cu2}$**a** is the resting state of the catalytic cycle. a.u., arbitrary units. (**C**) Same as (B), but of $\mathbf{2}_{Cu}$**a** and **3** using $\mathbf{1}_{Cu}$**a** as catalyst. (**D** and **E**) Et_3N, as a proton scavenger, allows for the rapid formation of $\mathbf{1}_{Cu2}$**a** from (CAAC)CuOTf and phenyl acetylene (D), and consequently shortens the induction period of the CuAAC reaction described in (A) using (CAAC)CuOTf (E).

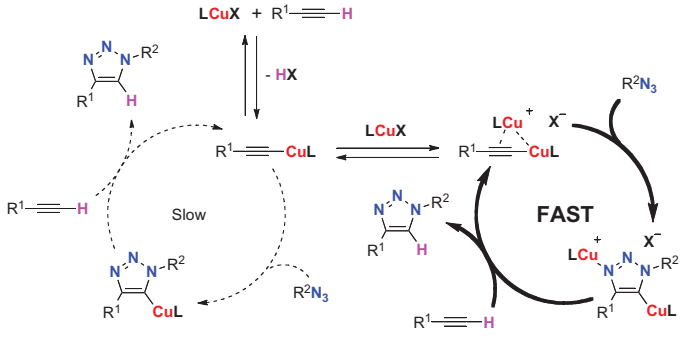

Fig. 3. Mechanistic conclusions: Both the mono- and bis-copper pathways are active in the CuAAC reaction, but the latter is kinetically favored. The protodemetallation is performed by the alkyne, which regenerates the metallated acetylide, thereby excluding the σ-copper acetylide from the preferred catalytic cycle.

although kinetic data demonstrate their involvement. Moreover, when the trifluoromethanesulfonate is used, investigations of the dinuclear pathway permitted the isolation of a never-postulated bis(copper) triazole complex of type $\mathbf{2}_{Cu2}$, which is the resting state of the catalytic cycle. The alkyne serves as the proton source for the demetallation of $\mathbf{2}_{Cu2}$, which regenerates the π,σ-bis(copper) acetylide of type $\mathbf{1}_{Cu2}$, leaving out complexes of type $\mathbf{1}_{Cu}$ from the catalytic cycle. These results led to the broader question of whether bis(metallic) complexes of type $\mathbf{1}_{Cu2}$ are also key species in other copper-catalyzed organic reactions (*33*).

MATERIALS AND METHODS

General

^1H and ^{13}C NMR spectra were recorded on Bruker Avance 300, Jeol ECA 500, and Varian Inova 500 spectrometers. NMR multiplicities are abbreviated as follows: *s* = singlet, *d* = doublet, *t* = triplet, *q* = quartet, *sept* = septet, *m* = multiplet, *br* = broad signal. Chemical shifts are given in parts per million (ppm) and are referenced to $SiMe_4$ (^1H, ^{13}C) and $CFCl_3$ (^{19}F). All spectra were obtained at 25°C in the solvent indicated. Coupling constants *J* are given in hertz (Hz). Mass spectra were performed at the University of California San Diego Mass Spectrometry Laboratory. Melting points were measured with an electrothermal MEL-TEMP apparatus. Single crystal x-ray diffraction data were collected on a Bruker Apex II CCD (charge-coupled device) detector using Mo-Kα radiation (λ = 0.71073 Å). Crystals were selected under

oil, mounted on nylon loops, and then immediately placed in a cold stream of nitrogen. Structures were solved and refined using Olex2 and SHELXTL. The CAAC and 3,3-diphenyl-1-propyne were prepared following literature procedures, whereas all other starting materials were purchased from commercial sources.

Synthesis of (CAAC)CuCCPh $\mathbf{1_{Cu}a}$

n-BuLi (2.4 mmol, 2.5 M in hexane) was slowly added to a solution of phenyl acetylene (234 mg, 2.3 mmol) in THF (15 ml) at −78°C. After 30 min, a solution of (CAAC)CuOAc (1.0 g, 2.3 mmol) in THF (10 ml) was added, and the mixture was stirred at ambient temperature for 1 hour. Volatiles were removed under vacuum, and the remaining solid was extracted with benzene (3 × 10 ml). After removal of benzene under vacuum, the solid was washed with hexane (20 ml). $\mathbf{1_{Cu}a}$ was obtained as a light yellow solid. Yield 88% (970 mg). mp 152°C [decomposition (dec.)]. ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.48 (t, *J* = 7.8 Hz, 1 H, *p*-*H*), 7.34 (d, *J* = 7.8 Hz, 2 H, *m*-*H*), 7.23 (br d, *J* = 7.1 Hz, 2 H, *o*-H_{C6H5}), 7.14 (br t, *J* = 7.1 Hz, 2 H, *m*-H_{C6H5}), 7.08 (br t, *J* = 7.1 Hz, 1 H, *p*-H_{C6H5}), 2.88 (sept, *J* = 6.9 Hz, 2 H, C*H*Me$_2$), 1.98 (s, 2 H, CH_2), 1.96 to 1.87 (m, 2 H, CH_2), 1.86 to 1.74 (m, 2 H, CH_2), 1.39 to 1.30 (m, 18 H, CH_3, CHCH_3), 1.11 (t, *J* = 7.5 Hz, 6 H, CH_3); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 253.5 ($C_{carbene}$), 145.6 (C_q), 135.1 (C_q), 131.8 (CH_{C6H5}), 129.9 (CH_{Ar}), 128.1 (CH_{C6H5}), 127.7 (PhCCCu), 125.7 (CH_{Ar}), 125.0 (CH_{C6H5}), 121.9 ($C_{q\text{-}C6H5}$), 106.3 (PhCCCu), 81.3 (C_q), 63.3 (C_q), 42.8 (CH_2), 31.4 (CH_2), 29.5, 29.4, 27.3, 22.4, 9.9; high-resolution mass spectrometry (HRMS) [electrospray ionization–time-of-flight mass spectrometry (ESI-TOFMS)]: mass/charge ratio (*m*/*z*) calculated for $C_{30}H_{40}CuNNa^+$ 500.2349, found 500.2355.

Synthesis of bis(copper) acetylide complexes $\mathbf{1_{Cu2}a}$

(CAAC)CuOTf (530 mg, 1 mmol) was added to a solution of $\mathbf{1_{Cu}a}$ (480 mg, 1 mmol) in methylene chloride (20 ml). The reaction was stirred for 5 min at ambient temperature. After removing the solvent under vacuum, $\mathbf{1_{Cu2}a}$ was obtained as a white solid. Yield 95% (952 mg). mp 174°C (dec.). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.44 (t, *J* = 7.8 Hz, 2 H, *p*-H), 7.26 (d, *J* = 7.8 Hz, 4 H, *m*-H), 7.22 (t, *J* = 7.6 Hz, 1 H, *p*-H), 7.04 (t, *J* = 7.6 Hz, 2 H, *m*-H), 6.41 (d, *J* = 7.6 Hz, 2 H, *o*-H), 2.82 (sept, *J* = 6.9 Hz, 4 H, C*H*Me$_2$), 2.05 (s, 4 H, CH_2), 1.96 to 1.83 (m, 4 H, CH_2), 1.80 to 1.68 (m, 4 H, CH_2), 1.38 (s, 12H, CH_3), 1.29 (d, *J* = 6.9 Hz, 12 H, CHCH_3), 1.18 to 1.02 (m, 24 H); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 249.4 ($C_{carbene}$), 145.3 ($C_{q\text{-}Aro}$), 134.7 ($C_{q\text{-}Aro}$), 132.0 ($CH_{\text{-}Aro}$), 130.4 ($CH_{\text{-}Aro}$), 129.4 ($CH_{\text{-}Aro}$), 128.7 ($CH_{\text{-}Aro}$), 125.4 ($CH_{\text{-}Aro}$), 122.2 (PhCCCu$_2$), 118.9 ($C_{q\text{-}Aro}$), 110.8 (PhCCCu$_2$), 82.5 (C_q), 63.1 (C_q), 42.1 (CH_2), 31.5 (CH_2), 29.4, 27.2, 22.4, 9.9; HRMS (ESI-TOFMS): *m*/*z* calculated for $C_{52}H_{75}Cu_2N_2^+$ 853.4517, found 853.4507.

Synthesis of bis(copper) triazole complexes $\mathbf{2_{Cu2}a}$

Benzyl azide (40.0 mg, 0.30 mmol) was added to a solution of $\mathbf{1_{Cu2}a}$ (250 mg, 0.25 mmol) in methylene chloride (0.5 ml). After 1 hour, diethyl ether (15 ml) was added to induce the precipitation of the product. After filtration, $\mathbf{2_{Cu2}a}$ was isolated as a pale yellow solid. Yield 87% (246 mg). mp 175°C (dec.). ^{1}H NMR (CD_2Cl_2, 500 MHz): δ = 7.48 to 7.38 (m, 2 H, *p*-H), 7.34 to 7.14 (m, 12 H), 6.82 (br, 2 H), 5.11 (s, 2 H, CH_2Ph), 2.77 (sept, *J* = 6.9 Hz, 4 H, C*H*Me$_2$), 2.01 (s, 2 H, CH_2), 1.96 (s, 2 H, CH_2), 1.85 to 1.73 (m, 2 H, CH_2), 1.73 to 1.61 (m, 4 H, CH_2), 1.61 to 1.51 (m, 2 H, CH_2), 1.34 (br, 12 H, CH_3), 1.29 to 1.20 (m, 12 H, CHCH_3), 1.04 to 0.86 (m, 24 H); ^{13}C NMR (CD_2Cl_2, 125 MHz): δ = 252.7 ($C_{carbene}$), 249.3 ($C_{carbene}$), 156.7 ($C_{triazolide}$), 155.1 ($C_{triazolide}$), 145.4 (C_q), 145.3 (C_q), 136.7 (C_{qAr}), 135.2 (C_q), 134.8 (C_q), 133.3 (C_{qAr}), 130.3 (CH_{Ar}), 130.2 (CH_{Ar}), 129.1 (CH_{Ar}), 128.8 (CH_{Ar}), 128.2 (CH_{Ar}), 128.1 ($C_{q\text{-}Ar}$), 128.0 (CH_{Ar}), 127.1 (CH_{Ar}), 125.2 (CH_{Ar}), 125.1 (CH_{Ar}), 82.3 (C_q), 81.9 (C_q), 63.3 (C_q), 63.0 (C_q), 57.1 (CH_2Ph), 42.4 (CH_2), 31.3 (CH_2), 29.4, 27.0, 22.3, 9.7. HRMS (ESI-TOFMS): *m*/*z* calculated for $C_{59}H_{82}Cu_2N_5^+$ 986.5157, found 986.5161.

Protodemetallation of $\mathbf{2_{Cu2}a}$ leading to the regeneration of $\mathbf{1_{Cu2}a}$

Phenyl acetylene (15 mg, 0.15 mmol) was added to the solution of $\mathbf{2_{Cu2}a}$ (136 mg, 0.12 mmol) in methylene chloride (5 ml). After stirring for 16 hours at room temperature, the solvent was removed under vacuum. The remaining solid was washed with diethyl ether (3 × 10 ml) to remove triazole **3**, and after drying, $\mathbf{1_{Cu2}a}$ was obtained as a yellow solid. Yield 91% (108 mg). NMR data are identical to those of a sample prepared as described above.

SUPPLEMENTARY MATERIALS

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/1/5/e1500304/DC1

Supplementary text

Fig. S1. ^{1}H NMR of (CAAC)CuOAc in CD_2Cl_2.

Fig. S2. ^{13}C NMR of (CAAC)CuOAc in CD_2Cl_2.

Fig. S3. ^{1}H NMR of (CAAC)CuCl in CD_2Cl_2.

Fig. S4. ^{13}C NMR of (CAAC)CuCl in CD_2Cl_2.

Fig. S5. ^{1}H NMR of (CAAC)CuOTf in $CDCl_3$.

Fig. S6. ^{13}C NMR of (CAAC)CuOTf in $CDCl_3$.

Fig. S7. ^{1}H NMR of $\mathbf{1_{Cu}a}$ in CD_2Cl_2.

Fig. S8. ^{13}C NMR of $\mathbf{1_{Cu}a}$ in CD_2Cl_2.

Fig. S9. ^{1}H NMR of $\mathbf{1_{Cu2}a}$ in CD_2Cl_2.

Fig. S10. ^{13}C NMR of $\mathbf{1_{Cu2}a}$ in CD_2Cl_2.

Fig. S11. ^{1}H NMR of $\mathbf{2_{Cu2}a}$ in CD_2Cl_2.

Fig. S12. ^{3}C NMR of $\mathbf{2_{Cu2}a}$ in CD_2Cl_2.

Fig. S13. ^{1}H NMR of $\mathbf{1_{Cu2}b}$ in CD_2Cl_2.

Fig. S14. ^{3}C NMR of $\mathbf{1_{Cu2}b}$ in CD_2Cl_2.

Fig. S15. ^{1}H NMR of $\mathbf{2_{Cu}a}$ in CD_2Cl_2.

Fig. S16. ^{13}C NMR of $\mathbf{2_{Cu}a}$ in CD_2Cl_2.

Fig. S17. Evolution of the annulation reaction monitored by ^{1}H NMR.

Fig. S18. Evolution of the protodemetallation reaction monitored by ^{1}H NMR.

Fig. S19. Evolution of the catalytic reaction between benzyl azide and phenyl acetylene monitored by ^{1}H NMR.

Table S1. Crystal data and structure refinement for $\mathbf{1_{Cu2}a}$.

Table S2. Crystal data and structure refinement for $\mathbf{2_{Cu2}a}$ (X = BF4).

Table S3. Crystal data and structure refinement for $\mathbf{1_{Cu2}b}$ (X = BF4).

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