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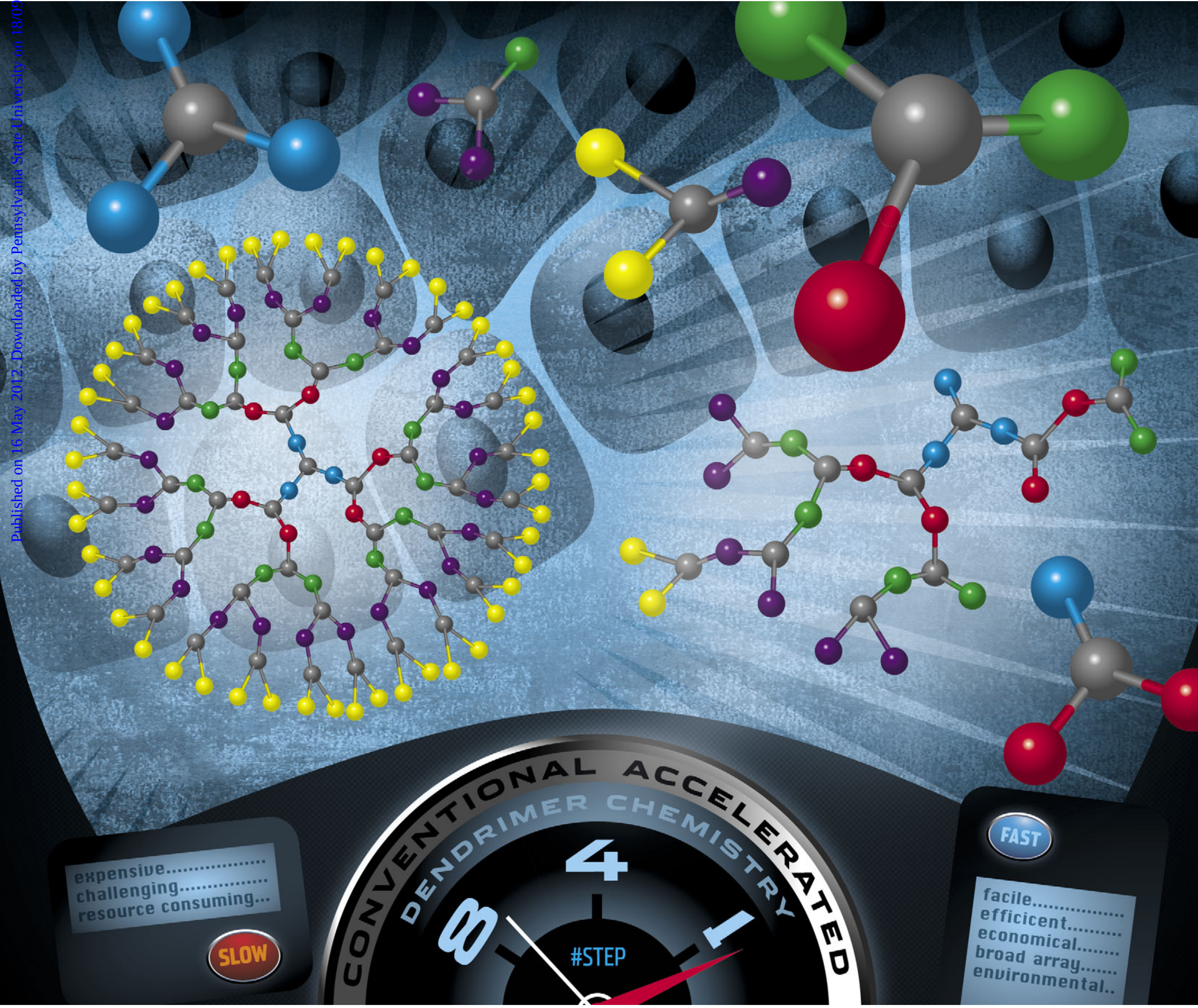

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TUTORIAL REVIEW

Simplifying the synthesis of dendrimers: accelerated approaches

Marie V. Walter and Michael Malkoch*

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Dendrimers are highly branched and monodisperse macromolecules that display an exact and large number of functional groups distributed with unprecedented control on the dendritic framework. Based on their globular structure, compared to linear polymers of the same molecular weight, dendrimers are foreseen to deliver extraordinary features for applications in areas such as cancer therapy, biosensors for diagnostics and light harvesting scaffolds. Of the large number of reports on dendrimer synthesis only a few have reached commercial availability. This limitation can be traced back to challenges in the synthetic paths including a large number of reaction steps required to obtain dendritic structures with desired features. Along with an increased number of reaction steps come not only increased waste of chemical and valuable starting materials but also an increased probability to introduce structural defects in the dendritic framework. This tutorial review briefly covers traditional growth approaches to dendrimers and mainly highlights accelerated approaches to dendrimers. A special focus capitalizes on the impact of the click chemistry concept on dendrimer synthesis and the promise it has to successfully accomplish highly sophisticated dendrimers, both traditional as well as heterofunctional, in a minimum number of chemical steps. It is clear that accelerated synthetic approaches are of greatest importance as these will encourage the scientific community to synthesize and access dendrimers for specific applications. The final goal of accelerated synthesis is to deliver economically justified dendritic materials for future applications without compromising the environmental perspective.

1. Introduction

Synthetic polymers are macromolecules that are typically constructed from interconnected chemical reactions of a large number of monomers (building units). The initial introduction of synthetic polymers in the 1830's is today reflected by an infinite number of structural variations that have ended in key components in products that us humans need to function in a modern society. Based on the tremendous requirements for future material breakthroughs, polymer scientists are currently focusing on assessing novel chemistries that can deliver polymers with accurate structural control and enhanced functions.

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Marie V. Walter was born in Mulhouse, France, in 1985. She graduated from Ecole Nationale Supérieure de Chimie de Paris (ENSCP), France, in 2008 with a MSc in chemistry. She is currently pursuing her PhD under the supervision of Associate Professor Michael Malkoch and Professor Anders Hult at KTH Royal Institute of Technology, in Stockholm, Sweden. Her research focuses on the design and synthesis of advanced dendritic macromolecules, their assembly into ordered and porous films, and their assessment as bioactive surfaces for biological applications.

Michael Malkoch

Michael Malkoch is an Associate Professor in functional macromolecules at KTH Royal Institute of Technology, Sweden. In 2003, he received his PhD in Polymer Technology from KTH which was followed by a post-doctoral visit to the US working closely with Prof. Craig J. Hawker at IBM Almaden, Stanford University and UC Santa Barbara 2003 to 2005. In 2007, he was awarded an independent grant from Swedish Research Council (VR) in materials science. Most recently, Malkoch received a prestigious personal grant from VR as a senior researcher in the field of biomedical engineering.

Dendritic polymers are a prime example of an important scientific breakthrough for the synthesis of sophisticated macromolecules.[1–3] These polymers are among the latest additions to the polymer family and are highly branched macromolecules, whose name originates from the Greek word "Dendron" meaning tree. The synthetic work on this class of materials was first approached by Vögtle *et al.* in 1978 who reported the synthesis of a branched polypropylene-amine structure: "cascade molecules" were generated through repetitive monomer addition and activation of the obtained branched molecule.[4] Even though the final branched structure was simple and of low molecular weight, their work is today recognized as the starting point for the research on dendritic polymers. Today, dendritic structures are typically divided into monodisperse dendrimers and dendrons, and polydisperse hyperbranched polymers, dendrigrafts and dendritic-linear hybrids such as dendronized polymers, Fig. 1.

The current research activities on dendritic polymers can be traced back to two original experimental reports published in the mid 1980's. These parallel synthetic investigations on high molecular weight and branched macromolecules were reported by Tomalia *et al.*[5] (Dow Chemical company) and Newkome *et al.*[6] who described on monodisperse poly(amidoamine) (PAMAM) dendrimers and on poly(etheramide) arborols, respectively. Within the class of dendritic polymers, dendrimers are today by far one of the most exciting structures to synthesize and access. In comparison to their linear analogues, with random coil conformations and polydisperse nature, dendrimers have attracted a lot of interest due to their high branching, multiple end-groups represented at the periphery of the framework and most importantly, their structural perfection. The flawless nature of a dendrimer can, in the simplest form, best be demonstrated by mass spectrometry analysis (MALDI-TOF). Fig. 2 (top) exemplifies the level of structural control for a water soluble polyester dendrimer, based on 2,2-bis(methylol) propionic acid (bis-MPA), with 96 reactive hydroxyl groups at the periphery and a theoretical molecular weight of 10 926.5 g mol^{-1}. The single peak detection for this dendrimer, including sodium as the counter ion, is remarkably precise with a molecular weight of 10 953.9 g mol^{-1}. For a direct comparison, a MALDI-TOF spectrum of a well-defined and water-soluble linear polymer, polyethylene glycol (PEG), with an average molecular weight of 10 000 g mol^{-1} and a polydispersity index (PDI) below 1.05, can be seen in Fig. 2 (bottom). Interestingly, the main inflection point for the linear polymer is detected around 11 000 g mol^{-1} and

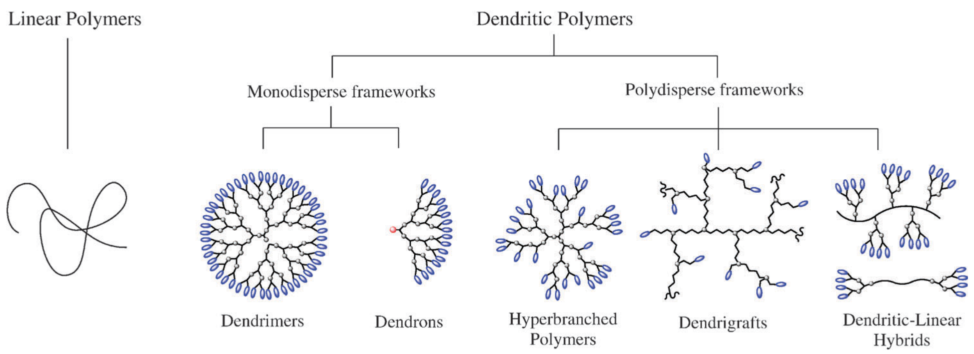


Fig. 1 Schematic overview of the sub-classes of the family of dendritic polymers.

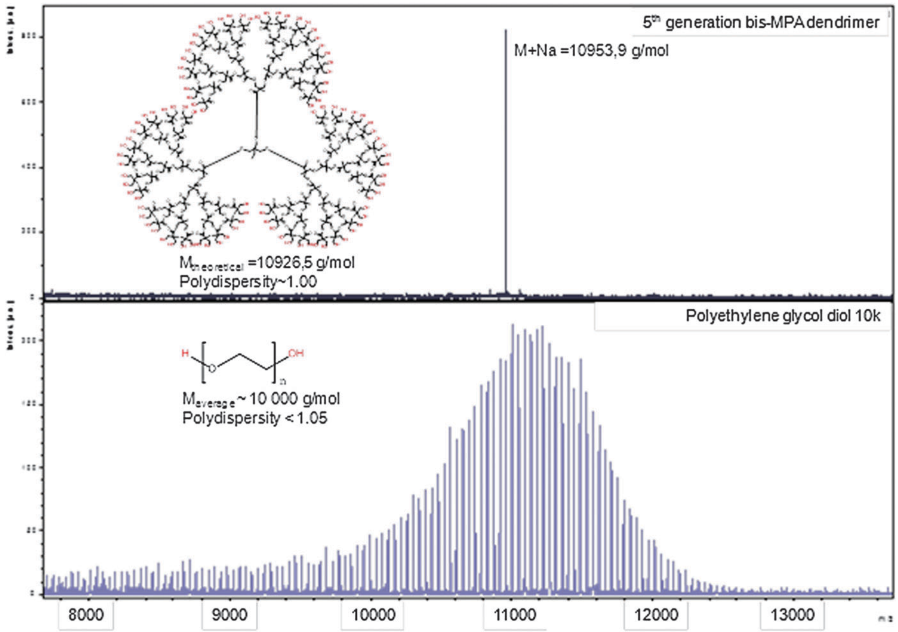


Fig. 2 MALDI-TOF spectra of a monodisperse generation five bis-MPA dendrimer (top) and well-defined linear polyethylene glycol (bottom).

molecular weight variations are found over a range of several thousand daltons.

As a result of the unique properties of dendritic polymers, scientists are foreseeing an exciting potential in cutting-edge applications such as sensors, moieties for light-harvesting, surface engineering, enzyme-like catalysis, targeted drug-delivery, macromolecular carriers, and in biomimetic applications among others.[7–11] An intriguing recent application that makes use of the structural perfection of dendrimers can be found in the commercially available mass spectrometry calibrants Spherical®. These storage stable and premixed calibrant kits are organo soluble that find use in simple analysis of both oligopeptides as well as polymers.[12]

The framework of a dendrimer consists of interconnected AB_n monomers where A and B are two different functionalities and n is a number higher than or equal to two. A dendrimer consists of a multifunctional core moiety, typically di-, tri- or tetra-functional, capped with several layers of branched monomers, each layer being called a generation (G). The regularly branched framework has an outer layer that is decorated with a large number of activated functional groups that can undergo further growth or post-functionalizations. The structure of the dendrimer can also be divided into fragments called dendrons, which are wedges going from the core to the periphery of the dendrimer. A schematic picture of a four generation dendrimer is presented in Fig. 3.

Even though dendrimers are considered one of the most exciting and sophisticated synthetic macromolecules for application driven research,[7] their commercial breakthrough is to date limited. This can be traced back to the challenging synthetic schemes required to obtain structurally perfect dendrimers. This tutorial review intends to give an insight into accelerated synthetic strategies that can minimize the number of reaction steps to dendrimer synthesis and thereby also increase their availability.

2. Conventional synthesis

Dendrimers are usually synthesized using a chain of iterative growth and activation steps. Because of their perfectly branched structure, the synthesis of dendrimers requires the use of robust organic reactions that can efficiently proceed even at a macromolecular level. There are two main synthetic strategies to accomplish dendrimers, the divergent and the convergent growth approach. These strategies, as well as, their revised versions are described below in Fig. 4.

a. Divergent growth

The first reports on dendrimer synthesis[4–6] employed the divergent growth strategy. In the divergent growth approach, also called the inside-out approach, the growth of the dendrimer is initiated from a multifunctional core, B_n ($n \geq 2$). The monomer used is of the AB_n type ($n \geq 2$) where A is an activated group while B is deactivated/protected to permit controlled growth. The active B functionalities of the core are reacted with an excess of the A functionalities of the AB_n monomer, forming the first dendritic layer. In order to continue the growth, the B functionalities of this first layer are activated/deprotected, resulting in a first generation reactive dendrimer. Thereafter a new monomer layer can be added to the macromolecule which results in a generation two dendrimer. Repetition of these growth and activation steps leads to an increase in dendrimer generation, as well as an increase in the number of functional end-groups, Fig. 4. Upon reaching the desired generation, the functional groups at the periphery are available for further post-functionalization. A major drawback of the divergent growth strategy is the risk of building dendrimers with structural defects, which are impossible to separate from perfect dendrimers. Structural defects are the result of incomplete conversion of all the end-groups, which is mainly caused by surface crowding occurring for high generation dendrimers. However, since the divergent growth approach only requires an excess of inexpensive monomers and reagents, most of the commercially available dendrimers are prepared using this strategy.

b. Convergent growth

In the 1990's, Hawker and Fréchet introduced the convergent growth approach as an alternative route to construct dendrimers.[13] This method relies on the construction of perfectly branched dendrons (dendrimer wedges), which are finally coupled to a core moiety after activation of their focal point. The dendrons are obtained by either the convergent or the divergent route *via* growth and activation steps. In order to enable further functionalization of the dendrimer after coupling of the dendrons to the core, the end-groups need to be activated, Fig. 4. In comparison to the divergent method, the monitoring of the dendron growth is more straightforward *via* this strategy since dendrons are intrinsically less complicated than dendrimers. As a result, the risk of structure defects within the dendron is lower. However, with increased dendron size follows lower reaction efficiency of the dendron core because of steric hindrance.

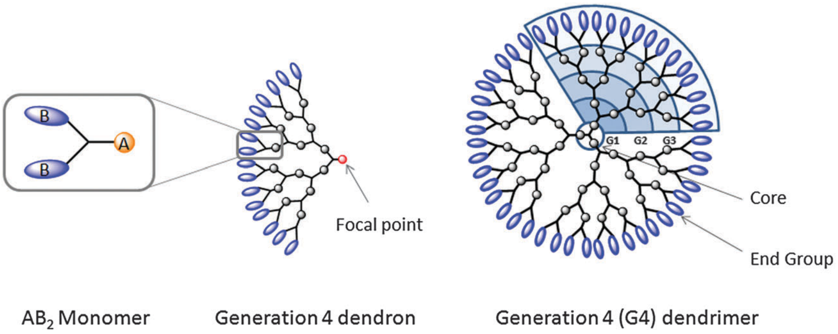


Fig. 3 Schematic drawing of an AB_2 monomer and its subsequent use for the synthesis of a generation four dendron and a generation four dendrimer with a tri-functional core.

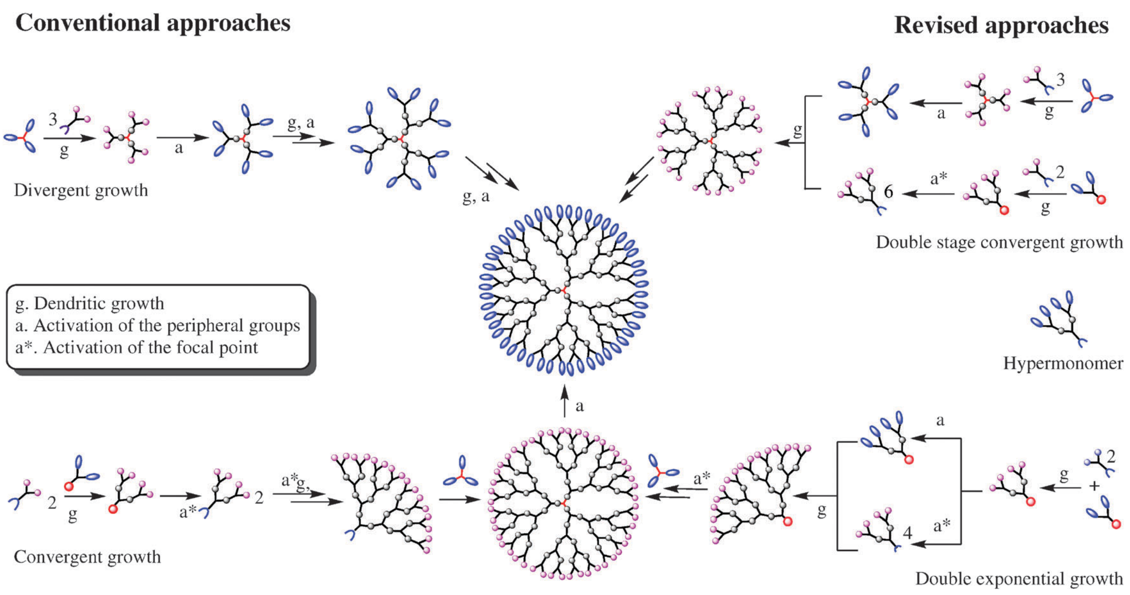


Fig. 4 Schematic overview of conventional and revised growth strategies, including growth (g) and activation (a, a*) steps, for the synthesis of dendrimers.

This leads to partly substituted dendrimers in the final reaction step. To suppress defects and drive the reactions to completion, it may be necessary to use a larger excess of dendrons and/or include a core moiety of a more extended nature. The main drawback of this approach is the loss of valuable high generation dendrons coupled with lower yields for higher generation dendrimers. This limits the use of the convergent growth strategy for the production of commercial dendrimers.

3. Accelerated synthesis

a. The need of efficient synthetic protocols

The two conventional approaches described earlier are based on a repetition of growth and activation steps, which makes the synthesis of dendrimers tedious and time-consuming. With increasing generation, the risk of introducing defects within the structure increases. As a result, the perfect and monodisperse nature of a dendrimer can be jeopardized by each extra reaction step. For example, starting from a tri-functional core and an AB_2 monomer, the synthesis of a generation four dendrimer, having 48 active end-groups, requires no less than eight synthetic steps. Moreover, at a higher generation, the dendrimer synthesis will require a larger excess of reagents and key dendritic building blocks to ensure full substitution of all reactive groups. It is obvious that an accelerated strategy to dendrimers, with focus on reducing the number of reaction steps, will not only lower the consumption of chemicals and valuable starting materials but also be more time- and cost-effective. From a scientific point of view, a reduction in the number of reaction steps will make dendrimers less challenging to obtain and their availability larger to a broader scientific community. Commercially, the acceleration will provide a larger worldwide use of dendrimers at lower production costs and most importantly their construction by a more environmentally friendly route.

Therefore new strategies have been and continuously are introduced to facilitate new and already reported dendrimers syntheses using accelerated approaches. These strategies are the object of the session below.

b. Defining what is accelerated in dendrimer chemistry

The field of dendrimer synthesis is progressing towards faster and simpler synthetic methodologies to obtain dendrimers of high molecular weights without compromising the large number of functional groups. The definition of accelerating the synthesis of dendrimers is obtaining a higher branching and/or number of functional groups through fewer reaction steps. Today, several parameters have been identified to accelerate the synthesis of dendrimers.

- The *selection of building-blocks* is crucial, since the composition, number and nature of the functional groups dramatically affect the dendrimer structure. The monomers are used in excess during the synthesis and commercially available molecules are therefore preferred. Monomers that can be synthesized in a straightforward manner and on a large scale can also be considered. More complicated and exclusive building-blocks would counteract the concept to accelerate the synthesis of dendrimers and therefore limit future research investigations of such dendrimers.
- The *number of reactions* leading to a new generation is significant. In the conventional strategies, two iterative steps, growth and activation, are necessary for generating a new dendrimer generation (layer). Performing the growth without the need of an activation step would yield dendrimers in half the number of reaction steps.
- *One-pot chemistries* are other alternatives to consider, since the number of purification steps required can be severely decreased thus shortening the overall reaction time and particularly the time needed for purification of target dendrimers.

c. Revised traditional approaches

Three different accelerated growth approaches to dendrimers make use of the traditional growth and activation strategies.

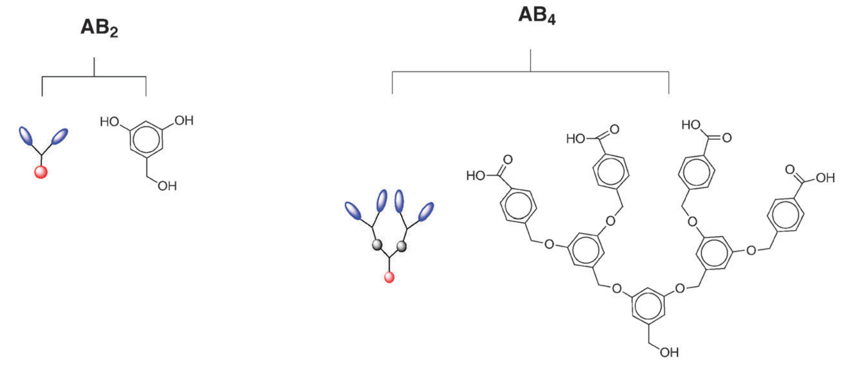
These approaches were reported in the early 1990's, since scientists had already then recognized the need for simpler routes to construct dendrimers without risking their perfection.

i. Hypermonomer strategy. The hypermonomer strategy employs monomers having a higher number of functional groups as compared to the conventional AB_2 monomer, Fig. 5. Typically, monomers such as AB_4 or AB_8 have been used. As a result, a dendrimer having a high number of functional groups can be obtained in fewer steps. For example, while a dendrimer of generation four built from a trifunctional core and AB_2 monomers requires 8 synthetic steps, the use of AB_4 monomers results in a dendrimer having the same number of functional groups in only four steps. However, the hypermonomers are usually dendrons of low generation, whose synthesis requires several growth and activation steps. Therefore, the acceleration is in this case limited to generating dendrimers in fewer steps, without considering the time required for monomer synthesis.

The hypermonomer approach was first reported by Fréchet *et al.* who coupled a third generation dendron (AB_8 hypermonomer) to an AB_4 hypermonomer to obtain a fifth generation dendron. However, the final product was obtained in low yield due to steric hindrance and low reaction efficiency.[14] The same group also investigated the synthesis of a poly(aryl ether) dendron by reacting a second generation dendron with an AB_4 hypermonomer. The fourth generation poly(aryl ether) dendron was obtained after only 6 synthetic steps.[15] Dendrimers based on an AB_3 monomer, methyl 3,4,5-trihydroxybenzoate[16] and on an AB_4 monomer having four dienophile units and one diene function[17] have successfully been reported. However, the synthesis of hypermonomers is still a tedious process and therefore this strategy has not been extensively used.

ii. Double stage convergent growth. The double stage convergent growth strategy relies on the parallel synthesis of a hypercore (low generation dendrimer) and low generation dendrons, which are coupled to each other in a final step, Fig. 4. The advantage of this strategy relies on the use of a hypercore, which limits the problems of steric hindrance and thereby facilitates access to higher generation dendrimers. Using this approach, Fréchet *et al.* reported the synthesis of a seventh generation dendrimer in only one coupling step.[18] They synthesized a third generation dendrimer using the conventional convergent growth, which was subsequently used as a hypercore to which fourth generation dendrons were attached. The seventh generation dendron was obtained in 61% yield. The reaction was made possible by the introduction of spacers between the benzyl rings of the hypercore, which resulted in a less compact structure, Fig. 6. Even though this approach seems promising, the synthesis of the hypercore required 10 steps. Using a similar strategy, Bair *et al.* prepared a third generation dendrimer by coupling second generation dendrons to a hexafunctional core. They observed that the coupling of the first three dendrons occurred rapidly, while the substitution of the remaining functional groups was difficult, probably because of a higher number of non-productive collisions.[19] This route was also used by Moore *et al.* for the synthesis of a fourth generation dendrimer by coupling of second generation dendrons to a second generation dendrimer.[20] A well-defined macromolecule was in this case observed by SEC and attributed to the fully substituted product. Despite the limited number of coupling steps necessary for the synthesis of a high generation dendrimer, this method has not been extensively used since the preparation of the dendrons and the hypercore is time consuming. These structures are usually prepared using the conventional growth approach and their synthesis therefore requires many synthetic steps. For example, the preparation of the hypercore and dendrons used by Moore *et al.* required four synthetic steps each. Consequently, the fourth generation dendrimer was obtained after a total of nine steps. Because of the tedious preparation of the dendrons and the hypercore, the use of this method should be limited to the preparation of dendrimers of higher generations that cannot be obtained through conventional methods.

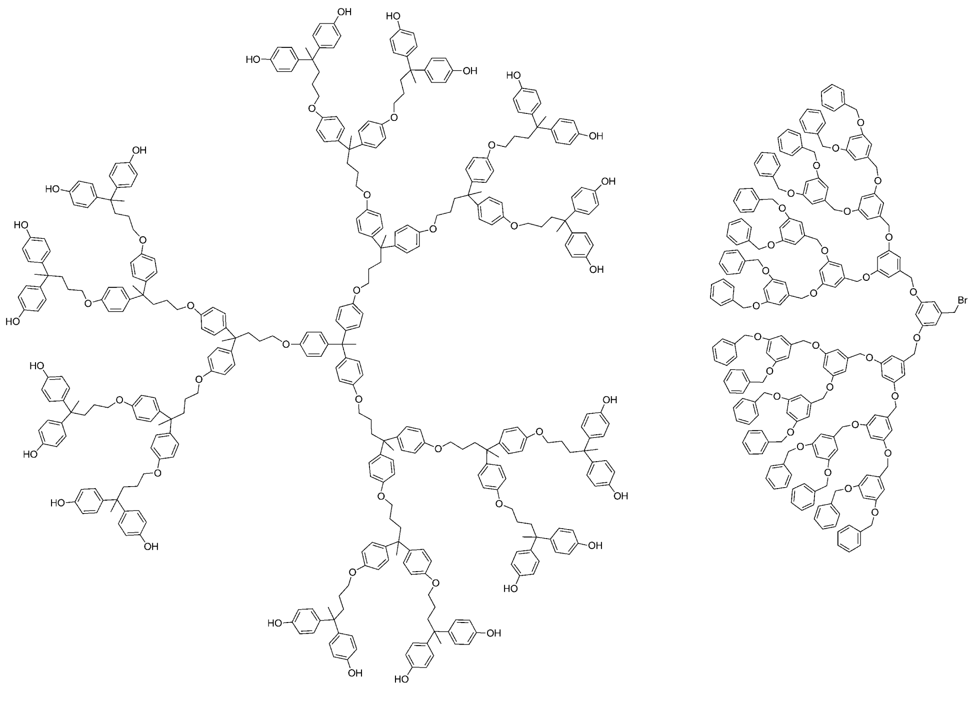
iii. Double exponential growth. The double exponential growth strategy relies on the preparation of fully protected/deactivated low generation dendrons. The dendrons are later activated selectively, either at their focal point or at the periphery and then coupled together to obtain a higher generation of a fully protected dendron. These steps are repeated and, in a final step, the focal points of the dendrons are activated and coupled to a multifunctional core, Fig. 4. This concept was first developed by Moore *et al.* in 1995.[21] Theoretically, using this approach, a generation seven dendrimer can be obtained after 9 synthetic steps whereas fourteen synthetic steps would be necessary to obtain a similar structure with a conventional approach. Hult *et al.* further developed this approach for the synthesis of a hydroxyl activated 2,2-bis(methylol)-propionic acid (bis-MPA) dendrimer, Scheme 1.[22]



Conventional monomer

Hypermonomer
(low generation dendron)

Fig. 5 Example of a conventional monomer and a hypermonomer for dendrimer synthesis.[14]



Hypercore

Fourth generation dendron

Fig. 6 Fréchet's hypercore and fourth generation dendron used for the synthesis of a seventh generation dendrimer.[18]

They initially synthesized a second generation dendron, bearing two acetonide protective groups at the periphery and a single benzyl ester protective group at the focal point, using a conventional growth approach. After selective deprotection at the focal point or at the periphery, the two dendrons were coupled to yield a fully protected fourth generation dendron. Finally, the activation of the core enabled the attachment of three dendron wedges to a trifunctional core, which resulted in a fully protected fourth generation bis-MPA dendrimer. After deprotection, a fourth generation dendrimer, comprising 48 hydroxyl groups, was obtained in a total of seven synthetic steps, not including the activations of the monomer unit. However, with increasing generations the yield of the reactions decreases, suggesting that applying this method to high generation dendrimers might be difficult. Identical dendrimers are currently synthesized *via* the divergent growth approach which can deliver a generation four bis-MPA dendrimer in 8 steps and on a multigram scale.[23]

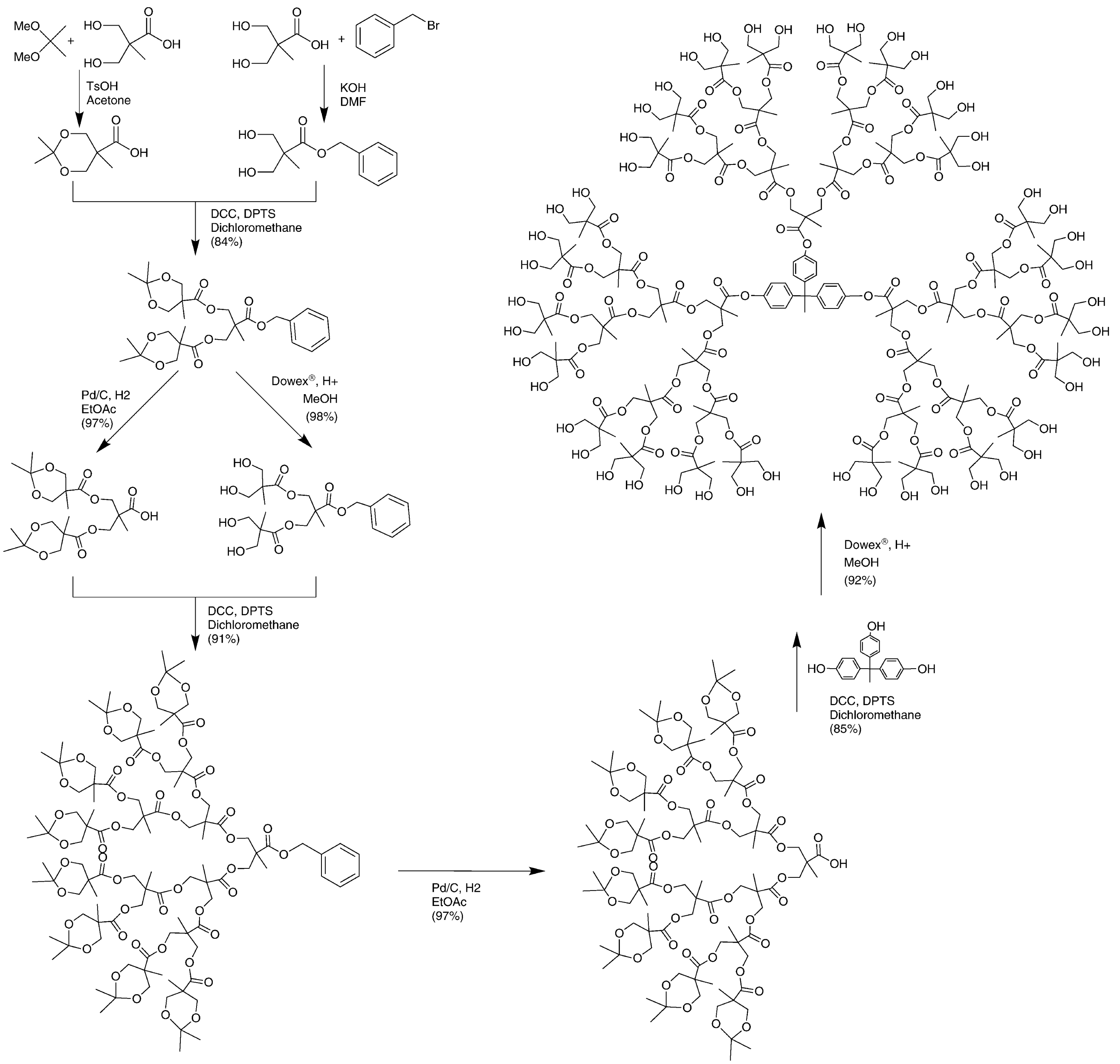
4. Orthogonal and chemoselective growth strategies

It is apparent that the acceleration is limited for the revised traditional strategies. To fully accelerate the synthesis, it is of utmost importance to eliminate the iterative activation steps. This can be and has been accomplished by introducing two or more robust and chemoselective reactions that can coexist during orthogonal growth of dendrimers. Several orthogonal growth concepts will be discussed below.

a. Chemoselective reactions

Nature's important macromolecules, such as proteins, natural products or DNA, are constructed in complex environments *via* simultaneous and/or cascade reactions. Scientists are today considering this chemoselective strategy as the new promising route for the synthesis of complex macromolecular architectures in a limited number of steps. The concept of chemoselectivity was introduced and coined in 1977 by Barany and Merrifield through the definition of an orthogonal system.[24] While this strategy has typical use in peptide synthesis, its use for the construction of dendritic materials was first attempted in 1993 by Spindler and Fréchet, who combined carbamate and etherification reactions for the orthogonal growth of arylic dendrons.[25] Unfortunately, the poor efficiency and chemoselectivity of both reactions resulted in dendrons of low generations.

The number of dendrimers constructed using chemoselective and orthogonal approaches has increased dramatically as a consequence of the recent introduction of the click chemistry concept. The initial click concept was introduced in 2001 by K. B. Sharpless and co-workers[26] and is now integrated in most research fields related to chemistry, as can be seen by the large number of reviews published on this subject.[27–31] The click chemistry concept applies to a range of reactions that form stable products with no or few by-products. Furthermore, to be considered as a click reaction, the reaction must be highly efficient with yields close to 100%, wide in scope, and tolerant to other functional groups. To date, the most studied click reaction is the copper catalyzed Huisgen 1,3-dipolar cycloaddition between azides and primary acetylenes (CuAAC), which selectively forms the 1,4-substituted 1,2,3-triazole, Scheme 2. The exothermic CuAAC reaction displays a large thermodynamic driving force (84 kJ mol^{-1}) to favor a single product. In 2004, the CuAAC reaction was first reported

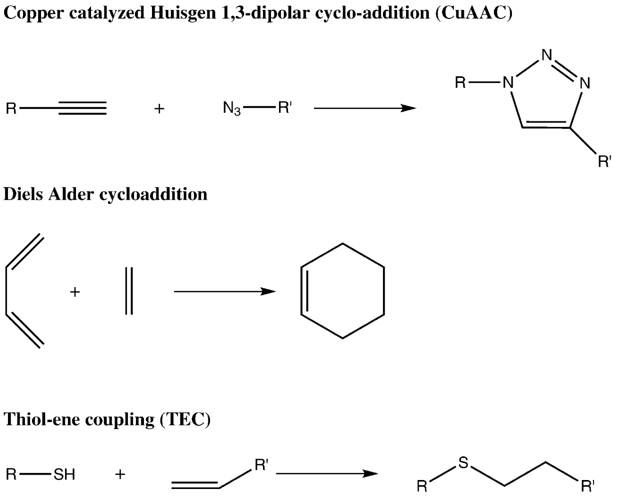


Scheme 1 Seven consecutive steps to construct a generation four bis-MPA dendrimer *via* the double exponential growth method as reported by Hult *et al.*[22]

as a chemical reaction for the conventional growth synthesis of triazole containing dendrimers.[32] Furthermore, the advantages of this reaction include unprecedented features, such as high yields and simple purification through extraction. Presently, the click concept has proven to be a reliable synthetic platform to deliver complex macrostructures.[33–35] The concept is today extended to include the Diels–Alder (DA) cycloaddition as well as the thiol–ene coupling (TEC), Scheme 2. The potential of the DA addition reaction for dendrimer synthesis has already been demonstrated in 1997 by Müllen *et al.* in the preparation of a polyphenylene dendrimer.[36] In 2008, Hawker *et al.* illustrated the power of UV initiated TEC for the divergent growth of a generation four polythioether dendrimer.[37] Chemists are still proposing new chemical reactions as click reactions, which has initiated a debate on the subject in order to protect the concept.[38]

b. Orthogonal growth

The orthogonal strategy relies on the divergent growth approach of dendrimers using different monomers, for example AB_x and CD_y, instead of a single AB_n monomer. The monomers have chemoselective groups appropriately chosen so that the A functionality selectively reacts with the D functionality, while the B functionality only reacts with the C functionality, Fig. 7. Such chemoselectivity makes the deprotection/activation steps obsolete, thereby reducing the number of reaction steps during dendrimer growth. The obtained dendrimer is characterized by



Scheme 2 Schematic representation of common click reactions.

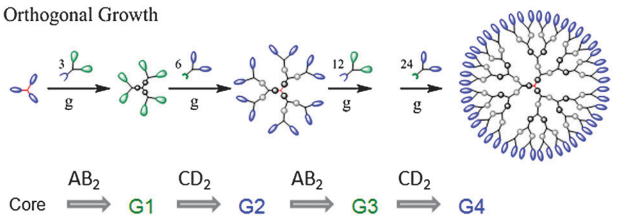


Fig. 7 Schematic overview of the orthogonal growth (g) approach.

a layered structure containing different covalent linkages between the layers. The nature of the monomers also results in alternating reactive chain-end functionalities being displayed with each generation. Using this method, a generation four dendrimer can be synthesized in 4 steps.

A comparison of the increase in the number of functional groups for different types of monomer combinations is presented in Fig. 8. When using a conventional approach a combination of an AB_2 monomer and a multifunctional core for the growth is followed by an activation step. This step is herein represented by a CD monomer and therefore does not affect the number of functionalities. The resulted increase in the number of end-groups is relatively slow, doubling only with every second step. By reacting an AB_2 monomer with a CD_2 monomer the number of functional groups is doubled with each generation. Further increasing the functionalities of the monomers will dramatically affect the number of end groups. For instance, the combination of AB_5 and CD_5 monomers with a trifunctional core results in 375 end groups after only three steps. Interestingly, such a comparison was reported by Majoral *et al.* in 2005 on inorganic phosphorus-containing dendrimers. In the same report, the synthetic growth versatility was successfully accomplished by changing the functionality of the core to a B or D type and consequently inverting the order of the reaction steps between AB_2 and CD_2 monomers.[39]

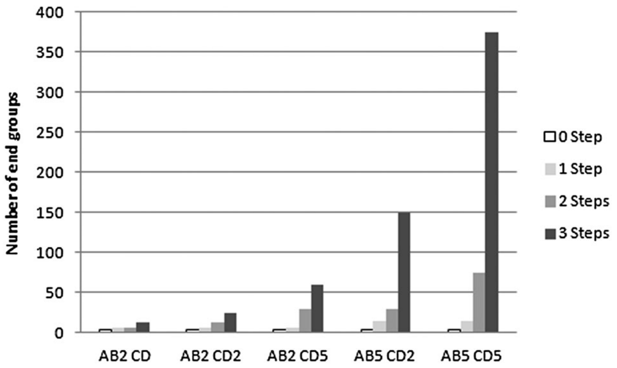


Fig. 8 Effect of the monomer structure on the final number of functional groups located at the outer layer of a dendrimer built from a trifunctional core.

The marriage of the click concept and the orthogonal strategy was initially introduced by Malkoch *et al.* in 2007, who reported on the accelerated synthesis of three sets of generation four dendrimers, two bis-MPA based and one Fréchet type.[40] The accelerated divergent growth strategy relied on the use of AB_2 and CD_2 monomers. It is apparent from the number of structures presented in Table 1 that the orthogonal growth approach is an important and permanent breakthrough in dendrimer synthesis, since this approach dramatically reduced the number of consecutive reaction steps necessary for the preparation of a high generation dendrimer while maintaining a large number of functional groups. One of the most recent synthetic accomplishments in dendrimer chemistry was jointly reported by Malkoch and Hawker, who demonstrated the power of this strategy by synthesizing a dendrimer of generation six in one day.[41] They designed two new monomers, AB_2 having one thiol and two azide functional groups and the other, CD_2, having one alkyne and two alkene functionalities. By successively combining two different click reactions, thiol–ene and CuAAC, they could efficiently synthesize a generation six dendrimer in less than 24 hours, each reaction step, including purification, being performed in less than 3 hours.

c. One pot synthesis

In order to facilitate the synthesis of dendrimers in fewer steps, scientists have been looking at the possibility of eliminating the need for purification steps. This is made possible through the use of one pot synthesis. One pot multi-step reactions can be divided into two main categories: the non-tandem reactions (NTRs) and the tandem reactions (TRs). NTRs are based on chemical reactions that take place consecutively, one at a time. Unlike NTRs, TRs are based on chemical reactions that take place independently of one another, and can therefore occur simultaneously. A more complete description of these systems can be found in the review by Malkoch *et al.*[49] The first attempt to synthesize dendrimers in a one pot system was made in the 1990's, but this attempt resulted in non-perfect dendrimers with PDI values of up to 1.4.[50] The first successful synthesis of a dendrimer *via* a one pot process was reported by Rannard and Davis who prepared a third generation carbonate dendrimer in four steps employing a convergent growth approach and NTRs with sequential additions of the reagents.[51] The synthesis was performed on a large scale (100 g) and after simple purification the dendrimer was obtained in 89% yield. At the same time, the synthesis of a fourth generation phosphorous dendrimer through a divergent

Table 1 Overview of the AB_x and CD_y systems where x and $y \geq 2$[25,39–48]

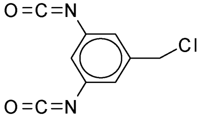
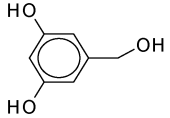
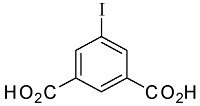
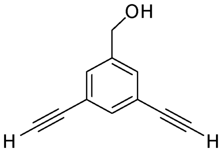
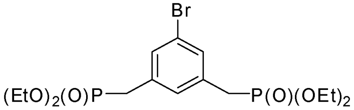
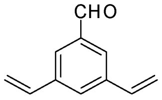
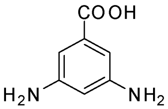
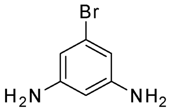
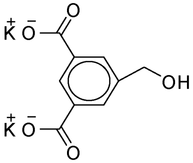
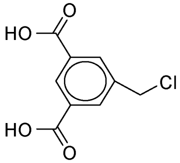
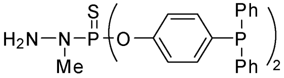
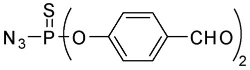
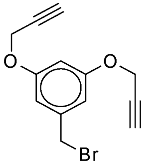
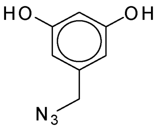
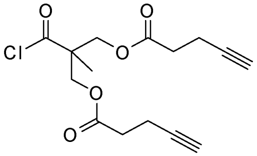
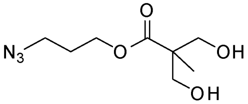
Dendrimer	AB_x monomer	CD_y monomer	Reaction sequence	Number of reactions	Generation	Core functionality	Number of end groups	Mw g mol^{-1}	Ref.
Fréchet type			Carbamate formation/ etherification	3	G3 (dendron)	—	8	1766	25
Zimmerman			Mitsunobu esterification/ Sonogashira reaction	4	G4 (dendron)	—	16	5169	42
Poly(phenylenevinylene)			Horner-Wadsworth-Emmons reaction/Heck coupling	4	G4 (dendron)	—	16	4966	43
Fréchet type			Condensation/CO insertion	4	G4 (dendron)	—	16	3736	44
Fréchet type			Carboxylate salt alkylation/ esterification	3	G3 (dendron)	—	16	4151	45
Phosphorous			Staudinger reaction/ condensation	4	G4	3	48	19 674	46
Fréchet type			Etherification/CuAAC	4	G4	3	48	8240	40
Bis-MPA type			Esterification/CuAAC	4	G4	3	48	10 962	40

Table 1 (*continued*)

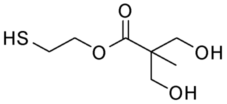
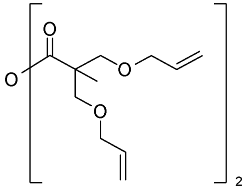
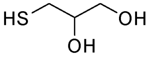
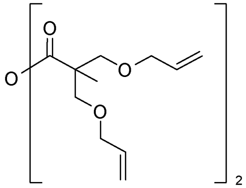
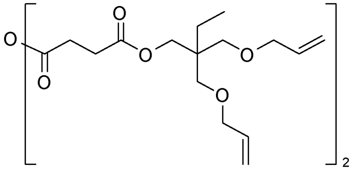
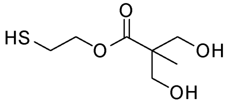
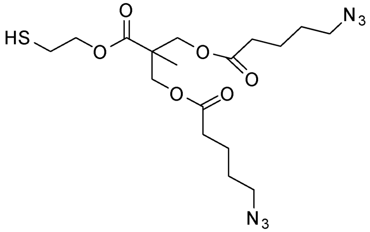
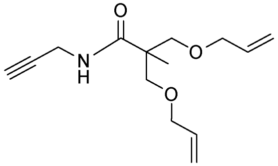
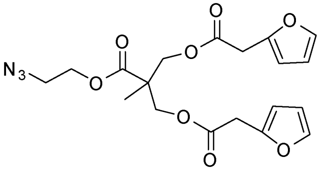
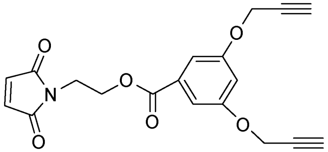
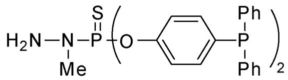
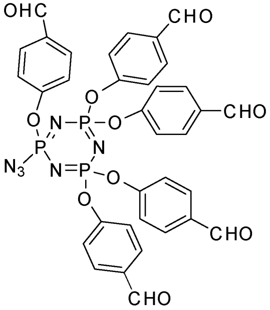
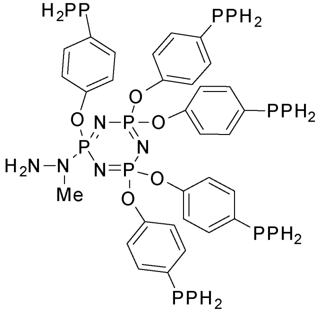
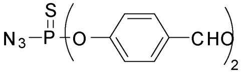
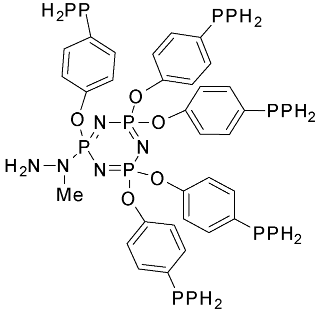
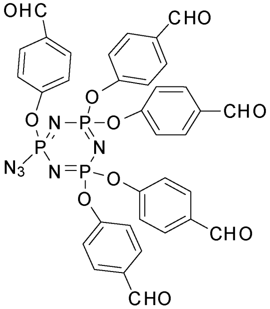
Dendrimer	AB$_x$ monomer	CD$_y$ monomer	Reaction sequence	Number of reactions	Generation	Core functionality	Number of end groups	Mw g mol^{-1}	Ref.
Bis-MPA type			Thiol-ene/Esterification	5	G5	3	96	18 372	47
Hybrids			Thiol-ene/Esterification	4	G4	3	48	7759	47
Hybrids			Esterification/Thiol-Ene	5	G5	3	96	24 616	47
Bis-MPA type			Thiol-Ene/CuAAC	6	G6	3	192	59 919	41
Bis-MPA type			CuAAC/Diels Alder	3	G3	3	24	8132	48

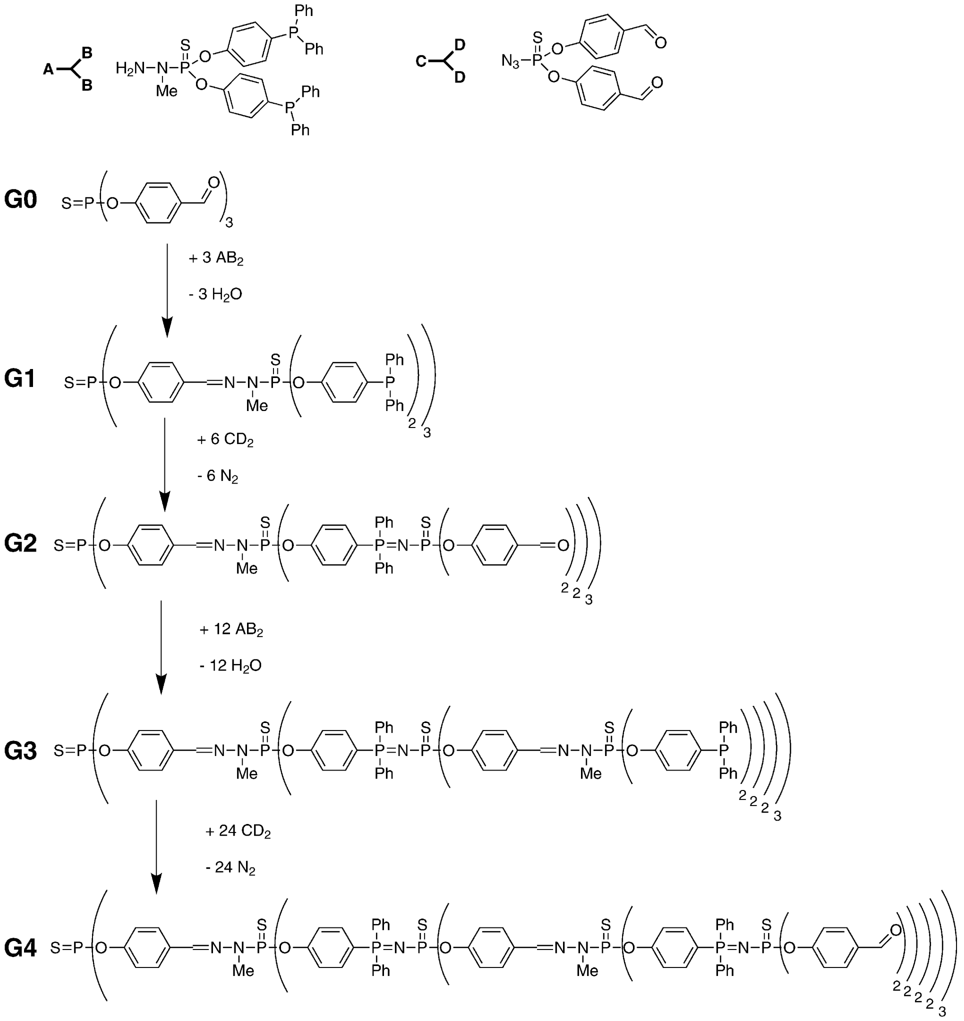
Table 1 (*continued*)

Dendrimer	AB_x monomer	CD_y monomer	Reaction sequence	Number of reactions	Generation	Core functionality	Number of end groups	Mw g mol^{-1}	Ref.
Phosphorous			Staudinger reaction/ condensation	4	G4	6	600	143 006	39
Phosphorous			Staudinger reaction/ condensation	4	G4	6	600	208 417	39
Phosphorous			Staudinger reaction/ condensation	3	G3	6	750	265 048	39

growth approach and a one pot multi-step reaction strategy was presented by Majoral *et al.*[46] This strategy takes advantage of two orthogonal reactions, namely the condensation reaction between an aldehyde and a hydrazine and the Staudinger reaction between an azide and a phosphine. Interestingly, the only byproducts during the one pot synthesis are water and nitrogen gas, Scheme 3. A fourth generation dendrimer could be obtained after four steps and its monodispersity was confirmed by SEC. However a slight broadening of the peak was observed, as compared to a fourth generation dendrimer synthesized through a step-by-step process. Moreover, a strict control of the stoichiometry was necessary to avoid the formation of byproducts such as low molecular weight dendrimers and dendrons. One pot synthesis can also be applied for the post-modification of traditional dendrimers. For instance, Hawker and co-workers successfully post-functionalized the end-groups of a generation four amino functionalized polypropylenimine dendrimer (PPI). They performed an amidation reaction followed by a CuAAC click reaction to obtain the final fully PEG-ylated dendrimer in 78% yield.[52] Despite the many advantages of these strategies, the synthesis of a perfect structure *via* one-pot reactions is still difficult to execute because of the need to perfectly control the stoichiometry of the reagents to avoid the formation of byproducts. Therefore, the number of reports on one pot strategies for the synthesis of monodisperse dendrimers is low.

d. Heterofunctional dendrimers

One of the main benefits of dendrimers is the ability to include a large and exact number of different functional (heterofunctional) groups within the framework without compromising the structural perfection. The initial proposal of heterofunctional dendrimers (HFDs) having dual-purpose properties was in fact a fourth generation convergently grown polyether dendron that was finally coupled to a fullerene core.[53] The resulted fullerene–dendritic hybrid, as described by Fréchet, combined the conductive properties of fullerene and insulating properties of the dendron shell. Similar structures have been synthesized using chiral, fluorescent or photochemically responsive molecules as a core.[54] HFDs are today recognized as state-of-art multipurpose scaffolds having a larger number of potential applications than traditional dendrimers.[55] As a consequence of their potential, scientists have successfully established accelerated synthetic protocols for the development of HFDs having heterofunctionalities that are expressed differently within the dendritic framework.



Scheme 3 Majoral's synthesis of a fourth generation dendrimer using orthogonal chemistries.[46]

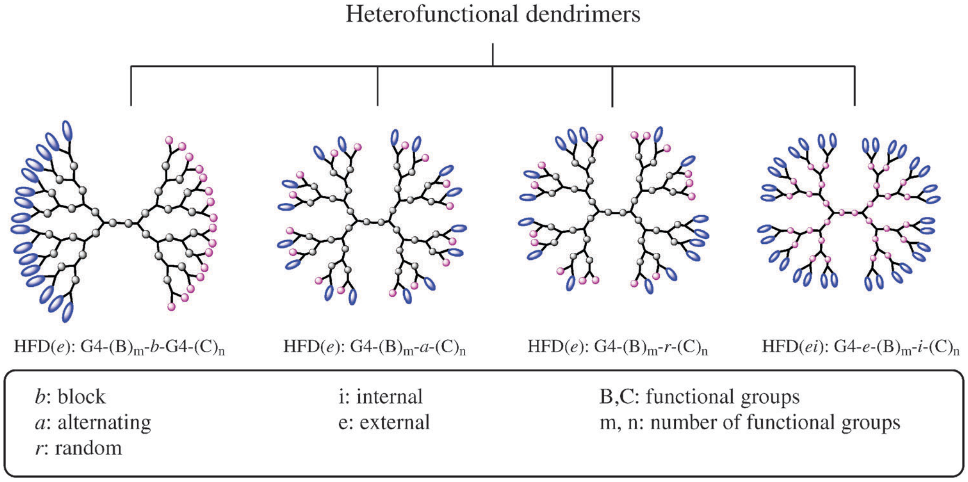


Fig. 9 Schematic representation of possible heterofunctional dendrimers of fourth generation expressing dual-functionality.

To clarify the structural variations found in the literature, a nomenclature for HFDs is of importance and proposed below. A fourth generation HFD is used as a model system, expressing bifunctionality and based on a dual-functional core, Fig. 9. The typical variations found for such structures can be divided into four subgroups and prioritized by: (i) the type of dendrimer (HFD), (ii) the location of the heterofunctionality (external (*e*) or internal (*i*) or their combination (*ei*)), (iii) the generation (G4 in this case) of the dendrimer or dendron and its functional group (in this case B or C) and the number of functional groups (*m* or *n*), and (iv) the location of the different functionalities with respect to each other (block (b); alternating (a) or random (r)). These structures are divided into four different subgroups, namely HFD expressing external functionality that separates the groups in blocks, HFD with external functionality with either alternating or random distribution of the groups and HFD with external and internal functional groups, Fig. 9.

The consequence of architectural alternations, as are illustrated in Fig. 10, has a dramatic impact on the number of functional groups with respect to generation. In the cases shown, a fifth generation HFD(*e*) synthesized from an AB$_2$-type monomer will possess a total of 64 peripheral groups. This can have an equal number of (32 + 32) B and C functionalities either distributed in two separate dendron blocks (HFD(*e*)-G5-$(B)_{32}$-*b*-G5-$(C)_{32}$) or alternating (HFD(*e*)-G5-$(B)_{32}$-*a*-$(C)_{32}$) with respect to each other. While equal in the number of external functional groups, the major difference between these two dendrimers is the number of reaction steps as the HFD(*e*)-alternating can be accomplished in half the number of reaction steps. To further accelerate the accessibility of HFDs, alternative scaffolds making use of both the external (*e*) and the internal (*i*) framework can be constructed, HFD(*ei*). These structures rely on AB$_2$C-type monomers that, if successfully grown from a difunctional core, will generate a fifth generation dendrimer displaying a total of 126 functional groups distributed between 64 external B and 62 internal C groups (HFD(*ei*)-G4-*e*-$(B)_{64}$-*i*-$(C)_{62}$). The choice of the core molecule also dramatically influences the number of functional groups: a dendrimer with

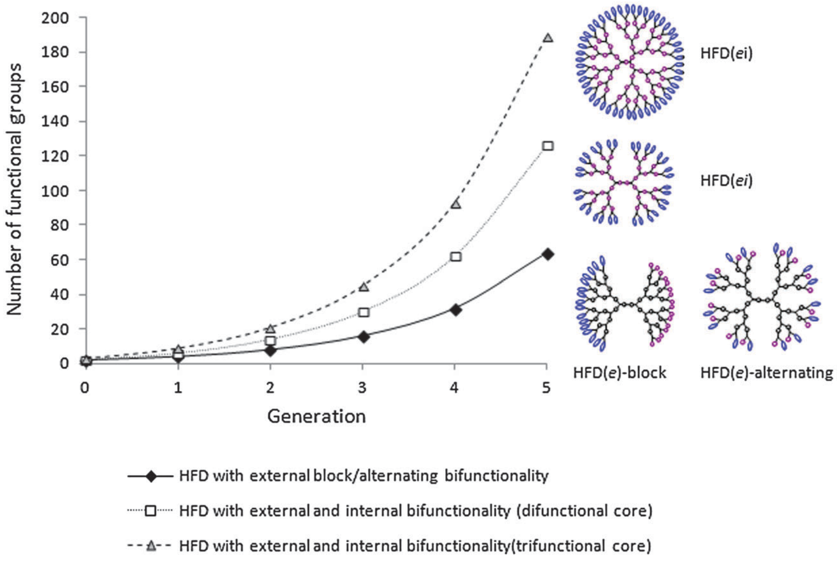
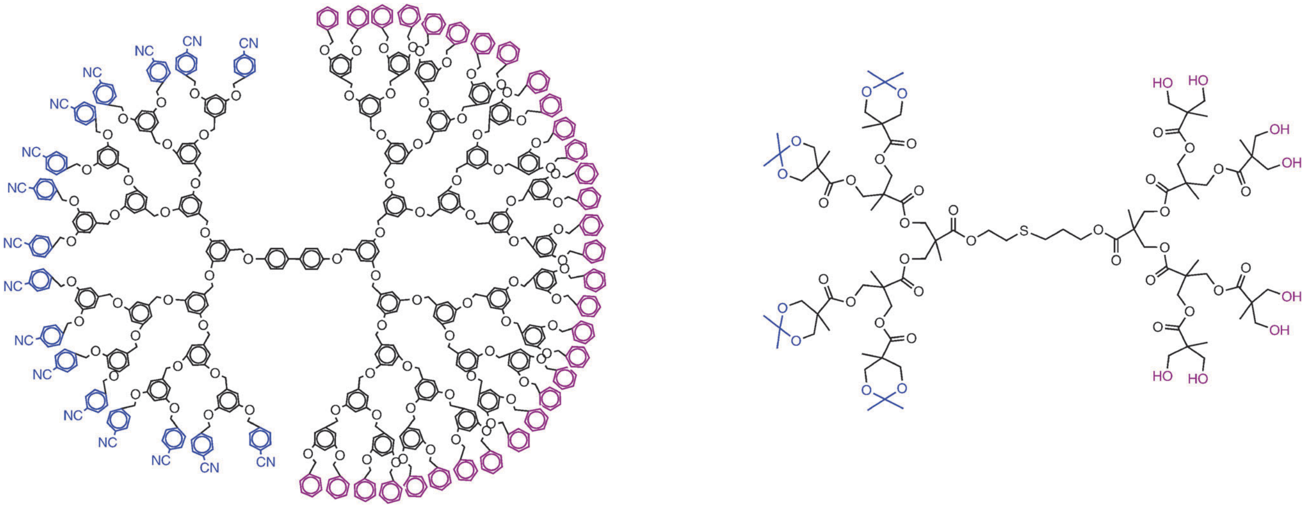


Fig. 10 Increase in functionality with generation for different HFDs, grown from either an AB$_2$ monomer or an AB$_2$C monomer and from a difunctional or a trifunctional core.

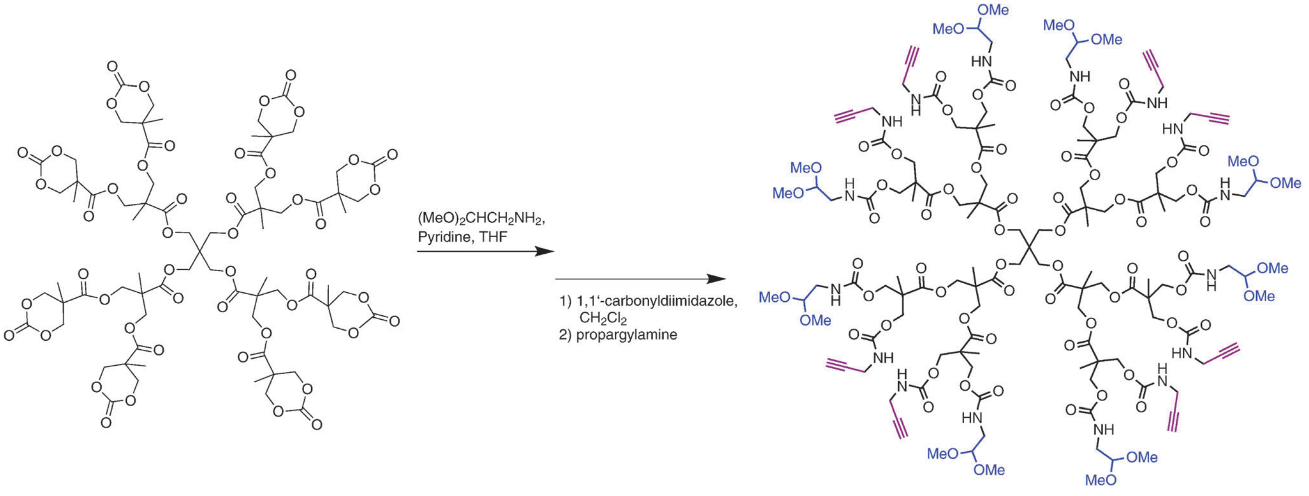


Scheme 4 Example of the HFD(*e*)-block obtained by coupling of dendrons to a core moiety Fréchet-Type HFD(*e*)-G4-(cyano)$_{16}$-*b*-G5-(benzyloxy)$_{32}$[56] (left) or direct coupling of two dendrons *via* click chemistry bis-MPA HFD(*e*)-G3-(acetonide)^{4}-*b*-G3s-(hydroxyl)$_8$[61] (right).

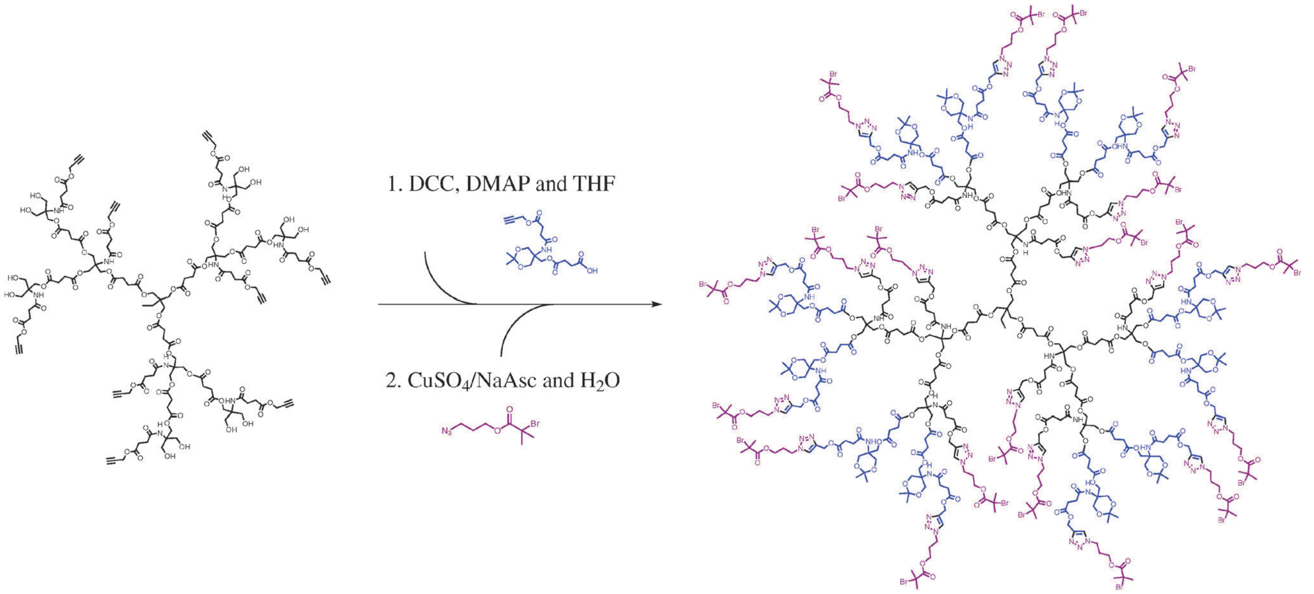
peripheral and internal functionality of fifth generation will present a total of 189 functional groups wherein 96 are external groups when built from a trifunctional core (HFD(*ei*)-G4-*e*-(B)$_{96}$-*i*-(C)$_{93}$).

i. Exterior (HFD(*e*)). Fréchet and co-workers reported the first synthesis of a HFD(*e*)-block already in 1993. Using a convergent/convergent approach, they synthesized two benzyl ether dendrons bearing different end-groups: a 4th generation dendron having 16 cyano groups on one hand and a 5th generation dendron bearing 32 benzyloxy groups on the other hand. In a last step, the two dendrons were coupled to a difunctional core to yield the final Fréchet-type HFD(*e*)-G4-(cyano)$_{16}$-*b*-G5-(benzyloxy)$_{32}$ after a total of 20 reaction steps, Scheme 4.[56] Considering the broad possibilities offered by this type of structures, HFD(*e*)-blocks with various end-groups have been developed using a similar strategy for different dendritic structures such as PAMAM,[57] polyether[56] or polyester dendrimers.[58] The emergence of the click concept has enabled a more straightforward introduction of these structures including reports utilizing the CuAAc,[59] DA[60] or most recently TEC[61] click reaction, Scheme 4. Tomalia *et al.* have presented another strategy for the coupling of two dendrons, relying on the complementarity of DNA bases.[62] They synthesized PAMAM dendrons functionalized with single stranded DNA (ssDNA) at the focal point. By combining complementary ssDNA, they selectively obtained the HFD(*e*)-block that could be hemi-spherically differentiated both as a function of generation or end-groups functionality.

Majoral *et al.* were the first to report the synthesis of a HFD(*e*)-alternating using the reactivity of the P(X)Cl$_2$ (X = S, O) terminal fragments of phosphorus dendrimers.[63] They were able to introduce tri- or tetra-functionality by substitution of the phosphorus atom with a variety of reagents. More recently, Fréchet and co-workers described the accelerated synthesis of a heterofunctional bis-MPA dendrimer by introducing alternating peripheral functionalities, Scheme 5.[64] The proposed strategy included a key activation step of the exterior with a cyclic carbonate. The obtained scaffold was further subjected to two selective chemical reactions to yield a second generation bis-MPA dendrimer with 8 protected aldehydes and 8 alkynes, bis-MPA



Scheme 5 Fréchet's approach for the construction of the bis-MPA dendrimer with external bifunctionality, bis-MPA HFD(*e*)-G2-(acetylene)$_8$-*a*-(aldehyde)$_8$.[64]



Scheme 6 One-pot growth and post-functionalization of a polyester HFD(*ei*)-G3-*e*-(acetonide)$_{12}$-*i*-(tertiary-Br)$_{21}$ as described by Malkoch *et al.*[69]

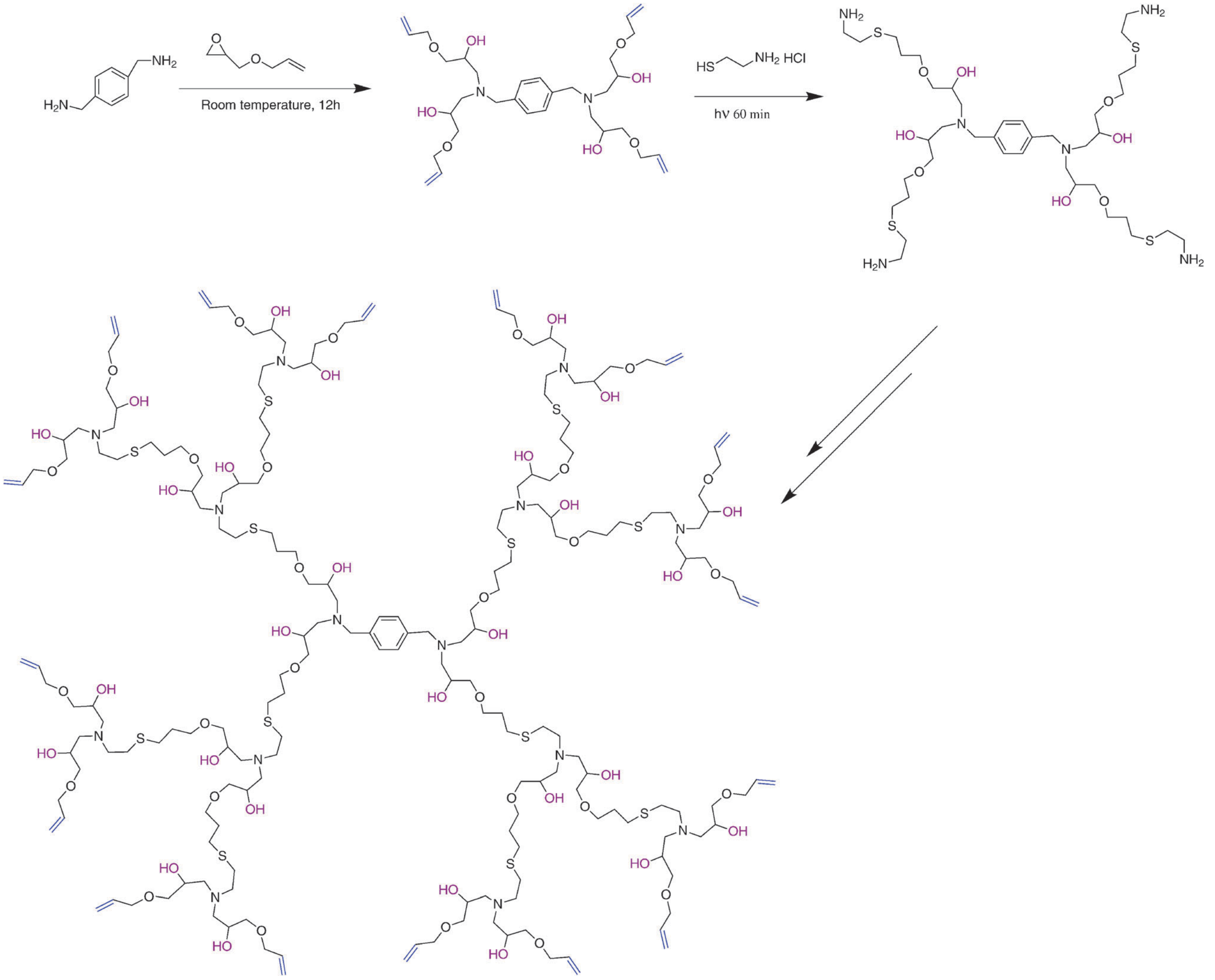
HFD(*e*)-G2-(acetylene)$_8$-*a*-(aldehyde)$_8$. As a result, the number of reaction steps to obtain a HFD(*e*) based on bis-MPA dramatically decreases with the alternating approach when compared to the HFD(*e*)-block.

ii. Interior and exterior (HFD(*ei*)). Even though the interior of the dendritic framework represents a major part of the dendritic scaffold, it is usually inactive independently of the synthetic approach or structure of the final dendrimer. This has been a major limitation to really make use of dendrimer's full potential, independently of the size or the building-block. Therefore, scientists have been looking for different routes to incorporate functionality within the internal framework. The first attempt was introduced by Fréchet and co-workers already in 1993.[65] The report described the metallation of fourth generation poly(benzyl ether) dendrons using superbases. Their study revealed that mostly the peripheral benzylic protons were prone to metallation, probably because of poor reagent accessibility inside the framework. To increase the accessibility, scientists have overcome the challenges by designing new monomers of an AB_2C structure, where C is an additional functional group represented in the interior of the dendritic scaffold. The introduction of these novel monomers enabled a remarkable increase in the number of functional groups *via* a divergent growth approach and without adding extra synthetic steps. This approach was first developed by McGrath and co-workers who introduced internal acetonide protected diols into a second generation poly(benzyl ether) dendrimer.[66–68] However, the deprotected dendrimer was obtained in low yield and trans-esterification reactions occurred during the deprotection. Taking advantage of the selective nature of the CuAAC click reaction, Malkoch *et al.* constructed new AB_2C monomers where A is a carboxylic acid, B are acetonide protected hydroxyl groups and C is either an azide or a primary alkyne group. Two different third generation dendrimers were constructed in six reaction steps that could later be post-functionalized without a deprotection step.[69] The orthogonality of the proposed reaction strategy, combining esterification and CuAAc click reactions, permitted a one-pot growth and postfunctionalization reactions to isolate third generation polyester HFD(*ei*)-G3-*e*-(acetonide)$_{12}$-*i*-(tert-Br)$_{21}$, Scheme 6. Later, Hawker *et al.* combined two orthogonal chemistries, namely epoxy–amine and thiol–ene reactions, during the growth to obtain internally functionalized dendrimers from commercially available monomers. The final dendrimer possessed internal hydroxyl groups and peripheral allyls, Scheme 7.[70] For a more detailed overview of the subject, the reader is directed towards a review by Hecht.[71]

5. Summary and outlook

Dendrimers, with their unique properties, have attracted the interest of the scientific community, who foresee their use in a wide range of future applications. The great need of dendrimers for research purposes has lead to the appearance of several start-up companies commercializing different dendrimer families. PAMAM dendrimers have been commercially available since 1990's through Dendritech® as well as Dendritic nanotechnologies, Inc. Bis-MPA based structures, including dendrimers, dendrons and hyperbranched materials, are commercialized by Polymer Factory Sweden AB. The Netherland based Symo-Chem BV has since the beginning of 2000 been commercializing PPI dendrimers. Moreover, Sigma Aldrich can provide a selection of different dendritic structures today, including PAMAM and bis-MPA scaffolds. With the emergence of new and robust chemistries, dendrimer synthesis has matured and new concepts are constantly being proposed for more efficient and reliable synthetic routes for the construction of novel dendrimers.

For instance, the first synthesis of a generation four bis-MPA dendrimer *via* the convergent growth approach was performed on a milligram scale[72] and required over a month of experimental work with great emphasis on the purification steps including multiple column chromatography procedures. Today, with the development of the orthogonal strategy exploiting the full use



Scheme 7 Hawker's accelerated strategy to a dendrimer with internal hydroxyl groups and peripheral allyl groups, HFD(*ei*)-G3-*e*-(allyl)$_{16}$-*i*-(hydroxyl)$_{28}$.[70]

of different click chemistries, a generation six dendrimer can be obtained in one day[41] and on a multi-gram scale. Furthermore, the development of a library of AB_2C type monomers has unlocked multipurpose dendrimers in an accelerated fashion. In this case, a generation six dendrimer can theoretically be constructed in 12 consecutive reaction steps, generating a macromolecule with an incredible number of functional groups distributed between 192 peripheral functionalities and 189 internal functional groups.

In conclusion, the increased accessibility to sophisticated and structurally perfect dendrimers is today successfully achieved using accelerated growth approaches. These strategies enable the broader community of scientists to access the unique features of dendrimers, which eventually lead to a larger number of potential applications. While still seen as exclusive macromolecules, accelerated approaches change the mindset of chemists encouraging them to undertake the synthesis of dendrimers and optimization of dendrimer synthesis. A grand breakthrough, which is seen as a holy grail by dendrimer chemists, is a large scale synthesis of a high generation monodisperse dendrimer in a one-pot system with a single and simple purification step.

Acknowledgements

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