Macromolecules
ARTICLE

Macromolecules **2010**, *43*, 6625–6631 **6625**
DOI: 10.1021/ma101242u

Pushing the Limits for Thiol−Ene and CuAAC Reactions: Synthesis of a 6th Generation Dendrimer in a Single Day

Per Antoni,[†,‡] Maxwell J. Robb,[‡] Luis Campos,[‡] Maria Montanez,[†] Anders Hult,[†] Eva Malmström,[†] Michael Malkoch,*[,†] and Craig J. Hawker*[,‡]

[†] *Royal Institute of Technology, School of Chemistry and Chemical Science, Division of Coating Technology, Teknikringen 56-58, 10044 Stockholm, Sweden, and* [‡] *Department of Chemistry and Biochemistry, Materials Department, and Materials Research Laboratory (MRL), University of California, Santa Barbara, California 93106*

Received June 3, 2010; Revised Manuscript Received July 7, 2010

ABSTRACT: Dendrimer synthesis should not be tedious and time-consuming. By utilizing an AB_2-CD_2 approach and having orthogonal, "clickable" groups on each monomer, the time for dendrimer assembly can be drastically reduced. This was shown by preparation of a sixth generation dendrimer from starting monomer units in a single day.

Introduction

The field of branched, globular polymers such as dendrimers has undergone a remarkable development since they were first postulated by Flory in 1952.[1] Flory's early ideas were synthetically realized almost 30 years later when the divergent growth approach was introduced, followed in 1990 by the convergent strategy for the synthesis of dendrimers.[2−5] In recent years, the dendrimer field has expanded with numerous scientific publications discussing the use of these unique macromolecules in various applications such as multivalent affinity probes,[6] microelectronics,[7,8] and in light harvesting systems.[9]

An ongoing challenge in developing applications for dendritic macromolecules is the elaboration of new methodologies for their synthesis. Ideally, dendrimer synthesis should be fast, efficient, and rely on simple purification methods with these attributes being absent from many of the original divergent or convergent growth approaches. A number of accelerated strategies have been developed ranging from a branched AB_4 monomer approach to the rapid synthesis of dendrimers by an orthogonal coupling strategy.[10,11] In the latter strategy, Zimmerman combined different AB_2 and CD_2 monomers with orthogonal Mitsunobu esterification and Sonogashira chemistry to construct dendritic macromolecules at a rate of one generation per step. While accelerated, many of these strategies still suffer from issues related to efficiency and complicated purification steps which leads to a considerable time investment. To overcome the long held view that dendrimer synthesis is tedious, expensive, and time-consuming, a robust and highly efficient strategy for the synthesis of dendritic macromolecules based on the combination of two orthogonal click reactions is presented. This approach takes advantage of the quantitative nature of the coupling reactions, an AB_2/CD_2 strategy, and facile purification requirements to allow a sixth generation dendrimer to be prepared in a single day from starting monomer units. While other approaches have accelerated dendrimer synthesis by reducing the number of steps, it is proposed that this focus on acceleration in terms of steps, efficiency and most importantly, time, will further facilitate the academic and commercial availability of dendritic materials.[12,13]

The introduction of click chemistry in 2001 brought with it a wide range of opportunities for dendrimer synthesis[14−16] with these highly efficient, robust, and orthogonal reactions being ideal for the rapid and facile preparation of dendrimers.[17] Within this family of reactions are copper catalyzed azide alkyne cycloaddition (CuAAC) and photochemical radical thiol−ene coupling.[18−22] The effectiveness of these reactions for dendrimer synthesis has already been proven. In 2008, Hawker successfully synthesized fourth generation dendrimers using thiol−ene coupling reactions[23] and in 2007, Malkoch demonstrated the accelerated assembly of a fourth generation dendrimer in 4 steps using CuAAC coupling reactions in combination with esterification chemistry.[24] In an elegant expansion of this approach, Shen exploited the kinetically asymmetric reactivity of 2-[(methacryloyl)-oxy]ethyl acrylate (AB monomer) via Michael additions with cysteamine as a CD_2 monomer. The key to this approach is the orthogonality of the methacrylate unit which undergoes quantitative reaction with the thiol and no reaction with the amino group.[25] A consistent feature in all of these accelerated approaches is the cessation of dendrimer growth at the fourth generation and prolonged reaction/purification times.

In this report, we present the synthesis of a sixth generation dendrimer using the accelerated AB_2/CD_2 approach employing both CuAAC and thiol−ene coupling reactions. We present a new methodology for dendritic growth including time efficient and benign reaction conditions coupled with simplified purification. The end result is the preparation of a sixth generation dendrimer in a single day.

Experimental Section

General Methods. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded using either a Bruker 200, 300, or 500 MHz or Varian 400 or 500 MHz spectrometer with the solvent signal as internal reference. Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. $CDCl_3$ was used unless otherwise noted. Column chromatography was performed on a Biotage SP1 Flash Purification System using FLASH 40+M cartridges. Gel permeation chromatography

---

*Corresponding authors. E-mail: (M.M.) Malkoch@kth.se; (C.J.H.) Hawker@mrl.ucsb.edu.

(GPC) was performed in *N,N*-dimethylformamide (DMF) on a Waters 2690 separation module equipped with a Waters 2414 refractive index detector. Molecular weights were calculated relative to linear PS standards. Differential scanning calorimetry (DSC) was performed on a TA Instruments DSC Q2000 fitted with a RCS90 refrigerated cooling system at a sampling rate of 10 °C/min in the temperature range of −90 to 70 °C. Thermogravimetric analysis (TGA) was performed on a TA Instruments Q50 thermogravimetric analyzer under a nitrogen atmosphere at a heating rate of 10 °C/min. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 with a Universal ATR sampling accessory. The MALDI−TOF mass spectra were collected on a Bruker UltraFlex MALDI−TOF MS with SCOUT−MTP Ion Source (Bruker Daltonics, Bremen) equipped with a N_2-laser (337 nm), a gridless ion source and reflector design. Spectra of the first and second generation dendrimers were acquired using a reflector-positive method with an acceleration voltage of 25 kV and a reflector voltage of 26.3 kV. Higher generation (third generation and higher) dendrimers were monitored using a linear mode. The detector mass range was set to 500−20000 Da in order to exclude high intensity peaks from the lower mass range. The laser intensity was set to the lowest value possible to acquire high resolution spectra. Spectra were analyzed with FlexAnalysis Bruker Daltonics, Bremen, version 2.2. A Hamamatsu L5662−01 equipped with a 200W Hg−Xe lamp (230−436 nm), $\lambda_{max} = 365$, was used as a UV-light source. ESI mass spectrometry was performed on a Micromass QTOF2 quadrupole/time-of-flight tandem mass spectrometer with the cone voltage set to 45 V and the source temperature at 80 °C. Chemicals were purchased from Sigma-Aldrich (St. Louis, MO) and used without further purification unless otherwise noted.

2,2′-Disulfanediylbis(ethane-2,1-diyl) Bis(2,2,5-trimethyl-1,3-dioxane-5-carboxylate), HED-bis-MPA-Ac, 1. Acetonide-protected bis-MPA(methyloypropionic acid) (42.6 g, 0.245 mol, 2.4 equiv) was dissolved in 150 mL of DCM (dichloromethane) together with HED (2,2′-bis(hydroxyethyl)dimercaptan) (15.75 g, 0.102 mol, 1 equiv) and DMAP (4-dimethylaminopyridine) (4.98 g, 0.041 mol, 0.4 equiv). The solution was kept at 0 °C upon addition of DCC (dicyclohexylcarbodimide) (50.50 g, 0.245 mol, 2.4 equiv). The reaction was left overnight to reach room temperature. The slurry was filtered and the crude solution was concentrated and purified by flash chromatography eluting the product in 20:80 EtOAc:hexanes as a viscous oil. Yield: 40.5 g (85%). ^{1}H NMR: δ 1.19 (s, 6H, $-CH_3$), 1.38 (s, 6H, $-CH_3$), 1.42 (s, 6H, $-CH_3$), 2.93 (t, 4H, $-SCH_2CH_2O-$), 3.63 (d, 4H, J = 12 Hz, $-CH_2O-$), 4.18 (d, 4H, J = 12 Hz, $-CH_2O-$) and 4.40 (t, 4H, $-SCH_2CH_2O-$) ppm. ^{13}C NMR: δ 18.6, 22.5, 24.7, 37.0, 41.9, 62.4, 65.9, 98.0, and 174.0 ppm, MS (ESI): m/z $[M + Na]^+$ calcd for $[C_{20}H_{34}O_8S_2 + Na]^+$, 489.16; found, $[M + Na]^+$ 489.16.

2,2′-Disulfanediylbis(ethane-2,1-diyl) Bis(3-hydroxy-2-(hydroxymethyl)-2-methylpropanoate), HED-bis-MPA−OH, 2. 1 (30.0 g) was dissolved in 300 mL of MeOH and stirred overnight vigorously with 30 g of prewashed acidic Dowex. The full deprotection of the end-groups was monitored by TLC. The polymer resin was filtered off and the solution was concentrated and used without any further purification. Yield: 24.6 g (99%). ^{1}H NMR (acetone-d_6): δ 1.11 (s, 6H, $-CH_3$), 2.98 (t, 4H, $-SCH_2CH_2O-$), 3.64 (d, 4H, J = 10 Hz, $-CH_2O-$), 3.67 (d, 4H, J = 10 Hz, $-CH_2O-$), 3.80 (bs, 4H, -OH), and 4.31 (t, 4H, $-SCH_2CH_2O-$) ppm. ^{13}C NMR: δ 17.2, 37.2, 49.4, 62.4, 68.0, and 175.6 ppm. MS (ESI): m/z $[M + Na]^+$ calcd for $[C_{14}H_{26}O_8S_2+Na]^+$, 409.08; found $[M + Na]^+$, 409.08.

2,2′-(2,2′-Disulfanediylbis(ethane-2,1-diyl)bis(oxy))bis(oxomethylene)bis(2-methylpropane-3,2,1-triyl) Tetrakis(5-azidopentanoate), HED-bis-MPA-N$_3$, 3. 2 (10.0 g, 0.026 mol, 1 equiv), 5-azidopentanoic acid (17.8 g, 0.124 mol, 4.8 equiv), and DMAP (2.50 g, 0.022 mol, 0.8 equiv) were dissolved in 300 mL of DCM and cooled in an ice bath. DCC (25.6 g, 0.124 mol, 4.8 equiv) was dissolved in 50 mL of DCM and added dropwise to the 0 °C solution. The reaction was left overnight and the white precipitate was filtered off the following morning. The crude solution was washed with 3 × 50 mL 10 wt % $NaHSO_4$ (aq) and 3 × 50 mL 10 wt % $NaHCO_3$ (aq). The organic phase was washed once more with brine, dried using $MgSO_4$, concentrated, and purified by flash chromatography eluting the product in 30:70 EtOAc: hexanes as a colorless oil. Yield: 20.6 g (91%). ^{1}H NMR: δ 1.24 (s, 6H, $-CH_3$), 1.56−1.71 (m, 16H, $-CH_2CH_2-$), 2.34 (t, 8H, $-C{=}OCH_2-$), 2.90 (t, 4H, $-SCH_2CH_2O-$), 3.28 (t, 8H, $-CH_2N_3$), 4.19 (d, 4H, J = 12 Hz, $-CH_2O-$), 4.23 (d, 4H, J = 12 Hz, $-CH_2O-$), and 4.37 (t, 4H, $-SCH_2CH_2O-$) ppm. ^{13}C NMR: δ 17.8, 22.0, 28.3, 33.4, 36.9, 46.3, 51.0, 62.6, 65.2, 172.4, and 172.5 ppm. MS (ESI): m/z $[M + Na]^+$ calcd for $[C_{34}H_{54}N_{12}O_{12}S_2 + Na]^+$, 909.31; found, $[M + Na]^+$ 909.36.

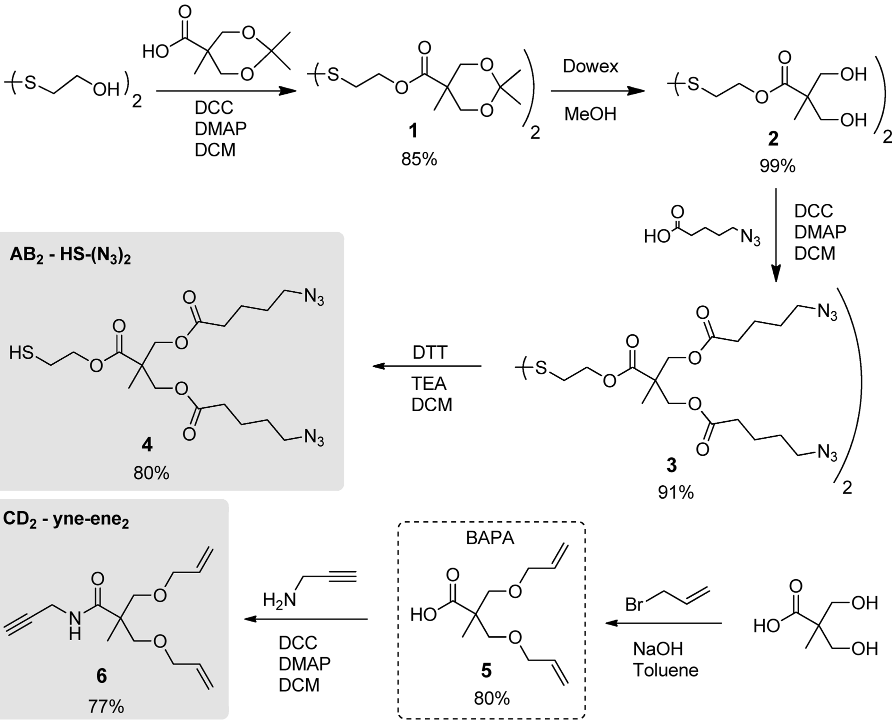
2-((2-Mercaptoethoxy)carbonyl)-2-methylpropane-1,3-diyl Bis-(5-azidopentanoate), HED-bis-MPA-N$_3$, 4. 3 (14.0 g, 15.8 mmol, 1 equiv), dithiothreitol (DTT) (4.87 g, 31.6 mmol, 2 equiv), and TEA (6.38 g, 63.2 mmol, 4 equiv) were dissolved in 100 mL of DCM and flushed with argon for 15 min. The reaction was left to stir overnight and then concentrated. The crude product was purified by flash chromatography eluting the product in 30:70 EtOAc:Hexanes as a colorless viscous oil. Yield: 11.2 g (80%). ^{1}H NMR: δ 1.24 (s, 3H, $-CH_3$), 1.46 (t, 1H, $-SH$), 1.56−1.72 (m, 8H, $-CH_2CH_2-$), 2.33 (t, 4H, $-OCH{=}OCH_2-$), 2.73 (q, 2H, $-SCH_2CH_2O-$), 3.27 (t, 4H, $-CH_2N_3$), 4.20 (d, 2H, $-CH_2O-$), 4.22 (t, 2H, $-SCH_2CH_2O-$), and 4.23 (d, 2H, $-CH_2O-$) ppm. ^{13}C NMR: δ 17.8, 21.9, 23.1, 28.2, 33.4, 46.3, 50.9, 65.2, 65.3, 172.3, and 172.5 ppm. MS (ESI): m/z $[M + Na]^+$ calcd for $[C_{17}H_{28}N_6O_6S + Na]^+$, 467.15; found, $[M + Na]^+$ 467.17.

3-(Allyloxy)-2-(allyloxymethyl)-2-methylpropanoic Acid, BAPA, 5. Bis-MPA (20.0 g, 0.149 mol, 1 equiv), NaOH (59.6 g, 1.49 mol, 10 equiv), and allyl bromide (125.3 g, 1.04 mol, 7 equiv) were added to 300 mL of toluene and left to reflux overnight under vigorous stirring. The reaction was removed from heat and 100 mL of H_2O was added to the crude solution followed by dropwise addition of concentrated HCl until pH = 1 was established. The reaction was washed with H_2O (2 × 50 mL), dried over $MgSO_4$, and concentrated. The pure product was isolated as a yellow viscous oil. Yield: 25.6 g (80%). ^{1}H NMR: δ 1.22 (s, 3H, $-CH_3$), 3.54 (d, 2H, $-CH_2O-$), 3.57 (ABq, 2H, $-CH_2O-$), 3.98 (dt, 4H, J = 6 Hz, $-OCHH_2CHCH_2$), 5.10−5.30 (m, 4H, $-CHCH_2$), 5.75−5.96 (m, 2H, $-CHCH_2$), and 9.68 (bs, 1H, $-OH$) ppm. ^{13}C NMR: δ 17.9, 48.1, 71.8, 72.3, 116.9, 1345, and 180.4 ppm. MS (ESI) m/z $[M + Na]^+$ calcd for $[C_{11}H_{18}O_4 + Na]^+$, 237.09; found $[M + Na]^+$, 237.12.

3-(Allyloxy)-2-(allyloxymethyl)-2-methyl-*N*-(prop-2-ynyl)propanamide, BAP-Acet, 6. 5 (14.0 g, 0.065 mol, 1 equiv), DMAP (1.59 g, 0.0131 mol, 0.2 equiv), and propargylamine (3.59 g, 0.065 mol, 1 equiv) were dissolved in 100 mL of DCM and cooled down to 0 °C. DCC (13.47 g, 0.065 mol, 1 equiv) was dissolved in 20 mL of DCM and added to the cold solution where after the reaction was left to stir overnight. The white precipitate was filtered off and the crude solution was concentrated and purified by flash chromatography eluting the colorless, slightly viscous oil in 30:70 EtOAc:hexanes. Yield: 12.6 g (77%). ^{1}H NMR: δ 1.17 (s, 3H, $-CH_3$), 2.18 (t, 1H, $-CCH$), 3.50 (d, 2H, $-CH_2O$), 3.52 (ABq, 2H, $-CH_2O$), 3.98 (m, 6H, $-OCHH_2CH-$ and $-NCH_2CCH$), 5.13−5.28 (m, 4H, $-CHCH_2$), 5.80−5.91 (m, 2H, $-CHCH_2$), and 7.28 (bs, 1H, $-NHC{=}O-$) ppm. ^{13}C NMR: δ 18.3, 29.0, 47.2, 71.2, 72.4, 73.0, 79.8, 117.1, 134.2, and 174.6 ppm. MS (ESI): m/z $[M + Na]^+$ calcd for $[C_{14}H_{21}NO_3+Na]^+$, 274.12; found, $[M + Na]^+$ 274.15.

Dendrimer Synthesis. *General Procedure for Synthesizing Azide-Functional Dendrimers.* The alkene-functional dendrimer, AB$_2$-monomer (2 equiv/alkene for G1, 4 equiv/alkene for G3 and 7 equiv/alkene for G5,), and DMPA (0.2 equiv/alkene) were

Scheme 1. Synthesis of AB_2, 4, and CD_2, 6, Monomers Used for Dendritic Growth



dissolved in inhibitor free THF. The vessel was sealed using a rubber septum and the solution was sparged with argon for 15 min before exposure to 365 nm UV-light for 45 min with stirring. The first and third generation dendrimers were purified by filtration through a silica plug while the fifth generation dendrimer was purified by precipitating two times into diethyl ether.

General Procedure for Synthesizing Alkene-Functional Dendrimers. The azide-functional dendrimer, CD_2-monomer (1.1 equiv/azide for G2 and G4, 1.6 equiv/azide for G6), and NaAsc (0.3 equiv/azide) were dissolved in an inhibitor free THF/H_2O mixture. The vessel was sealed using a rubber septum and purged with argon for 10 min. $CuSO_4$ (0.1 equiv/azide) was dissolved in H_2O and added to the solution. The reaction was kept under stirring for 1 h where after the two phases were left to separate followed by removal of the water phase. The second and fourth generation dendrimers were purified by filtration through a silica plug. For the sixth generation dendrimer, the organic phase was first diluted with DCM, extracted with H_2O (2 × 2 mL) and brine (1 × 2 mL), dried over $MgSO_4$, and partially concentrated. The dendrimer solution was precipitated two times into diethyl ether.

Results and Discussion

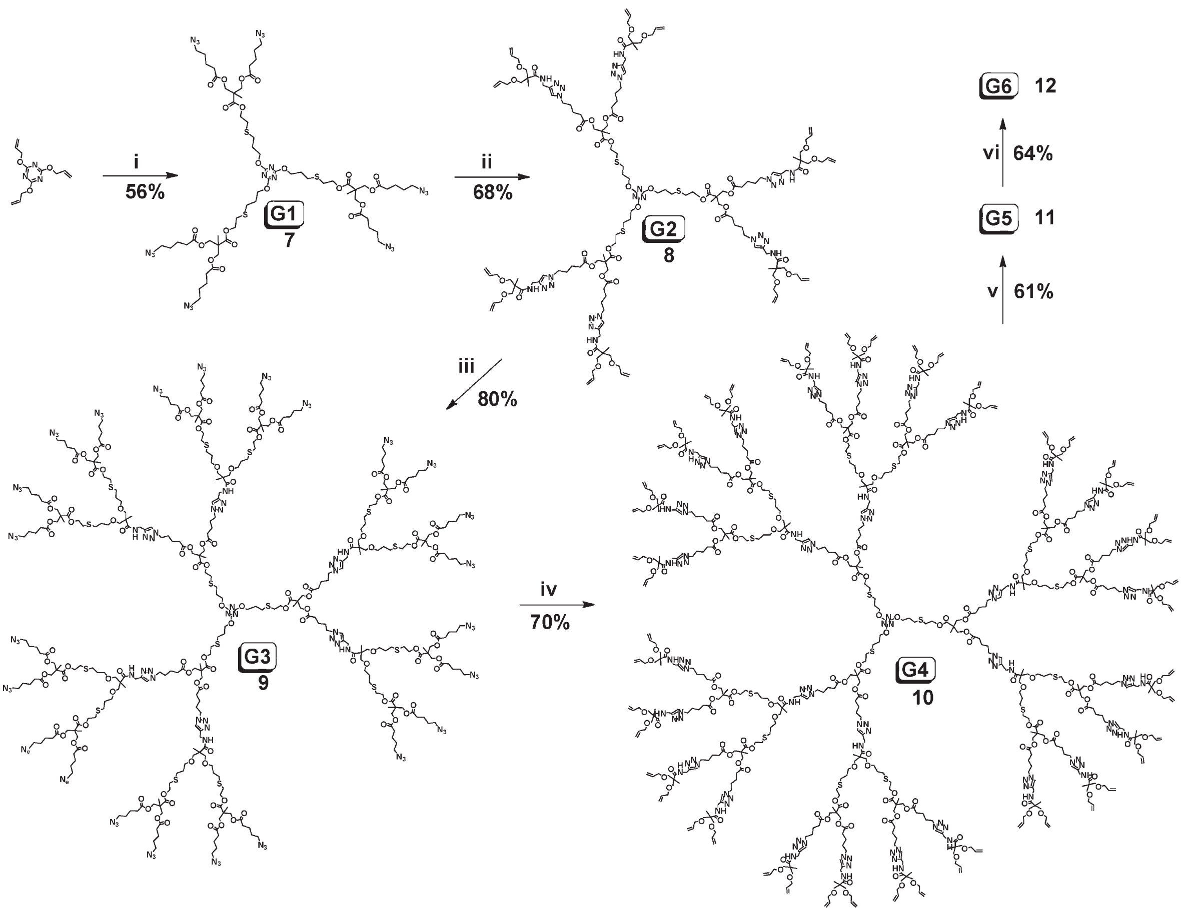
The syntheses of the starting AB_2 and CD_2 monomers were accomplished according to Scheme 1. The inexpensive and commercially available starting material 2,2-bis(hydroxymethyl)-propionic acid, bis-MPA, was used in both cases with the AB_2 monomer **4**, containing a single thiol and 2 azide groups, being prepared in four steps with an overall isolated yield of 61%. Similarly, the CD_2 monomer **6**, containing one alkyne and two alkene groups, was prepared in just two steps with an overall isolated yield of 62%. The structure and purity of the AB_2 and CD_2 monomers were confirmed by NMR spectroscopy and mass spectrometry.

The first generation dendrimer **7**, Scheme 2, was obtained via a thiol−ene reaction between 2.0 equiv of **4** per core alkene functionality and tris(allyloxy)triazine (TAT), in the presence of the radical initiator, 2,2-dimethoxy-2-phenylacetophenone (DMPA). The reaction solution was sparged with argon for 15 min prior to irradiation with 365 nm UV light for 45 min followed by simple filtration through a plug of silica to remove excess **4**. The IR spectrum of the purified first generation dendrimer, **7**, showed a strong absorption peak at 2091 cm^{-1} corresponding to the azide end-groups and the complete disappearance of the core alkene absorption at 923 cm^{-1}. Similar spectral changes, for example appearance of a triplet at 3.29 ppm corresponding to the methylene protons adjacent to the azide end-groups and loss of resonances for the olefinic protons, were observed in the ^{1}H NMR spectra (Figure 1) demonstrating that full addition to the peripheral alkenes was achieved. Significantly, the high efficiency/facile purification of the thiol−ene reaction, coupled with short reaction times, allows full generation growth and product purification to be accomplished in 2−3 h.

The pure first generation dendrimer **7** was then reacted with 1.1 equiv of **6** per azide unit in THF/H_2O with $CuSO_4$ and sodium ascorbate (NaAsc). The $CuSO_4$/NaAsc system[15] was chosen because of its proven robust nature and monitoring of the CuAAC reaction using ^{1}H NMR and FT-IR spectroscopy revealed full conversion of the peripheral azides. Concomitant with the loss of the CH_2N_3 resonance at 3.3 ppm, new peaks in the region of 5.1−5.9 ppm corresponding to the terminal alkenes of the fully converted second generation dendrimer **8** were observed in the ^{1}H NMR spectrum (Figure 1). Additionally, FT-IR showed complete disappearance of the azide stretch at 2091 cm^{-1} and reappearance of the terminal alkene vibrational transition at 923 cm^{-1}, confirming the quantitative nature of the second generation growth step. In analogy with the thiol−ene reaction, the time required for synthesis and purification of the alkene-terminated second generation dendrimer **8**, was minimal and the pure dendrimer was obtained in less than 3 h. With the exception of the reaction to form G6, the ratio of 1.1 alkyne/N_3 was kept constant throughout the synthesis. A slightly higher ratio of 1.6 equiv of **6**/N_3 and a slightly increased reaction time of 2 h was required to completely convert the fifth generation dendrimer in the final growth step.

This facile and time efficient synthetic strategy greatly facilitates the preparation of higher generation dendrimers with this iterative sequence of AB_2/CD_2 monomer additions

Scheme 2. Synthesis of a Sixth Generation Dendrimer[a]



[a] Key: (i) 2 equiv of **4**/ene, UV light for 0.75 h; (ii) 1.1 equiv of **6**/N$_3$, 1 h; (iii) 4 equiv of **4**/ene, UV light for 0.75 h; (iv) 1.1 equiv of **6**/N3, 1 h; (v) 7 equiv of **4**/ene, UV light for 0.75 h; (vi) 1.6 equiv of **6**/N$_3$, 2 h.

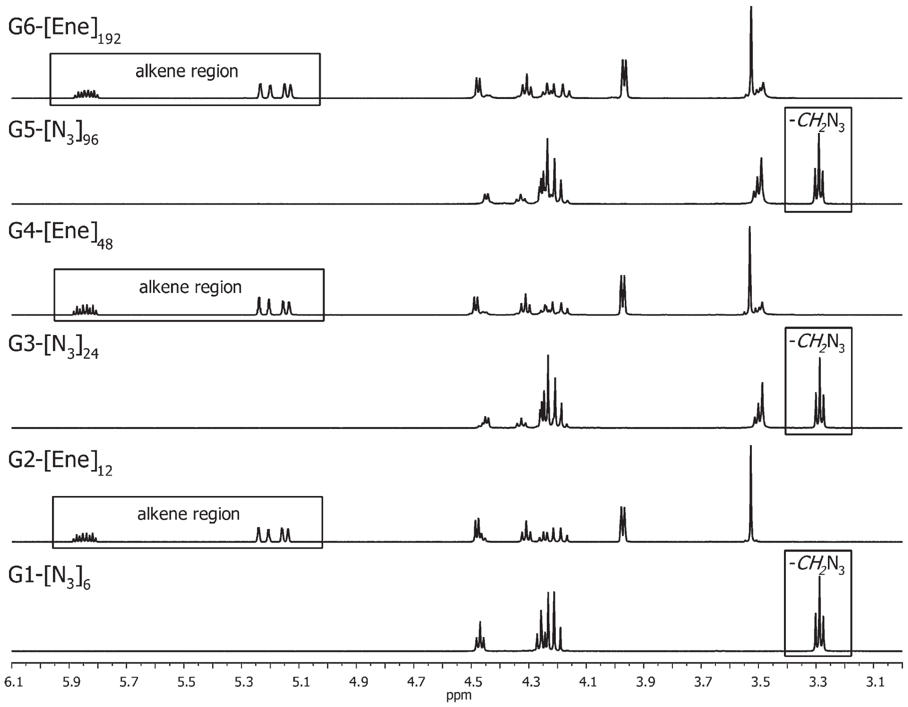


Figure 1. Sequence of ^{1}H NMR spectra for first through sixth generation dendrimers showing the appearance and disappearance of chain end functional groups.

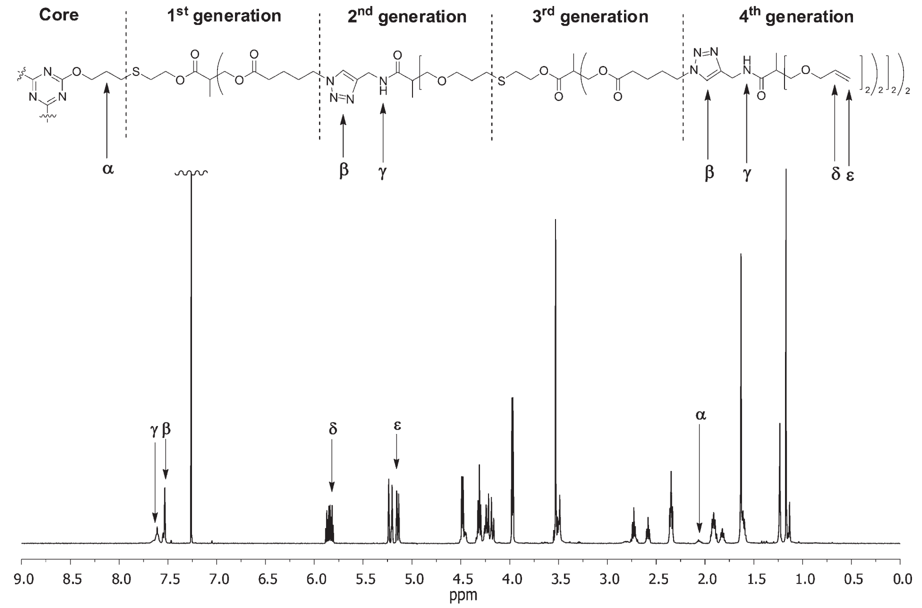


Figure 2. ^{1}H NMR spectrum of the fourth generation dendrimer, **10**.

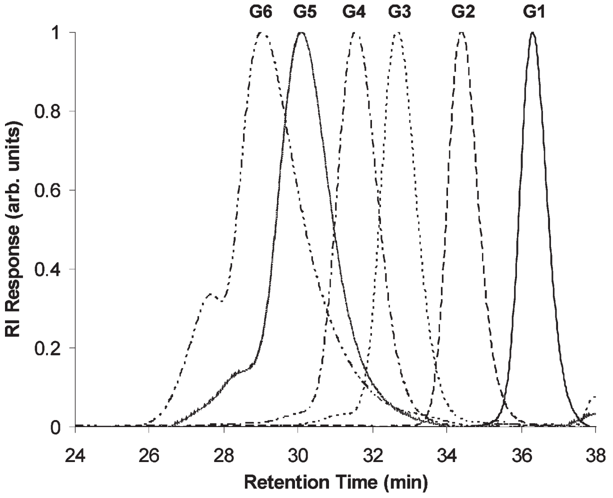


Figure 3. GPC chromatograms illustrating generational growth from the first to sixth generation dendrimer.

being repeated to ultimately obtain a sixth generation dendrimer (Scheme 2). To illustrate the robust nature, generations 1−4 were synthesized on multigram scales and purified by filtration through a silica plug while generations 5 and 6 were purified by simple precipitation or a combination of extraction and precipitation. Isolated yields were high for each growth step where the complete sequence of reaction, purification and isolation could be performed in less than 3 h. A direct consequence of this is that a sixth generation dendrimer was prepared in *less than* a single 24 h time period from the starting monomers, **4** and **6**.

Critical to the success of this accelerated approach to dendrimers was not simply a dramatic reduction in the time required for preparation but also the need to maintain a high level of purity for the dendritic macromolecules from G1 to G6. Structural evolution and purity was monitored using a variety of techniques. For example, the quantitative exchange of chain end functional groups was monitored throughout the synthesis by ^{1}H NMR spectroscopy with Figure 1 showing the alternating appearance and disappearance of alkene and azide end groups. The high fidelity of the accelerated growth process based on the combination of thiol−ene and CuAAC chemistry can also be gauged by comparison of the integration values for the various generation layers within the dendritic structures with Figure 2 showing the high degree of resolution that can be obtained for the ^{1}H NMR spectrum of the fourth generation alkene functional dendrimer, **10**.

Table 1. Molecular Weight and Thermal Characterization Data

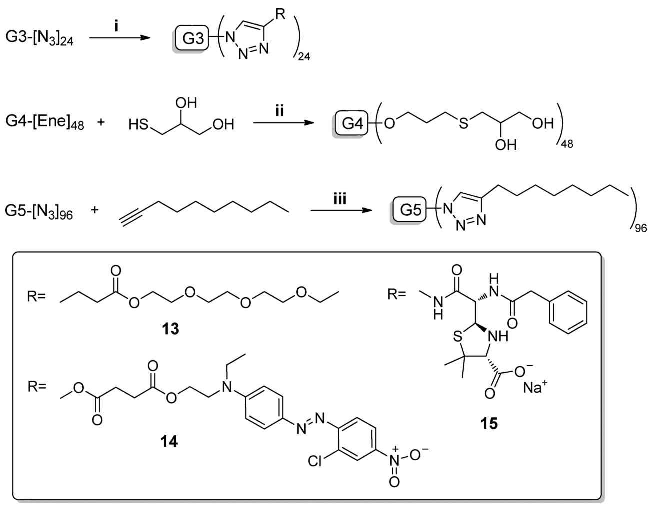
	dendrimer	$M_{\mathrm{w,theoretical}}$[a]	$M_{\mathrm{w,MALDI}}$[a]	$M_{\mathrm{n,GPC}}$[a]	PDI	T_g
7	G1-$[\mathrm{N_3}]_6$	1 582.80	1605.2	3350	1.02	−72
8	G2-$[\mathrm{Ene}]_{12}$	3 090.72	3112.9	6210	1.02	−34
9	G3-$[\mathrm{N_3}]_{24}$	8 424.78	8557.5	10 700	1.03	−54
10	G4-$[\mathrm{Ene}]_{48}$	14 456.46	14 985	16 200	1.03	−23
11	G5-$[\mathrm{N_3}]_{96}$	35 792.94	35 900	26 600	1.21	−51
12	G6-$[\mathrm{Ene}]_{192}$	59 919.66	60 200	34 300	1.29	−13

[a] Molecular weights reported in g/mol.

Characterization of the dendrimers by mass spectrometry (MALDI) and gel permeation chromatography (GPC) showed essentially single molecular ions and narrow polydispersity peaks for generations 1 through 4 (Figure 3). The end-group variation between generations affected the selection of the MALDI−TOF matrix. The alkene functional dendrimers were analyzed using dihydroxybenzene (DHB) as matrix whereas the azide functional dendrimers were analyzed using 9-nitroanthracene. The theoretical molecular weights expected for the dendrimers were confirmed by MALDI−TOF (Table 1); however, a linear mode was used for the higher generations which resulted in poor isotopic resolution for the fifth and sixth generation dendrimers **11** and **12**. Evaluation of these materials by GPC showed increasing amounts of coupled products at generation 5 and generation 6 which correlates with dendrimer-dendrimer cross coupling reactions (radical combination) in the fifth generation growth step. With 7.0 equiv of thiol per alkene for the synthesis of the fifth generation dendrimer, thiol−ene reaction with the 48 chain end alkene units resulted in a small (~10%) high molecular weight fraction. These coupled impurities are a direct result of the divergent growth strategy (percent is consistent with the level of failure sequences observed for other divergent dendrimers such as PAMAM) and our deliberate attempt to eliminate any complicated purification strategies. This level of coupled products could be significantly reduced by column chromatography if required.

The ability to accelerate the synthesis of dendrimers by combining click reactions not only results in a dramatic increase

Scheme 3. Post Functionalization of a Third, Fourth, and Fifth Generation Dendrimer[a]



[a] Key: (i) 1.1-2 equiv of post-functionalizing reagent/N_3, 45 min; (ii) 7 equiv of 1-thioglycerol/ene, UV light for 1 h; (iii) 1.6 equiv of 1-decyne/N_3, 3 h.

in time efficiency but also allows higher generation materials to be prepared more readily. This is a critical feature as many reported dendrimer syntheses proceed only to generation 3 or 4 where the true benefit of the dendritic architecture may not be apparent. This is especially true in the examples described above where comparison of the absolute molecular weights with the polystyrene equivalent molecular weights clearly demonstrates the power of proceeding to higher generations. For generation 1 to 4, the polystyrene equivalent molecular weight is larger than the actual molecular weight (i.e., for $G = 3$; $MW_{actual} = 8560$ amu; while $MW_{pst} = 10\,700$ amu), a direct result of the larger, less compact AB_2 and CD_2 repeat units. It is only when the dendrimers are grown to generation 5 and 6 that the traditional and expected dendritic effect of a significant reduction in polystyrene equivalent molecular weight when compared to the actual molecular weight is observed. For the sixth generation dendrimer, the polystyrene equivalent molecular weight of 34 300 amu is significantly less that the theoretical molecular weight of 59 900. As a result, the novel dendritic properties for these materials, resulting from the globular and compact nature of the macromolecule would only be expected to become fully apparent at $G = 5$ and above, again demonstrating the power of this accelerated approach.

The thermal properties of the different dendrimer generations, **7**−**12**, were analyzed using thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC). Interestingly, alkene functional dendrimers **8**, **10**, and **12** depicted a higher onset for thermal degradation of 270, 250, and 260 °C respectively, corresponding to the degradation of the polyester backbone. The azide terminal dendrimers **7**, **9** and **11** exhibited a significantly decreased onset temperature for thermal degradation of 200 °C for **7** and **9** and 140 °C for **12**. These low temperature decompositions are assigned to azide fragmentation and release of N_2 at elevated temperatures. For example, the observed mass loss of 13 wt % was in good correlation with the theoretical mass loss of 11 wt % corresponding to six N_2 molecules ($6 \times 28 = 168$ g/mol) evolved from **7** (1582.78 g/mol). The T_g's for the dendrimers were also found to be highly dependent on the end group functionality rather than molecular weight with alkene functional dendrimers displaying higher T_g's than the azide terminal generations (Table 1).

The presence of "click-ready" groups at the chain ends for each generation also allows a range of post functionalization reactions to be conducted on the third (alkene), fourth (azide), and fifth (alkene) generation dendrimers **9**−**11**. This demonstrates the versatility of this thiol−ene/CuAAC reaction sequence and the ease with which these materials can be chemically modified at each stage of the synthesis (Scheme 3). Transformation of the native dendrimers yielded an assortment of new materials ranging from dendrimers with hydrophilic (**13** and **16**) and hydrophobic (**17**) surfaces to those having bioactive groups at the chain ends (**14** and **15**). All of the post functionalization reactions showed good yields and required simple purification protocols (i.e., precipitation, dialysis, etc.).

Conclusions

A highly orthogonal and time efficient protocol for the assembly of high generation, high molecular weight dendrimers has been demonstrated based on the combination of orthogonal click reactions. The full assembly and purification of each dendrimer generation was realized within 3 h resulting in an overall sixth generation dendrimer with a total assembly time of less than a day from the corresponding branched monomer units. The power of this accelerated AB_2/CD_2, dual click strategy is the demonstration that dendrimer synthesis should not be tedious and time-consuming, breaking a long held viewpoint concerning dendritic macromolecules and allowing high generation dendrimers to be readily accessed.

Acknowledgment. Financial support from the NSF (CHE-0957492, the MRSEC Program DMR-0520415 (MRL-UCSB)), UC Regents for a President's Fellowship (L.M.C.) and Graduate Fellowship (M.J.R.), the Swedish Research Council (M.M.) (Grant 2006-3617), Bengt Lundqvists Minnesfond (P.A.), and Instituto de Salud Carlos III (M.I.M.) is greatly acknowledged.

Supporting Information Available: Text giving detailed experimental procedures and figures showing chemical structures and ^1H NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Flory, P. J. *J. Am. Chem. Soc.* **1952**, *74*, 2718–2723.
(2) Buhleier, E.; Wehner, W.; Voegtle, F. *Synthesis* **1978**, 155–159.
(3) (a) Newkome, G. R.; Yao, Z.; Baker, G. R.; Gupta, V. K. *J. Org. Chem.* **1985**, *50*, 2003–2004. (b) Tomalia, D. A.; Baker, H.; Dewald, J.; Hall, M.; Kallos, G.; Martin, S.; Roeck, J.; Ryder, J.; Smith, P. *Polym. J.* (*Tokyo, Japan*) **1985**, *17*, 117.
(4) (a) Li, W.; Wu, D.; Schlüter, A. D.; Zhang, A. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 6630–6640. (b) Lonsdale, D. E.; Whittaker, M. R.; Monteiro, M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 6292–6303. (c) Wang, G.; Luo, X.; Zhang, Y.; Huang, J. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 4800–4810. (d) Katritzky, A. R.; Song, Y.; Sakhuja, R.; Gyanda, R.; Meher, N. K.; Wang, L.; Duran, R. S.; Ciaramitaro, D. A.; Bedford, C. D. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3748–3756.
(5) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638–7647.
(6) Helms, B. A.; Reulen, S. W. A.; Nijhuis, S.; de Graaf-Heuvelmans, P. T. H. M.; Merkx, M.; Meijer, E. W. *J. Am. Chem. Soc.* **2009**, *131*, 11683–11686.
(7) Ito, Y.; Higashihara, T.; Ueda, M. *J. Photopol. Sci. Tech* **2008**, *21*, 799–803.
(8) Magbitang, T.; Lee, V. Y.; Cha, J. N.; Wang, H. L.; Chung, W. R.; Miller, R. D.; Dubois, G.; Volksen, W.; Kim, H. C.; Hedrick, J. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 7574–7580.
(9) Kawa, M.; Fréchet, J. M. J. *Chem. Mater.* **1998**, *10*, 286–296.
(10) Wooley, K. L.; Hawker, C. J.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **1994**, *33*, 82–85.
(11) Zeng, F.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1996**, *118*, 5326–5327.
(12) Ihre, H.; Hult, A.; Soderlind, E. *J. Am. Chem. Soc.* **1996**, *118*, 6388–6395.
(13) (a) Malkoch, M.; Malmstrom, E.; Hult, A. *Macromolecules* **2002**, *35*, 8307–8314. (b) Bosman, A. W.; Heumann, A.; Klaerner, G.;

Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2001**, *123*, 6461–6466.

(14) Dondoni, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8995–8997.

(15) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.

(16) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.

(17) Brauge, L.; Magro, G.; Caminade, A.; Majoral, J. *J. Am. Chem. Soc.* **2001**, *123*, 6698–6699.

(18) (a) Rosen, B. M.; Lligadas, G.; Hahn, C.; Percec, V. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3940–3948. (b) Rosen, B. M.; Lligadas, G.; Hahn, C.; Percec, V. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3931–3939.

(19) (a) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad, E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, 5775–5777. (b) Malkoch, M.; Vestberg, R.; Gupta, N.; Mespouille, L.; Dubois, P.; Mason, A. F.; Hedrick, J. L.; Liao, Q.; Frank, C. W.; Kingsbury, K.; Hawker, C. J. *Chem. Commun.* **2006**, 2774–2776. (c) O'Reilly, R. K.; Joralemon, M. J.; Wooley, K. L.; Hawker, C. J. *Chem. Mater.* **2005**, *17*, 5976–5988.

(20) (a) Gu, W.; Chen, G.; Stenzel, M. H. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 5550–5556. (b) Li, C.; Ge, Z.; Liu, H.; Liu, S. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 4001–4013. (c) Antoni, P.; Hed, Y.; Nordberg, A.; Nyström, D.; von Holst, H.; Hult, A.; Malkoch, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2126–2130.

(21) (a) Iha, R. K.; Wooley, K. L.; Nyström, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J. *Chem. Rev.* **2009**, *109*, 5620–5686. (b) Lutz, J.-F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1018–1025. (c) Binder, W. H.; Sachsenhofer, R. *Macromol. Rapid Commun.* **2007**, *28*, 15–54.

(22) (a) Sumerlin, B. S.; Vogt, A. P. *Macromolecules* **2010**, *43*, 1–13. (b) Yu, B.; Chan, J. W.; Hoyle, C. E.; Lowe, A. B. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 3544–3557. (c) Wiltshire, J. T.; Qiao, G. G. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 1485–1498. (d) Gacal, B. N.; Koz, B.; Gacal, B.; Kiskan, B.; Erdogan, M.; Yagci, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2009**, *47*, 1317–1326.

(23) Killops, K. L.; Campos, L. M.; Hawker, C. J. *J. Am. Chem. Soc.* **2008**, *130*, 5062–5064.

(24) (a) Antoni, P.; Nystrom, D.; Hawker, C. J.; Hult, A.; Malkoch, M. *Chem. Commun.* **2007**, 2249–2251. (b) Kang, T.; Amir, R. J.; Khan, A.; Ohshimizu, K.; Hunt, J. N.; Sivanandan, K.; Montanez, M. I.; Malkoch, M.; Ueda, M.; Hawker, C. J. *Chem. Commun.* **2010**, *46*, 1556–1558. (c) Urbani, C. N.; Bell, C. A.; Lonsdale, D. E.; Whittaker, M. R.; Monteiro, M. J. *Macromolecules* **2007**, *40*, 7056–7059. (d) Urbani, C. N.; Lonsdale, D. E.; Bell, C. A.; Whittaker, M. R.; Monteiro, M. J. *J. Polym. Sci., Part A: Polym. Chem.* **2008**, *46*, 1533–1547. Whittaker, M. R.; Urbani, C. N.; Monteiro, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 11360–11361.

(25) Ma, X.; Tang, J.; Shen, Y.; Fan, M.; Tang, H.; Radosz, M. *J. Am. Chem. Soc.* **2009**, *131*, 14795–14803.