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# A Photoreducible Copper(II)-Tren Complex of Practical Value: Generation of a Highly Reactive Click Catalyst

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**Abstract:** A detailed study on the photoreduction of the copper(II) precatalyst **1** to generate a highly reactive cuprous species for the copper(I)-catalyzed alkyne-azide cycloaddition (CuAAC) click reaction is presented. For the photoactive catalyst described herein, the activation is driven by a photoinduced electron transfer (PET) process harnessing a benzophenone-like ketoprofenate chromophore as a photosensitizer, which is equally the counterion. The solvent is shown to play a major role in the $Cu^{II}$ to $Cu^{I}$ reduction process as the final electron source, and the influence of the solvent nature on the photoreduction efficiency has been studied. Particular attention was paid to the use of water as a potential solvent, aqueous media being particularly appealing for CuAAC processes. The ability to solubilize the copper-tren complexes in water through the formation of inclusion complexes with β-CDs is demonstrated. Data is also provided on the fate of the copper(I)-tren catalytic species when reacting with $O_2$, $O_2$ being used to switch off the catalysis. These data show that partial oxidation of the secondary benzylamine groups of the ligand to benzylimines occurs. Preliminary results show that when prolonged irradiation times are employed a $Cu^{I}$ to $Cu^{0}$ over-reduction process takes place, leading to the formation of copper nanoparticles (NPs). Finally, the main objective of this work being the development of photoactivable catalysts of practical value for the CuAAC, the catalytic, photolatent, and recycling properties of **1** in water and organic solvents are reported.

**Keywords:** click chemistry • copper • homogeneous catalysis • photoinduced electron transfer • photochemistry • photolatent catalyst

## Introduction

The design of chemical processes that can be controlled by light is a research area with strong potential for development.[1] Catalysts whose activity can be switched on/off upon light irradiation are of particular interest.[2] Considering transition-metal catalysts, the generation of a highly active catalytic species on demand by the light irradiation of an inactive precatalyst presents several key benefits: 1) handling metal species that are stable under ambient conditions; 2) switching on catalysis at a given time and place; 3) tuning the onset of the generated active catalyst by controlling the photoactivation process, which would be valuable for highly exothermic reactions conducted on a large scale. To date, most examples of photocontrolled transition-metal catalysts are the so-called photocaged catalysts, which rely on the photodissociation or photodecomposition of ligands in coordinatively saturated metal complexes to generate vacant active sites.[2,3]

Most of the transition-metal catalysts exhibit an oxidation-state dependent activity. Notable examples include palladium-catalyzed coupling reactions for which the active species is the reduced $Pd^{0}$, whereas the oxidized $Pd^{II}$ is inactive. Typically in these reactions a $Pd^{II}$ precatalyst is employed, the active $Pd^{0}$ species being generated in situ, typically through phosphine ligand oxidation or reductive elimination processes.[4] Electrochemical reduction has also emerged as a powerful activation method.[4] Rather surprisingly, photoinduced electron transfer (PET) to a metal cation as a way to activate a catalyst has been largely unexplored. We recently reported the synthesis, preliminary sensitized photoreduction studies and catalytic activity of [Cu($t$BuBz$_3$tren)ketoprofenate]ketoprofenate complex **1** (Figure 1), a prototype photolatent catalyst whose activation is driven by a PET process.[5] The copper(I)-catalyzed alkyne–azide cycloaddition (CuAAC) is an example of a reaction for which the catalyst is inactive in its oxidized cupric state but active in its reduced cuprous form.[6] This click reaction is now widely employed in all areas of the chemical sciences.[7,8] Within the last ten years a range of catalytic systems have been developed, most of them being based on either copper(II) precatalysts to which an external sacrificial reductant, such as sodium ascorbate, is added or directly reduced copper(I) catalysts.[9] In recent years, light-induced click reactions have received special attention,[10] and a few examples of photodriven CuAAc processes have been re-

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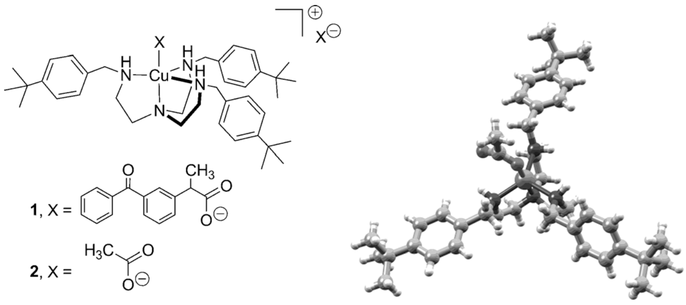


Figure 1. Structural formulas of complexes **1** and **2** (left) and molecular structure of the [Cu(*t*BuBz$_3$tren)acetate]$^+$ cation (right).

ported.[11] Of particular interest is the use of free-radical photoinitiators to mediate the copper(II) to copper(I) reduction, which were applied to the preparation of polymers.[11b,c]

In our preliminary communication we have shown that although **1** is inactive as a catalyst at room temperature in methanol, it is quantitatively and rapidly reduced to its cuprous state upon light irradiation (TLC lamp, $\lambda = 365$ nm) to provide a highly reactive click catalyst (Figure 2).[5] The photogenerated cuprous [Cu(*t*BuBz$_3$tren)]$^+$ species proved to be extremely sensitive towards $O_2$. Consequently, by simply introducing air into the reaction medium the catalysis could be switched off, and then subsequently switched on by bubbling Ar followed by irradiation (Figure 2). Preliminary flash photolysis studies reveal that the photoreduction process involves the triplet benzophenone chromophore, which is efficiently quenched ($k_q = 1.0 \times 10^8\,s^{-1}$), most likely by a charge-transfer process from the copper(II) ion.

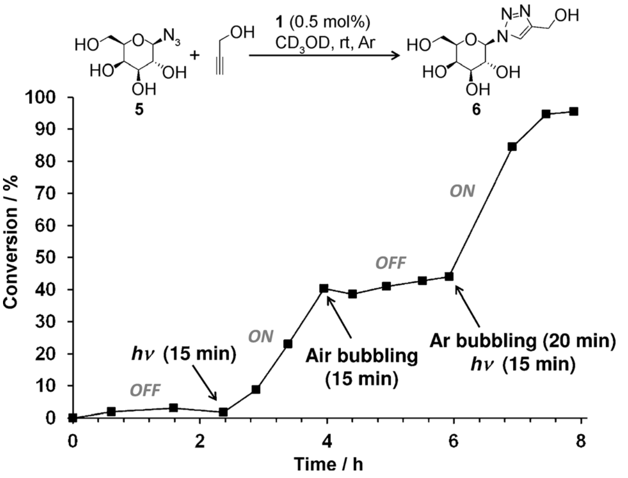


Figure 2. Reaction profile showing the reversible photolatent properties of **1** for the CuAAC.

In the present article, we present the scope and limitations of the first generation of copper-tren-ketoprofenate photolatent click catalysts. The influence of the solvent nature on the photoreduction efficiency has been studied in detail, with the solvent playing a major role in the process because it represents the terminal electron source. As water is a particularly appealing reaction medium for the CuAAC, special attention was paid to the solubilization of the copper(II) precatalysts in water, exploiting the formation of inclusion complexes with β-cyclodextrins (β-CDs). Preliminary results showing the formation of copper nanoparticles (NPs) under prolonged irradiation times are described. Data is provided on the fate of the catalyst when the highly reactive photogenerated copper(I) catalyst reacts with $O_2$, $O_2$ being used to switch off the catalysis. Finally, the main objective of this work being the development of photoactivable catalysts of practical value for the CuAAC, the catalytic, photolatent, and recycling properties of **1** in aqueous and organic solvents are reported.

## Results and Discussion

**Design, synthesis, and characterization of complexes 1–4**: With the aim of developing a photoactivable catalyst of practical value, precatalyst **1** was designed to have a simple preparation, yet present three key structural/functional features: 1) A tetradentate tren-derived ligand, which should favor the stabilization of the $Cu^I$ reduced species, thus limiting the formation of colloidal $Cu^0$, which may occur during the photoreduction process. Moreover we,[12] and others,[13] have previously shown that the copper(I)-tren complexes are excellent click catalysts; 2) Three available *tert*-butylbenzyl (*t*BuBz) substituents are incorporated on the tren unit, which are excellent guests for β-CDs. This should allow the solubilization of **1** in both organic solvents and water, in a strategy inspired by the seminal work of Monflier and coworkers who exploited such supramolecular interactions not only to solubilize organometallic complexes in water, but also modulate the catalyst selectivities;[14] 3) A ketoprofenate ligating counterion as photosensitizing group. The ketoprofen 2-(3-benzoylphenyl)propionic acid is a well-known commercially available non-steroidal anti-inflammatory drug containing the benzophenone chromophore and a carboxylic acid group. This choice was prompted by the work of Chow and Buono-Core who reported that certain aromatic ketones, in particular benzophenones, could sensitize the photoreduction of transition-metal complexes $ML_2$ such as $[Cu(acac)_2]$[15] and $[Ni(acac)_2]$ (acac = acetylacetonate),[16] or $[Cu(Bp)_2]$ (Bp = dihydrobis(1-pyrazolyl)borate) in hydrogen-donating solvents.[17]

In our preliminary account we reported the synthesis and characterization of the copper(II) complex [Cu(*t*BuBz$_3$tren)ketoprofenate]ketoprofenate **1** and its non-photoactivable structural analogue [Cu(*t*BuBz$_3$tren)acetate]acetate **2**.[5] The precatalyst (compound **1**) was obtained in 90% yield by treating the *t*BuBz$_3$tren ligand in methanol with the copper(II)-carboxylate complex $[Cu_2(\text{ketoprofenate})_4(H_2O)_2]$ (**3**) (Figure 3). Complex **3** is prepared by treating $[Cu(OTf)_2]$ (OTf = trifluoromethanesulfonate) with two equivalents of the sodium salt of keto-

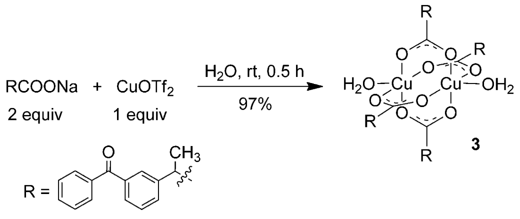


Figure 3. Synthesis and proposed structure of the copper(II)-ketoprofenate complex **3**.

profen in water. The precipitate that immediately forms is filtered and dried affording **3** as a green powder in 97 % yield. Complex **3** was characterized by elemental analysis, UV/Vis, FTIR, and EPR spectroscopies. In particular, the X-band EPR spectrum of a solid, powdered sample of **3** measured at room temperature (Figure S1, the Supporting Information) is characteristic of a magnetic copper(II) dimer possessing the typical "paddle-wheel" structure with four carboxylates symmetrically bridging the copper(II) ions.[18] The complex [Cu(*t*BuBz$_3$tren)acetate]acetate **2** was obtained in a similar manner as its structural analogue **1** by treating the *t*BuBz$_3$tren ligand with [$Cu_2(OAc)_4(H_2O)_2$]. The X-ray analysis of single crystals of **2** (Figure 1) revealed a monomeric structure with the copper(II) ion in a distorted trigonal-bipyramidal geometry and an acetate occupying the axial coordination site in a *syn* monodentate mode. By analogy, and in agreement with characterization, we proposed a similar structure for **1**. Finally, the complex [Cu(*t*-BuBz$_3$tren)Cl]•Cl **4**, was prepared in 91 % yield from [$CuCl_2$]•5$H_2O$ and *t*BuBz$_3$tren.

**Supramolecular complexes between 1–2, 4 and β-CDs in water**: Major applications of the CuAAC reactions involve biomolecule substrates (notably polypeptides, oligosaccharides, and oligonucleotides), which are intrinsically water-soluble.[19] The search for highly reactive click catalysts that are compatible with water-soluble reactants is thus of special interest.[20] Exploiting supramolecular host–guest interactions between the β-CDs and the *t*BuBz substituents of the tren ligand should provide a photolatent catalyst useful for both organic and aqueous reaction conditions. The photolatent precatalyst **1** is a lipophilic complex, which is soluble in most organic solvents except alkanes. Complex **1** is completely insoluble in water (as verified by UV/Vis spectroscopy, see Figure 4), whereas [Cu(*t*BuBz$_3$tren)Cl]•Cl (**4**) is slightly soluble (<1 mM), and **2** is moderately soluble (up to 10 mM). Consequently, the solubilization studies were conducted with complexes **1** and **4**, employing the highly water-soluble randomly-methylated β-cyclodextrin (RAME-β-CD) as the host. Rapid solubilization occurs when the RAME-β-CD is added to aqueous suspensions of **1** or **4**. Titration experiments revealed that the addition of 5 and 3 equivalents of the CD was enough to solubilize 90–95 % of complexes **1** (Figure 4) and **4** (Figure S2, the Supporting Information), respectively. These results suggest that for complex **4**, a supramolecular [Cu(*t*BuBz$_3$tren)⊂3RAME-β-CD]$^{2+}$ assembly forms in which each *t*BuBz substituent is included in a RAME-β-CD. The molecular models presented in Figure 5 show that 3 RAME-β-CDs could easily fit around the [Cu(*t*BuBz$_3$tren)]$^{2+}$ cation, and that steric hindrance should not hamper the formation of such an assembly. For **1**, the 5:1 ratio between the CD and the complex, necessary to achieve almost complete solubilization, suggests that not only the *tert*-butylphenyl groups, but also the benzophenone moiety of the ketoprofenate anions, are encapsulated by the RAME-β-CD. Confirmation was sought through MS studies (see below).

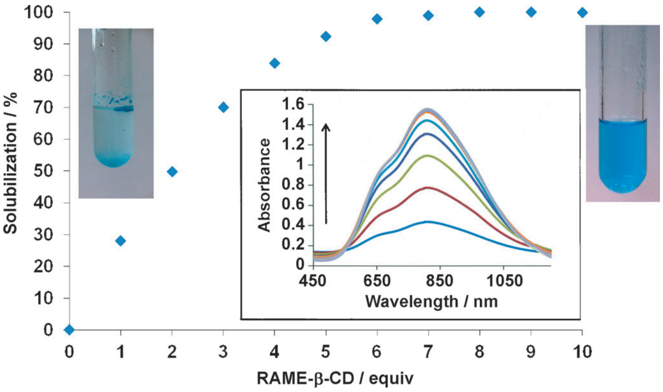


Figure 4. Photographs of aqueous solutions of **1** before (left) and after addition (right) of 10 equivalents of RAME-β-CD (final concentration 5.2 mM), and graph showing the percentage of solubilized **1** upon addition of 1 to 10 equivalents of RAME-β-CD. The inset shows the evolution of the visible absorption spectrum of the solution after each addition of one equivalent of CD.

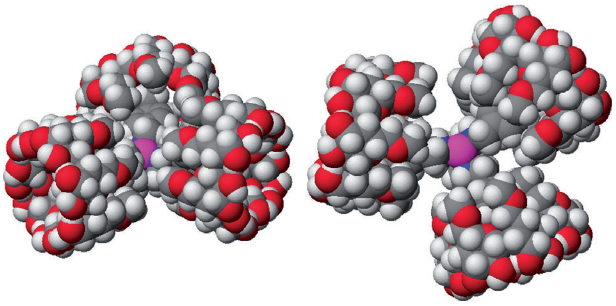


Figure 5. Side and top views of CPK models of the minimized (MM2, CaChe 3.1) supramolecular [Cu(*t*BuBz$_3$tren)⊂3β-CD]$^{2+}$ cation. A β-CD with permethylated primary $-CH_2OH$ functions has been considered for this study to reflect the steric hindrance of the smaller rim found in the RAME-β-CD.

Nuclear Overhauser spectroscopy (2D NOESY) and diffusion-ordered spectroscopy (DOSY) NMR experiments did not afford direct evidence of such an interaction in solution. This is ascribed to the paramagnetic nature of the copper(II) ion, affording $^1$H NMR spectra in which the $Ph-CH_2-N$, $N-CH_2CH_2-N$, and $-CHCH_3-CO_2$ resonances are not observed, whereas all the others are very broad (see the Supporting Information, Figures S3 and S4 for the 600 MHz

$^1$H NMR spectra of **1** in MeOD, **1**+10 equiv RAME-β-CD in $D_2O$, and RAME-β-CD in $D_2O$). Interestingly, the 1D NMR spectra show that the anomeric protons of the RAME-β-CD are shifted upfield by about $\delta = 0.1$ ppm when **1** is present, indicating that an interaction with a guest effectively takes place (Figure S4, the Supporting Information). The 2D NOESY and DOSY experiments conducted on the diamagnetic *t*BuBz$_3$tren ligand confirmed the formation of inclusion complexes. Addition of three equivalents of RAME-β-CD to a suspension of the *t*BuBz$_3$tren ligand in $D_2O$ led to fast and complete solubilization (the 600 MHz $^1$H NMR spectrum of the resulting solution is given in Figure S3, the Supporting Information). The 2D NOESY spectrum (Figure 6) reveals intense cross-peaks between the protons of the *tert*-butylphenyl groups of the ligand and the −CH−, $-CH_2-$ and $-OCH_3$ protons of the CD. The DOSY experiments (Figure 6) confirmed the clean formation of a supramolecular [*t*BuBz$_3$tren⊂3RAME-β-CD] complex diffusing at a much slower rate ($D = 3.54\times10^{-11}$ m$^2$s$^{-1}$) than the free RAME-β-CD ($D = 1.77\times10^{-10}$ m$^2$s$^{-1}$), corresponding to a hydrodynamic radius about five times higher.

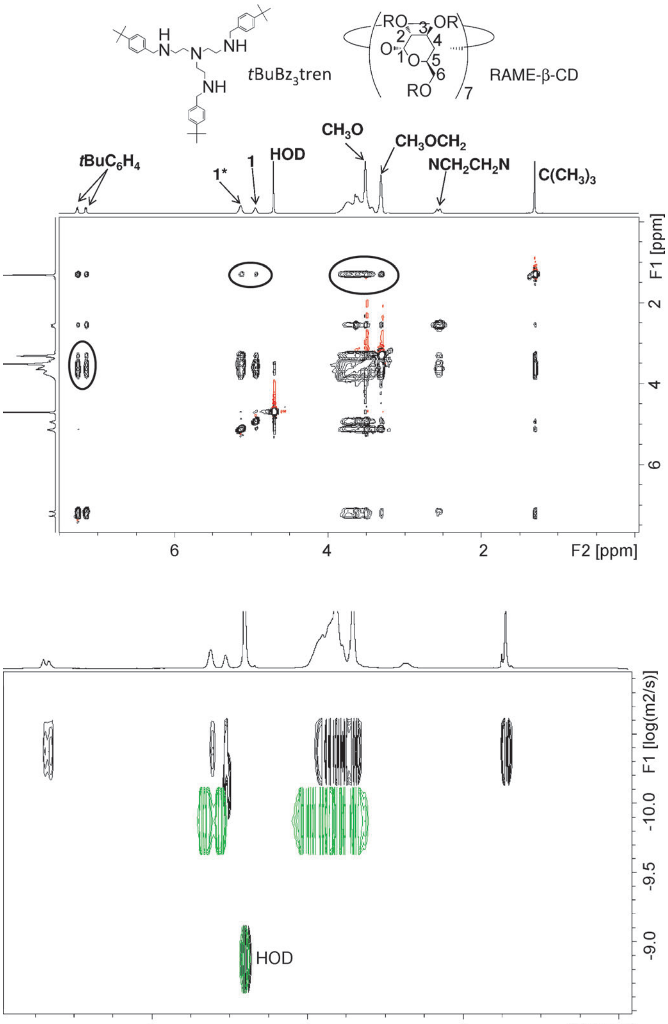


Figure 6. a) 2D NOESY NMR spectrum (400 MHz) of a $D_2O$ solution of *t*BuBz$_3$tren (20 mM)+3 equiv RAME-β-CD (60 mM); b) DOSY spectrum of the solution (black) superimposed with the DOSY spectrum (green) of the RAME-β-CD alone (60 mM).

Mass spectrometry studies have been conducted on aqueous solutions of **1** and **4** in the presence of β-CD. For the MS studies, β-CD instead of RAME-β-CD was employed, the latter being a mixture of randomly-methylated CDs, with the major product bearing 14 methyl groups. The β-CD was found to be less efficient in solubilizing **1** and **4** in water. Only approximately 40% of **4** was solubilized with three equivalents of β-CD, compared to approximately 95% when employing RAME-β-CD. Nonetheless, the ESI-MS of an aqueous solution of **4** and β-CD shows a peak at $m/z = 1819.7$ ascribed to the [Cu(*t*BuBz$_3$tren)Cl⊂β-CD]$^+$ supramolecular cation (Figure S5, the Supporting Information). With complex **1**, the peak could not be observed in the positive mode as the [Cu(*t*BuBz$_3$tren)ketoprofenate⊂β-CD]$^+$ supramolecular cation would afford a peak at $m/z = 2034.9$, which is above the upper detection limit for ESI, that is, 2000 Da. However, in the negative mode an intense peak at $m/z = 1387.5$ Da assigned to the anionic inclusion complex [ket⊂CD]$^-$ is observed (Figure S5, the Supporting Information).

**Photoreduction studies of complexes 1 and 2**: The main objective of this study was to assess the solvent scope and thus determine the best conditions for the click reactions. Indeed, the solvent plays a major role in the photoreduction process as the potential terminal electron donor. Chow, Buono-Core and co-workers, extensively studied the impact of the solvent in the benzophenone photosensitized photoreduction of transition-metal complexes $ML_2$ such as [Cu(acac)$_2$],[15] [Ni(acac)$_2$],[16] or [Cu(Bp)$_2$].[17] The photoreduction proved to be particularly efficient in hydrogen-donating solvents such as alcohols (MeOH, EtOH, *i*PrOH). Mechanistic studies showed that photoreduction involves quenching of the triplet aromatic ketone [Eq. (1)], most likely by a charge-transfer complex intermediate [Eq. (2)], performing a monoelectronic oxidation of the ligand (L) to generate a ligand-centered radical [Eq. (3)], which abstracts a hydrogen atom [Eq. (4)] from the solvent ($RCH_2OH$). Overall, the process generates the reduced complex ML, the protonated ligand L−H and an α-hydroxy radical R$^\bullet$CHOH.

$$Ph_2CO \xrightarrow{h\nu} Ph_2CO^* \tag{1}$$

$$Ph_2CO^* + [M^{II}(acac)_2] \rightarrow Ph_2CO^{\bullet-} + [M^{III}(acac)_2] \tag{2}$$

$$Ph_2CO^{\bullet-} + [M^{III}(acac)_2] \rightarrow Ph_2CO^{\bullet-} + [(acac)^{\bullet+}M^{II}(acac)] \tag{3}$$

$$\begin{aligned} &Ph_2CO^{\bullet-} + [(acac)^{\bullet+}\ M^{II}(acac)] + RCH_2OH \rightarrow \\ &Ph_2CO + [M^{I}(acac)] + Hacac + R^\bullet CHOH \end{aligned} \tag{4}$$

*Photoreduction followed by UV/Vis spectroscopy*: In our preliminary work,[5] the photoreduction and catalytic studies

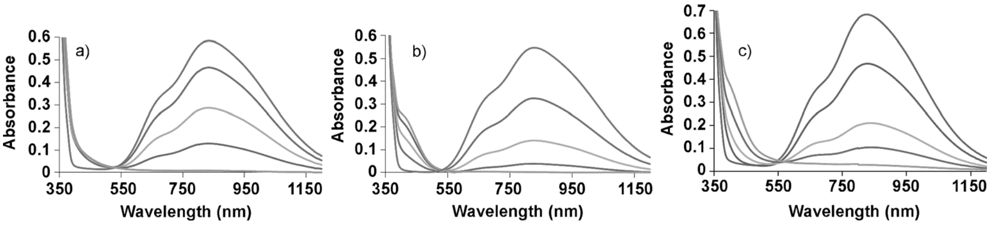


Figure 7. Photoreduction of **1** in various solvents (1.85 mM, $\lambda = 365$ nm, deoxygenated by freeze–pump–thaw cycles, sealed quartz cuvettes) followed by UV/Vis absorption spectroscopy: a) in THF (irradiation times = 0, 4, 8, 12, 16 min from top spectrum to bottom spectrum, respectively); b) in toluene (irradiation times = 0, 8, 16, 24, 30 min from top spectrum to bottom spectrum, respectively); c) in $CH_3CN$ (irradiation times = 0, 10, 30, 52, 70 min from top spectrum to bottom spectrum, respectively).

were conducted in MeOH, a good H-donating and a green solvent,[21] which are two favorable characteristics for the title study. Irradiations were conducted at $\lambda = 365$ nm in strictly anaerobic conditions (solutions degassed by freeze–pump–thaw cycles, sealed cell) to eliminate $O_2$ which, if present, would react very rapidly with the copper(I) species ultimately leading to ligand oxidation (see below). The copper photoreduction process in MeOH proved to be very efficient, the quantum ($\Phi_{red}$) yield being estimated at 0.17. Typical reductions of MeOH solutions of **1** (3 mL, 1.85 mM) in 1 cm quartz UV cuvettes proceed in approximately 30 min, affording colorless solutions in agreement with the formation of a $[Cu(tBuBz_3tren)]^+$ cationic species. Importantly, the photoinduced reduction did not occur in **2** (in which acetate replaces the ketoprofenate), which showed the fundamental photostability of the inorganic moiety when irradiating at 365 nm. In $CH_2Cl_2$, a poor H-donating/oxidizable solvent, the photoreduction was sluggish, approximately 75% of **1** being reduced after 3 h of irradiation. We report here that in THF the reduction is very efficient, a colorless solution being obtained after irradiating for less than 20 min (Figure 7). In toluene the complex **1** is rapidly photoreduced in about 30 min, whereas in $CH_3CN$, a poorer H-donating solvent, the reduction was completed in about 1 h (Figure 7).

The photoreduction in water was tested by using a solution (3 mL) containing **1** (1.84 mM) and 10 equiv of RAME-β-CD. As shown by UV/Vis spectroscopy (Figure S6, the Supporting Information) the reduction does not occur in water, as expected for a poorly oxidizable/H-donating solvent. Nonetheless, we hypothesized that in CuAAC reaction conditions, the alkyne could potentially serve as the sacrificial reductant and hence favor the reduction. When the photoreduction is conducted in the presence of 200 equivalents (conditions of catalysis experiments), the solution turns colorless within minutes with the concomitant formation of an amorphous yellow precipitate (Figure S7, the Supporting Information). The yellow precipitate, which is stable to air and insoluble in any common solvent, is characteristic of polymeric alkynyl-copper(I) complexes, possessing an infinite Cu−Cu ladder structure with bridging RC≡C groups.[22] Interestingly, a range of such alkynyl-copper(I) complexes have been previously prepared by Chow and Buono-Core through the benzophenone-sensitized photoreduction of $[Cu(acac)_2]$ in the presence of various acetylenes or, by treating a copper(I) species with acetylenes.[15a] Importantly, when complex **2** is irradiated in water in the presence of RAME-β-CD and excess propargyl alcohol, no reduction occurs (Figure S7, the Supporting information), confirming that with **1** the reduction is driven by the benzophenone sensitizer.

*Photoreduction followed by $^1H$ NMR spectroscopy*: Similarly to observations in MeOD, sharp resonances, in particular those of the benzylic $-CH_2-$ and $-NCH_2CH_2N-$ groups, which are not observable with **1**, emerge in the $^1H$ NMR spectra upon irradiation of a [D$_8$]toluene solution, in agreement with the formation of a diamagnetic ($d^{10}$) cuprous $[Cu(tBuBz_3tren)]^+$ cationic species (Figure 8). Concomitantly, the broad resonances of **1**, such as those of the *tert*-butyl groups, disappear while the corresponding upfield-shifted sharp resonances appear.

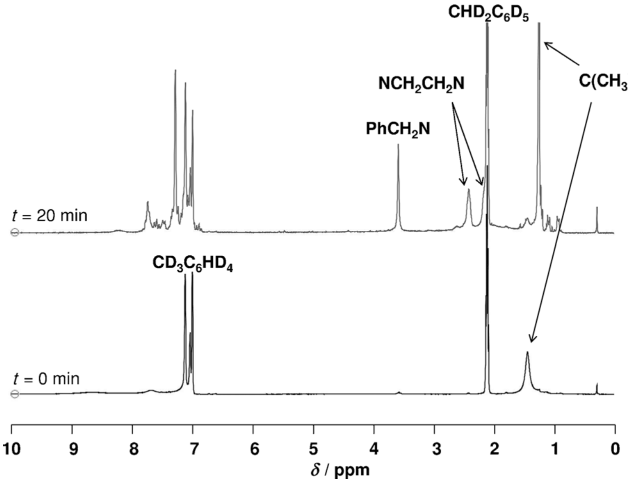


Figure 8. Evolution of the $^1H$ NMR spectrum of a [D$_8$]toluene solution of **1** (5 mM, deoxygenated by Ar bubbling) upon irradiation of the NMR tube at 365 nm.

**Behavior of the cuprous $[Cu(tBuBz_3tren)]^+$ species in the presence of $O_2$**: We previously showed that the photogenerated cuprous species was extremely sensitive towards $O_2$, and that such reactivity could be exploited to switch off the reaction. After having been stopped, the reaction could be switched on after deoxygenation of the reaction mixture followed by irradiation (Figure 2). The reaction of copper(I)-

polyamino complexes with $O_2$ frequently leads to hydroxylation reactions at oxidizable positions of the ligand, implying copper(II)-superoxo, -hydroperoxo, or -peroxo intermediates.[23] It was thus considered important to determine whether these oxidative processes were taking place when reduced **1** was treated with $O_2$, and to see if major alteration of the catalyst structure occurred. When a colorless toluene solution of reduced **1** is exposed to air, the solution instantaneously turned green, indicating that the generated cuprous species rapidly reacts with $O_2$. Analysis of the ESI-MS spectrum of the resulting solution (Figure 9) shows peaks at $m/z = 898.5$ and 896.5, that is, 2 and 4 mass units less than expected for the $[Cu(t\text{BuBz}_3\text{tren})\text{ketoprofenate}]^+$ ion, but also peaks at $m/z = 641.4$ (minor), 643.4 (100%) and 645.4 (60%), that is, at 2, 4 and 6 mass units lower than the $[Cu(t\text{BuBz}_3\text{tren})]^+$ cation. This agrees with the partial oxidation of the benzylic amines into imines, resulting from the reaction of the cuprous $[Cu(t\text{BuBz}_3\text{tren})]^+$ cation with $O_2$. Hydroxylation products that should afford peaks at 662.4 and 916.5 (+16 mass units) are not observed. The occurrence of oxidation processes was further confirmed by reacting complex **1** with 45 equivalents of $H_2O_2$ in MeOH for 3 h. The ESI-MS spectrum of the resulting solution (Figure S9, the Supporting Information) showed an intense peak at $m/z = 641.4$ attributed to the tris(imine) $[Cu(t\text{BuBz}_3\text{tren})-6H]^+$ cation.

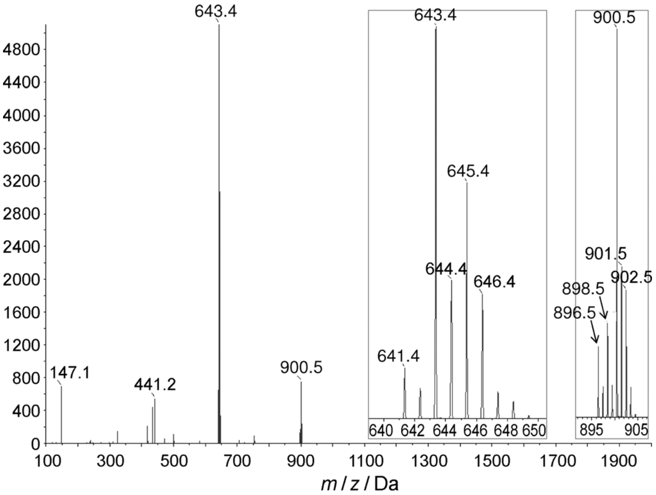
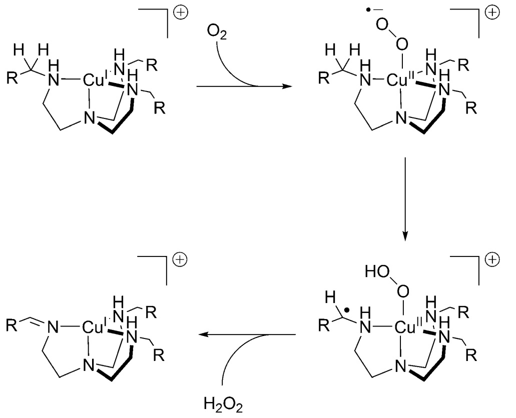


Figure 9. ESI-MS spectrum of a toluene solution of **1** (1 mM) that was photoreduced (deoxygenated by Ar bubbling) and subsequently reoxidized with air. A comparative spectrum of the native complex **1** is given in Figure S8 (the Supporting Information).

The appearance of imine functions can be observed when following the photoreduction process by UV/Vis spectroscopy. For instance, in the spectra recorded during the reduction in toluene (Figure 7), while the absorption band corresponding to the d–d copper(II) transition is disappearing a new band appears at approximately 410 nm. The appearance of this absorption band is correlated to the residual $O_2$ present in the toluene solution of the sealed cuvette degassed by multiple freeze–pump–thaw cycles. Accordingly, when less-effective degassing is conducted (Ar bubbling), a more intense absorption at 410 nm is obtained (Figure S10, the Supporting Information). This new absorption is characteristic of a metal-to-ligand charge-transfer (MLCT) band involving the copper(I) and a coordinating imine group that originates from the oxidation of the benzylic amines of the ligand by the oxidizing species produced when $O_2$ reacts with $Cu^I$. The attribution of this band was confirmed by recording the UV/Vis spectrum of the cuprous [Cu(trisiminetren)Br] complex (Figure S11, the Supporting Information), prepared in situ by treating CuBr and the trisimine ligand in toluene under strictly anaerobic conditions. The resulting spectrum shows an intense MLCT band at 410 nm ($\varepsilon = 4200\,\text{M}^{-1}\text{cm}^{-1}$). From this ε value, it was estimated that approximately 10% of the amine groups in **1** were oxidized into imines during the photoreduction process conducted from the solution degassed by Ar bubbling and closed with a rubber stopper. For the reduction conducted in a sealed cell degassed by freeze–pump–thaw cycles, the amount of imine that forms due to traces of $O_2$ is estimated to be approximately 2.5%.

The amine-to-imine oxidation is thus favored when reduced **1** reacts with $O_2$. Such reactivity is most probably related to that occurring in the copper(I)-catalyzed aerobic oxidation of alcohols to aldehydes.[24] Based on our observations and previous extensive studies on related copper(I)/$O_2$ systems, a tentative mechanism to account for the imine formation is proposed in Scheme 1. Further studies, which go beyond the scope of this work, should be conducted to characterize the reaction intermediates and confirm this mechanism. Overall these results show that when adventitious traces of $O_2$ are present in the reaction medium, or when air is introduced to stop the reaction, a rather efficient oxidative process occurs leading to the formation of substantial amounts of the oxidized imine ligand.



Scheme 1. Proposed mechanism for the aerobic amine-to-imine ligand oxidation.

**Formation of copper nanoparticles (NPs) by prolonged irradiation**: Chow and Buono-Core previously reported that prolonged irradiation in the benzophenone-sensitized reduction of $[Cu(acac)_2]$,[15] and $[Cu(Bp)_2]$,[16] gave rise to the formation of metallic copper particles due to disproportionation and/or photolysis of the cuprous species. They showed that in the presence of strongly coordinating ligands (L) such as phenanthroline, bipyridine, or triphenylphosphine, copper(I) could be trapped to afford the corresponding $[Cu(acac)L_x]$ complexes, which proved to be much less prone to decomposition into metallic copper. The presence of the tetradentate tren ligand in **1** might limit the over-reduction process, by lowering the reduction potential of the $Cu^{II}/Cu^{I}$ and $Cu^{I}/Cu^{0}$, compared with copper salts. The $E_{1/2}$ of the $Cu^{II}/Cu^{I}$ couple for **1** measured in acetonitrile was found at a rather low value of −0.34 V vs. SCE.[5] Nonetheless, we observed that prolonged irradiation of **1** leads to $Cu^{I}$ to $Cu^{0}$ reduction and the formation of copper NPs. This is clearly illustrated when following the photoreductions in THF (Figure 10) or toluene (Figure S12, the Supporting Information). After typically 30–45 and 60 min of irradiation in THF and toluene, respectively, the solutions turn progressively to a henna color, with Plasmon resonances appearing at 563 and 569 nm that are characteristic of dispersed Cu NPs (particle diameter > 4 nm).[25] To try to determine whether the $Cu^{0}$ was produced by disproportionation or photoreduction of the $Cu^{I}$ species, a yellowish toluene solution of reduced complex **1** (degassed by freeze–pump–thaw cycles, sealed cuvette), obtained after 26 min of irradiation, was left in the dark. The solution slowly recovers its initial blue color, whereas fine particles of metallic copper appear concomitantly. The UV/Vis spectrum of the supernatant after seven days reveals that approximately 55 % of the original absorption at 826 nm has been recovered (Figure S13, the Supporting Information), that is, close to the 50 % theoretical value expected for a disproportionation process. These results show that disproportionation of the cuprous $[Cu(tBuBz_3tren)]^+$ occurs, but that this is a rather slow process compared with the kinetics of appearance of the Cu NPs (Figure 10). It can thus be assumed that the $Cu^{I}$ to $Cu^{0}$ over-reduction is mostly due to a photoreduction process rather than disproportionation. It should also be underlined that under catalytic conditions, the photogenerated copper(I) species will be rapidly "trapped" by the alkyne and azide present in large excess and then engaged in the catalytic cycle, thus probably limiting the formation of copper(0).

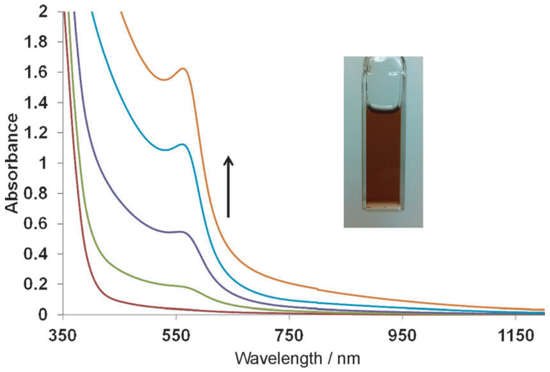
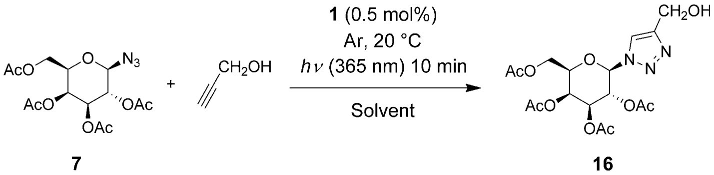


Figure 10. UV/Visible spectra of a THF solution of **1** (1.85 mM, deoxygenated by freeze–pump–thaw cycles, sealed cell) recorded after irradiation times = 30, 45, 60, 75, and 90 min ($\lambda$ = 365 nm) in order of increasing intensity at 550 nm, and photograph of the resulting homogeneous solution.

**Photolatent and catalytic properties of 1**: In our preliminary report, reactions were conducted in methanol under an inert atmosphere (Ar bubbling). The precatalyst was activated by irradiating the reaction mixture at 365 nm (TLC lamp) for 15–30 min. The cuprous species generated was very active, the reaction between the unprotected sugar β-D-galactopyranosyl azide **5** and propargyl alcohol being completed in about 3 hours with a catalyst loading of 0.5 mol %. From the azide **5**, a range of triazoles were isolated in good to excellent yields. Interestingly, the reaction could be stopped immediately at any time by simply introducing air in the reaction medium. Degassing followed by irradiation switched on the reaction (Figure 1).

Table 1. Reactivity of **1** in various solvents.



| Solvents | Reaction times to 100 % conversion[a] |
|---|---|
| $[D_8]$THF | < 10 min |
| $CD_2Cl_2$ | < 10 min |
| $[D_8]$toluene | < 60 min |
| $CD_3CN$ | ≈ 40 h |

[a] Followed by using $^1$H NMR spectroscopy (reaction conditions given in the Supporting Information).

The latent behavior and click reactivity of **1** was further probed in various organic solvents, namely the reaction between the soluble peracetylated β-D-galactopyranosyl azide **7** and propargyl alcohol substrates (Table 1). Click reactions were run in NMR tubes at room temperature (20 °C) in deoxygenated deuterated solvents (Ar bubbling, 20 min) with **1** (0.5 mol %). It is noteworthy that under ambient conditions **1** exhibits no residual background activity, a crucial parameter when considering effective photoswitchable catalysts (the $^1$H NMR spectra recorded at various times for the reaction conducted in THF are provided in Figure S14, the Supporting Information). Catalyst activation was carried out by irradiating the NMR tube for 10 min at 365 nm by using a TLC lamp. The reactions conducted in THF and $CH_2Cl_2$ proved to be extremely fast; the triazole **16** being formed quantitatively at the end of the irradiation time, that is, within 10 min. Interestingly, this shows that the reaction medium is not limited to good H-donating solvents. Indeed, the photoreduction of **1** in $CH_2Cl_2$ in the absence of the reactant is sluggish, as approximately 75 % of **1** is reduced after 3 h irradiation.[5] However, as described above for the photoreduction in water, under the reaction conditions, the alkyne may serve as a sacrificial reductant. In toluene the reaction proceeded very effectively (less than 60 min), whereas in acetonitrile the reaction was very slow, with complete conversion being reached after approximately 40 h.

Click reactions implying a range of alkynes and azides were conducted in round-bottom flasks at low catalyst loading (0.5 mol %, except for **13** which required 1 mol %) and irradiation times of 30 min. Toluene was chosen as the solvent, in which the triazoles that form are usually poorly soluble. The triazoles (**8**–**16**) were obtained in good to excellent yields, the products being conveniently isolated by filtration after precipitation at −18 °C (Figure 11). A catalyst recycling experiment was attempted in the following manner. The filtrate recovered after isolation of the triazole **9** (1st run) was loaded with the reactants, degassed (20 min Ar bubbling) and irradiated for 30 min. After 24 h, the solution was placed at −18 °C and the triazole isolated by filtration (2nd run). A third and fourth run were conducted in the same manner. Yields of the isolated products of 89, 81, 78, and 71 % were obtained for the 1st, 2nd, 3rd, and 4th run, respectively, showing a satisfactory recyclability for **1**.

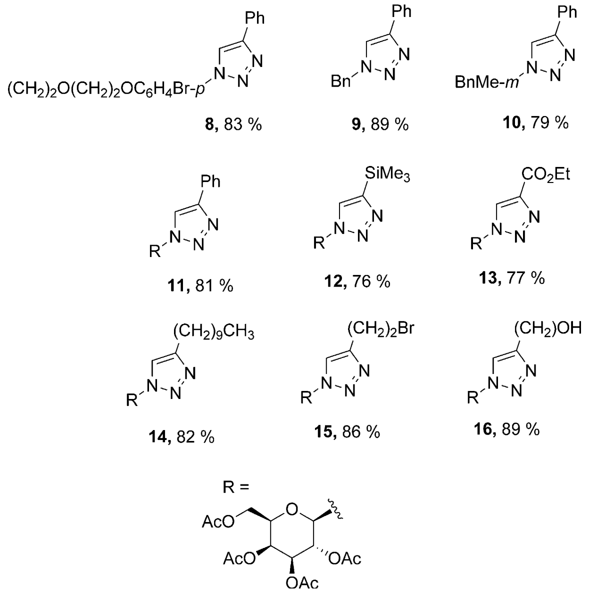


Figure 11. Structures and reaction yields for triazoles **8**–**16**.

As azide **5** and propargyl alcohol are both water-soluble, the reaction was finally tested in "in water" conditions ($D_2O$, reaction profile followed by $^1H$ NMR spectroscopy given in the Figure S14) using 0.5 mol % **1** in the presence of 10 equivalents of RAME-β-CD. Both an excess of propargyl alcohol (2 equiv) and continuous irradiation were necessary for the reaction to proceed effectively. Under these conditions, approximately 90 % conversion was observed in 10 h, the triazole **6** (Figure 2) being isolated in 83 % yield after chromatography.

## Conclusion

PET processes could represent a powerful strategy for the photoactivation of copper catalysts that are active in their low-valent cuprous state. A benzophenone-like chomophore proved to be a particularly useful photosensitizer to efficiently generate a highly reactive click copper(I) species on-demand from the copper(II)-tren precatalyst **1** upon light irradiation at 365 nm. The convenient introduction of the benzophenone chromophore in **1** through the ketoprofenate counterion represents a rather general strategy, which could be extended to other cationic metal complexes. We have shown that the reaction medium is not limited to good H-donating solvents, such as MeOH, THF, or toluene. Indeed, under the reaction conditions, the alkyne may serve as a sacrificial reductant, opening the way to photolatent click catalysis in aqueous media. The preliminary results reported herein, exploiting the supramolecular precatalyst formed between **1** and the β-RAME-CD have shown that photolatent click catalysis based on PET can indeed be conducted in water. This study has shown that the photogenerated cuprous-tren species is highly sensitive to $O_2$. Although this reactivity can be exploited to efficiently switch off the catalytic activity, by simply introducing air into the reaction medium, it also induces side-oxidative reactions leading to ligand oxidation with the formation of imines, thus raising concerns on the chemical integrity of the catalyst. We also noticed that over-reduction processes, ascribed to a photosensitized process rather that disproportionation, may occur leading to the formation of copper(0) and, ultimately, to copper NPs. Although these are possible limitations, the photoactivable precatalyst **1**, which can be stored indefinitely under ambient conditions, has strong potential for applications in click chemistry. These results may pave the way to the development of a new generation of photoactivable catalysts, not only for copper chemistry, but for other transition-metal-catalyzed reactions. Studies along these lines are currently under investigation in our group.

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