

# Dendritic architectures based on bis-MPA: functional polymeric scaffolds for application-driven research

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Dendritic polymers are highly branched, globular architectures with multiple representations of functional groups. These nanoscale organic frameworks continue to fascinate researchers worldwide and are today under intensive investigation in application-driven research. A large number of potential application areas have been suggested for dendritic polymers, including theranostics, biosensors, optics, adhesives and coatings. The transition from potential to real applications is strongly dictated by their commercial accessibility, scaffolding ability as well as biocompatibility. A dendritic family that fulfills these requirements is based on the 2,2-bismethylolpropionic acid (bis-MPA) monomer. This critical review is the first of its kind to cover most of the research activities generated on aliphatic polyester dendritic architectures based on bis-MPA. It is apparent that these scaffolds will continue to be in the forefront of cutting-edge research as their structural variations are endless including dendrons, dendrimers, hyperbranched polymers, dendritic-linear hybrids and their hybridization with inorganic surfaces.

## 1. Introduction

Historically, highly branched polymers were first mentioned by Flory in 1952 when he theoretically described the condensation

of AB<sub>x</sub>-monomers to give polydisperse, statistically composed, highly branched architectures with a large number of end-groups.<sup>1</sup> Interestingly, Flory assumed that this class of polymers would not be of significant interest, due to their poor material properties. Contradictory to Flory's assumption and as a complement to linear polymers, dendritic polymers with branched architectures and multiple representations of functional groups have emerged with a variety of structural variations and their

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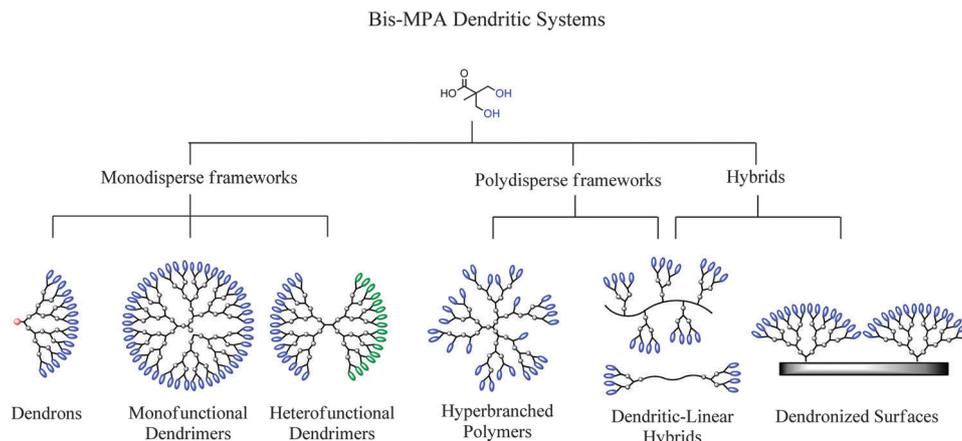


Fig. 1 Schematic overview of the sub-classes of dendritic polymers generated from bis-MPA.

use in potential cutting-edge applications is today widely assessed.<sup>2–4</sup> It is apparent that current challenges in application-driven research are strongly dependent on the accessibility of complex and highly functional materials that can be tailored to an array of applications in a straightforward manner. This class of polymers was revisited by Vögtle *et al.*<sup>5</sup> in 1978, describing the synthesis of branched polypropylene–amine structure followed by two parallel studies in 1985 from Tomalia *et al.*<sup>6</sup> and Newkome *et al.*<sup>7</sup> Currently, the family of dendritic polymers comprises a number of different architectures, including subclasses of monodisperse dendrons and dendrimers as well as polydisperse hyperbranched polymers and dendritic-linear hybrids. The intensive research on these scaffolds can be traced to the number of published scientific reports. As an illustrative example, a recent search, 8th of March 2013, on the keyword “dendrimers” on Web of Science, resulted in over 14 000 reports not including patents.

From the large number of reports on dendritic materials, a family that has been of particular interest is based on 2,2-bis(methylol)propionic acid (bis-MPA) as the building block.

This simple aliphatic, pro-chiral, molecule with a molecular weight of  $134.06 \text{ g mol}^{-1}$  comprises two hydroxyls and one carboxylic group. It is readily available in bulk quantities and plays an important role in the synthesis of functional aliphatic polyesters. The bis-MPA molecule, being an  $\text{AB}_2$  monomer, has successfully been explored for the construction of a large number of dendritic materials, ranging from monodisperse dendrons and dendrimers to polydisperse hyperbranched polymers and dendritic-linear hybrids, Fig. 1. Furthermore, their hybridization with organic and inorganic surfaces has been accomplished to generate highly functional dendronized surfaces. Today, bis-MPA based dendritic polymers are commercially available, including hyperbranched Boltorn<sup>TM</sup> as well as bis-MPA dendrimers and dendrons. The commercial availability of these highly functional polymers is a strong incitement on their potential use in both industry as well as academia for a wide array of applications, ranging from milligram to multi-ton scales. This critical review is the first of its kind detailing the overall research activities, in chronological order with respect to original reports, which have been generated on dendritic materials based on the bis-MPA monomer.



Michael Malkoch

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## 2. The chemistry of dendritic polymers based on bis-MPA

### a. Hyperbranched polymers

Hyperbranched polymers (HBPs) have fascinated scientists and industrialists as a “poor man’s alternative to dendrimers”. In contrast to the tedious and demanding synthetic protocols that are required to accomplish flawless and monodisperse dendrimers, the synthesis of hyperbranched polymers is often based on one-pot reactions, requiring essentially no work-up. The properties of hyperbranched polymers are similar to those of dendrimers; although polydisperse, their highly branched structure do not generally form chain entanglements and the branching also results in high solubility and low melt- and solution viscosity. The ease by which hyperbranched polymers are synthesized and their intrinsically different properties



compared to linear polymers have spurred significant interest in HBP over the last few decades and there are several excellent review chapters and books summarizing the area.<sup>8–10</sup>

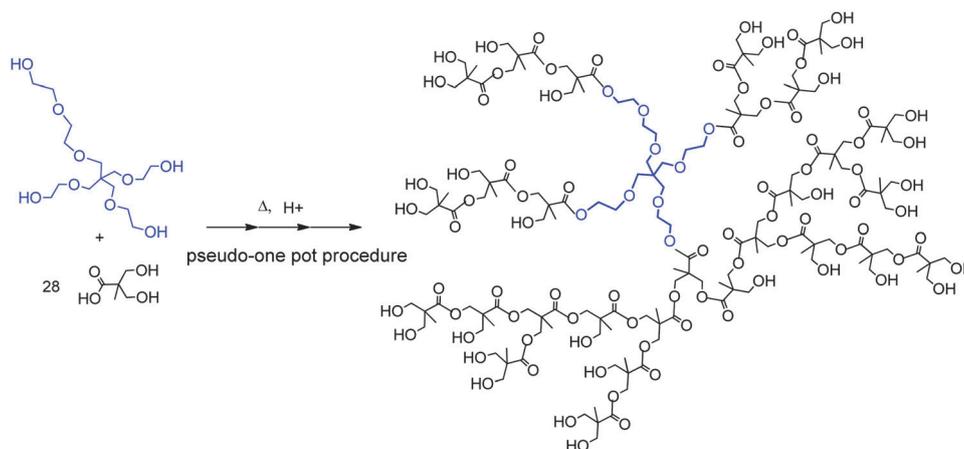
The first report describing the use of bis-MPA as an AB<sub>2</sub>-monomer for the construction of a dendritic macromolecule was published by Hult *et al.* in 1993.<sup>11</sup> In this study, bis-MPA based allyl-functional oligoesters were used in coating applications. A modification of the synthetic strategy was later described, where bis-MPA was copolymerized with trimethylolpropane (TMP) in an acid-catalyzed condensation reaction to provide more control of the molecular weight and polydispersity.<sup>12</sup> The reaction was carried out as a pseudo one-step reaction, by successive addition of monomers, in one-pot to increase the probability of building TMP-cored hyperbranched polyesters. In the first step, one equiv. of TMP and three equiv. of bis-MPA, corresponding to the stoichiometric ratio in a first generation dendrimer [G1], were reacted at 140 °C. However, since the outcome of the condensation reaction is based on statistics, a range of isomers and species having different molecular weights will form as the reaction progresses. After approximately 3 hours under reduced pressure, another portion of bis-MPA, corresponding to the theoretical amount required for the [G2] dendrimer, was added together with another catalytic portion of the acid and could be repeated several times to reach the desired bis-MPA to core ratio. The pseudo-one pot procedure was utilized to favor chain growth on the already formed oligoester backbone, rather than forming new oligoester skeletons. The copolymerization of bis-MPA with the polyol core (or chain stopper) is important to reduce the polydispersity of the final polymer, and to improve the molecular weight control, and also, to some extent, reduce the risk of unwanted side-reactions, such as cyclizations and etherifications. The straightforward synthetic procedure is still valid, and can be utilized for various suitable core moieties and end-groups and their combinations. Although hyperbranched polymers are simple to construct, challenging characterizations comes with the price due to their complex polydisperse nature.

These HBPs are often described in the literature by their trade name Boltorn™ and are globally provided by Perstorp AB, making them one of the mostly utilized HBPs in the literature. The original Boltorn™s are comprised of hydroxyl functionalities at the periphery and are named H20, H30 and H40, indicating that the stoichiometric ratio between the core and bis-MPA corresponds to the generation 2 [G2], 3 [G3] and 4 [G4] dendrimer accordingly. Scheme 1 conceptually depicts Boltorn H30. Other Boltorn derivatives include U3000, W3000, H2003, H2004, P1000, *etc.* The vast interest in the synthesis of hyperbranched polymers has fuelled the development of new characterization protocols that allow for the understanding of the structure–property interplay as summarized in a comprehensive review by Zagar and Zigon.<sup>13</sup>

## b. Dendrimers

The monodisperse nature of dendrimers typically requires robust chemical reactions coupled with tedious workup procedures. Consequently, most of the research activities have been limited to a few dendrimer scaffolds provided by a selected number of world-wide commercial sources. With their current commercial availability, dendrimers based on the bis-MPA monomer are today one of the most utilized dendritic platforms. While bis-MPA is the most commonly used abbreviation, alternative widely-used acronyms are bisMPA, BMPA, bis-HMPA dendrimers as well as PBisMPA. Since the initial synthetic report by Hult *et al.* in 1996,<sup>14</sup> bis-MPA dendrimers have been constructed up to [G6], with a myriad of bis-MPA based dendritic structures published, including both traditional as well as heterofunctional dendrimers (HFDs). The introduction of the “click” concept by K. Barry Sharpless has provided a facile synthetic tool for the construction of dendrimers,<sup>15,16</sup> which is today routinely used for the synthesis of sophisticated bis-MPA dendrimers.<sup>17,18</sup> The most critical synthetic reports are described below and briefly summarized in Table 1.

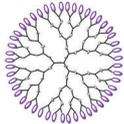
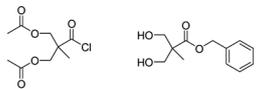
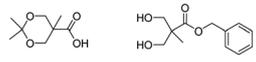
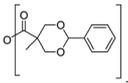
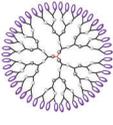
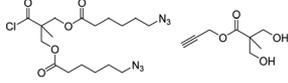
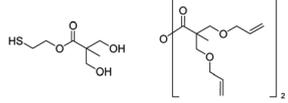
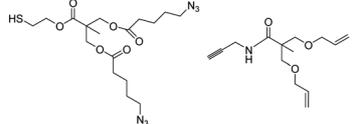
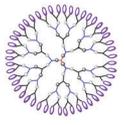
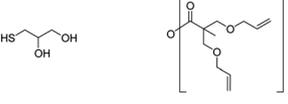
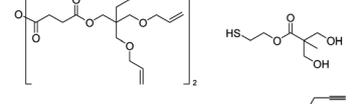
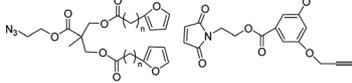
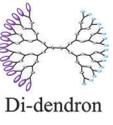
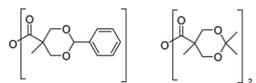
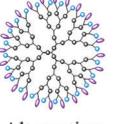
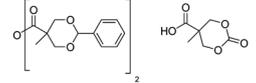
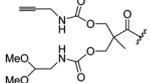
**I. Homofunctional traditional bis-MPA dendrimers.** Successful synthesis of bis-MPA dendrimers has been accomplished *via* convergent, double exponential and divergent growth approaches, Fig. 2.



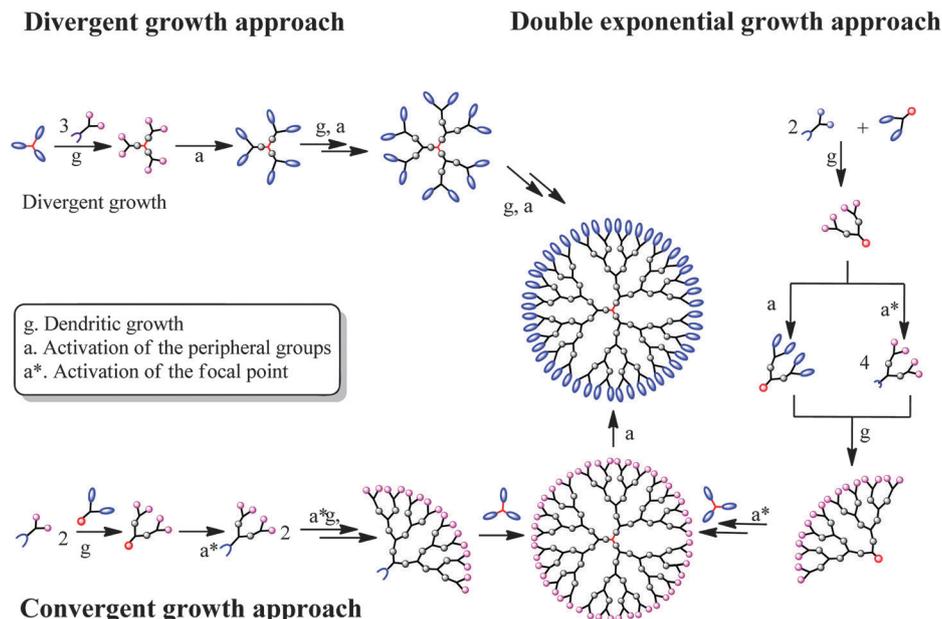
**Scheme 1** Idealized structure of one isomer of a pseudo-third generation [G3] hyperbranched polyester based on bis-MPA and PP50. The synthesis is conducted using 3 addition of bis-MPA, each corresponding to the theoretical amount of the corresponding dendrimer.



**Table 1** A detailed summary of different bis-MPA dendrimer architectures reported in the literature

Dendrimer	Strategy	Building blocks	Reaction	Steps	Generation	End groups	Total yield (%)	Year
<b>Homofunctional</b>								
 Traditional bis-MPA dendrimer	Convergent		Esterification	10	[G4]		15	1996 <sup>14</sup>
	Double exponential		Esterification	7	[G4]		56	1998 <sup>19</sup>
	Divergent		Esterification	8	[G6]		48	2001 <sup>20</sup>
	Divergent		Esterification	8	[G4]		47	2002 <sup>21</sup>
 Bis-MPA dendrimer with different linkages	Orthogonal		Esterification/ CuAAC	4	[G4]		69	2007 <sup>25</sup>
	Orthogonal		TEC/esterification	5	[G5]		12	2010 <sup>27</sup>
	Orthogonal		TEC/CuAAC	6	[G6]		8	2010 <sup>28</sup>
 Bis-MPA dendrimer hybrids	Orthogonal		TEC/esterification	4	[G4]		26	2010 <sup>27</sup>
	Orthogonal		Esterification/TEC	5	[G5]		19	2010 <sup>27</sup>
	Orthogonal		CuAAC/DA	3	[G3]		27	2010 <sup>29</sup>
<b>Heterofunctional</b>								
 Di-dendron	Divergent		Esterification	12	[G3-G3]		39	2002 <sup>31</sup>
	Divergent/ convergent		Esterification/ CuAAC	12	[G4-G4]		57	2005 <sup>32</sup>
	Divergent/ convergent		Esterification/SPAAC	14	[G3-G2]		55	2011 <sup>33</sup>
	Divergent/ convergent		Esterification/TEC	12	[G3-G3]		20	2011 <sup>22</sup>
 Alternating bifunctionality	Divergent		Esterification	6	[G2]		46	2007 <sup>35</sup>





**Fig. 2** Overall strategies that have successfully been employed for the construction of homofunctional traditional bis-MPA dendrimers.

In the first report, the construction of a bis-MPA dendrimer employed a convergent growth approach and resulted in a [G4] polyester dendrimer based on a trisphenolic core and 48 peripheral acetyl groups, Fig. 2.<sup>14</sup> To overcome the termination related to the acetyl groups and to obtain a reactive bis-MPA dendrimer, a double exponential growth strategy was developed by the introduction of an acetonide diol protecting group.<sup>19</sup> The combination of DCC esterification reactions and mild acidic deprotection steps resulted in a [G4] dendrimer with 48 reactive hydroxyl groups. Two major drawbacks of both the convergent and the double exponential growth strategies are poor yield of higher generation dendrimers as well as the loss of valuable dendron precursors. Consequently, a divergent growth approach was reported by Fréchet *et al.*, exploiting the inexpensive, anhydride activated benzylidene protected bis-MPA. Iterative esterification and hydrogenolysis deprotection reactions resulted in a monodisperse [G5] dendrimer displaying 96 hydroxyl groups that was isolated by simple extractions in a total yield of 52%, Scheme 2A.<sup>20</sup> While highly efficient with >90% yields in each step, the hydrogenolysis steps required a hydrogenation PARR vessel. As a result, a synthetic improvement was reported by Hult *et al.* capitalizing on the employment of an anhydride activated acetonide protected bis-MPA for the divergent growth synthesis of a [G4] dendrimer in 8 consecutive reaction steps.<sup>21</sup>

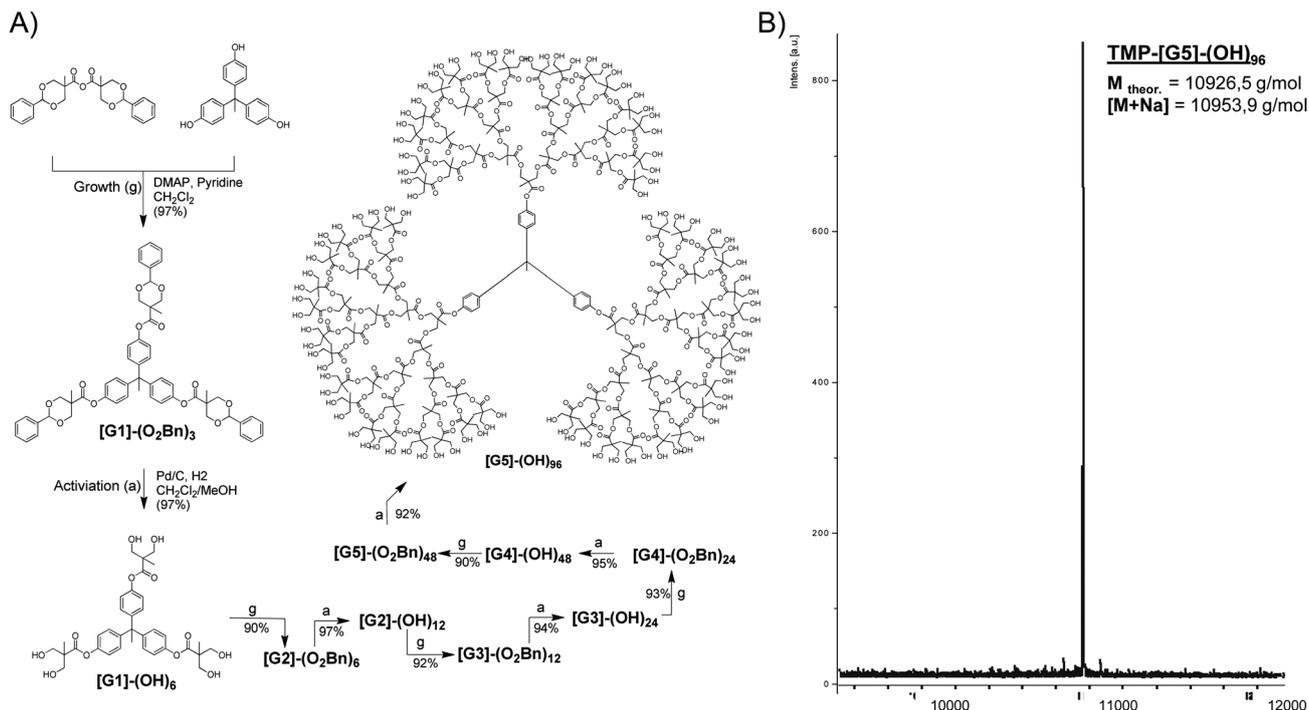
Most recently, Malkoch *et al.* reported on the synthesis of traditional bis-MPA dendrimers that were divergently grown and contained a cleavable disulfide core. Upon reaching the desired generation, the dendrimers were selectively cleaved by dithiothreitol (DDT) in high yields generating dendritic macrothiols that were further reacted *via* UV initiated thiol–ene coupling (TEC) chemistry to result in sophisticated dendritic materials, in both organic as well as aqueous solutions.<sup>22</sup>

Today, all traditional bis-MPA dendrimers are commonly synthesized and accurately characterized *via* the divergent growth approach. The structural integrity of all monodisperse dendrimers is routinely analyzed by both NMR and MALDI-TOF MS. A typical MALDI spectrum displaying a single peak corresponding to a [G5] bis-MPA dendrimer is shown in Scheme 2B.

## II. Accelerated approaches of homofunctional dendrimers.

Dendrimer chemistry has matured in the last decade as a consequence of the introduction of novel chemical reaction concepts that are both high yielding and proceed with unprecedented efficiency. A critical advancement that today enables the synthesis of larger arrays of dendritic scaffolds and in a more reliable fashion is related to the proposed family of click reactions including the copper-catalyzed azide–alkyne cycloaddition (CuAAC), TEC, as well as the Diels–Alder reaction (DA).<sup>3,18,23</sup> These robust reactions are highly selective, known to proceed in a variety of solvents and with simple purification protocols. Hawker *et al.* first evaluated CuAAC click reaction as a universal methodology for the postfunctionalization of various types of dendritic structures.<sup>24</sup> In this context, a [G2] homofunctional bis-MPA dendrimer decorated with 12 primary acetylenes was efficiently reacted with a 5% molar excess of ethyl 2-azidoacetate in a THF–water mixture, using Cu(I) as a catalyst. The fully reacted dendrimers were isolated by column chromatography in 91% yield. The chemoselective nature of click reactions was further explored by Malkoch *et al.* for the construction of bis-MPA as well as Fréchet type dendrimers *via* an accelerated growth strategy, Scheme 3a.<sup>25</sup> Different from the traditional iterative growth and activation steps that inherently include the possibility of introducing defects, the accelerated strategy relies on the use of AB<sub>2</sub> and CD<sub>2</sub> monomers in which functionality A reacts only with D and B only with C. As a result,





**Scheme 2** (A) Divergent growth approach for the construction of fully activated bis-MPA dendrimers utilizing an anhydride activated bis-MPA monomer. (B) Structural purity of a fifth generation bis-MPA dendrimers with 96 peripheral hydroxyl groups as shown by MALDI-TOF.

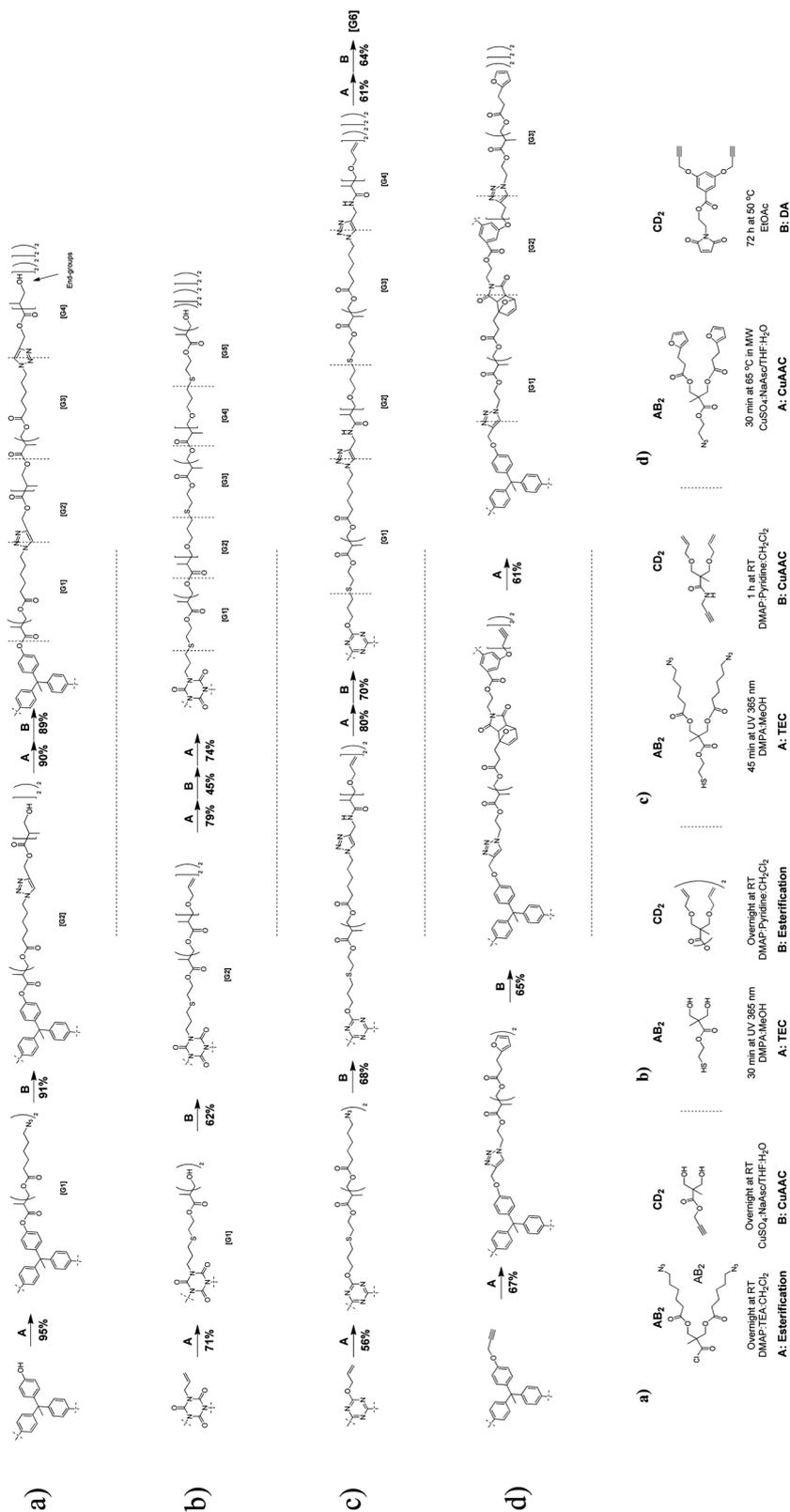
continued growth of fully reactive dendrimers is obtained with each reaction step. The initial concept exploited different bis-MPA monomers that allowed a divergent growth approach *via* esterification and CuAAC reactions. Two different bis-MPA dendrimers were synthesized up to the [G4] in 4 reaction steps with excellent yields of >90% for each reaction step. In contrast to traditional bis-MPA dendrimers, the isolated dendrimers comprised both ester as well as triazole linkages. The recently discovered utility of the photoinitiated TEC chemistry as a powerful reaction tool for the construction of dendrimers<sup>26</sup> was further adapted to accelerate the synthesis of homo-functional bis-MPA dendrimers. As can be seen in Scheme 3b, sequential TEC and esterification reactions resulted in a [G5] bis-MPA dendrimer with 96 peripheral alkene groups.<sup>27</sup> To date, one of the most robust examples of accelerated dendrimer synthesis was reported by Hawker and Malkoch on the bis-MPA platform. The strategy combined both the TEC and CuAAC click reactions and yielded a [G6] dendrimer in a single day displaying 192 alkene peripheral groups and a molecular weight of *ca.* 60 000 g mol<sup>-1</sup>, Scheme 3c.<sup>28</sup> Each reaction reached completion within 1 h and the fully activated dendrimers, having either azide or alkene peripheral groups, were isolated through simple purification procedures. Interestingly, the 7.0 equiv. excess of thiol to ene required to reach a fully substituted [G5] dendrimer was found (by SEC) to generate 10% fraction of dendrimer-dendrimer intermolecular cross-coupled.

Based on the modular nature to construct bis-MPA dendrimer scaffolds utilizing benign and accelerated reaction approaches, hybridization strategies with complementary monomers have also been reported. For instance, Kakkar *et al.* reported the

successful construction of a fully clicked [G3] dendrimer utilizing CuAAC and DA reactions based on bis-MPA (AB<sub>2</sub>) and aromatic (CD<sub>2</sub>) monomers, Scheme 3d.<sup>29</sup> The obtained dendrimers exhibited thermoresponsivity in which the dendritic scaffold disassembled *via* a retro-DA at physiologically relevant pH. As can be seen in Table 1, other bis-MPA dendrimer hybrids have been accomplished *via* orthogonal growth approaches with both thioglycerol as well as trimethylol propane as paired monomers.<sup>27</sup> Most recently, hybridization *via* accelerated approaches combined both esterification and Michael addition reactions which resulted in a [G5] dendrimer with 128 hydroxyl peripheral groups.<sup>30</sup>

**III. Heterofunctional dendrimers (HFDs).** The fascination to explore dendrimers in cutting edge research capitalizes on their structural perfection that can bear a large and exact number of functionalities within a confined space and at a sub-nanoscale range. The homofunctional dendrimers are by far the most synthetically assessed, however, their single function is sought to be a limitation for their use as multipurpose scaffolds in more advanced applications. Consequently, the constructions of more sophisticated multipurpose dendrimers that express more than one type of functionality are of great importance today. From a small number of reports, different synthetic approaches have successfully been executed for the design of heterofunctional dendrimers (HFDs), tailored with dual functionality located differently within the dendritic architecture.<sup>17</sup> Indeed, the bis-MPA platform has been in the frontier to efficiently deliver HFDs with dual functionality that have distinctly different functionalities located separately as blocks or alternating at the outer shell.



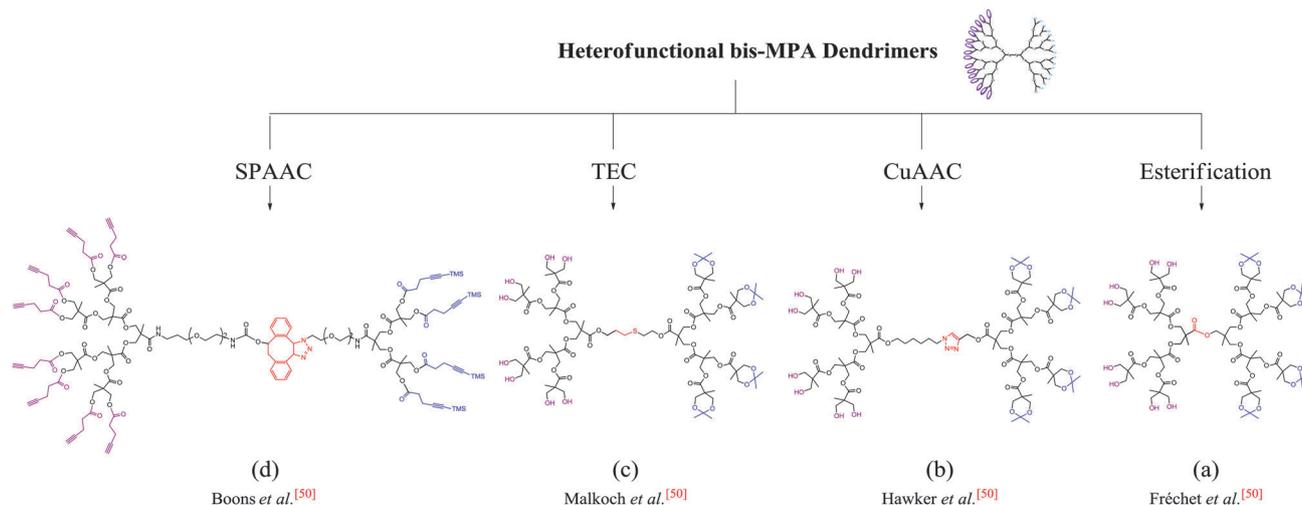


**Scheme 3** Different accelerated and orthogonal growth strategies to homofunctional bis-MPA dendrimers employing (a) esterification and CuAAC; (b) TEC and esterification reactions; (c) TEC and CuAAC and (d) CuAAC and DA.

The first original paper on the construction of heterofunctional bis-MPA dendrimers was reported by Gillies and Fréchet in 2002.<sup>31</sup>

By combining the anhydride activated benzylidene and the acetonide protected bis-MPA monomers, a [G3] didendron



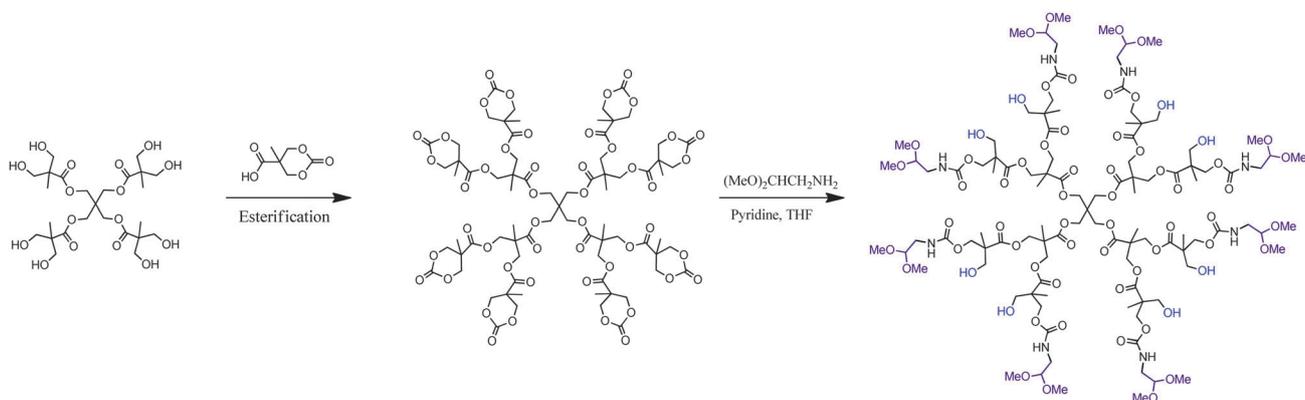


**Fig. 3** Third generation [G3] HFD scaffolds based on bis-MPA and with exterior block dual functionalities, (a) HFD(e)-G3-(hydroxyl)<sub>8</sub>-b-G3-(acetone)<sub>4</sub>; (b) HFD(e)-G3-(hydroxyl)<sub>8</sub>-b-G3-(acetone)<sub>4</sub>, HFD(e)-G3-(hydroxyl)<sub>8</sub>-b-G3-(acetone); (c) HFD(e)-G3-(acetylene)<sub>8</sub>-b-G2-(acetylene-TMS)<sub>4</sub> based on the nomenclature proposed by Walter and Malkoch for HFDs.<sup>17</sup>

based HFD was synthesized *via* esterification reactions in 12 consecutive steps employing both the convergent and divergent growth approaches, Fig. 3a. The HFD based on two dendrons was isolated in an overall yield of 39% and displayed 4 acetone and 8 hydroxyl end groups. An alternative synthetic strategy was proposed by Hawker *et al.* in 2005 utilizing the chemoselectivity of the CuAAC reaction. Two separate dendrons were grown divergently to [G3] comprising in one end a single azide and eight hydroxyl groups and in the other end a primary acetylene in the focal point with 4 acetone protective groups. The two dendrons were efficiently coupled in THF and isolated in 92% yield, Fig. 3b.<sup>32</sup> Following a similar synthetic methodology as for the CuAAC strategy, both the UV initiated TEC as well as the strain-promoted azide-alkyne cycloaddition (SPAAC) have successfully been explored as alternate click reactions for the synthesis of HFDs based on didendrons with dual functionalities, Fig. 3c and d.<sup>22,33</sup> The potential use of these scaffolds as *in vivo* drug delivery vehicles<sup>34</sup> makes the TEC and

SPAAC strategies of importance as they exclude the use of potentially toxic copper.

Though HFDs based on didendron blocks have efficiently been constructed and characterized, their major drawback is coupled to the large number of required iterative reaction steps. For all the third generation dendrimers shown in Fig. 3, a minimum number of 10 reaction steps are required, not including monomer synthesis or further functionalization. An apparent consequence of the number of reaction steps limits their accessibility for the larger scientific audience. To simplify the synthesis, HFDs that display alternating peripheral dual functionality have been suggested as alternative scaffolds. By employing the divergent growth approach, a [G2] bis-MPA dendrimer was synthesized expressing eight cyclic carbonates, Scheme 4. A number of different amine functional substituents were selectively reacted *via* ring opening of the cyclic carbonates, resulting in HFDs in only four reaction steps and with 16 alternating heterofunctionalities at the periphery.<sup>35</sup>



**Scheme 4** A simplified strategy for the construction of bis-MPA HFD(e)-G2-(hydroxyl)<sub>8</sub>-a-(acet)<sub>8</sub> with externally (e) alternating (a) dual functionality as proposed by Fréchet *et al.*<sup>35</sup>



### c. Dendritic-linear polymer hybrids

Dendritic-linear polymer hybrids are sophisticated polymer structures containing linear chains as well as dendritic segments. These structures have been investigated since the first reports by Fréchet *et al.* in the early 1990's<sup>36–38</sup> and since then, several fascinating structures have been produced over the years. Their synthesis require chemists skilled in both organic and polymer chemistry. The linear and dendritic segments can be combined in several different manners, resulting in an array of functional structures, many of which can be found in a review by Gitsov.<sup>39</sup> An important aspect of their synthesis, compared to dendrimers, is the purification protocols employed which typically require simple precipitations in poor solvent. Due to the unique rheological, solution and solid-state properties of these polymers, it is hypothesized that they could find applications as nanometer-sized reactors, nanoporous sized thin-films, nanosponges and for non-covalent and site-specific modifications of glycoproteins, *etc.*<sup>39</sup>

One great advantage of using the bis-MPA building block to produce hybrid structures is the intrinsic availability of hydroxyl end-groups, which can easily be functionalized in a benign fashion by a number of chemical reactions. Furthermore, the bis-MPA dendritic structures can be divergently grown from any type of hydroxyl or amine group. Below follows a summary of bis-MPA based dendritic-linear polymer hybrids reported in the literature.

**I. Star-like dendritic-linear polymers.** There are several reports in the literature where bis-MPA-based dendritic structures have been utilized as macroinitiators for the polymerization of linear polymer chains, Scheme 5. This results in dendritic-linear polymer hybrids of a star-like nature, where the number of arms is determined by the number of groups at the periphery of the dendritic structure. Since the bis-MPA-based dendritic structures have OH-groups at the periphery, these can easily be used either directly for the ring-opening polymerization (ROP) of  $\epsilon$ -caprolactone ( $\epsilon$ -CL) and lactide acid (L-LA), for example, or be converted into initiators for reversible-deactivation radical polymerizations (RDRP). The hydroxyl groups could also be utilized for coupling reactions, in which pre-formed polymer chains are coupled to the bis-MPA dendritic core. However, both of these approaches present challenges, especially in terms of end-group functionalization of the dendritic core. It is desirable that all the end-groups at the periphery of the dendritic structure initiate polymerization or are coupled with linear chains. Uncompleted coupling or initiation is difficult to avoid, and hybrids with these types of defects are impossible to separate from the complete functionalized ones. Furthermore, characterization of the hybrids is also a difficult task, and in many cases the defects cannot be detected utilizing conventional analytical tools such as NMR, SEC or MALDI-TOF.

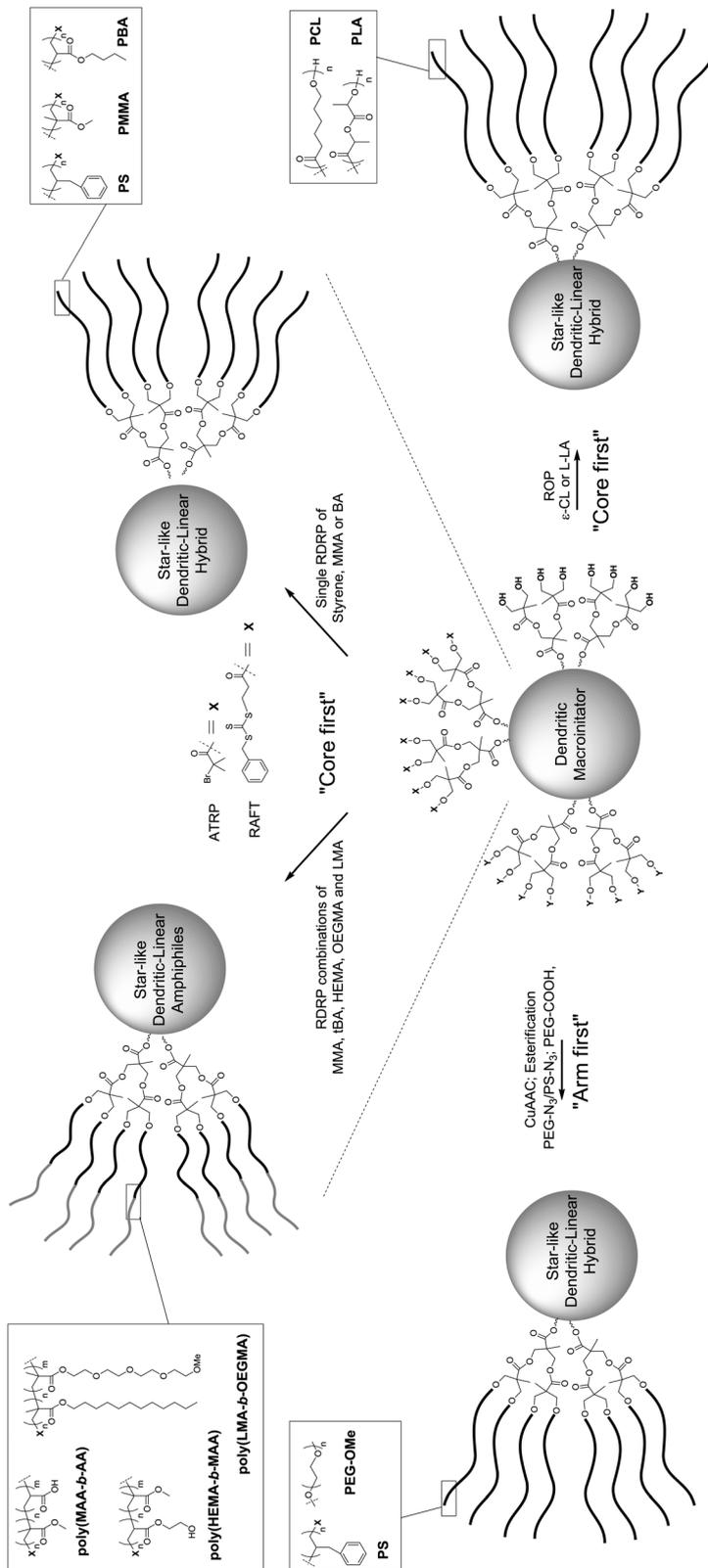
Hedrick *et al.* reported the first ROP of a bis-MPA-based core molecule, polymerizing  $\epsilon$ -CL from [G1] and [G2] dendritic macroinitiators.<sup>40</sup> In an extension of this work, both L-LA and  $\epsilon$ -CL were polymerized at 110 °C from G1–G4 bis-MPA dendrimers utilizing a catalytic amount of Sn(Oct)<sub>2</sub>, Scheme 5.<sup>41,42</sup> Hence, in the case of the G4 dendrimer, 48 linear chains were grown from the core molecule with a resulting molecular weight as high as

115 kDa and polydispersities as low as 1.17.<sup>42</sup> The resulting hybrid structures were semicrystalline and formed films. Measurements of the relationship between hydrodynamic volume *vs.* molecular weight showed a deviation from linearity, typically seen in dendrimers of higher generation. Hult *et al.* further expanded this methodology to include HBP Boltorn H30, a [G3] bis-MPA dendrimer and a dendron as macroinitiators for ROP of  $\epsilon$ -CL.<sup>43</sup> In this study it could be concluded that with lower  $M_w$  of the grafted PCL, unreacted OH-groups of the macroinitiators remained. The hybrid structures were compared to the linear PCL and the rheological properties were evaluated, showing that the branched structures had a considerably lower zero shear rate viscosity ( $\eta_0$ ) than the linear PCL of the same molecular weight.

Bis-MPA scaffolds have also been utilized as macroinitiators in RDRP. In the first reports, Hedrick and Miller *et al.* synthesized [G1] and [G2] dendrimer macroinitiators where the hydroxyl groups were converted to *tert*-Br groups to be exploited as initiating sites for Atom Transfer Radical Polymerization (ATRP) of methyl methacrylate (MMA)<sup>44</sup> and for block-copolymer amphiphiles composed of poly(MMA-*b*-AA).<sup>45</sup> In an alternative approach, two ATRP initiating groups were first attached to the bis-MPA monomer followed by the attachment to [G1] and [G2] dendrimers and dendrons.<sup>46</sup> ATRP of MMA was successfully performed from all initiating sites except for the [G2] dendrimer having an average of 10–12 polymer chains of 12 possible initiating sites. Similarly, Grayson *et al.* utilized first and second generation bis-MPA dendrimers with six and 12 reactive sites for ATRP of oligo (ethylene glycol) methacrylate (OEGMA) and lauryl methacrylate (LMA). The resulting star-like amphiphilic block-copolymers were evaluated as transdermal carriers.<sup>47</sup> Reversible-Addition Fragmentation Chain Transfer (RAFT) polymerizations have also been explored in a similar manner by Barner-Kowollik *et al.* The peripheral hydroxyl groups of lower generation bis-MPA dendrons<sup>48</sup> as well as hyperbranched Boltorn H20<sup>49</sup> were converted into RAFT agents by a reaction with 3-benzylsulfanylthiocarbonylsulfanylpropionic acid. The macroinitiators were utilized for RAFT polymerization of butyl acrylate (BA) and styrene (S).

The “arm-first” approach has also been successfully investigated for the construction of star like dendritic-linear hybrids. A direct esterification coupling between carboxylic acid monofunctional PEG of 5 kDa or 10 kDa in molecular weight and Boltorn H30 and H40 was successfully reported by Nyström *et al.*<sup>50</sup> Anti-cancer agent doxorubicin (DOX) was entrapped within the hybrids and the structures were evaluated in terms of morphology, particle size, drug encapsulation efficiency, *in vitro* release, cellular uptake, cytotoxicity and apoptosis induction. Boltorn H30 with PEG10k chains was found to be the most promising in terms of controlled release and stability. A similar esterification methodology was further adapted by Shen *et al.* and resulted in a [G5] orthogonally grown bis-MPA dendrimer with 56 peripheral 2 kDa PEG chains.<sup>30</sup> The “arm-first” strategy has also been exploited *via* click chemistry. Grayson *et al.* decorated first and second generation bis-MPA dendrimers with primary acetylenes that were subsequently reacted *via* CuAAC reactions with azido functional PS and PEG.



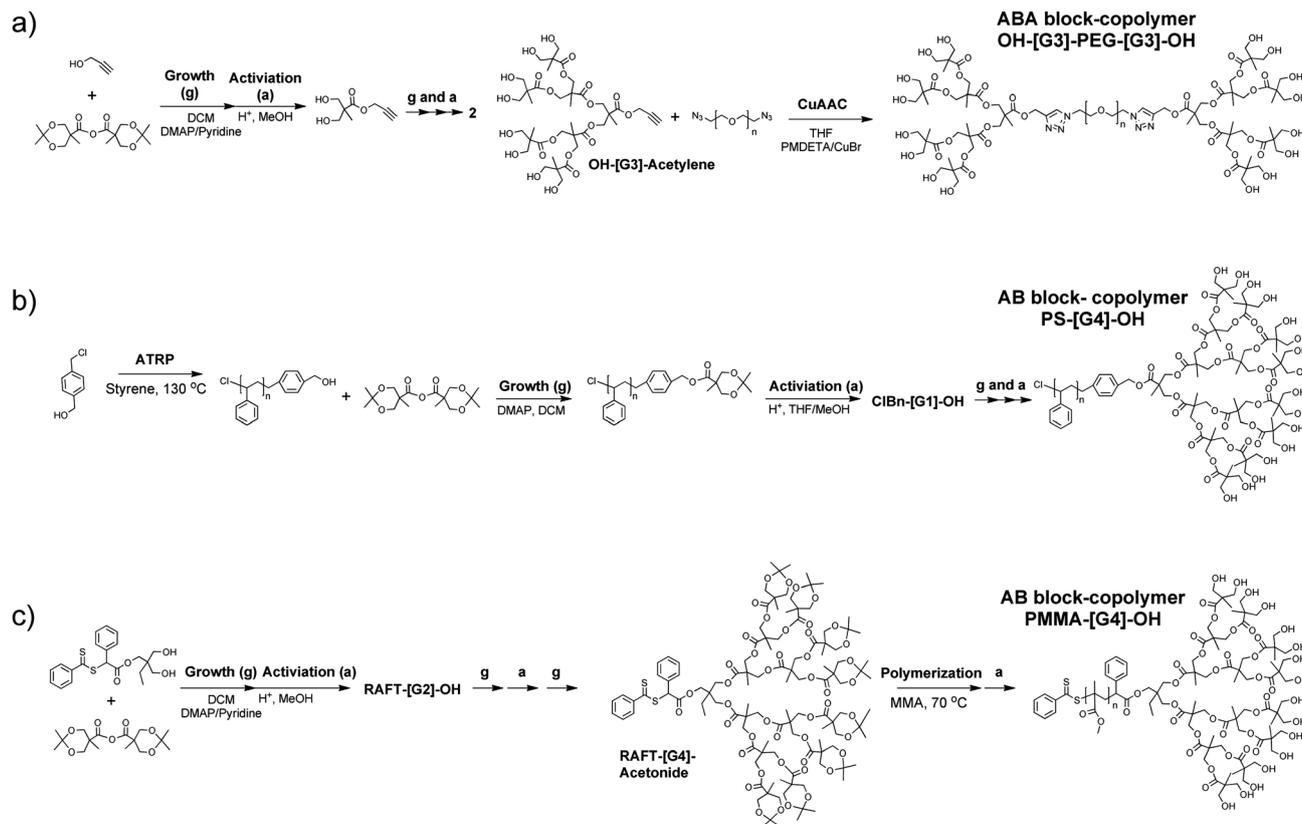


**Scheme 5** Overall strategies described in the literature for the construction of star-like dendritic-linear hybrids based on bis-MPA.

These star-structures were carefully investigated using MALDI-TOF, revealing the formation of "perfect" stars.<sup>51</sup>

**II. Dendritic-linear block-copolymers.** These hybrids are typically linear chains that are end-functionalized with





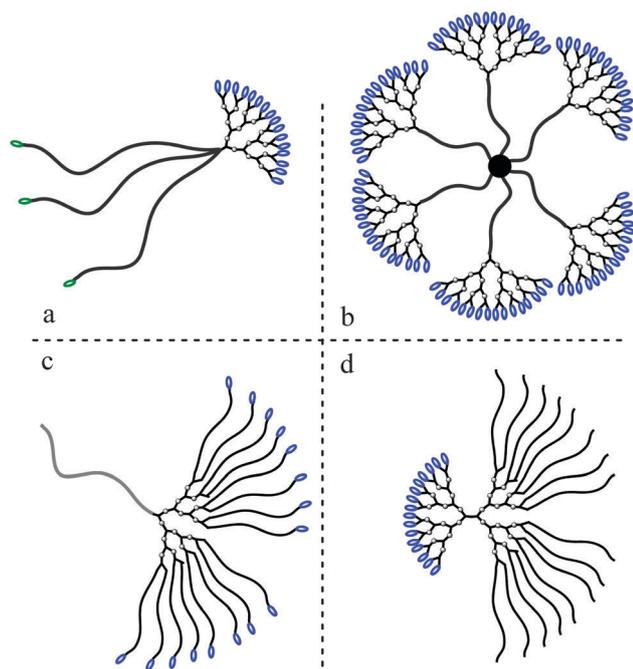
**Scheme 6** Different approaches to generate dendritic-linear hybrids as AB, ABA and ABC block-copolymers.

dendritic segments. Several groups have reported on benign synthetic approaches for the delivery of hybrid structures that are obtained in excellent yields and contain a bis-MPA dendritic part (A) together with a linear polymer (B). One of the first examples employed the anhydride activated benzylidene protected bis-MPA for the divergent growth of dendrons from mono-, di and tetra hydroxylated PEG.<sup>20</sup> The resulted library covered dendritic-linear hybrids of AB, ABA and A<sub>4</sub>B block-copolymers. Similar AB and ABA hybrids based on PEG have successfully been constructed *via* CuAAC and TEC click chemistries. For these materials, the PEG end-groups were first converted to contain either a primary acetylene,<sup>52</sup> allyloxy<sup>24</sup> or azido<sup>53</sup> (Scheme 6a) intermediate followed by convergent coupling reactions to dendrons, comprising single complementary click groups in the core. UV initiated TEC reactions have also been described for the synthesis of ABA hybrids containing 3 kDa PCL as a B block and [G4] dendrons as A blocks.<sup>22</sup> Linear-dendritic hybrids of AB block-copolymers have also been constructed by utilization of RDRP techniques. Ahn *et al.* reported on the synthesis of hydroxyl end-functionalized PS by ATRP and its use as a scaffold for the divergent growth approach of bis-MPA dendrons up to the [G4], Scheme 6b. The obtained AB block-copolymers were subsequently cleaved from the PS chain using palladium(II) acetate catalyst under H<sub>2</sub> atmosphere regenerating PS and the intact dendrons.<sup>54</sup> In an alternative approach, bis-MPA dendrons, ranging from generation one to four, have been constructed to exhibit a single RAFT or ATRP core as an

initiating site. For both systems, hybrid materials were accomplished to include PS and PMMA linear chains, Scheme 6c.<sup>55,56</sup>

Dendritic-linear hybrids based on dendritic bis-MPA structures which do not fall within the categories mentioned above have also been reported. For example, Hedrick *et al.* produced dendritic-linear AB, A<sub>2</sub>B, AB<sub>2</sub>, A<sub>2</sub>B<sub>2</sub> and A<sub>3</sub>B<sub>3</sub> hybrid structures, where the A-block is a bis-MPA dendron of [G1] to [G3] and the B-block is a linear polymer chain, for example PCL.<sup>57</sup> The macroinitiators, *i.e.* the OH-functional dendrons, were orthogonally protected, meaning that ROP<sup>57</sup> and ATRP<sup>58</sup> could be performed from selected end-groups of the dendron structure, leaving a set number of the OH-end groups un-grafted. A schematic representation of an AB<sub>3</sub> with dual-functionality can be seen in Fig. 4a. Hawker and Qiao described the construction of a core cross-linked star polymer in which an AB block-copolymer, *tert*-Br-PS-[G4]-acetonide, was crosslinked at the Br-chain site by copolymerization with divinyl benzene, Fig. 4b.<sup>59</sup> ABC<sub>x</sub> hybrids were recently produced by Malkoch *et al.*, using either CuAAC or thiol-ene chemistry.<sup>60</sup> In their approach, bis-MPA dendrons, having an alkyne group or an ene-group in the focal point, were synthesized up to the fourth generation. The peripheral OH-groups were used as macroinitiators for ROP of  $\epsilon$ -CL and subsequently PEG chains, either azide or thiol functionalized, were coupled to the focal point of the dendron. Hence, ABC<sub>x</sub> amphiphilic structures were produced, having a single PEG chain coupled to a dendron having 2, 4, 8, or 16 PCL chains attached to it. In Fig. 4c, a schematic representation of ABC<sub>16</sub>





**Fig. 4** Various complex linear-dendritic hybrids as described by (a) Hedrick *et al.*,<sup>57,58</sup> (b) Hawker and Qiao *et al.*,<sup>55</sup> (c) Malkoch *et al.*,<sup>60</sup> and (d) Gillies and Fréchet.<sup>31</sup> Blue and green ellipses represent reactive sites available for further functionalization.

hybrids based on a [G4] dendron with 16 PCL chains is shown. Fréchet *et al.* have coined the term “bow-ties” for a class of dendritic hybrid structures, which are based on heterofunctional dendrimers (HFDs).<sup>31,61</sup> The structure consists of two, covalently attached, dendritic segments, which may be of different generation, and linear chains are attached to one of the dendritic segments, examples are shown in Fig. 4d. Structures based on dendritic segments of bis-MPA and linear segments of PEG have been synthesized, using both convergent and divergent methods and the generation of the dendritic segments was varied as well as the molecular weight of the PEG chains.<sup>31</sup>

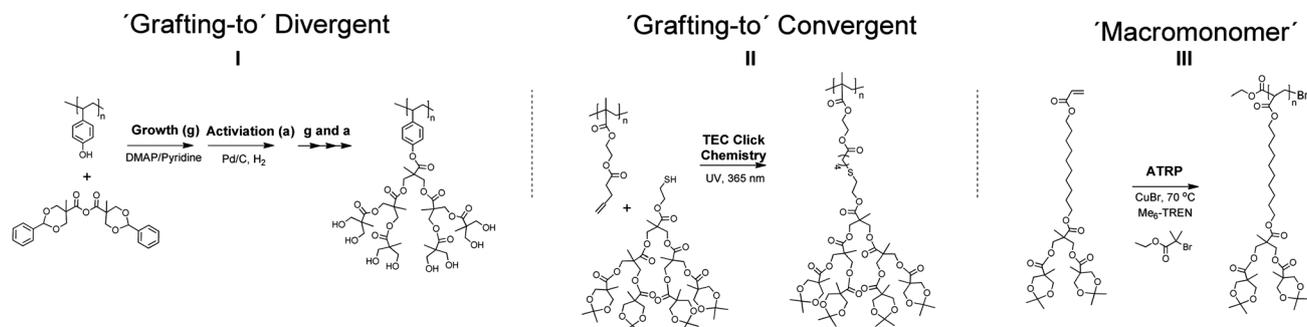
#### d. Dendronized polymer hybrids

Dendronized polymers can be considered a subgroup of dendritic-linear polymer hybrids, as they are a form of comb-polymers

composed of a linear backbone onto which dendrons have been attached to each repeating unit.<sup>62</sup> However, since these macromolecular hybrids predominantly consist of dendritic components they are often considered as an isolated subgroup of dendritic polymers. The field of dendronized polymers has been extensively studied and reviewed by Schlüter *et al.*<sup>63–65</sup> After the first, published, reports of these materials,<sup>66,67</sup> they have attracted great interest due to their rod-like and cylindrical shapes and their potential to be used as catalyst supports, energy transfer, light harvesting, and/or electrically conducting materials, nanoobjects for surface patterning, gene-delivery, *etc.*<sup>65,68</sup>

Dendronized polymers based on bis-MPA have been produced both through the ‘grafting-to’<sup>69</sup> and the ‘macromonomer’ methodology.<sup>70</sup>

**I. ‘Grafting-to’ approach.** In the ‘grafting-to’ approach, dendrons are convergently coupled to or divergently grown from a functional group of each repeat unit of a linear chain. The first example of dendronized polymers based on bis-MPA was reported by Grayson and Fréchet<sup>71</sup> describing the divergent growth approach from poly(*p*-hydroxystyrene). By iterative reactions using anhydride activated benzylidene protected bis-MPA for the growth and hydrogenolysis *via* Pd/C for hydroxyl activations, dendrons up to [G4] were obtained, Scheme 7(I). A major advantage of the divergent growth is the loss of inexpensive reactive building blocks as well as the isolation of the final polymers, which are simply purified by precipitation. Adronov *et al.* utilized an RDRP method, nitroxide mediated polymerization (NMP) to synthesize carborane functionalized dendronized polymers.<sup>72</sup> In a first step, carborane-functionalized styrene was polymerized. Dendronization of the resulting polymer was accomplished through the divergent growth of bis-MPA to the [G4]. Interestingly, this paper also reports on the big discrepancy between molecular weight calculations based on SEC and NMR. For the [G4] dendrimer,  $M_w$  was measured to be 23 kDa by SEC, with a dispersity of 1.16, but NMR-calculations gave a molecular weight of 164 kDa. The results elucidate the difficulties in the characterization of these complex macromolecules. Similarly, Malmström *et al.*<sup>73</sup> detailed the divergent growth of fully activated [G3] dendronized polyacrylate having a C10 spacer between the main chain and the dendron wedges. The final polymer reached molecular weight ( $M_n$ ) close to 84 kDa



**Scheme 7** (I) Grafting-to *via* divergent growth utilizing iterative esterification/deprotection reactions<sup>71</sup> and (II) grafting-to through convergent coupling of a third generation [G3] macrothiol dendron to allyloxy poly(HEMA) exploiting the UV initiated TEC click chemistry.<sup>22</sup> (III) ATRP polymerization *via* the macromonomer approach of a second generation [G2] bis-MPA dendron with a flexible spacer to the polymerizable group.<sup>73</sup>



as obtained by SEC. The attempt to obtain higher generation dendronized polymers failed due to steric hindrance. In fact, for both the divergent growth as well as the convergently coupled approaches, the obtained structural integrity is strongly dictated by the efficacy of the chemical reactions and the inherent sterical parameters found at higher generation constrained dendronized polymers. For the divergent approach, structural defect will be generated at the periphery while for the convergent strategy incomplete functionalization of the polymer chain will be found with increased generation of the dendron.

A critical drawback of the convergent methodology is the employment of large excess dendron precursors that are onerous to construct. Nonetheless, the convergent approach in which bis-MPA dendrons are efficiently coupled to linear polymers has been described briefly in the literature. Malmström *et al.* utilized a cellulose derivative, hydroxypropyl cellulose (HPC), as the backbone to which bis-MPA dendrons were convergently coupled, up to [G3].<sup>74</sup> The size of the dendronized polymers was studied in solid states by spin-casting on mica and graphite surfaces followed by investigation of the surfaces with tapping-mode AFM. The polymers adopted a spherical shape and their diameters were estimated to be *ca.* 30–70 nm. In another synthetic route, Malkoch *et al.* utilized the UV initiated TEC click chemistry to successfully couple “macrothiol” to fully allylated poly(HEMA). All allyls were consumed within 1.5 h of UV exposure, resulting in a [G3] dendronized polymer with a theoretical molecular weight of about 76 000 g mol<sup>-1</sup>, Scheme 7(II). Dendronized polymers that display the hybridization between bis-MPA and Fréchet-type arylether dendrons have also been successfully described in the literature. Bis-MPA dendrons were divergently grown from poly(*p*-hydroxystyrene) followed by an activation step with primary acetylene to which the [G3] arylether dendron with a single azido group was convergently clicked together resulting in a [G6] dendronized polymer with a detected molecular weight of 7020 kDa.<sup>75</sup> More recently, Grayson *et al.* exploited CuAAC reactions for the development of a new class of cyclic dendronized polymers which were successfully constructed from both octanol deep-cavity cavitand<sup>76,77</sup> as well as cyclic poly(*p*-hydroxystyrene).<sup>78</sup>

**II. Macromonomer approach.** In the ‘macromonomer’ route, dendronized monomers, *i.e.* monomers containing a dendron with a single polymerizable group, are polymerized using different polymerization procedures such as radical polymerization, RDRP, ring-opening metathesis polymerization (ROMP), Suzuki polycondensations, *etc.* The great advantage with this approach is the complete dendronization of each repeat unit, and the fact that the generation growth can be carefully controlled. However, the dendronized monomers are tedious to prepare and require an increased number of chromatographic purification steps with increasing dendron generation. Furthermore, it has been shown that macromonomers bearing more than a [G2] dendron usually require highly efficient polymerization techniques in order to obtain dendronized polymers otherwise only oligomers or no polymerization occurs. One solution to this problem is the incorporation

of a flexible spacer in between the polymerizable group and the dendron, however; the resulting dendronized polymers may not be able to form stiff, cylindrical shapes.

In 2004, Malmström *et al.* reported the first dendronized polymers based on bis-MPA through the ‘macromonomer’ route.<sup>73</sup> In this case, Scheme 7(III), dendronized bis-MPA monomers of [G1] to [G3] with an acrylic polymerizable group separated by a flexible 10 C spacer were polymerized by ATRP.<sup>79</sup> All three macromonomers followed first-order kinetics and were polymerized to high conversions. Following the same synthetic concept, Hult *et al.* produced dendronized polymers where a G1 macromonomer was synthesized by reaction of HEMA with bis-MPA, which was subsequently polymerized by ATRP. From the resulting G1 dendronized polymer, now only having a 2 C spacer in between the polymer backbone and the dendron side-chain, dendrons were divergently grown up to [G4].<sup>80–82</sup> The bulk<sup>82</sup> and solution<sup>80</sup> properties of the dendronized polymers were carefully studied, where <sup>1</sup>H NMR self-diffusion and longitudinal relaxation data showed that the polymers had an elongated rod-like structure in solution and that the higher generation dendronized polymers had a larger rod diameter, which approximately doubled when the generation was increased from two to four. The same group synthesized macromonomers from 5-norbornene-2-methanol, to which bis-MPA was divergently grown from [G1] to [G4].<sup>83</sup> The resulting dendronized norbornene macromonomers were subsequently polymerized by ROMP, employing Grubb’s first or second generation catalyst. The first generation catalyst resulted in polymers having fairly controlled dispersity (ranging between 1.2 and 3.7) and molecular weights of the dendronized polymers obtained from the [G4] macromonomer were in the range of 120 kDa. Similarly, Choi *et al.* synthesized a bis-MPA based macromonomer having a norbornene unit in the structure, although a biphenyl group was incorporated as a rigid spacer in between the polymerizable norbornene unit and the dendron.<sup>84</sup> Macromonomers up to [G5] were successfully polymerized by ROMP, utilizing Grubb’s third generation catalyst. The resulting polymers had low dispersities, between 1.04 and 1.51, and molecular weights as high as 1036 kDa were reported for the [G5] macromonomer. Furthermore, the rod-like conformation was confirmed and visualized as individual polymer chains by AFM.

Most recently, Malkoch and Barner-Kowollik *et al.* investigated the combination of dendrons and high temperature acrylate polymerization to obtain dendronized polymers.<sup>85</sup> Bis-MPA-based dendronized acrylate macromonomers ranging from [G1] to [G3] were synthesized by CuAAC, incorporating a flexible 6 or 9 carbon spacer in the structure. The acrylate monomers were then polymerized by auto-initiated high temperature polymerization resulting in vinyl terminated oligomers, where the degree of polymerization decreased with increasing generation.

#### f. Dendronized surfaces based on bis-MPA

The immobilization of dendritic structures on solid surfaces creates dendronized surfaces, sometimes denoted forests. This topic has been thoroughly investigated as dendronized surfaces



can amplify functional groups and surface area, resulting in highly controlled nanostructures.<sup>68</sup> The dendritic structures can be immobilized either *via* physisorption or by covalent attachment. In physisorption the dendritic structure normally self-assembles onto the surface, forming either monolayers or multilayers. In the covalent attachment approach, the dendritic structures, typically a dendron, can be chemically bonded to the surface through the focal point or by the peripheral groups. Furthermore, the covalent attachment of dendrons to surfaces can be performed through both 'graft-to' and the 'grafting-from' approaches. In the 'graft-to' route, preformed dendrons or dendrimers are convergently, chemically bound to the surface, and in the 'grafting-from' method, the dendrons are grown from the surface. This can occur either similar to dendritic growth, where generations are divergent grown from the surface, or by forming a hyperbranched polymer directly on the surface through, for example, self-condensing vinyl polymerization or normal condensation polymerization.<sup>86</sup> Considering the facile preparation of bis-MPA based dendritic structures with any hydroxyl functionalities there are surprisingly few reports in the literature detailing their attachment to solid surfaces.

**I. 'Grafting-to' strategy.** In 2001, Tsukruk *et al.* investigated physisorbed hyperbranched polymers Boltorn H30 and H40 from silicon wafers, which were found to exhibit typical Langmuir adsorption isotherms.<sup>87</sup> The surface morphology and microstructure were initially investigated and, in a continuation of this work, the nanomechanical properties of the dendronized surfaces were studied.<sup>88</sup> Malmström *et al.* formed a self-assembled dendritic monolayer (SADM) by initially synthesizing monodisperse bis-MPA based dendrons of generation [G1] to [G3] containing a disulfide core and subsequently allowing their adsorption onto gold surfaces using the 'grafting-to' approach.<sup>89</sup> Ellipsometry showed that the thickness of the monolayer increased with increasing generation. Layers with both acetonide-protected end-groups as well as deprotected, hydroxyl, end-groups were investigated and it was shown that they exhibited very different wetting properties. Employing the same strategy, Malkoch *et al.* reported on the evaluation of a comprehensive library of bis-MPA dendrimers with extended disulfide linkage decorated with carbohydrates as well as dendrons displaying a single thiol as a core.<sup>90</sup> Surface plasmon resonance (SPR) analysis detailed the fabrication of dendronized gold surfaces with molecular covering densities ranging from 0.33–2.2 molecules nm<sup>-2</sup> and functional availability of 0.95–5.5 groups nm<sup>-2</sup>. In an alternative strategy, the robustness of CuAAC click reaction was investigated to generate dendronized bis-MPA monolayers on the silicon wafer surface. Micrometer dendronized features were generated through AFM mediated dip-pen nanolithography of which bis-MPA dendrons with azide focal point were covalently attached to acetylene functionalized silicon surfaces.<sup>91</sup> Malkoch *et al.* also utilized the CuAAC reaction for the dendronization of cellulose surfaces with bis-MPA based dendrons.<sup>92</sup> Acetylene-functional dendrons up to [G5] were attached to azide-functional cellulose surfaces, both in the form of filter paper and of cellulose model surfaces

using the Quartz-Crystal Microbalance (QCM). The terminal hydroxyl groups of the dendrons were further functionalized *via* the 'grafting-from' approach with an AB<sub>2</sub>C monomer providing dual functional surface templates, Scheme 8A. Carbohydrates, antibiotics, dyes and oligoethylene glycol chains were finally attached to the surfaces.

**II. 'Grafting-from' approach.** The 'grafting-from' of hyperbranched bis-MPA architectures by polycondensation protocols of the bis-MPA monomer has been reported for the development of dendronized surfaces. Liu *et al.* detailed a straightforward strategy to develop dendronized blocks on silanized silicon oxide particles,<sup>93</sup> clay (attapulgitite)<sup>94</sup> as well as calcium carbonate (CaCO<sub>3</sub>) nanoparticles.<sup>95</sup> In the case of CaCO<sub>3</sub> these could be grafted through a one-pot condensation method where the bis-MPA was used as both the surface modifying agent, attaching to the CaCO<sub>3</sub> by ionic bonds, and the monomer for the reaction. Adronov *et al.* have also investigated the divergent growth of bis-MPA dendrons from gold surfaces.<sup>96–98</sup> In their approach, a self-assembled monolayer of PEG, thiolated in one end and hydroxyl-functional in the other, was first formed on the gold surface. From the OH-terminus, [G4] bis-MPA dendrons were sequentially grown using iterative growth/activation chemistry, as is outlined in Scheme 8B. In an extension of the work, the periphery groups of the surface-bound dendrons were EDC-coupled with PEG-chains of varying length.

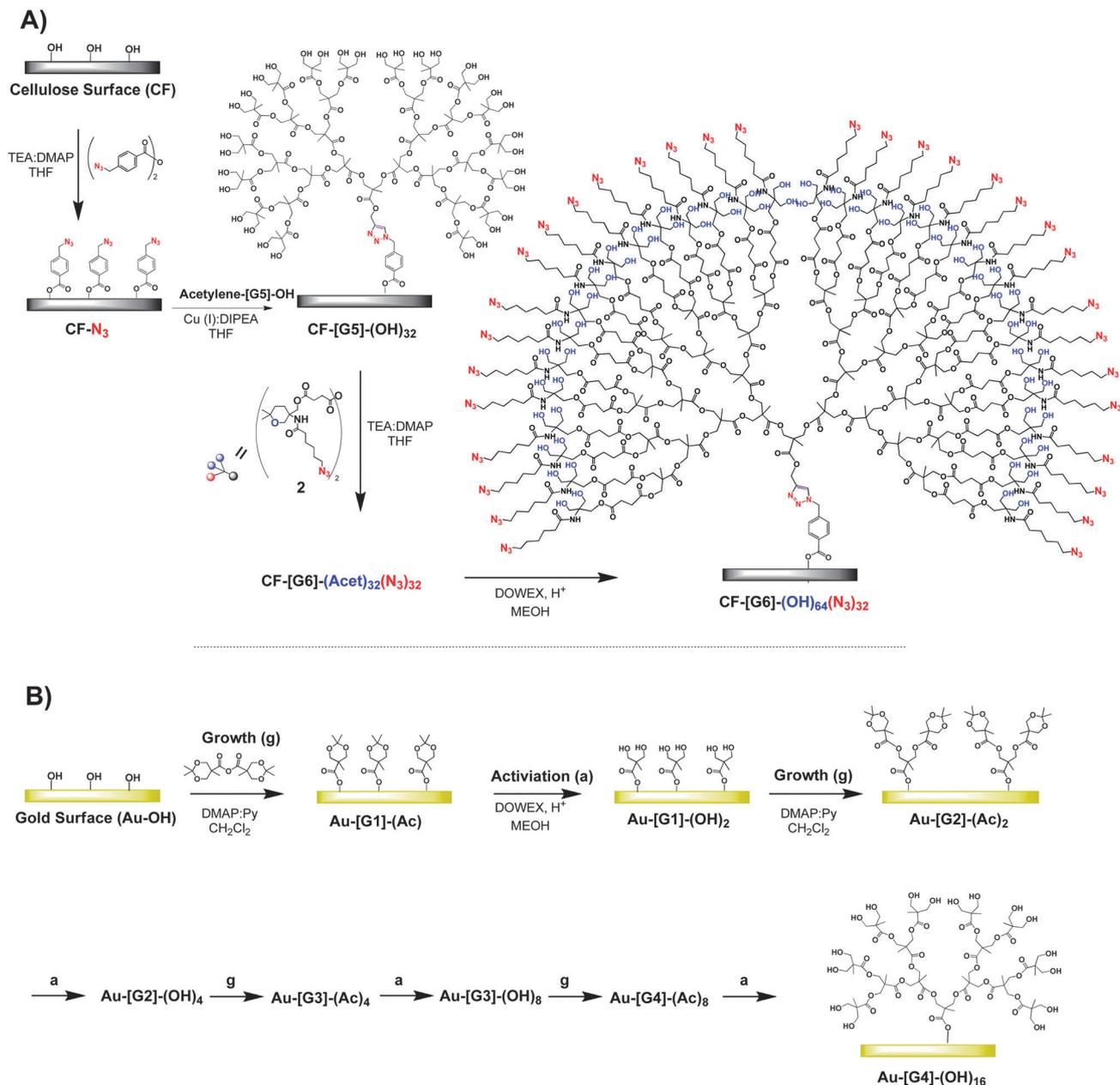
### 3. Foreseen applications of dendritic materials based on the bis-MPA platform

From the number of available scientific papers it is apparent that dendritic materials based on bis-MPA have potential in an array of applications. Their facile synthesis, postfunctionalization and hybridization are a continuous topic towards application driven research. Currently, a large number of carefully selected substituents, not including polymeric hybrids, have successfully been attached, both as a core as well as peripheral groups, Fig. 5, resulting in advanced dendritic frameworks for the evaluation in solution, networks as well as thin film applications.

#### a. Optical

The branched and layered architecture of bis-MPA dendrimers displaying multiple reactive hydroxyl groups at the periphery has enabled their exploitation as functional probes in optical applications. Ferroelectric liquid coralline dendrimers up to [G3] with 24 mesogene containing groups were successfully synthesized revealing a variety of mesophases including the smectic C\* phase as well as ferroelectricity.<sup>99,100</sup> Peripheral chiral<sup>101</sup> as well as fluorinated<sup>102</sup> bis-MPA dendrimers have been synthesized providing site isolation of divalent and trivalent lanthanides in which their luminescence efficiency was evaluated. Metal-ion containing macrocycles have also been introduced as core moieties of bis-MPA dendrimers. Optically active porphyrin was successfully decorated with a dendritic





**Scheme 8** (A) Sixth generation [G6] dual functional dendronized cellulose surface by a combination of grafting to and grafting from approach. (B) Grafting from methodology for the fabrication of fourth generation [G4] dendronized Au surfaces.

shell *via* the divergent growth approach.<sup>103</sup> Nonlinear optical (NLO) chromophore platinum(II) acetylides were impeded in a bis-MPA dendritic shell and optical-power limiting (OPL) measurement showed improved OPL properties with increased generation.<sup>104,105</sup> Arylthiophene cored bis-MPA dendrimers were straightforwardly synthesized *via* the divergent growth strategy to [G4] and their optical-power limiting (OPL) properties were observed at 532 nm, Fig. 6a.<sup>106</sup> The emergence of the click concept was also reported for the convergent coupling of the [G4] dendron to cyclen.<sup>107</sup> An increase in luminescence decay time was detected for higher generation dendrimers with incorporated lanthanide metal ion Europium. Furthermore, the stable

triazole linkage generated from the click reaction was found to act as a sensitizer. Employing a similar strategy, [G2] and [G3] bis-MPA dendrons were efficiently coupled to an azide functional cyanine dye.<sup>108</sup> Photophysical characterization elucidated an intense absorption and emission in the near-infrared. Linear-dendritic block-copolymers comprising a single PEG chain ( $M_w$  1, 2 and 5 kDa) coupled to [G1] to [G4] bis-MPA dendrons were decorated with mesogenic and photochromic cyanazobenzene units and the aggregation behavior of the amphiphilic hybrid structures was studied in water solution.<sup>109</sup> In this case, the hybrids were found to form cylindrical micelles, sheet-like micelles, tubular micelles as



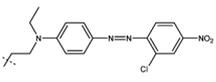
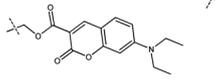
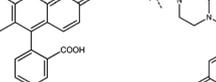
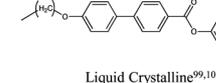
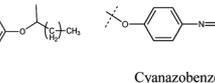
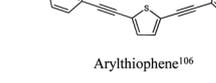
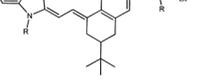
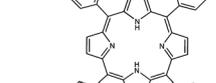
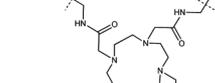
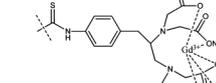
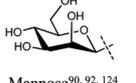
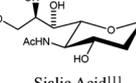
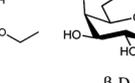
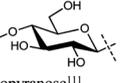
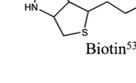
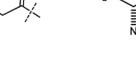
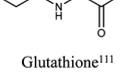
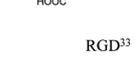
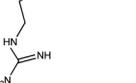
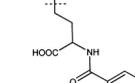
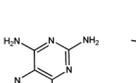
Type	Reported functionalities attached to bis-MPA dendritic scaffolds					
Reactive	 Alkene <sup>27, 28, 111, 128</sup>	 Alkyne <sup>24, 32, 33</sup>	 Azide <sup>232, 91</sup>	 Thiol <sup>22, 89, 90</sup>	 Amine <sup>127, 131</sup>	 Carboxyl <sup>156, 129, 130</sup>
	 Carbonate <sup>35, 112, 114</sup>	 Guanidine <sup>127, 131</sup>	 Phosphine <sup>56</sup>	 Phosphonic <sup>56</sup>	 Disulfide <sup>22, 56</sup>	
Optical	 Disperse Red <sup>1328, 92</sup>	 Coumarin <sup>32</sup>	 Fluorescein <sup>33, 118</sup>	 Rhodamine <sup>125</sup>		
	 Liquid Crystalline <sup>99, 100</sup>	 Cyanazobenzene <sup>109</sup>	 Fluorinated <sup>102</sup>			
	 Arylthiophene <sup>106</sup>	 Platinum(II) acetylides <sup>104, 105</sup>	 Cyanine dye <sup>108</sup>	 Chiral <sup>101</sup>		
	 Porphyrin <sup>103</sup>	 Cyclen <sup>107</sup>	 Gd(III) Chelates <sup>126</sup>			
Bioactive	 Mannose <sup>90, 92, 124</sup>	 Sialic Acid <sup>111</sup>	 β-D-lactopyranose <sup>111</sup>	 Cysteine <sup>27</sup>		
	 Biotin <sup>53</sup>	 Glutathione <sup>111</sup>	 Amoxicillin <sup>28, 92</sup>			
	 RGD <sup>33</sup>	 Folic Acid <sup>118</sup>	 MTX <sup>118</sup>	 Doxorubicin <sup>50, 113, 123, 124</sup>		

Fig. 5 Selection of substituents attached to bis-MPA architectures.

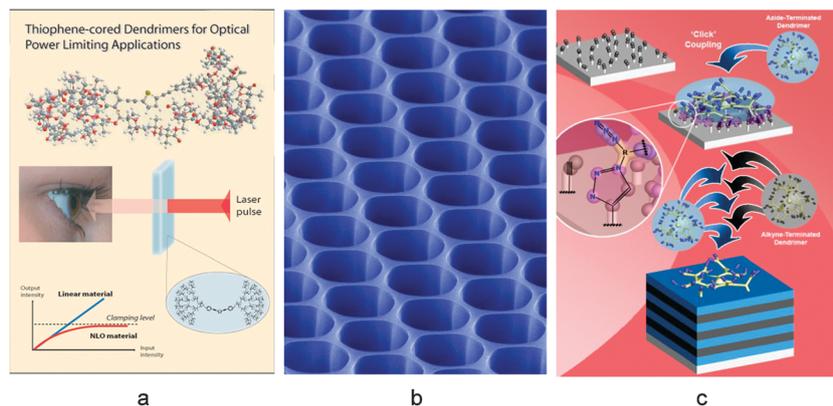
well as polymer vehicles, depending on the generation of dendrons and  $M_w$  of the PEG chain.

### b. Biological

Today dendritic structures based on bis-MPA are intensively considered as promising macromolecular probes in biological research.<sup>34</sup> This capitalizes on their aliphatic polyester structure,

yielding a biocompatible and hydrolytically degradable architecture.<sup>110</sup> Today, a large number of bioactive substituents have successfully been covalently attached to these scaffolds including carbohydrates,<sup>16,33,111</sup> peptides,<sup>33,111</sup> anticancer doxorubicin (DOX),<sup>31,112,113</sup> and antibiotic penicillin derivative amoxicillin.<sup>28</sup> To accomplish accurate postfunctionalizations, the peripheral hydroxyl groups are converted to reactive





**Fig. 6** (a) Arylthiophene cored [G4] bis-MPA dendrimers for optical-power limiting (OPL) applications,<sup>106</sup> (b) ordered honeycomb membranes from core crosslinked star AB block-copolymer hybrids consisting of PS and bis-MPA dendrons<sup>55</sup> and (c) ultrathin films *via* LBL methodology from monodisperse bis-MPA dendrimers.<sup>145</sup> Copyright permission from John Wiley and Sons.

intermediates including alkenes,<sup>27,28,111</sup> acetylenes<sup>24,32,33</sup> and *p*-nitrophenyl carbonates.<sup>112,114</sup> The latter resulted in facile introduction of both polyethylene glycol chains<sup>115</sup> and DOX, with pH-sensitive hydrazone linkages,<sup>113</sup> into a library of HFDs, Fig. 4d. In cell culture, a carefully selected HFD drug delivery vehicle with the nomenclature<sup>17</sup> HFD(*e*)-G3-(PEO5k)<sub>8</sub>-*b*-G4-(DOX)<sub>16</sub> was found to be more than 10 times less toxic than free DOX. Furthermore, the efficacy of the carrier, containing 20 mg kg<sup>-1</sup> DOX, on albino house mouse (BALB/c)e bearing C-26 tumors *via* intravenous administration was found to exhibit a nine fold higher accumulation in tumor than free DOX after 48 h. Remarkably, a single injection of the DOX loaded HFD carrier, at 20 mg kg<sup>-1</sup> DOX equivalents 8 days after tumor implantation, caused complete tumor regression and 100% survival of the mice.<sup>113</sup> A hetero-functional dendrimer decorated with sixteen mannose units and two coumarin chromophores, HFD(*e*)-G4-(mannose)<sub>16</sub>-*b*-G1-(coumarin)<sub>2</sub>, was evaluated by Hawker *et al.* as a recognition/detection agent for the inhibition of hemagglutination. The multivalent representation of the carbohydrates was found to exhibit 240-fold greater potency than monomeric mannose *i.e.* a relative activity of 15 per sugar group when compared to mono-mannose.

Since hydroxyl-functional hyperbranched polyesters have a significant resemblance to the corresponding dendrimers they have also been evaluated in biological applications. A blocking agent based on Boltorn H30, pseudo [G3], with mannose peripheral groups suggested inhibition at nanomolar concentrations between cell-specific intercellular adhesion molecular 3-grabbling nonintegrin (DC-SIGN) and Ebola virus (EBOV).<sup>116,117</sup> Dual functional hyperbranched polyester based on Boltorn H2003 has also been accomplished to introduce combinations of fluorescein, folic acid and MTX for use as a drug delivery vehicle.<sup>118</sup> One area where the interest for hyperbranched polymers has emerged significantly is encapsulation of dyes or drug moieties.<sup>119</sup> The structural characteristics of hyperbranched polymers, their low viscosity and their relatively low price make them potential candidates for successful encapsulation applications. Karatsos *et al.* have modeled Boltorn H20's and H30's capability to host the pharmaceutical molecule 'Shikonon' using fully atomistic molecular

dynamics simulation.<sup>120</sup> It was found that a higher pseudo-generation gave rise to a more efficient drug loading and that conformational characteristics and the solution's concentration may affect the polymer-drug complexation. A higher loading capacity is interpreted as an effect of increased hydrogen bonding capacity.

In more recent work by Nyström *et al.*, Boltorn H30 and H40 were modified with an average of 5 PEG chains (5 or 10 kDa) prior to the encapsulation of DOX. The resulting constructs were evaluated as passive drug delivery vehicles and found to exhibit enhanced drug efficacy and a higher degree of apoptosis compared to free drug.<sup>121</sup> These Boltorn based drug delivery systems were taken up *via* clathrin- and macropinocytosis-mediated endocytosis.<sup>122</sup> The same group successfully encapsulated DOX in PCL and PEG containing linear-dendritic hybrids.<sup>123</sup> The resulting self-assembled micelles were approximately 100 nm in diameter and capable of achieving DOX loading efficiencies of up to 22 wt%. The loading amount of DOX was largely influenced by the size of the dendron. The encapsulation of DOX was also successful in polymer based theranostic systems, built from non-toxic star-like dendritic-linear polymer hybrids consisting of [G1] and [G2] bis-MPA dendrimers decorated with hydrophilic and fluorinated poly(PEGMA-*co*-TFMA) chains. With larger hydrophobic dendrimer cores, the release kinetics of DOX could be tailored revealing cellular uptake of the DOX loaded micelles into breast cancer cells.<sup>124</sup> Gillies *et al.* have also elegantly reported on the introduction of dendritic blocks comprising rhodamine and Gd(III) chelates to PCL-PEG based micelles.<sup>125,126</sup> The Gd(III) surface functionalized micelles were proposed as high-relaxivity MRI contrast agents. In an alternative approach, superparamagnetic iron oxide (SPIO) nanoparticles were decorated with [G3] dendrons comprising guanidine end groups.<sup>127</sup> The dendrons displayed enhanced uptake of SPIO into GL261 mouse glioma cells.

### c. Thin films and crosslinked networks

The branched architectures expressing a large number of functional groups and low viscosity in solution have enabled the utilization of dendritic polymers in coating applications.



In thin film applications, the hyperbranched bis-MPA polymers are the most assessed and reviewed.<sup>128,129</sup> The peripheral exposed functional groups of the dendritic scaffolds eliminate the formation of chain entanglements which is crucial for efficient film formation.

**I. Hyperbranched polymers.** Boltorn™ P1000 compound was successfully used to accomplish a series of multifunctional and hyperbranched polyesters, carrying benzophenone, acrylates and tertiary amine moieties for further use as photoinitiating polymers in the fabrication of UV-cured films.<sup>130</sup> In another approach, Boltorn™ materials were used to intercalate with unmodified sodium montmorillonite clay (Na-MMT) in water to generate a broad range of polymer clay nanocomposite films.<sup>131–135</sup> For instance, it was found that exfoliation could only be obtained with clay loadings less than 5% wt/wt.<sup>131</sup> No correlation between interlayer spacings and the generation number was found, although the interlayer distances increased in a step-like fashion, explained by the flattened conformation of the hyperbranched polyester. Wooley *et al.* end-functionalized Boltorn™ H30 with alkene groups and the final branched structure was UV-cured with thiol-ene coupling into films using a combination of 4-armed poly(ethylene glycol) (PEG) tetrathiol (0–25 wt%) and varying equivalents of pentaerythritol tetrakis(3-mercaptopropionate) (PETMP) (0–64 wt%). The cured films were evaluated for their antifouling properties and it was suggested that the Boltorn-PEG-PETMP systems are low cost, environmentally benign, antibiofouling coatings.<sup>136</sup> Thiol-yne click chemistry has also been employed for the fabrication of films based on acetylene modified Boltorn™ H20 and its subsequent crosslink using PETMP under UV.<sup>137</sup> 2D micro-patterned surfaces were accomplished by direct laser writing (DLW) hence allowing topographical evaluation on cell proliferation. Nanofiltration membranes for water purification have been developed by a reaction between Boltorn™ H40 and glutaraldehyde.<sup>138,139</sup> The membranes showed high water permeability and salt rejection. Rhodamine B and xylene dyes were used to evaluate the separation of small organic molecules. Thin film composite membranes for nanofiltration were developed by crosslinking Boltorn™ H40 and terephthaloyl chloride on a polyacrylonitrile support and the membrane performance was evaluated.<sup>140</sup> As compared to other membranes, the hyperbranched membranes exhibited relatively high permeate flux.<sup>141</sup>

**II. Dendritic-linear hybrids.** These scaffolds have also been evaluated for the construction of thin films. A star-like dendritic-linear polymer hybrid based on Boltorn™ H20 with PS chains was self-assembled to honeycomb microarrays with pore sizes close to 1.5 μm in diameter.<sup>49</sup> Perfectly ordered honeycomb membranes were successfully accomplished from core cross-linked star AB block-copolymer hybrids consisting of PS and bis-MPA dendrons, Fig. 6b. The dendrons were decorated with protective acetanilides, hydroxyl and hydrophobic pentadecafluorooctanoyl end-groups.<sup>55</sup> In a more recent work, amphiphilic ABC<sub>x</sub> structures having a balanced mass ratio of PEG chain to PCL interconnected *via* a bis-MPA dendritic linker enabled the construction of ordered arrays *via* a breath figure method.<sup>142</sup> AB block-copolymer hybrids have also been investigated as dispersing agents for a variety of inorganic particles such as TiO<sub>2</sub>,

Au and CdSe. By decorating the dendron end-groups with phosphonic, carboxylic, disulphide, *etc.*, even dispersion of discrete inorganic nanoparticles was noted in both solutions as well as in PMMA matrices.<sup>56</sup> AB block-copolymers based on a 5 kDa PEG and carboxylated dendrons up to [G4] were employed as CaCO<sub>3</sub> crystallization growth modifiers. Spherical particles of gradually reducing size with increasing number of generation of the dendritic segment were obtained.<sup>143</sup> Environmentally friendly non-covalent crosslinked hydrogels have also been reported by Aida *et al.* utilizing ABA block-copolymers as dendritic binders.<sup>144</sup> An aqueous solution of < 0.4 wt% of the dendritic component decorated with positively charged guanidinium ion groups and 2–3 wt% of anionically charged clay sheets resulted in self-healing hydrogels within 3 min. Chemically crosslinked hydrogels from similar block-copolymers have also been accomplished *via* CuAAC resulting in functionalizable hydrogels for interaction with proteins.<sup>53</sup>

**III. Dendrons and dendrimers.** Dendrons and dendrimers assessment as crosslinked film is strongly coupled to ultrathin or monolayer fabrications. Exploring the highly efficient CuAAC click reaction, Hawker *et al.* coupled azide- and alkyne-terminated bis-MPA dendrimers of different generation to silicon wafers, Fig. 6c.<sup>145</sup> The dendrimers were iteratively coupled *via* Layer-by-Layer (LbL) methodology to an alkyne-functionalized surface initially with azide-functional dendrimers. In the second step, alkyne-functional dendrimers were covalently attached to the azide-functional dendrimer surfaces and the procedures were revisited for further film growth. Excellent control over the film growth was obtained by the dendrimer size, ranging from 0.46 nm for [G2] dendrimers to 1.22 nm for [G5] dendrimers. The films were highly regular and defect-free, compared to linear analogues.

Dendronized Au surfaces with monolayer of bis-MPA dendrons of different generation and PEG chain length were also evaluated by Adronov *et al.* with respect to protein resistance, cell adhesion and proliferation.<sup>96–98</sup> The protein resistance increased with increasing generation of dendrons and increasing chain length of PEG to 2 kDa. The PEG-functionalized dendronized surfaces exhibited a significant reduction in cell growth, whereas the hydroxyl functional dendronized surfaces showed a considerably higher affinity for the cells. A potential biosensor with self-assembled dendritic monolayer (SADM) of bis-MPA dendrons that display mannose carbohydrates was also evaluated, by Malkoch and Berglin *et al.*, for their multivalent interaction and scavenging ability towards *Escherichia coli* MS7fim+ bacteria.<sup>90</sup> The carbohydrate decorated sensors based on [G3] dendrons revealed 2.5 times enhanced recognition of bacteria, when compared to hydroxyl functional surfaces. The same group also explored bifunctional dendronized cellulose surfaces as biosensors.<sup>92</sup> A 10-fold stronger multivalency to lectin protein Concanavalin A was detected for the biosensors based on [G5] bis-MPA dendrons displaying multiple mannose substituents when compared to the monomeric counterpart. Self-assembled arrays of [G4] carboxylated bis-MPA dendrimers onto gold surfaces were accomplished with a defined separation of 17 or 28 nm.<sup>146</sup> The surfaces were found to enhance the growth of endothelial cells and binding of proteins from the cell media



**Table 2** Commercial sources of available bis-MPA based scaffolds

Bis-MPA based dendritic scaffolds	Perstorp	Polymer Factory	Sigma-Aldrich
Monomers	×		×
HBP	× <sup>a</sup>	×	×
Dendrons		×	×
Homofunctional dendrimers		×	
Heterofunctional dendrimer		×	
Dendritic-linear hybrids		×	×
Tailor-made dendritic polymers		×	

<sup>a</sup> Large scale availability for customers with final applications.

when compared to commercially available poly(acrylic acid) of the same molecular weight.

#### 4. Commercial availability

All the bis-MPA based dendritic architectures described here have academically been reported supported by detailed experimental protocols. As a result, an experienced dendrimer or polymer chemist can reproduce many of the elegant examples found in the literature. However, for the broad scientific community with limited knowledge in specific synthesis of bis-MPA based dendritic structures, the commercial route is an alternative to facilitate their evaluation in desired cutting-edge research. Today, the producers Perstorp AB and Polymer Factory Sweden AB along with the distributor Sigma Aldrich Corporation are three global providers of a selection of these scaffolds, Table 2.

#### 5. Summary and outlook

Bis-MPA based dendritic materials belong to one of the most utilized dendritic families. This is ultimately related to their facile synthesis and hybridization using most known polymerization techniques. As a result, a remarkable number of sophisticated architectures have successfully been accomplished including monodisperse dendrons and dendrimers as well as polydisperse hyperbranched and dendritic-linear hybrids. The introduction of the click concept has further expanded the number of suggested bis-MPA dendritic architectures and active substituents by benign postfunctionalization to include optical and bioactive groups. With the commercial availability and excellent biocompatibility, researchers are presently exploring these frameworks for a wide variety of applications. However, the use of suggested new polymeric materials for *in vivo* medicinal applications is not straightforward since that has to pass the hurdle of various clinical phases. To the best of our knowledge, FDA or other entities have not yet approved any dendritic carrier based on bis-MPA for use as a drug delivery vehicle.

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