A chemoselective approach for the accelerated synthesis of well-defined dendritic architectures†

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A chemoselective and layered growth approach has been developed for the synthesis of dendrimers, combining Click chemistry with traditional esterification/etherification reactions, without the need for activation steps and with excellent overall yields.

Dendrimers are highly branched polymers that have gained increasing attention in a variety of nanotechnology applications from microelectronics to biomedical devices.[1] It is generally known that dendrimers are time consuming and expensive to construct using traditional multi-step techniques which limits their commercial availability to PAMAM®, DAB®, Phosphorous PMMH and 2,2-bis(methylol)propionic acid (bis-MPA) dendrimers.[2,3] Nevertheless, their well-defined, modular structure with high functional group density and 3-dimensional shape make these synthetically challenging scaffolds extremely attractive molecular targets. For example, PAMAM dendrimers have been modified with sulfonic acid end groups to afford a novel dendritic HIV/AIDS[4] drug while the same PAMAM scaffolds with hydrophilic oligo(ethylene glycol) end groups have been used as pore generating agents for the development of dielectric layers for advanced microelectronic devices.[5]

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Traditionally, two synthetic strategies are available for the preparation of dendrimers, either the divergent[6] or convergent[7] growth approach. Both strategies yield high generation dendritic structures from AB_x-monomers through repetitive growth and activation steps. To achieve 'perfect' structures, the chosen chemistry needs to be essentially quantitative as inefficient reactions lead to defects in the dendritic structures and may give rise to tedious purification procedures. As a result, new synthetic strategies and versatile coupling reactions that will enable the preparation of dendritic macromolecules under accelerated conditions and with unprecedented control are of significant interest. A reaction that has gained tremendous attention since it was reported by Fokin and Sharpless in 2002 and which fulfills all the criteria for the construction of dendritic structure is the Cu catalyzed Click reaction of azides with terminal alkynes.[8] This reaction is highly efficient and occurs under benign conditions in the presence of other reactive groups with no byproducts. Due to its orthogonal, robust nature, this example of Click chemistry has attracted significant attention in the materials science community, especially for the construction of complex polymeric materials.[9] For example, the construction of multifunctional AB-diblock dendrimers with both targeting ligands and imaging agents for investigating the binding with cell surfaces was successfully accomplished in high yields using Click chemistry.[10] Nonetheless, while the introduction of new chemical reactions has greatly enabled the efficient construction of dendrimers,[11] the synthetic approaches employed still involve the traditional multi-step, divergent or convergent approaches.

To greatly increase the availability of functionalized dendrimers and to accelerate their use in a variety of applications the development of new methodologies for their synthesis is required. The requirements for such an approach are that it should involve

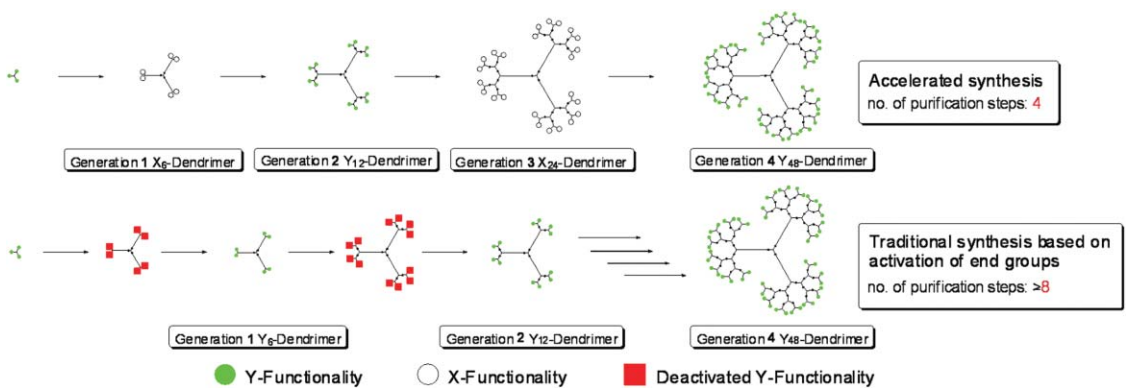


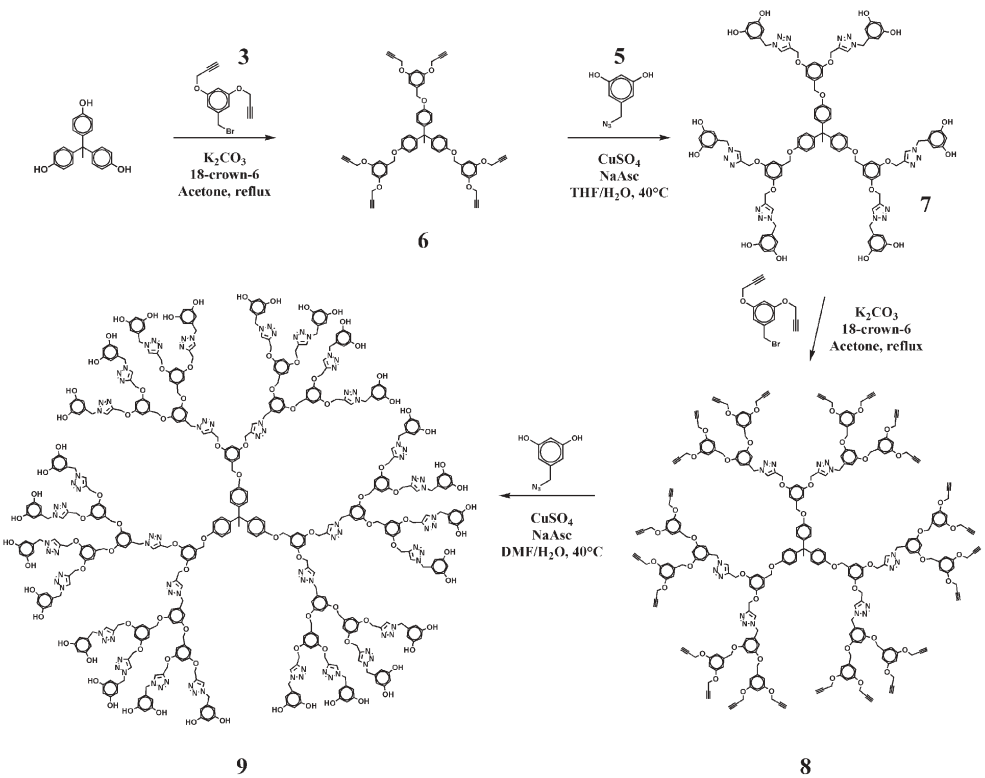
Fig. 1 Graphical representation of the number of synthetic steps required for the preparation of a Gen = 4 dendrimer using an accelerated chemoselective synthesis (top) *versus* a traditional divergent dendrimer synthesis (bottom).

fewer reaction steps, be quantitative in nature, compatible with a variety of functional groups and occur under mild reaction conditions. This can be accomplished through the synthesis of AB_2- and CD_2-monomers that selectively react with each other and employ reactions that proceed in very high yield (Fig. 1). If this chemoselectivity can be achieved, $AB_2 + CD_2$ systems lead to generation growth involving only a single reaction with little or no purification required. The orthogonality required in the selection of the A, B, C and D functional groups also dictates a high degree of flexibility in the incorporation of reactive functional groups.

This communication describes the development of an accelerated growth approach[12] to dendrimers based on the combination of Click chemistry with traditional esterification/etherification reactions, for the synthesis of dendrimer derivatives of the classical Fréchet-type and bis-MPA dendritic macromolecules. These structures were chosen due to their use in dendrimers as well as to demonstrate the modular nature of this synthetic approach and its applicability to different chemistries and monomer units. To illustrate the efficiency of the accelerated approach methodology the synthesis of analogs of Fréchet-type dendrimers was initially examined through the combination of Click and etherification reactions. The required monomer units for one-step generation growth are 1-(bromomethyl)-3,5-bis(prop-2-ynyloxy)benzene, **3**, as nominally the AB_2-monomer, and 5-(azidomethyl)benzene-1,3-diol **5**, as the CD_2-monomer unit.

In this case, orthogonal reactivity is achieved by the Click reaction of the terminal acetylenes with the azide group of **5** in the presence of the phenolic moieties of **5** followed by the etherification of the terminal phenolic groups of the growing dendrimer, **7**, with the bromomethyl group of **3** with the terminal acetylenes of **3** giving rise to the third generation dendrimer **8**, containing 24 terminal acetylene groups (Scheme 1). This synthetic strategy allows the divergent preparation of a fourth generation dendrimer **9**, containing 48 terminal phenolic groups, in only four steps and in multi-gram quantities with an overall yield of 70% from the starting triphenol, resulting in a layered dendritic block copolymer with alternating layers of benzyl ether, triazole and benzyl ether groups. The orthogonality and efficiency of this strategy were demonstrated by monitoring each reaction with NMR and Maldi-TOF techniques. As can be seen in Fig. 2, the growth progress of the fourth generation dendrimer **9** was monitored by ^{1}H NMR and the Click reaction was found to reach completion within 12 h at RT. This was confirmed since the peak corresponding to the acetylene terminal groups at 3.55 ppm in DMSO was not detectable. It should be noted that a traditional divergent growth approach would require at least eight steps with multiple purification procedures for the synthesis of a similar fourth generation structure.

Moreover, the dendritic products obtained have alternating end groups, either acetylene or phenolic, depending on the generation number which allows for convenient and efficient post modifications without the need for elaborate activation of dormant species. To further demonstrate the versatility of this concept, the accelerated synthesis of analogs of bis-MPA type dendrimers was addressed. Traditionally, bis-MPA dendrimers require growth/activation steps involving esterification and deprotection reactions. To develop bis-MPA type dendrimers *via* this accelerated approach, esterification reactions were coupled with Click chemistry. Initially, a bis-MPA based AB_2-monomer containing both an acyl chloride and azide functionalities was designed, **13**, and coupled with the corresponding CD_2-monomer, **15**, which is the propargyl ester of bis-MPA (Fig. 3). Generation growth was



Scheme 1 Chemoselective synthesis of a Gen = 4 Fréchet-type dendrimer using an accelerated $AB_2 + CD_2$ approach.

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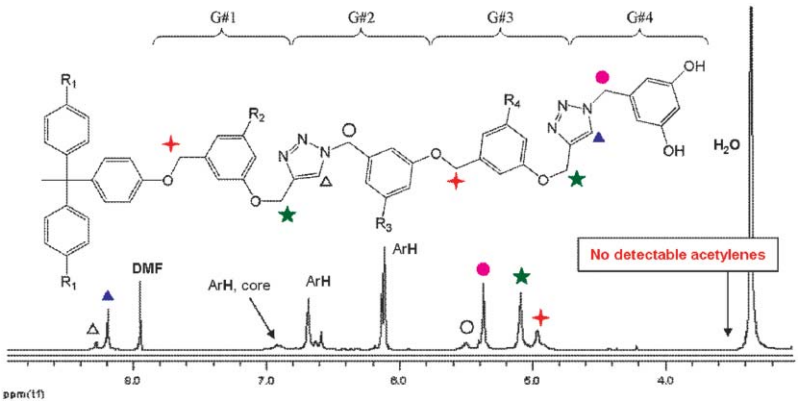

Fig. 2 Crude ^{1}H NMR spectra of a Gen = 4 Fréchet-type dendrimer, **9**, containing 48 terminal hydroxyl groups.

accomplished *via* an esterification reaction of **13** with the trisphenolic hydroxyl core followed by a Click reaction of **15** to yield a second generation bis-MPA type dendrimer with 12 terminal hydroxyl groups. Repetition of this sequence of reactions gives the fourth generation dendrimer, **19**, which again is obtained in excellent yield with high levels of purity after only four reaction steps.

The distinct difference between this chemoselective accelerated approach and the traditional strategies for dendrimer synthesis is the repetitive utilization of two highly versatile reactions in sequence which avoids numerous activation or deprotection steps. As a result, growth is not only accelerated but a much richer family of functionalized dendritic structures can be prepared. This versatility is demonstrated by the accelerated synthesis of two different types of dendrimers, analogs of bis-MPA-type and Fréchet-type dendrimers. The simple and orthogonal nature of these strategies also allows the synthesis of a wide variety of other macromolecular architectures and hybrid materials where monomers from different families are combined to generate new materials with unique features.

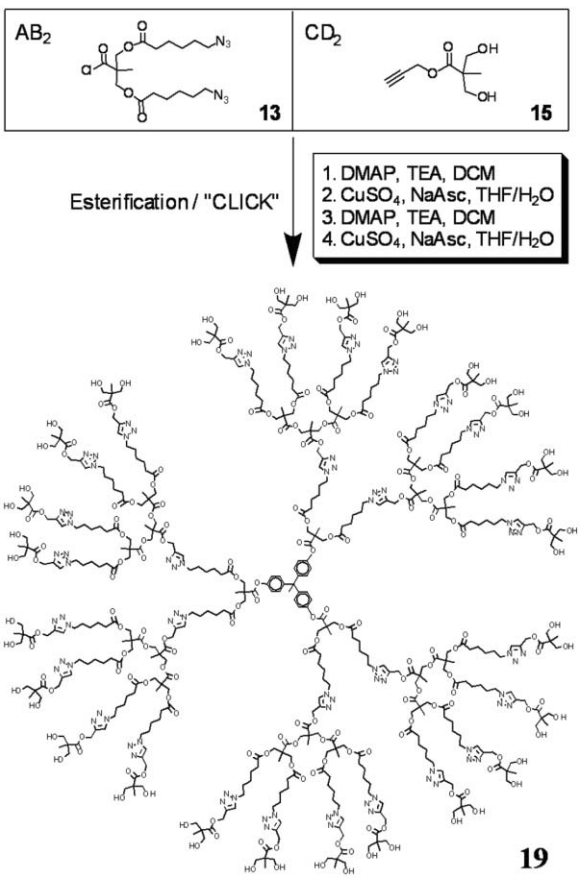

Fig. 3 Accelerated synthesis of a Gen = 4 bis-MPA dendrimer synthesized in only four steps from **13** and **15**.

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