Incorporation of Functional Guest Molecules into an Internally Functionalizable Dendrimer through Olefin Metathesis

Catherine O. Liang and Jean M. J. Fréchet*

Department of Chemistry, University of California, Berkeley, California 94720-1460, and Material Sciences Division, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, California 94720

Received April 18, 2005; Revised Manuscript Received May 18, 2005

ABSTRACT: A poly(aryl ether) dendrimer bearing 22 allyl groups throughout the interior of the molecule has been prepared using a convergent synthetic approach. The internal functionalities of this dendrimer can be used to attach small molecule guests to the interior of the dendrimer using olefin metathesis. A ruthenium-based Grubbs catalyst was used to covalently attach an allylated pyrene and imidazolidinone via cross-metathesis. The extent of coupling was estimated by UV, NMR, and elemental analysis data. The high tolerance of cross-metathesis to a range of functional groups enables the incorporation of a wide range of molecules and provides access to different inner environments in one step from a single source of dendrimer.

Introduction

In the 20 years that have followed their discovery, dendrimers have been the object of numerous studies seeking to exploit the unique molecular architecture and physical properties of these macromolecules.[1] The highly branched, monodisperse dendrimers are characterized by a globular morphology at higher generations and can be segmented into periphery, interior, and core sections. The well-developed anatomy of dendrimers has encouraged their use in a variety of applications including site isolation,[1−7] drug delivery,[8−12] biomimetics,[2,13−15] and catalysis.[2,4,16−21]

Dendrimer repeat units and branches have traditionally functioned as a skeleton and a connection between the periphery and core; however, they also largely control the characteristics of the nanoenvironment generated within the dendrimer.[18,19,22−24] Such local environment is greatly influenced by the chemical makeup and polarity of the repeat unit as well as its chemical differentiation from the surrounding medium in order to provide a unique interior context. For instance, the influence of poly(aryl ether) branches on the local nanoenvironment surrounding a solvatochromic probe located at the focal point or core of a family of dendrimers was noted[3] more than a decade ago as the absorbance of the probe shifts with increasing dendrimer generation. Aside affecting local polarity, dendrimer repeat units may also provide a platform for cooperativity between branches.[25−30] The recognition of their utility has prompted investigations into internal manipulation and functionalization of the dendrimer.[19,22,23]

Functionalization of the dendrimer interior can be achieved via either pre-[19] or postmodification[31] methods. In the premodification strategy, monomer units that contain the desired functional group are used in the construction of the dendrimer framework. Including functional groups at the start of the synthesis allows for layering of different functionalities through the stepwise growth sequence. However, functional groups incorporated at the beginning of dendrimer synthesis may be sensitive to the reaction sequence required for dendrimer growth and may complicate preparation. In the postmodification approach, a monomer repeat unit bearing a functional "handle" that is capable of further derivatization may be used in the construction of the dendrimer. Once construction of the dendrimer has been completed, the "handle" is modified to provide a functionalized macromolecule in a single step and avoids exposure of the newly incorporated functionality to the dendrimer growth steps.[22]

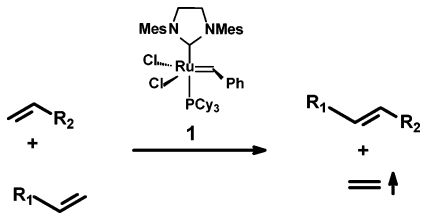
This report describes the incorporation of an internally functionalizable handle that is compatible with both dendrimer growth and subsequent transformation steps into other functionalities. In line with the postmodification approach, a poly(benzyl ether) dendritic platform containing internal allyl ether groups at each branched monomer was selected. The allyl group was chosen as an internal moiety that is inert to dendrimer growth steps and serves as a precursor to other functionalities. The robust polyether backbone[24] is rugged enough to endure many different reaction conditions and provides an electron-rich environment. A key advantage of this approach is the ease of introduction of the functionality of interest by modification of the reactive handle, thus transforming the "generic" dendrimer into an internally functionalized macromolecule in a single step.

Derivatization of the macromolecule can be accomplished by olefin metathesis, which has become an important carbon−carbon bond forming reaction in organic synthesis.[32−34] A particularly useful form of olefin metathesis is cross-metathesis (CM) in which an olefinic product is formed after joining two substituted alkenes (Scheme 1), a reaction driven to completion by evolution of volatile ethylene byproduct when terminal olefins are selected as reactive partners. The ruthenium-based catalysts used in olefin metathesis have exceptional functional group tolerance and are selective toward olefins over alcohols, esters, aldehydes, acids, and ketones.[32] The utility of this metal-catalyzed reaction for the preparation of polymers and natural products has been reviewed,[32−34] and its application to the

* Corresponding author. E-mail frechet@berkeley.edu.

10.1021/ma050818a CCC: $30.25
Published on Web 06/23/2005

Scheme 1. Cross-Metathesis of Terminal Olefins Results in an Unsaturated Product and Ethylene Gas[a]



[a] The second-generation Grubbs catalyst 1 is shown above.

preparation of unusual dendrimers has been pioneered by Zimmerman and co-workers.[35−40]

Therefore, the internal allyl-functionalized dendrimers prepared in this work have been tested in intermolecular cross-couplings experiments between the allyl handle and complementary small molecule guests. A pyrene derivative was selected for incorporation into the dendrimer since its UV absorbance could be used to monitor and quantify its loading into the dendrimer. Similarly, the covalent attachment of a catalytic molecule, an allyl imidazolidinone derivative useful in the catalysis of Diels−Alder reactions, was studied with generations 3 and 5 dendrimers.

Results and Discussion

Preparation of an Internally Functionalizable Dendrimer. The dendrimer was prepared using a convergent synthesis[41] and a monomer bearing allyl groups. Commercially available 3,5-dihydroxymethylbenzoate (**2**) was reacted with a substoichiometric amount of allyl bromide to afford the mono- and bis-allylated compounds **3** and **4**, respectively, which were separated through flash chromatography (Scheme 2). Heating the monoallyl ether intermediate **3** furnished the allyl-substituted Claisen rearranged products **5** and **6** isolated in a 1:2.7 ratio, respectively, after separation by flash chromatography.[42−44]

The bis-allylated intermediate **4** was also subjected to Claisen rearrangement conditions and the crude purified to yield isomeric products **7** and **8** in an approximately 1:2 ratio. At first glance, the doubly allylated compound **8** appears very attractive for its symmetry and its ability to introduce two allyl groups simultaneously in the dendrimer layers. However, when **8** was used in the convergent synthesis of the dendrimer, routine reactions on the ester focal point became difficult to carry out. For example, reduction of the focal ester groups to the corresponding primary alcohol with lithium aluminum hydride required very long reaction times at elevated temperatures, and activation of the benzylic alcohol through a bromination step did not proceed at all under routine conditions.[41] These problems were attributed to the steric hindrance resulting from the allyl substituents flanking both sides of the reactive focal group in **8**. To avoid the reactivity issues encountered with the doubly substituted monomers such as **8**, dendrimer syntheses were exclusively carried out with the monoallylated building blocks **5** and **6**.

The convergent growth sequence of a generation 5 dendrimer began with the preparation of the peripheral groups. Tetradecyl chain ends were chosen to ensure compatibility with nonpolar solvents and to assist with subsequent encapsulation of the interior functionalities. To that end, monomer **6** was coupled to tetradecyl bromide to yield compound **9** (Scheme 3).

The ester focal point of compound **9** was then reduced to furnish the benzylic alcohol **10** and activated through a bromination step to give **11**. The electrophilic site of **11** was then allowed to react with diol **2** in a single growth step, yielding a generation 2 dendron **12**. Repetition of the reduction, bromination, and ether coupling steps through three more cycles afforded the generation 5 dendrimer **21**.

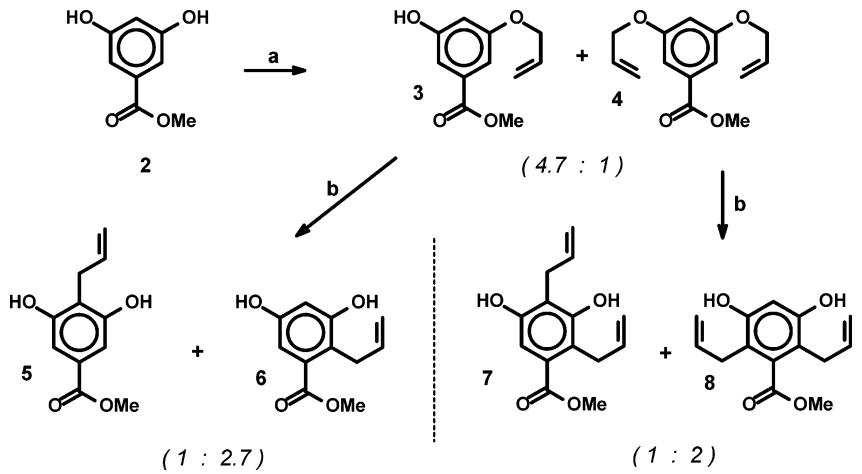
As a result of its versatility, the convergent synthesis enabled the preparation of precisely layered dendrimers with allyl functional handles at all, or some, of the layers. The increase in molecular weight between dendrimer generations was reflected in the size-exclusion chromatography (SEC) peaks, which indicated decreased elution volumes as the size of the dendrimer increased (Figure 1). The narrow SEC peaks were characterized by a low polydispersity index (PDI) for each generation of dendrimer and was measured as 1.02 for generation 5 dendrimer **21** obtained after four consecutive growth cycles. Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry data of compound **21** revealed a mass of 11 002 Da, which is within 0.04% of the expected mass (Figure 2). Overall, both the SEC and MALDI data support the identity of generation 5 dendrimer **21** having a low polydispersity.

In addition, atomic force microscopy (AFM) images of dendrimer **21** in the dry state were obtained (Figure 3) showing large and small aggregates and perhaps even isolated molecules on the mica surface. Images of two different sized aggregates that are relatively uniform in shape and size are observed and remain unchanged after 24 h. Aggregation of the dendrimers may be attributed to the attractive hydrophobic interactions between the molecules and chain entanglement of the tetradecyl periphery. A cross-sectional analysis of the smaller structures (circled) reveals a height of ≈3.5 nm. This is in accordance with the estimated size of a generation 5 Fréchet-type dendrimer.[45]

Intramolecular Metathesis of the (G-5) Dendrimer. Recent advances in the development of catalysts for metathesis reactions include a ruthenium-based molecule containing a substituted N-heterocyclic carbene ligand referred to as "Grubbs second-generation catalyst" **1**.[46] This catalyst is particularly attractive as its attributes include high activity, broad functional group compatibility, mild reaction conditions, and ease of use.

Intramolecular metathesis reactions were initially explored with the (G-5) dendrimer **21**. In the absence of small molecule guests the dendrimer containing 22 allyl groups was treated with the Grubbs catalyst (Scheme 3). A maximum of 11 "cross-links" between the repeat units bearing allyl groups within the dendrimer was possible. The resulting MALDI mass spectrum (Figure 4) of the intramolecularly metathesized dendrimer **22** showed a molecular weight of 10 787 Da (M + H), which represent a mass loss of 211 Da from the starting material (10 998, M + H). This reduction in weight corresponds to between 7 and 8 molecules of ethylene (196−224), which in turn indicates the possible formation of an equivalent amount of bonds within the dendrimer. 7−8 internal "cross-links" per dendrimer out of a possible 11 translates into 64−73% of allyl groups participating in the metathesis reaction. In addition, the SEC trace of compound **22** showed a monomodal peak with a M_w/PDI of 8644 Da/1.02, which represents a mass loss of 812 Da from the precursor **21** (Figure 4, inset).

Scheme 2. Preparation of Allyl-Containing Monomer Repeat Units[a]



[a] Reagents and conditions: (a) allyl bromide; K_2CO_3, 18-crown-6, acetone 60 °C, 2 days; (b) *o*-dichlorobenzene, 180 °C, 2 days.

The lack of dendrimer "dimers" suggested that cross-coupling between dendrimer molecules was avoided at the reaction concentration of 2.0 mM even without having to carry the reaction at ultrahigh dilutions.[47,48]

The ^{1}H NMR spectrum of the metathesized compound **22** after metathesis was characterized by broadening of the peaks (Figure 5i) when compared to the spectrum of the (G-5) dendrimer precursor (Figure 5ii). Comparison of the integration values from the ^{1}H NMR spectrum of **22** provides quantitative information on the degree of cross-linking within the dendrimer. Signals in regions A, B, and C (Figure 5ii) correspond to the allyl group (C*H*, 22 H), aromatic protons (Ar*H*, 70 H), and ester/tetradecyl protons (CO_2CH_3, $(-OCH_2(CH_2)_{12}CH_3)_{32}$, 67 H), respectively. After metathesis, the remaining unreacted allyl units in the dendrimer (Figure 5i, A) were calculated from the integration value. This value was normalized to the integration values from regions B or C, which remain theoretically unchanged because they do not participate in the reaction. This leads to an estimated formation of 6.5−7.2 internal bonds, suggesting that ca. 59−74% of the allyl groups participated in olefin metathesis. These values correlate well with the MALDI mass spectral data discussed previously.

Cross-Metathesis with an Allylated Pyrene Derivative. To investigate the ability of the dendrimer to covalently incorporate guest molecules, a small molecule guest that can be quantified by ultraviolet (UV) spectroscopy in an absorbance region distinct from the absorbance signals of the dendrimer was chosen. The absorbance maximum of allylated pyrene **24**, easily prepared from pyrene butanol **23**, is at 344 nm, which is within the transparent region of the UV spectrum of the dendrimer. In addition to its UV characteristics and ease of preparation, allylated pyrene **24** is aromatic, which, we speculate, may promote its accumulation within the polyaryl dendrimer through π-stacking. Preparation of the guest molecule was accomplished through treatment of the alcohol **23** with base and allyl bromide to furnish **24** (Scheme 4).

Generation 5 dendrimer (G-5) **21** was mixed with 10 equiv of allylated pyrene **24** in the presence of Grubb's catalyst **1** to afford dendrimer conjugate **25** containing bound dye molecules (Scheme 3). This metathesis process was expected to lead to both intermolecular coupling reactions involving the small molecule and the dendrimer as well as intramolecular coupling reactions within the dendrimer. Because of the competitive intramolecular pathway and the limitations on selectivity of the reactive partners, a mixture of products with varying degrees of incorporation of both intramolecular "cross-links" and pyrene moieties was expected. Following purification of the dendrimer−pyrene conjugate, SEC analysis of the purified product afforded a monomodal peak of molecular weight 9.0 kDa (based on polystyrene standards) with a narrow polydispersity of 1.02.

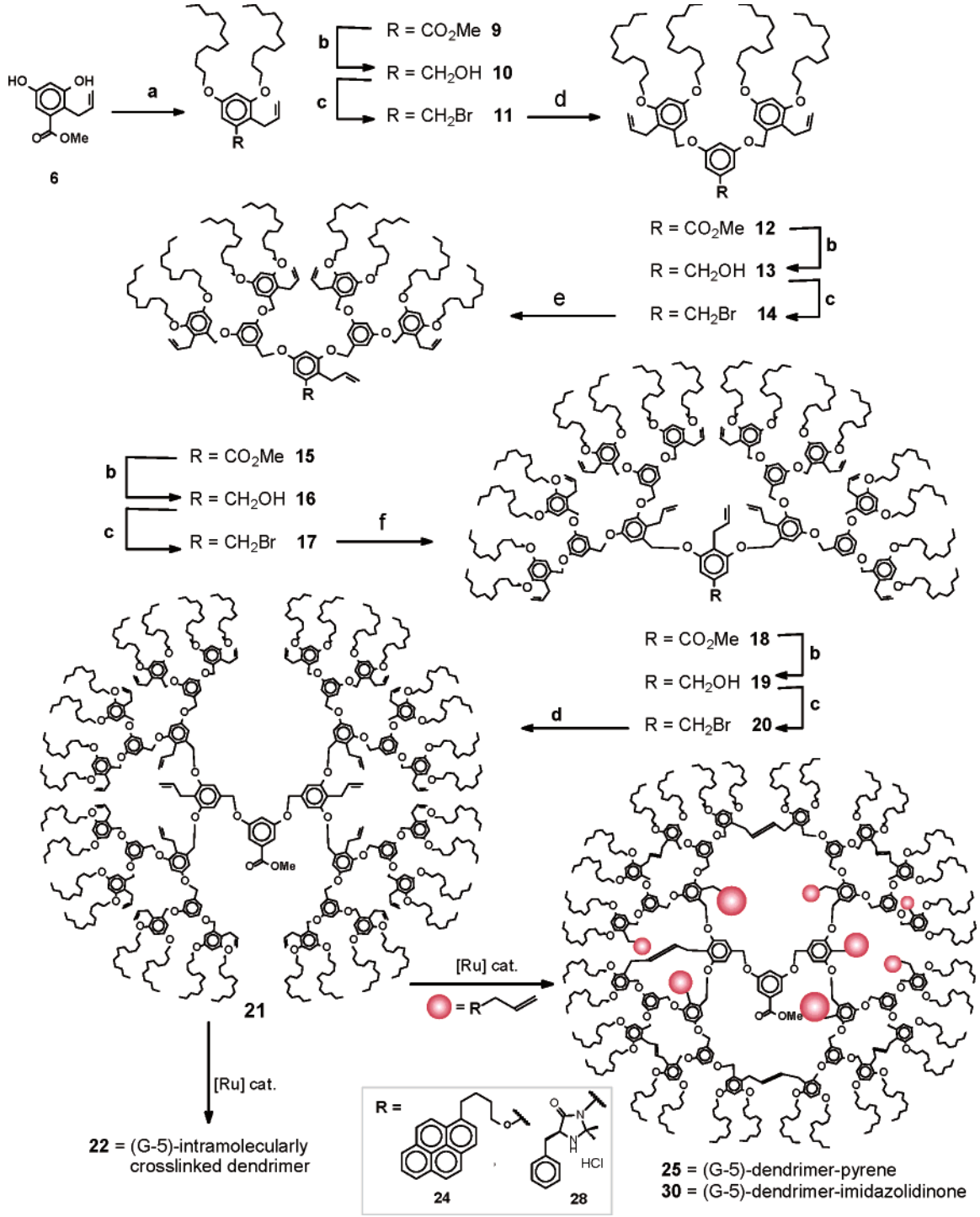
Quantification of incorporated pyrene per gram of conjugate material **25** was determined using UV measurements. First, the molar absorptivity of the small molecule pyrene derivative **24** was determined by measuring the absorption of a series of dilutions. The absorption intensity (344 nm) was plotted as a function of sample concentration in THF. Applying Beer's law, the coefficient (ϵ = 46 234 M^{-1} cm^{-1}) was determined from the slope of the line (Figure 6).

With the extinction coefficient of the allylated pyrene determined, the amount of the pyrene incorporated inside the dendrimer−pyrene conjugate **25** was quantified. The absorption intensity of a series of dendrimer−pyrene conjugate **25** dilutions was measured at the pyrene absorption maximum of 344 nm (Figure 7).

Applying the previously determined molar absorptivity coefficient suggests a loading of 460 ± 20 μmol of pyrene per gram of conjugate. This value translates to an average of ca. 5.7 molecules of pyrene per dendrimer molecule; therefore, nearly 60% of the guest molecules were incorporated into the dendrimer, which is significant given that the dendrimer undergoes a competing metathesis reaction through intramolecular cyclization.

Cross-Metathesis with a Catalytically Active Imidazolidinone Derivative. The second functional molecule chosen for inclusion within the dendrimer was an imidazolidinone derivative. This organocatalytic molecule has been shown to catalyze enantioselective Diels−Alder additions, 1,3-dipolar cycloadditions, and Friedel−Crafts alkylations.[49−51] In addition to the catalytic properties of the imidazolidinone derivative, this molecule was chosen as a guest because it can be easily synthesized with a pendant allyl group, and the nitrogen content of the conjugate can be used to help quantify the loading. Therefore, the imidazolidinone guest molecule was prepared via a convenient two-step procedure from commercially available L-phenylalanine methyl ester hydrochloride **26** (Scheme 5). Formation of the amide **27** was followed by acid-catalyzed ring closure

Scheme 3. Convergent Growth of Generation 5 Dendrimer Containing 22 Inner Allyl Groups[a]



[a] Reagents and conditions: (a) tetradecyl bromide, K_2CO_3, acetone, 40 °C, 2.5 days; (b) $LiAlH_4$, THF, 0 °C−RT; (c) CBr_4, PPh_3, iPr_2NEt, THF; (d) **2**, K_2CO_3, acetone, 60 °C, 2 days; (e) **6**, K_2CO_3, acetone, 60 °C, 2 days; (f) **5**, K_2CO_3, acetone, 60 °C, 2 days.

and treatment with HCl to give the product **28**. An excess of the guest molecule **28** was combined with the (G-3) dendrimer **15** or the (G-5) dendrimer **21** in the presence of the second-generation Grubbs catalyst **1**. The dendrimer−imidazolidinone conjugate products (G-3)-imid. **29** and (G-5)-imidazolidinone **30** were precipitated from methanol as a low-melting solid while excess small molecule impurities were soluble in methanol and eliminated in the filtrate.

Reaction of the small molecule guest **28** with the (G-3) macromolecule **15** can only lead to a maximum theoretical loading of five imidazolidinones per dendrimer if one assumes that no intramolecular metathesis occurs within the dendrimer itself. However, since intramolecular "cross-linking" of the dendrimer is a competing reaction, a mixture of intra- and intermolecular coupled products was again expected. Analysis of the product by MALDI mass spectrometry revealed discrete peaks corresponding to the attachment of 1−4 small molecules to the macromolecule (Figure 8). The peak labeled **29a** with a mass of 2831 matches that expected for a dendrimer with two internal "cross-links" and one imidazolidinone derivative. Peak **29e** with a mass of 3536 Da, also visible in the spectrum, matches

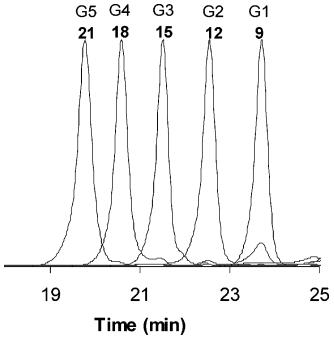


Figure 1. Overlapping SEC traces comparing generation 1−5 compounds with methyl ester focal points (**9**, **12**, **15**, **18**, **21**).

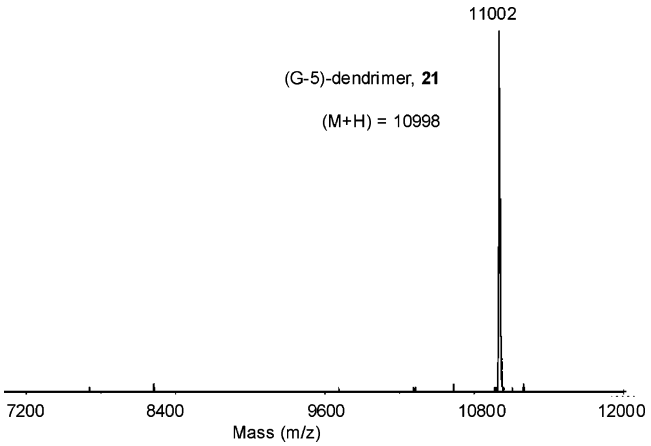


Figure 2. MALDI mass spectrum of the generation 5 compound **21**.

the mass of a dendrimer containing four imidazolidinone units and no "cross-links". While MALDI was a helpful technique in detecting single ion mass peaks (Table 1), actual isolation of discrete products by SEC or silica gel chromatography could not be achieved.

Nitrogen analysis also proved convenient to estimate the amount of catalytic residues per gram of conjugate. Therefore, elemental analysis of the (G-3)-imidazolidinone product **29** indicated a nitrogen content of 2.32%. This value corresponds to 829 μmol of imidazolidinone groups per gram of product. On the basis of this calculation, an average incorporation of close to three catalytic residues per dendrimer molecule or 60% functionalization of the allyl bearing sites can be calculated. This average is in line with MALDI mass spectra data, which confirmed the presence of products containing between 1 and 4 guest molecules.

To further favor intermolecular cross-coupling reactions and maximize guest loading, the (G-5)-dendrimer **21** was reacted with 9 equiv of the imidazolidinone derivative **28** per allyl site within the macromolecule. This metathesis reaction could theoretically lead to the incorporation of 22 guest molecules or, in the absence of intermolecular couplings, the formation of 11 "cross-links". Once again, a mixture of intra- and intermolecular metathesis products was expected. The large number of possible cross-metathesis products from (G-5)−imidazolidinone couplings result in a broad, undefined distribution as observed by MALDI MS (Figure 9). In theory, the lowest and highest MW products that can possibly be generated from the reaction are the completely internally "cross-linked" molecule at 10.7 kDa and the fully cross-coupled 22 imidazolidinone containing product at 15.7 kDa, respectively. The lower limit of the broad peak, 10.6 kDa, approximates a completely internally "cross-linked" particle with no imidazolidinones (10 682 Da). The detectable upper limit of the observed distribution, 13.7 kDa, corresponds to the incorporation of ≈13 molecules of **28** per dendrimer with formation of up to four internal "cross-links" (13 686 Da).

Although MALDI mass spectrometry is not a quantitative measurement, it does provide relative abundances as in this example where the ionization efficiency of the various products was likely to be similar to one another. The most abundant peak at 12.2 kDa corresponded to approximately 7 molecules of **28** per dendrimer and 7 internal "cross-links" (12 307 Da). As in the case of the reaction with the lower generation dendrimer, separation of the individual products by SEC or silica gel chromatography was not feasible.

The nitrogen content of compound **30** (1.38%), corresponding to 493 μmol of imidazolidinone residue per gram of conjugate material, suggests an average of six cross-couplings per macromolecule, in agreement with the MALDI data. This suggests that 27% of all possible olefinic sites within dendrimer **21** were cross-coupled with the imidazolidinone derivative **30**.

Complete loading of the dendrimer **21** with small molecule guests **24** or **28** is unlikely considering the fact that the competing metathesis coupling is an intramolecular reaction. The compact, globular nature of the larger dendrimer results in close packing of the allyl-containing branches, which aids in the reaction between allyl units on proximal branches. In addition, contraction of the dendrimer morphology may be further encouraged by the tendency of the dendrimer to minimize the interaction between the electron-rich poly(aryl ether) interior and the nonpolar hexane solvent, enhancing proximity between branches. The effective increase in local concentration of allyl groups belonging to the branches of the macromolecule favors intramolecular coupling within the dendrimer over intermolecular dendrimer−guest coupling. Another factor limiting the amount of the imidazolidinone salt **28** incorporated into the dendrimer cavities is the charge−charge repulsion that is experienced by the small molecule. The tendency of charged molecules to repel one another would make it unlikely for the imidazolidinone HCl salt to accumulate into the interior of the dendrimer, reducing both the local concentration of allylated **28** and the likelihood of **28** cross-coupling with a dendritic allyl group. Given these considerations, the ability to incorporate an average of 4 and 6 guest molecules **28** into (G-3) and (G-5) dendrimers, respectively, is significant since the competitive intramolecular "cross-linking" path of the dendrimer is likely to be favored.

SEC chromatograms of the (G-5) product **30** have an observed polystyrene equivalent molecular weight (M_w) of 9087 Da and M_w/M_n 1.02. The data acquired from SEC greatly underestimate molecular weight when compared to the MALDI mass data, which clearly show the presence of products with MW ranging from 10.5 to 13.7 kDa. The underestimation of SEC data is expected given that linear polystyrene standards were used for calibration and that the higher generation globular dendrons exhibit a decreased hydrodynamic volume due to their globular shape.

For the lower generation dendrimers, the observed SEC data is closer to the theoretical value. In the case of the (G-3)-imidazolidinone conjugate **28**, the observed

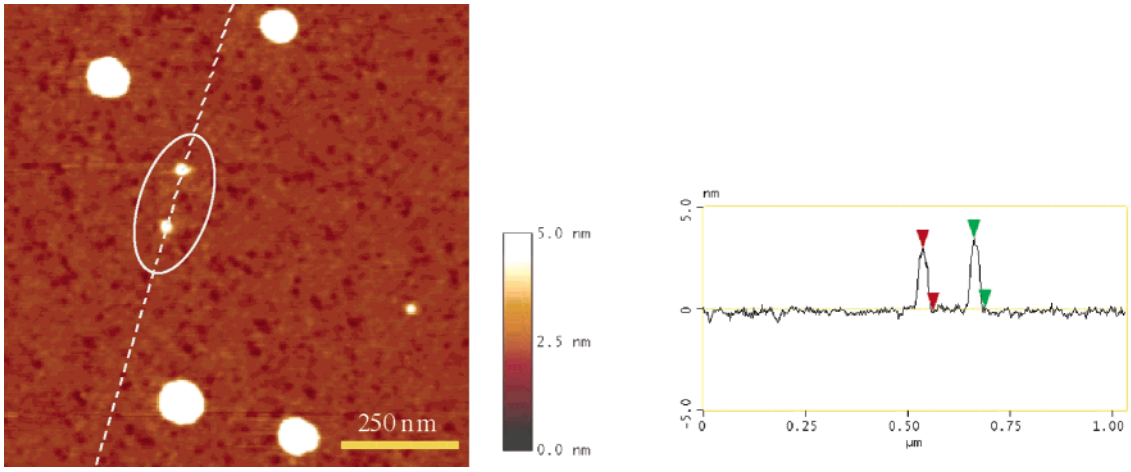


Figure 3. AFM image of large and small aggregates of generation 5 dendrimer **21** (left). Cross-sectional analysis of small aggregate (right).

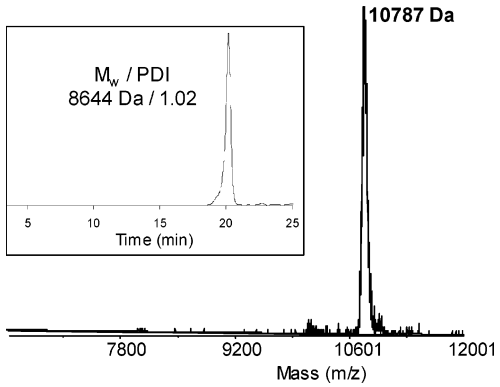


Figure 4. MALDI mass spectrum and SEC trace (inset) of metathesized (G-5)-dendrimer **22**.

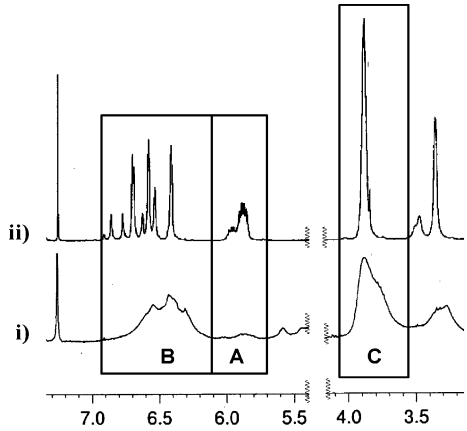
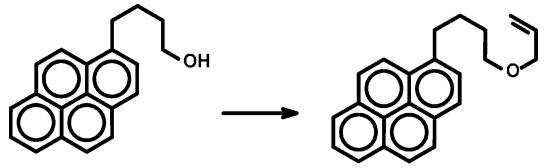


Figure 5. ^{1}H NMR spectra of (i) intramolecularly metathesized product **22** and (ii) (G-5)-dendrimer **21** in $CDCl_3$.

polystyrene equivalent M_w of 3770 Da and M_w/M_n 1.01 is comparable to MALDI mass data (2.8−3.5 kDa).

Further analysis of the SEC chromatograms indicated a monomodal peak for both products **29** and **30**. The chromatography data showed a narrow polydispersity (1.01−1.02) and the absence of molecular weight species corresponding to dimerized macromolecules. Although olefin metathesis of allyl-containing dendrimers can result in unwanted dimerization between macromolecules especially at high reaction concentrations,[35,38,48] intermolecular metathesis between (G-5) dendrimers bearing 22 allyl groups was avoided with reaction concentrations up to 3 mM. The ability to prevent

Scheme 4. Preparation of Allyl Pyrene Butyl Ether Compound 24[a]



23 **24**

[a] Reagents and conditions: KH, dichloromethane, allyl bromide, 6 h, 0 °C−RT.

"dimer" formation between the macromolecules may be attributed to the presence of the long chain ends, which may help encapsulate the core, and to the position of the allyl groups buried deep throughout the interior of the dendrimer.

Evaluation of the Imidazolidinone-Loaded Dendrimer. To test whether intramolecular "cross-linking" impaired access to the dendrimer, the dendrimer−imidazolidinone conjugate **30** was evaluated for its ability to catalyze the [4 + 2] cycloaddition between cinnamaldehyde and cyclopentadiene in decane (Scheme 6). Reaction progress was monitored through consumption of the aldehyde and followed by gas chromatography. Although the kinetic investigation was complicated due to the complexity of the dendrimer system, which contains a number of different catalytic species, a comparison of reaction progress with time provided some qualitative insight into the performance of the different catalysts.

At a 1.0 M reaction concentration in decane and in the presence of 5 mol % of catalyst, the conversion of cinnamaldehyde after 3 days was 73% for the small molecule catalyst **28** and 69% for the (G-5)−imidazolidinone conjugate **30** containing reactions (Table 2). Because of the intrinsic reactivity of the two molecules used in this Diels−Alder reaction, the uncatalyzed control reaction proceeded to an extent of 42%. The macromolecular catalyst **30** could be recovered from the reaction mixture by precipitation in methanol and reused under the same reaction conditions. Progress of the reaction after 1 day reached 32% for the recycled catalyst, which was comparable to the 35% conversion observed for the freshly prepared material.

To verify that the structural integrity of the imidazolidinone was not affected by the conditions used

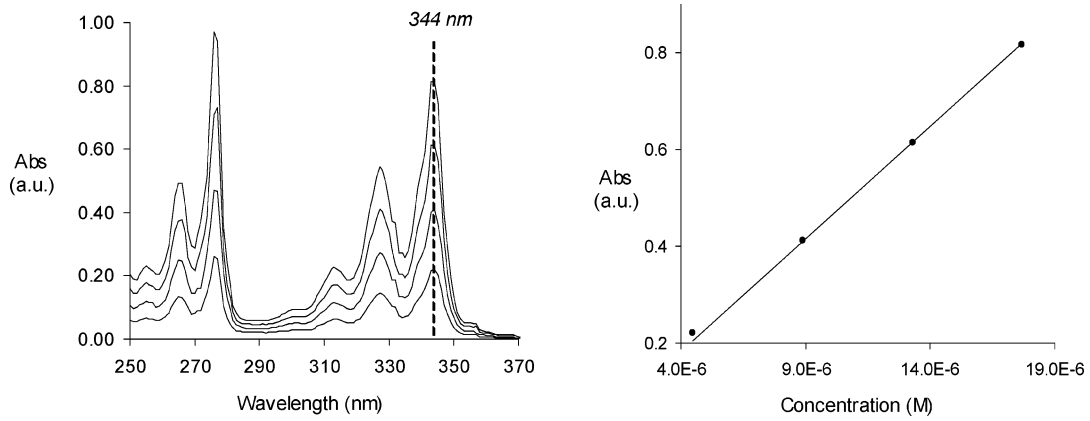


Figure 6. Absorbance spectra of allylated pyrene **24** at various concentrations (left). Beer's law plot of absorbance intensity at 344 nm with respect to concentration (right).

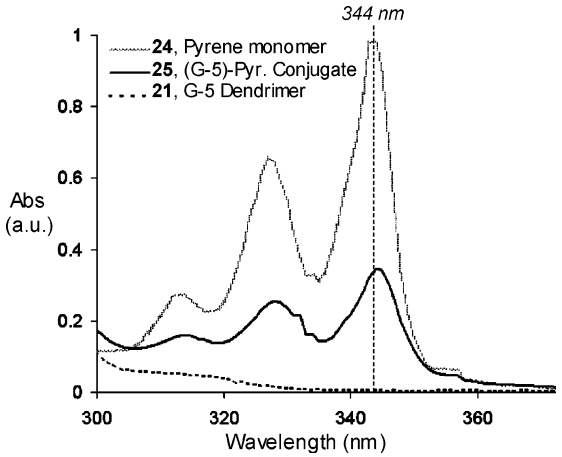
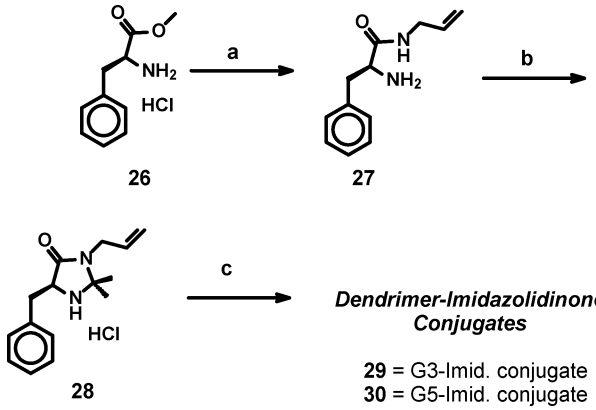


Figure 7. UV absorption spectra of the allylated pyrene monomer **24**, dendrimer–pyrene conjugate **25**, and dendrimer **21**.

Scheme 5. Preparation of Compound 28 and Subsequent Coupling with Dendrimers[a]



[a] Reagents and conditions: (a) allylamine, RT, N_2, 1 day; (b) acetone, methyl alcohol, p-TSA, 60 °C, 1.5 days; (c) dendrimer 21 or 15, Grubbs catalyst 1, dichloromethane, 45 °C.

during its coupling by metathesis, thus affecting its potential as a catalyst, the monomeric catalyst **28** was homocoupled to give the dimer **31** (Scheme 7) and then tested in the same Diels–Alder reaction.

Because **31** had limited solubility in decane, the reaction had to be carried out in methanol, a medium in which the reaction proceeds at a significantly faster rate. Therefore, conversion of the cinnamaldehyde in the presence of catalyst **31** reached 96% within 22 h while

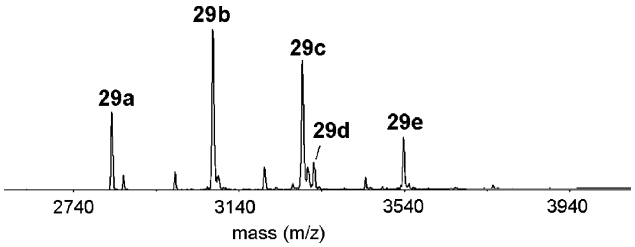


Figure 8. MALDI mass spectrum of (G-5)–imidazolidinone conjugate **29**.

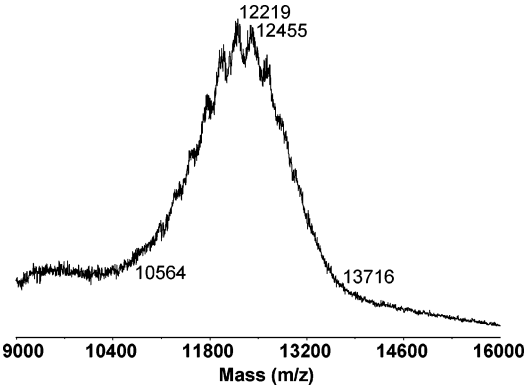


Figure 9. MALDI mass spectrum of (G-5)–imidazolidinone conjugate compound **30**.

Table 1. Products Identified in the MALDI Mass Spectrum for Compound 29

	imidazolidinone residues per dendrimer	cross-links	obsd value	calcd value $(M + H)^+$
29a	1	2	2831	2831
29b	2	1	3076	3075
29c	3	1	3292	3292
29d	3	0	3319	3320
29e	4	0	3536	3536

the uncatalyzed control reaction reached a conversion of 20% (Figure 10). As can be seen in Figure 10, the conversion achieved with the monomeric catalyst **28** essentially matched that obtained with the dimer, indicating that exposure of the imidazolidinone to metathesis conditions does not impair its catalyst activity.

The data obtained in these experiments also confirms that the formation of intramolecular "cross-links" by metathesis within the dendrimer does not noticeably impair transport of small molecule reagents into the interior of the dendrimer.

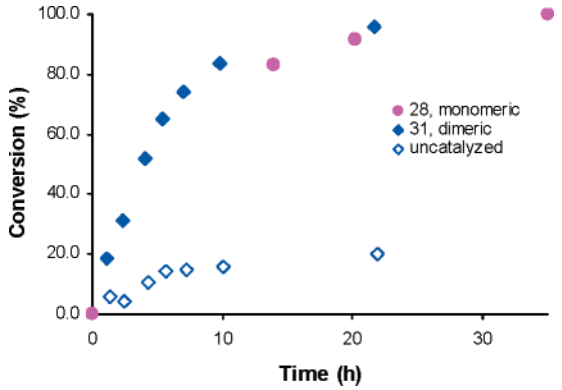


Figure 10. Reaction progress of [4 + 2] cycloaddition in methanol between cyclopentadiene and cinnamaldehyde in the presence and absence of 5 mol % monomeric **28** and dimerized imidazolidinone **31** catalyst.

Scheme 6. Diels–Alder Reaction between Cinnamaldehyde and Cyclopentadiene Used in the Evaluation of Allylimidazolidinone Catalysts 28 and 30

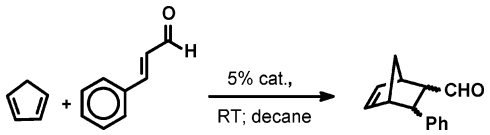
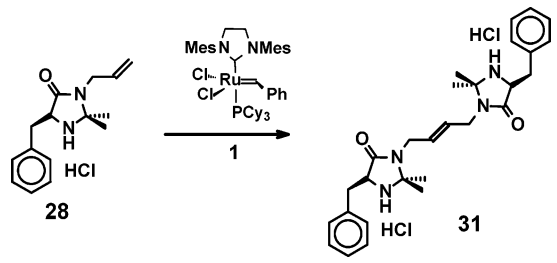


Table 2. Percent Conversion of Cinnamaldehyde in Its Diels–Alder Reaction with Cyclopentadiene 1.0 M in Decane after 1 and 3 days under Different Catalytic Conditions

	time (days)	
	1	3
uncatalyzed	14	42
28, imid	41	73
30, G5-imid	35, 32[a]	69

[a] Recycled catalyst.

Scheme 7. Homocoupling of Allylimidazolidinone 28 and the Dimer Product 31



Conclusion

The convergent preparation of a monodisperse poly(aryl ether) dendrimer containing allyl groups located throughout the interior of the molecule enables the attachment of guest molecules through olefin metathesis. A significant advantage of this methodology is the functional group tolerance of the metathesis reaction, permitting the incorporation of a wide variety of substrates that could benefit studies involving encapsulation or catalysis, for example. This synthetic strategy of inclusion of guest molecules at the final step of the synthetic sequence allows introduction molecules that would not normally tolerate the dendrimer growth steps. In addition, different dendrimers characterized by their respective "inner" functionality can be created rapidly from a "generic" allyl-containing dendrimer through a single metathesis step.

Acknowledgment. Funding for this research was provided by the National Science Foundation (DMR-0317514) and, in part, the Biomolecular Program of the Department of Energy at LBNL (DE-AC03-76SF00098). C.L. also thanks the Eastman-Kodak Company for fellowship support.

Supporting Information Available: Details on the synthesis and characterization of dendrimers, guest molecules, dendrimer–guest conjugates, and catalysis experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendrimers and Dendrons*; Wiley-VCH: Weinheim, 2001. Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and other Dendritic Polymers*; John Wiley and Sons: New York, 2001.

(2) Hecht, S.; Fréchet, J. M. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 74–91. Fréchet, J. M. J. *Prog. Polym. Sci.*, in press.

(3) Cameron, C. S.; Gorman, C. B. *Encycl. Nanosci. Nanotechnol.* **2004**, *2*, 327–335. Gorman, C. B.; Smith, J. C. *Acc. Chem. Res.* **2001**, *34*, 60–71. Gorman, C. B. *C. R. Chim.* **2003**, *6*, 911–918.

(4) Crooks, R. M.; Zhao, M.; Sun, L.; Chechik, V.; Yeung, L. K. *Acc. Chem. Res.* **2001**, *34*, 181–190. Garcia-Martinez, J. C.; Lezutekong, R.; Crooks, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 5097–5103. Scott, R. W. J.; Wilson, O. M.; Crooks, R. M. *J. Phys. Chem. B* **2005**, *109*, 692–704. Scott, R. W. J.; Wilson, O. M.; Oh, S.-K.; Kenik, E. A.; Crooks, R. M. *J. Am. Chem. Soc.* **2004**, *126*, 15583–15591. Niu, Y.; Crooks, R. M. *C. R. Chim.* **2003**, *6*, 1049–1059.

(5) Hawker, C. J.; Wooley, K. L.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 4375–4376.

(6) Furuta, P.; Brooks, J.; Thompson, M. E.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2003**, *125*, 13165–13172. Harth, E. M.; Hecht, S.; Helms, B.; Malmstrom, E. E.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 3926–3938. Lee, L. F.; Adronov, A.; Schaller, R. D.; Fréchet, J. M. J.; Saykally, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 536–540. Hecht, S.; Vladimirov, N.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 18–25. Freeman, A. W.; Koene, S. C.; Malenfant, P. R. L.; Thompson, M. E.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2000**, *122*, 12385–12386. Pollak, K. W.; Leon, J. W.; Fréchet, J. M. J.; Maskus, M.; Abruna, H. D. *Chem. Mater.* **1998**, *10*, 30–38. Kawa, M.; Fréchet, J. M. J. *Chem. Mater.* **1998**, *10*, 286–296.

(7) Vutukuri, D. R.; Basu, S.; Thayumanavan, S. *J. Am. Chem. Soc.* **2004**, *126*, 15636–15637. Mueller, C.; Ackerman, L. J.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2004**, *126*, 14960–14963. Nierengarten, J.-F. *C. R. Chim.* **2003**, *6*, 725–733. Balzani, V.; Vogtle, F. *C. R. Chim.* **2003**, *6*, 867–872. Morgan, M. T.; Carnahan, M. A.; Immoos, C. E.; Ribeiro, A. A.; Finkelstein, S.; Lee, S. J.; Grinstaff, M. W. *J. Am. Chem. Soc.* **2003**, *125*, 15485–15489. Hahn, U.; Gorka, M.; Vogtle, F.; Vicinelli, V.; Ceroni, P.; Maestri, M.; Balzani, V. *Angew. Chem., Int. Ed.* **2002**, *41*, 3595–3598.

(8) Gillies, E. R.; Fréchet, J. M. J. *Drug Discovery Today* **2005**, *10*, 35–43. Duncan, R. *Nature Rev. Drug Discov.* **2003**, *2*, 347–360. Patri, A. K.; Majoros, I. J.; Baker, J. R. *Curr. Opin. Chem. Biol.* **2002**, *6*, 466–471. Esfand, R.; Tomalia, D. A. *Drug Discovery Today* **2001**, *6*, 427–436. Liu, M.; Fréchet, J. M. J. *Pharm. Sci. Technol. Today* **1999**, *2*, 393–401. Kim, Y.; Zimmerman, S. C. *Curr. Opin. Chem. Biol.* **1998**, *2*, 733–742. Schultz, L. G.; Zimmerman, S. C. *Pharm. News* **1999**, *6*, 25–29.

(9) Pan, G.; Lemmouchi, Y. Akala, E. O.; Bakare, O. *J. Bioact. Compat. Polym.* **2005**, *20*, 113–128. Aulenta, F.; Hayes, W.; Rannard, S. *Eur. Polym. J.* **2003**, *39*, 1741–1771.

(10) Shaunak, S.; Thomas, S.; Gianasi, E.; Godwin, A.; Jones, E.; Teo, I.; Mireskandari, K.; Luthert, P.; Duncan, R.; Patterson, S.; Khaw, P.; Brocchini, S. *Nat. Biotechnol.* **2004**, *22*, 977–984. Malik, N.; Wiwattanapatapee, R.; Klopsch, R.; Lorenz, K.; Frey, H.; Weener, J. W.; Meijer, E. W.; Paulus, W.; Duncan, R. *J. Controlled Release* **2000**, *65*, 133–148. Malik, N.; Evagorou, E. G.; Duncan, R. *Anti-Cancer Drugs* **1999**, *10*, 767–776.

(11) Gillies, E.; Dy, E. E.; Fréchet, J. M. J.; Szoka, F. C. *Mol. Pharm.* **2005**, *2*, 129–138. Gillies, E. R.; Fréchet, J. M. J.

Bioconjugate Chem. **2005**, *16*, 361−368. Lee, C. C.; Yoshida, M.; Fréchet, J. M. J.; Dy, E. E.; Szoka, F. C. *Bioconjugate Chem.* **2005**, *16,* 535−541. Gillies, E. R.; Jonsson, T. B.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2004**, *126*, 11936−43. Gillies, E. R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137−14146. Gillies, E. R.; Fréchet, J. M. J. *Chem. Commun.* **2003**, 1640−1641. Gillies, E. R.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2002**, *124*, 14137−14146. Padilla De Jesús, O.; Ihre, H. R.; Gagne, L.; Fréchet, J. M. J.; Szoka, F. C., Jr. *Bioconjugate Chem.* **2002**, *13*, 453−61. Ihre, H. R.; Padilla De Jesús, O.; Szoka, F. C., Jr.; Fréchet, J. M. J. *Bioconjugate Chem.* **2002**, *13*, 443−52.

(12) Kono, K.; Akiyama, H.; Takahashi, T.; Takagishi, T.; Harada, A. *Bioconjugate Chem.* **2005**, *16*, 208−214. Kim, T.-I.; Seo, H. J.; Choi, J. S.; Jang, H.-S.; Baek, J.; Kim, K.; Park, J.-S. *Biomacromolecules* **2004**, *5*, 2487−2492. Patri, A. K.; Myc, A.; Beals, J.; Thomas, T. P.; Bander, N. H.; Baker, J. R., Jr. *Bioconjugate Chem.* **2004**, *15*, 1174−1181. D'Emanuele, A.; Jevprasesphant, R.; Penny, J.; Attwood, D. *J. Controlled Release* **2004**, *95*, 447−453. Vandamme, Th. F.; Brobeck, L. *J. Controlled Release* **2005**, *102*, 23−38.

(13) Chow, H. F.; Mong, T. K. K.; Wan, C. W.; Wang, Z. Y. *Adv. Dendritic Macromol.* **1999**, *4*, 107−133. Fréchet, J. M. J. *Macromol. Symp*. **2003**, *201*, 11−22. Tomalia, D. A.; Brothers, H. M., II.; Piehler, L. T.; Durst, H. D.; Swanson, D. R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5081−5087.

(14) Smith, D. K.; Diederich, F. *Top. Curr. Chem.* **2000**, *210*, 183−227. Smith, D. K.; Diederich, F. *Chem.—Eur. J.* **1998**, *4*, 1353−1361. Kim, Y.; Zimmerman, S. C. *Curr. Opin. Chem. Biol.* **1998**, *2*, 733−742.

(15) Knecht, M. R.; Wright, D. W. *Langmuir* **2004**, *20*, 4728−4732. Takasu, D.; Tomioka, N.; Jiang, D.-L.; Aida, T.; Kamachi, T.; Okura, I. *J. Inorg. Biochem.* **1997**, *67*, 242.

(16) Twyman, L. J.; King, A. S. H.; Martin, I. K. *Chem. Soc. Rev.* **2002**, *31*, 69−82. Astruc, D.; Chardac, F. *Chem. Rev.* **2001**, *101*, 2991−3023.

(17) Fréchet, J. M. J. *J. Polym. Sci., Part A* **2003**, *41*, 3713−25. Kreiter, R.; Kleij, A. W.; Gebbink, R. J. M. K.; van Koten, G. *Top. Curr. Chem.* **2001**, *217*, 163−199. Hearshaw, M. A.; Hutton, A. T.; Moss, J. R.; Naidoo, K. J. *Adv. Dendritic Macromol.* **1999**, *4*, 1−60.

(18) Hecht, S.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6959−6960. Liang, C. O.; Fréchet, J. M. J. *Prog. Polym. Sci.* **2005**, *30*, 385−402. Liang, C. O.; Helms, B.; Hawker, C. J.; Fréchet, J. M. J. *Chem. Commun.* **2003**, 2524−5. Helms, B.; Liang, C. O.; Hawker, C. J.; Fréchet, J. M. J. *Macromolecules*, in press.

(19) Piotti, M. E.; Rivera, F.; Bond, R.; Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1999**, *121*, 9471−9472.

(20) Delort, E.; Darbre, T.; Reymond, J.-L. *J. Am. Chem. Soc.* **2004**, *126*, 15642−15643. Douat-Casassus, C.; Darbre, T.; Reymond, J.-L. *J. Am. Chem. Soc.* **2004**, *126*, 7817−7826. Liu, L.; Breslow, R. *J. Am. Chem. Soc.* **2003**, *125*, 12110−12111.

(21) Mizugaki, T.; Miyauchi, Y.; Murata, M.; Ebitani, K.; Kaneda, K. *Chem. Lett.* **2005**, *34*, 286−287. Touzani, R.; Alper, H. *J. Mol. Catal. A: Chem.* **2005**, *227*, 197−207. Scott, R. W. J.; Sivadinarayana, C.; Wilson, O. M.; Yan, Z.; Goodman, D. W.; Crooks, R. M. *J. Am. Chem. Soc.* **2005**, *127*, 1380−1381.

(22) Freeman, A. W.; Chrisstoffels, L. A. J.; Fréchet, J. M. J. *J. Org. Chem.* **2000**, *65*, 7612−7617. Hecht, S. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1047−1058.

(23) Severac, M.; Leclaire, J.; Sutra, P.; Caminade, A.-M.; Majoral, J.-P. *Tetrahedron Lett.* **2004**, *45*, 3019−3022. Ghorai, S.; Bhattacharjya, A.; Basak, A.; Mitra, A.; Williamson, R. T. *J. Org. Chem.* **2003**, *68*, 617−620. Fréchet, J. M. J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4782−4787. Larre, C.; Donnadieu, B.; Caminade, A.-M.; Majoral, J.-P. *J. Am. Chem. Soc.* **1998**, *120*, 4029−4030. Newkome, G. R.; Gross, J.; Moorefield, C. N.; Woosley, B. D. *Chem. Commun.* **1997**, 515−516.

(24) Fréchet, J. M. *Science* **1994**, *263*, 1710−1715.

(25) Baker, L. A.; Crooks, R. M. *Macromolecules* **2000**, *33*, 9034−9039.

(26) Baker, L. A.; Sun, L.; Crooks, R. M. *Bull. Korean Chem. Soc.* **2002**, *23*, 647−654.

(27) Francavilla, C.; Drake, M. D.; Bright, F. V.; Detty, M. R. *J. Am. Chem. Soc.* **2001**, *123*, 57−67.

(28) Breinbauer, R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2000**, *39*, 3604−3607.

(29) Lagnoux, D.; Delort, E.; Douat-Casassus, C.; Esposito, A.; Reymond, J. L. *Chem.—Eur. J.* **2004**, *10*, 1215−1226.

(30) Kleij, A. W.; Gossage, R. A.; Jastrzebski, J. T. B. H.; Boersma, J.; van Koten, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 176−178.

(31) Lochmann, L.; Wooley, K. L.; Ivanova, P. T.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 7043−7044. Larre, C.; Bressolles, D.; Turrin, C.; Donnadieu, B.; Caminade, A.-M.; Majoral, J.-P. *J. Am. Chem. Soc.* **1998**, *120*, 13070−13082. Twyman, L. J. *Tetrahedron Lett.* **2000**, *41*, 6875−6878.

(32) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29.

(33) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043.

(34) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2037−2056.

(35) Wendland, M. S.; Zimmerman, S. C. *J. Am. Chem. Soc.* **1999**, *121*, 1389−1390.

(36) Zimmerman, S. C.; Lawless, L. J. *Top. Curr. Chem.* **2001**, *217*, 95−120.

(37) Zimmerman, S. C.; Wendland, M. S.; Rakow, N. A.; Zharov, I.; Suslick, K. S. *Nature (London)* **2002**, *418*, 399−403.

(38) Zimmerman, S. C.; Zharov, I.; Wendland, M. S.; Rakow, N. A.; Suslick, K. S. *J. Am. Chem. Soc.* **2003**, *125*, 13504−13518.

(39) Kim, Y.; Mayer, M. F.; Zimmerman, S. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1121−1126.

(40) Mertz, E.; Zimmerman, S. C. *J. Am. Chem. Soc.* **2003** *125*, 3424−3425.

(41) Hawker, C. J.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1990**, *112*, 7638−7647. Hawker, C.; Fréchet, J. M. J. *Chem. Commun.* **1990**, 1010−1013.

(42) Claisen, L.; Tietze, E. *Ber.* **1926**, *59B*, 2344−2351.

(43) Claisen, L.; Tietze, E. *Ber.* **1925**, *58B*, 275−281.

(44) Tarbell, D. S. *Chem. Rev.* **1940**, *27*, 495−546.

(45) Mourey, T. H.; Turner, S. R.; Rubinstein, M.; Fréchet, J. M. J.; Hawker, C. J.; Wooley, K. L. *Macromolecules* **1992**, *25*, 2401−2406.

(46) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(47) Mecerreyes, D.; Lee, V.; Hawker, C. J.; Hedrick, J. L.; Wursch, A.; Volksen, W.; Magbitang, T.; Huang, E.; Miller, R. D. *Adv. Mater.* **2001**, *13*, 204−208.

(48) Schultz, L. G.; Zhao, Y.; Zimmerman, S. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1962−1966.

(49) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875.

(50) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 4243−4244.

(51) Paras, N. A.; MacMillan, D. W. *J. Am. Chem. Soc.* **2001**, *123*, 4370−4371.

MA050818A