Dendrimer design using Cu^{I}-catalyzed alkyne–azide "click-chemistry"

Grégory Franc and Ashok Kakkar*

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The chemoselective [3 + 2] cycloaddition of an azide on to an alkyne, catalyzed by Cu^{I}, has become known as "click-chemistry". The ease with which this reaction can be carried out and the formation of pure product without the need for further purification, offer a tremendous potential in developing monodisperse 1,4-disubstituted 1,2,3-triazole heterocycle based macromolecules of a diverse nature. The versatility of this approach in designing dendrimers or functionalizing them at the periphery with desired molecules has rekindled hopes in developing nanomaterials, at scales that can accelerate their entry into industrial usage.

Introduction

Hyperbranched macromolecules that are monodisperse in nature and are characterized by a high density of peripheral groups, constitute a topical area of research.[1] These intriguing globular architectures were first reported by Vögtle and co-workers[2] in 1978 and referred to as cascade macromolecules. Subsequently, the term dendrimer was coined by Tomalia[3] due to their structural similarity to a tree. Much effort has been devoted to develop synthetic methodologies that either follow a growing pattern from a multivalent core in an iterative sequence (divergent),[2–4] or a dendron is grafted on to the core (convergent).[5] The diversity of backbones and peripheral groups that can be included into their overall structure has provided great impetus in exploiting their novel exo- and endo-receptor properties. It makes these nanoscale macromolecules competitive candidates for applications in a variety of fields including catalysis, biology or materials science.[6]

Despite an explosion of activity in dendrimer research, very few dendrimer based products have reached an industrial development stage. To our knowledge, a gel-based formulation (VivaGel™) to protect women from sexually transmitted infections by Starpharma®, is proposed to be the only future commercialization of dendrimers. Some of the reasons for the slow progress in this area are the multi-step synthetic routes commonly employed for the synthesis of dendrimers, and purification processes required to remove excess of reagents

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Grégory Franc was born in Paris, France, in 1981. After obtaining a preparatory degree in chemistry at the Orsay University (1999–2001), he joined the Ecoles des Mines d'Albi and received his "Ingénieur" title in 2004. The same year, he finished his MSc at the Institut National Polytechnique at Toulouse. During his PhD studies under the supervision of Dr Jean-Pierre Majoral and Dr Anne-Marie Caminade at the Laboratoire de Chimie de Coordination in Toulouse, his research dealt with the versatility afforded by phosphorus-containing dendrimers in fields including fluorescence, materials science and nanoparticles. He obtained his PhD degree from Paul Sabatier University in 2007. He is currently work ing as a post-doctoral fellow at McGill University on developing novel synthetic methodologies to hyperbranched macromolecules.

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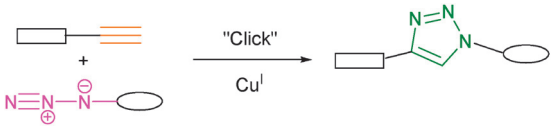

Scheme 1 "Click" reaction: Cu^{I}-catalysed [3 + 2] Huisgen cycloaddition between alkyne and azide to form 1,4-disubstituted 1,2,3-triazole heterocycles.

as well as by-products at each generation build-up. There has been progress made in this regard including the polyamidoamine (PAMAM) dendrimers reported by Tomalia,[7] phosphorus-containing dendrimers by Majoral and co-workers,[8] aliphatic polyester dendrimers by Fréchet and co-workers,[9] and the 3,5-dihydroxybenzyl alcohol based dendrimers by Bourrier and Kakkar.[10] However, much still needs to be done to make these processes viable for industrial scale applications.

Considering the wide variety of possible applications offered by these hyperbranched and monodisperse macromolecules, development of a versatile methodology to render the synthesis of dendrimers more adaptable to specific needs is necessary to their eventual commercialization. An appealing alternative started to emerge with the advent of what has been coined as "click-chemistry".[11] The latter, for the purposes of this review, refers to Huisgen type [3 + 2] cycloaddition leading to the formation of triazole heterocycles.[12] Among these cycloaddition reactions, Cu^{I}-catalyzed "click-chemistry" between acetylenes and azides[13] has lagged somehow behind for a while with respect to the other types of cycloaddition due to some potential dangers associated with azides. However, since Sharpless and Meldal's independent reports in 2002,[14] this chemoselective [3 + 2] cycloaddition, providing 1,4-disubstituted 1,2,3-triazole heterocycles (Scheme 1), has started to expand at a fast pace. It has revealed itself as an astonishing tool to functionalize a myriad of molecules.

The application of "click-chemistry" to dendrimers was advanced in 2004 when the first example of a convergent synthesis of dendritic macromolecules bearing triazole rings at each layer with quantitative yields was reported.[15] Since then, this simple 1,3-dipolar cycloaddition has started to emerge as a valuable alternative for constructing a diverse range of dendritic macromolecules, and has raised realistic expectations for exploring their potential for industrial applications. This review aims at highlighting and giving an up-to-date overview of the significance and versatility of "click-chemistry", and the options it provides for the construction and functionalization of a wide variety of dendrimers.

Proof of concept

Convergent approach

After describing the concept of Cu^{I}-catalyzed alkyne–azide "click-chemistry", Sharpless in collaboration with Hawker and co-workers demonstrated in 2004 the viability of this approach to build dendrimers. Using the convergent methodology, they synthesized several new series of dendritic macromolecules bearing triazole heterocycles in each layer.[15] Starting from AB_2 type monomers containing two alkyne groups and a chloride moiety, dendrimers were constructed through a two-step process. The latter involved formation of

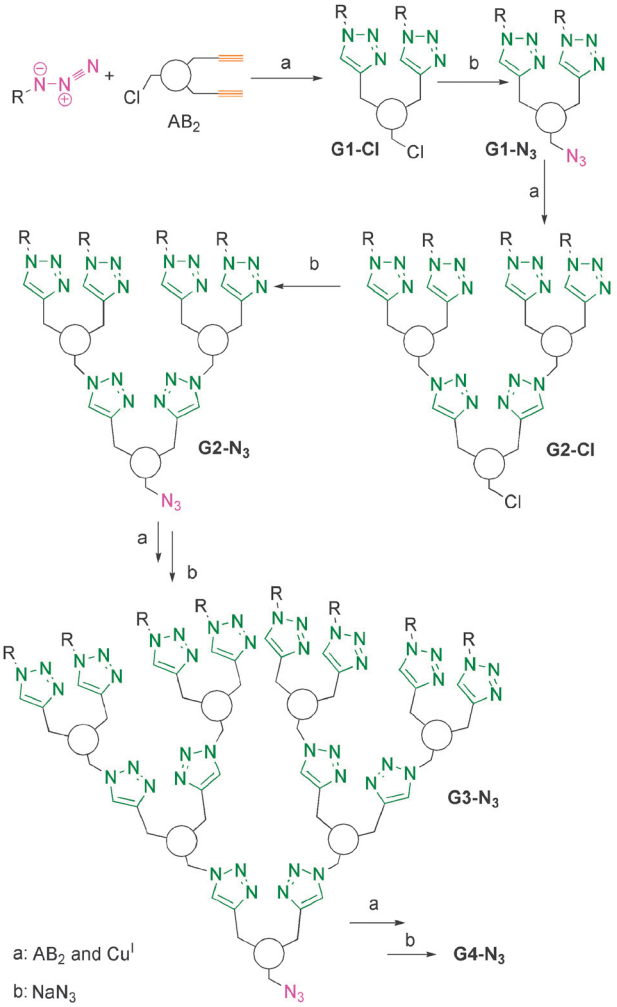

Fig. 1 First examples of triazole dendrimers synthesized using a convergent methodology.

the bis-triazole intermediate through cycloaddition in the presence of Cu^{I} ($CuSO_4$ reduced by sodium ascorbate (SA)), followed by conversion of the chloride extremity to an azide. The sequence was then repeated iteratively to generate dendrons of up to the fourth generation (Fig. 1).

Many factors combine to make this a particularly elegant methodology. From a practical perspective, the monomer loading is convenient and the work-up is minimal, with no flash chromatography being required for purification. Moreover, considering the versatility and polyvalence of the convergent approach, it offers significant potential in developing a variety of backbone architectures in excellent yields. Finally, because these dendrimers can be functionalized with a variety of different peripheral groups, it is possible to tailor their properties including solubility and ease of nanomaterial fabrication.

Divergent approach

Using a three-step divergent process, Hawker and co-workers applied the "click-chemistry" concept to synthesize 1,4-disubstituted triazole dendrimers.[16] Lack of any by-products as well as the fidelity and reliability of the "click" reaction reduce the usual drawbacks of the divergent methodology that lends itself,

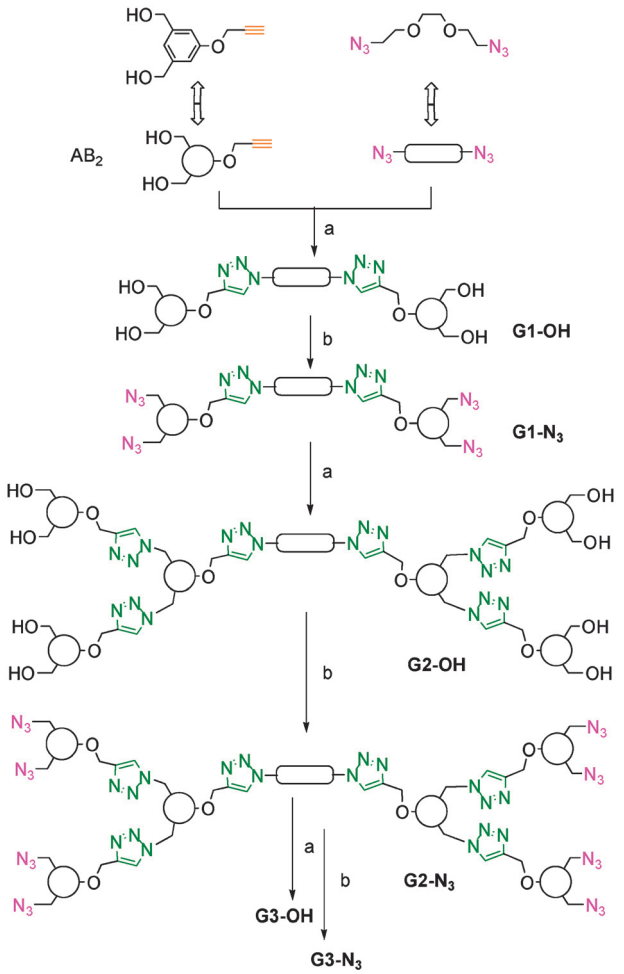

Fig. 2 Divergent build-up of dendrimers using "click-chemistry".

in general, to defects in the evolving dendrimer architecture. Starting from a bis(azide) core and an AB_2 monomer that contained propargyl ether and two alcohol functionalities, a first-generation dendrimer bearing 4 OH-groups at the periphery was obtained through the cycloaddition reaction. Then, in a one-pot process, the four hydroxyl extremities were transformed *in situ* to benzyl chlorides using $SOCl_2$ as the halogenating agent. This was followed by conversion to azides upon reaction with an excess of NaN_3. The azide functionalized dendrimer was then "clicked" with the AB_2 monomer to synthesize the second-generation dendrimer. This iterative process could then be repeated to build the desired *n*th generation (n = 1–3) of the dendrimers (Fig. 2). Purification by extraction or precipitation was found to be sufficient to afford the desired compounds.

The divergent approach as described above, although successful and efficient to build a variety of dendrimers, still involved traditional multi-step route requiring the need of an activating agent to generate reactive extremities at each additional cycle. To address this issue, Malkoch and co-workers reported using an accelerated strategy with an AB_2 + CD_2 system to synthesize dendrimers of up to fourth generation (Fig. 3).[17] This concept is similar in principle to the construction of phosphorus dendrimers as previously demonstrated by Majoral and co-workers.[8] Using building blocks that contain orthogonal functional

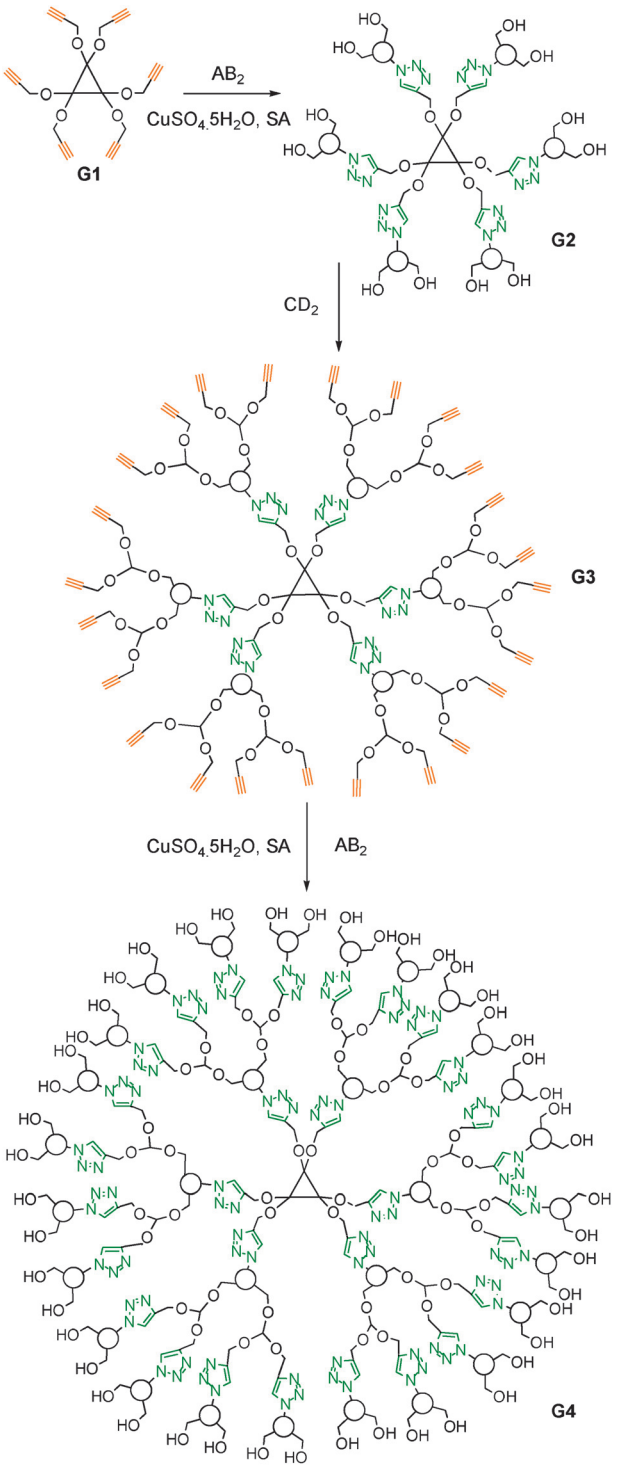

Fig. 3 Accelerated synthesis of dendrimers using AB_2 + CD_2 systems.

groups eliminates the need for protection/deprotection steps, affording desired macromolecules in high yields.

As demonstrated by these cited examples, "click-chemistry" affords a facile and efficient method to covalently link dendrimer generations, divergently or convergently. It can lead to robust and well-defined dendritic architectures with a wide variety of backbone structures without requiring flash chromatography for the purification process.

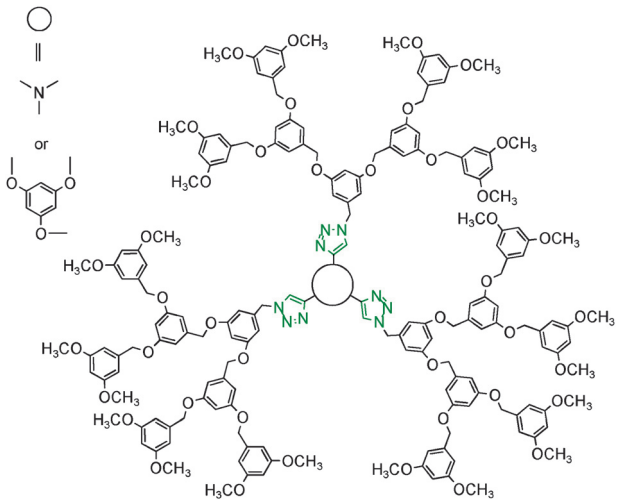

Fig. 4 Linked dendrons using "click-chemistry".

Dendrons clicked together at their focal point

Research groups have now adopted "click-chemistry" in stitching dendrons together and/or core units. This strategy that results in high yields with lack of by-products affords the possibility to obtain polyvalent architectures building for novel nanomaterials. Lee *et al*. have demonstrated that dendrons can be linked together convergently and very efficiently using "click-chemistry". For example, they reacted a tripodal acetylene core, tripropargyl amine, with methoxy terminated Fréchet type dendrons containing azide functionality at the focal point (Fig. 4). The formation of symmetric triazole dendrimers was carried out in DMF–H_2O solution (4 : 1) at 50–60 °C in the presence of $CuSO_4{\cdot}5H_2O$, and using SA as the reducing agent. The 1,4-disubstituted 1,2,3-triazole heterocycles were obtained in excellent yields (G1 = 93% and G2 = 88%) after column chromatography. It was noted that for the third-generation dendron yield was relatively low (40–42%).[18]

Subsequently, they changed the core to a 1,3,5-tris(prop-2-ynyloxy)benzene (Fig. 4), and obtained up to fourth-generation triazole dendrimers with yields between 93 and 86% after column chromatography.[19]

To demonstrate the versatility of the approach, they subsequently 'inverted' the process by placing a tri(azide) core, with Fréchet type dendritic wedges bearing acetylene groups at the focal point. Using similar reaction conditions as described above, dendrimers from generation 1 to 4 were synthesized with yields ranging from 80 to 89% after purification *via* silica gel chromatography. Higher generation dendrimers were found to take longer times, probably due to the bulkiness of G3 and G4 dendrons. They reported that FT-IR spectroscopy proved to be a useful technique to monitor these reactions, with the disappearance of the alkyne (3285 cm^{-1}) and azide (2100 cm^{-1}) stretching bands. In addition, as for previous examples, polydispersity index (PDI) was found to be narrow (1.01–1.04).[20]

They subsequently turned their attention to develop PAMAM dendrimers using the same methodology. After synthesizing divergently azide-functionalized PAMAM dendrons, the latter were successfully grafted on to a variety of multi-alkyne cores.[21–23] Interestingly, for first-generation PAMAM

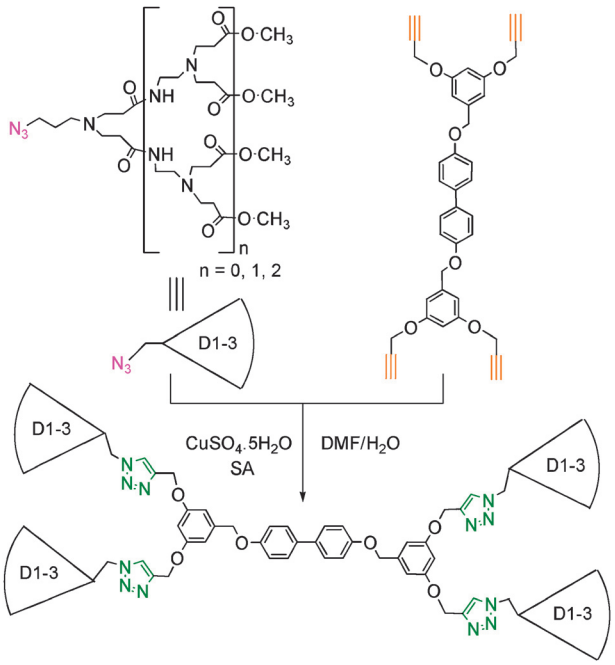

Fig. 5 Grafting of PAMAM dendrons on alkynyl cores.

dendron and the tetrafunctional core (Fig. 5), "click" reaction did not take place with CuI at room temperature in THF. The reaction temperature had to be subsequently raised to 50 °C. However, using $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in a 4 : 1 mixture of DMF/H_2O, triazole formation could be initiated at room temperature. It was completed at 60 °C in 9 h with a yield of 97% for generation 1, 12 h for generation 2 (91% yield) and 18 h for generation 3 (86% yield).[22]

A reverse methodology, as described previously for Fréchet type dendrons, was then adopted by the same group for the PAMAM dendrons containing alkyne or azide moieties at the focal point (Fig. 6). To enhance their collection of cores available, they reported a study with tri(azide) and two tetra-(azide) cores.[24] An important feature of the PAMAM dendrimers is that the presence of an amine inside the dendrons

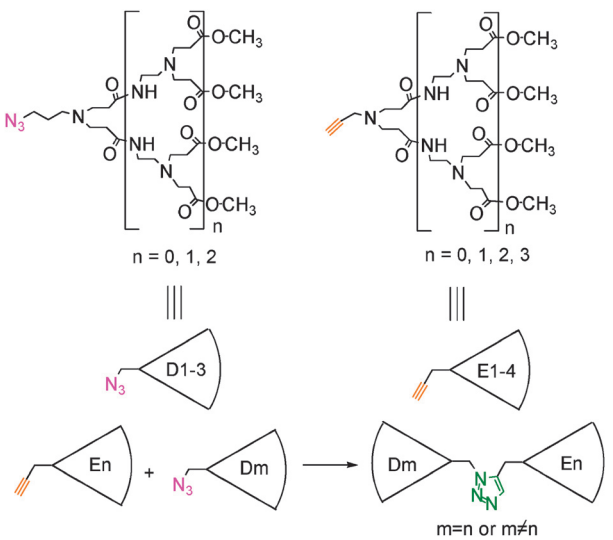

Fig. 6 Constructing symmetrical/unsymmetrical dendrimers using dendrons with azide and alkyne moieties at the focal points.

confers an anchimeric (neighboring group) assistance, allowing the "click" reactions to occur at room temperature and relatively faster, even for the higher generations. For example, to "click" alkyne- and azide-PAMAM dendrons of the third generation, only 4 h were needed resulting in 94% yield after purification.[25] The polydispersity index (PDI) for this family remains once again excellent with values ranging from 1.01 to 1.02.[25] It was noted that when a tetrafunctional core was employed, purification by dialysis compared with column chromatography afforded much better yields.[24,25] This may be related to the retention of the final product on silica gel.

To modify the multivalency of dendrimers, Lee's group synthesized unsymmetrical dendrimers with two different types of PAMAM[25] and Fréchet type[20,26] dendrons, by following the strategies reported earlier (Fig. 6). These included stitching azide and alkyne terminated dendrons of different generations,[20,25,26] or using a bivalent core through a two-step process.[27] In the stitching method, yields were very good (>84% for Fréchet type dendrons and 76% for PAMAM dendrons). In the two-step synthesis, formation of the intermediate dendrons of third or fourth generation was achieved readily in very high yield using an excess of the divalent core. The latter yielded the desired unsymmetrical PAMAM dendrimers upon simple addition of a dendron to the other.[27]

Bifunctional dendrimers such as those originally described by Fréchet and Hawker,[28] often required lengthy purifications, and as a result are obtained in low yields. Lee *et al.* developed the "click" strategy to link efficiently Fréchet type and PAMAM type dendrons of similar generations. Later on they demonstrated that different generations of each type could also be clicked to form diblock co-dendrimers. Their strategy was based on the fusion of azido-PAMAM or Fréchet type dendrons with the corresponding alkyne-PAMAM or Fréchet type dendrons of the same or a different generation (Fig. 7) with excellent yields.[29,30]

Hawker, Sharpless and co-workers used a similar strategy of "clicking" two dendrons together to synthesize symmetrical/unsymmetrical multivalent macromolecules. This resulted in controlled repartition of peripheral groups, one side bearing a protecting group while the other ready for further polyvalent functionalization.[31]

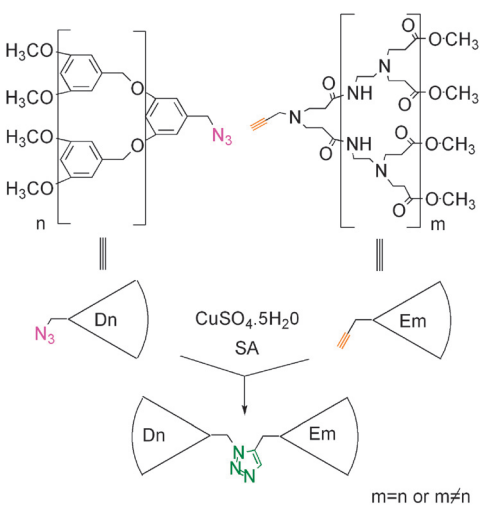

Fig. 7 Bifunctional dendrimers with variable dendron arms.

Peripheral functionalization through "click-chemistry"

Considering that the physicochemical properties (such as solubility) of dendrimers are generally dictated by the groups on the outer shell, easy, convenient, consistent and fast tailoring of their surfaces is an area of great current interest. In addition, dendritic effects in catalysis or biology depend often on the density due to multivalency. Thus effortless and reliable modification of the periphery of dendrimers are crucial concerns for chemists working in this area. "Click-chemistry" has brought great perspectives in this regard.

The concept of chain end functionalization of dendritic macromolecules was elegantly demonstrated in 2005 by Malkoch *et al.* Dendrimers containing peripheral acetylene groups were functionalized using "click-chemistry" and chemoselective formation of 1,4-disubstituted 1,2,3-triazole rings, to provide access to a library of extremities (Fig. 8).[32] Synthesis of acetylene terminated Fréchet type, polyester and PAMAM backbones, and their subsequent functionalization, offered potential in developing nanomaterials with unique features. They also tailored reaction conditions for the "click-chemistry" to demonstrate polyvalence of the method. Thus, (i) copper(I)-catalysts soluble in organic solvents ($CuP(OEt)_3I$ or

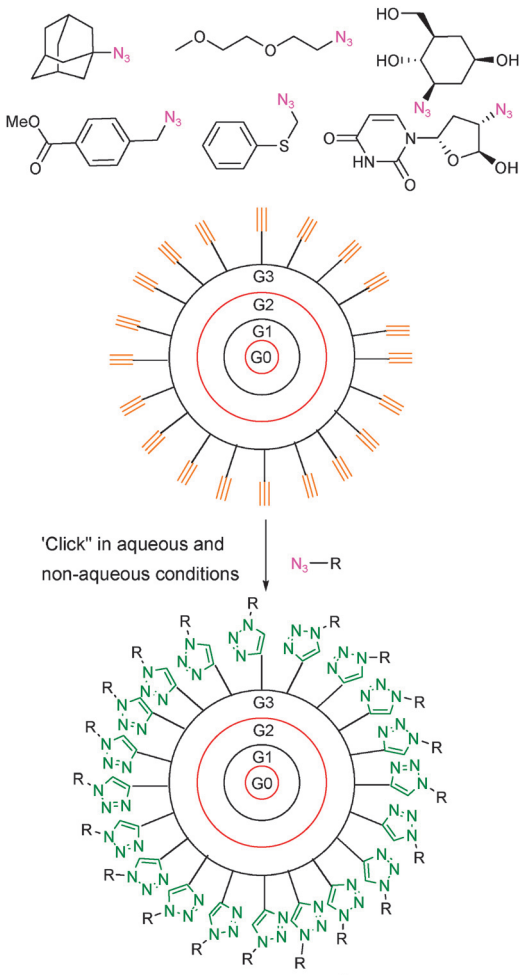

Fig. 8 Tailoring the periphery of dendrimers with "click-chemistry".

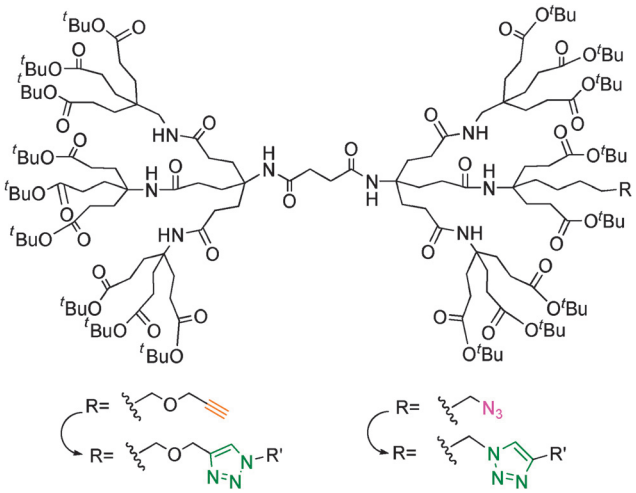

Fig. 9 Targeted monofunctionalization of the periphery using click-chemistry.

$Cu(PPh_3)_3Br$) were developed for non-aqueous "click-chemistry"; (ii) typical water-soluble $CuSO_4$ with SA as a reducing agent in presence of THF–water mixture for aqueous "click-chemistry", and (iii) the assistance of microwaves to quicken or complete reactions that were slow. The inclusion of a variety of end-groups including dyes, adamantane or aryl methyl ester, and bioactive molecules or azido-dendrons, broadened the field for peripheral modification of dendrimers.

Weck and co-workers demonstrated even further high fidelity of this chemoselective 1,3-dipolar cycloaddition method. The latter allowed them to carry out monofunctionalization of a dendrimer outer shell after using microwave irradiation. This novel approach allowed targeted tailoring of dendrimer surfaces with a single azido- or alkyne-group in extremely high yields (Fig. 9).[33]

Dendrimers for biological applications have also attracted significant interest due to their potential in the treatment of certain cancers[34] or the amplification of NK human cells.[35] Similarly, peptide- and glycol-dendrimers[36] have aroused intense interest due to the multivalent effect-enhancing interaction and affinity of a single entity.[37] Most common routes for dendrimer functionalization include peptide coupling, chemoselective reaction of sulfhydryl groups of peptides with maleimide or iodoacetamides functionalities.[38] Nonetheless, covering a dendritic scaffold with a high density of functional groups can be problematic, due to incomplete modification of the periphery, solubility or purification. In order to circumvent this problem, "click-chemistry" brings a new and highly useful route to tailor the dendrimer surface with desired extremities efficiently. "Click-chemistry" is beginning to be employed extensively for tailoring biologically active moieties.[39]

Triazole-based peptide dendrimers[40] are also starting to emerge.[41] In 2005, Liskamp and co-workers, starting from an amino-acid based dendrimer functionalized with propargyl groups, succeeded to graft a variety of 2–16 azidopeptides at the periphery. Major improvement consisted in using microwaves to promote cycloaddition, and reduction in the reaction times to sometimes 10 min with fair to excellent yields (46–96%) depending on the size of the peptides.[42] This multivalent approach to covalently bind bioactive molecules to a scaffold,

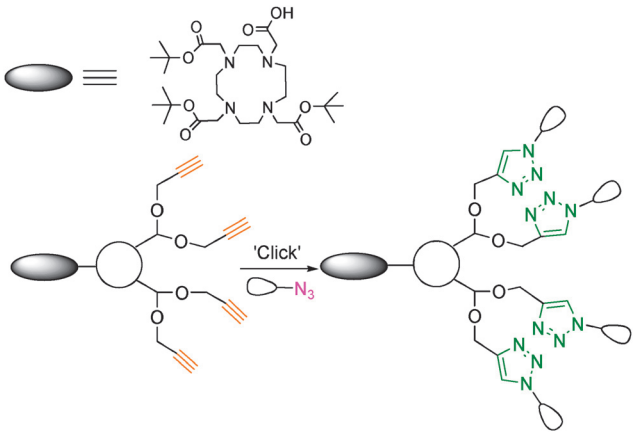

Fig. 10 Small glycodendrimers with a labelling agent at the focal point for tumour imaging.

has proven to be successful in synthesizing many such examples. Magainin-azide derivatives (long antimicrobial oligomeric peptides) were clicked to amino acid based dendrimers using microwave irradiations at a constant temperature of 80 °C in 5–20 min. Adopting this strategy, a 23-amino acid antimicrobial peptide was used for efficient construction of pore membranes.[43]

Liskamp and co-workers in 2007, synthesized mono-, di- and tetravalent dendrimers capped chemoselectively with *N*-ε-azido *cyclo*(Arg-Gly-Asp-D-Phe-Lys) using "click-chemistry" (Fig. 10). The presence of an additional DOTA–conjugate moiety was also accomplished for further radiolabelling with ^{111}In. The 1,3-dipolar cycloadditions were carried out in 10–30 min using a DMF–H_2O mixture in the presence of $CuSO_4$ and SA. The assistance of microwaves was required to obtain complete conversions. Using these functionalized dendrimers, they demonstrated better tumor targeting properties *in vivo* and *in vitro*, especially with the tetrameric adduct.[44]

The use of a mixture of organic solvents–water has also provided great impetus for the synthesis of glycodendrimers. In 2006, a divergent synthesis starting from a water-soluble azide-terminated core comprised of gallic acid and triethylene glycol, with three different alkyne-derived carbohydrates, was reported. After ultrafiltration, triazole glycodendrimers of generations 1 to 3 were grafted with 3 to 27 α-L-fucose, α-D-mannose and β-D-lactose residues in good to excellent yields (75–92%).[45] Given the success of this methodology, a long PEG chain at the focal point was subsequently added to form dendritic block copolymers. Modification of the periphery of these dendritic polymers led to the formation of glycoextremities with yields ranging from 80 to 92%.[46]

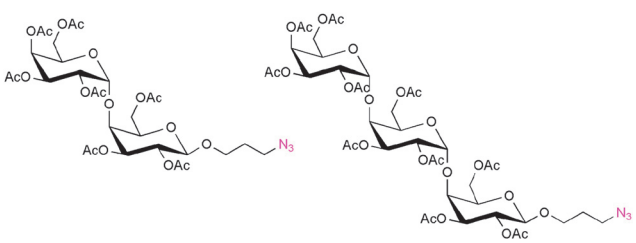

Fig. 11 Examples of large azido-disaccharides and trisaccharides "clicked" at the periphery of dendrimers with the assistance of microwave irradiations.

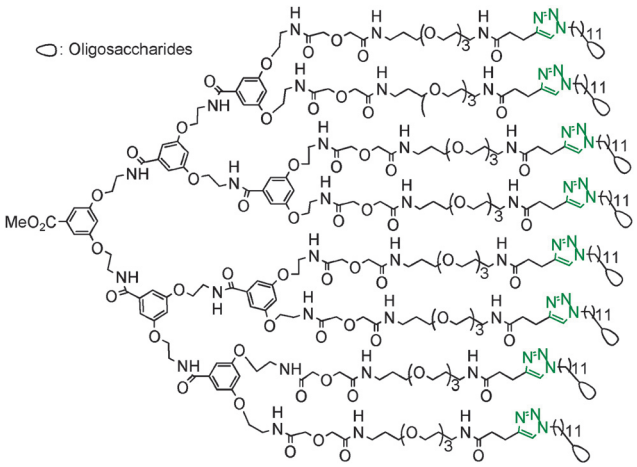

Fig. 12 Example of multivalent bioactive structures functionalized with oligosaccharide for the inhibition of cholera toxin (by Pieters and co-workers[49]).

Liskamps, Pieters and co-workers reported the use of microwave irradiation to graft protected and unprotected azido carbohydrates to their amino acid based scaffolds. The reactions were highly selective and efficient, and they obtained a series of dendrimers by combining $CuSO_4$, SA with microwaves with yields above 90% in most of the cases.[47] They later used the same methodology to functionalize the periphery of dendrimers with disaccharide and trisaccharides (Fig. 11). The latter were evaluated as inhibitors of adhesion of a pathogen with binding activities in the low nanomolar range.[48]

The strategy to include microwaves to accelerate the reaction was also demonstrated by coupling galactose as well as oligosaccharides functionalized with a long linear alkyl arm ending with an azide extremity, to generation 0, 1, 2 and 3 alkyne-terminated dendrimers. The use of microwaves for a G1 dendrimer afforded the desired compound after 1 min.[49] This group synthesized a library of novel macromolecules bearing one to eight residues with unprecedented binding ability to cholera toxin (Fig. 12).[49,50] These examples show that divergent ligation through the "click-chemistry" route is a very valuable tool. It avoids the long processing times required especially with protected glycosides, and leads to probably greater purity and easy access to desired compounds.

A new approach to triazole glycodendrimers has been developed by Roy and co-workers, by grafting acylated protected carbohydrates onto the periphery before deprotecting them. Two of their reports[51,52] deal with the interesting synthesis of small azido- and alkyl-based cores allowing them to obtain three or six mannose residues per molecule. These multivalent triazole macromolecules were built on pentaerythritol bearing aliphatic and/or aromatic spacers (Fig. 13). During the course of their studies, as previously reported by Sharpless, they determined that the use of Cu^{II} ($CuSO_4$) reduced by SA gave generally higher yields than a direct source of Cu^{I} (CuI). Wang's group had also reported the synthesis of small-acetylated glycoconjugate clusters in aqueous conditions.[53]

The same group also synthesized azido-terminated dendrons and dendrimers bearing amide linkage in their interior. It allowed them to functionalize the surfaces of different scaffolds with prop-2-ynyl α-L-fucoside in the presence of $CuSO_4$ and SA.

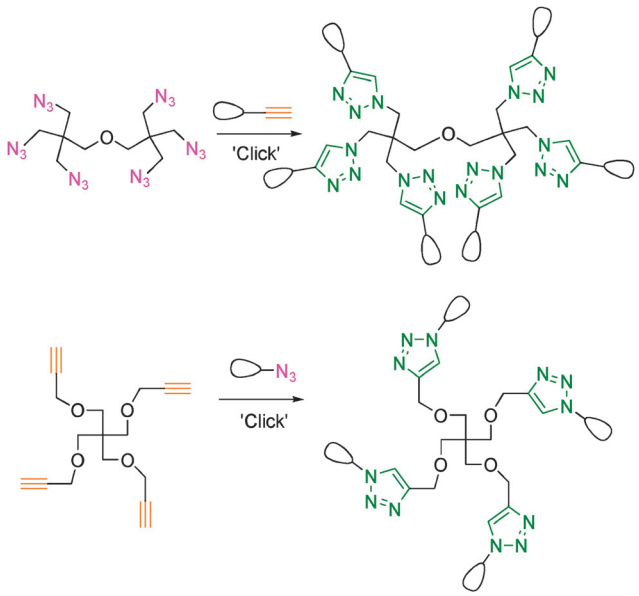

Fig. 13 Small triazole glycoconjuagte clusters by Roy and co-workers.[51,52]

They also designed symmetrical bifunctional dendrimers with a combination of α-L-fucoside and D-(+)-galactoside residues. BOC-protected focal point dendrons bearing two or four galactoside extremities were conveniently deprotected in order to allow a peptidic coupling to take place with focal point dendrons bearing two or four azido peripheral groups, respectively. These two or four groups were 'clicked' with the corresponding alkyl-based fucosides to afford symmetrical bis-dendrons with four or eight carbohydrate moieties (Fig. 14). The latter were de-*O*-acetylated using standard Zemplén conditions (NaOMe, MeOH), to afford the desired final compounds, which demonstrated very good binding affinities with Pa-IL and Pa-IIL lectins from *Pseudomonas aeruginosa*.[54]

A report by Sharpless and Hawker on bifunctional dendrimers mentioned above,[31] gives a good insight into what "click-chemistry" can contribute to enhancing the scope of dendrimer field. They demonstrated that they were able to modify

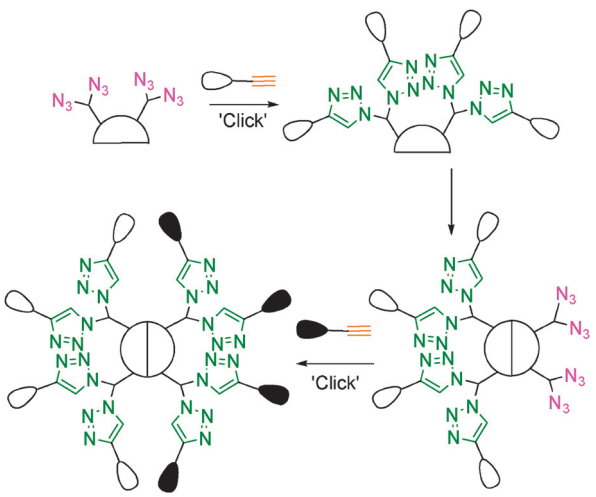

Fig. 14 Synthesis of a bifunctional dendrimers decorated with two kinds of galactoside residues.

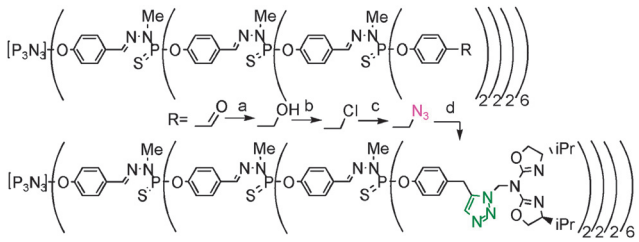

Fig. 15 Peripheral modification of a third-generation phosphorus dendrimers capped with azabis(oxazoline) ligands.

the periphery of symmetrical/unsymmetrical dendrimers at will, by tailoring protection/deprotection steps to afford, on the one hand fluorescent dyes, and on the other hand mannoside residues. This example demonstrated the strength of "click-chemistry" for the purpose developed in this review. These well-defined dendrimers represent potentially useful therapeutic agents due to their multivalent binding abilities. Making their synthesis simpler through "click-chemistry" probably affords a greater future to develop this area of research.

Dendrimers have offered an advantageous platform in catalysis due to their unique properties.[55] The positioning of the catalytic sites on a support often has significant influence on their activity. Binding catalytic moieties to a dendritic backbone can be problematic at times. For example, if large loading of monomers is necessary for a chiral ligand, it will dampen any perspective for this method due to high costs of dendritic catalysts. "Click-chemistry" offers an opportunity to resolve this problem. However, one must consider potential impairing of the catalytic site since triazole moieties can interact with transition metals. Caminade, Majoral and co-workers through their work have provided some insight into this. They grafted 12, 24 and 48 alkyne-based azabis(oxazoline) ligands to their dendrimer backbone containing azide moieties (Fig. 15), using CuI. They demonstrated that catalytic asymmetric benzoylations of a diol was not interfered with and any ligation of Cu^{II} with the triazole that proved to be problematic in other tests systems was completely avoided.[56]

More recently, it has been demonstrated that small Fréchet type dendrimers bearing acetylene end-groups can be functionalized with ((2*R*,4*S*)-4-azidopyrrolidine-2-yl)diphenylmethanol (Fig. 16), for the asymmetric borane reduction of prochiral ketones. A dendrimer containing six chiral catalyst sites was shown to give excellent yields and *ee* values for a large group of ketones. Additionally, easy recovery of dendrimers by precipitation allowed the catalyst to be reused for four re-runs while keeping its activity and excellent selectivity.[57]

Astruc and co-workers have demonstrated that triazole dendrimers are a valuable tool for catalysis. Their first report dealt with the synthesis of triazole dendritic macromolecules starting from a nona-allyl core, which was transformed to a nona-azide core. Triallylphenol functionalized with propargyl bromide was then readily added through a Cu^{I}-induced "click-chemistry" step to afford the aromatic triazole rings and 27-allyl peripheral substituents. This two-step three-reaction iterative process was then repeated to obtain the second generation with 81 terminal allyls and 36 triazole rings inside the scaffold. They mentioned that a stoichiometric amount of

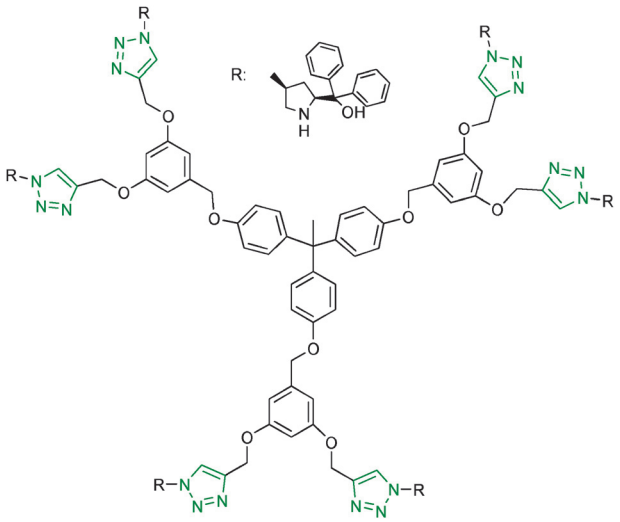

Fig. 16 Small Fréchet type dendrimer after click reaction with six ((2*R*,4*S*)-4-azidopyrrolidine-2-yl)diphenylmethanol groups for asymmetric catalysis.

Cu^{I} was necessary, since the metal remained trapped and could only be removed with aqueous ammonia solution.[58] They then used their azido intermediate to functionalize the periphery by synthesizing poly-1,2,3-triazolylferrocenyl macromolecules with 9, 36, 117 triazole groups for G0, G1, G2, respectively (Fig. 17). Subsequently they demonstrated the ability of several metals to bind to the aromatic triazoles using cyclic voltammograms (redox recognition). Pd^{II} showed the best ability as a guest inside the dendritic structure.[58,59] In a later study, they demonstrated that $Pd(OAc)_2$ can bind selectively to this series of dendrimers in a one-to-one fashion between a triazole unit and a metal atom. After reduction with MeOH or

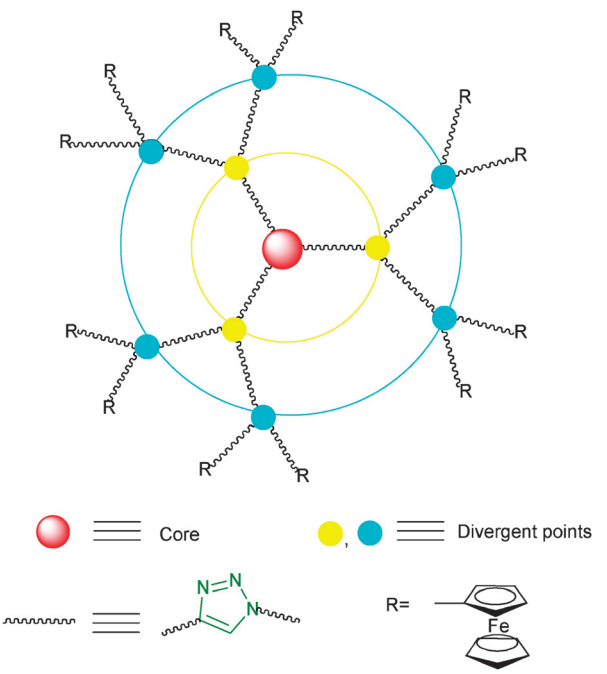

Fig. 17 Second-generation triazole-containing dendrimer for binding in a one-to-one fashion between triazole moieties and metal.

$NaBH_4$ they were able to generate catalytically active palladium nanoparticles with a controlled repartition and encapsulation of the metal. This ability of Pd atoms to be inserted into the triazole dendrimer allowed them to readily control the precise size of their nanoparticles that led to very good catalytic activity for the reduction of styrene,[59] cyclohexadiene,[59] or Myaura–Suzuki C–C bond formation.[60]

The same group then modified the periphery to form water-soluble 1,2,3-triazolylsulfonate dendrimers by clicking sodium propargyl sulfonate in the presence of $CuSO_4$ and SA to the azido-terminal group. This series was then used to stabilize (but not encapsulate) water-soluble Pd nanoparticles. This strategy could not afford the same control of the morphology and size as before. The nanoparticles nonetheless still presented, even with a very low loading, excellent properties for the hydrogenation of allyl alcohol and Suzuki coupling reactions under ambient conditions.[61]

Conclusions

This review has aimed at depicting the highly versatile nature of the so-called "click" reaction between acetylenes and azides, which continues to provide access to a variety of multivalent dendritic architectures. It has offered a simple and convenient methodology to link dendrimer generations, stitch dendrons together and modify the periphery of dendrimers. The demonstrated potential of this synthetic technique has given realistic expectations in developing competitive macromolecules for industrial usage, and for a variety of applications. Through this highlight of "click-chemistry", we have made an attempt to assemble a library of reaction optimizations in dendrimer synthesis. A review of these makes it clear that this methodology does not necessitate high monomer loading, and in general the purification of the desired products does not require tedious and lengthy chromatographic separations. It is also obvious that Cu^I-catalyzed "click-chemistry" does not generate considerable waste (virtually no by-product). It has thus fulfilled one important aspect of the atom economy requirements that is the object of Green Chemistry. For all these reasons, this strategy is a complete and fertile methodology to authorize further development of dendrimers at an industrial scale.

Considering ongoing developments in the area of "click-chemistry", a highly active and reusable Cu^I-tren catalyst $[Cu(C_{18}H_{37})_6tren)]Br$ (Fig. 18) for Huisgen 1,3-dipolar cycloaddition of azides with alkynyl groups has been reported. The activity of this catalyst has been demonstrated to be compatible with dendrimer synthesis, broadening the scope of this new strategy. Moreover, low catalyst loading (0.1 mol%) employed here can be advantageously combined with "click-chemistry" for cost reduction in future industrial build-up of dendrimers.[62]

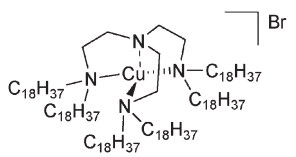

Fig. 18 Cu^I-tren catalyst.

This review has also established that the inclusion of 1,2,3-triazole moieties inside dendritic scaffolds does not impair the properties of the dendrimers. There are in fact advantages to have such heterocycles inside dendrimer structures. When catalysis is the intended goal, nitrogen centers in these heterocycles can bind a variety of transition metals including Pd^{II} or $Cu^{I/II}$. It has also been shown that the nitrogen heterocycle is relatively stable to metabolic degradation,[63] and there are no reports of loss of activity when such dendrimers are employed for biological applications.

In conclusion, dendrimer design using Cu^I-catalyzed "click-chemistry" is a very powerful, accessible and affordable method. In addition, many more potential aspects of this reaction are still awaiting discovery, as the number of publications dealing with this strategy continues to grow at a fast pace.

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