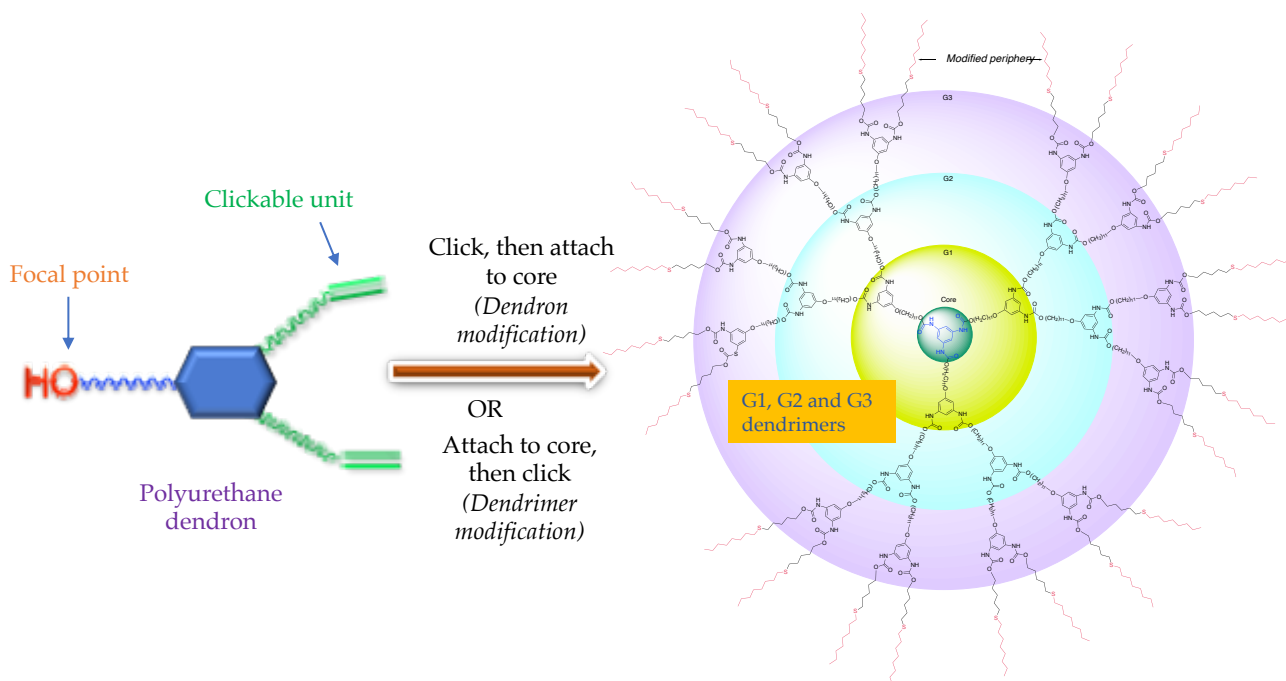# Thiol-Ene Click Inspired Late-stage Modification of Long-chain Polyurethane Dendrimers

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ABSTRACT: Compared to the synthesis of polyurethane polymers, construction of well-defined polyurethane dendrimers is challenging due to the high reactivity of externally added or in-situ formed isocyanates leading to the formation of side products. For this reason, the synthesis of dendritic polyurethanes is limited to very few reports. With primary focus of dendrimer research on the interaction of the periphery and the core, we report the synthesis of a common polyurethane dendron, which allows for late-stage variation of both the periphery and the core. The periphery can be varied simply by installing a clickable unit in the dendron and then attaching to the core and vice-versa. Thus, a common dendron allows for varying periphery and core in just two steps. To accomplish this, protecting group free one-pot multicomponent Curtius reaction was utilized to afford a robust and versatile AB_2 type polyurethane dendron employing commercially available simple molecules 5-hydroxyisophthalic acid, 11-bromoundecanol, and 4-penten-1-ol. Subsequent late-stage modification of either dendrons or dendrimers via thiol-ene click reaction gave surface-functionalized alternating aromatic-aliphatic polyurethane homodendrimers to generation-three (G3). The dendrons and the dendrimers were characterized by NMR, mass spectrometry, and FT-IR analysis. A bifunctional AB_2 type dendritic monomer demonstrated this approach's versatility that can either undergo a thiol-one click or attachment to the core. This approach enables the incorporation of functionalities at the periphery and the core that may not withstand the dendrimer growth for the synthesis of polyurethane dendrimers and other dendritic macromolecules.

INTRODUCTION

Dendrimers are highly branched multivalent, star-shaped polymeric macromolecules.[1–4] These monodispersed dendritic polymers exhibit wide applications in the field of catalysis, sensing, molecular electronics, photonics, fluorescence, and therapeutics.[5–19] After Tomalia's first report on poly(amidoamine) (PAMAM) dendrimers in 1985,[20] many research groups have reported the synthesis dendritic macromolecules using ether, ester, carbosilane, amide, and alkyne linkages.[21–33] Nevertheless, very few have reported the synthesis of dendrimers having urethane linkage. It is noteworthy that, as of now, SciFinder® reveals less than 100 references showing the entry of polyurethane dendrimers, which is negligible as compared to the references reported on polyurethane polymers (more than 340,000). This data indicates that polyurethane dendrimers[34] have not been

studied extensively, which discloses both tremendous opportunities and significant challenges in the field of dendrimer chemistry. The construction of a well-defined architecture of a polyurethane dendrimer is challenging due to isocyanates' high reactivity.[35] Pleasingly, the pioneering works published simultaneously in 1993 by two research groups established the synthetic routes to polyurethane dendrimers. The first route described by Spindler and Fréchet[36,37] used isocyanate chemistry. In contrast, the second route described by Kumar and Ramakrishnan[38] employed an isocyanate-free approach to synthesize polyurethane dendrimers. Following these pioneering works, a few more dendritic polyurethanes have been reported.[39–46] Recently, Nasar and coworkers have reported synthesis of hyperbranched polyurethanes and polyurethane dendrimers based on blocked isocyanate chemistry.[47–52]

However, the dendrimers have been synthesized equally *via* well-established convergent and divergent methods; the convergent method involves a small number of reactions per molecule during the coupling and activation dendrons.[53] This provides greater structural control than with divergent protocol. First reported by Hawker and Fréchet for the synthesis poly(phenyl benzyl ether) dendrimers,[54] convergent method ensures precise placement of functional groups throughout the dendritic structure that enables the synthesis of functional macromolecules. Though several dendrimers are reported recently employing the convergent method of synthesis,[25,31,55–72] there are very few reports on polyurethane dendrimers using this method.[40,73–75]

Scheme 1. General representation of synthetic strategy
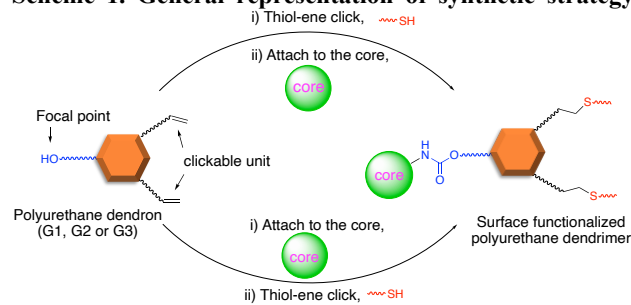
Thiol-ene click reaction, one of the idealized click reactions, is most frequently photoinduced, proceeds with quantitative yield in presence of small concentration of benign catalyst, undergoes with rapid reaction rate, insensitive to moisture, and yields a single stereoselective product.[76,77] For this reason, thiol-ene click reactions have been widely exploited for synthesis, functionalization, and post-modification/surface modification of dendrimers abd for the formation of cross-linkages in hyperbranched macromolecules.[51,78–107] Nevertheless, this powerful tool far from its application in the field of polyurethane chemistry. There are only two reports of thiol-ene click reaction employed for the synthesis of hyperbranched aliphatic polyurethanes.[108,109] To the best of our knowledge, the use of thiol-ene click reaction has not been reported previously.

Our group reported the convergent synthesis of polyurethane dendrimers having dodecyl end groups, using a protection-deprotection strategy two decades ago.[110,111]

Herein, we report on a fast, efficient, and protecting-group free approach to synthesize polyurethane dendrimers to the third generation (G3) using the convergent method. A common polyurethane dendron was synthesized utilizing a one-pot multicomponent Curtius reaction,[112,113] which allowed for late-stage modification of both the periphery and the core. Using this approach, while the periphery can be varied simply by installing a clickable unit in the dendron followed by its attachment to the core, the convergent method allows for varying the core itself. Thus, a common dendron allows for varying the periphery and the core in just the final two steps. Commercially available 5-hydroxyisophthalic acid, 4-penten-ol, and 11-bromoundecanol were subjected to Curtius reaction to furnish an AB$_2$ type common polyurethane dendron. The subsequent late-stage modification of either dendron or dendrimer via thiol-ene click reaction gave surface-functionalized alternating aliphatic-aromatic polyurethane homodendrimers. As shown in Scheme 1, an AB$_2$ type dendritic monomer can either undergo a thiol-ene click followed by attachment to the core or vice-versa to yield post-modified dendrimers. Previously, we demonstrated this strategy in detail concerning generation-one (G1) dendrimers. In this work, we extend our previous approach to synthesize the polyurethane dendrimers to G3.

RESULTS AND DISCUSSION

Synthesis of linking agent and core. Commercially available 5-hydroxyisophtalic acid **1** was used as a building block to synthesize generation-one dendritic wedge **(G1W)$_{ene}$** (or simply a dendron), whereas unprotected 5-hydroxy-1,3-diacyldiazide 4 was utilized as a linking group or branching point to afford G2 or G3 dendron (Scheme 2). Linking group **4**, a white amorphous solid, was synthesized in a three-step sequence starting from **1** with an overall yield 79%, where **1** was esterified using methanol followed by nucleophilic substitution with hydrazine and treatment with sodium nitrite under acidic medium. To synthesize a trifunctional core **6**, 1,3,5-benzenetricarbonyltrichloride was treated with sodium azide forming acyl azide at room temperature, which underwent Curtius rearrangement on affording 1,3,5-triisocyanatobenzene **6**[114] as needle-shaped crystals on heating (87% yield).

Scheme 2. Synthesis of linking group 4 and core 6
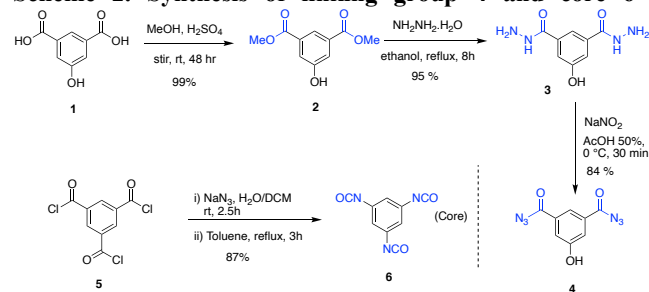
Synthesis of G1 dendrimer. With a core and a building block in hand, we started synthesizing a series of polyurethane dendrimers starting from G1 dendrimer. In this study, 4-penten-1-ol and 11-bromoundecanol are used as peripheral and spacer groups, respectively. Accordingly, the G1 dendron required for this operation was prepared from **1** in two steps (Scheme 3). One-pot multicomponent Curtius reaction using

commercially available starting materials **1**, 4-penten-1-ol, and DPPA (diphenylphosphoryl azide) in the presence of a base like Et$_3$N formed an isocyanate on heating due to rearrangement of acyl azide. *In situ* formed isocyanate was trapped by 4-penten-1-ol to afford phenolic diurethane **7** with 39% yield over three steps (*reaction details in the previous paper-ref to be added*). On refluxing **7** with 11-bromoundecanol in acetone furnished G1 dendron **(G1W)$_{ene}$**. It's noteworthy that the diurethane **7** can also be used as a dendron, but the reactivity is lower than that of alcoholic OH. Also, the installation of the undecyl group increases the solubility even for higher generation dendrons and dendrimers.

Scheme 3. Synthesis of G1 dendron using one-pot multicomponent Curtius reaction
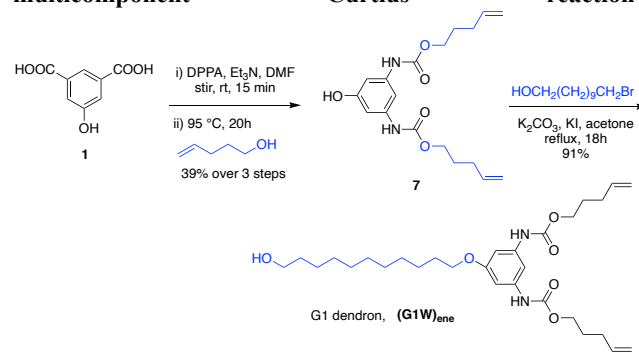
The advantages of this strategy of dendron formation are that the reaction proceeds smoothly in one-pot without the need of separating intermediate isocyanate, and the byproduct, diphenylphosphoric acid, can be separated from the desired product simply using flash chromatography. Our group has already succeeded in preparing polyurethane dendrimers employing this method.[111] However, the current approach does not require any protection at the focal point of the dendron, which significantly reduces the synthetic steps. Moreover, the current strategy allows one to synthesize dendron on a multigram scale.
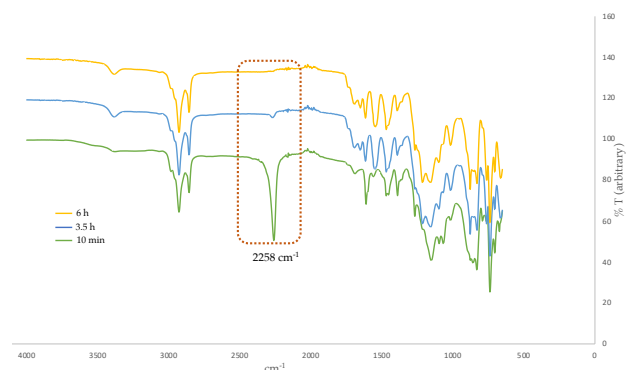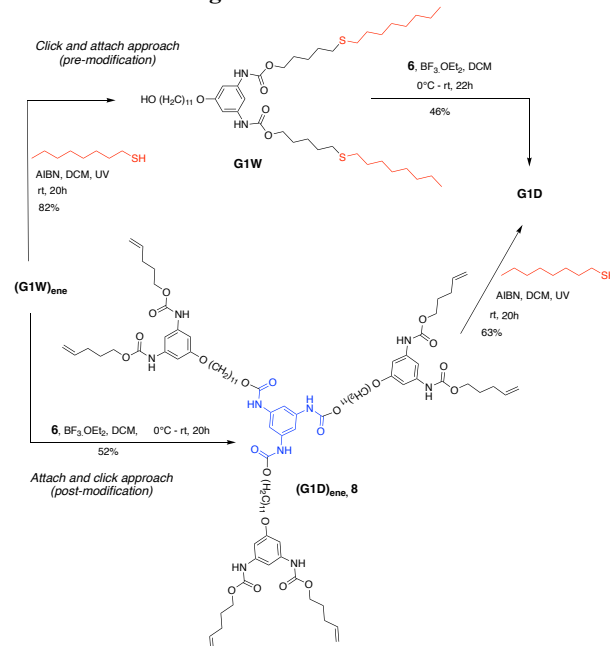

Figure 1. Progress of BF$_3$.OEt$_2$-catalyzed reaction involving the attachment of dendron to the core monitored by FT-IR spectroscopy. The isocyanate N=C=O stretch at 2258 cm^{-1} disappears over time.

Scheme 4. Late – stage modification of G1 dendron and dendrimer using thiol – ene click reaction

Convergent synthesis has been widely used in the construction of functional macromolecules because it permits to modification of dendrons both at focal points and at the chain ends. Moreover, this approach allows post derivatization of peripheral groups without disturbing the core and repeating units' functionality.[53] Exploiting this theme, we previously demonstrated our late-stage modification strategy's versatility by synthesizing G1 dendrimers using thiol-ene click chemistry.[76] As shown in Scheme 4, dendrimer **G1D** can be constructed via two different routes – i) click and attach approach (pre-modification), and ii) attach and click approach (post-modification)- starting from dendron **(G1W)$_{ene}$**. Our previous method of dendron formation allows us to change both the periphery and core in just two steps. The peripheral groups can be changed by installing a different clickable unit, whereas a different core can be used during the dendron's attachment to it.

Synthesis of G2 and G3 dendrimers. A convergent synthesis is a stepwise assembly of building blocks or monomer units leading to different generation dendrons' formation. Subsequent attachment of a dendron to the core moiety results in a dendrimer with well-defined architecture. As depicted in Scheme 5, growth of higher generation dendritic wedges commenced with coupling **1** with G1 dendron **(G1W)$_{ene}$** under Curtius reaction conditions using DPPA as an azide source, and Et$_3$N as a base gave G2 phenolic dendron **9**. However, the yield of this reaction was significantly lower than that of **7** (Scheme 3). Such low yield could be attributed partially to the less reactivity of larger attacking nucleophile **(G1W)$_{ene}$** compared with 11-bromoundecanol and partially to the side product, diphenyl phosphoric acid produced from DPPA during the reaction. Our attempt to an efficient synthesis of **9** was unsuccessful using OH protected **1** as a linking group, i.e., 5-

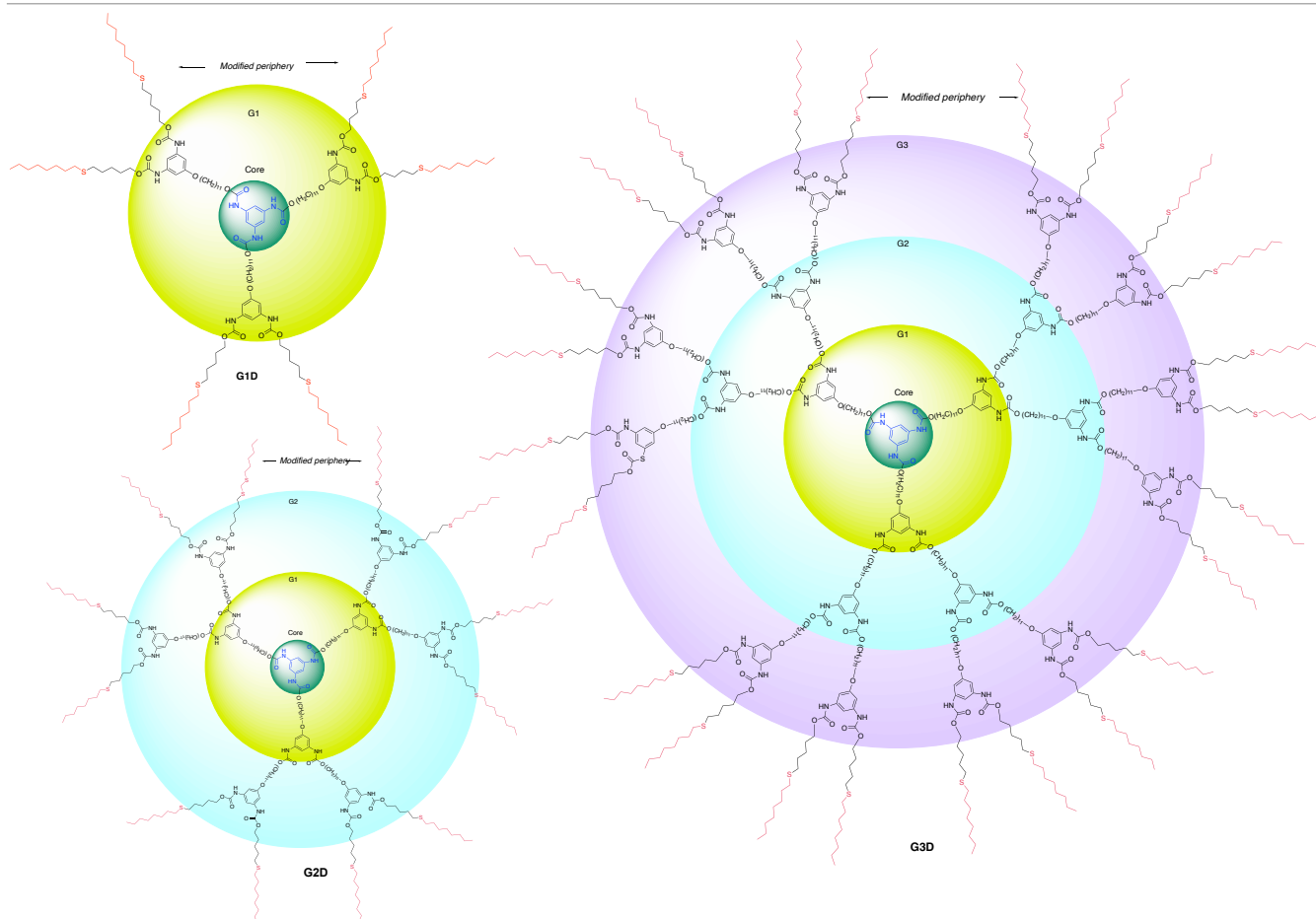acetoxyisophthalic acid, because we lose the acetate group within

Figure 2. Structure of synthesized G1, G2, and G3 dendrimers showing modified periphery.

an hour on heating at 80 °C (Et$_3$N catalyzes the deprotection). To overcome these difficulties, we synthesized **4** as the linking group with a free OH group on it (Scheme 2), which undergoes Curtius reaction without any catalyst to form **9** with good yield.

## Scheme 5. Synthesis of G2 dendron from 5-hydroxyisophthalic acid
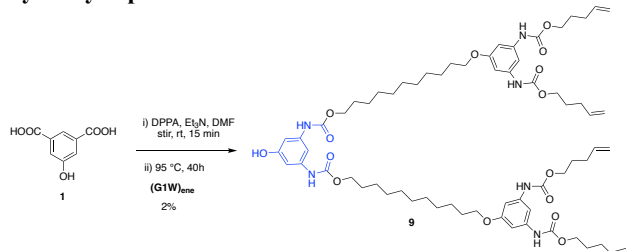
Having optimized the proper reaction conditions, we started coupling of G1 dendron **(G1W)$_{ene}$** with linking agent **4** that preceded smoothly on heating under at 95 °C Curtius reaction

conditions in DMF to afford G2 phenolic urethane **9**. G2 dendron **(G2W)$_{ene}$** with pentene periphery was produced when **9** was heated with 11-bromoundecanol, a spacer group used in this study. *In situ* formed isocyanate during Curtius rearrangement could be activated by adding a Lewis acid like BF$_3$.OEt$_2$ as a catalyst, however, it did not accelerate the formation of product because of solvent (DMF) coordinating with catalyst. Moreover, a base like Et$_3$N as a catalyst would render unprotected phenolic OH more nucleophilic, leading to the phenolic attack on *in situ* formed isocyanate, thereby increasing the side products' yield. Therefore, we carried out this particular reaction without any catalyst, and better results were obtained over a longer time. Thiol-ene functionalization of peripheral alkene moieties with 1-octanethiol in the presence of 2,2'-azobis(2-methylpropionitrile) (AIBN) free-radical initiator under UV light formed G2 dendron **G2W** containing thioether functionality in end groups. In its final step, periphery-modified **G2W** was attached to the trifunctional core **6** in the presence of Lewis acid catalyst BF$_3$.OEt$_2$ to afford generation-two dendrimer **G2D** as highly viscous, transparent gel. Figure 1 shows FT-IR monitored-progress of BF$_3$.OEt$_2$-catalyzed reaction involving attachment of dendron to the core.

Iteration of Curius reaction followed by undecyl group attachment (steps i and ii, Scheme 6) to the so-formed phenolic wedge **10** produced generation-three dendron **(G3W)ene** starting from generation-two dendritic wedge **(G2W)ene** and linking group **4**. Peripheral pentene moieties of this G3 dendron was subjected to thiol-ene click conditions as in G1 and G2 steps to form a modified G3 dendron **G3W**, which was then attached to trifunctional core **6** to generate G3 dendrimer, **G3D**.

Scheme 6. Synthesis showing the growth of G2 – G3 dendrons and dendrimer.
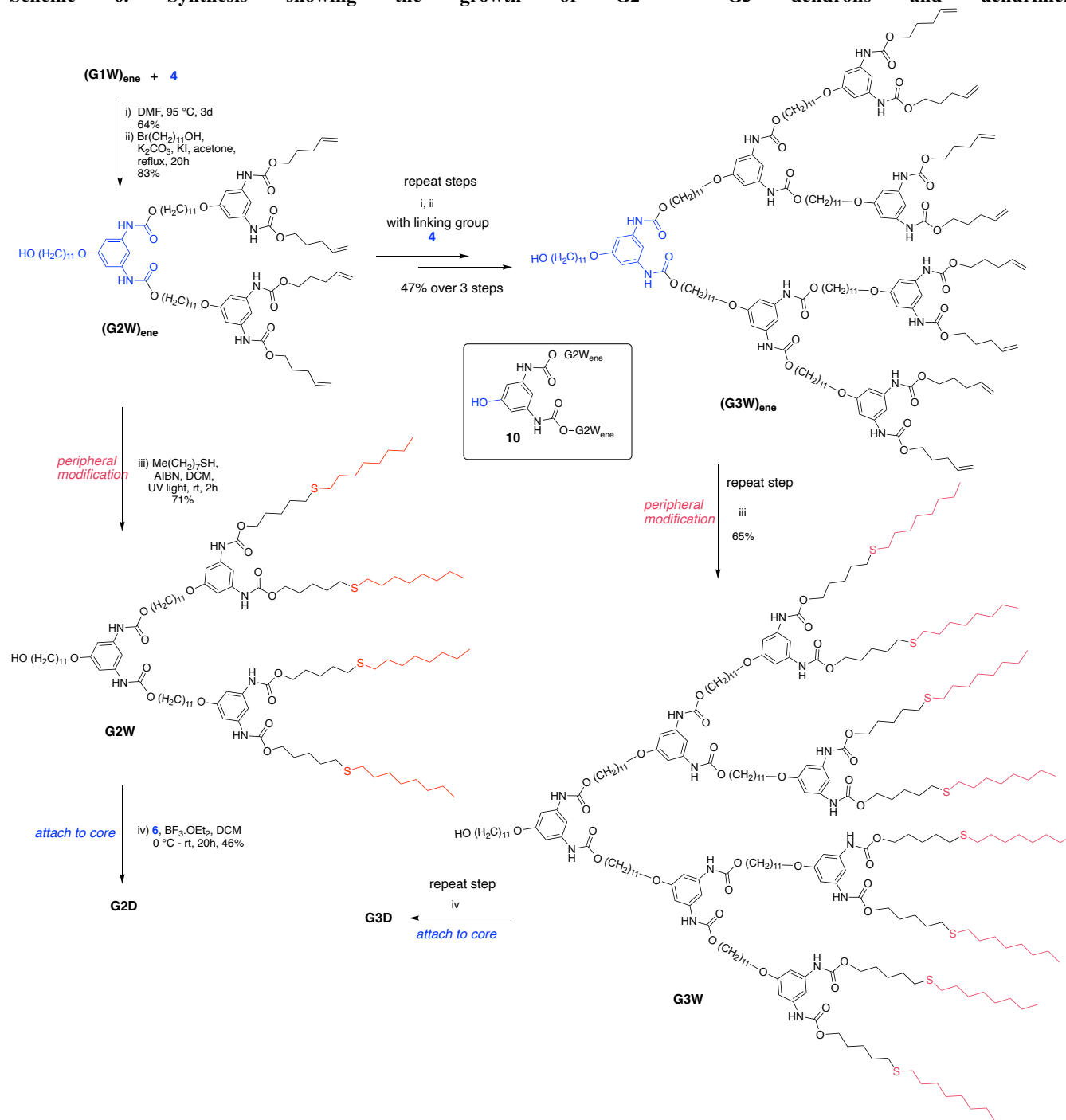
Our strategy allows for the growth of a new generation dendron in every two steps, thereby furnishing G3 dendron (with an alkene periphery in this case) only over six steps. The first of the two steps involve Curtius reaction that generates urethane linkage via nucleophilic attack of alcohol on *in situ* formed isocyanate (obtained from internal rearrangement of acyl azide), and the second step involves attachment of undecyl group as a tail. Both of these reactions do not require protection – deprotection and the products can be purified easily using silica gel chromatography. The advantage of using a clickable periphery is that these groups remain unreactive during the growth of dendron.

As shown in Scheme 6, we opted click and attach approach to synthesize G2 and G3 dendrimers. The reasoning behind this can be explained in terms of yield and the complexity of the reaction. Our study showed that the click-then-attach approach proceeds with better yields than that of the attach-then-click approach (Scheme 4). Attachment of dendron to a trifunctional core involves the same number of reactions per molecule in both approaches; however, end group modification by thiol-ene click during attach-then-click approach requires a large number of reactions per molecule to undergo completion. Such transformations suffer from the same complications as divergent synthesis as the
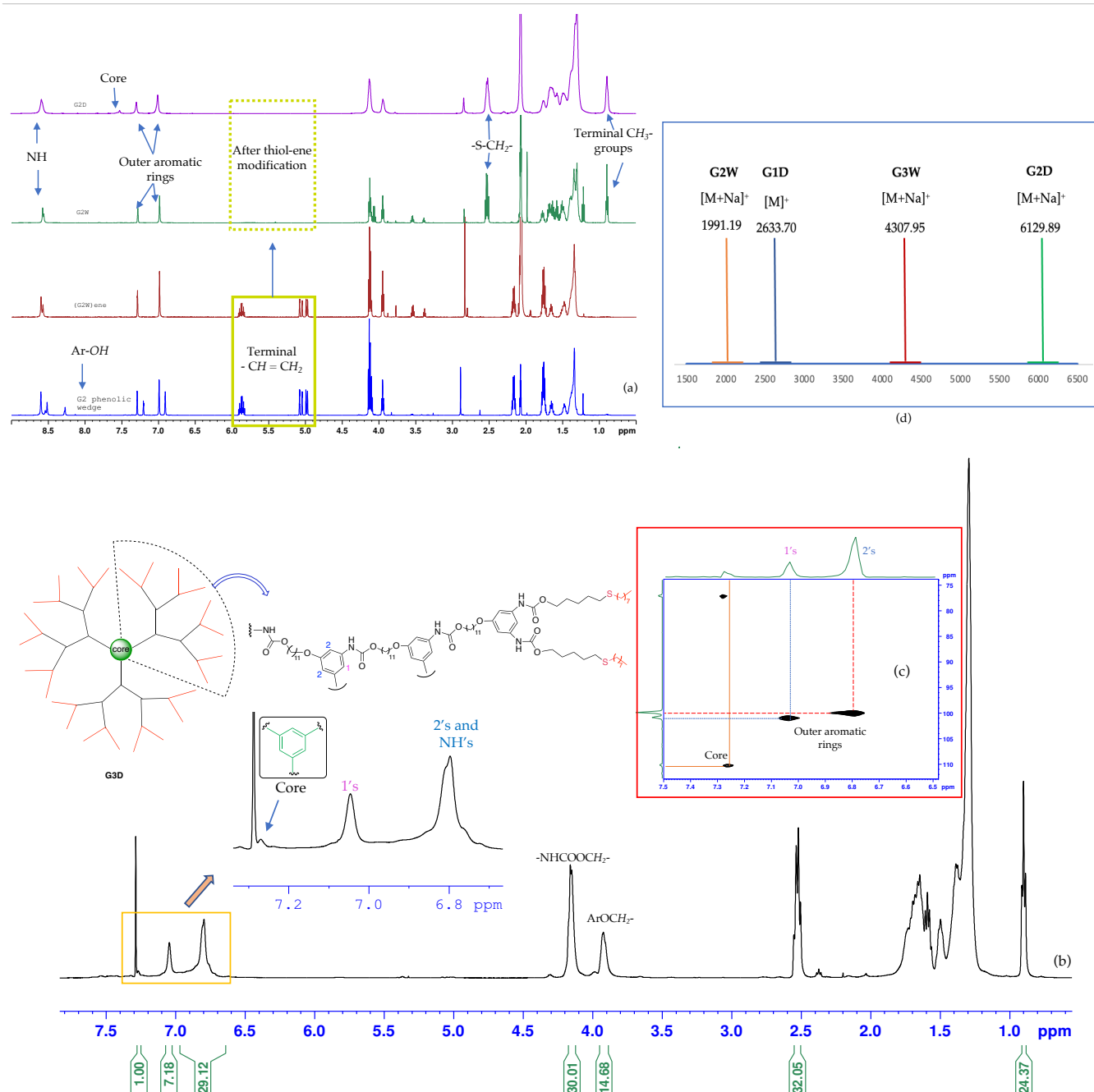
Figure 3. (a) Representative ^{1}H NMR spectra (stacked) showing G2 phenolic wedge **9**, **(G2W)$_{ene}$**, **G2W**, and **G2D** respectively from bottom to top, (b) ^{1}H NMR spectrum of **G3D**: integrals in full spectrum show the one-third portion of this C3 symmetric molecule whereas the expanded region depicts aromatic protons of both core and peripheral groups, (c) a portion of HSQC of **G3D** showing heternonuclear ^{1}H-^{13}C coupling at aromatic region, and (d) MALDI-TOF spectra of G1-G3 denrons and dendrimers (*NMR spectra were recorderd in 500MHz spectrometer at 298K using CD$_3$COCD$_3$ as deuterated solvent*).

multiplicity of end groups increases with higher generation resulting in incomplete or side reactions or even degradation of branches, which burdens the purification of the dendrimer.

Characterization of dendritic structures. Thiol-ene click modified polyurethane dendrimers **G1D-G3D** were first characterized by one-dimensional multinuclear (^{1}H and ^{13}C) as well as two-dimensional (2D) homonuclear and heteronuclear NMR spectroscopy. As shown in the ^{1}H NMR spectra (Figure 3 and S18, S19, and S27), over 0.0 ppm, the peaks of protons assigned to **G1D-G3D** remain unchanged, indicating the identical structures of the dendrimers. However, these peaks became broader with increasing generations, possibly because the protons became non-equivalent, going from the first to the third-generation dendrimer. In the stacked ^{1}H NMR of G2 dendrimeric structures (Figure 3a), the peaks at ∼5.9 – 5.0 ppm assigned to the terminal alkenes disappeared, ultimately indicating that the thiol-ene reaction went successfully to completion. This formtion of new peaks - a quartet at ∼2.5 ppm and a triplet at ∼0.9 ppm assigned to -SCH_2- and the terminal -CH_3 groups, respectively – further supports the completion of thiol-ene reaction. Attachment of dendrons **G1W-G3W** to the trifunctional core was evidenced by the appearance of a new ^{1}H peak at the aromatic region (figure 3a *purple spectrum* and 3b). Expanded region of figure 3b shows aromatic protons' peaks of **G3D** where a more shielded broad peak at ∼6.8 ppm is assigned to both NH's and aromatic protons ortho to aryl ethers. In contrast the most deshielded peak at ∼7.3 ppm accounts for aromatic protons of the core. Over 0.0 ppm, ^{1}H NMR of G1-G3 dendrimers were also characterized by two-dimensional homonuclear and heteronuclear NMR spectroscopy. Figure 3c shows an aromatic region of two-dimensional heteronuclear single quantum coherence (HSQC) spectroscopy of **G3D** where more downfield peak (∼7.25 ppm, 110 ppm) corresponds to the aromatic proton of the trifunctional core.

Mass spectrometric investigation of polyurethane dendrimers **G1D-G3D** was performed by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF-MS), which supported the existence of these dendrimers. In the MALDI-TOF-MS spectrum (Figure S37-41), the peak of m/z = 2633.70 detected was consistent with the theoretical mass of [G1D + H]+ ion (m/z = 2632.70). The peak at m/z = 6129.89 detected in the MALDI-TOF-MS spectrum (Figure S..) corresponded to the [G2D+Na]+ ion (theoretical m/z = 6125.94). For the polyurethane dendrimer **G3D** (theoretical mass = 13043.46), the MALDI-TOF-MS spectrum provided unsatisfactory mass data, possibly because the dendrimer absorbed the laser wavelength (355 nm) used in the instrument subsequently fragmenting the coumpond before it gives [G3D]$^+$ signal. (As shown in the Figure S51, the **G3D** has broad absorption from 280-360 nm with an emission maxima at 382 nm, Figure S52).

To further determine the structure of **G1D** – **G3D**, we also employed two-dimensional (2-D) diffusion-ordered spectroscopy (DOSY). The observation of a distinct spectral band in the DOSY spectrum (Figure S31-S36) of the dendrimers implied the existence of **G1D**, **G2D**, or **G3D**. Moreover, a gradual decrease in the diffusion coefficient (*D*) observed – 4.47 × 10^{-10} (**G1D**), 1.86 × 10^{-10} (**G2D**), and 1.38 × 10^{-10} (**G3D**) – in the spectrum provided further evidence of a progressive increase in the size of the dendrimers with increasing generations.

Late – stage modification of dendrimers. Also termed as post-synthetic modification, the late-stage modification is a powerful synthetic method to produce functional materials of wide applications.[115] This approach not only enables the synthesis of a material that cannot be synthesized directly but also ensures the synthesis of combinatorial materials. For example, a library of G1 – G3 polyurethane dendrimers can be produced just in the final two steps using the thiol-ene click reaction followed by attachment to the core. Although the post-synthetic functionalization can be brought both at the focal point[116] and the periphery of the dendrimers, the modification at the periphery is of particular interest. This is because, with the growing generation of a dendrimer, the core along with repeating units get shielded, and peripheral units are the only means of communication with an external environment. As a result, the properties of the dendrimer solely depends on the peripheral units. Thiol-ene click-inspired orthogonal surface modification of a dendrimer furnishes a dendrimer with different physical and chemical properties.[117]

CONCLUSION

In summary, we demonstrated a thiol-ene click-inspired, protecting group-free approach towards the convergent synthesis of polyurethane dendrimers. One-pot multicomponent Curtius reaction followed by a spacer group's attachment gave a new generation common dendron in every two-step, which allowed for late-stage modification of both the periphery and the core. As a representative of the proposed approach, thioether surface-functionalized polyurethane G1 dendrimers were synthesized via both 'click then attach' and 'attach then click' approaches using a trifunctional core. Higher generation dendrimers, **G2D** and **G3D**, were synthesized employing the 'click then attach' strategy to minimize the incomplete reactions and possible degradations at the periphery that could be associated with the 'attach then click' approach. Access to this type of investigation will contribute to a concise and efficient synthesis of not only the polyurethane dendrimers but also for other dendritic macromolecules. Our ongoing research also involves the synthesis and characterization of dendrimers with alkyne moieties, which undergo late-stage modification using azide-alkyne click chemistry.

EXPERIMENTAL ESCTION

General information. Starting materials were used as obtained from commercial sources: Sigma Aldrich (NaN$_3$, AIBN, 1-octadecanethiol, triethylamine), TCI (4-penten-1-ol, 1-bromoundecanol, benzene-1,3,5-trcicarbonyltrichloride, 1-octanethiol, BF$_3$.OEt$_2$), and Alfa Aesar (5-hydroxyisophthalic acid, DPPA). Whereas anhydrous solvents were used in the dendrimer synthesis, DMF (Acros Organics), DCM (Fischer Scientific), and acetone (Acros Organics) were used as received, reagent toluene was used without distillation. Curtius reaction was set in a Carousel reactor, and all other reactions were performed using classical batch process using oil bath (if heat 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 Thermo Scientific MelTemp 3.0 instrument.

^{1}H, ^{13}C, and 2D NMR spectra were recorded with a Bruker Advance 500 MHz NMR instrument at 298K. NMR spectra were recorded using either acetone-d_6 or CDCl$_3$ as a deuterated solvent, and accordingly, the solvent residual peaks were obtained at δ 2.05 ppm (qn) and δ 7.26 ppm (s) respectively in ^{1}H NMR. In ^{13}C NMR, solvent residual peaks were recorded at δ 206.68 ppm (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 in 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 PerkinElmer Spectrum One FT-IR Spectrometer.

HRMS spectra of small molecules, including dendrons, were obtained from FTMS plus CESI mass spectrometer using DCM as a solvent. MALDI of larger molecules was recorded with a Bruker Autoflex 3 instrument using dithranol and ferulic acis 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 auto-column flash cartridges packed with 12g or 40g silica of 40-75 μm, 60 Å (obtained from Sorbtech and Supelco Technologies). Flow rate was 10 mL/min - 30 mL/min. The mobile phase used in these separations was ethyl acetate, hexane, DCM, or a mixture of these solvents.

General procedure of Curtius reaction. *Method 1.* An oven-dried carousel tube was charged with 5-hydroxyisophthalic and a magnetic stirrer. After degassing and backfilling the tube with nitrogen, anhydrous DMF was added. The compound was dissolved completely, followed by the slow addition of Et$_3$N and dropwise addition of DPPA under stirring at ambient temperature. After stirring the solution for 15 min, **(G1W)$_{ene}$** was added, and the tube was transferred to carousel reactor maintained at 95 °C. The reaction was monitored with TLC. After 40h, the solution was cooled to room temperature, diluted 20 times with water, and extracted with EtOAc (3 times). Combined organic layers were washed with water (5 times) and brine (once), concentrated under reduced pressure and purified by flash chromatography.

Method 2. An oven-dried carousel tube was charged with 5-hydroxy-1,3-dicarbonyl diazide **4** and a dendron, **(G1W)$_{ene}$** or **(G2W)$_{ene}$**. After degassing and backfilling the tube with nitrogen, anhydrous DMF was added, and then the solution was transferred to the carousel reactor maintained at 95 °C. The reaction was monitored with TLC. After 72h, work-up was performed similarly to method 1.

General procedure of thiol-ene click reaction. The dendron having an alkene periphery was dissolved in anhydrous DCM in a glass vial. 1-Octanethiol (1.1 eq/double bond) and AIBN (0.1 eq/double bond, as a free-radical initiator) were added to the solution. The vial was then capped and placed under a broad spectrum UV lamp under stirring at ambient temperature. After 2h, the solvent was evaporated, and the crude was purified by flash chromatography.

General procedure of attachment of dendron to the core. An oven-dried RB flask was charged with 1,3,5-triisocyanatobenzene and magnetic stirrer. After degassing and backfilling the flask with nitrogen, anhydrous DCM was added via syringe. The flask was then placed under an ice-

bath and three drops of BF$_3$.OEt$_2$ was added. After stirring 10 min, a solution of dendron in anhydrous DCM was added dropwise, and stirring was continued for 10 min. The ice bath was removed, and the stirring was continued for 20h. The progress of the reaction was monitored using FT-IR observing the isocyanate peak (~2200 cm^{-1}). When the peak disappeared, the stirring was stopped, the solvent was evaporated, and the crude was purified by flash chromatography.

(Synthetic procedure of compounds from 7 to G1D has been reported previously.[118])

5- Hydroxy- 1,3- benznedicarbonyl diazide **4**. Dimethyl-5-hydroxyisophthalte **2** (10 g, 47.6 mmol, 1.0 eq) was dissolved in ethanol (100 mL) in a 250 mL – RB flask containing a magnetic stir bar. Hydrazine hydrate (14.65 mL, 51%, 142.8 mmol, 5.0 eq) was added, and the mixture was refluxed. The progress of the reaction was checked with TLC (1:1 EtOAc/hexane). After 8h, white solid formed was filtered, washed with cold ethanol, and dried under vacuum overnight to get white powder as product **3** (9.54 g, 45.4 mmol, 95% yield, m.p. 257 °C). It was carried to the next step without further purification.

5-Hydroxy-1,3-benzenedicarboxylic acid-1,3-dihydrazide **3** (9.54 g, 45.43 mmol, 1.0 eq) was dissolved in 50% v/v acetic acid (120 mL) in a 250 mL – RB flask containing a magnetic stir bar. The solution was placed at an ice-bath, and NaNO$_2$ (9.40 g in 90 mL MQ water, 136.29 mmol, 3.0 eq) was added dropwise at 0 °C. Stirring was continued for 30 min at the same temperature. The white solid formed was filtered, washed with cold water, and dried under vacuum to give compound **4** as amorphous white solid (8.86 g, 38.16 mmol, 84% yield). It was pure enough for further reactions. TLC (35% EtOAc in hexane): R$_f$ 0.46. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 9.42 (s, 1H, OH), 8.05 (t, *J* = 1.43 Hz, 1H), 7.72 (d, *J* = 1.45 Hz, 2H). ^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 171.0, 158.2, 132.7, 121.0, 120.8. HRMS (ESI-LTQ-Orbitrap): *m/z* calcd for C$_8$H$_3$N$_6$O$_3^-$ [M-H]$^-$ 231.0272; found 231.0270.

Generation – two phenolic wedge 9. General procedure of Curtius reaction (*method 1*) was employed using 5-hydroxyisophthalic acid 1 (66 mg, 0.362 mmol, 1.0 eq), anhydrous DMF (08 mL), Et$_3$N (106 μL, 0.760 mmol, 2.1 eq), DPPA (165 μL, 0.760 mmol, 2.1 eq), and **(G1W)$_{ene}$** (375.2 mg, 0.724 mmol, 2.0 eq) to give a transparent viscous oil as the product **9** (22 mg, 0.018 mmol, 5%) after purification (40% EtOAc/hexane as mobile phase.)

General procedure of Curtius reaction (*method 2*) was employed using 5-hydroxy-1,3-benzenedicarbonyl diazide **4** (579.3 mg, 2.500 mmol, 1.0 eq), **(G1W)$_{ene}$** (1941.5 mg, 3.743 mmol, 1.5 eq), and DMF (8 mL) to get a transparent viscous oil as the product **9** (763.3 mg, 0.63 mmol, 34%) after purification (40% EtOAc/hexane as mobile phase.) TLC (40% EtOAc in hexane): R$_f$ 0.44. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 8.58 (t, 6H, -NH-), 8.28 (s, 1H, OH), 7.29 (s, 2H), 7.20 (q, *J* = 1.9 Hz, 1H), 6.99 (s, 4H), 6.90 (s, 2H), 5.89 – 5.84 (m, 4H), 5.07 – 4.97 (qd, *J* = 17.1, 11.1, 9.2, 1.7 Hz, 8H), 4.12 (t, 12H), 3.95 (t, *J* = 6.5 Hz 4H), 2.19 – 2.14 (m, 8H), 1.78 – 1.74 (m, 12H), 1.67 – 1.64 (m, 4H), 1.49 – 1.46 (m, 4H), 1.43 – 1.29 (m, 24H). ^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 160.1, 158.1, 153.54, 153.51, 153.46, 140.7, 140.6, 137.9, 114.6, 114.5, 100.7, 100.0, 99.9, 99.2, 67.6, 64.3, 63.7, 63.6, 61.6, 29.8,

28.1, 25.9, 25.7. MALDI-TOF-MS (*dithranol* as matrix): *m/z* calcd for $C_{66}H_{96}N_6O_{15}$ [M+Na]$^+$ 1235.68, found [M+Na]$^+$ 1235.67.

Generation two dendron, **(G2W)$_{ene}$**. An oven-dried 50 mL RB flask was charged with 11-bromoundecanol (156.0 mg, 0.620 mmol, 1.5 eq), K_2CO_3 (285.4 mg, 2.065 mmol, 5.0 eq), KI (13.8 mg, 0.083 mmol, 0.2 eq), anhydrous acetone (5 mL), and a magnetic stir bar. After degassing and filling the flask with nitrogen, **9** (501.1 mg, 0.413 mmol, 1.0 eq) in 1.5 mL anhydrous acetone was transferred into the flask via syringe. The reaction mixture was set to reflux under nitrogen. Progress of reaction was checked with TLC (3:2 hexane/EtOAc). After 20 h, solvent was evaporated, crude was extracted with EtOAc, washed with brine, dried with anhydrous $MgSO_4$, concentrated, and finally purified by flash chromatography using 40% EtOAc in hexane as mobile phase to give slightly yellow viscous oil as product (475.5 mg, 0.344 mmol, 83% yield). TLC (40% EtOAc in hexane): R$_f$ 0.41. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 8.58 (d, 6H, NH), 7.29 (s, 3H), 6.99 (s, 6H), 5.91 – 5.82 (m, 4H), 5.08 – 4.97 (dq, *J* = 17.1, 10.2, 1.5 Hz, 8H), 4.12 (q, *J* = 6.7 Hz, 12H, overlapped triplet), 3.95 (t, *J* = 6.5 Hz, 6H), 3.55 (q, *J* = 18.4, 5.7 Hz, 2H), 3.40 (t, *J* = 5.3 Hz 1H, OH), 2.19 – 1.80 (m, *J* = 7.2 Hz, 8H), 1.80 – 1.73 (m, 16H), 1.67 – 1.63 (m, *J* = 14.3 Hz, 4H), 1.53 – 1.29 (m, 53H). ^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 160.1, 153.6, 153.5, 140.7, 140.6, 137.9, 114.6, 100.7, 99.2, 67.7, 64.4, 63.7, 61.6, 32.9, 29.8, 281., 25.9, 25.8, 25.7. MALDI-TOF-MS (*dithranol* as matrix): *m/z* calcd for $C_{77}H_{118}N_6O_{16}$ [M+Na]$^+$ 1405.85, found 1405.99.

Surface functionalized generation-two dendron, **G2W**. General procedure of thiol-ene click reaction was employed using **(G2W)$_{ene}$** (101 mg, 0.073 mmol, 1.0 eq), anhydrous DCM (0.4 mL), 1-octanethiol (112 µL, 0.584 mmol, 4.0 eq) and AIBN (5 mg, 0.029 mmol, 0.4 eq) to give highly viscous, transparent oil as product (123.9 mg, 0.063 mmol, 86% yield) after purification (40% EtOAc/hexane as mobile phase). TLC (30% EtOAc in hexane): R$_f$ 0.41. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 8.58 (d, 6H, NH), 7.28 (s, 3H), 6.99 (s, 6H), 4.12 (qn, *J* = 6.5 Hz, 12H, overlapped triplet), 3.95 (t, *J* = 6.5 Hz, 6H), 3.55 (q, *J* = 18.4, 5.5 Hz, 2H), 3.39 (t, 1H, *J* = 5.3 Hz, OH), 2.53 (q, *J* = 7.5 Hz, 16H), 1.77 (qn, *J* = 14.4, 6H), 1.72 – 1.25 (m, 136H), 0.89 (t, *J* = 6.9 Hz, 12H). ^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 160.1, 153.60, 153.57, 160.66, 140.64, 100.8, 99.2, 67.6, 64.4, 64.2, 61.6, 59.7, 32.9, 31.7, 31.6, 31.4, 25.9, 25.8, 25.7, 25.0, 22.4, 13.6, 13.5. MALDI-TOF-MS (*dithranol* as matrix): *m/z* calcd for $C_{109}H_{190}N_6O_{16}S_4$ [M+Na] 1990.30, found 1991.19.

Generation-two dendrimer, **G2D**. General procedure of attachment of dendron to the core was employed using 1,3,5-triisocyanatobenzene **6** (7.3 mg, 0.036 mmol, 1.0 eq), **G2W** (233.9 mg, 0.119 mmol, 3.3 eq), BF$_3$.OEt$_2$ (3 drops), and anhydrous DCM (1.5 mL) to give highly viscous transparent oil as product (101.3 mg, 0.017 mmol, 46% yield) after purification (30% EtOAc/hexane as mobile phase). TLC (30% EtOAc in hexane): R$_f$ 0.56. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 8.58 (s, 21H), 7.53 (s, 3H), 7.29 (s, 9H), 6.99 (s, 18H), 4.13 (s, 42H), 3.94 (s, 18H), 2.52 (d, *J* = 6.8 Hz, 48H), 1.76 – 1.31 (m, 378H), 0.90 (s, 36H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 160.3, 153.5, 139.6, 139.5, 99.1, 68.1, 65.4, 65.2, 32.2, 32.0, 31.8, 29.7, 29.5, 29.4, 29.3, 29.2, 29.1, 29.0, 28.9, 28.6, 26.0, 25.2, 22.7, 14.1. MALDI-TOF-MS (*ferulic acid* as matrix):

m/z calcd for $C_{336}H_{573}N_{21}O_{51}S_{12}$ [M+Na]$^+$ 6125.94, found 6129.89.

Generation – three phenolic wedge **10**. General procedure of Curtius reaction (*method 2*) was employed using 5-hydroxy-1,3-benzenediacrbonyl diazide **4** (104.9 mg, 0.452 mmol, 1.0 eq), **(G2W)$_{ene}$** (875.4 mg, 0.633 mmol, 1.4 eq), and anhydrous DMF (5 mL) to give highly viscous transparent oil as product **10** (827.7 mg, 0.270 mmol, 62% yield) after purification (40% EtOAc/hexane as mobile phase). TLC (40% EtOAc in hexane): R$_f$ 0.38. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 8.56 (s, 14H, NH), 8.25 (s, 1H), 7.30 (s, 6H), 7.22 (s, 1H), 7.00 (s, 12H), 6.92 (s, 1H), 5.89 – 5.83 (m, 8H), 5.02 (dd, *J* = 17.1, 10.2 Hz, 16H), 4.12 (q, *J* = 6.7 Hz, 28H), 3.94 (t, *J* = 6.3 Hz, 12H), 2.16 (q, *J* = 7.2 Hz, 16H), 1.80 – 1.72 (m, 30H), 1.70 – 1.60 (m, 12H), 1.50 – 1.27 (m, 98H). ^{13}C NMR (125 MHz, CDCOCD$_3$): δ 160.1, 158.2, 158.1, 153.6, 153.5, 140.65, 140.62, 137.9, 114.6, 100.7, 100.0, 99.9, 99.2, 67.6, 64.4, 64.3, 63.7, 29.8, 28.1, 25.9, 25.7. MALDI-TOF-MS (*dithranol* as matrix): *m/z* calcd for $C_{162}H_{240}N_{14}O_{35}$ [M+Na]$^+$ 2964.73, found 2966.58.

Generation – three dendron, **(G3W)$_{ene}$**. The procedure reported for **(G2W)$_{ene}$** was employed using 11-bromoundecanol (68.4 mg, 0.2721 mmol, 1.5 eq), K$_2$CO$_3$ (125.4 mg, 0.907 mmol, 5.0 eq), KI (9.0 mg, 0.0544 mmol, 0.3 eq), G3 phenolic wedge **10** (534.0 mg, 0.1814 mmol, 1.0 eq), and anhydrous acetone (8 mL) to give gel-like transparent product (297.0 mg, 0.0954 mmol, 75% yield) after purification (40% EtOAc/Hexane as mobile. Phase). TLC (40% EtOAc in hexane): R$_f$ 0.33. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 8.60 (d, *J* = 12.2 Hz, 14H, NH), 7.30 (s, 7), 6.99 (s, 14H), 5.91 – 5.82 (m, 8H), 5.02 (dd, *J* = 17.1, 10.1 Hz, 16H), 4.12 (t, *J* = 6.8, 28H, overlapped triplets), 3.94 (t, *J* = 6.4 Hz, 14H), 3.55 (q, *J* = 5.7 Hz, 2H), 3.40 (t, 1H, OH), 2.16 (q, *J* = 7.2 Hz, 16H), 1.78 – 1.72 (m, 32H), 1.69 – 1.62 (m, 14H), 1.50 – 1.27 (m, 122H). ^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 160.1, 158.1, 153.6, 153.5, 140.6, 137.9, 114.5, 100.7, 100.0, 99.1, 67.6, 64.4, 64.3, 63.7, 59.6, 29.8, 29.5, 28.1, 25.9, 25.7. MALDI-TOF-MS (*ferulic acid* as matrix): *m/z* calcd for $C_{173}H_{262}N_{14}O_{36}$ [M+Na]$^+$ 3134.90, found 3136.66.

Surface functionalized generation-three dendron, **G3W**. General procedure of thiol-ene click reaction was employed using **(G3W)$_{ene}$** (274.8 mg, 0.088 mmol, 1.0 eq), 1-octanethiol (184 µL, 1.059 mmol, 12.0 eq and AIBN (10 mg, 0.058 mmol, 0.8 eq), and anhydrous DCM (1.5 mL) to give gel-like transparent product (244 mg, 0.057 mmol, 65%) after purification (30% EtOAc/hexane as mobile phase). TLC (30% EtOAc in hexane): R$_f$ 0.58. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 8.58 (d, *J* = 7.1 Hz, 14H, NH), 7.30 (s, 7H), 7.01 (s, 14H), 4.12 (qn, *J* = 6.4 Hz, 28H, overlapped triplet), 3.94 (t, *J* = 6.2 Hz, 14H), 3.55 (q, *J* = 6.1 Hz, 2H), 3.42 (t, 1H, OH), 2.53 (q, *J* = 7.3 Hz, 32H), 1.80 – 1.72 (m, 16H), 0.89 (t, *J* = 6.8 Hz, 24H). The large aliphatic multiplet portion was not integrated. ^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 160.1, 153.6, 153.5, 140.6, 100.7, 99.1, 67.6, 64.4, 64.3, 61.7, 32.9, 31.7, 31.6, 31.5, 29.6, 25.9, 25.8, 25.7, 25.0, 22.5, 13.5. MALDI-TOF-MS (*ferulic acid* as matrix): *m/z* calcd for $C_{237}H_{406}N_{14}O_{36}S_8$ [M+Na]$^+$ 4303.80, found 4307.95.

Generation-three dendrimer, **G3D**. General procedure of attachment of dendron to the core was employed using 1,2,3-triisocyanatobenzene **6** (1.8 mg, 0.00918 mmol, 1.0 eq), **G3W** (118.0 mg, 0.02754 mmol, 3.0 eq), BF$_3$.OEt$_2$ (3 drops), and

anhydrous DCM (1 mL) to give highly viscous transparent oil as product (77.9 mg, 0.0060 mmol, 65% yield). TLC (5% acetone in DCM): R_f 0.22. ^{1}H NMR (500 MHz, CD$_3$COCD$_3$): δ 7.27 (s, 1H), 7.05 (s, 7H), 6.80 (s, 29H, broad), 4.15 (d, J = 5.2 Hz, 30H, overlapped triplets), 3.92 (s, 14H, broad triplets), 2.52 (q, J = 7.7 Hz, 32H), 0.90 (t, J = 13.0 Hz, 24H) (large aliphatic hydrocarbon portion was not integrated). ^{13}C NMR (125 MHz, CD$_3$COCD$_3$): δ 160.3, 153.5 (broad), 139.54, 139.48, 100.9, 99.9, 69.3, 68.0, 65.4, 65.2, 32.2, 32.0, 31.8, 29.9, 29.7, 29.6, 29.5, 29.4, 29.3, 29.24, 29.21, 29.0, 28.9, 28.6, 26.0, 25.9, 25.2, 22.7, 14.1. MALDI-TOF-MS: unsatisfactory data was obtained even with different matrices like dithranol, ferulic acid, sinapic acid, HABA, HCCA, and DHB.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge.

^{1}H NMR, ^{13}C NMR, 2D NMR, and IR spectra as well as mass spectrometric data of the novel compounds described (PDF).

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Notes

The authors declare no competing financial interest.

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