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A Model for Late-Stage Modification of Polyurethane Dendrimers Using Thiol−Ene Click Chemistry

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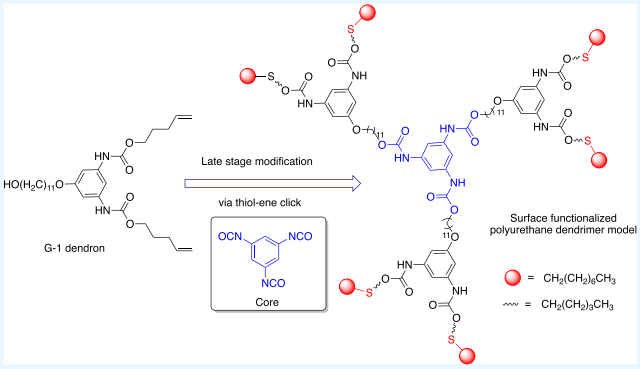
ABSTRACT: Dendritic materials possessing urethane linkage are surprisingly more stable than similar structures having functional groups such as ether, ester, amide, or carbosilane. This generates profound interest in dendritic polyurethanes. Construction of a well-defined polyurethane dendrimer is, however, challenging because of isocyanates' high reactivity. As a model of our ongoing dendrimer-research, herein, we report a protecting group-free one-pot multicomponent Curtius reaction to furnish a robust and versatile AB_2-type dendron, which ensures late-stage modification of both the dendron and dendritic macromolecule yielding a surface functionalized polyurethane dendrimer. While 5-hydroxyisophthalic acid, 11-bromoundecanol, and 4-penten-1-ol were utilized in the construction of the dendron, thiol−ene click chemistry was employed for the late-stage modification. Novel dendrons and dendrimers synthesized were characterized by NMR (1D and 2D) and high-resolution MALDI-TOF analysis. This strategy allows an easy late-stage modification of dendritic macromolecules and is highly useful in the synthesis of both symmetrical and unsymmetrical dendrimers (Janus dendrimers).



INTRODUCTION

Since the first successful synthesis of poly(amidoamine) dendrimers by Tomalia et al. in 1985,[1] development of dendritic macromolecules, including dendrimers and hyperbranched polymers, has developed rapidly in the field of macromolecular chemistry[2] because of their extensive applications in the chemical[3] and biomedical fields.[4,5] Dendritic macromers have been reported for a wide variety of compounds like polyethers, polyamines, polyamides, polyarylenes, polycarbosilanes, and polycarbonates. Though a few such structures are reported in the field of polyurethanes, construction of a well-defined architecture of polyurethane dendrimers (PUDs)[6] is challenging owing to high reactivity of externally added or in situ formed isocyanates toward nucleophiles. Pleasingly, two seminal works published simultaneously in 1993 by two research groups found synthetic routes to PUDs, which are valid to date. The first route described by Spindler and Fréchet[7] using isocyanate chemistry assured the synthesis of dendritic structures via growth of two generations in a single synthetic operation. The second route described by Kumar and Ramakrishnan[8] using Curtius rearrangement as an isocyanate-free approach trapped in situ formed isocyanate by an alcohol affording a urethane.

PUDs have been synthesized employing both divergent[9−13] and convergent[14−17] methods in the last two and a half decades after the aforementioned pioneering works. First reported by Hawker and Fréchet,[14] the convergent synthesis involves a small number of reactions per molecule during the coupling of dendron and activation of the functional group at the focal point. This ensures greater structural control than in the divergent synthesis appraoch.[18] Moreover, the functional groups can be precisely placed throughout the dendritic structure, an attribute required to construct functional macromolecules. Nevertheless, fewer reports have been reported on PUDs employing the convergent method. Previously, our group reported convergent syntheses of PUDs containing dodecyl as end groups using a protection/deprotection strategy.[19,20] This work reports a fast, efficient, and protecting group-free approach to the synthesis of PUDs where terminal pentene functionalized end groups of dendron can further undergo pre- or post-modification via thiol−ene click chemistry. This enables easy modification of the dendritic periphery, which could be of particular interest because these peripheral groups are the moieties to come in frequent contact with the external environment.

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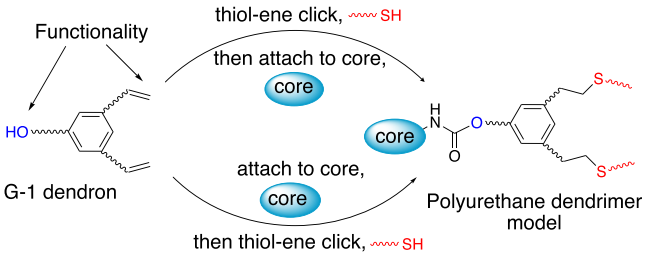
As a proof of concept, herein, we report the synthesis of the first-generation dendritic wedge, its attachment to a core structure, and pre-and post-modification using thiol−ene reaction. The versatility of this approach is depicted by an AB_2 type dendritic monomer that can undergo either a thiol−ene click reaction[21] or attachment to the core. As shown in Scheme 1 "hydroxy" and "ene" functionalized dendrons can be

Scheme 1. General Representation of the Strategy Employed



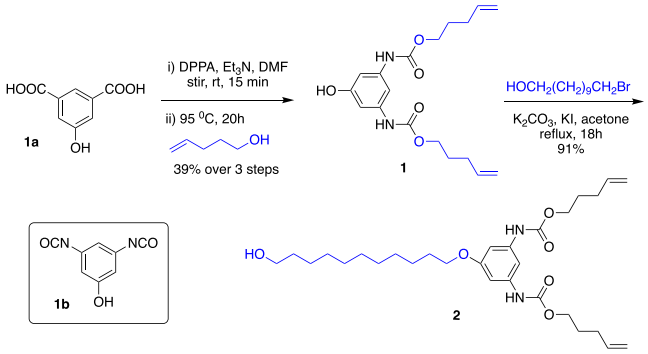
utilized in either of the two ways—click and attach to the core or attach to the core and click—to synthesize a polyurethane dendrimer.

RESULTS AND DISCUSSION

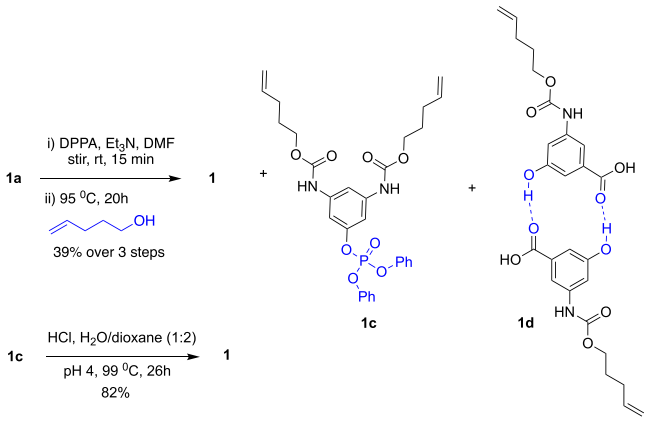
To build an AB_2 type dendron or branching monomer, we selected three molecules, 5-hydroxyisophthalic acid, 4-penten-1-ol, and 11-bromoundecanol, as the branching unit, peripheral group, and spacer group, respectively. Accordingly, the branching monomer was prepared in a two-step sequence of reactions. We exploited the Curtius reaction[22] to synthesize the phenolic diurethane **1**. The formation of **1** involved one-pot multicomponent Curtius reaction in which 5-hydroxyisophthalic acid (1 equiv.) **1a** was converted to an isocyanate analogue **1b** through an acyl azide intermediate under mild conditions using diphenyl phosphoryl azide[23] (DPPA, 2.1 equiv.) and triethylamine (2 equiv.) (Scheme S1). Organic isocyanates are electrophilic reactive intermediates, which can be trapped easily by nucleophiles in situ, thereby forming the urethane linkage. The hydroxy diisocyanate **1b** was trapped by 4-penten-1-ol to afford the phenolic diurethane **1**, which in turn furnished branching monomer **2** with an excellent yield when refluxed with 11-bromoundecanol. Unlike the previously reported synthetic protocol,[19,20] this strategy is concise and does not require any protection-deprotection of functional groups.

Protecting group-free Curtius reaction is a key step to form the urethane linkage in this approach, and we spent some time investigating the efficacy of this reaction. The protecting group-free approach reduces an extra step required to activate the dendron at its focal point. Since the reaction intermediate **1b** (Scheme 2) has a nucleophilic phenolic group, it could potentially compete with 4-penten-1-ol to react with its own isocyanate leading to the formation of polymeric side products. This directed us to optimize the reaction conditions. The unprotected phenolic hydroxy group in **1b** resulted in two minor side products—diurethane phosphate **1c** and the dimer of monourethane **1d** (Scheme 3). Taking advantage of the difference between pK_b values of aromatic hydroxy (∼4) and carboxylic groups (∼9−11), we anticipated that a base with pK_b larger than that of phenolic −OH (∼4) could prevent the potential formation of urethane phosphate. Surprisingly, the

Scheme 2. Synthesis of Branching Monomer



Scheme 3. Optimization of Curtius Reaction



bases with larger pK_b values did not increase the yield of **1** (Table 1; entries 1−3) and the base with smaller pK_b

Table 1. Effect of Base on Curtius Reaction[a]

			yield (%)		
entry	base	pK_b	1	1c	1d
1	pyridine	8.8	19	11	2
2	PVP	8.4	5	11	36
3	DMAP	4.4	20	12	5
4	Et_3N	3.2	39	10	4
5	no base		1	24	1

[a]Conditions: **1a** (1.0 equiv.), DPPA (2.1 equiv.), triethylamine (2.0 equiv.), 4-penten-1-ol (1.5 equiv.). The crude was purified by flash chromatography using ethyl acetate/hexane as eluting solvent.

(triethylamine) gave better yields (Table 1; entry 4). This reaction did require a base as depicted by entry 5 in Table 1, where the yield of **1** is negligible in the absence of a base. In addition, while good yields were obtained at temperatures of 85−95 °C, side products were formed in higher amounts at higher temperature. However, one of the side products, **1c**, can be recycled back to **1**.

Being a green reaction, thiol−ene click chemistry has been widely used in the efficient growth of dendrimers.[24−28] We utilized thiol−ene click here as a tool to ascertain the robustness of monomer **1** toward synthesis of PUDs by functionalizing the dendritic surface via different methods. Accordingly, **4** was synthesized via two different routes as shown in Scheme 4. To accomplish this, 1-octanethiol and 1,3,5-triisocyanatobenzene **3b** (Scheme S3) were selected as

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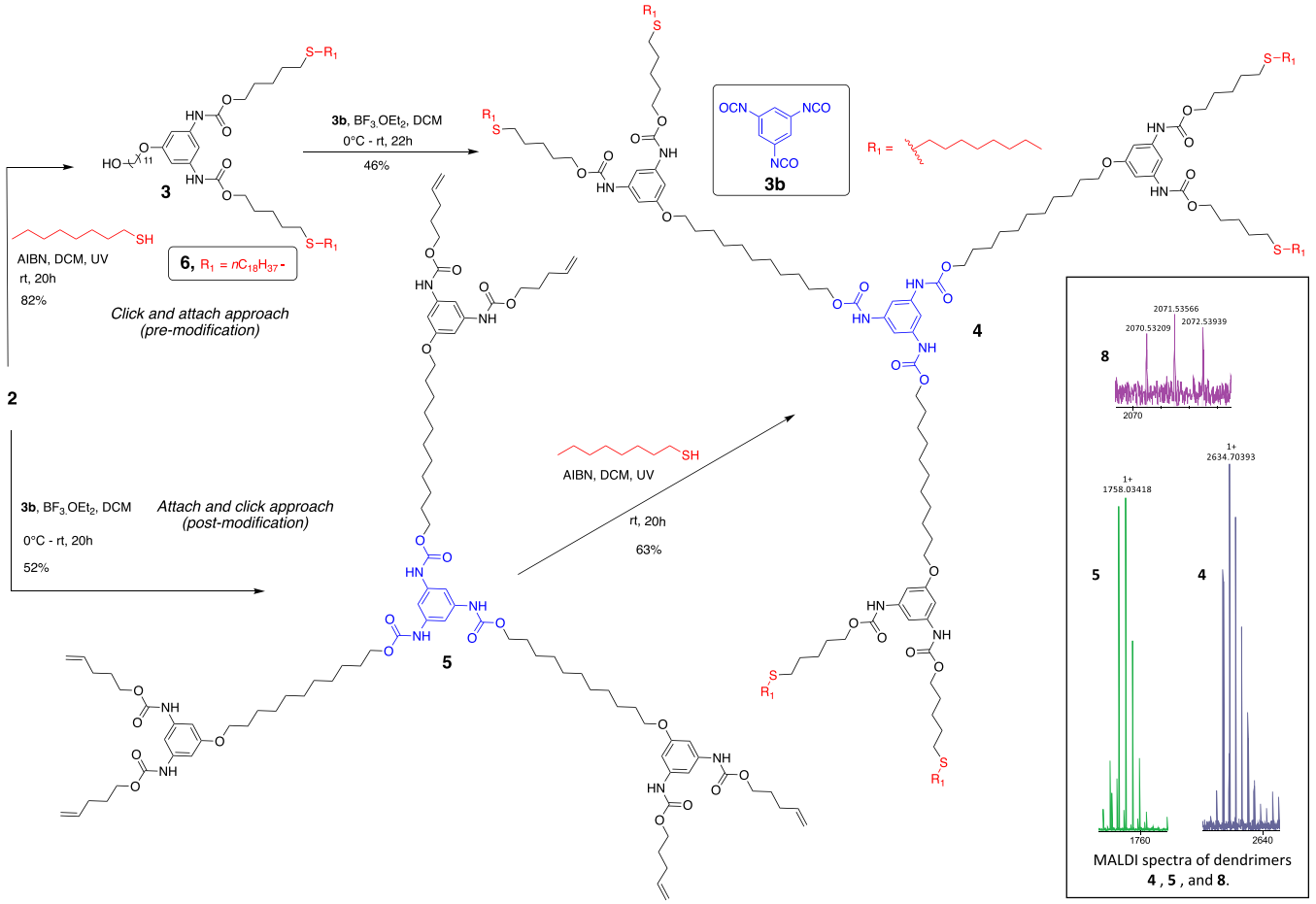
Scheme 4. Synthetic Routes to Polyurethane Dendrimers



the thiol−ene click partner and a simple trifunctional core, respectively. In its click-and-attach approach, the wedge **2** was irradiated with 1-octanethiol under UV light in the presence of free radical initiator 2,2′- azobis (2-methylpropionitrile) (AIBN) to obtain thioether functionalized dendron **3** in high yield (82%). The convergent synthesis of **4** was accomplished when dendron **3** was attached to the core **3b** in the presence of Lewis acid $BF_3{\cdot}OEt_2$. In the attach-and-click approach, dendron **2** was attached to the core **3b** under identical conditions to furnish a dendrimer **5** with pentene peripheral groups, which underwent subsequent thiol−ene click with 1-octanethiol under identical reaction conditions to produce dendrimer **4**. It is noticeable that the overall yield of the post-modification route is lower because of the larger number of reactions required to undergo completion at the periphery.

The most powerful feature of convergent synthesis lies on its ability to selectively modify both focal point and chain ends. This strategy allows one to vary the number of functional moieties and the type of functional moiety in the resultant dendrimers. In this study, we modified the chain ends without changing its focal point, which in turn resulted in surface modified dendrimer **4**. There are two possible approaches for the installation of the functionality at the core—introduction of end groups prior to and after the dendritic growth. The structural features of dendron **2** guarantee both pre- and post-modification routes.

All novel compounds including dendritic wedges and dendrimers were characterized by ^1H, ^{13}C NMR, and mass spectrometry (HRESI-MS or MALDI-TOF) (details in the Supporting Information). Figure 1 shows the solution state ^1H NMR spectra of branching monomers (**2** and **3**) and

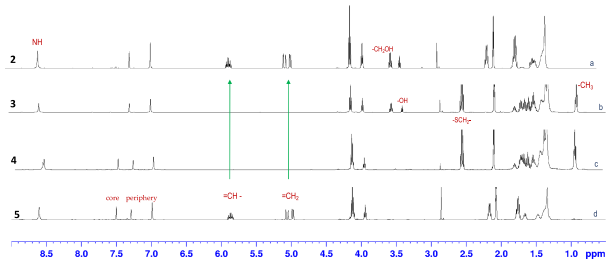


Figure 1. Typical ^1H NMR of branching monomers and dendrimers: (a) dendron **2**, (b) dendron **3**, (c) dendrimer **4**, and (d) dendrimer **5**. All spectra were taken in a 500 MHz spectrometer using CD_3COCD_3 as a solvent.

dendrimers (**4** and **5**) in deuterated acetone as a solvent before and after thiol−ene functionalization. The disappearance of peaks with chemical shifts at 5.0 and 5.9 ppm ($-CH{=}CH_2$) (Figure 1a,d) and the appearance of new peaks at 2.6 ($-SCH_2-$) and 0.9 ppm ($-CH_3$) (Figure 1b,c) provided evidence that thiol−ene click proceeded successfully. Moreover, a new peak assigned at 7.5 ppm (aromatic C*H*) (Figure 1c,d) furnished further evidence of successful attachment of dendron **2** or **3** to the trifunctional core.

To further exploit the potential of this approach, we embarked on the search for successful functionalization of a

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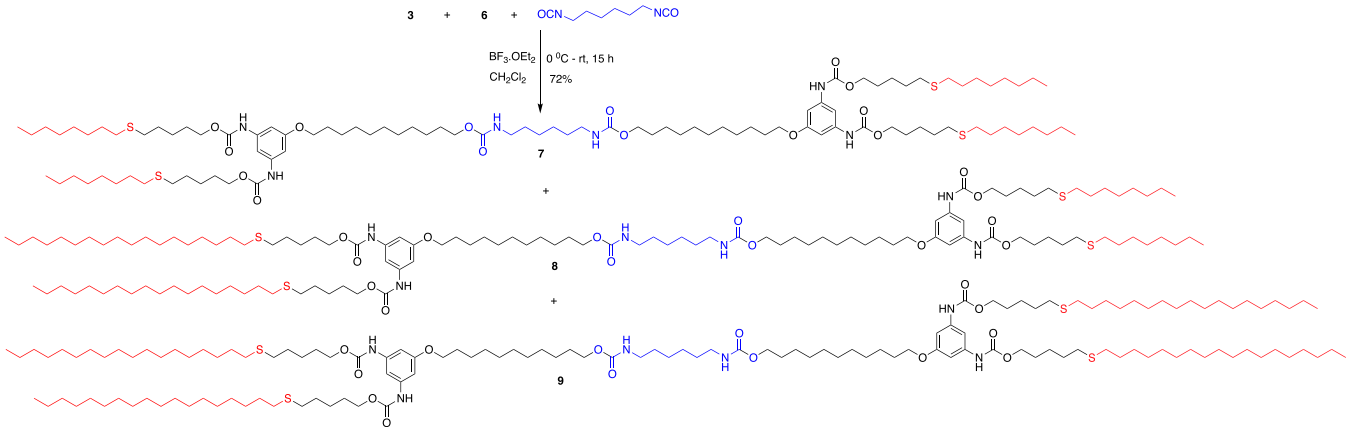
Scheme 5. Functionalization of the Core with Different Dendrons



different core, hexamethylene diisocyanate (HDI), using two different dendrons (Scheme 5). 1-Octanethiol and 1-octadecanethiol clicked dendritic monomers **3** and **6** were allowed to attach to the bifunctional core HDI at ambient temperature in the presence of $BF_3{\cdot}OEt_2$ that produced three different dendrimers (**7**, **8**, and **9**complete structure in the Supporting Information) as an amorphous white solid (72% yield) including a Janus dendrimer **8**.[29,30] Separation turned out to be simple and convenient with flash chromatography using hexane/ethyl acetate as the eluent. At this point, we utilized the click-and-attach approach as the overall yield of this approach was higher than that of the attach-and-click approach. It is noteworthy that the proportion of products **7**:**8**:**9** is 1:2:1, in agreement with statistical distribution of their attachment to the core. Thus, we anticipate that this approach will allow access to hetero- or Janus dendrimers.[29]

CONCLUSIONS

In summary, we presented a thiol−ene click inspired protecting group-free approach to the convergent synthesis of polyurethane dendrimers. As a representative of the proposed approach, generation one dendrimers were synthesized via click-and-attach and attach-and-click methods under mild conditions. An efficient and robust bifunctional dendron synthesized from a one-pot multicomponent Curtius reaction enabled late-stage modification of itself and accompanying dendrimers. Additionally, functionalization of a bifunctional core with two different dendrons furnished a mixture of three dendrimers including a Janus dendrimer. Access to this type of investigation will contribute to concise and versatile synthesis of dendritic macromolecules.

EXPERIMENTAL SECTION

General Information. Starting materials were used as received from commercial sources. Curtius reaction was set in a Carousel reactor, and all other reactions were performed using a classical batch process using an oil bath (if heat was needed). A UV lamp from American Ultraviolet Company (model: PC-100S; 120 V, 60 Hz, 5 Amp; S/N: 9902L3669) was used to carry out the thiol−ene click reaction. Melting points were determined using a Thermo Scientific MelTemp 3.0 instrument.

^1H, ^{13}C, and 2D NMR spectra were recorded with a Bruker Avance 500 MHz NMR instrument at 298 K. NMR spectra were recorded using either acetone-d_6 or $CDCl_3$ as deuterated solvent, and accordingly, the solvent residual peaks were obtained at δ 2.05 (qn) and δ 7.26 ppm (s), respectively, in ^1H NMR. In ^{13}C NMR, solvent residual peaks were recorded at δ 206.68 (s) and δ 29.92 ppm (septet) for acetone-d_6 and δ 77.23 ppm (s) for $CDCl_3$. Coupling constants (J) are given in hertz (Hz), whereas chemical shifts are given on the δ scale (ppm). Moreover, the multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), or m (multiplet). IR spectra were obtained from a PerkinElmer Spectrum One FT-IR Spectrometer.

HRMS spectra of small molecules including dendrons were obtained from an FTMS plus CESI mass spectrometer using DCM as solvent. MALDI spectra of larger molecules were recorded with a Bruker 15 FT-ICR instrument using HCCA as the matrix in positive ion mode.

Purification of compounds was carried out using flash chromatography with irregular silica of 40−60 μm, 60 Å. Small-scale purification was achieved using autocolumn flash cartridges packed with 12 or 40 g of silica of 40−75 μm, 60 Å (obtained from Sorbtech and Supelco Technologies). The flow rate was 10−30 mL/min. The mobile phase used in these separations was ethyl acetate, hexane, DCM, or a mixture of these solvents.

Phenolic Diurethane 1. 5-Hydroxyisophthalic acid (5.0 g, 27.45 mmol, 1.0 equiv.) was dissolved in anhydrous DMF (20 mL) under nitrogen in an oven-dried Carousel flask equipped with a magnetic stir bar. After complete dissolution, Et_3N (12.4 mL, 54.90 mmol, 2.0 equiv.) was added slowly followed by dropwise addition of DPPA (18.9 mL, 54.90 mmol, 2.0 equiv.) at rt. This reaction is exothermic and turns the solution yellow. Stirring was continued for 15 min before adding 4-penten-1-ol (5.1 mL, 49.41 mmol, 1.8 equiv.) at rt. The solution was heated to 95 °C for 20 h, then diluted 20 times with water, and extracted with EtOAc (4 × 150 mL). The combined organic layers were washed multiple times with water to remove DMF, washed with brine, dried with anhydrous $MgSO_4$, concentrated, and purified by flash chromatography using 7:3 hexane/EtOAc (mobile phase) to give phenolic diurethane **1** as a light purple solid (3.39 g, 39% yield). The diurethane phosphate 10% (slightly yellow solid) and the dimer of monourethane 4% (white solid) were also isolated as side products. This reaction can be monitored by FTIR. (*Caution*: During Curtius rearrangement ($-CON_3$ to $-NCO$), the reaction proceeds violently releasing N_2 gas. The reaction vessel should not be sealed completely in this step to avoid possible explosion.)

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Phenolic Diurethane ***1***. M.p. 86−89 °C. TLC (30% EtOAc in hexane): R_f 0.34. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.54 (s, 2H, aromatic −NH−), 8.29 (s, 1H, −OH), 7.20 (t, J = 1.8 Hz, 1H), 6.91 (d, J = 1.6 Hz, 2H), 5.82−5.90 (m, 2H), 4.96−5.08 (m, 4H), 4.12 (t, J = 6.6 Hz, 3H), 2.14−2.18 (m, 4H), 1.72−1.77 (m, 4H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 158.1, 153.6, 140.6, 137.8, 114.6, 100.2, 63.7, 29.8, 28.1, 28.0. HRMS-ESI (m/z): $[M + Na]^+$ Calcd for $C_{18}H_{24}N_2O_5Na$ 371.1577; found 371.1573.

Diurethane Phosphate ***1c***. TLC (30% EtOAc in hexane): R_f 0.40. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.89 (s, 2H, OH), 7.66 (s, 1H), 7.45 (t, J = 7.5 Hz, 4H), 7.40 (s, 2H), 7.36 (dd, J = 8.6, 1.0 Hz, 4H), 7.29 (dt, J = 6.9, 1.1 Hz, 4H), 5.90−5.83 (m, 2H), 5.08−4.97 (m, 4H), 4.15 (t, J = 6.6 Hz, 4H), 2.19−2.15 (m, 4H), 1.79−1.74 (m, 4H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 157.9, 157.8, 153.6, 153.5, 151.1, 151.1, 150.7, 150.6, 141.1, 137.8, 130.1, 130.0, 125.7, 120.2, 114.8, 114.0, 105.0, 104.2, 104.1, 64.6, 64.4, 64.1, 64.0, 29.8, 28.0. LRMS-ESI (m/z): $[M + Na]^+$ Calcd for $C_{30}H_{33}N_2O_8PNa$ 603.2; found 603.3.

Dimer of Monourethane ***1d***. TLC (30% EtOAc in hexane): R_f 0.29. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.75 (s, 2H, −NH−), 7.75 (t, J = 3.2, 2H), 7.48 (s, 2H), 7.21 (q, 2H, J = 0.9 Hz), 5.90−5.85 (m, 2H), 5.09−4.97 (m, 4H), 4.15 (t, J = 6.6 Hz, 4H), 2.20−2.15 (qn, J = 6.8 Hz, 4H), 1.80−1.74 (qn, J = 8.1 Hz, 4H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 166.6, 157.8, 153.5, 140.8, 137.8, 132.1, 114.6, 110.9, 110.6, 109.6, 63.9, 59.6, 19.9, 13.6. LRMS-ESI (m/z): $[M−H]^-$ Calcd for $C_{13}H_{15}NO_5$ 264.0; found 263.9.

Recycling 1 from 1c. Phosphate compound **1c** (1.97 g, 3.40 mmol) was dissolved in 1,4-dioxane/water (2:1) in a Carousel flask equipped with a magnetic stir bar. HCl (37.4%, 2 mL) was added to the flask, and the heterogeneous solution was stirred vigorously at 99 °C in a Carousel reactor. After 26 h, the reaction mixture was extracted with EtOAc, washed with water and brine, dried with anhydrous $MgSO_4$, concentrated, and purified by silica gel chromatography using 7:3 hexane/EtOAc as the mobile phase. A slightly pink solid was obtained as product **1** (980 mg, 82% yield).

Branching Monomer 2. An oven-dried 100 mL RB flask equipped with a magnetic stir bar was charged with 11-bromoundecanol (1.5 g, 5.9 mmol, 1.2 equiv.), K_2CO_3 (3.3 g, 22.5 mmol, 5.0 equiv.), and KI (166 mg, 0.2 mmol, 0.2 equiv.). The flask was placed under nitrogen, and **1** (1.7 g, 4.9 mmol, 1.0 equiv.) in acetone (20 mL) was transferred into it *via* syringe. The reaction mixture was refluxed for 18 h, and the progress of reaction was monitored by TLC (7:3 hexane/EtOAc). After completion, acetone was evaporated, and the residue was extracted with EtOAc, washed with brine, dried with anhydrous $MgSO_4$, and concentrated. The crude was purified by flash chromatography gradient elution using silica gel as the stationary phase and 10−30% EtOAc in hexane as the mobile phase to give transparent viscous oil as the product (2.32 g, 91% yield). TLC (1:1 hexane/EtOAc): R_f 0.55. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.60 (s, 2H), 7.29 (t, J = 1.8 Hz, 1H), 6.98 (d, J = 1.4 Hz 2H), 5.83−5.91 (m, 2H), 4.97−5.08 (m, 4H), 4.13 (t, J = 6.6 Hz, 3H), 3.95 (t, J = 6.5 Hz, 2H), 3.54 (q, J = 5.4 Hz, 2H), 3.41 (t, J = 5.2 Hz, 1H), 2.15−2.19 (m, 4H), 1.73−1.79 (m, 6H), 1.47−1.54 (m, 4H), 1.36−1.42 (m, 14H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 160.1, 153.5, 140.6, 137.9, 114.5, 99.2, 67.6, 63.7, 61.6, 32.9, 29.9, 29.8, 29.5, 29.4, 29.2, 28.1, 25.9, 25.8. HRMS-ESI (m/z): $[M + H]^+$ Calcd for $C_{29}H_{47}N_2O_6$ 519.3429; found 519.3421.

1,3,5-Triisocyanatobenzene 3b. Trifunctional core **3b** was prepared by modifying the procedure reported by Davis.[31] Briefly, at 0 °C, sodium azide (4.30 g, 66 mmol, 3.3 equiv.) was dissolved in water (8 mL), and 1,3,5-benzenetricarbonyl chloride (5.31 g, 20 mmol, 1.0 equiv.) in DCM (60 mL) was added slowly over 30 min. After addition, the ice-bath was removed and the solution was stirred at room temperature for 2.5 h. DCM was evaporated under reduced pressure, and the residue was dissolved in toluene (60 mL) and refluxed for 3 h. Evaporating the toluene under reduced pressure gave fine, needle-shaped crystals as the product (3.27 g, 87% yield). M.p. 83−85 °C (lit. 84−85 °C). Spectral data were in agreement with that reported previously. The product was pure enough for the next step.

General Procedure of Thiol−Ene Click Reaction. The dendron or dendrimer with alkene periphery was dissolved in dry DCM in a vial equipped with a magnetic stir bar to which thiol and AIBN were added. The reaction mixture was then placed under UV light and stirred at rt. for 20 h. Solvent was evaporated, and the crude was purified by flash chromatography.

Thiol−Ene Clicked Dendron 3. The general procedure of thiol−ene click reaction was employed using dendron **2** (285.5 mg, 0.55 mmol, 1.0 equiv.), 1-octanethiol (382 μL, 2.2 mmol, 4.0 equiv.), AIBN (18 mg, 0.11 mmol, 0.2 equiv.), and dry DCM (1.5 mL) to furnish a white solid (364.5 mg, 82% yield) after flash chromatography (7:3 hexane/EtOAc). M.p. 46 °C. TLC (30% EtOAc in hexane): R_f 0.26. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.58 (s, 2H, −NH−), 7.29 (s, 1H), 6.99 (s, 2H), 4.13 (t, J = 6.6, 4H), 3.96 (t, J = 6.5, 2H), 3.54 (q, J = 18.4, 5.5, 2H), 3.39 (t, J = 5.3, 1H, −OH), 2.54 (q, J = 8.6, 8H), 1.79 (m, 2H), 1.72−1.46 (m, 22H), 1.43−1.26 (m, 34H), 0.89 (t, J = 6.8, 6H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 160.1, 153.5, 153.4, 140.7, 140.6, 140.5, 100.7, 99.1, 6.5, 64.2, 61.6, 61.5, 32.9, 31.6, 31.5, 31.4, 29.6, 25.8, 25.0, 22.2, 13.5. HRMS-ESI (m/z): $[M + H]^+$ Calcd for $C_{45}H_{83}N_2O_6S_2$ 811.5687; found 811.5675.

Thiol−Ene Functionalized PUD 4 (Attach-then-Click Approach). The general procedure of thiol−ene click reaction was employed using dendrimer **5** (117.6 mg, 0.067 mmol, 1.0 equiv.), 1-octanethiol (139 μL, 0.803 mmol, 12.0 equiv.), AIBN (13.2 mg, 0.080 mmol, 1.2 equiv.), and dry DCM (0.6 mL) to afford highly viscous transparent oil as the product (110.3 mg, 63% yield) on flash chromatography (4:1 hexane/EtOAc). TLC (20% EtOAc in hexane): R_f 0.46. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.59 (s, 9H, −NH−), 7.49 (s, 3H), 7.29 (s, 3H), 6.99 (s, 6H), 4.12 (t, J = 6.4 Hz, 18H), 3.95 (t, J = 6.4 Hz, 6H), 2.53 (q, J = 7.5 Hz, 24H), 1.80−1.74 (m, 6H), 1.72−1.45 (m, 64H), 1.43−1.24 (m, 110H), 0.89 (t, J = 6.8 Hz, 18H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 160.1, 153.6, 153.5, 140.6, 140.5, 140.1, 103.0, 100.7, 99.2, 67.5, 64.3, 64.2, 31.7, 31.6, 31.5, 29.6, 25.9, 25.7, 25.0, 22.4, 13.5. MALDI-TOF (m/z): $[M + H]^+$ Calcd for $C_{144}H_{250}N_9O_{21}S_6$ 2633.70901; found 2633.69930.

Thiol−Ene Clicked Dendron 6. The general procedure of thiol−ene click reaction was employed using **2** (195.5 mg, 0.375 mmol, 1.0 equiv.), 1-octadecanethiol (322.4 mg, 1.125 mmol, 3.0 equiv.), AIBN (12.3 mg, 0.075 mmol, 0.2 equiv.), and dry DCM (2 mL) to afford a white waxy solid (350.0 mg, 85% yield) after flash chromatography (4:1 hexane/EtOAc). M.p. 69 °C. TLC (30% EtOAc in hexane): R_f 0.42. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 7.03 (s, 1H), 6.79 (s, 2H), 6.73 (s, 2H), 4.16 (t, J = 6.6 Hz, 4H), 3.94 (t, J = 6.5 Hz, 2H), 3.66 (t,

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J = 6.6 Hz, 3H), 2.52 ($t_{overlapped}$, J = 14.8, 11.0 Hz, 8H), 1.77−1.27 (m, 102H), 0.90 (t, J = 6.9 Hz, 3H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 160.4, 153.5, 139.5, 100.8, 99.9, 68.1, 65.2, 63.1, 32.8, 32.2, 32.0, 31.9, 29.7, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.2, 28.9, 28.6, 25.9, 25.7, 25.2, 22.7, 14.1. HRMS-ESI (m/z): $[M + H]^+$ Calcd for $C_{65}H_{123}N_2O_6S_2$ 1091.8817; found 1091.8810.

General Procedure of Attachment of Dendron to the Core. The di- or trifunctional core was dissolved in dry DCM in an oven-dried RB flask equipped with a magnetic stir bar and transferred the flask to an ice-bath. To this solution were added the corresponding dendron (in dry DCM) dropwise and a catalytic amount of $BF_3{\cdot}OEt_2$ at 0 °C. The reaction mixture was allowed to warm up and stirred at ambient temperature for 20 h. Progress of reaction was monitored by FT-IR for the isocyanate peak at ∼2250 cm^{-1}. After the completion of reaction, solvent was evaporated, and the crude was purified by flash chromatography to obtain the title compound.

Dendrimer 5. The general procedure of dendron's attachment to the core was employed using 1,3,5-triisocyanatobenzene **3b** (45.0 mg, 0.244 mmol, 1.0 equiv.), $BF_3{\cdot}OEt_2$ (35 μL, 0.13 mmol, 0.6 equiv.) in dry DCM (0.5 mL), dendritic wedge **2** (383.0 mg, 0.740 mmol, 3.3 equiv.), and dry DCM (1 mL) to afford highly viscous colorless oil **5** as the product (203.4 mg, 52% yield) after flash chromatography using 10−40% EtOAc in hexane (gradient elution). TLC (40% EtOAc in hexane): R_f 0.58. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.60 (s, 9H, −NH−), 7.50 (s, 3H), 7.29 (t, 3H), 6.99 (d, 6H), 5.89−5.83 (m, J = 10.3, 10.2 Hz, 6H), 5.08−4.97 (m, J = 17.1, 10.2, 1.4 Hz, 12H), 4.12 (t, J = 6.6 Hz, 18H, overlapped), 3.95 (t, J = 6.5 Hz, 6H), 2.19−2.14 (m, J = 7.2 Hz, 12H), 1.70−1.63 (m, 6H), 1.79−1.73 (m, 18H), 1.51−1.44 (m, 6H), 1.43−1.30 (m, 40H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 160.1, 153.6, 153.5, 153.4, 140.6, 140.2, 137.9, 137.8, 114.6, 114.5, 103.1, 100.7, 99.2, 67.6, 64.2, 63.7, 29.8, 28.1, 25.9, 25.7. MALDI-TOF (m/z): $[M + H]^+$ Calcd for $C_{96}H_{142}N_9O_{21}$ 1757.03148; found 1757.03092.

Thiol−Ene Functionalized PUD 4 (Click-then-Attach Approach). The general procedure of attaching dendron to the core was employed using 1,3,5-triisocyanatobenzene **3b** (30.4 mg, 0.15 mmol, 1.0 equiv.), dendritic wedge **3** (405.3 mg, 0.500 mmol, 3.3 equiv.) in dry DCM (1 mL), $BF_3{\cdot}OEt_2$ (23 μL, 0.09 mmol, 0.6 equiv.), and dry DCM (0.5 mL) to furnish title compound **4** as highly viscous transparent oil (183.2 mg, 46%).

Linear Dendrimers 7, 8, and 9. The general procedure of dendron's attachment was employed using hexamethylene 1,6-diisocyanate (34.2 μL, 0.214 mmol, 1.0 equiv.), dendron **3** (208.3 mg, 0.257 mmol, 1.2 equiv.) in dry DCM (1.25 mL), dendron **6** (280.4 mg, 0.257 mmol, 1.2 equiv.) in dry DCM (1.25 mL), $BF_3{\cdot}OEt_2$ (11 μL, 0.0428 mmol, 0.2 equiv), and dry DCM (0.5 mL) to afford three dendrimers **7**, **8**, and **9** as white solids after flash chromatography (5−30% EtOAc in hexane).

*Dendrimer **7***. M.p. 64−66 °C. TLC (30% EtOAc in hexane): R_f 0.20. ^{1}H NMR (500 MHz, CD_3COCD_3): δ 8.58 (s, 4H, aromatic −NH−), 6.99 (s, 4H), 7.29 (s, 2H), 6.12 (s, 2H, aliphatic −NH−), 4.13 (t, J = 6.5 Hz, 8H), 3.96 (t, J = 6.5 Hz, 8H), 2.54 ($t_{overlapped}$, J = 8.8, 6.2 Hz, 16H), 1.81−1.75 (m, 4H), 1.72−1.46 (m, 50H), 1.43−1.25 (m, 100H), 0.90 (t, J = 6.9 Hz, 12H). ^{13}C NMR (500 MHz, CD_3COCD_3): δ 160.1, 156.6, 153.6, 140.7, 100.8, 99.2, 66.6, 64.2, 63.8, 40.4, 31.8, 31.7, 31.6, 31.5, 29.86, 26.2, 25.9, 25.8, 25.0, 22.4, 13.5. MALDI-TOF (m/z): $[M + H + K]^+$ Calcd for $C_{98}H_{177}N_6O_{14}S_4K$ 1829.18427; found 1829.17646.

*Janus Dendrimer **8***. M.p. 71−73 °C. TLC (30% EtOAc in hexane): R_f 0.31. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 2H), 6.79 ($s_{overlapped}$, 8H), 4.73 (s, 2H, aliphatic −NH−), 4.16 (t, J = 6.6 Hz, 8H), 4.05 (t, J = 6.4 Hz, 4H), 3.94 (t, J = 6.5 Hz, 4H), 3.16 (t, J = 6.4 Hz, 4H), 2.55−2.50 ($t_{overlapped}$, J = 10.4 Hz, 16H), 1.78−1.24 (m, 132H), 0.90 (t, J = 6.9 Hz, 12H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 160.4, 156.9, 153.5, 139.5, 100.8, 99.9, 68.1, 65.1, 64.9, 40.8, 32.2, 32.0, 31.9, 31.8, 29.9, 29.7, 28.6, 29.5, 29.5, 29.3, 29.2, 29.1, 29.0, 28.9, 28.6, 26.3, 26.0, 25.9, 25.2, 22.7, 22.6, 14.1. MALDI-TOF (m/z): $[M + H]^+$ Calcd for $C_{118}H_{217}N_6O_{14}S_4$ 2070.53302; found 2070.53209.

*Dendrimer **9***. M.p. 78−80 °C. TLC (30% EtOAc in hexane): R_f 0.42. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (s, 2H), 6.79 (s, 4H), 6.71 (s, 4H, aromatic −NH−), 4.71 (s, 2H, aliphatic −NH−), 4.16 (t, J = 6.6 Hz, 8H), 4.06 (t, J = 6.4 Hz, 4H), 3.94 (t, J = 6.5 Hz, 4H), 3.17 (q, J = 6.4 Hz, 4H), 2.54 (dt, J = 14.8, 10.9 Hz, 16H), 1.80−1.25 (m, 196H), 0.90 (t, J = 6.9 Hz, 12H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 160.4, 156.9, 153.4, 139.5, 100.7, 99.8, 68.1, 65.1, 64.9, 40.8, 32.2, 32.0, 31.9, 31.8, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.6, 26.3, 26.0, 25.9, 25.2, 22.7, 22.6, 14.1. MALDI-TOF(m/z): $[M + H + Na]^+$ Calcd for $C_{138}H_{257}N_6O_{14}S_4Na$ 2373.83633; found 2373.82192.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c01609.

Experimental procedures, ^{1}H NMR, ^{13}C NMR, and IR spectra, and mass spectrometric data of the novel compounds described (PDF)

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Notes

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