Gradient Polymer Elution Chromatographic Analysis of α,ω-Dihydroxypolystyrene Synthesized via ATRP and Click Chemistry

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Introduction. In the past decade, the development of controlled/living radical polymerizations (CRP)[1] allows the synthesis of (co)polymers not only with a predetermined degree of polymerization and narrow molecular weight distribution (low polydispersity, M_w/M_n) but also with high functionality and desired microstructure. One of the most efficient CRP methods is atom transfer radical polymerization (ATRP).[2−4] The polymers produced by ATRP preserve the terminal halogen atom(s) and can be successfully converted into various end groups through appropriate transformation, especially nucleophilic substitutions.[5] For instance, the substitution of a halogen atom from a polymer chain end by an azide anion is very efficient.[6] The obtained organic azido group can be used for a variety of chemical transformations to produce numerous types of end functional moieties,[5,7−10] such as amino, hydroxy, or carboxy groups.

One particular reaction of organic azides that has garnered increased attention is the 1,3-dipolar cycloaddition of azides and terminal alkynes.[11] Two groups recently reported that with the use of a Cu(I) catalyst this coupling reaction results in the highly specific and efficient preparation of 1,4-disubstituted 1,2,3-triazole products under moderate reaction conditions.[12,13] These reactions can be conducted in aqueous or organic media, and little or no side reactions are observed. The practicality and versatility of the Cu(I)-catalyzed coupling reaction led to its inclusion in the class of efficient and specific organic reactions, commonly termed "click reactions", as coined by Sharpless et al.[14] Click reactions have emerged as a powerful method to modify chain-end and/or chain-side groups for functionalization of various (co)polymers.[15−17]

Because of its utility for the preparation of functional telechelic polymers, ATRP, combined with the efficiency of click chemistry, is an interesting and promising strategy to synthesize various end-functionalized polymers.[18] Recently, several groups have reported the synthesis of functional (co)polymers via ATRP and subsequent click reactions.[19−21,46] Notably, Lutz et al. described the preparation of monofunctional polymers by reacting various alkynes with azide-derivatized polymers prepared by ATRP.[20]

The development and optimization of procedures for the synthesis of well-defined functional polymers is vitally dependent on effective analytical methods to determine the molecular weight distribution (MWD) as well as the functionality-type distribution (FTD). Characterization of chain-end functionality is generally difficult since most traditional analytical techniques, such as NMR, UV−vis spectroscopy, and specific titration of −OH or −COOH groups, are limited to low molecular weight polymers, i.e., polymers with low degree of polymerization. Moreover, all these methods only determine the average functionality, not the FTD.[22]

High-performance liquid chromatography (HPLC), especially gradient polymer elution chromatography (GPEC)[23,24] and liquid chromatography under critical conditions (LCCC),[25,26] has emerged as a powerful technique to analyze the FTD of telechelic (co)polymers.[22,27,28] Several reports have detailed the use of LCCC to separate poly(methyl methacrylate) (PMMA)[29−31] and poly(*n*-butyl acrylate) (PBA)[32] linear polymers according to their chain-end functionality. However, the resolution of the separation, especially the elution curve of the difunctional polymer, i.e., α,ω-dihydroxy-terminated PMMA, was incomplete. Instead of giving rise to a narrow and sharp peak, the dihydroxy-containing PMMA eluted as a broad peak when analyzed at the critical conditions of nonhydroxy-functionalized PMMA standards. Such a phenomenon is often observed during the LCCC analysis of block copolymers when the "visible" block elutes in adsorption mode.[33,34] As an alternative HPLC technique, GPEC shows wide applicability for polymer separation according to their molar mass, chemical composition, and functionality.[24,35] The GPEC separation mechanism is based on precipitation and then redissolution.[22,28,36,37] The polymer sample is dissolved in a solvent or solvent mixture and injected into a column filled with a nonsolvent for the polymer. With such a poor solvent as the mobile phase, the polymer chains precipitate and adsorb onto the column. As the eluent composition is gradually changed to an increasingly higher concentration of a good solvent for the analyzed polymer, the precipitated polymer redissolves into the mobile phase and is eventually eluted. Thus, the polymer chains are separated according to their partition coefficient between column and mobile phase.

Telechelic polymers are distributed not only in chain-end functionality but also in molar mass. Transferring the eluate from GPEC analysis into a size exclusion chromatography (SEC) column can further separate the polymer chains according to their hydrodynamic volume. Thus, GPEC×SEC two-dimensional liquid chromatograms (2D-LC)[27,38,39] can be obtained, leading to information on both functionality distribution and molecular weight distribution of the synthesized telechelic (co)polymers. It was shown previously that various 2D-LC methods allowed for efficient separation of block copolymers, showing the presence of homopolymers and coupling products that were not fully resolved by SEC alone.[40−42]

Herein, we report the synthesis of α,ω-dihydroxy-terminated polystyrene (PS) by combination of ATRP and subsequent modification via click reactions. GPEC and GPEC×SEC 2D-LC techniques were then employed to extensively characterize the obtained polymer product, quantifying the fractions of different telechelic PS

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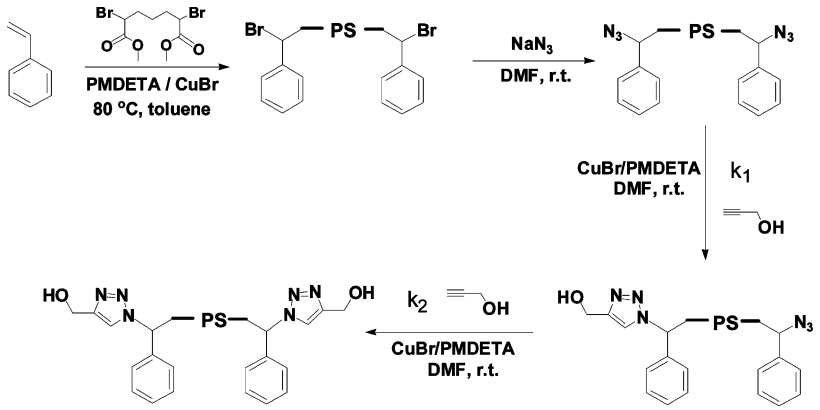
Scheme 1. Outline for the Synthesis of α,ω-Dihydroxy-Terminated PS Linear Polymers



species at various reaction times and determining the apparent rate constants (k_1 and k_2) of the consecutive click reactions of propargyl alcohol with the α,ω-diazido-terminated PS.

Results and Discussion. The synthetic strategy applied for preparation of the α,ω-dihydroxy-terminated PS is shown in Scheme 1. α,ω-Dibromo-terminated PS was synthesized by ATRP using CuBr/*N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA) as the catalyst and dimethyl 2,6-dibromoheptanedioate as the initiator (M_n = 2340 g/mol, M_w/M_n = 1.08).[21] The polymerization was stopped at low monomer conversion to ensure a high degree of bromine chain-end functionality.[43,44] After purification, the two bromo groups were transformed to azido groups by nucleophilic substitution with sodium azide. Finally, the reaction between the azido groups and an excess of propargyl alcohol in *N,N*-dimethylformamide (DMF) with CuBr/PMDETA as the catalyst led to α,ω-dihydroxy-PS via click reactions. SEC results indicated that the molecular weight of the polymer did not change during the postpolymerization reactions. On the basis of ^{1}H NMR spectra, the transformation reaction from bromo to azido chain-end groups was complete, and the azido groups were undetectable after the click reactions (Supporting Information).

In-situ ^{1}H NMR spectroscopy was employed to monitor the kinetics of the reaction between the α,ω-diazido-PS and propargyl alcohol as a function of reaction time. Figure 1 shows that with CuBr/PMDETA as the catalyst 96% of the azido groups were transformed to hydroxy

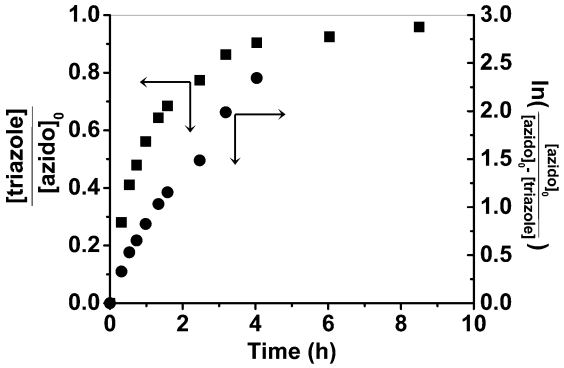


Figure 1. Formation of triazole groups as a function of reaction time during the reaction of α,ω-diazido-terminated PS and excess propargyl alcohol in DMF-d_7. ([triazole]/[azido]$_0$) = 3 × $A_{triazole}/A_{ini}$, where $A_{triazole}$ and A_{ini} are the peak areas from the protons of triazole rings and methyl ester groups from the ^{1}H NMR spectrum (cf. Figure S3 in Supporting Information).

chain-end groups after 8.5 h. A semilogarithmic kinetic plot had an initial slope of (1.53 ± 0.07) × 10^{-4} s^{-1}. Curvature could potentially be due to the loss of the Cu(I) catalyst by air oxidation or due to differences in the reactivity of the two azido groups. Regardless, the functionalization reaction seems to be efficient, and most of the PS should contain two hydroxy chain-end groups after 8.5 h. However, the results from NMR spectra cannot provide the distribution of different PS species during the reactions. In other words, only the average number of hydroxyls per PS chain can be determined by NMR spectroscopy. Hence, GPEC and GPEC×SEC 2D-LC were employed to characterize the obtained PS product in order to determine the distribution of the hydroxy groups in the PS products and its change with reaction time.

GPEC separates polymers according to their interaction with the stationary column. As the mobile phase gradually changes from a poor solvent to a good solvent, the chains with weaker column interactions are expected to elute first. A normal phase bare-silica column was used as the stationary phase. When the eluent composition changed from hexane to THF, the linear PS chains containing fewer hydroxy end groups should elute earlier than the chains containing more hydroxy end groups. It is worth noting that the enthalpic interaction energy between the PS chains and the stationary phase is determined by both the molecular weight and the hydroxyl functionality. The GPEC retention behavior of nonhydroxy-PS standards was determined in adsorption mode (Supporting Information). However, with the existence of hydroxy groups at the chain end, the elution behavior of the PS chains was mainly determined by the hydroxyl functionality.

Figure 2A shows the GPEC chromatograms of the α,ω-dibromo-, diazido-terminated PS, and the PS products from the click reactions at different reaction times. The elution volume of the dibromo-PS was similar to that of the diazido-PS (peak I, 13.7 mL), which indicates the bromo and azido groups have similar interaction with the bare-silica column under the GPEC conditions. Upon the introduction of hydroxy groups onto the PS chain ends, the PS containing more hydroxy groups should elute later. On the basis of Figure 2A, it is reasonable to expect that peak I represents nonhydroxy-functionalized PS and peaks II and III represent monohydroxy- and dihydroxy-functionalized PS chains, respectively. During the click reactions, PS samples were withdrawn from the reaction vial periodically. After evaporation of the solvent, the polymers were analyzed by GPEC to determine the fractions of different PS

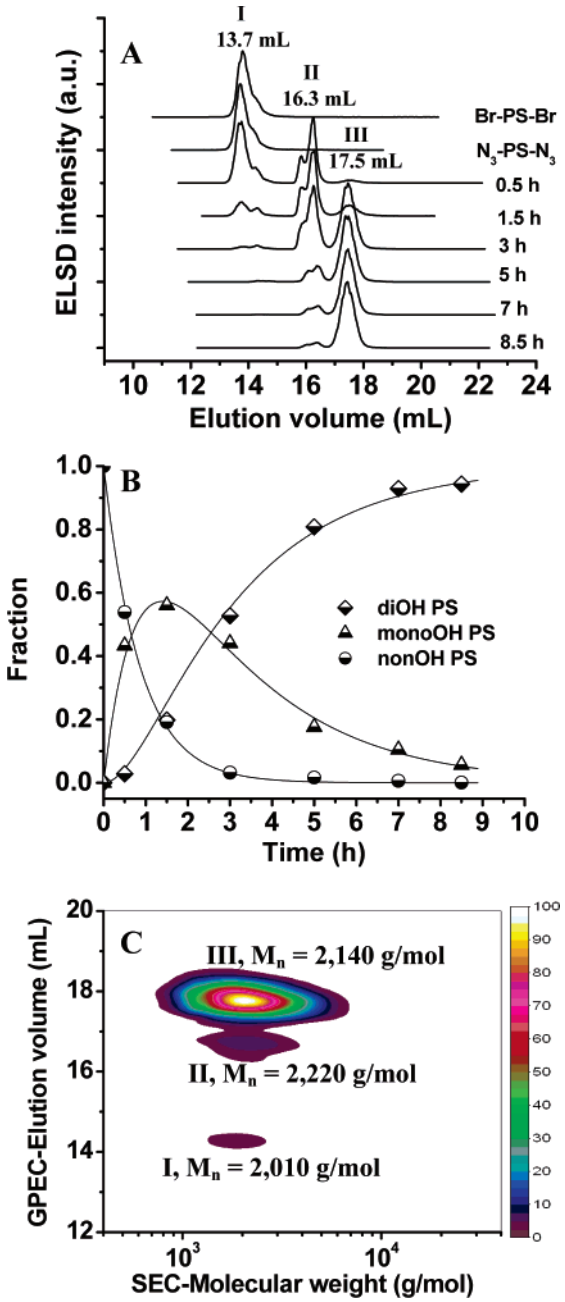


Figure 2. GPEC elution chromatograms of α,ω-dibromo-, α,ω-diazido-terminated PS, and α,ω-dihydroxy-terminated PS at different reaction times (A); fraction of dihydroxy-, monohydroxy-, and nonhydroxy-PS as a function of reaction time with solid lines as fitting results (B); and GPEC×SEC 2D chromatogram of α,ω-dihydroxy-terminated PS after 8.5 h (C).

species. The amount of unreacted α,ω-diazido-PS decreased with increasing reaction time, confirmed by the diminishing intensity of peak I. The intensity of peak II first increased with reaction time and then decreased. At the same time, peak III appeared at higher elution volume, and its intensity increased gradually. The small splitting in peaks I and II was presumably caused by the columns not being fully equilibrated during the gradual change of eluent composition.

Because the evaporative light scattering detector (ELSD) usually has a nonlinear response to polymer concentration, calibration curves of the three elution peaks in Figure 2A were established carefully. Integration results of these peaks provided quantitative information about the fractions of different PS species as a function of reaction time (Figure 2B). At the beginning of the reaction with propargyl alcohol, all of the polymer was nonhydroxy-PS. With increased reaction time, the population of nonhydroxy-PS decreased and the population of dihydroxy-PS increased. The fraction of monohydroxy-PS reached its maximum at ca. 1.5 h and then decreased with reaction time. Since the propargyl alcohol was in 10 times excess to the azido group, it is possible to assume a constant concentration of propargyl alcohol (i.e., pseudo-first-order conditions) and consider the click reactions as consecutive reactions, shown in Scheme 1. The apparent rate constants (k_1 and k_2) were determined as $(3.2 \pm 0.2) \times 10^{-4}$ s^{-1} and $(1.1 \pm 0.1) \times 10^{-4}$ s^{-1}. These results semiquantitatively suggested that the second click reaction on a PS chain was 3 times slower than the first one. To the best of our knowledge, this is the first example in which the rate constants of consecutive click reactions between propargyl alcohol and diazido telechelic polymer chains were measured. The slower reaction of the second azido group is interesting since there have been reports that click reactions conducted in the absence of additionally added ligand are often autocatalytic due to complexation of the copper catalyst by the triazole product.[45] If this were the case for the current system, the second chain end might be expected to react faster than its predecessor. However, the distance between the end groups may be too great, and the presence of PMDETA may preclude such an effect. Rather, decreased mobility of the monohydroxy-containing PS chains could potentially be responsible for the apparent reduced reactivity of the second chain end. The kinetics of the reactions (fraction of formed hydroxy chain-end groups as a function of reaction time) was also determined from Figure 2B. For example, after 8.5 h, 97% of the chain ends contained hydroxy groups. This result is in excellent agreement with the value of 96% functionalization determined from ^{1}H NMR data (Figure 1).

The GPEC traces demonstrated successful separation of dihydroxy-PS from monohydroxy- and nonhydroxy-PS. To ensure that the separation observed by GPEC was primarily due to the chain-end functionality and not differences in molecular weight, GPEC×SEC 2D-LC was conducted through transferring the eluates from the GPEC to a SEC column. Figure 2C shows the 2D chromatogram of PS product obtained from click reaction after 8.5 h, which provided information on both molecular weight and the distribution of hydroxyl functionality. It is seen that the three types of PS products represented by I, II, and III, had similar molecular weights. Their only significant difference was the hydroxyl functionality.

Conclusions. α,ω-Dihydroxy-terminated PS was synthesized by the combination of ATRP, nucleophilic substitution, and click chemistry. GPEC and GPEC×SEC 2D-LC techniques were employed to precisely characterize the functionality of the polymers. Under GPEC, the elution behavior of the α,ω-dibromo-PS was similar to that of the α,ω-diazido-PS, which indicated their similar interaction with the stationary column. GPEC analysis successfully separated the dihydroxy-PS from monohydroxy- and nonhydroxy-PS. The apparent rate constants ($k_1 = 3.2 \times 10^{-4}$ s^{-1}, $k_2 = 1.1 \times 10^{-4}$ s^{-1}) of the consecutive click reactions between propargyl alcohol and diazido-PS were determined through quantification of these three species at different reaction times, information which is not available by conventional

spectroscopic techniques. The results indicated the second click reaction on a PS chain was ~3 times slower than the first reaction. After 8.5 h, both NMR spectroscopy and GPEC showed 96−97% of hydroxy groups at the PS chain-ends. GPEC×SEC 2D analysis ensured that these species retained their molecular weight during the postpolymerization modification and demonstrated the utility of GPEC for separation of polymers based on chain-end functionality.

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Supporting Information Available: Procedures for preparation and analysis of α,ω-dibromo-, α,ω-diazido-, and α,ω-dihydroxy-terminated PS; their SEC plots and ^{1}H NMR spectra and GPEC elution traces of PS standards. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Matyjaszewski, K., Davis, T. P.; Eds. *Handbook of Radical Polymerization*; Wiley: Hoboken, NJ, 2002.
(2) Wang, J.-S.; Matyjaszewski, K. *J. Am. Chem. Soc.* **1995**, *117*, 5614.
(3) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921.
(4) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689.
(5) Coessens, V.; Pintauer, T.; Matyjaszewski, K. *Prog. Polym. Sci.* **2001**, *26*, 337.
(6) Coessens, V.; Matyjaszewski, K. *J. Macromol. Sci., Pure Appl. Chem.* **1999**, *A36*, 667.
(7) L'Abbe, G. *Chem. Rev.* **1969**, *69*, 345.
(8) Matyjaszewski, K.; Nakagawa, Y.; Gaynor, S. G. *Macromol. Rapid Commun.* **1997**, *18*, 1057.
(9) Coessens, V.; Nakagawa, Y.; Matyjaszewski, K. *Polym. Bull.* **1998**, *40*, 135.
(10) Matyjaszewski, K. *Polym. Int.* **2003**, *52*, 1559.
(11) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 742.
(12) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596.
(13) Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057.
(14) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
(15) O'Reilly, R. K.; Joralemon, M. J.; Nugent, A. K.; Matson, J. B.; Hawker, C. J.; Wooley, K. L. *Polym. Prepr.* **2004**, *45*, 292.
(16) O'Reilly, R. K.; Hawker, C. J.; Wooley, K. L. *Polym. Prepr.* **2004**, *45*, 780.
(17) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928.
(18) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200.
(19) Opsteen, J. A.; van Hest, J. C. M. *Chem. Commun.* **2005**, 57.
(20) Lutz, J.-F.; Boerner, H. G.; Weichenhan, K. *Macromol. Rapid Commun.* **2005**, *26*, 514.
(21) Tsarevsky, N. V.; Sumerlin, B. S.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 3558.
(22) Philipsen, H. J. A. *J. Chromatogr., A* **2004**, *1037*, 329.
(23) Glockner, G. *Gradient HPLC and Chromatographic Cross-Fractionation*; Springer: Heidelberg, 1991.
(24) Philipsen, H. J. A.; Klumperman, B.; German, A. L. *J. Chromatogr., A* **1996**, *746*, 211.
(25) Belen'kii, B. G.; Gankina, E. S.; Tennikov, M. B.; Vilenchik, L. Z. *J. Chromatogr.* **1978**, *147*, 99.
(26) Pasch, H. *Adv. Polym. Sci.* **1997**, *128*, 1.
(27) Pasch, H.; Trathnigg, B. *HPLC of Polymers*; Springer: Heidelberg, 1997.
(28) Berek, D. *Prog. Polym. Sci.* **2000**, *25*, 873.
(29) Jiang, X.; Lima, V.; Schoenmakers, P. J. *J. Chromatogr., A* **2003**, *1018*, 19.
(30) Peters, R.; Mengerink, Y.; Langereis, S.; Frederix, M.; Linssen, H.; van Hest, J.; van der Wal, S. *J. Chromatogr., A* **2002**, *949*, 327.
(31) Jiang, X.; van der Horst, A.; Lima, V.; Schoenmakers, P. J. *J. Chromatogr., A* **2005**, *1076*, 51.
(32) Jiang, X.; Schoenmakers, P. J.; Lou, X.; Lima, V.; van Dongen, J. L. J.; Brokken-Zijp, J. *J. Chromatogr., A* **2004**, *1055*, 123.
(33) Evreinov, V. V.; Gorshkov, A. V.; Prudskova, T. N.; Gur'yanova, V. V.; Pavlov, A. V.; Malkin, A. Y.; Entelis, S. G. *Polym. Bull.* **1985**, *14*, 131.
(34) Pasch, H.; Gallot, Y.; Trathnigg, B. *Polymer* **1993**, *34*, 4986.
(35) Teramachi, S.; Hasegawa, A.; Shima, Y.; Akatsuka, M.; Nakajima, M. *Macromolecules* **1979**, *12*, 992.
(36) Karanam, S.; Goossens, H.; Klumperman, B.; Lemstra, P. *Macromolecules* **2003**, *36*, 3051.
(37) Lee, W.; Cho, D.; Chun, B. O.; Chang, T.; Ree, M. *J. Chromatogr., A* **2001**, *910*, 51.
(38) Kilz, P.; Krueger, R. P.; Much, H.; Schulz, G. *Polym. Mater. Sci. Eng.* **1993**, *69*, 114.
(39) van der Horst, A.; Schoenmakers, P. J. *J. Chromatogr., A* **2003**, *1000*, 693.
(40) Li, M.; Jahed, N. M.; Min, K.; Matyjaszewski, K. *Macromolecules* **2004**, *37*, 2434.
(41) Lutz, J.-F.; Jahed, N.; Matyjaszewski, K. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 1939.
(42) Min, K.; Gao, H.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2005**, *127*, 3825.
(43) Lutz, J.-F.; Matyjaszewski, K. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 897.
(44) Gao, H.; Tsarevsky, N. V.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 5995.
(45) Rodionov, V. O.; Fokin, V. V.; Finn, M. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2210.
(46) Sumerlin, B. S.; Tsarevsky, N. V.; Louche, G.; Lee, R. Y.; Matyjaszewski, K. *Macromolecules* **2005**, *38*, 7540.

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