Metal-Free Synthesis of Responsive Polymers: Cloud Point Tuning by Controlled ''Click'' Reaction

C. REMZI BECER,[1,2,3] KENTA KOKADO,[4] CHRISTINE WEBER,[1,3] AYDIN CAN,[1,2,3] YOSHIKI CHUJO,[4] ULRICH S. SCHUBERT[1,2,3]

[1]Laboratory of Organic and Macromolecular Chemistry, Friedrich-Schiller-University Jena, Humboldtstrasse 10, 07743 Jena, Germany

[2]Laboratory of Macromolecular Chemistry and Nanoscience, Eindhoven University of Technology, Den Dolech 2, 5612 AZ Eindhoven, The Netherlands

[3]Dutch Polymer Institute (DPI), John F. Kennedylaan 2, 5612 AB Eindhoven, The Netherlands

[4]Department of Polymer Chemistry, Graduate School of Engineering, Kyoto University, Katsura, Nishikyo-ku, Kyoto 615-8510, Japan

ABSTRACT: Nitroxide-mediated radical polymerization has been used for the preparation of pentafluorostyrene (PFS) homopolymers and random copolymers of PFS and oligo(ethyleneglycol) methacrylate (OEGMA$_{8.5}$). The poly(pentafluorostyrene) homopolymers were reacted with thiophenol at different ratios at room temperature in the presence of triethylamine. The "clicked" polymers were characterized by ^{1}H and ^{19}F NMR spectroscopy and size exclusion chromatography. Moreover, the copolymerization kinetics of the PFS and OEGMA$_{8.5}$ copolymers was followed, and the phase transition behavior of random copolymers with different compositions was discussed. Furthermore, copolymers of PFS and 2-(dimethylamino) ethyl methacrylate (DMAEMA) were prepared at various mole ratios, and the copolymer with a 10:90 ratio, respectively, was soluble in water at room temperature. Turbidimetry measurements were performed for PFS and OEGMA$_{8.5}$ or DMAEMA copolymers to determine their cloud points. Finally, the PFS and OEGMA$_{8.5}$ copolymer with a mole ratio of 60:40 was reacted further with thiophenol to increase the hydrophobic part in the copolymer. The cloud points of the obtained copolymers could be tuned from 87 to 33 °C by using not only the controlled radical polymerization but also the "click" reaction in a controlled fashion. © 2010 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 48: 1278–1286, 2010

KEYWORDS: controlled radical polymerization; fluoropolymers; living polymerization; lower critical solution temperature; metal-free click reaction; stimuli-responsive polymers; stimuli-sensitive polymers

INTRODUCTION Macromolecular engineering has become more and more popular in the last decade with the desire to gain absolute control over the molecular structures.[1] Several synthetic techniques have been developed to synthesize tailor-made macromolecules decorated with specific functionalities.[2] In particular, the nitroxide-mediated radical polymerization (NMP) provides metal-free polymerization conditions of monomers, unlike metal-mediated living radical polymerization techniques.[3] On the other hand, there is an increasing interest in metal-free "click" reactions to functionalize well-defined polymer backbones.[4] By combining the selected metal-free synthesis techniques, it is possible to synthesize stimuli-responsive polymers with controlled architectures.

Controlled/living radical polymerization techniques are in general preferred over living ionic polymerization techniques because of their extensive purification requirements. Metal-mediated living polymerization techniques require the use of ruthenium, copper, or cobalt salts to establish the equilibrium between active and dormant species.[5] However, NMP requires only the use of stable-free nitroxide compounds for the controlled propagation of the chains. The most widely and successfully used nitroxide compounds are TEMPO, TIPNO, Bloc Builder, and their derivatives for the polymerization of styrene and acrylates.[6] Moreover, Bloc Builder, a commercially available free nitroxide, provides a reasonable control over the polymerization of methacrylates by addition of a few mole percent of styrene to the polymerization medium. NMP is mostly the preferred technique for the synthesis of glycopolymers or polymers that are aimed to be used in biological applications.[7]

NMP and other controlled/"living" radical polymerization (CRP) techniques allow the synthesis of well-defined polymers with desired initiating or terminating groups. However, these techniques are mostly only tolerant to a limited

number of functionalities, most commonly the desired functionalities are being introduced to the polymer with postpolymerization reactions.[8] The "click" chemistry concept has been introduced by Sharpless and coworkers in 2001, and these reactions are highly efficient and provide high yields with readily available starting materials.[9] In the last years, there has been an enormous effort on the discovery of new type of "click" reactions that do not require the use of metal catalyst. Most of the studies have been focused on reacting azides with various activated alkyne compounds in the absence of copper salts.[10] There is also significant amount of research carried out on the reaction of thiols, which can proceed not only by radical addition but also by nucleophilic substitution.[11] Hawker and coworkers as well as Schlaad and coworkers demonstrated the suitability of the thiol-alkene reaction as a "click" reaction by synthesizing fifth-generation dendrimers or by introducing side-chain functionalities to a polyoxazoline backbone under UV irradiation.[12] The nucleophilic substitution reaction of thiols and *para*-fluoro phenyl groups has been recently reported by Schubert and coworkers.[13] They have described the synthesis of glycopolymers based on a pentafluorostyrene (PFS) backbone, which reacted with thiol-glucose at room temperature in the absence of a metal salt. As a consequence, the thiol-*para* fluoro type of metal-free "click" reaction is used further in this study for the synthesis of thermoresponsive copolymers based on PFS and oligo(ethyleneglycol) methacrylate (OEGMA) or 2-(dimethylamino) ethyl methacrylate (DMAEMA).

Stimuli-responsive polymers present a phase transition upon changing the temperature, the pH value, the ion concentration, or the medium.[14] These functional polymers are smart materials and are used in various applications, that is, drug delivery systems or cell culturing.[15] Thermoresponsive polymer solutions exhibit a sudden phase transition at the so-called cloud point because of the polymer–solvent interactions that weaken upon increasing the temperature. Therefore, selected classes of monomers have been widely used in the synthesis of responsive polymers, that is, poly(N-isopropyl acrylamide), poly(ethyleneglycol) (PEG), poly(2-alkyl-2-oxazoline), poly[2-(dimethylamino) ethyl methacrylate] (DMAEMA), and poly[oligo(ethyleneglycol) methacrylate] (OEGMA).[16] Different combinations of these monomers with each other and also with hydrophobic monomers have been prepared even in libraries to systematically investigate the effect of the comonomer composition.[17] It is possible to tune the lower critical solution temperature (LCST) behavior of the polymers not only by altering the copolymer composition but also by introducing side groups or end groups to the backbone.[18]

In this report, we discuss the copolymerization of PFS and OEGMA$_{8.5}$ or DMAEMA at different percentages to obtain well-defined copolymers with a LCST behavior. Moreover, homopolymer of PFS has been reacted with thiophenol at different mole percentages to follow the efficiency of the "click" reaction. Finally, the LCST of a PFS and OEGMA$_{8.5}$ copolymer has been tuned by reacting it with thiophenol at different mole percentages.

EXPERIMENTAL

Materials

Pentafluorostyrene (99%, Aldrich), oligo(ethyleneglycol) methyl ether methacrylate (OEGMA$_{475}$, $M_n \sim 475$ g/mol, Aldrich), and 2-(dimethylamino) ethyl methacrylate (98%, Aldrich) were purified by passing over a neutral aluminum oxide column. Bloc Builder^{TM} (Arkema), triethylamine ($\geq$99%, Merck), thiophenol ($\geq$98%, Aldrich), and all solvents were used as received.

Instruments

GC measurements were performed on a Shimadzu GC used with a Trace column RTX-5 and an autosampler for the determination of the PFS monomer conversions. NMR spectroscopy was recorded on a Bruker Avance 250 MHz in deuterated methylene chloride. The chemical shifts were calibrated with respect to the residual solvent signal. The size exclusion chromatography (SEC) was equipped with triple detectors that are a diode array detector, a reflective index detector, and a multiangle light scattering detector. Two PSS SDV (5 μm pore size) columns were placed in series. DMA with 5 mmol LiCl was used as an eluent at 1 mL/min flow rate, and the column oven was set to 40 °C. The reported number-average molar masses were calculated according to polystyrene standards. Turbidimetry measurements were performed in a Crystal 16 from Avantium Technologies or an UV–vis spectrometer Specord 250 from Analytik Jena. For the first method, four blocks of parallel temperature-controlled sample holders were connected to a Julabo FP40 cryostat, allowing 16 simultaneous measurements. Turbidity of the solutions at a concentration of 5 mg/mL was measured by the transmission of red light through the sample vial as a function of the temperature. Solutions of the polymers were prepared in deionized water and were stirred at room temperature until all polymeric material was dissolved. Two heating cycles were applied from 0 to 100 °C at 1 °C/min with hold steps of 5 min at the most extreme temperatures. The cloud points are given as the 50% transmittance point during the first heating ramp of the aqueous polymer solutions.

Synthesis of the PPFS Homopolymer (H1)

PFS (5 mL, 36.25 mmol), Bloc Builder (277 mg, 0.725 mmol), and tetrahydrofuran (THF) (5 mL) were added in a 25-mL pressure-resistant round-bottom flask. The mixture was bubbled gently with argon while stirring at least for 30 min. Afterward, the flask was capped and placed into a preheated oil bath at 110 °C. The reaction was continued for 3 h. The flask was cooled down immediately after the reaction, and samples were withdrawn for the analysis by GC and SEC. The solution was precipitated twice into methanol, filtered, and dried. ($M_{n,SEC} = 4100$ g/mol, PDI = 1.05, conversion = 42%)

Synthesis of the P(PFS)-*r*-(OEGMA$_{8.5}$) Copolymers (R1–R6)

For the preparation of random copolymers, the required amounts of PFS, OEGMA$_{8.5}$, Bloc Builder, and toluene were added into a flask. Different molar ratios of PFS and

TABLE 1 Selected Characterization Data for the Clicked Homopolymer of PPFS

Run	[PhSH]/[PFS]	[NEt₃]/[PFS]	Conv. (%) ¹⁹F NMR	Conv. (%) ¹H NMR	$M_{n,GPC}$ (g/mol)	PDI
H1	–	–	–	–	4,100	1.05
H2	0.25	1.25	16	11	4,400	1.05
H3	0.50	2.5	40	47	4,400	1.06
H4	1.00	5.0	86	>99	4,500	1.05
H5	2.00	10.0	98	>99	4,550	1.04

All thiophenol "click" reactions were performed in THF at room temperature for 15 h.

OEGMA₈.₅ were used as listed in Table 2. Total monomer to initiator ratio was kept as 100:1. The reaction was performed at a concentration of 4 mol/L in toluene as solvent. All reactions were conducted at 110 °C for 6 h. The polymerization was terminated by cooling down the vial with tap water. The obtained polymers were precipitated into cold hexane and dried under vacuum. The monomer conversion of PFS was calculated from both GC and ¹H NMR spectroscopy, whereas only the spectroscopy technique was used for the conversion of OEGMA₈.₅ to obtain reliable data. The vinylic protons of PFS and OEGMA₈.₅ were compared with respect to toluene protons for the initial and the end samples.

### Synthesis of the P(PFS)-*r*-(DMAEMA) Copolymers (R7–R10)

Similar to the synthesis of the P(PFS)-*r*-(OEGMA)₈.₅ copolymers described earlier, different mole ratios of PFS and DMAEMA were used as listed in Table 3. The polymerizations were conducted at 110 °C for 6 h, in toluene as solvent, at a concentration of 4 mol/L. The monomer conver-

sions were determined by using both GC and ¹H NMR spectroscopy.

"Click" Reaction with Thiophenol and PPFS₁₉ (H1) or P(PFS)₄₆-*r*-(OEGMA₈.₅)₃₁ (R3)

The thiophenol "click" reaction was performed using different molar ratios of thiophenol and the corresponding homo or copolymer. PPFS₁₉ (**H1**) homopolymer (97 mg, 0.5 mmol PFS) was dissolved in THF (0.8 mL). Subsequently, triethylamine (87 μL, 0.625 mmol) and thiophenol (13 μL, 0.125 mmol) were added into the solution in this order and the flask was capped immediately. The amounts and ratios provided here are for the synthesis of **H2**. The corresponding amounts can be calculated for **H3**, **H4**, and **H5** by multiplying the aforementioned ratios by 2, 4, and 8, respectively, as listed in Table 1.

The P(PFS)-*r*-(OEGMA) (**R3**) copolymer (96 mg) was dissolved in THF (2 mL). Subsequently, triethylamine (251 μL, 1.8 mmol) and thiophenol (62 μL, 0.6 mmol) were added into the solution in this order and the flask was capped immediately. The added amounts mentioned here are the same
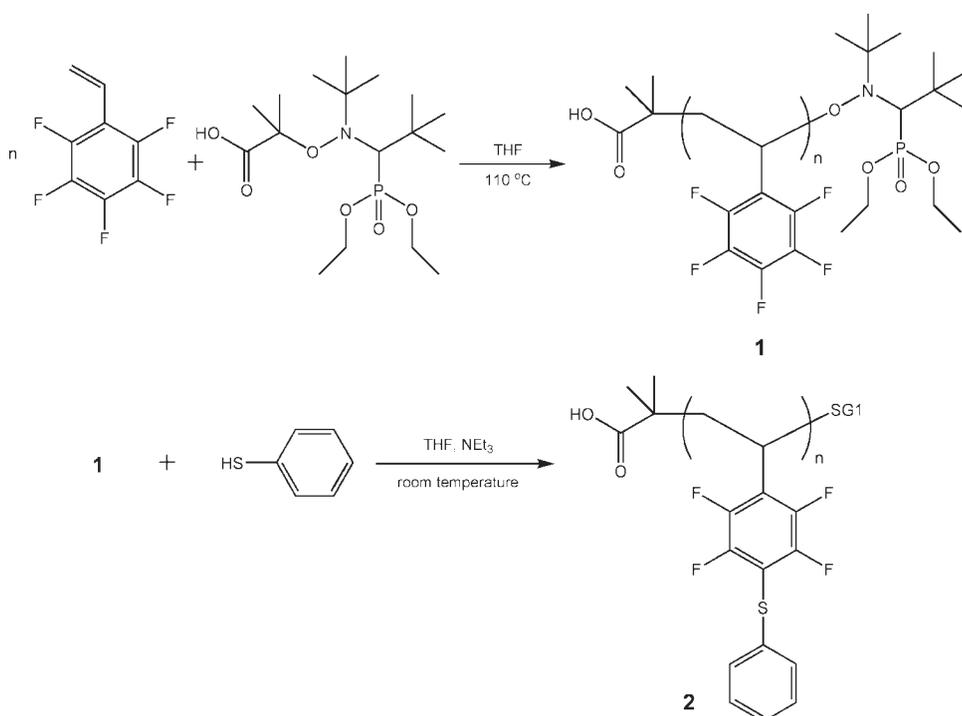
SCHEME 1 Schematic representation of the nitroxide-mediated polymerization of pentafluorostyrene initiated by Bloc Builder (top), thio-*para* fluoro "click" reaction on PPFS (bottom).
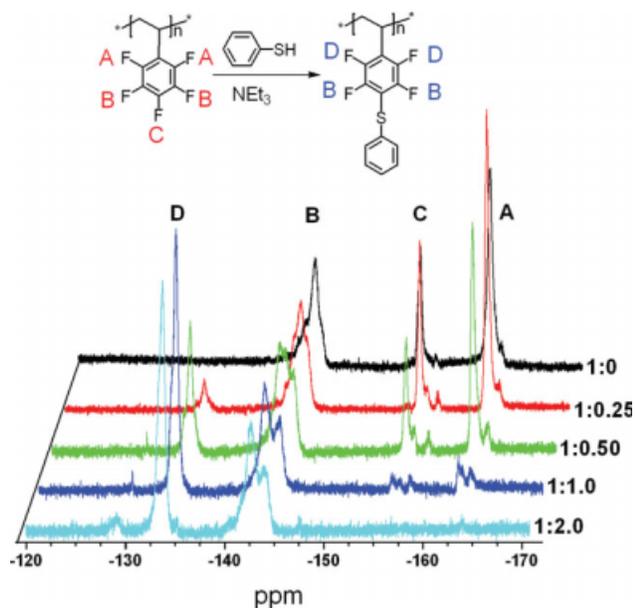
FIGURE 1 ^{19}F NMR spectra of PPFS homopolymers reacted with different amounts of thiophenol. The ratios show the amount of thiophenol used per PFS repeating unit. (A) o-fluorine, (B) m-fluorine, and (C) p-fluorine of the starting material, (D) o-fluorine, and (B) m-fluorine of the product. All spectra are normalized according to (B) signals.

as for the synthesis of **C1**. The corresponding amounts can be calculated for **C2** and **C3** by multiplying the aforementioned ratios by 2 and 4, respectively.

RESULTS AND DISCUSSION

The NMP of PFS was performed using Bloc Builder as an alkoxyamine initiator as depicted in Scheme 1. The polymerization was performed at 110 °C and in THF as solvent. The

homopolymer of PFS **H1** was obtained as white powder with a gravimetric yield of 42%, after precipitated twice into methanol. The resulting polymer was characterized by SEC, and the molar mass was calculated according to polystyrene standards (**H1**, $M_{n,SEC}$ = 4100 g/mol, PDI = 1.05). Subsequently, this polymer **H1** was dissolved in THF and used further for "click" reactions with thiophenol. **H1** was reacted with different molar ratios of thiophenol (0.25, 0.50, 1.00, and 2.00 per PFS) in the presence of triethylamine (fivefold in respect to thiophenol). The "click" reaction was performed at room temperature for 15 h for all homopolymers and copolymers.

Subsequent to the "click" reaction, the solutions were precipitated into cold methanol to terminate the reaction. The conversion values are listed in Table 1 and show the percentage of PFS units that are reacted with thiophenol. The maximum conversion for **H2** and **H3** aimed to be 25 and 50%, respectively, as calculated. Therefore, it is also possible to "click" **H2** or **H3** with another functionality to obtain multifunctional polymers. The conversion values were calculated from the ratio of p-fluorine of PFS (shown as C in Fig. 1), which are decreasing with higher conversion values, to a constant amount of m-fluorine atoms (shown as B in Fig. 1). Corresponding ^{19}F NMR spectra of the obtained polymers are depicted in Figure 1. It was also possible to follow the reaction with ^{1}H NMR spectroscopy measurements as unreacted thiophenol could be separated from the polymer by precipitation. The amount of phenyl groups introduced to **H1** allows to determine the conversion of the thio-p-fluoro "click" reaction. The calculated conversion values using ^{1}H NMR spectra are in good correlation with the ^{19}F NMR spectroscopy measurements. The PPFS homopolymer is not soluble in water, and introducing phenyl groups on the side chains does not improve its solubility in water, as expected. Consequently, as described later in the discussion part,
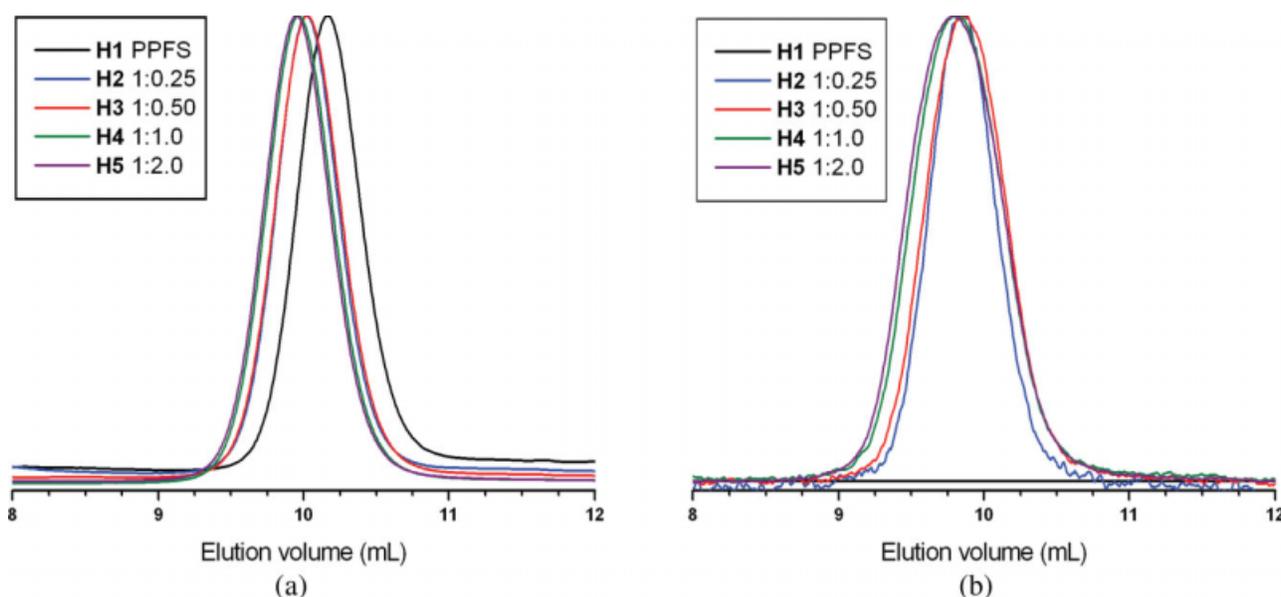
FIGURE 2 SEC traces of PPFS "clicked" with different ratios of thiophenol. RI response (left), UV response at 254 nm (right).
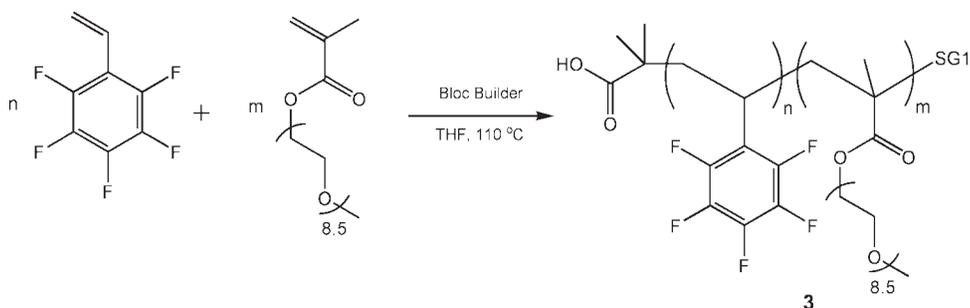
SCHEME 2 Schematic representation of NMP of pentafluorostyrene and oligo-(ethyleneglycol) methacrylate (M_n = 475 g/mol) at various ratios initiated by Bloc Builder.

copolymerizing PFS with more than 40 mol % OEGMA$_{8.5}$ provides sufficient hydrophilicity to the copolymer to solubilize in water at room temperature. Moreover, it is possible to tune the LCST of these copolymers by introducing different amounts of phenyl groups to the side chains. Therefore, we performed thiophenol reactions with the homopolymer **H1** as model reactions prior to the "click" reactions with copolymers.

The polymers were further characterized using SEC, which was equipped with both a RI and an UV detector. The resulting chromatograms for **H1–H5** are shown in Figure 2. The hydrodynamic volume of the "clicked" polymers showed a slight increase in comparison to the **H1** homopolymer. However, the calculated number-average molar mass values did not differ significantly for **H2–H5**. This might be due to the fact that the hydrodynamic volume of PPFS **H1** is not increasing after incorporation of additional phenyl groups to the side chains of the polymer. It should also be noted that the backbone length did not increase with the "click" reaction, but the repeating units became more bulky. Nevertheless, the UV signal obtained in the SEC measurements is a clear indication that thiophenol was incorporated into the polymer **H1** as the starting homopolymer did not show any absorbance at 254 nm.

The nitroxide-mediated copolymerization of PFS and OEGMA$_{8.5}$ has been performed for the first time, as illustrated in Scheme 2. The polymerization was conducted in toluene as solvent and initiated with Bloc Builder, which is a very efficient alkoxyamine initiator for the polymerization of styrene, acrylates, and their derivatives.[19] However, the poly-merization of methacrylates using this initiator is not straightforward to obtain polymers with narrow polydispersity indices (PDIs). Detailed studies of Charleux et al. showed that control over the polymerization of methyl methacrylate (MMA) could be achieved by adding few percentages (~8.8% in respect to MMA) of styrene to the polymerization medium.[20] A similar approach was used for the NMP of OEG-MAs, and comb-like polymers with moderate PDI values could be obtained.[21] Lessard and Maric prepared comb-like polymers using oligo(ethyleneglycol) acrylates (OEGA$_8$) instead of OEGMA by taking into account that acrylates are better compatible with the Bloc Builder than methacry-lates.[22] Moreover, they have demonstrated further the living-ness of polyOEGA homopolymers by reacting them with styrene yielding diblock copolymers. Nevertheless, to the best of our knowledge, there is no example in the literature combining PFS with OEGMA or DMAEMA monomers using the NMP technique.

Copolymerization of PFS and OEGMA$_{8.5}$ was performed at various ratios, as listed in Table 2. All copolymerizations were performed in THF as solvent and reacted for 15 h. The molar masses of the obtained polymers were determined by measuring SEC. Copolymers with higher ratio of OEGMA$_{8.5}$ showed higher molar mass values as the molar mass of the OEGMA$_{8.5}$ monomer is more than double compared with the PFS monomer (475 g/mol for OEGMA$_{8.5}$ vs. 194 g/mol for PFS). Besides, the calculations were performed according to linear PS standards, which might not be very accurate for OEGMA-containing graft-shaped copolymers. Nevertheless, the molar masses and the PDI values of the obtained

TABLE 2 Random Copolymerization of PFS and OEGMA$_{8.5}$ at Various Ratios

| Run | Feed Ratio | | $M_{n,GPC}$[a] (g/mol) | PDI | Conv.$_{GC}$ PFS (%) | Conv.$_{NMR}$ PFS (%) | Conv.$_{NMR}$ OEGMA$_{8.5}$ (%) | Sol.[b] | Composition |
	PFS	OEGMA$_{8.5}$							
R1	90	10	6,100	1.22	0.29	0.30	0.44	−	P(PFS)$_{27}$-r-(OEGMA$_{8.5}$)$_4$
R2	75	25	10,900	1.27	0.35	0.32	0.41	−	P(PFS)$_{24}$-r-(OEGMA$_{8.5}$)$_{10}$
R3	60	40	17,400	1.27	0.75	0.76	0.77	+	P(PFS)$_{46}$-r-(OEGMA$_{8.5}$)$_{31}$
R4	50	50	19,500	1.73	0.69	0.68	0.67	+	P(PFS)$_{34}$-r-(OEGMA$_{8.5}$)$_{34}$
R5	25	75	24,000	1.52	0.93	0.94	0.90	+	P(PFS)$_{24}$-r-(OEGMA$_{8.5}$)$_{68}$
R6	10	90	23,700	1.47	0.91	0.88	0.82	+	P(PFS)$_9$-r-(OEGMA$_{8.5}$)$_{74}$

[a] Calculated according to polystyrene standards.
[b] "Sol." stands for solubility and is determined in water at room temperature at a concentration of 5 mg/mL.
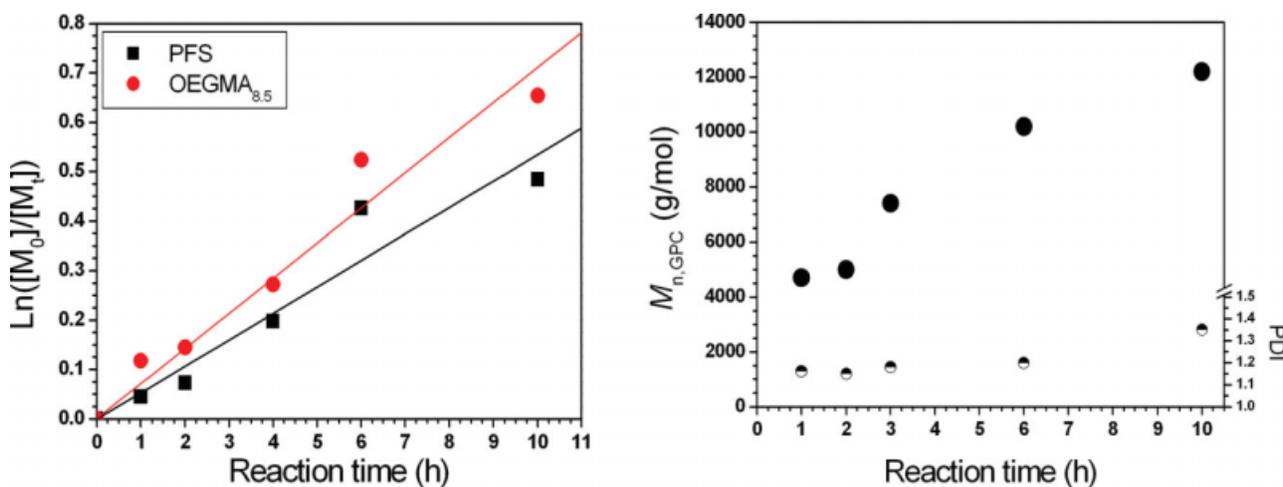
FIGURE 3 Semilogarithmic kinetic plot for the NMP of PFS/OEGMA$_{8.5}$ with a respective ratio of 75:25 (left). Molar mass (M_n) and polydispersity index (PDI) versus reaction time plot (right) of the obtained copolymers. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

polymers showed an increasing trend. PDI values increased from 1.22 to 1.73 with higher amounts of the OEGMA$_{8.5}$ monomer. Interestingly, the PDI values are relatively lower at very low content (10%) **R6** and at very high content (90%) **R1** of PFS. A lower PDI value is expected at lower PFS content as an improved control over the SG-1-mediated copolymerization of OEGMA (91.2 mol %) and styrene (8.8 mol %) has been observed by addition of small amount of styrene, as reported in the literature.[21] However, the authors have performed the polymerization either in bulk or in ethanol and kept the monomer conversion below 70%, which both may have significant effects on the polymerization kinetics and the control over the PDIs.

The monomer conversions were calculated using both GC and ^{1}H NMR spectroscopy, and the calculated values are all in good correlation. The copolymers were precipitated in hexane to remove the unreacted monomers and solvent. Afterward, the solubility behaviors of **R1**–**R6** were examined in water at room temperature. It was observed that copolymers with more than 40 mol % OEGMA$_{8.5}$ content are soluble in water, whereas copolymers with lower OEGMA$_{8.5}$ content are not soluble because of the high amount of fluorinated repeating units.

The nitroxide-mediated copolymerization kinetics of a random copolymer **R2** has been followed as a representative example. As illustrated in Figure 3, both monomers exhibit linearly increasing trends in the semilogarithmic kinetic plot, although the conversion values of OEGMA$_{8.5}$ are slightly higher than those of PFS. This is a good indication that both monomers are incorporated randomly in the copolymer and are not forming di- or quasi-block copolymers. Moreover, the molar masses and the PDI values were followed by SEC measurements. The molar masses increased in time, and the PDI values stayed below 1.4 throughout the polymerization. However, it should be noted that the molar mass calculations were performed according to linear polystyrene calibrations,

and the hydrodynamic volume of the graft-shaped copolymers may not increase linearly with their corresponding absolute molar mass. Unfortunately, MALDI-TOF MS measurements did not provide a well resolved spectrum, and the proton peaks that belong to the initiator or free nitroxide (SG1) could not be detected separately in the ^{1}H NMR spectrum.

The synthesized copolymers of PFS and OEGMA$_{8.5}$ were examined for their phase transition behavior in aqueous solution. For this purpose, a solution of each copolymer was prepared in pure water with a concentration of 5 mg/mL. Subsequently, the transmission through the vial during the turbidimetry measurement was recorded. The turbidity measurements were performed using a Crystal 16 or an
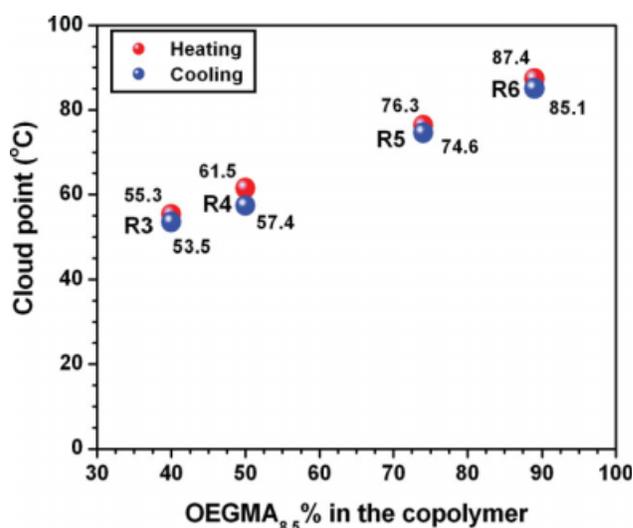
FIGURE 4 Cloud points of P(PFS)-*r*-(OEGMA$_{8.5}$) copolymers measured in water. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]
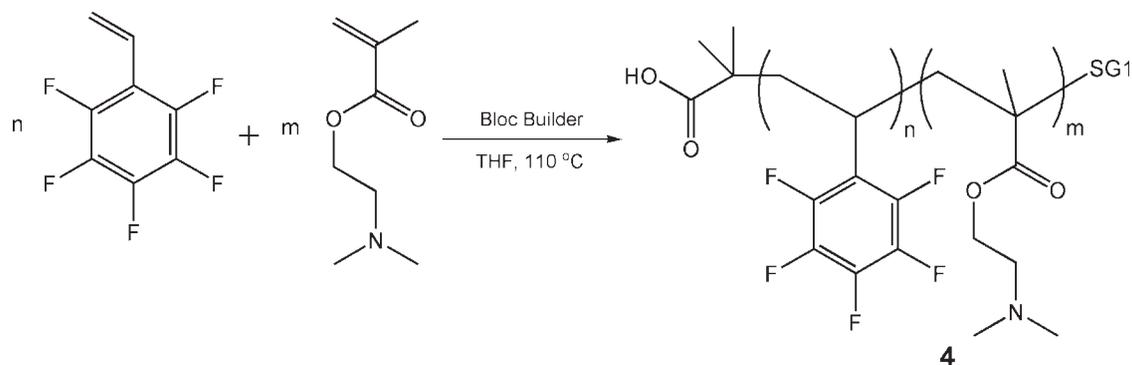
SCHEME 3 Schematic representation of NMP of pentafluorostyrene and 2-(dimethylamino) ethyl methacrylate at various ratios initiated by Bloc Builder.

UV–vis spectrometer. The samples were heated from 0 to 100 °C with a heating ramp of 1 °C/min, held for 5 min, cooled down to 0 °C, held for 5 min, and the same cycle was repeated twice. The transmittance decreased sharply because of the precipitation of the polymer as soon as the cloud point of the solution was reached. The cloud points are reported at 50% transmittance. It is known that the cloud points can be tuned by incorporation of hydrophobic monomers into the water-soluble copolymers.[16(a),23] Similarly, the cloud points of the copolymers synthesized in this study were increased from 53 to 87 °C with higher content of $OEGMA_{8.5}$ (Fig. 4). Besides, there is a slight hysteresis observed between the heating and cooling cycles, in particular for the copolymers having a lower $OEGMA_{8.5}$ content.

The SG-1-mediated copolymerization of PFS and DMAEMA was performed in toluene using Bloc Builder as an initiator (Scheme 3). The reactions were conducted in pressure-resistant vials at 110 °C for 6 h and immediately cooled down after the reaction. The solutions were precipitated into hexane to remove the unreacted monomer and solvent. As listed in Table 3, copolymerizations were performed using different molar ratios of PFS and DMAEMA ranging from 75:25 to 10:90, respectively. The molar masses of the copolymers were determined by SEC measurements according to a PS calibration. PDI values were increased with higher content of DMAEMA. The monomer conversions were determined by both GC and ^{1}H NMR spectroscopy, and the values found with both the techniques are in good correlation. Subse-

quently, the solubility behavior of the purified PFS-r-DMAEMA copolymers was investigated. Unfortunately, only **R10** was found to be soluble in water at room temperature. The turbidity measurement of **R10** revealed a cloud point at 32.0 °C. The cloud point of the homopolymer solution of DMAEMA was determined as 46.6 °C at pH 7 in our previous studies.[24] Incorporation of 10 mol % of PFS resulted in a 14 °C decrease of the cloud point. Therefore, the insolubility of copolymers with more than 25 mol % PFS content was expected.

Furthermore, the p(PFS)$_{33}$-r-(OEGMA$_{8.5}$)$_{22}$ copolymer **R3** was functionalized via the thiol-para fluoro click reaction. The cloud point of the aqueous solution of the **R3** copolymer was determined to be at 55.3 °C and is expected to decrease by the use of a controlled "click" reaction. The hydrophobic content of the copolymer could be increased by introducing phenyl rings to the side chains. Recently, Cooper and co-workers reported a similar approach where they systematically end functionalized pDMAEMA with different alkyl end groups.[18] The authors followed a high-throughput approach and were able to determine the structure–LCST relationships. In our approach, the side groups of the copolymers were functionalized at different ratios to vary their phase transition behaviors. The schematic representation of the "click" reaction is depicted in Scheme 4. The reactions were performed in THF as solvent and at room temperature for 15 h. Different amounts of thiophenol were used with respect to the copolymer. The polymers were characterized by SEC and

TABLE 3 Random Copolymerization of PFS and DMAEMA at Various Ratios

|	Feed Ratio				Conv.$_{GC}$ (%)		Conv.$_{NMR}$ (%)			
Run	PFS	DMAEMA	$M_{n,GPC}$[a] (g/mol)	PDI	PFS	DMAEMA	PFS	DMAEMA	Sol.[b]	Composition
R7	75	25	4,700	1.21	0.10	0.25	0.12	0.24	−	P(PFS)$_9$-r-(DMAEMA)$_6$
R8	50	50	10,600	1.28	0.54	0.65	0.53	0.62	−	P(PFS)$_{27}$-r-(DMAEMA)$_{31}$
R9	25	75	12,600	1.38	0.70	0.70	0.70	0.66	−	P(PFS)$_{18}$-r-(DMAEMA)$_{50}$
R10	10	90	9,500	1.55	0.68	0.63	0.64	0.62	+	P(PFS)$_6$-r-(DMAEMA)$_{56}$

[a] Calculated according to polystyrene standards.
[b] Solubility is determined in water at room temperature at a concentration of 5 mg/mL.

^{19}F NMR spectroscopy. Complete conversion of thiophenol was observed for all click reactions, according to ^{19}F NMR spectroscopy. Thus, the **R3** copolymer was functionalized with 56, 80, and 100% thiophenol to yield **C1**, **C2**, and **C3**, respectively, as listed in Table 4. Furthermore, based on the SEC measurements, the hydrodynamic volume of the copolymers did not change after clicking different amounts of thiophenol. This might be due to the polymeric architecture, which is a graft-shaped copolymer. Relatively long PEG side chains might form the hydrodynamic sphere of the copolymer, and introducing phenyl groups to the PFS units does not affect the overall hydrodynamic volume of the polymer. However, it does influence the solubility behavior of the copolymer in water. Nevertheless, we detected the absorbance of the phenyl ring at 254 nm in the UV detector, which is also a direct indication for the successful "click" reaction.

The cloud points of the random copolymers clicked with thiophenol were detected by measuring transmittance at 500 nm in the UV–vis spectrometer. The solution of the starting random copolymer **R3** exhibited a cloud point at 55.3 °C. This copolymer was reacted with a certain amount of thiophenol to synthesize **C1** with 55% of the PFS units decorated with phenyl rings. Therefore, the cloud point of **R3** decreased to 43.3 °C for **C3**. Further incorporation of phenyl groups decreased the cloud point of these copolymer solutions to 33.1 °C. The obtained cloud points are listed in Table 4.

CONCLUSIONS

We reported here for the first time the nitroxide-mediated radical copolymerization of PFS and OEGMA or DMAEMA. These copolymers exhibited a thermoresponsive behavior at certain monomer compositions, and the cloud points could be varied from 87 to 53 °C by controlling the incorporation of more fluorophilic monomeric units into OEGMA$_{8.5}$- or DMAEMA-containing copolymers. Moreover, the thiol-*para* fluoro "click" reaction was performed using both the homopolymer of PFS and also its copolymer with OEGMA$_{8.5}$. The reaction was followed by ^{1}H and ^{19}F NMR spectroscopy techniques and SEC. The cloud point of P(PFS)-*r*-(OEGMA)$_{8.5}$ could be decreased from 55.3 to 33.1 °C by controlled clicking of thiophenol groups at different ratios. We have demonstrated here that cloud points of well-defined copolymers could be tuned not only by the CRP of responsive monomers but also by using the "click" reaction in a controlled fashion.
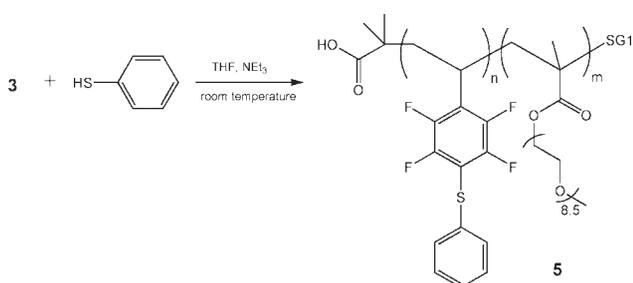
SCHEME 4 Schematic representation of the thiol-*para* fluoro "click" reaction using thiophenol and PPFS$_{46}$-*r*-PEGMA$_{31}$ copolymer.

TABLE 4 Cloud Points of PPFS$_{46}$-*r*-PEGMA$_{31}$ Copolymers Clicked with Different Ratios of PhSH

	Conv. (%) ^{19}F NMR	$M_{n,GPC}$ (g/mol)	PDI	Cloud Point (°C)
R3	–	17,400	1.27	55.3
C1	56	18,200	1.26	43.3
C2	80	18,200	1.27	35.7
C3	100	16,900	1.32	33.1

These results will be the basis for the synthesis of stimuli-responsive glycopolymers. Moreover, the absolute molar mass of these copolymers will be investigated further in detail.

REFERENCES AND NOTES

1 (a) Hawker, C. J.; Wooley, K. L. Science 2005, 309, 1200–1205; (b) Förster, S.; Antonietti, M. Adv Mater 1998, 10, 195–217; (c) Balazs, A. C.; Emrick, T.; Russell, T. P. Science 2006, 314, 1107–1110.

2 (a) Moad, G.; Rizzardo, E.; Thang, S. H. Acc Chem Res 2008, 41, 1133–1142; (b) Kamigaito, M.; Ando, T.; Sawamoto, M. Chem Rev 2001, 101, 3689–3745; (c) Xia, J. H.; Matyjaszewski, K. Chem Rev 2001, 101, 2921–2990; (d) Ouchi, M.; Takaya, T.; Sawamoto, M. Chem Rev 2009, 109, 4963–5050; (e) Rosen, B.; Percec, V. Chem Rev 2009, 109, 5069–5119; (f) Percec, V. Chem Rev 2009, 109, 4961–4962.

3 (a) Hawker, C. J.; Bosman, A. W.; Harth, E. Chem Rev 2001, 101, 3661–3668; (b) Sciannamea, V.; Jerome, R.; Detrembleur, C. Chem Rev 2008, 108, 1104–1126.

4 (a) Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Angew Chem Int Ed 2009, 48, 4900–4908; (b) Lutz, J.-F. Angew Chem Int Ed 2008, 47, 2182–2184; (c) Tunca, U.; Ozyurek, Z.; Erdogan, T.; Hizal, G. J Polym Sci Part A: Polym Chem 2004, 42, 4228–4236; (d) Durmaz, H.; Colakoclu, B.; Tunca, U.; Hizal, G. J Polym Sci Part A: Polym Chem 2006, 44, 1667–1675; (e) Durmaz, H.; Dag, A.; Erdogan, E.; Demirel, A. L.; Hizal, G.; Tunca, U. J Polym Sci Part A: Polym Chem 2010, 48, 99–108. (f) Lowe, A. Polym Chem, in press; DOI: 10.1039/b9py00216b; (g) Iha, R. K.; Wooley, K. L.; Nystrom, A. M.; Burke, D. J.; Kade, M. J.; Hawker, C. J Chem Rev 2009, 109, 5620–5686; (h) Sumerlin, B. S.; Vogt, A. P. Macromolecules, in press; DOI: 10.1021/ma901447e.

5 (a) Debuigne, A.; Poli, R.; Jerome, C.; Jerome, R.; Detrembleur, C. Prog Polym Sci 2009, 34, 211–239; (b) Percec, V.; Guliashvili, T.; Ladislaw, J. S.; Wistrand, A.; Stjerndahl, A.; Sienkowska, M. J.; Monteiro, M. J.; Sahoo, S. J Am Chem Soc 2006, 128, 14156–14165; (c) Haddleton, D. M.; Crossman, M. C.; Dana, B. H.; Duncalf, D. J.; Heming, A. M.; Kukulj, D.; Shooter, A. J. Macromolecules 1999, 32, 2110–2119.

6 TEMPO: 2,2,6,6,-tetramethyl-1-piperidinyloxy nitroxide; TIPNO: tert-butyliso-propylphenyl.

7 (a) Ohno, K.; Tsujii, Y.; Miyamoto, T.; Fukuda, T.; Goto, M.; Kobayashi, K.; Akaike, T. Macromolecules 1998, 31, 1064–1069; (b) Miura, Y.; Koketsu, D.; Kobayashi, K. Polym Adv Technol 2007, 18, 647–651; (c) Narumi, A.; Matsuda, T.; Kaga, H.; Satoh, T.; Kakuchi, T. Polymer 2002, 43, 4835–4840; (d) Chen, Y. M.; Wulff, G. Macromol Chem Phys 2001, 202, 3426–3431; (e) Gotz, H.; Harth, E.; Schiller, S. M.; Frank, C. W.; Knoll, W.; Hawker, C. J. J Polym Sci Part A: Polym Chem 2002, 40, 3379–3391; (f) Ohno, K.; Izu, Y.; Yamamoto, S.; Miyamoto, T.; Fukuda, T. Macromol Chem Phys 1999, 200, 1619–1625; (g) Ohno, K.; Fukuda, T.; Kitano, H. Macromol Chem Phys 1998, 199, 2193–2197.

8 (a) Yagci, Y.; Tasdelen, M. Prog Polym Sci 2006, 31, 1133–1170; (b) Bernaerts, K.; Du Prez, F. Prog Polym Sci 2006, 31, 671–748.

9 Kolb, H. C.; Finn, M. G.; Sharpless, K. B. Angew Chem Int Ed 2001, 40, 2004–2021.

10 (a) Laughlin, S. T.; Baskin, J. M.; Amacher, S. L.; Bertozzi, C. R. Science 2008, 320, 664–667; (b) Ning, X.; Guo, J.; Wolfert, M. A.; Boons, G. J. Angew Chem Int Ed 2008, 47, 2253–2254; (c) Sawoo, S.; Dutta, P.; Chakraborty, A.; Mukhopadhyay, R.; Bouloussa, O.; Sarkar, A. Chem Commun 2008, 5957–5959; (d) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. Proc Natl Acad Sci USA 2007, 104, 16793–16797; (e) Rosen, B. M.; Lligadas, G.; Hahn, C.; Percec, V. J Polym Sci Part A: Polym Chem 2009, 47, 3931–3939.

11 (a) Chan, J. W.; Yu, B.; Hoyle, C. E.; Lowe, A. B. Chem Commun 2008, 4959–4961; (b) Li, M.; De, P.; Gondi, S. R.; Sumerlin, B. S. J Polym Sci Part A: Polym Chem 2008, 46, 5093–5100.

12 (a) Gress, A.; Völkel, A.; Schlaad, H. Macromolecules 2007, 40, 7928–7933; (b) Killops, K. L.; Campos, L. M.; Hawker, C. J. J Am Chem Soc 2008, 130, 5062–5064.

13 Becer, C. R.; Babiuch, K.; Pilz, K.; Hornig, S.; Heinze, T.; Gottschaldt, M.; Schubert, U. S. Macromolecules 2009, 42, 2387–2394.

14 (a) Mathur, A. M.; Drescher, B.; Scranton, A. B.; Klier, J. Nature 1998, 392, 367–370; (b) Zhang, L.; Guo, R.; Yang, M.; Xiqun, J.; Liu, B. Adv Mater 2007, 19, 2988–2992; (c) You, Y. Z.; Zhou, Q. H.; Manickam, D. S.; Wan, L.; Mao, G. Z.; Oupicky, D. Macromolecules 2007, 40, 8617–8624; (d) Dimitrov, I.; Trzebicka, B.; Mueller, A. H. E.; Dworak, A.; Tsvetanov, C. B. Prog Polym Sci 2007, 32, 1275–1343.

15 (a) Schmaljohann, D. Adv Drug Delivery Rev 2006, 58, 1655–1193; (b) Thijs, H. M. L.; Becer, C. R.; Guerrero-Sanchez, C.; Fournier, D.; Hoogenboom, R.; Schubert, U. S. J Mater Chem 2007, 17, 4864–4871.

16 (a) Schild, H. G. Prog Polym Sci 1992, 17, 163–249; (b) Robinson, D. N.; Peppas, N. A. Macromolecules 2002, 35, 3668–3674; (c) Lutz, J. F.; Weichenhan, K.; Akdemir, O.; Hoth, A. Macromolecules 2007, 40, 2503–2508; (d) Jones, J. A.; Novo, N.; Flagler, K.; Pagnucco, C. D.; Carew, S.; Cheong, C.; Kong, X. Z.; Burke, N. A. D.; Stoever, H. D. J Polym Sci Part A: Polym Chem 2005, 43, 6095–6104; (e) Lutz, J. F.; Andrieu, J.; Uzgun, S.; Rudolph, C.; Agarwal, S. Macromolecules 2007, 40, 8540–8543; (f) Goh, E. C. C.; Stoever, H. Macromolecules 2002, 35, 9983–9989; (g) Aoshima, S.; Kanaoka, S. Adv Polym Sci 2008, 210, 169–208; (h) Tan, B. H.; Gudipati, C. S.; Hussain, H.; He, C.; Liu, Y.; Davis, T. P. Macromol Rapid Commun 2009, 30, 1002–1008.

17 (a) Eggenhuisen, T. M.; Becer, C. R.; Fijten, M. W. M.; Eckardt, R.; Hoogenboom, R.; Schubert, U. S. Macromolecules 2008, 41, 5132–5140; (b) Becer, C. R.; Hahn, S.; Fijten, M. W. M.; Thijs, H. M. L.; Hoogenboom, R.; Schubert, U. S. J Polym Sci Part A: Polym Chem 2008, 46, 7138–7147; (c) Weber, C.; Becer, C. R.; Hoogenboom, R.; Schubert, U. S. Macromolecules 2009, 42, 2965–2971; (d) Becer, C. R.; Schubert, U. S. Adv Polym Sci, in press; DOI:10.1007/12_2009_16.

18 Jana, S.; Rannard, S. P.; Cooper, A. I. Chem Commun 2007, 2962–2964.

19 (a) Becer, C. R.; Paulus, R. M.; Hoogenboom, R.; Schubert, U. S. J Polym Sci Part A: Polym Chem 2006, 44, 6202–6213; (b) Vinas, J.; Chagneux, N.; Gigmes, D.; Trimaille, T.; Favier, A.; Bertin, D. Polymer 2008, 49, 3639–3647; (c) Couvreur, L.; Lefay, C.; Belleney, J.; Charleux, B.; Guerret, O.; Magnet, S. Macromolecules 2003, 36, 8260–8267; (d) Lessard, B.; Maric, M. J Polym Sci Part A: Polym Chem 2009, 47, 2574–2588; (e) Lessard, B.; Schmidt, S. C.; Maric, M. Macromolecules 2008, 41, 3446–3452.

20 (a) Charleux, B.; Nicolas, J.; Guerret, O. Macromolecules 2005, 38, 5485–5492; (b) Nicolas, J.; Dire, C.; Mueller, L.; Belleney, J.; Charleux, B.; Marque, S. R. A.; Bertin, D.; Magnet, S.; Couvreur, L. Macromolecules 2006, 39, 8274–8282.

21 Nicolas, J.; Couvreur, P.; Charleux, B. Macromolecules 2008, 41, 3758–3761.

22 Lessard, B.; Maric, M. Macromolecules 2008, 41, 7870–7880.

23 (a) Yin, J.; Ge, Z.; Liu, H.; Liu, S. J Polym Sci Part A: Polym Chem 2009, 47, 2608–2619; (b) Pietsch, C.; Hoogenboom, R.; Schubert, U. S. Angew Chem Int Ed 2009, 48, 5653–5656.

24 Fournier, D.; Hoogenboom, R.; Thijs, H. M. L.; Paulus, R. M.; Schubert, U. S. Macromolecules 2007, 40, 915–920.