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The Efficient Copper(I) (Hexabenzyl)tren Catalyst and Dendritic Analogues for Green "Click" Reactions between Azides and Alkynes in Organic Solvent and in Water: Positive Dendritic Effects and Monometallic Mechanism

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Abstract: An easily synthesized, copper(I) (hexabenzyl)tren complex **1** is an efficient catalyst for the copper(I)-catalyzed Huisgen-type 1,3-cycloaddition between azides and alkynes (CuAAC) reaction in toluene. Alternatively, a convenient procedure involves mixing copper(I) bromide (CuBr) with hexabenzyltren and the substrates in toluene which gives, for instance, 100% yield of triazole in 10 min using 0.1 equiv. catalyst with phenylacetylene and benzyl azide at room temperature. The toluene-soluble catalyst **1** is recyclable and is applied, for example, to the CuAAC synthesis of an 81-branched dendrimer that previously required the use of a stoichiometric amount of copper(II) sulfate ($CuSO_4$) + sodium ascorbate "catalyst". Dendritic copper(I)-centered analogues **2** and **3** of the first and second generations (G1 and G2, respectively) containing respectively 18 and 54 branch termini, including a 54-branched water-soluble metallodendrimer **5**, are also very efficient catalysts for the CuAAC reaction. With the metallodendritic Cu(I) derivatives **2** and **3**, the dendritic frame brings about steric protection against the well-known inner-sphere aerobic oxidation of Cu(I) to bis(μ-oxo)-bis-Cu(II). The metallodendrimers **2** and **3** are also sometimes more efficient than the parent catalyst, as shown by kinetic studies. Catalysis in water without co-solvent of the CuAAC reactions of water-insoluble substrates was achieved under ambient conditions in good yields with the recyclable catalyst **5**. Efficient catalysis of the CuAAC reaction by these bulky Cu(I) metallodendrimers emphasizes the monometallic mechanism. The difference of kinetic behavior between **1** and CuBr + hexabenzyltren suggests, however, that whereas a monometallic mechanism is working for **1**, the mixture of CuBr + hexabenzyltren might involve the bimetallic mechanism proposed by Fokin and Finn.

Keywords: alkynes; azides; catalysis; click chemistry; copper; mechanism; metallodendrimers; water

Introduction

Dendrimers are useful supports for catalysis, because they allow high catalyst loading at the periphery of the dendritic framework and subsequent recycling.[1] Intradendritic catalysis is also intriguing, because the metal centers are then protected by the dendrimer, although the steric bulk of the dendrimer frame often results in a kinetic drop. This latter strategy has been successfully developed in particular by Crooks who demonstrated the use of the dendrimer as a nanoreactor in which the periphery plays the role of a nanofilter,[2] and by Fréchet with intradendritic organic reactions for which a radial polarity gradient in the dendrimer induces a favorable catalytic effect.[3] As shown by these seminal studies, intradendritic catalysis is indeed promising, because the dendrimer interior can function as a complex supramolecular nanoreactor whereby the key-and-lock principle, in addition to the steric protection, might provide biomimetic conditions.[4]

A dramatic example of the need of steric protection is Cu(I) catalysis, because oxygen from air binds Cu(I) to form μ-peroxo-dicopper(II), then bis(μ-oxo)-dicopper(II). Thus the unprotected Cu(I) complexes are very air-sensitive, which inhibits catalysis.[5] The Cu(I)-catalyzed Huisgen-type 1,3-cycloaddition between azides and alkynes (CuAAC)[6–9] has become

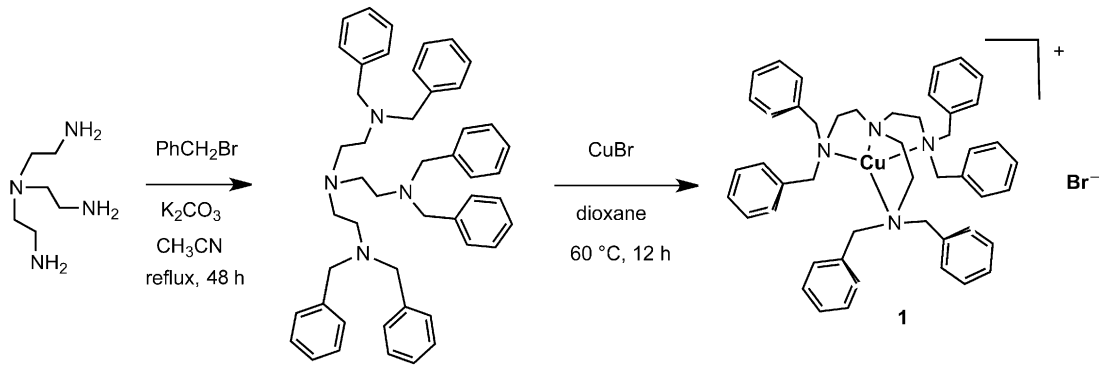
one of the most convenient and popular "click" reactions to link organic and bio-organic fragments[10] following the independent finding of the efficiency of Cu(I) catalysis by the groups of Meldal and of Fokin and Sharpless.[6] The catalytically active Cu(I) species is usually generated from $CuSO_4$ and sodium ascorbate in excess, a very convenient system initially reported by the Fokin–Sharpless group that works well in aqueous solvents.[7] Various genuine Cu(I) catalysts that do not require a sacrificial reductant are also known, the advantage of liganded Cu(I) being the rate acceleration provided by various polyamine ligands.[11] Efficient accelerating ligands are the tris-(pyrazolylmethyl)amines,[12] discovered by the Fokin–Sharpless group, and more recently improved with the closely related tris(2-benzimidazolylmethyl)-amines reported by the Finn group.[13] We have been interested in the simple, commercial ligand $N(CH_2CH_2NH_2)_3$, abbreviated as tren. The Cu(I) complex of the hexamethyltren ligand $N(CH_2CH_2NMe_2)_3$ (Me_6tren) has been shown by Matyjaszewski's group[14] to be an efficient catalyst for the click reactions. Matyjaszewski et al. have compared various polyamine ligands and shown that the Me_6tren ligand provided a 50-fold increase of the click rate constant compared to CuBr. Recently, the complex [Cu(I)tren($C_{18}H_{37})_6$][Br][15] **4** has also been probed for its efficiency. Dendritic protection of the Cu(I) center, however, is a rational strategy that involves intradendritic catalysis and has not been addressed so far. Yet, supramolecular effects involving weak bonds are well known in dendrimer chemistry[16] and are likely to play a role because of the interactions, besides coordination, that influence the catalytic reaction pathway within the metallodendrimer interior. An additional interest in sterically protecting the catalytic Cu(I) center is to check whether a monometallic mechanism is viable for this click reaction and to search for information provided by the dendritic effects on the catalysis. Indeed, fine studies have pointed out the complexity of the mechanism, and in particular the implication of several Cu species involved in the transition state and requiring some partial decoordination of polydentate nitrogen ligand.[13]

Following our interest for metallodendritic catalysts[17] and the frequent use of click reactions in the synthesis of nanomaterials (dendrimers[18] and gold nanoparticles[19]), we have now designed dendritic ligands for catalysts of the click reaction with benzyl substituents on the nitrogen atoms of tren. Thus, we are reporting here the new parent catalyst [Cu(I)-tren($Bn)_6$][Br] (**1**) and the dendritic derivatives **2**, **3** and **5** containing, as a core, the framework of **1** and dendritic substituents located in the *para* position of the phenyl groups of **1**. This series of CuAAC catalysts includes a water-soluble metallodendritic catalyst **5** for CuAAC reactions in water. The catalyst **1** will turn out to be of great interest for its efficiency *per se*, ease of preparation, solubility in toluene and recycling properties, and a comparison will be carried out with the catalytic properties of the metallodendrimers.

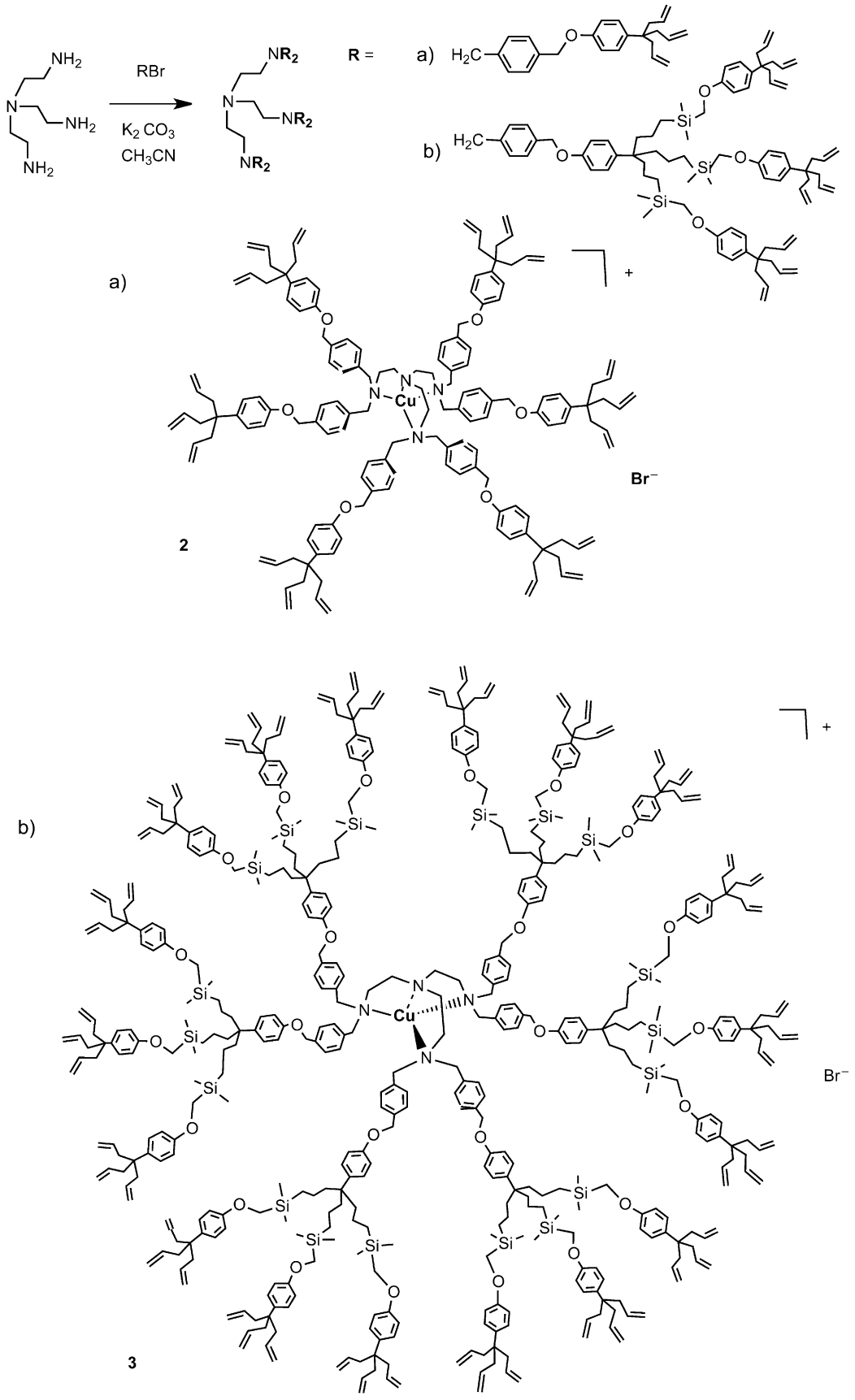
Results

Synthesis and Characterization of [Cu(I)tren($Bn)_6$][Br] (1) and Dendritic Analogues

The hexabenzyltren ligand was easily synthesized by refluxing commercial tren with benzyl bromide in acetonitrile in the presence of K_2CO_3, and the Cu(I) complex **1** was then also easily obtained by heating CuBr with the hexabenzyltren ligand in dioxane at 60 °C overnight (Scheme 1). The complex **1** is well soluble in toluene, which is very practical for click reactions, because the 1,2,3-triazole products precipitate from this solvent, and it is then easily separated from the reaction products by filtration. Both the ligand and the complex **1** were characterized *inter alia* by the molecular ion peaks in their MALDI-TOF mass spectrua, UV-vis. spectroscopy ($\lambda = 316$ nm, $\varepsilon = 2689.8\ L\,mol^{-1}\,cm^{-1}$), cyclic voltammetry {electrochemically irreversible oxidation at $E_{pa} = 0.30$ V *vs.* $[Fe(C_5Me_5)_2]^{+/0}$ on Pt in CH_2Cl_2, using 0.1 M [(*n*-



Scheme 1. Synthesis of the complex [Cu(hexabenzyl)tren][Br] (**1**).



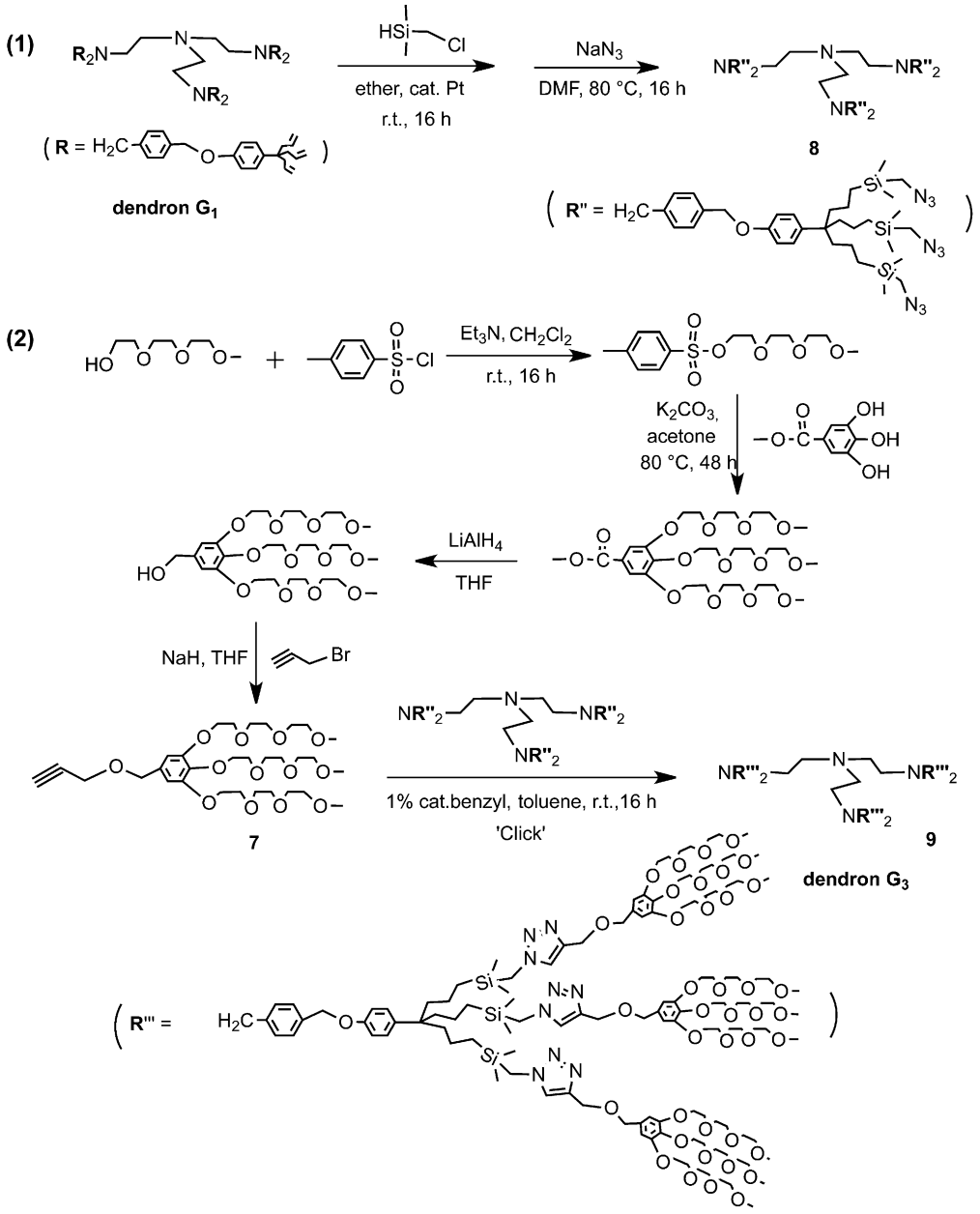
Scheme 2. Syntheses of the tren ligands **G1** and **G2** and structures of their CuBr complexes **2** (**G1**) and **3** (**G2**).

$Bu)_4N][PF_6]$ as the supporting electrolyte; $\Delta E_p =$ 0.40 V} and elemental analysis.

The dendritic analogues **2** and **3** of **1** were designed by introducing dendrons in the *para*-position of benzyl bromide.[20] Thus, dendrons containing 3 allyl termini for the first generation and 9 allyl termini for the second generation (with 1→3 connectivity)[21] were linked to the tren amino groups *via* their bromobenzyl focal points, resulting in the formation of dendritic ligands that contain 18 and 54 terminal groups for the first and second generations G1 and G2, respectively (Scheme 2).

The water-soluble dendritic tren ligand **9** (**G′2**) containing 27 triethylene glycol termini was synthesized according to Scheme 3 by a 'click' reaction between the tren derivative **8** functionalized with 9 azido termini and the propargyl-functionalized dendron **7** containing three triethylene glycol termini.

Finally, the Cu(I) catalysts **2**, **3** (Scheme 2) and **5** (Figure 1) were prepared by heating CuBr with these dendritic tren ligands **G1**, **G2** and **G′2** in freshly distilled dioxane at 60 °C overnight. These ligands and the metallodendritic catalysts **2**, **3** and **5** were characterized by ^1H and ^{13}C NMR, UV-vis. spectroscopy and elemental analysis, and the sizes of the ligands were determined by DOSY NMR (1.92 nm for **G1**) and dynamic light scattering (4.1 nm for **G2**). As it is often the case for relatively large dendrimers, the elemental analyses show slightly lower found values, due to the encapsulation of residual water and inorganic salts.



Scheme 3. Synthesis of the **G′2** dendron **9**.

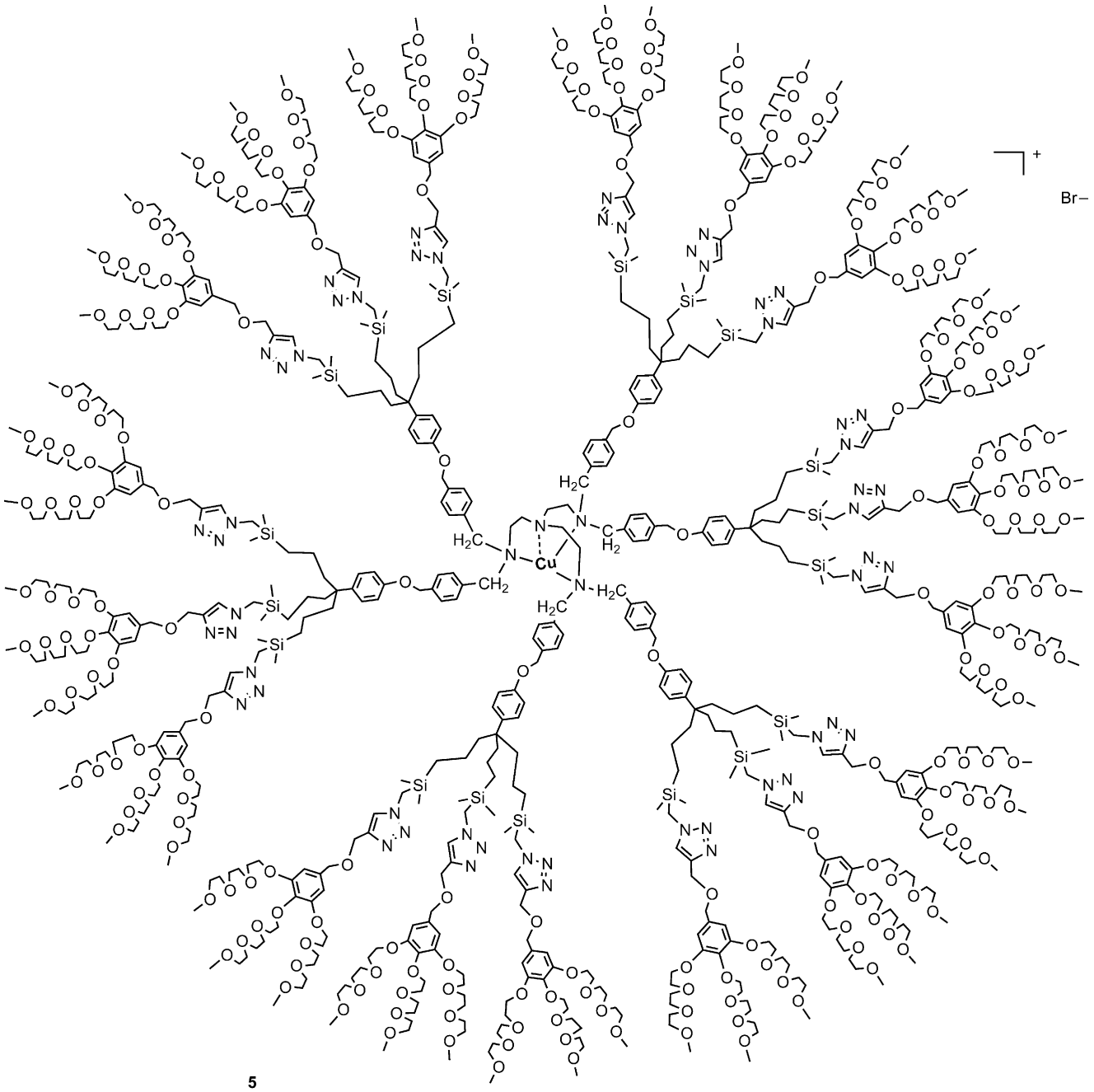


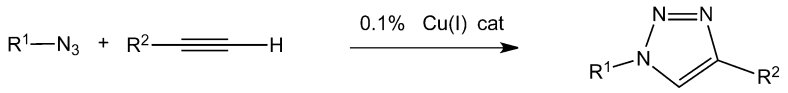
Figure 1. Structure of the water-soluble dendritic Cu(I) catalyst **5** (from the **G′2** dendron **9**+CuBr; see Scheme 3 for the synthesis of the **G′2** dendron **9**).

This trend is more marked, however, for the dendrimer **5** terminated by triethylene glycol termini.

Catalysis of the Click Reaction in Toluene by the Cu(I) Complexes 1–4

The CuAAC reactions between various terminal alkynes and azides catalyzed by the dendritic catalysts **1**–**4** proceed quantitatively or in high yields using only 0.1% catalyst under various conditions. Internal alkynes are completely unreactive. In Table 1, the yields with the new Cu(I) catalysts are compared to those obtained in the present study using the known catalyst [Cu(I)tren($C_{18}H_{37}$)$_6$][Br], **4** under the same conditions and with those obtained in the absence of catalyst. The yields recorded at 0.1% mol catalyst per mol substrate allow a differentiation of the efficiencies of the various catalysts with various substrates and reaction conditions. All the reactions of Table 1 were also carried out using 1% mol of catalyst **1** at 22 °C, and these reactions were quantitative or nearly

Table 1. Compared yields and selectivities of CuAAC reactions catalyzed by 0.1 mol% equiv. dendritic and non-dendritic complexes Cu(I)(tren)Br and without catalyst.



N°	R^1	R^2	s	T [°C]	t [h]	Cat. **1**[a] Product [%][b]			Cat. **2**[a] Product [%][b]			Cat. **3**[a] Product [%][b]			Cat. **4**[a] Product [%][b]			No catalyst[a] Product [%][b]		
						M	*S*	*T*	*M*	*S*	*T*	*M*	*S*	*T*	*M*	*S*	*T*	*M*	*S*	*T*
1	Bn	Ph	t	60	24	100	0	100	99	1	100	100	0	100	83	0	83	28	3	31
2	Bn	Ph	t	22	24	100[c]	0	100	100	0	100	81	0	81	71	0	71	0.4	0.2	0.6
3	Bn	Ph	n	60	14	100	0	100	99	1	100	100	0	100	100	0	100	7	3	10
4	Bn	Ph	n	22	24	100	0	100	100	0	100	95	0	95	85	0	85	1	1	2
5	Bn	Ph	p	22	48	–	–	–	100	0	100	94	0	94	80	0	80	1	0	1
6	Bn	CO_2Et	t	22	24	99	1	100	91	1	92	92	8	100	38	8	46	13	4	17
7	Bn	*n*-Bu	t	60	24	100	0	100	100	0	100	91	1	92	46	2	48	2	1	3
8	Bn	$SiMe_3$	t	60	24	98[d]	2	100	60	1	61	78	2	80	40	1	41	29	1	30
9	Bn	Fc	t	60	72	93	0	93	100	0	100	99	0	99	100	0	100	0	0	0
10	R^3	CO_2Et	t	60	14	90	10	100	90	10	100	91	9	100	78	22	100	58	21	79
11	R^3	CO_2Et	t	22	24	98	2	100	97	3	100	96	4	100	50	8	58	22	7	29
12	R^3	CH_2OH	t	60	24	97	3	100	98	2	100	98	2	100	93	2	95	13	3	16
13	R^3	R^4	t	60	24	100[d]	0	100	100	0	100	97	0	97	96	0	96	13	0	13
14	R^3	R^5	t	60	72	100[d]	0	100	97	0	97	100	0	100	88	0	88	0	0	0
15	Ad	CO_2Et	t	60	24	99[d]	1	100	85	6	91	93	7	100	72	12	84	41	11	52

[a] 1 mmol of each reactant and 0.1% mmol of the catalysts were used for the click reaction in 1 mL solvent when toluene or pentane was used.

[b] Determined by GC, two runs, ±3%. Isolated yields are 1% to 10% lower. The turnover numbers (TONs) are ten times larger than the yields%.

[c] In the presence of sodium ascorbate (2 equiv *per* mol catalyst).[d] 1% of cat. **1** was used. Cat. **4**: [Cu(I) tren($C_{18}H_{37}$)$_6$][Br].[15] Fc = ferrocenyl. s = solvent, t = toluene, p = pentane, n = neat, M = major product; S = side product (minor 1,5-isomer), T = total product, R^3 = *m*-MeBn; R^4 = *p*-$CH_3OC_6H_4$; R^5 = *p*-$CHOC_6H_4$.

so without formation of the minor triazole isomer. The yields obtained with 0.1% mol catalyst are most of the time significantly higher with the dendritic catalysts than with the non-dendritic catalysts **1** and **4**. In the case of the catalyst **1**, this may eventually be due to its air sensitivity, and these yields could be slightly but significantly increased upon using 0.1% mol sodium ascorbate in order to inhibit catalyst oxidation. This advantage of the dendritic catalysts **2** and **3** over the non-dendritic analogues **1** and **4** is more marked for the reactions carried out at 22 °C than at 60 °C. In some cases, the catalyzed reaction with the **G1** dendritic complex **2** produces better yields than **G2**, **3**, and in some others it is the opposite. Thus it appears that at least at 22 °C the dendritic catalysts are selective for some substrates, although this aspect is leveled off when reactions are carried out at 60 °C and for a sufficient amount of time at 0.1% catalyst *vs.* substrate (TON values equal or close to 1000).

The catalysts **2** and **3** could be recharged with the substrates of entry 1 at least ten times (Table 2), giving high yields of products, which increased the turnover numbers to close to 10^4.

Alternatively, the Cu(I) catalyst could be recycled, even with only 0.1% mol catalyst, by filtration at −18 °C of the toluene-insoluble reaction product and re-used giving a quantitative yield of product upon recycling **1** three times and recycling **2** twice. On the other hand, the result was less successful for **3**, possibly for solubility reasons (Table 3).

Table 2. Recharging of both dendritic catalysts **2** and **3** (PhCCH + BnN_3, 0.1 mol% catalyst, toluene, 60 °C, 24 h).

Recharging run[a]	1	2	3	4	5	6	7	8	9	10
Catalyst **2** (yield [%])[b]	98	98	95	98	99	99	95	96	93	91
Catalyst **3** (yield [%])[b]	99	99	97	98	98	97	89	82	83	84

[a] Recharging the catalyst for the reaction of entry 1, Table 1.

[b] ±3%.

A convenient alternative consists in using a mixture of CuBr + hexabenzyltren in toluene instead of **1**. For instance, using 10% mol of this catalyst yielded 100% yield of the triazole 1,4-isomer in 10 min at room temperature with phenylacetylene and benzyl azide. With 0.1% mol of this amount *vs.* substrates, a quantitative yield was obtained at 22 °C in 24 h including the for-

Table 3. Yields of the CuAAC reactions between PhC≡CH and BnN_3 using 0.1% mol of catalyst **2** and **3**, and 1% mol of catalyst **1** in toluene at 22 °C.

Run[a]	Cat. **1** Product [%]		Cat. **2** Product [%]		Cat. **3** Product [%]	
	M	S	M	S	M	S
1	100	0	100	0	81	0
2	100	0	100	0	41.7	0
3	100	0	91	0	30	0

[a] M = major product; S = side product (minor 1,5-triazole isomer).

mation of only 0.7% of minor isomer (compare entry 2 of Table 1, no trace of minor isomer), whereas the same reaction without ligand (CuBr alone) produced an 18% yield of the major isomer and 1% of the minor 1,5-isomer.

Table 1 also shows the formation of a minute amount of the minor 1,5-triazole isomer, this isomer being formed in larger amounts, as it is known, in the non-catalyzed reactions. In order to investigate the influence of the amount of catalyst not only on the reaction yields, but also on the selectivity, the CuAAC reaction has been carried out using lower amounts of catalysts, and the selectivities and yields are given in Table 4. The reaction giving the largest amount of minor isomer in the catalyzed reaction and the best yield of the non-catalyzed reaction were selected as examples. Table 4 shows that when the amount of catalyst is decreased there is a mixture of the catalyzed and non-catalyzed reactions. This selectivity was recorded in the less favorable case as indicated above, but for instance with PhC≡CH, the yield was quantitative without formation of any trace of the minor isomer with only 0.01% mol catalyst **1** *vs.* substrates in the presence of sodium ascorbate. The effect on the selectivity of the aerobic sensitivity of catalyst **1** is also all the more hazardous as its amount is lower, but the addition of one mol sodium ascorbate *vs.* the catalyst **1** is a good protection against the risk of aerobic oxidation of this catalyst.

Table 4. From catalyzed to non-catalyzed reactions: influence of the variation of the concentration of the catalyst **1** on the selectivity of the reaction between *m*-$MeBnN_3$ and $HCC(CO_2Et)$ at 100% total yield (60 °C).

Mol% of **1** *vs.* substrates	Time [h]	Main product [%]	Minor isomer [%]	Selectivity
1	16	99	1	99
0.1	15	90	10	9
0.01	15	85.6	14.4	5.9
0.001	45	75.6	24.4	3.1
0.0005	48	73.5	26.5	2.8
0.00001	48	71	29	2.4
0	72	69.2	30.8	2.2

It is important to note that at 60 °C the non-catalyzed reaction is efficient when the substituent on the alkyne is electron-withdrawing (CO_2Et), yields being even sometimes close to quantitative (entry 10 of Table 1). The non-catalyzed reaction is not very selective, unlike the catalyzed reaction, but again the selectivity of the non-catalyzed reaction increases upon decreasing the temperature. For instance with R^3 and $R^2 = CO_2Et$ in toluene, the ratio of major isomer/minor isomer is 2.8 with 100% yield at 60 °C but is raised to 3.5 with 77% yield at 22 °C. This non-catalyzed reaction also occurs at 60 °C, but to a lesser extent when the alkyne substituent is phenyl (entry 1 of Table 1) than when it is the electron-withdrawing substituent CO_2Et.

A kinetic study was carried out for the four catalysts **1**–**4** under the conditions of entry 1 of Table 1 (0.1% mol catalyst, 22 °C, PhC≡CH + BnN_3). The plots of the inverse of the concentrations as a function of time (Figure 2) show that the reactions catalyzed by the metallodendritic catalysts **2** and **3** are faster than those carried out using the non-dendritic catalysts **1** and **4**, the fastest reaction being observed with the 54-branch dendrimer **G2** in the case of these substrates. The mixture of CuBr + hexa(benzyl)tren gives a faster kinetics than the isolated catalyst **1** (*vide infra*, Discussion section). The mixture of CuBr + dendron **G1** gives slow kinetics, and it is noticed that CuBr is solubilized much more slowly in toluene with dendron **G1** than with hexa(benzyl)tren.

In these reactions, the yields were quantitative for cat. **2** and high for the other catalysts after 20 h. It was suspected that these uncompleted reactions were

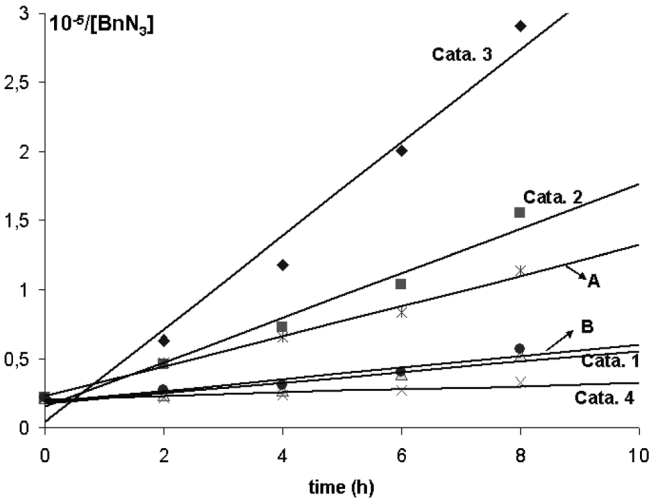


Figure 2. Compared kinetics of the CuAAC reaction between PhCCH and BnN_3 at 22 °C in toluene using with 0.1% catalysts **1**–**4** or CuBr + tren ligand. **A** CuBr + $(benzyl)_6$tren; **B**: CuBr + tren dendron **G1**.

due to aerobic oxidation of the catalysts used in very low amounts. Thus the reaction catalyzed by **1** was also carried out in the presence of two equiv.of sodium ascorbate per mol catalyst. The kinetics was exactly the same in the presence and absence of sodium ascorbate, except that at the end of the reaction, the reaction became quantitative in the presence of sodium ascorbate. In their study, Matyjasewski et al. used hydrazine as an efficient oxidation inhibitor.[14] Here, sodium ascorbate is not soluble in toluene, but is also efficient as an oxidation inhibitor.

Given the ease of preparation of **1**, it was probed as a click catalyst for the synthesis of an 81-branch dendrimer by 1→3 connectivity between a 27-branch azido-terminated dendrimer and a phenol dendron that was propargylated at the focal point. This reaction had previously required a quantitative amount of $CuSO_4$ in the presence of excess sodium ascorbate for completion, and lower amounts were not efficient. It was believed that chelating coordination of Cu ions by the dendritic triazole heterocycles forming tripods inhibited their use as catalyst. Attempts to use the catalyst **4** under various conditions for this reaction also failed, presumably because of steric effects of the alkyl branches of the tren ligand. Indeed, 6% of complex **1** successfully catalyzed the quantitative synthesis of the 81-allyl dendrimer (Scheme 4).

Catalysis of the Click Reaction of Water-Insoluble Substrates on Water by the Water-Soluble Cu(I) Complex 5 without Cosolvent

The CuAAC reaction of water-insoluble substrates was also catalyzed on water under air by 0.1% mol of the water-soluble catalyst **5** at 22 °C (Table 5). Under these conditions, the selectivity was either total or very high. Again, the selectivity results of Table 1 can be improved by simply raising the amount of catalyst used as in Table 1 in toluene. Under the reaction conditions, the catalyst **5** is not air sensitive. Note that the non-catalyzed reaction is also quite efficient on water with several substrates. In some cases such as the reaction between 1-adamantyl azide and ethoxycarbonylacetylene, the non-catalyzed reaction proceeds equally well on water and in the absence of water, whereas the non-catalyzed reaction between benzyl azide and phenylacetylene proceeds much more easily on water than in the absence of water.

The catalyst **5** was easily separated by filtration of the water-insoluble product and re-used twice in 0.1% molar amount *vs.* substrates providing 100% yield and selectivity for the reaction between benzyl azide and phenylacetylene.

Attempts to carry out reactions in a 1/1 THF/H_2O mixture led to results that were worse than on water alone. For comparison, the CuAAC reaction catalyzed by 0.1% $CuSO_4$ + sodium ascorbate was carried out between benzyl azide and phenylacetylene on water under N_2 at 22 °C for 24 h and yielded 5% of triazole product.

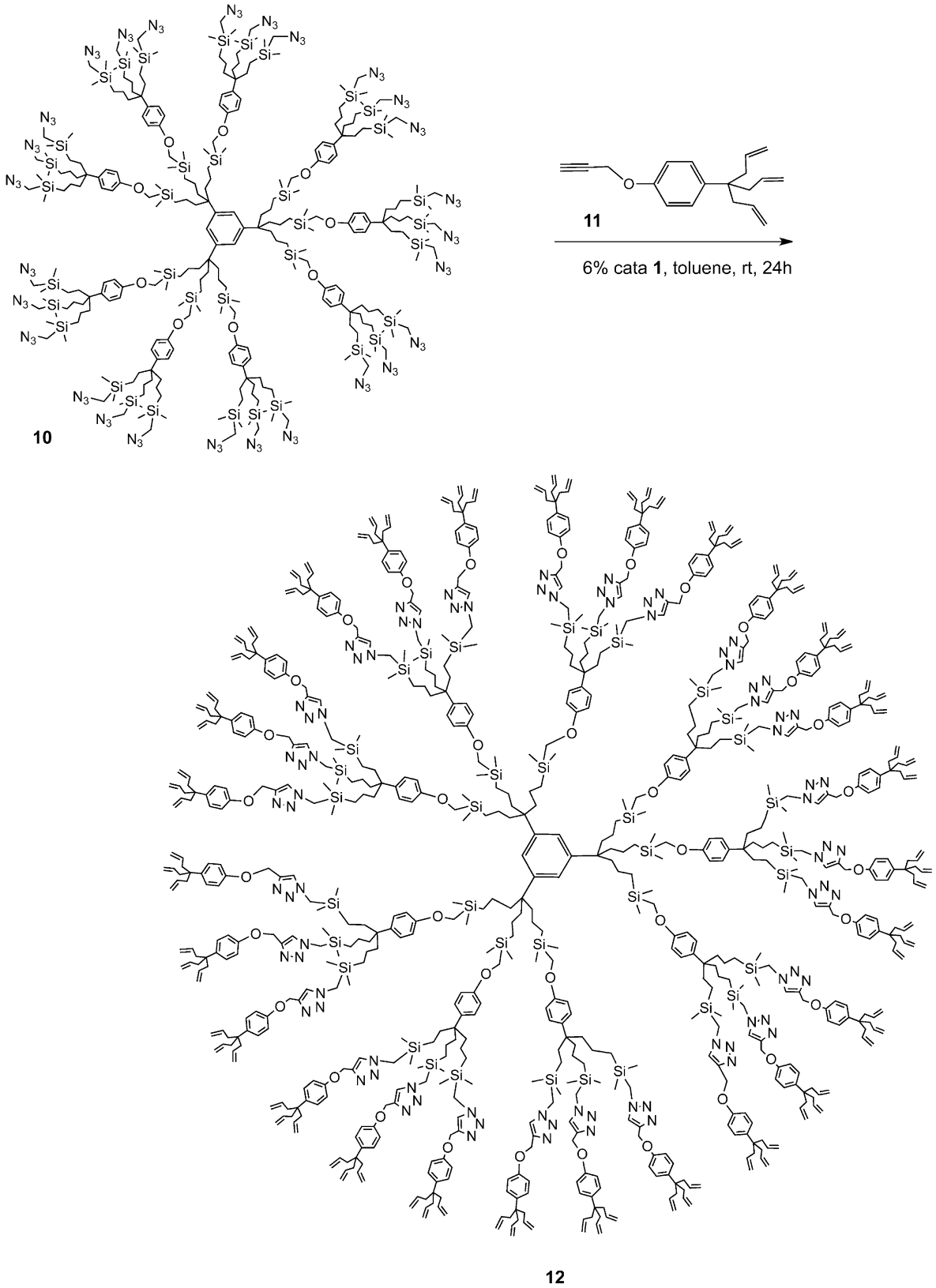
Discussion

The CuAAC reaction has been shown during the last decade to be of considerable use to assemble chemicals and materials,[6–15] but key issues remained concerning pollution of product by copper residues and mechanistic aspects. This work contributes to the group of known valuable Cu catalysts by the synthesis, characterization and study of both a new, very convenient Cu(I) catalyst and of the first dendritic Cu(I) catalysts. It also addresses the "greenness" of the CuAAC process and the mechanistic problem.

The Very Easily Synthesized, Efficient, Convenient, Soluble and Recyclable Catalyst 1

The catalyst **1** is of the Cu(I)(polyamine) catalyst family including [Cu(I)(hexamethyltren)][Br] that has been disclosed by the Matyajeswski group,[14] but the very easily synthesized complex **1** is toluene soluble unlike [Cu(I)(hexamethyltren)][Br], which allows its easy separation from the triazole products by filtration. It is important to remove the copper catalyst from the triazole product for both toxicity and recycling reasons. Thus, it has been possible to show its re-use. Although **1** is somewhat air sensitive, it has been demonstrated that it could be used here in very low amounts such as 0.1 mol% *vs.* substrates and even recycled or recharged with substrates under nitrogen ten times even in the absence of an oxidation inhibitor. In this way, turnover numbers of the order of 10^4 were obtained. For a more comfortable use, it is also possible to add sodium ascorbate as the oxidation inhibitor. The latter does not change the mechanism as shown by superposition of the kinetic diagrams, but the reaction yields can be improved if the amount of catalyst is very low, and maximum selectivity is then guaranteed. Another caution in using catalytic amounts lower than 0.1 mol% amount *vs.* substrate concerns the selectivity that decreases at too low catalyst concentrations because of the mixture between the catalyzed and non-catalyzed reactions for which data have also been searched here and reported in the tables for comparisons.

Compared to the very practical Fokin–Sharpless catalyst $CuSO_4$ + sodium ascorbate,[6] the catalyst **1** not only provides ligand acceleration of the reaction, but much more importantly, it protect the Cu(I) catalyst against coordination by the 1,2,3-triazole heterocycles that are formed in these click reactions. In



Scheme 4. Synthesis of the 81-branch dendrimer **12** using catalytic amounts of **1**.

simple cases, this coordination does not inhibit catalysis, because it is reversible, that is, weak enough. In some nanomaterial click syntheses, the problem becomes crucial, however, to such an extent that the use of the $CuSO_4$/sodium ascorbate catalyst no longer works in catalytic amounts but must be used stoichio-

Table 5. CuAAC reactions catalyzed by **5** in water without co-solvent.

No.	R^{1}[a]	R^{2}[a]	T [°C]	t [h]	Yields[b] with cat. **5,** in water			Yields[b] without catalyst, on water			Yields[b] without catalyst, neat		
					M	S	T	M	S	T	M	S	T
1	Bn	Ph	22	24	100	0	100	1	2	3	0.5	0.6	1.1
2	Bn	Ph	60	24	100	0	100	82	16	98	6.8	3.2	10
4	Bn	*n*-Bu	22	24	99	1	100	2	0	2	1.7	0	1.7
5	Bn	$SiMe_3$	60	24	91	0	91	25	1	26	37	2	39
6	Bn	$SiMe_3$	22	48	78	0	78	22	1	23	10	0	10
7	Bn	Fc	22	72	99	0	99	0	0	0	0	0	0
8	R^3	CH_2OH	22	24	97	3	100	0	0	0	0	0	0
9	R^3	R^4	22	24	96	0	96	34	0	34	4	0	4
10	R^3	R^5	22	72	100	0	100	8	0	8	0	0	0
11	Ad	CO_2Et	22	24	96	2	98	56	6	62	66	6	72

[a] R^1 and R^2 are defined in the CuAAC equation of Table 1. 1 mmol of each reactant and 0.1% mmol of the catalyst **5** were used for the click reaction in 1 mL H_2O.

[b] Determined by GC, two runs, ±3%. Isolated yields are 1% to 10% lower. The turnover numbers (TONs) are ten times larger than the yields%. M = major isomer, S = minor 1,5-triazole isomer, T = total product. Fc = ferrocenyl. R^3 = *m*-MeBn; R^4 = *p*-$CH_3OC_6H_4$; R^5 = *p*-$CHOC_6H_4$.

metrically. This is what we have experimented in the recent past with both click dendrimer synthesis[18] and gold nanoparticle click fonctionalization.[19] The problem is related to the fact that Cu(I) is only weakly liganded by the solvent and/or ascorbate. These very weak ligands are displaced by stronger chelating triazole ligands that bind the copper ions in chelating dendritic branches more strongly than monodentate triazoles.[18] Similar effects and/or aggregation with the metal core in gold nanoparticle syntheses also provoke the need of stoichiometric amounts of $CuSO_4$ + sodium ascorbate "catalyst".[19] In both areas, medicinal applications of the click reaction have enormous potential, and thus the use of stoichiometric amounts of Cu "catalyst" is prohibited.

Catalyst **1** is possibly not as efficient as the Cu(I)[tris(triazolylmethyl)amine] and related catalysts of the Script's group,[12,13,17], but its efficiency is excellent as exemplified by its use in low amount (0.1%) in standard reactions and successful use in the synthesis of an 81-branch dendrimer whereas the use of $CuSO_4$ + sodium ascorbate was previously required in stoichiometric amounts. Thus **1** is far from unique, but its solubility, recyclability, efficiency and simplicity of synthesis are remarkable, and we have been able to show here its efficient specific use. Finally, an even simpler use involves the addition of CuBr and hexabenzyltren in catalytic amounts providing a catalytic system in toluene that is very efficient. The latter alternative is all the more useful as there is no need to store the catalyst away from air, because neither CuBr nor the ligand is air sensitive.

Metalloenzyme Mimic by Cu(I)-Centered Metallodendrimers: The Positive Dendritic Effect

It is remarkable that the kinetics is faster for some substrates with the bulky dendritic catalysts **2** and **3** than with the related non-dendritic parent analogue **1** as shown here upon comparing the reaction rates of the Cu(I)(tren) catalysts **1**–**4**. This property is reminiscent of metalloenzyme caytalysis.[4] Supramolecular metal-substrate arrangements and forces are responsible for this trend. It is probable that orientation of substrates in key rate-limiting (transition) states are rendered more favorable at the metallodendritic center due to conformational and steric effects within the dendrimer interior.[16] This property has very rarely been disclosed in metallodendrimer chemistry,[22] because the dendritic steric bulk usually considerably slows down the reaction kinetics, and dendrimer chemists prefer to load their catalysts at the dendrimer periphery for dendritic recycling.[16] Here, not only is the kinetics faster with the **G1** dendrimer **2** than with the parent catalyst **1**, but also the **G2** dendrimer **3** provides a faster reaction than the **G1** dendrimer **2**, that is, the dendritic effect is continuously positive. In addition, the dendritic Cu(I) catalysts **2** and **3** are much more air stable than **1**. Obviously, only a few substrates can serendipitously be observed to show faster kinetics in this catalytic metallodendrimer series compared to the parent catalyst **1**, because steric effects of larger substrates facing dendritic bulk around the Cu(I) center rapidly dominate the reaction kinetics. An extreme case is the click reaction in the dendritic branches for the construction of the 81-branched dendrimer that can only be catalyzed by a small non-dendritic catalyst such as **1**, whereas

larger catalysts of the same Cu(I)(tren) family such as **4** have failed to catalyze this latter reaction.

Catalysis in Water by the Recyclable Water-Soluble, Air-Stable Dendritic Catalyst 5

CuAAC catalysis in water without co-solvent of the water-soluble air-stable dendritic catalyst **5** in 0.1 mol% amount *vs.* substrate can be followed by easy recovery of the catalyst by filtration of the water suspension of the product, then re-use of the catalyst. Thus, only very minute amounts of a robust Cu complex are engaged in the reaction, and this catalyst is easily removed and re-used. The stability in air, use in water only at 22 °C (ambient, biocompatible conditions), recyclability, and very small quantity of copper used and recovered are fine advantages in the context of green chemistry.

Reactions "on" water are well documented in the literature, and a recent excellent review is available.[23] In the present case, the dendrimer works in the fashion of a molecular micelle, a concept developed by Newkome.[21a,24] The hydrophobic substrates are stabilized inside the hydrophobic dendrimer interior where they can meet at the dendritic Cu(I) center for catalytic formation of the products. There is an equilibrium between the insoluble substrates and the dendrimer-encapsulated substrates, and this equilibrium is displaced by the "click" reaction towards the product formation. Such an example has recently been demonstrated for olefin metathesis whereby the molecular catalyst, that is not attached to the dendrimer, is also hydrophobic.[25] In a different approach, catalysis in water of the CuAAC reaction between the water-soluble substrates azidopropanol and propargyl alcohol using 8% Cu per substrates has very recently been shown to proceed with >95% conversion in 1–3 h using Cu(I)/Cu(0) loaded in polyamidoamine (PAMAM) dendrimers PAMAM-OH and PAMAM-NH_2 with Cu:ligand ratios of 1:1 and 30:1, respectively.[26] More generally, several Cu catalysts have recently been reported in the context of "green chemistry".[27]

Efficient Metallodendritic Catalysts: Evidence for a Monometallic CuAAC Mechanism

It has been well emphasized that oligomeric Cu-alkynyl species in fast interconversion between fragments of various nuclearities are involved in the CuAAC catalysis by the very efficient Cu(I) catalysts containing a ligand of the tris(triazolylmethyl)amine (TBTA) family.[13] Among these species, alkynyl-bridged bis(copper) species were believed to be key species undergoing the attack by the azide. Detailed and in-depth kinetic studies by the groups of Finn and of Fokin have shown the mechanistic complexity of this reaction, and in particular it has been suggested that several mechanisms with close energies of transition states could be involved.[13] In the present study, the polydentate dendritic polyamine ligands isolate the Cu(I) center, and the large bulk around the metal center inhibits the approach of a second copper atom. Consequently, there is no room here for an alkynyl-bridged intermediate or transition state. One might argue that a very small amount of copper could escape from the coordination sphere of the ligand, but CuBr is not soluble, and is a very poor catalyst under the reaction conditions, as we have checked. There is also obviously too much bulk to allow two dendritic Cu(I)tren complexes to approach each other and share a bridging alkynyl and a polyamine ligand such as in the key species suggested by Fokin and Finn.[13] Another argument is the positive dendritic effect on the catalysis kinetics, the rate acceleration by the tren ligand being all the greater, as the dendrimer is larger, whereas the approach of any other Cu species is rendered more difficult because of the increased steric effect of the dendrimer. Thus, it appears that no bimetallic catalyst, but only a monometallic Cu(I)(tren) center, is responsible for catalysis in the series of Cu(I)(tren) catalysts **1**–**5** examined here. This view is not conflicting with the mechanism proposed for the Cu(I)-TBTA catalysis in non-dendritic complexes, because it is probable that the nuclearity of the CuAAC catalysis depends on the structure of the catalyst and reaction conditions. Indeed, an intriguing point in this respect is the different kinetics observed for CuBr + hexabenzyltren compared to the preformed catalyst **1**. The faster rate observed with CuBr + hexabenzyltren could be due to the occurrence of the Fokin–Finn bimetallic mechanism, because in the presence of both tren and the alkyne, the competition of complexation could lead to direct formation of the Cu(I)-acetylide oligomers before complexation of tren, so that the species $Cu(I)_2$-σ,μ-alkynyl(tren) of Figure 3, analogous to the proposition of Finn and Fokin, could be the key active species with bimetallic tren coordination. This species has been proposed by Finn and Fokin to better acti-

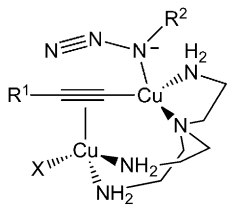
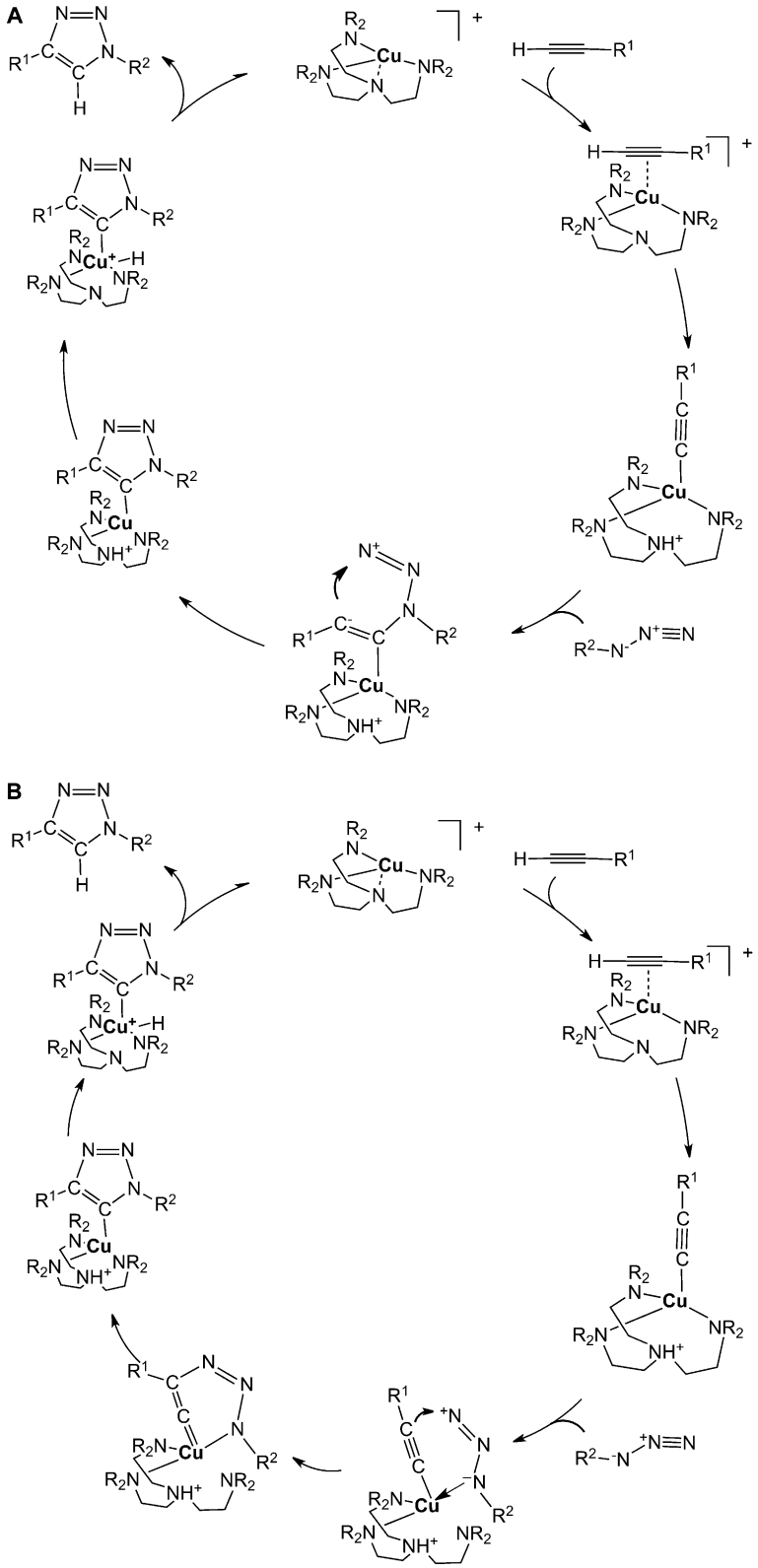


Figure 3. Key catalytically active bimetallic species proposed by Finn and Fokin[13] for the CuAAC reaction (extended here to tren).



Scheme 5. Proposed mechanisms for the CuAAC reaction catalyzed by the Cu(I)(tren) catalysts **1**–**5.** **A**: Azide attack on the α alkynyl carbon. **B**: Azide attack on the metal (Fokin–Finn-type mechanism adapted to tren).[13]

vate the alkyne towards azide attack, and the faster reaction observed under the present CuBr + ligand conditions could be taken into account by such a bimetallic activation that is inhibited in the cases of the pre-formed Cu(I)-tren catalysts.

The [Cu(I)(tren)][Br] catalysts can have either a 16-electron or an 18-electron configuration depending on whether three or four tren nitrogen atoms are coordinated to the Cu(I) center, that is, there could be a doubt concerning the coordination of the apical nitrogen. However, Matyajeswski's group has shown that the tridentate nitrogen ligands provided a significantly faster kinetics than the tetradentate ligands such as tren. Since it is well recognized that the first step is π coordination of the alkyne onto Cu(I),[7] this step must involve a rate-limiting ligand substitution of the apical nitrogen ligand of tren by the π-alkyne ligand, because otherwise an improbable high-energy 20-electron configuration would need to be reached by Cu(I). The acidity of the π-alkyne is enhanced by the coordination to Cu(I), and the free apical nitrogen then becomes a good base for deprotonation of the π-alkyne ligand to give the neutral 18-electron σ-alkynyl-Cu(I) intermediate. DFT calculations had shown that the acidity of the alkyne was, as expected, considerably enhanced (lowering of the pK_a by 9.8 units) by π-coordination to the cationic Cu(I) center.[28] In such σ-alkynyl complexes, the σ-alkynyl polarization brings a small fractional positive charge on the α carbon atom, and a LUMO of this ligand is polarized on the α carbon atom. Therefore, this situation is favorable for a direct azide attack onto this α carbon atom (Scheme 5, **A**). Upon approaching the α carbon atom of the alkynyl ligand, the negatively charged nitrogen atom of the azide can favorably polarize the π electronic cloud of the triple bound before N–C bond formation. It has been proposed that the azide attacks a Cu(I) center before its migration to the α carbon atom, and this possibility is also alternatively adequate (Scheme 5, **B**).[7]

It does not appear as mechanistically indispensable, however, partly because the azide would then have to displace another nitrogen ligand in the 18-electron Cu(I)-σ-alkynyl species (which is also eventually feasible) and partly because nucleophilic attacks on the α carbon atoms of ligands are widespread in organometallic chemistry.[29,30] This polarization of the σ-alkynyl ligand and disymmetrization of the alkyne explains the regioselectivity for the formation of the 1,4-triazole isomer. A bimetallic mechanism proposed earlier in which the alkynyl ligand binds one Cu(I) center and the azide the other one[31] cannot occur either here at the bulky Cu(I)-center of metallodendrimers for the reason stated above. The remaining known steps of the mechanism[13] are metal-heterocycle formation followed by protonation of the Cu(I) center by the nearby ammonium center of the salt [trenH][Br] to give the Cu(III) cationic copper-hydride intermediate and reductive elimination of the triazole from the cationic $[Cu(III)(triazolyl)(H)]^+$ species (Scheme 5).

Conclusions

The new CuAAC catalyst [Cu(hexabenzyl)tren[[Br] (**1**) is very easy to synthesize, toluene soluble, efficient, easy to separate from products and recyclable even if it is used in only 0.1 mol% amount *vs.* substrates. TONs of the order of 10^4 can be reached upon recharching substrates. Below this molar amount per substrate, some substrates lead to traces of the minor 1,5-triazole isomer due to a small amount of non-catalyzed reaction. The presence of sodium ascorbate eventually optimizes the CuAAC reaction by preventing aerobic oxidation. The catalyst **1** is impressively convenient for the click synthesis of nanomaterials such as large dendrimers that previously required the use of stoichiometric amount of $CuSO_4$ and sodium ascorbate or could not be synthesized using large molecular catalysts such as $[Cu(C_{18}H_{37})_6tren]Br$ (**4**).

Another very convenient alternative is the use of CuBr + (hexabenzyl)tren in toluene that, remarkably, proceeds with faster kinetics than the preformed catalyst **1** (100% yield in 10 min with 0.1 equiv. catalyst for the reaction of phenylacetylene with benzyl azide), probably due to a bimetallic mechanism related to that proposed by Finn and Fokin.[13]

The catalyst **1** serves as a model for the construction of the robust Cu(I)-centered dendrimers **2** and **3** in which aerobic Cu(I) oxidation to μ-oxo-bridged dicopper species is sterically prevented. These metallodendrimers catalyze the CuAAC reaction between azidomethylbenzene and phenylacetylene more rapidly than the non-dendritic complexes **1** or **4** with a positive dendritic effect recalling enzymatic catalysis. The water-soluble Cu(I) dendritic complex **5** catalyzes the click reaction of water-insoluble substrates at 0.1 mol% per mol substrate at 22 °C on water in air, and is recyclable with quantitative yield even at such a low catalyst concentration. The robustness of these Cu(I) catalysts compared to the very poor catalytic activity of CuBr under the same conditions together with the above data show that a monometallic mechanism proceeds in the case of the dendritic or star Cu(I)(tren) catalysts **2**–**5**.

Experimental Section

General data

See the Supporting Information.

Synthesis of the Ligand (Benzyl)$_6$tren

A suspension of bromomethylbenzene (1.5 g, 8.8 mmol), tris(2-aminoethyl)amine (0.18 g, 1.3 mmol) and K_2CO_3 (1.9 g, 13.8 mmol) was refluxed in CH_3CN under N_2. After 48 h, the mixture was cooled in an ice bath, the solid residue was washed with acetonitrile, water, and MeOH and then

dissolved in hot toluene. The toluene phase was washed with brine, dried over Na_2SO_4, the solvent was removed under vacuum, and the resulting solid was precipitated in methanol giving (benzyl)$_6$tren as a light-yellow gel; yield: 0.84 g (97.7%). ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.34$ (30 H, C*H*, arom.), 3.50 (12 H, NCH_2Cq), 2.46, (12 H, NCH_2CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 138.7$ (NCH$_2$*C*q), 127.7, 127.0, 125.7 (*C*H arom.), 57.7 (N*C*H$_2$Cq), 51.9 (N*C*H$_2$CH$_2$N*), 50.3 (NCH$_2$*C*H$_2$N*); anal. calcd. for $C_{48}H_{54}N_4$: C 83.92, H 7.92; found: C 83.64, H 7.96; MS (MALDI-TOF): $m/z = 687.5$, calcd. for $C_{48}H_{54}N_4$: 686.2.

Synthesis of the Ligand G1

A suspension of **14** (0.55 g, 1.34 mmol), tris(2-aminoethyl)-amine (28 mg, 0.19 mmol) and K_2CO_3 (0.29 g, 2.1 mmol) was refluxed in CH_3CN under N_2. After 48 h, the mixture was cooled in an ice bath, the solid residue was washed with acetonitrile, water, and MeOH and then dissolved in hot toluene. The toluene phase was washed with brine, dried over Na_2SO_4, the solvent was removed under vacuum, and the resulting solid was precipitated in methanol giving the ligand **G1** as a colorless solid; yield: 0.3 g (75%). ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.42$ (24 H, C*H*, arom.), 7.32 and 7.02 (24 H, C*H* arom.), 5.64 (18 H, CH$_2$C*H*=CH$_2$), 5.1 (48 H, CH$_2$CH=CH_2 and CH_2O), 3.56 (12 H, CH_2Cq), 2.52, 2.43 (48 H, NCH_2CH_2N and CH_2CH=CH$_2$); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 156.9$ (*C*qO), 139.7 (*C*qCH$_2$O), 138.0 (*C*qC*), 135.8 (NCH$_2$*C*q), 134.7 (CH$_2$*C*H=CH$_2$), 129.0, 127.8 (*C*H arom.), 117.7 (CH$_2$CH=*C*H$_2$), 114.3 (*C*H arom.), 69.9 (*C*H$_2$O-Cq), 58.6 (N*C*H$_2$Cq), 53.2 (N*C*H$_2$CH$_2$N*), 51.6 (NCH$_2$*C*H$_2$N*), 42.8 (*C*H$_2$CH=CH$_2$), 42.1 (benzylic quaternary C of the core); MS (MALDI-TOF): $m/z = 2129$, calcd. for $C_{150}H_{174}O_6N_4$: 2126; anal. calcd. for $C_{150}H_{174}O_6N_4$: C 84.67, H 8.18; found: C 84.24, H 8.14; DOSY: diffusion coefficient $D = KBT/6\pi\eta r_H$, $D = 1.96\ (\pm 0.1) \times 10^{-10}$ m^2/s, $r_H = 1.92\ (\pm 0.1)$ nm.

Synthesis of the Ligand G2

A suspension of **16** (see the Supporting Information) (0.58 g, 0.44 mmol), tris(2-aminoethyl)amine (9.2 mg, 0.063 mmol) and K_2CO_3 (96 mg, 0.70 mmol) was refluxed in CH_3CN under N_2. After 48 h, the mixture was cooled in an ice bath, the solid residue was washed with acetonitrile, water, and MeOH and then dissolved in hot toluene. The toluene phase was washed with brine, dried over Na_2SO_4, the solvent was removed under vacuum, and the resulting solid was precipitated in methanol giving the ligand **G2** as a colorless solid; yield: 0.27 g (57.4%). ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.39$, 7.23, 6.92 (120 H, C*H*, arom.), 5.57 (54 H, CH$_2$C*H*=CH$_2$), 5.03 (120 H, CH$_2$CH=CH_2 and Cq-CH_2O), 3.53 (48 H, NCH_2Cq and Si(CH$_3$)$_2$CH_2O), 2.45, (120 H, NCH_2CH_2N and CH_2CH=CH$_2$), 1.68 (36 H, C*CH_2CH$_2$CH$_2$), 1.19 (36 H, C*CH$_2$CH_2CH$_2$), 0.63 (36 H, C*CH$_2$CH$_2$CH_2), 0.08 [108 H, Si(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 159.5$ [Si(CH$_3$)$_2$CH$_2$O-*C*q], 156.5 (CqCH$_2$O*C*q), 137.3 (*C*qCH$_2$O, *C*qC*), 134.8 (NCH$_2$*C*q, CH$_2$*C*H=CH$_2$), 127.5 (*C*H arom. of Cq), 117.5 (CH$_2$CH=*C*H$_2$), 113.6 (*C*H arom. of Cq), 69.9 (Cq-*C*H$_2$O-Cq), 60.2 [NCH$_2$Cq and Si(CH$_3$)$_2$*C*H$_2$O], 53.2 (N*C*H$_2$CH$_2$N*), 51.8 (NCH$_2$*C*H$_2$N*), 43.2 (C**C*H$_2$CH$_2$CH$_2$), 42.7 (*C*H$_2$CH=CH$_2$), 42.1 (benzylic quaternary of the core), 17.8 (C*CH$_2$*C*H$_2$CH$_2$), 14.7 (C*CH$_2$CH$_2$*C*H$_2$), −4.5 [Si(*C*H$_3$)$_2$]; anal. calcd. for $C_{492}H_{678}O_{24}N_4Si_{18}$: C 78.45, H 9.01; found: C 76.44, H 9.11; DLS: r = 4.1 nm (PDI = 0.34).

Synthesis of the Ligand G′2

The dendron **8** (210 mg, 5×10^{-5} mol, 1 equiv.) and the dendron **7** (683 mg, 1.08×10^{-3} mol, 20 equiv.) were dissolved in 5 mL toluene, then the catalyst **1** (9 mg, 1.08×10^{-5} mol, 0.2 equiv., 1 mol%) was added. The light brown solution was stirred for 24 h at 22 °C under nitrogen. After removing toluene under vacuum, the mixture was washed several times with dried diethyl ether to remove the excess of dendron **7**, then precipitated in toluene giving the ligand **G′2** as a yellow-brown gel; yield: 0.63 g (51.6%). The infrared spectrum shows the disappearance of the band at 2098 cm^{-1} that is characteristic of the azide function and of the band at 2112 cm^{-1} for the terminal alkyne group. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.42$ (18 H, C*H* of triazole), 7.35 (24 H, C*H* of intern. arom), 7.14, 6.9 (24 H, C*H* of middle arom.), 6.57 (36 H, C*H* of extern. arom.), 4.93 (12 H, CH_2O-arom), 4.63 (36 H, triazole-CH_2), 4.46 (36 H, O-CH_2-arom), 4.13 (144 H, arom-OCH_2 and Si-CH_2-N), 3.83–3.54 (552 H, OCH_2CH_2O and NCH_2-arom), 3.35 (162 H, OCH_3), 2.52 (12 H, NCH_2CH_2N), 1.6 (36 H, CH_2CH$_2$CH$_2$Si), 1.06 (36 H, CH$_2$CH_2CH$_2$Si), 0.59 (36 H, CH$_2$CH$_2$CH_2Si), 0.04 [108 H, Si(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 156.4$ (*C*qO middle), 152.5 (*C*qO extern.), 144.6 (*C*q of triazole), 139.3 (*C*qCH$_2$O intern and *C*q of middle arom), 137.7 (OCH$_2$*C*q extern), 135.6 (NCH$_2$*C*q), 133.3 (O*C*H$_2$Cq extern), 128.9, 127.3 (*C*H of intern. arom), 127.6, 114 (*C*H middle arom), 123.4 (*C*H of triazole), 107.2 (*C*H of arom extern), 71.8–69.6 (OCH_2CH_2O), 68.7 (CH_2O-arom), 63.5 (triazole-CH_2O), 58.9 (NCH_2Cq and OCH_3), 53.6 (NCH_2CH_2N), 43 (CH_2CH$_2$CH$_2$Si), 41.6 (*C*qCH$_2$CH$_2$CH$_2$Si), 40.9 (SiCH_2N), 17.3 (CH$_2$CH_2CH$_2$Si), 14.7 (CH$_2$CH$_2$CH_2Si), −4.03 [Si(CH_3)$_2$]; anal. calcd. for $C_{762}H_{1272}O_{240}N_{58}Si_{18}$: C 58.7, H 8.22; found: C 58.19, H 7.87.

General Procedure for the Synthesis of the Cu(I)(tren) Catalysts[15]

The complex CuBr/ligand tris(2-aminoethyl)amine (tren) was prepared by using a slight excess (1.1/1) of CuBr and the tren ligand in freshly distilled 1,4-dioxane at 60 °C overnight. Then, the solution was filtered under nitrogen to remove the excess of CuBr. After removing the solvent under vacuum, the product (off-white gel) was kept under nitrogen.

Catalyst 1: ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.31$ (30 H, C*H*, arom.), 3.49 (12 H, NCH_2Cq), 2.47, 2.23 (12 H, NCH_2CH_2N); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 137.9$ (NCH$_2$*C*q), 127.7, 127.0, 125.7 (*C*H arom.), 59.5 (N*C*H$_2$Cq), 52.8 (N*C*H$_2$CH$_2$N*), 49.4 (NCH$_2$*C*H$_2$N*); anal. calcd. for $C_{48}H_{54}N_4CuBr$: C 69.57, H 6.52; found: C 68.71, H 6.52; MS (MALDI TOF): $m/z = 830$, calcd. for $C_{48}H_{54}N_4CuBr$: 829. The cyclic voltammogram (see the Supporting Information) shows an electrochemically irreversible oxidation wave at $E_{pa} = 1.10$ V *vs.* $[Co(C_5H_5)_2]^{+/0}$ reference using $[Co(C_5H_5)_2][PF_6]$[32] as the internal reference and $[n\text{-}Bu_4N][PF_6]$ 0.1 M as the supporting electrolyte in CH_2Cl_2 on Pt. The E_{pa} value is 0.30 V *vs.* $[Fe(C_5Me_5)_2]^{+/0}$,[32] $\Delta Ep = 0.40$ V, partial chemical reversibility ($i_c/i_a = 0.5$ at the scan rate of 0.1 V s^{-1}). For in-

terconversion of the metallocene reference potentials, see ref.[32] UV-vis.: $c = 0.0004$ mol/L in CH_2Cl_2, $\lambda = 316$ nm, $\varepsilon = 2690$ L. mol^{-1} cm^{-1} for cat.**1** (see Figure 2 in the Supporting Information).

Catalyst 2: ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.34$ (24H, C*H*, armo.), 7.21 and 6.94 (24H, C*H* arom.), 5.57 (18H, CH_2CH=CH_2), 5.0 (48H, CH_2CH=CH_2 and CH_2O), 3.49 (12H, CH_2Cq), 2.44, 2.42 (48H, NCH_2CH_2N and CH_2CH=CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 155.7$ (*C*qO), 138.8 (*C*qCH$_2$O), 136.9 (*C*qC*), 135.4 (NCH$_2$*C*q), 133.2 (CH$_2$*C*H=CH$_2$), 128.7, 126.8 (*C*H arom. of Cq), 116.2 (CH$_2$CH=*C*H$_2$), 113.1 (*C*H arom. of Cq), 68.5 (*C*H$_2$O-Cq), 58.1 (N*C*H$_2$Cq), 52.1 (N*C*H$_2$CH$_2$N*), 51.1 (NCH$_2$*C*H$_2$N*), 41.7 (*C*H$_2$CH=CH$_2$), 41.0 (benzylic quaternary of the core); UV-vis.: $\lambda = 262$ nm, $\varepsilon = 2003$ L mol^{-1} cm^{-1}; anal. calcd. for $C_{150}H_{174}O_6N_4CuBr$: C 79.37, H 7.67; found: C 78.53, H 7.59; DOSY: $D = KBT/6\pi\eta r_H$, $D = 5.81$ $(\pm 0.1) \times 10^{-10}$ m^2/s, $r_H = 0.65$ (± 0.01) nm.

Catalyst 3: ^{1}H NMR ($CDCl_3$, 250 MHz): $\delta = 7.41$, 7.20, 6.92 (120H, C*H*, armo.), 5.57 (54H, CH$_2$C*H*=CH$_2$), 5.0 (120H, CH$_2$CH=CH_2 and Cq-CH_2O), 3.54 (48H, NCH_2Cq and Si(CH$_3$)$_2$CH_2O), 2.43, (120H, NCH_2CH_2N and CH_2CH=CH$_2$), 1.68 (36H, C*CH_2CH$_2$CH$_2$), 1.22 (36H, C*CH$_2$CH_2CH$_2$), 0.64 (36H, C*CH$_2$CH$_2$CH_2), 0.09 [108H, Si(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 159.3$ [Si(CH$_3$)$_2$CH$_2$O-*C*q], 156.4 (CqCH$_2$O*C*q), 137.1 (*C*qCH$_2$O, *C*qC*), 134.5 (NCH$_2$*C*q, CH$_2$*C*H=CH$_2$), 127.3 (*C*H arom. of Cq), 117.2 (CH$_2$CH=*C*H$_2$), 113.5 (*C*H arom. of Cq), 60.0 [N*C*H$_2$Cq and Si(CH$_3$)$_2$*C*H$_2$O], 43.1 (C**C*H$_2$CH$_2$CH$_2$), 42.6 (*C*H$_2$CH=CH$_2$), 41.9 (benzylic quaternary of the core), 17.6 (C*CH$_2$*C*H$_2$CH$_2$), 14.5 (C*CH$_2$CH$_2$*C*H$_2$), −4.6 [Si(*C*H$_3$)$_2$]; UV-vis.: $\lambda = 275$ nm, $\varepsilon = 2648$ L mol^{-1} cm^{-1}; anal. calcd. for $C_{492}H_{678}O_{24}N_4Si_{18}CuBr$: C 76.99, H 8.84; found: C 76.10, H 8.92.

Catalyst 5: ^{1}H NMR ($CDCl_3$, 600 MHz): $\delta = 7.32$, 7.06, 6.8 (66H, C*H* of triazole and C*H* of arom intern), 6.5 (36H, C*H* of arom extern.), 4.86 (12H, CH_2O-arom), 4.57, 4.38 (72H, triazole-CH_2 and O-CH_2-arom), 4.04 (144H, arom-OCH_2 and Si-CH_2-N), 3.54 (552H, OCH_2CH_2O and NCH_2-arom), 3.25 (162H, OCH_3), 1.47 (36H, CH_2CH$_2$CH$_2$Si), 0.94 (36H, CH$_2$CH_2CH$_2$Si), 0.47 (36H, CH$_2$CH$_2$CH_2Si), −0.06 [108H, Si(CH_3)$_2$]; ^{13}C NMR ($CDCl_3$, 150 MHz): $\delta = 156.4$ (*C*qO middle), 152.5 (*C*qO extern.), 144.8 (*C*q of triazole), 139.3 (*C*qCH$_2$O intern and *C*q of arom in middle), 137.7 (OCH$_2$*C*q extern), 135.8 (NCH$_2$*C*q), 133.3 (O*C*H$_2$Cq extern), 129.8, 128.8 (*C*H of arom intern), 127.4, 114.1 (*C*H of arom in middle), 123.4 (*C*H of triazole), 107.3 (*C*H of arom extern), 71.8–69.6 (OCH$_2$*C*H$_2$O), 68.7 (*C*H$_2$O-arom), 63.5 (triazole-*C*H$_2$O), 58.9 (N*C*H$_2$Cq and O*C*H$_3$), 43 (*C*H$_2$CH$_2$CH$_2$Si), 41.6 (*C*qCH$_2$CH$_2$CH$_2$Si), 41 (Si*C*H$_2$N), 17.3 (CH$_2$*C*H$_2$CH$_2$Si), 14.6 (CH$_2$CH$_2$*C*H$_2$Si), −4.02 [Si(*C*H$_3$)$_2$]; anal. calcd. for $C_{762}H_{1272}O_{240}N_{58}Si_{18}CuBr$: C 58.16, H 8.15; found : C 53.48, H 7.47, showing the presence of dendrimer-encapsulated water and inorganic salts.

Procedure for the 'Click' Reaction

In a 10-mL Schlenk flask fitted with a stirring bar, the catalyst [Cu(C$_7$H$_7$)$_6$tren]Br (**1**), [Cu(C$_{24}$H$_{27}$O)$_6$tren]Br (**2**), [Cu(C$_{81}$H$_{111}$O$_4$)$_6$tren]Br (**3**), [Cu(C$_{18}$H$_{37}$)$_6$tren]Br (**4**), or [Cu(C$_{126}$H$_{210}$O$_{40}$N$_9$Si$_3$)$_6$tren]Br (**5**) (0.1 mmol% equiv.), the azide (1 mmol) and the alkyne (1.05 mmol) were stirred in freshly distilled toluene or pentane (1 mL) (or neat) or water at 22 °C or at 60 °C under pressure of nitrogen in the sealed Schlenk flask. The reaction was monitored by GC (see Table 1).

Procedure for Recycling the Cu(I) Catalysts

In a 10-mL Schlenk flask fitted with a stirring bar, the catalyst [Cu(C$_{24}$H$_{27}$O)$_6$tren]Br (**2**), [Cu(C$_{81}$H$_{111}$O$_4$)$_6$tren]Br (**3**), or [Cu(C$_{126}$H$_{210}$O$_{40}$N$_9$Si$_3$)$_6$tren]Br (**5**) (0.1 mmol% equiv.), the azide (1 mmol) and the alkyne (1.05 mmol) were stirred in freshly distilled toluene for **2** and **3** (1 mL) or H$_2$O for **5** at 22 °C, and the reaction was monitored by GC. After each 24 h, the reaction mixture was cooled at −18 °C for 30 min in order to complete precipitation of the product, then filtered and washed three times in order to recyle the catalyst, then the catalyst solution was concentrated to 1 mL, which allowed us to reload the substrates for the next reaction (see Table 3).

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