# New methodologies in the construction of dendritic materials

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Dendritic polymers are highly branched polymer structures, with complex, secondary architectures and well-defined spatial location of functional groups. Due to their unique physical and chemical features, applications in areas such as targeted drug-delivery, macromolecular carriers, catalysis, sensors, light harvesting, surface engineering and biomimetic materials have been proposed. However, only a few dendritic materials have been exploited commercially due to time consuming syntheses and the generation of significant waste/presence of unreacted starting materials. This *tutorial review* describes traditional synthesis of dendritic materials as well as recent advances in synthetic strategies, for example the use of Click chemistry, as a tool to efficiently obtain complex, functional dendritic structures.

## Introduction

In today's society the demand for ever more complex and highly specific materials is increasing at a rapid rate. Currently, these functional polymers are key components with great potential, as they can efficiently be tailored to function in a wide variety of applications with the architecture of a polymer having a great influence on its final properties. Due to this, the progress and advances in polymeric architecture are important steps towards novel, multifunctional materials.[1] A consequence of the increased demand for sophisticated macromolecules is a focus on highly branched dendritic polymers. These structures are amongst the newest additions to macromolecular chemistry and are a result of the growing synergy between advanced organic chemistry and polymer synthesis. Dendritic materials comprise sub-classes such as dendrimers, dendrons, hyperbranched polymers, dendrigraft polymers and dendronized polymers, Fig. 1.[2] Highly branched dendritic polymers exhibit very different properties compared to their linear analogues. These polymeric architectures have been carefully studied since Vögtle *et al.*[3] reported the first concept of branching by repetitive growth and the first dendrimers were synthesized by Tomalia and co-workers at Dow Chemical in the early 1980s in parallel with Newkome's "arborol" systems.[4,5] The presence of a highly branched structure gives these polymers unique properties and it is foreseen that they will find use in specialized applications, for example; targeted drug-delivery, macromolecular carriers, enzyme-like catalysis, sensors, light harvesting, surface engineering and biomimetic applications.[2,4,6]

Presently, there are over 10 000 scientific reports and 1000 patents dealing with dendritic structures. Still, complex polymer structures, including dendritic materials, have struggled to be commercialized on a large scale by industry. The main reason is that they are, in most cases, exceptionally tedious to synthesize, leading to extremely high production costs. Therefore, a continuous improvement of synthetic methodologies for dendritic polymers is a crucial step towards their commercial success. Recent synthetic advances in the field of organic and polymer chemistry have provided researchers with new

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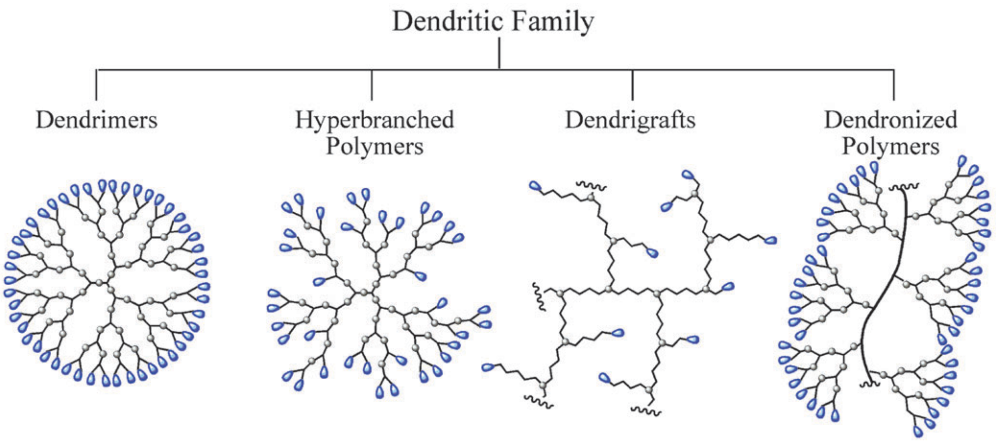

**Fig. 1** Schematic picture of sub-classes in the dendritic family.

tools to more efficiently prepare these intricate structures, as will be discussed herein.

## The dendritic family

Dendritic structures can be divided into several sub-groups with a myriad of structures and sizes possible. Below, we briefly summarize and describe some of the most important groups within the dendritic family.

### Dendrimers and dendrons

When dendritic polymers are perfectly branched they are either dendrons or dendrimers. The dendrimers comprise a single core that is capped with layers of repeat units which are radially branched. Each layer is called a generation, as can illustratively be seen in Fig. 2. Much like proteins and natural products, dendrimers are near monodisperse with predictable molecular weights and nano-scale dimensions. The unique properties of dendrimers are attributed to their globular structure, resulting from internal structures in which all bonds emerge radially from a central core, and a large number of end-groups are present at its surface.[7] Due to their globular structures, dendrimers can be seen as nano-particles with the ability of core encapsulation. In contrast to linear polymers, these macromolecules do not entangle, showing unusual viscosity behaviours, such as low solution viscosity and functional groups can be either protected or exposed.[4]

Associated with dendrimers are dendrons which represent a structural component of the parent dendrimer, and are also monodisperse, wedged-shaped sections of a dendrimer. Hence, a dendrimer is made up of a number (≥ 2) of dendrons. Each functional group in a dendritic core gives rise to one dendron. Furthermore, dendrons of higher generations (≥ G4) can be seen as dendrimers but with an active core moiety that can be further functionalized.[2] Examples of dendrimers: Tomalia-type poly(amidoamine) (PAMAM),[8] Fréchet-type poly(benzylether),[8] Newkome's arborol dendrimers,[9] phosphorus-containing dendrimers[10] and the poly(2,2-bis(hydroxymethyl)propionic acid) (P(bis-MPA) dendrimer).[8] In Fig. 3 a G2 PAMAM dendrimer is shown (a) and a G4 P(bis-MPA) dendrimer (b).

### Hyperbranched polymers

Hyperbranched polymers are highly branched polymer structures, much like the dendrimers, but contain imperfections in the branching points due to their traditional one-pot synthesis.[11,12] Hence, the polymers contain dendritic sites as well as linear sites with the structure being poorly controlled in comparison to

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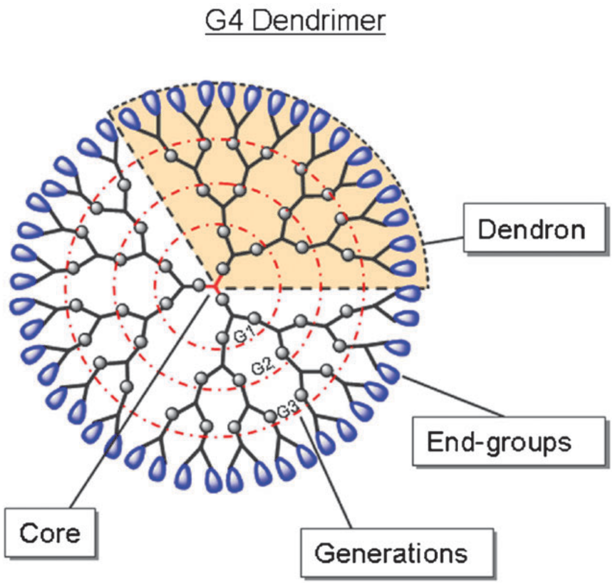


**Fig. 2** Different structural components of the dendrimer.

dendrimers and typical polydispersities are about 2 or higher. However, these polymers possess many of the properties of dendrimers, in that they are highly branched, have a multitude of end-groups, a globular structure and they show similar viscosity behaviours attributable to significantly reduced entanglements.[13] Additionally, hyperbranched polymers have much higher solubility than their linear analogues due to their many end-groups.

Examples of hyperbranched polymers: Boltorn® (P(bis-MPA) hyperbranched polymer),[12] Hybrane™ (poly(ester amide)),[12] poly(phenylenes),[13] *etc.*

## Dendrigraft polymers

Dendrigraft polymers, sometimes referred to as arborescent polymers, are a relatively new addition to the dendritic family, combining features of dendrimers and hyperbranched polymers with linear polymers.[14] While dendrigraft polymers are grown in generations, much like dendrimers, the repeating unit is an oligomer or a polymer chain, rather than a small monomer unit. Due to this, flexible polymers with very high molecular weights are obtained rapidly.[1] The group of dendrigraft polymers will not be further discussed herein and is the subject of a recent review by Gauthier.[15]

Examples of dendrigraft polymers: Comb-burst®,[14] arborescent polybutadiene,[14] *etc.*

## Dendronized polymers

Dendronized polymers, sometimes termed "rod-shaped polymers", are structures having a linear backbone with dendritic side-chains.[16] They are in fact a sub-class of comb-polymers where the "comb's teeth" are dendrons instead of linear polymer chains. Depending on the density and size of the attached dendrons, the dendronized polymers can have either random-coil or fully stretched out conformation. These latter rod-like cylindrical polymers ("nanotubes") are believed to have new and interesting properties, since they have dimensions reminiscent of several biological functional units, such as the mosaic virus (lengths up to 400 nm and diameters up to 6 nm). Furthermore, this exceptionally high aspect ratio is another remarkable feature of dendronized polymers compared to the globular dendrimers, *i.e.* they are not only molecular objects; they are also form-anisotropic nanoscopic objects.[16,17]

Examples: PAMAM-based dendronized polymers,[17] P(bis-MPA)-based dendronized polymers,[18] Fréchet-type dendronized polymers,[17] Percec-type dendronized polymers,[17] *etc.*

## Traditional synthetic strategies

A common theme for all the dendritic structures described above is that the monomers contain more than one functional group. Traditionally, they are of the type $AB_x$, where A denotes one type of functional group and B denotes another type of functional group. The A-functionality cannot react with itself, only with the B-functionality, and *vice versa.* X is the number of reactive B-functional groups and is $\geq 2$, which results in the branching (AB-type monomers yield linear polymers and $AB_x$-types yield branched polymers). As a

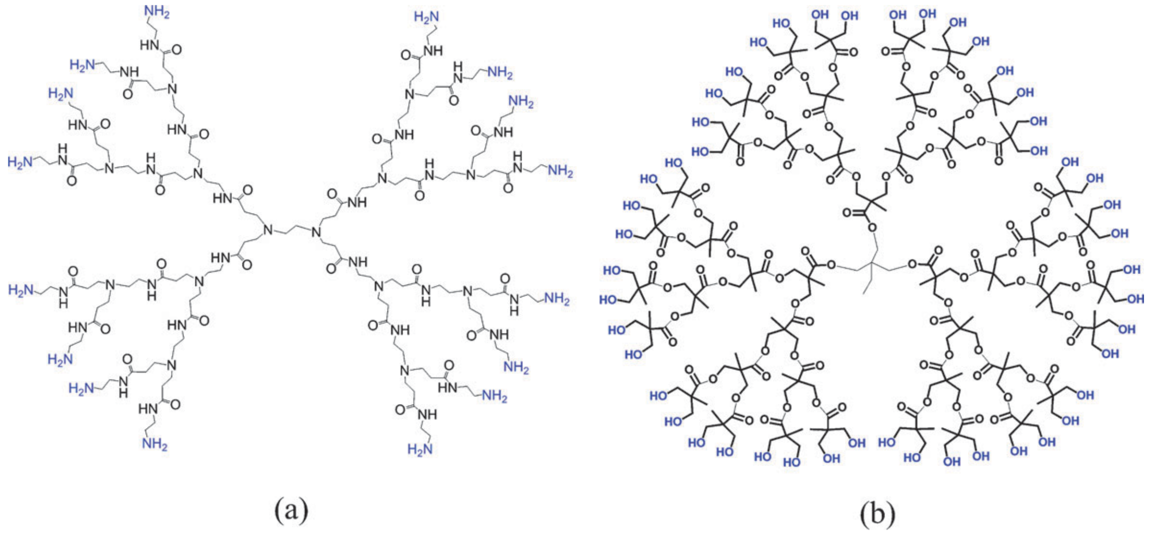
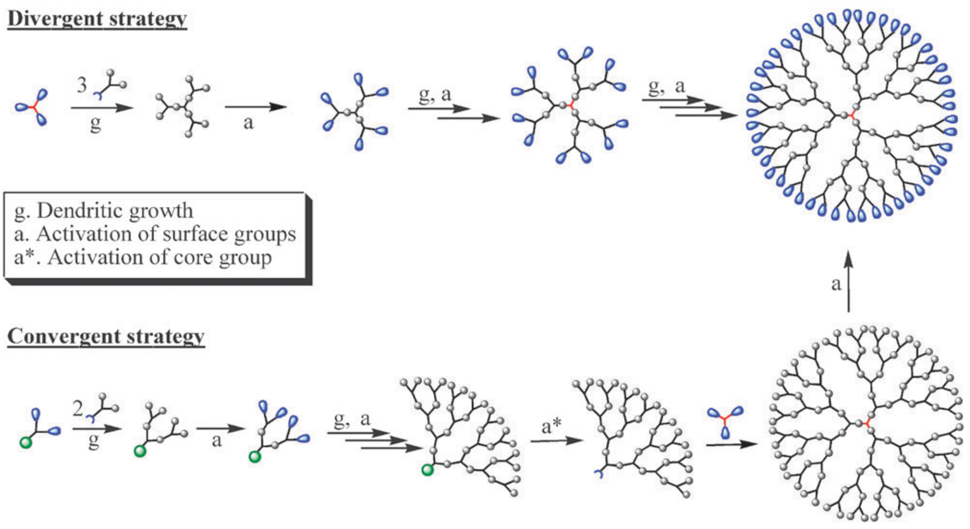


**Fig. 3** (a) 2nd generation PAMAM dendrimer; (b) 4th generation P(bis-MPA) dendrimer.



**Scheme 1** Divergent *vs.* convergent growth approach. A 4th generation dendron typically requires a minimum of 8 reaction steps.

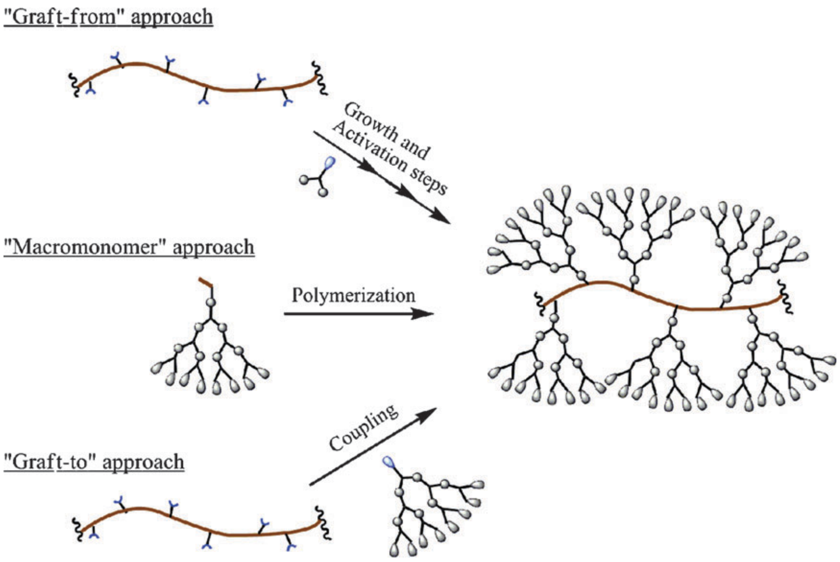
result, coupling of the AB$_x$-monomers forms a highly branched dendritic structure.[19]

### Dendrimers and dendrons

As mentioned above, syntheses of dendrimers and dendrons are tedious and require the skills of an organic chemist. Traditional syntheses involve repetitive stepwise growth and deprotection/activation protocols with careful purification procedures between each generation.[6] Typically, 4th generation dendrimers require a minimum of 8 reaction steps, not including the monomer synthesis, making them very time consuming and generating significant waste. Today, dendrimers are synthesized utilizing either divergent or convergent growth, Scheme 1.

**Divergent growth.** During the genesis of dendritic macromolecules, the divergent growth strategy, which starts from a core molecule, was developed with chosen core multiplicity ($N_c$), from which generations were grown.[1] The core multiplicity is 2 or higher ($N_c \geq 2$), meaning that it contains two or more reactive groups of the same functionality. Each reactive group represents the start of a dendron and if the core has a core multiplicity of three ($N_c = 3$), the dendrimers will be made up of three dendrons, Fig. 2. The first step is to grow the first generation, denoted G1. Here, the B-functionality of the AB$_x$-monomer needs to be protected/deactivated from reacting with A, making it possible for the A-functionality of the monomer to only react with reactive sites on the core. After the first generation has been grown it is necessary to purify the dendrimers, in order to remove by-products, unreacted starting materials and defect dendrimers, *i.e.*, dendrimers that have only been partially derivatized. This is typically performed by column chromatography, eluting with solvents of different polarity. After purification, the activation of the B-functionality on the first generation dendrimer is performed in one step, whereupon the "activated" dendrimer can be reacted with a new set of AB$_x$-monomers again, giving rise to a 2nd generation dendrimer (G2) with a new set of protected/deactivated B-functionalities. After purification to remove by-products and dendrimers with partial derivatization, the pure dendrimer is activated again. Repetitive steps are employed until the desired generation of dendrimers is reached.[20,21] However, the increasing number of end-groups with increasing generation generally requires large excesses of monomers and reagents, in order to drive the reaction to completion. With increasing generation the risk of incomplete derivatization also increases, resulting in enhanced amount of non-perfect dendrimers that are essentially impossible to efficiently remove by standard purification techniques. Nevertheless, upon identifying efficient reactions for growth and activation steps, the divergent growth approach is preferable. In fact, all commercially available dendrimers today are constructed *via* this approach.

**Convergent growth.**[22] In the convergent method the individual dendrons are synthesized first and then coupled to a core molecule. The dendrons are typically constructed by the same activation/deactivation strategies as for the divergent growth described above, and once the dendrons have reached the desired generation they are coupled to a small polyfunctional core molecule. The dendron core is deactivated until this final coupling step.[8] The advantages are that the growth of each dendron can be more carefully monitored and controlled since the dendrons are structurally less complicated. As a result, the risk for partial derivatization is severely lowered. However, due to steric hindrance, the last coupling step is potentially difficult, requiring versatile organic coupling reactions or even an extended spacer in the dendron core. Potentially, not all core molecules will have all their reactive groups coupled with dendrons and the product mixture could therefore contain dendrimers with a lower number of dendrons attached to it. Consequently, a purification step is necessary. However, as the partly derivatized dendrimers are much smaller than the desired dendrimers, the purifications are more straight forward. The preparation of very large dendrimers (≥ G6) is complicated utilizing this approach and only gives rise to small amounts of material.[23] The most attractive feature of the convergent method is the ability to prepare well-defined, bifunctional dendrimers, where two dendrons exhibit multiple groups of different functionality.



**Scheme 2** The three strategies to synthesize dendronized polymers.

## Hyperbranched polymers

Hyperbranched polymers are by far the least challenging of all dendritic structures from a synthetic viewpoint, as they are produced in a one-pot reaction that does not require the protection/deprotection procedure necessary for dendrimers and dendrons, nor do they require tedious work-up procedures.[11,12] They can be synthesized with most known polymer-forming reactions of $AB_x$-monomers, such as condensation reactions, cationic procedures, ring-opening polymerization and free radical polymerization, in which the A-functionality can only react with the B-functionality and *vice versa*. The most common synthetic method involves polycondensation of $AB_x$-monomers in the presence of a catalyst, such as an acid or transesterification reagent.[12] To achieve a more controlled polycondensation process, another approach involves utilizing a core molecule in the polymerization of $AB_x$-monomers. By adding a functional core, with a $B_y$-functionality, the polydispersity of the final polymer is lowered and the molecular weight can better be controlled.[11] For hyperbranched polymers the term "degree of branching" (DB) is an important parameter, that determines the properties of the polymer. The higher the DB-value, the more the hyperbranched polymers behave like dendrimers, which can be controlled by the reactivity of the functional groups in the starting $AB_x$-monomer.[11,13]

A wide variety of monomers have been used for the synthesis, such as: bis-MPA, (3,5-dibromophenyl)boronic acid, 3,5-diacetoxybenzoic acid, *etc*.

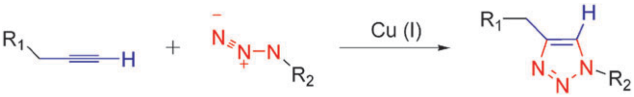
## Dendronized polymers

Dendronized polymers have been synthesized utilizing three main strategies, a macromonomer route and "graft-to" or "graft-from" approaches, Scheme 2.[17]

In the macromonomer route, dendrons of desired generation bearing a polymerizable focal point are first synthesized (*i.e.*, the macromonomer) and then used in a polymerization reaction, resulting in a dendronized polymer bearing a dendron side-chain on each repeating unit. Advantages of this approach are that all repeating units contain the desired dendron. However, the macromonomers (the dendronized monomers) are tedious to make, and become increasingly difficult to obtain with increasing generation.[16] Typically macromonomers of generation 1–3 are found in the literature.[17] Polymerization techniques that have been used are step-growth polymerization, polycondensation/polyaddition, Suzuki polycondensations, free-radical polymerization, anionic- and cationic polymerization, ring-opening metathesis polymerization (ROMP), atom transfer radical polymerization (ATRP) and reversible addition fragmentation chain-transfer (RAFT).[24] The latter mentioned controlled polymerization procedures, anionic- and cationic polymerization, ROMP, ATRP and RAFT, allow controlled degrees of polymerization (DP) as well as low polydispersity index (PDI) and control over the end-groups of the linear polymer.

Another disadvantage with the macromonomer approach is that at higher generations of the dendronized side-group, the polymerizations become increasingly difficult to perform, often resulting in low yields and incomplete polymerization.[17] This is probably due to shielding of the polymerizable group by the dendron, as well as steric hindrance when incorporating another large monomer to the growing chain end. Macromonomers up to the 4th generation have been found to polymerize, whereas higher generation dendronized macromonomers do not.[16] To overcome this problem, a spacer can be incorporated between the polymerizable group and the dendron side-chain.[18] However, it is doubtful if the resulting dendronized polymer in truth behaves like a rod-like polymer, taking on a stretched out conformation, or if this polymer instead will form a random coil.[24]

In the graft-to and graft-from approaches, a functionalized linear polymer is utilized to which dendrons are coupled, either by step-wise divergent growth from the linear polymer (graft-from) or convergently, by the coupling of pre-made dendrons to the linear polymeric backbone (graft-to).[16] In this approach, polymerization of a linear polymer is first



**Scheme 3** The copper(I)-catalyzed Click-reaction between a terminal alkyne and an azide, resulting in triazoles.

performed and the resulting linear polymer contains functional groups along its back-bone that are designed to react with the A-functionality of the $AB_x$-monomers (for the graft-from route) or the focal point of the pre-made dendrons (for the graft-to route). Preferably, the linear polymer should be synthesized using a controlled polymerization procedure, for control over molecular weigh, PDI and end-groups.

The advantage of the graft-from strategy is the much easier purification procedure, the polymer is purified through precipitation only, and no column chromatography is needed during dendron growth.[16] Also, since small molecules are reacted onto the polymer backbone, steric hindrance is suppressed using this approach. However, if the reaction employed is of low efficiency, there is risk of partial derivatization with increasing dendron generation, which is difficult to analyze. In the graft-to route the dendrons are pre-made, utilizing the same purification procedures as for dendrimers leading to a high degree of control over the substituents; however, the final coupling step is still prone to partial functionalization which increases with increasing generation of the dendrons.[16]

## Click chemistry: an emerging concept for complex dendritic structures

As the field of dendrimer chemistry matures, the structural complexity increases as functionality and applications are emphasized. However, enhanced complexity raises the demand for robust and versatile synthetic methods. By combining recent developments in organic and polymer chemistry with traditional strategies, more and more tailored, complex structures can be prepared and made available to the broader materials community.

In 2001, Sharpless and co-workers coined the term Click chemistry as a common name for a number of extremely versatile coupling reactions that posses high thermodynamic driving force ($>20$ kcal $mol^{-1}$).[25] The requirements of a Click-reaction are: (1) robust and quantitative, *i.e.*, the reactions are highly selective and the yields are near 100%: (2) the reactions are able to proceed in the presence of a variety of solvents such as water, organic solvents, *etc.*, irrespective of their protic/aprotic or polar/non-polar character: (3) high tolerance to other functional groups and (4) the reaction proceeds at various types of interfaces such as solid/liquid, liquid/liquid or even solid/solid.[26] Another advantage of these reactions is the requirement of only stoichiometric amounts of starting materials with virtually no by-products being formed, which greatly simplifies the purification procedures. These reactions are often performed at room temperature and are purified by filtration or simple extraction. The use of heat or microwave irradiation can further accelerate the reaction towards completion. The most widely studied example of "Sharpless-Type Click-reactions" are a variant of the Huisgen 1,3-dipolar cycloaddition reaction between C–C triple bonds, C–N triple bonds, and alkyl-/aryl-/sulfonyl azides.[27]

Sharpless and Hawker jointly recognized that the *C*u(I)-catalyzed *a*zide–*a*lkyne 1,3-dipolar *c*ycloaddition (CuAAC), which results in an aromatic triazole heterocyclic, Scheme 3, is a superior synthetic reaction for preparing complex polymeric structures.[28] Since then, Click chemistry has developed as an important reaction for polymer scientists to prepare functionalized macromolecular architectures. Several dendritic polymers have been constructed in recent years as a proof that synthetically challenging macromolecules can be obtained by utilizing the CuAAC reaction.[28–31] In reported approaches, the A- and B-functionalities of the $AB_x$-monomer units are azides and acetylenes, respectively, and the resulting triazole ring appears as part of the repeating unit in the final dendritic structure.[28,29]

The significant interest in Click chemistry has allowed new complex dendritic concepts such as unsymmetrical dendrimers, dendritic–linear hybrids, layered dendritic structures and dendrimer functionalization to be easily obtained. Below follows an overview of current development of these structures, achieved *via* Click chemistry.

### Dendrimers

Dendrimers have been synthesized by Click chemistry using both the divergent and convergent growth approaches. In the first report by Hawker, Sharpless *et al.*[28] the convergent method was utilized starting from $AB_2$-monomers in which the A-functionality was a chloromethyl group and the $B_2$-functionalities were acetylenes. After each Click-reaction, the chloride atom was easily replaced with an azide moiety, activating it for the next coupling step. As a result, the dendrons contain numerous 1,4-disubstituted 1,2,3-triazole linkages and in a final step, 4th generation dendrons were coupled to a range of different core molecules. The major achievement of this work was to concretely demonstrate the utility of Click chemistry and the level of efficiency that could be achieved during a traditionally difficult synthetic process.

Subsequently, Wooley *et al.*[30] reported on the divergent growth approach to Fréchet-type dendrimers using Click chemistry, resulting in either azide or acetylene terminated dendrimers.

Recently, Hawker *et al.* described the utilization of another Click-reaction, thiol–ene Click chemistry, for the divergent synthesis of poly(thioether) dendrimers.[32] The synthesis was carried out under mild reaction conditions and without the use of a metal catalyst, making the process even more environmentally friendly.

### Dendronized polymers

The efficiency of Click chemistry makes it an ideal reaction for the synthesis of dendronized polymers. In 2004 Fréchet *et al.*[33] constructed dendronized polymers *via* CuAAC reaction utilizing a graft-to convergent growth approach. This was achieved by synthesizing a linear polymer poly(vinlyacetylene), bearing acetylene groups on each repeating unit, to which dendrons (G1–G4) with an azide group in the focal point were coupled through the CuAAC reaction. It was found that for generations 1–2 the coupling reaction was quantitative, and for generation 3 it proceeded in >98% yield. However, the G4-dendrons were

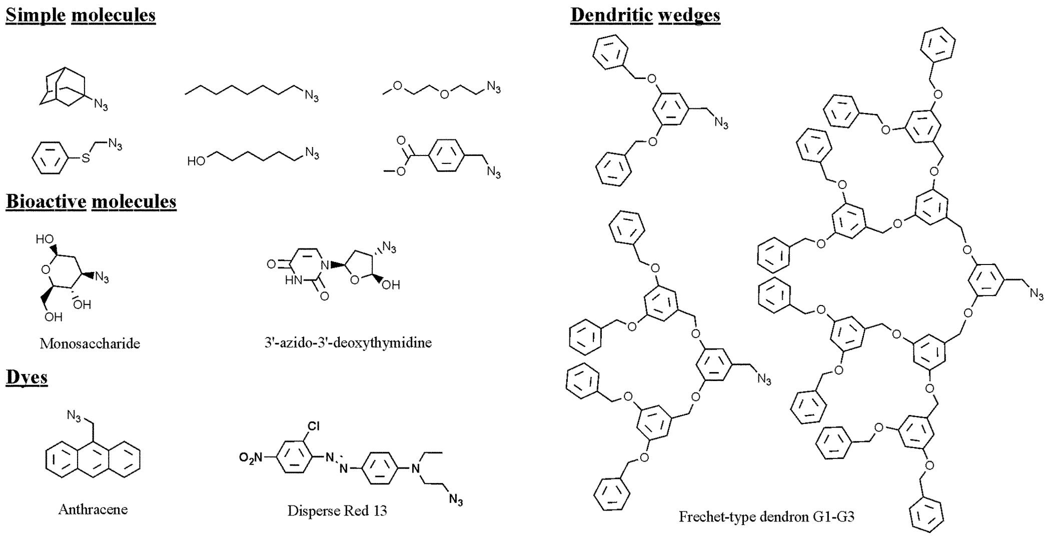


**Fig. 4** Functional molecules attached to dendritic structures *via* Click chemistry.

unreactive under the conditions employed. The resulting G3-dendronized polymer, with an $M_w$-value of about 290 kDa, was suggested to have a rod-like morphology, based on AFM-analysis.[33]

### Robust functionalization of dendrimers

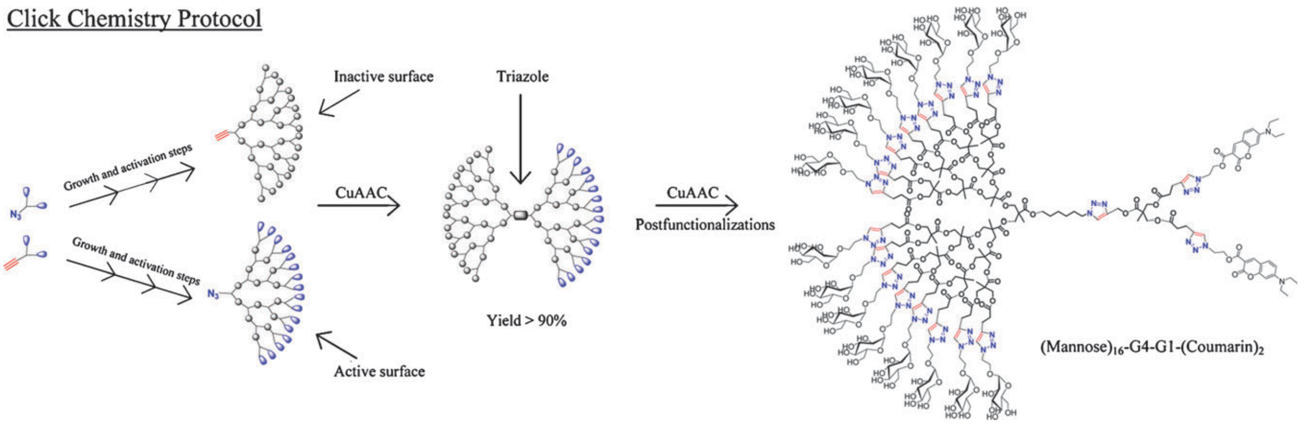
One of the key features of dendrimers is their multitude of chain end/surface groups and by modifying the end-groups of a dendrimer, the physical and chemical properties change dramatically. Hence, the functionalization of a parent dendrimer with a library of different chain end-groups is an efficient route to materials with novel properties.

Previously, functionalization of dendrimers has been problematic, due to insufficient functionalization of higher generation dendrimers and the utilization of chemistries that have been incompatible with the repeating units of the dendritic core. This has resulted in either low yields of the functionalized dendrimers, or the need to use large excess of the reagents coupled with long reaction times.[34]

In 2005 Hawker *et al.*[35] published a general approach to the efficient functionalization of structurally different dendritic macromolecules including PAMAM dendrimers, poly(benzylether) dendrimers, and P(bis-MPA) hyperbranched polymers using CuAAC chemistry. Acetylene functional dendritic materials were first synthesized and utilized as scaffolds for the reactions with a library of azide functional molecules including norbornene, alkyl, functionalized dyes, benzyl ether dendrons, *etc.* (Fig. 4). The CuAAC reaction between primary acetylenes and azides showed exceptionally high yields and incorporation of chain-ends was performed without the use of protection chemistry and with only a minimum of purification steps.

### Unsymmetrical dendrimers

Unsymmetrical dendrimers, also referred to as bifunctional or “bow-tie” dendrimers, are dendrimers in which the attached dendrons have different structures. This difference could be related to the repeat structure of the dendron or the dendrons could potentially contain different end-groups and/or functional groups while being based on the same repeat unit. These structures are fundamentally interesting and from an applications viewpoint contain multiple functionalities which can be exploited as dual purpose systems, for example as recognition/detecting agents for biological systems.



**Scheme 4** Convergent synthesis of unsymmetrical dendrimers *via* Click chemistry.

Unsymmetrical dendrimers are amongst the most sophisticated dendritic structures and are traditionally difficult to synthesize. In 2002 Fréchet *et al.*[36] described an elegant strategy for the creation of unsymmetrical polyester dendrimer–poly(ethylene oxide) structures synthesized by first growing two types of dendrons using two different protecting groups and which, in a final step, were coupled together, convergently. The deprotection of one type of protecting group gave rise to partly activated dendrimer that could undergo functionalization reactions. However, as this approach involves the use of two different protecting groups, close monitoring is required to ensure that no undesired deprotection is taking place. As a result, the synthetic methodology to obtain these structures can be seen as complicated, giving rise to tedious purification procedures. The group of Hawker *et al.*[37] reported in 2005 a robust and simplified synthetic protocol for the construction of unsymmetrical dendrimers by taking advantage of the efficiency and orthogonality of the CuAAC reaction. In this strategy, two types of dendrons were grown using anhydride chemistry; one dendron comprised acetylene in the core and the other an azide. As the CuAAC can be performed selectively in the presence of other functional groups, dendrons could be convergently coupled in which one dendron was activated (Scheme 4). Unsymmetrical P(bis-MPA) dendrimers up to the fourth generation were constructed in >90% yields in both organic as well as aqueous solutions. To further elevate the structural complexity, functionalization *via* the Click chemistry approach was employed. In a specific application for the detection and imaging of bacteria, the dendrons were tailored with a targeting functionality and with a detecting functionality. For example; a G4–G1 unsymmetrical dendrimer was synthesized, tailored with 16 mannose units on the G4 dendron and with two coumarin chromophores on the G1 dendron.

The group of Jin *et al.*[38] also employed the convergent Click chemistry approach to obtain Tomalia-type PAMAM dendrimers, both symmetrical and unsymmetrical, and reported high, overall yields. In their approach, dendrons of different generations were coupled together through Click chemistry, resulting in unsymmetrical dendrimers.

## Hybrid structures

Polymers containing both linear chains and dendritic parts are often referred to as "dendritic–linear polymer hybrids" or just "hybrid materials", Fig. 5. In fact, dendronized polymers are often referred to as hybrids, as they contain a linear backbone with dendritic side groups. However, dendronized polymers are usually highly ordered and when the dendron is present on every repeating unit the "linearity" in the polymer backbone is difficult to identify.

Structures in which linear chains are attached to dendritic scaffolds have been studied extensively in recent years. These structures are of great interest, combining the uniqueness of both the dendritic and the linear polymer. For instance, Frechet *et al.* devised hybrid PEG-unsymmetrical dendrimers with covalently attached cancer drugs and the resulting branched structure affords greater solubility and bioavailability which allows maximized performance in physiological environments.[34] One approach to obtain hybrid structures is by turning the core or the multiple end-groups of the dendritic polymer into initiating moieties for ATRP,[39] RAFT,[40] nitroxide-mediated polymerization,[41] ring-opening polymerization[39] or ring-opening metathesis polymerization,[42] for example, and subsequent grafting-from polymerization. However, this approach is coupled with potential problems. The polymerization rate from the core of sterically hindered high generation dendrons (Fig. 5A) is often decreased as the initiating sites become less available. As a result, long reaction times and elevated temperatures are necessary to obtain the desired hybrids (Fig. 5B). It is also highly uncertain if linear chains will grow from each of the chain-ends of the dendritic structure.

Another method utilizes a grafting-to strategy, in which pre-formed polymer linear chains are coupled to a dendritic core. Previously, this approach has suffered from low grafting density when traditional synthetic coupling procedures were used. However, if a highly versatile reaction, such as the CuAAc reaction, is utilized in combination with convergent growth, the risk of partial coupling of the active sites in the dendritic core is diminished. For example, Shabat *et al.*[43] reports on the convergent attachment of PEG-chains to a dendritic core *via* Click chemistry using only stoichiometric amounts of the linear polymer.

Another type of hybrid material is that in which a dendron is attached to one or several chain-ends of a linear polymer (Fig. 5A and C). In this case the linear polymer is often synthesized by a controlled polymerization, in which the end-groups can be turned into functionalities that will react with a focal point of a dendron. Riguera *et al.*[44] reported on the use of Click chemistry to prepare PEG–dendritic block copolymers up to generation three. All reactions were performed at room temperature and under aqueous conditions

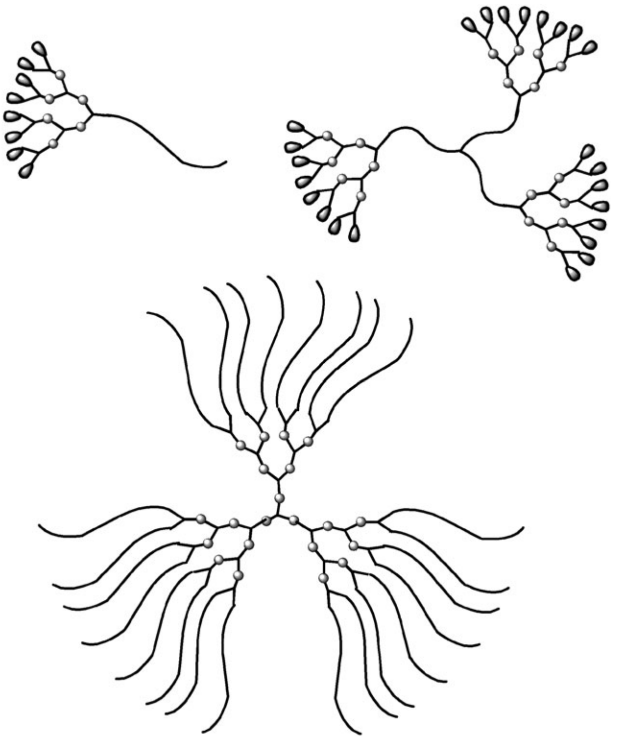


**Fig. 5** Examples of hybrid structures.

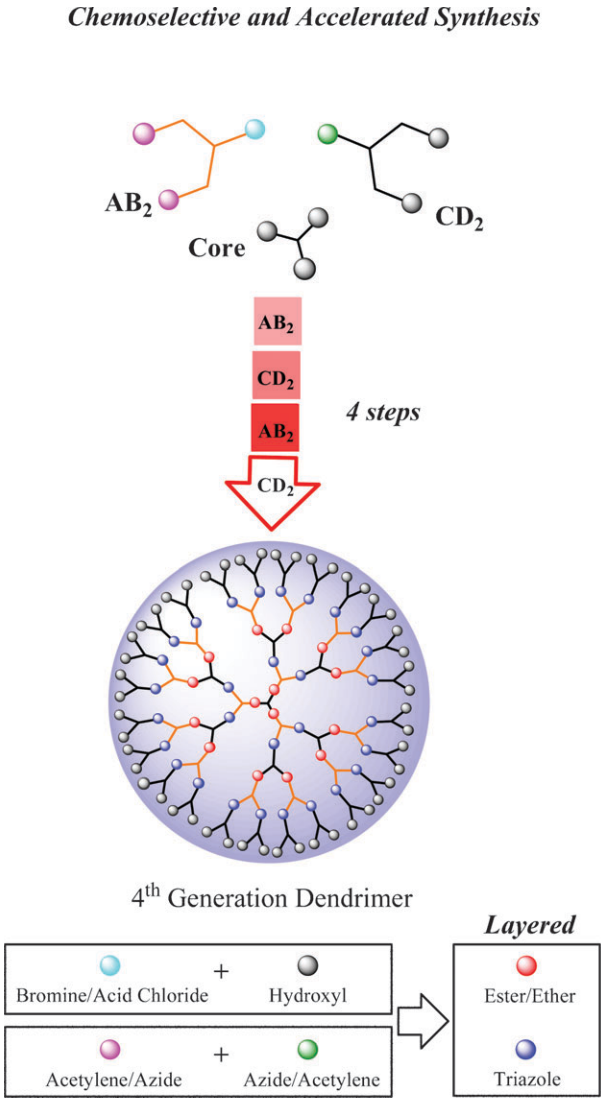
with the hybrids purified through precipitation, again illustrating the efficiency of Click chemistry.

### Layered dendritic structures

As mentioned above, dendrimers are traditionally constructed *via* a growth and activation strategy. However, the synthetic procedure can be accelerated by utilizing two different kinds of monomers, instead of only a single $AB_x$-type monomer. In this approach monomers of $AB_2$-functionality are coupled to monomers with $CD_2$-functionality. Here, A can selectively react with D and B can only react with C. Due to this, no protection/deprotection steps are required in the procedure and a dendrimer having a layered structure composed of two alternating repeat units is obtained.

This approach was initially reported by Caminade and Majoral *et al.*[10] for the synthesis of phosphorus-containing dendrimers. The reactions utilized were the condensation between an amine ($NH_2$, the A-functionality) and an aldehyde (CHO, the D-functionality) and the Staudinger reaction between phosphine ($PPh_2$, B-functionality) and azide ($N_3$, the C-functionality). The orthogonality was inherent in that neither A nor D could react with either B or C, and *vice versa*, completely excluding the need for protection chemistry in the growth of the dendrimers. By this method, 4th generation dendrimers were produced in only 4 reaction steps compared to a traditional synthetic strategy that requires 8 steps.

Capitalizing on the efficiency and selectivity of the CuAAC reaction, Malkoch *et al.*[45] further applied this approach for the coupling of two well-studied repeat units, Bis-MPA and Fréchet-type systems, Scheme 5. In this report, Click chemistry was utilized in conjunction with traditional esterification/etherification reactions and a bis-MPA $AB_2$-monomer, in which the A-functionality was an acyl chloride and the B-functionality was azide, together with a bis-MPA $CD_2$-monomer, in which the C-functionality was an acetylene and the D-functionality was hydroxyl. In this case, the A-functionality (acyl chloride) will only react with the D-functionality (hydroxyl) through an esterification reaction and the B-functionality (azide) will only react with the C-functionality (acetylene) through a CuAAC reaction. Similarly, to generate the Fréchet-type dendrimers, an $AB_2$-monomer, (1-(bromomethyl)-3,5-bis(prop-2-ynyloxy)benzene), having a bromide as the A-functionality and an acetylene as the B-functionality and a $CD_2$-monomer, 5-(azidomethyl)benzene-1,3-diol, having an azide as the C-functionality and phenolic as the D-functionality were allowed to react through alternating Click-reactions and Williamson etherification reactions. The resulting 4th generation dendrimers were obtained in 4 steps and with good overall yields. Furthermore, the resulting dendrimers have reactive chain-ends which can be subsequently functionalized to give a library of different structures.



**Scheme 5** Layer dendritic structures through an $AB_2$/$CD_2$-approach utilizing Click chemistry.

### Dendritic ultrathin films *via* layer-by-layer deposition

A major advantage of dendritic macromolecules when compared to other polymeric systems is their well-defined structure which allows them to be used as nanoscale building blocks. As an illustration of this potential, the field of layer-by-layer (LbL) deposition of polymers on surfaces is now extensively studied to devise future smart surfaces. Typically, cationic and anionic linear polymers are deposited in repetitive steps, giving layered films with physical properties that rely on the interaction between the polymer species. Another approach for LbL deposition is the use of two types of polymers with multiple functional groups, which can covalently react with each other in a stepwise fashion. Consequently, Hawker *et al.*[46] explored the use of Click chemistry in LbL deposition by constructing two sets of P(bis-MPA) dendrimers (G2–G5), comprising either acetylene or azide chain-end functionalities. In the initial step, acetylene-functionalized Si-wafers were dipped into a Click-reaction solution containing azide-functionalized dendrimers (100 mg dendrimer/20 mL DMF). After thorough washing of the wafer, the surface, now bearing covalently attached azide-functionalized dendrimers, was dipped in a Click-reaction solution containing acetylene-functionalized dendrimers (100 mg dendrimer/20 mL DMF). These steps were repeated up to 30 layers and an ultrathin film of dendrimers was obtained. It was found that the dendritic growth of the layers was significantly more controlled when compared to random coiled linear analogues and

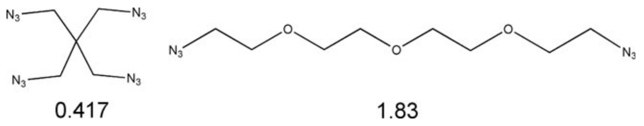


**Fig. 6** Two azide-containing compounds evaluated by Smith's rule.

the surfaces more uniform. Hence, this approach produced tailor-made surfaces under benign conditions and with multiple functionalities that can undergo robust and efficient functionalization reactions.

### Working with azides

As the CuAAC reaction is becoming more popular, the use of azides is increasing dramatically. However, as organic molecules with high nitrogen content, *e.g.* containing $-N_3$ or $NO_2$, are documented explosives, it is essential to consider their properties before designing them. An assessment for explosive risks based on specific organic azides or heavy-metal azides can be evaluated using Smith's rule,[47] eqn (1), (see also Fig. 6) and by consulting the literature.[48]

$$\frac{(N_C + N_O)}{N_N} > 3 \tag{1}$$

$N_C$ = Number of carbon atoms, $N_O$ = number of oxygen atoms, $N_N$ = number of nitrogen atoms

## Applications

As future applications for nanostructures and nanomaterials increases, the need for well-defined polymeric building blocks assumes a more critical role. Currently, the synergy of organic chemistry and materials science has led to exciting new fields of research including dendritic materials, carbon nanotubes and selectively functionalized nanoparticles. Dendritic materials, with their unique structures and high functional group density, are perfect scaffolds that can be designed for a variety of different applications.[49] The dendritic scaffolds available today range from biodegradable to thermally stable for high-performance applications. It is foreseen that these scaffolds will find use in high-value applications, for example: drug-delivery, tissue engineering, markers for imaging, optical devices, semiconductor and catalysis. In fact, the Australian Nanobiotech Company, Starpharma Holdings Ltd, has devised a vaginal microbicide gel, VivaGel, that is in clinical trial for HIV prevention.[49] The active compound is based on a polylysine dendrimer decorated with 32 naphthalene disulfonate units at its periphery.

## Commercial availability

The commercial availability of dendritic materials is still limited due to their tedious syntheses. Nevertheless, as more efficient chemical methodologies are appearing their availability are foreseen to increase. Polymer Factory Sweden AB has commercialized dendrons, dendrimers and hyperbranched materials based on bis-MPA, while PAMAM dendrimers are available from Dendritic Nanotechnology Inc. In addition, Sigma-Aldrich is a world-wide distributor of a selection of dendrimers, dendrons and hyperbranched materials. Their library includes P(bis-MPA) dendrimers and dendrons, PAMAM dendrimers, PPI dendrimers, and phosphorus-containing dendrimers.

## Concluding remarks

Dendritic polymers possess unique qualities, making them ideal candidates as materials in a number of nanoscale and high value added applications. Since the commercialization of monodisperse dendritic structures have been restricted by their tedious and costly syntheses, research addressing the development of accelerated and more efficient synthetic procedures for the production of these materials is imperative. Click chemistry is a prime example of a recent innovation in organic/material synthesis which is ideally suited as a synthetic tool for obtaining complex dendritic structures. Utilizing Click chemistry allows the syntheses to be accelerated, lowering the number of reaction steps and the need for tedious purification procedures, while at the same time diminishing the necessity for large excess of reagents. By exploiting other robust and versatile synthetic tools, dendritic structures are well on their way to greater levels of commercialization and use in new applications.

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