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PERSPECTIVE

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Dendritic and Hyperbranched Polymers from Macromolecular Units: Elegant Approaches to the Synthesis of Functional Polymers

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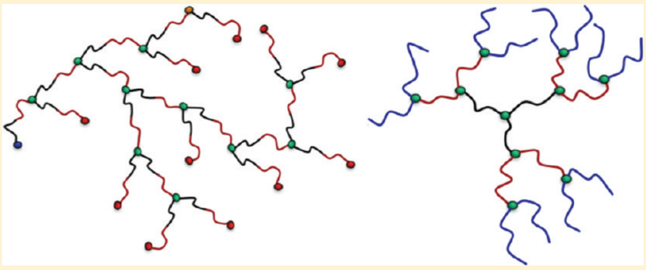

ABSTRACT: This perspective presents the state-of-the-art techniques to synthesize highly branched polymers such as dendrimers and hyperbranched polymers with well-defined linear chains between branch points. These highly branched polymers are essentially the long-chain analogues of conventional dendrimers and hyperbranched polymers and have been given many names, including dendrimer-like, DendriMac, HyperMac, etc. We cover the various synthetic strategies: the direction of synthesis (i.e., core outward or periphery inward) and the building of hyperbranched polymer either through iterative chain growth/branching reactions or from well-defined and reactive building blocks. The first section of this paper focuses on the iterative chain growth/branching reactions. These reactions have been used to create long-chain analogues of dendrimers. The second section highlights the modular synthesis of long-chain analogues of dendrimers following traditional dendrimer chemistry, based on divergent or convergent synthesis, and using linear polymers, or macromonomers, as building units. The third section outlines the modular synthesis of hyperbranched polymers via single step addition of macromonomers. The final section of this perspective highlights other related syntheses of long-chain hyperbranched polymers that do not fit within the groups described above.

1. INTRODUCTION

Recent advances in polymer science have provided new synthetic tools to design a wide range of polymeric architectures, differing in composition and extent of branching. The degree of branching in polymers can dramatically influence their physical properties. For instance, low-density polyethylene has many branches leading to a low degree of crystallinity, making it a soft material. Conversely, high-density polyethylene (a hard material) is essentially linear with a high degree of crystallinity.[1,2] These observations highlight the possibility that a particular material can be tuned for a given application by simply varying the architecture of the polymeric chains.

Highly branched polymers (e.g., dendrimers and hyperbranched polymers) have many unique features, such as high densities, low viscosities, and many functional end-groups.[3−7] These features make such highly branched polymers attractive candidates for many material applications including targeted drug delivery, viscosity modifiers, supports for catalysts, and scaffolds for further synthesis.[7−11] Dendrimers have well-ordered treelike structures with branches arranged into layers or generations.[6] A hyperbranched polymer also has many branch points, but unlike the regular branching structure found in a dendrimer, these branches are randomly distributed throughout the macromolecule.[6,12] In general, highly branched polymers are synthesized from multifunctional monomers.[13] In the case of a divergent dendrimer synthesis, each new layer (i.e., generation) in the dendrimer is added sequentially. In contrast, hyperbranched polymers are relatively simple to synthesize, and the reaction can often be completed in one pot.[5]

Dendrimer formation can typically be categorized into one of two synthetic strategies. The first approach is to grow the dendrimer "divergently" from the core outward.[14,15] In this approach, the generational layers are added sequentially; the first generational layer is added to the core unit followed by further subsequent generational layers. The other approach to dendrimer synthesis is to grow the polymer "convergently" from the terminal groups inward.[16] In this synthesis, the terminal groups are initially prepared, followed by the addition of the penultimate generation, with subsequent inward growth of the dendrimer. The final step is to link the dendrons together to a core unit to complete the dendrimer.

Hyperbranched polymers can be synthesized using a variety of approaches, although in most cases the reaction can be described as either an explicit or implicit reaction based on AB_n monomers, where the group A can react with the B groups.[13] Examples of hyperbranched polymer syntheses include polycondensation reaction,[5,13] ring-opening polymerizations,[17] self-condensing vinyl polymerization,[18] "click" reactions,[19] or reactions that involve a combination of mono- and difunctional monomers in the presence of a chain transfer agent.[20,21]

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However, if highly branched polymers with a variety of functional groups are desired, the multifunctional monomer must be specifically made in each case using a different reaction scheme in most cases. Furthermore, if the properties of the material are to be tuned by the introduction of spacers between the branch points, a potentially complex synthesis of the small organic molecule may have to be devised. These spacers alter the degree of branching[22,23] and allow the properties of the material to be fine-tuned between the extremes of a linear and dendritic polymer. These factors highlight some of the limitation of only using relatively small organic multifunctional monomers as building blocks for more complex highly branched polymers. These concerns can be addressed by making the spacer unit between the branch points a well-controlled linear polymer or macromolecule. Other advantages of these branched polymers with well-controlled linear spacers between the branch points is that they can combine the advantageous properties of linear polymers and branched polymers. For instance, these long-chain branched polymers can entangle like their linear segments.[24] For instance, these long-chain branched polymers can entangle like their linear segments,[24] making them less brittle materials than their short-chain analogues.[25,26] However, they still have many branch points and viscometric profiles similar to regular highly branched polymers.[27]

These well-controlled linear polymers can be easily prepared using a (pseudo)-"living" polymerization. "Living" polymerization was first used to describe polymers synthesized in the absence of termination or transfer events.[28] These "living" polymerizations gave polymers with predictable molecular weights, narrow distributions, and well-defined end-groups.[29] Strictly speaking, only ionic polymerizations fully satisfied the criteria of a "living" system, and indeed for many decades polymer with "living"-like characteristics could only be made using only ionic polymerizations.[29−32] In recent decades, a new class of free-radical polymerizations has been developed to create polymers with the control similar to that of a "living" polymer. These "living" radical polymerizations (LRP) can be used to create polymers with similar control over molecular weight and end-group functionality to that of a true "living" polymerization, with a reduced influence of side reactions.[33] They have the added advantages of flexibility and tolerance to functional groups and impurities of a conventional free-radical polymerization.[34] Examples of these LRP methods include nitroxide-mediated polymerization (NMP),[35,36] atom transfer radical polymerization (ATRP),[37−39] and reversible addition−fragmentation chain transfer polymerization (RAFT).[40−42] The major advantage of these "living" and pseudo-"living" polymerizations is that they can be used to create well-defined polymers. This approach has allowed the synthesis of a variety of complex architectures, including block and gradient polymers, as well as branched architectures such as star, hyperbranched, and dendritic.[30,32,36,39,41−45]

This perspective focuses on highly branched polymers, in particular dendrimers and hyperbranched polymers with well-defined linear chains between branch points. These highly branched polymers are essentially the long-chain analogues of conventional dendrimers and hyperbranched polymers and have been given many names including dendrimer-like, DendriMac, HyperMac, etc. The well-controlled linear polymers can be synthesized using any (pseudo)-"living" polymerization technique, although in most cases the polymer is synthesized by either anionic or LRP. This paper will also highlight the different approaches to the "linking" or branching of these linear chains, including traditional condensation-type reactions,[5,13] as well as the more recent "click" reactions.[46−48] This perspective complements other articles reviewing the field of star and branched polymers made from linear chains, including articles by Taton et al.,[49,50] Hirao et al.,[51,52] and Hutchings.[53]

There are several key strategies to the synthesis of dendritic and hyperbranched polymers that contain well-defined spacers. These strategies vary in the direction of synthesis, i.e., core outward or periphery inward, and whether the polymer is made by iterative chain growth/branching reactions or from well-defined and reactive building blocks. This perspective highlights the various strategies available to the production of these complex structures, and each approach is illustrated using either seminal articles or examples that we believe exemplifies a particular stratergy. The first part of this paper focuses on the iterative chain growth/branching reactions, which have been used to create long-chain analogues of dendrimers. The second section will highlight the modular synthesis of long-chain analogues of dendrimers following traditional dendrimer chemistry, based on divergent or convergent synthesis using linear polymers or macromonomers as building units. The third section will outline the synthesis of hyperbranched polymers from macromonomers. The final part of the paper will highlight alternative original synthetic pathways to dendritic structures with long spacers between branching points.

2. SEQUENTIAL SYNTHESIS: POLYMERS BASED ON SEQUENTIAL INITIATION AND GROWTH

This sequential strategy involves the synthesis of dendritic structures similar to dendrimers, in which each branching points is separated by a long polymeric chain. This approach is typically performed divergently, i.e., from an initiator with multiple functionalities, which is grown to a star polymer. The terminal groups of the star are then reacted with a branching agent, for instance an AB_2 group, effectively transforming each terminal group to yield at least twice as many initiating groups, which can be used to grow the next generation of the polymer. This process of reacting the terminal groups of a polymer with branching agents to yield a molecule with at least twice as many initiating sites followed by chain extension can be repeated many times to give a long-chain dendrimer-like polymer with many generations (Figure 1). Alternatively, a convergent synthetic approach can be used. In this case, the terminal generation is grown first, followed by the linking of two such terminal generations to a branch point, and reinitiation to grow the penultimate generation. This process is repeated until the dendrons are finally linked to a core unit (Figure 2).

2.1. Long-Chain Analogues of Dendrimers Based on Poly(ethylene oxide). In the initial synthesis of this class of polymers, ring-opening polymerization of ethylene oxide was combined with branching reactions to create long-chain analogues of dendrimers. The original approach to the synthesis of dendrimer-like polymers was outlined by Six and Gnanou,[54] who combined anionic ring-opening polymerization to reactions that generate branch points. In their approach, only relatively low-generation dendrimer-like polymers could be synthesized due to solubility issues.[50,54] Their subsequent work demonstrated multiple generations from long-chain analogues of poly(ethylene oxide).[55] The methodology involved the growth of the first generation as a star polymer, followed by the conversion of the terminal groups to a difunctional initiator, and then extension to give the second

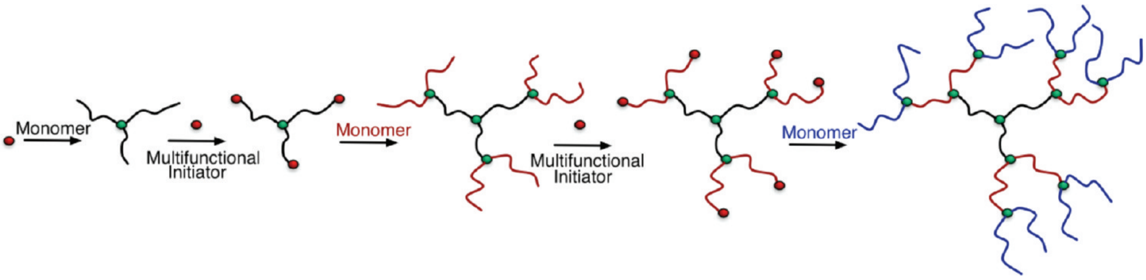


Figure 1. Schematic depiction of the divergent sequential synthesis of the long-chain analogue of dendrimers. The different colored chains represent potentially different monomers. The red sphere represents an active difunctional initiator, and the green represents a formed branching point.

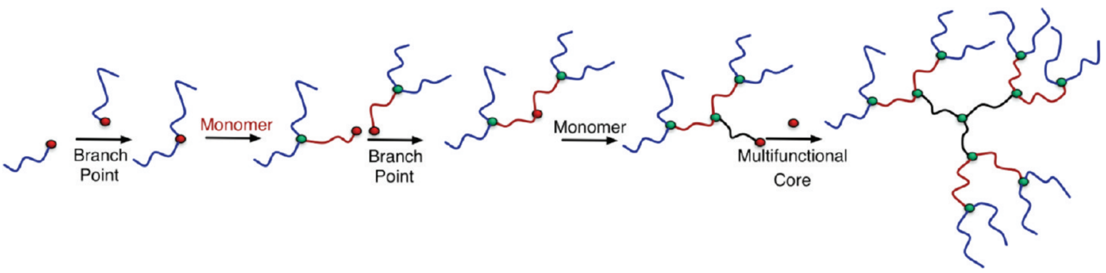


Figure 2. Schematic depiction of the convergent sequential synthesis of the long-chain analogue of dendrimers. The different colored chains represent potentially different monomers. The red sphere represents an active end-group or branch point, and the green represents an already branched point.

generation. They extended the concept to generate up to the eight generations with good control over the molecular weight: with polydispersities below ~1.1 for the first 5 generations and typically below ~1.2 for generations 6−8.[56] A subsequent study further confirmed the efficiency of the reaction involving poly(ethylene oxide) by MALDI-ToF analyses.[57] This strategy for high-generation poly(ethylene oxide) is shown in Scheme 1. In addition, the physical properties of these molecules were studied. The intrinsic viscosities were similar to conventional dendrimers, but the maximum intrinsic viscosity appeared to shift for generations of eight and above,[56] most probably due to the large radii of 20−30 nm.[56]

Another synthetic approach outlined by Gnanou and coworkers[58] allowed the production of dendrimer-like poly(ethylene oxide) polymers of up to four generations, consisting of hydroxy terminal groups and an aldehyde central point. Reaction of the aldehyde with aniline demonstrated the accessibility of the central point.[58] This is an important feature for coupling biomolecules into the dendrimer for applications such as targeted delivery.

Further developments in the synthesis of these polymers included an approach by Feng et al.[59] to synthesize a dendrimer-like polymer with a Janus or two-faced character. This structure was achieved from a core exhibiting two different functionalities, and growing each face of the dendrimer-like polymer orthogonally, resulting in a two-faced dendrimer-like polymer with two different types of terminal groups.[59] A variety of terminal groups were introduced into the poly(ethylene oxide) dendrimer-like polymers, with one of the most interesting being the introduction of an azide functionality onto one face and an alkyne onto the other face. This allowed the dendrimer-like polymers to be linked into a “necklace” polymer by a Cu(I)-catalyzed “click” reaction.[59]

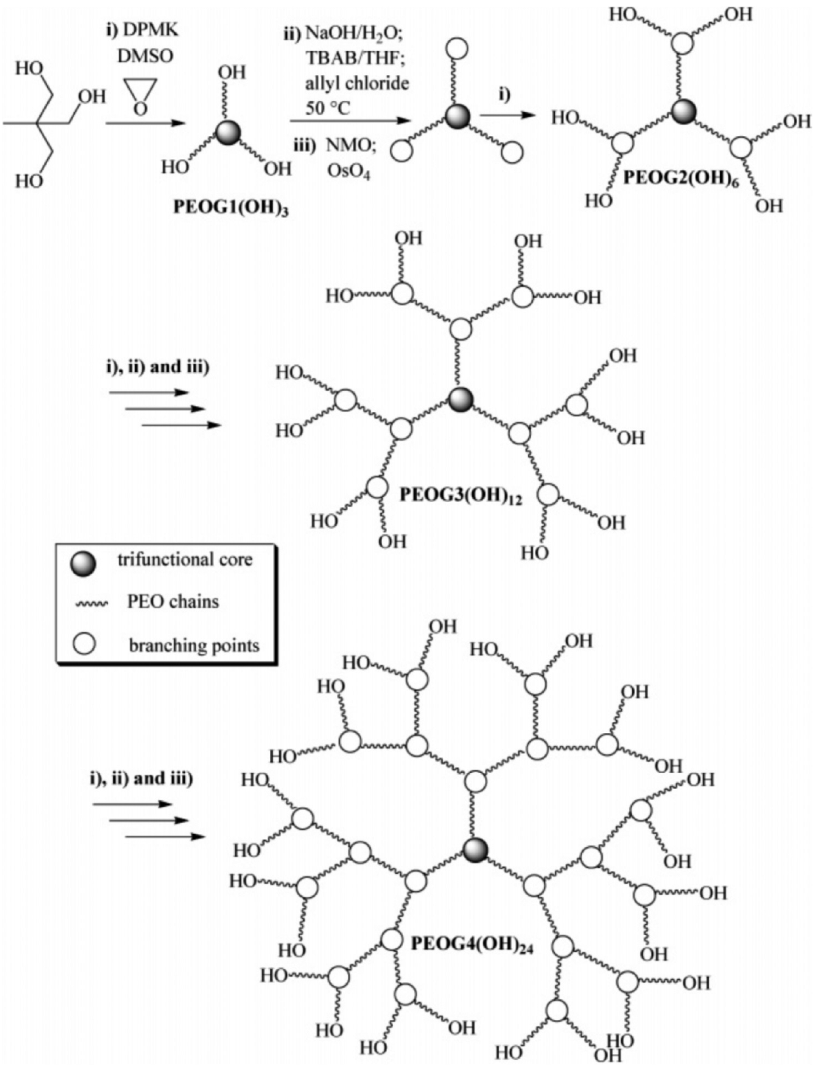
A further efficiency improvement of these reaction was achieved by Feng et al.,[60] who synthesized third-generation dendrimer-like polymers based on poly(ethylene oxide) in one pot. This was achieved by sequential growth of linear chain segments followed by addition of a glycidol molecule that acts as a branch point, with propylene oxide added to limit the extent of aggregation of the terminal alkoxides.[60] They could then grow higher generations by the addition of ethylene oxide, followed by a subsequent branching reaction, and so on.[60]

The development of dendrimer-like polymers based on ethylene oxide has progressed significantly since the initial synthesis by Six and Gnanou.[54] On their own, these dendrimer-like polymers highlight the control that can be achieved in these dendrimer-like polymers. Although at high generations, the PDI can increase to ~1.25,[56] this value is still very low given the number of functionalization steps. These dendrimer-like poly(ethylene oxide) polymers are interesting due to their water solubility. For instance, if biomolecules are included in or bound to the polymer, these polymers could be efficient delivery vectors. Also, the ability to grow a Janus dendrimer[59] is of particular interest to the field of material science and biochemistry due to the fact that two different molecules could be attached to the periphery of the molecule. Various applications could be conceived in addition to the unique necklace morphology;[59] for instance, two different block copolymers could be attached, giving a triblock copolymer for self-assembly studies, or a drug and receptor molecule could be attached for efficient delivery of drugs.

2.2. Long-Chain Analogues of Dendrimers Based on Poly(lactones) and Poly(lactides).

Similar routes as described in the previous section were applied to lactones and lactides.[61] In their seminal paper, Hedrick et al.,[61] who first coined the name dendrimer-like polymers, produce poly(ε-caprolactone)-based dendrimers up to three generations via living ring-opening polymerization. Furthermore, they explored the physical properties of the resulting materials and demonstrated their semicrystalline behavior via differential scanning calorimetric analyses.[61] This synthesis is shown in Scheme 2.

Scheme 1. Synthesis of High-Generation Poly(ethylene oxide) Dendrimer-like Polymer (Reproduced from Ref 56)



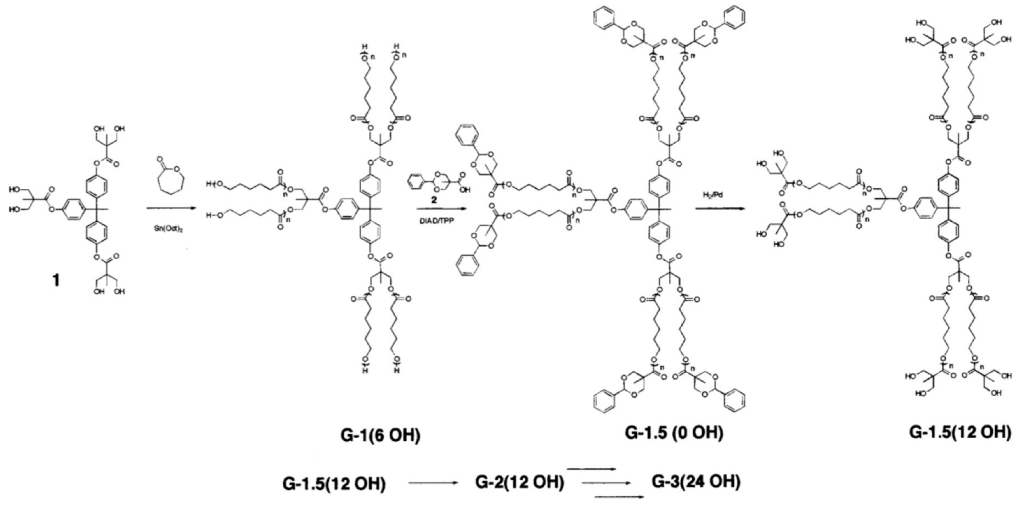
A similar synthesis was outlined by Trollsås et al.,[62] although these polymers had an initial generation of poly(ε-caprolactone), followed by a third-generation (conventional) dendron with protected hydroxy terminal groups. Once attached, these dendrons were used to grow a final and outer generational layer of poly(ε-caprolactone).[62] A further extension of this concept was outlined by Trollsås et al.,[63] where several dendrimer-like poly(ε-caprolactone) polymers were synthesized. The resulting polymers were similar in terms of number of branch points and molecular weights but differed in the branch arrangements. In general, these polymers were found to agree well with the predicted structure of a many armed star polymer when analyzed by DLS and SAXS.[63] Interestingly, the molecular architecture was also found to have a significant influence on the apparent molecular weight measured by SEC, which is expected (Figure 3). Additionally, the architecture was also found to have a significant influence on the melt temperature of the poly(ε-caprolactone) segments (Figure 3).

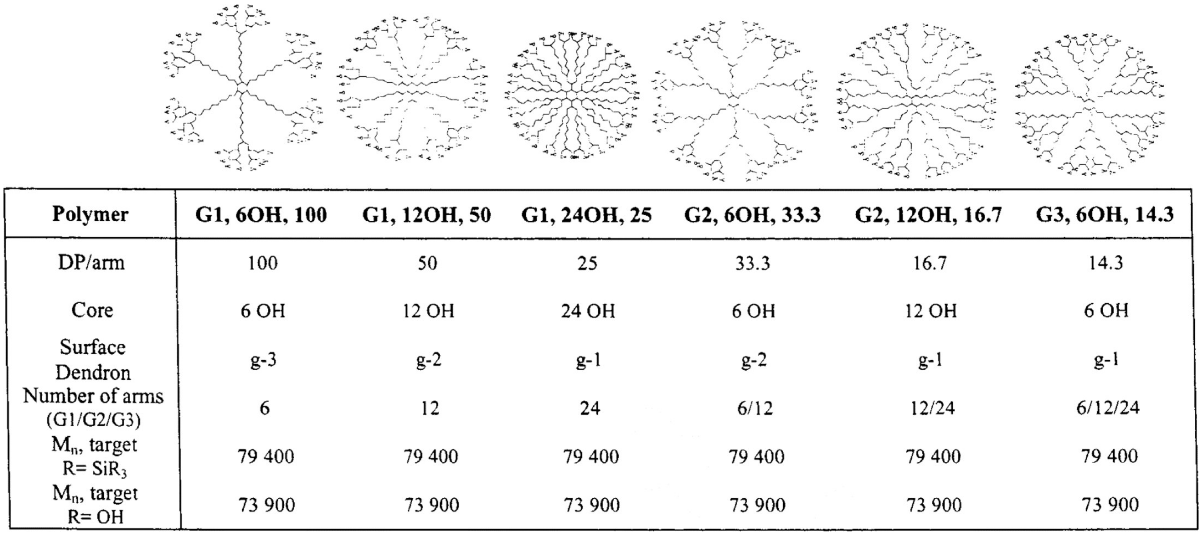
SANS studies[64] on these dendrimer-like polymers indicated that the radius of gyration of the polymer grew linearly with the number of generations and that the overall size and compactness of the molecule could be tuned by changing the spacer length. Interestingly, these dendrimer-like polymers showed the linear increase in the radius of gyration with generation number, similar to highly branched polymer models,[12,65−67] and the observed scaling was also consistent with the complex size−mass scaling functions predicted by many dendrimer models and simulations.[68] However, the radius of gyration for a third-generation dendrimer-like polymer with 20 ε-caprolactone units as the spacer is ∼9 nm,[64] whereas third-generation conventional PAMAM and poly(ether) dendrimers have radii of 1.5 nm.[6,69] Poly(ester) dendrimers are expected to have similar sizes. This increase of almost 1 order of magnitude in size is due to the long linear spacer between the branch points.

A similar approach to the ones described earlier can be used to generate H-shaped block copolymers using appropriate catalysts.[70] For instance, a poly(ethylene oxide) central unit was first synthesized, followed by functionalization with a multifunctional brancher, and growth of a poly(rac-lactide) second block, which effectively corresponds to the second generation.[70]

The advantage of using these dendrimer-like materials based on lactides and lactones is that they offer degradability. As highlighted by Hedrick et al.,[63] tuning the architeture can alter the properties of the material such as its melt temperature or its size in solution. One of the most significant limitations is the

Scheme 2. Synthesis of Third-Generation Dendrimer-like Poly(ε-caprolactone) (Reproduced from Ref 61)





Polymer	G1, 6OH, 100	G1, 12OH, 50	G1, 24OH, 25	G2, 6OH, 33.3	G2, 12OH, 16.7	G3, 6OH, 14.3
DP/arm	100	50	25	33.3	16.7	14.3
Core	6 OH	12 OH	24 OH	6 OH	12 OH	6 OH
Surface Dendron	g-3	g-2	g-1	g-2	g-1	g-1
Number of arms (G1/G2/G3)	6	12	24	6/12	12/24	6/12/24
M_n, target R= SiR_3	79 400	79 400	79 400	79 400	79 400	79 400
M_n, target R= OH	73 900	73 900	73 900	73 900	73 900	73 900

Figure 3. Effect of architecture on apparent molecular weight, melt temperature, and glass transition temperature for poly(ε-caprolactone) dendrimer-like polymers synthesized by Hedrick et al. (Reproduced from ref 63.)

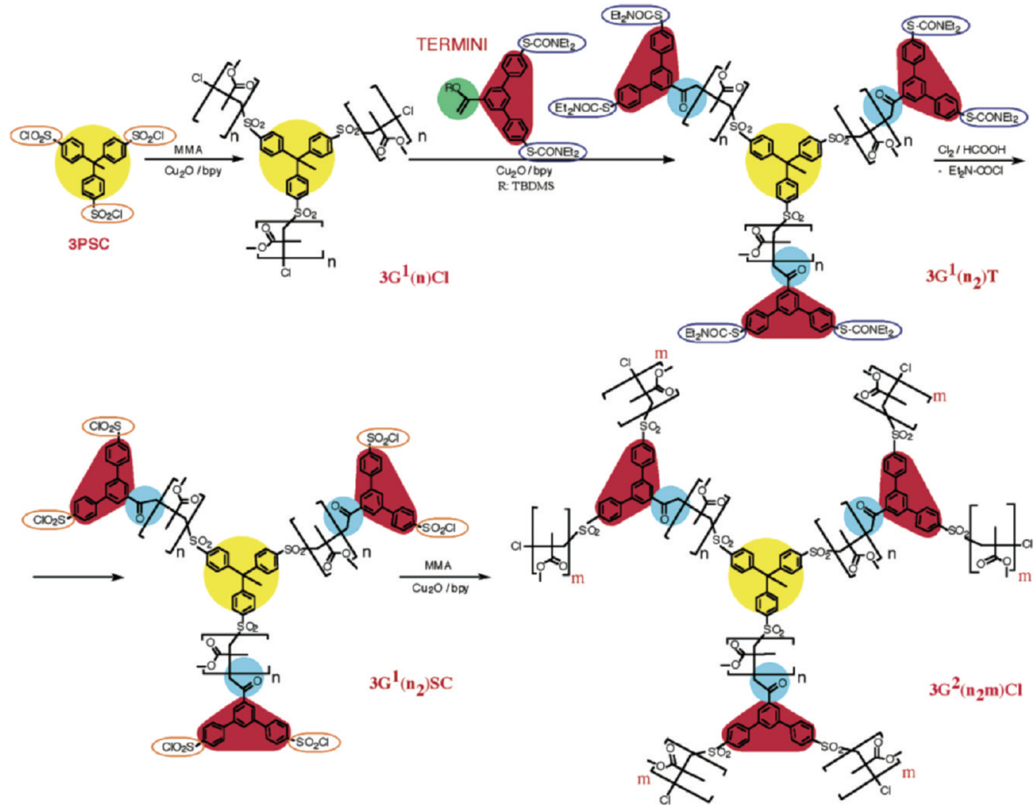
relatively small number of monomer functionalities available for traditional ring-opening polymerization. However, combination with conventional dendrons[62] highlights the breadth of monomer functionality that could be incorporated by combining materials made by traditional ring-opening polymerization with other dendritic structures.

2.3. Long-Chain Analogues of Dendrimers Based on Vinyl Monomers. In these systems, the same concepts of linear chain growth followed by conversion of the terminal groups to branch points is applied to reactions that utilize "living" radical polymerizations of vinyl monomers rather than ring-opening polymerizations.

An interesting application of this approach is the synthesis of dendrimer-like polystyrene by using ATRP to grow the polystyrene chains and transforming the terminal groups to a difunctional initiator and then further chain extending with styrene.[71] This method was used to create third-generation polystyrene dendrimer-like molecules with different number of arms in the initial generation.[71] Macromolecules containing four arms in the initial generation had an intrinsic viscosity profile similar to that of conventional dendrimers. On the other hand, polymers with a larger number of arms in the initial generation did not show a decrease in intrinsic viscosity at high generation, although this may occur at higher generations than synthetically attainable.[71] Other examples include up to third-generation dendrimer-like polymers containing polystyrene as the core generation and *tert*-butyl acrylate as the final generation.[72] Upon hydrolysis of the *tert*-butyl esters to carboxylic acid, a pH-responsive material was formed that was barely water-soluble at low pH but easily water-soluble at high pH. In addition, surface studies showed that the poly(*tert*-butyl acrylate) polystyrene dendritic polymers form stable monolayers on an air—water interface. Under certain conditions these molecules can form pseudomicelles as indicated by AFM.[72]

One elegant approach to the synthesis of long chain-dendritic polymers was outlined by Percec et al.,[73] who combined copper-mediated LRP with the efficient thio—bromo "click" reaction.

Scheme 3. The TERMINI Approach to the Synthesis of Dendrimer-like Macromolecules (Reproduced from Ref 75)



Initially, thio—bromo "click" reactions were used to make dendrimers from small molecules,[74] but in subsequent work the concept was used to make dendritic polymers with poly(methyl acrylate) spacers. The poly(methyl acrylate) chains in each generation was grown using copper-mediated LRP, and after polymerization the bromine end-groups were transformed to a diol by the addition of a thiol containing two hydroxy groups. After the functionalization to an initiator, the subsequent dendritic generation of poly(methyl acrylate) could be grown.[73] This method gave good control over structure of the polymer and showed a lower than theoretical molecular weight based on linear polymer size exclusion chromatography calibration, as expected for dendritic polymer.

The high tolerance to functional groups and impurities makes these dendrimer-like polymers synthesized by LRP attractive. In principle, anionic polymerization of many of these monomers is possible and will give better-controlled structures with less contamination from terminated polymers. On the other hand, the ease with which LRP reactions can be implemented may make the higher polydispersities of ∼1.3 acceptable for most applications. The other advantage of these LRP processes is their tolerance to many functional groups, especially in (bio)materials synthesis. The use of "click"-like reactions is particularly interesting, since these reactions offer simple formation of the branch points needed to create these dendrimer-like polymers. As highlighted in a subsequent section, an even broader range of functionalities can be incorporated by combining two different living polymerizations, such ring-opening and LRP.

2.4. The TERMINI Approach. This technique was developed and coined by Percec et al., describing an irreversible TERminator Multifunctional INItiator.[75] In general, the TERMINI method is used in conjunction with LRP, although ionic polymerization variations exist.[27] In the TERMINI approach, a molecule containing two initiating groups is chosen to react fully and irreversibly with the terminal groups of a living polymer. Each added end-group is then used to initiate a new polymer chain, allowing the addition of a new generation to the polymer. In the original implementation of the TERMINI method, dendrimer-like polymers of methyl methacrylate up to four generations were synthesized by a combination of ATRP and a TERMINI molecule, which contained a reactive vinyl group and two masked ATRP initiators. In general, the TERMINI approach yielded large dendritic polymers of high molecular weight (up to 460 000 g/mol) with good control (polydispersities <1.3).[75] The TERMINI approach is shown in Scheme 3.

The TERMINI approach may follow two routes: (1) the addition of TERMINI unit after the chain growth reaction, i.e. in the absence of monomer, followed by deprotection and reinitation and (2) the addition of the TERMINI unit after some allotted reaction time with the monomer. The first approach gives better defined materials but adds synthetic complexity, while the second approach is simpler but leads to some uncertainty over the exact chain length.[75] In the original implementation of TERMINI, dendritic macromolecules with different linear chain spacers were generated, and interestingly the longer spacers tended to promote the transition to dense globular polymers at lower generations than their shorter chain analogues. As subsequently outlined by Percec et al.,[76] the TERMINI approach can be applied to make a wide variety of materials, for instance by changing the number of unit in the focal point. In a further development of the method, Percec et al.[77] created TERMINI molecules which are much easier to synthesize and optimized living radical polymerization conditions, both of which greatly reduce the time needed to create these branched structures.

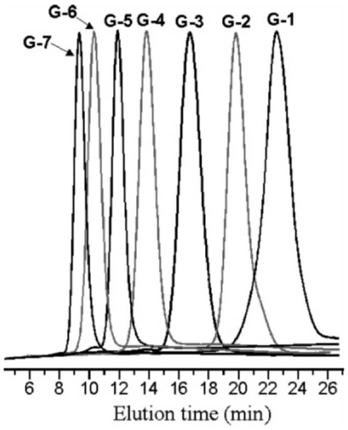


Figure 4. High-temperature size exclusion chromatography traces of generation 1 to generation 7 dendrimer-like polystyrenes, synthesized by the anionic TERMINI method of Matmour and Gnanou.[27] All polymers have low polydispersity, with the generation 7 polymer having number-averaged molecular weight of 1.92 × 10^6 g/mol and polydisperisty index of 1.04. (Reproduced from ref 27.)

An anionic version of the TERMINI approach was outlined by Matmour and Gnanou,[27] who generated both miktoarm star polymers and dendrimer-like polymers of poly(styrene) and poly(butadiene) of up to seven generations for poly(styrene) and three generations for poly(butadiene).[27] Interestingly, the polystyrene dendrimer-like polymers showed the characteristic increase followed by decrease in intrinsic viscosity with generation number, typical of conventional dendrimers.[27] These polymers exhibit very low polydispersity as well as controlled structures and molecular weights (Figure 4). In most cases, the polydispersity index is below 1.1, and the generation 7 dendrimer-like polymer had a PDI of 1.04.

The TERMINI method is interesting since the polymerization and branching happen in quick succession, often in one pot,[75] allowing the facile synthesis of high molecular weight dendrimer-like polymers. One particularly interesting feature of the TERMINI approach is the fact that it is applicable to both ionic and living radical systems, and it highlights the relative merits of these two approaches. The anionic TERMINI gave polystyrenes with excellent control, as seen by polydispersities below 1.05. However, this comes at the cost of the stringent conditions needed to perform multiple anionic polymerizations. In contrast, the radical polymerization gives higher polydispersities, often in the order of 1.3, although they require less stringent reaction conditions. The main disadvantage of the TERMINI approach is that the TERMINI molecule must be synthesized in most cases, while there are often simpler branching reactions such as the thio−bromo click, followed by standard functionalization.

2.5. Long-Chain Analogues of Dendrimers Based on Ring-Opening and Living Radical Polymerizations. Conceptually, the method outlined in this section is very similar to those outlined earlier, namely using living polymerizations to create well-defined long-chain analogues of dendrimers by growing a linear chains from a multifunctional core, followed by a conversion of the terminus of each chain to a branch point, with subsequent growth of new linear chains. However, the materials in this section utilize two or more different growth mechanisms, typically ring-opening polymerization of monomers such as lactones or ethylene oxide, and LRP of a vinyl monomer.

One early study in these polymers focused on different architectures of poly(ε-caprolactone) and poly(methyl methacrylate) from star to third generation dendrimer-like polymers.[78] These studies confirmed that the properties of the polymer such as its radius of gyration and fractal dimension can be influenced by changing architecture and that at higher concentrations these polymers can display liquidlike charcteristics.[78] These poly(ε-caprolactone)-based dendrimer-like polymers have been further studied in terms of their dynamics in subsequent work.[79]

These materials can also be designed with true block-type structure. For instance, Hedrick et al.[25] functionalized a first-generation (star) polymer of poly(ε-caprolactone) to form a branch point at each terminal group. Each newly formed branch point contains an ATRP initiator, which can be used to initiate a methyl methacrylate block, with the optional addition of hydrophilic polymers such as hydroxyethyl methacrylate or a poly(ethylene oxide) methacrylate macromonomer.[25] The amphiphilic properties of these materials were exploited to generate unimolecular micelles.[25] These materials also showed interesting thermal properties, with the branches preventing phase separation in some cases, as evidenced by the block copolymer showing only one T_g, when the methyl methacrylate block has a component of hydroxyethyl methacrylate, while a dendrimer-like polymer of poly(ε-caprolactone)−poly(methyl methacrylate) has two T_gs when the block lengths are sufficiently large. Two T_gs are also observed in dendrimer-like polymers that contain a poly(ethylene oxide) methacrylate component attached to the methyl methacrylate block. A similar approach was used to generate second generation dendrimer-like block copolymers based on substituted poly(caprolactone) and poly(L-lactide), with the substituted poly(ε-caprolactone) block as the first generation and the poly(L-lactide) as the second generation.[80] This material showed two T_gs with each T_g corresponding well to the that of each block.[80]

Another application of this method was performed by Gnanou et al. to create dendrimer-like polymers with different functionalities in various generations by a combination of polymerization techniques.[81] In particular, anionic polymerization was used to create a well-controlled star polymer of poly(ethylene oxide). The end-groups of the poly(ethylene oxide) blocks were then functionalized with either a mono- or difunctional ATRP initiator, and a block of polystyrene was grown from each ATRP initiator. A monofunctional ATRP initiator led to a star block copolymer, and a difunctional ATRP initiator led to a second generation dendrimer-like block copolymer.[81,82] Since these materials possess a hydrophilic block and a hydrophobic block, they can self-assemble depending on the solvent. The authors showed that in a polar solvent such as methanol the NMR signal of the styrene groups disappears, in less polar solvents, both blocks can be seen by NMR, and in solvents that are better for the polystyrene units, a decrease in the poly(ethylene oxide) units is observed.[81,82]

The same group subsequently expanded this approach by reversing the order of the blocks.[83] In that work a star polymer of polystyrene was first synthesized by ATRP, followed by transformation of the terminal group to either a mono- or difunctional initiator for anionic polymerization of ethylene oxide.[83] When a difunctional initiator is used, then dendrimer-like polymers are generated with the first generation being a polystyrene and the second generation being a poly(ethylene oxide) block.[83] Surface characterizations showed the influence of the architecture on the size and compactness of the macromolecule, in particular demonstrating that the dendrimer-like molecule occupies a smaller area than a lower molecular weight star polymer.[83]

This methodology of synthesizing a star polymer of one monomer, followed by modification of the terminal groups to a difunctional initiator, has further been used to create doubly hydrophilic block copolymers.[84] In this synthesis a star polymer of ethylene oxide is first synthesized by anionic polymerization, followed by addition of a difunctional initiator, and growth of *tert*-butyl acrylate chains. After hydrolysis of the *tert*-butyl groups, this yielded a dendrimer-like block copolymer, where the first generation is a poly(ethylene oxide) and the second generation is acrylic acid.[84]

A similar responsive material was outlined by Gnanou et al.[85] In this method dendrimer-like poly(ethylene oxide) polymers were synthesized, from generation 1 to generation 5. These dendrimer-like molecules contained allylic groups that were then converted to ATRP initiators, from which chains of *tert*-butyl acrylate were grown. After hydrolysis of the *tert*-butyl esters, the resulting poly(ethylene oxide)−poly(acrylic acid) dendrimer-like polymers were studied by DLS in water. The size of these molecules increased at higher pHs, as the carboxylic acid groups become ionized, and this effect is greatest when the acid groups comprise a large proportion of the total polymer mass.[85]

One alternative and interesting approach was outlined by Luan et al.[86] In this case a dendrimer-like polymer of up to the third generation was synthesized. These polymers were made by the first creating a multifunctional core, followed by polymerization of styrene by ATRP. Each bromine terminal group could be converted to a difunctional hydroxy group which could be used to initiate ring-opening polymerization of poly(L-lactide). After this reaction, the end groups could again be transformed into a difunctional bromine group, capable of initiating a styrene block by ATRP.[86] These block materials were studied by DSC, showing thermal characteristics consistent with the poly(L-lactide) block, although the styrene units and architecture show a clear influence on the exact temperature of the various phase transitions. A similar concept was used by Kong and Pan[87] to create third-generation dendrimer-like polymers. In this case, the first generation was a polystyrene block, the second generation was a poly(L-lactide), and the third generation was a random copolymer of poly(styrene) and poly(*N*-acryloyloxysuccimide).[87] When the final generation was cross-linked by the addition of a diamine, and the central poly(L-lactide) block was decomposed, an interesting hollow particle results. These particles are due to aggregates of the initial polymers, rather than unimolecular particles, since these particles have sizes in the range of a hundred nanometers.

The idea of combining two different reaction mechanism is both elegant and useful since it gives access to a very wide range of monomer functionalities that can be polymerized by both ring-opening and radical reactions. This can be seen by the various kinds of hydrophobic/hydrophilic block copolymers and phase-separating polymers synthesized by this approach. Another advantage of this approach is that the terminal groups of one polymer can often be easily functionalized to the branch point for the next generation, which is synthesized by the alternative mechanism. The main disadvantage of this approach is that the ring-opening polymerization must be performed under stringent conditions, unlike the purely radical reactions that are typically more tolerant to impuritites. However, the very wide range of functional materials that can be synthesized by this approach makes it attractive in materials synthesis.

2.6. Convergent Approaches Based upon Chain Extension. In this approach linear chains are grown by a (pseudo)-living polymerization. In this convergent approach, linear polymers are first synthesized and then linked to a branching unit to create the terminal generation. In general, it appears that the convergent approach has not been as readily used as the divergent approach, possibly due to the more stringent reactions conditions. Hadjichristidis et al.[88,89] used anionic polymerization to create linear chains of either poly(styrene), poly(isoprene), or poly(butadiene). These linear chains are then linked to a chlorosilane molecule, which also contains a vinyl group, leading to a macromonomer. This macromonomer can then be added to the end of a living anionic polymer and chain extended with another monomer. This approach can be repeated several times to generate dendrimers-like polymers of up to the second generation.[88] If higher generation dendrimer-like polymers are desired, then a similar approach is taken, although the initial anionic chains are added to a dichlorosilane monomer. This creates a macromonomer containing a two-polymer chain. After anionic initiation, for instance via a butyllithium, a new polymer chain can be grown, which can be grown to a higher generation following the method above or coupled to a multifunctional core.[89] The convergent synthesis of the second-generation dendrimer like polymer is shown in Scheme 4.

This approach is very interesting from a synthetic chemistry perspective, since it demonstrates that dendrimer-like polymers can be both grown convergently and divergently. However, at present this method requires very stringent reaction conditions, and in many cases a polydisperity of 1.15 can be seen for a third-generation dendrimer.[89] This is higher than the value seen by other methods such as the anionic TERMINI.[27] However, the possibility of synthesizing dendrimer-like polymers convergently provides an additional layer of flexibility to the synthetic chemist.

3. MODULAR SYNTHESIS: POLYMERS BASED ON THE COUPLING OF MACROMONOMERS

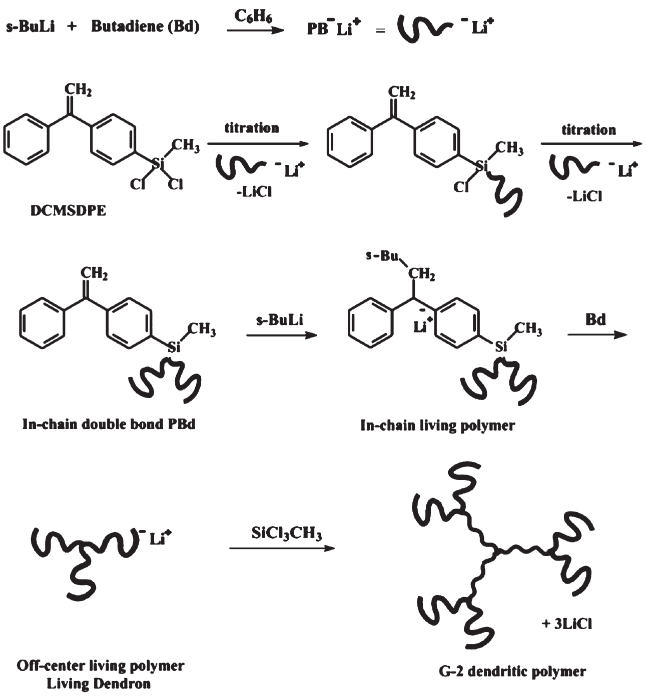
The modular synthesis mimics typical syntheses of hyperbranched polymers and dendrimers, by using linear polymeric chains as macromonomers rather than small molecules, as building blocks. These polymeric chains typically exhibit functionalities of the type AB_2 at the α- and ω-chain end that are used for the coupling reactions. Multistep strategies follow the principles of dendrimer synthesis via protection−deprotection procedures. These methods rely on either a divergent synthesis, where the branched structure is built from the core, or a convergent synthesis, where the macromonomers are added from the periphery toward the focal point. Single-step syntheses mimic hyperbranched synthetic strategies, since all the macromonomers are reacted at the same time.

3.1. Multiple-Step Syntheses. The multiple-step modular syntheses can proceed by very similar methods to the iterative growth and branching methods. However, in these methods the macromonomer are grown first, and then subsequently branched together. The polymer can be grown either divergently as shown in Figure 5 or convergently as shown in Figure 6. The advantages of this method are that the components of each generation can be characterized, although if very large polymers are used coupling slow due to steric factors.

3.1.1. Multiple-Step Syntheses Using Traditional Couplings. Hirao et al. reported the synthesis of dendrimer-like polymers up to the third generation, based on PMMA obtained by anionic polymerization.[90] This group typically uses anionic polymerization of methacylates and coupling of the anionic chain to a benzyl bromide. Dendrimer-like polymers exhibiting repeating units of MMA in the central two generations, and repeating units of protected HEMA as the third generation could also be created by the same approach. After deprotection of the HEMA the resulting amphiphilic molecules were observed to form unimolecular micelles.[90] These MMA dendrimer-like polymers also showed intrinsic viscosities significantly lower than their linear equivalents.[90,91] This approach was subsequently extended to create dendrimer-like polymers based on MMA up to the seventh generation (Scheme 5).[92] These high molecular weight dendrimer-like polymers could be made with excellent control over the architecture, as seen by the very narrow SEC traces shown in Figure 7, and polydispersities as low as 1.02.

Similar approaches were applied to generate dendrons of MMA and a perfluorinated methacrylate.[93] These materials altered the contact angle between the material and water or dodecane.[93] A further extension of these methods was to generate dendrimers up to the third generation, but with a branch functionality of 4 units, rather than the usual dual functional brancher.[94] In addition, fourth-generation dendrimer-like polymers of MMA and block copolymers of *tert*-butyl methacrylate, (2,2-dimethyl-1,3-dioxolan-4-yl)methyl methacrylate, and 2-vinylpyridine were synthesized by this approach.[95] These block copolymers were then transformed to hydrophilic blocks, thus leading to amphiphilic branched structures. The MMA polymers were analyzed by RALLS, SAXS, viscometry, and AFM.[95] Additionally, the technique was used to create fifth-generation dendrimer-like polystyrene[96] and third-generation dendrimer-like block copolymers, where the first and third generation are polystyrene and the second generation is PMMA.

Scheme 4. Synthesis of Second-Generation Dendrimer-like Polymer of Butadiene by a Convergent Approach (Reproduced from Ref 89)



AFM studies of the interaction between fourth-generation tetrafunctional block copolymers of styrene and 3-*tert*-butyldimethylsilyloxymethylstyrene[97] and graphite showed the formation of monolayers separated into four lobes,[97] where the size is consistent with the expected size of these dendrimers when spread out on the graphite surface.

Hutchings first coined the term "DendiMacs" to describe dendrimers obtained from linear polymeric chains. In their seminal paper, Hutchings et al. describes an iterative convergent strategy involving condensation coupling reactions of AB_2 macromonomers. The macromonomers were synthesized by living anionic polymerization, initiated with 3-*tert*-butyldimethylsiloxy-1-propyllithium and end-capped with 1,1-bis(4-*tert*-butyldimethylsiloxyphenyl)ethylene. Following a deprotection reaction, the macromonomer, functionalized with two phenol groups and one primary alcohol group, were assembled into a dendritic structure by a series of Williamson coupling reactions and subsequent end-group modification reactions (Scheme 6).[98] In following work, the same group extended the synthetic procedure to polybutadiene (PBd) to form a first-generation polybutadiene DendriMac in three steps. The first step involved the synthesis of a three-arm PBd miktoarm star in which one arm has a terminal hydroxy group introduced by the use of a protected functionalized initiator. Following fractionation of the star, the hydroxy group was deprotected and converted into an alkyl bromide moiety before coupling the star to a trifunctional core (1,1,1-tris(4-hydroxylphenyl)ethane) by a Williamson coupling reaction catalyzed by cesium carbonate to yield a first-generation PBd DendriMac.[99]

These syntheses of high molecular weight high-generation dendrimers from macromonomers highlight the excellent control over polymer architecture attainable by synthetic chemists. Anionic polymerization allows precise control over the structure of the macromonomer. In many cases the polymers made by this

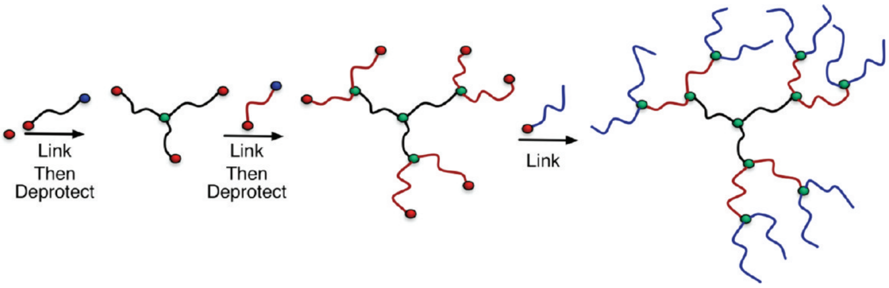


Figure 5. Schematic depiction of the divergent modular synthesis of the long-chain analogue of dendrimers. The different colored chains represent the potentially different monomer functionalities. The red spheres represent an active group, the green spheres represent already formed branches, and the blue spheres represent groups that can be activated with the appropriate treatment.

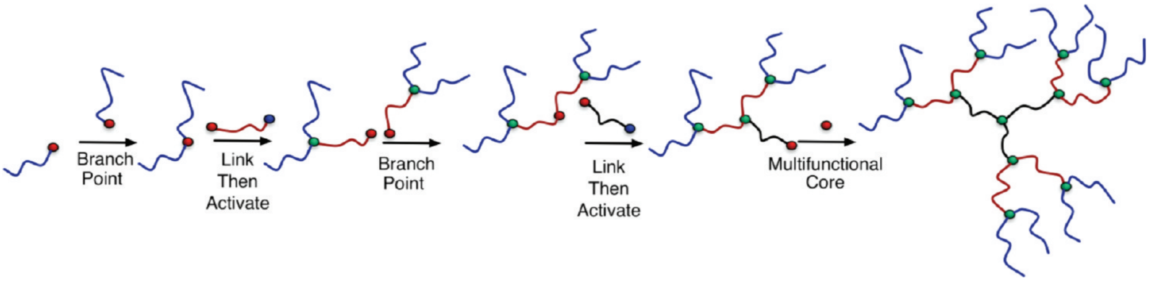
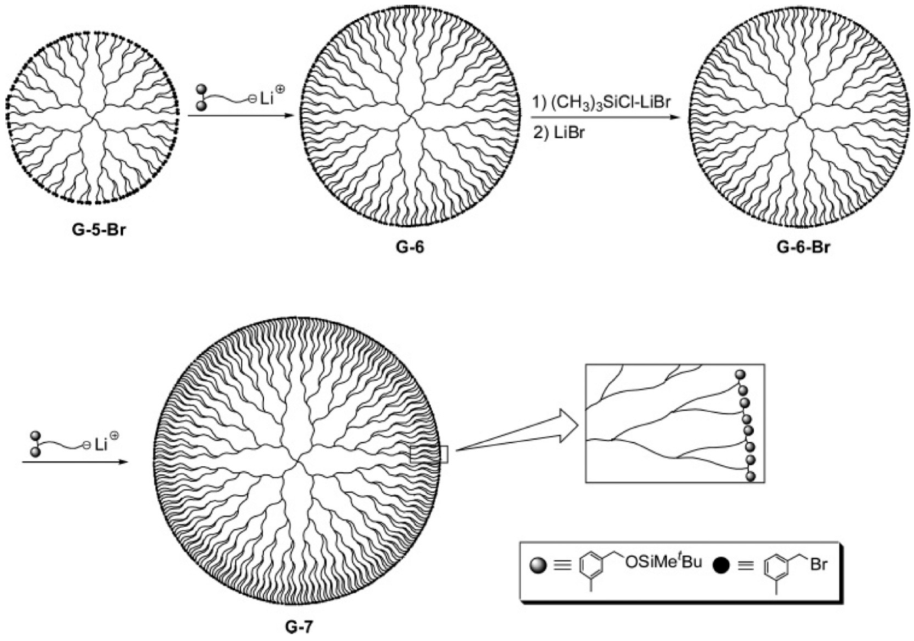


Figure 6. Schematic depiction of the convergent modular synthesis of the long-chain analogue of dendrimers. The different colored chains represent the potentially different monomer functionalities. The red spheres represent an active group, the green spheres represent already formed branches, and the blue spheres represent groups that can be activated with the appropriate treatment.

Scheme 5. Synthesis of Seventh-Generation Dendrimer-like Poly(methyl methacrylate) Polymers Outlined by Hirao et al. (Reproduced from Ref 92)



method have very low polydispersities (<1.05), although in some cases the molecular weights are so high that the polymer approaches the exclusion limit of typical SEC systems.[97] A drawback of the approached outlined here is that sometimes harsh coupling conditions[98] are needed that can lead to solvent degradation and side reactions. Although optimization of conditions is possible, leading to lower amounts of degradation, an alternative is to use "click" reactions that typically proceed under milder reactions and are compatible with a wide variety of functional groups.

3.1.2. Multiple-Step Syntheses Utilizing "Click"-like Reactions. The rise of click reactions had a major impact on the ability to engineer polymeric dendrimers and hyperbranched polymers. In particular, CuAAC reactions allowed miktoarm stars and first-generation dendrimers to be made from polystyrene, poly(*tert*-butyl acrylate), and poly(methyl acrylate).[100] The main issue in these reactions was not the efficiency of the CuAAC reaction, but the accuracy in determining the concentration of polymer chains based on the SEC measurements. This was overcome by using reactive alkyne and azide solid supports to remove excess unreacted polymer after the CuAAC reaction and allowed the product to be isolated in high purity.[101,102] The combination of ATRP/CuAAC and the reactive supports enabled Monteiro et al. to prepare a range of dendritic-type structures via a multistep procedure (Scheme 7).[103,104] The building polymer blocks synthesized using ATRP produced polymer chains with bromine end-group, which were subsequently converted to azides. Coupling these azide end-groups with a range of small molecules created polymer chains with desired functional end-groups. This produced the basic building blocks in which these polymer chains coupled through a divergent process to form dendron or dendrimer structures.

One issue that became apparent was the high levels of copper catalyst used in these reactions, especially when such structures have potential uses in biological applications. An alternative method to significantly reduce the level of Cu(I)Br was the use of copper wire in the absence of conventional ligand to produce AB-type miktoarm dendrimers via a convergent process.[105] The coupling rate was slower than Cu(I)Br/PMDETA but gave highly efficient CuAAC coupling. For this reaction to work efficiently, triazole rings that act as ligands must be initially present in the starting polymer. It was found that the coupling

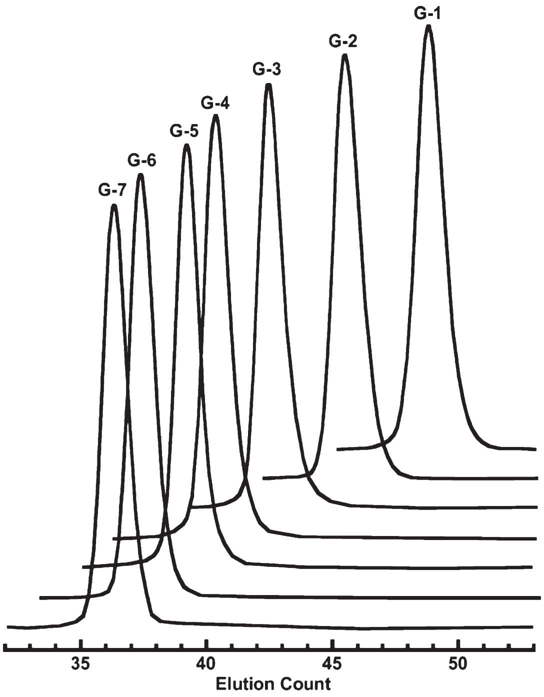
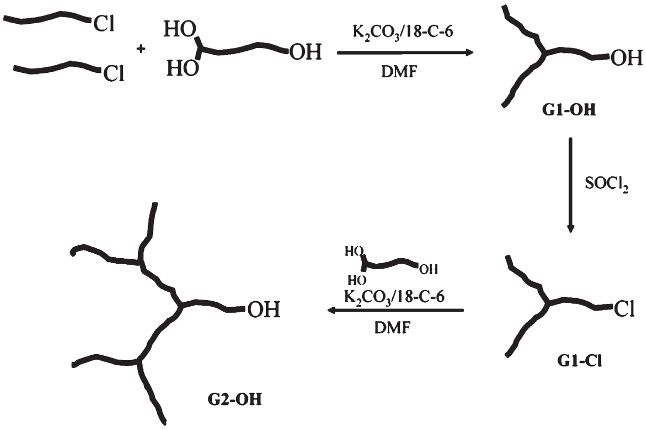


Figure 7. Size exclusion chromatography traces for generation 1 to generation 7 dendrimer-like poly(methyl methacrylate) polymers synthesized by Hirao et al.[92] The molecular weight of the generation 7 sample has weight-average molecular weight of 1.97×10^6 g/mol and polydispersity index of 1.02. (Reproduced from ref 92.)

Scheme 6. Synthesis of Second-Generation Polystyrene Dendron (Reproduced from Ref 98)[a]



[a] Upon coupling the dendron to a multifunctional core, following a similar reaction scheme to the one above, a second-generation "DendriMac" is formed.

rate increased with increasing triazole ring formation. The simple removal of copper wire from the reaction without the use of tedious purification methods (e.g., column chromatography) represents an advantage over previous methods.

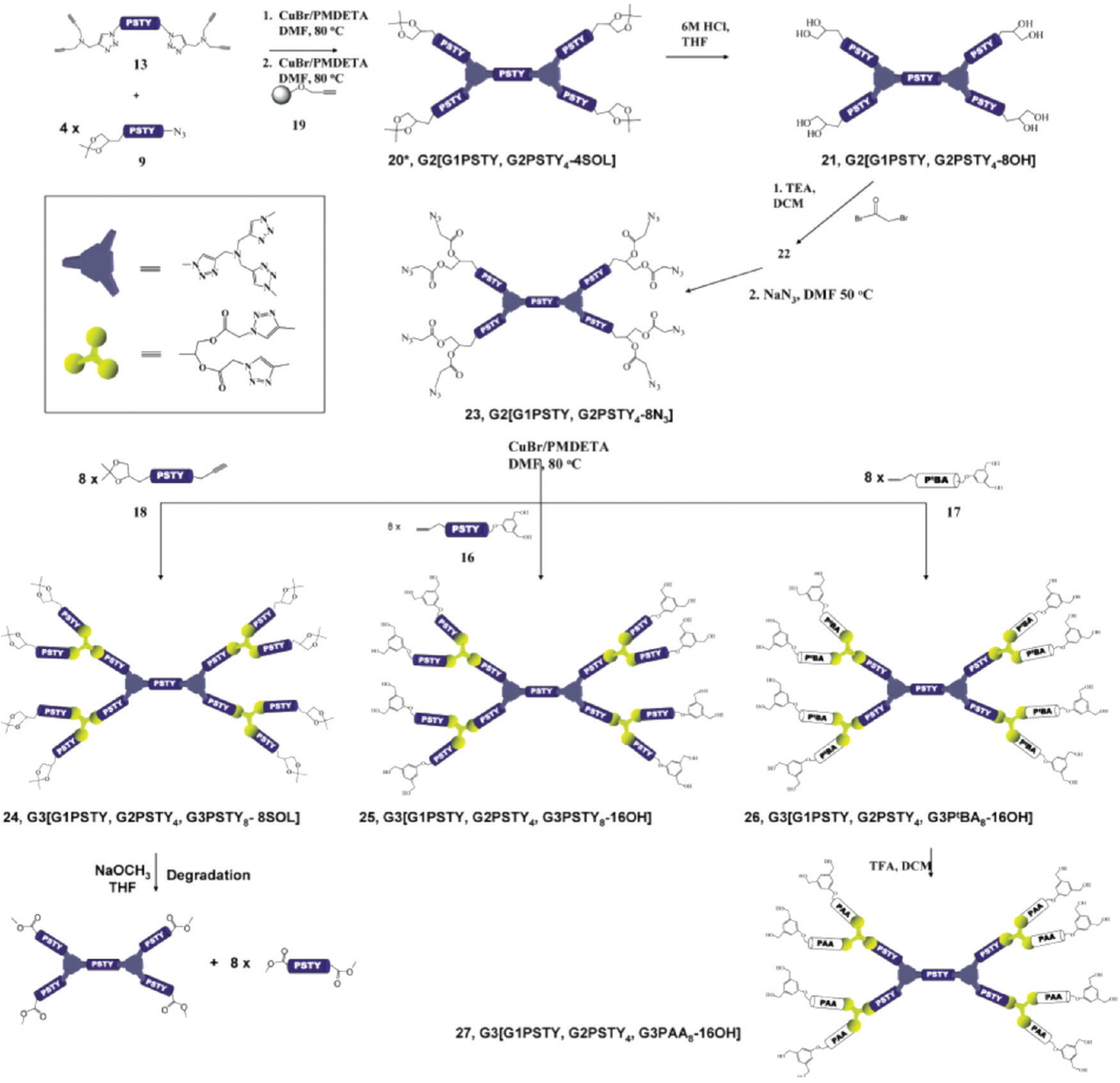
Wang et al. also used CuAAC to synthesize highly complex dendrimer-like copolymers based on the miktoarm star copolymer [polystyrene−poly(ethylene oxide)−poly(ethoxyethyl glycidyl ether)] [PS−PEO−(PEEGE-alkyne)]. The alkyne moiety present at the chain end of the PEEGE block was reacted with 1,4-diazidobutane and pentaerythritol tetrakis(2-azidoisobutyrate) to form dendrimer-like structures containing PEEGE as first generation and PS and PEO as second generation. Both azide groups of 1,4-diazidobutane were reacted to form [PEEGE−(PS/PEO)]$_2$, while only three of the four azide groups of pentaerythritol tetrakis(2-azidoisobutyrate) were reacted, presumably because of steric hindrance, to form [PEEGE−(PS/PEO)]$_3$.[106]

Additionally, Altintas et al.[107] used click reactions to synthesize various dendrimer-like miktoarm star polymers. In their work, second-generation dendrimer-like polymers could be synthesized by a combination of ATRP and ring-opening polymerization. In particular, the central block was synthesized by ATRP to create either poly(*tert*-butyl acrylate) or poly(styrene) with subsequent transformation of the bromine end-group to an azide. The second generation had the alkyne in the center of a block copolymer with one block of poly(*tert*-butyl acrylate) synthesized by ATRP or poly(styrene) synthesized by NMP and the second block of poly(*ε*-caprolactone) or poly(ethylene oxide) synthesized by ring-opening polymerization. The polymers were subsequently "clicked" together, yielding two materials: one with poly(styrene) core with poly(*tert*-butyl acrylate) and poly(ethylene oxide) as the outer generation and one with poly(*tert*-butyl acrylate) core and poly(styrene) and poly(*ε*-caprolactone) as the shell.[107]

Monteiro's group has recently developed the SET-NRC (single electron transfer−nitroxide radical coupling) method for extremely rapid coupling between polymer chains with halides to ones with nitroxide end-groups at 25 °C within minutes.[108,109] This method is a based on the earlier developed ATNRC (atom transfer nitroxide radical coupling) method.[110,111] Monteiro et al. extended these reactions to include CuAAC (copper-catalyzed azide/alkyne cycloaddition) and thiol−ene reactions to make third-generation dendrimers in one pot (see Scheme 8). The authors showed that this method of dendrimer formation could be controlled through careful choice of solvent and ligand.[112] The dendrimers could be formed via a convergent, divergent, or parallel approach through controlling the rates of the two "click" reactions. The efficiency, yield, and purity were all very high, and purification was by simple precipitation. This methdology was extended to polymeric systems to make third-generation dendrimers with equal efficiency and yields, in one pot at 25 °C. The polymers used in this construction consisted of polystyrene, PEG, poly(acrylic acid) , poly(*N*-isopropylacrylamide), and poly(methyl methacrylate).[113]

These approaches based on "click"-like reactions applied to reactive macromonomers offer significant flexibility to the synthetic chemist. In many cases the macromonomer is synthesized using a living radical polymerization, which can introduce some heterogeneities such as incomplete chain-end functionality and polydispersities of 1.1−1.2. However, the range of functional groups that living radical polymerizations are compatible with justifies the use of these reactions. Furthermore, "click" reactions are also compatible with many functional groups, making this approach one of the most robust in terms of the variety of materials synthesized and tolerance to reaction conditions. A particularly attractive concept is to use orthogonal "click"-like reactions[113,114] to produce high-generation polymers with greater ease. The tolerance to a variety of functional groups makes this approach ideal for the synthesis of dendrimer-like materials with interesting self-assembly properties as well as potentially in biomaterials applications. However, if the regular dendritic structure is not a requirement, then it is possible to complete the reaction in one pot and create a long-chain hyperbranched polymer.

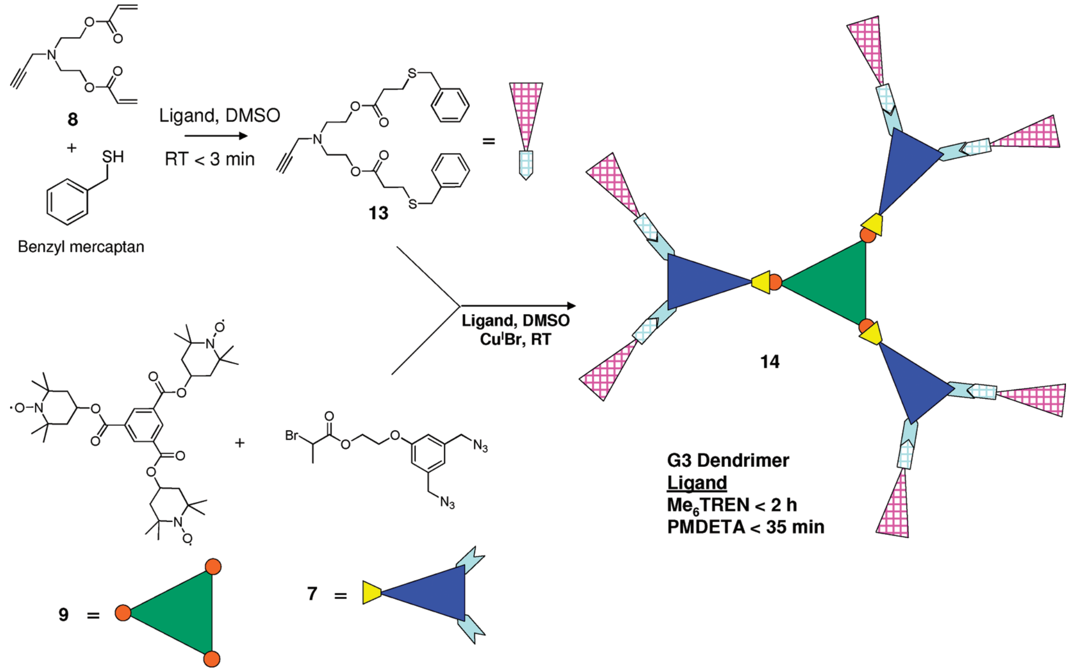
Scheme 7. Synthesis of Second- and Third-Generation Polymeric Dendrimers with Selectively Cleavable Linkages (Reproduced from Ref 103)



3.2. Single-Step Syntheses. In these syntheses a macromonomer is created to have effectively an AB$_n$-type functionality. These macromonomers can be coupled together using a variety of approaches including conventional polycondensation type reactions as well as the more recently explored "click" reactions. The advantage of the "click" approaches is that the coupling of macromonomers is highly efficient and can be achieved under relatively mild conditions, often within a very short time frame.[46] The key concepts in the synthesis of long chain analogues of hyperbranched polymers are presented in Figure 8. It illustrates how reactive macromonomers can be coupled together, in much the same way as their small molecule analogues to create high molecular weight hyperbranched polymers. Figure 9 shows an interesting extension of this concept by performing the same polycondensation on a linear block copolymer. This leads to an alternating block copolymer structure, which will be discussed later in this section.

3.2.1. Use of Polycondensation Reactions To Synthesize Long-Chain Analogues of Hyperbranched Polymers: HyperMacs. The concept of HyperMacs was introduced by Hutchings et al.[115] HyperMacs are based on the coupling of macromonomers by a condensation reaction.[115] In the original implementation, these HyperMacs were created from polystyrene macromonomers, synthesized by anionic polymerization.[115] The end-groups were functionalized to a biphenol and chloro group, allowing the coupling of macromonomers by a Williamson reaction. These

Scheme 8. Synthetic Pathways for the Formation of a G3 Dendrimer in One Pot at 25 °C Using Three "Click"-Type Reactions (i.e., Thiol−Ene, CuAAC, and ATNRC or SET-NRC)



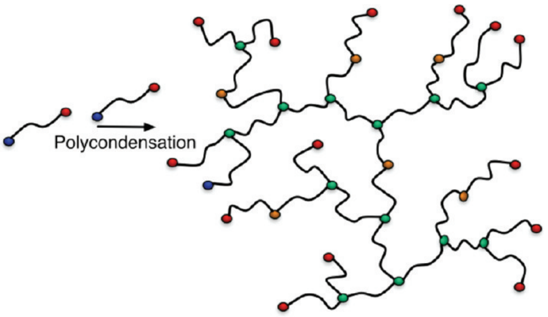


Figure 8. Schematic depiction of the modular synthesis of the long chain analogue of hyperbranched polymers. Here the blue sphere represents the A group, the red represents the B_2 group in the AB_2 macromonomer, the green represents an already formed branch point, and the orange the semireacted units.

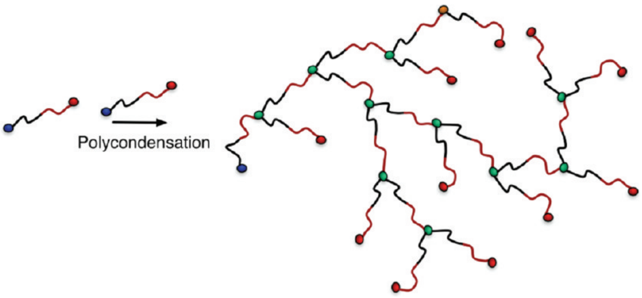


Figure 9. Schematic depiction of the modular synthesis of the long-chain analogue of hyperbranched polymers from block copolymers. This leads to an alternating block copolymer structure. Here the blue sphere represents the A group, the red represents the B_2 group in the AB_2 macromonomer, the green represents an already formed branch point, and the orange the semireacted units.

HyperMacs could be synthesized from polystyrene macromonomers with a variety of molecular weights, giving branched polymers with weight-averaged molecular weights over 500 000 g/mol. However, these HyperMacs have polydispersity indices in the order of 3,[115] which is significantly higher than dendrimer-like polymers that typically have polydispersity indices below 1.3.

An interesting feature of these HyperMacs is that their intrinsic viscosities are significantly lower than their linear equivalents.[115] Another interesting outcome of these HyperMac syntheses is that the proportion of cyclized material can be decreased by increasing the molecular weight of the macromonomer. Another way of minimizing the extent of cyclized material was to increase the concentration of the polymer.[115,116] The choice of solvents was also important. The principal requirements for solvents are good solubility of polystyrene and aprotic properties with high dielectric constant. THF and DMF meet the requirements, and reactions were faster in refluxing DMF than that in refluxing THF, not only because of the difference in temperature (153 °C for DMF and 67 °C for THF) but also because of the difference in dielectric constant (7.58 and 36.71 for THF and DMF at 25 °C, respectively), since the coupling reaction is favored by solvents with high dielectric constants.[115] In subsequent work, the synthetic conditions for HyperMacs were improved by altering the leaving group on the macromonomer from a chlorine to a bromine and by using cesium, rather than potassium, carbonate.[24] This allowed for milder reaction conditions and lower degrees of solvent degradation during synthesis, which reduced the extent of side reactions.[24] In a subsequent paper, the HyperMac methodology was applied to synthesize HyperMacs based on butadiene and methyl methacrylate.[117]

When polystyrene HyperMacs were studied by rheology, these materials showed simple thermorheology characteristics with shear thinning properties and relaxations consistent with a treelike dissipation of the stress.[118] In addition, the determining factor on chain entanglement appears to be the molecular weight of the linear segments and whether that linear chain length is longer than the entanglement length.[24] A subsequent study of polystyrene HyperMacs shows that under appropriate reaction conditions a significant proportion (~15%) of the materials derived are actually gelled and insoluble in a good solvent for the constituent polymer.[119] Although in theory AB_2 polymerizations should not gel, Hutchings et al.[119] suggest that the reactions are so efficient that gels or insoluble materials can indeed be formed by these reactions.

An additional elegant application of the HyperMac approach was outlined by the same group.[117] In this work, HyperMacs were synthesized from block copolymers of poly(styrene) and poly(isoprene). These resulting highly branched block copolymers had many branches, molecular weights of almost 1 000 000 g/mol,[117] and they showed phase separation, but a lack of long-range order.[117] In contrast, the linear macromonomer, and other similar polymers, precursor showed a distinct cylindrical morphology.[117] These poly(styrene)-*b*-poly(isoprene) highly branched copolymers also showed high stress at break values, and when blended with commercial polymers of poly(styrene)-*b*-poly(isoprene), they showed higher strain a break, and decreased Young's modulus.[117]

HyperMacs are very interesting since a wide variety of long-chain hyperbranched polymers can be synthesized in one pot. As with the DendriMacs, initially harsh conditions were needed for the coupling reactions leading to side reactions, although ultimately the reaction conditions were optimized for the synthesis of high molecular weight polymers in a single step. The polymeric structures are less well-defined than their dendrimer-like analogues, but the simpler reaction conditions makes these HyperMacs attractive. Interestingly the HyperMac based on block copolymers showed unique self-assembly properties and tensile properties, suggesting that these materials could be used extensively in applications due to the simple synthesis and interesting properties.

3.2.2. Use of "Click" Reactions To Synthesize Long-Chain Analogues of Hyperbranched Polymers. As outlined by Sharpless et al., click reactions are ones that give high yields, proceed under mild conditions, and are tolerant to many functional groups.[46] Therefore, these reactions are ideally suited to polymer—polymer reactions such as the coupling of many macromonomer. One interesting application of this method was outlined by Konkolewicz et al.,[120] where the thiol—yne reaction was used to create hyperbranched polymers from both small organic molecules and polystyrene oligomers synthesized by RAFT, which contain both a thiol and alkyne group on the molecule (Scheme 9). These reactions were rapid, reaching high conversion within 3 h, and proceeded at room temperature with UV radiation as an initiating source.[120] Another interesting outcome of these reactions was that the resulting hyperbranched polymer has a very high degree of branching, almost as high as a dendrimer. This was evidenced by essentially no signal from the vinyl intermediate formed from the addition of one thiol to the alkyne, suggesting that the degree of branching was very close to 1.[120] This concept was subsequently extended by the same group,[121] which applied the thiol—yne reaction to block copolymers containing both a thiol and alkyne (Scheme 9).[121]

This approach leads to an alternating block copolymer structure between branch points. In that work, one block was chosen to be hydrophobic (styrene), while the other was chosen to be hydrophilic (dimethylacrylamide or acrylic acid). The acrylic acid—styrene hyperbranched block copolymer was formed by hydrolysis of a hyperbranched *tert*-butyl acrylate—styrene polymer. The dimethylacrylamide—styrene system self-assembled into structures that were significantly larger than those formed by their linear analogues, while the acrylic acid—styrene system showed distinct pH responsiveness. At low pH the system self-assembled into large, ill-defined structures, while at relatively high pH the system self-assembled into small, possibly unimolecular particles or micelles.[121] The dendritic polymers also feature highly reactive alkyne peripheral groups that can be utilized for further reaction. For instance, the numerous alkyne end-groups were reacted with gold(I) to obtain gold(I)—acetylide end-groups which provide luminescent properties.[122]

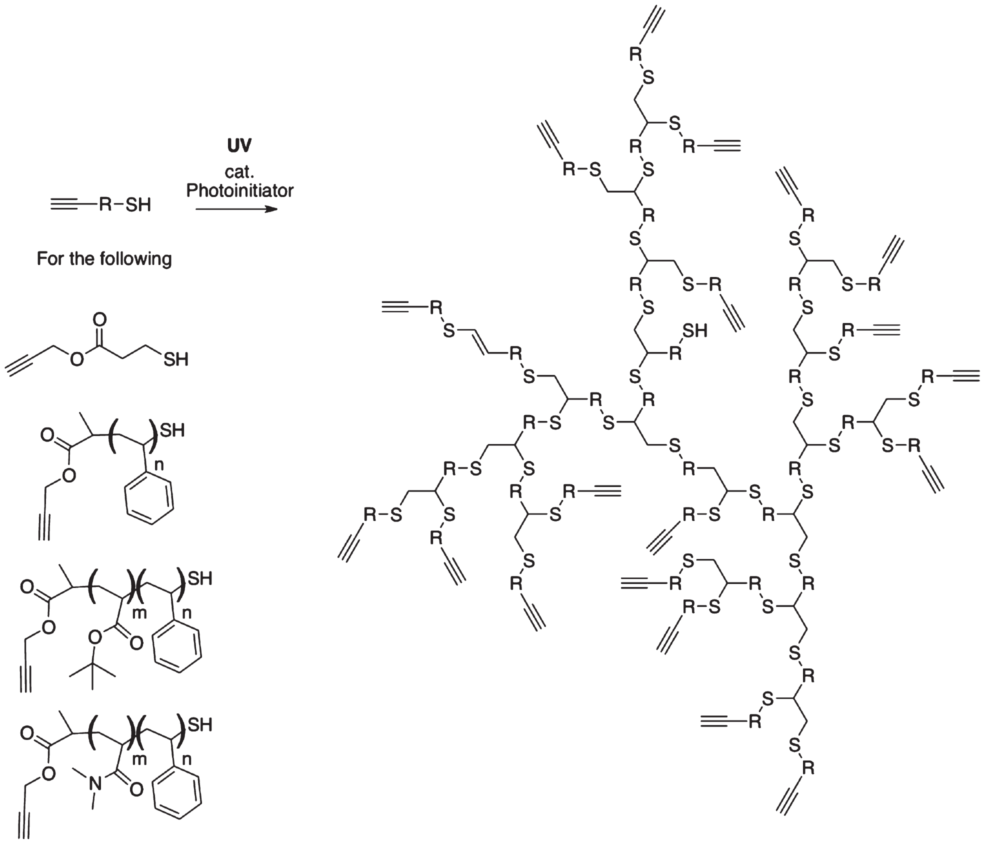
Another interesting application of the click methods for synthesizing hyperbranched structures was outlined by Xu et al.[123] In this approach, a RAFT agent containing two bromine groups was synthesized and used to polymerize methyl acrylate. Upon aminolysis of the RAFT agent, the resulting thiol created an AB_2 macromonomer, with the thiol reacting rapidly with the bromine groups.[123] However, depending on the nature of the bromo groups, a structure that was more linear or more branched could be formed.

Very recently, Yan et al. reported a novel method to reversibly change topologies of long-chain analogues to hyperbranched polymers, from linear to branched to cross-linked structures. The authors used RAFT polymerization to build a telechelic poly(*N*,*N*-dimethylacrylamide) incorporating an average of one 2-(pyridin-2-yldisulfanyl)ethyl acrylate unit per chain. Aminolysis of the dithioeteser end groups led to polymeric chains exhibiting two thiol end-groups and one thiol midchain. Disulfide bond formation led to the restructuring of the functional linear polymer into branched polymers and reversible cross-linked gel. This process has the advantage of being simple, although it does not offer strict control over the spacer between branching points, since the 2-(pyridin-2-yldisulfanyl)ethyl acrylate unit is incorporated randomly in the linear chain, and it is possible that more than one unit is present in each linear chain.[124]

The synthesis of long-chain hyperbranched polymers through "click"-like reactions is very attractive due to the mild reaction conditions, tolerance to many functional groups, and high yields. These methods can be used to create interesting architectures such as alternating block copolymers and materials with almost complete branching. The use of "click"-like reactions in the synthesis of long-chain hyperbranched polymers is relatively new, and already there have been several functional materials with interesting self-assembly properties highlighted.[121] This approach is expected to be utilized extensively in materials applications and even in bio applications due to the possibility of incorporating biocompatible functional groups.

3.2.3. Other Approaches to Long-Chain Analogues of Hyperbranched Polymers. One interesting approach was outlined by Trollsås et al.,[80] who used two different AB_2 block copolymers and coupled these polymers together. These blocks were based on substituted poly(lactone)s and poly(L-lactide)s. This approach yielded interesting random block hyperbranched polymers (see Scheme 10). Interestingly, when the block copolymers contain two different substituted poly(lactone) blocks, there is typically only one T_g, and the system is still able to form crystalline phases, although the block choice can influence the melt temperature and the presence of one or two melt temperatures.

Scheme 9. Polymerization of a Molecule Bearing an Alkyne and Thiol To Give a Hyperbranched Polymer[120,121]



In contrast, when a block of poly(L-lactide) is combined with a block of a substituted poly(lactone), the system showed phase separation, as seen by the presence of two T_gs in all cases and a melt temperature which corresponds to closely to the poly(L-lactide).[80]

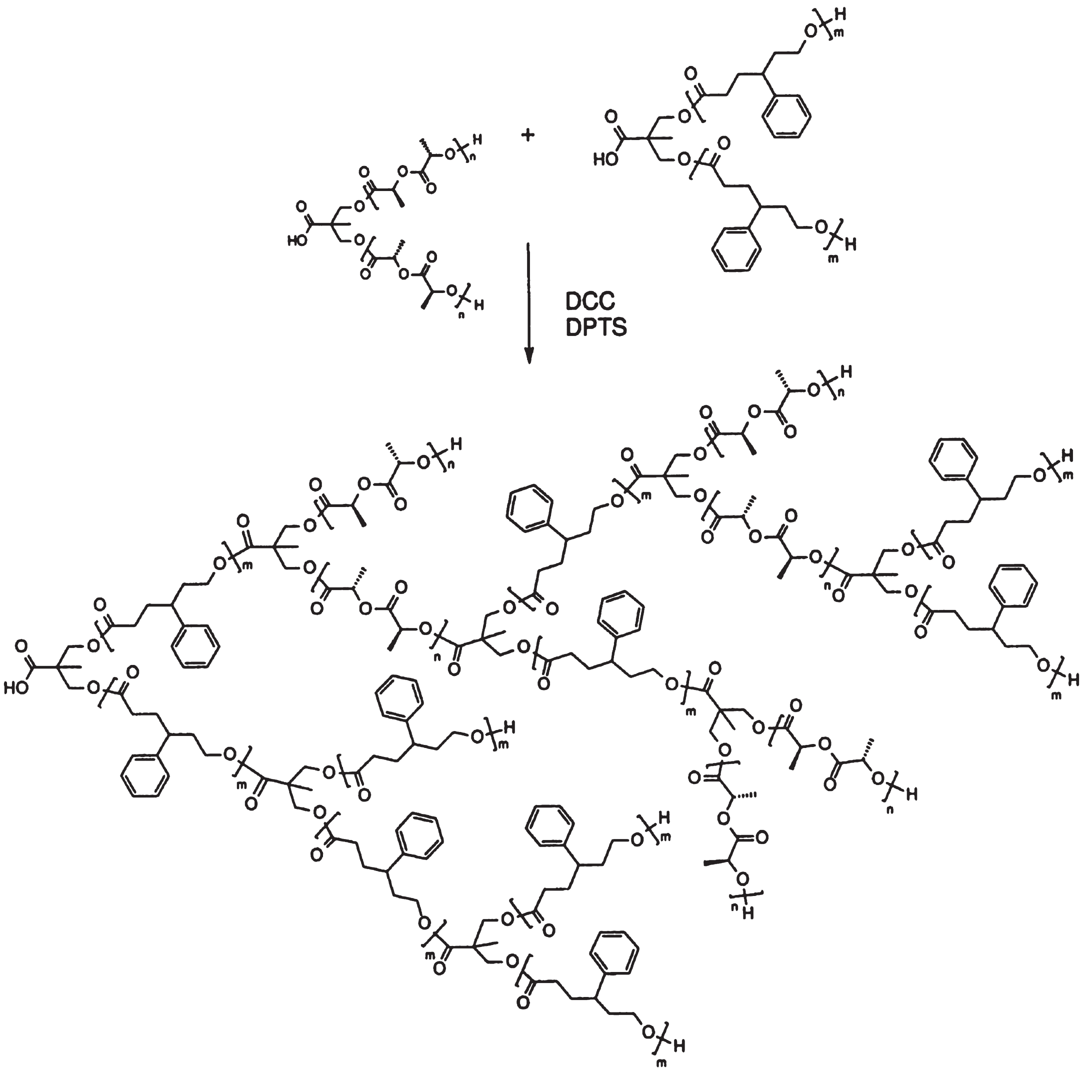
Frey et al.[125] synthesized hyperbranched polymers from macromonomers based on poly(isoprene), by first synthesizing a linear macromonomer of poly(isoprene), followed by capping with a silane. This creates an AB$_n$ monomer for a hydrosilylation reaction. Although this method is elegant and relatively straightforward, it does not create polymers with well-defined spacing between branch points. This method was subsequently extended by the same group,[126] to generate poly(butadiene) and poly(isoprene) macromonomers, with a silane cap. These macromonomers were coupled using a hydrosylation, with a ferroceneyl comonomer, leading to ferrocene-functionalized polymers. These materials again did not have well spaced branch points, although they did show interesting electrical properties.[126]

One other elegant approach was outlined by Hong et al.[127] In their approach, the authors generated a relatively short macromonomer with an alkene and two secondary amines of different reactivities. Depending on the external conditions, temperature, etc., either one or both of these amines can participate in the coupling reactions. If only one amine reacts with the alkene, then linear polymers are formed, while if both amines react with the alkene, then hyperbranched polymers can form. Another interesting approach of these materials was outlined by Guo et al.,[128] where linear oligomers of anilene, with one reactive group at either end of the molecule, was reacted with either tri- or tetrafunctional poly(ε-caprolactone). This results in a $A_2 + B_n$ polymerization.[128]

Choi et al. synthesized hyperbranched polymers based on poly(ε-caprolactone).[129−132] In their initial study, Choi and Kwak synthesized hyperbranched poly(ε-caprolactone), from macromonomer containing 5, 10, and 20 ε-caprolactone units. The macromonomers were coupled together using a polycondensation reaction.[130] These polymers were found to have sizes significantly smaller than a linear equivalent polymer, and the more highly branched polymers were found to melt at lower temperatures than their linear equivalents as well as displaying increased thermal stability. In later studies, the same authors studied the crystallization kinetics of different architectures of poly(ε-caprolactone).[131] The crystallization mechanism was found to be the same regardless of architecture, although the very highly branched samples were found to crystallize at the slowest rate, with the linear polymer crystallizing at a rate between that of a moderately and very weakly branched poly(ε-caprolactone).[131] Subsequently, the same group investigated the effect of branch spacing on the cooperative chain mobility by dynamic light scattering.[132] They found that polymers with higher degree of branching (achieved by shorter spacers between branch points) had faster mobility compared to polymers with a lower degree of branching.[132] In addition to synthesizing these hyperbranched poly(ε-caprolactone), Choi et al. also studied their crystallization properties in the presence of the noncrystallizing poly(vinyl chloride), finding that the hyperbranched architecture crystallizes faster than their linear equivalent under those conditions.[129]

Overall the synthesis of long-chain hyperbranched polymers is attractive due to the ease of implementation. These syntheses can give hyperbranched block copolymers or materials with improved thermal stability. These reactions highlight the variety of functional

Scheme 10. Synthesis of Hyperbranched Block Copolymer by a Polycondensation of Two Different Macromonomers (Reproduced from Ref 80)



materials that can be achieved simply by varying the architecture. In all cases the facile synthesis makes long-chain hyperbranched polymers attractive, particularly for larger scale applications, as a means to combine the advantageous properties of hyperbranched and linear polymers as well as gaining some unique properties.

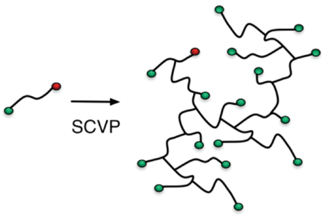


Figure 10. Schematic depiction of the self-condensing vinyl polymerization. Here the green groups represent the initiator component and the red the vinyl group.

4. OTHER RELATED SYNTHESES OF LONG-CHAIN HYPERBRANCHED POLYMERS

4.1. Arborescent and Dendrigraft Polymers. Introduced by Gauthier and Moeller,[100] this strategy can produce interesting materials, although it is based upon several grafting reactions, which do not lead to well-defined spaces between branch points. This method has been adapted to the synthesis of various hyperbranched type polymers;[127,133−138] however, these materials are not the key feature of this perspective due to the unspecified spacing between branch points. An excellent review on the subject has been published by Teertstra and Gauthier.[139]

4.2. Self-Condensing Vinyl Polymerization. An additional method of synthesizing hyperbranched polymers with long linear spacer units is the self-condensing vinyl polymerization method (SCVP).[18] In its simplest form SCVP uses inimers, which are molecules that contain both an initiating and a propagating functionality. However, it is also possible to add a comonomer, which allows the introduction of long linear chains between branch points.[5,140] Although this approach can be used to create various functional hyperbranched polymers with linear spacers, it does not lead to well-defined spacing between branch points

Table 1. Advantages of the Various Synthetic Options for the Long-Chain Branched Polymers Highlighted in This Perspective[a]

	advantages	disadvantages
dendrimer-like polymers by sequential growth and functionalization	well-controlled structures with low polydispersities	multiple steps needed
	ability to make a variety of architectures including blocks	requires very high yield reactions in the synthesis of the branch point
dendrimer-like polymers by coupling macromonomers	well-controlled structures with low polydispersities	multiple steps needed
	ability to make a variety of architectures including blocks	requires very high yield macromonomer coupling reactions
long-chain hyperbranched polymers	facile, one-pot synthesis of branched architecture with linear spacers	less well-defined structures and higher polydispersities
	ability to make a variety of architectures including blocks	requires very high yield reactions in the synthesis of the branch point
linear chains by anionic polymerization	well-controlled linear chains, with little to no dead chains	applicable to a relatively small number of functional groups
	very low polydisperisties	requires very stringent reaction conditions
linear chains by living radical polymerization	tolerance to a very wide variety of functional groups	contamination by dead chains and higher polydispersities
	milder and less stringent reaction conditions	
traditional coupling reactions	well-established high yield reactions	often require harsh reaction conditions and not compatible with all functional groups
	easy to implement protection—deprotection reactions	
"click" couplings	mild reaction conditions and high yields	can require additional reactions to introduce the reactive "click" groups
	tolerance to many functional groups	

[a] The choice of polymer, linear chain polymerization method, and coupling will depend on the desired material.

(Figure 10), and it is therefore out of the scope of this perspective. Instead, we refer the interested reader to the excellent recent review published by England and Rimmer.[140]

5. CONCLUSION, APPLICATIONS, AND OUTLOOK

We have reviewed the various synthetic techniques for long-chain analogues of dendrimers and hyperbranched polymers. In general, the long-chain analogues of dendrimers can be synthesized by two strategies. The first strategy is the sequential growth of linear chains followed by reaction of the terminal groups with a branching agent to give a molecule with twice as many initiating sites. These new initating sites are then used to grow the subsequent generation. The second strategy is to first create a library of macromonomers, and sequentially link these macromonomers, in a modular approach to give a long-chain analogue of a dendrimer. These two reactions can be performed either divergently or convergently. These reactions can be used to create both long-chain homopolymer dendrimers and polymers that have different functionalities in different generations.

Long-chain analogues of hyperbranched polymers can be created from reactive macromonomers that exist as AB_n macromonomers. These materials can be easily synthesized in one pot and be used to create a variety of hyperbranched polymers with different degrees of branching from a variety of monomers. Alternatively, the same method can be applied to reactive block copolymers and lead to alternating block copolymers.

Table 1 highlights the various advantages of the different approaches summarized in this perspective. Ultimately, the best combination of techniques depends on the material and application. In some cases a very well-defined polymer is needed, in which case anionic polymerization of the linear chain segments may be implemented in a dendrimer-like polymer. Alternatively, the branched structure may be needed with hydrophilic functional groups, but polydispersity is not a concern, in which case a long-chain hyperbranched polymer synthesized by living radical methods may be appropriate.

As synthetic techniques to achieve these unique architectures are being developed, examples of application are now appearing. For instance, Gnanou et al.[141] used both star and dendrimer-like polymers of poly(ethylene oxide) to functionalize them with glycopolymers. The resulting branched polymers offered a multivalent display of the glycopolymers, which could trigger anti-inflammatory reponse.[141] The same group studied the surface characteristics of second-generation dendrimer-like polymers based on *tert*-butyl acrylate—styrene and acrylic acid—styrene.[142] In these materials, the styrene units were used in the first generation and the acrylic units in the second generation. In general, the *tert*-butyl acrylate polymers aggregated near an air—water interface with a circular micelle-like morphology,[142] while the acrylic acid system showed similar properties, but only when the acid group was unionized.[142] When ionized, the polymer fully dissolved in the aqueous phase. These results indicate the wide variety of self-assemblies possible from two related polymers, by simply varying the pH of the system or introducing a more hydrophobic group.[142]

Similary, the poly(styrene), poly(*tert*-butyl acrylate), poly(ethylene oxide), and poly(ε-caprolactone) miktoarm dendrimer-like polymers synthesized by Altintas et al. have shown interesting thermal and phase separation behaviors when characterized by a variety of techniques such as DSC, AFM, and SAXS.[107] The material with poly(*tert*-butyl acrylate) core and periphery of poly(styrene) and poly(ε-caprolactone) did not show significant self-assembly, and this was attributed to the miscibility of the peripheral segments, whereas the polymer with poly(styrene) core and poly(*tert*-butyl acrylate) and poly(ethylene oxide) periphery showed self-assembly with a period of 13 nm.[107]

The unique architecture of dendrimer-like polymers have also made them ideal model systems for various rheological studies[143,144] and studies that focused on viscoelastic and dielectric relaxations.[145] Other applications include using different generations of dendrimer-like polymers based on poly(ε-caprolactone) to study the transport properties of the materials.[146] In another example, dendrimer-like polymers from dendrons of MMA and a perfluorinated methacrylate were used to alter the contact angle between the material and water or dodecane.[93] Finally, an elegant application reported by Guo et al.[128] uses linear oligomers of anilene, which had one reactive group at either end of the molecule reacted with tri- and tetrafunctional poly(ε-caprolactone). The electrical conductivity of the resulting alternating hyperbranched block copolymers was found to be higher than that of equivalent linear block copolymers, which was justified by the branched structure facilitating many connections and leading to a high conductivity.[128]

Synthetic polymer chemists have paved the way for the development of a new family of polymeric structures classified as long chain analogues of dendrimers and hyperbranched polymers. In particular, the combination of living radical polymerization techniques and click reaction has had a dramatic impact on the synthesis of these structures and streamlined their production. Although to date the unique properties of the resulting materials have been investigated by only a handful of research groups, there is no doubt they will find growing applications over the next few years as these structures become easier to obtain.

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Dominik Konkolewicz received his B.Sc. with Honours in 2006 from the University of Sydney and his PhD in 2011 from the same university, under the supervision of A/Prof. Sébastien Perrier and Dr Angus Gray-Weale. At present, he is a visiting assistant professor at Carnegie Mellon University, under the guidance of Prof. Krzysztof Matyjaszewski. His interests include various aspects of polymer science including the mechanism and kinetics of reversible addition−fragmentation chain transfer polymerization and atom transfer radical polymerization, theoretical models for the structure of polymers, and development of efficient for the synthesis of complex polymer architectures and functional materials.

Prof. Michael J. Monteiro is currently an Australian Research Council Future Fellow at The University of Queensland, Brisbane, Australia. His first Postdoctoral Fellowship was with Prof. Ken O'Driscoll at the University of Waterloo on determining the effects of solvent on k_p by PLP. In 1999, he was an Assistant Professor at Eindhoven University of Technology, The Netherlands, where he started with living radical polymerization using RAFT. His group was the first to study and synthesize polymer nanoparticles in water with controlled composition and morphology using the RAFT technology. He worked with Prof. Virgil Percec (University of Pennsylvania) in 2001 on SET-LRP. He completed his PhD at Griffith University, Australia, on nitroxide trapping of small radical intermediates in polymerization systems. He was awarded the Queen Elizabeth II Fellowship in 2004−2009, J. G. Russell award from the Australian Academy of Sciences, and The University of Queensland Research Excellence Award.

Associate Professor Sébastien Perrier graduated with his PhD in 2002 from the University of Warwick, England, in polymer chemistry. After one year as a postdoctoral fellow at the University of New South Wales, Australia, he was appointed as lecturer at the University of Leeds, UK, and was promoted to senior lecturer in 2005. In October 2007, he moved to the University of Sydney and was appointed as director of the Key Centre for Polymers & Colloids. A/Prof Perrier leads a team of 15−20 researchers working at the interface of organic chemistry, polymer synthesis, and material science. He has published over 100 research papers and book chapters and over 50 conference papers/abstracts. He is a member of the editorial boards of *Soft Matter*, *Macromolecules*, *European Polymer Journal*, and *Polymer Chemistry*. Awards include an ARC international fellowship (2002) and the Macro Group UK Young Researcher Award (2006), the Young Tall Poppy Science Award (2009), the Rennie Memorial Medal (2009), and the David Sangster Polymer Science and Technology Award (2009). In 2011, he was appointed on the Australian Research Council College of Experts. His research interests lie at the interface of polymer synthesis, materials/soft matter science, and biology.

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