Terminal Functionalization of Polymers via Single Electron Oxidation of *N*-Alkoxyamines

Greg O'Bryan and Rebecca Braslau*

Department of Chemistry, University of California, Santa Cruz, California 95064

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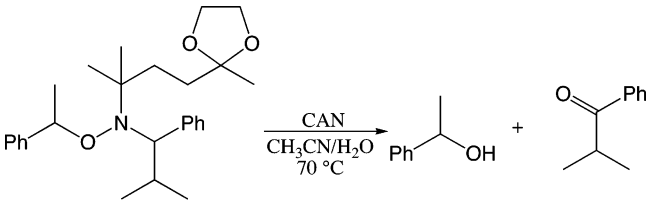
ABSTRACT: Polymers prepared by nitroxide-mediated polymerization undergo single electron oxidation of the *N*-alkoxyamine end group upon treatment with ceric ammonium nitrate. This facile reaction proceeds efficiently under mild conditions to produce monotelechelic polymers. A mechanism for cleavage of the *N*-alkoxyamine is proposed, and the utility of this process is explored through derivatization with various end groups.

Introduction

Controlled free radical polymerization (CRP) has become a method of choice for the production of designed macromolecular constructs. An advantage of CRP over ionic polymerizations is tolerance to moisture and compatibility with many sensitive functional groups. The most widely recognized methods of CRP are reversible addition fragmentation transfer (RAFT),[1] atom transfer radical polymerization (ATRP),[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.[3a,4] For NMP using unimolecular initiators, chain end functionalization commonly involves the synthesis of functionalized initiators prior to polymerization. This functionality can be introduced onto either the initiating α alkyl portion (typically a 1-phenethyl derivative) or the capping ω nitroxide portion of the *N*-alkoxyamine. The most common strategies have employed preparation of 1-phenethyl groups bearing alcohols[5] or benzyl chlorides.[6] An interesting example of the latter is that of Schubert et al., who synthesized a terpyridine functionalized *N*-alkoxyamine[7] from the corresponding benzyl chloride. The resulting polymers, bearing a terpyridine at the α terminus, can be utilized as supramolecular building blocks. Long et al. developed another supramolecular building block strategy utilizing multiple hydrogen-bonding uracils built onto the α polymer end.[8] In these systems the Lewis basic nature of the terpyridine and uracil groups are incompatible with ATRP due to competing ligand binding of the metal catalyst. Billion et al. have used an ester derivatized initiator bearing a silyl group for surface grafting.[9] A few examples utilize the carboxylic acid-bearing AIBN analogue V-501 to form carboxylic acid α-terminated polymers in the presence of free nitroxides.[10]

There are only a few methods that involve the removal of the *N*-alkoxyamine cap to introduce functionality as a postpolymerization modification. These methods entail heating the polymer to achieve nitroxide dissociation and subsequent trapping of the active radical chain end with various species. Maleimide derivatives[11] as well as thiuram disulfides[12] have been used to introduce a variety of different functional groups through this method. Turro utilized postpolymerization nitroxide exchange[13] as another means to introduce functionality. Postpolymerization functionalization reactions allow for the preparation of a family of monodisperse polymer samples differing only in labeled end groups. An important aspect of these works is the extent of retention of the ω-nitroxide after the polymerization process. This was evaluated by Hawker et al. by surveying the fidelity of dye labeled *N*-alkoxyamines.[14] For polymers having molecular weights less than 60 000 g/mol, it was found that greater than 95% of *N*-alkoxyamine end groups were preserved.

Scheme 1. Attempted Ketal Deprotection Leading to *N*-Alkoxyamine Degradation



1 **2** **3**

The investigation of single electron oxidation of *N*-alkoxyamines came about during the removal of a ketal protecting group on a functionalized *N*-alkoxyamine (Scheme 1).[15] Many ketal deprotection methods involve acidic conditions, which at elevated temperatures might decompose the *N*-alkoxyamine. However, the CAN-mediated deprotection procedure of Marko et al.[16] is carried out at 70 °C under mildly acidic conditions. Thus, *N*-alkoxyamine **1** bearing a ketal was treated with ceric ammonium nitrate (CAN) in aqueous acetonitrile. It was surprising to see complete disappearance of the initiator within 5 min to produce a relatively clean NMR spectrum of 1-phenylethanol (**2**) and isobutyrophenone (**3**) (Scheme 1). Intrigued by this facile decomposition under such mild conditions, this reaction was explored as a method to remove the nitroxide end cap and to introduce functionality onto the terminus of polymers prepared via NMP. Previously reported postpolymerization modifications of *N*-alkoxyamine end groups require thermolysis of the labile C−ON bond. Herein we present a strategy which utilizes a chemical process that requires little or no heating to achieve substitution of the ω-nitroxide.

Experimental Section

General Materials and Methods. Ammonium ceruim(IV) nitrate (98%) was purchased from Aldrich. Monomers styrene (St) (99%, Acros Organics), *n*-butyl acrylate (*n*BA) (99+%, Acros Organics), and *tert*-butyl acrylate (*t*BA) (98%, Aldrich) were distilled prior to use. Unless otherwise noted, all other reagents were used as received. Tetrahydrofuran (THF) was distilled from sodium/benzophenone, and acetonitrile and dichloromethane were distilled from calcium hydride when anhydrous conditions were

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required. 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).

Analytical Techniques. NMR spectra were recorded at 250 MHz (Bruker ACF dual probe 250 MHz, 62.5 MHz ^{13}C NMR) or 500 MHz (Varian 500 MHz, 125 MHz ^{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−vis 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, 100−5000 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.

General Procedure for the Oxidation of *N*-Alkoxyamines with CAN. 2,2,5-Trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (**4**)[17] (100 mg, 0.31 mmol) was dissolved in 3 mL of acetonitrile and heated to 70 °C. A solution of CAN (422 mg, 0.77 mmol) in 2 mL of acetonitrile and a minimum amount of water to dissolve the solid (~200 μL) was added all at once. Upon addition of CAN, the color of the reaction mixture changed immediately from yellow to dark orange and then over the course of 2 min changed to a pale yellow color. After 5 min the reaction was cooled to room temperature and poured into 10 mL of water, and the aqueous layer was extracted three times with 8 mL of dichloromethane. The combined organic layer was washed with 10 mL of saturated $NaHCO_3$ (to precipitate excess cerium) followed by 10 mL of brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to afford 107.3 mg of crude material. Analysis of the ^{1}H NMR and the low-resolution mass spectra of the crude product showed several constituents (percent composition determined by integration): 34% 1-phenylethanol (**2**), 4.91 ppm (q, 1 H), (fragments in MS not observed); 33% *N*-*tert*-butyl-α-isopropyl-α-phenylnitrone (**10**), 3.89 ppm (m, 1 H), *m*/*z* $[M + 1]^+$ 220.2; 24% isobutyrophenone (**3**), 3.56 ppm (m, 1 H), *m*/*z* $[M + 1]^+$ 149.1; 5% *N*-(1-phenethyl)-acetamide (**8**), 5.13 ppm (q, 1 H), *m*/*z* $[M + 1]^+$ 164.1; and 2% *N*-(1,1-dimethylethyl)acetamide (**12**), 1.91 ppm (s, 3 H), *m*/*z* $[M + 1]^+$ 116.1.

One-Pot Oxidation of *N*-Alkoxyamines with CAN and Subsequent Oxidation of 1-Phenylethanol with CAN/TEMPO. 2,2,5-Trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (**4**) (60 mg, 0.18 mmol) and 6 mg (0.04 mmol) of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) were dissolved in 3 mL of acetonitrile and heated to 70 °C. A solution of CAN (246 mg, 0.37 mmol) in 1 mL of acetonitrile was added in one portion. After 1 h, the reaction mixture was poured into 10 mL of water, and the aqueous layer was extracted three times with 8 mL of dichloromethane. The combined organic layer was washed with 10 mL of saturated $NaHCO_3$ and 10 mL of brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated to obtain 38 mg of an orange oil. Analysis of the ^{1}H NMR spectrum of the crude product showed two major constituents (percent composition determined by integration): acetophenone **18**, 2.61 ppm (q, 3 H, 52%), and isobutyrophenone **3**, 3.56 ppm (m, 1 H, 48%).

***N*-(1-Phenethyl)chloroacetamide (15).** 2,2,5-Trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (879 mg, 2.7 mmol) in 30 mL of chloroacetonitrile was heated to 70 °C. A solution of CAN (3.70 g, 6.75 mmol) in 30 mL of chloroacetonitrile and 40 mL of 10 M nitric acid was added. The reaction mixture was stirred at 70 °C for 30 min and then poured into 100 mL of water. The organic phase was separated, and the remaining aqueous layer was extracted three times with 50 mL of dichloromethane. The combined organic layer was washed with 80 mL of saturated $NaHCO_3$ and 80 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated. Excess chloroacetonitrile was removed in vacuo (100 mTorr) while heating at 50 °C. The product was purified by flash column chromatography [4:1 hexanes:EtOAc → 2:1 hexanes:EtOAc → EtOAc → 10:1 EtOAc:MeOH], affording *N*-(1-phenethyl)-1-chloroacetamide[18] as a slightly yellow crystalline solid (93.4 mg, 18%). TLC: 1:1 hexanes:EtOAc, UV, *p*-anisaldehyde, $R_f = 0.56$. IR ($CDCl_3$): 3415 (N−H), 2930 (C−H), 1671 (C═O), 1524 cm^{-1} (N−H). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.33$ (m, aromatic, 5 H), 5.15 (m, $CH_3C\mathbf{H}$(NH)Ph, 1 H), 4.05 (d, $J = 14.0$ Hz, $ClC\mathbf{H}_2C$(O), 2 H), 1.54 (d, $J = 6.5$ Hz, $C\mathbf{H}_3CH$, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.2$ (s, $CH_2\mathbf{C}$(O)NH, 1 C), 142.4 (s, *ipso*-Ar, 1 C), 130.1 (s, *o*-Ar, 2 C), 127.8 (s, *p*-Ar, 1 C), 126.2 (s, *m*-Ar, 2 C), 49.4 (s, $CH_3\mathbf{C}H$(NH)Ph), 42.8 ($Cl\mathbf{C}H_2C$(O)), 21.8 ($\mathbf{C}H_3CH$(NH)-Ph). HRMS: *m*/*z* $[M + 1]^+$ calcd for $C_{10}H_{12}ClNO$: 197.0607; found 197.0600.

3-(1-Phenylethoxy)propyne (19). To a solution of 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (**4**) (200 mg, 0.61 mmol) in freshly distilled propargyl alcohol (1.78 mL, 31 mmol) was added a solution of CAN (1.003 g, 1.83 mmol) in 8 mL of dry acetonitrile. The reaction mixture was stirred at room temperature for 30 min and then poured into 30 mL of water. The aqueous phase was extracted three times with 15 mL of dichloromethane. The combined organic layers were washed twice with 15 mL of saturated $NaHCO_3$ and once with 15 mL of brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography eluting with hexanes to afford 64 mg (66% yield) of a colorless oil. TLC: 4:1 Hex:EtOAc, UV, *p*-anisaldehyde, $R_f = 0.61$. IR (neat): 3307 (C≡C−H), 2250 (C≡C), 1091 (C−O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.37$ (m, aromatics, 5H), 4.67 (q, $J = 6.5$ Hz, $CH_3C\mathbf{H}(OCH_2C{\equiv}CH)Ph$, 1 H), 4.10 (dd, $J = 2.5$ Hz, $J = 15.5$, $OC\mathbf{H}_2C{\equiv}CH$ 1 H), 3.89 (dd, $J = 2.5$ Hz, $J = 15.5$ Hz, $OC\mathbf{H}_2C{\equiv}$CH 1 H), 2.42 (t, $J = 2.5$ Hz, $C{\equiv}C\mathbf{H}$, 1 H), 1.50 (d, $J = 6$ Hz, $C\mathbf{H}_3CH$, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 142.5$ (s, *ipso*-Ar, 1 C), 128.7 (s, *o*-Ar, 2 C), 127.9 (s, *p*-Ar, 1 C), 126.6 (s, *m*-Ar, 2 C), 80.1 (s, $CH_2\mathbf{C}{\equiv}CH$, 1 C), 76.8 (s, $CH_3\mathbf{C}H(Ph)CH_2$, 1 C), 74.1 (s, $CH_2C{\equiv}\mathbf{C}H$, 1 C), 55.6 (s, $O\mathbf{C}H_2C{\equiv}CH$, 1 C), 23.9 (s, $\mathbf{C}H_3CH(Ph)CH_2$).

2,2,5-Trimethyl-3-(ethyl-2-oxypropionate)-4-phenyl-3-azahexane (23). Following the general procedure of Matyjaszewski et al.,[19] a 50 mL Schlenck flask was charged with 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (1.00 g, 4.54 mmol), ethyl-2-bromopropionate (684 mg, 3.78 mmol), 4,4′-*tert*-butyl-2,2′-bipyridine (40 mg, 0.15 mmol), copper triflate (14 mg, 0.04 mmol), copper metal (45 μm powder, 260 mg, 3.97 mmol), and 20 mL of benzene. The solution was degassed by three freeze−pump−thaw cycles under argon. The solution was stirred and heated to 75 °C for 20 h. Volatiles were removed in vacuo, and the resulting material was purified by flash column chromatography (neutral alumina adsorbent, 95:5 hexanes:dichloromethane) to afford 990 mg (82% yield) of a colorless oil as a 7:3 mixture of diastereomers. A small amount of a single diastereomer was also isolated and used for spectral characterization. TLC: 8:1 hexanes:EtOAc, UV, *p*-anisaldehyde, $R_f = 0.33$. IR (neat): 2978 (C−H), 1748 (C═O), 1453 cm^{-1} (N−O). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.25$ (m, aromatics, 5 H), 4.55 (q, $J = 6.5$ Hz, $NOC\mathbf{H}(CH_3)C$(O), 1 H), 4.19 (q, $J = 7$ Hz, $OC\mathbf{H}_2CH_3$, 2 H), 3.39 (d, $J = 10.5$ Hz, $CH(CH_3)_2C\mathbf{H}PH$, 1 H), 2.18 (m, $CH_3C\mathbf{H}(CH)CH_3$, 1 H), 1.57 (d, $J = 7$ Hz, NOCH(C(O))-$C\mathbf{H}_3$, 3 H), 1.34 (t, $J = 7$ Hz, CH_2CH_3, 3 H), 1.23 (d, $J = 6$ Hz, $(C\mathbf{H}_3)_2CH$, 3 H), 0.94 (s, $(C\mathbf{H}_3)C$, 9H), 0.53 (d, $J = 6.5$ Hz, $(C\mathbf{H}_3)_2$-CH, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.0$ (s, $CH\mathbf{C}$(O)O, 1 C), 142.1 (s, *ipso*-Ar, 1 C), 131.1 (s, *o*-Ar, 2 C), 128.4 (s, *m*-Ar, 2 C), 126.6 (s, *p*-Ar, 1 C), 81.6 (s, $O\mathbf{C}H$(C(O))CH_3, 1 C), 72.6 (s, $N\mathbf{C}H(Ph)CH(CH_3)_2$, 1 C), 72.1 (s, $\mathbf{C}(CH_3)_3$, 1 C), 60.5 (s, $CH_3\mathbf{C}H_2O$, 1 C), 32.1 (s, $\mathbf{C}H(CH_3)_2CH$, 1 C), 28.0 (s, $C(\mathbf{C}H_3)_3$, 3 C), 21.9 ($CH(\mathbf{C}H_3)_2CH$, 1 C), 21.3 ($CH(\mathbf{C}H_3)_2CH$, 1 C), 19.0 (s, $OCH(C(O))\mathbf{C}H_3$, 1 C), 14.3 (s, $OCH_2\mathbf{C}H_3$. HRMS *m*/*z* $[M + 1]^+$ calcd for $C_{19}H_{31}NO_3$: 321.2304; found 321.2297.

Ethyl-2-(2,2,6,6-tetramethyl-1-piperidinyloxy)propionate (25). The same procedure used in the synthesis of **22** was followed, with TEMPO in place of TIPNO to afford 6.15 g (87% yield) of a

colorless oil. IR (neat): 2977 (C−H), 1749 (C═O), cm^{-1} 1454 (N−O). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 4.28$ (q, $J = 6.8$ Hz, NOC**H**(C(O))CH_3, 1 H), 4.16 (q, $J = 7.5$ Hz, OC**H**$_2$$CH_3$, 2 H), 1.44 (m, C**H**$_2$C**H**$_2$C**H**$_2$, 6 H), 1.37 (d, $J = 6.8$ Hz, CHC**H**$_3$, 3 H), 1.25 (t, $J = 7.5$ Hz, OCH_2C**H**$_3$, 3 H), 1.18 (s, C(C**H**$_3$)$_2$, 3 H) 1.12 (s, C(C**H**$_3$)$_2$, 6 H), 1.04 (s, C(C**H**$_3$)$_2$, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 174.3$ (s, O**C**(O)CH, 1 C), 81.9 (s, O**C**H(C(O))CH_3, 1 C), 60.4 (s, O**C**H_2CH_3, 1 C), 60.0 (s, N**C**$(CH_3)_2CH_2$, 1 C), 59.5 (s, N**C**$(CH_3)_2CH_2$, 1 C), 40.4 (s, CH_2**C**$H_2C(CH_3)_2$, 1 C), 40.2 (s, CH_2**C**$H_2C(CH_3)_2$, 1 C), 33.7 (s, C(**C**$H_3)_2$, 1 C), 33.1 (s, C(**C**$H_3)_2$, 1 C), 20.3 (s, **C**H_3CH(O)C(O), 1 C), 18.3 (s, C(**C**$H_3)_2$, 2 C), 17.2 (s, CH_2**C**H_2CH_2, 1 C), 14.2 (s, OCH_2**C**H_3, 1 C).

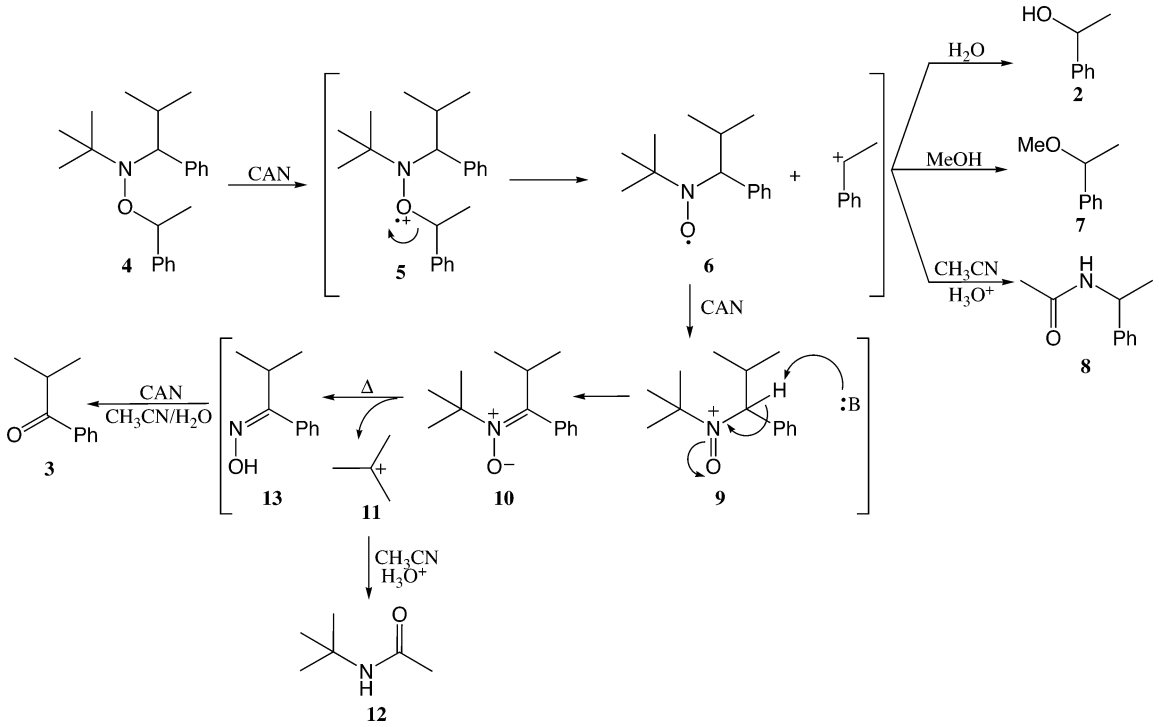
Ethyl-2-nitrooxypropionate (24). Ethyl 2-(2,2,6,6-tetramethylpiperidinyloxy)propionate (**21**) (500 mg, 1.94 mmol) was subjected to the general oxidation procedure with CAN (4.25 g, 7.76 mmol). The crude mixture was purified by flash column chromatography (20:1 hexanes:EtOAc) to provide 145 mg (46% yield) of a slightly yellow oil. For spectral comparison, the authentic nitrate was prepared by refluxing ethyl-2-bromopropionate (500 mg, 2.8 mmol) and silver nitrate (951 mg, 5.6 mmol) in 8 mL of dry acetonitrile. Silver bromide was removed by filtration and the solvent removed in vacuo; 351 mg (77% yield) of a colorless oil was obtained. IR (neat): 2984 (C−H), 1752 (C═O), 1646 cm^{-1} (N═O). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 5.23$ (q, $J = 7.5$ Hz, CH_3C**H**(ONO_2)C(O), 1 H), 4.27 (q, $J = 7.5$ Hz, OC**H**$_2$$CH_3$, 2 H), 1.56 (d, $J = 7.5$ Hz, C**H**$_3$CH, 3 H), 1.31 (t, $J = 7.5$ Hz, OCH_2C**H**$_3$, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 169.1$ (s, CH**C**(O)O, 1 C), 76.0 (s, CH_3**C**H(ONO_2)C(O), 1 C), 62.2 (s, OCH_2CH_3, 1 C), 14.8 (s, **C**H_3CH(ONO_2)C(O), 1 C), 14.1 (s, OCH_2**C**H_3, 1 C).

Alcohol Functionalized Polystyrene (PS-A). Polystyrene made by nitroxide-mediated polymerization initiated with 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (**4**) (M_n: 6574 g/mol, polydispersity index (M_w/M_n) = 1.12, 150 mg, 0.011 mmol) was dissolved in 4 mL of tetrahydrofuran and heated to reflux. A solution of CAN (126 mg, 0.23 mmol), dissolved in 1 mL of tetrahydrofuran and 400 μL of water was added to the polystyrene solution and stirred at reflux for 20 h. The reaction mixture was concentrated in vacuo, and the polymer precipitated by the addition of 30 mL of ice cold methanol. The methanol layer was decanted and the resulting material was dried under vacuum. The polymer was then redissolved in a minimum amount of THF, and the precipitation process repeated three more times to provide 141 mg (96%) of a white flaky polymer. GPC: $M_n = 6234$, polydispersity index (M_w/M_n) = 1.12.

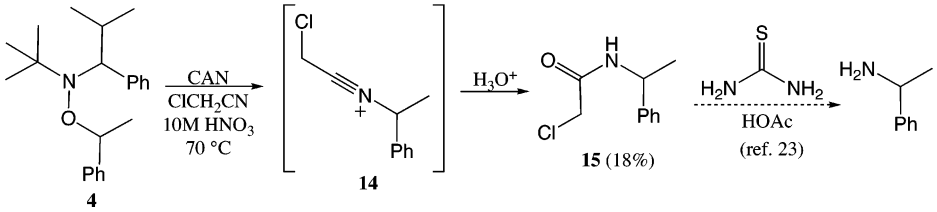
Pyrene Functionalized Polystyrene (PS-Py). 1-Pyrenebutyric acid (32 mg, 0.11 mmol), dicyclohexylcarbodiimide (34 mg, 0.165 mmol), and dimethylaminopyridine (1 mg, 0.011 mmol) were dissolved in 2 mL of freshly distilled anhydrous dichloromethane. To this was added a solution containing alcohol functionalized polystyrene PS-A (70 mg, 0.011 mmol) dissolved in 5 mL of anhydrous dichloromethane. The reaction mixture was stirred for 18 h under inert atmosphere and then filtered through celite. The filter cake was washed twice with 8 mL of dichloromethane and then concentrated. The crude material was redissolved in a minimum amount of tetrahydrofuran and precipitated with ice cold methanol. The methanol layer was decanted, and the resulting material was dried under vacuum. The polymer was then redissolved in a minimum amount of THF, and the precipitation process repeated four times to afford 74 mg (100% yield) of white flaky polymer. UV−vis spectroscopy ($\lambda = 345$ nm, $\epsilon = 38\,507$, $CHCl_3$) indicated 86% incorporation of pyrene onto the end of the polymer chain. GPC: $M_n = 6249$, polydispersity index (M_w/M_n) = 1.12.

4-Pyren-1-yl-butyric Acid 1-Phenethyl Ester (26). 1-Pyrenebutyric acid (300 mg, 1.04 mmol), dicyclohexylcarbodiimide (321 mg, 1.56 mmol), and (dimethylamino)pyridine (12 mg, 0.10 mmol) were dissolved in 15 mL of freshly distilled anhydrous dichloromethane and stirred at room temperature under inert atmosphere for 20 min. To this solution was added 1-phenylethanol (152 mg, 1.24 mmol), and the reaction mixture was stirred at room temperature until the starting acid was no longer observed by TLC (18 h). The reaction mixture was then filtered through celite, and the filter cake washed twice with 5 mL of dichloromethane. The filtrate was concentrated and purified by flash column chromatography (1:1 hexanes:dichloromethane) to give 333 mg of oil. ^1H NMR analysis revealed 23% to be 1,3-dicyclohexylurea as determined by integration, resulting in a 63% yield of the desired product. TLC: dichloromethane, UV ($\lambda = 344$ nm), *p*-anisaldehyde, $R_f = 0.76$. IR ($CDCl_3$): 2935 (C−H), 1724 cm^{-1} (C═O). ^1H NMR (500 MHz, $CDCl_3$): $\delta = 8.29-7.8$ (m, aromatics, 10 H), 7.42 (m, aromatics, 5 H), 6.01 (q, $J = 6.5$ Hz, CH_3C**H**(OC(O))Ph, 1 H), 3.40 (m, ArC**H**$_2$$CH_2$, 2 H), 2.52 (m, CH_2C**H**$_2$$CH_2$, 2 H), 2.24 (m, CH_2C**H**$_2$C(O)O, 2 H), 1.61 (d, $J = 6.5$ Hz, CHC**H**$_3$, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.9$ (s, CH_2**C**(O)O, 1 C), 141.9 (s, *ipso*-

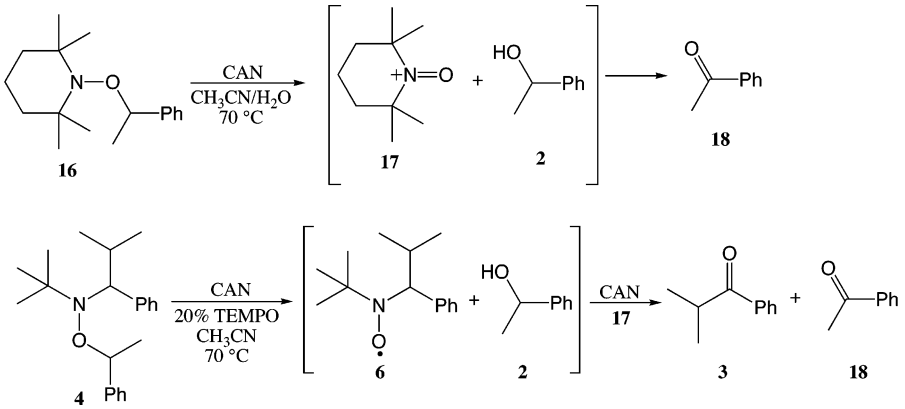
Scheme 2. Proposed Mechanism of Oxidative Degradation of an α-Hydrogen *N*-Alkoxyamine



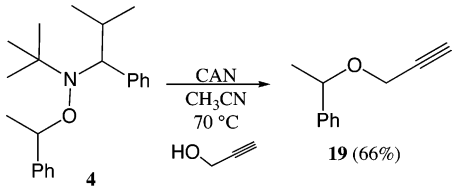
Scheme 3. Trapping Phenethyl Cation with Chloroacetonitrile as the Reaction Solvent



Scheme 4. Oxidative Cleavage of *N*-Alkoxyamines and Subsequent Oxidation of 1-Phenylethanol to Acetophenone via the Oxomonium Salt of TEMPO



Scheme 5. Trapping Benzylic Cation Intermediate To Form Propargyl Ether



pyrene, 1 C), 135.9 (s, *ipso*-Ar, 1 C), [131.6, 131.0, 130.1, 128.9, 128.7, 128.1, 127.6, 127.5, 126.9, 126.3, 126.0, 125.2, 125.1, 125.1, 125.0, 124.9, 123.5] (s, aromatics, 20 C), 72.5 (s, O**C**H(Ph)CH_3, 1 C), 35.1 (s, pyrene**C**H_2CH_2, 1 C), 34.3 (s, CH_2**C**H_2C(O), 1 C), 27.0 (s, CH_2**C**H_2CH_2, 1 C), 22.4 (s, **C**H_3CH(Ph)O, 1 C). HRMS *m*/*z* $[M + 1]^+$ calcd for $C_{28}H_{24}O_2$: 392.1776; found 392.1770.

Results and Discussion

Mechanism of Single Electron Oxidation of *N*-Alkoxyamines. The ability to chemoselectively oxidize the *N*-alkoxyamine terminus of polymers prepared by NMP provides the opportunity to modify the "living" chain end once polymer growth is complete. In order to probe this reaction, *N*-alkoxyamine **4** was oxidized as a small molecule model of an *N*-alkoxyamine-capped polystyrene. A proposed mechanism is shown in Scheme 2. Since CAN is a common one-electron oxidant,[20] the initial step is likely formation of radical cation **5**. Resonance structure **5** is shown for mechanistic simplicity, although the resonance structure in which the radical cation resides on the nitrogen is more representational of the electronic distribution. Cleavage of the oxygen−carbon bond of this intermediate can occur through either homolytic cleavage to directly form an oxomonium species and a benzyl radical or, alternatively, ionic cleavage to form a stable nitroxide radical and a benzyl cation. Both pathways would lead to the formation of the observed products **2** and **3**. Also observed in a small amount in the crude reaction mixture was *N*-(1-phenethyl)acetamide (**8**), which is presumably produced by trapping of the benzylic cation with the reaction solvent in a Ritter reaction. To explore this further, the reaction solvent was changed to anhydrous methanol, which led to the formation of 1-phenethyl methyl ether (**7**). Also observed under methanolic conditions was isobutyrophenone **3**, nitrone **10**, and a very small amount of unhydrolyzed oxime **13**. The formation of the methyl ether **7** and the Ritter product **8** provide evidence that the mechanism proceeds through ionic cleavage to form a benzylic cation. The other intermediate formed from ionic cleavage is nitroxide radical **6**. The fate of the nitroxide under these oxidation conditions was examined by treating TIPNO **6** with CAN in aqueous acetonitrile. Following aqueous workup isobutyrophenone **3** and nitrone **10** were the sole products observed. The nitrone derives from a two-step process in which the nitroxide is first oxidized by CAN to oxomonium salt **9**. The oxomonium isomerizes to the nitrone by deprotonation of the benzylic hydrogen. This nitrone is only marginally stable,[21] decomposing further to give isobutyrophenone oxime **13**. Hydrolysis of an oxime to a ketone is known to occur under the acidic aqueous conditions of the CAN reaction.[22] Further evidence of nitrone decomposition is the isolation of amide **12**, which arises from trapping of *tert*-butyl cation with acetonitrile in a second Ritter reaction. Nitrone **10** was observed in larger quantities when the reaction was conducted at room temperature.

Addition of Functionality through Trapping of the Benzylic Cation. The observed Ritter product **8** and the methanol trapping experiment to form ether **7** provide strong evidence that radical cation **5** fragments to give a benzyl cation. With the goal of introducing useful functionality onto the *N*-alkoxyamine terminus of polymers produced by NMP, three different strategies were explored. The first was another Ritter reaction using chloroacetonitrile as the reaction solvent during oxidative cleavage of **4** (Scheme 3). The benzylic cation is trapped by the nitrile and the unstable intermediate **14** is hydrolyzed to the acetamide. The α-chloroacetamide **15** was isolated in low yield following flash column chromatography. Hydrolysis of the α-chloroacetamide can be carried out under very mild conditions using thiourea via a ligation mechanism.[23] This provides a method to terminally functionalize the end of polystyrene chains with a monosubstituted amine for use in further chemical transformations.

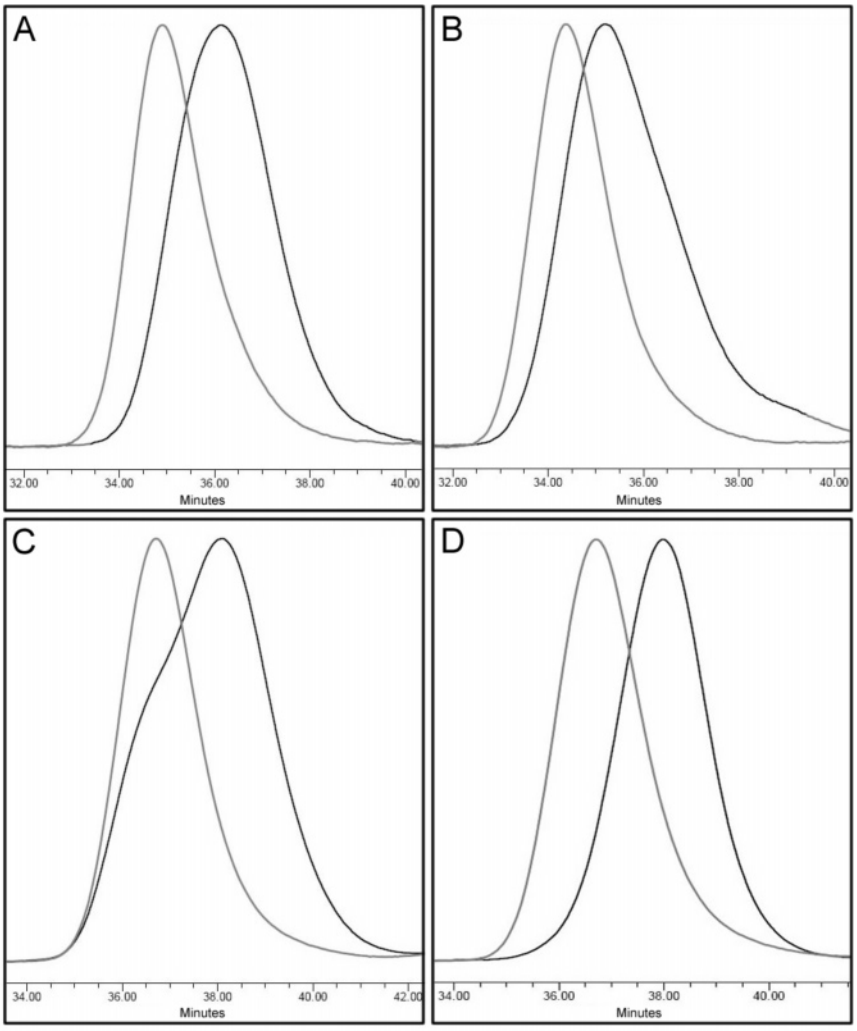


Figure 1. Gel permeation chromatographs of polymer samples containing a central bis-nitroxide and cleaved products. In each case the original polymer sample is on the left, and the cleaved polymer is shifted to the right, showing a decrease in molecular weight. (A) Poly(*n*-butyl acrylate), **21a** (0.003 mmol, 50 mg), is cleaved with CAN (0.03 mmol, 17 mg) in wet acetonitrile to give **22a**. (B) Poly(*tert*-butyl acrylate), **21b** (0.003 mmol, 50 mg), is cleaved with CAN (0.03 mmol, 17 mg) in wet acetonitrile to give **22b**. (C) Polystyrene, **21c** (0.007 mmol, 50 mg), gives incomplete cleavage with CAN (0.07 mmol, 38 mg) in wet acetonitrile to give **22c**. (D) Polystyrene, **21c** (0.007 mmol, 50 mg), in a mixture of 2.5:1 benzonitrile: acetonitrile is cleaved with CAN (0.07 mmol, 38 mg) to give solely **22c**.

Next, a one pot oxidation of the product benzylic alcohol using catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[24] and CAN[25] was explored as a route to introduce a ketone onto the polymer terminus. Ketone end groups are valuable as they can be chemoselectively converted to the corresponding hydrazones or oximes as a method for attaching a wide selection of useful reporter molecules or affinity labels.[26] The TEMPO-based *N*-alkoxyamine **16** was utilized as a small molecule model (Scheme 4) to explore this strategy. As expected, 1-phenylethanol (**2**), produced from the initial oxidation of **16**, is further oxidized to acetophenone **18** via oxomonium salt **17**. The oxomonium salt of TEMPO does not contain any hydrogen atoms α to the nitrogen and therefore cannot isomerize to a nitrone as with oxomonium salt **9** derived from TIPNO. Taking advantage of this catalytic reaction, CAN oxidation of TIPNO-based *N*-alkoxyamine **4** was carried out with the addition of 0.2 equiv of TEMPO. Following oxidation, acetophenone was isolated in a mixture with isobutyrophenone (Scheme 4).[27]

Finally, addition of propargyl alcohol as a nucleophile to trap the benzylic cation under anhydrous conditions was investigated (Scheme 5). The addition of an alkyne to a polymer terminus provides a useful handle for Huisgen 1,3-dipolar cycloadditions. This cycloaddition has gained increasing attention as the conditions are efficient, high yielding, and tolerant to a variety of solvents and functional groups, and the product 1,2,3-triazole is very stable.[28] Following CAN oxidation, the benzylic cation was trapped by propargyl alcohol to form propargyl ether **19**, isolated in 66% yield.

Oxidative Cleavage of Polymer Samples with CAN. To test this methodology on polymer samples, it was advantageous to select substrates in which a significant change in molecular weight would be observed upon cleavage. Polymers prepared by the bis-nitroxide-based bidirectional initiator **20** developed in these labs[23] provides an ideal substrate. Polymers grown using this "outside-in" approach result in samples in which the *N*-alkoxyamine resides in the middle of the polymer. Upon oxidative cleavage, the molecular weight should decrease by half: a change that would be clearly observed by gel permeation chromatography (GPC). Samples composed of poly(*n*-butyl acrylate) (**21a)**, poly(*tert*-butyl acrylate) (**21b**), and polystyrene (**21c**) prepared from bidirectional initiator **20** were subjected to the CAN oxidative conditions (Scheme 6). Figure 1 shows the GPC chromatographs of polymer samples before and after cleavage. Initial attempts at cleaving polystyrene **21c** did not go to complete conversion due to the moderate solubility of

Scheme 6. Cleavage of Bidirectional Polymers with CAN

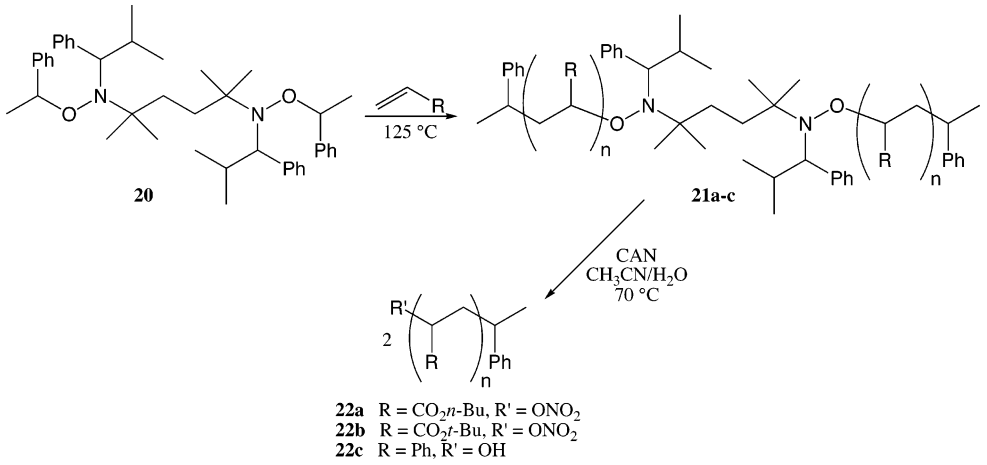
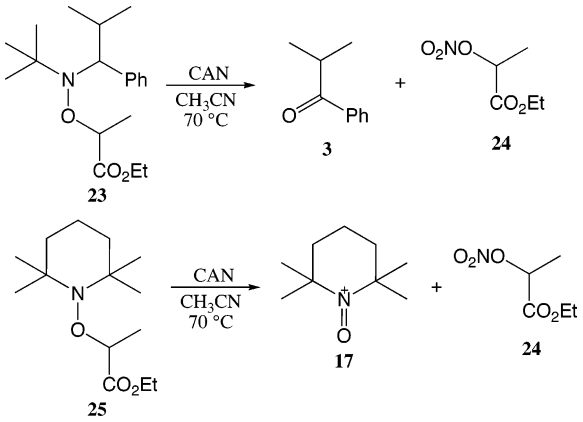


Table 1. Summary of Molecular Weights and Polydispersities of Polymers 21a−c before and after Cleavage with CAN

polymer substrate	R	M_n[a] (g/mol)	PDI[b]	polymer after cleavage	R′	M_n[a] (g/mol)	PDI
21a	CO_2*n*-butyl	17127	1.21	**22a**	ONO_2	10293	1.24
21b	CO_2*tert*-butyl	22599	1.22	**22b**	ONO_2	13928	1.31
21c	Ph	7209	1.23	**22c**	OH	4654	1.21

[a] Number-average molecular weight, measured by gel permeation chromatography (GPC). [b] Polydispersity index (M_w/M_n), measured from GPC.

Scheme 7. Oxidative Cleavage of a Small Molecule Polyacrylate End-Group Model



polystyrene in acetonitrile. Changing the solvent to a 2.5:1 mixture of benzonitrile and acetonitrile increased the solubility, resulting in complete cleavage of the polymer sample. Polydispersities of polymer samples obtained after cleavage remained virtually unchanged.

Model Study for Oxidation at the Polyacrylate Terminus. Given the success in cleaving polyacrylate samples **21a** and **21b**, a small molecule model bearing an ester group was synthesized to explore the decomposition fate of the polyacrylate terminus. The mechanism for decomposition of an ester-terminated *N*-alkoxyamine differs from that shown in Scheme 2, since formation of a carbocation adjacent to a carbonyl group is unlikely. Model compound **23** was prepared with TIPNO and ethyl-2-bromopropionate under atom transfer radical coupling conditions.[19] Treatment with CAN produced a complex mixture of components in which the only clearly observed product was isobutyrophenone **3** (Scheme 7). Isobutyrophenone was previously obtained from the decomposition of nitroxide **6** (Scheme 2), implying that either nitroxide **6** or oxomonium salt **9** is produced during the reaction. To explore this further, *N*-alkoxyamine **25** was synthesized and subjected to the same conditions. Oxidative cleavage of **25** produced TEMPO, which was oxidized further to oxomonium salt **17**. The oxomonium salt was removed upon aqueous workup, and nitrate ester **24** was isolated in 46% yield. Addition of pure nitrate ester **24** to the crude NMR samples obtained from decomposition of initiator **23** showed an increase in the suspected resonances.

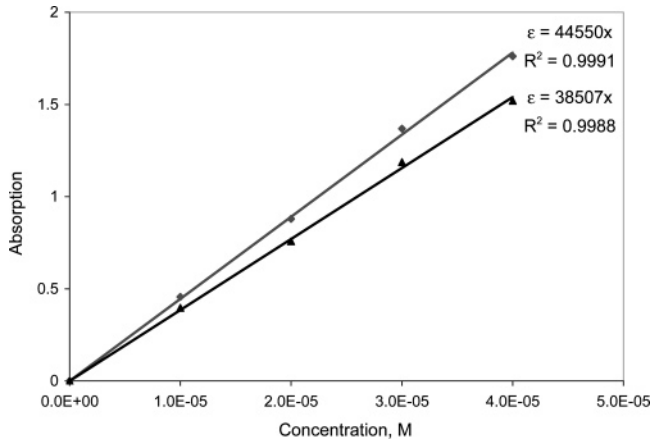
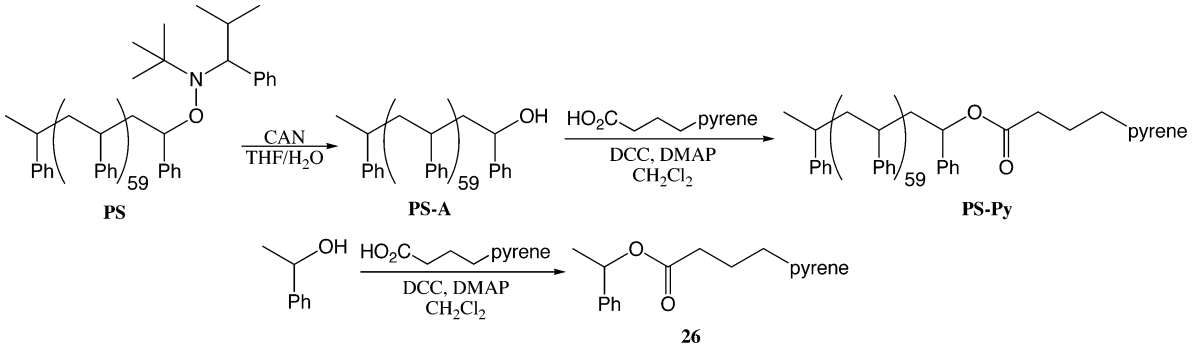


Figure 2. Comparison of the molar extinction coefficients of pyrene-labeled polystyrene (**PS-Py**, ▲) vs the phenethyl ester of 1-pyrenebutyric acid (**26**, ◆).

Terminal Functionalization of Polystyrene following Cleavage with CAN. The small molecule model indicates that the oxidative cleavage of polystyrene proceeds by trapping of a benzylic cation at the polymer terminus with water to form benzylic alcohol **PS-A**. To demonstrate the utility of this method, derivatization of the secondary benzyl alcohol of **PS-A** was performed by esterification with 1-pyrenebutyric acid to give the pyrene-terminated polystyrene **PS-Py** (Scheme 8). For spectral comparison, the analogous 1-phenethyl ester of pyrenebutyric acid was prepared. To quantify the amount of derivatization on the end of the polystyrene,[29] samples of increasing concentration were prepared for both **PS-Py** and **26**. The absorbance of each sample was measured at $\lambda_{max} = 345$ nm to

Scheme 8. Terminal Functionalization and Pyrene Labeling of Polystyrene



determine the molar extinction coefficients. The ratio of the polystyrene extinction coefficient to that of **26** indicated 86% incorporation of pyrene onto the end of the polymer (Figure 2).

Conclusion

Treatment of *N*-alkoxyamines with CAN effects oxidative cleavage. Polystyrene samples prepared by NMP fragment to form secondary benzylic cations at the polymer terminus, which can be trapped by water, alcohols, or nitriles to form the corresponding alcohol, ether, or amide chain end functionalized polymers. In the presence of catalytic TEMPO, secondary benzyl alcohols are oxidized in situ to the corresponding ketones. Polyacrylates bearing *N*-alkoxyamines also undergo oxidative cleavage to form nitrate esters; however, the mechanism of fragmentation is not yet clear. The utility of this method for postpolymerization functionalization of polystyrene has been demonstrated by labeling the resulting secondary benzyl alcohol at the polymer terminus with a fluorescent dye.

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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.

(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) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688. (b) Bosman, A. W.; Vestberg, R.; Heumann, A.; Frechet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715−728.

(4) (a) Matyjaszewski, K. *Macromol. Symp.* **2003**, *195*, 25−31. (b) Perrier, S.; Takolpuckdee, P. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 5347−5393.

(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. Sco.* **2000**, *122*, 1844−1845. (e) Miura, Y.; Hirota, K.; Moto, H.; Yamada, B. *Macromolecules* **1999**, *32*, 8356−8362. (f) 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. (g) Gravert, D. J.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 1513−1516. (h) Manksy, P.; Liu, Y.; Huang, E.; Russell, T. P.; Hawker, C. *Science* **1997**, *275*, 1458−1460.

(6) (a) Dao, J.; Benoit, D.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 2161−2167. (b) Gotz, H.; Harth, E.; Schiller, S. M.; Frank, C. W.; Knoll, W.; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 3379−3391. (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.

(7) (a) Lohmeijer, B. G. G.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 4016−4027. (b) Lohmeijer, B. G. G.; Schubert, U. S. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 6331−6344.

(8) Mather, B. D.; Lizotte, J. R.; Long, T. E. *Macromolecules* **2004**, *37*, 9331−9337.

(9) Laruelle, G.; Parvole, J.; Billon, F. L. *Polymer* **2004**, *45*, 5013−5020.

(10) (a) Lepoittenvin, B.; Perrot, X.; Masure, M.; Hemery, P. *Macromolecules* **2001**, *34*, 425−429. (b) Baumert, M.; Mülhaupt, R. *Macromol. Rapid Commun.* **1997**, *18*, 787−794.

(11) Harth, E.; Hawker, C. J.; Fan, W.; Waymouth, R. M. *Macromolecules* **2001**, *34*, 3856−3862.

(12) Beyou, E.; Chaumont, P.; Chauvin, F.; Devaux, C.; Zydowicz, N. *Macromolecules* **1998**, *31*, 6828−6835.

(13) Turro, N. J.; Lem, G.; Zavarine, I. S. *Macromolecules* **2000**, *33*, 9782−9785.

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

(15) O'Bryan, G.; Nilsen, A.; Braslau, R., manuscript in preparation.

(16) Ates, A.; Gautier, A.; Leroy, B.; Plancher, J. M.; Quesnel, Y.; Vanherck, J. C.; Marko, I. E. *Tetrahedron* **2003**, *59*, 8989−8999.

(17) Prepared in accordance to the following procedure: Benoit, D.; Chaplinski, V.; Braslau, R.; Hawker, C. J. *J. Am. Chem. Soc.* **1999**, *121*, 3904−3920.

(18) For spectral comparison, see: Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1992**, *57*, 6532−6536.

(19) Matyjaszewski, K.; Woodworth, B. E.; Zhang, X.; Gaynor, S. G. Metzner, Z. *Macromolecules* **1998**, *31*, 5955−5957.

(20) (a) Zhang, Y.; Flowers, R. A., II. *J. Org. Chem.* **2003**, *68*, 4560−4562. (b) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21−30.

(21) Nilsen, A.; Braslau, R. *J. Polym. Sci., Part A: Polym. Chem.* **2006**, *44*, 697−717.

(22) Bird, J. W.; Diaper, G. M. *Can. J. Chem.* **1969**, *47*, 145−150.

(23) Hill, N. L.; Braslau, R. *Macromolecules* **2005**, *38*, 9066−9074.

(24) Braslau, R.; Anderson, M. O. "Nitroxides". In *Free Radicals in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 2, Chapter 3, pp 127−149.

(25) Kim, S. S.; Jung, H. C. *Synthesis* **2003**, *14*, 2135−2137.

(26) (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) 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.

(27) Solubility issues became problematic when these conditions were applied to polystyrene prepared with initiator **4.** The solvent was changed to THF in an attempt to increase the solubility of the polymer sample. UV analysis indicated 27% of ketone-terminated polystyrene was produced as determined by preparation of the 2,4-dinitrophenylhydrazone. Oxidation of small molecule model **4** in THF also showed very little acetophenone formation by ^{1}H NMR.

(28) (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596−2599.

(29) Bosman, A. W.; Vestberg, R.; Heumann, A.; Frechet, J. M.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715−728.

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