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Convergent Synthesis of Second Generation AB-Type Miktoarm Dendrimers Using "Click" Chemistry Catalyzed by Copper Wire

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Dendrimers synthesized from small molecules form macromolecules of well-defined size and architecture.[1] The high density of functional groups on the periphery of the dendrimers makes them useful as carriers for multiple copies of biologically active compounds for drug/vaccine delivery or probe molecules for detection applications.[2] However, the typical synthetic procedure for obtaining dendrimers from small molecules limits their size to about 5−15 nm as each new generation is increasingly difficult to add and contributes only to a relatively small increase in dimensions. In addition, traditional dendrimers are difficult to purify and as a consequence costly. Thus, the focus in synthetic dendrimers has shifted from using small molecule to polymeric building blocks made by living radical polymerization.[3] However, there is still a need in precise synthetic tools that would allow one to combine polymeric blocks with diverse functionality into one structure to create advanced products for biomedical and coatings applications.

"Click" chemistry using the copper-catalyzed Huisgen[4] dipolar cycloaddition reaction between alkyne and azide groups to form 1,2,3-triazol rings catalyzed by Cu(I)/N-based ligand complexes[5,6] has provided researchers with a methodology to divergently synthesize stars[7] and dendrimers[8] from coupling well-defined linear polymeric chains (see Scheme 1). Since the divergent method results in proliferation of reactive groups on the periphery with each additional generation, higher levels of Cu(I) and ligand are therefore required for efficient "click" reactions at each successive generation synthesis. Therefore, many purification steps are required to remove excess copper species through column chromatography, resulting in loss of dendritic product. Also problematic is the high levels of N-based ligands that can reduce the product yield through base cleavage of ester linkages (*vide supra*) or difficulty in removal of residual ligand. It has also been found (not only in our work) that fresh Cu(I) was required for each new "click" reaction.[9] Therefore, a methodology is required that provides (i) a simple means of removal of excess copper, (ii) that the same copper species can be used in all subsequent "click" reactions, and (iii) elimination of the use of ester cleavable N-based ligands.

In this work, we demonstrate an efficient and high yielding "click" methodology for the synthesis of second generation homo-, block-, and amphiphilic miktoarm block-dendrimers (Scheme 2) in pure form via a convergent strategy[10] of coupling dendrons to a base labile core compound using copper wire (Cu (wire)[5]) in the absence of added N-based ligand. The convergent method has the advantages that the number of reactive groups is low (i.e., low amount of copper is required), and additionally a diverse range of dendrimers can be prepared with mixed chemical compositions (i.e., miktoarm dendrimers of hydrophobic or amphiphilic composition). This methodology has allowed us to synthesize miktoarm dendrimers in much higher yields as compared to those in the presence of CuBr/PMDETA complexes, especially when "clicking" acrylate-type polymers together. This latter result is important for high yield synthesis of amphiphilic miktoarm[11] dendrimers. The major advantage of using Cu (wire) is the ease of removal of excess copper from the final product, the reuse of the same Cu (wire) in all subsequent reactions, and in the absence of base (i.e., N-based ligand) the base cleavable ester linkages at the core remain intact.

Controlling the chain length and functionality of the building polymeric blocks provides a toolbox (Scheme 1) for producing structurally complex architectures. See Supporting Information for experimental details. To this end, we used several techniques to explore the effect of reaction conditions on copper-catalyzed "click" reactions for convergently making chemically diverse miktoarm dendrimers (Scheme 2), ranging from blocks of polystyrene (PSTY), poly(methyl acrylate) (PMA), poly(*tert*-butyl acrylate) (P^{t}BA), and poly(acrylic acid) (PAA), demonstrating the wide variety of polymer chemical composition that can be "clicked" to form high order structures. Pure dendrimers were obtained via fractionation by size exclusion chromatography (SEC).

The synthesis of **12** was carried out using either CuBr/PMDETA or Cu (wire)/PMDETA. Cu (wire) in the absence of PMDETA gave no coupling of tripropagylamine to the azide on the polymer end group (**11**). However, in the preparation of dendrons (**13**−**15**) where a triazol ring was initially present as part of the polymer, Cu (wire) in the absence of PMDETA gave similar purities between 83 and 92% as for CuBr/PMDETA (Scheme 1, Table 1 and Supporting Information for SEC chromatograms). This suggests that the triazol rings either act as a base to catalyze triazol ring formation or act as a ligand for the copper species. We carried out atomic absorption spectroscopy (AA) to determine the amount of copper bound to **13** formed from copper catalyzed "click" reaction between **8** and **12** using three different catalytic methods: CuBr/PMDETA (10 times excess to propagyl end groups, method A), CuBr/PMDETA (0.5 times excess to propagyl end groups, method B), and Cu (wire) (method C). The polymer (**13**) was precipitated into cold methanol and filtered and dried before AA readings were taken. It was found that regardless of the type and amount of copper catalyst used, the percentage of copper to polymer was similar and close to 0.045%, which suggests that there is one copper species for every nine dendrons.

The azide chain-end modified 3-arm stars (**19**−**21**) in excess were convergently coupled to **22** to form G2 dendrimers **23**−**25** (in Scheme 2 and Supporting Information for SEC chromatograms). It should be noted that the starting polymers used for each method were prepared by the same route. The purity of **23** was low (57%) and did not increase after a further reaction for 1 h when high levels of CuBr and PMDETA were used (method A in Table 1). There was an increase in purity at both a lower level of CuBr and PMDETA (64% after 4 h) or copper wire (76% after 4 h). There are two possible reasons for this high yield in the presence of Cu (wire): (1) Cu (wire) provides a constant source of active copper, and (2) the ester linkages in

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Scheme 1. Synthesis of Starting Linear and Three-Arm Star Polymers (PMDETA = *N,N,N′,N′,N″*-Pentamethyldiethylenetriamine)

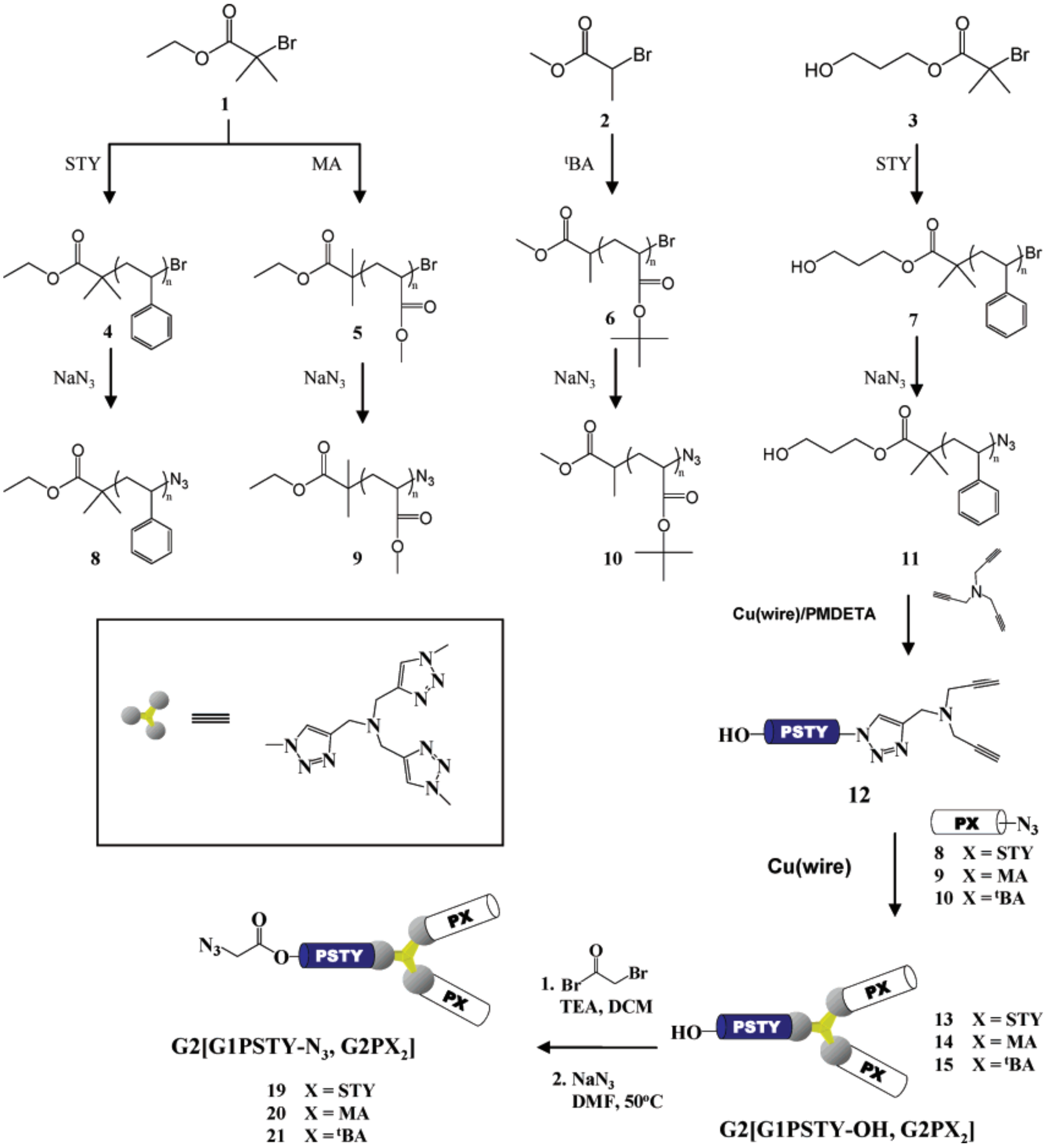


Table 1. Purity of Reactive Three-Arm Stars and G2-Dendrimer Products after "Click" Reactions Using CuBr/PMDETA or Copper Wire (with No Added Ligand)

	method A (10CuBr/PMDETA)		method B (0.5CuBr/PMDETA)		method C (Cu wire)		SEC data method C		
product	time (h)	purity (%)	time (h)	purity (%)	time (h)	purity (%)	PDI	M_p	$M_{p,theory}$
3-arm stars									
13	2	90	3	91	4	85	1.27	16 650	16 800
14	2	92	3	90	4	87	1.31	18 480	18 940
15	2	86	3	83	4	85	1.27	12 880	14 360

	method A (10CuBr/PMDETA)		method B (0.5CuBr/PMDETA)		method C (Cu wire)		SEC data method C		
								after fractionation	
product	time (h)	purity (%)	time (h)	purity (%)	time (h)	purity (%)	PDI	M_p	$M_{p,theory}$
G2 dendrimers									
23	1	57	2	66	2	62			
	2	57	4	64	4	76	1.17	47 620[a]	50 400
24	2	56	4	24	4	71	1.16	47 013[a]	45 520
25	2	52	4	7	4	63	1.19	57 253[a]	54 680

[a] Peak molecular weight (M_p) determined using triple detection SEC (light scattering). [b] Purity was calculated from the relative ratio of starting to final products based on a weight distribution.

the core remain intact due to the absence of base (i.e., PMDETA).

Coupling the acrylate dendrons (**20** or **21**) to **22** produced G2 miktoarm dendrimers with low purities in the presence of

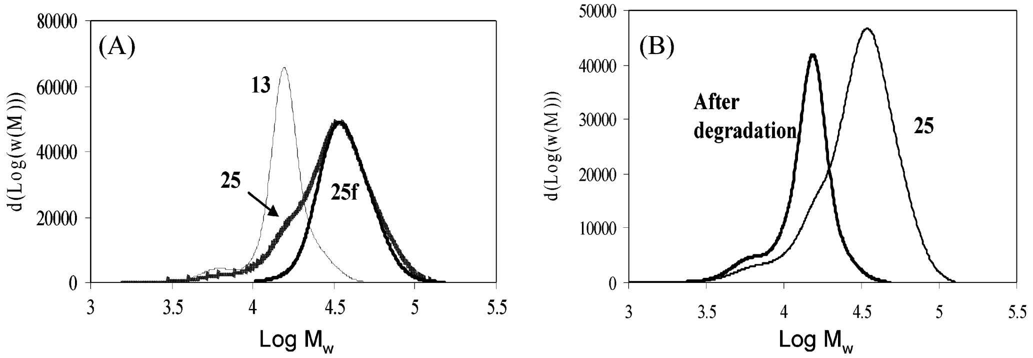
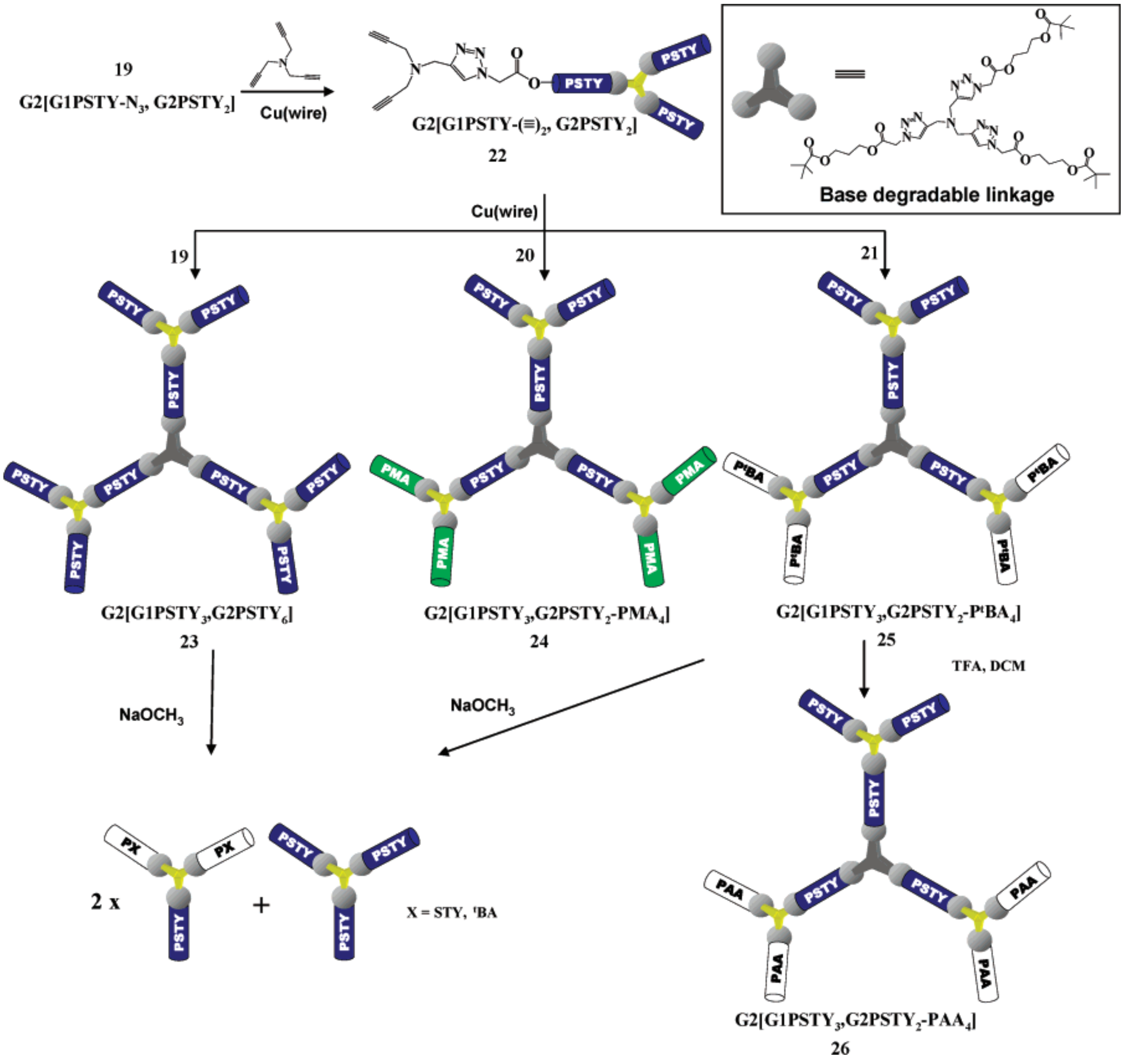


Figure 1. Size exclusion chromatography (SEC) for (A) the synthesis of G2[G1PSTY$_3$,G2PSTY$_2$-P^{t}BA$_4$] (**25**) and after fractionation using SEC (**25f**), and (B) base degradation of the core of **25** in the presence of NaOCH$_3$ in THF for 16 h.

Scheme 2. Synthesis of G2 Dendrimers



high levels of CuBr/PMDETA (~56%, method A), most probably due to degradation of the ester linkages. Surprisingly, low amounts of CuBr/PMDETA (method B) gave extremely low purities (24 and 7% for **24** and **25**, respectively), and the same result was found even after the experiment had been carried out in triplicate. The reason for this is not clear but could be due to some preferential binding of the CuBr to the acrylate side groups. When Cu (wire) was used, the purity significantly increased to greater than 71% for **24** and 63% for **25**, suggesting that again the constant source of active copper overcame the low "clicking" efficiency when using low concentrations of CuBr/PMDETA. Pure G2 dendrimers were obtained through fractionation by SEC (e.g., **25f** in Figure 1A). The molecular weight data (i.e., M_n, M_p, PDI) for copper wire catalyzed reactions is given in Table 1, and show that after fractionation the polydispersity index is low and below 1.2 for all dendrimers and that the peak maximum molecular weight, M_p, is close to theory. It should be noted that the M_p and PDI values are based on absolute molecular weights determined from triple detection SEC, and as such the agreement between theory and experiment M_p's is strong proof that miktoarm and other G2 dendrimers have been synthesized.

The results using Cu (wire) as the catalyst suggests that the triazol rings act as strong ligands for the most likely species, Cu(I). Chan et al.[12] showed that polytriazolylamines both stabilized Cu(I) from oxidation in air and disproportionation to give significantly faster rates of "click" coupling reactions and higher yields (>84%). The mechanism by which Cu (wire) or Cu(0) is converted to Cu(I) is still unclear. Our results show that using Cu (wire) gives a constant source of copper species that is available in the "click" reactions. Himo et al.[5] postulated that Cu(I) could be formed through comproportionation of Cu(0) + Cu(II) → Cu(I). Our results support this postulate as our "click" reactions with wire are carried out in air. First, there is initial oxidation of the wire surface to Cu(I) species. Second, the surface catalyzes the "click" reaction to form Cu(II) species that then undergo comproportionation with Cu (wire) to form Cu(I). The triazol rings additionally stabilize the Cu(I) species further driving the equilibrium to the right.

The dendrimers were designed to undergo base cleavage at their central core. Sodium methoxide (an agent known to cleave ester groups) was added to solutions of **23** and **25** in THF at room temperature for 16 h. SEC analysis (Figure 1B) showed that all G2 dendrimer (peak molecular weight of 57200) was degraded only at the core, resulting in polymer material with the same peak molecular weight as the starting 3-arm star precursor. This provides an additional design parameter when designing dendrimers for (slow) controlled release in drug and vaccine delivery applications. An amphiphilic miktoarm dendrimer (**26**) was prepared from the hydrolysis of the *tert*-butyl groups on **25** to carboxylic groups using TFA.

In summary, we have shown for the first time that polymer structures with unprecedented chemical diversity (hydrophobic or amphiphilic) and complexity (G2 miktoarm dendrimers with a degradable core) consisting of PSTY, PMA, P^{t}BA, and PAA were synthesized with high purity using copper wire as the "click" catalyst via a convergent strategy. The advantages of carrying out "click" reactions with Cu (wire) are (a) higher purity and greater "click" efficient reactions are obtained, (b) "click" reactions can be carried out in the absence of N-based ligands, although triazol rings must be present and part of the starting polymers, (c) excess copper species can be easily removed from the reaction mixture, and (d) reuse of the same copper wire in all subsequent "click" reactions. There is still a small amount of copper species (0.045% w/w of copper/polymer) remaining in the polymer structures after precipitation. The convergent strategy provides a tool to prepare dendrimers with chemical diversity in each generation that cannot be achieved using a divergent strategy. Our results also support that comproportionation provides a constant source of Cu(I) species to give high yields from "click" reactions using Cu (wire). This is additionally aided through the strong stabilization of the Cu(I) species with the preformed triazol rings in starting polymer structures.

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Supporting Information Available: Text giving synthetic and experimental details, schemes showing the synthetic routes, a table of SEC data, and figures showing SEC chromatograms, NMR spectra, and AT FTIR chromatograms. This information is available free of charge via the Internet at http://pubs.acs.org.

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