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A Facile Route to Functional Hyperbranched Polymers by Combining Reversible Addition−Fragmentation Chain Transfer Polymerization, Thiol−Yne Chemistry, and Postpolymerization Modification Strategies

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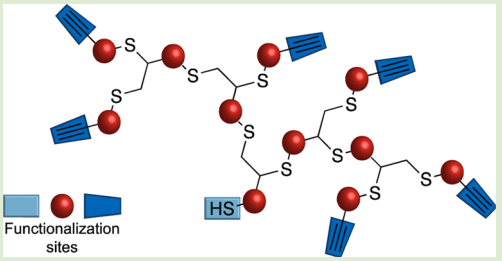
Supporting Information

ABSTRACT: This contribution reports on the preparation of functional hyperbranched polystyrene-based materials via a combination of reversible addition−fragmentation chain transfer (RAFT) polymerization, thiol−yne chemistry, and postpolymerization modification reactions. The thiol−yne approach allows the rapid preparation of hyperbranched polymers under mild reaction conditions from polymeric chains bearing a thiol group at one chain end and an alkyne moiety at the other. Postpolymerization modifications of the focal thiol and peripheral alkyne functionalities present within the hyperbranched structures were conducted using two highly efficient strategies, i.e., phosphine-catalyzed thiol−ene reaction and copper-catalyzed azide−alkyne cycloaddition (CuAAC), respectively. In addition to introducing functionalities by postpolymerization modification onto the periphery of the hyperbranched polymers, the interior of the globular structure could also be functionalized by taking advantage of the isocyanate chemical handle of a poly(styrene-*co*-3-isopropenyl-α,α-dimethylbenzyl isocyanate) (P(S-*co*-TMI)) copolymer. The combination of these strategies provides an elegant tool for the elaboration of a wide variety of multifunctional hyperbranched structures.



Dendritic structures such as dendrimers or hyperbranched polymers are globular macromolecules that are characterized by a highly branched structure and a high density of functional chain ends.[1−4] These specific characteristics, which give these structures markedly different properties in comparison to their linear analogues, render dendrimers and hyperbranched polymers very attractive candidates for a wide range of applications, including in, but not restricted to, nanomedicine, catalysis, and biosensing.[4−17] In contrast to dendrimers, which are defined by a strictly regular generational structure and the preparation of which typically requires tedious, sequential syntheses and intermediate purification steps, hyperbranched polymers can be prepared via more straightforward synthetic routes.[1−3,5,6,18] Despite having randomly distributed branches, hyperbranched polymers are promising alternatives to dendrimers since they also possess a high branching density and a large number of functional terminal groups, allowing for example the design of multivalent macromolecules.[19−21]

Recently our group developed a strategy for the synthesis of hyperbranched polymers based on the UV irradiation of molecules bearing a thiol moiety at one end and an alkyne group at the other in the presence of a photoinitiator.[22,23] Such molecules act as an AB_2 monomer where the thiol is the A unit and each of the π bonds of the alkyne are the B units. The thiol−yne mechanism proceeds via the double addition of thiyl radicals to the unsaturated carbon−carbon bonds, thus producing asymmetric dithioether branching points.[24,25] One of the most remarkable features of dendritic polymers prepared by this means is that they possess many residual alkyne moieties in the periphery of their structure. Indeed, each peripheral group in the dendritic polymer, except the one remaining thiol group (focal point), is a reactive alkyne (Scheme 1). These two chemical groups can act as potential handles for further postpolymerization functionalization.

In this report, a strategy for the preparation of multifunctional hyperbranched polymers via a combination of reversible addition−fragmentation chain transfer (RAFT) polymerization,[26−29] thiol−yne chemistry, and postpolymerization modification strategies is presented. The thiol focal point and alkyne peripheral moieties of polystyrene-based hyperbranched polymers obtained by means of the thiol−yne approach are modified using two efficient techniques, i.e., a phosphine-catalyzed thiol−ene reaction[30−32] and a copper-catalyzed azide−alkyne cycloaddition (CuAAC),[33−35] respectively. In addition to the functionalization of the outer periphery, a method to introduce functionalities within the interior volume of the globular structure by utilizing a poly(styrene-*co*-3-isopropenyl-α,α-dimethylbenzyl isocyanate) (P(S-*co*-TMI))

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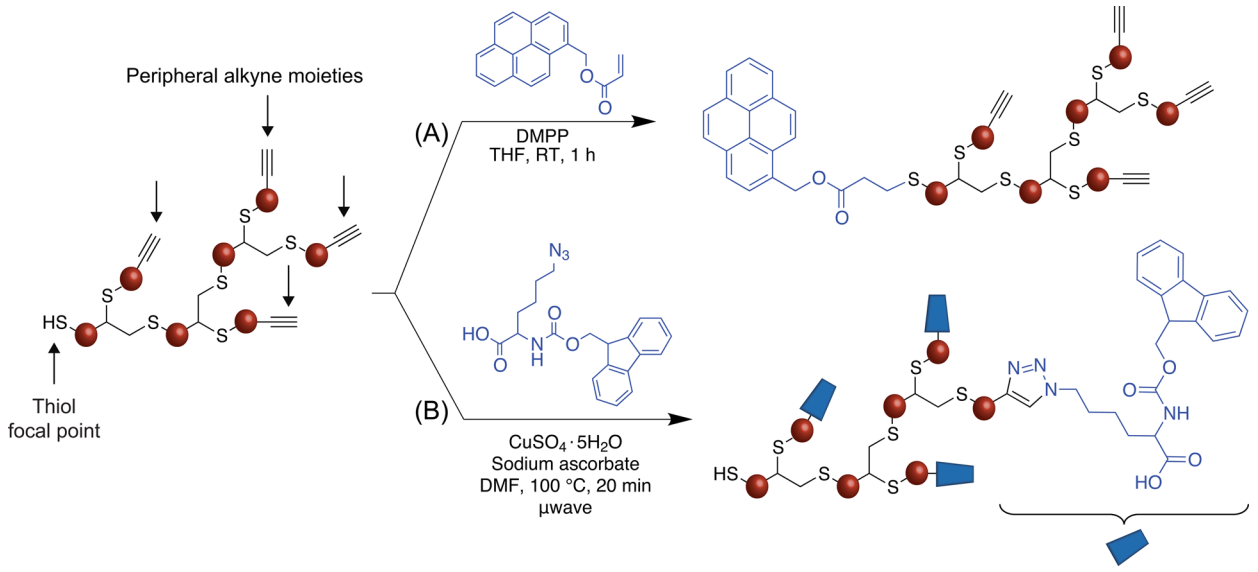
Scheme 1. Schematic Representation of the Postpolymerization Modification of the Hyperbranched Polymers: (A) Phosphine-Catalyzed Reaction of an Acrylate Derivative of Pyrene onto the Thiol Focal Point (Thiol−Ene) and (B) Copper-Catalyzed Azide−Alkyne Cycloaddition of Fmoc-L-azidolysine onto the Peripheral Alkyne Groups[a]



[a]DMPP: dimethylphenylphosphine; THF: tetrahydrofuran; RT: room temperature; $CuSO_4 \cdot 5H_2O$: copper(II) sulfate pentahydrate; DMF: *N*,*N*-dimethylformamide; μwave: microwave irradiation.

copolymer as a platform for the preparation of functional thiol/yne building blocks is also described.

The hyperbranched polymers used in this study have been produced by photopolymerization of polystyrene macromonomers bearing an alkyne moiety at one chain end and a thiol group at the other. The synthesis of such macromonomers relies on the use of an alkyne-containing chain transfer agent, prop-2-yn-1-yl 2-(((butylthio)carbonothioyl)thio) propanoate, to mediate RAFT polymerization. This strategy allowed the preparation of linear chains with well-controlled molecular weight and narrow molecular weight distribution (M_n = 2510 g·mol^{-1}, $Đ$ = 1.14) exhibiting an alkyne moiety at their α-chain end. The thiol moiety was generated at the other end of the polymer chain by reducing the trithiocarbonate group using a large excess (~40 equiv relative to the number of polymer chains) of isopropylamine. The successful and complete aminolysis of the polymer was ascertained by ^{1}H NMR spectroscopy (Figure S3, Supporting Information). The monomodal, well-defined polymer distribution obtained (M_n = 2510 g·mol^{-1}, $Đ$ = 1.14), as well as the comparison of the size exclusion chromatograms of the polymer before (PS) and after (PS-SH) aminolysis (Figure 1), indicate that no detectable amount of disulfide bonds were formed during the process. The UV irradiation at room temperature of a 0.15 M solution of the aminolyzed polymer in a DMF/toluene (4/1, *v*/*v*) solvent mixture in the presence of ~0.5 equiv (relative to the number of polymeric chains) of photoinitiator (2,2-dimethoxy-2-phenylacetophenone, DMPA) led to the production of dendritic structures in which each branching unit is linked to the other by the polymeric chain (Scheme S3, Supporting Information). Figure 1 shows the response of the differential refractive index (DRI) detector as a function of the retention time for the hyperbranched polystyrene (*hb*PS) obtained via the thiol−yne strategy. The molecular weight and molecular weight distribution of the hyperbranched structures (M_n = 8700 g·mol^{-1}, M_p = 18400 g·mol^{-1}, $Đ$ = 4.22) were determined by conventional calibration and are reported relative to linear

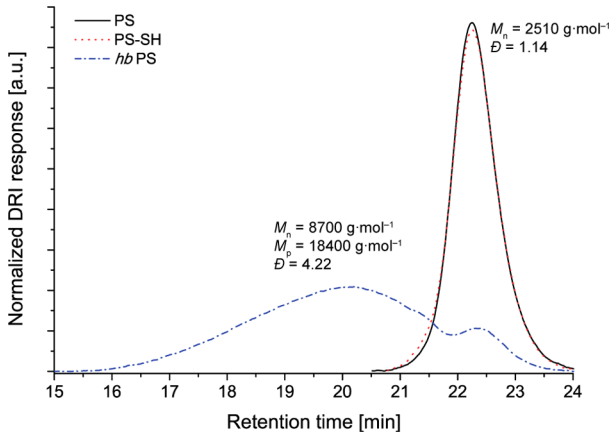


Figure 1. Size exclusion chromatograms (differential refractive index detector) of polystyrene prepared by RAFT polymerization (PS), polystyrene after aminolysis (PS-SH), and hyperbranched polystyrene (*hb*PS) produced by thiol−yne photopolymerization.

polystyrene standards. It is worth noting that hyperbranched polymers possess hydrodynamic radii that are smaller than those of their linear analogues (for equivalent molecular weights). As a consequence, molecular weights of hyperbranched polymers determined by size exclusion chromatography (SEC) relative to linear polymer standards (as reported here) are significantly underestimated.

A remarkable feature of the dendritic structures produced by the thiol−yne approach is that they possess many residual alkyne groups in their periphery, as well as a thiol focal point, which can both be exploited to introduce a high density of functionalities via postpolymerization modifications. The feasibility of using the hyperbranched polystyrene as a platform for postpolymerization modification was explored with two proof-of-concept experiments involving two orthogonal, highly efficient ("click"-type) reactions (Scheme 1).

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The functionalization of the thiol focal point was performed via a phosphine-catalyzed Michael reaction, which has been proven to proceed in an extremely rapid and quantitative manner.[30] A THF solution of hyperbranched polystyrene was allowed to react with pyren-1-ylmethyl acrylate in the presence of dimethylphenylphosphine at room temperature for 1 h. After precipitation, the modified hyperbranched polymer was thoroughly washed with cold methanol to remove any potentially physisorbed, unreacted pyren-1-ylmethyl acrylate. The successful introduction of the fluorescent probe onto the hyperbranched structure was visually observed by comparing the glow produced under 365 nm UV light by a 3 mg·mL^{-1} solution of the pyrene-containing *hb*PS to a solution of the same concentration of the unmodified *hb*PS (Figure 2). Further

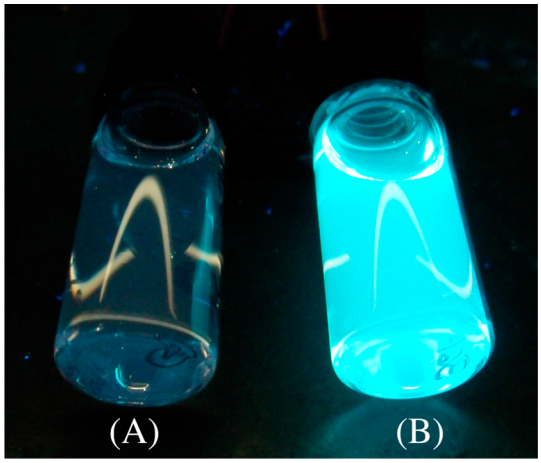

Figure 2. Solutions (3 mg·mL^{-1} in THF) under UV light (365 nm) of the hyperbranched polystyrene (A) before and (B) after postpolymerization modification with pyren-1-ylmethyl acrylate.

evidence is given in the ^{1}H NMR spectrum of the modified *hb*PS (Figure S4, Supporting Information). The presence of a new set of peaks that correspond to the protons of the pyrenyl ring (7.9−8.2 ppm), as well as the absence of peaks in the olefinic region of the spectrum (typically between 5 and 6 ppm), prove that the pyren-1-ylmethyl acrylate reacted with the thiol group of the hyperbranched polymer and that any residual, unreacted acrylate was removed. The pyrene-functionalized hyperbranched structures were also analyzed by size exclusion chromatography. The DRI response shows that the phosphine-catalyzed thiol−ene reaction did not disrupt the structure of the hyperbranched polymer (Figure S5, Supporting Information), and the UV response clearly indicates a higher absorbance intensity for the pyrene-containing hyperbranched polymer at 343 nm as compared to its unmodified analogue (Figure S6, Supporting Information).

The introduction of functionalities onto the peripheral alkyne moieties was conducted in a microwave reactor using the copper-catalyzed azide−alkyne cycloaddition (CuAAC), following a protocol adapted from Poon et al.[36] The reaction between the alkyne-terminated hyperbranched polystyrene and Fmoc-L-azidolysine was performed in DMF under microwave irradiation, employing copper(I), which was generated in situ by the reduction of copper(II) sulfate with sodium ascorbate, as a catalyst. After 20 min, the reaction mixture was cooled and precipitated twice in cold methanol, yielding the Fmoc-L-lysine-functionalized *hb*PS. The coupling between the alkyne and azide partners was confirmed by fluorescence spectroscopy

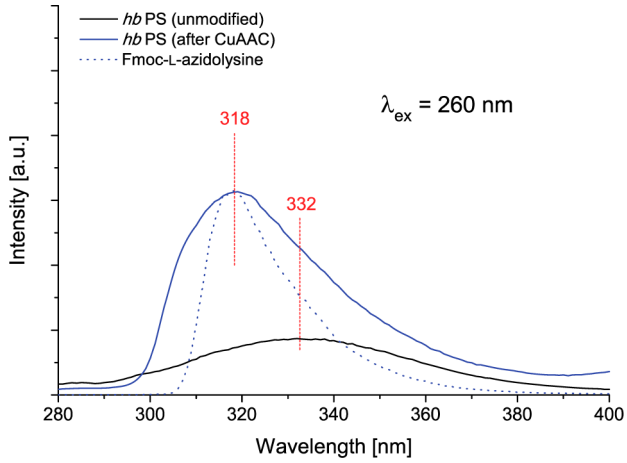

Figure 3. Fluorescence intensity as a function of the wavelength for Fmoc-L-azidolysine, for the unmodified hyperbranched polystyrene, and for the hyperbranched structure after the postpolymerization modification with Fmoc-L-azidolysine. Excitation wavelength: 260 nm.

(Figure 3). When subjected to an excitation wavelength of 260 nm, the fluorenyl group emits its maximal intensity at 318 nm, as evidenced by the spectrum of Fmoc-L-azidolysine. The presence of this characteristic peak intensity in the emission spectrum recorded for the functionalized *hb*PS definitively indicates the successful conjugation of the azido compound to the hyperbranched structure.

The effective coupling of the Fmoc-L-azidolysine to the alkyne-terminated hyperbranched polymer was further evidenced by ^{1}H NMR spectroscopy (Figure S7, Supporting Information). The disappearance of the signal at 4.4−4.5 ppm corresponding to the two protons adjacent to the alkyne moiety (−CH_2−C≡CH) is a clear indication that the alkyne groups have been consumed. In addition, the appearance of the characteristic peaks of the fluorenyl group (two doublets in the 7.7 ppm region and two triplets between 7.28 and 7.38 ppm), as well as the presence of peaks at 7.45 ppm (C*H* of the triazole ring), 5 ppm (CH_2 on the polymer next to the triazole ring), and 4.2 ppm (CH_2 on the amino acid next to triazole ring), prove that the alkyne functionalities readily reacted with the Fmoc-L-azidolysine. Finally, the size exclusion chromatogram of the functionalized hyperbranched structure was compared to that of its unmodified counterpart (Figure S8, Supporting Information). The two chromatograms are essentially identical, indicating that the conditions chosen for the microwave irradiation neither were destructive for the hyperbranched polymer nor induced further polymerization of the alkyne moieties.

In addition to the functionalities that can be introduced onto the periphery of the hyperbranched structure via postpolymerization modifications (vide supra), the use of functional thiol/yne macromonomers also offers the opportunity to introduce functionalities into the core of the final dendritic polymer. The strategy developed in this report resides in the synthesis of linear polymers bearing reactive moieties in their side chains that can be utilized as a platform to prepare functional thiol/yne macromonomers. To demonstrate the feasibility of this approach, a statistical copolymer formed of styrene and 3-isopropenyl-α,α-dimethylbenzyl isocyanate (P(S-*co*-TMI)) was prepared by RAFT polymerization using the alkyne-containing chain transfer agent as a mediator (Scheme S4, Supporting Information), with the objective of using the isocyanate

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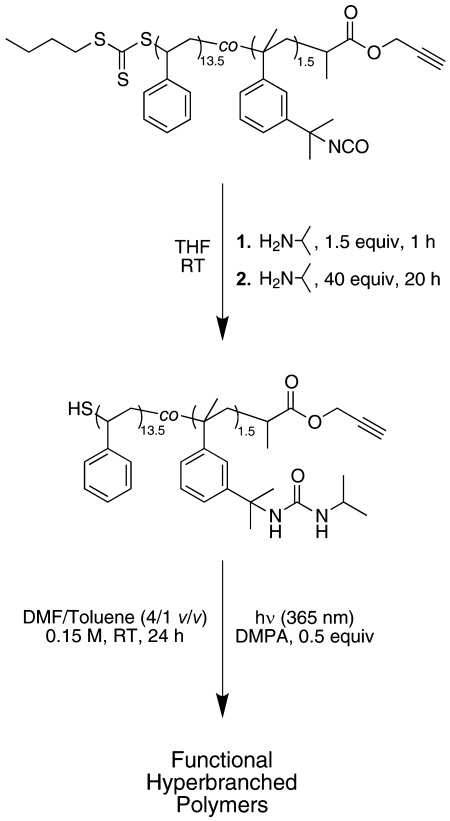
reactivity toward nucleophiles as a functionalization platform. Scheme 2 highlights the synthetic strategy that was followed for the preparation of functional hyperbranched structures from P(S-*co*-TMI) copolymers.

Scheme 2. Schematic Representation of the Procedure for the Functionalization, Aminolysis, and Photopolymerization of the P(S-*co*-TMI) Copolymer[a]



[a]THF: tetrahydrofuran; RT: room temperature; DMF: *N*,*N*-dimethylformamide; DMPA: 2,2-dimethoxy-2-phenylacetophenone.

The well-defined (M_n = 2080 g·mol^{-1}, $Đ$ = 1.24) P(S-*co*-TMI) copolymer was first functionalized with a nearly quantitative amount (~1.5 equiv) of isopropylamine, leading to the transformation of all isocyanate pendant groups of the copolymer into isopropylurea moieties. Indeed, the reaction between the isocyanate pendant group and isopropylamine can be easily monitored by Fourier transform infrared (FTIR) spectroscopy, by following the decrease in intensity of the isocyanate peak at 2250 cm^{-1}. The consumption of the isocyanate moieties was shown to proceed in an extremely rapid and efficient fashion. The characteristic isocyanate peak almost completely vanished after 2 min of reaction, and after 5 min the peak was no longer discernible (Figure 4A). Moreover, the appearance of the amide bands at 1640 and 1550 cm^{-1}, as well as the N−H stretching signal in the 3300−3500 cm^{-1} region, is indicative of the formation of the expected urea bonds. The functionalization of the P(S-*co*-TMI) with isopropylamine was also confirmed by ^{1}H NMR spectroscopy with the appearance of new, broad signals due to the isopropylurea in the 3.4−4.1 ppm region of the spectrum (Figure S9B, Supporting Information). It is also worth noting that under these conditions and even if the reaction is prolonged for 24 h no aminolysis could be detected as no

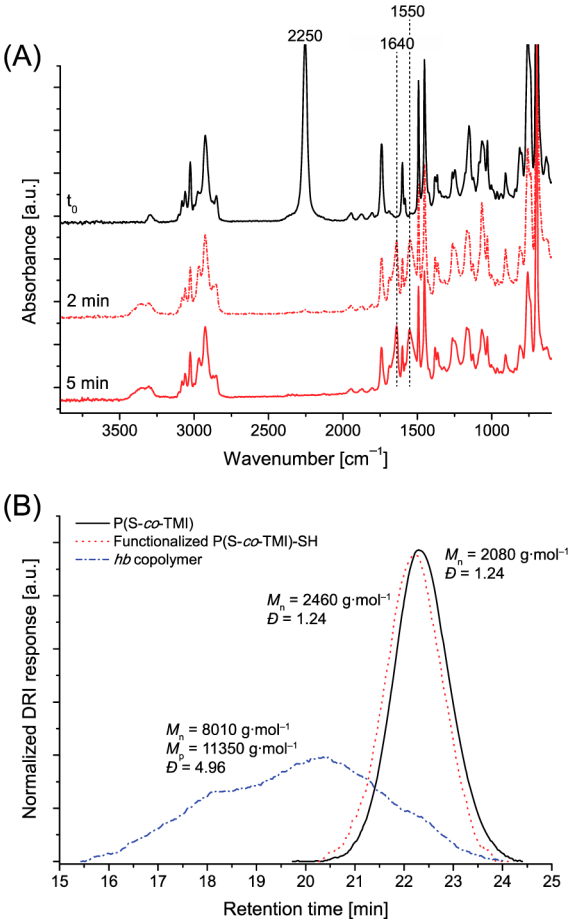


Figure 4. (A) FTIR absorbance spectra of P(S-*co*-TMI) as a function of reaction time with ~1.5 equiv of isopropylamine. (B) Size exclusion chromatograms (differential refractive index detector) of P(S-*co*-TMI) prepared by RAFT polymerization, the copolymer after functionalization with isopropylamine and aminolysis, and the hyperbranched copolymer produced by thiol−yne photopolymerization.

decrease in the peak intensity at ~3.3 ppm (i.e., CH_2 next to the trithiocarbonate) could be observed.

The aminolysis of the trithiocarbonate group on the ω-chain end of the functionalized copolymer was achieved in a second step by adding a large excess (~40 equiv) of isopropylamine to the mixture. The reaction was let to proceed for 20 h, after which the aminolyzed functional P(S-*co*-TMI) copolymer was precipitated twice in ice-cold hexane. The completion of the reaction was evidenced by ^{1}H NMR spectroscopy with the disappearance of the peak at 3.3 ppm (Figure S9C, Supporting Information), and the molecular weight and molecular weight distribution of the aminolyzed functional copolymer were determined by size exclusion chromatography (M_n = 2460 g·mol^{-1}, $Đ$ = 1.24). The narrow molecular weight distribution and the symmetry of the size exclusion chromatogram observed for the copolymer after aminolysis (Figure 4B) indicated that the formation of disulfide bonds between polymeric chains did not occur to a noticeable extent.

The UV irradiation (365 nm) of a 0.15 M solution of the aminolyzed copolymer in a DMF/toluene (4/1, *v*/*v*) mixture for 24 h yielded functional hyperbranched polymers, where the functionalities are located within the core of the structure. The size exclusion chromatogram of the postmodified hyperbranched polymer is displayed in Figure 4B. The molecular

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weight and dispersity of the dendritic material were determined relative to linear polystyrene standards as M_n = 8010 g·mol^{-1}, M_p = 11350 g·mol^{-1}, and $Đ$ = 4.96.

In conclusion, this work established synthetic strategies for the preparation of multifunctional hyperbranched polymers produced by thiol−yne chemistry. Three high-yielding reactions were discussed with specific, proof-of-concept examples. It is predicted that combining the different strategies will allow the fabrication of dendritic systems with great versatility. As suggested in this report, the extremely high reactivity of the isocyanate moiety, as compared to the trithiocarbonate group, toward primary amines could for example be utilized as a tool to introduce more expensive and functional amino compounds in a one-pot, two-step protocol, where the reactive copolymer would be functionalized quantitatively with the functional amine first, followed by the aminolysis of the copolymer by the addition of a large excess of an inexpensive, sacrificial primary amine. It is also anticipated that providing the right reaction conditions, the outer periphery of the dendritic structure could be decorated with any azide-containing compound and/or functional molecules bearing reactive alkene bonds, using copper-catalyzed azide−alkyne cycloaddition (CuAAC) or phosphine-catalyzed thiol−ene reaction, respectively. The possibility to functionalize the internal core as well as the outer periphery of the hyperbranched structure, and to potentially tune the properties of the dendritic system almost indefinitely by introducing specific functionalities, may open new avenues in the design and synthesis of materials for applications that require multifunctional and/or multivalent specificities.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental methods, ^{1}H NMR and ^{13}C NMR spectroscopy spectra, DMF-SEC and THF-SEC chromatograms, and reaction schemes. 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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