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Recyclable Catalytic Dendrimer Nanoreactor for Part-Per-Million Cu^{I} Catalysis of "Click" Chemistry in Water

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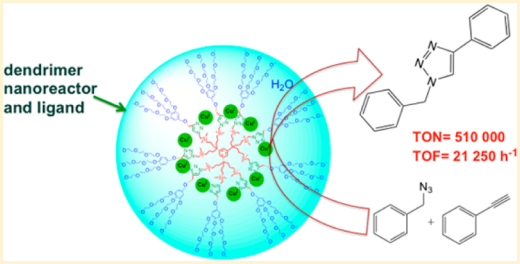
Supporting Information

ABSTRACT: Upon catalyst and substrate encapsulation, an amphiphilic dendrimer containing 27 triethylene glycol termini and 9 intradendritic triazole rings serves as a catalytic nanoreactor by considerably accelerating the Cu^{I}-catalyzed alkyne−azide cycloaddition (CuAAC) "click" reactions of various substrates in water using the catalyst Cu(hexabenzyltren)Br (tren = triaminoethylamine). Moreover this recyclable nanoreactor with intradendritic triazole rings strongly also activates the simple Sharpless−Fokin catalyst $CuSO_4$ + sodium ascorbate in water under ambient conditions leading to exceptional TONs up to 510 000. This fully recyclable catalytic nanoreactor allows to considerably decrease the amount of this cheap copper catalyst down to industrially tolerable residues, and some biomedical and cosmetic applications are exemplified.



INTRODUCTION

Since Breslow's concept of supramolecular nanoreactors with cyclodextrins,[1] nanoreactors are becoming increasingly investigated in catalysis as illustrated by Fujita's capsule M_6L_4,[2] Rebek's soft ball,[3] cucurbit[6]uril,[4] and biresorcinarenes,[5] respectively, studied by Mock and Warmuth, porphyrin[6] used by Reek and Van Leuuwen, Sanders' porphyrine macrocycle[7] and Bergman and Raymond's capsule.[8,9] Surfactants and ionic liquids,[10] copolymers that form micelles and polymersomes,[11] and dendrimers[12−29] are useful for the encapsulation or stabilization of catalytically active nanoparticles.[12−18] In particular, Newkome has proposed dendritic molecular micelles,[19−21] and Crooks has used dendrimers as nanofilters for nanoparticle catalysis.[12−14] Along this line, dendrimers have the potential to serve as molecular containers,[22−24,29] and dendrimers with internal triazole rings on their tethers have been shown to facilitate the catalysis by Pd nanoparticles of C−C cross-coupling reactions.[18,23−27,30]

It was then of interest to examine whether these dendritic nanoreactors are of general application in catalysis and, in particular, if they can also facilitate or activate catalysis by molecular catalysts. Therefore, we have now addressed their utility in the Cu^{I}-catalyzed Huisgen-type azide−alkyne 1,3-cycloaddition (CuAAC), the most commun "click" reaction allowing to link together two organic, bioorganic, or other functional molecular fragments.[31,32] The catalytically active Cu^{I} species is usually generated from $CuSO_4$ and sodium ascorbate in excess, a very convenient system that works well in aqueous solvents.[32] Various genuine Cu^{I} catalysts that do not require a sacrificial reductant are also known, the advantage of liganded Cu^{I}, particularly with nitrogen ligands, being the rate acceleration, for instance with the efficient polytriazoles[33,34] and tris(2-aminoethyl)amine derivatives (tren).[35−38] The nitrogen ligands allow the use of Cu^{I} catalysts in amounts that are much reduced (most often of the order of 1%) compared to the original, simple, and practical catalyst $CuSO_4$ + sodium ascorbate that is still the most commonly utilized catalyst but in much larger quantities that are often even stoichiometric or superior to stoichiometry.[25−27] The large quantity of metal catalyst used in the CuAAC "click" reaction and its difficult complete removal presently remain the main problems, inhibiting the utilization of such "click" chemistry in electronics and biomedicine.

Now the use of the dendrimer **1** terminated by 27 triethylene glycol (TEG) termini[39] (Scheme 1a) is proposed as an amphiphilic micellar nanoreactor, stabilizer, and activator of CuAAC reactions in water leading to a considerable decrease of the required Cu^{I} catalyst for these reactions. The water-soluble dendrimer **1** is also fully recyclable and reusable many times without consumption or decomposition.

Two approaches are shown here to be extremely efficient for this purpose. First, the reactions of various substrates are catalyzed in water using the complex [hexabenzyltren-Cu]Br, **2**,[37] with the dendrimer **1** taking advantage of its molecular-micelle effect. In this strategy, it is possible to catalyze click reactions with down to only 0.1% of the Cu^{I} catalyst **2** and to localize this hydrophobic solid catalyst **2** inside the dendrimer in D_2O by 600 MHz ^1H NMR, bringing an enlightening support for the role of **1** as a nanoreactor. Second, now utilizing both advantages of micellar dendritic encapsulation and catalytic activation of "naked" Cu^{I} by intradendritic triazole ligands, the recyclable dendrimer **1** in very small quantities allows the use of only part-per-million Cu^{I} catalyst ($CuSO_4$ + sodium ascorbate) at 30 °C in only water, an exceptional efficacy of this convenient, simple, and commercial catalyst.

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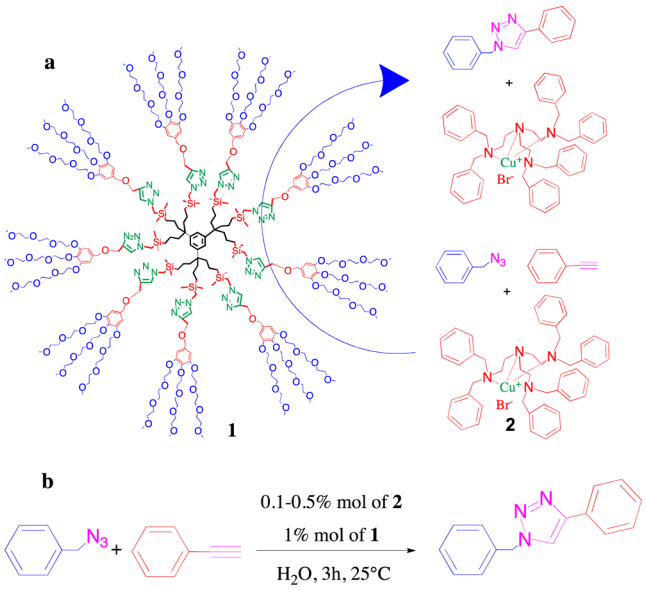
Scheme 1. CuAAC Reaction between Benzyl Azide and Phenyl Acetylene Catalyzed by the Cu^{I} Complex 2 in the Presence of Small Amounts of the Dendrimer 1 (a, b).



RESULTS AND DISCUSSION

Activation of Click Catalysis by Micellar Dendrimer Effect: the Dendrimer 1 As a Nanoreactor. The CuAAC reaction is first conducted in water during 3 h between the water-insoluble substrates benzyl azide and phenyl acetylene with various amounts of catalyst **2** in the presence of 1% mol of **1** (Scheme 1a,b and Table 1).

Table 1. CuAAC Reactions between Benzyl Azide and Phenyl Acetylene[a]

entry	catalyst **2** (mol %)	dendrimer **1** (mol %)	yield (%)[b]
1	0.1	0	2
2	0.1	1	91[c]
3	0.2	1	92
4	0.5	1	98

[a]From Scheme 1b. All the reactions were carried out with 0.1 mmol of azide, 0.105 mmol of alkyne, 2 mL of water at 25 °C during 3 h. [b]Isolated yield. [c]This reaction was repeated 10 times with the same recycled dendrimer **1**, and after reusing **1** ten times, the yield remained 91%.

According to Table 1, the "click" reaction with 1% of **1** works well when the amount of catalyst **2** is in the range 0.1−0.5% mol (yields: 92−98%). When the same reaction is conducted without **1**, the reaction does not work under these conditions, the yield being only 2% (entry 1).

The water/organic compatible TEG termini render the dendrimer **1** water-soluble, and the hydrophobic core allows solubilization in water of the hydrophobic catalyst **2** and the substrates. The results from Table 1 confirm that the hydrophobic substrates and catalyst **2** meet more easily in the hydrophobic core of **1** than outside **1** in water. Scheme 1a illustrates the schematic principle of the reaction. The insolubility of **1** in diethyl ether allows the complete extraction of the organic products from the reaction medium upon keeping **1** in the water phase. In this way, **1** was recycled more than ten times without change of structure during the catalysis (the experiment of entry 2 was repeated 10 times, with the same recycled dendrimer **1** without change in reaction yield). The next-generation dendrimer **3**[39] containing a hydrophobic core and 81 TEG termini (see structure in the Supporting Information Scheme S1) was also used in the test CuAAC reaction between benzyl azide and phenyl acetylene under the conditions indicated in Table 1 in order to check its behavior as a nanoreactor. The reaction performed in the presence of **3** was nearly quantitative (90%) after 3 h as in the presence of **1** (91%, entry 2), indicating that the micellar effect of **1** and **3** in the catalysis of CuAAC reactions was similar. Because the synthesis of **3** is longer than that of **1**, the following studies of the "click" reactions were only conducted with the dendrimer **1**.

The CuAAC reaction has been conducted using the nanoreactor **1** in water for seven other substrates in order to check the applicability and generality of the method for this reaction (eq 1 and Table 2)

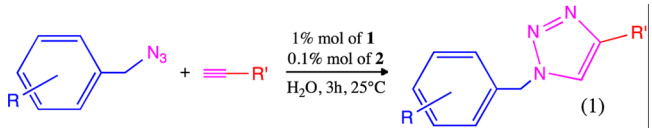
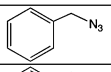
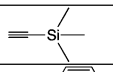
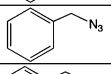
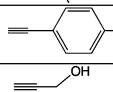
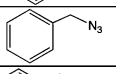
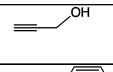
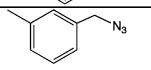
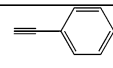
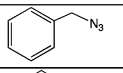
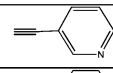
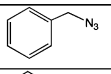
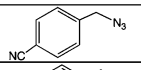
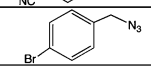
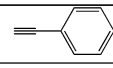


Table 2. CuAAC Reactions between Various Azides and Alkynes Using 0.1 Mol % of Catalyst 2 in the Presence of Catalytic Amounts of Dendrimer 1[a]

Entry	Azide	Alkyne	Yield/**conv.** (%)[b]
5			89/**97**
6			93/**100**
7			93/**100**
8			90/**97**
9			95/**100**
10			91/**98**
11			90/**97**
12			96/**100**

[a]See eq 1. All the reactions are carried out with 0.1 mmol of azide, 0.105 mmol of alkyne, 1% mol of dendrimer **1**, 0.1% mol of **2**, and 2 mL of water at 25 °C, during 3 h. [b]Isolated yield/^{1}H NMR conversion.

The method that is proposed here is efficient for the "click" reaction of various substrates, leading to yields of around 90% or more for classic nonactivated substrates. Finally the catalyst **2** was used during the "autocatalytic" synthesis of the nanoreactor **1** itself. Remarkably, with only 8% mol of **2** per branch, the "click" reaction between the nona-core azide and the tris-TEGylated alkynyl dendron (eq 2) is completed in 570 min at 30 °C in the presence of only 1 mol % **1** per branch, leading to **1** in 81% isolated yield. If **1** is absent at the beginning of the reaction, the yield under these conditions is only 39% (in 1200 min), clearly showing the strong autocatalytic effect of very small amounts of **1** on its own formation. The kinetic study of the reaction (see Supporting Information, Figures S29

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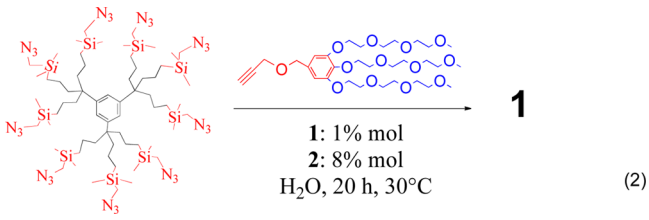

(2)

and S30) shows that after 90 min, the conversion of the starting material is already 45.8% in the presence of **1** against only 2% without **1** at the beginning of the reaction. In the absence of **1** at the beginning of the reaction, its synthesis using catalyst **2** requires 2 days to reach completion; thus, the presence of **1** at the beginning of the reaction clearly accelerates its synthesis.

^{1}H NMR Characterization of the Solubilization of the Hydrophobic Catalyst 2 in Water and Encapsulation in the Dendrimer 1. In order to provide further insight into the catalytic activation by the dendrimer **1**, ^{1}H NMR and DOSY NMR studies of **1** have been conducted.

The ^{1}H NMR study of **1** in D_2O shows a minute shift of the triazole proton (from 7.79 to 7.76 ppm) upon diluting **1** 32 times (from 2.8×10^{-3} to 8.7×10^{-5} M, Figure 1a). This experiment suggests that, when **1** is concentrated, assemblies of dendrimers are formed with interdendritic interlocked TEG termini, whereas in diluted conditions, these assemblies are split. This observation is also confirmed by DOSY NMR experiments that show different diffusion coefficients when **1** is concentrated (2.8×10^{-3} M) or diluted (8.7×10^{-5} M). The hydrodynamic diameter of concentrated **1** calculated from the diffusion coefficient using the Stokes–Einstein law is 13.3 (±0.2) nm, and 10.2 (±0.2) nm when **1** is diluted (the calculated maximum diameter of **1** at full extension is approximately 6 nm).

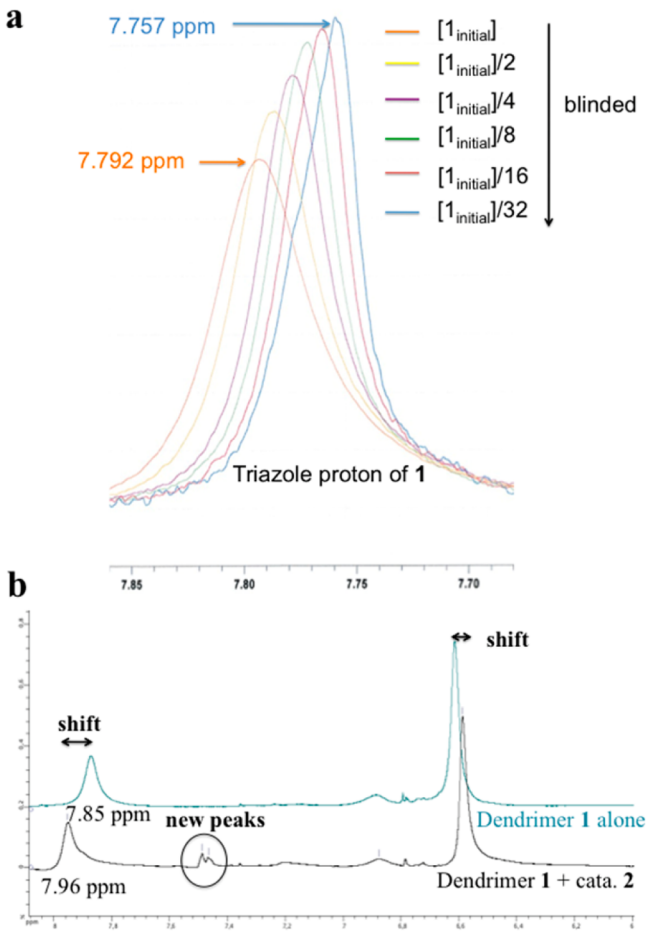

Figure 1. ^{1}H NMR characterization of the solubilization of the hydrophobic catalyst **2** in water and its encapsulation in the dendrimer **1**. (a) 600 MHz ^{1}H NMR in D_2O of **1** from concentrated solution [**1**] = 2.8×10^{-3} M (left) to diluted solution [**1**] = 8.7×10^{-5} M (right). (b) 600 MHz ^{1}H NMR of **1** + **2** in D_2O. New peaks appear around 7.5 ppm and shifts are observed, inter alia in the portion of the spectrum represented here, for two types of protons (triazole at 7.85 ppm and aromatic rings of the TEG dendron 6.62 ppm).

The ^{1}H NMR spectrum of **1** + **2** in D_2O presents, compared to that of **1** alone, the appearance of new signals at 7.47–7.49 ppm (Figure 1b) corresponding to the protons of the phenyl groups of **2**, showing the solubilization in water of the hydrophobic complex **2**. It is also remarkable that in the presence of **2** the signals of the protons of the hydrophobic groups of the tethers of **1** (red and green regions of Scheme 1a) are slightly shifted (0.03 ppm in the red region, see Figure S2/Table S1 of the Supporting Information), especially the triazole proton (around 0.1 ppm shift, see Figure 1b). This latter shift possibly results from interaction of this triazole with the Cu atom of **2** subsequent to reversible decoordination of a nitrogen ligand of **2**. This would eventually add to the driving force provided by the hydrophobic shelter for the encapsulation of **2** by **1**. NOESY NMR shows a weak interaction between the new peaks of **2** and the CH_3 substituents of the Si groups of **1**, which also confirms the presence of the catalyst **2** very close to the hydrophobic interior of **1** (see Figure S4 of the Supporting Information). The bulk of the core and the barrier of the methyl substituents of the Si atoms prevent significantly deeper interaction of **2** beyond the $SiMe_2$ groups near the dendrimer core.

Upon diluting the solution **1** + **2** from [**1**] = 2.8×10^{-3} M to [**1**] = 3.2×10^{-4} M (condition of the CuAAC reactions) the ratio of water-soluble **2** per mol **1** increases from 1/15 to 1/5 (Supporting Information, Figure S3), which is in agreement with the stoichiometry used during the catalytic CuAAC reaction with 1% dendrimer **1** and 0.1–0.2% catalyst **2** (Table 1, entries 1–3 and Table 2, entries 5–12).

Intradendritic Triazole Ligands of 1 As Additional Activators of Cu^I Catalysis. The second strategy uses, in addition to and in synergy with the micellar effect of the amphiphilic dendrimer illustrated above, the intradendritic triazole activation of the Cu^I catalysis. In this case, it is not necessary to synthesize a Cu^I catalyst such as **2** with a nitrogen ligand because this role is played by the nine intradendritic triazole ligands of **1**. In precedent work on catalytically efficient dendrimer-encapsulated Pd nanoparticles, the role of the triazole ligands was the stabilization of the nanoparticles.[18,39] On the other hand, here, the intradendritic triazole ligands activate Cu^I by increasing the electronic density for improved catalytic efficiency. Thus, the classic $CuSO_4 \cdot 5H_2O$ source can advantageously be used as precatalyst of the CuAAC reaction, and sodium ascorbate (NaAsc) as reducing agent of Cu^{II} to Cu^I, that is, the initially reported conditions.[51] As **1** contains nine triazolyl rings, 9 equiv. Cu^{II} per dendrimer are used. After adding $CuSO_4 \cdot 5H_2O$ to an aqueous solution of **1**, Cu^{II} coordinates the intradendritic triazolyl ligands, then Cu^{II} is reduced in situ to Cu^I for intradendritic catalysis (Figure 2). The coordination of Cu^{II} to the triazole rings of **1** has been checked by ^{1}H NMR spectroscopy. After adding $CuSO_4 \cdot 5H_2O$ to a deuterium oxide solution of **1** (1 equiv per triazole), the NMR signal of the triazole proton of **1** at 7.90 ppm vanishes to

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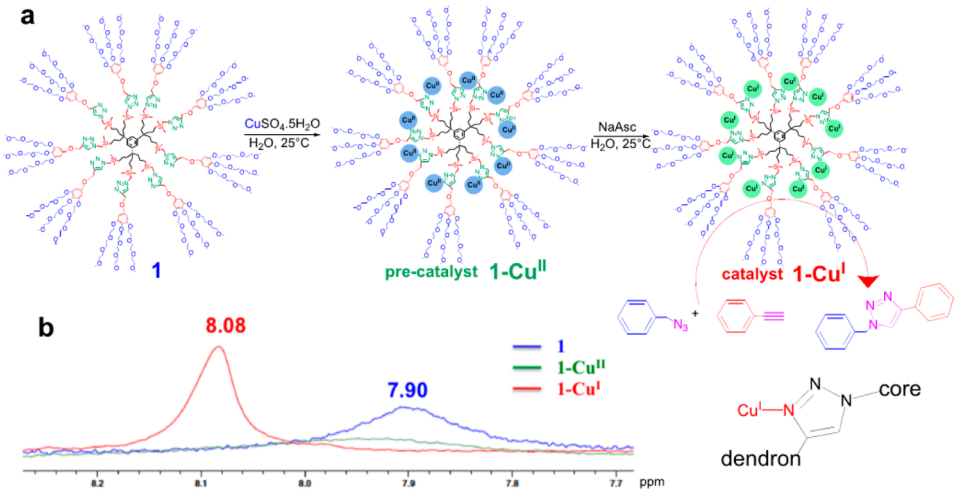


Figure 2. (a) Dendrimer **1** as nanoreactor/ligand for CuAAC catalysis. (b) Comparison of the NMR signals of the triazole proton of **1** alone (7.90 ppm), with Cu^{II} (very broad due to the paramagnetism) and Cu^{I} (shift to 8.08 ppm) showing the coordination of the intradendritic triazoles of **1** to the copper ions.

give a very broad signal due to the paramagnetic Cu^{II} species. When NaAsc is added to reduce Cu^{II} to Cu^{I}, the NMR signal of the triazole proton of **1** reappears but is shifted (8.08 ppm instead of 7.90 ppm when **1** is alone) showing the coordination of all the triazole rings to Cu^{I} (Figure 2b and Figure S8 of the Supporting Information).[40]

The efficiency of the CuAAC catalyst involving this system has been tested again for the classic reaction between benzyl azide and phenyl acetylene with various amounts of catalyst, down to 1 ppm of copper. When the quantities of **1** and $CuSO_4{\cdot}5H_2O$ are 1%, the yield is 100% in 2.5 h of reaction against only 15% when the reaction is conducted without **1**. The reaction is quantitative with only 4 ppm of Cu^{I} in water at 30 °C during 24 h (entry 18) and reaches 50% of yield with 1 ppm of Cu^{I} (Table 3).

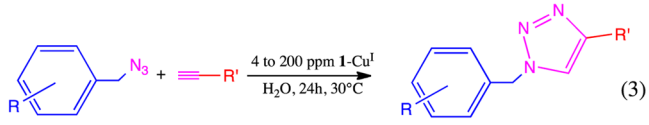
Table 3. CuAAC Reactions between Benzyl Azide and Phenyl Acetylene Using Various Amounts of 1−Cu^{I} [a]

entry	Cu^{I} ppm	time (h)	yield (%)	TON	TOF (h^{-1})
13[b]	10000 (1 mol %)	2.5	99	99	39.6
14[b]	2000	19	99	495	26.0
15	200	19	99	4 950	260
16	40	19	99	24 700	1 300
17	20	19	99	49 500	2 600
18	4	24	99	247 000	10 300
19	1	24	50	510 000	21 200
20	0	24	0	0	0

[a]All the reactions were carried out with 1 mmol of azide, 1.05 mmol of alkyne in 1 mL of H_2O. [b]The reaction was carried out with 5 mL of water.

Such an extremely low quantity of copper has never been successfully used in only water at 30 °C for CuAAC reactions before the present study. At such extremely low catalyst amounts, the noncatalyzed Huisgens reaction is in competition with the CuAAC reaction at high temperature using the standard substrates.[37] At 30 °C, however, neither the Huisgen reaction in the absence of Cu^{I} catalyst nor the CuAAC reaction (entry 20) proceeds. In the case of very small amounts of copper, an excess of sodium ascorbate vs the low catalyst amount is added to the reaction in order to avoid oxidation of Cu^{I} that is air sensitive.

The CuAAC reaction is also carried out in water at 30 °C between various alkynes and azides (aromatic and aliphatic) with parts-per-million amounts of Cu^{I} (eq 3 and Table 4)



(3)

In order to check if the dendritic effect is positive and to distinguish between the micellar dendrimer effect and the Cu^{I} activation by coordination of a nitrogen atom of the "clicked" triazole in water, the results obtained in the presence of the Cu^{I} complex of dendrimer **1** were compared on one hand with those obtained with the Cu^{I} complex of the nondendritic molecule **4** (Scheme 2a), and on the other hand with those obtained with Cu^{I} in the presence of the water-soluble dendrimer **5**[41] that does not contain triazole ligands (Scheme 2b).

With Cu^{I} stabilized by the nondendritic triazole ligand of **4**, the same conditions as in entry 15 (200 ppm of Cu^{I}) are followed, and the yield is also quantitative. When the amount of catalyst is reduced to 4 ppm as in entry 18, however, no reaction is observed upon several attempts, which emphasizes the key molecular micelle role of the dendritic nanostructure. With dendrimer **5** that does not contain triazole rings (Scheme 2b), Cu^{I} is introduced under the same conditions as with **1** and as in entry 17 (20 ppm of Cu^{I}). After 24 h, only 27% of isolated yield is obtained, whereas with **1**−Cu^{I} 99% is obtained in 19 h. This shows the crucial activation role of the triazole ring. When the reaction is performed without any dendrimer (using only the water solution of Cu^{I}), the isolated yield is 9%. These experiments show that both the micellar effect of the dendrimer **1** and the activation by coordination of Cu^{I} by the intradendritic triazole ligands have a very positive effect on the catalytic efficiency and that these two effects are cumulative, resulting in the considerable benefit of the dendritic nanoreactor **1** on the "click" reactions with the simple Sharpless-Fokin catalyst $CuSO_4{\cdot}5H_2O$ + sodium ascorbate in water.

These results advantageously compare with relatively recent ones (2008−2014) from the literature in Table 5, a large number of active catalysts for the CuAAC reactions being known.

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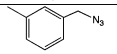
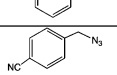
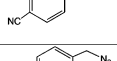
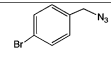
Table 4. CuAAC Reactions between Various Azides and Alkynes with 1−Cu^{I} [a] (See eq 3)

Entry	Azide	Alkyne	Cu^{I}	Yield (%)[c]
21			4 ppm	99
22			20 ppm	87
23 [d]			20 ppm	81
24			20 ppm	89
25			4 ppm	90
26			4 ppm	82
27			50 ppm	90
28 [d]			50 ppm	89
29			100 ppm	98
30			20 ppm	98
31			200 ppm	98

[a]All the reactions are carried out with **1**−Cu^{I} at 30 °C during 24 h in 1 mL of H_2O. [b]Pent-1-yne is hydrophobic and has a low boiling point, so that it is difficult to conduct experiments with a lower amount of catalyst. [c]Isolated yield. [d]Reaction performed at 35 °C.

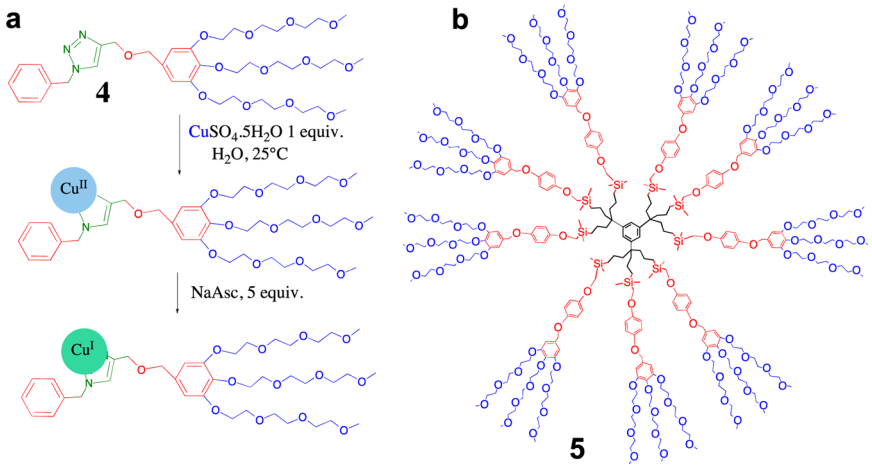
Table 5. Examples of Recent Efficient CuAAC Reactions in the Presence of Various Catalysts and Reaction Conditions[a]

catalyst[ref]	Cu (% mol)	time (h)	solvent	temperature (°C)
Cu/Fe[42]	5 wt %	8	CH_2Cl_2	30
Cu-NHC/Phen[43]	1	18	*t*-BuOH/H_2O 2/1	20
Cu/AlO(OH)[44]	3	6	*n*-hexane	25
Cu_2O/benzoic acid[45]	1	0.13	H_2O	20
poly(imidazole-acrylamide)/$CuSO_4$/NaAsc[46]	0.25	1.5	*t*-BuOH/H_2O 1/3	50
poly(imidazole-acrylamide)/$CuSO_4$/NaAsc[46]	0.00045	31	*t*-BuOH/H_2O 1/3	50
bis-NHC-dicopper complex[47]	0.5	0.75	CH_2Cl_2	20
TBTA-Cu^{I}[33]	0.25−1	24	*t*-BuOH/H_2O 2/1	20
nano-FGT-Cu[48]	2.4	0.16	H_2O	Mw 120
Fe_2O_3−NHC-Cu^{I}[49]	0.25	18	H_2O	20
β-CD/$CuSO_4$,NaAsc[50]	5	0.25	H_2O	20
$[Cu_8(l4\text{-}H)\{S_2P(OEt)_2\}_6](PF_6)$[51]	0.4	4	CH_3CN	20
$CuSO_4/N_2H_4$−H_2O[52]	0.0025	4	No	20
ammonium NHC-Cu^{I}[53]	5	3	H_2O	20
Fe_2O_3/SiO_2 *Tris*(triazolyl) Cu^{I}[54]	0.5	20	H_2O	20
PS/SiO_2*Tris*(triazolyl) methane−Cu^{I}[55]	0.5	4	H_2O	20
SBA-15-imine/Cu^{I}[56]	0.1	6	H_2O	20
$Cu(PPh_3)NO_3$[57]	0.5	0.66	H_2O	20
$[(NHC_{Cy})Cu]PF_6$[58]	2	1.5	H_2O	20
Catalyst **2**[37]	0.1	24	$PhCH_3$	22

[a]All the above results correspond to the CuAAC reaction between benzyl azide and phenylacetylene. NHC: N-heterocyclic carbene, TBTA: tris(benzyltriazolylmethyl)amine, FGT: ferrite-glutathione, *β*-CD: *β*-cyclodextrin, SBA-15: mesoporous silica, NHC_{Cy}: NHC ligand with cyclohexyl substituents on the nitrogen atoms. Yields are between 90 to 100% except with Cu-NHPhen (78%) and $CuSO_4/N_2H_4$−Cu (82%).

One of the best results has been recently reported by Yamada et al., who have described the synthesis of an amphiphilic self-assembled polymeric copper catalyst. This catalyst is active in the CuAAC reaction between benzyl azide and phenyl acetylene with 4.5 ppm of copper at 50 °C during 32 h in the mixed solvent *t*-BuOH/H_2O (1/3).[45] The presence of *t*-BuOH as cosolvent and 50 °C are necessary for a complete reaction. Another remarkable example was also recently reported by Shin et al. using *β*-cyclodextrin as nanoreactor for "click" reactions in water in the presence of $CuSO_4$ and sodium ascorbate at rt, but 5% mol of copper was needed in that case for a quantitative reaction in only water.[49] The catalysts $Cu(PPh_3)NO_3$[56] and $[(NHC_{Cy})Cu]PF_6$[57] are also active in water but 0.5% mol and 2% mol respectively are necessary for a complete reaction between benzyl azide and phenyl acetylene. Generally, the CuAAC "click" reaction is possible in water when the amount of liganded copper exceeds 0.1% mol (see Table 5); therefore, the activity of the present system is incomparable.

Scheme 2. (a) Complexation of the reference compound 4 by Cu^{II} followed by reduction to water-soluble, catalytically active Cu^{I}-triazole for CuAAC reactions. (b) Structure of dendrimer 5 that does not contain triazolyl groups.



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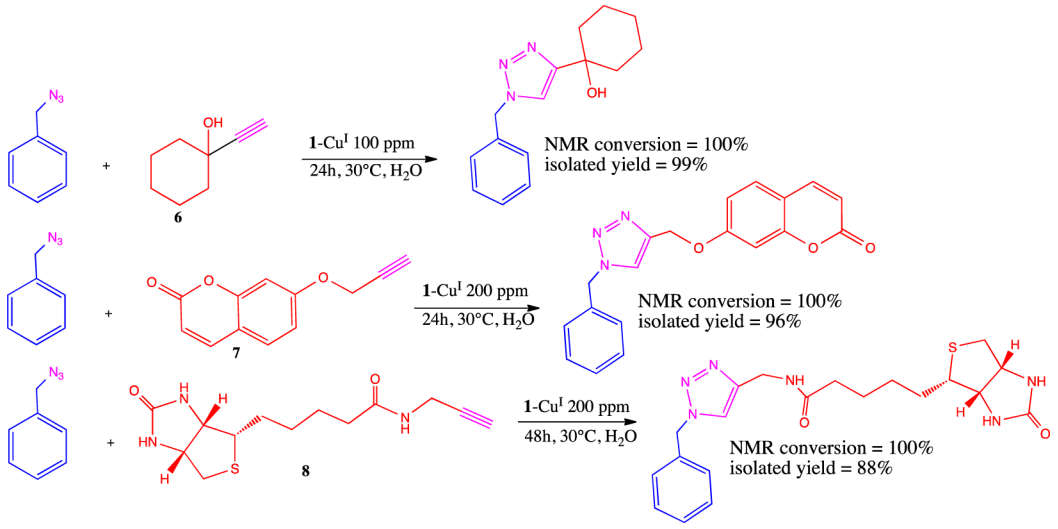
Scheme 3. CuAAC Reactions with 1−Cu^{I} As Catalyst for Various Applications



To evaluate the scope and the applicability of the present system, the CuAAC reaction with **1**−Cu^{I} was tested on hydrophobic biomolecules with medicinal, targeting, and labeling interests (Scheme 3). As a candidate, the 1-ethynylcyclohexanol **6** was chosen because of its simple structure and because it is an active metabolite of the old central nervous system depressant drug ethinamate. The 7-(propargyloxy)coumarin **7** belonging to the coumarin family was also tested in the CuAAC "click" reaction with **1**−Cu^{I}. Coumarins are often used for their anti-oedematous properties, and their flavor properties have rendered this family famous in the perfume industry. Moreover coumarins are known as fluorescence dyes. The 3-(D-biotinylamido)-1-propyne **8** is an alkyne derivative of biotin that is known for instance for its role as a vitamin and coenzyme in the synthesis of fatty acids. Biotin is also known for its extremely high affinity with avidin. As exposed in Scheme 3, the catalyst **1**−Cu^{I} is very active for the CuAAC "click" reaction even for these three biological molecules with only 100−200 ppm of Cu^{I}.

CONCLUDING REMARKS

The water-soluble dendrimer **1** acts as a molecular micelle nanoreactor in catalytic quantities (1% vs substrates or less) and is recycled and reused many times without any loss or decomposition. Under these conditions (water, 25 °C, 3 h), it considerably facilitates catalysis by [Cu(hexabenzyltren)]Br (0.1% vs substrate) of the CuAAC reactions that are nearly quantitative in the presence of this dendritic nanoreactor and do not work in its absence. Along this line, the "autocatalyzed" dendritic nanoreactor synthesis of **1** is remarkable.

This catalytic nanoreactor effect is confirmed by ^{1}H NMR evidence of the solubilization of the hydrophobic catalyst **2** in water in the presence of the dendrimer **1**, and the catalyst−dendrimer interaction is shown by the selective NMR shifts of intradendritic protons in the hydrophobic region, providing a proof for the solubilization role of **1**.

In addition to and in synergy with this effect, the presence of intradendritic triazole ligands allows catalyzing CuAAC reactions at 30 °C with down to 4 ppm of commercial $CuSO_4{\cdot}5H_2O$ and sodium ascorbate for quantitative yields and 1 ppm with 50% yield. The reaction with hydrophobic biomolecules has also been performed in only water at 30 °C, leading to quantitative yields. Comparisons of **1** with the nondendritic triazole ligand **4** and with the water-soluble dendrimer **5** that has a hydrophobic core but does not contain triazole ligands show that both the micellar and intradendritic triazole coordination share key roles in the considerable catalyst activation in water. This opens the route to future biomedical and nanomaterials applications of the common CuAAC reaction with the cheap Sharpless−Fokin catalyst $CuSO_4{\cdot}5H_2O$ + sodium ascorbate, as already exemplified here in a few examples of biomedical or cosmetic interest.

ASSOCIATED CONTENT

Supporting Information

General data, syntheses of the catalysts **2** and **1**−Cu^{I}, procedure and data for the encapsulation of catalyst **2** in **1**, complexation of Cu^{I} to the triazoles of **1**, syntheses and ^{1}H NMR spectra and data of the "click" reaction products, spectroscopic characterization of **3**−**5**, kinetic study of the autocatalytic synthesis of **1**, and characterization of **1** after reuse. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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