Synthesis and Characterization of a Novel Bisnitroxide Initiator for Effecting "Outside-In" Polymerization

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ABSTRACT: A new bis-α-hydrogen nitroxide based initiator for use in nitroxide-mediated free radical polymerization (NMRP) has been synthesized and is demonstrated to effect controlled polymerizations. The bisnitroxide forms "living" systems; the resulting polymers are formed with low polydispersities. The addition of a second block is facile, forming symmetrical ABA triblock copolymers. Monomer addition occurs at the center of the living polymer. This "outside-in" strategy overcomes previous restrictions in sequence specificity encountered in preparing ABA triblock copolymers using NMRP by the more traditional, complementary "inside−out" bidirectional nitroxide initiators.

Introduction

"Living" polymerization techniques including nitroxide-mediated radical polymerization[1] (NMRP), atom transfer radical polymerization[2] (ATRP), and reversible addition fragmentation transfer[3] (RAFT) have evolved as excellent methods for the controlled growth of polymeric materials. These methods are often complementary, as each has advantages and disadvantages. For example, functionality such as nitriles and free amines, which can act as ligands on copper, are compatible with NMRP. ATRP has the advantage that it functions at lower temperatures, while RAFT provides controlled polymerization of monomers such as vinyl acetate that are not compatible with NMRP and ATRP. A disadvantage of NMRP is that it must be run at relatively high temperatures. ATRP and RAFT systems may be contaminated with components of the initiators after the polymerization; polymers produced with ATRP usually contain trace metal contaminates while polymers constructed with RAFT may be contaminated with highly colored sulfur byproducts. All of these systems are commonly considered "living" as once an initial polymer is generated, the entire chain can be utilized as a macroinitiator for subsequent polymerizations.[4]

Block copolymers have specialized and highly tunable properties; they are often constructed via "living" polymerization techniques. One class of block copolymers of particular interest are ABA triblock copolymers in which the A blocks are hydrophilic and the B block is hydrophobic. With judicious choice of block length and monomer selection, these polymers can self-assemble to form vesicles and membranes.[5] Using NMRP, traditional *N*-alkoxyamine initiators can generate triblock copolymers in a linear, three-step fashion. An attractive alternative is the development of bidirectional initiators capable of growing in two directions simultaneously. In addition to being convergent, the use of a bidirectional initiator ensures that both outside blocks are of the same length and that the polymer chain ends are identical, forming symmetrical polymers (Scheme 1).

A number of bisnitroxide initiators have been developed (Figure 1). Catala et al.[6] first presented initiator **2** based on di-*tert*-butyl nitroxide radical with a styryl-like linker in 1996 and demonstrated the "living" polymerization of styrene. Also in 1996, Priddy et al.[7] reported a similar initiator **3** built with TEMPO. Cleavable carbonate and dicarbonate linked bis-TEMPO initiators **4** and **5** were developed by Knauss et al.[8] and Korn and Gagne,[9] respectively. Gnanou et al.[10] developed the SG1-based bisnitroxide initiator **6** containing central hydrolyzable ester linkages. Schmidt-Naake et al.[11] developed both bis-TEMPO **7a** and bis-TIPNO **7b** *N*-alkoxyamine initiators. All of these initiators grow from the "inside-out", resulting in polymers bearing nitroxide caps at both chain termini.

The complementary "outside-in" approach generates polymers in which a bisnitroxide resides at the center of the resulting polymer chain. Charleux et al.[12] and Rassat et al.[13] have synthesized and studied the polymerization of initiators **8** and **9**, respectively, and Long et al.[14] have developed initiator **10**, which is similar to **8** but contains carbamate instead of ester linkages (Figure 1). All of these "outside-in" bisnitroxide initiators are TEMPO-based and are therefore limited to the use of styrenic monomers.

The distinction between the "inside-out" vs the "outside-in" approach is very important, as there is a limiting sequence specificity observed in NMRP.[15] The use of TIPNO[16] or SG1[17] type nitroxides allows the use of a variety of monomers to design copolymers with highly tunable properties; however, the order of block construction is important. It is possible to add either a polystyrene or a polyisoprene B block to a polyacrylate or polyacrylamide macroinitiator, but a polystyrene or polyisoprene macroiniator will not readily add a polyacrylate or polyacrylamide B block with adequate control. Thus, the development of an "outside-in" initiator based on an α-hydrogen-containing nitroxide makes it possible to prepare amphiphilic ABA triblock copolymers with a hydrophilic A block derived from a wide variety of monomers including acrylates or acrylamides. Herein we present a novel bis-*N*-alkoxyamine **1** that polymerizes in an "outside-in" fashion built on a TIPNO type of bisnitroxide (Figure 1), therefore permitting access to a wide variety of monomer building blocks. Triblock copolymers that were previously unaccessible by the traditional NMRP bisnitroxide initiators are now easily prepared.

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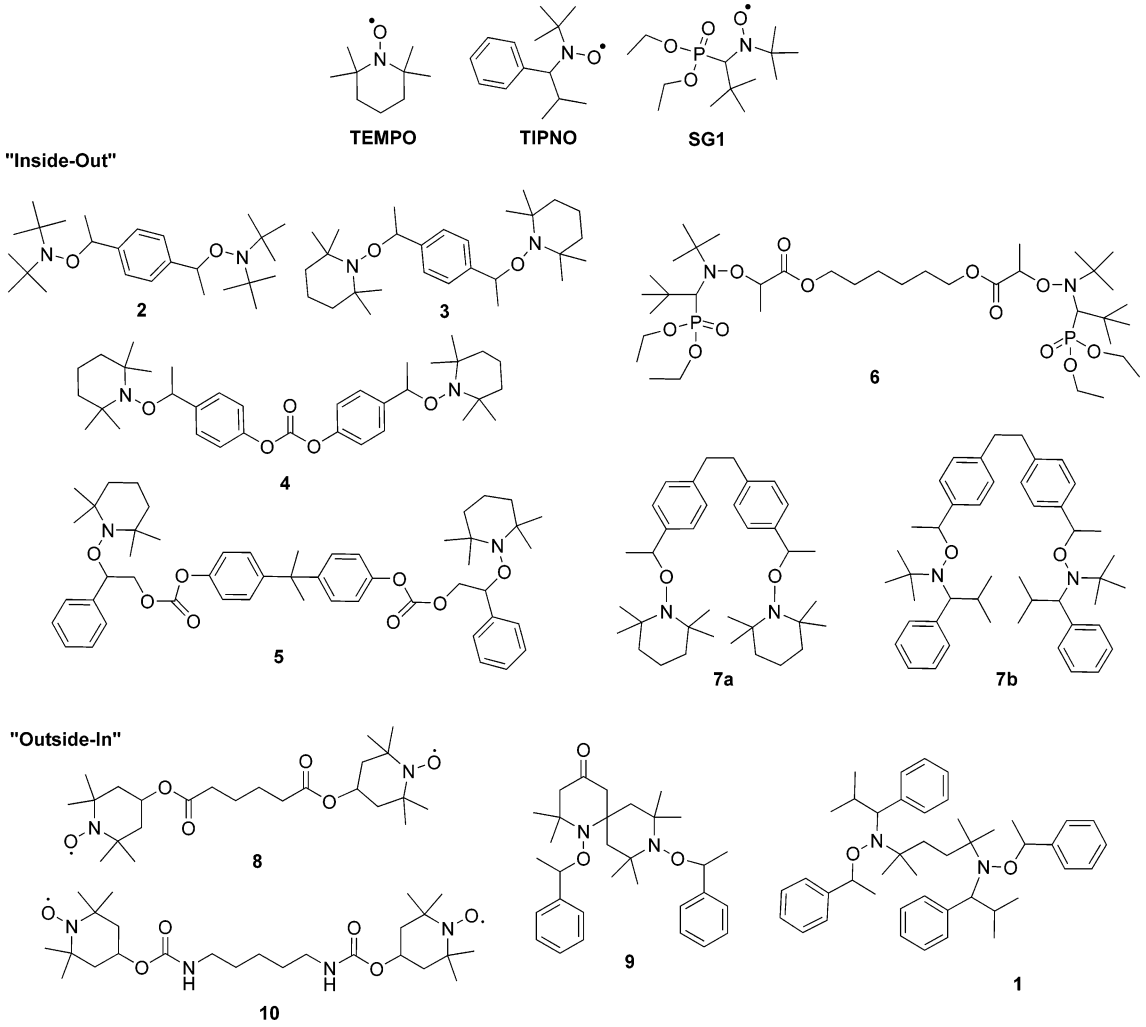
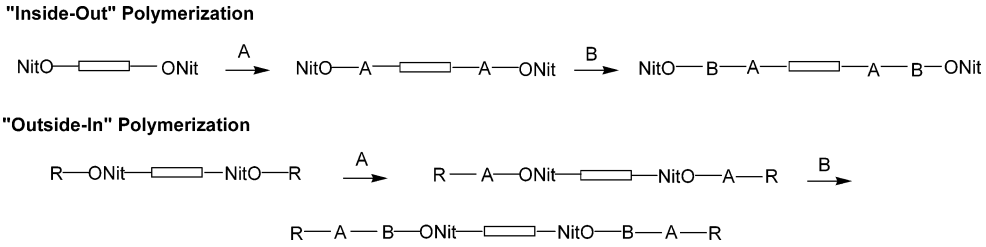


Figure 1. Bisnitroxide initiators that polymerize "inside-out" or "outside-in".

Scheme 1. "Inside-Out" vs "Outside-In" Polymerization



Experimental Section

General Materials and Methods. Styrene (St) (99%, Acros Organics), *n*-butyl acrylate (*n*BA) (99+%, Acros Organics), *tert*-butyl acrylate (*t*BA) (98%, Aldrich), and dimethylacrylamide (DMA) (99%, Aldrich) were distilled immediately before use under vacuum. Trimethylsilyl chloride (Acros, 98%) was freshly distilled from poly(vinylpyridine). 2,5-Dimethylhexane-2,5-diol (97%), chloroacetonitrile (99%), isopropylmagnesium chloride, and sodium borohydride were purchased from Aldrich. Benzaldehyde (98%) was purchased from Alfa Aesar. Cupric acetate was purchased from Mallinchkrodt Chemical Works. All others—thiourea, *m*-chloroperbenzoic acid (70−75%), 1,4-diazobicyclo[2.2.2]octane (97%), and Jacobsen's catalyst (*R*,*R*)—were purchased from Acros. Unless otherwise noted, all other reagents were used as received. Tetrahydrofuran (THF) was distilled from sodium/benzophenone when anhydrous conditions were required. Acetonitrile was distilled over calcium hydride. Water was deionized. Flash chromatography was performed using EM Science Silica Gel 60. Analytical TLC was performed using commercial Whatman plates coated with silica gel (0.25 nm thick). Reactions were carried out under a nitrogen atmosphere unless otherwise noted. Polymerizations were carried out in sealed ampules.

Analytical Techniques. NMR spectra were recorded at 250 MHz (Bruker ACF dual probe 250 MHz) or 500 MHz (Varian 500 MHz) as noted in $CDCl_3$. Mass spectra were obtained on an electrospray ionization time-of-flight (ESITOF) mass spectrometer (Mariner Biospectrometry workstation from Applied Biosciences). Melting points are uncorrected. FTIR spectra were recorded in deuteriochloroform on a Perkin-Elmer 1600 FTIR spectrometer. Elemental analysis was performed by M-H-W Laboratories in Phoenix, AZ. Gel permeation chromatography (GPC) was performed using a Waters apparatus equipped with five Styragel columns (300 × 4.6 mm, 5 μm bead size), HR 0.5 (pore size 50 Å, 0−1000 Da), HR 1 (pore size 100 Å, 100−5000 Da), HR 2 (pore size 500 Å, 500−20 000 Da), HR 4 (pore size 10 000 Å, 50−100 000 Da), HR 5E (linear bed, mixed pore sizes, 2000−4 × 10^6 Da). Tetrahydrofuran (THF) was used as the eluent at a flow rate of 0.35 mL/min at ambient temperature. A refractive index detector

was used, and the molecular weights were calibrated against seven polystyrene standards ranging from 2000 to 156 000 Da.

Bis-*N*,*N*′-(2-chloroacetyl)-2,5-dimethylhexane-2,5-diamine (12). 2,5-Dimethylhexane-2,5-diol, **11** (10.00 g, 68.39 mmol), was combined with chloroacetonitrile (20.51 g, 273.5 mmol) in 22 mL of glacial acetic acid. The solution was placed in an ice bath, and 22 mL (410 mmol) of concentrated sulfuric acid was added dropwise, causing the solution to turn amber in color. The reaction was allowed to warm to room temperature and stirred overnight. Next, 275 mL of ice-chilled water was added, forming a white precipitate. The precipitate was filtered and washed twice with 140 mL of saturated $NaHCO_3$ solution and three times with 140 mL of water. The solid was recrystallized from aqueous ethanol, affording 13.68 g (46.21 mmol, 68% yield) of white crystals; mp = 153 °C. TLC: 1:1 hexanes:EtOAc, UV, molybdate, $R_f = 0.39$. IR ($CDCl_3$): 3413 (N−H), 1682 cm^{-1} (C=O). ^1H NMR (250 MHz, $CDCl_3$) δ: 6.28 (br s, 2H), 3.94 (s, 4H), 1.73 (s, 4H), 1.32 (s, 6H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 165.2, 54.0, 43.0, 33.2, 27.0 ppm. HRMS: M + 1 ($C_{12}H_{23}N_2O_2Cl_2$) 297.113 calcd; 297.112 obsd.

2,5-Dimethylhexane-2,5-diamine (13). Bis-*N*,*N*′-(2-chloroacetyl)-2,5-dimethylhexane-2,5-diamine, **12** (13.68 g, 46.21 mmol), was dissolved in 275 mL of ethanol, and 8.44 g (111 mmol) of thiourea was added. Glacial acetic acid (55 mL) was added, and the solution was refluxed overnight, forming a white precipitate. Ice-cold water (650 mL) was added to the mixture, and the precipitate was filtered. The filtrate was made basic by the addition of 6 M NaOH until the pH was between 10 and 11. The filtrate was extracted twice with 700 mL of $CHCl_3$. The organic layers were combined and dried over $MgSO_4$, and the volatiles were removed in vacuo affording 4.53 g (31.0 mmol, 67% yield) of a clear yellow oil. TLC: 1:1 methanol:EtOAc, UV, cobalt TLC dip, $R_f = 0.13$. IR ($CDCl_3$): 3358 (N−H), 2855 (C−H), 1368 cm^{-1} (C−N). ^1H NMR (250 MHz, $CDCl_3$) δ: 1.38 (s, 4H), 1.27 (br s, 4H), 1.09 (s, 12H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 49.2, 39.2, 30.3 ppm. HRMS: M + 1 ($C_8H_{21}N_2$) 145.170 calcd; 145.170 obsd.

***N*,*N*′-Dibenzylidene-2,5-dimethylhexane-2,5-diamine (14).** Benzaldehyde (4.60 mL, 45.2 mmol), 2,5-dimethylhexane-2,5-diamine, **13** (3.00 g, 20.5 mmol), and activated 4 Å molecular sieves were added to a flame-dried round-bottom flask with stir bar. Anhydrous THF (20 mL) was added via syringe, and the solution was refluxed overnight. After cooling, the resulting mixture was filtered through a sintered glass funnel, and the filter cake was washed with diethyl ether until it appeared white in color. The filtrate was concentrated in vacuo, affording 7.43 g of a yellow solid which was recrystallized from hexanes to give 5.88 g (18.4 mmol, 89% yield) of pale yellow crystals; mp = 93 °C. TLC: CH_2Cl_2, UV, $R_f = 0.60$. IR: ($CDCl_3$) 2947 (C−H), 1642 cm^{-1} (C=N). ^1H NMR (250 MHz, $CDCl_3$) δ: 8.23 (s, 2H), 7.75 (m, 4H), 7.39 (m, 6H), 1.59 (s, 4H), 1.26 ppm (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 155.5, 137.4, 130.2, 128.6, 128.0, 59.5, 37.7, 27.4 ppm. HRMS: M + 1 ($C_{22}H_{29}N_2$) 321.233 calcd; 321.236 obsd.

***N*,*N*′-Dibenzylidene-2,5-dimethylhexane-2,5-bisoxaziridine (15).** *N*,*N*′-Dibenzylidene-2,5-dimethylhexane-2,5-diamine, **14** (694.1 mg, 2.167 mmol), was combined with 11 mL of $CHCl_3$, followed by 919 mg (8.67 mmol) of Na_2CO_3, and the solution was placed in an ice bath. An anhydrous solution of *m*-chloroperbenzoic acid (*m*CPBA) was made by dissolving 1.28 g (5.20 mmol) of *m*CPBA in 43 mL of $CHCl_3$, washing with brine, drying over $MgSO_4$, and filtering. This *m*CPBA solution was added via an oven-dried addition funnel to the ice-cooled reaction flask, and the mixture was stirred overnight at room temperature. The reaction mixture was washed twice with saturated Na_2CO_3 solution prior to being run three times through a 2 cm plug of basic alumnia. The solution was dried over $MgSO_4$ and filtered, and the volatiles were removed in vacuo, giving 458 mg of **15** as a clear blue oil (1:1 mixture of diastereomers). This residue solidified and was recrystallized from hexanes to afford white crystals in 44% yield (335 mg, 0.950 mmol); mp = 71−73 °C. TLC: 9:1 hexanes:EtOAc, UV, molybdate, $R_f = 0.27$. IR: ($CDCl_3$) 3114 (C−H aromatic) 2933 cm^{-1} (C−H). ^1H NMR (500 MHz, $CDCl_3$, inseparable mixture of diastereomers) δ: 7.38 (m, 10H), 4.67 (s, 1H, diast A), 4.65 (s, 1H, diast B), 1.68 (m, 4H), 1.14 (s, 6H, diast B), 1.13 (s, 6H, diast A), 1.07 (s, 6H, diast A), 1.06 ppm (s, 6H, diast B). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 158.4, 129.7, 128.4, 127.5, 70.1, 34.9, 22.9, 21.1 ppm. HRMS: M + 1 ($C_{22}H_{29}N_2O_2$) 353.222 calcd; 353.221 obsd.

***N*,*N*′-Dibenzylidene-2,5-dimethylhexane-2,5-bisnitrone (16).** *N*,*N*′-Dibenzylidene-2,5-dimethylhexane-2,5-bisoxaziridine, **15** (2.60 g, 7.38 mmol), was added to a flame-dried round-bottom flask with a stir bar. Anhydrous acetonitrile (25 mL) was added via syringe, and the mixture was refluxed for 3 days. During this time the reaction turned dark brown. Upon cooling, light-colored crystals formed which were recrystallized from acetonitrile to give the dinitrone as light-brown crystals in 54% yield (1.41 g, 3.99 mmol), mp = 187 °C. TLC: 1:1 hexanes:EtOAc, UV, $R_f = 0.43$. IR ($CDCl_3$): 2951 (C−H), 1579 (nitrone), 1190 cm^{-1} (nitrone). ^1H NMR (250 MHz, $CDCl_3$) δ: 8.29 (m, 4H), 7.5 (s, 2H), 7.41 (m, 6H), 1.86 (s, 4H), 1.58 (s, 12H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$) δ: 158.6, 130.8, 130.2, 128.8, 128.4, 72.9, 34.2, 26.6 ppm. HRMS: M + 1 ($C_{22}H_{29}N_2O_2$) 353.222 calcd; 353.220 obsd.

2,5,5,8,8,11-Hexamethyl-3,10-diphenyl-4,9-diazadodecane-4,9-bishydroxylamine (17). *N*,*N*′-Dibenzyl-2,5-dimethylhexane-2,5-bisnitrone, **16** (2.00 g, 5.67 mmol), 1,4-diazobicyclo[2.2.2]octane (DABCO) (1.28 g, 11.4 mmol), and 100 mL of THF were added to a flame-dried round-bottom flask with stir bar. The solution was sonicated for 30 min to help solubilize the nitrone. Trimethylsilyl chloride was added (1.45 mL, 11.4 mmol), and the mixture was cooled in an ice bath. Isopropylmagnesium chloride (17 mL, 2.0 M solution in THF) was added, and the solution was allowed to warm to room temperature and stirred for 3.5 h. Afterward, 100 mL of a saturated NH_4Cl solution and 45 mL of concentrated NH_4OH were added, and the solution was extracted twice with 100 mL of CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and filtered, and the volatiles were removed in vacuo. The product was purified via flash chromatography (hexanes to 10:1 hexanes:ethyl acetate), affording 1.80 g (4.10 mmol, 72% yield) of the hydroxylamine. TLC: 4:1 hexanes:EtOAc, UV, molybdate, $R_f = 0.60$. ^1H NMR (500 MHz, $CDCl_3$) δ: 7.44−7.27 (m, 10H), 5.22 (br s, 2H), 3.41 (d, 2H, J = 9.5 Hz), 2.40 (m, 2H), 2.06 (m, 2H), 1.16 (d, 6H, J = 6 Hz), 1.06 (s, 6H), 1.02 (m, 2H), 0.64 (d, 6H, J = 6 Hz), 0.59 ppm (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 4° ipso: 141.8, CH (aromatic): 130.4, 128.0, 126.9, CH−N: 70.9, 4°: 61.4, CH_2: 35.3, CH (*i*Pr): 32.0, CH_3: 24.8, 23.0, 22.1, 20.9 ppm.

2,5,5,8,8,11-Hexamethyl-3,10-diphenyl-4,9-diazadodecane-4,9-bisnitroxide (18). 2,5-Dimethyl-*N*,*N*′-bis(2-methyl-1-phenylpropyl)hexane-2,5-bishydroxylamine, **17** (1.70 g, 3.89 mmol), was dissolved in 8 mL of MeOH, 16 mL of EtOH, and 1 mL of 2-propanol. Concentrated NH_4OH (574 μL) and catalytic $Cu(OAc)_2$ (39 mg, 0.19 mmol) were added. Air was bubbled through the suspension until it turned blue. The solid yellow dihydroxylamine **17** did not completely dissolve. Volatiles were removed in vacuo; the residue was dissolved in 8 mL of $CHCl_3$ and 2.3 mL of saturated $NaHSO_4$ solution. The organic layer was washed with 8 mL of saturated $NaHCO_3$ solution and dried over $MgSO_4$, and volatiles were removed in vacuo, affording 1.57 g (3.60 mmol, 92% yield) of **18** as a bright yellow solid; mp = 98−109 °C (decomposition). TLC: 4:1 hexanes:EtOAc, UV, *p*-anisealdehyde, R_f = 0.29. IR: ($CDCl_3$) 2872 (C−H), 1387 cm^{-1} (N−O). HRMS: M + 1 ($C_{28}H_{43}N_2O_2$) 439.332 calcd; 439.337 obsd.

2,5,5,8,8,11-Hexamethyl-4,9-(1-phenylethoxy)-3,10-diphenyl-4,9-diazadodecane (1). 2,5-Dimethyl-*N*,*N*′-bis(2-methyl-1-phenylpropyl)hexane-2,5-bisnitroxide, **18** (500 mg, 1.14 mmol), was dissolved in 5.7 mL of toluene and 5.7 mL of EtOH followed by the addition of styrene (317 μL, 2.74 mmol). Jacobsen's catalyst (*R*,*R*) (290 mg, 0.460 mmol) was added followed by sodium borohydride (129 mg, 3.40 mmol); the reaction was stirred overnight open to the atmosphere. Volatiles were removed in vacuo, and the residue was dissolved in 6 mL of $CHCl_3$ and 6 mL of H_2O. A small amount of a 10% HCl solution was added to reduce emulsions within the separatory funnel. The organic layer was dried over $MgSO_4$, and volatiles were removed in vacuo. The product was purified

by three consecutive flash chromatography columns in hexanes to give the product as a highly viscous green oil in 43% yield (316 mg, 0.490 mmol) as a mixture of multiple diastereomers. TLC: 10:1 hexanes:EtOAc, UV, *p*-anisealdehyde, $R_f = 0.46$. IR: ($CDCl_3$) 2956 (C−H), 1452 (N−O), 1364 (N−O), 1064 cm^{-1} (C−N). Elemental analysis: $C_{44}H_{60}N_2O_2$ calcd: C, 81.43; H, 9.32; N, 4.32. Found: C, 81.65; H, 9.43; N, 4.14. ^1H NMR (500 MHz, $CDCl_3$, mixture of diastereomers) δ: 7.45−7.13 (m, 20H), 4.92 (m, 2H, 2 diast), 4.81 (m, 2H, 2 diast) [3.42 (d, 2H, J = 11 Hz), 3.29 (d, 2H, J = 10.5 Hz), 3.25 (d, 2H, J = 10.5 Hz), 3.16 (d, 2H, J = 10.5 Hz) 4 diast], 2.33 (m, 2H) [note: other diast d of sept. is buried around 1.4 ppm], [1.64 (d, 6H, J = 6.5), 1.57 (d, 6H, J = 7 Hz), 1.55 (d, 6H, 8 Hz), 1.48 (d, 6H, J = 7 Hz) 4 diast], [0.76 (s, 6H), 0.75 (s, 6H), 0.68 (s, 6H), 0.67 (s, 6H) 4 diast], [0.55 (d, 6H, J = 6.5 Hz), 0.51 (d, 6H, J = 5.5 Hz), 0.20 (d, 6H, J = 6.5 Hz), 0.17 (d, 6H, J = 6.5) 4 diast], 1.52−0.84 ppm (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of 4 diastereomers) δ [4° ipso: 146.2, 146.0, 145.3, 143.1, 142.8] [CH (aromatic): 130.9, 128.2, 127.63, 127.58, 127.5, 127.4, 127.2, 127.1, 126.8, 126.6, 126.4, 126.3, 126.2, 126.1] [CH−O: 83.5, 83.3, 83.1, 83.0] [CH−N: 71.9, 71.7] [4°: 63.3, 63.2] [CH_2: 35.7, 35.5, 35.2, 34.9] [CH_3: 32.4, 31.9, 31.8, 26.5, 26.4, 26.2, 26.1, 25.8, 25.7, 25.6, 25.5, 25.3, 23.7, 23.6, 22.5, 22.3, 22.2, 21.5, 21.3] ppm.

General Polymerization Procedure. A representative example is as follows: A mixture of *N*-alkoxyamine (0.087 mmol, 1 equiv), styrene (17.46 mmol, 200 equiv), and bisnitroxide (when added) (0.0044 mmol, 0.05 mol equiv) was degassed in an ampule by three consecutive freeze/pump/thaw cycles and sealed under argon. The vial was heated to 120−125 °C until the solution became just slightly viscous. After cooling, a small aliquot was taken for a crude ^1H NMR to calculate percent conversion based on integrating the remaining monomer vs polymer peaks, which indicated 72% monomer conversion in this case. The remainder of the polymer sample was dissolved in a minimum amount of CH_2Cl_2 (unless otherwise noted below) and the ice-chilled precipitation solvent (6−10 mL) was added dropwise. The precipitated polymer was separated by decantation, and volatiles were removed in vacuo. This precipitation procedure was repeated two times to give 1.4 g of purified polymer which was analyzed by ^1H NMR and GPC (M_n = 16 200 g/mol, polydispersity index (M_w/M_n) = 1.21). Polymers were precipitated as follows: PS with methanol, PDMA with hexanes, P*t*BA was dissolved in THF and precipitated with 50% aqueous methanol, and P*n*BA was dissolved in THF and precipitated with methanol.

P*t*BA−PS−P*t*BA Triblock Copolymer. The procedure to make the ABA triblock copolymer P*t*BA−PS−P*t*BA (second entry Table 4) is typical using 100 mg (0.0052 mmol) of the P*t*BA macroinitiator with 400 equiv of styrene for 1 h. The ABA polymer was dissolved in THF and precipitated with methanol (M_n = 41 300, polydispersity index (M_w/M_n) = 1.25).

P*t*BA−P*n*BA−P*t*BA Triblock Copolymer. The procedure to make the ABA triblock copolymer P*t*BA−P*n*BA−P*t*BA (fourth entry Table 4) is typical using 470 mg (0.030 mmol) of the P*t*BA macroinitiator with 200 equiv of *n*BA for 3 h. The polymer was dissolved in CH_2Cl_2 and precipitated with methanol (M_n = 28 700, polydispersity index (M_w/M_n) = 1.26).

PDMA−P*n*BA−PDMA Triblock Copolymer. The procedure to make the ABA triblock copolymer PDMA−P*n*BA−PDMA (sixth entry Table 4) is typical using 514 mg (0.035 mmol) of the PDMA macroinitiator with 400 equiv of *n*BA in 500 μL of DMF as solvent. The polymerization was run for 4 h, and the polymer was dissolved in CH_2Cl_2 and precipitated with diethyl ether (M_n = 46 200, polydispersity index (M_w/M_n) = 1.43).

[P*t*BA-*r*-PDMA]−P*n*BA−[P*t*BA-*r*-PDMA] Triblock Copolymer. The procedure to make the ABA triblock copolymer [P*t*BA-*r*-PDMA]−P*n*BA−[P*t*BA-*r*-PDMA] (eighth entry Table 4) is typical using 260 mg (0.029 mmol) of the P*t*BA/PDMA macroinitiator with 200 equiv of *n*BA for 4 h. The polymer was dissolved in CH_2Cl_2 and precipitated with diethyl ether (M_n = 29 200, polydispersity index (M_w/M_n) = 1.27).

Example Procedure for Nitroxide Exchange. The polymer sample **8** (50.0 mg, 0.0055 mmol, 1 equiv), TEMPO (13.7 mg. 0.0873 mmol, 16 equiv), and 8 mL of anisole were combined and placed in a 100 °C oil bath for 16 h open to the atmosphere. The majority of the anisole was then removed by vacuum distillation. A 50 μL aliquot of the residue was taken for GPC analysis (M_n original = 11 200 g/mol; M_n after cleavage = 5900 g/mol).

Example Procedure for Thermal Decomposition. Polymer sample **8** (50.0 mg, 0.0055 mmol) was dissolved in 2 mL of *p*-xylene and heated to 130 °C for 16 h. The majority of the *p*-xylene was removed by vacuum distillation. A 50 μL aliquot of the residue was taken for GPC analysis (M_n original = 16 200 g/mol; M_n after cleavage = 10 900).

Cleavage of PDMA with Zn°/HOAc. Polymer sample **4** (300.0 mg, 0.026 mmol, 1 equiv) and freshly activated zinc metal (washed sequentially three times each with 5% HCl, water, methanol, and diethyl ether) (900.0 mg, 13.77 mmol) were combined in 100 mL of 60% aqueous acetic acid. The solution was heated to 60 °C open to the atmosphere for 16 h. After cooling, 100 mL of 5 M KOH was added followed by addition of KOH pellets until the pH was between 11 and 13. This mixture was extracted twice with 150 mL of CH_2Cl_2, washed with brine, and dried over $MgSO_4$, and volatiles were removed in vacuo yielding 30 mg (0.0055 mmol) of cleaved polymer, which was analyzed by GPC (M_n original = 11 500 g/mol; M_n after cleavage = 7000 g/mol).

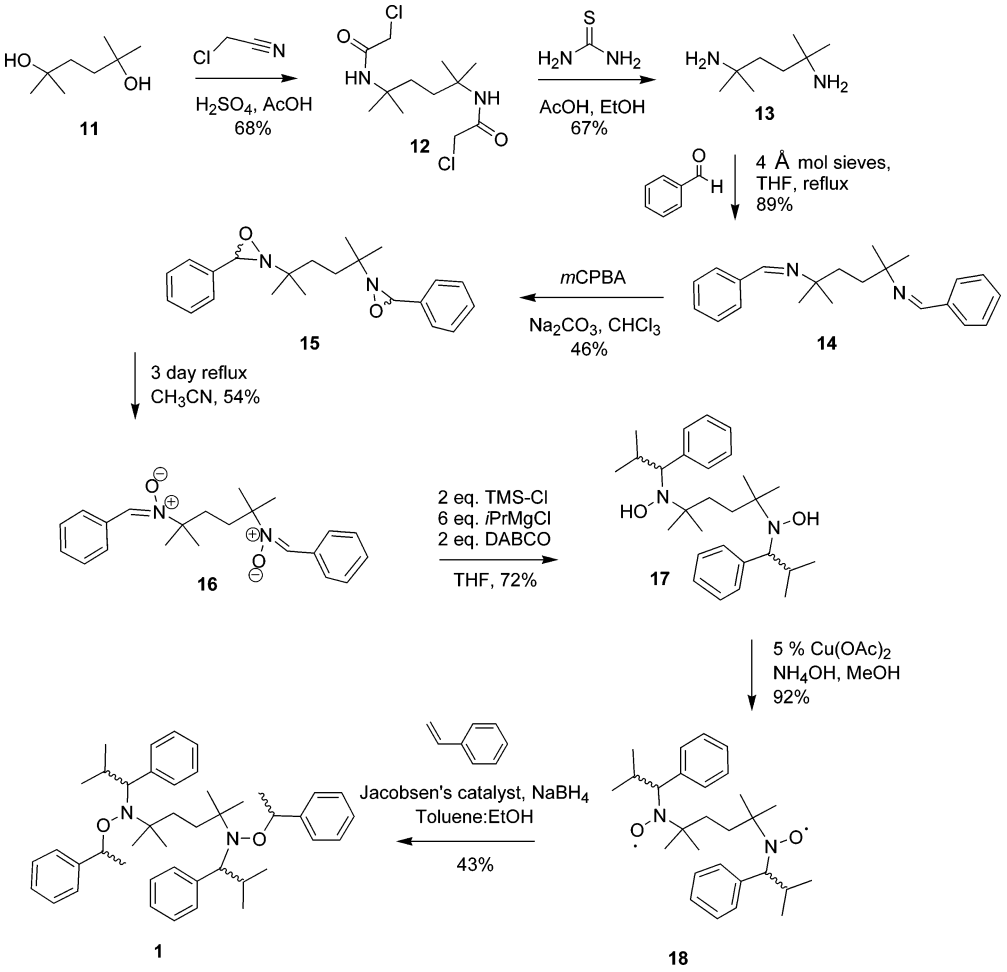
Results and Discussion

The synthesis of initiator **1** began with a modified Ritter reaction[18] on the tertiary bisdiol **11** using chloroacetonitrile under strongly acidic conditions to give the α-chloro amide **12**. Chloride displacement by thiourea followed by intramolecular transamidification in acidic ethanol gave bisamine **13** (Scheme 2). This tertiary amine was condensed with benzaldehyde to give bisimine **14** in 89% yield. Oxidation of the imine bond was performed with *m*CPBA to form bisoxaziridine **15** as a mixture of diastereomers. Thermolysis[19] in refluxing acetonitrile provided bisnitrone **16** in 54% yield. The next step of the synthesis required the nucleophilic introduction of an isopropyl group to the nitrone functionality, which proved challenging. After examining the addition of isopropyl Grignard with several Lewis acids ($CeCl_3$, $ZnCl_2$, and various copper reagents), it was found that addition of freshly distilled TMS-Cl resulted in a satisfying 72% yield of the adduct **17** after purification. Oxidation of the hydroxylamine species with air and catalytic $Cu(OAc)_2$ gave the bisnitroxide **18**. Last, formation of the *N*-alkoxyamine initiator using styrene and Jacobsen's catalyst following the method of Hawker[20] gave bidirectional initiator **1** in 43% yield after purification (Scheme 2).

An alternative approach to the preparation of a bisnitroxide similar to TIPNO was envisioned to begin with a nitro compound. Bisnitro **19** is commercially available and was examined as a possible starting material following the standard procedure developed in these labs for the preparation of TIPNO.[16] Thus, reduction with zinc and acid converted the nitro groups to hydroxylamines in situ, which condensed with isobutylaldehyde. However, instead of forming the desired bisnitrone **21**, the cyclic aminal **20** was formed; the oxidation product led to the formation of a brillant pink reaction mixture (Scheme 3).[21] This undesired cyclization was probably enhanced by the gem dimethyl effect.[22] Thus, the route beginning with this nitro starting material was abandoned.

With bisnitroxide initiator **1** in hand, polymerizations were carried out with styrene (St), *tert*-butyl acrylate (*t*BA), *n*-butyl acrylate (*n*BA), and dimethylacrylamide (DMA) (Table 1). The molecular weights predicted on

Scheme 2. Synthetic Route to the "Outside-In" Bidirectional Initiator 1



Scheme 3. Attempted Route to a Bisnitroxide Using the Commercially Available Bisnitro Compound 19

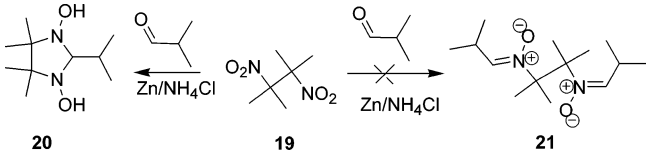


Table 1. Polymerization of Various Monomers Using Bidirectional Initiator 1 at 120−125 °C

entry	monomer[a]	time (min)	$M_{n,calc}$[b] (g/mol)	M_n[c] (g/mol)	M_w[d] (g/mol)	PD[e]
1	St	120	15 600	16 200	19 600	1.21
2	*t*BA[f]	180	19 100	22 600	27 600	1.22
3	*n*BA[f]	105	16 300	17 100	20 700	1.21
4	DMA[f]	105	16 100	11 500	13 700	1.19

[a] 200 equiv was used, all polymerizations were run neat. [b] Number-average molar mass calculated from percent conversion determined by ^{1}H NMR; see Supporting Information for an example calculation. [c] Number-average molar mass measured by GPC. [d] Weight-average molar mass measured by GPC. [e] Polydispersity index (M_w/M_n) by GPC. [f] 5% of bisnitroxide **18** was added (St = styrene, *t*BA = *tert*-butyl acrylate, *n*BA = *n*-butyl acrylate, DMA = dimethylacrylamide).

the basis of ^{1}H NMR percent conversion correlate with those observed via gel permeation chromatography (GPC), and good polydispersities were obtained. A linear relationship exists between $\ln([M]_0/[M])$ and time in the polymerization of styrene (Figure 2) and *tert*-butyl acrylate (Figure 3), indicating no significant termination. Figures 4 and 5 graphically represent the linear relationship between the predicted molecular weights based on ^{1}H NMR data and the experimental molecular weights obtained from GPC during the polymerization of both styrene and *tert*-butyl acrylate with initiator **1**, indicating an absence of chain transfer events (Table 2). The polydispersities are also presented in these figures. During the polymerization of styrene, a low molecular weight shoulder is observed in the GPC traces as the polymerization proceeds (vide infra). During the polymerization of *tert*-butyl acrylate, the polydispersities continue to improve throughout the polymerization, which is consistent with statistical predictions. From these data, it is clear that initiator **1** behaves as a "living" system. While clearly initiator **1** effects polymerization in a living manner and polymerizes a variety

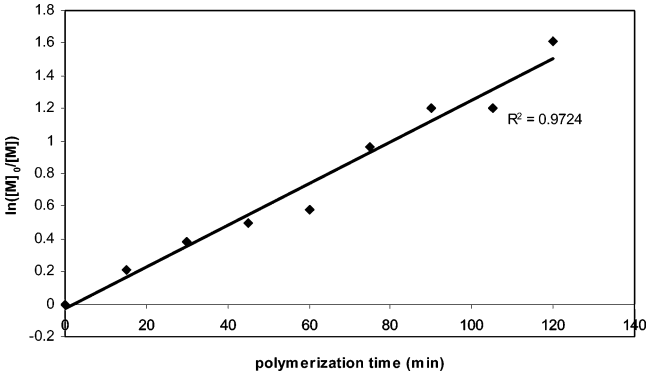


Figure 2. Styrene polymerization with initiator **1**, neat at 120 °C, as a function of $\ln([M]_0/[M])$ and time.

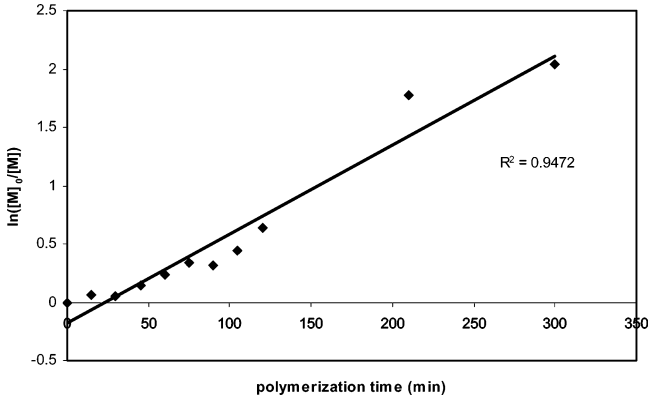


Figure 3. *tert*-Butyl acrylate polymerization with initiator **1**, neat at 120 °C, as a function of $\ln([M]_0/[M])$ and time.

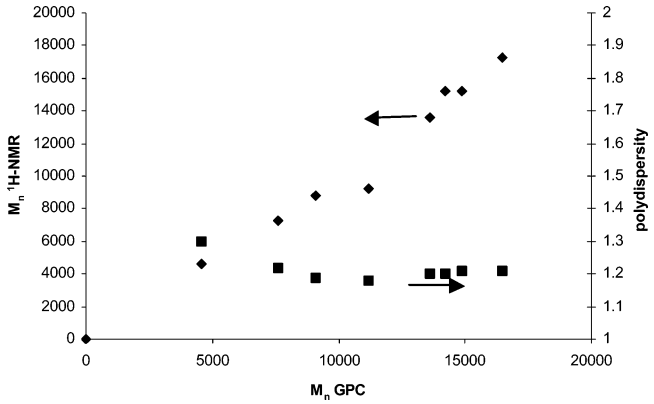


Figure 4. Evolution of M_n (molecular weight as calculated by ^{1}H NMR) and polydispersity (M_w/M_n) as a function of M_n determined by GPC for the polymerization of styrene neat at 120 °C with bidirectional initiator **1**.

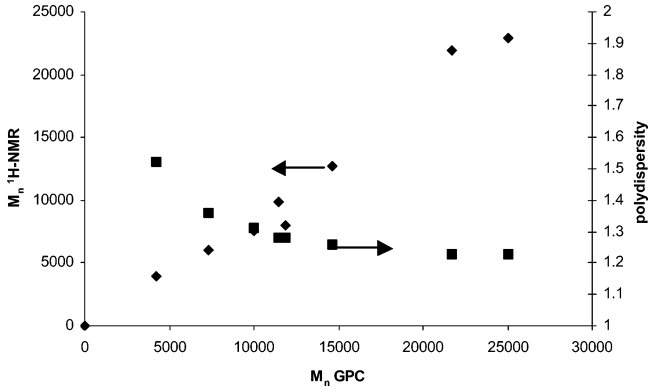


Figure 5. Evolution of M_n (molecular weight as calculated by ^{1}H NMR) and polydispersity (M_w/M_n) as a function of M_n determined by GPC for the polymerization of *tert*-butyl acrylate neat at 120 °C with bidirectional initiator **1**.

of monomers, it was still necessary to demonstrate growth at both ends of the initiator.

Crossover experiments have clearly demonstrated that nitroxide exchange during NMRP is a facile process.[23] Thus, heating a polymer prepared with bidirectional initiator **1** in the presence of a large excess of TEMPO should result in nitroxide exchange. As α-hydrogen-substituted nitroxides such as TIPNO and bisnitroxide **18** decompose upon prolonged heating, whereas TEMPO is stable at polymerization temperatures, over time all polymer chains should be capped by TEMPO and should be half the length of the initial polymer (Scheme 4). Thus, a sample of polystyrene **22** prepared with initiator **1** (entry 8 from Table 2) (M_n = 11 200, PD = 1.18) was heated with 16 equiv of TEMPO at 100 °C for 16 h. The resulting polymer **23** showed a single peak by GPC (M_n = 5900, PD = 1.21) (Figure 6).

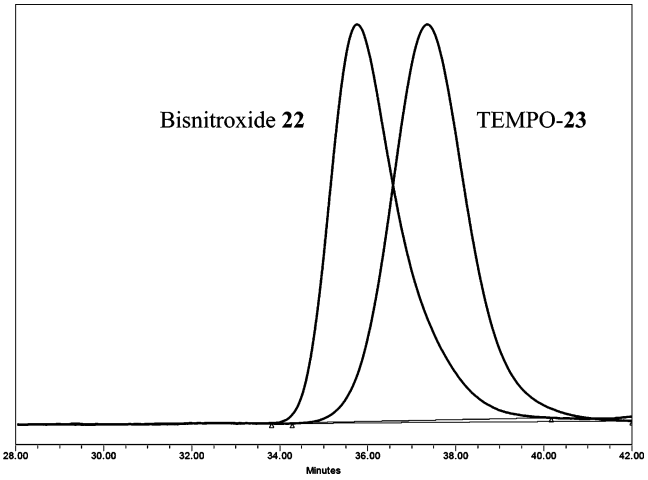


Figure 6. Exchange of internal bisnitroxide in polysytrene sample **22** with excess TEMPO in anisole at 100 °C: the resulting polymer is approximately half the original molecular weight. Bisnitroxide **22**: M_n = 11 200 g/mol; TEMPO-**23**: M_n = 5900 g/mol.

Another way to remove the nitroxide moiety from the polymer is by extended heating to effect nitroxide thermal decomposition following the method of Long.[14] Thus, each of the polymer samples 1, 2, 3, 4, and 8 from Table 2 were subjected to heating at 130 °C in *p*-xylene for 16 h. As can be seen in Table 3, each sample was cleaved to form a polymer of approximately half the original molecular weight. Finally, it is common to reductively cleave nitrogen−oxygen bonds using zinc and acetic acid.[24] However, solubility problems arise when this procedure is applied to hydrophobic polymer samples. Although polystyrene and poly(*n*-butyl acrylate) samples were recovered unchanged upon treatment with activated zinc and acetic acid, the water-soluble poly(dimethyacrylamide) was successfully cleaved (last entry of Table 3).

Convinced that initiator **1** does indeed grow polymer chains in both directions, the formation of block copolymers was investigated (Table 4). An inside B block of styrene or *n*-butyl acrylate was added to A block macroinitiators consisting of poly(*tert*-butyl acrylate), poly(dimethyacrylamide), and a random 1:1 copolymer of poly(*tert*-butyl acrylate)-*r*-poly(dimethylacrylamide)

Scheme 4. Exchange of Internal Bisnitroxide with Excess TEMPO

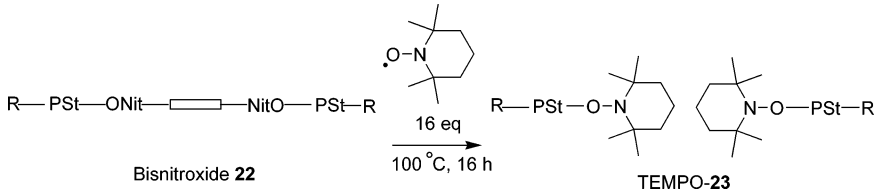


Table 2. Polymerization with Bidirectional Initiator 1 of Styrene and *tert*-Butyl Acrylate

entry	monomer[a]	time (min)	monomer % conv[b]	$M_{n,calc}$[c] (g/mol)	M_n[d] (g/mol)	PD[e]
5	St	15	19	4 600	4 600	1.30
6		30	32	7 300	7 600	1.22
7		45	39	8 800	9 100	1.19
8		60	44	9 200	11 200	1.18
9		75	62	13 600	13 600	1.20
10		90	70	15 200	14 200	1.20
11		105	70	15 200	14 900	1.21
12		120	80	17 300	16 500	1.21
13	*t*BA[f]	45	13	4 000	4 200	1.52
14		60	21	6 000	7 300	1.36
15		75	29	8 000	11 900	1.28
16		90	27	7 600	10 000	1.31
17		105	36	9 900	11 500	1.28
18		120	47	12 700	14 600	1.26
19		210	83	21 900	21 700	1.23
20		300	87	22 900	25 000	1.23

[a] 200 equiv was used. [b] Calculated by ^{1}H NMR. [c] Number-average molar mass calculated from percent conversion determined by ^{1}H NMR. [d] Number-average molar mass measured by GPC. [e] Polydispersity index (M_w/M_n) from GPC. [f] 5% of bisnitroxide **18** was added (St = styrene, *t*BA = *tert*-butyl acrylate).

(Table 4). An example GPC trace is shown in Figure 7. To ensure the B blocks were adding to both internal C−O *N*-alkoxyamine bonds of the macroinitiators, three of the triblock copolymers were subjected to the nitroxide crossover reaction with excess TEMPO (Table 5). In each case, the resulting AB diblock copolymers were of significant lower molecular weight and showed similar polydispersities to the original ABA triblocks.

Other groups who have developed "outside-in" bisnitroxide initiators have found that the GPC traces for these polymers often display a shoulder on the right side of the peak.[12,14] If one of the chains of the bidirectional nitroxide terminates as the polymerization proceeds, the resulting unidirectional polymer chains would be approximately half the molecular weight of the rest of the sample. All of the previously developed bisnitroxide initiators are TEMPO based; therefore, the polymerizations were performed with styrenic monomers. Bidirectional initiator **1** also displays this shoulder in the GPC traces of polystyrene starting at ~60% conversion (Figure 8), however not in the GPC traces of acrylate or acrylamide polymers, even at high conversions (Figure 9). This is a particularly interesting observation; further work is necessary to understand this phenomenon. Another interesting property of initiator **1** is that

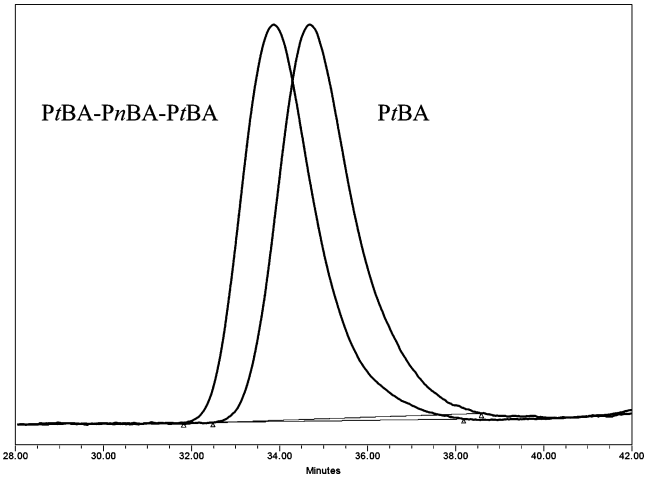


Figure 7. GPC trace of P*t*BA−P*n*BA−P*t*BA triblock copolymer. M_n of P*t*BA = 18 900 g/mol; M_n of P*t*BA−P*n*BA−P*t*BA = 28 700 g/mol.

Table 3. Central Cleavage of Polymers Prepared with Bidirectional Initiator 1

sample	monomer	original M_n[a] (g/mol)	M_n[a] after cleavage (g/mol)	PD[b]	method
8	St	11 200	5 900	1.21	100 °C, TEMPO
1	St	16 200	10 900	1.14	130 °C, 16 h
2	*t*BA	22 600	14 600	1.32	130 °C, 16 h
3	*n*BA	17 100	14 000	1.33	130 °C, 16 h
4	DMA	11 500	8 000	1.43	130 °C, 16 h
8	St	11 200	5 600	1.22	130 °C, 16 h
4	DMA	11 500	7 000	1.42	60 °C, Zn°/HOAc

[a] Number-average molar mass measured by GPC. [b] Polydispersity index (M_w/M_n) from GPC after cleavage (St = styrene, *t*BA = *tert*-butyl acrylate, *n*BA = *n*-butyl acrylate, DMA = dimethylacrylamide).

Table 4. Addition of B Blocks To Form ABA Triblock Copolymers

		$M_{n,calc}$[a] (g/mol)	M_n[b] (g/mol)	PD[c]
A block	P*t*BA	19 100	22 600	1.22
A−B−A triblock	P*t*BA−PS−P*t*BA	29 500	41 300	1.25
A block	P*t*BA	15 800	18 900	1.22
A−B−A triblock	P*t*BA−P*n*BA−P*t*BA[d]	28 100	28 700	1.26
A block	PDMA	14 800	14 800	1.28
A−B−A triblock	PDMA−P*n*BA−PDMA[d]	61 700	46 200	1.43
A block	[P*t*BA-*r*-PDMA][d,e]	9100	9400	1.29
A−B−A triblock	[P*t*BA-*r*-PDMA]−P*n*BA−[P*t*BA-*r*-PDMA][d]	29 600	29 200	1.27

[a] Number-average molar mass calculated from percent conversion determined by ^{1}H NMR. [b] Number-average molar mass measured by GPC. [c] Polydispersity index (M_w/M_n) from GPC. [d] 5% of bisnitroxide **18** was added. [e] 100 equiv of each monomer was used. For equivalents of monomer used and polymerization times, please see Experimental Section (St = styrene, *t*BA = *tert*-butyl acrylate, *n*BA = *n*-butyl acrylate, DMA = dimethylacrylamide).

Table 5. Nitroxide Exchange to Cleave ABA Triblock Copolymers to AB Diblock Copolymers with Excess TEMPO

sample	original M_n[a] (g/mol)	M_n[a] after cleavage (g/mol)	PD[b] original	PD[b] cleaved
P*t*BA−P*n*BA−P*t*BA	28 700	20 000	1.26	1.24
PDMA−P*n*BA−PDMA	46 200	31 100	1.43	1.58
[P*t*BA-*r*-PDMA]−P*n*BA−[P*t*BA-*r*-PDMA]	29 200	19 300	1.27	1.26

[a] Number-average molar mass measured by GPC. [b] Polydispersity index (M_w/M_n) from GPC.

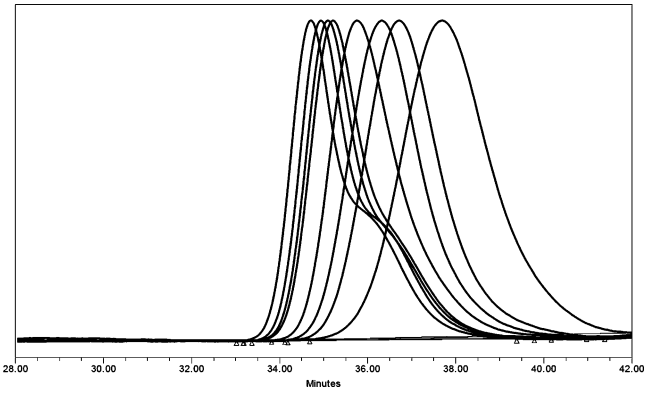


Figure 8. Time study GPC traces for polystyrene using initiator **1**. Percent conversions based on ^{1}H NMR data are (beginning from first peak on the right) 19, 32, 39, 44, 62, 70, 70, and 80: note a shoulder develops at high conversions. Each polymerization was run with 200 equiv of styrene, neat at 120 °C.

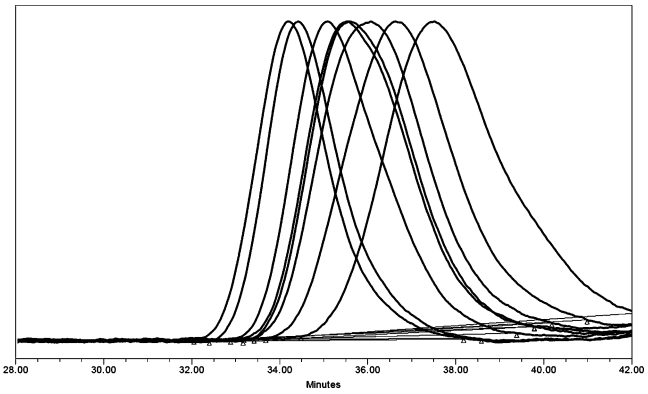


Figure 9. Time study GPC traces for poly(*tert*-butyl acrylate) using initiator **1**. Percent conversions based on ^{1}H NMR data are (beginning from first peak on the right) 13, 21, 29, 27, 36, 47, 83, and 87: no shoulder develops even at high conversion. Each polymerization was run with 200 equiv of *tert*-butyl acrylate and 5% of bisnitroxide **18**, neat at 120 °C.

polymerizations proceed much faster than with unidirectional TIPNO. For example, during the polymerization of styrene, TIPNO reaches 68% conversion after 8 h while initiator **1** with twice as much monomer reaches 70% conversion after only 1.5 h. The two initiators have very similar structures; therefore, this difference in rate is intriguing. Further work will be necessary to explain this difference in rate.

Conclusion

The new "outside-in" bisnitroxide initiator **1** was synthesized, beginning with the conversion of a tertiary bisalcohol to a tertiary bisamine and proceeding through a key oxaziridine to nitrone rearrangement, to provide a new synthetic route to *N*-alkoxyamines. This new bidirectional initiator effects polymerization of several types of monomers in a "living", well-controlled manner. Symmetrical ABA triblock copolymers are easily prepared in two steps, with the second B block inserted into the center of the macroinitiator.

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Supporting Information Available: Spectra with full assignments and example calculations. This material is available free of charge via the Internet at http://pubs.acs.org.

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