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Tandem Functionalization in One Highly Branched Polymer with Layered Structure

Xiaosong Cao, Yi Shi, Weiping Gan, and Haifeng Gao*

Dedication ((optional))

Abstract: In this report, we developed a hyperbranched polymer with multi-layer structure to demonstrate the possibility of highly efficient tandem functionalization reactions at different domains within one nanostructured platform. The polymer scaffold was constructed using the chain-growth copper-catalyzed azide-alkyne cycloaddition (CuAAC) polymerization of three functional monomers with sequential monomer addition in one pot. Subsequent reactions onto different monomer units exhibited efficient functionalization in each segment, constructing a highly sophisticated polymer structure via a robust procedure. As a proof of concept, we demonstrated the ability of this polymer structure to quantitatively load six species of guest molecules through three different types of conjugation reactions.

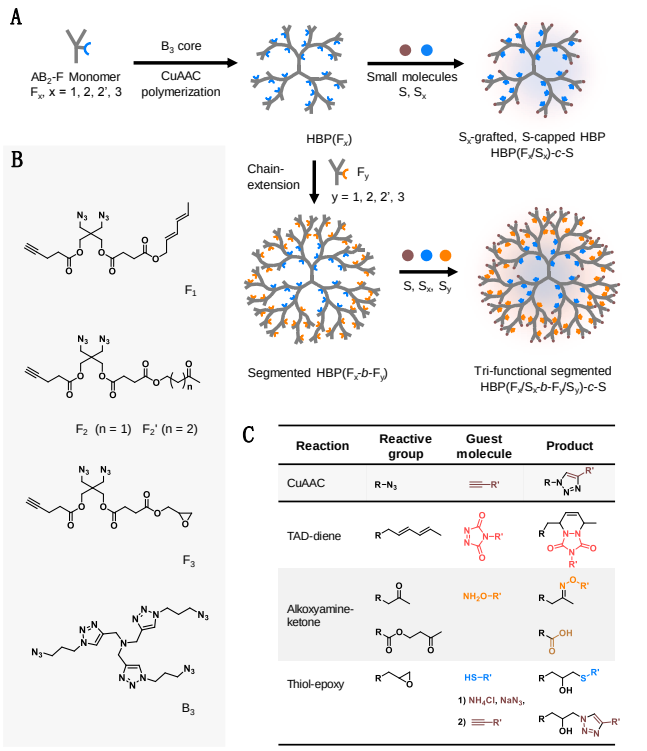
Introduction

Incorporation of functional groups into polymers significantly determines the properties and applications of polymeric materials.[1] As the choices of functional monomer species are often limited by their compatibility in the polymerization techniques,[1d, 2] the strategy of post-polymerization modification becomes attractive, which provides alterative options to introduce functional groups into well-structured polymers, especially by using several efficient click reactions.[1a, 1e, 3]

Highly branched polymers that have a compact nanostructure and multiple terminal groups are intriguing candidates as unimolecular containers in diverse fields such as theranostic reagents,[4] catalysts[5] and optoelectronic materials.[6] Further functionalization of the backbones and the interior of these highly branched polymers brings up opportunities to increase the density and diversity of active guest species in these unimolecular containers.[7] However, different from linear polymers whose functionalization is less affected by the polymer structure, functionalization of highly branched polymers, especially sequential functionalization of the inside structure becomes rare and challenging, mainly due to the steric hindrance of polymer structures on the reaction efficiency.[6a, 8]

We have an intention to develop an applicable highly branched polymer platform that could efficiently, orthogonally, and quantitatively load cargo molecules bearing different types of functional groups in minimum synthetic effort.[1a, 9] The traditional hyperbranched polymers synthesized from step-growth polymerization of AB_m ($m \geq 2$) monomers show difficulty in this goal because of the poorly defined structure (both interior and exterior) and the inability to incorporate reactive groups into specific segments. As a matter of fact, a versatile chain-growth polymerization of AB_2 monomers (where A represents an alkynyl group and B_2 represents a di-azido unit) using the efficient copper-catalyzed azide-alkyne cycloaddition (CuAAC) reaction has been recently developed in our group, producing hyperbranched polytriazoles with low dispersity (M_w/M_n ~1.05) and up to a million molecular weight.[10] More importantly, the use of a tris-triazoleamine-based trifunctional B_3 core during the CuAAC polymerization accurately control the polymer's degree of polymerization (DP) following $DP = [AB_2]_0/[B_3]_0 \times$ conversion, allowing sequential addition of different AB_2 monomers in multiple batches to produce segmented hyperbranched copolymers.[11] In this progress, we see the chance to introduce multiple functional sites through sequential chemical conjugations on the polytriazole skeleton, which can reach never-reported sorphitication of hyperbranched structures carrying an array of reactive groups.[12]

Herein, three types of AB_2-F functional monomers carrying diene,



Scheme 1. **A**) Schematic illustration of the synthesis of multifunctional hyperbranched polytriazoles, **B**) structure of the AB_2 monomers and B_3 core, and **C**) summary of reactions used for backbone construction and post-polymerization functionalization.

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ketone, and epoxy groups (denoted as F_1, F_2, and F_3 with synthesis details in the supporting information, Figures S1-S2) were designed for use in the CuAAC (co)polymerization to construct hyperbranched polymers with layered structure and periphery azido groups. Correspondingly, three efficient metal-free click reactions, including triazolinedione (TAD)-diene reaction,[3f, 13] alkoxyamine-ketone reaction,[14] and thiol-epoxy reaction,[15] were carefully adopted for the post-polymerization modification. The highly efficient nature of these reactions and their orthogonality was demonstrated in details using many transformation reactions (Scheme 1).

Results and Discussion

The chain-growth mechanism in the CuAAC polymerization of AB_2 monomers was based on the rapid complexation between in-situ formed triazole groups and the Cu catalyst, which efficiently confines the catalyst in the polytriazole polymers[16] and selectively favors the polymer-monomer reaction rather than monomer-monomer reaction. To demonstrate the compatibility of several highly reactive groups, the CuAAC polymerization of each functional monomer in the presence of the B_3 core was conducted at molar ratios of $[F_x]_0$:$[B_3]_0$:$[CuSO_4{\cdot}5H_2O]_0$:[ascorbic acid]$_0$ = m:1:10:10 with constant monomer concentration $[F_x]_0$ = 0.5 mol L^{-1} in DMF solution at 45 °C, where the B_3 molecule functions as an initiator to define the DP of polymers in proportion to monomer conversion.[10b] For instance, when m = 300, all polymerizations reached nearly complete conversion (conv. > 95%) in 4~6 min, producing hyperbranched polymers with very low dispersity M_w/M_n ~ 1.04. More importantly, the absolute molecular weight of these highly branched polymers, $M_{n,MALLS}$, determined by size exclusion chromatography (SEC) in THF equipped with a multi-angle laser light scattering (MALLS) detector, were all very close to the theoretical values, $M_{n,theo}$ = FW_{B3} + m×FW_{Fx}×conv. (FW_{B3} and FW_{Fx} standing for the formula weights of B_3 core and F_x monomer, respecitvely), confirming the controlled chain-growth polymerization during the processes (Table S1, Figures S3-S5). ^{1}H NMR spectroscopy of the purified HBPs (Figure S6) confirmed the quantitative preservation of dangling reactive groups during the polymerization. The degree of branching (DB) of polymers was calculated as DB ~ 0.8 (Figure S7), representing a highly arborescent and dense polymer structure.

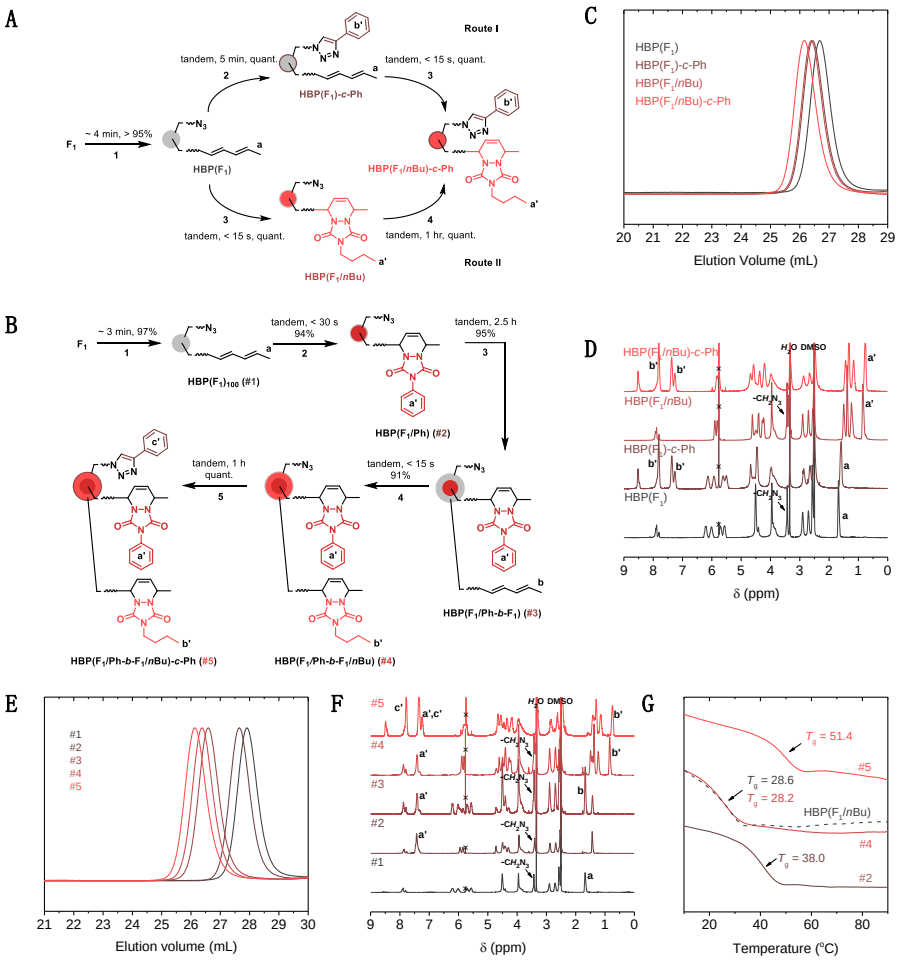

Figure 1. A) Rapid CuAAC polymerization of F_1 monomer and subsequent functionalization reactions, conditions: 1. $[F_1]_0$:$[B_3]_0$:$[CuSO_4{\cdot}5H_2O]_0$:[ascorbic acid]$_0$ = 300:1:10:10, $[F_1]_0$ = 0.5 M in DMF, 45 °C; 2. phenylacetylene (1 equiv.), 45 °C; 3. *n*BuTAD (1.1 equiv.), DMF, r.t.; 4. phenylacetylene (1 equiv.), $CuSO_4{\cdot}5H_2O$ (0.03 equiv.), ascorbic acid (0.03 equiv.), 45 °C; **B**) one-pot sequential synthesis of tri-functionalized segmented hyperbranched polymer using F_1 monomer, conditions: 1. $[F_1]_0$:$[B_3]_0$:$[CuSO_4{\cdot}5H_2O]_0$:[ascorbic acid]$_0$ = 100:1:10:10, $[F_1]_0$ = 0.5 M in DMF, 45 °C; 2. PhTAD (1 equiv.), r.t.; 3. $[F_1]_0$:$[CuSO_4{\cdot}5H_2O]_0$:[ascorbic acid]$_0$ = 200:10:10, $[F_1]_0$ = 0.5 M in DMF, 45 °C; 4. *n*BuTAD (1 equiv.), r.t.; 5. phenyl acetylene (1 equiv.), $CuSO_4{\cdot}5H_2O$ (0.03 equiv.), ascorbic acid (0.03 equiv.), 45 °C; **C**) DMF SEC traces (crude products, RI signal) and **D**) ^{1}H NMR spectra (purified products, DMSO-d_6) of the precursor HBP(F_1) and its functionalized derivatives; **E**) DMF SEC traces (crude products, RI signal) and **F**) ^{1}H NMR spectra (purified products, DMSO-d_6) of individual product in the sequential synthesis of tri-functionalized segmented hyperbranched polymer; **G**) Differential scanning calorimetry (DSC) curves of purified HBP(F_1/*n*Bu), HBP(F_1/Ph), HBP(F_1/Ph-*b*-F_1/*n*Bu) and HBP(F_1/Ph-*b*-F_1/*n*Bu)-*c*-Ph.

Tandem functionalization of hyperbranched polymers on periphery and at interior was first demonstrated using HBP(F_1) (m = 300) as an example (Table 1, Figure 1A). By the end of the polymerization, adding 1 equiv. of phenylacetylene in situ quantitatively reacted all peripheral azido groups on HBP(F_1) in 5 min (Route I, Figure 1A), evidenced by complete disappearance of the methylene proton signal adjacent to azido units (δ = 3.43 ppm) in ^{1}H NMR spectroscopy (Figure 1D) and the azido signal at 2100 cm^{-1} in IR spectroscopy (Figure S11A). The produced HBP(F_1)-*c*-Ph with phenyl (Ph) groups capped at periphery showed smooth shift of SEC trace (Figure 1C) with $M_{n,app}$ = 54.1k and remained low dispersity M_w/M_n = 1.03 as compared to HBP(F_1): $M_{n,app}$ = 49.1k and M_w/M_n = 1.03, determined by DMF SEC based on linear poly(methyl

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methacrylate) (PMMA) standards. Meanwhile, the absolute molecular weight increased from the $M_{n,MALLS}$ = 112.6k of HBP(F_1) to $M_{n,MALLS}$ = 139.1k of HBP(F_1)-*c*-Ph, as recorded by SEC-MALLS, in which the latter value was very close to the theoretical value of $M_{n,MALLS}$ of HBP(F_1) + m×FW of phenylacetylene = 112.6k + 300×102 = 143.2k. If we purified the polymer HBP(F_1)-*c*-Ph by removing the Cu^I catalyst and excess ascorbic acid, the second TAD-diene reaction[3f, 17] inside the polymer could be complete in 15 seconds by reacting with 1 equiv. of 4-*n*-butyl-1,2,4-triazole-3,5-dione (*n*BuTAD), quantitatively producing HBP(F_1/*n*Bu)-*c*-Ph polymer with grafted *n*Bu groups at interior. The 2nd step TAD-diene reaction could also be accomplished in tandem without any purification of HBP(F_1)-*c*-Ph when using 1.1 equiv. of *n*BuTAD since some of the TAD groups was reduced to urazole by the ascorbic acid and Cu^I present in the solution (Figure S8). The reaction could be carried out in many aprotic solvents, e.g., dichloromethane, chloroform, THF, DMSO, and the final product HBP(F_1/*n*Bu)-*c*-Ph showed a monomodal SEC trace with $M_{n,app}$ = 56.9k, $M_{n,MALLS}$ = 179.8k and M_w/M_n = 1.03. The sequence of these tandem reactions could be reversed without any influence on the functionalization efficiency (Route II in Figure 1A, and Figure S9). With the interest of using one single monomer to construct a sophisticated core-shell polymer structure, the synthesis of a hyperbranched polymer tri-functionalized at different layers was demonstrated merely using F_1 monomer (Table 1, Figure 1B). The crude HBP(F_1) with m = 100 was synthesized and subsequently modified with 1 equiv. of 4-phenyl-1,2,4-triazole-3,5-dione (PhTAD) to produce HBP(F_1/Ph). This polymer without any purification could serve as the inner core for chain-extension polymerization with another batch of F_1 (m = 200) to produce HBP(F_1/Ph-*b*-F_1) before a subsequent step of decoration with *n*BuTAD to get HBP(F_1/Ph-*b*-F_1/*n*Bu). In the chain-extension step, it was noticed that additional Cu catalyst should be added since the acidic urazole groups (pK_a ~ 5) generated in the previous reaction could complex Cu^I catalysts.[18] The "living" chain-growth feature was retained in this step as confirmed by linear increase of apparent molecular weights over conversions (Figure S10). Finally, the copolymer was end-capped with phenylacetylene to obtain well-defined final polymer HBP(F_1/Ph-*b*-F_1/*n*Bu)-*c*-Ph with $M_{n,app}$ = 57.3k, and M_w/M_n = 1.04 (Figure 1E). During these sequential chain-extension and functionalizations, the crude and purified polymers after each step were carefully characterized using ^{1}H NMR spectroscopy (Figure 1F), demonstrating more than 95% monomer conversion in each polymerization, as well as 94%, 91%, and 100% incorporation of PhTAD, *n*BuTAD and phenylacetylene units in each layer from inside to outside, respectively. As a further proof, the absolute molecular weight for the four precursors and the final product were also measured, with gradually increased $M_{n,MALLS}$ = 37.2k, 54.7k, 124.9k, 152.8k and 175.3k, respectively. Thermal properties of the polymers HBP(F_1/Ph), HBP(F_1/Ph-*b*-F_1/*n*Bu), HBP(F_1/Ph-*b*-F_1/*n*Bu)-*c*-Ph were strongly influenced by the attached peripheral functional moieties, with an up-and-down change of the glass transition temperature (T_g) from 38.0 °C to 28.2 °C and 51.4 °C, respectively (Figure 1G). Intriguingly, the bilayered HBP(F_1/Ph-*b*-F_1/*n*Bu) showed nearly identical T_g as the mono-functionalized HBP(F_1/*n*Bu) (T_g = 28.6 °C), confirming the segmented structure of the polymers and the dominant effect of outermost layer on the polymer's thermal property.[11]

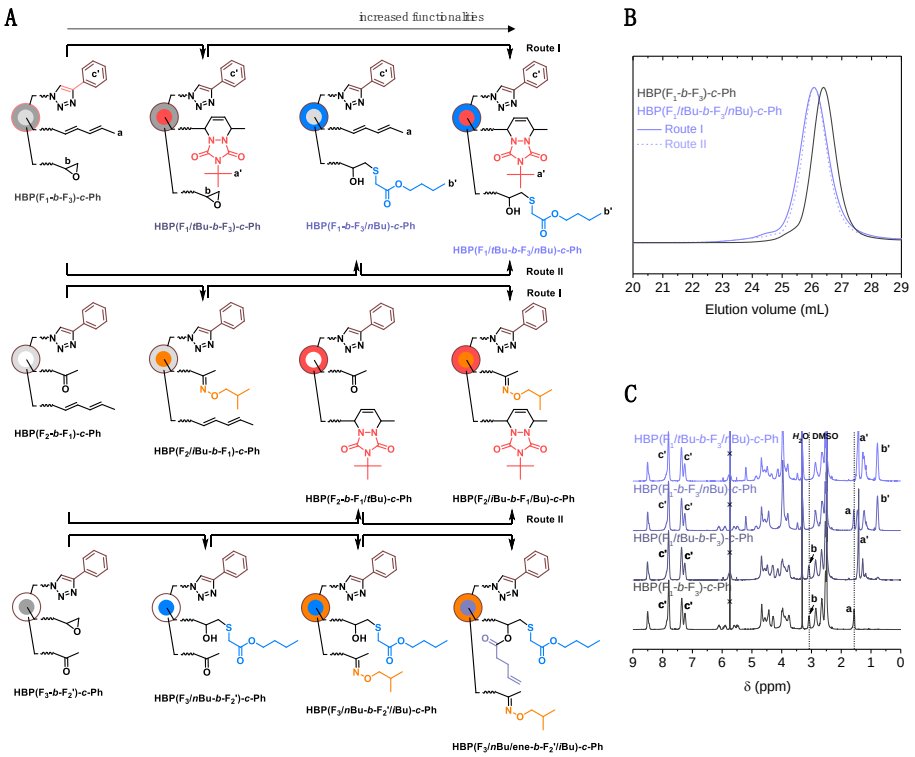

Figure 2. A) A list of segmented hyperbranched polymers synthesized from chain-extension polymerization of two different monomers with subsequent chemo-selective functionalization; **B**) DMF SEC traces (crude products, RI signal) and **C**) ^{1}H NMR spectra (purified products, DMSO-d_6) of the precursor HBP(F_1-*b*-F_3) and its functionalized derivatives.

In a parallel effort, the two-step tandem functionalization of HBP(F_2) was demonstrated complete and efficient by reacting azido groups with 1 equiv. of phenylacetylene and reacting ketone units with 1.2 equiv. of hydroxylamine compounds at room temperature, regardless of the order (Scheme S5, Figure S12).[19] Several interesting features are worth of mentioning during these tandem reactions. First, the HBP(F_2) polymer with 2-butanone as dangling group could serve as the precursor of polyacids, which underwent complete *β*-elimination reaction in the presence of a mild base e.g., triethylamine (Et_3N),[20] as confirmed by successful amidation of the polymer with *n*-butylamine (Scheme S6, Figure S14). However, HBP(F_2') with 2-pentanone as dangling group remained stable under the basic condition, indicating that adding one more methylene unit blocked the *β*-elimination pathway (Fig. S13, S14C). Second, the dynamic covalent character of the oxime bond was demonstrated by exchange reaction between polymer HBP(F_2'/*n*Bu)-*c*-Ph and large excess of *O*-benzyl hydroxylamine, yielding HBP(F_2'/Ph)-*c*-Ph with more than 95% benzyl groups incorporated (Scheme S7, Figure S15).[21] The two-step tandem functionalization of HBP(F_3) was carried out using thiol-epoxy reaction and phenylacetylene coupling reactions (Scheme S8, Figure S17).[22] The ring-open epoxides by reacting with thiols also generated a pendant secondary hydroxyl unit that could undergo further esterification or isocyanate-hydroxyl reaction. Similarly, epoxide ring-opening reaction using sodium azide in the presence of ammonium chloride was also efficient to introduce azido groups for subsequent CuAAC reaction (Scheme S9, Figure S19).[6a]

Table 1. Summary of products from functionalization of hyperbranched homopolymers

	Precursor	Reaction Type	Time	Conv. [%][e]	$M_{n,app}$ [×10^{-3}][f]	M_w/M_n[f]
HBP(F_1)-*c*-Ph	HBP(F_1)[a]	CuAAC	4 min	>99	54.1	1.03
HBP(F_1/*n*Bu)	HBP(F_1)[a]	TAD-diene	15 s	>99	53.2	1.03
HBP(F_1/*n*Bu)-*c*-Ph	HBP(F_1)-*c*-Ph[a]	TAD-diene	15 s	>99	56.9	1.03
HBP(F_1/*n*Bu)-*c*-Ph	HBP(F_1/*n*Bu)[a]	CuAAC	1 hr	>99	57.1	1.03
HBP(F_1/Ph)	HBP(F_1)[a,c]	TAD-diene	1 min	>99	30.1	1.03
HBP(F_1/Ph -*b*-F_1)	HBP(F_1/Ph)[a,c]	CuAAC	2.25 hr	94	48.1	1.03
HBP(F_1/Ph-*b*-F_1/*n*Bu)	HBP(F_1/Ph-*b*-F_1)[a,d]	TAD-diene	15 s	95	51.6	1.04
HBP(F_1/Ph-*b*-F_1/*n*Bu)-*c*-Ph	HBP(F_1/Ph-*b*-F_1/*n*Bu)[a,d]	CuAAC	2 hr	91	57.3	1.04
HBP(F_2)-*c*-Ph	HBP(F_2)[a]	CuAAC	6 min	>99	52.7	1.03
HBP(F_2/*n*Bu)	HBP(F_2)[b]	alkoxyamine-ketone	8 hr	>99	48.3	1.03
HBP(F_2/*n*Bu)-*c*-Ph	HBP(F_2)-*c*-Ph[b]	alkoxyamine-ketone	8 hr	>99	54.6	1.02
HBP(F_2/*n*Bu)-*c*-Ph	HBP(F_2/*n*Bu)[b]	CuAAC	30 min	>99	54.2	1.04
HBP(F_{acid})-*c*-Ph	HBP(F_2)-*c*-Ph[b]	*β*-elimination	8 hr	>99	40.6	1.03
HBP(F_{acid}/*n*Bu)-*c*-Ph	HBP(F_{acid})-*c*-Ph[b]	amidation	12 hr	>99	55.4	1.03
HBP(F_2')-*c*-Ph	HBP(F_2')[a]	CuAAC	9 min	>99	54.8	1.03
HBP(F_2'/*n*Bu)	HBP(F_2')[b]	alkoxyamine-ketone	8 hr	>99	52.9	1.04
HBP(F_2'/*n*Bu)-*c*-Ph	HBP(F_2')-*c*-Ph[b]	alkoxyamine-ketone	8 hr	>99	57.3	1.04
HBP(F_2'/Ph)-*c*-Ph	HBP(F_2'/*n*Bu)-*c*-Ph[b]	ligand-exchange	24 hr	95	56.3	1.03
HBP(F_3)-*c*-Ph	HBP(F_3)[a]	CuAAC	4 min	>99	52.9	1.06
HBP(F_3/*n*Bu)-*c*-Ph	HBP(F_3)-*c*-Ph[b]	thiol-epoxy	12 hr	>99	56.7	1.05
HBP(F_3/*n*Bu/ene)-*c*-Ph	HBP(F_3/*n*Bu)-*c*-Ph[b]	esterification	36 hr	>99	60.2	1.07
HBP(F_{azide})-*c*-Ph	HBP(F_3)-*c*-Ph[b]	azidation	36 hr	>99	60.4	1.07
HBP(F_{azide}/*n*Bu)-*c*-Ph	HBP(F_{azide})-*c*-Ph[b]	CuAAC	30 min	>99	63.6	1.08

a Precursor that was directly post-functionalized via sequential addition of reactants in one pot without any purification process from the previous step. b Precursor that was purified prior to use. c Precursor from CuAAC polymerization with m = 100. d Precursor from CuAAC chain-extension with m = 200 for the 2nd batch of F_1 monomer. e Conversion of functionalizable groups in the purified product, or conversion of the second batch monomer for CuAAC chain-extention of HBP(F_1/Ph), as determined by ^{1}H NMR spectroscopy. f Apparent number-average molecular weight and dispersity measured by DMF SEC with RI detector, calibrated with linear PMMA standards. Unless noted otherwise, initial homopolymers were prepared from CuAAC polymerization with m = 300.

Table 2. Sequential functionalization of hyperbranched copolymers with segmented structure

	Precursor	Reaction Type	Time	Conv. [%][c]	$M_{n,app}$ [×10^{-3}][d]	M_w/M_n[d]
HBP(F_1-*b*-F_3)-*c*-Ph	HBP(F_1-*b*-F_3)[a]	CuAAC	25 min	>99	56.4	1.06
HBP(F_1/*t*Bu-*b*-F_3)-*c*-Ph	HBP(F_1-*b*-F_3)-*c*-Ph[b]	TAD-diene	15 s	>99	59.5	1.09
HBP(F_1-*b*-F_3/*n*Bu)-*c*-Ph	HBP(F_1-*b*-F_3)-*c*-Ph[b]	thiol-epoxy	12 hr	>99	63.0	1.10
HBP(F_1/*t*Bu-*b*-F_3/*n*Bu)-*c*-Ph	HBP(F_1/*t*Bu-*b*-F_3)-*c*-Ph[a]	thiol-epoxy	12 hr	>99	64.5	1.13
HBP(F_1/*t*Bu-*b*-F_3/*n*Bu)-*c*-Ph	HBP(F_1-*b*-F_3/*n*Bu)-*c*-Ph[b]	TAD-diene	15 s	>99	64.2	1.11
HBP(F_1-*b*-F_3)-*c*-Glu	HBP(F_1-*b*-F_3)[a]	CuAAC	25 min	>99	64.9	1.06
HBP(F_1/Boc-*b*-F_3)-*c*-Glu	HBP(F_1-*b*-F_3)-*c*-Glu[b]	TAD-diene	15 s	>99	68.3	1.09
HBP(F_1/Boc-*b*-F_3/SAc)-*c*-Glu	HBP(F_1/Boc-*b*-F_3)-*c*-Glu[a]	thiol-epoxy	36 hr	>99	70.2	1.11
HBP(F_2-*b*-F_1)-*c*-Ph	HBP(F_2-*b*-F_1)[a]	CuAAC	40 min	>99	53.5	1.03
HBP(F_2/*i*Bu-*b*-F_1)-*c*-Ph	HBP(F_2-*b*-F_1)-*c*-Ph[b]	alkoxyamine-ketone	8 hr	>99	55.1	1.04
HBP(F_2-*b*-F_1/*t*Bu)-*c*-Ph	HBP(F_2-*b*-F_1)-*c*-Ph[b]	TAD-diene	15 s	>99	57	1.03
HBP(F_2/*i*Bu-*b*-F_1/*t*Bu)-*c*-Ph	HBP(F_2/*i*Bu-*b*-F_1)-*c*-Ph[b]	TAD-diene	15 s	>99	57.1	1.04
HBP(F_2/*i*Bu-*b*-F_1/*t*Bu)-*c*-Ph	HBP(F_2-*b*-F_1/*t*Bu)-*c*-Ph[a]	alkoxyamine-ketone	8 hr	>99	58.1	1.05
HBP(F_2-*b*-F_1)-*c*-(PEO$^{0.42}$*n*Bu$^{0.58}$)	HBP(F_2-*b*-F_1)[a]	CuAAC	40 min	>99	60.6	1.05
HBP(F_2-*b*-F_1/Ph$^{0.75}$*n*Bu$^{0.25}$)-*c*-(PEO$^{0.42}$*n*Bu$^{0.58}$)	HBP(F_2-*b*-F_1)-*c*-(PEO$^{0.42}$*n*Bu$^{0.58}$)[b]	TAD-diene	1 min	>99	61.9	1.06
HBP(F_2/Dan$^{0.16}$*n*Bu$^{0.84}$-*b*-F_1/Ph$^{0.75}$*n*Bu$^{0.25}$)-*c*-(PEO$^{0.42}$*n*Bu$^{0.58}$)	HBP(F_2-*b*-F_1/Ph$^{0.75}$*n*Bu$^{0.25}$)-*c*-(PEO$^{0.42}$*n*Bu$^{0.58}$)[a]	alkoxyamine-ketone	18 hr	>99	63.8	1.08
HBP(F_3-*b*-F_2')-*c*-Ph	HBP(F_3-*b*-F_2')[a]	CuAAC	40 min	>99	59.9	1.05
HBP(F_3/*n*Bu-*b*-F_2')-*c*-Ph	HBP(F_3-*b*-F_2')-*c*-Ph[b]	thiol-epoxy	12 hr	>99	58.6	1.06
HBP(F_3/*n*Bu-*b*-F_2' /*i*Bu)-*c*-Ph	HBP(F_3/*n*Bu-*b*-F_2')-*c*-Ph[b]	alkoxyamine-ketone	8 hr	>99	60.8	1.05
HBP(F_3/*n*Bu/ene-*b*-F_2' /*i*Bu)-*c*-Ph	HBP(F_3/*t*Bu-*b*-F_2'/*i*Bu)-*c*-Ph[b]	esterification	36 hr	>99	61.3	1.06
HBP(F_3-*b*-F_2')-*c*-EtHex	HBP(F_3-*b*-F_2')[a]	CuAAC	40 min	>99	62.5	1.06
HBP(F_3/Gly-*b*-F_2')-*c*-EtHex	HBP(F_3-*b*-F_2')-*c*-EtHex[b]	thiol-epoxy	36 hr	>99	60.6	1.06
HBP(F_3/Gly-*b*-F_2' /DEG)-*c*-EtHex	HBP(F_3/Gly-*b*-F_2')-*c*-EtHex[b]	alkoxyamine-ketone	12 hr	>99	61.5	1.05

a Precursor that was directly post-functionalized via sequential addition of reactants in one pot without any purification process. b Precursor that was purified prior to use. c Conversion of reactive groups in the purified product determined by 1H NMR spectroscopy. d Apparent number-average molecular weight and dispersity of crude product measured by DMF SEC with RI detector, calibrated with linear PMMA standards. All copolymer precursors were synthesized from CuAAC polymerization with m = 100 for the 1st monomer and m = 200 for the 2nd monomer.

The "living" CuAAC polymerization allows sequential addition of functional monomers in one pot and renders the possibility to place desired reactive groups in specific domain while minimizing the synthetic effort. Three types of segmented hyperbranched copolymers HBP(F_1-*b*-F_3)-*c*-Ph, HBP(F_2-*b*-F_1)-*c*-Ph, HBP(F_3-*b*-F_2')-*c*-Ph, with different monomer placement sequences were prepared by sequential addition of the 1st monomer in m = 100 followed by chain-extension polymerization of the 2nd monomer (m = 200) and end capping using 1 equiv. of phenylacetylene to the azido groups (Table 2, Figure 2A). No loss of functional group was observed in all cases. ^{1}H NMR characterization (Figure S21) confirmed that the molar ratios of the two monomer units and the terminal phenyl units exactly matched the feed ratio of 1:2:3 in each copolymer. Sequential functionalization was carried out on each copolymer. For example, treating the HBP(F_1-*b*-F_3)-*c*-Ph with equimolar *t*BuTAD (to F_1 monomer units) completely disappeared the diene peaks (δ = 6.21~5.42 ppm, Figure 2C) and introduced the *t*-butyl proton peak at δ = 1.48~1.12 ppm. Subsequent addition of *n*-butyl thioglycolate in basic condition into the polymer solution disappeared the characteristic proton signal of epoxide at δ = 3.08 ppm but quantitatively produced a new peak at δ = 0.78 ppm, representing the CH_3- protons from the *n*-butyl group (Figure 2C). In both reactions, the reactive groups were compatible in the other reactions and did not introduce any side product. The sequential functionalization of HBP(F_1-*b*-F_3)-*c*-Ph was also successful to produce HBP(F_1/*t*Bu-*b*-F_3/*n*Bu)-*c*-Ph in either synthetic pathway as demonstrated by ^{1}H NMR spectroscopy with molar ratio of $f_{t\mathrm{Bu}}$: $f_{n\mathrm{Bu}}$ ≈ 1:2 and SEC measurements ($M_{n,app}$ = 64.5k, M_w/M_n = 1.13, Route I, or $M_{n,app}$ = 64.2k, M_w/M_n = 1.11, Route II, Table 2, Figures 2B, S22). To demonstrate that our strategy is applicable for other guest molecules with tunable reactivity and polarities, HBP(F_1-*b*-F_3) was capped with glucose, modified with a Boc-protected amine derived TADs and thiol acetic acid which could be easily transformed to amine and thiol groups (Figure S23).

Hyperbranched polymer with a radial polarity gradient could also be prepared through three-step modifications by using HBP(F_3-*b*-F_2') as the parent scaffold (Figure S24). In all cases, complete conversions of functional groups were achieved with no side reactions (Table 2). In another example, tetra-functionalized polymer ($M_{n,app}$ = 61.3k, M_w/M_n = 1.06) was synthesized through sequential modification of the HBP(F_3-*b*-F_2')-*c*-Ph with *n*-butyl thioglycolate, *O*-*i*-butyl hydroxylamine, and 4-pentenoic acid for reacting with epoxy, carbonyl and hydroxyl groups (after epoxide ring-opening reaction), respectively (Table 2, Figure S25).

For advanced applications (e.g. catalysis, diagnosis and therapy), it is often desirable to formulate the dosages of multiple reactive species into one nanostructure.[23] In our study, the three efficient click reactions between alkyne and azide, triazolinediones and diene, hydroxylamine and ketone provide possibility to use mixed substrates for one reaction to simultaneously introduce two functional groups into one domain. To test this versatility, the HBP(F_2-*b*-F_1) (m_{total} = 300 with theoretical ratio of F_2:F_1 as 1:2) immediately after polymerization was functionalized in situ via end-capping reaction with a mixture of alkynyl-terminated poly(ethylene glycol) with average molar mass 350 g/mol (ay-PEG_{350}) and propynyl *n*-butyrate at 0.4:0.6 molar ratio (1 equiv. to the azido groups on polymer). The polymer after purification was further functionalized on the shell using a mixture of PhTAD: *n*BuTAD at molar ratio 0.75:0.25 (totally 1 equiv. to the diene units) and in the core using a mixture of dansyl (Dan)-hydroxlamine and *O*-*n*Bu hydroxylamine at molar ratio 0.3:0.9 (1.2 equiv. to the ketone units, Figure 3A), producing final product HBP(F_2/Dan$^{0.16}$*n*Bu$^{0.84}$-*b*-F_1/Ph$^{0.75}$*n*Bu$^{0.25}$)-*c*-(PEO$^{0.42}$*n*Bu$^{0.58}$) ($M_{n,app}$ = 63.8k, M_w/M_n = 1.08, Table 2, Figure S27). The evolution of ^{1}H-NMR spectra after individual modification exhibited complete consumption of the clickable groups, the ratio of guest molecules incorporated via CuAAC and TAD-diene reactions exactly matched with the initial feed ratio (Figure 3B).

Conclusions

In this study, we developed a robust polymer platform to construct structurally defined hyperbranched polymers with an array of densely functionalized groups at different spatial layers. The employed chain-growth CuAAC polymerization of three types of AB_2-F_x (x = 1, 2, 2" and 3) functional monomers and various types of subsequent orthogonal modifications, including ultrafast TAD-diene reaction, alkoxyamine-ketone reaction, and thiol-epoxy reaction, were all conducted under mild conditions with high efficiency. In addition, successful combination of four chemo-selective reactions allowed accurate and quantitative allocation of several model guest molecules within one polymer nanostructure at different placements. By simply varying the monomers, the guest molecules and their ratios, all structural and compositional parameters within these hyperbranched polymers could be adjusted. Considering the extensive applications of dendritic polymers, increasingly demanding requirements of complexity for high-performance polymers, as well as tedious synthetic procedure of traditional dendrimers, this development will become a useful toolbox that enables a facile access to unlimited types of polytriazoles with desired functions. We envisage that many other functionalization techniques could be possibly compatible with the current CuAAC polymerization, which may further enrich the elements in this toolkit for preparing advanced materials.

Experimental Section

Preparation of segmented HBP(F_2-*b*-F_1)-c-Ph via CuAAC polymerization in one pot. The inner core HBP(F_2) was firstly synthesized at molar ratios of $[F_2]_0$:$[B_3]_0$:$[CuSO_4{\cdot}5H_2O]_0$:[ascorbic acid]$_0$ = 100:1:10:10. F_2 (305.3 mg, 0.7 mmol), B_3 (3.6 mg, 7.0 μmol), $CuSO_4{\cdot}5H_2O$ (17.5 mg, 70.0 μmol) and 1.2 mL DMF were charged in a 10 mL schlenk flask equipped with a magnetic stirring bar. The flask was subjected to three freeze-pump-thaw cycles, back-filled with nitrogen and immersed in a thermostatic oil bath at 45 °C. The reaction was initiated by quickly addition of a degassed solution of ascorbic acid (12.3 mg, 70.0 μmol) in 0.2 mL DMF ($[F_2]_0$ = 0.5 mol L^{-1} in total amount of DMF). After 4 min, 98% monomer conversion was reached, and a 2nd batch of deoxygenated F_1 monomer (624.7 mg, 1.4 mmol, m = 200) in 2.4 mL DMF was added into the system and allowed to react for 40 minutes to reach completion.

The chain-end azido units of the resulted hyperbranched polymer were subsequently modified by adding deoxygenated phenylacetylene (214.3 mg, 2.1 mmol) to the mixture via a 1 mL syringe, and allowed to react at 45 °C for another 40 min before dilution with 10 mL CH_2Cl_2.

The Cu catalyst was then removed by adding two equivalents of 2,2'-bipyridyl (bpy) ligand followed by passing through a flash neutral alumina column. The catalyst-free solution of hyperbranched polymers were precipitated into 40 mL diethyl ether three times, dried *in vacuo* to a constant mass, yielding 1.06 g product as a white solid (93%), which was stored in a freezer at -20 °C before further usage.

Preparation of HBP(F_2-*b*-F_1/*t*Bu)-c-Ph via TAD-diene reaction. 408.7 mg purified HBP(F_2-*b*-F_1)-c-Ph (750.0 μmol of total monomer units) was dissolved in 1.5 mL anhydrous DMF in a 10 mL round-bottom flask equipped with a magnetic stirring bar. To this stirring solution was added dropwise a freshly prepared solution of 77.5 mg *t*BuTAD (500.0 μmol, 1.0 equiv. to the diene groups) in 1.5 mL anhydrous DMF at room temperature, with instant disappearance of the characteristic reddish color of TAD. The resulting pale yellow solution was evenly separated into two portions, with one precipitated into 20 mL ethyl ether three times to remove the DMF and then dried *in vacuo*, yielding 238.1 mg pale brown solid (98%), while the other half was directly used for next-step reaction.

Preparation of HBP(F_2/*i*Bu-*b*-F_1)-c-Ph via alkoxyamine-ketone reaction. To the above solution was sequentially added *O*-*i*-butylhydroxylamine hydrochloride (18.8 mg, 150.0 μmol, 1.2 equiv. to the ketone groups), Et_3N (15.2 mg, 150.0 μmol) and *p*-phenylenediamine (32.4 mg, 300.0 μmol, 0.2 mol L^{-1} in DMF) under nitrogen atmosphere. The mixture was stirred continuously for 8 hours at room temperature, before being precipitated into 20 mL of ethyl ether three times, redissolved in 5 mL CH_2Cl_2 and passed through a flash neutral alumina column. After dried *in vacuo* to a constant mass, the product was 236.9 mg in pale brown solid (94%).

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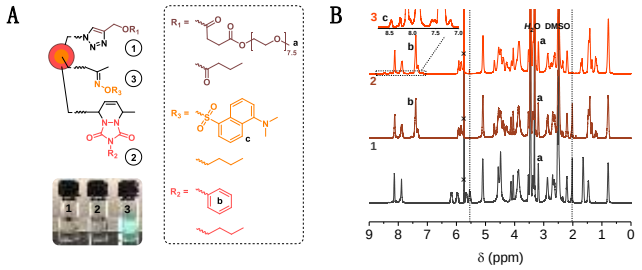

Figure 3. A) The HBP(F_2/Dan$^{0.16}$*n*Bu$^{0.84}$-*b*-F_1/Ph$^{0.75}$*n*Bu$^{0.25}$)-*c*-(PEO$^{0.42}$*n*Bu$^{0.58}$) synthesized from sequential loading of mixtures of guest molecules on segmented HBP(F_2-*b*-F_1) polymers, conditions: 1. PEO_{350}-alkyne (0.4 equiv.), propynyl *n*-butyrate (0.6 equiv.), 45 °C, no purification after polymerization in situ; 2. PhTAD (0.75 equiv.), *n*BuTAD (0.25 equiv.), DMF, r. t., with purified polymer; 3. dansyl-hydroxlamine (0.3 equiv.), *O*-*n*-butyl hydroxylamine hydrochloride (0.9 equiv.), Et_3N (0.9 equiv.), *p*-phenylenediamine (100 mM), DMF, r. t., with purified polymer; inset photos: the DMF solutions of the final products after each step with concentrations of monomer units = 0.3 mmol L^{-1}, illuminated by portable UV lamp (excitation at 365 nm). **B**) ^{1}H NMR spectra (purified products, DMSO-d_6) of the corresponding polymers.

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Keywords: Click Chemistry • Hyperbranched Polymer • Functionalization • Layered Structure

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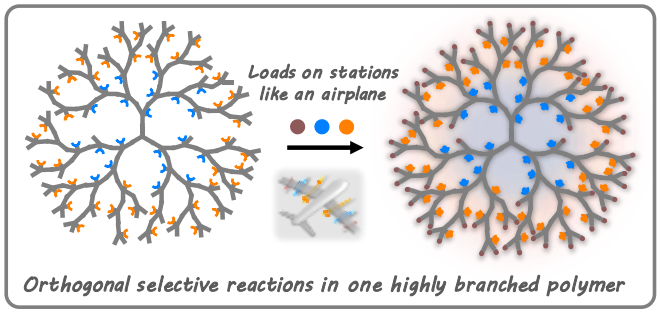

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