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Efficient halogen–lithium exchange reactions to functionalize poly(alkyl aryl ether) dendrimers

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Abstract—Poly(alkyl aryl ether) dendrimers were functionalized with bromophenyl groups at their peripheries, so as to have 3, 6, 12, and 24 groups in the zero, first, second, and third generation dendrimers, respectively. The new bromophenyl functionalized dendrimers were assessed for their reactivities in C–heteroatom and C–C bond forming reactions. For this purpose, the bromophenyl functionalized dendrimers were converted quantitatively to their polylithiated derivatives, using *n*-BuLi in benzene. The polylithiated dendrimers were reacted either with D_2O or with CO_2, so as to afford the corresponding deuterated and carboxylic acid functionalized dendrimers, respectively. The carboxylic acid functionalized dendrimers were modified further to the methyl esters during their characterization.

1. Introduction

Alkyl- and aryllithium derivatives are versatile intermediates in organic and organometallic synthesis.[1] Most often the lithium derivatives are derived by exchange reactions involving alkyl- or arylhalide and a lithium source.[2] Lithiation of an alkyl- or an aryl substrate is one of the important reaction in the course of many C–C bond forming, C–heteroatom bond forming and C–varied metal bond forming reactions.[3] Many theoretical and synthetic studies have been reported due to wide utility of organolithium compounds.[4] Polylithiation of macromolecules represents a system wherein multiple simultaneous lithiations are performed and such polylithiated intermediates are then used to prepare a variety of functionalized macromolecules.[5] Uniformly branched dendritic macromolecules[6] are recent additions in polylithiations. Carbosilane-based dendrimers were the only ones explored thus far in terms of their polylithiation and further functionalization.[7] As a strategy to functionalize poly(alkyl aryl ether) dendrimers,[8] polylithiations of the dendrimers were undertaken, in an effort to exploit the rich lithiation chemistry as applicable to this class of dendrimers. The polylithiated dendrimers, obtained by a halogen–metal exchange reaction, were subjected to reactions with a few electrophiles. The syntheses and reactions of polylithiated dendrimers up to the third generation, which exhibit 24 peripheral lithiated arenes, are presented herein.

2. Results and discussion

Poly(alkyl aryl ether) dendrimers are constituted with phloroglucinol as the core and branching component and a pentamethylene as the linker connecting the branches. *endo*- and *exo*-Receptor properties of these dendrimers have been explored and beneficial effects of the dendritic architectures have been previously identified.[9] The poly(alkyl aryl ether) dendrimers exhibit multiple phenolic hydroxyl groups at their peripheries and the zero, first, second, and third generation dendrimers present 3, 6, 12, and 24 such groups, respectively.[8] These phenolic hydroxyl groups were utilized to install functionalities necessary for polylithiations. Bromophenyl functionality was chosen for its subsequent bromide–lithium exchange reaction. Multiple phenolic O-alkylation of the dendrimer peripheries with a bromophenyl group containing monomer was thus conducted across different generations of the poly(alkyl aryl ether) dendrimers.

2.1. Synthesis of bromophenyl group functionalized monomer

The bromophenyl group containing derivative **2** was obtained upon reaction of 1,5-dibromopentane with 4-bromophenol (**1**) (Scheme 1). The mono-O-alkylated product **2** was utilized to alkylate the peripheral phenolic groups of the dendrimers.

Keywords: Alkylation; C–C bond formation; Dendrimers; Lithiation.
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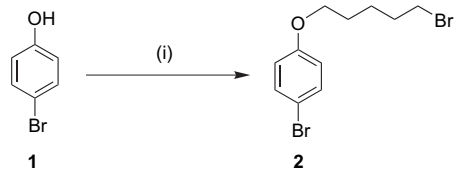
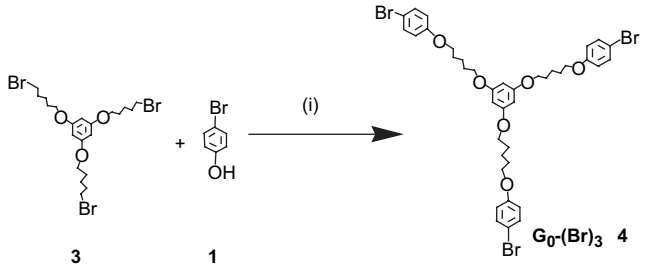


Scheme 1. (i) 1,5-Dibromopentane, K_2CO_3, 18-C-6, Me_2CO, 70 °C, 7 h, 80%.

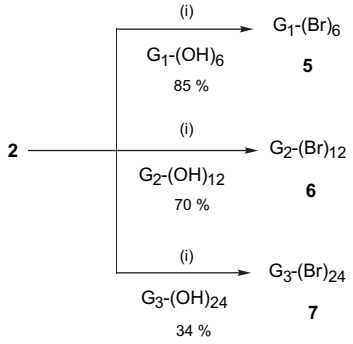
2.2. Synthesis of bromophenyl group functionalized dendrimer

The zero-generation dendrimer **4**, containing the bromophenyl group, was obtained by a three-fold alkylation of a tribromide **3** with 4-bromophenol, in good yields (Scheme 2).



Scheme 2. (i) K_2CO_3, 18-C-6, 2-butanone, 70 °C, 12 h, 86%.

The first, second, and third generation bromophenyl group containing dendrimers were obtained by multiple O-alkylation of the corresponding phenolic dendrimers with monomer **2**. The O-alkylations were performed in the presence of K_2CO_3 and 18-C-6 (cat.) in 2-butanone (DMF) and the bromophenyl terminated first (**5**), second (**6**), and third generation (**7**) dendrimers were obtained in moderate yields. The zero, first, second, and third generation dendrimers were thus functionalized with 3, 6, 12, and 24 bromophenyl groups at their peripheries, respectively (Scheme 3 and Fig. 1).



Scheme 3. (i) K_2CO_3, 18-C-6 (cat.), 2-butanone, DMF, reflux.

Dendrimers **4**–**7** were freely soluble in solvents such as, THF, PhMe, and MeOH whereas, their solubilities in MeOH, Et_2O, and hexane were moderate to poor. In terms of loading, the bromophenyl group constituted 3.53, 2.78, 2.52, and

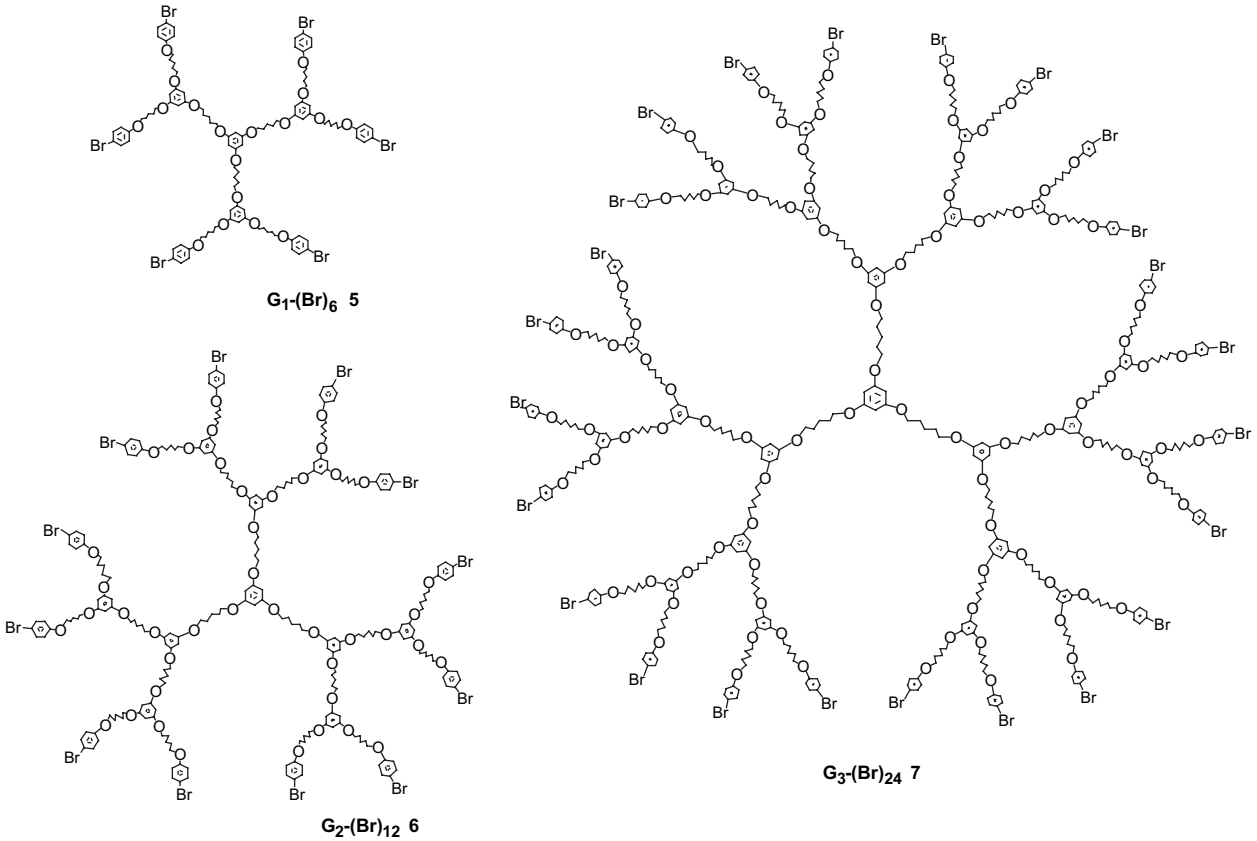


Figure 1. Molecular structures of bromophenyl group functionalized G_1-$(Br)_6$ (**5**), G_2-$(Br)_{12}$ (**6**), and G_3-$(Br)_{24}$ (**7**) dendrimers.

2.40 mmol/g in zero (**4**), first (**5**), second (**6**), and third (**7**) generation dendrimers, respectively.

2.3. Characterization

The constitutions and the structural homogeneities of the dendrimers were ascertained by ^{1}H and ^{13}C NMR spectroscopies and elemental analyses. Specifically, the phloroglucinol protons appeared as a singlet at 6.05 ppm and the bromophenyl moiety at ~6.70 and ~7.30 ppm, as a pair of doublets in the ^{1}H NMR spectra of the dendrimers. The CH (methine) and C (q) carbons of the phloroglucinol moiety appeared at ~93.5 and 160.5 ppm, respectively, in the ^{13}C NMR spectra. The resonances of CH (methine) and C (q) of the peripheral bromophenyl moieties were observed at ~116.0, ~132.0 and ~112.5, ~158.8 ppm, respectively. Mass spectral analysis by MALDI-TOF and ES methods, could not be accomplished even after several trials. Gel permeation chromatography was conducted to assess the GPC profiles of the dendrimers in THF as the eluant. The retention times of various generations were: **7**: 6.81 min; **6**: 7.37 min; **5**: 8.09 min; **4**: 9.13 min and monomer **2**: 10.63 min, consistent with the proposed M_r values.

2.4. Lithiations of bromophenyl functionalized dendrimers

Lithiation of the bromophenyl functionalized dendrimers was followed using lithium metal. The lithiated dendrimers would allow incorporation of various electrophiles in the course of carbon–heteroatom and carbon–carbon bond formation. Thus, lithiation reactions were conducted with the most widely used reagent and solvent, namely, *n*-BuLi and THF. Lithiation, followed by a subsequent reaction with an electrophile, was conducted across a series of dendrimers. In the event, it turned out that the electrophilic substituent on the product could not be identified. Rather, only the debromination of the bromophenyl functionality occurred. On the other hand, use of Et_2O as the solvent, in place of THF, allowed the reaction to proceed in the anticipated manner, leading to incorporation of the electrophile at the carbon subjected to the halogen–lithium exchange reaction. However, the successful reaction in Et_2O for the zero-generation dendrimer with three bromophenyl functionalities could not be extended to other dendrimers, due to the insolubility of the dendrimers in Et_2O. Benzene as the solvent of the reaction at ~50 °C was then identified for the lithiation reaction. Thus, the reaction of bromophenyl functionalized dendrimers **4**–**7**, in benzene at ~50 °C, afforded the lithiated derivatives **8**–**11** (Scheme 4).

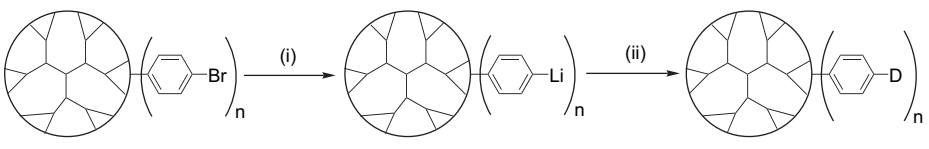
The lithiated derivatives precipitated as a white solid from the reaction mixture. Without isolation, lithiated products were reacted with electrophiles, so as to yield the C–heteroatom or C–C bond formed product. In one series, the lithiated derivatives were treated with D_2O (Scheme 4) and the deuterated dendrimers were obtained in good to excellent yields as the only isolable product of the reaction (Fig. 2).

Complete deuteration of the dendrimer peripheries was confirmed by the characteristic double doublet resonances, centered at 6.89 and 7.27 ppm, of the peripheral phenyl groups of the dendrimers in the ^{1}H NMR spectra. The corresponding ^{13}C NMR resonances for the deuterated phenyl group were observed at ~114.4, 129.3, 129.4, and 159.0 ppm. Elemental analyses of the deuterated products confirmed the structural homogeneities of the dendrimers.

Upon accomplishing deuteration of the lithiated dendrimers, efforts were focused to subject them to a C–C bond forming reaction. Specifically, the reaction mixture containing the lithiated product was treated with CO_2 (g), at 0 °C for ~45 min and left to stir further at room temperature for 15 h. Acidification of the reaction mixture with aq HCl afforded a precipitate, which was then triturated with ice-cold water. The precipitate was dried further to afford the carboxylic acid functionalized dendrimers **16**–**19** (Scheme 5 and Fig. 3).

Dendrimers **16**–**19** were viscous hygroscopic solids and thus were derivatized as the methyl ester derivatives (Scheme 5). Treatment of the carboxylic acid functionalized dendrimers with MeOH, in the presence of H_2SO_4 (cat.), refluxing the reaction mixture for ~24 h, work-up, and purification afforded the carboxylic acid methyl ester derivatives of the dendrimers **20**–**23** (Fig. 3). The constitutions of the methyl ester functionalized dendrimer were ascertained by spectroscopic methods and elemental analysis. Syntheses of a series of deuterated and carboxylic acid functionalized dendrimers thus illustrated the efficient formation of lithiated dendrimers from the corresponding bromide derivatives.

Only the polysilane dendrimers have thus far been explored for their lithiation reactions, followed by reactions with electrophiles.[7] Within the polysilane dendrimers, the largest dendrimer contained up to 12 lithiated centers at the peripheries of the dendrimers. The studies reported herein add to the



n = 3 **4**
n = 6 **5**
n = 12 **6**
n = 24 **7**

n = 3 **8**
n = 6 **9**
n = 12 **10**
n = 24 **11**

n = 3 **12**
n = 6 **13**
n = 12 **14**
n = 24 **15**

Scheme 4. (i) *n*-BuLi, PhH, 50 °C, 45 min and (ii) D_2O, rt, 15 h.

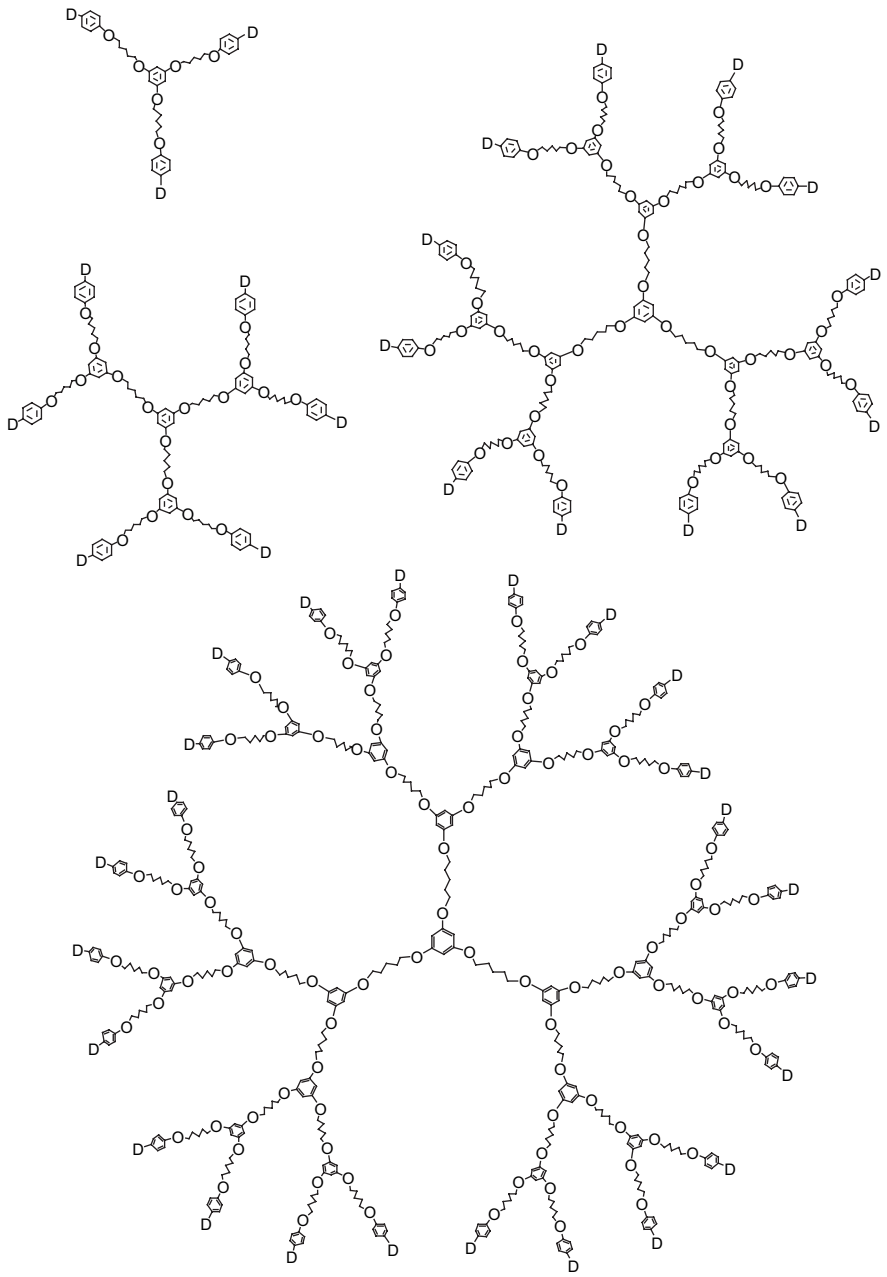
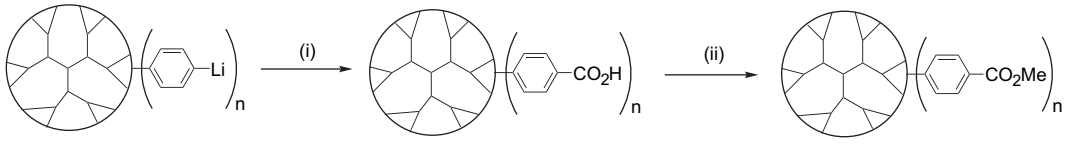


Figure 2. Molecular structures of deuterated G_0-$(D)_3$ (**12**) and G_1-$(D)_6$ (**13**) and G_2-$(D)_{12}$ (**14**) and G_3-$(D)_{24}$ (**15**) dendrimers.



n = 3 **8**
n = 6 **9**
n = 12 **10**
n = 24 **11**

n = 3 **16**
n = 6 **17**
n = 12 **18**
n = 24 **19**

n = 3 **20**
n = 6 **21**
n = 12 **22**
n = 24 **23**

Scheme 5. (i) CO_2 (gas), rt, 15 h and (ii) MeOH, H_2SO_4 (cat.), reflux, 24 h.

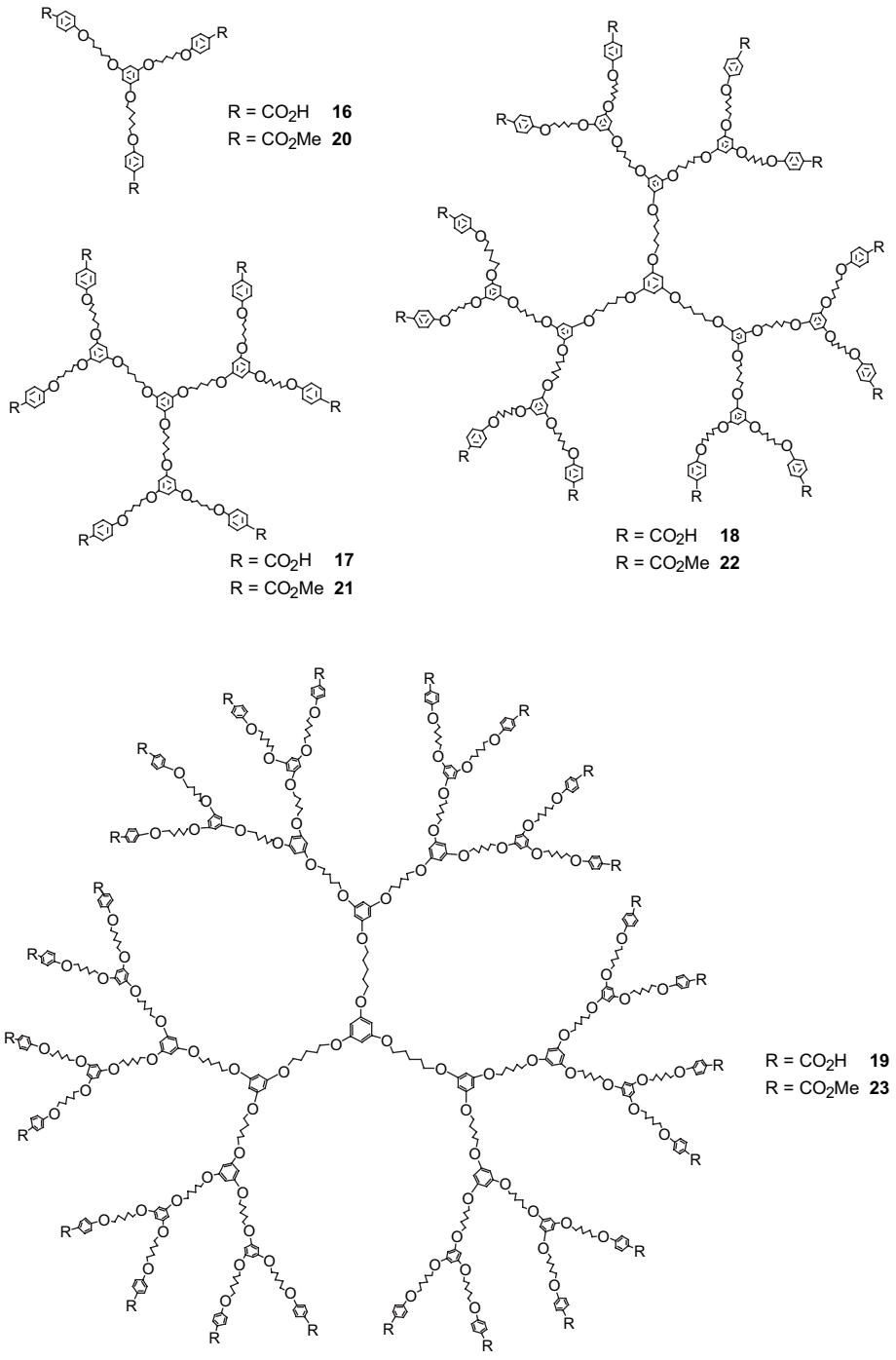


Figure 3. Molecular structures of carboxylic acid and methyl ester functionalized poly(alkyl aryl ether) dendrimers.

efforts targeting the widely practiced lithiations into the general area of dendrimer chemistry.

3. Conclusion

Poly(alkyl aryl ether) dendrimers, having up to 24 bromophenyl functionalities at their peripheries, were explored for their efficacies in lithiation reactions. The halide–lithium exchange reaction was found to be facile and the resulting lithiated dendrimers underwent reactions with deuterium and carbon electrophiles, leading, respectively, to deuterated and carboxylated dendrimers. Having established the formation of lithiated dendrimers, reaction of such dendrimers with varied electrophiles will be conducted further.

4. Experimental

4.1. General methods

Chemicals were purchased from commercial sources and were used without further purification. Powdered K_2CO_3 (Ar grade) was dried at 120 °C for 24 h before being used.

Solvents were dried and distilled according literature procedures.[10] Analytical TLC was performed on commercial Merck plates coated with silica gel GF_{254} (0.25 mm). Silica gel (230–400 mesh) was used for column chromatography. Melting points determined are uncorrected. Microanalyses were performed on an automated C, H, N analyzer. Benzene is a carcinogenic substance. Experiments involving this solvent were performed using safety gloves and in a well-ventilated fume hood. ^1H and ^{13}C NMR spectral analyses were performed on a 300 MHz or 400 MHz and 75 MHz spectrometer, respectively, with residual solvent signal acting as the internal standard. The following abbreviations are used to explain the multiplicities: s, singlet; d, doublet; t, triplet; m, multiplet; band, several overlapping signals, and br, broad. In addition, the following abbreviations are used to denote various carbon nuclei: Ar. (q) and Ar. (t) for phloroglucinol (quaternary) and phloroglucinol (tertiary), respectively; periphery Ar. (q) and periphery Ar. (t) for peripheral aromatic (quaternary) and aromatic (tertiary), respectively.

4.1.1. Synthesis of monomer 2. 4-Bromophenol (3.0 g, 17.3 mmol), 1,5-dibromopentane (8.44 g, 36.77 mmol), K_2CO_3 (2.4 g, 17.3 mmol), and 18-crown-6 (cat.) were dissolved in acetone (50 mL) and refluxed for 7 h. The reaction mixture was cooled, filtered, the solvents were removed under reduced pressure, and the residue was dissolved in $CHCl_3$ (100 mL) and washed with H_2O (2×100 mL). The organic layer was concentrated, dried (Na_2SO_4), and purified by column chromatography (100–200 mesh, SiO_2, petroleum ether/EtOAc=95:5) to afford the required mono-alkylated monomer **2** as a waxy solid (4.5 g, 80%, relative to 4-bromophenol). R_f 0.60 (petroleum ether/EtOAc=95:5). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.58 (m, 2H), 1.78 (m, 2H), 1.91 (m, 2H), 4.32 (t, J=6.6 Hz, 2H), 3.91 (t, J=6.3 Hz, 2H), 6.75 (d, J=9.3 Hz, 2H), 7.34 (d, J=9.3 Hz, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 24.8, 28.3, 32.4, 33.5, 67.8, 112.7 (periphery Ar. (q)), 116.3 (periphery Ar. (t)), 132.2 (periphery Ar. (t)), 158.1 (periphery Ar. (q)); Anal. Calcd for $C_{11}H_{14}OBr_2$: C, 41.03; H, 4.38. Found: C, 41.07; H, 4.57.

4.1.2. G_0-Br_3 (4). A mixture of **3** (0.618 g, 1.079 mmol), **1** (0.671 g, 3.88 mmol), K_2CO_3 (0.536 g, 3.88 mmol), and 18-C-6 (cat.) in 2-butanone (20 mL) was stirred at 70 °C for 12 h. The reaction mixture was filtered and solvents were then removed in vacuo, the resulting residue was dissolved in CH_2Cl_2, washed with water, dried, concentrated, and purified (SiO_2, PhMe/EtOAc=98:2) to afford **4**, as a white solid (0.84 g, 92%). Mp: 67–69 °C. TLC R_f 0.62 (PhMe/EtOAc=98:2). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.63 (m, 6H), 1.82 (m, 12H), 3.92 (t, J=6.6 Hz, 12H), 6.05 (s, 3H), 6.75 (d, J=9.3 Hz, 6H), 7.34 (d, J=9.3 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.8, 28.9, 67.7, 67.9, 93.8 (Ar. (t)), 112.6 (periphery Ar. (q)), 116.2 (periphery Ar. (t)), 132.1 (periphery Ar. (t)), 158.1 (periphery Ar. (q)), 160.8 (Ar. (q)); GC–MS m/z: 850 $[M]^+$; Anal. Calcd for $C_{39}H_{45}Br_3O_6$: C, 55.14; H, 5.34. Found: C, 55.27; H, 5.34.

4.1.3. G_1-Br_6 (5). A mixture of G_1-$(OH)_6$ (0.3 g, 0.423 mmol), **2** (1.05 g, 3.04 mmol), K_2CO_3 (0.42 g, 3.04 mmol), and 18-C-6 (cat.) in 2-butanone (20 mL) and DMF (2 mL) was heated at 70 °C for 36 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated. Excess of **2** was removed by triturating the crude residue with Et_2O and the resulting residue was purified further (SiO_2, PhMe/EtOAc=95:5) to afford **5**, as a colorless oil (0.77 g, 85%). TLC R_f 0.71 (PhMe/EtOAc=96:4). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.64 (m, 18H), 1.83 (m, 36H), 3.93 (t, J=6.3 Hz, 36H), 6.06 (s, 12H), 6.76 (d, J=9.3 Hz, 12H), 7.34 (d, J=9.3 Hz, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 67.7, 68.0, 93.9 (Ar. (t)), 112.7 (periphery Ar. (q)), 116.3 (periphery Ar. (t)), 132.2 (periphery Ar. (t)), 158.2 (periphery Ar. (q)), 160.7 (Ar. (q)); Anal. Calcd for $C_{105}H_{126}Br_6O_{18}$: C, 58.51; H, 5.89. Found: C, 58.77; H, 6.19.

4.1.4. G_2-Br_{12} (6). A mixture of G_2-$(OH)_{12}$ (0.2 g, 0.423 mmol), **2** (0.527 g, 1.536 mmol), K_2CO_3 (0.21 g, 1.536 mmol), and 18-C-6 (cat.) in 2-butanone (15 mL) and DMF (5 mL) was heated at 70 °C for 36 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated. Excess of **2** was removed by triturating the crude residue with Et_2O and the resulting residue was purified further (SiO_2, PhMe/EtOAc=95:5) to afford **6**, as a colorless oil (0.374 g, 70%). TLC R_f 0.54 (PhMe/EtOAc=98:2). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.60 (m, 42H), 1.80 (m, 84H), 3.92 (m, 84H), 6.06 (s, 30H), 6.75 (d, J=9.0 Hz, 24H), 7.34 (d, J=9.0 Hz, 24H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 15.2, 22.7, 65.8, 67.6, 67.9, 93.8 (Ar. (t)), 112.6 (periphery Ar. (q)), 116.2 (periphery Ar. (t)), 132.1 (periphery Ar. (t)), 158.1 (periphery Ar. (q)), 160.8 (Ar. (q)); Anal. Calcd for $C_{237}H_{288}Br_{12}O_{42}$: C, 59.71; H, 6.09. Found: C, 59.27; H, 5.92.

4.1.5. G_3-Br_{24} (7). A mixture of G_3-$(OH)_{24}$ (0.15 g, 0.036 mmol), **2** (0.353 g, 1.03 mmol), K_2CO_3 (0.143 g, 1.03 mmol), and 18-C-6 (cat.) in 2-butanone (15 mL) and DMF (2 mL) was heated at 100 °C for 96 h. Solvents were then removed in vacuo and the resulting residue was dissolved in CH_2Cl_2, washed with water, dried (Na_2SO_4), and concentrated. Excess of **2** was removed by triturating the crude residue with MeOH and the resulting residue was purified further (SiO_2, PhMe/EtOAc=95:5) to afford **7**, as a brown oil (0.12 g, 34%). TLC R_f 0.40 (PhMe/EtOAc=98:2). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.61 (m, 90H), 1.81 (m, 180H), 3.92 (m, 180H), 6.05 (s, 66H), 6.74 (d, J=8.4 Hz, 48H), 7.33 (d, J=8.4 Hz, 48H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 29.0, 67.6, 67.9, 93.8 (Ar. (t)), 112.6 (periphery Ar. (q)), 116.2 (periphery Ar. (t)), 132.1 (periphery Ar. (t)), 158.1 (periphery Ar. (q)), 160.8 (Ar. (q)); Anal. Calcd for $C_{501}H_{612}Br_{24}O_{90}$: C, 60.22; H, 6.17. Found: C, 59.90; H, 6.29.

4.2. General procedure for the synthesis of deuterated dendrimers

Dendrimer (1.0 equiv) was dissolved in benzene (2 mL) and the system was charged with an inert atmosphere (N_2 atm). *n*-BuLi (2.0 equiv per bromophenyl group) was added and warmed to 50 °C for 45 min. The white precipitate was cooled to 0 °C and D_2O (99.9 atom %, Aldrich, 2.0 equiv per bromophenyl group) was added slowly over a period of 5 min and the reaction mixture was allowed to stir at room temperature for another 15 h. Solvents were removed under reduced pressure, washed with $CHCl_3$ (10 mL), and

H_2O (2×5 mL). The organic layer was dried (Na_2SO_4) and concentrated to afford the required deuterated dendrimers in good yield.

4.2.1. G_0-$(D)_3$ (12). G_0-$(Br)_3$ (62 mg, 0.073 mmol). G_0-$(D)_3$ (40 mg, 90%). TLC R_f 0.50 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64 (m, 6H), 1.88 (m, 12H), 3.94 (m, 12H), 6.07 (s, 3H), 6.89 (d, J=8.7 Hz, 6H), 7.27 (d, J=8.7 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 29.0, 29.1, 67.6, 67.7, 93.8 (Ar. (t)), 114.4 (periphery Ar. (t)), 129.3 (periphery Ar. (t)), 129.4 (periphery Ar. (t)), 159.0 (periphery Ar. (q)), 160.8 (Ar. (q)); HRMS *m/z*: 850 $[M]^+$; Anal. Calcd for $C_{39}H_{45}D_3O_6$: C, 76.06; H, 8.35. Found: C, 76.00; H, 8.37.

4.2.2. G_1-$(D)_6$ (13). G_1-$(Br)_6$ (40 mg, 0.019 mmol). G_1-$(D)_6$ (27 mg, 86%). TLC R_f 0.55 (PhMe/EtOAc=96:4). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64 (m, 18H), 1.82 (m, 36H), 3.97 (m, 36H), 6.06 (s, 12H), 6.89 (d, J=8.4 Hz, 12H), 7.26 (d, J=8.4 Hz, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 29.0, 67.6, 67.7, 68.0, 93.8 (Ar. (t)), 114.5 (periphery Ar. (t)), 129.4 (periphery Ar. (t)), 129.5 (br Ar. (t)), 159.0 (periphery Ar. (q)), 160.8 (Ar. (q)); Anal. Calcd for $C_{105}H_{126}D_6O_{18}$: C, 74.70; H, 8.24. Found: C, 74.39; H, 7.93.

4.2.3. G_2-$(D)_{12}$ (14). G_2-$(Br)_{12}$ (35 mg, 7.34 μmol). G_2-$(D)_{12}$ (20 mg, 71%). TLC R_f 0.51 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.64 (m, 42H), 1.84 (m, 84H), 3.94 (m, 84H), 6.06 (s, 30H), 6.88 (d, J=8.4 Hz, 24H), 7.26 (d, J=8.4 Hz, 24H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 29.0, 67.6, 67.7, 93.8 (Ar. (t)), 114.4 (periphery Ar. (t)), 129.3 (periphery Ar. (t)), 129.4 (br Ar. (t)), 159.0 (periphery Ar. (q)), 160.8 (Ar. (q)); Anal. Calcd for $C_{237}H_{288}D_{12}O_{42}$: C, 74.26; H, 8.20. Found: C, 74.10; H, 7.98.

4.2.4. G_3-$(D)_{24}$ (15). G_3-$(Br)_{24}$ (30 mg, 3.0 μmol). G_3-$(D)_{24}$ (18 mg, 75%). TLC R_f 0.35 (PhMe/EtOAc=98:2). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.62 (m, 90H), 1.81 (m, 180H), 3.91 (m, 180H), 6.05 (s, 66H), 6.78 (br d, 48H), 7.25 (br d, 48H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 29.0, 67.6, 67.8, 93.8 (Ar. (t)), 114.6 (periphery Ar. (t)), 129.3 (periphery Ar. (t)), 129.4 (periphery Ar. (t)), 159.0 (periphery Ar. (q)), 160.8 (Ar. (q)); Anal. Calcd for $C_{501}H_{612}D_{24}O_{90}$: C, 74.08; H, 8.19. Found: C, 72.87; H, 7.96.

4.3. General procedure for the synthesis of carboxylic acid functionalized dendrimers

Dendrimer (1.0 molar equiv) was dissolved in benzene (2 mL) and the system was charged with inert atmosphere (N_2 atm). *n*-BuLi (2.0 molar equiv) was added and warmed to 50 °C for 45 min. The white precipitate was cooled to 0 °C and CO_2 (g) was passed over a period of 45 min and allowed to stir at room temperature for 15 h. The reaction mixture was cooled to 0 °C, ice was added, allowed to stir for 30 min, followed by the addition of concd HCl (0.5 mL). The pink color precipitate was separated by filtration, washed with ice-cold water (50 mL), co-evaporated with benzene (5×2 mL), and dried to afford the acid functionalized dendrimers, as a light pink color solid.

4.3.1. G_0-$(CO_2H)_3$ (16). G_0-$(Br)_3$ (60 mg, 0.071 mmol). G_0-$(CO_2H)_3$ (40 mg, 63%). Mp: 81.4–83.4 °C. IR (KBr, cm^{-1}): 3430.7, 1685.5, 1606.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.55 (m, 6H), 1.76 (m, 12H), 3.97-4.03 (m, 12H), 6.21 (s, 3H), 6.99 (d, J=8.0 Hz, 6H), 7.87 (d, J=8.0 Hz, 6H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 22.0, 22.1, 22.2, 28.1, 28.3, 67.7, 68.0, 92.1 (Ar. (t)), 114.1 (periphery Ar. (t)), 123.1 (periphery Ar. (q)), 131.3 (periphery Ar. (t)), 156.6 (Ar. (q)), 162.2 (periphery Ar. (q)), 167.1 (carbonyl).

4.3.2. G_1-$(CO_2H)_6$ (17). G_1-$(Br)_6$ (56 mg, 0.026 mmol). G_0-$(CO_2H)_3$ (45 mg, 90%). IR (KBr, cm^{-1}): 3436.5, 1685.5, 1604.5; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.64 (m, 18H), 1.82 (m, 36H), 4.03–4.06 (m, 36H), 6.26 (s, 12H), 7.01 (d, J=8.4 Hz, 12H), 7.94 (d, J=8.4 Hz, 12H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 21.7, 22.0, 22.2, 28.1, 28.2, 28.3, 67.7, 67.9, 92.1 (Ar. (t)), 114.2 (periphery Ar. (t)), 114.4 (periphery Ar. (t)), 122.9 (periphery Ar. (q)), 131.3 (periphery Ar. (t)), 156.6 (Ar. (q)), 162.2 (periphery Ar. (q)), 167.1 (carbonyl).

4.3.3. G_2-$(CO_2H)_{12}$ (18). G_2-$(Br)_{12}$ (50 mg, 0.011 mmol). G_2-$(CO_2H)_{12}$ (38 mg, 84%). IR (KBr, cm^{-1}): 3436.5, 1637.5, 1604.5; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.49 (m, 42H), 1.71 (m, 84H), 3.94 (m, 84H), 6.17 (s, 30H), 6.92 (br s, 24H), 7.85 (br s, 24H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 22.0, 22.1, 22.2, 28.2, 28.3, 67.7, 68.0, 92.1 (Ar. (t)), 114.2 (periphery Ar. (t)), 114.4 (periphery Ar. (t)), 123.2 (Ar. (q)), 131.4 (periphery Ar. (t)), 156.7 (Ar. (q)), 162.2 (periphery Ar. (q)), 167.2 (carbonyl).

4.3.4. G_3-$(CO_2H)_{24}$ (19). G_2-$(Br)_{12}$ (36 mg, 3.6 μmol). G_2-$(CO_2H)_{12}$ (20 mg, 60%). IR (KBr, cm^{-1}): 3424.8, 1683.6, 1606.4; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.62 (m, 90H), 1.81 (m, 180H), 3.91 (m, 180H), 6.05 (s, 66H), 6.78 (br d, 48H), 7.25 (br d, 48H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ: 21.9, 22.0, 28.2, 28.3, 67.7, 68.0, 92.2 (Ar. (t)), 114.2 (periphery Ar. (t)), 114.4 (periphery Ar. (t)), 123.1 (periphery Ar. (q)), 131.3 (periphery Ar. (t)), 156.6 (Ar. (q)), 162.2 (periphery Ar. (q)), 167.1 (carbonyl).

4.4. Esterification of carboxylic acid functionalized dendrimers

To a solution of acid functionalized dendrimer in methanol a catalytic amount of concd H_2SO_4 was added and refluxed for 24 h. Solvents were removed in vacuo, the crude reaction mixture was washed with $CHCl_3$ and H_2O. The organic layer was dried (Na_2SO_4), concentrated, and purified by column chromatography (SiO_2, 100–200 mesh) to afford the corresponding ester functionalized dendrimers as a glassy material.

4.4.1. G_0-$(CO_2Me)_3$ (20). Yield: 81%. TLC R_f 0.48 (PhMe/EtOAc=9:1). IR (KBr, cm^{-1}): 1724.1; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.67 (m, 6H), 1.87 (m, 12H), 3.88 (s, 9H), 3.94 (t, J=6.3 Hz, 6H), 4.03 (t, J=6.3 Hz), 6.06 (s, 3H), 6.90 (d, J=9.0 Hz, 6H), 7.98 (d, J=9.0 Hz, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 51.80, 67.7, 67.9, 93.8 (Ar. (t)), 114.03 (periphery Ar. (t)), 122.4 (periphery Ar. (q)), 131.6 (periphery Ar. (t)), 160.9 (Ar. (q)), 162.8 (Ar. (q)), 166.9 (carbonyl); HRMS *m/z*: 809.1497 $[M+Na]^+$; Anal. Calcd for $C_{45}H_{54}O_{12}$: C, 68.68; H, 6.92. Found: C, 68.87; H, 7.04.

4.4.2. G_1-$(CO_2Me)_6$ (21). Yield: 90%. TLC R_f 0.37 (PhMe/EtOAc=8:2). IR (KBr, cm^{-1}): 1724.1, 1712.5; ^{1}H NMR

(300 MHz, $CDCl_3$) δ: 1.67 (m, 18H), 1.84 (m, 36H), 3.88 (s, 18H), 3.94 (m, 12H), 4.02 (m, 24H), 6.06 (s, 12H), 6.89 (d, J=9.3 Hz, 12H), 7.97 (d, J=9.3 Hz, 12H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.8, 28.9, 51.80, 67.7, 67.9, 93.8 (Ar. (t)), 114.0 (periphery Ar. (t)), 122.4 (periphery Ar. (q)), 131.5 (periphery Ar. (t)), 160.8 (Ar. (q)), 162.8 (periphery Ar. (q)), 166.9 (carbonyl); Anal. Calcd for $C_{117}H_{144}O_{30}$: C, 69.21; H, 7.15. Found: C, 69.37; H, 7.08.

4.4.3. G_2-$(CO_2Me)_{12}$ (22). Yield: 84%. TLC R_f 0.45 (PhMe/EtOAc=7:3). IR (KBr, cm^{-1}): 1724.1, 1716.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.67 (m, 42H), 1.84 (m, 84H), 3.88 (s, 36H), 3.94 (m, 60H), 4.02 (m, 24H), 6.06 (s, 30H), 6.89 (d, J=9.3 Hz, 24H), 7.97 (d, J=9.3 Hz, 24H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 29.0, 51.9, 67.7, 67.9, 93.9 (Ar. (t)), 114.0 (periphery Ar. (t)), 122.4 (periphery Ar. (q)), 131.6 (periphery Ar. (t)), 160.9 (Ar. (q)), 162.8 (periphery Ar. (q)), 166.9 (carbonyl); Anal. Calcd for $C_{261}H_{324}O_{66}$: C, 69.39; H, 7.23. Found: C, 69.53; H, 7.07.

4.4.4. G_3-$(CO_2Me)_{24}$ (23). Yield: 76%. TLC R_f 0.41 (PhMe/EtOAc=7:3). IR (KBr, cm^{-1}): 1724.1, 1716.6; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.63 (m, 90H), 1.85 (m, 180H), 3.88 (s, 72H), 3.94 (m, 132H), 4.03 (t, J=6.3 Hz, 48H), 6.06 (s, 66H), 6.89 (d, J=10.8 Hz, 48H), 7.97 (d, J=10.8 Hz, 48H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ: 22.7, 28.9, 29.2, 29.5, 51.8, 67.9, 93.8 (Ar. (t)), 114.0 (periphery Ar. (t)), 120.1 (periphery Ar. (q)), 131.6 (periphery Ar. (t)), 160.9 (Ar. (q)), 162.8 (periphery Ar. (q)), 165.6 (carbonyl); Anal. Calcd for $C_{549}H_{684}O_{138}$: C, 69.47; H, 7.26. Found: C, 69.63; H, 7.06.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.052.

References and notes

1. (a) Mallan, J. M.; Bebb, R. L. *Chem. Rev.* **1969**, *69*, 693; (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300; (c) *Top. Curr. Chem.* **1987**, *138*, 1–226.
2. (a) Sotomayer, N.; Lete, E. *Curr. Org. Chem.* **2003**, *7*, 275; (b) Strohmann, C.; Schildbach, D. *Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, UK, 2004; p 941.
3. Najera, C.; Sansano, J. M.; Yus, M. *Tetrahedron* **2003**, *59*, 9255.
4. (a) Maercker, A.; Theis, M. *Top. Curr. Chem.* **1987**, *138*, 1; (b) Jemmis, E. D.; Gopakumar, G. *Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, UK, 2004; p 1.
5. (a) Brix, B.; Clark, T. *J. Org. Chem.* **1988**, *53*, 3365; (b) Itsuno, S.; Shimizu, K.; Ito, K. *Tetrahedron Lett.* **1992**, *33*, 6339; (c) Yus, M.; Gomez, C.; Candela, P. *Tetrahedron* **2003**, *59*, 1909; (d) Quirk, R. P.; Guo, Y.; Wesdemiotis, C.; Arnould, M. A. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 2435; (e) Matmour, R.; Lebreton, A.; Tsitsilianis, C.; Kallitsis, I.; Heroguez, V.; Gnanou, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 284.
6. (a) *Top. Curr. Chem.* **1998**, *197*, 1–240; (b) *Top. Curr. Chem.* **2000**, *210*, 1–311; (c) *Top. Curr. Chem.* **2001**, *212*, 1–298; (d) *Top. Curr. Chem.* **2002**, *217*, 1–243.
7. (a) Vasilenko, N. G.; Getmanova, E. V.; Myakushev, V. D.; Rebrov, E. A.; Moller, M.; Muzafarov, A. M. *Vysokomol. Soedin., Ser. A Ser. B* **1997**, *39*, 1449; (b) Wijkens, P.; Jastrzebski, J. T. B. H.; van der Schaaf, P. A.; Kolly, R.; Hofner, A.; van Koten, G. *Org. Lett.* **2000**, *2*, 1621; (c) Meijboom, R.; Hutton, A. T.; Moss, J. R. *Organometallics* **2003**, *22*, 1811.
8. Nithyanandhan, J.; Jayaraman, N. *J. Org. Chem.* **2002**, *67*, 6282.
9. (a) Nithyanandhan, J.; Davis, R.; Das, S.; Jayaraman, N. *Chem.—Eur. J.* **2004**, *10*, 689; (b) Kaanumalle, L. S.; Nithyanandhan, J.; Pattabiraman, M.; Jayaraman, N.; Ramamurthy, V. *J. Am. Chem. Soc.* **2004**, *126*, 8999; (c) Nithyanandhan, J.; Jayaraman, N. *Tetrahedron* **2005**, *61*, 11184; (d) Kaanumalle, L. S.; Ramesh, R.; Murthy Maddipatla, V. S. N.; Nithyanandhan, J.; Jayaraman, N.; Ramamurthy, V. *J. Org. Chem.* **2005**, *70*, 5062.
10. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.