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Convergent Synthesis of Dendrimers via the Passerini Three-Component Reaction

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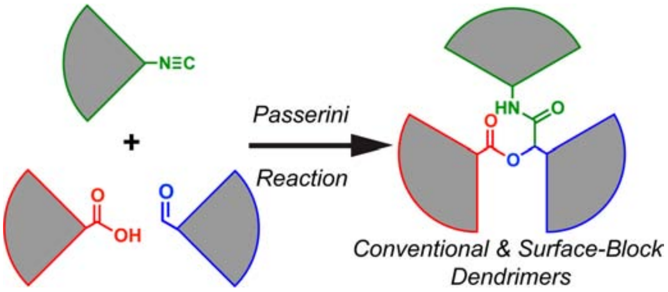
ABSTRACT



Tuning properties by programming the surface functional group composition of surface-block dendrimers has been limited to dendrimers with only two types of surface functionality (i.e., surface-diblock dendrimers). The Passerini reaction provides dendrimer products from precursor dendrons in reasonable yields. This proof-of-principle experiment opens the door to making surface-triblock dendrimers.

Dendrimers are highly branched, globular, and monodisperse macromolecules whose physical and chemical properties are governed by the surface functional groups.[1] Strategies to selectively tune the surface group composition of dendrimers present opportunities in supramolecular materials[1d−f] and nanomedicine.[1f,g,2] Surface-block dendrimers,[3] which contain clusters of functional groups that are different from the other surface groups (Figure 1), offer tailored physical properties[4] and orthogonal reactivity for subsequent modification of the dendrimers.[5] Surface-diblock dendrimers (Figure 1) are sometimes referred to as Janus-type dendrimers,[6] bow-tie dendrimers,[5] or codendrimers.[7] Unanticipated liquid crystal mesophases,[8] vesicular self-assemblies for potential drug delivery,[7,9] soluble drug delivery vehicles,[5,10] organogels,[11] and complex interfacial assemblies[12] have been obtained from

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surface-diblock dendrimers. Surface-block dendrimers having more than two different clusters of surface groups (e.g., surface-triblock dendrimers (Figure 1)) remain an unresolved synthetic challenge. Herein, we describe the convergent synthesis of dendrimers via the Passerini three-component reaction.[13,14] This proof-of-principle experiment establishes a strategy by which surface-triblock dendrimers can be synthesized.

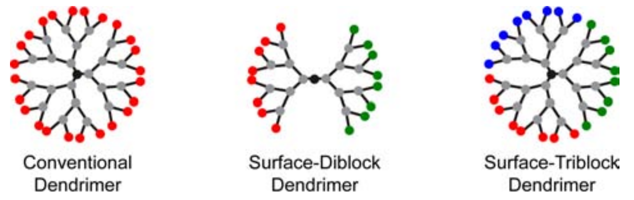
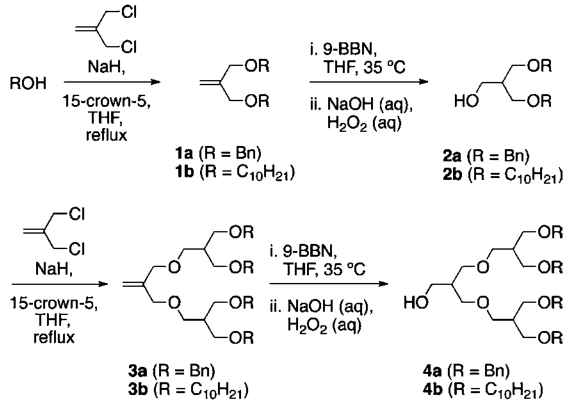


Figure 1. Surface group composition of dendrimer architectures.

Symmetry designed to facilitate the synthesis of dendrimers is the Achilles' heel when synthesizing surface-block dendrimers. Maximizing the number of equivalent reaction sites per molecule through symmetry minimizes the number of synthetic steps required to obtain high molecular weight and large diameter dendrimers. Synthesis of surface-block dendrimers by sequential addition of different dendrons to a symmetric core becomes increasingly laborious as the valency of the core increases (e.g., divalent to trivalent), even when large excesses of reagents are used.[3,4] Difficulty separating mixtures of dendritic products is a significant liability for these linear reaction sequences. Stoichiometric reaction conditions conserve valuable dendritic intermediates and can be combined with high-dilution techniques that suppress formation of unwanted byproducts.[6] Matching the symmetry of the core molecule to that of the desired surface-block dendrimer has yielded efficient syntheses of surface-diblock dendrimers.[8d,15] Nonetheless, coupling of two dendrons bearing complementary apex functional groups[16] remains the most heavily exploited strategy by which to prepare surface-diblock dendrimers.[7,8,16]

Given the widespread adoption of synthesis methods that directly couple dendrons, we were intrigued by the prospect of employing multicomponent reactions in the final step of a convergent synthesis of a dendrimer. Isocyanide multicomponent reactions, such as the Passerini reaction,[13] are established reactions by which three or more components are combined in a single operation.[14] The Passerini reaction is a high fidelity reaction suitable for polymer synthesis[17] and divergent synthesis of dendrimers.[18] The Passerini reaction opens the door to surface-diblock dendrimer compositions not possible via methods described above and, most importantly, a route to surface-triblock dendrimers.

Scheme 1. Synthesis of the Alcohol Precursors of the Passerini Reaction Components



1,3-Propanediol dendrons were selected as a representative case study for the convergent synthesis of dendrimers culminating in a Passerini reaction. The dendrons were synthesized in a convergent manner following the strategy introduced by Fréchet and co-workers.[19] We employed modified literature procedures for the synthesis of second-generation dendrons containing either benzyl[20] or linear alkyl[21] peripheral groups (Scheme 1). In refluxing THF, methallyl dichloride was treated with an excess of either benzyl alcohol or 1-decanol in the presence of NaH. Extended reaction times were encountered when decanol was the nucleophile source. Reaction times were reduced from 22 to 5 h when 15-crown-5 was added as a catalyst. Even under these conditions, careful chromatographic separation was required to remove small amounts of the monoalkylated intermediate. The resulting first-generation alkenes (**1a** and **1b**) were subjected to hydroboration with 9-BBN followed by oxidation by H_2O_2 in the presence of NaOH. The first-generation alcohols (**2a** and **2b**) provided the nucleophile source in a subsequent Williamson ether synthesis with methallyl dichloride in the presence of NaH

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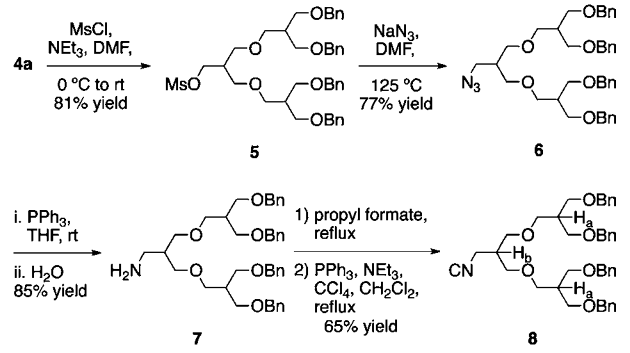
and 15-crown-5. Subjecting the second-generation alkenes (**3a** and **3b**) to hydroboration–oxidation provided the corresponding alcohols (**4a** and **4b**) from which the Passerini reaction components were derived.

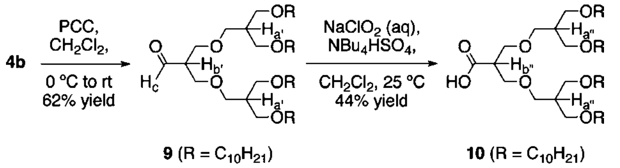
Scheme 2. Synthesis of the Isocyanide Passerini Reaction Component



Isocyanide component **8** was prepared from the second-generation alcohol **4a** (Scheme 2). Alcohol **4a** was transformed to the amine **7** in a manner similar to that reported by Cho and co-workers.[22] Alcohol **4a** was converted to the corresponding sulfonate **5** when treated with mesyl chloride and NEt$_3$. Nucleophilic substitution of the mesylate with azide was achieved in DMF at 125 °C. The azide **6** was reduced to the amine **7** under Staudinger conditions.[23] The dendritic amine **7** was converted to the corresponding formamide in refluxing propyl formate, and the formamide intermediate was dehydrated to the isocyanide **8** by treatment with PPh$_3$, CCl$_4$, and NEt$_3$.[24]

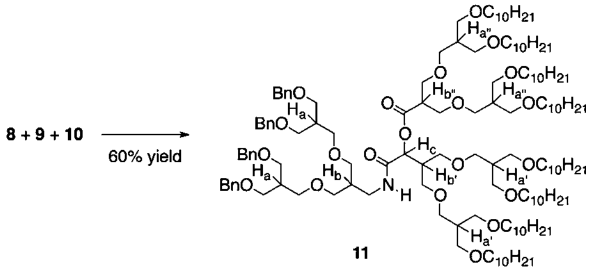
The aldehyde and carboxylic acid components **9** and **10** were prepared from the second-generation dendron **4b** (Scheme 3). Oxidation of the alcohol to the aldehyde **9** with PCC in CH$_2$Cl$_2$ was accomplished in satisfactory yields. Upon storage, the aldehyde **9** undergoes further reaction to yield a higher molecular weight impurity that cannot be removed by chromatography on SiO$_2$. Oxidation of **4b** with PDC in DMF[25] did not yield **10**. However, oxidation of aldehyde **9** to carboxylic acid **10** by NaClO$_2$ under phase transfer conditions was successful.

Scheme 3. Synthesis of the Aldehyde and Carboxylic Acid Passerini Reaction Components



The dendritic components **8**, **9**, and **10** react to yield the anticipated Passerini reaction product.[13] We obtained dendrimer **11** when the reaction was performed neat or in THF solution (Scheme 4). The reaction was difficult to monitor by ^{1}H NMR spectroscopy because signals overlap, but thin layer chromatography (TLC) provided sufficient evidence for the disappearance of starting materials. No other intermediates or byproducts were observed from TLC of the reaction mixture. The product dendrimer was isolated in 60% yield from column chromatography.

Scheme 4. Passerini Reaction Between Dendron Components



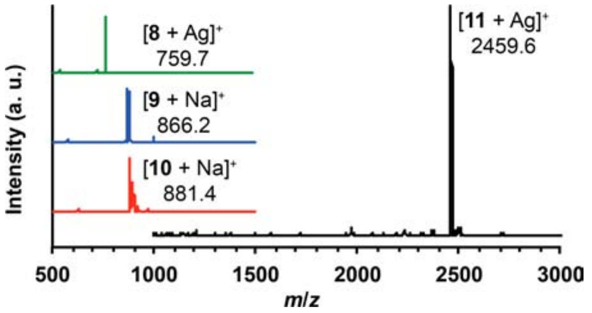


Figure 2. MALDI-TOF Spectra of the component dendrons and the Passerini dendrimer **11**.

Evidence for the identity of the dendrimer was obtained from MALDI-TOF mass spectrometry and elemental analysis. A single mass peak above m/z 1000 is observed in the MALDI-TOF spectrum (Figure 2). The mass peak at m/z 2459.6 corresponds to the expected mass for the $[M + Ag]^+$ ion. Elemental analysis of the dendrimer was also consistent with the expected molecular formula (see Supporting Information).

Resonances unique to the dendrimer product of the Passerini reaction were observed in both ^{1}H and ^{13}C NMR spectra. Figure 3 presents portions of the ^{1}H NMR spectra for the components **8**, **9**, and **10** and for dendrimer **11** in CDCl$_3$. A resonance for the α-acyloxyamide α-*H* (*c*) is observed as a doublet at δ 5.34 ppm. The methine proton resonances of the 1,3-propanediol dendrons provide further evidence that the product dendrimer has incorporated one of each of the three component

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dendrons. Resonances for the outermost, first-generation layer of methine protons (*a*, *a*′, and *a*″) at δ 2.22 ppm and δ 2.09 ppm in **11** are essentially unchanged relative to the component dendrons **8** (δ 2.22 ppm), **9** (δ 2.11 ppm), and **10** (δ 2.15 ppm). An upfield shift of the aldehyde α-*H* methine resonance (*b*′) from δ 2.73 ppm in **10** to δ 2.64 ppm in dendrimer **11** is consistent with reduction of the aldehyde carbonyl. A small downfield shift of the acid α-*H* methine resonance (*b*″) from δ 2.91 ppm in **9** to δ 2.96 ppm in dendrimer **11** is consistent with the apex functional group transformation to an ester. The second-generation methine resonance (*b*) of the isocyanide component is shifted upfield from δ 2.12 ppm in **8** to δ 1.98 ppm in **11**. From these chemical shifts in $CDCl_3$ and relative integration of the peripheral methyl groups, peripheral benzyl groups, and α-acyloxyamide α-*H* resonances of **11** measured in CCl_4 solution,[26] we conclude that the dendrimer has the structure and composition expected from the Passerini reaction.

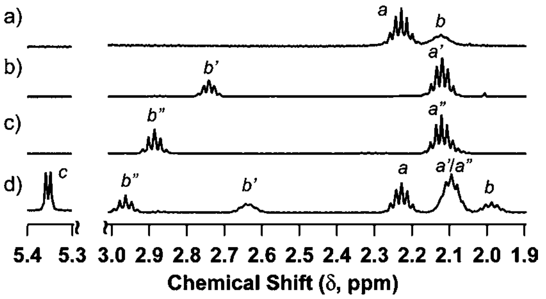

Figure 3. Partial ^{1}H NMR spectra of the Passerini reaction components (a) **8**, (b) **9**, (c) **10**, and (d) product **11** in $CDCl_3$.

Gel permeation chromatography (GPC) provides insight to the purity of dendrimer **11** because the dendrimer is significantly larger than each of the component dendrons (i.e., **8**, **9**, and **10**). Figure 4 compares chromatograms of **8**, **9**, **10**, and **11**. Peak retention times reflect the expected size differences. Dendron **8**, which has peripheral benzyl groups, is smaller than dendrons bearing peripheral decyl chains (i.e., **9** and **10**). Dendrimer **11** elutes faster than each of the components. There is no indication of smaller dendrimers or dendrons in any of the chromatograms. The number-average molecular weight (M_n) and the molecular weight distribution (M_w/M_n) for **8**, **9**, **10**, and **11** were determined relative to polystyrene standards. The narrow molecular weight distributions reported in Figure 4 indicate the purity of each compound.

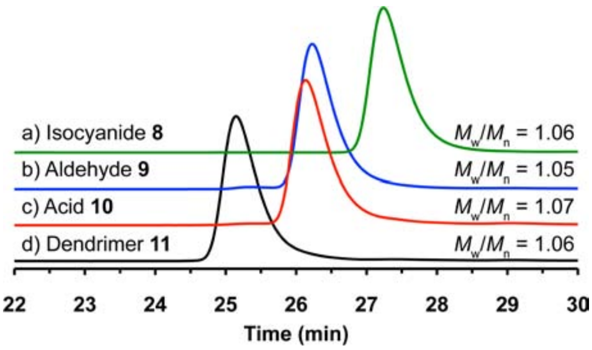

Figure 4. Elution profiles and molecular weight distributions (M_w/M_n) of the component dendrons and the Passerini reaction product obtained from GPC in THF.

Isocyanide multicomponent reactions of dendrons yield dendrimers having precisely controlled surface group compositions. In our proof-of-concept experiment, the dendrons and dendrimer were prepared following the convergent strategy developed for 1,3-propanediol dendrons. We expect that this Passerini reaction can be extended to dendrons based on other types of branched repeating units because of the benign reaction conditions. Slower reaction kinetics at higher generations, and diminishing yields attributed to steric congestion at the periphery of the dendrimer will affect the scope of this strategy. The advantage of this multicomponent reaction to synthesize dendrimers is that surface-triblock dendrimers, having three distinct clusters of surface functional groups, can be prepared in a single synthetic transformation. Surface-triblock dendrimers are an unprecedented dendritic architecture. The Passerini reaction described herein shows the feasibility of accessing libraries of surface-triblock dendrimers.

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Supporting Information Available. Detailed synthetic procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(26) Overlap of the residual $CHCl_3$ resonance with the aromatic protons prevented integration of the complete ^{1}H NMR spectrum recorded in $CDCl_3$. Spectra recorded in solvents that allowed integration of the full spectrum are reported in the Supporting Information.