Dendrons on insoluble supports: synthesis and applications†‡

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The range of composite materials, integrating insoluble organic or inorganic solids and fragments based on dendritic architecture, has been expanded considerably during the last decade. Though the dendritic parts of these hybrids often constitute only a minor portion of the total volume, these components can dramatically alter the properties of the support, imparting new features and functions on the materials. In most cases, organic or metalloorganic dendrons are tethered through their focal point to silica, polystyrene, or other insoluble support, and the formed hybrid materials are used as synthetic intermediates, high-loading supports for solid-phase synthesis, heterogeneous catalysts, and stationary phases in separation processes. This *perspective* surveys the different types of such materials, both from the synthetic and applicative points of view.

1 Introduction

Dendrimers and dendrons, highly branched and ordered oligomers, offer—in addition to their aesthetic beauty—a variety of interesting architecture-dictated properties for a wide range of applications.[1] These properties include high degree of structural control, well-defined shape, molecular weight and size, multivalency, high loading and proximity of the peripheral groups, and specific, isolated microenvironment in the interior.

Among the various materials, fully or partially based on the dendritic architecture, the share of hybrids composed of dendritic molecules and insoluble organic or inorganic support has notably increased during the past decade. These composite materials are used today in chemistry, material sciences, biology and medicine for such applications as synthesis, catalysis, chromatographic separation, drug design and vaccine development. Whereas the dendritic fragments of these materials constitute usually only a minor part of the total volume, these components can significantly alter the support properties, imparting entirely new features and functions on the hybrid composites.

There are a number of modes for conjugation of the dendritic moiety to a support. Dendritic wedges can be coupled to the support through the focal point or through the peripheral functionalities, whereas dendrimers are usually immobilized through the peripheral functional groups (Fig. 1).[2,3] In this *perspective*, we choose to focus on the dendritic structures branching outwards from the support (*i.e.*, hybrid materials in which the dendrons are connected to the support *via* their focal point) (Fig. 1(a)).

In this article, we will first discuss the synthetic approaches and sequences that lead to such architecture and some of the properties of the formed hybrids. Afterwards, we will review the applications of these materials. A number of earlier review articles surveyed some of the topics that are brought together and summarized in this *perspective*.[4]

2 Synthesis

2.1 General synthetic schemes

The materials of the chosen architecture can be assembled through the synthesis of the dendrons in solution, followed by

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Kerem Goren was born in 1984. She studied chemistry at Tel Aviv University and accomplished her BSc degree cum laude in 2006. She then started PhD studies in the group of Dr Moshe Portnoy, working on supported dendritic organocatalysis.

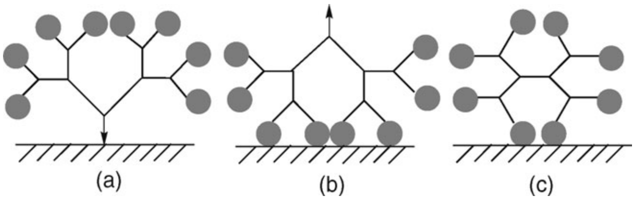


Fig. 1 Possible modes of coupling dendritic fragments to support. Dendrons coupled through the focal point (a) or the peripheral groups (b). Dendrimers coupled through the peripheral groups (c).

their post-synthetic immobilization on the support through a reactive group at the focal point. Alternatively, the hybrid structure can be constructed *via* stepwise growth of the dendron on the support, applying the technique of solid-phase synthesis. The latter approach is used in the majority of the cases and is the leading route to most dendritic motifs used for the dendronization of insoluble supports.

2.1.1 Solid-phase synthesis of dendrons. Solid-phase synthesis of dendrons is mostly carried out on polystyrene, polyacrylamide or silica supports. While in solution dendrons and dendrimers are assembled *via* both divergent and convergent routes, the former is much more suitable for the synthesis of polymer-supported dendrons and most such systems are indeed assembled *via* the divergent approach (Scheme 1).[1,5] In solution, the divergent approach suffers, particularly for higher generations, from incomplete conversion at the growth step and the difficulty in purifying "perfect" dendrimers from similar defective structures. The technique of synthesis on solid support (a.k.a. solid-phase synthesis) has a number of inherent advantages over orthodox solution synthesis.[6] Two of the advantages—the possibility to drive the reaction to completion using a large excess of soluble reagents and the ease of separation/purification—are used to reduce or entirely eliminate the aforementioned obstacles in divergent solid-phase dendron synthesis. Many of the reported synthetic schemes for the solid-phase dendron synthesis are characterized by very high conversions at each step and high homogeneity of the dendritic grafts.

In a single report, one of the first, dealing with solid-phase dendron synthesis, Moore and co-workers used a convergent approach.[7] According to this strategy, the assembly of each dendron generation on support is followed by the dendron cleavage and coupling of the cleaved dendritic wedge to the resin-bound branching unit, thus forming the next generation dendron (Scheme 2).

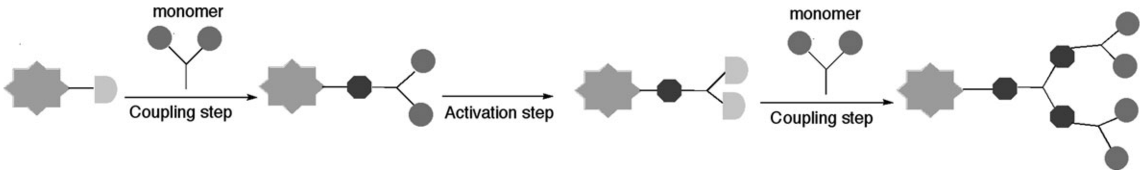
A few years later, again in a single report, a combined divergent/convergent strategy was introduced by Wang and co-workers.[8] According to this approach, generation assembly is followed by the division of the resin into two portions. Dendrons of the *n*th generation are cleaved from one portion (as in the convergent approach) and their focal point is covalently attached to the activated termini of the supported dendrons of the second portion, thus rapidly forming the generation 2*n* (Scheme 3). Although conceptually elegant, the divergent/convergent approach, as well as the convergent strategy, may suffer from the same characteristic feature of solid-phase synthesis that constitutes an advantage for the divergent approach—the need to use a large excess of soluble reagents for each synthetic step. Accordingly, the cleaved dendritic wedges, designated for reassembly on the resins, must be produced in large amounts. This demands a very efficient and high purity synthesis and the use of relatively high loading on the support.

Moshe Portnoy studied organometallic chemistry and catalysis in the Weizmann Institute of Science under the guidance of Prof. D. Milstein. Upon receiving his PhD degree in 1994, he joined the group of Prof. I. Willner in the Hebrew University of Jerusalem for postdoctoral study. In 1995 he received a Rothschild postdoctoral fellowship and moved to the Stanford University to study Ru-catalyzed organic reactions with Prof. B. M. Trost. In 1997, he returned to Israel to start his independent career at Tel Aviv University. His research interests include the synthetic methodology for solid-phase synthesis, catalysis and dendrimers. Since 2000, his group has been actively involved in preparing and studying new dendritic structures on solid supports and investigating supported dendritic catalysts. Dr Moshe Portnoy is a recipient of the Allshwang Award administered by the Israel Science Foundation.

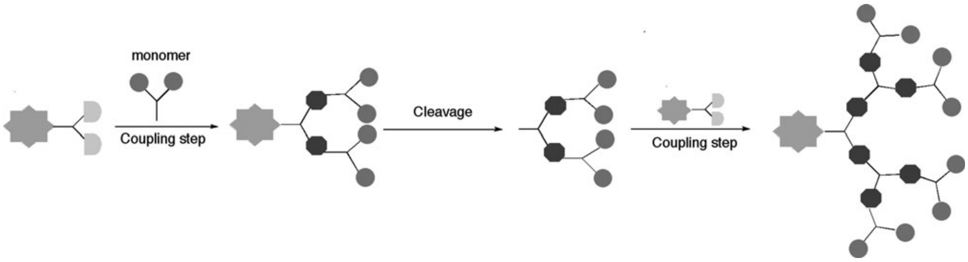
2.1.2 Attachment of dendrons pre-synthesized in solution. As aforementioned, in a few cases dendrons have been prepared in solution and only thereafter coupled to the support (Scheme 4). The hybrid materials, prepared *via* this route, were mostly assembled on silica and gold support. Though only some of these dendrons were prepared by the convergent route, the last step, immobilization on support through the focal point, is conceptually the same as the last step of the convergent synthetic approach in solution.[5] Accordingly, some of the authors using the post-synthetic dendron assembly on a support, name such a synthetic route "convergent". In order not to confuse this approach with the one introduced by Moore and based solely on solid-phase synthesis,[7] we avoid using the term "convergent" for the post-synthetic immobilization technique.

2.1.3 Hyperbranched polymers grafted onto solid support. Conceptually related to dendronized supports are supports grafted with irregular hyperbranched polymers ("cousins" of dendrons).[9] Although less ordered and uniform than dendrons, such polymers usually reach higher formal generation and benefit from an easier preparation. Though beyond the scope of this *perspective*, the hybrids formed by this technique are structurally very similar to dendronized insoluble materials. In fact, some of the dendronized supports reported during the past decade incorporated actually highly branched grafts better described as hyperbranched polymers, rather than perfectly built dendrons (see subsequent sections 2.3 and 2.9).

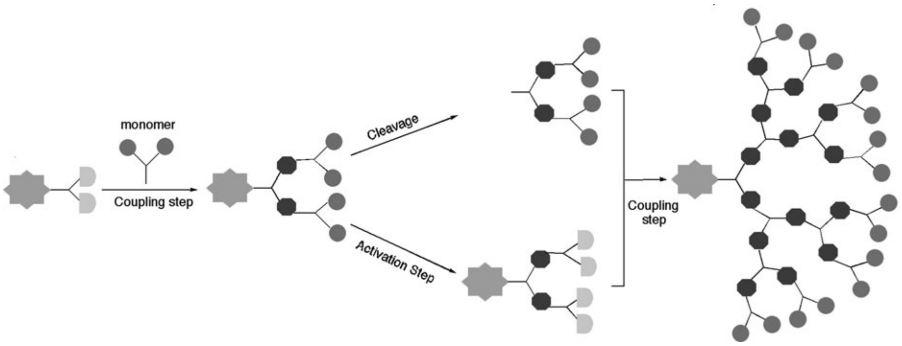
The technique of graft-on-a-graft is similar to the divergent approach for dendrimer growth on surfaces,[9a] whereas the



Scheme 1 The divergent approach to dendron assembly on solid support.



Scheme 2 The convergent approach to dendron assembly on solid support.

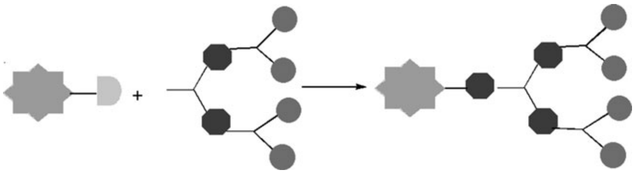


Scheme 3 The divergent/convergent approach to dendron assembly on solid support.

more powerful and fast—but relatively unexplored technique—is surface-initiated polymerization. The latter is mostly based on strained ring opening polymerization. It was applied recently by Park and co-workers and Linden and co-workers for hyperbranched poly(ethyleneimine) grafting of silica, silicon and glass using aziridine monomer and for grafting of hyperbranched polyglycerol on silica (Huck and Khan) and on polystyrene (Haag and co-workers) using glycidol monomer.[10,11] Polycondensation from the aminopropyl silica using 2,2-bis(hydroxymethyl)propionic acid monomer was recently carried out by Liu.[12] As in the case of dendrimers, hyperbranched polymers, prepared in solution, can be immobilized on a support after their synthesis.

2.2 Preparation of polyamide dendrons

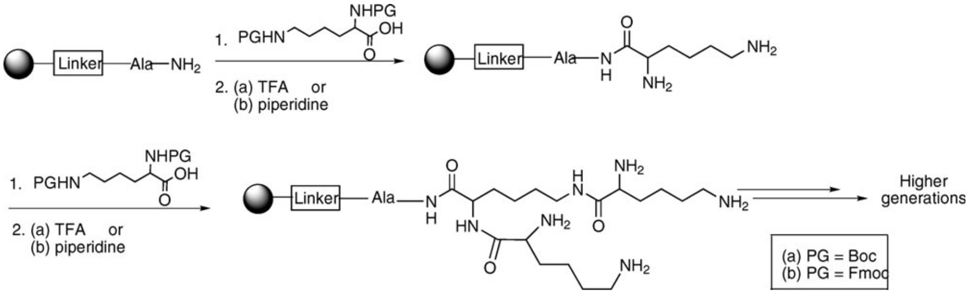
Many dendrons immobilized on insoluble support are, in fact, peptides or related structures. Three recent reviews extensively surveyed peptide dendrimers, both soluble and support-bound.[13]



Scheme 4 Post-synthetic immobilization approach to preparation of dendronized supports.

2.2.1 Polylysine dendrons. The most prominent of the support-bound peptidic dendrons is polylysine. The synthesis of up to tenth-generation dendritic polylysine was patented in 1981 by Denkewalter *et al.*,[14] but this structures remained largely unexplored until the pioneering reports of Tam and co-workers, published in 1988.[15] The dendrons were prepared on phenylacetamidomethyl (PAM) polystyrene with a β-Ala spacer by a divergent approach through a conventional solid-phase peptide synthesis (SPPS). Although based on a non-symmetrical monomer, these structures are true dendrons and were prepared to the third (and later the fourth) generation. The major emphasis in these reports was on the application; the novelty of the synthetic concept and the dendritic nature of the polylysine were only recognized latter.[16]

Polymer-bound polylysine dendritic cores have been widely used as synthetic intermediates and, accordingly, a number of schemes for their synthesis have been reported. Initially the dendrons were prepared *via* the Boc SPPS method, using a Boc-Lys(Boc)-OH building block (Scheme 5(a)).[15,17] Subsequently, a number of groups prepared the same dendrons *via* the Fmoc SPPS method, using a Fmoc-Lys(Fmoc)-OH building block (Scheme 5(b)).[18] In order to distinguish between the α- and ε-terminal amine groups of the dendron, the Boc strategy with a Boc-Lys(Fmoc)-OH building block in



Scheme 5 Synthetic scheme for the preparation of polylysine dendrons on solid support.[15,18]

the last coupling, was applied.[19] Tentagel™ (polyethylene glycol (PEG) grafted polystyrene) and polyethylene glycol-polyacrylamide copolymer (PEGA) resins, equipped with a range of linkers, have also been adopted as supports for polylysine synthesis.[20]

A variety of conjugate types incorporating polylysine dendrons have been generated on these supports. The first structures synthesized were those with peptides decorating the dendron periphery (Fig. 2, **I**).[15] Later peptides were introduced between the support and the dendritic focal point (Fig. 2, conjugates of types **II** and **III**).[21] In later works, carbohydrates were introduced as peripheral functionalities on the dendrons (leading to conjugates of types **IV** and **V**, Fig. 2).[20*a*,*c*]

Though the SPPS is, by far, the leading route to polylysine-dendronized supports, Smith and co-workers published in 2002 a convergent synthesis of up to third-generation polylysine dendrons in solution, followed by their immobilization on silica.[22] To our knowledge, this is the only example of a polylysine-dendronized silica support.

2.2.2 Polyglutamic acid dendrons. Another natural amino acid, L-glutamic acid, has also been used as a branching monomer unit in construction of the support-bound dendrons. Polyglutamate dendrons were prepared by Mitchell and co-workers in solution *via* a convergent approach up to the fourth generation.[23] Following the deprotection of the focal-point amine, the dendrons were reacted with succinic anhydride and then with aminopropyl-functionalized silica to form dendronized support (Scheme 6).

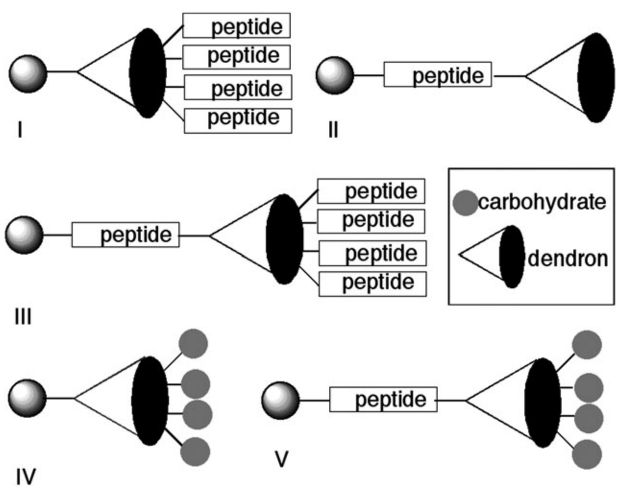
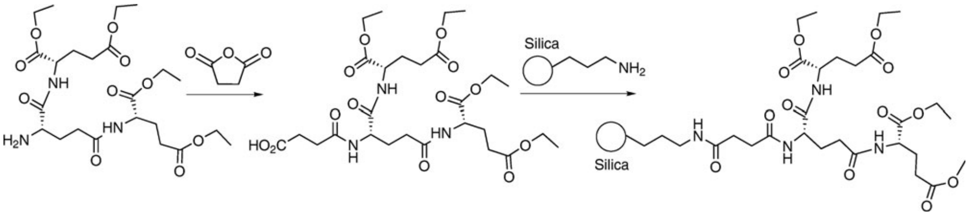


Fig. 2 Various types of conjugates generated on solid support with polylysine dendrons.

2.2.3 Dendrons combining natural and artificial amino acids. Of the naturally occurring amino acids only lysine and glutamic acid have been used as branching units in the solid support-bound dendrons; however a variety of other natural amino acids have been used for the construction of the dendron monomers. In a series of publications, Reymond and co-workers reported the preparation of peptide dendrimers *via* the straightforward divergent synthesis using the Fmoc SPPS technique on polystyrene or Tentagel supports. The first series of the peptide dendrons (dubbed "1.1.1" dendrons) were assembled on Rink amide polystyrene, using 2,3-diaminopropionic acid (DAP), (1,3-diaminoisopropyloxy) acetic acid, bis(aminomethyl)acetic acid or 3,5-diaminobenzoic acid as branching units.[24] The naturally occurring amino acids (mainly histidine, serine and aspartic acid, but also alanine, phenylalanine, threonine and others) connected the branching diamino acids, whereas cysteine was located near the focal point (Fig. 3(a)).

The second series of Reymond's peptide dendrons (dubbed "2.2.2.2" dendrons) were assembled on Tentagel with dipeptides (mostly His-Ser diad, but also other sequences) connecting the artificial branching units (DAP diamino acid).[25] Up to fourth-generation dendrons based on this design were prepared (Fig. 3(b)). These dendrons were also prepared in combinatorial format yielding a 65536-membered library of third-generation dendrons *via* "split and mix" approach.[25*a*,*b*]

A similar design, with artificial amino acids as branching units, separated by linear peptide segments, was applied in the synthesis of dendritic peptides on polystyrene by Albricio, Giralt, Royo, and co-workers (*e.g.* the synthesis in Scheme 7).[26] Mostly *cis*-4-amino-L-proline and imidazolidine-2-carboxylic acids were used as the branching units. Linear penta-proline segments connected the branching units into the dendritic structure. The dendrons were assembled by a Boc SPPS technique. The synthesis followed, in general, the divergent approach, though in some cases linear segments or even branched monomeric modules were prepared separately on the support. These units were cleaved and reassembled on the support into larger structures, thus imparting onto the synthesis some characteristics of the convergent approach. Introduction of the flexible Gly residue at the N-terminal position of the monomeric building block (*i.e.*, replacing the $(Pro)_5$ spacer connecting the branching amino acids by Gly $(Pro)_5$) resulted in a more efficient synthesis with a higher level

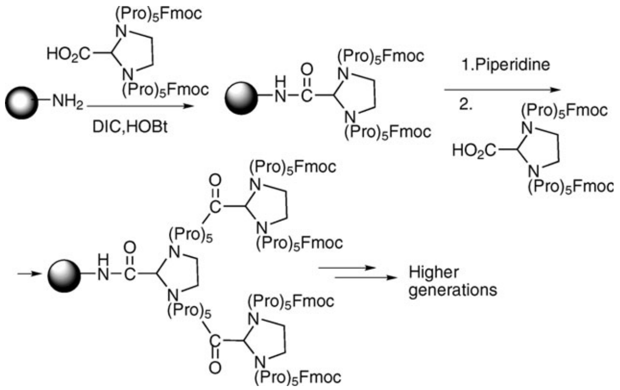


Scheme 6 Synthetic scheme for the preparation of polyglutamate dendrons on solid support.[23]

of purity, enabling construction of dendrons up to the fourth generation.[26d] While preparing the polyproline dendrons, Albericio and Royo observed fragility of the beads, suggested that the bead breakdown resulted from the "saturation of solid support" and proposed calling the phenomenon "stress of the bead".[27]

Dendrons based on the already mentioned 3,5-diaminobenzoic acid were among the first dendron types prepared on solid support. In 1991, Frechet and co-workers reported the preparation of polyamido dendrons on Merrifield polystyrene using Boc-protected 3,5-diaminobenzoic acid or its bis-β-alanine adduct as monomers (Scheme 8).[28]

Because of the low efficiency of coupling, the synthesis of the dendron based on the shorter unit stalled at the third generation (19% coupling yield only). With the second monomer, possessing elongated branches and somewhat more reactive terminal amine functionalities, the efficiency of the synthesis was improved and it proceeded with modest 70–80% coupling yields up to the fourth generation. However, it was not possible to proceed further. The cleavage of the dendritic molecules followed by size exclusion chromatography (SEC) revealed a broad molecular weight distribution and confirmed the non-uniform nature of the dendrons of higher generations. According to the authors, the incomplete couplings may be a result of the difficult coupling chemistry chosen for the propagation step, the restricted access of the reagents to the propagation sites on the polymer, or the steric crowding of the peripheral units frequently observed in dendrimer chemistry.



Scheme 7 Synthetic scheme for the preparation of polyproline dendrons on solid support.[26d]

Starting from 1999, Alper, Arya, and co-workers developed a variety of support-bound dendrons. Among other systems, polyamide dendrons, based on 3,5-diaminobenzoic acid branching units, were prepared to the third generation on a polystyrene support (Rink amide MBHA resin) *via* the

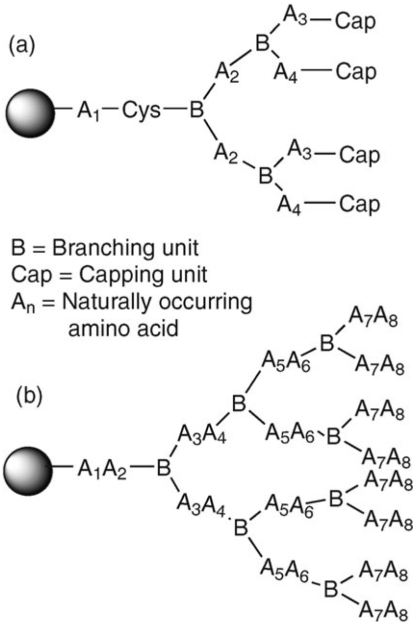
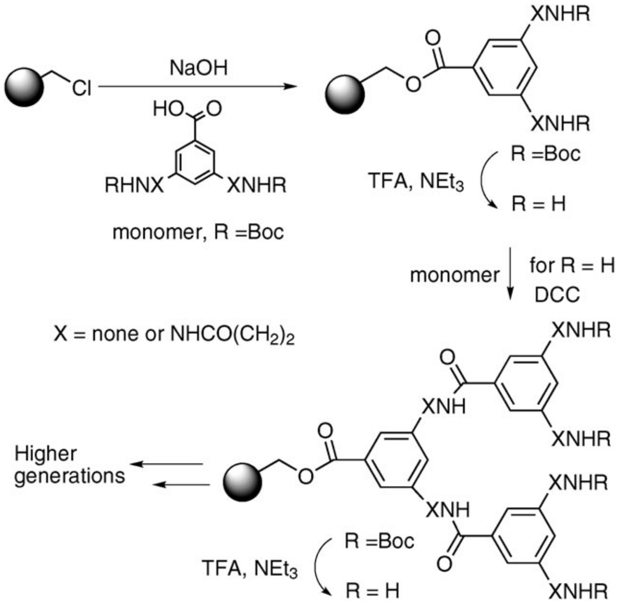


Fig. 3 Peptide dendrons prepared by Reymond and co-workers on solid support.[24,25]



Scheme 8 Synthetic scheme for the preparation of 3,5-diaminobenzoic acid-derived polyamide dendrons on solid support.[28]

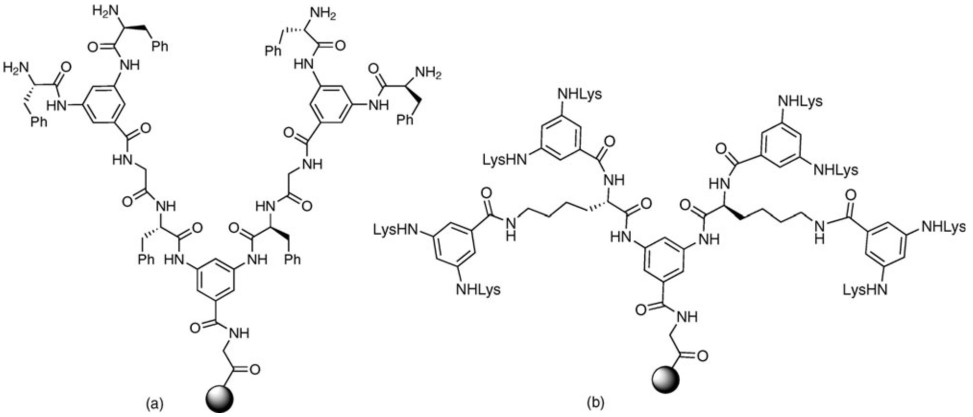


Fig. 4 Polyamide dendrons prepared by Alper and co-workers on polystyrene support.[29]

divergent, Fmoc chemistry-based approach.[29] In the first of the reported dendron types, the branching amino acid moieties were connected by the Gly-Phe dipeptide spacer (Fig. 4(a)).[29a] In the more advanced version of these polymer-bound dendrons, the repeating motif was Lys_2-3,5-diaminobenzoic acid-Gly; thus, an additional branching point was added and each generation provided an AB_4-type unit (Fig. 4(b)).[29c]

2.2.4 Dendrons made of artificial amino acids. A number of groups have reported preparation of support-bound dendrons based on trifurcated branching units. Chan and co-workers used a non-symmetric triamino acid, 4-azalysine, to prepare (*via* divergent growth) first- and second-generation peptide-like dendrons on polystyrene using Boc-chemistry (Fig. 5).[30] The dendrons prepared divergently by Lee and co-workers on Tentagel and PS-co-PEG-NH_2 resins are based on symmetric, TRIS-derived triamino acid monomer and were constructed up to the formal fifth and seventh generations, respectively (Fig. 6).[31] Since only the spectrophotometric determination of Fmoc release from the molecules, attached to the dendritic termini, was used to deduce the efficiency of dendron growth, the characterization of the dendrons was rather limited and no indication as to the dendron homogeneity was provided.

Silica-bound triple-branched dendrons based on amino triacid monomer were prepared by Newkome *et al.*[32] These dendrons were assembled divergently up to the third generation in solution and included an isocyanate functionality at the focal point (Scheme 9). Reaction of these molecules with aminopropyl-functionalized silica yielded dendronized support with a urea functional group connecting the dendrons to the spacer.

Publications from a few groups have described the preparation of other amide bond-linked dendrons on polystyrene, glass and polypropylene support.[33] These were based on diamino-, triamino- or pentaamino-carboxylic acid monomeric units.

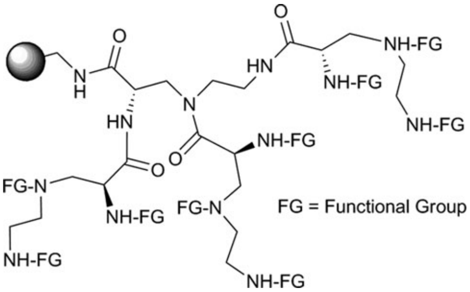


Fig. 5 Supported polyamide dendrons, derived from 4-azalysine.[30]

2.3 Preparation of polyamidoamine (PAMAM) dendrons

Thus far, all the dendritic structures presented in this review were constructed *via* the amide-bond forming reactions. A somewhat different synthetic strategy led to the synthesis of the polyamidoamine (PAMAM) dendrons on insoluble supports. In 1997 Bradley and co-workers introduced the solid-phase synthesis of PAMAM dendrons on organic polymer support. Initially, these dendrons were prepared on Tentagel up to the fourth generation (although the third generation was considered by the authors to be the optimal for synthetic

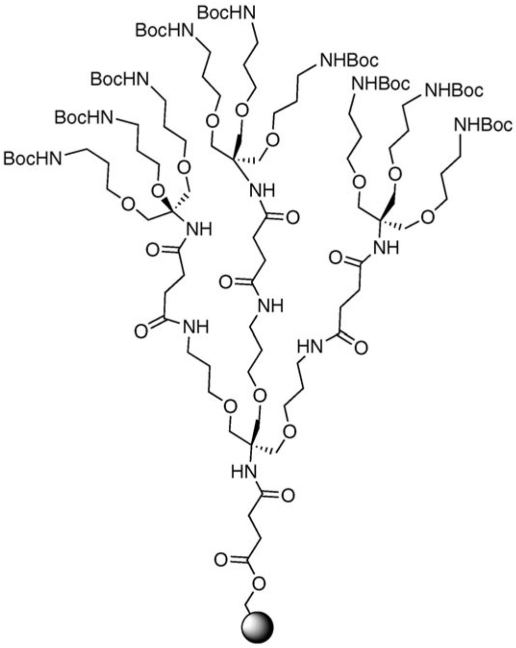
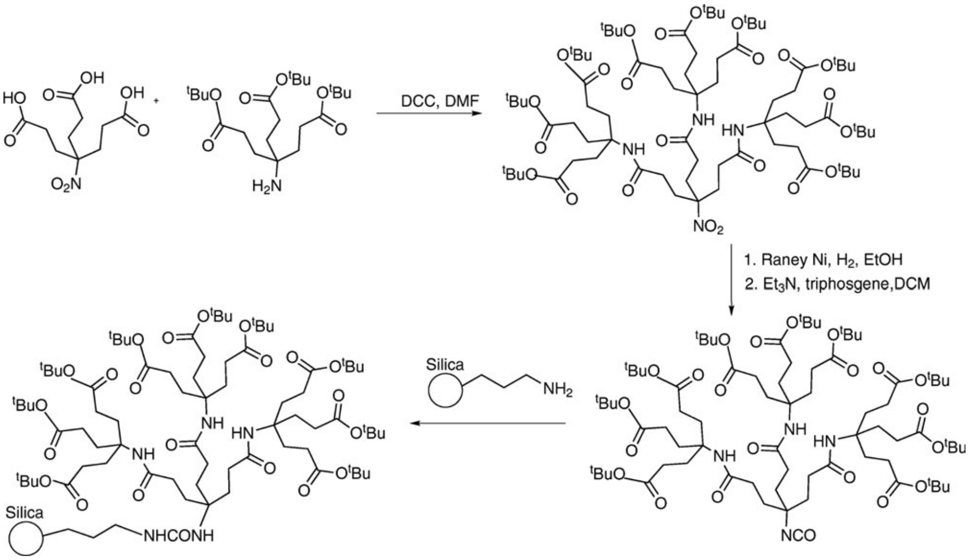


Fig. 6 Supported polyamide dendrons prepared by Lee *et al.*[31]

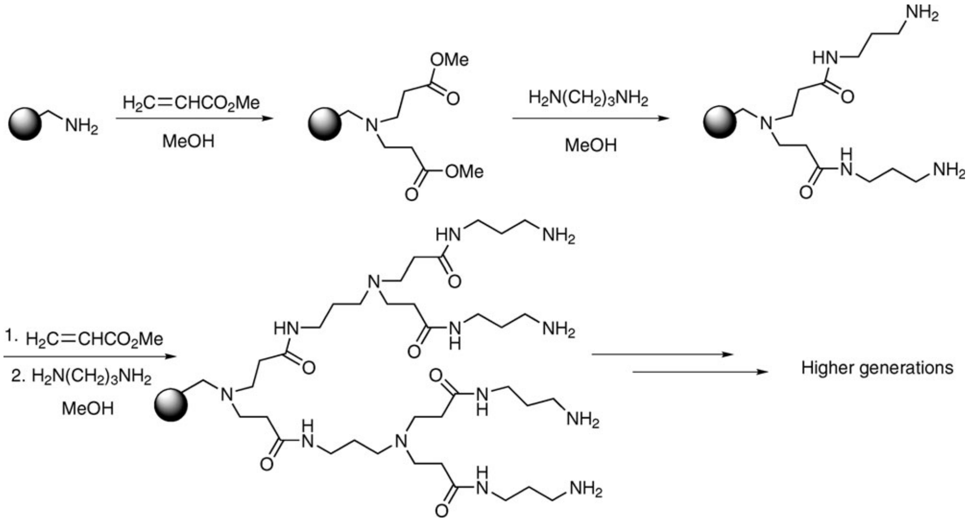


Scheme 9 Synthetic scheme for the preparation of the Newkome-type polyamide dendrons on solid support.[32]

purposes) (Scheme 10).[34] The assembly of the dendrons followed the divergent synthetic strategy developed by Tomalia *et al.* for PAMAM dendrimers in solution and was based on alternating steps of double Michael addition of terminal primary amines to methyl acrylate and aminolysis of the formed terminal esters with α,ω-alkanediamines (*e.g.*, 1,3-propanediamine).[35] Later, the approach was extended to PAMAM dendrons on polystyrene beads equipped with a short PEG spacer.[36] Basso and Bradley investigated the issue of unwanted site–site interactions on generation 3 (G3) PAMAM-dendronized Tentagel during solid-phase synthesis.[37] Although the G3-dendronized support proved somewhat more susceptible than the parent Tentagel to this type of side reactions, it was demonstrated that for reaction at ambient temperature, under reagent-excess conditions standard for solid-phase synthesis, the site–site interaction problem is negligible.

PAMAM dendrons were also prepared on silica, as early as 1998, by Tsubokawa *et al.* and by many other groups, among them those of Arya and Alper, Kunitake, Rhee, Bu and Qiu.[38–43] Usually, 3-aminopropyl-functionalized silica was employed as the parent support. In most studies, ethylenediamine-based PAMAM was constructed *via* the approach developed in solution by Tomalia *et al.* and pioneered on solid support by Bradley and co-workers.[34–36]

Using ultrafine silica (Tsubokawa *et al.*),[38a] and later regular amorphous silica (Rhee *et al.*; Alper *et al.*),[39c,d,41] the researchers examined the obtained content of the amino group (or other terminal group) per gram of silica (or total mass) and compared it with theoretical values. They found that the observed values were much lower than the theoretical ones and that the ratio of the two values declined rapidly as the generation increases. Thus, when second-generation dendrons were constructed on particles with an initial amine content of



Scheme 10 Synthetic scheme for the preparation of PAMAM dendrons on solid support.[34]

0.9 mmol/g SiO_2, the observed value was only 45% of the theoretical one, whereas for the fourth generation, it decreased to about 16%.[38a,41] Remarkably, when dendrons were constructed on silica with a lower initial loading of the amino groups, the deviation of the observed values from the theoretical ones was smaller and the decline of the ratio of the two values as a function of generation was less steep.[38a,41,42a]

The observed deviation most likely resulted from incomplete propagation reactions, which are caused by the increased steric hindrance in the pores and on the surface of the silica, accompanying the dendrimer growth. IR studies have supplied evidence of an incomplete amidation step.[38a] Bu *et al.* investigated the reaction kinetics of propagation of PAMAM dendrons on solid spherical silica gel.[42b] Their findings point to steric hindrance during the Michael addition step and a site–site cross-linking reaction, occurring during the amidation step, as the mechanistic reasons for structural defects of the dendrons. As in the previously described studies, data from this study demonstrated that the preparation of dendrons on a support with a reduced loading of the initiator amino groups proceeds with a remarkably enhanced efficiency and produces more perfect dendritic structures than synthesis on support with a higher initial loading. Zweni and Alper demonstrated that, indeed, the efficiency of the PAMAM dendron synthesis on silica decreases with the increase in the length of the diamine involved in the synthesis.[39d] This phenomenon can be explained by a higher percentage of the cross-linking side reaction accompanying lengthening of the diamine. Overall, the characterization results suggest that the PAMAM preparation on silica produced, at least in the earlier studies, a hyperbranched polymer rather than a perfect dendritic structure.[38a,39c]

A recently published detailed analysis of the PAMAM-on-silica synthesis and properties by Kunitake and co-workers pointed out that not only the generation and initial loading of the amino sites, but also the propagation step parameters, such as the reaction time and temperature, define the degree of branching and perfection of the dendrons.[40b] The structures with the highest degree of perfection seem to be those prepared at low temperatures with long reaction times and low loading of amine initiation sites.

An additional important factor, affecting the efficiency and perfection degree of the PAMAM dendron growth, is the nature of the support. In the earlier studies described above, amorphous silica with broad pore size distribution and average pore size of 6 nm was employed. A recent series of articles by Alper, Sayari, and co-workers described preparation of dendrons on a periodic MCM-41 silica (pore size 6.5 nm), a pore-expanded MCM-41 silica (pore size 10.6 nm) and large-pore Davisil silica (pore size 18 nm).[44] In-depth characterization of the dendronized silica, which included solid-state NMR, FTIR, nitrogen adsorption studies, elemental analysis and thermogravimetry, showed that the dendrons are grown inside the silica pores, completely filling them as the third or fourth generation is assembled. The physical limit on the dendron size, dictated by the pore dimension and shape, limits the propagation of the dendritic oligomers. Yet, for the pore-expanded silica an efficient synthesis of the fourth-generation dendrons with an overall yield of 71% could be achieved.[44b] Improvement of the PAMAM preparation process through quaternary ammonium salt catalysis was recently demonstrated by Qiu and co-workers on mesoporous silica.[43]

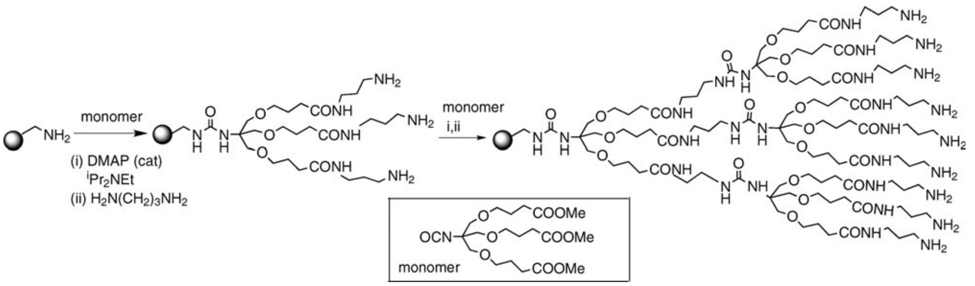
The PAMAM grown on silica can be used as is,[34,36,38a,40] or with small organic or organometallic moieties attached to the periphery of the dendrons.[38b,39,41,42a,44] Alternatively, a polymer (*e.g.*, vinyl polymer) can be grafted on the dendron termini, thus forming core–shell particles with the dendritic interface between the inorganic core and the organic outer shell.[38c]

In a number of cases PAMAM dendrons were also prepared from other polymer particle cores, such as chitosan, zirconia–urea–formaldehyde resin, silica-coated magnetite, and carbon nanotubes.[45] Like the silica support (*vide supra*), at least in the case of the chitosan, the theoretically predicted propagation of the dendrons was not achieved, presumably due to the steric hindrance in the support pores.

A different type of polyamidoamine dendron with a thiol group at the focal point was prepared in solution using iminodiacetate and bromoacetyl bromide submonomeric units.[46] Thereafter, these dendrons were immobilized on a gold surface.

2.4 Preparation of polyurea dendrons

Triply branched polyamidourea dendrons were developed by Bradley and co-workers in 2000 (Scheme 11).[47] The TRIS-derived monomer, an AB_3-type symmetrical isocyanato-triester, was prepared in three steps. The dendrimer growth involved attachment of the monomer to a resin-bound primary amine (thus converting the isocyanate into urea) followed by ester reaction with a propane-1,3-diamine spacer, forming an amide and restoring a primary amine terminus. The synthesis was monitored by both on-resin and cleavage



Scheme 11 Synthetic scheme for the preparation of polyamidourea dendrons on solid support.[47]

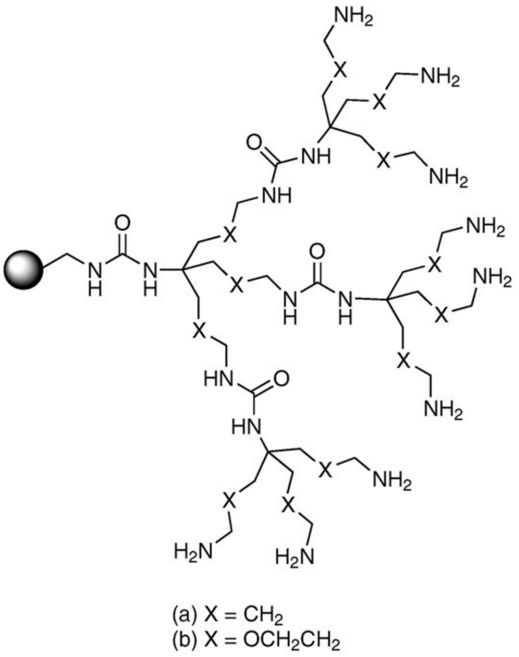
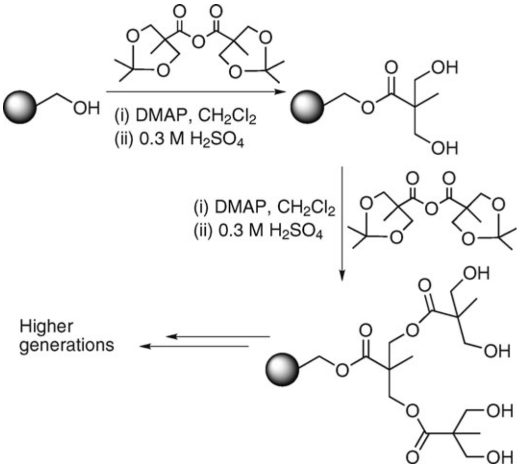


Fig. 7 Polyurea dendrons on solid support.[48]



Scheme 12 Synthetic scheme for the preparation of polyester dendrons on solid support.[49]

analysis, thus ensuring clean and uniform growth of dendritic wedges. Although the dendrons were constructed on aminomethyl polystyrene or diamine linker-bearing polystyrene only to the second generation, their triply-branched nature and the large size of the starting resin beads resulted in dendronized beads with a very high loading of the terminal groups (up to 230 nmol per bead).

To avoid possible macrocyclization during ester displacement by a diamine (a step also common to PAMAM synthesis), alternative monomers for preparing urea-bridged triply-branched dendrons were prepared and used.[48] The dendrons were assembled on solid support, up to the third generation, from Boc-protected monomeric triaminoisocyanates *via* a urea-connector formation, followed by deprotection of terminal amines (Fig. 7). The assembly took place on polystyrene as well as Tentagel resins with an up to 19-fold increase in the loading of the terminal groups.

The study of the properties of these dendronized beads revealed that dendronization increases the bead fragility. The attempts to assemble third-generation dendrons on large polystyrene beads (250–300 μm) resulted in breakage of the beads, as a result of isobutylene and CO_2 gas bubble evolution during the deprotection step. Increasing the length of the monomeric arms improved the situation only marginally. The authors assumed that electronic repulsion between the dendrimers (positively charged under these conditions) resulted in the rupture of the polystyrene matrix. These results correlate with the previously mentioned "stress of the bead" observed by Albericio and co-workers.[27] Replacement of the Boc protecting group by the Dde group enabled deprotection under milder conditions, without any gas evolution, thus improving the quality of the formed dendronized beads.[47b]

2.5 Preparation of polyester dendrons

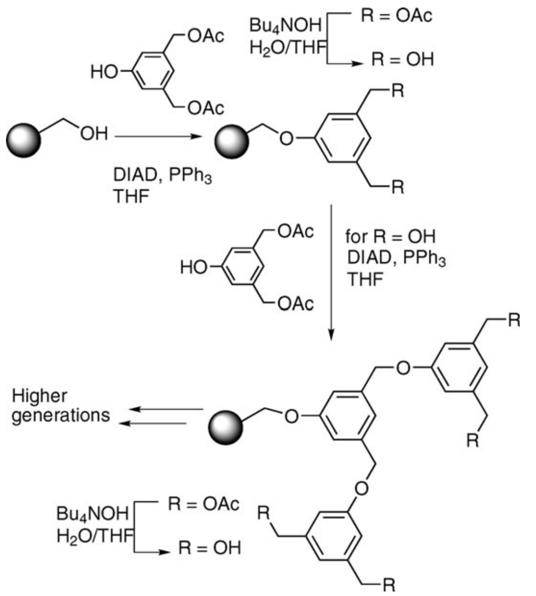
Fréchet and co-workers demonstrated the synthesis of polyester dendrons on solid support.[49] These dendrons, based on 2,2-bis(hydroxymethyl)propanoic acid units, were assembled up to the fourth generation on poly(2-hydroxyethyl methacrylate-co-ethylene dimethacrylate) resin and decorated with chiral proline derivatives. Two methods for preparation of these materials were reported. The solid-phase divergent approach (Scheme 12) yielded polymer with higher loading but a less precise architecture than the second approach. The second approach, the divergent synthesis of the dendrons in solution, followed by the focal point deprotection and then attachment to the solid support, led to well-defined structures on the polymer, but relatively low loading.

2.6 Preparation of polyether dendrons

The supported dendritic molecules, described thus far, have all been based on carbonyl-containing connecting groups (amides, ureas, esters). These groups are vulnerable to a variety of reaction conditions (reductive, hydrolytic, nucleophilic) and, therefore, are unsuitable for a wide range of synthetic and catalytic applications. Moreover, the coordinating nature of the amido group can affect the functioning of the constructs in some applications (*e.g.*, metal coordination and catalysis). For these reasons alternative dendritic motifs were considered.

Ethers are chemically and coordinatively more inert than amides. Indeed, Fréchet-type polyether dendrimers prepared in solution demonstrate a broad spectrum of chemical and coordinative compatibilities.[50] Accordingly, polyether dendron synthesis on solid supports was developed, initially by Bradley and co-workers and later by Portnoy and Dahan.[51,52] Instead of the 3,5-dihydroxybenzyl alcohol derivatives used in the soluble Fréchet-type dendrimers, a more SPOS-suitable 3,5-bis(hydroxymethyl)phenol unit was conceived as a building block for the dendron construction.

The first reported synthesis of the polystyrene-supported aryl benzyl ether dendrons was based on a 3,5-bis(acetoxymethyl)phenol building block, which was prepared from the



Scheme 13 Synthetic scheme for the preparation of polyether dendrons on solid support by Bradley and co-workers.[51]

commercially available dimethyl-5-hydroxyisophthalate in four steps. Using this building block, Bradley and co-workers constructed the dendrons up to the fourth generation through two repetitive steps (Mitsunobu coupling and ester hydrolysis, Scheme 13).[51]

Adopting an alternative synthetic strategy, Portnoy and Dahan prepared the dendron, again *via* two repetitive steps (Mitsunobu and ester reduction), using the dimethyl-5-hydroxyisophthalate itself without any need for building block preparation in solution (Scheme 14(a)).[52] Although the special betaine reagent imposes very high conversion and purity at the Mitsunobu coupling step of this synthetic scheme, it has to be prepared from costly starting materials and has a limited shelf life.[53] In order to avoid this obstacle, Portnoy and co-workers recently elaborated the synthetic scheme (Scheme 14(b)), adding a third synthetic step during each generation assembly and eliminating the need for Mitsunobu coupling.[54]

The same group recently introduced a tetrafurcated building block that can be incorporated into the dendritic structures.[55] Tetra-, octa- and hexadecaol dendritic grafts were prepared, starting from Wang resin or the aforementioned first- and second-generation polyether dendronized resins (Scheme 15).

The unit is built on hydroxyl-terminated resins in four highly efficient steps: attachment of the aldehyde (or oxidation of the terminal alcohol into aldehyde), Knoevenagel condensation with a malonate diester, Michael addition of the same diester and reduction, that restores the hydroxyl terminal groups. Combining this approach with the aforementioned polyether dendron synthesis, the loading of the terminal hydroxy groups can be increased up to ten-fold compared with the parent Wang resin.

While all the above mentioned support-bound polyether structures have been assembled *via* the divergent solid-phase synthesis, Yu and Guo prepared, *via* the traditional convergent approach in solution, first to third Fréchet-type polyether dendrons, bearing carboxylate at the focal point, and have grafted them onto the aminopropyl-modified nanometer silica.[56] Only a low degree of the amino groups functionalization was achieved by this method.

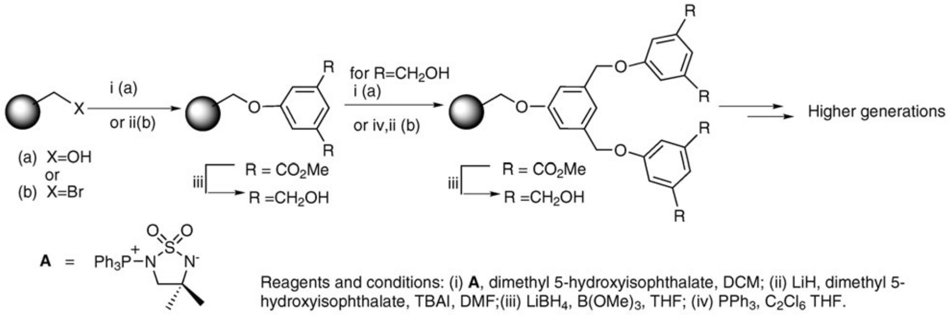
Third-generation Fréchet-type polyether dendrons, bearing at the focal point a long aliphatic chain terminated with thioether, were used by van Veggel, Reinhoudt and co-workers for insertion into the self-assembling thiol monolayers on gold surfaces.[57] The authors also used second-generation polyamidoether dendrons in a similar fashion.[58]

2.7 Preparation of polythioether dendrons

Polythioether dendrons, the sulfur analogues of the poly(aryl benzyl ether) dendrons, were assembled by Portnoy *et al.* to the fourth generation. These dendrons were prepared using the protected thiophenol monomer building block, which can be efficiently synthesized from the hydroxyisophthalate diester in multigram quantities.[59] The deprotection of the thiophenolate performed *in situ* is followed by three steps (similar to those previously described for the polyether dendrons in Scheme 14(b)) for each generation assembly (Scheme 16).[60] Thus far, there is only one example (only in solution) of another polythioether dendritic molecule.[61]

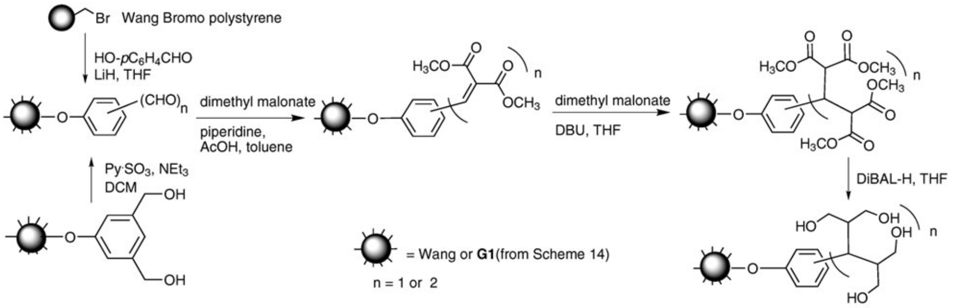
2.8 Preparation of polyamine dendrons

Portnoy and Dahan also prepared polyamine dendrons, analogous to the aryl benzyl ether and thioether dendrons.[4a,62] Although the 5-amino isophthalate diester is commercially available, its nucleophilicity is too weak to enable dendron assembly through a route analogous to those in Schemes 14(b) and 16. Following the attachment of the first module, the

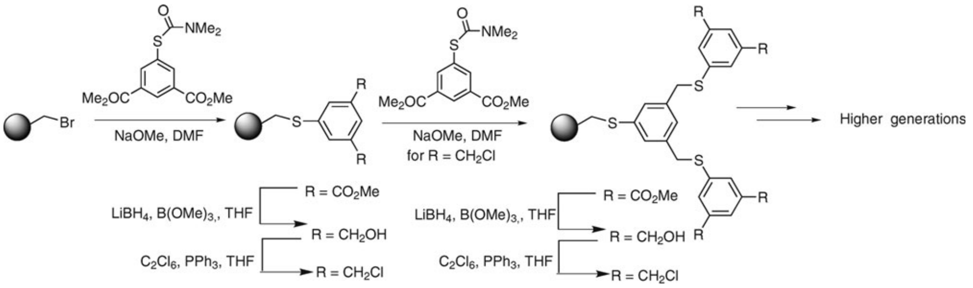


Reagents and conditions: (i) **A**, dimethyl 5-hydroxyisophthalate, DCM; (ii) LiH, dimethyl 5-hydroxyisophthalate, TBAI, DMF;(iii) $LiBH_4$, $B(OMe)_3$, THF; (iv) PPh_3, C_2Cl_6 THF.

Scheme 14 Synthetic scheme for the preparation of polyether dendrons on solid support by Portnoy and co-workers.[52,54]



Scheme 15 Synthetic scheme for the preparation of tetrafurcated polyether dendrons on solid support.[55]



Scheme 16 Synthetic scheme for the preparation of polythioether dendrons on solid support.[60]

growth of the dendron is achieved *via* a repetitive reduction, oxidation and reductive amination sequence (Scheme 17). These poly(aryl benzyl amine) dendrons were assembled divergently to the third generation.

Eilbracht and co-workers developed a synthesis of the aliphatic polyamine dendrons in solution *via* the synthetic sequence that includes tandem hydroformylation/reductive amination of olefins and phthalimide deprotection.[63] The feasibility of such a synthetic approach for solid-phase assembly of aliphatic polyamine dendritic structures was demonstrated when the authors prepared a first-generation dendron on Wang polystyrene.

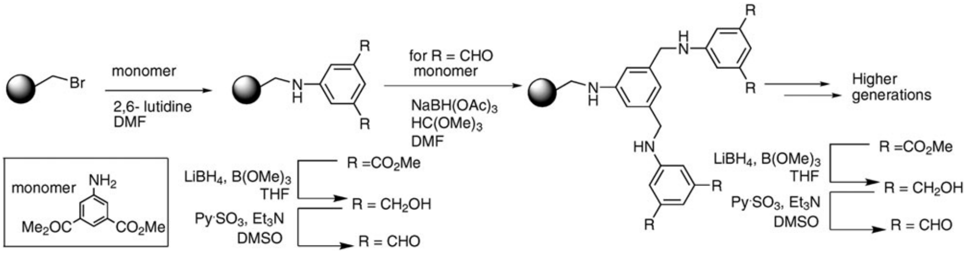
The "classic" poly(propylenimine) dendrons were prepared on silica gel by Liu *et al.* *via* a divergent approach that was based on a repeating sequence of amine Michael addition to acrylonitrile and nitrile reduction (Scheme 18),[64] a route pioneered in solution many years ago by Vogtle and Meijer.[65] Synthesis of fourth-generation dendrons was reported, though the publication lacked the characterization details to support the formation of truly dendritic architecture.

Hydroxyl-terminated polyamine dendrons of the first and second generations were recently obtained on macroporous polystyrene by Qu *et al.*[66] The authors used diethanolamine monomers for the divergent synthesis of the dendrons. The elemental analysis, used for quantification of the dendrimer loading, revealed 80–90% yield for each generation assembly.

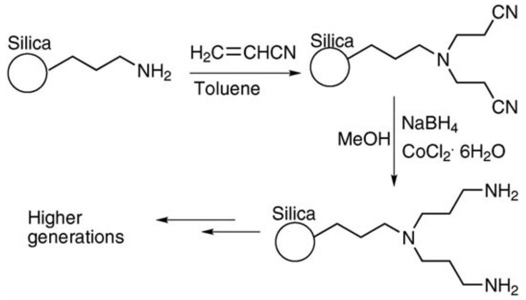
2.9 Preparation of dendrons based on 1,3,5-triazines

A number of research groups exploited use of substituted triazine units, and particularly the stepwise selective substitution pattern of triazine chlorides (*e.g.*, cyanuric chloride), to prepare a range of support-dendron composite materials.[67] Marsh *et al.* prepared first- and second-generation dendrons, assembled divergently from cyanuric chloride and bis(3-hydroxypropyl)amine on Wang polystyrene (Scheme 19).[68] In the first-generation shell two-fold branching originating from the oxy-diaminotriazine units was doubled by the branching of the aliphatic aminodiol spacer.

In the past three years, this synthetic approach was expanded, first by Su *et al.*, who prepared melamine (2,4,6-triamino-1,3,5-triazine) dendrons on silica, replacing the aminodiol spacer by a simple 1,6-hexanediamine.[69] These dendrons were assembled *via* a simple solid-phase divergent approach up to the fourth generation. Similarly, Marsh and co-workers themselves used cyanuric chloride and



Scheme 17 Synthetic scheme for the preparation of polyamine dendrons on solid support.[62]



Scheme 18 Synthetic scheme for the preparation of poly(propylenimine) dendrons on solid support.[64]

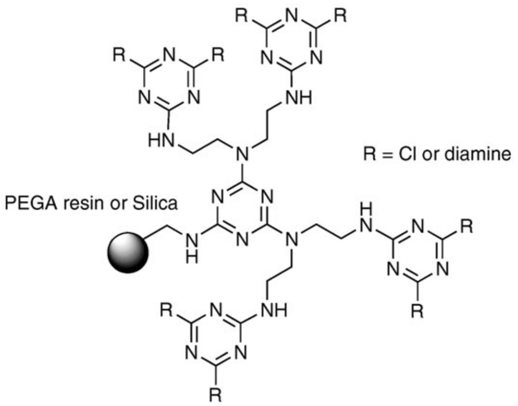


Fig. 8 Polymelamine dendrons prepared by Marsh and co-workers on solid support.[70]

ethylenediamine to prepare up to the third-generation melamine-based dendrons on polystyrene, PEGA and SynPhase resins, as well as silica gel.[70]

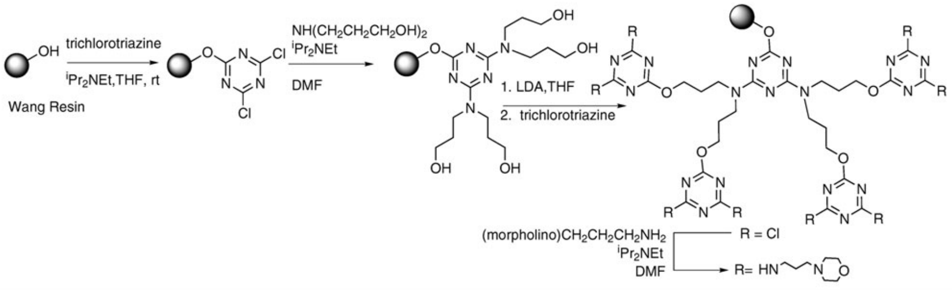
In the same work, it was demonstrated that replacement of a diamine spacer by diethylenetriamine bifurcated building block doubled the degree of branching for each generation, thus forming eight terminal group-bearing second-generation dendrons on PEGA (Fig. 8). The new strategy, which replaced the amino alcohol spacers by di- or triamines, enables more efficient and high-yielding synthesis to be carried out under less restrictive reaction conditions.

Somewhat more rigid melamine-based dendrons were synthesized by Simanek, Shantz, and co-workers, who used piperazine or 4-aminomethylpiperidine, instead of aliphatic straight-chain diamines, to connect the triazine units. Divergent synthesis on SBA-15 mesoporous silica afforded up to fourth-generation dendrons, mostly in the silica pores, forming organic–inorganic hybrids that were extensively characterized (Fig. 9).[71] The characterization included thermogravimetric, elemental and mass spectrometric analysis, IR spectroscopy, as well as nitrogen porosimetry and transmission electron microscopy (TEM). As in the case of PAMAM dendrons,[44] this characterization demonstrated gradual filling of the pores, with the fourth-generation dendrons reaching the ‘‘critical’’ size, as dictated by the pore diameter, beyond which it was not possible to further expand the dendritic structure.

In another study,[72] two approaches for synthesis of the polymelamine dendrons on silica gel were experimentally compared: the divergent solid-phase synthesis and the convergent solution assembly followed by focal point attachment to the support. Dendrons (up to the third generation) preparation was monitored and the hybrid products extensively characterized. Conclusions of the study were very similar to those reported earlier by Frechet and co-workers.[49] The post-synthetic attachment of the dendrons yields highly uniform, architecturally perfect structures, but is limited by the demanding solution synthesis and relatively low loading of the dendron on the support. On the other hand the divergent strategy benefits from the ease and technical simplicity of the solid-phase synthesis and yields higher dendron loading, but suffers from a relatively high degree of the structural defects—hyperbranched polymers are formed on the surface along with the perfect dendrons.

2.10 Preparation of poly(arylacetylene) dendrons

The purely solid-phase synthesis-based convergent and divergent/convergent approaches were used in the mid-1990s by Moore and co-workers and later by Wang and co-workers to prepare poly(phenylacetyene) dendrons on polystyrene.[7,8] Both synthesis used the Sonogashira coupling to assemble the next dendritic shell and MeI-induced cleavage of aryl triazenes for cleavage of the dendritic building blocks from the support (Schemes 20 and 21). Due to the divergent element in Wang's synthesis, the deprotection of the terminal acetylene groups from TMS was required in order to activate the polymer-bound dendrons for the next coupling. On the other hand, Moore's convergent approach was based on permanent ‘‘capping ‘‘of the dendritic termini with 3,5-di-*tert*-butylphenyl groups. The dendrons in both cases were prepared up to fourth generation (third, according to Moore, who used a different generation numbering). In the convergent case, efficient synthesis was reported, demonstrating the feasibility of



Scheme 19 Synthetic scheme for the preparation of 1,3,5-triazine-based dendrons on solid support.[68]

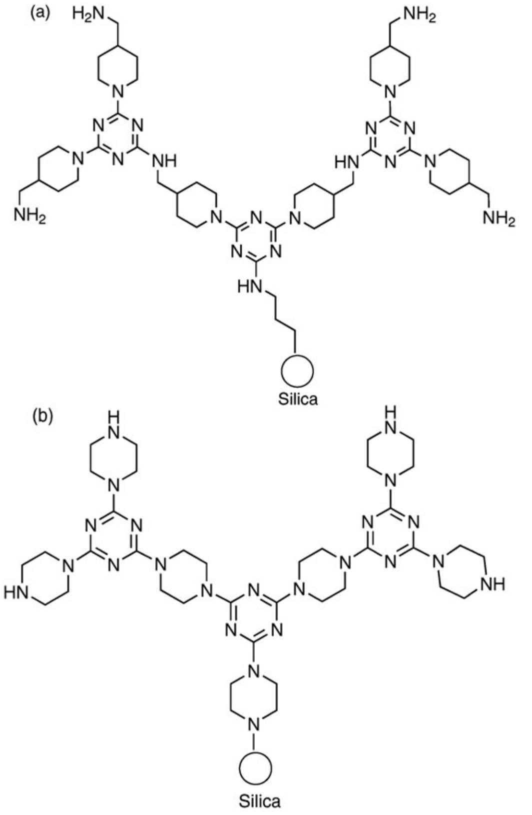


Fig. 9 Polymelamine dendrons prepared by Simanek and co-workers on solid support.[71,72]

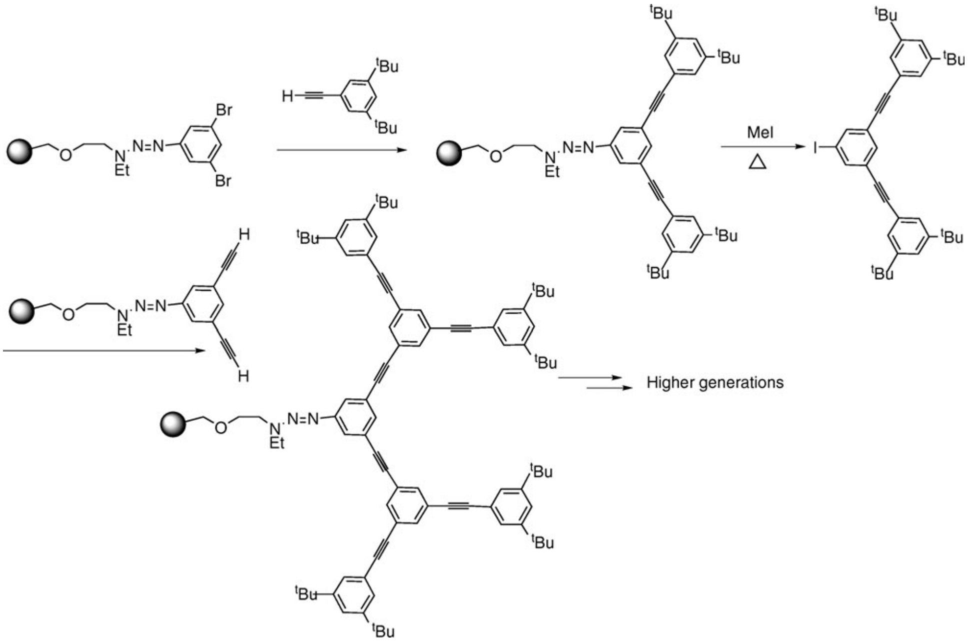
large-scale solid-phase synthesis of the low-generation dendrons. Attempts to proceed beyond the fourth-generation dendrons succeeded only on the resin, with a low loading of the resin-bound branching monomer, and were fruitless beyond the fifth generation. Though in the divergent/convergent approach the estimation of the success of each new layer assembly is straightforward (because of the cleavage step included in the synthesis), yields have not been reported.

2.11 Coordination-linked dendrons

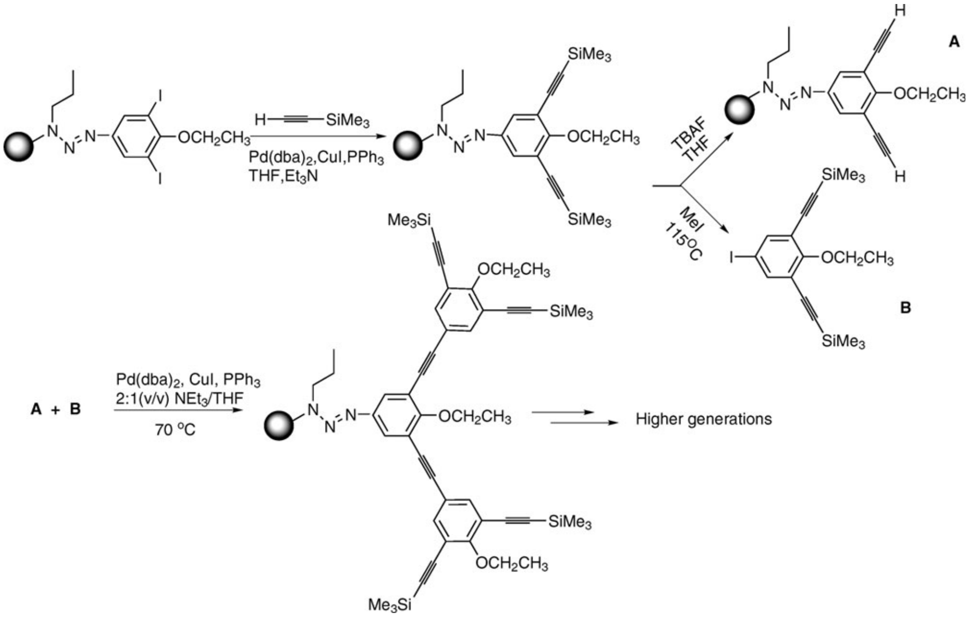
Reinhoudt, van Veggel, and co-workers prepared dendrons in solution, by assembly of individual monomers into the dendritic framework through a metal–ligand coordinative bond (Scheme 22).[73] The building blocks contained a pyridine (ligand) moiety at the focal point and pincer (S–C–S)PdCl complexes on the periphery. Chloride ligand abstraction was followed by pyridine–Pd coordination, leading to the next generation assembly. The dendrons, bearing at the focal point a long aliphatic chain terminated with thioether, were inserted into the thiol self-assembling monolayers (SAM) on gold.

A divergent growth of coordination dendrons on gold surfaces was recently reported by Rubinstein and co-workers.[74] Starting from disulfide bishydroxamate, inserted into the thiol SAM on gold, the dendron was repeatedly reacted with Zr^{4+} ions (from $Zr(acac)_4$ precursor) and trimesic acid-derived building block, bearing three bishydroxamate branches (Scheme 23).

Elipsometric, contact angle and atomic force microscopy (AFM) studies demonstrated that although high dilution of the anchoring units in the SAM ensures lateral separation between the dendrons of lower generation, at higher generation coalescence between individual dendrons occurs, and a growth mode, similar to that of multilayers prepared from SAMs of the anchoring units only, is observed. Though, in the study, the dendron assembly cycles were repeated up to the formal thirteenth generation and there was a good correlation between the generation and the dendron height (as demonstrated by AFM), it appears that for higher generations an



Scheme 20 Synthetic scheme for the preparation of poly(arylacetylene) dendrons on solid support *via* the convergent approach.[7]



Scheme 21 Synthetic scheme for the preparation of poly(arylacetylene) dendrons on solid support *via* the divergent/convergent approach.[8]

interlinked network of hyperbranched structures, rather than a landscape of isolated perfect dendrons, was obtained.

3 Applications of dendronized supports

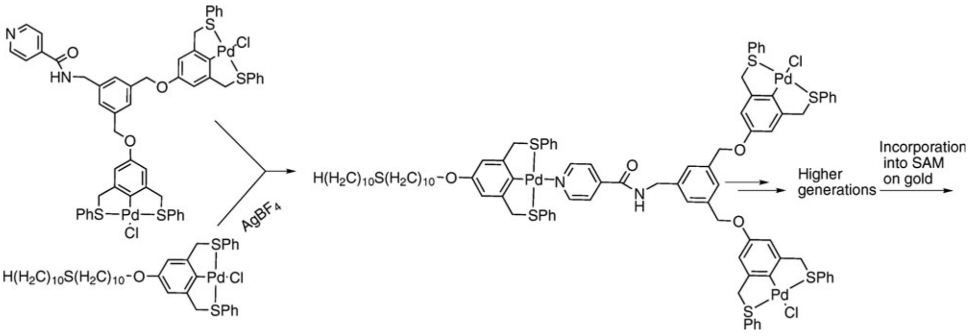
3.1 Dendronized supports as synthetic intermediates

Whereas the majority of the dendron-support hybrids are prepared for the subsequent use as new materials, in some cases, these constructs are only intermediates *en route* to production of soluble dendrons. In these cases the solid-phase synthesis technique was chosen as a synthetic approach to the preparation of dendrons, designated for application in solution.

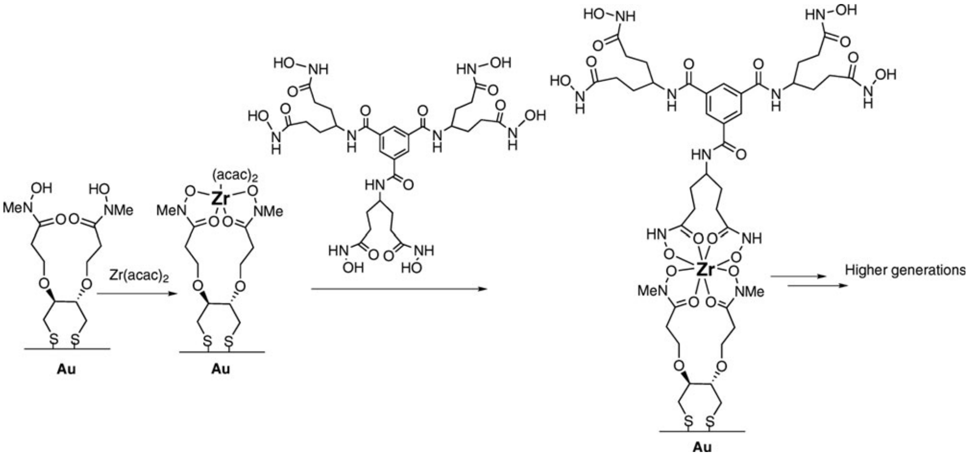
Some of these dendrons are cleaved immediately after formation; others are used as supported templates for preparation of soluble dendritic conjugates, which are initially constructed on support, but thereafter are cleaved together with the dendritic component. Formally, the applications of both types of such dendrons are beyond the scope of this *perspective*. However, since the dendron-support hybrid materials, which are the subject of the article, are crucial intermediates *en route* to these soluble dendritic oligomers, we will briefly review these applications.

The polylysine dendrons on solid support were used mostly for preparation of MAPs (multiple atigenic peptides, see section 2.2.1). The applications of MAPs were recently extensively reviewed.[13] Following cleavage from the support, peptide–polylysine dendron conjugates are used in a variety of biomedical applications, particularly as immunogens for the elicidation of cytotoxic immune response and antibody production. MAPs bearing pathogenic antigens have been used as synthetic vaccines. In these applications the dendron plays the role of an alternative hapten carrier.

The advantages of MAPs as immunogens, as summarized by Sadler and Tam, include simplicity in design and synthesis, versatility for investigating various immune responses, reliability of generating site-specific antibodies, and ease of generation in the laboratory.[13*a*] Antiparasite, antiviral, antimicrobial, antifungal, antiprion and antitumor immune system responses were induced by MAPs.[75] Some research groups produced mannose-conjugated, antigen-bearing polylysine dendrons (type **V**, in Fig. 2) to enhance the immunogenicity of the constructs.[20*a*,*c*] Among the related applications of



Scheme 22 Synthetic scheme for the preparation of coordination-linked dendrons on solid support.[73]



Scheme 23 Synthetic scheme for the preparation of coordination-linked dendrons on solid support *via* the divergent approach.[74]

MAPs, produced from support-dendron hybrids, are immunoassay and serodiagnosis reagents, and inhibitors of viral action.[75] MAPs themselves were used as antimicrobial agents.[18d]

MAP-like systems can also be used as biomineralization templates,[76] protein mimics,[77] and molecular probes for enzymatic activity.[78] Arginine-bearing polylysine dendrons demonstrated strong anti-angiogenic activity.[79] Similar arginine-decorated MAP-like polylysines, as well as loligomers, MAP-like dendrons decorated with cytoplasmic translocation signal and nuclear localization signal peptides, were studied as cell and nucleus membrane translocation agents and vehicles for delivery of exogenous molecules into cells and particular cell compartments.[80,81] Cationic lipidic polylysine dendrons, prepared by Florence and co-workers, self-assembled into higher order structures, "dendrisomes", which can be used as drug or oligonucleotide delivery vehicles.[21c,82]

Another type of supported dendrons, which were used for generation of dendritic gene delivery devices, are the polystyrene-bound polyurea dendrons.[47,48] Bradley and co-workers demonstrated that these dendrons, once cleaved from the support, complex efficiently plasmid DNA and transfect it successfully into cells.[83] The highest efficiency (95% of that displayed by the Superfect commercial transfection agent) was observed for one of the G3 dendrons; in general the efficiency increased with the dendron generation (positive effect).

Bradley and co-workers reported two techniques that make use of dendron–peptide conjugates equipped with fluorescent reporters for investigation of proteolytic activity of proteases.[84] The polyurea dendron constructs were prepared on support and cleaved for use in solution. The use of the dendritic core causes high local concentration of the fluorophore and leads to internal quenching of fluorescence in the intact proteolytic activity probe, without any need for a separate quenching moiety.[84a] This quenching between the fluorophores, decorating the dendron–multipeptide constructs, ceases upon enzymatic cleavage of the peptide tethering the fluorophore. The specific proteolysis results in both termination of the self quenching and amplification of the fluorescent signal, due to the release of multiple fluorophore-containing fragments.

The second technique was based on efficient quenching of the fluorescence of the fluorophore-terminated dendron by the quencher tethered to the focal point by the peptidic substrate of the protease.[84b] Upon cleavage, strong amplification of the fluorescence enables detection of the specific proteolytic activity. The normalized amplification observed with the first-generation dendritic conjugate surpassed that of the linear analogue.

The secondary structure of the polyproline dendrons (see section 2.2.3), cleaved after their assembly on solid support, was studied and found to be notably influenced by the dendritic architecture.[26b,d] Internalization of these dendrons by rat kidney cell and complexation of drugs by the dendrons suggest the possibility of their application as drug delivery agents.[26b]

The peptide dendrons prepared by Reymond and co-workers *via* solid-phase synthesis and cleavage (see Fig. 3) were examined in aqueous solution as artificial esterases (see also subsequent section 3.3.8).[24a–d,25] These histidine-containing dendritic structures displayed enzyme like esterolytic activity, cooperativity of the histidine residues, and a strong positive dendritic effect. The modular design enabled synthesis of structures based on His–Ser–Asp triad and His–Ser diad in the library format. "Mutant" structures, incorporating other amino acids, were prepared and examined, leading to His–Thr-based dendrons, which displayed superior catalytic properties.[25d] Peptide dendrons, incorporating Lys and Pro amino acids, were also catalytically active in asymmetric aldol addition.[25e] The dendrons of the "1.1.1" series were functionalized, subsequent to their SPPS synthesis and cleavage, with glycoside moieties on the periphery and colchicine alkaloid at the near-focal cysteine side chain (see Fig. 3(a)).[24e] These glycopeptide-colchicine conjugates were studied as drug delivery vehicles.

3.2 High-loading dendronized supports for solid-phase synthesis

In contrast to the hybrids discussed in the preceding section, which were used as synthetic intermediates and distinguished by the cleavage of the support–dendron bond after their synthesis on support, some of the dendronized insoluble materials are designed as high-loading supports for subsequent solid-phase synthesis. The cleavage that usually follows such synthesis will break the bond between the dendritic termini and substrate and leave the support–dendron bond intact.

Preparation of such high loading supports was extensively explored and promoted by Bradley and co-workers. The PAMAM, polyamidourea, and polyurea dendrons they prepared (see sections 2.3 and 2.4) were designed to increase the per-bead loading of the reactive sites (rather than per weight loading). Thus, the PAMAM dendrons on Tentagel increased the loading of the NH_2 groups on resin more than nine-fold with the loading per bead increasing up to 9.6 nmol per bead in the fourth generation.[34] The high per-bead loading of the support enabled the cleavage and analysis of the products from a single bead, using NMR, MS and HPLC techniques.[36b]

With the polyamidourea dendrons the increase in loading was even more dramatic (up to 230 nmol per bead).[47] The high per-bead loading of the terminal functional groups enabled the analysis of compounds cleaved from a single bead also for these dendrons (*e.g.*, biaryls prepared on the resin were analyzed by HPLC and NMR).

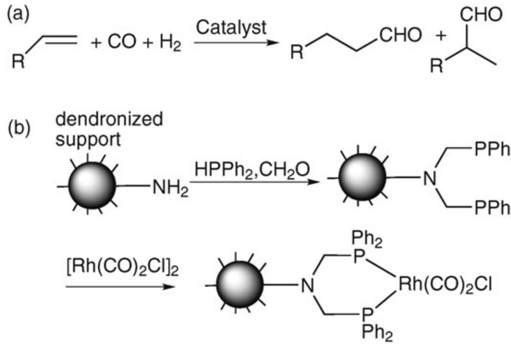
The high-loading dendronized supports were used by Bradley and co-workers to prepare peptides and biaryls, as well as amidine and aryl ether libraries.[34,47,48,85] Polyurea-dendronized polystyrene was used as a support for preparation of a library of antibacterial triazine-based compounds.[86] The high loading of the beads allowed screening of the antibacterial activity of compound released from a single bead. Similarly, a library of the (poly)arginine-lipid conjugates, prepared on high-loading polyurea-dendronized support, was screened by a "single bead release" technique for DNA transfection activity.[87]

The utility and versatility of the poly(4-azalyzine) dendron hybrids (see Fig. 5), prepared by Chan and co-workers as high-loading supports for solid-phase synthesis was shown for small molecules synthesis.[30] Lee and co-workers demonstrated the utility of high-loading support they prepared (see Fig. 6) for generation of pentapeptides.[31]

3.3 Supported dendritic catalysts

One of the most important applications of the dendronized supports is the preparation of support-bound dendritic catalysts. Such systems, based on outward-branching dendrons were prepared and explored by the groups of Alper and Arya, Portnoy, Kawi and Rhee.[4a,e] A number of heterogeneous dendritic catalysts based on a different design (*e.g.* polymerized dendrimers with catalytic units in their cores) are also known,[88] but are beyond the scope of this *perspective*. The discussion of the catalytic systems below is subdivided according to the catalytic reaction.

3.3.1 Hydroformylation. The first reaction tested using supported dendritic catalysts was hydroformylation. This reaction, extensively used in research and industry, converts terminal olefins, carbon monoxide, and hydrogen into linear or branched aldehydes (Scheme 24(a)).[89]



Scheme 24 The hydroformylation reaction (a) with supported catalysts prepared on dendronized supports (b).[29,30]

Between 1999 and 2005, Alper and co-workers prepared a number of Rh-based supported dendritic catalysts and tested them in the hydroformylation of styrene, vinyl acetate, vinyl benzoate, 1-octene, and a number of other olefins.[29a–c,39a,b,44a,c] On silica, PAMAM dendrons were converted into diphosphine ligands and further into Rh complexes (Scheme 24(b), see also section 2.3).[39a] Initially, only the ligands and complexes of the zeroth to second generation could effectively be formed. Due to steric hindrance, the functionalization and complexation of the third and fourth generation occurred with extremely low efficiency. The low-generation catalysts demonstrated high activity and strong selectivity towards the branched product. The third- and fourth-generation catalysts were only marginally active at room temperature, probably as a result of the very low metal loading on the silica. Nevertheless, at 75 °C, even these catalysts were active.

The improvement for the third- and fourth-generation catalysts was achieved through elongation of the diamine fragment of the branching module of the PAMAM dendron.[39b] The extension of the branch length, obtained by substitution of the 1,2-diaminoethane by 1,4-diaminobutane, 1,6-diaminohexane, or 1,12-diaminododecane in the PAMAM synthesis, relieved steric crowding and led to an increase in the metal catalyst loading for the higher dendron generations. The length extension, indeed, resulted in an additional improvement in the activity and recyclability of the catalysts. The best results were achieved for the diaminododecane-based fourth-generation catalyst, which could be recycled four times without a loss of activity.

Not only the loading of the active metal, but also the morphology of the support, influences the performance of the catalyst, as was demonstrated by Alper, Sayari and co-workers.[44a,c] PAMAM dendrons synthesized on a mesoporous or large pore silica and decorated with diphosphine–Rh complexes demonstrate a notably higher activity in the hydroformylation reaction, as compared to those prepared on amorphous silica. Whereas on MCM-41 silica only zeroth- and first-generation catalysts were active (the second-generation catalyst was non-active and the third-generation could not be prepared), on Davisil large-pore silica zeroth to third generation catalysts were prepared and compared. The first-generation catalyst was the most active one.

The observed dendritic effect on the effectiveness of the catalyst preparation and on the normalized activity of the systems is explained by the gradual filling of the silica pores for the higher generations and the difficulties in access to the reactive sites by the soluble reagents. Surprisingly, the recycling is possible only with MCM-41 and amorphous silica-supported catalysts, but could not be achieved for the Davisil-based systems. Thus, the type of the support also strongly influences the recycling parameter.

As detailed in the synthesis part (see section 2.2.3), the same cooperating groups also prepared polyamide dendrons on polystyrene.[29a] The dendrons, built of 3,5-diaminobenzoic acid-derived peptide-like monomers, were decorated with diphosphine chelate ligands and their Rh complexes, as described above for the silica systems (Scheme 24(b)). The hydroformylation reaction associated with this type of catalyst design again demonstrated high activity. The second- and third-generation catalysts were more active than the first-generation one and could be recycled a number of times without a loss of activity.

An additional study explored the influence of the isolation of the catalyst environment on the polystyrene-supported catalytic systems in the hydroformylation reaction. For this purpose, first- and second-generation dendrons (very similar to those described above) were constructed and the biphosphine–Rh complex was assembled on the first-generation module (Fig. 10).[29b] In the second-generation dendrons, the outer layer modules did not carry metal and were used to isolate the catalytic site from the environment. Although the metal loading of the second-generation catalyst was lower than that of the first, the reactivity and recyclability of the second generation-derived catalyst is notably better with some substrates (*e.g.*, vinyl benzoate). This interesting dendritic effect again emphasizes the influence of the dendritic template architecture on the catalytic outcome.

In a subsequent study,[29c] the polystyrene-bound lysine-incorporating dendrons with four propagation sites in each monomer (see Fig. 4(b)) were converted into first- and second-generation hydroformylation catalysts bearing 4 and 16 Rh complexes, respectively, on each of the dendrons. These new catalytic systems showed even higher reactivity (enabling room-temperature hydroformylation), excellent regioselectivity (higher than the first two systems, probably as a result of the lower reaction temperature), and outstanding recyclability.

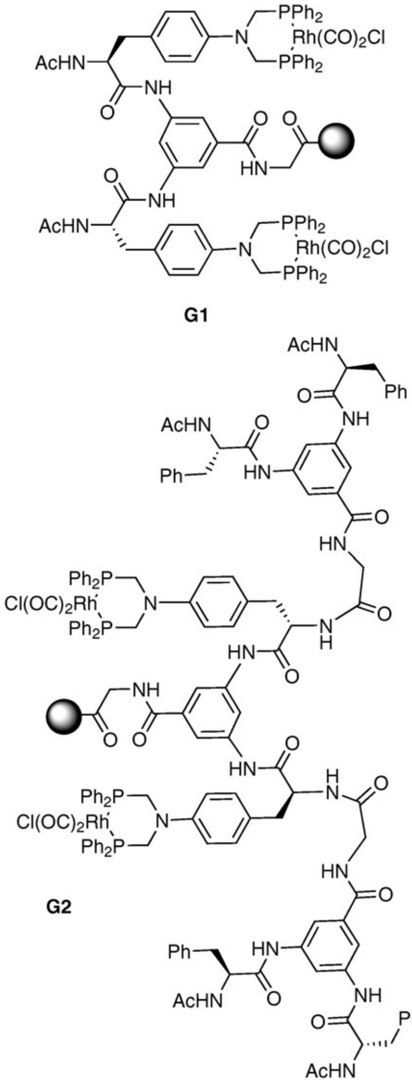
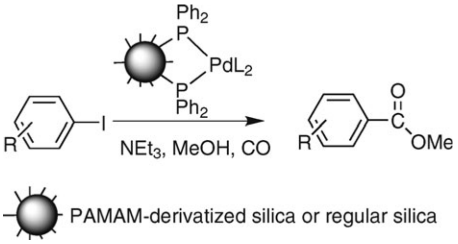


Fig. 10 Supported, internally-functionalized dendritic catalysts for hydroformylation.[29b]

3.3.2 Other carbonylation reactions. Other reactions that exploit CO chemistry are promoted by supported dendritic catalysts. In their paper from 2002, Alper and co-workers used the aforementioned phosphinated PAMAM-silica constructs to immobilize a number of Pd complexes. The formed structures were extensively studied and tested as heterogeneous catalysts in the iodoarene methoxycarbonylation reaction (Scheme 25).[90] Quantitative complexation was observed with zeroth- to second-generation-derived ligands for the $PdCl_2$ fragment. However, for higher generations and with bulkier Pd fragments, only partial functionalization was achieved. The catalytic reaction was optimized and quantitative conversions were readily obtained. With respect to the influence of the dendritic template structure on the reaction outcome, two trends were observed. First, higher generation-derived catalysts were characterized by lower Pd loadings and lower conversion per silica weight unit. However, the reactivity per Pd equivalent (or turnover number (TON) and turnover frequency (TOF), as presented by the authors) increased with the generation (Fig. 11). Second, the leaching of Pd from the support decreased upon the increase in the dendrimer generation. It is possible that some of the displayed activity resulted from Pd(0) nanoclusters, immobilized inside the silica/dendritic matrix, since blackening of the silica was usually observed



Scheme 25 The intermolecular carbonylation reaction with supported dendritic catalysts.[90]

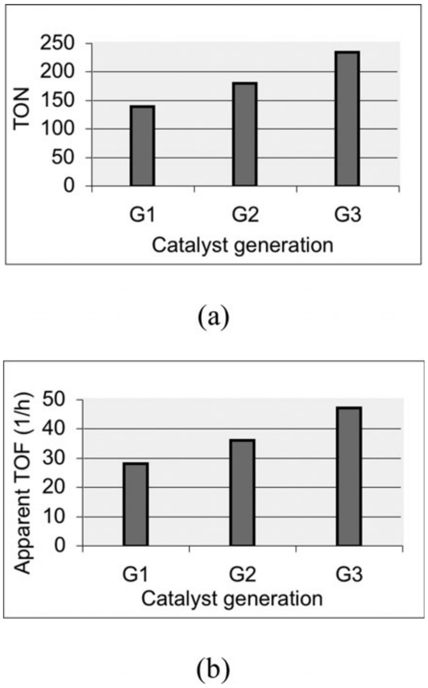


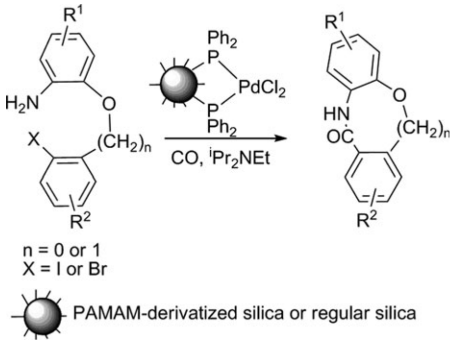
Fig. 11 The turnover number (a) and turnover frequency (b) dependence on the dendritic catalyst generation in the carbonylation reaction of iodobenzene.[90]

under these reaction conditions and bromobenzene substrates could not be used.[91]

The same group reported recently the intramolecular version of the iodoarene carbonylation reaction (Scheme 26).[92] In the intramolecular version amidocarbonylation, rather than alkoxycarbonylation, was carried out, thus enabling formation of six- to eight-membered fused heterocyclic lactams. Recyclability of the catalytic system was demonstrated. The first-generation dendron afforded the highest Pd loading and the best recyclability.

Another related transformation, intermolecular olefin hydroesterification, was also reported by the Alper group (Scheme 27(a)).[39c] The catalytic system prepared on silica was based on bisphosphine-$PdCl_2$ complexes, decorating the PAMAM dendrons with C_6-diamine spacers. Because of the longer diamine used in the PAMAM dendron construction, the phosphine–Pd catalyst could be prepared on zeroth- to fourth-generation dendrons. All the catalysts demonstrated high activity, a preference for the linear product, and moderate recyclability.

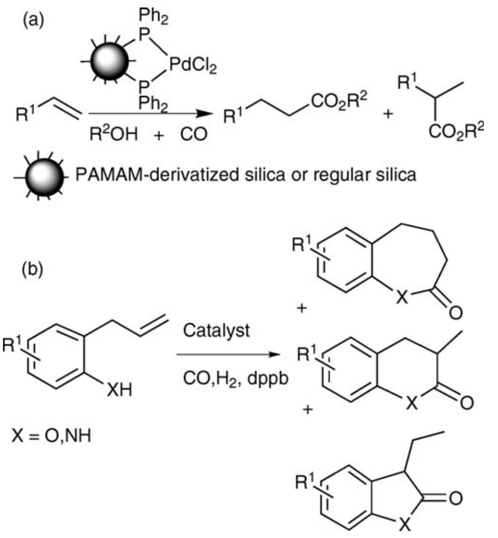
Intramolecular hydroesterification and hydroamidation of olefins was demonstrated by Alper's group on PAMAM-dendronized silica, using both bisphosphine–Pd chloride complexes and pincer PCP–Pd complexes (Scheme 27(b)).[93] In both cases, the presence of dppb ligand in solution was required and H_2 was usually added to CO atmosphere. In the case of pincer complexes,[93b] the dendritic catalysts showed higher activity than their non-dendritic analogue (G0), with the second-generation catalyst being the most active. Though differences in reactivity, selectivity and recyclability between the catalysts of different generations and between the heterogeneous catalysts and their homogeneous analogues were significant, one cannot rule out the possibility that the supported complexes serve only as Pd reservoirs for the minute amounts of highly catalytically active, homogeneous dppb–Pd complexes.



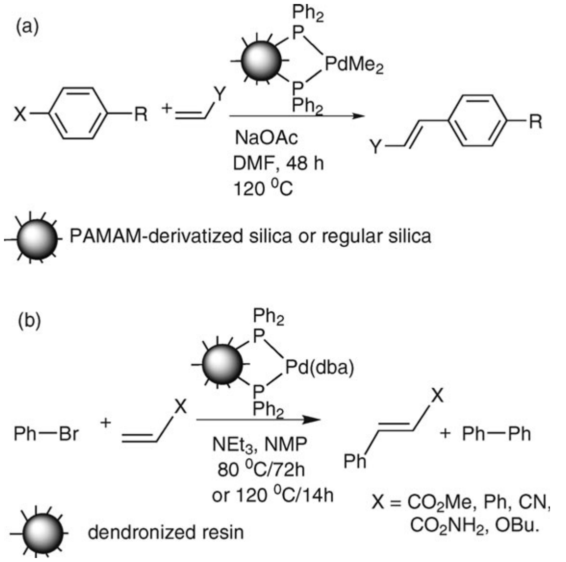
Scheme 26 The intramolecular carbonylation reaction with supported dendritic catalysts.[92]

A different type of carbonylation chemistry was carried out with bisphosphine–Rh complexes immobilized on polyamide-dendronized polystyrene. The supported dendrons with 3,5-diaminobenzoic acid and lysine branching units in each generation (see Fig. 4(b) and sections 2.2.3 and 3.3.1) were used to prepare the catalysts, which promoted the carbonylative ring expansion of aziridines to β-lactams.[94] Four and sixteen catalytic unit-bearing G1 and G2 catalysts were recovered and reused three times.

3.3.3 Heck reaction. An additional reaction catalyzed by Pd complexes immobilized on dendronized support is the Heck reaction.[95] Alper, Arya and co-workers prepared the already mentioned bisphosphine-terminated PAMAM-on-silica (see sections 2.3 and 3.3.1) and complexed it to a dimethylpalladium fragment, using (tmeda)$PdMe_2$ as a precursor.[96] Like in the case of Rh complexation, the poor functionalization of the third- and fourth-generation supported catalysts prevented their conclusive investigation. The zeroth to second generation supported catalysts demonstrated activity



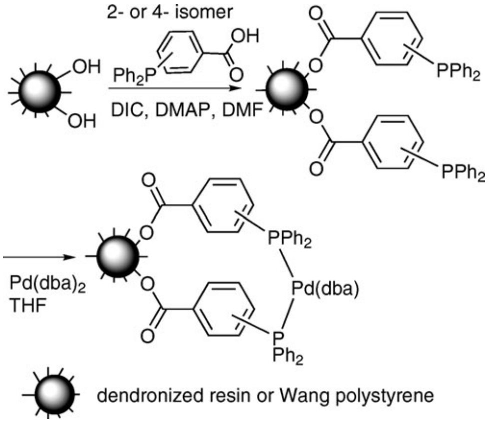
Scheme 27 The olefin hydroesterification and hydroamidation reactions with supported dendritic catalysts.[39c,93]



Scheme 28 The Heck reaction with supported dendritic catalysts.[96,97]

comparable with that of the homogeneous analogue in the Heck reaction of bromobenzene (Scheme 28(a)). This is noteworthy, as most supported Pd catalysts are only capable of activating iodoarenes or activated bromoarenes. Moreover, the reactivity of bromobenzene implies that it is highly likely that the catalysis is executed by monometallic Pd complexes decorating the dendrons rather than metal Pd black or Pd nanoclusters.[91] The faster decrease in the apparent turnover frequency observed for the non-dendritic (zeroth generation) catalyst, in comparison with the first- and second-generation ones, hints at the higher stability of dendritic systems.

Dahan and Portnoy also actively investigated the Heck reaction with supported dendritic catalysts. They used the previously described polystyrene-supported polyether dendritic template decorated with monodentate phosphines *via* an esterification reaction (Scheme 29, see also section 2.6).[97] For generations 1–3, as well as the analogue derived from the non-dendritic Wang resin, it was possible to effectively functionalize the termini with phosphines and complex them to a Pd(0) precursor [Pd(dba)$_2$]. Two phosphine ligands coordinated to each Pd center. The system was active for the Heck reaction of bromobenzene with various olefins (Scheme 28(b), Fig. 12). Remarkably, a strong positive dendritic effect was observed. The effect was particularly prominent at low reaction temperatures. Thus, for the reaction of bromobenzene with methyl acrylate at 80 °C, a five-fold increase in the yield was observed when the third-generation catalyst was compared with the non-dendritic catalyst. The increase in the yield reflected both the increase in the conversion and the selectivity toward the Heck product. At higher temperatures and with other substrates, similar effects, though of lesser magnitude, were observed. When analogous catalysts, based on the polythioether and polyamine dendritic framework, were examined, notably lower yields were obtained.[62] This observation, though not surprising, emphasizes the important impact of the dendritic template architecture on the catalytic outcome.



Scheme 29 Preparation of Pd(0) catalysts supported on polyether-dendronized resins.[97]

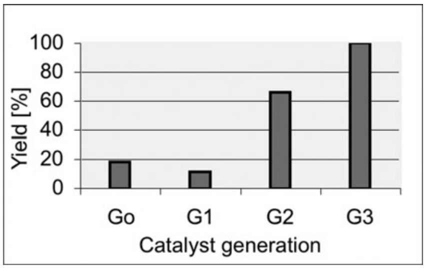
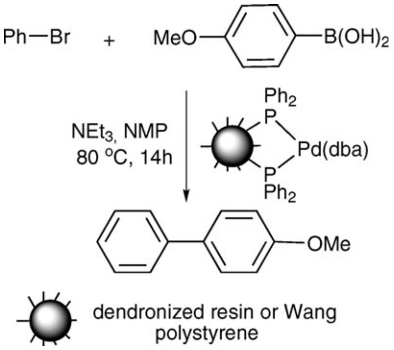


Fig. 12 The yield dependence on the dendritic catalyst generation in the Heck reaction of bromobenzene and methyl acrylate.[97]

3.3.4 Suzuki reaction. Portnoy and Dahan extended the study of the aforementioned supported dendritic phosphine–Pd complexes to the Suzuki cross-coupling reaction.[62,98] Bromobenzene was activated and coupled with *p*-methoxyphenylbenzoic acid (Scheme 30). As in the case of the Heck reaction, the system enabled the process to proceed under relatively mild conditions (at 80 °C, with NEt$_3$ as a base) and demonstrated a substantial positive dendritic effect (Fig. 13). Interestingly, the Suzuki reaction was less sensitive to the nature of the dendritic backbone than the Heck reaction, as the activities of the catalysts based on polythioether and polyamine dendritic backbone were similar to that of the polyether dendron-derived catalysts.

3.3.5 Oxidation of olefins. Bisphosphine-decorated PAMAM-on-silica complexed with a Pd(dba) fragment were used by Zweni and Alper for oxidation of terminal olefins to methyl



Scheme 30 The Suzuki reaction with supported dendritic catalysts.[62]

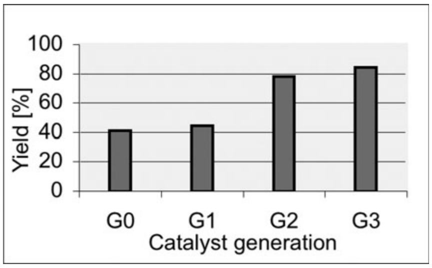


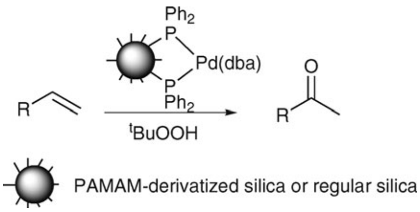
Fig. 13 The yield dependence on the dendritic catalyst generation in the Suzuki reaction.[62]

ketones (Scheme 31).[39d] *tert*-Butyl hydroperoxide was used as the oxidant under neat conditions. Zeroth- to second-generation catalysts, based on C_2, C_6 or C_{12} diamine spacers in the dendritic backbone, were examined for oxidation of α-olefins of varying length. Though the dendrons based on the longer diamines were grown on silica with lower efficiency than those based on ethylenediamine, they produced supported catalysts with higher loading of Pd and higher activity per Pd equivalent. On average, the G2 C_6-based catalyst was the most active.

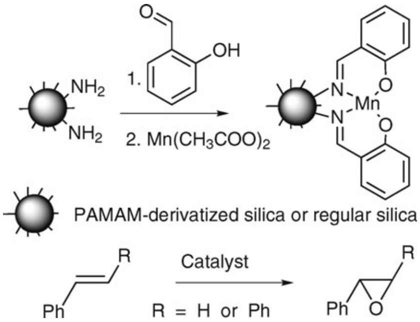
Kawi, Bu, and co-workers prepared a similar PAMAM-on-silica template with amino terminal groups converted into salicylimines.[42a] These salen-imitating ligands were complexed with Mn(II) and used as catalysts in olefin epoxidation (Scheme 32, Fig. 14), a reaction of growing importance in synthetic organic chemistry.[99] Remarkably, the catalytic activity per Mn equivalent increased dramatically with the dendron generation. Thus, in the epoxidation of styrene, the yield increased from 20% for generation zero to 75% for the fourth-generation catalyst. Even though the Mn loading per gram of silica was almost equal for the second-, third- and fourth-generation catalysts, the yield of the epoxidation increased more than two-fold in this series.

3.3.6 Hydrogenation of olefins.

The bisphosphine–Pd(dba)-decorated PAMAM dendrons on silica can be used not only for oxidation but for reduction as well. Zweni and Alper recently demonstrated that the same systems that were used for olefin conversion to methyl ketones (see the preceding section) can catalyze selective hydrogenation of dienes (cyclic and acyclic) to monoolefins under very mild conditions (*e.g.*, Scheme 33).[100] The second-generation dendritic catalyst, based on C_{12} diamine-derived dendron, demonstrated higher activity than the lower generation catalysts or catalysts based on a shorter diamine spacer in the dendron backbone. This G2 catalyst also demonstrated improved recyclability as compared to the non-dendritic analogue.



Scheme 31 The olefin oxidation with supported dendritic catalysts.[39d]



Scheme 32 The olefin epoxidation reaction with supported dendritic catalysts.[42a]

Gao and Jiang used a different approach to prepare supported dendritic hydrogenation catalyst.[101] Pd(0) nanoparticles were prepared and stabilized in the interior of the PAMAM dendrons grown on SBA-15 silica, using an approach pioneered in solution by Crooks and co-workers.[102] The dendrimers served as both template for the assembly of the metal particle and as a nanoreactor for controlling their reactivity. The second-generation heterogeneous catalyst was the most active and achieved the highest TOF in hydrogenation of allyl alcohols, surpassing the activity of the homogeneous dendrimer/Pd-nanoparticle analogue, whereas the third-generation catalyst exhibited the best chemoselectivity toward the hydrogenation product.

3.3.7 Pauson–Khand reaction.

Portnoy and Dahan applied the phosphine-decorated polyether dendrons on polystyrene (see sections 3.3.3 and 3.3.4) to the study of the Co-catalyzed Pauson–Khand reaction.[103] Both 4- and 2-diphenylphosphinobenzoate-bearing dendritic resins (generations 0–3) were complexed with $Co_2(CO)_8$ and the formed systems were tested in the intramolecular reaction of 1,6-enyne (Scheme 34).[104] Along with the regular Pauson–Khand cyclopentenone product, an Alder-ene byproduct was obtained in all experiments. The 4-diphenylphosphinobenzoate series of catalysts showed a remarkable increase (greater than twofold) in the yield of the Pauson–Khand product as a function of the dendron generation (Fig. 15). This increase reflects an improvement in both the activity and selectivity of the catalytic systems. The 2-diphenylphosphinobenzoate series demonstrated an unexplained lack of activity for the first-generation catalyst. The second- and third-generation catalysts in this series were, however, most active.

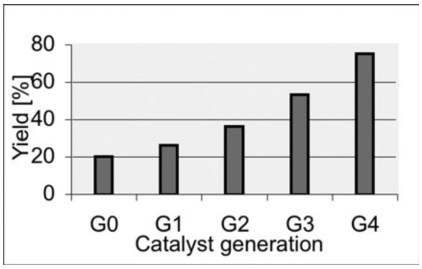
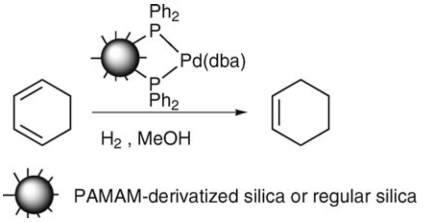


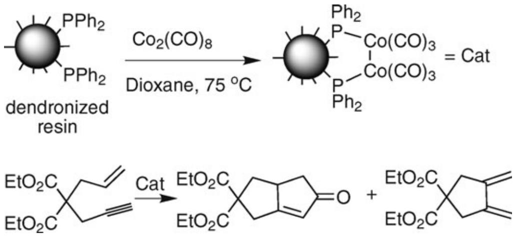
Fig. 14 The yield dependence on the dendritic catalyst generation in the styrene epoxidation.[42a]



Scheme 33 The diene hydrogenation reaction with supported dendritic catalysts.[100]

3.3.8 Enantioselective reactions. The only published example of an enantioselective reaction carried out with ligands immobilized on dendronized supports was described by Chung and Rhee.[41] The PAMAM-on-silica template was functionalized with a chiral aminoalcohol ephedrine, and the obtained systems were used to catalyze the enantioselective addition of diethylzinc to benzaldehydes (Scheme 35). The enantioselective addition of dialkylzinc reagents to aldehydes is one of the main approaches to the synthesis of chiral secondary alcohols and a yardstick for the chiral induction capability of amino alcohols and other related catalytic systems.[105] The first-to-fifth-generation catalysts were tested. A remarkable dependence on the generation and general loading of the dendrons was observed. When dendrons were prepared on silica with a 0.24 mmol g^{-1} initial loading of the amino groups, a strong positive dendritic effect on the conversion, chemoselectivity, and enantioselectivity of the catalytic reaction was observed (Fig. 16). Upon replacement of the first-generation catalyst by a fourth-generation one, the conversion increased from 63 to 92%, the chemoselectivity increased from 85 to 98%, and the enantiomeric excess (ee) increased from 11 to 56%. These increases were monotonic, and only for the fifth-generation catalyst was some deterioration in the performance observed. Moreover, the fourth-generation catalyst could be recycled three times without a loss of activity, chemoselectivity, or enantioselectivity. On the other hand, when the analogous catalysts were prepared on silica with an initial loading of 0.9 mmol g^{-1}, the opposite trend (a negative effect) was encountered, with the fifth-generation catalyst forming a practically racemic product. These dramatic differences might be in part a reflection of the differences in the perfectness of dendrimer growth, as extensively discussed for the PAMAM-on-silica in the Synthesis section.

Two additional examples of enantioselective supported dendritic catalysts were recently communicated at conference, but have not yet been published. A strong positive dendritic effect on the enantioselectivity of ketone reduction was demonstrated by chiral diamines supported on dendronized polystyrene and complexed with a $Ru(BINAP)Cl_2$ precursor.[106] Dendronization of polystyrene with polyether dendrons led to a dramatic improvement in the enantioselectivity of the aldol reaction catalyzed by immobilized proline derivatives.[107]



Scheme 34 The Pauson–Khand reaction with supported dendritic catalysts.[104]

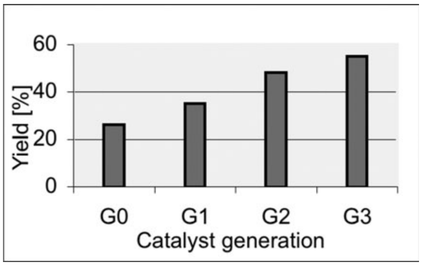


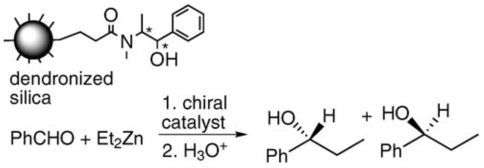
Fig. 15 The yield dependence on the dendritic catalyst generation in the Pauson–Khand reaction.[104]

3.3.9 Ester hydrolysis. Dendritic peptides, prepared by Reymond and co-workers (see sections 2.2.3 and 3.1), exhibited esterolytic activity not only in solution following their cleavage from the support, but also while still bound to the Tentagel resin.[25a,b] The dendrons of the library of the "2.2.2.2" series were subjected to the high-throughput screening of the ability to catalyze the hydrolysis of 8-butyryloxypyrene 1,3,6-trisulfonate (Scheme 36). Soaking the library beads with this fluorogenic substrate, followed by spreading on a dry surface, allowed direct selection of beads that carried the most active dendron structures. The consensus sequences of the most catalytically active dendrons included the His-Ser diad in the outermost layer and hydrophobic amino acids (Ile and Val) in the innermost part of the dendron. The presence of an additional histidine near the outermost layer enhanced the catalytic ability.

3.3.10 Other reactions. Similar peptide dendrons from the "2.2.2.2" series prepared in a library format were screened, while still on the beads, for aldolase potential activity.[25e] Probes forming colored enaminones or releasing fluorescent fragments *via* enolization or retro-aldol reactions were used for the screening. Lysine- and proline-rich sequences were identified with the enaminone-forming and enolization-sensitive probes.

3.4 Dendronized supports in separation processes

The potential of dendronized supports to serve as stationary phases for various separation techniques has been explored by a number of research groups. One of the applications is the use of dendron-modified support as chiral stationary phase (CSP)



Scheme 35 The enantioselective addition of diethylzinc to aldehydes with supported dendritic catalysts.[41]

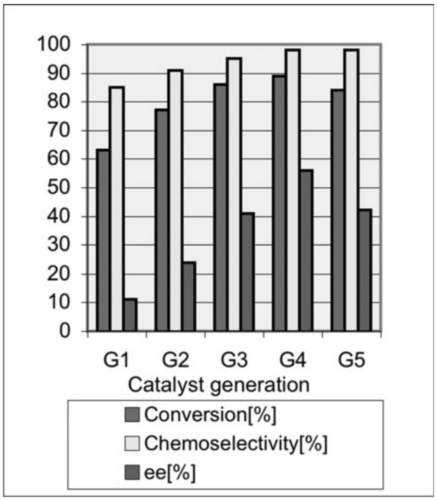
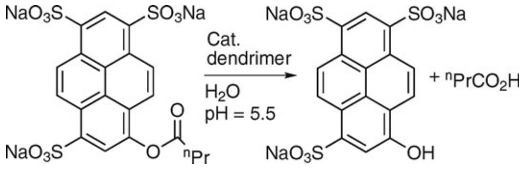


Fig. 16 The yield, chemoselectivity and enantiomeric excess dependence on the dendritic catalyst generation in the asymmetric addition of Et_2Zn to benzaldehyde.[41]

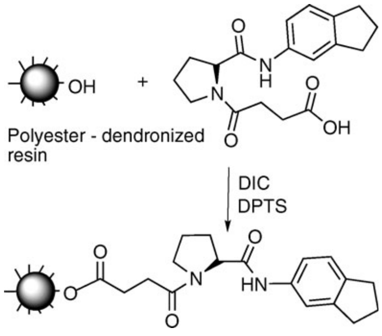
for separation of enantiomers. Mitchell and co-workers prepared poly-L-glutamate dendrons on silica (see section 2.2.2),[23] and in a subsequent chromatographic study the utility of these materials as stationary phases in reversed phase HPLC was demonstrated.[108] However, chiral resolution of racemic analytes was not achieved.

The use of dendronized polymers as CSPs was successfully established by Fréchet and co-workers.[49] The polymer-bound polyester dendrons (not chiral themselves, see section 2.5 and Scheme 12) were decorated with L-proline indananilide chiral selectors (Scheme 37). It was found that these materials enable effective separation of enantiomers of the tested protected amino acids with a very high separation factors. In general, the separation factor α increased with the selector loading. However, the structure and morphology of the dendritic interphase also plays a role, since there were some exceptions from this rule. It was demonstrated that the selectivity increases with the distance of the selector from the support core. The specific selectivity of the CSP (defined as the separation factor normalized by the selector loading) was notably higher for CSPs, built from perfect dendrons generated in solution, than for CSPs prepared by solid-phase divergent dendron synthesis. It was also enhanced for higher generations. The authors conclude that this validates the positive synergistic effect of multiple selectors located in well-defined positions within the dendritic CSP.

In another study, the behavior of PAMAM-dendronized silica (see section 2.3) as a stationary phase for size-exclusion chromatography demonstrated that its performance is governed by the local microstructure of the dendrons, which could be manipulated by the dendron growth conditions.[40b] It was suggested that modification of the dendrons by suitable ligands will generate column packing for multi-separation applications.



Scheme 36 Ester hydrolysis with supported dendritic catalysts.[25a,b]



Scheme 37 Preparation of CSPs with resin-supported dendrons.[49]

The use of dendronized silica as a stationary phase in capillary gas chromatography was pioneered in 2001 by Newkome *et al.*[32a] The triply-branched dendrons prepared in solution (see section 2.2.4) were immobilized on fused silica inside the capillary column. The dendritic architecture provides unique selectivity in separation of a Grob test mixture of compounds. The same dendron–silica hybrids were used by the authors for solventless capillary microextraction (CME) and preconcentration in chemical analysis.[32c] Using sol–gel dendrimer-coated extraction capillary, parts per trillion (ppt) detection limits were achieved in CME-coupled GC analysis of polar and nonpolar analytes in aqueous solutions.

Su and co-workers used silica gel with immobilized polymelamine, poly(amidoamine), or poly(propyleneimine) dendrons as the microcolumn packing for the flow injection preconcentration and separation of traces of Pt(IV) ions for flame atomic absorption spectroscopy determination.[64,69,109] Polyamine dendron-functionalized polystyrene was used for sequestering metal ions (Ag^+, Cu^{2+} and Hg^{2+}) from aqueous solutions.[66] The resins demonstrated good adsorption capacities, particularly for Cu^{2+}, due to the chelating nature of the polyamine dendrons. Such dendronized resins could potentially be applied for removal of metals from industrial wastewater.

Removal of another pollutant, atrazine herbicide, by polymelamine dendrons on silica was demonstrated by Simanek *et al.*[72] The authors revealed two trends. First, the dendrons of higher generation increased the sequestering ability of the dendron-support material relative to that of lower generations. Second, this ability was higher for the dendrons divergently grown on silica, as compared to the materials obtained by the focal-point immobilization of the dendrons pre-synthesized in solution (see section 2.9).

Materials composed of similar triazine-based dendrons and polystyrene were used by Marsh *et al.* as insoluble scavengers for removal of excess nucleophilic or electrophilic reagents from the reaction mixtures.[68] Dendrons, decorated with tertiary amines, effectively removed electrophiles (protons), whereas the similar resin with chlorotriazine terminal groups sequestered the excess nucleophile (amine).

3.5 Other applications

Poly(amidoamine) dendrons on gold surface cross-linked with poly(prolylenimine) dendrimers have been used as bioreactive surfaces for conjugation of biological macromolecules *en route* to fabrication of DNA microarrays, protein microchips, and other biosensors.[46] Polyamide pseudodendrons on glass and polypropylene were designed for similar purposes.[33c]

4 Summary and outlook

The composite support–dendron materials reviewed in this *perspective* display, a substantial structural and applicative diversity. Although these hybrids are usually prepared on polystyrene-based polymeric cores or silica, additional organic (PEGA, hydroxyethyl methacrylate) and inorganic (carbon nanotubes, glass) supports have recently been dendronized. The dendritic motifs, originally limited to polylysine and PAMAM, have lately been expanded to polyurea, polyester, polyether, polyamine, polymelamine, and other dendritic structures. The applications for these hybrid materials range far beyond synthetic intermediates of immunogenic polypeptides and now encompass drug delivery vehicles, catalysts, high-loading supports for synthesis, probes for enzymatic activity, stationary chromatographic phases, and a number of other applications. The uniqueness of the dendritic architecture, leading to dramatically altered performance of the hybrid materials as compared to the parent supports, has been prominent in a number of fields, particularly catalysis and separation.

Regarding the synthetic aspects of the field, we may expect continued activity. Though many synthetic schemes, discussed above, were brought to a very high efficiency, others are still far from optimal. It is possible that achieving perfect dendron growth in these cases requires alternative synthetic schemes (*e.g.*, "click chemistry" type reactions), different supports (*e.g.* macroporous resins), or a better match between the type of the support and the dendron or the chemistry used in its synthesis. One may expect that additional efforts will be devoted to preparation of dendronized supports with higher loading and lower level of structural defects.

On the other hand, recent studies of hyperbranched polymers, grafted on solid support (including silica-supported PAMAM, which is in some cases better described as a hyperbranched polymer rather than dendron) demonstrated their potential as comparable substitutes of perfectly dendronized supports. Taking into account that some of these hyperbranched grafts are generated in one-pot polymerization and possess high degrees of branching, it can be predicted that the routes to such composite materials and the studies of their applications will be substantially expanded in the future.

As to the applications of dendronized supports, it seems to-date only the "top layer" of their full potential has been revealed. Uses of MAPs, particularly as immunogenic conjugates, are well established and may have reached maturity, but some of the other applications, discussed in this article, are likely to be expanded. The positive dendritic effects on activity, selectivity, and recyclability observed in catalysis, and the broad range of the reactions tested with the supported dendritic catalysts are encouraging, as they point to the possibility of tailor-made suitable dendritic catalysts for improving a specific catalytic property for a given transformation. One may expect that the dendritic architecture will also open way to heterogeneous bifunctional catalysts, which are under-represented today in comparison to their soluble analogues. Dendritic architecture may add additional diversity elements to combinatorial studies of the supported catalysts (*e.g.*, Reymond's work).

The use of multivalency or preorganization of terminal groups has proven to be beneficial for various uses of the hybrid materials in separation studies. We may expect that the ability of chiral dendrons (internally chiral or bearing chiral terminal groups) to resolve enantiomer mixtures will be further exploited.

In addition to the already established or proposed applications, new ones may emerge, though naturally they are difficult to foresee. For instance, support-bound probes for investigation of enzymatic activity, which will exploit the multivalency and the proximity of the dendritic arms, may follow the examples of the detachable dendritic probes demonstrated by Bradley's group.[84] Supported dendron-incorporating constructs may emerge as important tools in discovering novel catalytic activities, because they enable preorganized immobilization of potential catalysts and multiple substrate units.

Today dendronized supports are well-established tools in the arsenal of synthetic, catalytic, and polymer chemists and their uses are extending to the areas of bio- and materials sciences. One may hope that new and fascinating synthetic schemes and applications will follow.

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