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'Click' cycloaddition catalysts: copper(I) and copper(II) tris(triazolylmethyl)amine complexes†

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The $\mathrm{Cu^{I}}$ complex of the 'click' ligand tris(benzyltriazolylmethyl)-amine is an unusual dinuclear dication with one triazole unit bridging two metal centers, and is an effective catalyst for the 'click' cycloaddition reaction.

The $\mathrm{Cu^{I}}$-catalyzed azide–alkyne cycloaddition (CuAAC),[1,2] a variant of the Huisgen azide–alkyne cycloaddition,[3] provides 1,4-substituted triazoles from azides and terminal alkynes with essentially perfect regioselectivity. This conjugation strategy has rapidly become a work-horse reaction finding application in polymer and materials science,[4] carbohydrate chemistry,[5] drug discovery,[6] and bioconjugation.[7] The reaction performs best in water and polytriazole ligands such as tris(benzyltriazolylmethyl)amine (TBTA) have been reported to stabilize the $\mathrm{Cu^{I}}$ oxidation state, thereby promoting catalysis.[8,9] Herein we report the preparation and X-ray structure determinations of $\mathrm{Cu^{I}}$ and $\mathrm{Cu^{II}}$ complexes of TBTA and investigate the ability of these complexes to promote the CuAAC reaction (Fig. 1).

Polytriazoles were identified as useful ligands for the CuAAC reaction through the observation of autocatalytic effects with polyvalent substrates.[8,10] In a seminal study, screening of a diverse range of mono-, bis-, and tristriazoles revealed TBTA as the most effective ligand for promotion of the reaction in the presence of air.[8] Phenanthroline and tripodal benzimidazole ligands provide rate enhancements over the "ligand free" case but can exhibit greater oxygen sensitivity.[11–13] Chan and co-workers have suggested that the tetradentate nature of TBTA allows it to completely envelop the $\mathrm{Cu^{I}}$ center, with the central basic tertiary amine being permanently coordinated during catalysis and the pendant triazole groups transiently dissociating from the metal center to allow formation of a $\mathrm{Cu^{I}}$-acetylide crucial to the catalytic cycle.[8]

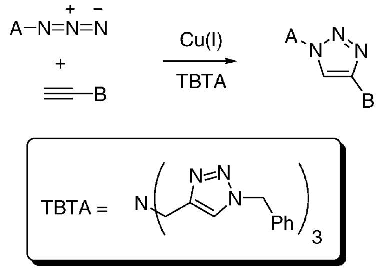

Fig. 1 The $\mathrm{Cu^{I}}$-catalyzed azide–alkyne cycloaddition is promoted in water by the tris(triazole) ligand TBTA.

The CuAAC reaction is commonly performed by mixing a source of $\mathrm{Cu^{II}}$, TBTA and a reducing agent, such as sodium ascorbate, to generate a $\mathrm{Cu^{I}}$ complex *in situ*.[1,8] Consequently, we initially investigated the $\mathrm{Cu^{II}}$ complex with TBTA. The green $\mathrm{Cu^{II}}$ salt, containing the cation **1** $[\mathrm{Cu^{II}Cl(TBTA\text{-}\kappa^4\text{-}}N,N^3,N^{3'},N^{3''})]^+$, was synthesized by the reaction of $\mathrm{CuCl_2}$ and TBTA in acetonitrile. The X-ray structure (Fig. 2) reveals the well-resolved cation **1** lying on a crystallographic three-fold axis. The copper is found in a distorted trigonal bipyramidal $\mathrm{CuN_4Cl}$ coordination environment, with the triazole fragments of the tripodal ligand occupying equatorial positions and the basic tertiary amine of TBTA and chloride in the apical positions. The counterions of the complex were modeled as 50% occupancy by chloride and hydroxide. Recently, a similar structure of [CuBr(TBTA)]Br was reported.[14]

To investigate the ease of conversion of the $\mathrm{Cu^{II}}$ complex to a catalytically active $\mathrm{Cu^{I}}$ species, the electrochemical behavior of **1** was investigated.‡ Cyclic voltammetry measurements in

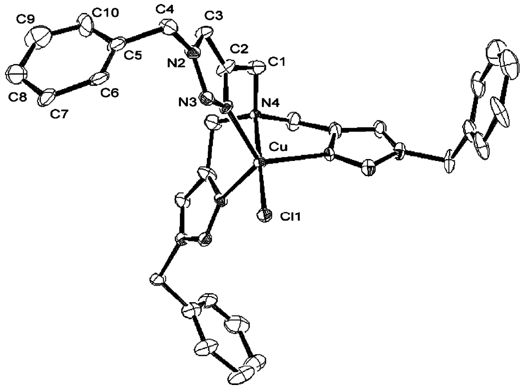

Fig. 2 An ORTEP representation, with ellipsoids at the 20% probability level, of the cation **1** $[\mathrm{Cu^{II}Cl(TBTA\text{-}\kappa^4\text{-}}N,N^3,N^{3'},N^{3''})]^+$. Pertinent bond lengths: Cu–N(1) = 2.078(7) Å; Cu–N(4) = 2.120(11) Å; Cu–Cl(1) = 2.233(5) Å. Anions omitted for clarity.

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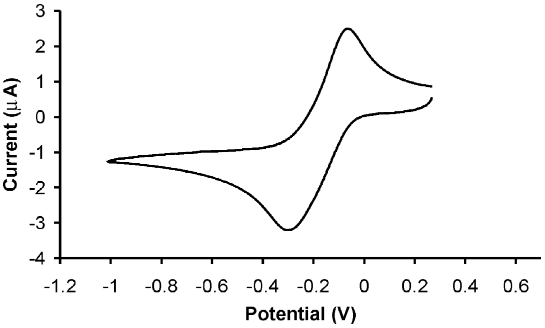


Fig. 3 Cyclic voltammogram of **1** in DMSO, 0.1 mol l^{-1} $(Bu_4N)(BF_4)$, scan rate = 0.01 V s^{-1}. Potentials quoted *vs.* Fc/Fc^+.

DMSO show that at very slow scan rates complex **1** undergoes a chemically reversible process centered at E = –0.18 V (*vs.* Fc/Fc^+) attributed to a Cu^{II}/Cu^{I} couple (ΔE = 225 mV) (Fig. 3). At faster scan rates the peak to peak separation increases suggesting that it might be possible to prepare a Cu^I complex but that significant reorganization at the metal center is expected to accompany reduction.

A Cu^I complex was prepared by the reaction of TBTA and $[Cu(CH_3CN)_4]BF_4$ in CH_3CN under anaerobic conditions. An X-ray crystal structure of colourless crystals of the dinuclear dication **2**, $[Cu^{I}_2(\mu\text{-TBTA-}\kappa^4\text{-}N^2,N^3,N^{3\prime},N^{3\prime\prime})_2]^{2+}$, as the tetrafluoroborate salt, reveals the cation lying about a crystallographic two-fold axis (Fig. 4). Each of the two Cu^I atoms has a distorted tetrahedral geometry, with three coordination sites satisfied by the proximal nitrogens (N1, N4 and N10; see Fig. 4) of the triazole groups of one TBTA molecule, and the fourth being supplied by the medial nitrogen (N7) of a triazole from the other bridging TBTA molecule within the dimer. Notably, the distance between the central tertiary amine and the copper center was 2.74 Å, significantly longer than a typical Cu–N bond. The Cu^I salt $\mathbf{2}\cdot(BF_4)_2$ is oxygen sensitive and rapidly oxidizes to give a green solution.

We next investigated the ability of the isolated complexes to catalyze a model CuAAC reaction between phenylacetylene and azidoacetanilide to give the triazole **3** (Table 1). In the absence of TBTA, the combination of 1 mol% $CuSO_4$ and 10 mol% sodium ascorbate afforded the triazole **3** in only 10% yield (entry 2). In the presence of TBTA, this same combination gave an excellent yield of **3** (entry 3). Similarly, the Cu^I source $[Cu(MeCN)_4]PF_6$ was ineffective in the absence of TBTA but in its presence gave a close to quantitative yield of **3** (entries 4 and 5). The isolated dinuclear dication Cu^I complex $\mathbf{2}\cdot(BF_4)_2$ was an effective catalyst for the CuAAC reaction (entry 6). Consistent with the facile reduction predicted by cyclic voltammetry, the Cu^{II} complex **1** could be converted to an active catalyst in the presence of sodium ascorbate (entry 7).

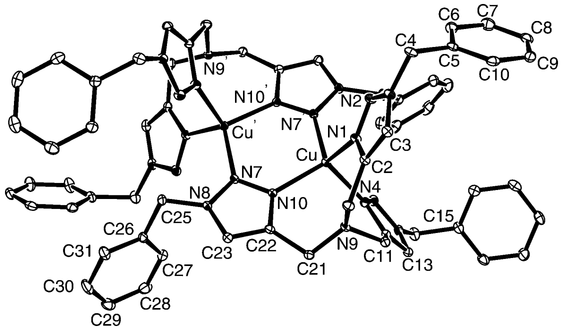
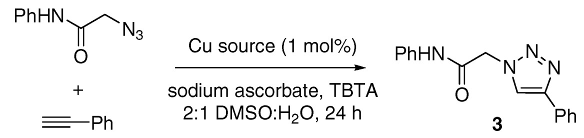


Fig. 4 An ORTEP representation, with ellipsoids at the 20% probability level, of the dication **2**. Pertinent bond lengths: Cu–N(1) = 2.049(2) Å; Cu–N(4) = 2.028(2) Å; Cu–N(10) = 2.0464(19) Å; Cu–N(7) = 2.038(2) Å. The prime character (′) indicates atoms at the symmetrically equivalent positions ($1 - x, y, \frac{1}{2} - z$). Solvent and counterions omitted for clarity.

Table 1 Effect of copper source on the cycloaddition synthesis of triazoles[a]



	Cu source	TBTA (mol%)	Sodium ascorbate (mol%)	Yield (%)[b]
1	$CuSO_4$	0	0	3
2	$CuSO_4$	0	10	10
3	$CuSO_4$	1	10	83
4	$[Cu(MeCN)_4]PF_6$	0	0	2
5	$[Cu(MeCN)_4]PF_6$	1	0	95
6	**2**	0	0	90
7	**1**	0	10	91

[a] Reactions were performed in glass flasks with no effort to exclude oxygen other than capping. [b] Yields were determined by ^1H NMR analysis of products isolated by dilution of reaction mixtures with water and filtration.

In summary, we report the structural characterization of Cu^I and Cu^{II} complexes of TBTA. The structure of **2** reveals that Cu^I does not coordinate with the tertiary amine of TBTA and that an unusual dinuclear coordination complex is formed with a triazole unit bridging two metal centers through the medial and proximal nitrogens. Recent studies have shown that the "ligand free" CuAAC reaction proceeds with a second order dependence on copper under catalytic conditions[10] and the involvement of di- and tetranuclear copper acetylide complexes has been suggested in ligand free and ligand accelerated cases.[12,15–18] By contrast the TBTA-assisted CuAAC reaction proceeds with a first order dependence on Cu^I concentration and thus the observed complex **2** is likely a precursor to the actual catalytic Cu^I species involved in the CuAAC, which is likely to be mononuclear and may involve hemi-labile coordination of the bridging triazole. Along with the recent report of a molecular Cu^I triazolide complex,[19] our study adds to the knowledge of copper species involved in the "ligand assisted" process. Finally, this work supports the proposed ability of TBTA to stabilize the Cu^I oxidation state and, along with the structural data, may lead to improved design of ligands for the promotion of the CuAAC reaction.

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Notes and references

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