ORGANIC
LETTERS

2000
Vol. 2, No. 11
1645−1648

A Facile Synthetic Route to a Third-Generation Dendrimer with Generation-Specific Functional Aryl Bromides

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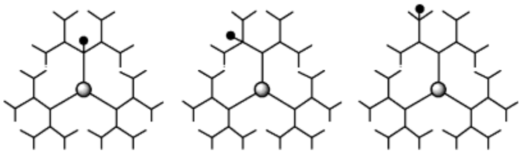
Received April 20, 2000

ABSTRACT



The synthesis of three third-generation dendrimers that selectively carry one aryl bromide functional group in the first, second, or third generation, respectively, is described. These functions, regardless of their location, can be chemically modified by Suzuki cross-coupling chemistry with *p-tert*-butylbenzene boronic ester.

Dendrimers are highly branched, globular, monodispersed macromolecules. They comprise a core, branching units, a large number of (functional) end groups, and free interior volume normally filled by solvent.[1] The expansion of these macromolecules to a range of several nanometers, the existence of usable “surface”, and transport possibilities in and with them have made dendrimers interesting candidates for various applications.[2] Many synthetic strategies have been developed for this class of compounds, with structure control and synthesis efficiency being the most important aspects. Functional groups were introduced at the periphery, typically one per terminus[3] (but also less),[4] in the interior at every generation (repeat unit),[5] at a certain generation,[6] or at the core.[7] Here we describe a synthetic strategy that allows for specific incorporation of a functional group at any given generation. These groups can then serve as anchors both for probes such as chromo-, fluoro-, and electrophores or catalytically active moieties and for modifying the interior of the dendrimer at predetermined positions. Facile access to a collection of third-generation polyether (Fréchet) type dendrimers with functional aryl bromides in the first (G1), second (G2), or third (G3) generation is provided. To prove that these functional groups can actually serve as anchors, *p-tert*-butylphenyl groups have been attached using Suzuki cross-coupling in all cases. To the best of our knowledge this is the first case where such a concept has been realized

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(1) Newkome, G. R.; Moorefield, C. N.; Vögtle, F. *Dendritic Molecules. Concepts, Syntheses, Perspectives*; VCH: Weinheim, 1996.

(2) Bosman, A. W.; Janssen, H. M.; Meijer, E. W. *Chem. Rev.* **1999**, *99*, 1665−1688. Schlüter, A. D.; Rabe, J. P. *Angew. Chem., Int. Ed.* **2000**, *39*, 864−883.

(3) For the numerous examples, see: Zeng, F.; Zimmerman, S. C. *Chem. Rev.* **1997**, *97*, 1681−1712. Newkome, G. R.; He, E.; Moorefield, C. N. *Chem. Rev.* **1999**, *99*, 1689−1746.

(4) Hawker, C. J.; Fréchet, J. M. J. *Macromolecules* **1990**, *23*, 4726−4279.

(5) For a dendrimer with hydroxy groups at every repeat unit and its use as a reverse micelle, see: Piotti, M. E.; Rivera, Jr., F.; Bond, R.; Hawker, C. J.; Fréchet, J. M. J.; *J. Am. Chem. Soc.* **1999**, *121*, 9471−9472. For a less specific incorporation of functionalities in a dendrimer, see: Lochmann, L.; Wooley, K. L.; Ivanova, P. T.; Fréchet, J. M. J. *J. Am. Chem. Soc.* **1993**, *115*, 7043−7044.

(6) Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Johnson, A. L.; Behera, R. K. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1176−1179. Newkome, G. R.; Moorefield, C. N. *Polym. Prepr.* **1993**, *34*, 75−76. Marx, H.-W.; Moulines, F.; Wagner, T.; Astruc, D. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1701−1704.

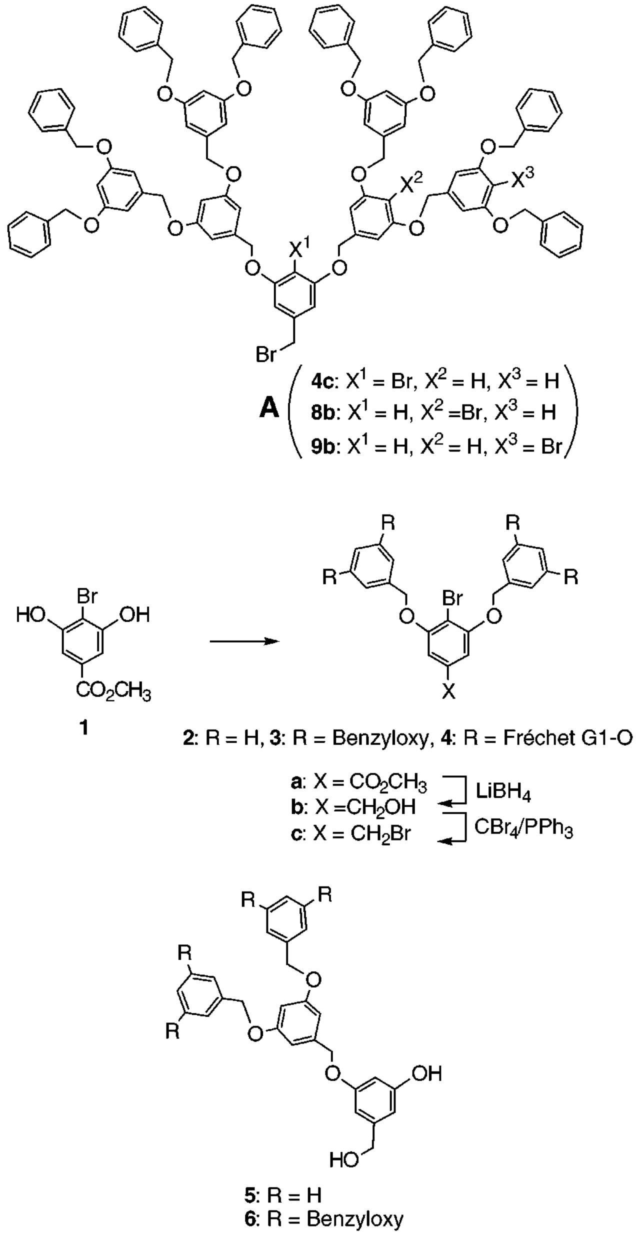
(7) For example, see: Jin, R.-H.; Aida, T.; Inoue, S. *J. Chem. Soc., Chem. Commun.* **1993**, 1260−1261. Dandliker, P. J.; Diederich, F.; Gross, M.; Knobler, K. B.; Lonati, A.; Sanford, E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1079−1083.

10.1021/ol005972q CCC: $19.00

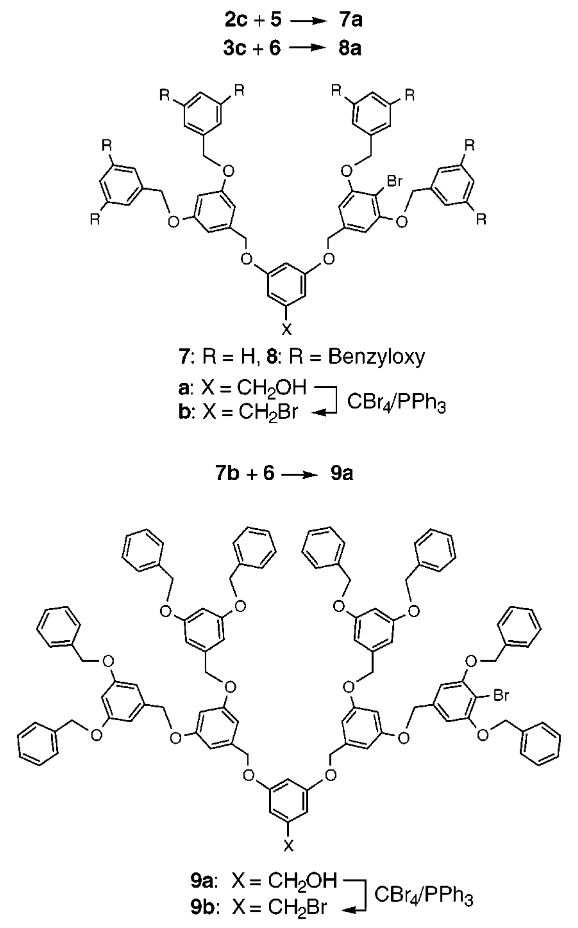
to the point where one can start to systematically explore and/or exploit the interior of a dendrimer in a generation-specific manner.[8]

The target G3 dendrons **A** have one bromo function at the branching point of the first (**4c**), second (**8b**), and third generation (**9b**), respectively (Scheme 1). Aryl bromides were chosen as anchor groups, because they easily undergo a Suzuki cross-coupling (SCC) reaction[9] in high yield, even in situations where considerable steric congestion can be expected in the interior of dendrimers. The synthetic sequence starts from the aromatic AB_2-type building block **1**, which already carries the required bromo function at C-4.[10] Reaction of **1** with benzyl bromide and Fréchet-type G1 and G2 bromides[11] under standard Williamson etherification conditions (K_2CO_3/acetone) gives the corresponding dendrons G1 (**2a**), G2 (**3a**), and G3 (**4a**) with esters at the focal point in high yields. $LiBH_4$ reduction furnishes the corresponding dendritic alcohols **2b**, **3b**, and **4b**, which are then converted to the corresponding bromides **2c**, **3c**, and **4c** by Appel bromination using CBr_4/PPh_3. The G2 and G3 dendrons **7a** and **8a** are obtained by reacting **2c** with phenol **5**, a "semi-dendron" [4] known in the literature, and **3c** with the corresponding "semi-dendron" **6**, respectively (Scheme 2). Appel bromination of **7a** and **8a** converts these alcohols into the corresponding bromides **7b** and **8b**. Finally, combination of the G2 bromide **7b** with **6** followed by Appel bromination yields the dendron **9b**.

Scheme 1



Scheme 2



For the synthesis of the target dendrimers **11a−c** (Scheme 3) the dendrons **4c**, **8b**, and **9b** are reacted with the last remaining phenoxy group of the trifunctional core, 1,1,1-tris(4′-hydroxyphenyl)ethane, which already carries two

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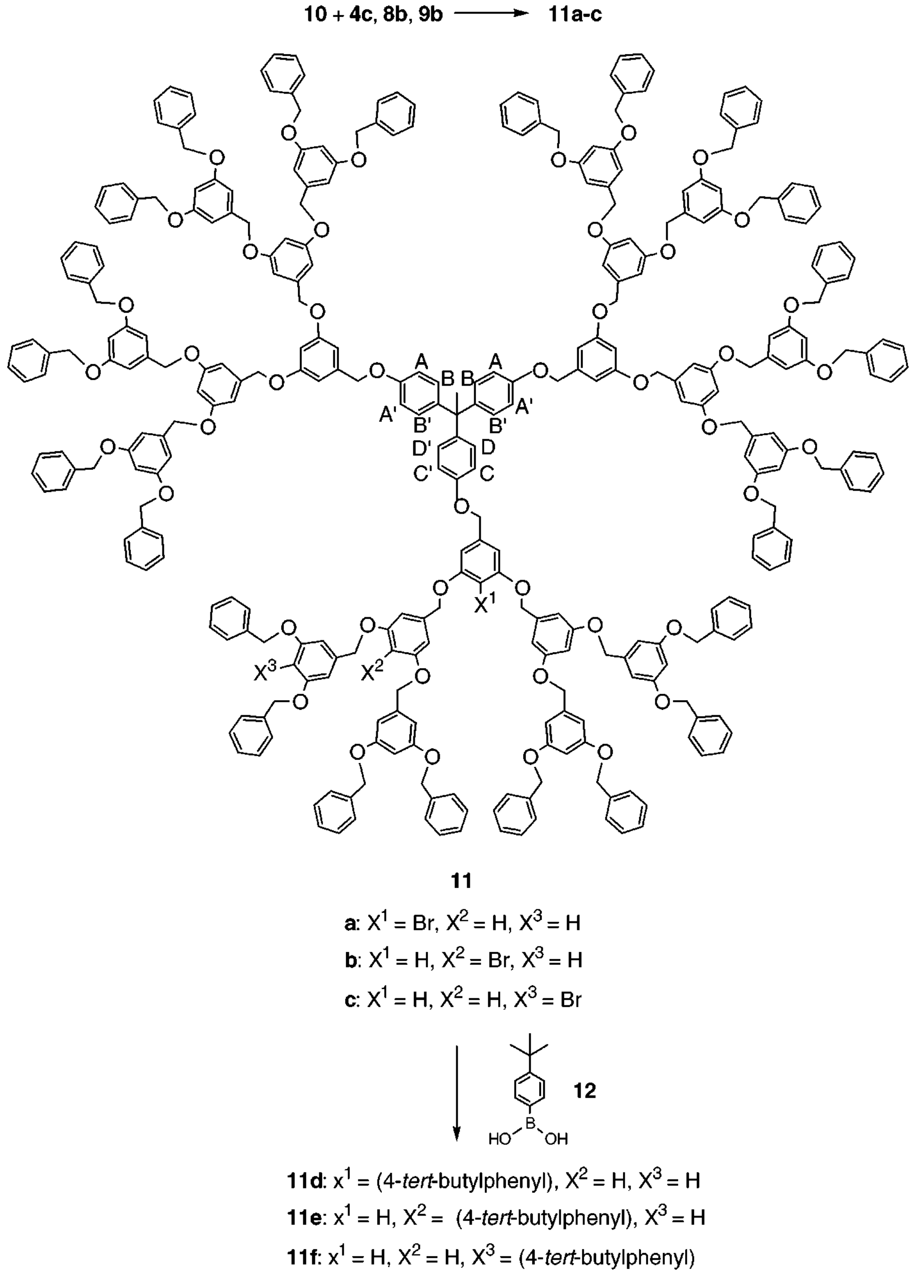
[8] Modrakowski, C.; Beinhoff, M.; Schlüter, A. D., manuscript in preparation.

[9] Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

[10] Compound **1** was obtained from the commercially available corresponding acid.

[11] Fréchet, J. M. J.; Wooley, K. L.; Hawker, C. J. *J. Am. Chem. Soc.* **1991**, *113*, 4252−4261.

Scheme 3



$10 + 4c, 8b, 9b \longrightarrow 11a\text{-}c$

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a: $X^1 = Br, X^2 = H, X^3 = H$

b: $X^1 = H, X^2 = Br, X^3 = H$

c: $X^1 = H, X^2 = H, X^3 = Br$

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11d: x^1 = (4-*tert*-butylphenyl), $X^2 = H, X^3 = H$

11e: $x^1 = H, X^2 =$ (4-*tert*-butylphenyl), $X^3 = H$

11f: $x^1 = H, X^2 = H, X^3 =$ (4-*tert*-butylphenyl)

regular (nonbrominated) Fréchet-type G3 dendrons (**10**,[4] structure not shown) under standard Williamson etherification conditions using Cs_2CO_3 as base and acetone as solvent. These dendrimers carry an aryl bromide function at one of the three branching units of the first (**11a**), at one of the six branching units of the second (**11b**), or at one of the 12 branching units of the third (**11c**) generation. The structure of the dendrimers was proven by high-field NMR spectroscopy, matrix-assisted laser desorption ionization time-of-flight (Maldi-tof), mass spectrometry, and elemental analysis. The purity was checked by gel permeation chromatography (GPC), NMR spectroscopy, and Maldi-tof. The GPC elution curves are monomodal with a polydispersity index of 1.01 in all three cases. The 500 MHz ^1H NMR spectra indicate a purity higher than 98%, and the mass spectra do not give any indication of side products. Specifically there is no signal for unreacted **10**.

In the next step we checked how far the bromo functions can be used as anchor groups. As a test reaction, dendrimers **11a**−**c** were reacted with 4-*tert*-butylbenzene boronic acid under SCC conditions. This boronic acid was chosen because its *tert*-butyl group can be easily and quantitatively identified by NMR spectroscopy. The SCC conditions were carried out for 5 d with a 5-fold excess of *p*-*tert*-butyl benzene boronic acid under standard reaction condition using 1−2 mol % of freshly prepared $Pd(PPh_3)_4$ and THF/1 M $NaHCO_3$ as the solvent system.

The crude products were purified by column chromatography and gave the modified dendrimers **11d**−**f** in isolated yields of 88%, 95%, and 97%, respectively (Scheme 3). The

GPC elution curves of these products are unchanged compared to those of their precursors, which is reasonable, because the spatial changes induced by the replacement of a bromo function result in a negligible change of the hydrodynamic volume.

The conversions of these reactions were determined by NMR integration to be 96% (**11d**), 97% (**11e**), and 99% (**11f**), respectively, and by comparing the intensities of the protons of the *tert*-butyl group ($\delta = 1.15$ ppm) with that of the 12 protons of the core AA′BB′ and CC′DD′ spin system centered at $\delta = 6.88$ ppm. Further support for the bromo group's complete replacement by *tert*-butylphenyl is the disappearance of the signal for the methylene protons near the bromo which absorbs in all cases baseline separated from all other methylenes at $\delta = 5.02$ (**11a**), 5.04 (**11b**), and 5.07 (**11c**).

Maldi-tof mass spectra of **11d−f** also reveal that the conversion is virtually quantitative. Only two peaks at 5190 and 5205 Da are observed, which are due to adducts of the respective dendrimer with sodium and potassium ions. Peaks of sodium or potassium adducts of the starting dendrimers at 5136 and 5152 Da of starting material cannot be observed. Thus, these replacements proceed quantitatively, which nicely underlines the potential as anchor groups for even the innermost bromine function.

Acknowledgment. This work was financially supported by the Deutsche Forschungsgemeinschaft (Sfb 448, TP A1) and the Fonds der Chemischen Industrie, which are gratefully acknowledged.

Supporting Information Available: Experimental details and spectroscopical data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL005972Q