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The Janus Face of the X Ligand in the Copper-Catalyzed Azide–Alkyne Cycloaddition

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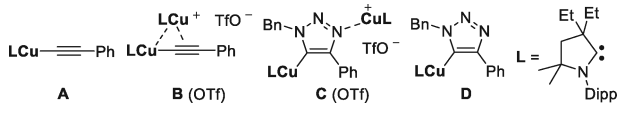
Supporting Information

ABSTRACT: To understand the effect of the anion (X) in the copper-catalyzed azide–alkyne cycloaddition (CuAAC) catalytic process, the kinetic profiles of the successive steps of the catalytic cycle have been studied by performing stoichiometric reactions using copper complexes LCuX in which L is a cyclic (alkyl)(amino)carbene (CAAC) ligand and X = OTf, Cl, OAc, OPh, or O*t*Bu. Basic ligands favor the metalation step but disfavor the formation of the catalytically active σ,π-bis(copper) acetylide, whereas non-nucleophilic ligands favor the latter but slowly promote the former. We show that acetate is a good compromise, and in addition, it is very efficient in the proto-demetalation step.

The copper-catalyzed 1,3-dipolar cycloaddition of an organic azide to a terminal alkyne (CuAAC)[1] is a highly versatile and efficient reaction[2] that has been applied in multiple fields of chemistry.[3] Its attractiveness is in part due to the cheap precatalysts used but also to its tolerance for a wide range of functional groups. However, despite many mechanistic studies,[4] it is only recently that the involvement of bis(copper) complexes was demonstrated. First, on the basis of indirect observations, Fokin and co-workers[4g] concluded that "*monomeric copper-acetylide complexes (i.e., A in Chart 1) are not reactive towards organic azides unless an exogenous copper catalyst is added.*" We then reported the isolation of the cyclic (alkyl)(amino)carbene (CAAC)[5,6] supported σ,π-alkyne bis(copper) **B** (OTf) and C,N-bis(copper)triazole **C** (OTf).[7] We demonstrated that although both **A** and **B** (OTf) are active in the catalytic cycle, the dinuclear complex **B** (OTf) is involved in the kinetically favored pathway, whereas **C** (OTf) is the resting state of the catalytic cycle. We realized that the isolation of complexes **B** and **C** was made possible by the electronic properties of the CAAC ligand[8] and, more importantly, because of the weakly coordinating trifluoromethanesulfonate anion. Furthermore, we showed that (CAAC)CuOTf is drastically less efficient than **B** (OTf) and **C** (OTf) for the CuAAC reaction of benzyl azide with phenylacetylene. Since the formation of the dinuclear complex **B** (OTf) from **A** is very fast, these observations clearly indicate that the formation of the mono(copper) acetylide **A** is the rate-limiting step of the catalytic cycle when (CAAC)CuOTf is the precatalyst.

Chart 1



These results prompted us to investigate the role of the anionic ligand in the individual steps of the copper-catalyzed azide alkyne cycloaddition, namely, (i) the metalation of the terminal alkyne, (ii) the formation of the σ,π-alkyne bis(copper) complex, (iii) the cycloaddition leading to the metalated triazole, and (iv) the protolysis of the latter to regenerate the active species and produce the final triazole. Using phenylacetylene and benzyl azide as substrates, we chose a set of anionic ligands (X = Cl, OAc, OPh, OtBu) that cover a broad range of basicity, and we compared our results to previously reported results obtained for X = OTf.[7]

First, we benchmarked the efficiency of various (CAAC)CuX precatalysts in the reaction of phenylacetylene and benzyl azide using a 5 mol % loading of the copper complex in dichloromethane at room temperature. The kinetic profiles of the reaction show that during the first 40 min (CAAC)CuOPh is the fastest precatalyst and that the rates of formation of triazole **1** parallel the basicities of the X ligands: OPh > OAc ≫ Cl ≈ OTf [(CAAC)CuO*t*Bu appeared to decompose in dichloromethane] (Figure 1, right). Then a drastic acceleration occurs with (CAAC)CuOAc, as the reaction reaches completion in 3 h (Figure 1, left). A similar phenomenon, although less pronounced, was observed with (CAAC)CuOPh and (CAAC)CuOTf, for which the reactions reach completion after 12 and 30 h, respectively, whereas (CAAC)CuCl[9] is

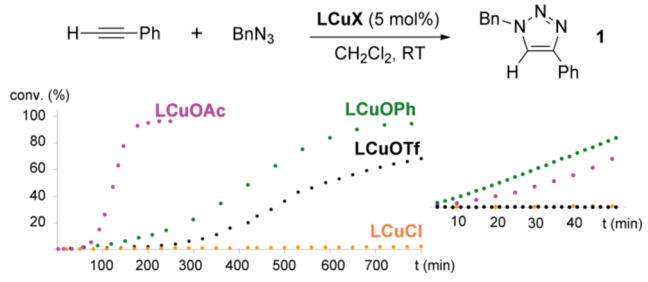


Figure 1. Kinetic profiles for the CuAAC of phenylacetylene with benzyl azide promoted by LCuX complexes [L = cyclic (alkyl)(amino)carbene (CAAC)].

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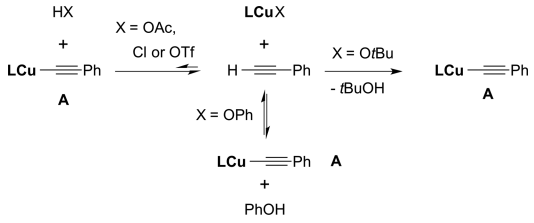
almost inept, with only a 3% yield of **1** after the same period of time.

To understand the effect of the anion on the kinetic profiles observed, we investigated the successive steps of the catalytic cycle by performing stoichiometric reactions, beginning with the metalation step.[10,11] When 1 equivalent of (CAAC)CuOTf, (CAAC)CuCl, or (CAAC)CuOAc was added to phenylacetylene, no apparent reaction was observed after 8 h at ambient temperature. In contrast, addition of (CAAC)CuO*t*Bu to a tetrahydrofuran (THF) solution of phenylacetylene led to the fast formation of *tert*-butanol and monocopper acetylide **A** (Scheme 1). In the case of (CAAC)CuOPh, a dynamic

Scheme 1. Stoichiometric Reactions of (CAAC)CuX Complexes with Phenylacetylene



equilibrium was evidenced by ^{13}C NMR spectroscopy at room temperature. These results perfectly explain the kinetic profiles observed during the first 40 min of the catalytic reactions, which correspond to deprotonation/complexation of the alkyne, a process that is favored by basic anions.

Next, we investigated the formation of the cationic bis(copper) complex by the reaction of **A** with a stoichiometric amount of (CAAC)CuX (Figure 2). As already reported, **B** (OTf) was formed quantitatively in a few minutes with (CAAC)CuOTf.[7] When the more coordinating anions X = Cl, OAc, and OPh were used, ^{1}H and ^{13}C NMR spectra indicated an equilibrium between **A**, (CAAC)CuX, and **B** (X). On the

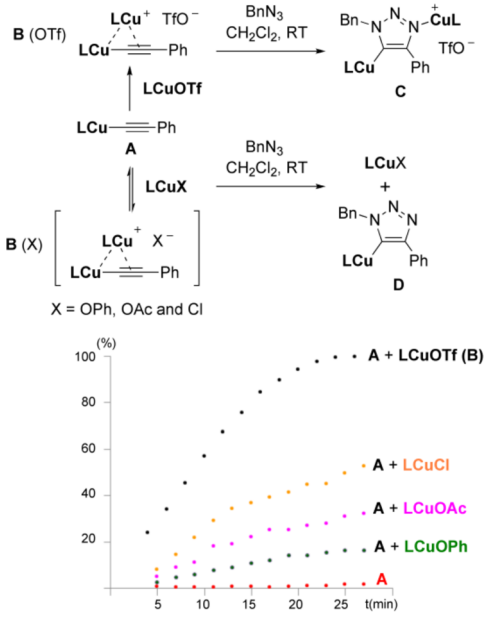


Figure 2. (top) Reaction of the monocopper acetylide **A** with LCuX and (bottom) kinetic profiles for the cycloaddition of benzyl azide to monocopper acetylide **A**, bis(copper) acetylide **B** (OTf), and equilibrated mixtures of **A** and (CAAC)CuX (X = Cl, OAc, OPh).

other hand, no interaction between **A** and (CAAC)CuO*t*Bu (in THF) was detected. Therefore, and not surprisingly, the order of difficulty of formation of the bis(copper) complex **B** follows the order of the basicities of the X ligands.

We then studied the addition of benzyl azide to monocopper acetylide **A**, bis(copper) acetylide **B** (OTf), and equilibrated mixtures of **A** and (CAAC)CuX (X = Cl, OAc, OPh). From **B** (OTf), the bis(metalated) triazole **C** was obtained, whereas with the other anions, the monometalated triazole **D** was produced (Figure 2). The reactions were monitored by ^{1}H NMR spectroscopy, and the kinetic profiles clearly show that the reaction is faster by far when **B** (OTf) is used. Then the rate decreases as the basicity of the X ligand increases, which is in line with the order of difficulty to form the bis(copper) complexes **B** (X).

From these sets of experiments (Scheme 1 and Figure 2), we can conclude that a basic X ligand at copper favors the alkyne metalation step to give **A** but simultaneously disfavors the formation of the key bis(copper) active catalyst **B**.

Finally, we turned our attention to the last step of the catalytic cycle, namely, the proto-demetalation of triazole **D**. We have previously reported that phenylacetylene is acidic enough to promote this reaction,[7] and thus, we investigated the reaction of **D** with phenylacetylene both in the absence and presence of (CAAC)CuX (X = OTf, Cl, OAc, OPh). The experiments were conducted by adding a 20-fold excess of phenylacetylene to **D** or to an equimolar mixture of **D** and (CAAC)CuX (X = OTf, Cl, OAc, OPh) in dichloromethane, and the formation of the metal-free triazole **1** was monitored by ^{1}H NMR spectroscopy over a period of 30 min (Figure 3). All

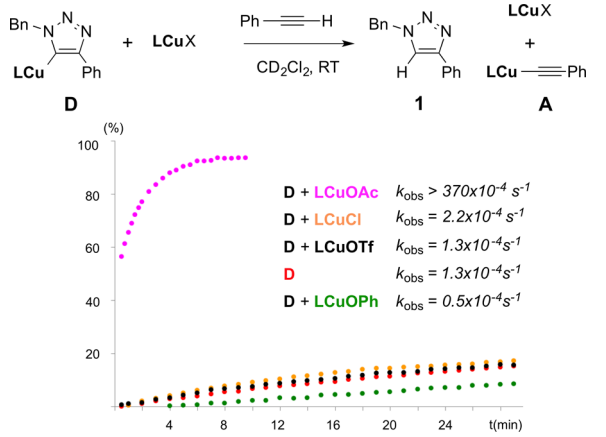


Figure 3. Kinetic profiles for the proto-demetalation of **D** by phenylacetylene in the absence or the presence of LCuX.

reactions occurred at very similar rates (k_{obs} between 0.5×10^{-4} s^{-1} and 2.2×10^{-4} s^{-1}) with the exception of the acetate complex ($k_{obs} > 370 \times 10^{-4}$ s^{-1}). Such acceleration is characteristic of a base assisted proton transfer mechanism usually observed in biological systems.[12]

On the basis of these results as a whole, it appears that the combination of monocopper acetylide **A** and (CAAC)CuOAc should be the most efficient catalytic system. Indeed, as can be seen in Figure 4, the addition of an equimolar amount of complex **A** to (CAAC)CuOAc bypasses the slow initial metalation of the alkyne by (CAAC)CuX, allows access to the bis(copper) active catalyst, and takes advantage of the fastest final proto-demetalation step.

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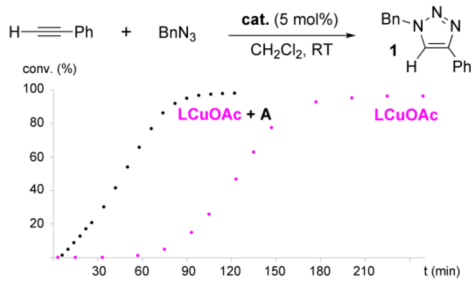

Figure 4. Comparison of the kinetic profiles for the reactions of phenylacetylene and benzyl azide with (CAAC)CuOAc or a 1:1 mixture of **A** and (CAAC)CuOAc (5 mol % Cu in each case).

This study has been made possible because CAAC ligands allow for the isolation of key intermediates. In addition, the CuAAC reactions promoted by CAAC-supported copper complexes are slow enough to be monitored. Our results demonstrate the Janus-face role of the X ligand in the CuAAC catalytic process. Basic ligands favor the metalation of the acetylene but disfavor the formation of the bis(copper) species, whereas non-nucleophilic ligands favor the latter but slowly promote the former. In this context, the acetate is a good compromise, and in addition, it is very efficient in promoting the proto-demetalation step; it should be noted that the acetate is often used in CuAAC reactions. Our results are in line with the work by Straub and co-workers,[2c,13] who recently reported that dinuclear copper complexes supported by bis(NHC) bidentate ligands and bearing a bridging acetate show excellent performance in different organic solvents with various alkynes and azides. We believe that the knowledge acquired in this study will enable both the improvement of known reactions[10,11,14] and also the design of novel copper-catalyzed chemical transformations. This hypothesis is under active investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b11028.

Full experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, and kinetic profiles (PDF)

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Notes

The authors declare no competing financial interest.

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