A highly active and reusable copper(I)-tren catalyst for the "click" 1,3-dipolar cycloaddition of azides and alkynes†

Nicolas Candelon, Dominique Lastécouères, Abdou Khadri Diallo, Jaime Ruiz Aranzaes, Didier Astruc and Jean-Marc Vincent*

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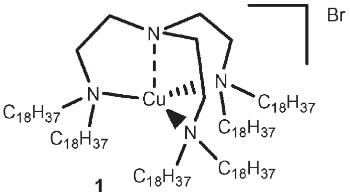
The copper(I) complex [Cu(C18$_6$tren)]Br 1 (C18$_6$tren = tris(2-dioctadecylaminoethyl)amine) which exhibits a good stability towards aerobic conditions is a versatile, highly reactive and recyclable catalyst for the Huisgen cycloaddition of azides with terminal or internal alkynes and is a useful catalyst for the preparation of "click" dendrimers.

Since the independent discovery by the groups of Sharpless[1] and Meldal[2] that Cu(I) was an efficient and regiospecific catalyst for the Huisgen 1,3-dipolar cycloaddition of azides and terminal alkynes,[3] this transformation has emerged as one of the most powerful "click" reactions.[4,5] Recently, Finn and coworkers reported that tris(2-benzimidazolylmethyl)amines were powerful accelerating ligands for the $CuSO_4$/sodium ascorbate catalytic system.[6] Some very active,[7] or recyclable[8] copper(I) catalytic systems which do not require a sacrificial reductant have been reported as well. However, the high reactivity of Cu(I) complexes towards dioxygen, in particular those bearing polyamino ligands, often make them very difficult to handle thus limiting their practical interest. Cu(I) complexes typically react with dioxygen to form unstable μ-peroxo-dicopper(II) intermediates evolving into highly reactive bis-μ-oxo-dicopper(III) which then decomposes irreversibly through oxidation processes.[9] By employing more crowded tetradentate tripodal ligands such as Me$_6$tren,[10] or a tris(tetramethylguanidino)tren (TMG$_3$tren),[11] the stability of the 1 : 1 $[Cu(L)O_2]^+$ Cu(II)-superoxo adducts can be greatly improved by lowering or inhibiting the formation of the $[Cu_2(L)_2O_2]^{2+}$ peroxo dimers. In the case of the very crowded TMG$_3$tren ligand, reversible binding of O_2 was demonstrated with no detectable decomposition of the copper(I) complex.[11a]

In 2004, we reported the preparation and catalytic activity of the highly crowded [Cu(C18$_6$tren)]Br complex **1** in atom transfer radical polymerization (ATRP) reactions.[12,13] The complex **1** proved to be highly reactive in ATRP, whilst an increased stability towards aerobic conditions was noticed. Whereas most of the copper(I) catalysts have to be prepared *in situ* for a given reaction to avoid decomposition, **1** is conveniently isolated as a colourless powder by filtration and can be handled in air. Moreover, **1** exhibits unusual solubility-based thermomorphic properties in polar solvents such as 1,4-dioxane allowing its recovery under an active form by simple filtration in air. We now report that **1** is a versatile, highly reactive and recyclable catalyst for the Huisgen cycloaddition of azides with terminal or internal alkynes and is a useful catalyst for the preparation of "click" dendrimers.



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Unlike **1**, the 1,4-disubstituted-1,2,3-triazoles products are polar products. Therefore we decided to run the reactions in solvents of low polarity (toluene or *n*-octane) to promote the selective precipitation of the products. The results reported in Table 1 for a range of azides **2** and acetylenes **3** show that in most cases the reactions can be carried out efficiently in these solvents using 0.05 mol% of catalyst affording the corresponding 1,4-disubstituted-1,2,3-triazoles **4** in good to excellent yields.‡

The reactions are run in air-equilibrated solutions under mild conditions (60 °C) showing the good stability of **1**. All the products reported in Table 1 were isolated with analytical purity *via* simple filtration under aerobic conditions after cooling the reaction mixture at −18 °C for 2 h. The choice of the solvent is governed by the nature of the product. For the less polar triazoles, the *n*-octane is favoured to ensure a good precipitation. The low polar catalyst **1** which is fully soluble in toluene or *n*-octane stays in the filtrate which can be reloaded with the substrates for a second reaction. The catalyst was reused two times, affording the triazoles with no decrease in the yield (Entries 4–6). This exemplifies the good stability of **1** under aerobic conditions. Importantly, inductively coupled plasma (ICP) analysis performed on the isolated triazole revealed a negligible contamination by copper (30 ppm) in agreement with an efficient recovery of the complex by the solid–liquid separation process. The efficiency and stability of **1** was further assessed by lowering the catalyst content (Entries 2–3). At 0.01 mol% loading, the triazole was isolated in 80% yield which represents a turnover number (TN) of 8000. Using as little as 10 ppm of **1** in neat conditions, the 1,4-disustituted triazole was still isolated in 54% yield corresponding to a turnover frequency of 2250 h^{-1} (TN = 54 000 in 24 h). In the case of the more crowded 1-azido adamantane, a higher catalyst loading (0.1 mol%) was required to achieve efficient transformations (Entries 15–17).

University Bordeaux-1, CNRS-UMR 5255, Institut des Sciences Moléculaires, 351 Cours de la libération, 33405 Talence, France. E-mail: jm.vincent@ism.u-bordeaux1.fr; Fax: +33 (0)5 40 00 61 58; Tel: +33 (0)5 40 00 89 42

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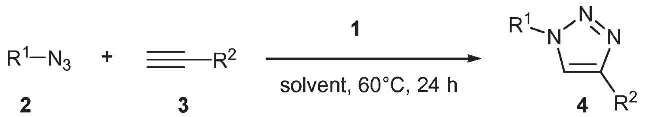
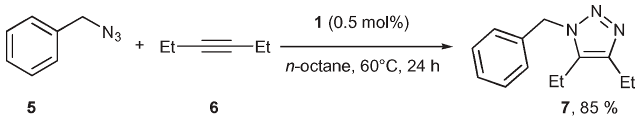
Table 1 Synthesis of triazoles **4** catalyzed by **1**



Entry	R^1	R^2	Solvent	**1** (mol%)	Yield[a] (%), TN[d] in parentheses
1	Bn	Ph	Toluene	0.05	86 (1720)
2	Bn	Ph	*n*-Octane	0.01	80 (8000)
3	Bn	Ph	Neat	0.001	54 (54000)
4	Bn	Ph	Toluene	0.1	93 (930)
5	Bn	Ph	Toluene	—[b]	92 (920)
6	Bn	Ph	Toluene	—[c]	95 (950)
7	Bn	$SiMe_3$	*n*-Octane	0.05	78 (1560)
8	Bn	*t*-Bu	*n*-Octane	0.05	87 (1740)
9	Bn	CO_2Et	Toluene	0.05	65 (1300)
10	Bn	*n*-Bu	*n*-Octane	0.05	80 (1600)
11	*m*-MeBn	*p*-$MeOC_6H_4$	Toluene	0.05	94 (1880)
12	*m*-MeBn	*p*-$CHOC_6H_4$	Toluene	0.05	78 (1560)
13	*m*-MeBn	CH_2OH	Toluene	0.05	91 (1820)
14	*m*-MeBn	CO_2Et	Toluene	0.05	68 (1360)
15	1-Ad	Ph	*n*-Octane	0.1	62 (620)
16	1-Ad	*p*-$CHOC_6H_4$	*n*-Octane	0.1	69 (690)
17	1-Ad	CO_2Et	*n*-Octane	0.1	77 (770)

[a] Isolated yields by filtration. [b] Recovered catalyst from entry 4. [c] Recovered catalyst from entry 5. [d] TN = Turnover number.

In 2006, Nolan and coworkers reported examples of 1,3-dipolar cycloadditions of an internal alkyne (3-hexyne) and benzyl azides catalyzed by a (NHC)CuBr (NHC = N-heterocyclic carbene) complex to afford 1,4,5-trisubstituted-1,2,3-triazoles.[7a] The same year, Weinreb and Majireck showed that $Cp^*RuCl(PPh_3)_2$ was a good catalyst for the [3 + 2] cycloadditions of alkyl azides with various unsymmetrical internal alkynes.[14] Reactions were conducted in refluxing benzene using 10 mol% of the catalyst affording, depending on the alkynes substituents, the triazoles with complete regioselectivity. The preliminary result reported in Scheme 1 reveals the potential of **1** for such transformation. Indeed, the triazole **7** was isolated in good yield by reacting, in rather mild conditions, equimolar amount of benzyl azide **5** and 3-hexyne **6** in the presence of 0.5 mol% catalyst. Further studies will attempt to specifically study the scope of such transformations.



Scheme 1 Formation of a trisubstituted triazole catalyzed by **1**.

Finally, we also tested **1** as catalyst in the synthesis of a 1,2,3-triazole-linked dendrimer. The copper(I)-catalyzed "click" reaction between azides and alkynes has emerged as a powerful synthetic tool for the preparation and functionalization of dendrimers.[15] Recently, Astruc and coworkers successfully exploited such reaction to prepare the first "click" metallodendrimers bearing up to 36 internal triazoles and up to 81 ferrocenyl units at the periphery.[16] These dendrimers were used as redox sensors for oxo anions ($H_2PO_4^-$, ATP^{2-}) and transition-metal cations (Pd^{2+}, $Cu^{+/2+}$) due to coordination to the internal triazoles.

For the synthesis of these dendrimers, the "click" reactions proceeded efficiently using the $CuSO_4$/ascorbate catalytic system. However, it was found that a stoichiometric amount of copper was needed to achieve high conversions, because the metal remained trapped in an inactive form inside the dendrimer. Subsequently, washings with aqueous ammonia were required in the purification step to remove the copper as $[Cu(NH_3)_6]^+$ ions. We hypothesized that the use of **1** in which the copper is caged inside a strongly coordinating tren ligand could greatly improve the synthesis of such compounds. As presented in Scheme 2, the dendrimer **9** was prepared in good yield from the nona-azido precursor **8** using as low as 0.1 mol% of **1**. This corresponds to a 10^3 times decrease in copper, with no need for a sacrificial reductant. Moreover the purification of the dendrimers was achieved by straightforward solid/liquid phase separation. After the reaction, the rather polar dendrimer **9** separates from the *n*-octane solution at low temperature as a colorless waxy solid sticking the wall of the flask. By simply removing the liquid phase, **9** was obtained in an analytically pure form with a copper content of 200 ppm as shown by ICP analysis.

In conclusion we have shown that **1** is a recyclable, highly reactive copper(I) catalyst for the Huisgen cycloaddition of azides with terminal alkynes affording high turnover numbers under aerobic reaction conditions. The complex **1** also showed very promising results for the preparation of 1,4,5-trisubstituted triazoles from internal alkynes. Moreover, because of its solubility and thermomorphic properties it can self-separate from the products in an efficient manner.[17] In our previous work on ATRP,[12] selective catalyst precipitation was favoured by running the reactions in a polar solvent, whilst in this study the use of apolar solvents was preferred to induce the selective precipitation of the products. We are now studying the reactivity of **1** in other important Cu(I)-catalyzed reactions.

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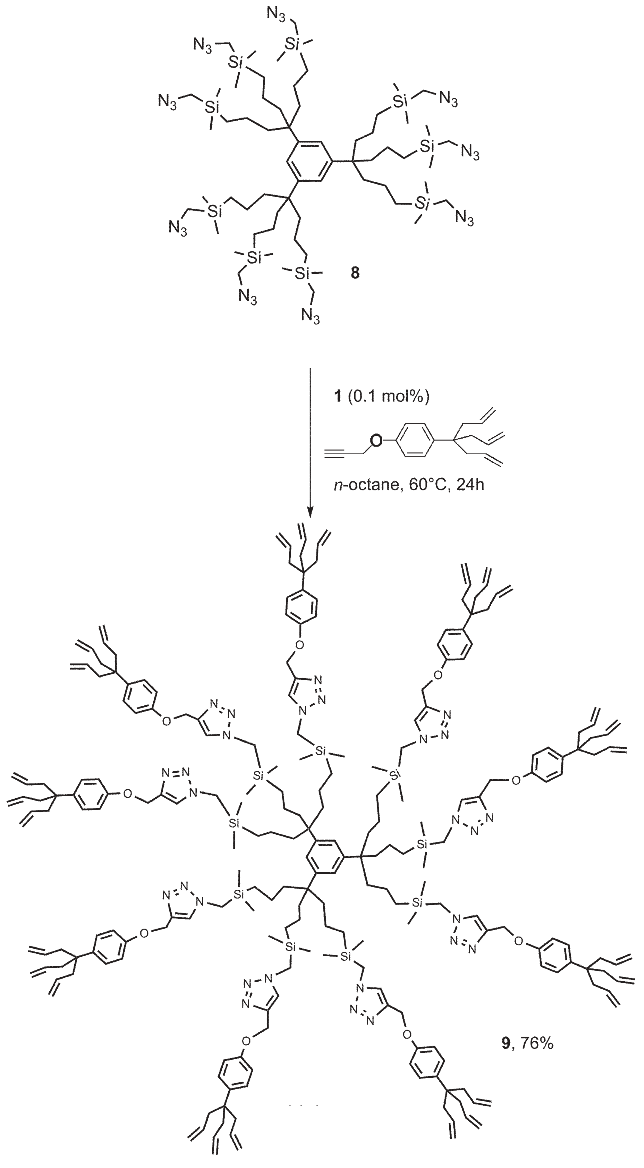

Scheme 2 Formation of a "click" dendrimer catalyzed by **1**.

Notes and references

‡ General procedure for the **1**-catalyzed "click" reactions: In a 2 mL flask fitted with a stirring bar and a rubber septum, the catalyst **1** (0.01–0.1 mol%) , the azide (1 mmol) and the alkyne (1 mmol) are stirred in the desired solvent (1 mL) at 60 °C. After 24 h the flask is placed at −18 °C for 2 h leading to the precipitation of the product which is recovered by filtration, washed twice and dried under vacuum.

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