ACS Macro Letters

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Combination of Orthogonal ABB and ABC Multicomponent Reactions toward Efficient Divergent Synthesis of Dendrimers with Structural Diversity

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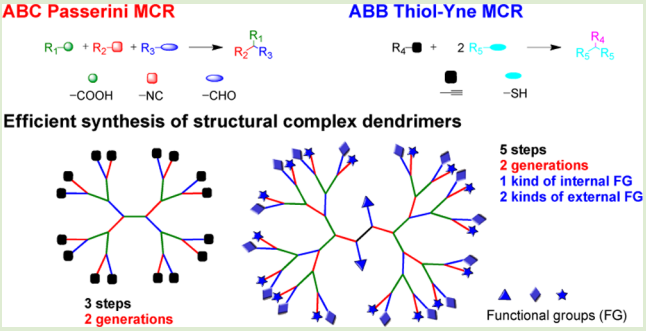
Supporting Information

ABSTRACT: Synthesis of dendrimers has been directed toward process efficiency and structural diversity. We report a divergent approach to the preparation of dendrimers with both ABC and ABB branching structures from nonbranching monomers by combination of efficient orthogonal ABC Passerini multicomponent reaction (MCR) and ABB thiol–yne MCR. Two kinds of dendrimers were synthesized efficiently: (1) dendrimers with two generations in three steps and (2) dendrimers with two generations containing one kind of internal functional group and two kinds of surface functional groups in five steps. This new synthetic method offers an efficient access to dendrimers with structural diversity.



Dendrimers are monodisperse, highly branched, three-dimensional synthetic polymers that exhibit unique features such as low intrinsic viscosity in solution, internal cavities for guest compounds, and large number of surface functionalities. These properties make them ideal materials for biomedical applications.[1] Especially dendrimers with complex structures such as internal functional groups or/and two kinds of peripheral functional groups have received increasing interest when they are applied in new fields.[2] Thus, efficient constructing diverse dendritic structures become important.[3]

Traditionally, dendrimers are synthesized by using repetitive steps of efficient synthetic protocols by either a divergent or a convergent approach.[4] In the divergent approach, the process efficiency to construct the dendritic scaffolds is strongly influenced by the tedious multistep procedures with repetitive protection–deprotection/activation and the chromatographic purification. Various new synthetic strategies aiming at enhancing the process efficiency have been developed, including those by the double stage[5] and double exponential growth,[6] using branched monomers[7] and orthogonal coupling.[3c,8] Recently, highly efficient click reactions such as copper-catalyzed [3 + 2] cycloaddition reaction between azides and alkynes,[9] thiol–ene reaction,[10] epoxy–amine reaction,[2d,e] aza-Michael addition reaction,[11] and thiol–yne reaction[2e,11b,12] have also been used for the synthesis of dendrimers. However, most of the previously reported divergent approaches introduce the branching structures in two ways: (1) the AB two-component reaction (AB 2CR, e.g., thiol–ene reaction) (Figure 1A) and (2) the ABB multicomponent reaction (ABB MCR,[13] e.g., thiol–yne reaction) (Figure 1B). These two ways can yield dendrimers with only the ABB branching structures and one kind of functional group located on the surface. Thus, the structural diversity of the synthesized dendrimers is limited.

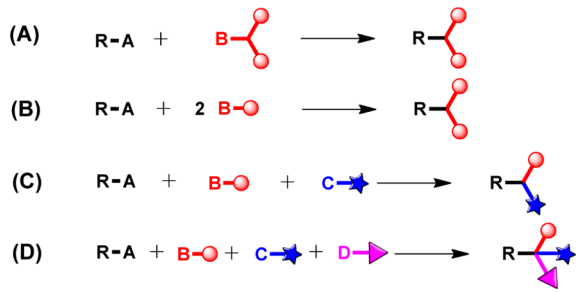


Figure 1. Strategies of introducing branching structures into dendrimers (divergent approach).

Several approaches have been reported to synthesize dendrimers with structural diversities. For example, the AB_2C monomer approach[2b,c] and the "epoxy–amine" reaction approach[2d] can offer access to internally functionalized dendrimers. However, the former needs the synthesis of complex monomers, and the latter requires postmodifications of the hydroxyl groups formed during the generation increase.

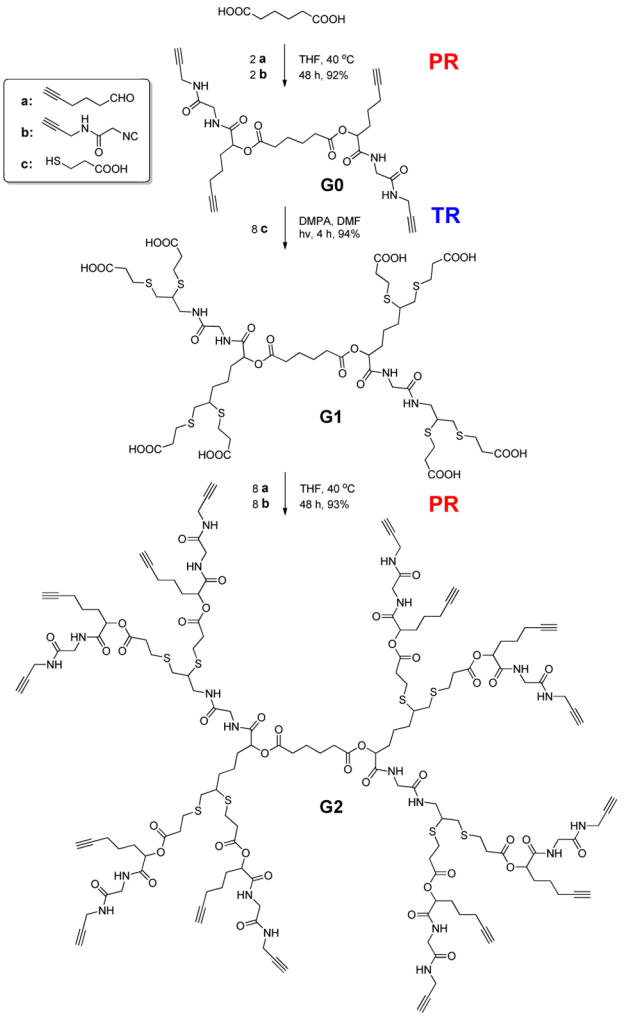
Received: April 7, 2014
Accepted: June 19, 2014
Published: June 20, 2014

   dx.doi.org/10.1021/mz500207z | ACS Macro Lett. 2014, 3, 667–670

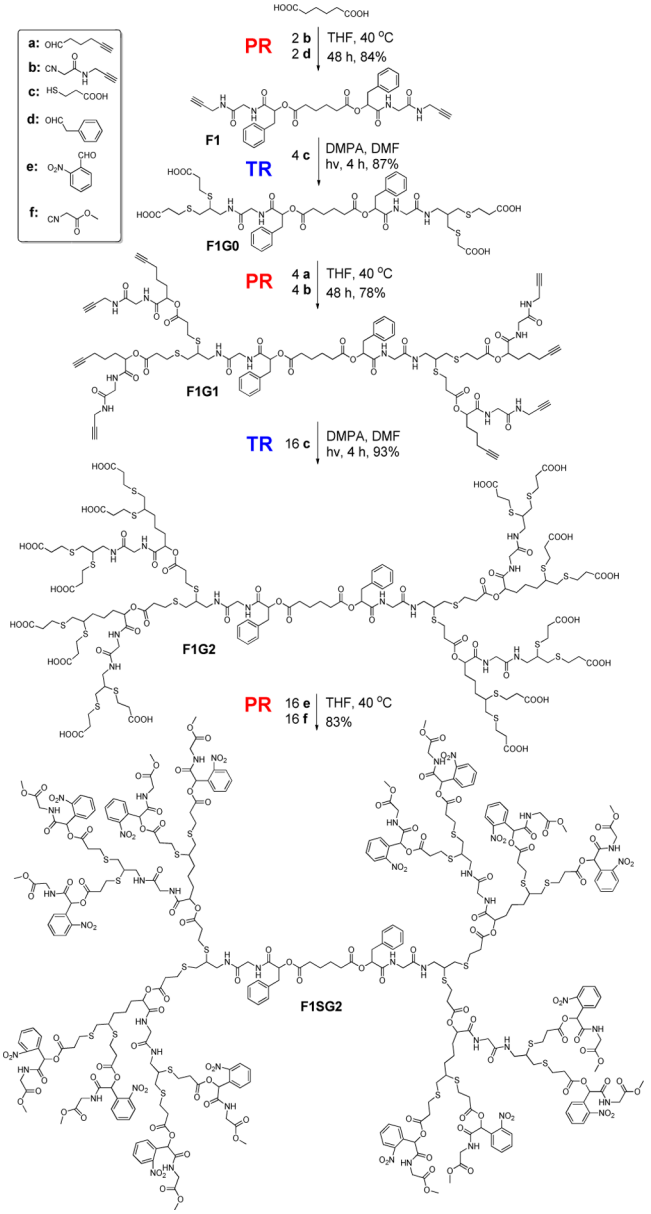
Meanwhile, the synthetic approach toward peripheral bifunctional dendrimers needs two steps for surface modifications.[2a,14] Recently, isocyanide-based multicomponent reactions (IMCRs) became rather popular in diversity-oriented macromolecular synthesis.[15−18] Wessjohann et al. reported the synthesis of structurally diverse dendrimers by multiple iterative IMCR (ABC-type Passerini reaction and ABCD-type Ugi reaction).[15c] Although the branching structures formed during the Passerini reaction and Ugi reaction can independently introduce internal and external functional groups into dendrimers (Figure 1C and 1D, respectively), the protection−deprotection protocols and chromatographic purification reduce the synthetic efficiency. Thus, synthesis of structurally diverse dendrimers with high process efficiency remains a challenge.

Herein, we report the first example of efficient synthesis of dendrimers with both ABB and ABC branching structures from nonbranching monomers by combination of the efficient orthogonal ABB thiol−yne MCR (Figure 1B) and ABC Passerini MCR (Figure 1C) under mild conditions. Two kinds of dendrimers were synthesized: (1) dendrimers with two generations via three steps (Scheme 1) and (2) dendrimers with two generations containing one kind of internal functional group and two kinds of surface functional groups via five steps (Scheme 2). Each step of the ABB or the ABC reaction can form branching structures and increase one generation, while the ABC Passerini reaction can also introduce internal functional groups or simultaneous anchoring of two kinds of peripheral functional groups.

Scheme 1. Divergent Synthesis of Dendrimers by Combination of ABB Thiol−Yne Reaction (TR) and ABC Passerini Reaction (PR)



Scheme 2. Divergent Synthesis of Functional Dendrimers by a Combination of ABB Thiol−Yne Reaction (TR) and ABC Passerini Reaction (PR)



The synthetic strategy for generation growth with high efficiency is illustrated in Scheme 1. First, the Passerini reaction of 1,6-hexanedioic acid, 5-hexyn-1-al (**a**), and propargyl isocyanoacetamide (**b**) conducted in THF at 40 °C for 48 h afforded compound **G0** with four terminal alkyne units. The isolation of **G0** can be simply done by precipitation into diethyl ether (Figure S1, Supporting Information (SI)), and the yield was 92%. Second, the thiol−yne reaction of **G0** with the commercially available 3-mercaptopropionic acid (**c**) under 365 nm UV light (photoinitiator DMPA, 4 h, rt) followed by precipitation in diethyl ether yielded **G1** with eight peripheral

dx.doi.org/10.1021/mz500207z | ACS Macro Lett. 2014, 3, 667−670

carboxylic acid groups in 94% yield. Finally, the Passerini reaction of **G1** with **a** and **b** afforded **G2** in 93% yield. The structures of **G0**, **G1**, and **G2** were confirmed by both ^{1}H NMR and ^{13}C NMR spectra (Figures S2 and S3, SI). For example, in the ^{1}H NMR spectrum of **G2** shown in Figure S2C (SI), all the signals can be assigned exactly, and the integrations are in accordance with the expected structure of **G2**. Especially, the integrations of the signals related to the typical protons (*b*, *i*, and *k*) indicated that **G2** has 4 + 4 alkyne groups. The GPC traces of **G0** and **G2** indicated the systematic increase in dendrimer size from **G0** to **G2** (Figures S4 and S5, SI). Moreover, the MALDI-TOF-MS spectra of **G0**, **G1**, and **G2** showed the expected peaks at 605.3, 1454.0, and 3202.2 ([M + Na^{+}]), respectively (Figure 2), further confirming the

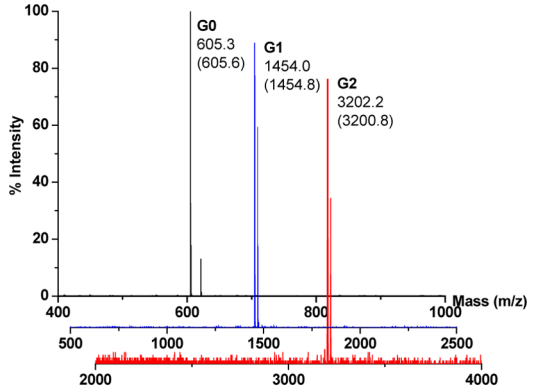


Figure 2. MALDI-TOF-MS of **G0**, **G1**, and **G2**. The calculated [M + Na^{+}] were shown in parentheses.

integration of the structures. Compounds **G0** and **G2** were subjected to silica column purification to get compounds **G0′** and **G2′**, and the corresponding characterizations of these two compounds are shown in the Supporting Information. Both the GPC trace and NMR spectrum of **G0′** were improved, but for compound **G2′**, almost identical results were obtained as compared to compound **G2**. Therefore, simple precipitation can guarantee the purity of high generation dendrimers. Further synthesis of **G3** from **G2** was tried in 360% excess of compound **c** (Scheme S1, SI). The MALDI-TOF-MS spectrum of the final product indicated that compound **G3** was formed (Figure S6, SI), but some defects existed. This is probably caused by the steric hindrance of the peripheral alkynyl groups. This strategy can also be extended to other types of dendrimers. As an example, a combination of the Passerini reaction of hexane-1,6-dial, 6-heptynoic acid with **b**, and the following thiol−yne reaction with **c** can generate another series of dendrimers (Scheme S2 and Figures S7−S10, SI).

After demonstrating the high efficiency of generation growth by combination of the ABC Passerini reaction and the ABB thiol−yne reaction, we next focus on enhancing the efficiency of both generation growth and functional group introduction. Scheme 2 illustrates a proof of concept design of functional dendrimers. In the first step, the Passerini reaction of 1,6-hexanedioic acid, **b**, and phenylacetaldehyde (**d**) generated **F1**, which contains a benzyl group and two peripheral alkyne groups. Again, simple precipitation is enough for successful purification (Figure S11, SI). Then, the thiol−yne reaction of **F1** with **c** under similar conditions as described above afforded **F1G0**. Thus, these two steps introduce one functional group at the specific position. Both steps are highly efficient with high yields. Repeating the above two steps can generate **F1G1** and **F1G2**, respectively. The structures of **F1**, **F1G0**, **F1G1**, and **F1G2** were characterized by ^{1}H NMR and ^{13}C NMR spectra (Figure S12 and Figure S13, SI). Typical signals related to the protons which were generated by the Passerini reaction in different generations were clear in the spectra. For instance, in Figure S12C (SI), the integrations of *c* and *n* indicated that during the synthesis of **F1G1** Passerini reactions occurred two and four times during the first and the third step, respectively. Again, the GPC traces of **F1** and **F1G1** showed a systematic increase in dendrimer size from **F1** to **F1G1** (Figure S14, SI). Moreover, the MALDI-TOF-MS spectra of **F1**, **F1G0**, **F1G1**, and **F1G2** showed the expected peaks at 653.0, 1077.5, 1950.3, and 3647.9 ([M + Na^{+}]), respectively, demonstrating the monodispersities of the compounds (Figure 3).

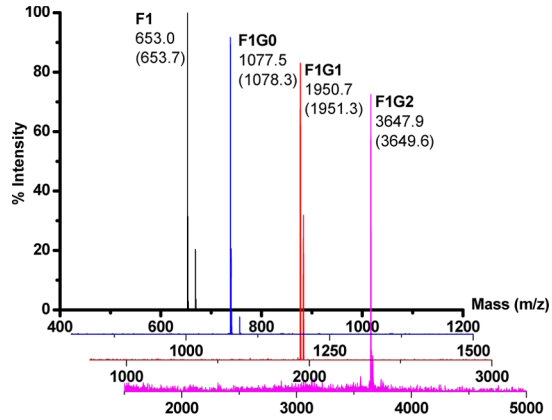


Figure 3. MALDI-TOF-MS of **F1G0**, **F1G0**, **F1G1**, and **F1G2**. The calculated [M + Na^{+}] were shown in parentheses.

To further demonstrate the high efficiency of introducing two kinds of peripheral functional groups by the Passerini reaction, **F1G2** was reacted with 2-nitrobenzaldehyde (**e**) and methyl isocyanoacetate (**f**) to generate **F1SG2**. It is worth noting that for the synthesis of **G0**, **G2**, **F1**, and **F1G1** the Passerini reaction was conducted with 1.2 equiv of aldehyde and isocyanide. However, for **F1SG2**, incomplete conversion of **F1G2** was detected by GPC even with 1.5 equiv of aldehyde and isocyanide (Figure S15, SI). Therefore, another 1.5 equiv of aldehyde and isocyanide were added, and the reaction was continued for another 48 h to get **F1SG2** with narrow polydispersity (Figure S16, SI). This indicated that the efficiency of Passerini reaction of high generation dendrimers was somehow reduced. The ^{1}H NMR spectra of **F1SG2** are shown in Figure S17 (SI). The integrations of *c*, *n*, and *v* indicated that the Passerini reactions occurred 2, 4, and 16 times during the first, third, and fifth step, respectively. Unfortunately, when **F1SG2** was characterized by MALDI-TOF-MS, the laser was operated at 337 nm, and thus partial photodegradation of **F1SG2** occurred.[19] Nevertheless, the molecular ion peak was observed in the MALDI-TOF-MS spectrum with high intensity (Figure S18, SI). Thus, two kinds of functional groups were introduced into the dendrimers by one step of Passerini reaction.

In conclusion, we demonstrated that a combination of the orthogonal ABB thiol−yne reaction and ABC Passerini reaction is a highly efficient divergent approach to dendrimers with structural diversity. This new method has several advantages. First, each step is highly efficient without protection−

dx.doi.org/10.1021/mz500207z | ACS Macro Lett. 2014, 3, 667−670

deprotection procedure. Second, the separation to remove the unreacted monomer is simple precipitation for high generation dendrimers. Third, highly efficient introduction of functional groups was demonstrated: introducing one kind of internal functional group or two kinds of external functional groups by one step. Dendrimers up to two generations were synthesized in three steps; however, for the synthesis of even higher generation dendrimers, this methodology has some limitations owing to the steric hindrance of the peripheral functional groups and the reduced efficiency of the Passerini reaction. Nevertheless, this approach will not only benefit dendrimer synthesis but also show great potential as a versatile synthetic tool for other functional branched macromolecules.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental section, Schemes S1 and S2, NMR spectra, GPC traces, and MS spectra. 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.

■ ACKNOWLEDGMENTS

This work is financially supported by National Natural Science Foundation of China (No. 21090351 and 21225416) and National Basic Research Program of China (No. 2011CB201402).

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