

클릭 화학에 의한 폴리(벤질에테르)덴드리머의 효율적인 합성

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Synthesis of Poly(benzyl ether) Dendrimers by Click Chemistry

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초록: 프레체형태 덴드리머의 합성을 위한 연결 방법이 알카인과 아지드기 사이의 클릭 화학을 이용하여 개발되었다. 덴드리머의 핵으로 작용할 수 있는 단위체인 4,4'-(3,5-비스(아지도프로필옥시)벤질옥시)비스페닐이 알카인 덴드론과 클릭 반응을 통해 덴드리머의 구축을 위해 사용되었다. 즉, 구리촉매 존재하에서 다중(아지드)화합물과 말단 알킨기를 가지는 폴리(벤질에테르)덴드론 사이의 클릭 반응을 통해 덴드리머의 합성 전략이 완성되었다.

Abstract: The stitching method for the synthesis of Fréchet-type dendrimers was elaborated using click chemistry between an alkyne and an azide. The core building block, 4,4'-(3,5-bis(azidopropoxy)benzyloxy)bisphenyl, was designed to serve as the azide functionalities for dendrimer growth via click reactions with the alkyne-dendrons. The synthetic strategy involved an 1,3-dipolar cycloaddition reaction between an azide and an alkyne-functionalized Fréchet-type dendrons in the presence of Cu(I) species which is known as the best example of click chemistry.

Keywords: alkyne, azide, click chemistry, fréchet-type dendrimers.

Introduction

Dendrimers, which are prepared by repetition of a given set of reactions using either divergent or convergent strategies, are highly branched and regular macromolecules with well-defined structures and have served as functional objects in nanotechnology and nanoscience.^{1,2} The convergent approach to dendrimer synthesis introduced by Fréchet and co-workers revolutionized the synthetic approaches to monodisperse dendrimers.^{3,4} The convergent methodology installs the core in the final step, enabling the incorporation of functionalities. It provides greater structural control than the divergent approach due to its relatively low number of coupling reactions at each growth step. The ability to prepare well-defined (un)symmetrical dendrimers is the most attractive features of the convergent synthesis. The convergent approach allows

for a large degree of chemical diversity such that functional groups can be incorporated at nearly central position in the dendritic architecture.

Although recent research emphasis seems to shift from the synthesis of novel dendrimers to their properties and potential applications, future more expanded applications of dendrimers rely on efficient and practical synthetic procedures. Recently, click chemistry,⁵ the copper-catalyzed 1,3-dipolar cycloaddition reaction between an alkyne and an azide, has attracted much attention in the synthesis of dendrimers^{6,7} and dendritic and polymer materials.⁸⁻¹⁰ In the convergent synthesis of the dendrimers, two feasible methods are the fusion of two dendrons and the stitch of multi-functional group with dendrons. We have developed the fusion and stitching methods for the synthesis of symmetric and unsymmetric dendrimers and diblock codendrimers using click chemistry between an alkyne and an azide.⁷ Taking advantage of this fact, herein we report the synthesis of Fréchet-type dendrimers by

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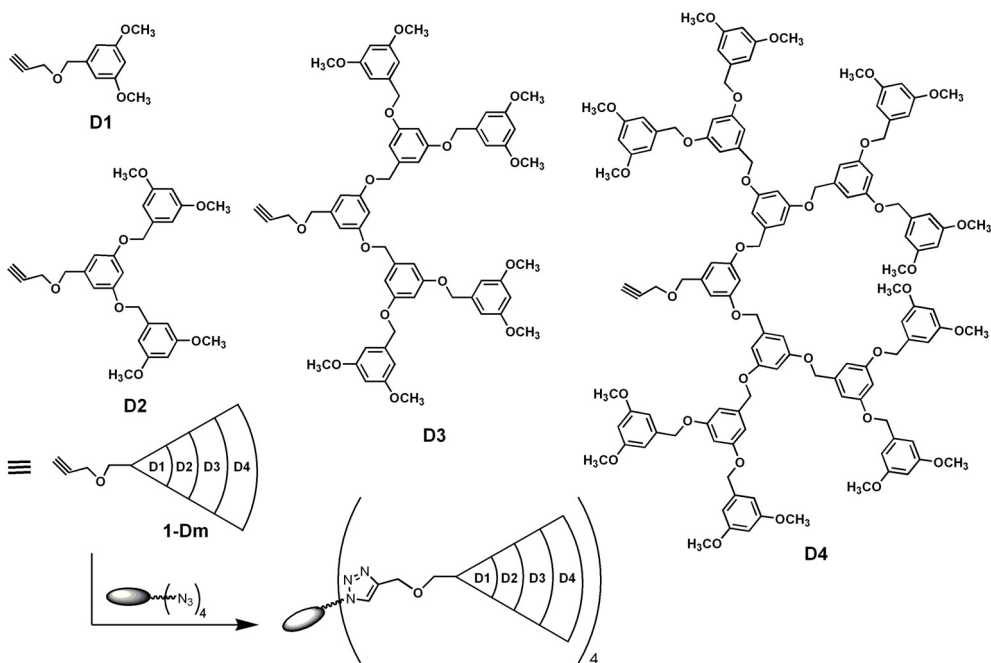


Figure 1. Structures of dendrons 1-Dm and synthetic strategy of dendrimers.

the stitching method of dendrons with tetra-core moiety (Figure 1). Because of the high yields and lack of byproducts provided by the click chemistry for stitching together dendrons and core unit, the various dendrimers having functional building block at core could be obtained easily and shown the characteristic behaviors.

Experimental

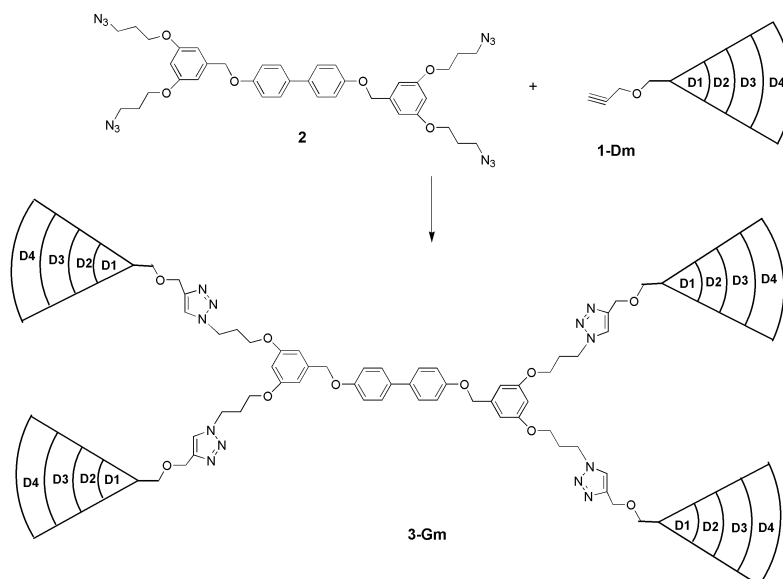
^1H -NMR spectra were recorded on a 300 or 500 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: *s*, singlet; *d*, doublet; *t*, triplet; *q*, quartet; *quin*, quintet; *d* of *d*, doublet of a doublet; *m*, multiplet; *br*, broad. ^{13}C -NMR spectra were proton decoupled and recorded on a 75 or 125 MHz NMR spectrometer using the carbon signal of the deuterated solvent as the internal standard. FAB and MALDI mass spectra were obtained from Korea Basic Science Institute (KBSI) in Daegu or Daejeon and POSTECH. Flash chromatography was performed with 37–75 μm silica gel. Analytical thin layer chromatography was performed on silica plates with F_{254} indicator and the visualization was accomplished by UV lamp or using an iodine chamber. Polydispersity (PDI) of dendrimers was determined by gel permeation chromatography (GPC) analysis relative to polystyrene calibration (Agilent 1100 series GPC, Plgel 5 μm MIXED-C,

refractive index detector) in THF solution.

General Procedure for the Preparation of Dendrimers 3-Gm from Alkyne-Dendrons 1-Dm and Tetra(azides) 2. A mixture of alkyne-dendrons 1-Dm (0.22 mmol) and 4,4'-(3,5-bis(azidopropoxy)benzyloxy)bisphenyl 2 (0.05 mmol) in THF-H₂O (4:1, 1 mL) in the presence of 20 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ with 40 mol% sodium ascorbate was stirred at 50 $^\circ\text{C}$ for ~100 h. The reaction mixture was poured into brine (20 mL) and the resulting solution was extracted with EtOAc (20 mL $\times$ 3). The combined organic phase was dried with sodium sulfate, concentrated, and purified by column chromatography to afford the desired product 3-Gm.

3-G1. 78% yield; A white solid; mp 72–74 $^\circ\text{C}$; IR 3001, 2939, 2862, 1597, 1458, 1366, 1157, 1057 cm^{-1} ; ^1H -NMR (500 MHz, CDCl_3) δ 2.38 (quin, $J=6.0$ Hz, 8H), 3.76 (s, 24H), 3.96 (t, $J=5.6$ Hz, 8H), 4.52 (s, 8H), 4.56 (t, $J=6.8$ Hz, 8H), 4.66 (s, 8H), 4.99 (s, 4H), 6.37 (m, 6H), 6.50 (d, $J=1.7$ Hz, 8H), 6.58 (d, $J=1.3$ Hz, 4H), 6.99 (d, $J=8.6$ Hz, 4H), 7.45 (d, $J=8.6$ Hz, 4H), 7.55 (s, 4H); ^{13}C -NMR (75 MHz, CDCl_3) δ 29.9, 47.0, 55.3, 63.6, 64.2, 69.8, 72.4, 76.6, 99.7, 100.8, 105.5, 106.0, 115.1, 123.0, 127.7, 133.7, 139.8, 140.2, 145.1, 157.7, 159.8, 160.9; MS (FAB): m/z 1587.0 [M^+]; HRMS (FAB) Calcd for $\text{C}_{86}\text{H}_{98}\text{N}_{12}\text{O}_{18}$: 1586.7122. Found: 1587.7232 [$\text{M}^+ + \text{H}$]. PDI: 1.01.

3-G2. 74% yield; A white solid; mp 60–62 $^\circ\text{C}$; IR 3008, 2939, 2839, 1597, 1458, 1373, 1149, 1049 cm^{-1} ; ^1H -NMR (500 MHz, CDCl_3) δ 2.36 (quin, $J=5.6$ Hz, 8H), 3.77 (s, 48H), 3.94 (t, $J=4.9$ Hz, 8H), 4.51 (s, 8H), 4.54 (t, $J=6.3$ Hz, 8H),



Scheme 1. Reagents and conditions: 20 mol% of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ /40 mol% of sodium ascorbate, THF/ H_2O (4:1), 50 °C.

4.65 (s, 8H), 4.95 (s, 20H), 6.37 (m, 2H), 6.40 (m, 8H), 6.53 (m, 4H), 6.56–6.58 (m, 20H), 6.59 (m, 8H), 6.97 (d, $J = 8.6$ Hz, 4H), 7.44 (d, $J = 8.5$ Hz, 4H), 7.53 (s, 4H); ^{13}C -NMR (75 MHz, CDCl_3) δ 29.8, 47.0, 55.2, 63.5, 64.2, 69.7, 69.9, 72.3, 76.6, 99.8, 100.8, 101.4, 105.1, 105.9, 106.6, 115.0, 122.9, 127.6, 133.5, 139.1, 139.7, 140.2, 145.0, 157.7, 159.7, 159.9, 160.9; MS (MALDI): Calcd for $\text{C}_{150}\text{H}_{162}\text{N}_{12}\text{O}_{34}$: 2675.1316. Found: 2676.1557 [$\text{M}^+ + \text{H}$], 2698.1112 [$\text{M}^+ + \text{Na}$]. PDI: 1.01.

3-G3. 75% yield; A white solid; mp 56–58 °C; IR 3008, 2939, 2839, 1597, 1458, 1373, 1149, 1049 cm^{-1} ; ^1H -NMR (500 MHz, CDCl_3) δ 2.33 (quin, $J = 5.6$ Hz, 8H), 3.76 (s, 96H), 3.92 (t, $J = 5.8$ Hz, 8H), 4.50–4.52 (m, 16H), 4.65 (s, 8H), 4.95 (s, 52H), 6.36 (m, 4H), 6.40 (m, 16H), 6.56 (m, 46H), 6.59 (m, 8H), 6.66 (m, 16H), 6.95 (d, $J = 8.2$ Hz, 4H), 7.41 (d, $J = 8.3$ Hz, 4H), 7.51 (s, 4H); ^{13}C -NMR (75 MHz, CDCl_3) δ 29.8, 47.1, 55.3, 63.6, 64.2, 69.9, 70.0, 72.3, 76.6, 99.9, 100.8, 101.4, 101.5, 105.2, 106.0, 106.3, 106.6, 115.0, 122.9, 127.6, 133.5, 139.1, 139.3, 139.7, 140.3, 145.0, 157.7, 159.8, 159.9, 160.0, 160.9; MS (MALDI): Calcd for $\text{C}_{278}\text{H}_{290}\text{N}_{12}\text{O}_{86}$: 4851.9705. Found: 4875.9343 [$\text{M}^+ + \text{H} + \text{Na}$]. PDI: 1.01.

3-G4. 73% yield; A white oil; IR 3008, 2939, 2839, 1597, 1458, 1373, 1203, 1149, 1049 cm^{-1} ; ^1H -NMR (500 MHz, CDCl_3) δ 2.29 (m, 8H), 3.75 (s, 192H), 3.89 (m, 8H), 4.46 (m, 8H), 4.50 (s, 8H), 4.63 (s, 8H), 4.93 (s, 116H), 6.39 (m, 36H), 6.55 (m, 96H), 6.60 (m, 8H), 6.66 (m, 46H), 6.94 (m, 4H), 7.40 (m, 4H), 7.49 (s, 4H); ^{13}C -NMR (75 MHz, CDCl_3) δ 29.8, 47.0, 55.3, 63.6, 64.2, 70.0, 72.3, 99.9, 101.6, 105.2, 106.4, 106.7, 115.0, 122.9, 127.6, 133.6, 139.1, 139.2, 139.3, 140.3, 144.8, 159.8, 159.9, 160.0, 160.9; PDI: 1.03.

Results and Discussion

The inward growth employed by the convergent synthesis is ideally suited for the attachment of diverse core moieties.⁴ As a result, building dendrimers via the convergent approach allows for the synthesis of symmetric dendrimers and for specific incorporation of function into the dendrimer interior. We decided to apply this methodology for the synthesis of dendrimer containing a kind of chromophore as a preliminary investigation. The synthetic strategy for Fréchet-type dendrimers, linked by the triazole units, utilized a convergent method using the alkyne-functionalized Fréchet-type dendrons **1-Dm** ($m = 1 \sim 4$: generation of dendron, Figure 1) are synthesized according to the reported procedure.^{7e} The 4,4'-(3,5-bis(azidopropoxy)benzyloxy) bisphenyl **2**, designed to present azide functionalities available for dendrimer growth via click reactions with the dendrons, was synthesized readily from the bis-alkylations of 4,4'-bisphenol with 3,5-bis(azidopropoxy)benzyl chloride¹² in the presence of a base.^{7m}

To demonstrate the effectiveness of the dipolar cycloaddition reactions of the tetra(azides) core **2** and alkyne-dendron **1-D1** (Scheme 1), we have screened with several conditions using various Cu(I) sources in different solvents.^{5,11} We have found that the reaction conducted from the condition of 5 mol% of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ with 10 mol% of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of THF

to H₂O for 24 h at 50 °C afforded the desired product **3-G1** in yield of 78%. The disappearance of tetra(azides) **2** as well as generation and disappearance of the mono, di, and triazole derivatives were monitored by TLC runs of the reaction mixture. The dendrimer **3-G1** was purified by column chromatography and the structure of dendrimer was confirmed by ¹H- and ¹³C-NMR spectroscopy, IR spectroscopy, and FAB mass spectra. Given the success in the synthesis of first generation dendrimer, we expanded this reaction to get higher generation dendrimers with 5 mol% of CuSO₄ · 5H₂O with 10 mol% of sodium ascorbate with respect to the alkyne in a 4:1 solvent ratio of THF to H₂O. Reactions of the tetra(azides) **2** with 4.4 equiv of **1-D2** and **1-D3** afforded the dendrimers **3-G2** and **3-G3** in yields of 74 and 75%, respectively, after 48 and 70 h, which were separated by column chromatography. In case of **1-D4**, the triazole dendrimer **3-G4** was obtained in 73% yield after 100 h. For completion of the reaction between the dendritic acetylene and the core, the higher generation dendron takes longer time than the lower generation dendron. This observation led us to imagine that the reaction between the dendritic acetylene and the azide core was kinetically controlled by the accessibility of acetylide due to the steric hindrance (bulkiness) of dendron and spatial congestion of the core region. This comparative efficiency of the click methodology is emphasized by the synthesis of the dendrimers with the tailed made core unit. Therefore this approach may provide new methodological insight into introduction of various functional cores and would greatly contribute to researches on the application side. We are now investigating for self-emissive dendrimer with a fluorescent or phosphorescent probe in core region.

Structural characterization of the dendrimers **3-Gm** with ¹H-NMR, ¹³C-NMR, and IR spectroscopy showed no defects due to incomplete reaction. From the ¹H-NMR spectra (CDCl₃), the peaks of the methylene protons adjacent to the nitrogen of triazole, the triazole proton, and the methylene protons adjacent to the carbon of triazole in dendrimers **3-Gm** were found at 4.56, 7.55, and 4.66 ppm for **3-G1**, 4.54, 7.53, and 4.65 ppm for **3-G2**, 4.52, 7.50, and 4.65 ppm for **3-G3**, and 4.50, 7.49, and 4.63 ppm for **3-G4**, respectively (Figure 2). The peaks of the methylene protons adjacent to the oxygen of bisphenyl in dendrimers **3-Gm** were found at 4.99 ppm for **3-G1**, 4.95 ppm for **3-G2**, 4.93 ppm for **3-G3**, and 4.93 ppm for **3-G4**, respectively. As the dendrimer generation increased, the peaks of all discussed protons shifted gradually to down-field which may be influenced by the dendritic microenvironment effect.¹³ Analysis of the dendrimers by mass spectrometry as well as by gel-per-

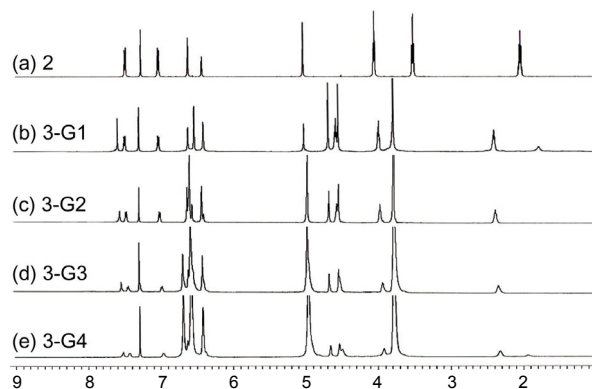


Figure 2. ¹H-NMR spectra for (a) **2**; (b) **3-G1**; (c) **3-G2**; (d) **3-G3**; (e) **3-G4**.

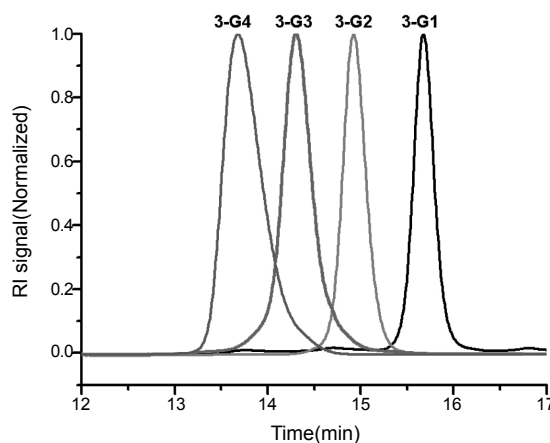


Figure 3. GPC diagrams of dendrimers **3-Gm** obtained from THF eluent.

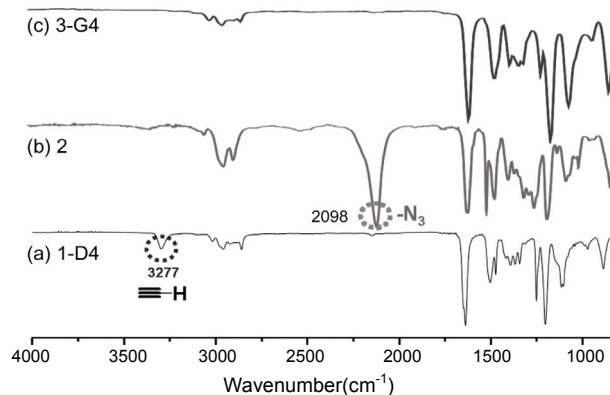


Figure 4. IR spectra for (a) **1-D4**; (b) **2**; (c) **3-G4**.

meation chromatography provides no signs of products with defects that would arise from incomplete coupling (Figure 3). As expected, the obtained dendrimer possessed a very well-defined molecular structure with very low polydispersity values (PDI=1.01–1.03). The IR spectra shows the disappearance of the acetylene peak at ~3277 cm⁻¹ and

the azide peak at $\sim 2098\text{ cm}^{-1}$ in the final dendrimer (Figure 4) while the ^1H -NMR revealed no alkyne peak at around δ 2.46 ppm.

Conclusions

We have demonstrated that click reactions between the tetra(azides) core and the alkyne-functionalized Fréchet-type dendrons lead to the formation of symmetric Fréchet-type dendrimers. This method can be applied for the fast synthesis of Fréchet-type dendrimers with functional units at core and may then provide an insight into designing various dendrimers with the functional cores.

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References

1. A. C. Grimsdale and K. Müllen, *Angew. Chem. Int. Ed.*, **44**, 5592 (2005).
2. D. A. Tomalia, *Prog. Polym. Sci.*, **30**, 294 (2005).
3. C. J. Hawker and J. M. J. Fréchet, *J. Am. Chem. Soc.*, **112**, 7638 (1990).
4. S. M. Grayson and J. M. J. Fréchet, *Chem. Rev.*, **101**, 3819 (2001).
5. (a) V. V. Rostovtsev, L. G. Green, V. V. Fokin, and K. B. Sharpless, *Angew. Chem. Int. Ed.*, **41**, 2596 (2002). (b) C. W. Tornøe, C. Christensen, and M. Meldal, *J. Org. Chem.*, **67**, 3057 (2002).
6. (a) P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Fréchet, K. B. Sharpless, and V. V. Fokin, *Angew. Chem. Int. Ed.*, **43**, 3928 (2004). (b) M. Malkoch, K. Schleicher, E. Drockenmüller, C. J. Hawker, T. P. Russell, P. Wu, and V. V. Fokin, *Macromolecules*, **38**, 3663 (2005).
7. (a) J. W. Lee and B. K. Kim, *Bull. Korean Chem. Soc.*, **26**, 658 (2005). (b) J. W. Lee, B. K. Kim, and S. H. Jin, *Bull. Korean Chem. Soc.*, **26**, 833 (2005). (c) J. W. Lee, B. K. Kim, J. H. Kim, W. S. Shin, and S. H. Jin, *Bull. Korean Chem. Soc.*, **26**, 1790 (2005). (e) J. W. Lee, J. H. Kim, B. K. Kim, W. S. Shin, and S. H. Jin, *Tetrahedron*, **62**, 894 (2006). (f) J. W. Lee, B. K. Kim, J. H. Kim, S. C. Han, W. S. Shin, and S. H. Jin, *Macromolecules*, **39**, 2418 (2006). (g) J. W. Lee, J. H. Kim, and B. K. Kim, *Tetrahedron Lett.*, **47**, 2683 (2006). (h) J. W. Lee, B. K. Kim, J. H. Kim, W. S. Shin, and S. H. Jin, *J. Org. Chem.*, **71**, 4988 (2006). (i) J. W. Lee, J. H. Kim, B. K. Kim, J. H. Kim, W. S. Shin, and S. H. Jin, *Tetrahedron*, **62**, 9193 (2006). (j) J. W. Lee, J. H. Kim, B. K. Kim, J. H. Kim, W. S. Shin, S. H. Jin, and M. Kim, *Bull. Korean Chem. Soc.*, **27**, 1795 (2006). (k) J. W. Lee, J. H. Kim, H. J. Kim, S. C. Han, J. H. Kim, W. S. Shin, and S. H. Jin, *Biocon. Chem.*, **18**, 579 (2007). (l) J. W. Lee, S. C. Han, J. H. Kim, Y. H. Ko, and K. Kim, *Bull. Korean Chem. Soc.*, **28**, 1837 (2007). (m) J. W. Lee, H. J. Kim, S. C. Han, J. H. Kim, and S. H. Jin, *J. Polym. Sci. Part A: Polym. Chem.*, **46**, 1083 (2008).
8. B. Helms, J. L. Mynar, C. J. Hawker, and J. M. J. Fréchet, *J. Am. Chem. Soc.*, **126**, 15020 (2004).
9. (a) H. Nandivada, H.-Y. Chen, L. Bondarenko, and J. Lahann, *Angew. Chem. Int. Ed.*, **45**, 3360 (2006). (b) J. E. Moses and A. D. Moorhouse, *Chem. Soc. Rev.*, **36**, 1249 (2007).
10. (a) M. A. Karim, Y.-R. Cho, J. S. Park, S. C. Kim, H. J. Kim, J. W. Lee, Y.-S. Gal, and S. H. Jin, *Chem. Commun.*, 1929 (2008). (b) D. Fournier, R. Hoogenboom, and U. S. Schubert, *Chem. Soc. Rev.*, **36**, 1369 (2007). (c) W. H. Binder and R. Sachsenhofer, *Macromol. Rapid Commun.*, **28**, 15 (2007).
11. V. D. Bock, H. Hiemstra, and J. H. van Maarseveen, *Eur. J. Org. Chem.*, 51 (2006).
12. J. W. Lee, S. C. Han, H. J. Kim, J. H. Kim, U. Y. Lee, B.-K. Kim, S. R. Sung, H.-S. Kang, J. H. Kim, and D.-S. Huh, *Polymer(Korea)*, **31**, 417 (2007).
13. (a) T. K.-K. Mong, A. Niu, H.-F. Chow, C. Wu, L. Li, and R. Chen, *Chem. Eur. J.*, **7**, 686 (2001).