Synthesis and Evaluation of a Functional, Water- and Organo-Soluble Nitroxide for "Living" Free Radical Polymerization

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ABSTRACT: The synthesis of a carboxy-functionalized nitroxide based on the 2,2,5-trimethyl-4-phenyl-3-azahexane-3-oxy (TIPNO) structure and the synthesis of two difunctional alkoxyamines have been achieved. Because of the presence of the carboxylic acid function, the nitroxide is organo-soluble in its acidic form and water-soluble in its basic form. Polymerizations of styrene and *n*-butyl acrylate mediated with the functional nitroxide exhibited all the expected features of a controlled system. The presence of an active chain end was demonstrated by reinitiation of a polystyrene block to form a polystyrene-*b*-poly(*n*-butyl acrylate) block copolymer. The ability of the new functional nitroxide to mediate polymerization in homogeneous aqueous solution has also been demonstrated. The polymerization of sodium styrenesulfonate was successfully achieved at temperatures below 100 °C and led to well-defined polymers, providing the first example of nitroxide-mediated radical polymerization (NMP) in homogeneous aqueous solution below the water boiling point.

Introduction

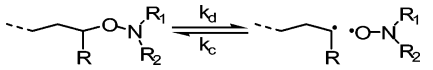
Nitroxide-mediated radical polymerization (NMP) is one of the most advantageous methods for synthesizing polymers of well-defined architectures.[1,2] Indeed, controlled free-radical polymerization (CRP) methods, including also atom transfer radical polymerization (ATRP)[3−5] and reversible chain transfer (i.e., iodine transfer polymerization,[6,7] reversible addition−fragmentation chain transfer (RAFT),[8,9] tellurium-mediated radical polymerization,[10−12] and quinone transfer radical polymerization[13]), combine some of the desirable attributes of traditional free radical systems (e.g., relative insensitivity to water and polar organic impurities) with the advantages of living ionic polymerization techniques (e.g., low polydispersity and preparation of chain-end functionalized and block copolymers).[14−16]

NMP is based on a reversible activation−deactivation equilibrium (Scheme 1) in which nitroxide reversibly deactivates the growing radical into dormant alkoxyamine. This equilibrium is highly shifted toward alkoxyamine, providing a low concentration of free radicals during the entire polymerization. This low radical concentration allows a decrease in the number of irreversible termination events. Furthermore, the activation reaction in NMP is a spontaneous thermal process, which represents a significant advantage since neither metallic catalyst nor bimolecular exchange between macromolecular species is required.

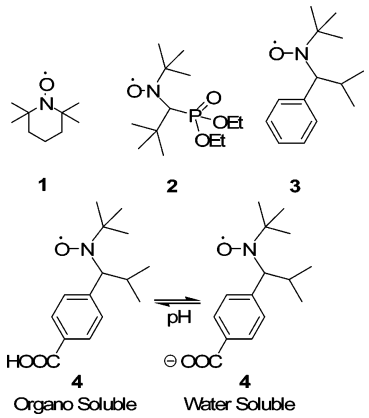
Since the initial reports by Rizzardo et al.[17] in 1985 and Georges et al.[1] in 1993 on the stable free radical polymerization (SFRP) of styrene (St), much progress has been made in this field. Indeed, as most of first generation nitroxides could only control the polymerization of styrene and styrene-like monomers, 2,2,6,6-tetramethylpiperidinyl-1-oxyl (TEMPO), **1** (Scheme 2), being a representative example of them, several groups have been working on the synthesis of new nitroxides to widen the scope of monomers polymerizable by NMP. Tordo et al. developed a phosphonate group bearing nitroxide, **2**[18−20] (Scheme 2), and Hawker and colleagues[21−23] synthesized a series of acyclic α-hydrogen-bearing nitroxides and corresponding alkoxyamines, which enabled the controlled radical polymerization of a wide range of monomers, like styrene, acrylates, acrylamides, 1,3-dienes, and acrylic acid.[24] Studer's group[25,26] and others[27−31] have also significantly improved the efficiency of NMP by developing a variety of nitroxides and alkoxyamines.

During the past few years, there has been a great tendency to replace the volatile, flammable, and toxic organic solvents used in synthetic reactions with "greener" ones, such as water,[32] supercritical carbon dioxide,[33] or ionic liquids.[34] The development of controlled radical polymerization in aqueous media (homogeneous or dispersed) is thus of great interest, not only for environmental reasons but also because water-soluble (co)polymers of controlled molar mass and structure cannot be prepared directly by other ''living" polymerization tech-

Scheme 1. Activation−Deactivation Equilibrium in NMP (Equilibrium Constant: $K = k_d/k_c$)



Scheme 2. TEMPO, 1, DEPN, 2, TIPNO, 3, and New Carboxy Functional Nitroxide, 4



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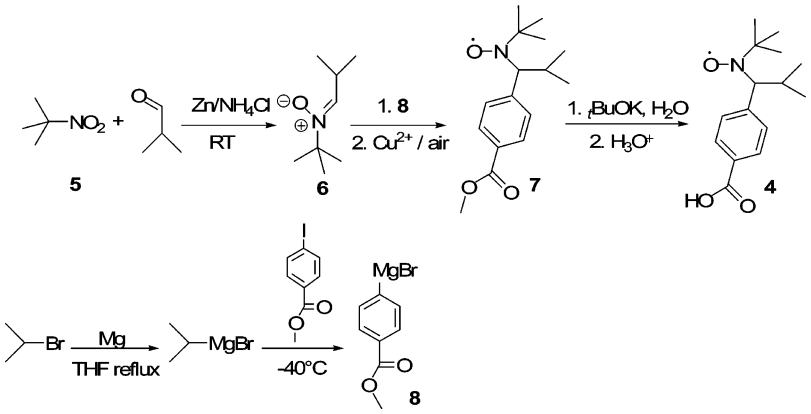
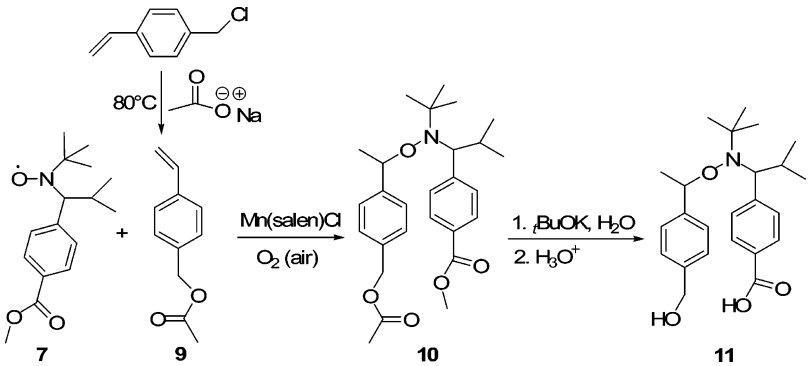
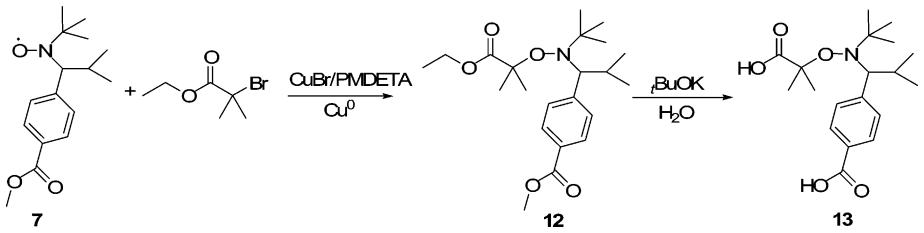
Scheme 3. Synthesis of the New Functional Nitroxide, 4



Scheme 4. Synthesis of Heterodifunctional Alkoxyamine 11 by Manganese Coupling



Scheme 5. Synthesis of Homodifunctional Alkoxyamine 13 by Atom Transfer Radical Cross-Coupling



niques.[35,36] Functional groups, which impart water solubility to monomers and polymers, are not compatible with ionic polymerizations and require chemical protection prior to polymerization.

Up to now, RAFT has emerged as the most powerful CRP technique for homogeneous aqueous polymerization due to the variety of monomers polymerizable with this process.[37]

Various ATRP systems have been studied,[35,38−40] but because of the occurrence of several side reactions, the number of water-soluble monomers polymerized in controlled fashion is still limited. Acidic monomers such as sodium methacrylate (NaMA) or sodium vinylbenzoate (NaVBA) are good examples to illustrate some of the difficulties encountered during homogeneous aqueous ATRP reactions.[35] With these monomers, the catalyst can be destroyed either by monomer coordination to the transition metal at high pH or by protonation of the ligand at low pH, resulting in a loss of the complexing ability. In addition to the catalyst, the end functionality of the initiator, or propagating chain end, can also be involved in side reactions. Typical initiators used for ATRP in aqueous solution are either alkyl chlorides or alkyl bromides. In the presence of water, these halides may undergo nucleophilic substitution by water, or elimination of hydrogen halide, particularly at high temperatures.[35]

In the case of NMP, trouble for polymerization in homogeneous aqueous solution comes from the fact that NMP is a thermal process. On one hand, NMP requires nitroxides that display high activation−deactivation equilibrium constant at the proceeding polymerization temperatures. On the other hand, the boiling point of the solvent is the highest temperature that cannot be risen above at atmospheric pressure. At the beginning of the investigation of NMP, the majority of available alkoxyamines were based on five- or six-membered-ring nitroxides, so that high temperatures (120 °C) were required to efficiently control and carry out the polymerization. As a result, polymerization in pure water at atmospheric pressure was not possible. Therefore, pressure vessels[41] or addition of a high boiling point solvent, such as ethylene glycol,[42] was necessary for aqueous polymerization.

With the discovery of second-generation nitroxides, which display higher activation−deactivation equilibrium constant than TEMPO, polymerization in "purely" homogeneous aqueous solution should be possible below water's boiling point. However, very few water-soluble alkoxyamines have been described. Furthermore, these alkoxyamines cleave into a hydrophobic nitroxide and a water-soluble initiating radical.[43] As a result, NMP has been mainly studied in dispersed aqueous media,[41] using bicomponent or monocomponent initiating

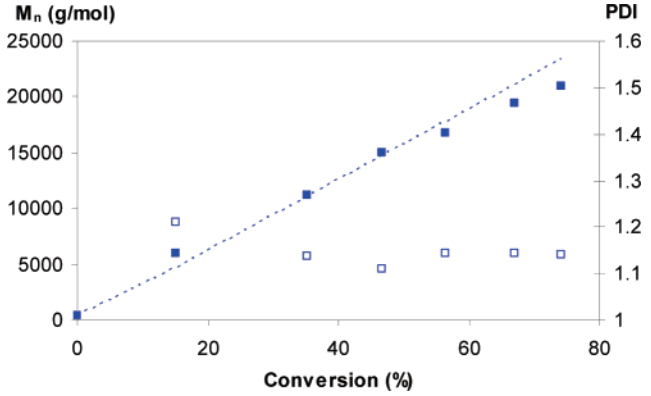


Figure 1. Plot of M_n and M_w/M_n vs conversion for bulk polymerization of styrene at 123 °C with alkoxyamine **11**. Experimental conditions: [**11**] = 30 mmol L^{-1}; bulk; T = 123 °C.

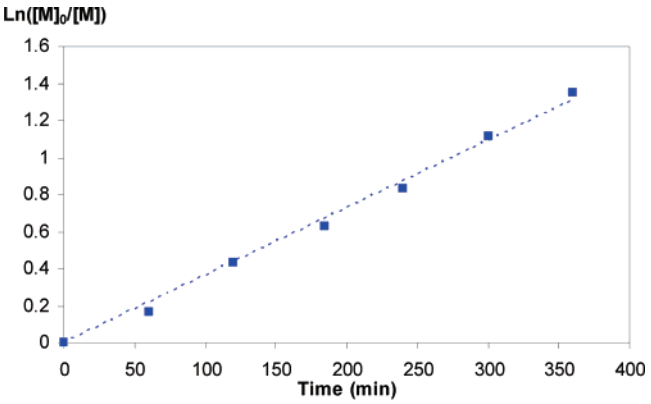


Figure 2. Kinetic plot for bulk polymerization of styrene at 123 °C with alkoxyamine **11**. Experimental conditions: [**11**] = 30 mmol L^{-1}; bulk; T = 123 °C.

systems. Nevertheless, only one report[44] about polymerization below water boiling point in dispersed aqueous media is available in the literature. To our knowledge, water-soluble alkoxyamines based on a water-soluble nitroxide are unknown.

The desire to prepare well-defined telechelic polymers that can be used for several applications, such as the synthesis of macrocycles[45] or multisegmented (co)polymers,[46] prompted us to develop a new functional nitroxide. The introduction of carboxylic acid function on the mediating agent was of interest, as it should confer water solubility to the nitroxide and thus allow various water-soluble monomers to be polymerized by NMP in homogeneous aqueous solution.

In this work, we present the synthesis of a new carboxy functional, water- and organo-soluble nitroxide, 2,2,5-trimethyl-4-*p*-carboxyphenyl-3-azahexane-3-nitroxide, **4**, based on the structure of the 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide, also known as TIPNO, **3**[21] (Scheme 2). The carboxylic acid function makes this compound water-soluble in its basic form and organo-soluble in its acidic form. We also report on the synthesis of difunctional water-soluble alkoxyamines and their use to prepare "homo"- and "hetero"telechelic polymers and copolymers (block and gradient copolymers). We finally demonstrate the ability of this new functional nitroxide to

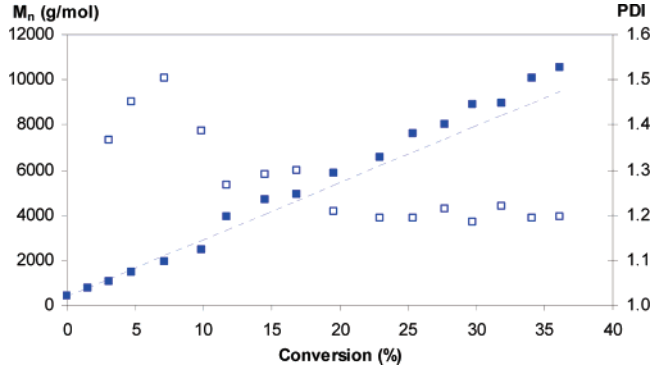


Figure 3. Plot of M_n and M_w/M_n vs conversion for bulk polymerization of *n*-butyl acrylate at 125 °C with alkoxyamine **11**. Experimental conditions: [**11**] = 37 mmol L^{-1}; [**4**] = 2.22 mmol L^{-1}; bulk; T = 125 °C.

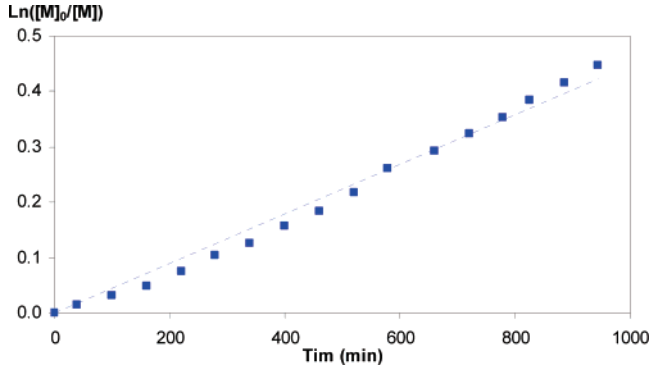


Figure 4. Kinetic plot for bulk polymerization of *n*-butyl acrylate at 125 °C with alkoxyamine **11**. Experimental conditions: [**11**] = 37 mmol L^{-1}; [**4**] = 2.22 mmol L^{-1}; bulk; T = 125 °C.

mediate the polymerization of sodium styrenesulfonate in homogeneous aqueous solution at temperature below 100 °C.

Results and Discussion

The synthesis of the nitroxide **4** was based on the strategy developed by Hawker and colleagues for the preparation of α-hydrogen-bearing nitroxides.[21] The reductive condensation of 2-methyl-2-nitropropane, **5**, with isobutyraldehyde gave *N*-*tert*-butyl-α-isopropylnitrone, **6**, in a single high-yielding step (Scheme 3). Addition of a functional organomagnesium reagent, **8**, to a solution of **6** in THF, at low temperature, followed by copper(II)-catalyzed oxidation under ambient atmosphere resulted in the formation of the protected nitroxide **7**, in 60% yield. The functional unsaturated Grignard reagent was prepared by iodine−magnesium exchange as described by Cahiez and Knochel[47] and reacted in situ with the nitrone **6**. The efficient reaction of i-PrMgX with a wide range of functionalized aryl iodides proceeds under mild conditions, so that various sensitive functional groups such as ester, nitrile, or amide function are tolerated during the organomagnesium reagent formation. Thus, this procedure allows the preparation of a wide range of functional nitroxides. The nitroxide was then deprotected by basic hydrolysis[48] to give finally the nitroxide **4** in 99% yield.

A heterodifunctional alkoxyamine, **11**, was synthesized in two supplementary steps. The diprotected alkoxyamine **10** was

Table 1. Synthesis of Styrene−*n*-Butyl Acrylate Random Copolymers, with Alkoxyamine 11

initial [styrene]/[butyl acrylate]	[styrene]/[butyl acrylate] in the copolymer	conversion (%)	M_n,NMR (g/mol)	M_n,SEC (g/mol)	PDI
71.3/28.7	73.4/26.6	65.7	19 430	17 220	1.15
50/50	58.9/41.1	66.55	21 350	15 440	1.24
31.8/68.2	44.4/55.6	63.2	21 360	22 620	1.17

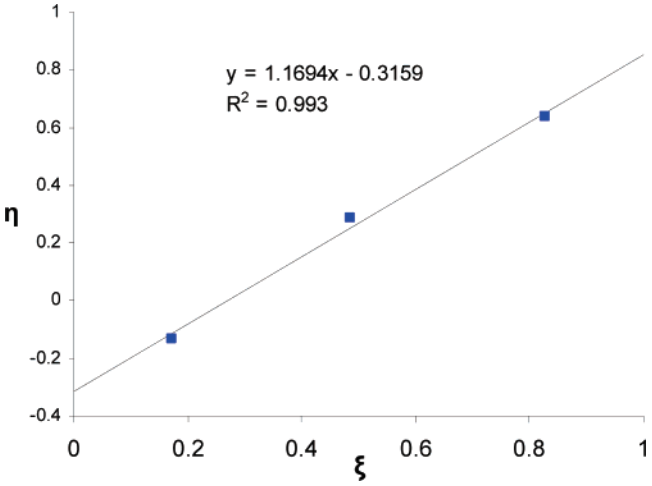


Figure 5. Kelen−Tüdos plot for bulk copolymerization of styrene and *n*-butyl acrylate mediated by alkoxyamine **11** at 125 °C.

obtained by coupling the nitroxide **7** with 4-vinylbenzyl acetate, **9**,[49] in the presence of a Salen−manganese complex[49] (Scheme 4). 4-Vinylbenzyl acetate, **9**,[49] was obtained in quantitative yield by reaction of sodium acetate with 4-vinylbenzyl chloride. The alkoxyamine **10** was then deprotected by basic hydrolysis of the two ester functions, to afford, after acidification, the α-hydroxy-ω-carboxyalkoxyamine **11** in 86% yield. This alkoxyamine was especially designed to obtain heterotelechelic polymers that can be used as precursors to cyclic[45] or multisegmented polymers.[46]

A homodifunctional alkoxyamine, **13**, was also synthesized by atom transfer radical cross-coupling[50] (Scheme 5). Reaction between the protected nitroxide **7** and ethyl 2-bromoisobutyrate in the presence of an excess of Cu(0) gave a diprotected alkoxymine, **12**, in 77% yield. The basic hydrolysis of **12** resulted, after acidification, in the formation of the dicarboxyalkoxyamine **13** in 89% yield. This alkoxyamine was especially designed for aqueous polymerizations, where the two carboxylic acid functions provide water solubility in their basic forms.

Polymerization of Styrene. The effectiveness of the difunctional alkoxyamine **11** for the living free radical polymerization of styrene was probed at 123 °C under bulk conditions. Good control was achieved up to high conversion. A linear increase of the molecular weight with conversion as well as low PDIs was observed (Figure 1). Using 30 mmol L^{-1} of **11**, polystyrene with $M_n = 20\,960$ g mol^{-1} and a polydispersity index of 1.14 was obtained after 6 h. A linear relationship between $\ln([M]_0/[M])$ vs time was observed, indicating that no detectable termination occurred in this system (Figure 2).

Polymerization of *n*-Butyl Acrylate. In contrast to TEMPO, the second generation of nitroxides, which includes the *N*-*tert*-butyl-*N*-(1-diethylphosphono-2,2-dimethylpropyl) nitroxide, also called SG1 or DEPN,[20,51] and TIPNO,[21] allows the control of not only styrene but also a wide range of monomers, such as acrylates, substituted acrylamides, and dienes.[20−22,51] The effectiveness of the difunctional alkoxyamine **11** for the living free radical polymerization of *n*-butyl acrylate was thus tested at 125 °C under bulk conditions. Good control was achieved with linear increase of the molecular weight and low polydispersity (Figure 3). Using 37 mmol L^{-1} of **11** with 6% of free nitroxide **4**, poly(*n*-butyl acrylate) with $M_n = 10\,900$ g mol^{-1} and a polydispersity index of 1.19 was obtained after 15 h 45 min. A linear relationship between $\ln([M]_0/[M])$ vs time was again observed, indicating that no detectable termination occurred in this system (Figure 4).

Random Copolymers. One of the major advantages of radical polymerization over most other forms of polymerization (anionic, cationic, coordination) is that statistical copolymers can be prepared from a wide range of comonomers containing various unprotected functionalities.[52] The good control obtained for styrene and *n*-butyl acrylate homopolymerizations using the heterodifunctional alkoxyamine **11** prompted us to investigate their random copolymerization for different ratios of styrene and *n*-butyl acrylate.

Using a constant [monomers]/[alkoxyamine] molar ratio of 285, styrene and *n*-butyl acrylate were copolymerized at 125 °C for 8 h without any free nitroxide. Well-defined copolymers, with low PDI, were obtained independent of the initial composition (Table 1).

In every case, a drift of the composition in the final copolymer was observed, as compared to the initial ratio of monomers (Table 1). The Kelen−Tüdos linearization method[53] was used to calculate reactivity ratios of styrene and *n*-butyl acrylate (Table 2). Plotting η against ξ gave a straight line which from $r_{n\mathrm{BA/S}}/\alpha$ and $r_{\mathrm{S}/n\mathrm{BA}}$ can be extracted as intercepts via extrapolation to $\xi = 0$ and $\xi = 1$ (Figure 5). Values of $r_{\mathrm{S}/n\mathrm{BA}}$ and $r_{n\mathrm{BA/S}}$ were found to be 0.854 and 0.124, respectively, in good agreement with Chambart et al.,[54] who reported values of $r_{\mathrm{S}/n\mathrm{BA}}$ 0.81 and $r_{n\mathrm{BA/S}}$ 0.23 at 120 °C.

Block Copolymers. To confirm the presence of dormant initiating centers at the chain end of linear polymers prepared with the new functional alkoxyamine **11**, block copolymers were synthesized.

An alkoxyamine-functionalized polystyrene block, **14** ($M_n = 15\,900$ g mol^{-1}, PDI = 1.10), was initially prepared and then used to polymerize 300 equiv of *n*-butyl acrylate, in the presence of an additional 0.06 equiv of nitroxide **4** at 125 °C for 16 h (Scheme 6). The polymerization gave the block copolymer **15**, which had the expected increase in molecular weight, while the polydispersity index remained low ($M_{n(th)} = 27\,875$ g mol^{-1}, $M_{n(exp)} = 27\,650$ g mol^{-1}, PDI = 1.19). Furthermore, no unreacted polystyrene was detectable by SEC (Figure 6).

Table 2. Kelen−Tüdos Linearization for Reactivity Ratios Calculation

expt	S_0[a]	A_0[a]	S_p[b]	A_p[b]	conv	x_0[c]	y[d]
1	71.3	28.7	73.4	26.6	0.657	2.484	2.759
2	50	50	58.9	41.1	0.666	1.000	1.433
3	31.8	68.2	44.4	55.6	0.632	0.466	0.799

expt	σ_2[e]	σ_1[f]	z[g]	F[h]	G[i]	η[j]	ξ[k]
1	0.612	0.679	1.203	1.908	1.463	0.636	0.829
2	0.557	0.799	1.967	0.370	0.220	0.288	0.485
3	0.529	0.905	3.133	0.081	−0.064	−0.135	0.171

[a] Relative initial monomer ratios. [b] Relative copolymer composition. [c] $x_0 = S_0/A_0$. [d] $y = S_p/A_p$. [e] $\sigma_2 =$ conv × $(M_{\mathrm{ABu}}/M_{\mathrm{St}} + x_0)/(M_{\mathrm{ABu}}/M_{\mathrm{St}} + y)$. [f] $\sigma_1 = y/x_0\sigma_2$. [g] $z = (\ln(1 - \sigma_1))/(\ln(1 - \sigma_2))$. [h] $F = y/(z^2)$. [i] $G = (y - 1)/z$. [j] $\alpha = (F_m F_M)^{1/2}$, where F_m and F_M are the lowest and highest F values; $\eta = (z(y - 1))/(\alpha z^2 + y)$. [k] $\xi = y/(\alpha z^2 + y)$.

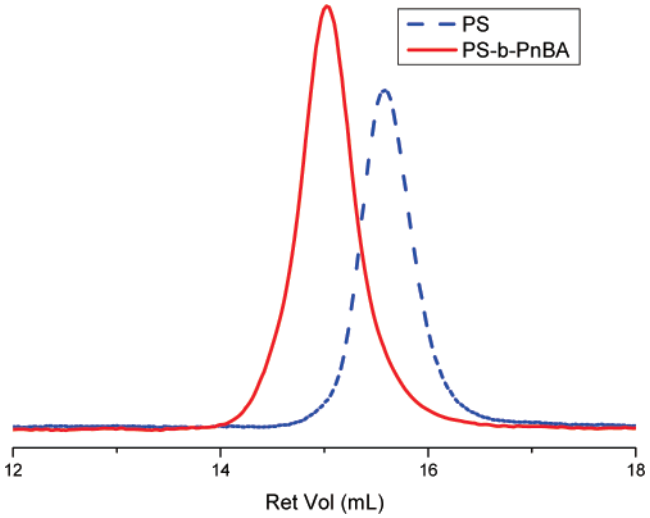


Figure 6. SEC traces of alkoxyamine-functionalized polystyrene block and poly(styrene)-*b*-poly(*n*-butyl acrylate) block copolymer. Experimental conditions: [*n*-BA]/[14]/[4] = 300/1/0.06; bulk; T = 125 °C.

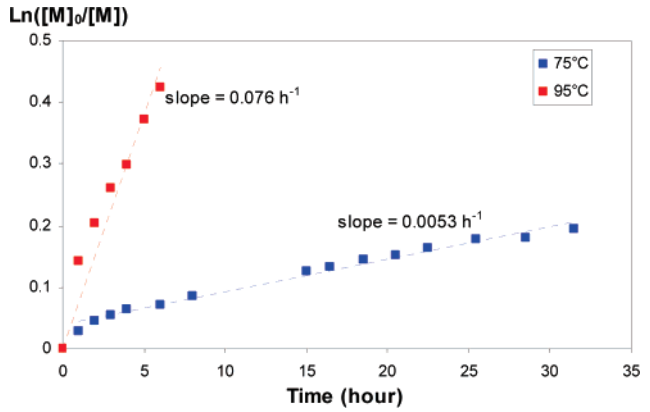


Figure 7. Kinetic plot for homogeneous aqueous polymerization of sodium styrenesulfonate at 75 and 95 °C with alkoxyamine **13**. Experimental conditions: [sodium styrenesulfonate]/[**13**] = 310; [**13**] = 1.6×10^{-3} mol L^{-1} in water; T = 75 and 95 °C.

Polymerization in Water. In many respects, water is an attractive solvent for radical polymerization. It is an inexpensive and environmentally friendly solvent that does not participate in radical transfer due to the high bond dissociation energy of its O−H bond (497 kJ mol^{-1}).[52]

Water-soluble (co)polymers of controlled molar mass and structure can only be prepared directly by CRP techniques.[35,36] Indeed, functional groups that impart water solubility to monomers and polymers are not compatible with ionic polymerizations.

It is thus very interesting to develop controlled radical polymerization in aqueous media. Various examples of heterogeneous NMP polymerizations in aqueous media have been reported. The NMP of styrene (at 90 °C)[44] and *n*-butyl acrylate[55] in miniemulsion have been described by Charleux et al. The same group has recently reported the emulsion polymerization of styrene and *n*-butyl acrylate with a water-soluble alkoxyamine initiator.[56,57]

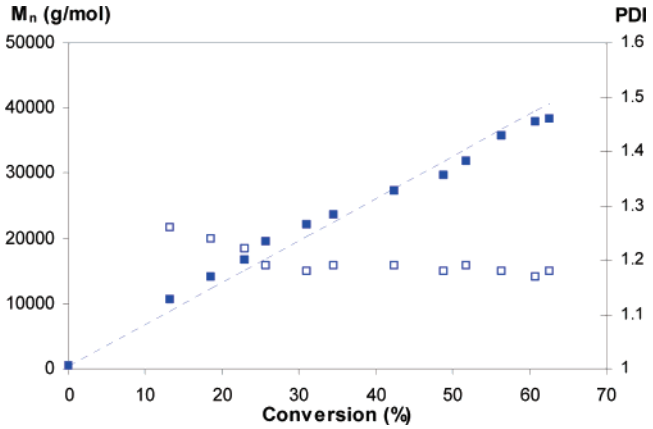


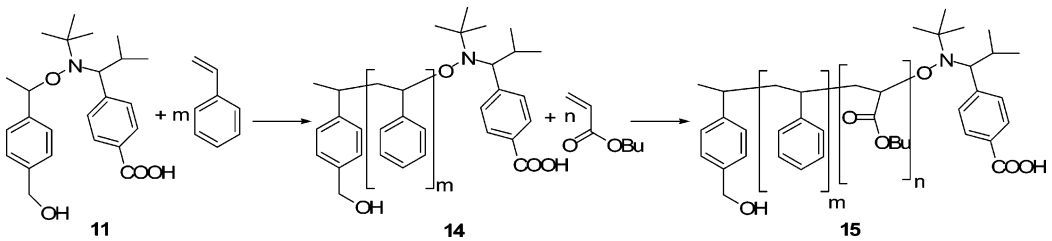
Figure 8. Plot of M_n and M_w/M_n vs conversion for homogeneous aqueous polymerization of sodium styrenesulfonate at 95 °C with alkoxyamine **13**. Experimental conditions: [sodium styrenesulfonate]/[**13**] = 310; [**13**] = 1.6×10^{-3} mol L^{-1} in water; T = 95 °C.

To our knowledge, there is only one example of NMP in "purely" homogeneous aqueous media.[58] This work reports on the synthesis of poly(sodium 4-styrenesulfonate) in water at 130 °C with nitroxides based on 1,1,3,3-tetramethylisoindolin-2-oxyl and 1,1,3,3-tetraethylisoindolin-2-oxyl with an ionic group on the aromatic ring. Yet, long polymerization times were required to prepare low molecular weight polymers (typically 6000 g/mol after 20 h). Several other examples of sodium styrenesulfonate polymerizations based on Keoshkerian's work are available in the literature.[42] However, in every case, a cosolvent was used (75−80% ethylene glycol or DMSO typically), and the polymerization temperature was around 125 °C. The new functional nitroxide **4**, which bears a carboxylic acid function, should allow us to overcome these two limitations, i.e., the use of a cosolvent and temperatures above 100 °C. On one hand, the carboxylic function will confer good water solubility to the nitroxide. On the other hand, as the structure of **4** is similar to TIPNO ($k_d = 3.3 \times 10^{-3}$ s^{-1} at 393 K in the case of phenylethyl-TIPNO-based alkoxyamine),[59] a lower dissociation constant of alkoxyamines derived from **4** compared to TEMPO-based alkoxyamines ($k_d = 5.2 \times 10^{-4}$ s^{-1} at 393 K in the case of phenylethyl-TEMPO-based alkoxyamine)[59] is expected. Controlled polymerizations at temperatures below 100 °C should thus be possible.

The ability of the new functional nitroxide **4** to mediate the polymerization of sodium styrenesulfonate at 95 and 75 °C in homogeneous aqueous solution was investigated using the difunctional alkoxyamine **13**. The two carboxylic acid functions provided good water solubility to the alkoxyamine.

Polymerization proceeded at 75 and 95 °C. As expected, the polymerization rate was significantly higher at 95 °C than at 75 °C. Indeed, the cleavage rate constant k_d depends on the

Scheme 6. Synthesis of Polystyrene-*b*-poly(*n*-butyl acrylate) Block Copolymer by NMP with Alkoxyamine 11



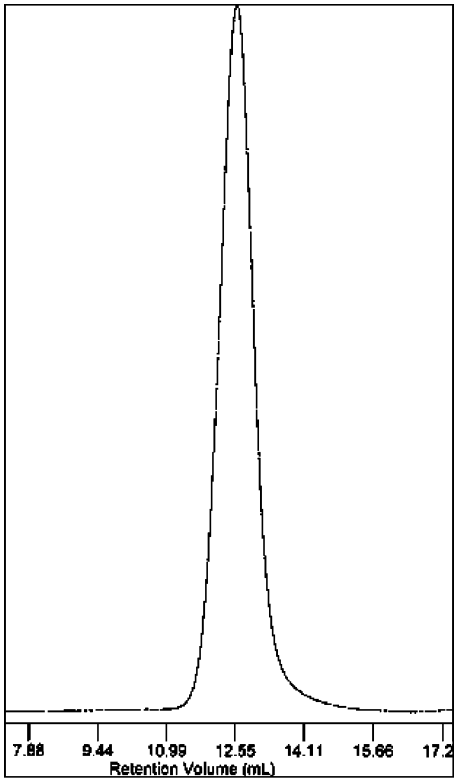


Figure 9. SEC traces of poly(sodium styrenesulfonate) obtained after 24 h of polymerization at 95 °C with alkoxyamine **13**. Experimental conditions: [sodium styrenesulfonate]/[**13**] = 310; [**13**] = $1.6.10^{-3}$ mol L^{-1} in water; T = 95 °C.

dissociation energy of the alkoxyamine bond and shows Arrhenius temperature dependencies while cross-combination constant k_c shows non-Arrhenius temperature dependencies.[60] A linear relationship between $\ln([M]_0/[M])$ vs time was observed in both cases, indicating the constant concentration of radicals in these systems (Figure 7).

A linear increase of the molecular weight with conversion as well as low PDIs and unimodal SEC traces could also be observed (Figures 8 and 9). Using 1.6×10^{-3} mol L^{-1} of alkoxyamine **13** and a ratio [monomer]/[initiator] = 310, poly(sodium styrenesulfonate) with M_n = 38 300 g mol^{-1} and a polydispersity index of 1.18 was obtained after 24 h at 95 °C (conversion 62.6%).

These results indicate that the new functional nitroxide **4** can efficiently mediate the polymerization of sodium styrenesulfonate in homogeneous aqueous solution at temperature below 100 °C.

Conclusion

The synthesis and characterization of a carboxy-functionalized nitroxide based on the structure of TIPNO have been described. Because of the presence of the carboxylic acid function, this new nitroxide is organo-soluble in its acidic form and water-soluble when deprotonated. Two functional alkoxyamines have been synthesized and characterized. The heterodifunctional alkoxyamine allows for synthesis, in one step, of heterotelechelic polymers that can be used for several applications, such as the synthesis of macrocycles,[45] multisegmented polymers,[46] or functionalized micelles. The latter could be of great interest for nanosized drug delivery systems.[61−63] The dicarboxyalkoxyamine was especially designed for aqueous polymerization. Polymerizations of styrene and *n*-butyl acrylate mediated with the new functional nitroxide exhibited all the expected features of a controlled system. The presence of an active chain end was demonstrated by reinitiation of a polystyrene block to form a polystyrene-*b*-poly(*n*-butyl acrylate) block copolymer. The ability of the new functional nitroxide to mediate polymerization in homogeneous aqueous solution was also confirmed. The polymerization of sodium styrenesulfonate was successfully achieved at temperatures below 100 °C and led to well-defined polymers, providing the first example of NMP in homogeneous aqueous solution below the water boiling point.

The NMP in water of other hydrophilic monomers with these new water-soluble alkoxyamines and the synthesis of macromolecular architectures are currently under investigation.

Experimental Section

Experimental Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on Bruker AC 200 MHz or ARX 250 MHz instruments. Proton and carbon chemical shifts are reported using the resonance of the deuterated solvent as internal standard. Elemental analyses were performed by the Service Central d'Analyses of the CNRS. Chemical ionization (CI, ammonia or methane) and electronic ionization (EI) mass spectra were obtained with a JMS-700 spectrometer.

Size exclusion chromatography (SEC) was performed at 40 °C with two columns (PSS SDV, linear MU, 8 mm × 300 mm; bead diameter, 5 μm; separation limits, $400-2 \times 10^6$ g mol^{-1}). The eluent was THF at a flow rate of 1 mL min^{-1}. A differential refractive index detector (LDC Analytical refracto-Monitor IV) was used, and molar mass distributions were derived from a calibration curve based on polystyrene (PS) standards from Polymer Standards Service.

Aqueous size exclusion chromatography (ASEC) was performed at 35 °C with two columns (Viscotek Viscogel G3000 PWXL and G4000 PWXL). The eluent was a mixture 80% 0.05 M Na_2SO_4 in water and 20% CH_3CN at a flow rate of 1 mL min^{-1}. A differential refractive index detector (Viscotek Refractive Index Detector) operating at 660 nm was used, and molar mass distributions were derived from a conventional calibration based on narrow NaPSS standards.

The monomer conversion for styrene and *n*-butyl acrylate polymerizations was determined by gravimetry after drying the polymer samples under vacuum for 48 h.

The monomer conversion for sodium styrenesulfonate polymerizations was determined by ^{1}H NMR spectroscopy in D_2O. Conversion was deduced from integration of the characteristic peaks of the vinyl protons of NaSS monomer at 5.34 (d), 5.82 (d), and 6.7 ppm (q) and of the alkyl protons of the polymer chain (broad peak centered at 1.5 ppm). Reaction samples were dried in vacuum at 50 °C prior to NMR analysis.

All reagents and chemicals were obtained from commercial suppliers without further purification: 4-vinylbenzyl chloride (technical, 90%, Aldrich), methyl 4-iodobenzoate (98%, Aldrich), and 2-methyl-2-nitropropane (Aldrich). *n*-Butyl acrylate (*n*BA, Aldrich, 99%) and styrene (S, Aldrich, 99%) monomers were distilled under reduced pressure before use. Sodium styrenesulfonate was recrystallized from a mixture MeOH/water (90/10). Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled under N_2 from sodium benzophenone, and DMF was distilled from CaH_2. Silica gel for column chromatography was Merck Kieselgel 60. Column chromatographic separations were carried out using Merck silica gel 60 (230−400 mesh) or alumina when indicated.

N-tert-Butyl-α-isopropylnitrone (**6**),[21] vinylbenzyl acetate (**10**),[49] and the Salen−manganese complex[49] were synthesized according to literature procedures.

Synthetic Procedures. Synthesis of 2,2,5-Trimethyl-4-*p*-methylbenzoate-3-azahexane-3-nitroxide TIPNO, 7. Under a nitrogen atmosphere, isopropyl bromide (10.9 mL, 116.6 mmol) was diluted in 10 mL of THF and added dropwise to a solution of magnesium (2.835 g, 116.6 mmol) in 20 mL of THF in order to have a smooth reflux. After the addition was completed, the solution was stirred

for 1 h at reflux. This solution was then added to a solution of methyl 4-iodobenzoate (27.76 g, 106 mmol) in THF (20 mL) at −40 °C. The solution was stirred for 1 h at −40 °C. A solution of *N*-*tert*-butyl-R-isopropylnitrone (10.1 g, 70.6 mmol) in 100 mL of THF was added over 10 min to the solution of methyl benzoate−magnesium bromide at −40 °C. The mixture was allowed to warm to −20 °C for 4 h. The excess Grignard reagent was decomposed by the addition of 10 mL of concentrated ammonium chloride solution followed by 30 mL of water until all solids had dissolved. The organic layer was separated, and the aqueous layer was extracted with 50 mL of diethyl ether. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated The residue obtained was then treated with a mixture of methanol (200 mL), of aqueous concentrated NH_4OH (15 mL), and of $Cu(OAc)_2$ (182 mg, 1 mmol) to give a pale yellow solution. A stream of air was bubbled through the yellow stirred solution until it became dark blue. Then the mixture was concentrated, and the crude nitroxide was purified by flash column chromatography (10:1:1 hexane/ethyl acetate/dichloromethane) to afford 11.733 g (59.8% yield) of **7**, as an orange solid. Elementary analysis: $C_{16}H_{24}NO_3^{\bullet}$ calculated: C, 69.04; H, 8.69; N, 5.03; O, 17.24, found: C, 69.04; H, 8.70; N, 4.80.

Synthesis of 2,2,5-Trimethyl-4-*p*-carboxyphenyl-3-azahexane-3-nitroxide TIPNO, 4. To a stirred suspension of potassium *tert*-butoxide (1 g, 8.9 mmol) in dry ether (10 mL), cooled to 0 °C, was added water (40 μL, 2.2 mmol) via syringe. This slurry mixture was stirred for 5 min. The nitroxide **7** (310 mg, 1.1 mmol) in solution in dry ether (5 mL) was added to this mixture. The ice bath was removed, and the reaction mixture was stirred at room temperature until the reaction was complete (over a night). The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated, acidified with concentrated hydrochloric acid, and evaporated under reduced pressure. The solid was dissolved in ethanol (15 mL), dried over anhydrous magnesium sulfate, and filtered. The solvent was evaporated to afford 294.2 mg (99.9% yield) of **4** as an orange solid. HRMS exact mass: calculated for $[M + 2]^+$ $C_{15}H_{23}NO_3$ 266.1756; found 266.1758.

Synthesis of 2,2,5-Trimethyl-3-(1-(4′-acetomethyl)phenylethoxy)-4-*p*-methylbenzoate-3-azahexane, 10. Functionalized TIPNO, **7** (3.823 g, 13.75 mmol), and 4-vinylbenzyl acetate (3.582 g, 20.35 mmol) were dissolved in 20 mL of isopropyl alcohol in an open flask. The solution was vigorously stirred, and finely ground Mn(salen)Cl catalyst (245 mg, 0.6876 mmol) was added, followed by $NaBH_4$ (0.845 g, 34.252 mmol) in small portions. After 24 h, the reaction mixture was partitioned between chloroform and 0.5 M HCl. The organic layer was separated and washed with water until it became acid-free. It was dried over $MgSO_4$, and the solvent was evaporated. The crude product was purified by column chromatography (10:1 pentane/ethyl acetate = >6/4) to afford 4.276 g (68.3% yield) of **10** as a colorless very viscous oil. ^{1}H NMR (250 MHz, $CDCl_3$, both diastereomers): δ 8.11−7.00 (m, 16H, both diastereomers), 4.89 (m, 2H, both diastereomers), 4.67 and 4.63 (each s, 4H, both diastereomers), 3.45 (d, 1H, J = 10.6 Hz, major diastereomer), 3.35 (d, 1H, J = 10.3 Hz, minor diastereomer), 2.31 (two m, 2H, both diastereomers), 2.00 and 1.92 (each s, 6H, both diastereomers), 1.60 (d, 3H, J = 6.1 Hz, major diastereomer), 1.51 (d, 3H, J = 5.9 Hz, major diastereomer), 1.28 (d, 3H, J = 5.9 Hz, minor diastereomer), 1.01 (s, 9H, major diastereomer), 0.95 (d, 3H, J = 5.9 Hz, major diastereomer), 0.75 (s, 9H, minor diastereomer), 0.50 (d, 3H, J = 6.4 Hz, major diastereomer) and 0.20 (d, 3H, J = 5.9 Hz, minor diastereomer). ^{13}C NMR (50 MHz, $CDCl_3$, both diastereomers): δ 167.49, 148.40, 148.19, 145.08, 144.23, 140.21, 139.48, 131.02, 128.61, 126.92, 126.38, 83.58, 82.65, 71.98, 65.27, 60.71, 52.01, 31.70, 28.55, 24.81, 23.25, 22.11, 21.95, 21.04. Elementary analysis: $C_{27}H_{37}NO_5$ calculated: C, 71.18; H, 8.19; N, 3.07; O, 17.56, found: C, 72.02; H, 8.46; N, 3.20.

Synthesis of 2,2,5-Trimethyl-3-(1-(4′-hydroxymethyl)phenylethoxy)-4-*p*-carboxybenzoate-3-azahexane, 11. To a stirred suspension of potassium *tert*-butoxide (770 mg, 6.857 mmol) in dry ether (10 mL), cooled to 0 °C, was added water (31 μL, 1.714 mmol) via syringe. This slurry mixture was stirred for 5 min, and a solution of functionalized alkoxyamine **10** (177 mg, 0.428 mmol) in 1 mL of dry ether was added. The ice bath was removed, and the reaction mixture was stirred at room temperature until the reaction was complete. The hydrolysis was monitored by TLC for the disappearance of the ester and was considered to be complete when the ester was no longer observed. The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The acidified solution was extracted three times with 50 mL portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered. The organic phase was evaporated to give 150 mg (87.7% yield) of **11** as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$, both diastereomers): δ 8.18−7.18 (m, 16H, both diastereomers), 6.94−5.97 (broad peak, 2H, OH, both diastereomers), 4.98 and 4.96 (m, 2H, both diastereomers), 4.73 and 4.69 (each s, 4H, both diastereomers), 3.54 (d, 1H, J = 10.33 Hz, major diastereomer), 3.43 (d, 1H, J = 10.58 Hz, minor diastereomer), 2.38 (m, 2H, both diastereomers), 1.65 (d, 3H, J = 6.15 Hz, major diastereomer), 1.56 (d, 3H, J = 6.4 Hz, minor diastereomer), 1.32 (d, 3H, J = 5.9 Hz, major diastereomer), 1.06 (s, 9H, minor diastereomer), 0.97 (d, 3H, J = 5.9 Hz, minor diastereomer), 0.80 (s, 9H, major diastereomer), 0.55 (d, 3H, J = 6.15 Hz, major diastereomer), and 0.24 (d, 3H, J = 6.37 Hz, minor diastereomer). ^{13}C NMR (50 MHz, $CDCl_3$, both diastereomers): δ 172.14, 149.01, 145.02, 144.22, 140.15, 139.41, 131.17, 129.49, 127.28, 126.46, 83.76, 82.84, 72.09, 65.33, 61.03, 32.00, 28.37, 24.81, 23.28, 22.01, 21.03. HRMS exact mass: calculated for $[M + 1]^+$ $C_{24}H_{34}NO_4$ 400.2488, found 400.2486.

Synthesis of 2,2,5-Trimethyl-3-(2-(ethyl-2-methyl-propionate)-ethoxy)-4-*p*-methylbenzoate-3-azahexane, 12. To a Schlenk flask was added ethyl 2-bromoisobutyrate (1 mL, 6.8 mmol), functionalized TIPNO **7** (2.273 g, 8.176 mmol), copper powder (2.224 g, 35 mmol), copper bromide (9.8 mg, 0.068 mmol), and 10 mL of toluene. The reaction solution was degassed by bubbling nitrogen, and PMDETA (14.25 μL) was added. The solution was then heated at 50 °C for 18 h. The solution was filtered and concentrated under vacuum. The crude product was purified by column chromatography (8/2/1 to 8/2/2 pentane/dichloromethane/ethyl acetate). 2.066 g (77.1% yield) of **12** as a lightly yellow very viscous oil that partially crystallizes below 5 °C was obtained. ^{1}H NMR (250 MHz, $CDCl_3$, both enantiomers): δ 8.18−7.48 (m, 4H, both enantiomers), 4.15 (m, 2H, both enantiomers), 3.90 (s, 3H, both enantiomers), 3.48 (d, 1H, J = 10.33 Hz, both enantiomers), 1.82 (m, 1H, both enantiomers), 1.62 and 1.58 (each s, 6H, both enantiomers), 1.27 (q, 3H, J = 6.63 Hz, both enantiomers), 1.16 (d, 3H, J = 6.15 Hz, major enantiomer), 0.92 and 0.80 (each s, 9H, both enantiomers) and 0.38 (d, 3H, J = 6.65 Hz, minor enantiomer). ^{13}C NMR (50 MHz, $CDCl_3$, both enantiomers): δ 175.42, 167.50, 148.19, 137.83, 131.28, 128.71, 82.32, 72.37, 60.96, 60.74, 52.04, 30.89, 28.54, 27.61, 25.30, 23.00, 22.14, 21.07, and 14.23. HRMS exact mass: calculated for $[M + 1]^+$ $C_{22}H_{36}NO_5$ 394.2593; found 394.2588.

Synthesis of 2,2,5-Trimethyl-3-(2-(2-methyl-propanoic acid)-ethoxy)-4-*p*-carboxybenzoate-3-azahexane, 13. To a stirred suspension of potassium *tert*-butoxide (5.87 g, 52.316 mmol) in dry ether (10 mL), cooled to 0 °C, was added water (235 μL, 13.08 mmol) via syringe. This slurry mixture was stirred for 5 min. To this solution was added the functionalized alkoxyamine **12** (1.285 g, 3.270 mmol) in solution in dry ether (25 mL). The ice bath was removed, and the reaction mixture was stirred at room temperature until the reaction was complete. The reaction was quenched by adding ice water until two clear layers formed. The aqueous layer was separated and acidified with concentrated hydrochloric acid. The acidified solution was extracted three times with 50 mL portions of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered. The organic phase was evaporated to give 1.021 g (89% yield) of **13** as white solid. ^{1}H NMR (250 MHz, DMSO, both enantiomers): δ 13.28−11.91 (broad peak, 2H, COOH, both enantiomers), 7.98−7.54 (m, 4H, both enantiomers), 3.57 (d, 1H, J = 10.0 Hz, both enantiomers), 1.93 (m, 1H, both enantiomers), 1.54 and 1.46 (each s, 6H, both enantiomers), 1.14

(d, 3H, $J = 6.4$ Hz, major enantiomer), 1.11 and 0.91 (each s, 9H, both enantiomers) and 0.35 (d, 3H, $J = 6.4$ Hz, minor enantiomer). ^{13}C NMR (250 MHz, DMSO, both enantiomers): δ 176.09, 167.42, 147.16, 137.56, 131.21, 128.09, 81.33, 71.07, 60.16, 31.29, 30.18, 28.10, 27.20, 25.55, 24.14, 22.54, and 20.71. MS (FAB): *m*/*z* calculated for $[M + 1]^+$ 352.2; found 352.3.

General Procedure for Styrene Polymerization; Preparation of Polystyrene. A mixture of the alkoxyamine **11** (399 mg, 1 mmol) and styrene (26.04 g, 250 mmol) was degassed by nitrogen bubbling for 30 min, sealed under nitrogen, and heated at 123 °C for 5 h. Samples were removed at different time intervals during polymerization, and conversion and molecular weights were determined by gravimetry and SEC, respectively. The polymerization was stopped ($M_n = 15\,910$ g mol^{-1}, $M_w/M_n = 1.10$, conversion = 59%) by quenching the reaction in an ice bath.

General Procedure for Acrylate Polymerization; Preparation of Poly(*n*-butyl acrylate). A mixture of the alkoxyamine **11** (42.3 mg, 0.106 mmol), the corresponding nitroxide, **4** (1.6 mg, 0.06 mmol), and *n*-butyl acrylate (2.671 g, 20.84 mmol) was degassed by three freeze/thaw cycles, sealed under nitrogen, and heated at 125 °C for 15 h 45 min. Samples were removed at different time intervals during polymerization, and conversion and molecular weights were determined by gravimetry and SEC, respectively. The polymerization was stopped ($M_n = 10\,900$ g mol^{-1}, $M_w/M_n = 1.19$, conversion = 36%) by quenching the reaction in an ice bath.

General Procedure for Styrene-*n*-Butyl Acrylate Random Copolymerization; Preparation of Polystyrene-*co*-poly(*n*-butyl acrylate). A mixture of the alkoxyamine **11** (11.2 mg, $2.8.10^{-2}$ mmol), styrene (583 mg, 5.6 mmol), and *n*-butyl acrylate (288 mg, 2.25 mmol) was degassed by three freeze/thaw cycles, sealed under nitrogen, and heated at 125 °C for 8 h. The polymerization was stopped ($M_n = 17\,200$ g mol^{-1}, $M_w/M_n = 1.15$, conversion = 66%) by quenching the reaction in an ice bath.

Procedure for Block Copolymer Formation; Preparation of Polystyrene-*b*-poly(*n*-butyl acrylate). A mixture of alkoxyamine-functionalized polystyrene (1.591 g, 0.1 mmol, $M_n = 15\,900$ g mol^{-1}, PDI = 1.10), initially prepared by polymerizing styrene with the alkoxyamine **11**, the corresponding nitroxide **4** (1.8 mg, 6.4 mmol), and *n*-butyl acrylate (3.924 g, 30.61 mmol) was degassed by three freeze/thaw cycles, sealed under nitrogen, and heated at 125 °C for 16 h. The polymerization was stopped ($M_n = 27\,650$ g mol^{-1}, $M_w/M_n = 1.19$, conversion = 30.5%) by quenching the reaction in an ice bath.

General Procedure for Sodium Styrenesulfonate Polymerization; Preparation of Poly(sodium styrenesulfonate). To a solution of sodium hydroxide (30.8 mg, 7.7×10^{-4} mol) in water (20 mL) was added the alkoxyamine **13** (11.2 mg, 3.2×10^{-5} mol) and sodium 4-vinylbenzenesulfonate (2.062 g, 0.01 mol). The mixture was degassed by bubbling nitrogen for 30 min and heated at 95 °C for 24 h. Samples were removed at different time intervals during polymerization, and conversion and molecular weights were determined by ^{1}H NMR and aqueous SEC, respectively. The polymerization was stopped ($M_n = 38\,300$ g mol^{-1}, $M_w/M_n = 1.18$, conversion = 62.6%) by quenching the reaction in an ice bath.

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