Ketone Functionalized Nitroxides: Synthesis, Evaluation of *N*-Alkoxyamine Initiators, and Derivatization of Polymer Termini

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ABSTRACT: Two ketone-bearing *N*-alkoxyamines have been prepared and evaluated as initiators in nitroxide-mediated polymerization. *N*-(1-Phenethyloxy)-5,5,8-trimethyl-7-phenyl-azanonan-2-one (**1**) forms polymers with excellent control of molecular weight and low polydispersities, whereas *N*-(1-phenethyloxy)-5,8-dimethyl-5,7-phenyl-azanonan-2-one (**2**) does not effect controlled polymerization at 125 °C. Polymers prepared from initiator **1** retain the ketone functionality on the nitroxide terminus. Near-quantitative functionalization is demonstrated via hydrazone formation.

Introduction

Controlled free-radical polymerization (CRP) has become a method of choice for the production of designed macromolecular constructs. The advantages of CRP over ionic polymerizations are tolerance to moisture and compatibility with many sensitive functional groups. The most widely recognized methods of CRP are reversible addition−fragmentation transfer,[1] atom-transfer radical polymerization,[2] and nitroxide-mediated polymerization (NMP).[3] These methods not only provide a means of generating well-defined macromolecular structures but also offer the opportunity to introduce chain-end functionality for a variety of applications.[4] In the field of NMP, polymer end-group functionalization is generally built into the initiator. These functional handles can be incorporated onto either the initiating α-alkyl end of the polymer chain (typically a 1-phenethyl derivative) or the capping *ω*-nitroxide. Throughout the literature, alcohols[5,6] and benzyl chlorides[6,7] are the most commonly used appendages for the introduction of a variety of functional groups. Among these examples there are notably few instances of functionality incorporated onto the *ω*-nitroxide. Hawker et al. evaluated the fidelity of the nitroxide cap by incorporating pyrene onto either the initiating phenethyl or the nitroxide-capping portions of *N*-alkoxyamines.[8] Dye labeling of the initiating alkyl radical segment showed no distinct changes (>95% end-group preservation) over a wide range of monomer conversions. Similarly, end-group fidelity of the capping *N*-alkoxyamines remained above 95% for monomer conversions below 80%; above this range, a sharp decline in end-group preservation was observed. These experiments demonstrate the ability to prepare monofunctionalized and telechelic polymers through the preparation of derivatized *N*-alkoxyamines.

Ketones are valuable functional handles because chemical moieties can be affixed through a number of chemoselective ligation reactions. A seminal demonstration of this is the work of Bertozzi et al., in which ketones were engineered into saccharides on cell surfaces.[9] Biotin hydrazide was then attached to cell surfaces by conversion of the ketones to hydrazones under physiological conditions. Similarly, Nishimura et al. functionalized bacterial cell surfaces with fluorescent labels through ketone derivatization to the corresponding hydrazone.[10] Another technique that has been utilized to probe biological systems is the conversion of carbonyls to oxime ethers via hydroxylamines.[11]

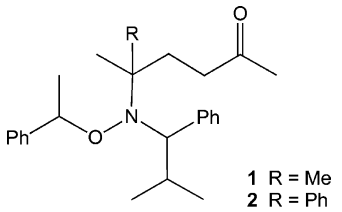

Figure 1. Ketone-functionalized *N*-alkoxyamines **1** and **2**.

Nitroxide-mediated radical polymerization allows for the production of block copolymers that can ultimately be used for self-assembly.[12] The "living" characteristic of NMP guarantees end-group preservation, which can be used for further chemical modification on surfaces of assembled macrostructures.[13] For example, self-assembled polymer micelles coated with ketone functionality can be envisioned for surface modification. This paper describes the synthesis of two novel *N*-alkoxyamines bearing ketones (**1** and **2**, Figure 1). These *N*-alkoxyamines are examined as initiators for NMP. Following polymerization, polymer chain ends are quantitavely analyzed, showing retention of the ketone functionality.

Experimental Section

General Materials and Methods. 2-Nitropropane (Aldrich, 97%), 3-buten-2-one (Aldrich, 99%), isobutyraldehyde (Aldrich, 98%), ethylene glycol (Mallinckrodt, 100%), tetrabutylammonium fluoride (TBAF, Acros, 1 M in THF, 5% water), (*R*,*R*)-(−)-*N*,*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cylcohexanediaminomanganese-(III) (Jacobsen's catalyst, Acros, 97.5%), *p*-toluenesulfonic acid (Aldrich, 99%), pyridine (Fisher, 99.9%), phenylmagnesium bromide (Aldrich, 3 M in THF), ammonium chloride (Fisher, 99.7%), ammonium hydroxide (Fisher, 14.8 N), copper(II) acetate monohydrate (Aldrich, 98%), sodium borohydride (Acros, 98%), and sodium hydrogen sulfate (Fisher, 97%) were used as received. Monomers styrene (St) (Acros, 99%), *n*-butyl acrylate (*n*BA, Acros, 99+%), *tert*-butyl acrylate (*t*BA, Aldrich, 98%), and *N*,*N*-dimethylacrylamide (DMA, Aldrich, 99%) were distilled under nitrogen prior to use. 5-Methyl-5-nitro-2-hexanone (**5**) and 5-nitro-5-phenylhexan-2-one (**6**) were prepared following the procedure of Miller et al.[14] and Puts et al.,[15] respectively. 2,4-Dinitrophenylhydrazine (Sigma, 30% water) was recrystallized from acetonitrile. Pyridinium-*p*-toluene sulfonate (PPTS) was prepared according to Miyashita et al.[16] Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and dichloromethane was distilled from calcium

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hydride when anhydrous conditions were required. Flash chromatography was performed by using EM Science Silica Gel 60. Analytical TLC was performed using commercial Whatman plates coated with silica gel (0.25 nm thick). TLC visualization was performed with a UV lamp irradiating at 254 nm and with either with *p*-anisaldehyde dip (PAA, 2.5 mL of *p*-anisaldehyde in 40 mL of 90:5:1 ethanol:concd sulfuric acid:glacial acetic acid) or molybdenum dip (21 g ammonium molybdate in 370 mL of water and 29 mL of concd sulfuric acid).

Analytical Techniques. NMR spectra were recorded at 250 MHz (Bruker ACF dual probe 250 MHz, 62.5 MHz for ^{13}C NMR) or 500 MHz (Varian 500 MHz, 125 MHz for ^{13}C NMR) as noted in $CDCl_3$. Mass spectra were obtained on an electrospray ionization time-of-flight (ESI-TOF) mass spectrometer (Mariner Biospectrometry workstation from Applied Biosciences). FTIR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer. UV−visible absorption spectra were recorded on a Cary 50 Varian spectrophotometer. 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, 100−5 000 Da), HR 2 (pore size 500 Å, 500−20 000 Da), HR 4 (pore size 10 000 Å, 50−100 000 Da), and HR5E (linear bed, mixed pore sizes, 2000−4106 Da). 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.

2-Methyl-2-(3-methyl-3-nitrobutyl)-[1,3]dioxolane (5). A 250 mL round-bottom flask was charged with *p*-toluenesulfonic acid (1.767 g, 9.289 mmol), 5-methyl-5-nitro-2-hexanone **3** (7.395 g, 46.45 mmol), ethylene glycol (7.26 mL, 139 mmol), and 105 mL of benzene. A Dean−Stark trap with a condenser was attached, and the reaction mixture was refluxed for 18 h under nitrogen. The reaction was then cooled to room temperature and then washed twice with 25 mL of saturated sodium bicarbonate solution. The aqueous layer was extracted with 25 mL of dichloromethane, the organic layers were combined and washed with 30 mL of brine, dried over magnesium sulfate, filtered, and then concentrated to give 9.34 g of a dark-brown oil. The oil was filtered through a plug of silica, and the solvent was removed in vacuo to provide 8.69 g (92.0% yield) of the product as a light-brown oil. TLC: 4:1 hexanes:EtOAc, UV, R_f = 0.51. IR ($CDCl_3$): 2941, 1543, 1374 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.89 (4 H, m, C(OC*H*$_2$C*H*$_2$O), 1.98 (2 H, m, C*H*$_2$C(OCH$_2$CH$_2$O)), 1.58 (2 H, m, C*H*$_2$CH$_2$C(OCH$_2$CH$_2$O)), 1.53 (6 H, s, (C*H*$_3$)$_2$C(NO$_2$)CH$_2$), 1.27 (3 H, s, C(OCH$_2$CH$_2$O)C*H*$_3$) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ 109.0 (*C*(OCH$_2$CH$_2$O)), 87.9 ((CH$_3$)$_2$*C*(NO$_2$)CH$_2$), 64.7 (C(O*C*H$_2$*C*H$_2$O)), 35.1 (C(NO$_2$)*C*H$_2$CH$_2$), 33.6 (CH$_2$*C*H$_2$ C), 25.9 ((*C*H$_3$)$_2$C(NO$_2$), 23.9 (C(OCH$_2$CH$_2$O)*C*H$_3$) ppm.

2-Methyl-2-(3-nitro-3-phenylbutyl)-[1,3]dioxolane (6). According to the procedure above, 5-nitro-5-phenyl-hexan-2-one **4** (11.4 g, 51.3 mmol), ethylene glycol (8.7 mL, 0.17 mol), and *p*-toluenesulfonic acid (0.98 g, 5.1 mmol) were employed to give 13.4 g of a viscous white oil (98% yield). TLC: 20% EtOAc in hexanes, UV, R_f = 0.29. IR ($CDCl_3$): 2943, 1549, 1351 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39 (5 H, m, Ar-*H*), 3.93 (4 H, m, C(OC*H*$_2$C*H*$_2$O)), 2.49 (2 H, m, CH$_2$C*H*$_2$C(OCH$_2$CH$_2$O)CH$_3$), 1.95 (3 H, s, C(OCH$_2$CH$_2$O)C*H*$_3$), 1.58 (2 H, m, C*H*$_2$CH$_2$C(OCH$_2$CH$_2$O)), 1.32 (3 H, C*H*$_3$C(Ph)(NO$_2$)CH$_2$) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 133.4 (*ipso*-Ar, 1C), 128.7 (*o*-Ar, 2C), 125.5 (*o*-Ar, 2C), 125.2 (*p*-Ar, 1C), 109.2 (*C*(OCH$_2$CH$_2$O)), 92.9 (*C*NO$_2$), 64.7 (C(O*C*H$_2$*C*H$_2$O)), 33.8 (*C*H$_2$*C*H$_2$C(OCH$_2$CH$_2$O)CH$_3$), 23.9 (*C*H$_3$CNO$_2$), 23.7 ((OCH$_2$CH$_2$O)*C*H$_3$) ppm.

***N*-[1,1-Dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-α-isopropylnitrone (7).** A solution of 2-methyl-2-(3-methyl-3-nitrobutyl)-[1,3]dioxolane **5** (8.686 g, 42.72 mmol), ammonium chloride (2.514 g, 46.99 mmol), and isobutyraldehyde (7.80 mL, 85.3 mmol) in 53 mL of water and 26 mL of isopropanol was chilled in an ice bath. Zinc powder (11.170 g, 170.79 mmol) was added batchwise over a period of 10 min. The ice bath was then removed. After 3 h of stirring at room temperature, the mixture was filtered through celite and the filter cake washed four times with 50 mL of dichloromethane. The organic layer was removed and washed with 70 mL of brine, dried over magnesium sulfate, filtered, and concentrated to give 10.343 g (99.5% crude yield) of the product nitrone as a light-gold oil. TLC: 1:1 hexanes:EtOAc, UV, R_f = 0.32. IR ($CDCl_3$): 3406, 2969, 2224, 1579, 1467 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.45 (1 H, d, J = 7.5 Hz, NC*H*CH(CH$_3$)$_2$), 3.78 (4 H, m, C(OC*H*$_2$C*H*$_2$O)), 3.02 (1 H, m, NCHC*H*(CH$_3$)$_2$), 1.74 (2 H, m, C*H*$_2$CH$_2$C(OCH$_2$CH$_2$O)CH$_3$), 1.38 (2 H, m, CH$_2$C*H*$_2$C(OCH$_2$CH$_2$O)CH$_3$), 1.31 (6 H, s, NC(C*H*$_3$)$_2$CH$_2$CH$_2$), 1.17 (3 H, s, CH$_2$C(OCH$_2$CH$_2$O)C*H*$_3$), 0.95 (6 H, d, J = 7.5 Hz, NCHCH(C*H*$_3$)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.6 (CH*C*HNO), 109.6 (*C*(OCH$_2$CH$_2$O)), 70.9 ((CH$_3$)$_2$*C*(N)CH$_2$), 64.6 ((C(O*C*H$_2$*C*H$_2$O)), 34.3 (C(N)*C*H$_2$CH$_2$), 33.3 (CH$_2$*C*H$_2$C), 26.1 ((*C*H$_3$)$_2$C(N)), 26.0 (CH(N)*C*H(CH$_3$)$_2$), 23.7 (C(OCH$_2$CH$_2$O)*C*H$_3$), 19.0 (CH(N)CH-(*C*H$_3$)$_2$) ppm. HRMS exact mass calcd for [M + 1]$^+$ $C_{13}H_{26}NO_3$, 244.1907; found 244.1905.

***N*-[1-Methyl-3-(2-methyl-[1,3]dioxolan-2-yl)-1-phenyl-propyl]-α-isopropylnitrone (8)**. According to the procedure above, 2-methyl-2-(3-nitro-3-phenylbutyl)-[1,3]dioxolane **6** (4.943 g, 18.63 mmol), isobutyraldehyde (3.40 mL, 37.2 mmol), ammonium chloride (1.096 g, 20.48 mmol), and zinc powder (4.865 g, 74.38 mmol) were employed. Purification by flash chromatography (4:1 hexanes: EtOAc) provided 2.378 g (41.86% yield) of the product nitrone as a light-brown oil. TLC: 1:1 EtOAc:dichloromethane, UV, R_f = 0.23. IR ($CDCl_3$): 2938, 1574, 1495 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (5 H, m, Ar-*H*), 6.38 (1 H, d, J = 7.0 Hz, N=C*H*CH(CH$_3$)$_2$), 3.87 (4 H, m, C(OC*H*$_2$C*H*$_2$O)), 3.15 (1 H, m, N=CHC*H*(CH$_3$)$_2$), 2.46 (2 H, m, CH$_2$C*H*$_2$C(OCH$_2$CH$_2$O)CH$_3$), 2.19 (2 H, m, CH$_2$C*H*$_2$C(OCH$_2$CH$_2$O)CH$_3$), 1.73 (3 H, s, CH$_2$C(OCH$_2$CH$_2$O)C*H*$_3$), 1.57 (2 H, m, C*H*$_2$CH$_2$C(OCH$_2$CH$_2$O)CH$_3$), 1.27 (3 H, s, C*H*$_3$C(Ph)(N)CH$_2$CH$_2$), 1.07 (6 H, d, J = 6.8 Hz, N=CHCH-(C*H*$_3$)$_2$), 1.05 (6 H, d, J = 6.8 Hz, N=CHCH(C*H*$_3$)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2 (*ipso*-Ar, 1C), 142.6 (N*C*HCH-(CH$_3$)$_2$), 128.7 (*o*-Ar, 2C), 127.9 (*p*-Ar, 2C), 126.2 (*m*-Ar, 2C), 109.7 (*C*(OCH$_2$CH$_2$O)), 64.7 (C(O*C*H$_2$*C*H$_2$O)), 33.8 (*C*H$_2$CH$_2$C), 33.3 (CH$_2$*C*H$_2$C), 26.2 ((*C*H$_3$)PhC(N)CH$_2$), 25.2 (NCH*C*H(CH$_3$)$_2$), 23.9 (C(OCH$_2$CH$_2$O)*C*H$_3$), 18.9 ((*C*H$_3$)$_2$CH) ppm. HRMS exact mass calcd for [M + 1]$^+$ $C_{18}H_{28}NO_3$, 306.2063; found 306.2045.

***N*-[1,1-Dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-N-(2-methyl-1-phenyl-propyl)-nitroxide (9).** *N*-[1,1-Dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-α-isopropylnitrone **7** (10.343 g, 42.50 mmol) was dissolved in 50 mL of anhydrous THF and then cooled to 0 °C while stirring. Phenylmagnesium bromide (3 M in Et$_2$O, 28.34 mL, 85.02 mmol) was added slowly over 10 min. The reaction was stirred at room temperature for 3 h, then excess reagent was cautiously quenched with 50 mL of saturated ammonium chloride solution, followed by 50 mL of water. The organic layer was separated, and the aqueous layer extracted four times with 50 mL of dichloromethane. The combined organic layers were washed with 100 mL of brine, dried over magnesium sulfate, filtered, and then concentrated. The residue was dissolved in 22 mL of methanol and to this was added concentrated ammonium hydroxide (29% w/w, 3.78 mL) and copper acetate monohydrate (424 mg, 2.33 mmol). A stream of air was bubbled through the mixture until the color changed to dark green (30 min). The reaction mixture was concentrated and partitioned between 50 mL of chloroform and 30 mL of concentrated sodium hydrogen sulfate. Enough water was added to dissolve all solids, and the organic layer was separated. The aqueous layer was extracted three more times with 30 mL of chloroform. The organic layers were combined and washed with 50 mL of saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered, and then concentrated to give 6.04 g of crude product. The nitroxide was purified by flash column chromatography (16:1 hexanes:EtOAc to 10:1 hexanes:EtOAc) to afford 6.036 g (44.31% yield) of the product as an orange oil. TLC 16:1 hexanes:EtOAc, UV, R_f = 0.54. IR ($CDCl_3$): 3406, 2974, 1594, 1469, 1378 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, with 5 μL of phenyl hydrazine added): δ 7.2−7.5 (5 H, m, Ar-*H*), 3.98 (4 H, m, C(OC*H*$_2$C*H*$_2$O)), 3.75 (1 H, s, NC*H*(Ph)CH(CH$_3$)$_2$), 2.20 (1 H, m, NCH(Ph)C*H*(CH$_3$)$_2$), 2.00 (2 H, m, CH$_2$C*H*$_2$C(OCH$_2$CH$_2$O)-

CH_3), 1.70 (2 H, m, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 1.33 (6 H, s, $C(CH_3)_2(N)CH_2CH_2$), 1.24 (3 H, s, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 1.19 (3 H, s, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 1.02 (6 H, s, NCH(Ph)CH(CH_3)$_2$), 0.64 (6 H, s, NCH(Ph)CH(CH_3)$_2$), 0.41 (6 H, s, NCH(Ph)CH(CH_3)$_2$). HRMS (with phenyl hydrazine) exact mass calcd for $[M + 1]^+$ $C_{19}H_{32}NO_3$, 322.2220; found 322.2213.

***N*-[1-Methyl-3-(2-methyl-[1,3]dioxolan-2-yl)-1-phenyl-propyl]-*N*-(2-methyl-1-phenyl-propyl)-nitroxide (10)**. Prepared according to the procedure above, *N*-[1-methyl-3-(2-methyl-[1,3]dioxolan-2-yl)-1-phenyl-propyl]-α-isopropylnitrone **8** (3.828 g, 12.53 mmol), phenylmagnesium bromide (3 M in THF, 8.35 mL, 25.1 mmol), and in the next step copper acetate monohydrate (125 mg, 0.688 mmol) were employed. Purification by flash chromatography (16:1 hexanes:EtOAc to 10:1 hexanes:EtOAc to 5:1 hexanes:EtOAc) provided 2.352 g (49.07% yield) of the product nitroxide as a viscous orange oil. TLC: 6% EtOAc in hexanes, UV, PAA, R_f = 0.11. IR ($CDCl_3$): 3315, 2934, 1596, 1455, 1378, 1294 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$ with 5 μL of phenyl hydrazine added): δ 7.33 (10 H, m, Ar-*H*), 3.88 (4 H, m, C(OCH_2CH_2O)), 3.08 (1 H, d, J = 7 Hz, NC*H*(Ph)CH(CH_3)$_2$), 2.88 (1 H, m, NCH(Ph)C*H*(CH_3)$_2$), 2.53 (2 H, m, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 2.27 (3 H, s, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 1.29 (m, 2 H, m, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 0.9 (s, 3 H, $CH_3C(Ph)(N)CH_2CH_2$), 0.8 (6 H, d, J = 6.8 Hz, CH(Ph)CH(CH_3)$_2$), 0.6 (6 H, d, J = 6.8 Hz, CH(Ph)CH(CH_3)$_2$), 0.4 (6 H, d, J = 6.8 Hz, CH(Ph)CH(CH_3)$_2$) ppm. HRMS (with phenyl hydrazine) exact mass calcd for $[M + 1]^+$ $C_{24}H_{34}NO_3$, 384.2539; found 384.2533.

***N*-(1-Phenethyloxy)-8-[1,3]-dioxolanyl-3-phenyl-2,5,5-trimethylazanonane (11).** To a solution of *N*-[1,1-dimethyl-3-(2-methyl-[1,3]dioxolan-2-yl)-propyl]-*N*-(2-methyl-1-phenyl-propyl)-nitroxide **9** (3.584 g, 11.19 mmol) and styrene (2.59 mL, 22.4 mmol) in 9 mL of 1:1 toluene:ethanol was added *R*,*R*-[*N*,*N*′-bis(3,5-di-*t*-butylsalicylidene)-1,2-cyclohexanediaminato] manganese(III) chloride (Jacobsen's catalyst, 1.423 g, 2.24 mmol) followed by sodium borohydride (1.269 g, 33.55 mmol). The reaction was then stirred open to atmosphere at room temperature until no more starting material was observed by TLC (~24 h). The mixture was then concentrated and partitioned between 50 mL of dichloromethane and 50 mL of water. The organic layer was separated and the aqueous layer was extracted three more times with 25 mL of dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and then concentrated to provide 6.197 g of crude material. The product was purified twice by flash column chromatography (hexanes to 16:1 hexanes:EtOAc) to obtain 4.659 g (97.81%) of the product as a viscous light-brown/green oil as an inseparable 1:1 mixture of diastereomers. TLC: 16:1 hexanes: EtOAc, PAA, R_f = 0.25. IR ($CDCl_3$): 2925, 2872, 1596, 1454, 1380, 1113, 1064 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, both diastereomers): δ 7.35 (10 H, m, Ar-*H*), 4.96 (1 H, m, PhC*H*(CH_3)-ON), 3.83 (4 H, m, C(OCH_2CH_2O)), 3.45 (1 H, d, J = 10 Hz, C*H*(Ph)CH(CH_3)$_2$), 3.28 (1 H, d, J = 10 Hz, C*H*(Ph)CH(CH_3)$_2$), 2.40 (1 H, m, CH(Ph)C*H*(CH_3)$_2$), 1.93, 1.81, 1.50 (4 H, m, $CH_2CH_2C(OCH_2CH_2O)CH_3$, both diastereomers), 1.65 (3 H, d, J = 5 Hz, PhCH(CH_3)ON), 1.58 (3 H, d, J = 5 Hz, PhCH(CH_3)-ON), 1.37 (6 H, d, J = 6.5 Hz, NCH(Ph)CH(CH_3)$_2$), 1.35 (6 H, s, $(CH_3)_2C(N)CH_2CH_2$), 1.21 (6 H, s, $(CH_3)_2C(N)CH_2CH_2$), 1.01 (3 H, s, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 0.94 (6 H, s, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 0.92 (6 H, d, J = 6.5 Hz, NCH(Ph)CH(CH_3)$_2$), 0.73 (3 H, s, $(CH_3)_2C(N)CH_2CH_2$), 0.69 (3 H, s, $(CH_3)_2C(N)CH_2CH_2$), 0.59 (3 H, d, J = 6.5 Hz, NCH(Ph)CH(CH_3)$_2$), 0.23 (3 H, d, J = 6.5 Hz, NCH(Ph)CH(CH_3)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, both diastereomers): δ 145.4 (*ipso*-Ar, 1C), 142.9 (*ipso*-Ar, 1C), 130.9 (*o*-Ar, 1C), 128.2 (*o*-Ar, 1C), 127.4 (*o*-Ar, 2C), 127.1 (*p*-Ar, 2C), 126.7 (*p*-Ar, 2C), 126.3 (*m*-Ar, 1C), 126.2 (*m*-Ar, 1C), 110.6 (*C*(OCH$_2$CH$_2$O)), 83.2 (PhCH(CH$_3$)O), 71.7 (PhCH(CH)N), 64.8 (C(OCH$_2$CH$_2$O)), 62.5 ((CH$_3$)$_2$*C*(CH$_2$)N), 33.6 (*C*H(CH$_3$)$_2$C), 32.3 (*C*H$_2$CH$_2$C), 31.7 (CH$_2$*C*H$_2$C), [26.6, 26.4] (*C*H$_3$)$_2$C(CH$_2$)N), 23.7 (C(OCH$_2$CH$_2$O)*C*H$_3$), 22.1 (*C*H$_3$CH(Ph)O), [21.4, 21.2] ((*C*H$_3$)$_2$-CHCN) ppm. HRMS exact mass calcd for $[M + 1]^+$ $C_{27}H_{40}NO_3$, 426.3003; found 426.3025.

***N*-(1-Phenethyloxy)-8-[1,3]-dioxolanyl-3,5-diphenyl-2,5-dimethylazanonane (12).** Prepared according to the procedure above, *N*-[1-methyl-3-(2-methyl-[1,3]dioxolan-2-yl)-1-phenyl-propyl]-*N*-(2-methyl-1-phenyl-propyl)-nitroxide **10** (2.046 g, 5.349 mmol), styrene (1.24 mL, 10.8 mmol), Jacobsen's catalyst (680 mg, 1.07 mmol), and sodium borohydride (607 mg, 16.1 mmol) were employed. Purification by flash column chromatography (20:1 hexanes:EtOAc to 16:1 hexanes:EtOAc) provided 2.197 g (84.21% yield) of the product as a brown viscous oil as an inseparable 1:1 mixture of diastereomers. TLC: 16:1 hexanes:EtOAc, UV, R_f = 0.18. IR ($CDCl_3$): 2952, 1492, 1453, 1374, 1293 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, both diastereomers): δ 7.52−7.14 (15 H, m, Ar-*H*), 5.22 (1 H, q, J = 7 Hz, PhC*H*(CH_3)ON), 5.11 (1 H, q, J = 7 Hz, PhC*H*(CH_3)ON), 3.87 (2 H, m, C(OCH$_2$CH$_2$O)), 3.64 (2 H, m, C(OCH$_2$CH$_2$O)), 3.02 (1 H, d, J = 10 Hz, NC*H*(Ph)CH(CH_3)$_2$), 3.93 (1 H, J = 10 Hz, NC*H*(Ph)CH(CH_3)$_2$), 2.34 (1 H, m, NCH(Ph)C*H*(CH_3)$_2$), 2.24 (2 H, m, $CH_2CH_2C(OCH_2CH_2O)CH_3$), 1.72 (3 H, d, J = 7 Hz, PhCH(CH_3)ON), 1.66 (3 H, d, J = 7 Hz), PhC*H*(CH_3)ON, 1.43 (2 H, m, $CH_2CH_2C(OCH_2CH_2O)CH_3$) 1.28 (3 H, d, J = 5 Hz, NCH(Ph)CH(CH_3)$_2$), 1.25 (3 H, s, $CH_3C(Ph)(N)CH_2CH_2$), 1.03 (3 H, s, $CH_3C(Ph)(N)CH_2CH_2$), 0.91 (6 H, d, J = 5 Hz, NCH(Ph)CH(CH_3)$_2$), 0.88 (3 H, s, $CH_2C(OCH_2CH_2O)CH_3$), 0.77 (3 H, s, $CH_2C(OCH_2CH_2O)CH_3$), 0.34 (3 H, d, J = 5 Hz, NCH(Ph)CH(CH_3)$_2$), 0.03 (3 H, d, J = 5 Hz, NCH(Ph)CH(CH_3)$_2$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, both diastereomers): δ [146.1, 145.1] (*ipso*-Ar, 1C), [144.7, 144.5] (*ipso*-Ar, 1C), [143.0, 142.9] (*ipso*-Ar, 1C), [130.8, 130.7] (*o*-Ar, 1C), 128.4−126.2 (Ar, 15C), [110.3, 110.0] (*C*(OCH$_2$CH$_2$O)), [84.4, 83.6] (PhC*H*(CH$_3$)O), [72.4, 72.3] (PhC*H*(CH$_3$)N), [69.9, 69.6] (PhC*H*(CH$_3$)N), [64.6, 64.5, 64.2, 64.1] (C(O*C*H$_2$*C*H$_2$O)), [38.1, 37.9] (*C*H$_2$CH$_2$C), [34.3, 33.8] (CH$_2$*C*H$_2$C), [32.6, 32.1] (NCH*C*H(CH$_3$)$_2$), [25.5, 24.0] (PhC-(*C*H$_3$)N), [23.7, 23.2] (C(OCH$_2$CH$_2$O)*C*H$_3$), [22.2, 21.9] (PhCH-(*C*H$_3$)O), [21.1, 21.0, 17.2, 16.6] (NCHCH(*C*H$_3$)$_2$) ppm. HRMS exact mass calcd for $[M + 1]^+$ $C_{32}H_{42}NO_3$, 488.3159; found 488.3348.

***N*-(1-Phenethyloxy)-5,5,8-trimethyl-7-phenyl-azanonan-2-one (1).** A solution of *N*-(1-phenethyloxy)-8-[1,3]-dioxolanyl-3-phenyl-2,5,5-trimethylazanonane **11** (1.00 g, 2.35 mmol) and pyridinium *p*-toluenesulfonate (135 mg, 0.71 mmol) in 30 mL of acetone and 1 mL of water was refluxed until the starting material was no longer observed by TLC (3 h). Next, 100 mL of diethylether was added and the organic phase was washed with 50 mL of saturated sodium bicarbonate solution and 50 mL of brine. The organic layer was dried over magnesium sulfate, filtered, and then concentrated to give 845 mg (94% yield) of the product as a light-yellow viscous oil as an inseparable 1.2:1 mixture of diastereomers. TLC: 4:1 hexanes: EtOAc, PAA, R_f = 0.58. IR ($CDCl_3$): 2958, 1781, 1682, 1597, 1493, 1453, 1383 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, both diastereomers): δ 7.30 (20 H, m, Ar-*H*), 4.88 (1 H, q, J = 5 Hz, PhC*H*(CH_3)ON, major diastereomer), 4.89 (1 H, q, J = 5 Hz, PhC*H*(CH_3)ON, major diastereomer), 4.84 (1 H, q, J = 5 Hz, PhC*H*(CH_3)ON, minor diastereomer), 3.34 (1 H, d, J = 11 Hz, NC*H*(Ph)CH(CH_3)$_2$, major diastereomer), 3.21 (1 H, d, J = 11 Hz, NC*H*(Ph)CH(CH_3)$_2$, minor diastereomer), 2.56 (1 H, m, CH(Ph)C*H*(CH_3)$_2$, both diastereomer), 2.38 (1 H, m, CH(Ph)C*H*(CH_3)$_2$, minor diastereomer), 2.33 (2 H, m, $CH_2CH_2C(O)CH_3$, both diastereomers), 2.09 (3 H, s, $CH_2CH_2C(O)CH_3$, minor diastereomer), 1.94 (3 H, s, $CH_2CH_2C(O)CH_3$, major diastereomer), 1.64 (3 H, d, J = 5 Hz, CH(Ph)CH(CH_3)$_2$, major diastereomer), 1.55 (3 H, d, J = 5 Hz, CH(Ph)CH(CH_3)$_2$, minor diastereomer), 1.47 (2 H, m, $CH_2CH_2C(O)CH_3$, both diastereomers), 1.34 (3 H, d, J = 5 Hz, CH(Ph)CH(CH_3)$_2$, major diastereomer), 0.99 (6H, s, $(CH_3)_2C(N)CH_2$, both diastereomers), 0.92 (3 H, d, J = 5 Hz, CH(Ph)CH(CH_3)$_2$,-minor diastereomer), 0.90 (6 H, s, $(CH_3)_2C(N)CH_2$, minor diastereomer), 0.81 (6 H, s, $(CH_3)_2C(N)CH_2$, major diastereomer), 0.57 (3 H, d, J = 5 Hz, CH(Ph)CH(CH_3)$_2$,major diastereomer), 0.22 (6 H, d, J = 5 Hz, CH(Ph)CH(CH_3)$_2$, minor diastereomer) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, all diastereomers): δ 209.6 (*C*(O)), 145.6 (*ipso*-Ar, 1C), 142.3 (*ipso*-Ar, 1C), 130.9 (*o*-Ar, 1C), 128.3 (*o*-Ar, 1C), 128.2 (*o*-Ar, 2C), 127.6 (*p*-Ar, 2C), 127.5 (*p*-Ar, 2C), 126.7 (*m*-Ar, 1C), 126.5 (*m*-Ar, 1C), 83.5 (PhC*H*(CH$_3$)O), 72.0 (PhC*H*-

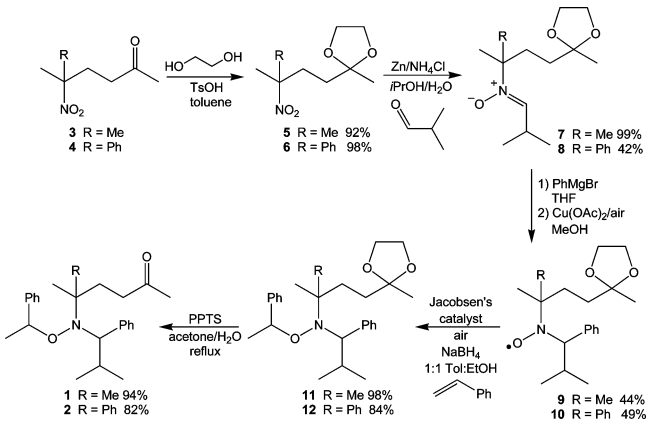
(CH)N), 62.0 ((CH$_3$)$_2$*C*N), 39.3 (CH$_2$*C*H$_2$C(O)), 35.1 (*C*H$_2$CH$_2$C(O)), 32.3 (PhCH*C*H(CH$_3$)$_2$), 26.7 ((*C*H$_3$)$_2$CN), 23.4 (C(O)*C*H$_3$), 22.3 (PhCH(*C*H$_3$)O), [21.4, 21.2] ((*C*H$_3$)$_2$CHCH) ppm. HRMS exact mass calcd for [M + 1]$^+$ $C_{25}H_{36}NO_2$, 382.2706; found 382.2695.

***N*-(1-Phenethyloxy)-5,8-dimethyl-5,7-phenyl-azanonan-2-one (2).** Prepared according to the procedure above, *N*-(1-phenethyloxy)-8-[1,3]-dioxolanyl-3,5-diphenyl-2,5-dimethylazanonane **12** (1.890 g, 3.876 mmol) and pyridinium *p*-toluenesulfonate (220 mg, 1.16 mmol) were employed to give 1.414 g (82.35% yield) of the product as a brown viscous oil as an inseparable mixture of diastereomers. TLC: 8:1 hexanes: EtOAc, PAA, R_f = 0.31. IR ($CDCl_3$): 2928, 1713, 1360 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, all diastereomers): δ 6.9−7.6 (15 H, m, Ar-*H*), 5.23 (1 H, q, J = 7 Hz, NC*H*(Ph)CH(CH$_3$)$_2$), 5.19 (1 H, q, J = 7 Hz, NC*H*(Ph)CH(CH$_3$)$_2$), 5.13 (1 H, q, J = 7 Hz, NC*H*(Ph)CH(CH$_3$)$_2$), 3.05 (1 H, d, J = 10 Hz, C*H*(Ph)CH(CH$_3$)$_2$), 2.96 (1 H, d, J = 10 Hz, C*H*(Ph)CH(CH$_3$)$_2$), 2.92 (1 H, d, J = 10 Hz, C*H*(Ph)CH(CH$_3$)$_2$), 2.46 (1 H, m, CH(Ph)C*H*(CH$_3$)$_2$), 2.37 (1 H, m, CH(Ph)C*H*(CH$_3$)$_2$), 2.27, 2.16 (4 H, m, C*H*$_2$C*H*$_2$C(O)CH$_3$, all diastereomers), 1.96 (3 H, s, CH$_2$CH$_2$C(O)C*H*$_3$), 1.75 (3 H, d, J = 7 Hz, PhCH(C*H*$_3$)ON), 1.72 (3 H, d, J = 7 Hz, PhCH(C*H*$_3$)ON), 1.69 (3 H, d, J = 7 Hz, PhCH(C*H*$_3$)ON), 1.63 (3 H, s, CH$_2$CH$_2$C(O)C*H*$_3$), 1.48 (3 H, s, CH$_2$CH$_2$C(O)C*H*$_3$), 1.33 (3 H, s, C*H*$_3$C(Ph)(N)CH$_2$CH$_2$), 1.32 (6 H, d, J = 7 Hz, NCH(Ph)CH(C*H*$_3$)$_2$), 1.26 (6 H, d, J = 7 Hz, NCH(Ph)CH(C*H*$_3$)$_2$), 1.25 (3 H, s, C*H*$_3$C(Ph)(N)CH$_2$CH$_2$), 1.24 (3 H, s, C*H*$_3$C(Ph)(N)CH$_2$CH$_2$), 1.00 (6 H, d, J = 7 Hz, NCH(Ph)CH(C*H*$_3$)$_2$), 0.92 (6 H, d, J = 7 Hz, NCH(Ph)CH(C*H*$_3$)$_2$), 0.36 (6 H, d, J = 7 Hz, CH(Ph)CH(C*H*$_3$)$_2$), 0.04 (6 H, d, J = 7 Hz, CH(Ph)CH(C*H*$_3$)$_2$). ^{13}C NMR (125 MHz, $CDCl_3$, all diastereomers): δ 208.8 (*C*(O)), [145.5, 145.0] (*ipso*-Ar, 1C), [142.9, 142.8] (*ipso*-Ar, 1C), [142.7, 142.6] (*ipso*-Ar, 1C), 130.7 (*o*-Ar, 1C), 128.5−125.9 (Ar, 15C), [110.4, 110.2] (*C*(OCH$_2$CH$_2$O)), [84.5, 83.8] (Ph*C*H(CH$_3$)O), [72.5, 71.8] (Ph*C*H(CH)N), [69.4, 69.3] (Ph*C*(CH$_3$)N), [40.4, 40.1] (*C*H$_2$C(O)), [38.7, 37.6] (*C*H$_2$CH$_2$C(O)), [32.5, 32.1] CH*C*H(CH$_3$)$_2$), [25.4, 24.7] (PhC(*C*H$_3$)N), [23.9 23.7] (C(O)*C*H$_3$), [22.2, 22.0] (PhC(*C*H$_3$)O), [20.9, 20.8, 17.2, 16.6] (CH(*C*H$_3$)$_2$) ppm. HRMS exact mass calcd for [M + 1]$^+$ $C_{30}H_{38}NO_2$, 444.2897; found 444.2963.

2,4-Dinitrophenylhydrazone of *N*-(1-phenethyloxy)-5,5,8-trimethyl-7-phenyl-azanon-2-one (18). A solution of **1** (50 mg, 0.13 mmol) in 0.5 mL of ethanol was slowly added to 1.5 mL of 2,4-dinitrophenylhydrazine (DNPH) reagent solution (2.145 g of DNPH dissolved in 7.5 mL of H_2SO_4, 10 mL of H_2O, and 35 mL of EtOH). The orange hydrazone precipitated immediately and was filtered and washed twice with chilled ethanol. The material was redissolved in dichloromethane, dried over magnesium sulfate, filtered, then and concentrated to give 63 mg (86% yield) of the product as an orange solid as an inseparable mixture of diastereomers. MP: 52−56 °C. IR ($CDCl_3$): 3155, 2981, 2254, 1619, 1594, 1337. ^{1}H NMR (500 MHz, $CDCl_3$ all diastereomers): δ [11.03, 10.93] (1 H, s, CH$_2$C(NN*H*)CH$_3$), 9.15 (1 H, m, Ar-*H*, meta NH, ortho di-nitro), 8.29 (1 H, d, J = 10 Hz, Ar-*H*, meta NH, ortho nitro), [7.95, 7.82] (1 H, m, Ar-*H*, ortho NH, both diastereomers), 7.31 (10 H, m, Ar-*H*), 4.93 (1 H, m, PhC*H*(CH$_3$)ON), 3.41 (1 H, d, J = 10 Hz, NC*H*CH(CH$_3$)$_2$Ph), 3.27 (1 H, d, J = 10 Hz, NC*H*CH(CH$_3$)$_2$Ph), [2.62, 2.40, 2.26, 1.37] (2 H, m, (CH$_3$)$_2$CC*H*$_2$C*H*$_2$C(NNH)CH$_3$, both diastereomers), 2.26 (1 H, m, (CH$_3$)$_2$C*H*CH(Ph)N), 1.79, 1.55 (3 H, s, C*H*$_3$C(NNH)CH$_2$CH$_2$, both diastereomers), 1.65, 1.56 (3 H, d, J = 5 Hz, PhCH(C*H*$_3$)O), [1.38, 0.95, 0.58, 0.22] (3 H, d, J = 5 Hz, (C*H*$_3$)$_2$CHCH(Ph)N, both diastereomers), [1.13, 1.04, 0.93, 0.71] (6 H, s, (C*H*$_3$)$_2$C(N)CH$_2$CH$_2$, both diastereomers). HRMS exact mass calcd for [M + 1]$^+$ $C_{31}H_{39}N_5O_5$, 562.3024; found 562.3060.

General Polymerization Method. A mixture of *N*-(1-phenethyloxy)-5,5,8-trimethyl-7-phenyl-azanon-2-one (**1**, 50 mg, 0.13 mmol) and styrene (1.363 g, 13.09 mmol) was degassed by four freeze−pump−thaw cycles and sealed under argon. The mixture was heated to 125 °C in an oil bath for 6 h. A small aliquot of the crude mixture was taken to determine the degree of polymerization by ^{1}H NMR. The polymer was dissolved in a minimum amount of dichloromethane and precipitated by the addition of chilled methanol.

Scheme 1. Synthesis of Ketone-Functionalized *N*-Alkoxyamines[a]



[a] TsOH = *p*-toluenesufonic acid, PPTS = pyridinium-*p*-toluene sulfonate, THF = tetrahydrofuran.

The precipitation procedure was repeated two times and dried under vacuum to give 858 mg of a white polymer. $M_{n(calcd)}$ (^{1}H NMR) = 9442. GPC: M_n = 9468, PDI = 1.13. For *n*-butyl acrylate, *t*-butyl acrylate, and *N*,*N*-dimethylacrylamide, 5% free ketal protected nitroxide (**9** or **10**) was added prior to polymerization. Precipitation of polyacrylates was effected with 70% methanol (aq), and poly(*N*,*N*-dimethylacrylamide) was precipitated from acetone by the addition of chilled diethyl ether.

Results and Discussion

Initiator Synthesis. Ketone functionalized initiators **1** and **2** were readily prepared by analogous syntheses from the corresponding nitro compounds (Scheme 1). Ketone functional groups of **3** and **4** were protected with ethylene glycol to give dioxolanes **5** and **6**. The nitro groups of **5** and **6** were then reduced with zinc to give the transient hydroxylamines, which condensed in situ onto isobutyraldehyde to produce nitrones **7** and **8**. Grignard addition with phenyl magnesium bromide to nitrones **7** and **8** provided hydroxylamine intermediates, which were directly oxidized with copper acetate and air to give nitroxides **9** and **10**. Coupling of **9** and **10** to styrene was accomplished through a modified version of Hawker's procedure[17] by employing Jacobsen's catalyst and sodium borohydride open to air to give *N*-alkoxyamines **11** and **12**. Ketone-functionalized initiators **1** and **2** were then revealed through removal of the dioxolane protecting groups with pyridinium *p*-toluene sulfonate.[18]

Polymerization Studies with 1 and 2. Initial polymerization studies with *N*-alkoxyamines **1** and **2** showed comparable rates in the polymerization of styrene (entries 1 and 2, Table 1). However, there was a distinct increase in the polydispersity index (PDI = M_w/M_n) of polystyrene prepared from **2**. Further polymerization experiments with other monomers showed similar results. In general, polymers prepared from **2** exhibited higher PDI values as well as decreased polymerizations times. An extreme example of the latter is during the polymerization of *N*,*N*-dimethylacrylamide, in which the entire sample solidified within 40 min of heating (entry 8, Table 1). The results observed from polymerizations initiated with **2** are consistent with other *N*-alkoxyamines, which also possess a phenyl ring at that position.[19] It is likely that mediating nitroxide **13** decomposes through α-scission to give stabilized tertiary benzyl radical **14** and nitroso **15** (Scheme 2). Ionic decomposition of the *N*-alkoxyamine or nitroxide by loss of the tertiary cation analogous to **14** cannot be excluded. The decomposition of **13** results in unmediated polymerization leading to radical termination (disproportionation and dimerization) and polydisperse polymers.

Table 1. Polymerization Results from Initiators 1 and 2 at with Various Monomers[a]

entry	initiator	monomer[b]	time (h)	% conversion[d]	M_n[e]	PDI[e]
1	1	St	6	87	9468	1.13
2	2	St	6	86	11 492	1.45
3	1[c]	NBA	20	72	12 822	1.15
4	2[c]	NBA	4	95	26 360	1.66
5	1[c]	TBA	20	74	12 310	1.17
6	2[c]	TBA	8	99	28 169	1.83
7	1[c]	DMA	4	80	10 649	1.23
8	2[c]	DMA	0.67	90	6840	1.58

[a] Experimental conditions: polymerizations were run neat in a 1:100 ratio of initiator to monomer at 125 °C. [b] St = styrene, NBA = *n*-butyl acrylate, TBA = *t*-butyl acrylate, DMA = *N*,*N*-dimethylacrylamide. [c] 5% free nitroxide of the corresponding dioxolane protected *N*-alkoxyamine was added. [d] Determined by ^{1}H NMR integration from an aliquot of the crude polymerization mixture. [e] Number-average molecular weight (M_n) and polydispersity index (PDI) were determined from gel permeation chromatography (GPC).

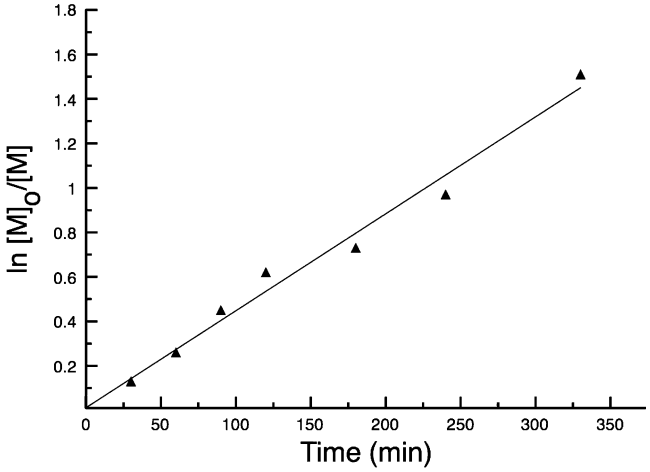
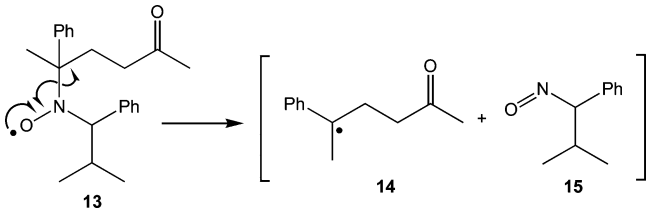


Figure 2. Styrene polymerization with initiator **1**, neat at 125 °C as a function of ln ($[M]_0/[M]$) and time.

Scheme 2. Possible Decomposition of Nitroxide Intermediate Nitroxide 13



Polymers terminated in this manner are unlikely to have an *ω*-chain end *N*-alkoxyamine, and therefore the "living" character of polymers prepared from **2** was not assessed.

The controlled nature of the polymerization was determined through a time study of the polymerization of styrene with initiator **1**. A linear relationship between ln ($[M]_0/[M]$) versus time indicated that this process follows first-order polymerization kinetics (Figure 2). This confirms that no significant termination events occur during polymerization. Figure 3 shows a linear relationship between molecular weight and monomer conversion exists, which implies controlled chain growth. A dramatic decrease is clearly observed in PDI for increasing monomer conversion. The low polydispersities observed for polymers prepared with **1** (PDI < 1.3, odd entries, Table 1) and the time study demonstrate that initiator **1** effects polymerization in a controlled manner.

To determine if polymers prepared from **1** retained an active initiator at the chain terminus, a second polymer block was

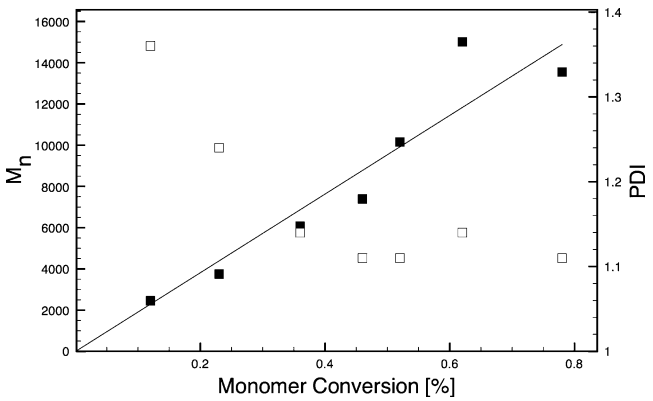


Figure 3. Plot of number average molecular weight (M_n, ■) and the polydispersity index (PDI, □) vs percent monomer conversion for polystyrene polymers prepared from **1**.

Scheme 3. Block Copolymer Synthesis from Macroinitiator 16

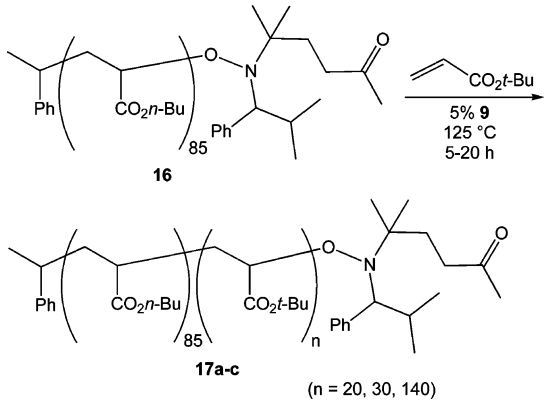


Table 2. Block Copolymers Grown from Poly(*n*-butyl acrylate) Macroinitiator 16[a]

polymer	monomer	time (h)	% conv[b]	M_n[c]	M_n[d]	PDI[d]
16		0		9610	12 822	1.15
17a	TBA	5	10	12 173	14 364	1.14
17b	TBA	10	15	13 455	15 162	1.16
17c	TBA	20	70	27 554	28 932	1.35

[a] Experimental conditions: polymerizations were run neat in a ratio 1:200:0.05 of macroinitiator to monomer to free nitroxide **9**, at 125 °C. [b] Determined by ^{1}H NMR integration from an aliquot of the crude polymerization mixture. [c] Calculated from the monomer conversions based on ^{1}H NMR integration. [d] Number-average molecular weight (M_n) and polydispersity index (PDI) were determined from gel permeation chromatography (GPC).

grown using a poly(*n*-butyl acrylate) macroinitiator (**16**, entry 3, Table 1). Polymer blocks of *t*-butyl acrylate were grown with macroinitiator **16** (Scheme 3) over time periods of 5, 10, and 20 h (Table 2). GPC chromatograms of the block copolymers showed comparable increases in molecular weight with respect to NMR conversions. Figure 4 shows sequential GPC traces of block copolymers grown from **16**. The observed increase in molecular weight demonstrates the ability of this novel initiator to grow block copolymers.

Post-Polymerization Chain-End Functionalization. The formation of diblocks from macroinitiator **16** confirmed the presence of an active *N*-alkoxyamine at the polymer terminus but does not provide any evidence that the ketone functionality survived polymerization. To investigate the integrity of the ketone on the polymer terminus, the well-established technique of hydrazone formation proved invaluable. Derivatization of ketones with 2,4-dinitrophenylhydrazine (DNPH) is well studied,[20] and preparation of hydrazones is straightforward.[21] 2,4-

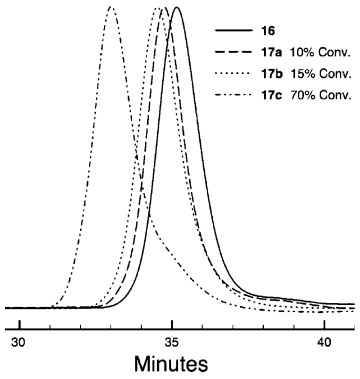
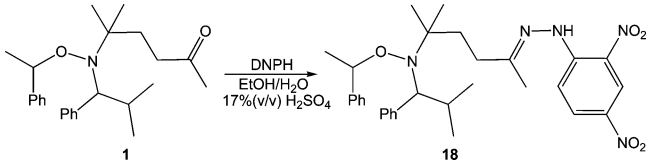
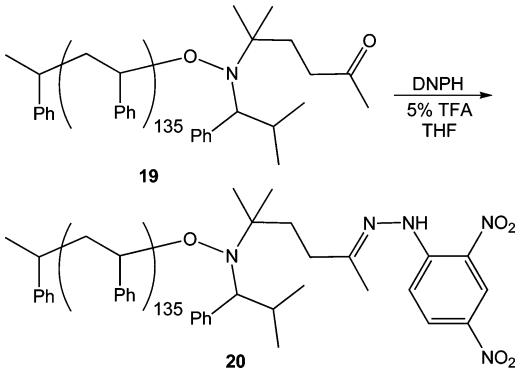


Figure 4. GPC chromatograms of poly(*t*-butyl acrylate) blocks grown from macroinitiator **16** at time intervals of 5 (**17a**), 10 (**17b**), and 20 h (**17c**).

Scheme 4. Preparation of 2,4-Dinitrophenylhydrazone of Initiator 1



Scheme 5. 2,4-Dinitrophenylhydrazine Derivatization of Ketone Terminated Polystyrene[a]



[a] Prepared from **1** and 200 equiv of styrene at 125 °C for 4 h. ^{1}H NMR analysis of an aliquot of the crude polymerization mixture indicated 74% monomer consumption. GPC: M_n = 12 945, PDI = 1.11.

Dinitrophenylhydrazones have intense molar absorptivities, which provides a method of quantification of functionalized polymer termini through UV−visible spectroscopy. Initially, a model compound was prepared by formation of the 2,4-dinitrophenylhydrazone of initiator **1** by conventional methods (Scheme 4).[14]

Applying this method in an attempted derivatization of polystyrene prepared with **1** resulted in immediate precipitation due to insolubility of the polymer in the reaction medium. The polymer sample was slightly yellow in color but showed negligible absorbance in the expected visible range. Therefore, a new method of hydrazone formation was developed that employed 5% (v/v) trifluoroacetic acid in tetrahydrofuran. The polymer was first dissolved in this acidic solution, followed by the addition of 10 equiv of DNPH (recrystallized from acetonitrile, Scheme 5). The reaction was stirred at room temperature for 24 h, after which the polymer was precipitated from the reaction by the addition of chilled methanol. A stark difference in color was observed in polymer samples prepared in this manner compared to those prepared by the traditional method. The extent of hydrazone formation on the polymer terminus

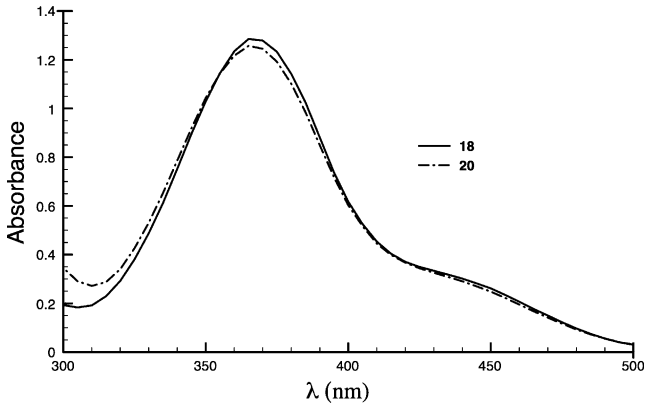


Figure 5. Overlay of absorption spectra of model hydrazone **18** and polymeric hydrazone **20**.

was quantified by comparing the absorptivity to that of model compound **18**. Because the hydrazone chromophores are the same in compounds **18** and **20**, the molar extinction coefficients should be identical, providing a precise determination of the degree of functionalized end-groups. An overlay of these absorption spectra is shown in Figure 5. The amount of functional end-groups was evaluated to be 98%, which correlates with the alkoxyamine fidelity observed by Hawker et al. for polymers prepared with monomer conversions below 80%.[7]

Conclusion

Two ketone functionalized *N*-alkoxyamines were synthesized and examined as initiators for nitroxide-mediated polymerization. Results with initiator **2** indicated uncontrolled polymerization. However, initiator **1** showed first-order polymerization kinetics, and the living character was confirmed through synthesis of diblock copolymers. The ability to modify the polymer end-group was demonstrated by derivatization of the pendant ketone with 2,4-dinitrophenylhydrazine. The quantitative nature of this postpolymerization functionalization was determined by measuring the absorptivity of the derivatized polymer sample versus a model compound. This demonstrates the capacity to add functionality as a postpolymerization modification of polymers prepared from **1**. The ketone group clearly survives the polymerization conditions but does not adversely affect the efficacy of the nitroxide in the NMP process. Facile decoration of the ω-terminus by hydrazone or oxime formation holds promise for the versatile manipulation of designed polymers produced by NMP for a variety of biomedical, biosensor, and nanotechnological applications.

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References and Notes

(1) (a) Moad, G.; Rizzardo, E.; Thang, S. H. *Aust. J. Chem.* **2005**, *58*, 379−410. (b) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559−5562. (c) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Chong, Y. K.; Moad, G.; Thang, S. H. *Macromolecules* **1999**, *32*, 6977−6980. (d) Mayadunne, R. T. A.; Rizzardo, E.; Chiefari, J.; Krstina, J.; Moad, G.; Postma, A.; Thang, S. H. *Macromolecules* **2000**, *33*, 243−245. (e) Barner-Kowollik, C.; Buback, M.; Charleux, B.; Coote, M. L.; Drache, M.; Fukuda, T.; Goto, A. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5809−5831.

(2) (a) Pintauer, T.; Matyjaszewski, K. *Coord. Chem. Rev.* **2005**, *249*, 1155−1184. (b) Patten, T. E.; Xia, J. H.; Abernathy, T.; Matyjaszewski, K. *Science* **1996**, *272*, 866−868. (c) Kato, M.; Kamigaito, M.; Sawamoto, M.; Higashimura, T. *Macromolecules* **1995**, *28*, 1721−1723. (d) Percec, V.; Barboiu, B. *Macromolecules* **1995**, *28*, 7970−7972. (e) Granel, C.; Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1996**, *29*, 8576−8582. (f) Wayland, B. B.; Basickes, L.; Mukerjee, S.; Wei, M. L.; Fryd, M. *Macromolecules* **1997**, *30*, 8109−8112. (g) Ando, T.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **1998**, *31*, 6708−6711. (h) Collins, J. E.; Fraser, C. L. *Macromolecules* **1998**, *31*, 6715−6717. (i) Percec, V.; Barboiu, B.; Van der Sluis, M. *Macromolecules* **1998**, *31*, 4053−4056. (j) Moineau, G.; Granel, C.; Dubois, P.; Jerome, R.; Teyssie, P. *Macromolecules* **1998**, *31*, 542−544. (k) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921−2990. (l) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689−3745.

(3) (a) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K. *Macromolecules* **1993**, *26*, 2987−2988. (b) Hawker, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 11185−11186. (c) Mansky, P.; Liu, Y.; Huang, E.; Russell, T. P.; Hawker, C. *Science* **1997**, *275*, 1458−1460. (d) Marque, S.; Mercier, C. L.; Tordo, P.; Fischer, H. *Macromolecules* **2000**, *33*, 4403−4410. (e) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688. (f) Bosman, A. W.; Vestberg, R.; Heumann, A.; Frechet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715−728. (g) Solomon, D. A. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5748−5764.

(4) (a) Coessens, V.; Pintauer, T.; Matyjaszewski, K. *Prog. Polym. Sci.* **2001**, *26*, 337−377. (b) Matyjaszewski, K. *Macromol. Symp.* **2003**, *195*, 25−31. (c) Harth, E.; Hawker, C. J.; Fan, W.; Waymouth, R. M. *Macromolecules* **2001**, *34*, 3856−3862. (d) Moad, G.; Chong, Y. K.; Postma, A.; Rizzardo, E.; Thang, S. H. *Polymer* **2005**, *46*, 8458−8468. (e) Lutz, J. F.; Borner, H. G.; Weichenham, K. *Macromol. Rapid Commun.* **2005**, *26*, 514−518.

(5) (a) Bartholome, C.; Beyou, E.; Bourgeat-Lami, E.; Chaumont, P.; Zydowicz, N. *Macromolecules* **2003**, *36*, 7946−7952. (b) Bowden, N. B.; Willets, K. A.; Moerner, W. E.; Waymouth, R. M. *Macromolecules* **2002**, *35*, 8122−8125. (c) Zhou, X. Z.; Shea, K.J.; *Macromolecules* **2001**, *34*, 3111−3114. (d) Husemann, M.; Morrison, M.; Benoit, D.; Frommer, J.; Mate, C. M.; Hinsberg, W. D.; Hedrick, J. L.; Hawker, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 1844−1845. (e) Miura, Y.; Hirota, K.; Moto, H.; Yamada, B. *Macromolecules* **1999**, *32*, 8356−8362. (f) Gravert, D. J.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 1513−1516. (g) Manksy, P.; Liu, Y.; Huang, E.; Russell, T. P.; Hawker, C. *Science*, **1997**, *275*, 1458−1460.

(6) Husseman, M.; Malmström, E. E.; McNamara, M.; Mate, M.; Mecerreyes, D.; Benoit, D. G.; Hedrick, J. L.; Mansky, P.; Huang, E.; Russell, T. P.; Hawker, C. J. *Macromolecules* **1999**, *32*, 1424−1431.

(7) (a) Dao, J.; Benoit, D.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 2161−2167. (b) Götz, H.; Harth, E.; Schiller, S. M.; Frank, C. W.; Knoll, W.; Hawker, C. J. *J. Poly. Sci., Part A: Polym. Chem.* **2002**, *40*, 3379−3391. (c) Götz, 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. (d) Blomberg, S.; Ostberg, S.; Harth, E.; Bosman, A. W.; Van, Horn, B.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1309−1320.

(8) Rodlert, M.; Harth, E.; Rees, I.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 4749−4763.

(9) (a) Mahal, L. K.; Yarema, K. J.; Bertozzi, C. R. *Science* **1997**, *276*, 1125−1128. (b) Lemieux, G. A.; Yarema, K. J.; Jacobs, C. L.; Bertozzi, C. R. *J. Am. Chem. Soc.* **1999**, *121*, 4278−4279. (c) Prescher, J. A.; Bertozzi, C. R. *Nat. Chem. Biol.* **2005**, *1*, 13−21.

(10) Sadamoto, R.; Niikura, K.; Sears, P. S.; Liu, H.; Wong, C.-H.; Suksomcheep, A.; Tomita, F.; Monde, K.; Nishimura, S.-I. *J. Am. Chem. Soc.* **2002**, *124*, 9018−9019.

(11) (a) Atamna, H.; Cheung, I.; Ames, B. N. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*(2), 686−691. (b) Chavez, J.; Wu, J.; Han, B.; Chung, W. G.; Maier, C. S. *Anal. Chem.* **2006**, *78*, 6847−6854.

(12) (a) Lutz, J. F. *Polym. Int.* **2006**, *55*, 979−993. (b) Qi, K.; Ma, Q.; Remsen, E. E.; C. G. Clark, J.; Wooley, K. L. *J. Am. Chem. Soc.* **2004**, *126*, 6599−6607.

(13) (a) Husseman, M.; Morrison, M.; Benoit, D.; Frommer, J.; Mate, C. M.; Hinsberg, W. D.; Hedrick, J. L.; Hawker, C. J. *J. Am. Chem. Soc.* **2000**, *122*, 1844−1845. (b) Blomberg, S.; Ostberg, S.; Harth, E.; Bosman, A.; Horn, B. V.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 1309−1320. (c) Bian, K.; Cunningham, M. F. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 2145−2154. (d) O'Reilly, R. K.; Joralemon, M. J.; Hawker, C. J.; Wooley, K. L. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 5203−5217.

(14) Clark, J. H.; Miller, J. M.; So, K. H. *J. Chem. Soc., Perkin Trans. 1* **1978**, *9*, 941−946.

(15) Puts, R. D.; Sogah, D. Y. *Macromolecules* **1996**, *29*, 3323−3325.

(16) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772−3774.

(17) (a) Dao, J.; Benoit, D.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 2161−2167. (b) Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3904−3920.

(18) Sterzycki, R. *Synthesis* **1979**, *9*, 724−725.

(19) Braslau, R.; O'Bryan, G.; Nilsen, A.; Henise, J.; Thongpaisanwong, T.; Murphy, E.; Mueller, L.; Ruehl, J. *Synthesis* **2005**, *9*, 1496−1506.

(20) (a) Allen, C. F. H. *J. Am. Chem. Soc.* **1930**, *52*, 2955−2959. (b) Johnson, G. D. *J. Am. Chem. Soc.* **1953**, *75*, 2720−2723. (c) Behforouz, M.; Bolan, J. L.; Flynt, M. S. *J. Org. Chem.* **1985**, *50*, 1186−1189.

(21) Shriner, R. L.; Hermann, C. K. F.; Morrill, T. C.; Curtin, D. Y.; Fuson, R. C. *The Systematic Identification of Organic Compounds*, 8th ed.; Wiley: New York, 2004.

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