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# Improved Copper(I)–NHC Catalytic Efficiency on Huisgen Reaction by Addition of Aromatic Nitrogen Donors

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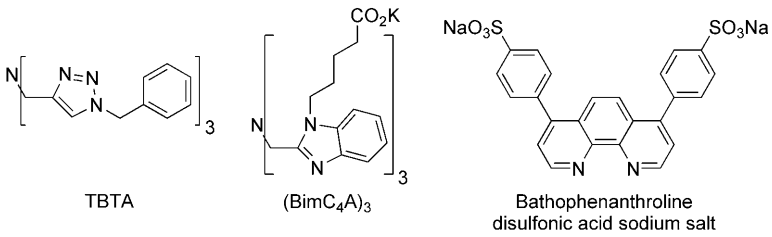
*Dedicated to Professor István E. Markó*

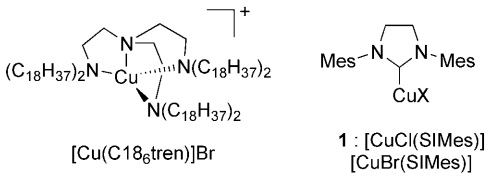
The recent emergence of "click chemistry" as a new paradigm for organic synthesis, invoking only simple, high-yielding and easily workable transformations, has facilitated an extraordinary increase in the number of molecules available for medicinal chemistry, biology, and material science.[1] Among these synthetic "click tools", the Huisgen-catalyzed cycloaddition, also called copper(I)-catalyzed azide alkyne cycloaddition (CuAAC), has received unrivalled attention.[2] Efficient CuAAC catalysts consist of a combination of copper and amino ligands (TBTA, $(BimC_4A)_3$, bathophenanthroline) in the presence of a sacrificial reducing reagent (Scheme 1).[3] Detailed studies have demonstrated the recruitment of a bimetallic species and showed that the ligands strongly accelerate the process.[3b,c]




Scheme 1. CuAAC accelerating ligands.

Very few systems are effective on CuAAC without the intervention of a reducing reagent. For example, Vincent and co-workers took advantage of the high stability of [Cu(C18$_6$tren)]Br in the presence of oxygen to synthesize 1,4-triazoles at low catalyst loading with a high turnover number in solution (Scheme 2).[4] Recently, Nolan and Díez have reported that *N*-heterocyclic carbenes (NHCs) are suitable ligands for copper(I) catalysis.[5] In a first report, among the copper(I)–NHCs screened, they showed that [CuX(SIMes)] (X = Cl, Br) functions particularly well under neat conditions; alternatively, the reaction can be carried out "on water".[5a] The Huisgen cycloaddition is an highly exothermic reaction and, for obvious safety reasons, reactions conducted in hydro-alcoholic solvents would be preferable, especially for performing large-scale synthesis. A second article reports the impressive catalytic activity of $[Cu(Icy)_2]PF_6$ that functions at 50 ppm loading, but still under neat conditions.[5b] Nevertheless, this catalyst suffers from the same safety limitations as [CuX(SIMes)]. Furthermore, neat conditions are not adapted to bioconjugation.

Closer examination of the binding mode of TBTA and $(BimC_4A)_3$ reveals that they share a central nitrogen σ-donor ligand connected to three




Scheme 2. Oxygen stable copper(I) catalysts.

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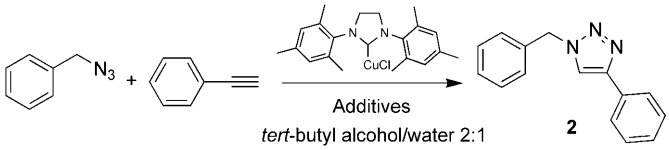
N-donor aromatic ligands. The helpful effect from N-donor aromatic ligands is also illustrated by the acceleration achieved by using bathophenanthroline.[6]

To overcome the above-mentioned limitations of copper(I)–NHC, we assumed that an association of the *N*-heterocyclic carbene (as the strong σ-donor ligand) with external N-donor aromatic ligand(s) would increase the catalysis efficiency. We thus selected several unsaturated nitrogen heterocycles: L-histidine, a ubiquitous amino acid residue associated to all types of copper enzymes, *N*-methylimidazole (NMI), 4-dimethylaminopyridine (4-DMAP), phenanthroline (Phen), and bathophenanthroline disulfonic sodium salt (Bathophen) to evaluate their influence on the course of the CuAAC catalyzed by [CuCl(SIMes)] (**1**).[7] For this purpose, we monitored the cycloaddition of benzyl azide and phenyl acetylene in a 2:1 *tert*-butyl alcohol/water mixture (Table 1).

Table 1. Effect of additives.

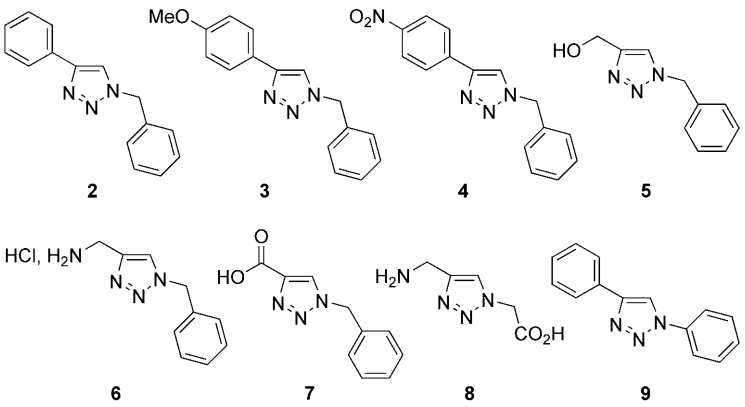



| Entry | Additive (ratio) | Loading [mol%] | Time [h] | *T* [°C] | Yield [%][a] |
|---|---|---|---|---|---|
| 1 | none | 1 | 18 | 20 | 10 |
| 2 | L-histidine (1:1) | 1 | 18 | 20 | 0 |
| 3 | NMI (1:1) | 1 | 18 | 20 | 76 |
| 4 | NMI (1:2) | 1 | 18 | 20 | 24 |
| 5 | 4-DMAP (1:1) | 1 | 18 | 20 | 63 |
| 6 | 4-DMAP(1:2) | 1 | 18 | 20 | 84 |
| 7 | Phen (1:1) | 1 | 18 | 20 | 78 |
| 8 | Phen (1:1) | 1 | 4 | 85 | 83 |
| 9 | Phen (1:1) | 0.1 | 72 | 50 | 73 |
| 10 | Bathophen (1:1) | 1 | 18 | 20 | 69 |

[a] Refers to pure isolated compounds.

Table 1, entry 1 shows the poor conversion obtained by using **1** alone in solution. Whereas histidine acted as a deleterious additive (Table 1, entry 2), pleasingly, the addition of one equivalent of NMI per copper–NHC afforded a good isolated yield (Table 1, entry 3). Unexpectedly, the addition of a second equivalent considerably decreased the yield (Table 1, entry 4).[8] Regarding 4-DMAP, optimum efficiency was reached for a ratio of ligand/**1** of 2:1 (Table 1, entries 5 and 6). A beneficial effect is also observed with the bidentate ligands phenanthroline (Table 1, entry 7), and bathophenanthroline (Table 1, entry 10). Importantly, the reaction also proceeds efficiently when the solvent was refluxed (85 °C, Table 1, entry 8). This highlights the well recognized ability of the NHC to protect copper(I) from oxidation. We were also satisfied to observe that the catalyst loading may be decreased to 0.1 mol% with an extended reaction time (Table 1, entry 9).[9]

Next, the scope of the reaction was examined with phenanthroline and 4-DMAP as additives (Scheme 3, Table 2).




Scheme 3. Triazoles obtained by **1**/4-DMAP (1:2) or **1**/Phen (1:1) catalyzed CuAAC.

Table 2. Catalyzed formation of triazoles.[a]

| | 2 | 3 | 4[b] | 5 | 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|---|
| 4-DMAP | 84 | 91 | 76 | 68 | 78 | 0[c],21[d] | 77 | 72 |
| Phen | 78 | 77 | 78 | 97 | 71 | 0[c],72[d] | 78 | 60 |

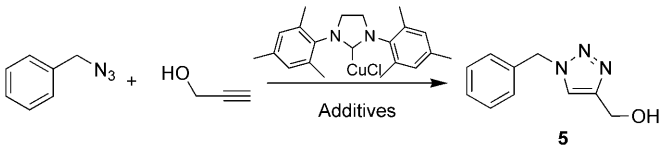
[a] All reactions were performed on 2 mmol scale during 18 h in an open vessel at room temperature using 1 mol% of **1** + 1 mol% of Phen or 2 mol% of 4-DMAP. Otherwise stated in supplementary material, products were isolated by simple filtration [b] In MeOH at 45 °C due to the poor solubility of the alkyne in *t*BuOH/water. [c] Using the free acid. [d] Using the triethylamonium salt.

Aromatic (**2**), electron-rich (**3**), electron-poor (**4**), and functionalized aliphatic (**5**, **6**) alkynes are well tolerated. The exception is propionic acid (**7**). This could be expected since propionic acid is likely to protonate the additives, thus annihilating any favorable effect.[10] Yield was increased in basic media (pH 9) by adding 1.1 equivalents of triethylamine. The low yield obtained with 4-DMAP is probably due to the competitive chelation of triethylamine, whereas the bidentate phenanthroline acting as a better binder allowed increased yield. Azidoacetic acid was also neutralized with propargylamine that can participate directly in the catalytic cycle; in this particular case a good yield was obtained (**8**). Finally, the reaction also proceeded well with phenyl azide as demonstrated by the formation of **9**.

The rate-accelerating effect of the additives was evidenced by monitoring the formation of the soluble triazole **5** during the CuAAC reaction, by $^1$H NMR spectroscopy (Scheme 4, Figure 1). After 7 h, a poor conversion was observed for the CuAAC catalyzed by **1** (2 mol%). The beneficial effect of the additive is evidenced by the simple addition of an equimolar amount of phenanthroline (2 mol%) into the solution. Subsequently, immediate formation of triazole **5** was observed.

We then compared the efficiency of Phen, NMI, and 4-DMAP (1 mol%) with the well known TBTA. For this, TBTA and copper sulfate (1:1) were mixed in the presence of 10 mol% of ascorbic acid, and completion of the reaction occurred after about 12 h. Comparison of the reaction with the different additives (without the addition of any reducing




Scheme 4. Catalyzed CuAAC formation of **5**.

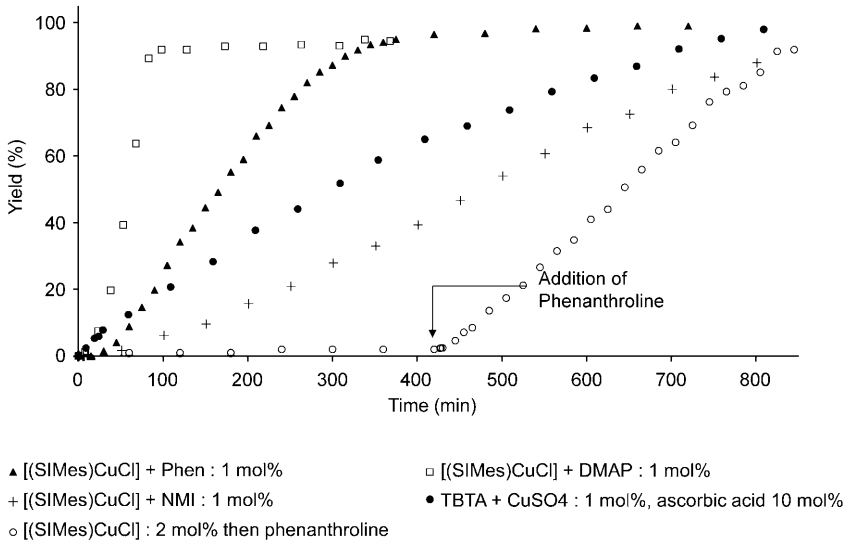



Figure 1. Kinetic study of the catalyzed formation of triazole **5.**

reagent) enabled us to establish a classification based on reaction rates: 4-DMAP > Phen > TBTA > NMI. Impressively, 4-DMAP afforded 100% completion in only 1.7 h, whilst 6 h are necessary for Phen, and 12 h for TBTA and NMI.

Gratifyingly, we were able to obtain red single crystals of the complex [CuCl(Phen)(SIMes)] (**10**), suitable for X-ray analysis, by saturating a solution of the complex in dichloromethane with diethyl ether. Representations of the structure are depicted in Figure 2 (hydrogen atoms are omitted for clarity).[11]

The copper atom lies in a distorted tetrahedral environment, which is in deep contrast with the linear structure of [CuCl(SIMes)]. This is not surprising as the same type of geometry is found for mixed σ, N-donor aromatic ligands complexes.[12] A comparison of the important structural features of **10** and **1** is given in Table 3. Interestingly, the carbene–copper bond remains unchanged, whereas the geometrical switch from **1** to **10** results in an elongation of the copper–chloride bond.

Inspection of the $^{1}H$ and $^{13}C$ NMR spectra of **1** in the presence of additives revealed an extreme broadening of Phen, 4-DMAP, or NMI signals, whereas the carbene signature remained unchanged. This typical ligand-exchange phenomenon occurring at the NMR time scale prompted us to use UV/Vis spectroscopy to gain more information. Among all ligands, phenanthroline is unique because the typical copper(I)-to-ligand d→π* charge-transfer band can be clearly observed at 450 nm in dichloromethane (Figure 3). This property enabled the determination of both the complex stoichiometry and the value of the association constant of phenanthroline with [CuCl(SIMes)].[13]

Evaluation of the complex stoichiometry by Job's continuous variation method, in dichloromethane, revealed the

Table 3. Representative distances and angles.

| Bond lengths [Å] | | | | |
|---|---|---|---|---|
| | Cu–Cl | Cu–$N^3$ | Cu–$N^4$ | Cu–$C^1$ |
| **10** | 2.347(2) | 2.114(5) | 2.128(5) | 1.916(7) |
| **1** | 2.099(1) | – | – | 1.882(4) |
| **Bond angles [°]** | | | | |
| | $N^3$-Cu-$N^4$ | $N^4$-Cu-Cl | $N^3$-Cu-Cl | $C^1$-Cu-Cl |
| **10** | 77.4(2) | 99.9(1) | 102.0(2) | 120.5(2) |
| **1** | – | – | – | 178.5(1) |

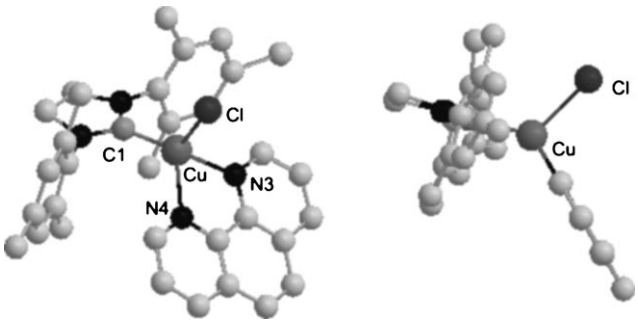



Figure 2. Views of [CuCl(Phen)(SIMes)] **10**.

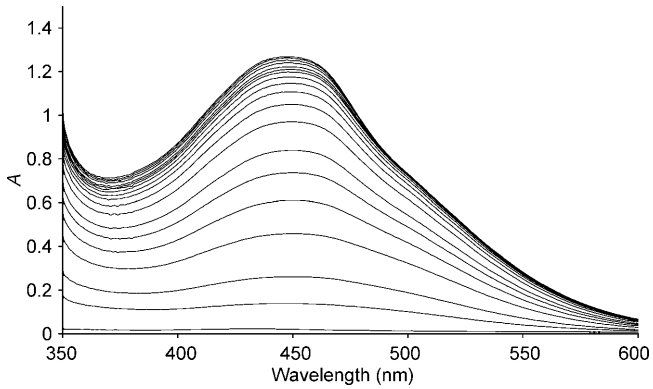
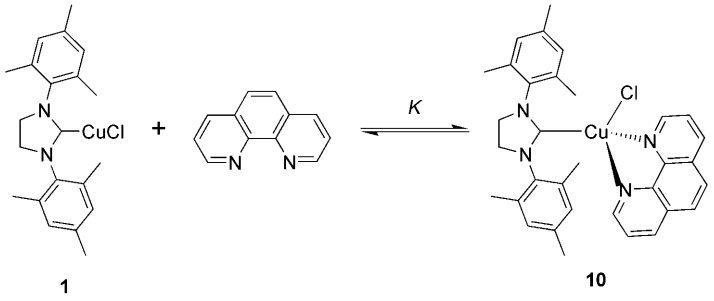



Figure 3. Copper(I) charge-transfer band increasing with the amount of phenanthroline (Curves from down to up: [Phen]/[**1**] from 0 to 50).




Scheme 5. Equilibrium between **1**, Phen and **10**.

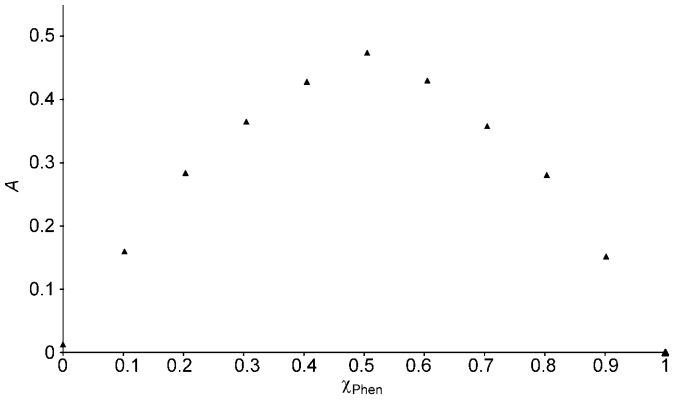



Figure 4. Stoichiometry: Job's plot for complex **10**.

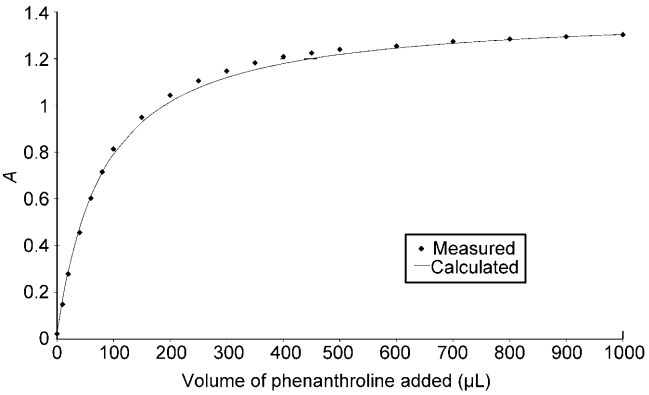



Figure 5. Titration curve of complex **10**, in $CH_2Cl_2$.

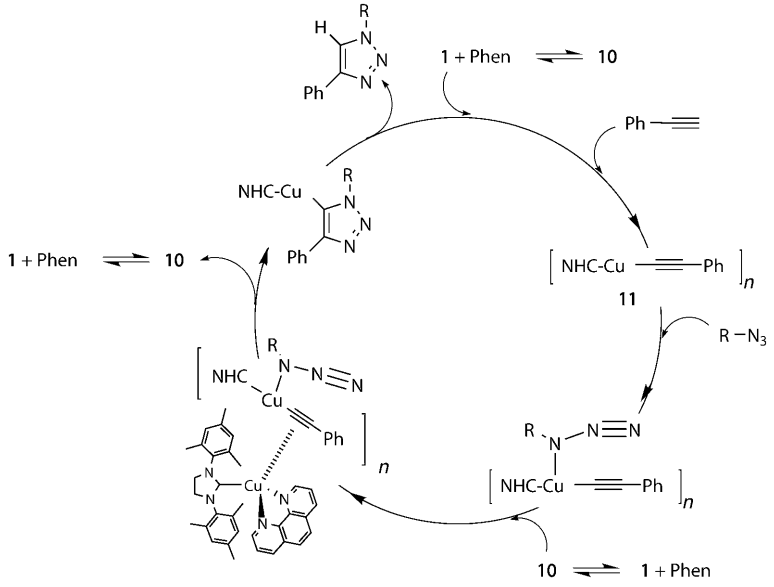
Table 4. Stoichiometry, association constants of **10**, in $CH_2Cl_2$.

| Stoichiometry Job's plot | $K$ [$M^{-1}$] Creswell-Allred | $K$ [$M^{-1}$] Benesi–Hildebrand |
|---|---|---|
| 1:1 | 254 ± 7 | 241 ± 3 |

typical formation of a 1:1 (host:guest) complex in agreement with our X-ray data (Scheme 5, Figure 4, and Table 4).

Surprisingly, **10** is a weak complex, based on a comparison (Figure 5 and Table 4) with literature values reported for $[Cu(Phen)]^+$ and $[Cu(Phen)_2]^+$.[14] Inspection of the distances deduced from single-crystal X-ray diffraction rules out the involvement of a steric effect to account for this low association. The weakness of complex **10** could be attributed to different electronic effects from the two ligands. It is important to remember here that a weak association of copper with its ligands is the key feature of the rate-accelerating effect displayed by tris-triazole, tris-benzimidazole, and related ligands.[3]

Regarding the CuAAC mechanism (Scheme 6), we propose that additional ligands form the saturated complex **10** (in which the chloride may be substituted by a solvent molecule). At this point, it seems unlikely that **10** may simultaneously accommodate azide and alkyne in a five-coordinate copper(I) complex and thus function as the sole catalytic species. Indeed, it seems rather difficult to propose an exact picture of the species involved, because of the particular complexity of the alkyne mode of complexation with copper(I). The most frequent arrangement reported includes three $Cu^I$ ions in a tetrahedral arrangement, but bimetallic complexes can also be found. In the particular case of [(IPr)Cu–C≡C–Ph], a 1:1 copper/acetylene stoichiometry has been proposed, but to the best of our knowledge, no X-ray structure analysis has been reported.[15] For the moment, the exact nature of the copper acetylene complex **11** formed from **1** and phenyl acetylene




Scheme 6. Outline of the assumed mechanism.

remains unclear. Therefore, it is more likely that the phenanthroline-containing complex **10** participates in the catalytic cycle as an additional copper center (whatever the nature of **11**), which associates through a π coordination of the acetylide in the rate-determining step.[3,16]

In conclusion, we report that simple addition of aromatic amines increases CuAAC catalytic activity of [CuCl(SIMes)] at a large range of temperatures in such a way that efficient catalysis can safely take place in hydro-alcoholic solvents. Phenanthroline and 4-DMAP are the additives of choice because the intrinsic stability of copper(I)–NHC may be maintained along the whole process, allowing a homogeneous CuAAC to proceed without the intervention of a reducing reagent. Current research in our laboratory focuses on the screening of a larger collection of additives and on delineating their effects on the CuAAC reaction catalyzed by copper(I)–NHC.

## Acknowledgements

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**Keywords:** azides · click chemistry · cycloaddition · homogeneous catalysis · N-heterocyclic carbenes

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[10] Interestingly, **7** has been synthesized using [CuCl(SIMes)] in solventless conditions: A. Maisonial, P. Serafin, M. Traïkia, E. Debiton, V. Théry, D. J. Aitken, P. Lemoine, B. Viossat, A. Gautier, *Eur. J. Inorg. Chem.* **2008**, 298–305. This reinforces the assumption that protonation of nitrogen additives annihilates the catalytic activity.

[11] Crystal data for **10**: $C_{33}H_{34}ClCuN_4$, $M_r = 585.65$, trigonal, space group $R\bar{3}$, $a = 42.0084(19)$, $c = 9.3049(4)$ Å, $V = 14220.5(1)$ Å$^3$, $Z = 18$, $\rho_{calcd} = 1.231$ g cm$^{-3}$, $\mu = 0.80$ mm$^{-1}$, $T = 293(2)$ K, $R(F^2 > 2\sigma(F^2)) = 0.053$, $R_w$ ($F^2$, all data) $= 0.209$, $S = 1.10$ for 3274 unique data ($\theta < 20.8°$; Bruker APEX-II CCD diffractometer, $Mo_{k\alpha}$ radiation, $\lambda = 0.71073$ Å) and 358 refined parameters; final difference synthesis $\Delta\rho_{max} = 0.54$e Å$^{-3}$, $\Delta\rho_{min} = -0.63$e Å$^{-3}$. CCDC-720889 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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[16] a) In our experimental conditions, the charge transfer band remains measurable during the reaction progress, attesting to the presence of complex **10** in solution; b) for a discussion on the association modes of acetylene and copper(I) see the excellent review from Meldal, ref. [2a]. For alternative mechanistic considerations on click chemistry, see ref. [2a,b].

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