Dendrimers

Efficiency and Fidelity in a Click-Chemistry Route to Triazole Dendrimers by the Copper(I)-Catalyzed Ligation of Azides and Alkynes**

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Unique properties of dendrimers, which are a direct consequence of their regular structure, have sparked significant interest in recent years.[1] A large number of dendritic structures varying in size, solubility, and function have been prepared. However, most dendrimer syntheses, particularly at later generations, require high monomer loading, rely on tedious and lengthy chromatographic separations, and generate considerable waste.[2] For example, the synthesis of polyether dendrimers,[3] based on a sequence of Williamson etherifications and halogenations, suffers from its incompatibility with various functional groups and complicated purifications.[4]

Herein, we report on an efficient and preparatively simple approach for the generation of diverse dendritic structures of high purity and in excellent yield. The unique aspects of this route arise from the near-perfect reliability of the Cu^I-

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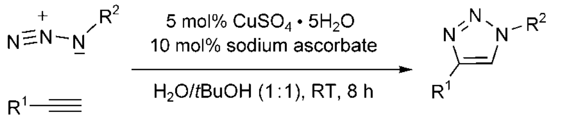
catalyzed synthesis of 1,2,3-triazoles from azides and alkynes (Scheme 1).[5] The reaction is experimentally simple—proceeding well in aqueous solutions without protection from oxygen, requiring only stoichiometric amounts of starting materials, and generating virtually no by-products. Equally important is the wide scope, high selectivity, and nearly quantitative yields of this transformation. In our procedure for the best click reaction to date,[6] the components and catalyst are simply mixed and stirred, whereupon pure products are isolated by filtration or simple extraction.

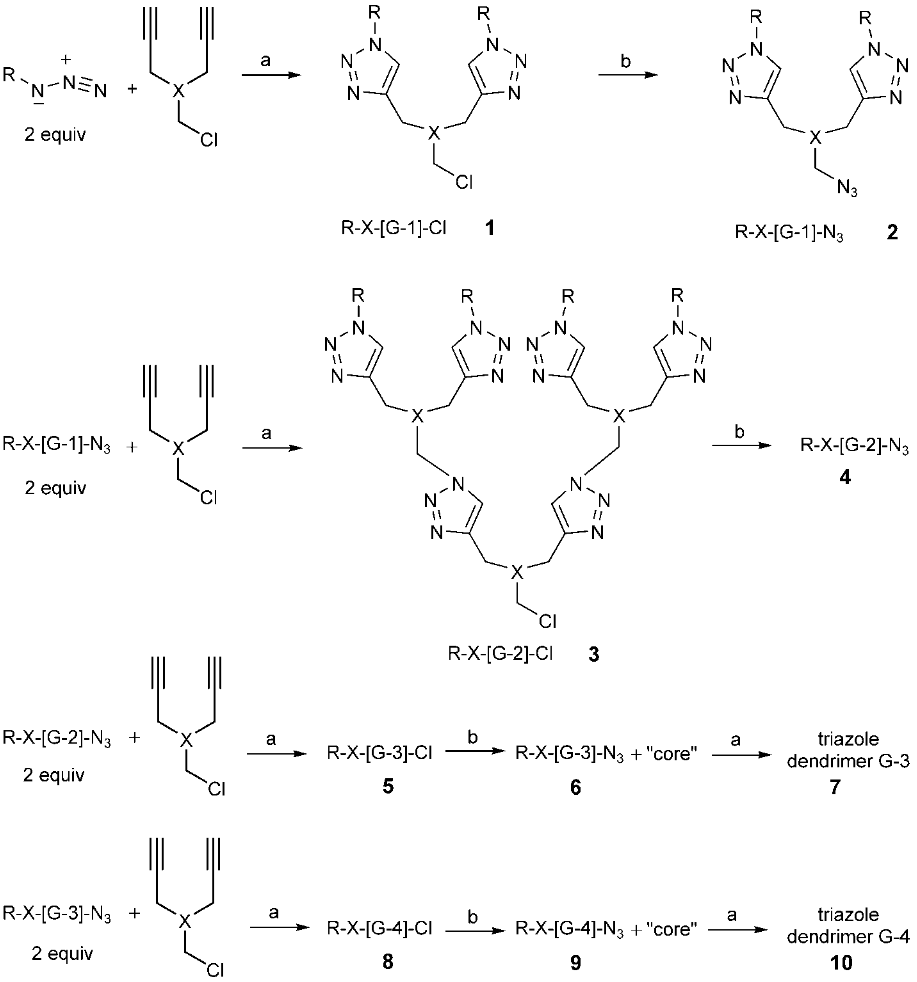


Scheme 1. Copper(I)-catalyzed synthesis of 1,4-disubstituted 1,2,3-triazoles.

Fréchet's convergent approach was utilized in our dendrimer synthesis.[7] Thus, the individual branches or dendrons were built sequentially, starting on the "outside" of the molecule. They were then coupled to a multivalent centerpiece ("core") in the last step, as outlined in Scheme 2, which led to a variety of dendrimers with different chain-end groups (R) and internal repeat units (X).

In exploiting Cu^I-catalyzed reaction for dendrimer construction, we envisaged a variety of AB_2 monomers based on terminal alkynes and alkyl halide functionalities. Readily available starting materials and simple synthetic strategies for the introduction of alkynyl groups lead to significant structural diversity (Figure 1). However, one structural feature was common to monomers **11**–**13**, namely the presence of a single chloromethyl group. This was specifically incorporated into our synthetic strategy to allow facile activation of the focal-point group during dendrimer construction by the convergent-growth approach. We envisaged that reaction of dendritic fragments containing a single chloromethyl group with sodium azide would lead to quantitative formation of the desired azidomethyl group, which could then be coupled with **11**, **12**, or **13** to give the next-generation dendron (Scheme 2). As with AB_2 monomer units, a variety of the chain ends with reactive functional groups ranging from carboxylic acid to alcohol could be employed in the construction of diverse triazole dendrimers (Figure 2).

Copper(I)-catalyzed reactions of AB_2 monomers and the chain-end units were carried out in the presence of $CuSO_4$ (2–5 mol%) and sodium ascorbate (5–10 mol%) in a 1:1 mixture of water and *tert*-butyl alcohol at room temperature to generate the desired bistriazoles in near-quantitative yields. Trace amounts of copper salts in the products were easily removed by washing with an ammonium hydroxide/citrate aqueous buffer. Owing to the high degree of efficiency, the reaction could be conducted with a stoichiometric amount (2.0 equiv) of the azides. Purifications were greatly simplified due to the absence of side products. This is in direct contrast with the classical synthesis of polyether dendrimers by the convergent-growth approach, where an excess of dendron (2.05–2.20 equiv) is typically used to increase yields of the next-generation dendritic fragment. Furthermore, purification by flash chromatography is usually required at each step.[7]



Scheme 2. Convergent approach toward triazole dendrimers. a) $CuSO_4$ (5 mol%), sodium ascorbate (10 mol%), $H_2O/tBuOH$ (1:1); b) 1.5 equiv NaN_3, CH_3COCH_3/H_2O (4:1), 60°C, 1–3 h.[8]

In the next step, the primary chlorides were converted into the corresponding azides by reaction with 1.5 equiv sodium azide in acetone/water.[9] This transformation was equally facile and typically resulted in yields of more than 95% with NaCl as the only by-product. The dendrons were then "grown" by the reaction of the

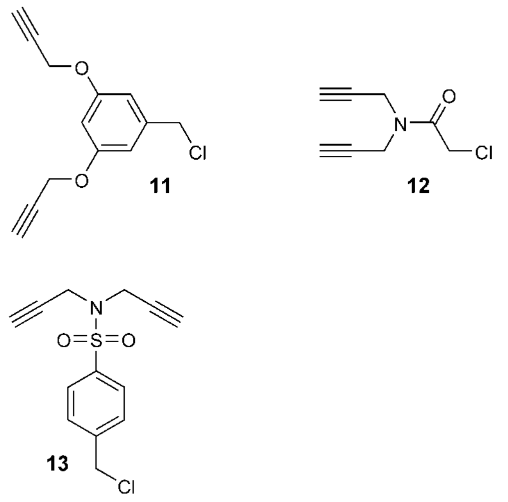


Figure 1. Structures of the AB$_2$ monomers **11–13** used in the synthesis of dendrimers based on click chemistry.

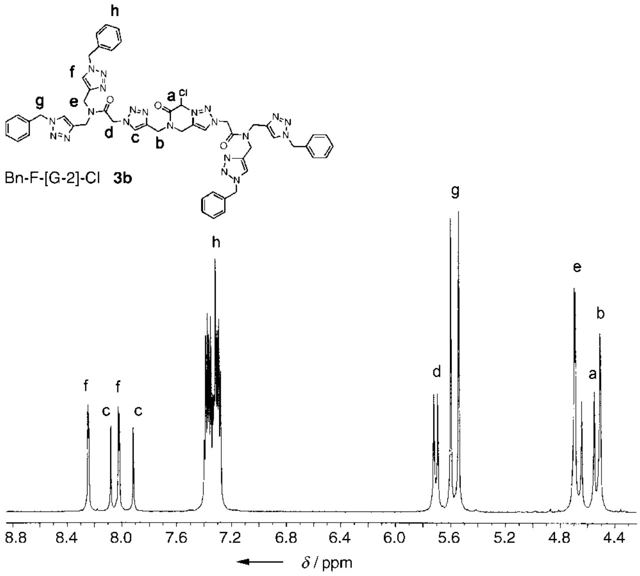


Figure 3. ^{1}H NMR spectrum of the crude reaction mixture containing dendron **3b**.

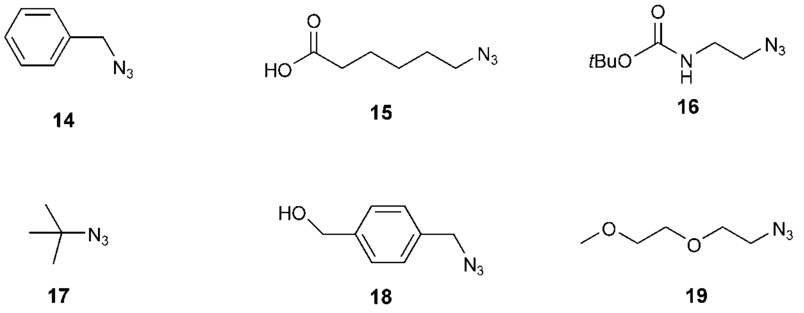


Figure 2. Azides **14–19** used in the synthesis of chain-end-functionalized dendrimers based on click chemistry.

resulting azides with the original monomers **11, 12**, or **13**. All second-generation dendrons were isolated as pure white solids by simple filtration or aqueous workup in yields exceeding 90% for the isolated products. As seen in the crude ^{1}H NMR spectrum of dendron Bn-F-[G-2]-Cl **3b** (Figure 3), the integration ratio for protons f and c is 2:1 which, in comparison with the spectrum of the mixture obtained from a purely thermal process, indicates 100% regioselectivity in its construction.

Following the same procedure, dendrons based on amide monomer **12** with *tert*-butyl azide **17** at the periphery as well as the benzyl ether monomer **11** with azide **19** were propagated to the fourth generation. Dendrons constructed from monomer **12** with the azides **16** and **19** at the periphery were propagated to the third generation. When the dendrimers were not soluble in aqueous mixtures, slight modification of the reaction conditions led to the same degree of efficiency and near-quantitative yields. For example, benzyl-terminated dendrons prepared from **14** and **11** were insoluble in 1:1 H_2O/THF solutions at the second generation and led to incomplete conversions. Similarly, conversion of the chloromethyl group to the azide group was unsuccessful with aqueous sodium azide. To overcome this difficulty, the copper-catalyzed reaction was performed in THF with an organosoluble Cu^I species, [$(PPh_3)_3CuBr$], under microwave irradiation, leading to quantitative yields of the next-generation dendritic fragment. Similar results for azide formation were obtained when the displacement was performed with sodium azide in dimethylformamide or dimethyl sulfoxide. Analysis of the dendrons by MALDI-TOF mass spectrometry as well as by gel-permeation chromatography (GPC) provides no signs of products with defects that would arise from incomplete branches (Figure 4).

Works by Tomalia, Fréchet, and others demonstrate that the solubility properties of dendritic molecules are dominated by their periphery.[2] As expected, our observations largely follow these trends. A unique property of

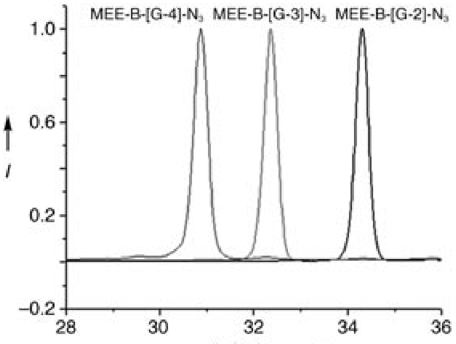


Figure 4. GPC traces for the crude reaction products MEE-B-[G-4]-N$_3$ **9d**, MEE-B-[G-3]-N$_3$ **6d**, and MEE-B-[G-2]-N$_3$ **4d**, obtained by dendritic growth from the benzyl ether monomer **11** and the azido di(ethylene glycol) derivative **19**.

these triazole-based dendrons is, as the molecules reach higher generations, they become less soluble in ethyl acetate and slightly more soluble in dichloromethane, chloroform, alcohols and, surprisingly, aqueous mixtures.[10]

Finally, several third- and fourth-generation triazole dendrimers were constructed by anchoring these dendrons to a variety of polyacetylene cores (Figure 5). A representative example is shown in Scheme 3, where the third-generation dendron *t*Bu-F-[G-3]-N_3 **6a** was coupled directly with 2,4,6-tris(prop-2-ynyloxy)-1,3,5-triazine (**23**) in the presence of the Cu^I catalyst generated in situ. It is noteworthy that even at these low concentrations (0.06 M in alkyne and azide), the reaction proceeded rapidly enough at room temperature and reached completion in less than 30 h as indicated by LC-MS analysis. Dendrimer **7a**, with 24 periphery units (M_w = 6322 Da), was isolated as a white solid in 92% yield. All dendrimers were characterized by ^1H and ^{13}C NMR spectroscopy, and the structure and purity were confirmed further by GPC and MALDI-TOF mass spectrometry (Figure 6). High polarity, good solubility in alcohol/water mixtures, and strong UV absorptions at $\lambda = 210$ and 229 nm are unique features of this new class of triazole dendrimers.

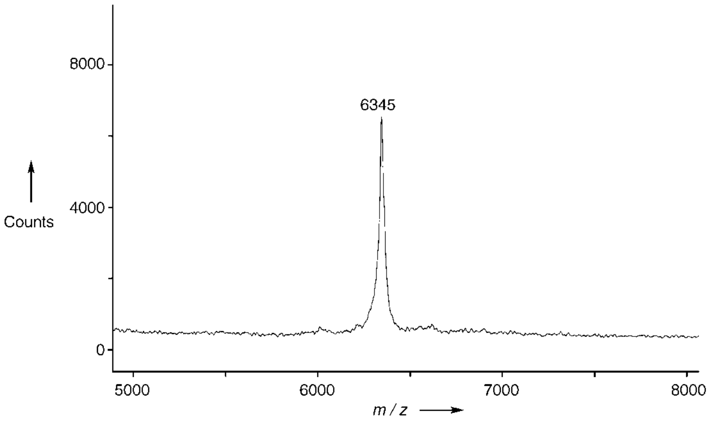


Figure 6. MALDI-TOF mass spectrum of **7a** (M+Na^+, resolution ± 0.1%).

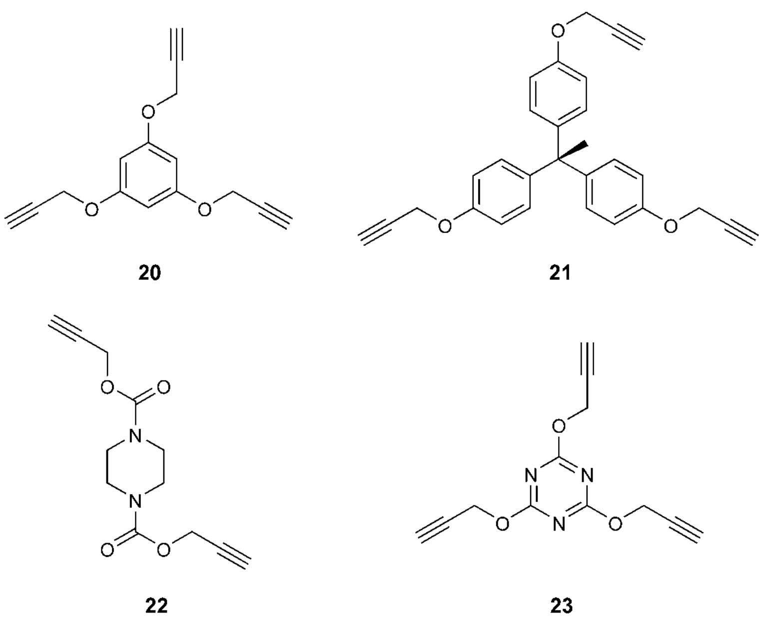
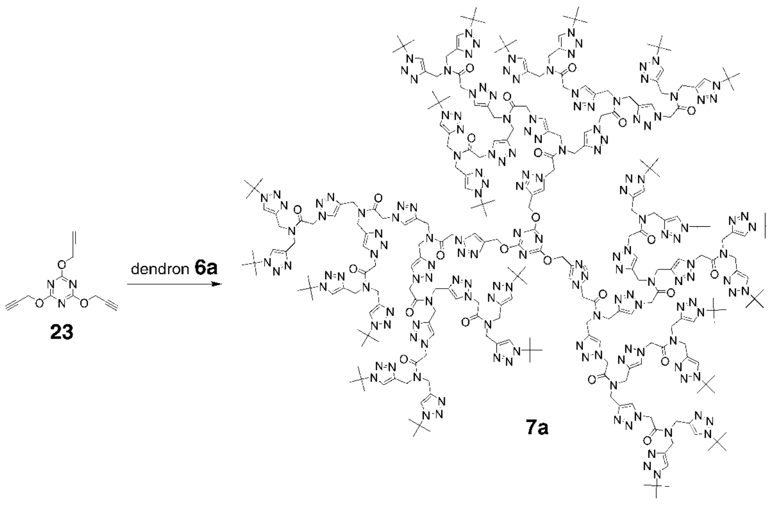


Figure 5. Polyacetylene cores used in the synthesis of chain-end-functionalized dendrimers based on click chemistry.



Scheme 3. Synthesis of dendrimer **7a**.

In summary, a highly efficient route to triazole-based dendrimers is now available thanks to the unprecedented reliability of the Cu^I-catalyzed ligation of terminal alkynes and azides. This chemistry is highly regioselective, resulting in 1,4-disubstituted triazoles. A variety of functional groups are compatible with the process, and the only major by-product formed in the reaction is NaCl. All second-generation and some third-generation dendrons were isolated directly as pure solids (i.e. without chromatographic separations), meeting the requirements for large-scale applications.

The recently discovered ability of polydentate 1,4-disubstituted 1,2,3-triazole ligands to stabilize Cu^I species even under aqueous aerobic conditions,[11] has already proven crucial in biological applications.[12] Exploration of the copper-binding ability of this new class of dendrimers and their ligand properties in homogeneous catalysis is underway.

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[4] Protic functional groups at the periphery, such as OH, COOH, and NH_2, are not compatible with Williamson etherifications and halogenations.

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[8] The nomenclature used for the dendritic framework is as follows: R-X-[G-*n*]-Y, where R describes the functional groups at periphery, Bn for benzyl, Boc for *tert*-butyl carbamate, MEE for (2-methoxyethoxy)ethane; X describes internal repeat units, B for 3,5-dioxybenzyl, F for formamide, S for benzenesulfonamide; *n* is the number for generations; Y describes functional group at the focal point, either chloride, Cl, or azide, N_3.

[9] Monochloride dendrons generated from benzenesulfonamide **13** were converted into the corresponding azides in wet DMF.

[10] In general, dendrons generated from benzenesulfonamide **13** are less soluble than dendrons made from acetamide **12** in all solvents tested, while the incorporation of **19** as a chain end increases the solubility substantially.

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