# HIGHLIGHT

# Functionalizing the Interior of Dendrimers: Synthetic Challenges and Applications

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**ABSTRACT:** Chemists' fascination with dendrimers mainly originates from their unique architecture and its exploitation for the design of well-defined functional macromolecules. Depending on the nature of the synthesis, functionalization is traditionally introduced at the core, the periphery, or both. However, the specific incorporation of functional groups at the interior layers, i.e., generations, represents a considerable synthetic hurdle that must be overcome for the full potential of dendrimers to be realized. This review covers recent advances in this emerging frontier of dendrimer science with a particular focus on covalent modifications. Monomer design, syntheses, and properties of various dendritic backbone types are discussed. Internal functionalization dramatically increases the degree of complexity that can be implemented into a dendrimer macromolecule and, therefore, promises to lead to smart materials for future applications in bio- and nanotechnologies. © 2003 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 41: 1047–1058, 2003

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## INTRODUCTION

Dendrimers[1–3] have been at the forefront of polymer research for almost 2 decades now. Once considered exotic molecules, they have extensively been studied in recent years and shown to exhibit exceptional characteristics in comparison with conventional polymers:

1. Because of their repetitive synthesis, reminiscent of well-established oligopeptide and oligonucleotide coupling chemistry, dendrimers represent precisely defined, monodisperse macromolecules, i.e., discrete entities, allowing the detailed investigation of structure–property relationships.
2. The highly symmetrical, branched architecture gives rise to a compact, globular shape at higher generations, allowing one to distinguish interior and exterior compartments.[4–7]
3. A single separated core is surrounded by a large number of terminal groups, the nature of which governs the interaction of the entire molecule with its environment.

To use these unique features of dendritic macromolecules,[8–10] the research community has shifted its main focus toward designing functional dendrimers[11–13] for specific high-end applications in both biotechnology and nanotechnology.[14–23] Most efforts have been based on the spatial segregation of the core and periphery for control over their interactions, which allows for the tuning of properties and the generation of new functions. Many fascinating phenomena unraveled so far in dendrimers have been inspired by nature, such as site isolation,[24] light harvesting,[24,25] and catalysis.[24,26–28]

Because of synthetic considerations, functionalization is usually introduced into the dendrimer framework at either the core or the periphery (or both). In almost all cases, the dendrimer backbone serves as a pure scaffold, arranging the functional units in space without having an inherent function. This role as an innocent spectator represents a serious limitation to the complexity and level of sophistication that could be achieved with these molecules. The modification of the interior has great promise for the incorporation of systematic changes localized between the core and periphery. For example, energy gradients could be established to facilitate cascade processes. Furthermore, the number of internal functional groups could be increased without the periphery being changed, and so cooperative phenomena within the interior could be investigated.

This review summarizes recent advances in the functionalization of the dendritic interior with a particular focus on *covalent* modifications using organic building blocks. The syntheses and properties of the resulting materials are discussed. For reasons of modularity, a distinction between functional and branching units is made, and so conjugated backbones[29–44] have been excluded. Alternative approaches using noncovalent interactions[45–52] between a functional guest and a dendritic host are not within the scope of this review.

## SYNTHETIC CONCEPTS

Dendrimers can be synthesized by either divergent or convergent growth approaches.[1,2] For the preparation of perfectly branched macromolecules that are free of defects and incorporate the desired functions, the convergent route appears to be superior;[53] however, there have been significant improvements in divergent procedures.[54–56] The functionalization of the interior can be envisaged before (premodification) or after (postmodification) the construction of the molecule (Fig. 1). Although both approaches support a modular synthesis allowing for the generation of a variety of molecules from similar building blocks, the choice of the approach is determined by the ultimate synthetic goal. Layered structures, having different functional groups located in adjacent generations, can be generated from a set of prefunctionalized monomer building blocks with the first approach. Alternatively, a variety of dendrimers differing in the nature of their respective internal functional groups can be accessed via postfunctionalization of one set of suitably protected precursor dendrimers with the latter approach.

The syntheses rely on the accessibility of a branched monomer ($AB_2FG$ or, in rare cases, $AB_3FG$) that carries either the functional group (FG) of choice or a moiety that can be readily functionalized. Because such branched molecular building blocks are sometimes difficult to prepare, the introduction of functional linear groups has enjoyed considerable attention. This allows for the use of established dendrimer growth procedures because the linear fragment (ABFG) is readily accessible from the original branched monomer ($AB_2$) by monofunctionalization.

The need to carry out a functionalization reaction that is chemically orthogonal to dendrimer growth represents a stringent requirement for such syntheses. Therefore, the incorporation of either orthogonal protecting groups or groups that can be selectively activated is necessary. This fact represents the major challenge for the further exploration of the dendritic interior for the construction of sophisticated functional molecules on the nanoscale.

In the following sections, several approaches are highlighted according to the utilized backbone type. Particular attention is given to the chosen monomers, their connection affording the respective dendrimers, and the

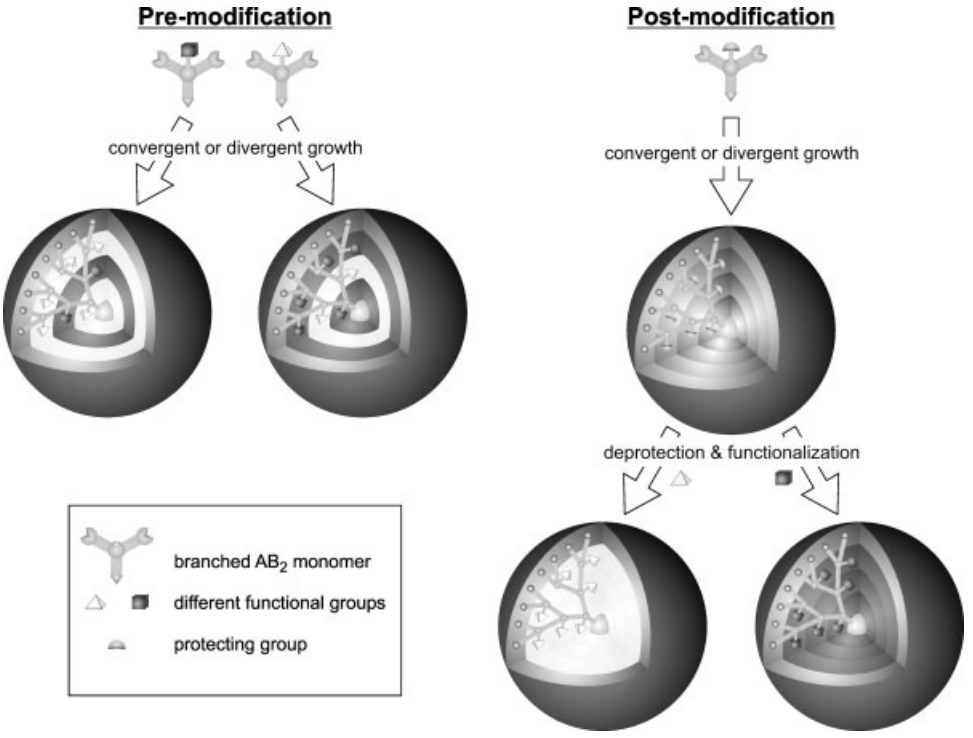


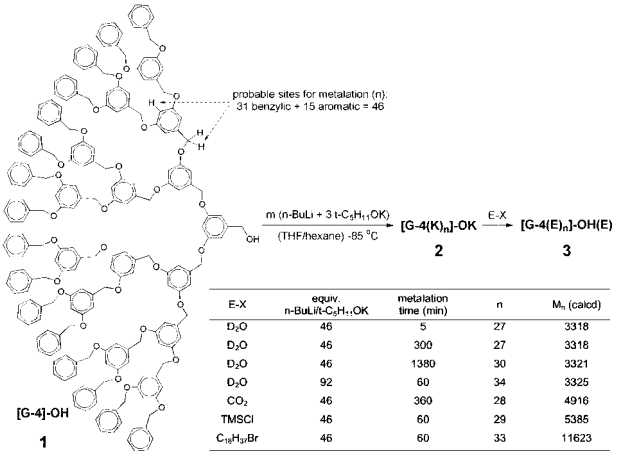

**Figure 1.** General synthetic access to internally functionalized dendrimers. Premodification with prefunctionalized branched monomers enables the construction of layered architectures (left), whereas postmodification with protected branched monomers allows for the modular introduction of functionality into a precursor dendrimer (right).

properties resulting from the architectural control over functional group placement.

## AROMATIC BACKBONES

By far, most examples concerning internally functionalized dendrimers are based on the poly(benzyl ether) type and are typically synthesized by the classical convergent approach pioneered by Hawker and Fréchet.[57,58] The relatively mild coupling and activation conditions in combination with the facilitated purification inherent in the convergent synthesis, as well as the wide variety of aromatic building blocks available, make this backbone ideally suited for the introduction of functionalities at the internal branch points.

The first attempts to modify the interior of Fréchet-type dendrons were reported by Lochmann et al.,[59] who studied the reaction of superbases, such as mixtures of *n*-butyl lithium and potassium *tert*-pentoxide, with fourth-generation poly(benzyl ether) dendron **1** (Fig. 2). Although 46 positions, 31 benzylic and 15 *o,o′*-dialkoxyphenyl, served as potential sites for metalation, not all sites proved to be reactive, with a maximum of 34 sites being successfully functionalized. NMR analysis revealed that peripheral benzylic protons were more readily abstracted, presumably because of reagent accessibility and electronic effects. Interestingly, metalation




| E-X | equiv. n-BuLi/t-$C_5H_{11}OK$ | metalation time (min) | n | $M_n$ (calcd) |
|---|---|---|---|---|
| $D_2O$ | 46 | 5 | 27 | 3318 |
| $D_2O$ | 46 | 300 | 27 | 3318 |
| $D_2O$ | 46 | 1380 | 30 | 3321 |
| $D_2O$ | 92 | 60 | 34 | 3325 |
| $CO_2$ | 46 | 360 | 28 | 4916 |
| TMSCl | 46 | 60 | 29 | 5385 |
| $C_{16}H_{33}Br$ | 46 | 60 | 33 | 11623 |

**Figure 2.** Statistical multifunctionalization of the interior of poly(benzyl ether) dendrons via metalation by superbases and subsequent reaction with various electrophiles. From 46 potential sites for metalation, a maximum of 34 sites could be functionalized to render, for instance, the dendrons soluble in either water or hexanes.[59]

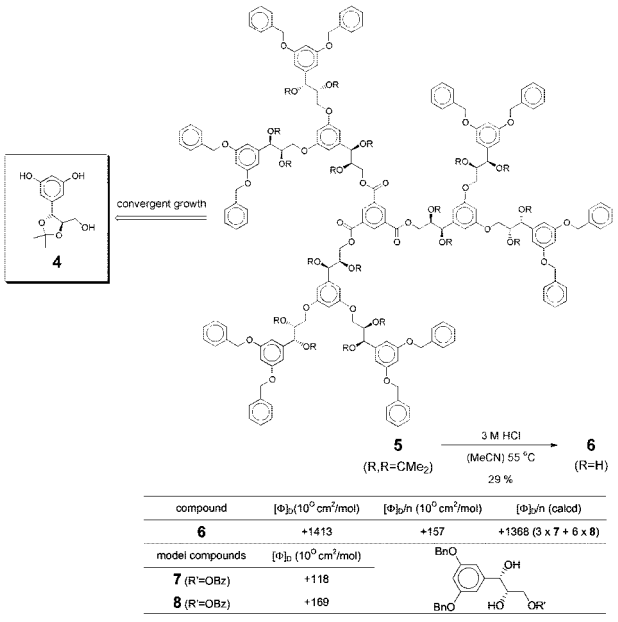



**Figure 3.** Incorporation of acetonide-protected vicinal diol units into the interior of poly(benzyl ether) dendrimers and subsequent deprotection.[64] The overall optical activity of the dendrimers resembles the superposition of the individual chiral subunits.

proceeded fairly rapidly, and the resulting polyanion **2** retained its structural integrity at low temperatures but underwent complete rearrangement, presumably of the Wittig type, without fragmentation at room temperature. Polyanion **2** was subsequently reacted with various electrophiles to yield dendrimer **3**. For example, the introduction of carboxyl groups via a reaction with carbon dioxide afforded a highly water-soluble dendrimer, whereas a reaction with octadecyl bromide rendered the resulting dendrimer soluble in hexane. This approach clearly benefits from its ease of synthesis and the relatively large number of various functional groups that can be introduced. However, because of its poor regioselectivity and consequently rather statistical nature, it is not suitable for the preparation of dendritic architectures with a well-defined placement of functional groups.

In their investigations concerning chiral dendrimers,[60] McGrath and coworkers[61–64] reported on the incorporation of acetonide-protected vicinal diol units in poly(benzyl ether) dendrimers (Fig. 3). The enantiomerically pure monomer building block **4** was readily accessible via asymmetric dihydroxylation and allowed for the convenient use of the convergent growth procedure.[57,58] Rather surprisingly, the acid-labile acetonide-protecting groups seemed to be compatible with the slightly acidic Appel-type bromination conditions (discussed later). Although much of the authors' primary attention was devoted toward the characterization of the acetonide-protected series,[61–63] some efforts were made to postmodify the synthesized dendrimers by the unmasking of the protected diol functionalities and by the investigation of the resulting compounds.[64] The deprotection of convergently grown dendrimer **5** under rather harsh conditions, i.e., 3 M HCl at 55 °C, afforded polyol **6** in a modest yield. Interestingly, more traditional mildly acidic cleavage routes led to extensive decomposition, most likely because of transesterification. Product **6**[64] and the corresponding first- and second-generation dendrons[61] were only soluble in highly polar media such as dimethyl sulfoxide and acetone. The key finding is related to the overall optical activity of dendrimer **6**, which is comparable to the superposition of suitable low molecular weight model compounds, i.e., **7** and **8**, which resemble the two different structural dendritic subunits. This implies that there is no additional chiral conformational order due to the dendrimer backbone. It should be noted that these polyhydroxylated compounds represent attractive target ligands for transition-metal-mediated catalysis within dendrimers.[24] Furthermore, it was possible to introduce chiral acetonide units at specific generations, but no deprotection attempts were reported.[65] These studies elegantly demonstrate the advantages resulting from precise control over the location and nature of the interior functionality and illustrate the importance of macromolecular architecture for tuning chirooptical properties.

With the aim of creating unimolecular chemical nanoreactors based on amphiphilic dendrimers, Piotti et al.[66] incorporated ester groups into tetradecyl-terminated Fréchet-type dendrimers (Fig. 4). Monomer **9**, with a focal tetrahydropyranyl-protected benzyl alcohol, was used to avoid oligomerization during Williamson etherification yet allowing the convenient one-step activation to the corresponding bromide under slightly acidic Appel-type bromination conditions (discussed previously). The fourth-generation dendrimer **10**, with 21 internal ester groups, was then reduced to the corresponding polyol **11**. Interestingly, saponification to the illusive polycarboxylate led to fragmentation. Presumably, the attack of the initially formed carboxylate at a neighboring benzylic site and the displacement of a phenolate lead to the formation of an ester linkage that is subsequently hydrolyzed and, therefore, results in scission. Because of its particular microenvironment, the carboxylate group displays enhanced nucleophilicity; in this case, the dendrimer catalyzes its own destruction.

By the study of the E1-type elimination of tertiary iodide **12**, it was found that **11** showed superior catalytic activity compared with polyester **10**, which slowly degraded under the reaction conditions (discussed previously). Various control experiments employing either no catalyst or first-generation dendrons with an equivalent

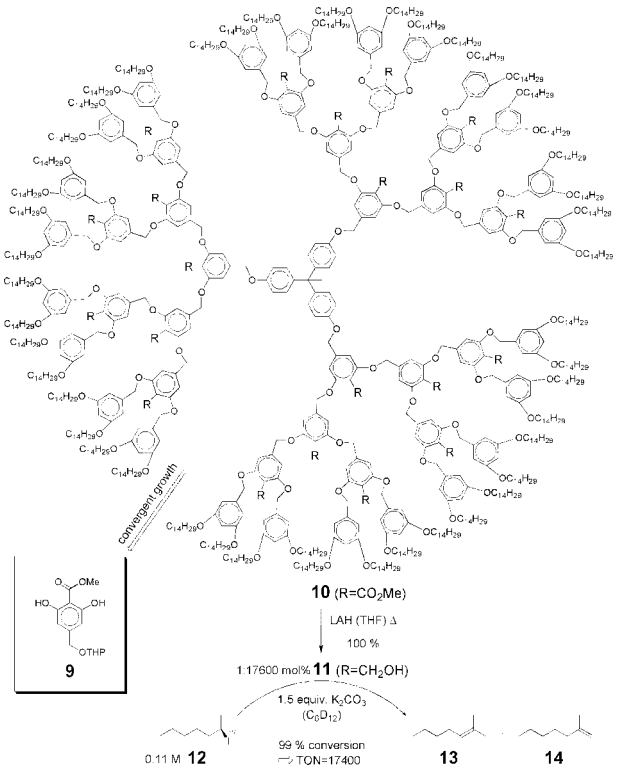



**Figure 4.** Reverse unimolecular micelle, consisting of long alkyl chain terminated poly(benzyl ether) dendrimers with internal ester groups, can be transformed into the corresponding polyols, which display high catalytic activity for elimination reactions of alkyl iodides.[66]

number of functional groups showed no reaction. In the presence of catalyst **11**, an impressive turnover number of 17,400 could be achieved. More interestingly, it was noted that the product distribution, i.e, Saytzeff **13** versus Hofmann olefin **14**, was sensitive to the catalyst loading, the nature of the internal functionality, and the structure of the dendrimer. Understanding such observed selectivities in dendrimer catalysis in general still remains a major and important challenge.[26–28]

This catalytic pump relies on a change in polarity during the course of a chemical transformation and uses the contrasting polar inner and nonpolar outer compartments of the dendritic architecture to preferentially concentrate substrates in the interior, stabilize transition states and intermediates, and expel the product to the surrounding solution. Since the initial proof of principle,[66] this concept has been extended more recently to excited-state catalysis with amphiphilic benzophenone-core dendrimers of the regular micellar structure type as singlet oxygen sensitizers for the conversion of cyclopentadiene to *cis*-2-cyclopentene-1,4-diol.[67] This conversion of excited-state energy localized at the dendrimer core into chemical energy can, in principle, be coupled to an efficient collection of photons by means of light-harvesting dendrimers[25] and therefore represents an important step toward mimicking nature's photosynthetic machinery.[24]

Although the presence of a large number of functional groups is desired for certain applications such as catalysis (discussed previously), the defined placement of one particular functional group at a specific location within the dendrimer[68] may be advantageous in some cases, such as probing the interior microenvironment. The generation-specific introduction of aryl bromide functionalities in poly(benzyl ether) dendrimers, allowing for further modification with orthogonal Pd-catalyzed cross-coupling chemistry, was accomplished by Bo et al.[69] (Fig. 5). Monomer **15** was chosen and embedded in the dendrimer framework at the first, second, or third layer, thereby granting access to structures **16–18**. Because the introduction of only one function was desired, the synthesis involved the statistical monocouplings of dendritic branches to the monomers and the final attachment to a trivalent core carrying two unfunctionalized branches, which was accessed via statistical functionalization as well. Most importantly, by the performance of high-

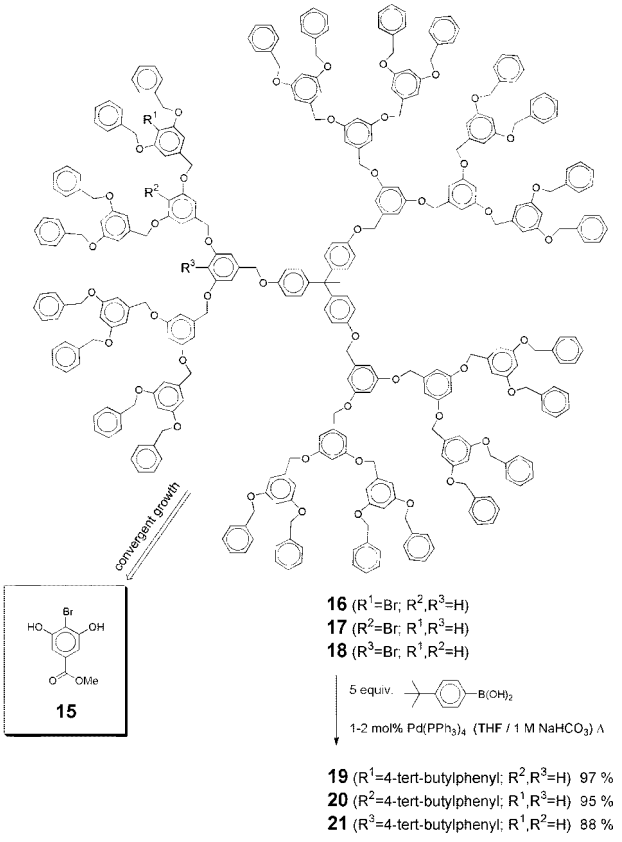



**Figure 5.** Generation-specific incorporation of aryl bromide functionalities into poly(benzyl ether) dendrimers and subsequent functionalization via Suzuki cross-coupling.[69]

yielding Suzuki cross-coupling reactions using 4-*tert*-butylphenylboronic acid, it was demonstrated that the internal aryl bromide functions could be used as anchor groups for postfunctionalization. Although structure–property relationships of these positional isomers have not been elucidated so far, the approach clearly illustrates the synthetic ability to precisely control the location of a functional group within a given dendritic structure.[70]

Combining architectural control with the ability to rapidly access a diverse array of macromolecules with accelerated growth strategies, Freeman et al. described a parallel monomer combination approach to prepare radial, i.e., layered, structures[71] employing both allylated and standard monomer building blocks **22** and **23**, respectively (Fig. 6).[72] Monomer **22** was readily available because methyl gallate could be selectively deprotonated and, therefore, allylated on account of the higher acidity of the 4-hydroxy group. All eight different combinations of inner dendrons **24–27** and outer dendrons **28–31** were prepared and then combined with a double-stage convergent growth approach[73–75] to afford a total of 16 fourth-generation dendron structures (**32–47**). Methyl benzoates, rather than benzylic alcohols, were used for growth because alkylations proceed with higher degrees of regioselectivity, i.e., no O-alkylation is observed, and the additional reduction step is facilitated by workup with Baeckström's reagent.[76] Although a detailed property screening of such a dendron library remains to be undertaken, this approach nicely demonstrates the power of parallel synthesis in this area of polymer science. Internal allylic groups were chosen because of their versatile chemistry, which potentially allows the preparation of an even more diverse set of dendrimers by postfunctionalization. Although modifications employing acidic conditions suffer from partial fragmentation of the structure, dihydroxylation to create internal diols units proved to be clean and high yielding.[77] Such materials display potentially interesting catalytic activity.

Positioning functional groups at the interior can also be advantageous if they are to be reacted with one another in an intramolecular fashion, i.e., in the same dendrimer molecule. This concept of concentrating intramolecular reaction space[78] and thereby minimizing intermolecular bond formation was demonstrated by Schultz et al.,[79] who investigated the ring-closing metathesis (RCM) of dendrimer **49** carrying internal allyl groups (Fig. 7). The linear unit **48**, having two allyl substituents, was terminated with a first-generation poly(benzyl ether)-type dendron and then incorporated in the standard convergent growth process[57,58] to afford **49**. A comparison of RCM of dendrimer **49** with internal crosslinking groups with RCM of dendrimers carrying such groups at their periphery showed that almost exclusively intramolecular crosslinking could be performed at

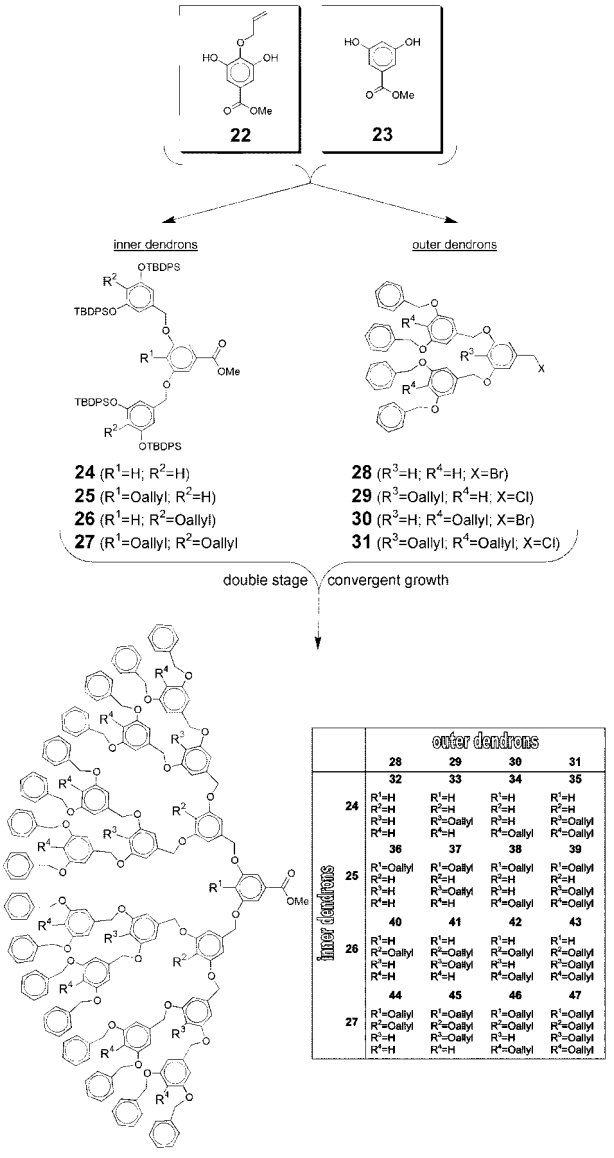



**Figure 6.** Construction of a dendron library with all possible combinations of generation-specific functionalization using an accelerated parallel monomer approach.[72]

significantly higher concentrations ($10^{-3}$ M) with only minor amounts of intermolecularly crosslinked material being formed. This represents a major improvement over the initial approach employing dendrimers with crosslinking groups located at their periphery, which required high dilution conditions ($10^{-5}$ M).[80] Taking advantage of recent developments in RCM catalyst design, the crosslinking density could be optimized to approximately 95% according to $^{1}$H NMR analysis. After this covalent bond formation between the individual dendron subunits, the core was removed by selective ester hydrolysis, which left the polyether backbone intact. The resulting cored dendrimers represent monomo-

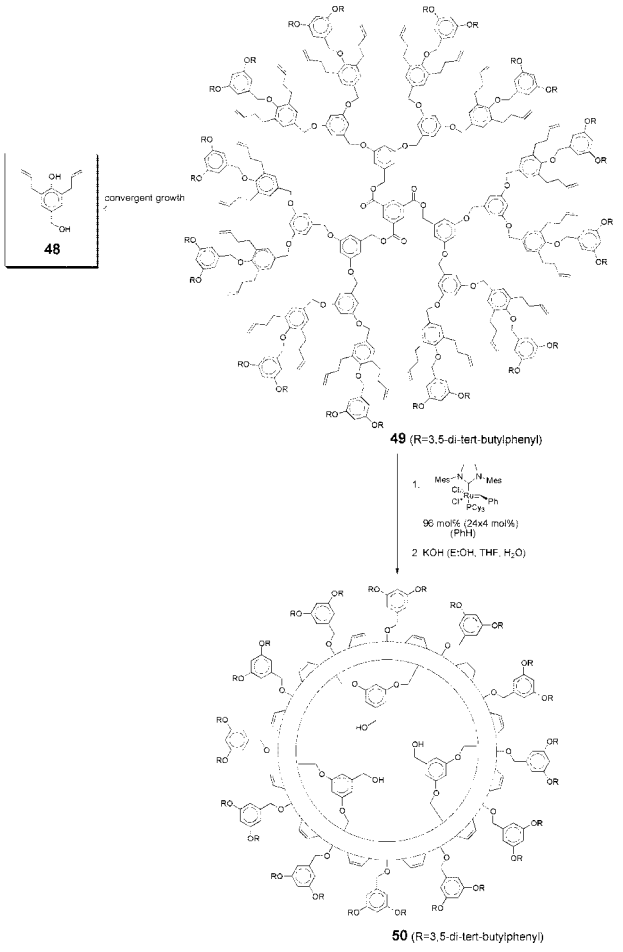



**Figure 7.** Introduction of crosslinking groups at the interior of poly(benzyl ether) dendrimers, which allows for the more practical preparation of cored dendrimers at higher concentrations.[79]

lecular imprints[81] within a well-defined macromolecule and so are interesting candidates for the design of synthetic host systems.[82]

## ALIPHATIC BACKBONES

The design of purely aliphatic dendrimers, although synthetically in some cases much more challenging, offers certain advantages, such as chemical robustness and UV transparency, necessary for specific applications, that is, catalysis and UV-photon harvesting, respectively. One important contribution to this area was made by Ford and coworkers,[83–86] who investigated the catalytic activity of poly(propylene imine) dendrimers that carried quaternized internal ammonium ions. Furthermore, there is one report about the reduction of an aromatic nitro group within an extended linear fragment of a first-generation dendrimer.[87] In this section, the examples that allow for synthetic flexibility and control over functional group placement in aliphatic dendrimers are presented.

Truly, the first example of controlled internal functionalization of dendrimers in general was reported by Newkome et al.[88] During their initial divergent synthesis of unimolecular micelles based purely on hydrocarbon dendrimers with peripheral carboxylate groups, the authors used Wurtz couplings of branched acetylide fragments (**51**) to a polyfunctional alkyl bromide core (Fig. 8).[89] Rather than removing the triple bond by complete hydrogenation as originally reported, the reaction with decaborane was used for the specific incorporation of *o*-carborane moieties within dendrimer **53**. Furthermore,

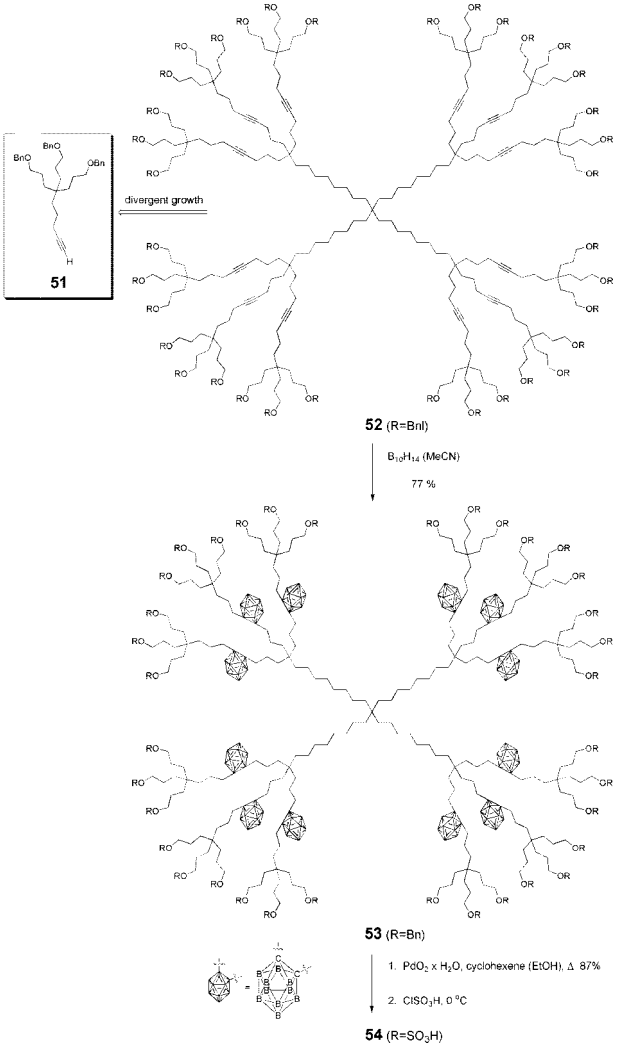



**Figure 8.** Generation of water-soluble polycarboranes for potential applications in boron neutron capture therapy using the generation-specific reaction of decaborane with polyalkyl dendrimers having internal alkine functionalities and the subsequent introduction of polar terminal groups.[88]

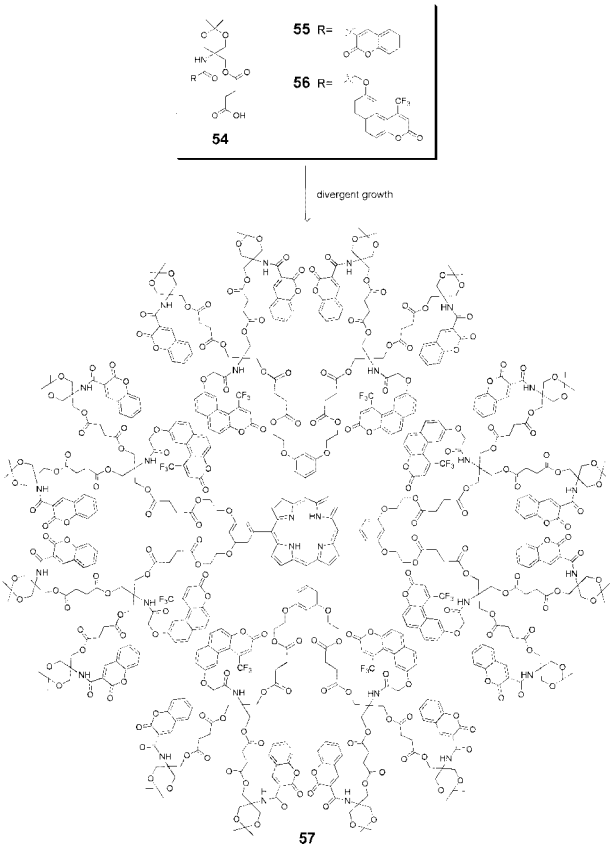



**Figure 9.** Construction of sophisticated light-harvesting dendrimers based on aliphatic polyesters with two sets of donor chromophores located in consecutive generations, both giving rise to nearly quantitative energy transfer to the porphyrin acceptor core.[90]

the molecule was rendered water-soluble by the introduction of sulfate groups at the periphery of dendrimer **54**. These materials, allowing for high local concentrations of boron clusters in an aqueous environment, represent interesting candidates for disease treatment based on boron neutron capture therapy.

Very recently, the aliphatic branched monomer **54**, which allows for the modular incorporation of a desired functional group at each generation of growth, has been designed for and applied to the construction of the multichromophore light-harvesting system **57** (Fig. 9).[90] The high yield and mild conditions used for the preparation of polyester dendrimers based on 2,2-bis(hydroxymethyl)propionic acid by convergent,[91] double-stage convergent,[92] or divergent protocols[56] allow for high functional group tolerance and are, therefore, well suited for the introduction of chromophores. Commercially available tris(hydroxymethyl)aminomethane hydrochloride was converted into the corresponding acetonide and, the remaining alcohol and amine functionalities were differentiated. This allowed for the incorporation of the desired functional group via an amide linkage followed by transformation into the required carboxylic acid to afford monomer **54**. Various functional monomers such as **55** and **56** are conveniently accessible by the incorporation of the desired carboxylic acid without any additional protection and deprotection steps.

The light-harvesting dendrimer **57** consists of two different types of donor chromophores, i.e., 16 coumarin and 8 naphthopyranone dyes, in a layered arrangement around a central porphyrin-core acceptor. Quantitative energy funneling is observed as indicated by exclusive emissions from the core. Energy migration seems to predominantly involve individual donor–acceptor energy-transfer events. This is in contrast to other recently reported sophisticated light-harvesting arrays that rely on efficient energy-transfer cascades.[93–95] In somewhat related work, Schlüter and coworkers[96,97] synthesized low-generation dendrimers equipped with generation-specific solvatochromic probes to elucidate local environments and, therefore, gain further insight into the controversially discussed density profile of dendrimers. Once a solvation/polarity gradient is established, this approach would allow for the generation of layered structures for directed energy or electron-transfer processes from one suitable solvation-responsive chromophore or electrophore.

## PHOSPHAZENE BACKBONES

Majoral and coworkers successfully applied the rich chemistry of phosphorus to the synthesis of heteroatom-based dendrimers,[98,99] and their accomplishments regarding the rational covalent functionalization of the dendritic interior[101] are particularly elegant and noteworthy. Although this chemistry has previously been reviewed,[98–100] the main synthetic concept is briefly illustrated in this section.

The use of monomers **58** and **59** allows for the rapid divergent synthesis of poly(phosphazene hydrazone) dendrimers such as **60** with internal P═N—P(═S) fragments (Fig. 10). Chemoselective methylation of the sulfur atom followed by MeS transfer leads to desulfurization and, therefore, generation of a specific chemical handle in the interior of **61**.[101] The Staudinger reaction of this P═N—P: fragment with a suitable branched azide initiates a second divergent dendrimer growth process originating from the interior and leading to the grafting of ''daughter'' dendrons within the ''mother'' dendrimer. The resulting gigantic dendrimer **62** consists of six fourth-generation dendrons within one third-generation dendrimer. The extremely versatile grafting-from-within approach[102] could further be used to incorporate for instance crown ether moieties in the dendritic interior.

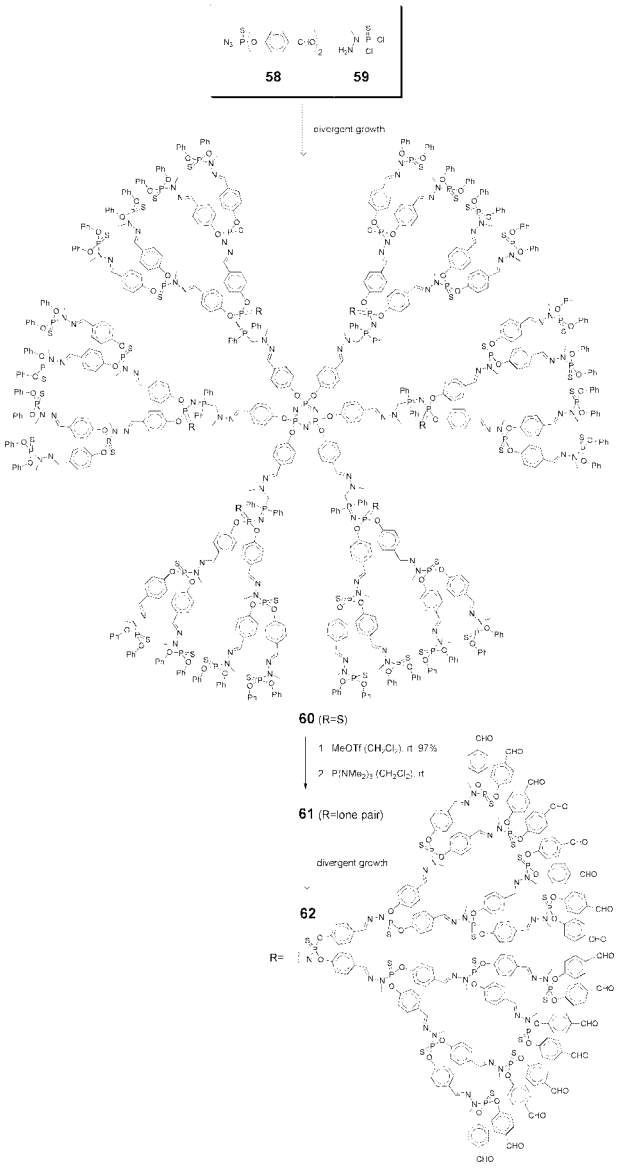



**Figure 10.** Generation-specific desulfurization of polyphosphazene dendrimers followed by the growth of dendrons from the interior via the highly chemoselective Staudinger reaction, affording dendrons within dendrimers.[101]

## OUTLOOK

The dendrimer field has undoubtedly blossomed and matured over the last decade, as evidenced by the ever increasing number of scientists working and publishing in this area. However, perhaps the most critical question still remains: what are dendrimers good for? Although dendrimers have already been implemented in a number of practical applications, namely in bio- and nanotechnologies,[14–23] a strong and continued effort of the community will be necessary to propel them out of the realm of being academic curiosities and niche products into a mainstream, commercially important class of polymers. To meet this ambitious yet inevitable measure of practicality, several important aspects have to be addressed.

The field is still in need of efficient and better syntheses. The enhanced performance of dendrimer-based materials cannot be overshadowed by extreme cost due to expensive preparation. Notable recent synthetic advances include improved divergent routes[54–56] and one-pot procedures,[103,104] as well as alternative approaches based on hyperbranched polymers,[8–10] chain walking,[105,106] and transfer.[107] Functional three-dimensional molecular entities in the dendrimer size range of a few nanometers have also been accessed with star-shaped polymers[108–113] and crosslinked linear block copolymers;[114–117] clearly demonstrating the tremendous utility of precision polymerization in combination with crosslinking methodologies.[118] Because of the often tedious preparation of dendritic macromolecules, it is necessary to compare them with their isomeric linear or less perfectly branched counterparts.[119–122] Such investigations can help to elucidate significant advantages of, perhaps even fundamental differences in, the perfect dendritic architecture over more readily accessible polydisperse alternatives, thereby justifying their use in high-end applications. Further improvements will originate from an increased level of complexity arising from functionalization at all regions of the dendrimer. Covalent modification of the dendritic interior, as highlighted in this review, can be supplemented by other alternative routes. For instance, sophisticated functional gradients throughout dendritic frameworks could elegantly be realized with either intrinsic backbone properties of sequentially elongated phenylacetylene dendrimers[123] or regiospecific complexation[124] and, in some cases, coordination chemistry.[47,48]

I am convinced that if exceptional performance is revealed and efficient and modular syntheses are found, more sophisticated dendrimers incorporating a functionalized interior will enjoy a bright future and certainly play a vital role in the creation of the next generation smart materials for tomorrow's technologies.

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