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Cyclization of α, ω heterotelechelic polystyrene prepared by nitroxide-mediated radical polymerization

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ABSTRACT

Polystyrene prepared by nitroxide-mediated radical polymerization (NMRP) bearing a benzyl chloride on the α-terminus was converted to an azide by S_N2 displacement, followed by oxidative replacement of the alkoxyamine with a terminal acetylene using ceric ammonium nitrate and propargyl alcohol at the ω-terminus. Macrocyclization using copper(I) catalyzed Huisgen 1,3-dipolar cycloaddition resulted predominately in macrocyclic polymers. Azidation of polystyrene prepared by NMRP upon thermolysis with ethanesulfonyl azide provided partial incorporation of azide in place of the terminal alkoxyamine.

1. Introduction

The facile copper(I) catalyzed Huisgen 1,3-dipolar cycloaddition reaction between an alkyl azide and a terminal acetylene, commonly referred to as a "click" reaction [1], has become an efficient method for the production of complex macromolecular structures. The seminal work of Sharpless et al. [2] in 2004 initiated the interest of many researchers in the field of macromolecular engineering, in demonstrating the preparation of a class of dendrimers consisting of 1,2,3-triazoles at the branch points. Hundreds of publications have since followed which employ "click" chemistry to functionalize polymers and prepare intricately designed macromolecules: a number of reviews have recently been published [3–14]. For example, Matyjaszewski et al. have contributed a number of examples of construction of designed materials through a combination of controlled radical polymerization, mainly atom transfer radical polymerization (ATRP), and "click" chemistry. Complex materials such as high molecular weight step-growth polymers [15], star polymers [16], graft copolymers [17], and multi-segmented block copolymers [18] have been prepared in this manner.

An interesting application of this strategy of controlling macromolecular topology is in the preparation of cyclic polymers. Due to constrained conformations, cyclic polymers have different physical characteristics than their linear counterparts [19,20]. This includes smaller effective hydrodynamic volumes, a property that can be exploited during chromatographic analysis to differentiate linear from cyclic polymers [21–24]. One of the first examples of the preparation of cyclic polymers involved the equilibration of linear and cyclic poly(dimethylsiloxane) chains [25]. A variety of methods for the preparation of cyclic polymers have since been published. A number of these publications rely on the difunctional nature of living anionic polymerization initiated with sodium naphthalene or other bidirectional initiators, followed by cyclization via addition of a linker molecule [26–31]. A number of examples of anionic polymerization to make α,ω-functionalized polymers that then are transformed to form macrocycles have appeared [32–35]. Anionic ring-opening polymerization has been used to make cyclic polyethers [36,37]. Multiple examples of the synthesis of macrocyclic polyesters [38–40] and thioesters [41] have emerged. Grubbs et al. demonstrated a straightforward synthesis of cyclic poly(butadiene) through an intramolecular variation of the ruthenium metathesis catalyst [42]. Shea et al. have used a boracyclane initiator to prepare cyclic polymers by methylene insertion [43]. Hemery et al. demonstrated the first example of utilizing a controlled radical polymerization to prepare cyclic polymers: polystyrene was prepared by nitroxide-mediated radical polymerization (NMRP) with 4-hydroxy-2,2,6,6-tetramethyl-piperidinooxy and 4,4′-azo-bis(4-cyanovaleric acid) as the initiator [44]. Ring closure was accomplished via esterification between the α-chain terminal

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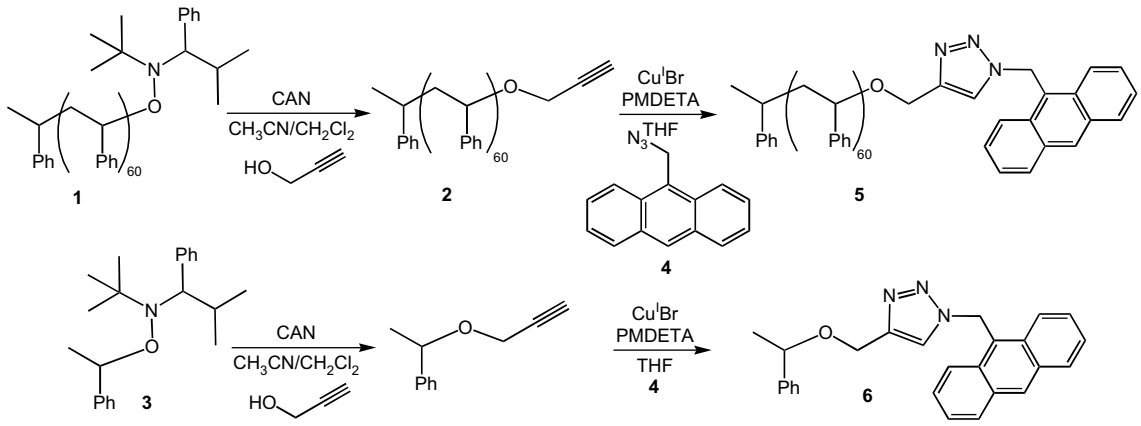


Scheme 1. Conversion of the terminal *N*-alkoxyamines on polystyrene **1** and the small molecule initiator **3** to propargyl ethers by oxidative cleavage with CAN, and subsequent labeling with anthracene via copper-catalyzed "click" chemistry.

carboxylic acid and the hydroxyl group of the capping ω-nitroxide. Cyclic dixanthates have been prepared to carry out reversible addition fragmentation transfer (RAFT) polymerization to form cyclic poly(methyl acrylate) upon γ-ray irradiation [45]. Our lab has investigated NMRP using cyclic alkoxyamines [46].

During the investigation of a "click" step-growth polymerization reaction of alkyne-azide α, ω heterotelechelic polystyrene, Matyjaszewski et al. observed the formation of polymers with lower hydrodynamic volumes than that of the linear precursors [15]. These slightly smaller polymers were attributed to intramolecular cycloaddition resulting in cyclic polymer chains. Grayson et al. demonstrated that this system could yield predominately cyclic polymers by slow addition of a dilute solution of heterotelechelic polymer to a solution of copper(I) catalyst at elevated temperature [47]. Recently, Winnik et al. utilized RAFT polymerization to prepare azide-alkyne α, ω heterotelechelic poly(*N*-isopropylacrylamide) (PNIPAM), a class of smart materials [48]. Likewise, Liu et al. have used ATRP to prepare α, ω heterotelechelic PNIPAM, followed by cyclization by "click" chemistry [49]. Another example employs RAFT polymerization followed by click chemistry to prepare cyclic polystyrenes [50]. An example of ATRP followed by Ring Closing Metathesis of the polymer termini has appeared [51].

Herein, we report the synthesis of azide-alkyne α, ω heterotelechelic linear precursor polymers prepared by NMRP. Cyclization of these linear precursors was achieved via a copper-catalyzed intramolecular azide alkyne cycloaddition under high dilution. Highlighted is the post-polymerization replacement of the terminal *N*-alkoxyamine cap with an alkyne to afford ω-chain end functionalization, via oxidative cleavage with ammonium cerium(IV) nitrate (CAN) in the presence of propargyl alcohol [52]. This process of *N*-alkoxyamine removal provides a general method to incorporate terminal alkynes onto polystyrene chains prepared via NMRP. Complimentary post-polymerization replacement of the nitroxide for an azide upon thermolysis with ethanesulfonyl azide was also investigated: azide incorporation was possible with polystyrenes, but not with polyacrylates.

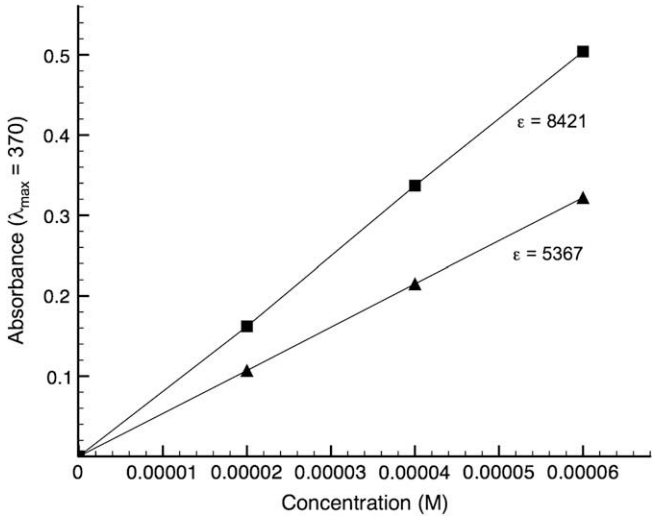


Fig. 1. Beer–Lambert plot of anthracene labeled polystyrene **5** (◆) compared to small model compound **6** (■).

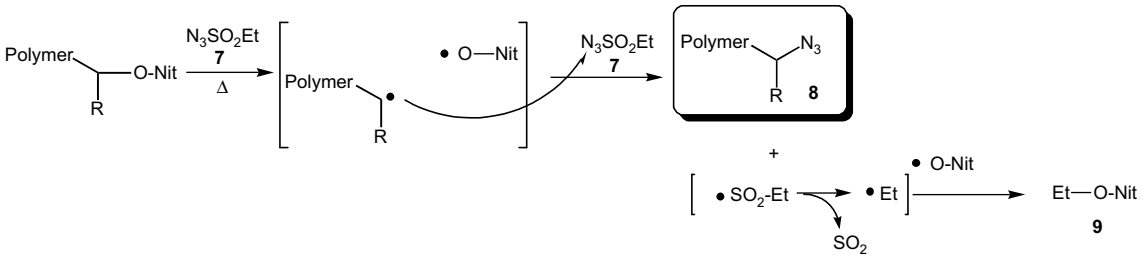
2. Experimental

2.1. Materials

Styrene (St) (Acros, 99%) was distilled under nitrogen prior to use. 2,2,5-Trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane, 2,2,5-trimethyl-3-(1′-*p*-chloromethylphenylethoxy)-4-phenyl-3-azahexane [53], **3**, and 9-(azidomethyl)anthracene **4** were prepared according to literature procedures [54,55]. Copper(I) bromide (Aldrich, 98%) was washed with glacial acetic acid followed by methanol purged with nitrogen prior to use. Ammonium cerium(IV) nitrate (CAN, Aldrich, 98%), *N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99%), and 2-bromoethyl benzene (Acros, 98%) were used as received. Ethanesulfonyl azide was prepared as described by Renaud and Ollivier [56]. Anhydrous dichloromethane, acetonitrile, and tetrahydrofuran were dried by filtration through an Innovative Technologies, Inc. Pure-Solv™ 400 system. Propargyl alcohol was distilled over potassium carbonate and stored over 4 Å molecular sieves before use. 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).

2.2. Characterization

NMR spectra were recorded on a Varian 500 MHz machine (125 MHz for ^{13}C NMR) or a Bruker 250 MHz (75 MHz for ^{13}C NMR) as noted in $CDCl_3$. UV–visible absorption spectra were recorded on a Cary 50 Varian spectrophotometer. FTIR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrometer. High-resolution mass spectrometry was obtained on an electrospray ionization time-of-flight (ESITOF) mass spectrometer (Mariner spectrometer from Applied Biosystems). Gel permeation chromatography (GPC) was performed using a Waters apparatus equipped with five Styragel



Scheme 2. Conversion of the terminal *N*-alkoxyamine of polymers prepared by NMRP to an azide.

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.

*2.2.1. General polymerization method by NMRP (**1**)*

The following example is representative: styrene (8.02 g, 77.0 mmol) and 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (500 mg, 1.54 mmol) were combined in a 5 mL glass ampoule with a magnetic stir bar and deoxygenated by three freeze–pump–thaw cycles. The vial was sealed under argon and heated to 125 °C for 3 h. An aliquot of the crude mixture was analyzed by ^{1}H NMR to determine the monomer conversion. The polymer was dissolved in a minimum amount of THF and precipitated in methanol (100 mL) and recovered by filtration. The precipitation process was repeated three times to give 3.28 g of a white powder. ^{1}H NMR: $M_{n,NMR} = 2929$. GPC: $M_n = 2058$, PDI = 1.27. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24–6.74 (br, 5H, polymer backbone Ar–H), 2.02 (br, 1H, polymer backbone –CH–), 1.59 (br, 2H, polymer backbone –CH_2–) ppm.

*2.2.2. General preparation of propargyl ether terminated polystyrene (**2**)*

To a solution of polystyrene **1** ($M_n = 2058$, PDI = 1.27, 200 mg, 0.068 mmol) in anhydrous dichloromethane (4 mL) and anhydrous acetonitrile (4 mL) was added propargyl alcohol (1.2 mL, 21 mmol) followed by the addition of solid CAN (373 mg, 0.68 mmol). The reaction was stirred at RT for 3 h. Dichloromethane (10 mL) was added and the precipitated cerium salts were removed by filtration. The filtrate was concentrated and the polystyrene was purified by precipitation into chilled methanol. The precipitation process was repeated two times and the resulting material was dried at 50 °C under vacuum to give 121 mg (64% yield) of a white powder. GPC: $M_n = 2032$, PDI = 1.26.

2.2.3. 3-(1-Phenylethoxy)propyne [57]

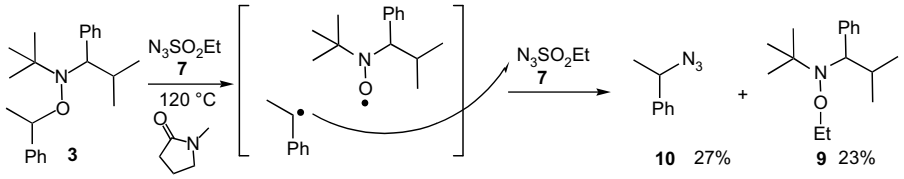
A heterogeneous solution of 2-bromoethyl benzene (1.0 g, 5.40 mmol), propargyl alcohol (1.513 g, 27 mmol) and poly (4-vinylpyridine) (50 mg) was heated to reflux (114 °C) for 30 min. This mixture was cooled, and hexanes (25 mL) were added and the organic layer was washed with water (3 × 10 mL). The organic layer was dried over magnesium sulfate, filtered, and concentrated. The crude material was purified by flash column chromatography (12:1 hexanes:ethyl acetate) to give 557 mg (64% yield) of a clear oil. TLC: 4:1 hexanes:ethyl acetate, $R_f = 0.61$. IR (neat): 3307, 2250, 1091 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (m, 5H, Ar–*H*), 4.67 (q, $J = 6.5$ Hz, 1H, CH_3CH(Ph)O–), 4.10 (dd, $J = 2.5$ Hz, $J = 15.5$ Hz, 1H, –OCH_2C≡CH), 3.89 (dd, $J = 2.5$ Hz, $J = 15.5$ Hz, 1H, –OCH_2C≡CH), 2.42 (t, $J = 2.5$ Hz, 1H, –C≡C*H*), 1.50 (d, $J = 6$ Hz, 3H, CH_3CH(Ph)O–) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.5, 128.7, 127.9, 126.6, 80.1, 76.8, 74.1, 55.6, 23.9 ppm.

*2.2.4. Labeling of alkyne terminated polystyrene with anthracene via copper-catalyzed Huisgen 1,3-dipolar cycloaddition ("click" reaction) (**5**)*

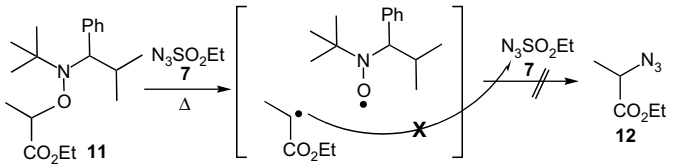
A 25 mL two neck flask was charged with propargyl ether terminated polystyrene **2** (100 mg, 0.036 mmol), 9-(azidomethyl)-anthracene **4** (17 mg, 0.072 mmol) and THF (5 mL), and deoxygenated by three freeze–pump–thaw cycles. The polystyrene solution was transferred via cannula to a flask containing copper(I) bromide under argon. The reaction was stirred at RT for 18 h and then filtered through neutral alumina. The filter cake was washed with THF (3 × 10 mL) and the filtrate was concentrated in vacuo. The resulting polymer was isolated by precipitation from THF into chilled methanol (30 mL) and filtered. The precipitation was repeated three more times to give 68 mg (63% yield) of an off-white powder. GPC: $M_n = 2018$, PDI = 1.26. UV ($CHCl_3$): $\lambda_{max} = 370$ nm, $\varepsilon = 5367$.

*2.2.5. 1-Athracen-9-ylmethyl-4-(1-phenylethoxymethyl)-1H-[1,2,3]triazole (**6**)*

To a 25 mL flask containing copper(I) bromide (30 mg, 0.21 mmol), PMDETA (43 μL, 0.21 mmol), and THF (10 mL) was added 9-(azidomethyl)anthracene **4** and (100 mg, 0.42 mmol) and 3-(1-phenylethoxy)propyne (101 mg, 0.63 mmol) under argon. The reaction was stirred at RT for 18 h and then filtered through neutral alumina. The filtrate was concentrated and purified by flash column chromatography (dichloromethane then dichloromethane:ethyl acetate 10:1) to give 119 mg (72%) of a light green solid. m.p. = 124–128 °C. UV ($CHCl_3$): $\lambda_{max} = 370$ nm, $\varepsilon = 8400$. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1H, Ar–*H*), 8.31 (d, $J = 8.5$ Hz, 2H, Ar–*H*), 8.29 (d, $J = 8$ Hz, 2H, Ar–*H*), 7.60 (m, 2H, Ar–*H*), 7.25 (m, 2H, Ar–*H*), 7.21 (m, 5H, Ar–*H*), 7.04 (s, 1H, –C=C*H*N(N)CH_2–), 6.50 (s, 2H, –NCH_2Ar),



Scheme 3. Conversion of small molecule *N*-alkoxyamine **3** to the benzyl azide **10**.



Scheme 4. Electron poor alkyl radicals do not react with ethanesulfonyl azide **7**.

4.42 (q, $J = 6.5$ Hz, 1H, CH_3CH(Ph)O–), 4.31 (ABC, $J_{AB} = 12$ Hz, $J_{AC} = 29$ Hz, $J_{BC} = 4.5$ Hz, 2H, –OCH_2C(N)CH–), 1.35 (d, $J = 6.5$ Hz, 3H, CH_3CH(Ph)O–) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 143.5, 141.9, 138.6, 137.8, 131.6, 130.9, 129.9, 129.6, 128.5, 128.2, 127.7, 127.6, 126.4, 125.5, 123.2, 122.1, 121.4, 78.0, 62.1, 46.5, 23.9 ppm.

2.2.6. Azidation of small molecule N*-alkoxyamine (**3**)*

To a 50 mL round bottom flask was added 2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane **3** (328 mg, 1.01 mmol), ethanesulfonyl azide **7** (1.329 g, 9.85 mmol) and 1-methyl-2-pyrrolidinone (8 mL). This mixture was purged with N_2 for half an hour and then gradually heated to 120 °C and held at that temperature for 4 h. After cooling, 30 mL of water was added and the reaction mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was combined, washed with brine, dried over magnesium sulfate and concentrated. Purification by column chromatography (silica gel, 1% EtOAc/hexanes) afforded 39.6 mg (27% yield) of 1-phenylethyl azide **10** as a colorless oil along with 57 mg (23%) of 2,2,5-trimethyl-3-(1-ethoxy)-4-phenyl-3-azahexane **9** as colorless oil.

*2.2.7. 1-Phenylethyl azide (**10**)*

TLC: 20% EtOAc/hexane, UV, *p*-anisealdehyde (violet), $R_f = 0.85$. IR (neat): 2981, 2933, 2105, 1493, 1454, 1377, 1306, 1248, 1068, 989, 911, 759, 700, 649 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H, Ar–H), 4.59 (q, $J = 4.5$ Hz, 1H, CH), 1.51 (d, $J = 4.5$ Hz, 3H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.9 (*ipso* of Ar), 128.8 (2 × CH–Ar), 128.2 (CH–Ar), 126.4 (2 × CH–Ar), 61.1 (*C*H), 21.7 (*C*H_3) ppm.

*2.2.8. 2,2,5-Trimethyl-3-(1-ethoxy)-4-phenyl-3-azahexane (**9**)*

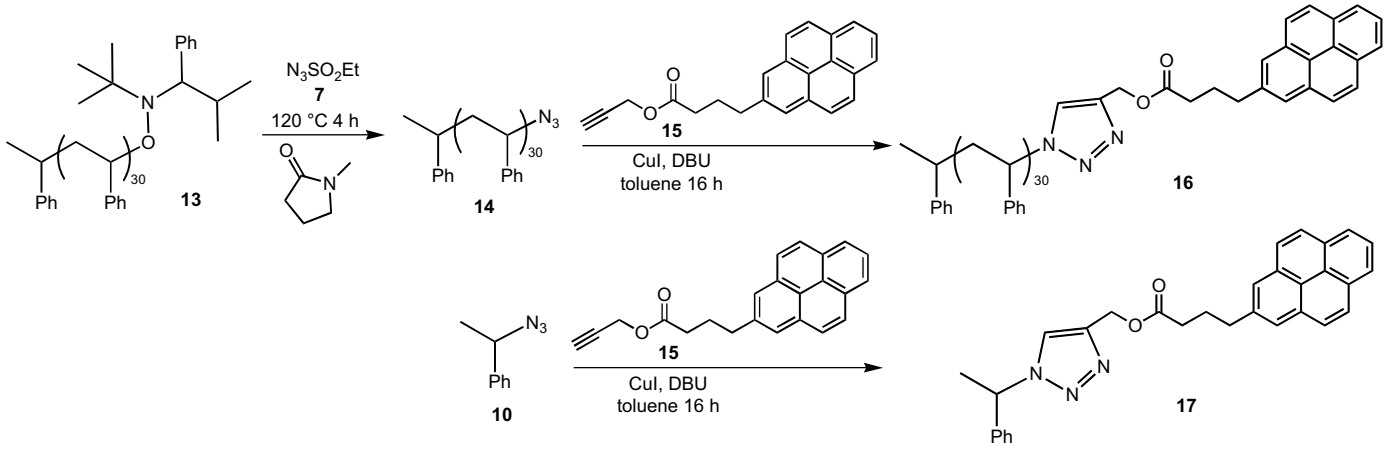
TLC: 1% EtOAc/hexanes, UV, *p*-anisealdhyde (violet), $R_f = 0.70$. IR ($CHCl_3$): 3025, 2972, 2930, 2106, 1681, 1601, 1493, 1452, 1216, 752, 700, 668 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.14 (m, 5H, Ar–H), 4.02 (m, 1H, OCH_2CH$_3$), 3.85 (m, 1H, OCH_2CH$_3$), 3.35 (d, $J = 10.0$ Hz, 1H, NC*H*Ph), 2.18 (m, 1H, C*H*(CH$_3$)$_2$), 1.23 (d, $J = 6.5$ Hz, 3H, CH(CH_3)$_2$), 1.19 (t, $J = 7.5$ Hz, 3H, OCH$_2$CH_3), 0.92 (s, 9H, C(CH_3)$_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 130.7. 127.5 (×2), 125.8 (×2), 72.2, 71.8, 60.2 (*C*(CH$_3$)$_3$), 32.0 (*C*H(CH$_3$)$_2$), 22.1 (OCH$_2$*C*H$_3$), 21.2 (C(CH$_3$)$_3$)14.2 (C(*C*H$_3$)$_3$) ppm.

*2.2.9. Prop-2-ynyl 4-(pyren-2-yl)butanoate (**15**)*

To a 50 mL round bottom flask containing a mixture of pyrenebutyric acid (289.7 mg, 1.00 mmol), dicyclohexylcarbodiimide (213 mg, 1.10 mmol) and *N*,*N*-dimethylaminopyridine (3 mg, 0.01 mmol) in 20 mL of anhydrous dichloromethane was slowly added propargyl alcohol (0.070 mL, 1.1 mmol) under N_2. The reaction mixture was allowed to react at RT for 18 h, then was filtered through Büchner funnel and washed thoroughly with dichloromethane. The filtrate was concentrated under reduced pressure and the crude mixture was purified by flash column chromatography (30% EtOAc/hexane). The product **15** (271.6 mg, 83.3%) was obtained as a pale yellow powder, m.p. 66–68 °C. TLC: 30% EtOAc/hexane, UV, *p*-anisealdhyde, $R_f = 0.50$. IR ($CHCl_3$): 3307 (CH stretch of alkyne), 3019, 2950, 2400, 2116 (C≡C stretch), 1739 (C=O stretch), 1603, 1522, 1435, 1418, 1214 (C–O stretch), 1160, 1143, 1029, 929, 847, 772, 669 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ 8.29 (d, $J = 9.0$ Hz, 1H, pyrene–H), 8.17–8.15 (m, 2H, pyrene–H), 8.12–8.10 (m, 2H, pyrene–H), 8.02 (s, 2H, pyrene–H), 7.99 (t, $J = 7.5$ Hz, 1H, pyrene–H), 7.85 (d, $J = 7.5$ Hz, 1H, pyrene–H), 4.70 (d, $J = 2.5$ Hz, 1H, OCH$_2$C≡CH), 3.39 (t, $J = 8$ Hz, 2H, pyrene–CH$_2$), 2.50 (t, $J = 7.5$ Hz, 2H, CH$_2$CO), 2.48 (t, $J = 2.5$ Hz, 1H, C≡CH), 2.21 (tt, $J = 7.5$, 7.5 Hz, 2H, CH$_2$CH$_2$CH$_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.4 (CO_2–), 135.6, 131.5, 131.0, 130.1, 128.8 (Cq–pyrene), 127.6, 127.5, 126.9, 126.0, 125.2, 125.1, 124.9, 123.4 (CH–pyrene), 77.8 (C≡CH), 75.0 (C≡CH), 52.0 (OCH$_2$C≡CH), 33.7 (pyrene–CH$_2$), 32.8 (CH$_2$CO$_2$), 26.8 (CH$_2$CH$_2$CH$_2$) ppm. HRMS: [M + 1] $C_{23}H_{19}O_2$ calc. 327.1385; found 327.1363.

*2.2.10. (1-(1-Phenylethyl)-1*H*-1,2,3-triazol-4-yl)methyl 4-(pyren-2-yl) butanoate (**17**)*

To a 100 mL round bottom flask containing a solution of prop-2-ynyl 4-(pyren-2-yl)butanoate **15** (175 mg, 0.537 mmol), 1-phenylethyl azide **10** (81 mg, 0.55 mmol), and 1,8-diazabicyclo[5.4.0]undec-7-ene (1.50 mL, 10.0 mmol) in 30 mL of dry toluene was added copper(I) iodide (28.6 mg, 0.15 mmol). The reaction was gently heated at 50 °C under N_2 for 16 h. The reaction was concentrated in vacuo, the crude mixture was purified by flash column chromatography (60% EtOAc/hexanes) to give 241 mg (94.4%) of triazole **17** as a pale yellow viscous oil. TLC: 60% EtOAc/hexane, UV, *p*-anisealdhyde, $R_f = 0.50$. IR ($CHCl_3$): 3017, 2939, 1732 (C=O stretch), 1604, 1587, 1496, 1456, 1382, 1215 (C–O stretch), 1160, 1143, 1047, 1025, 847, 770, 668 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (d, $J = 9.5$ Hz, 1H, pyrene–H), 8.13–8.12 (m, 2H, pyrene–H), 8.06–8.04 (m, 2H, pyrene–H), 7.98 (s, 2H, pyrene–H), 7.95 (t, $J = 7.5$ Hz, 1H, pyrene–H), 7.76 (d, $J = 7.5$ Hz, 1H, pyrene–H), 7.41 (s, 1H, CH–triazole), 7.25–7.17 (m, 5H, Ph–H), 5.70 (q, $J = 7.0$ Hz, 1H, CH$_3$*C*HPh), 5.18 (s, 2H, CO$_2$CH_2–triazole), 3.28 (t, $J = 7.5$ Hz, 2H, pyrene–CH$_2$),



Scheme 5. Azidation of polystyrene and subsequent attachment of a pyrene dye by "click" chemistry.

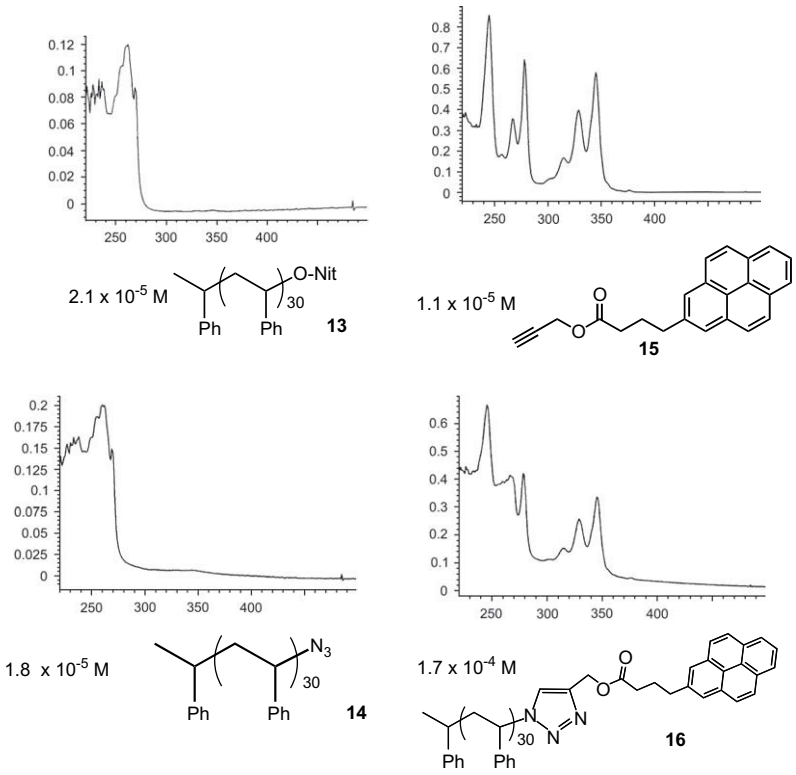
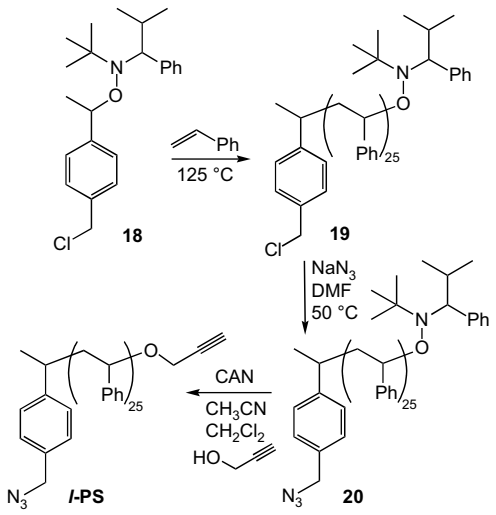


Fig. 2. UV–vis spectra of polystyrene **13** subjected to azidation to form **14**, and subsequent "click" chemistry to attach a pyrene dye to form triazole **16**, and the pyrene dye **15** for comparison.

2.43 (t, $J = 7.5$ Hz, 2H, CH_2CO), 2.14 (tt, $J = 7.5$, 7.5 Hz, 2H, $CH_2CH_2CH_2$), 1.89 (d, $J = 7.0$ Hz, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.4 (CO_2–), 163.4, 142.9, 139.7, 135.7, 131.5, 131.0, 129.1, 128.8, 128.7, 127.6, 127.55, 127.5, 126.8, 126.6 (×2), 126.0, 125.2, 125.1, 124.9 (×2), 123.4, 122.6, 60.5, 57.8, 33.8, 32.8, 26.8, 21.4 ppm. HRMS: [M + 1] $C_{31}H_{28}N_3O_2$ calc. 474.2181; found 474.2191.

2.2.11. Chloro α-chain end functionalized polystyrene (*19*)

According to the general polymerization method described above, *N*-alkoxyamine **18** (173 mg, 0.463 mmol) and styrene (2.584 g, 24.8 mmol) were employed. An aliquot of the crude mixture was analyzed by ^1H NMR to determine the monomer conversion. The polymer was purified by precipitation from THF into chilled methanol (100 mL) three times to give 1.102 g of **19** as a white powder. ^1H NMR: $M_{n,NMR} = 2978$. GPC: $M_n = 2895$, PDI = 1.20. ^1H NMR (500 MHz, $CDCl_3$): δ 4.54 (m, 2H, polymer α-chain end –ArCH_2Cl) ppm.



Scheme 6. Synthesis of azide-alkyne α, ω heterotelechelic polystyrene ***I*-PS**.

2.2.12. Azide α-chain end functionalized polystyrene (*20*)

A solution of chloro α-chain end functionalized polystyrene **19** ($M_n = 2978$, PDI = 1.20, 500 mg, 0.17 mmol) and sodium azide (44 mg, 0.67 mmol) in DMF (10 mL) was stirred at 50 °C for 17 h. The reaction was cooled to RT and then poured into diethyl ether (60 mL). The organic layer was washed with water (5 × 30 mL), dried over magnesium sulfate, filtered, and concentrated. The polymer residue was redissolved in THF and precipitated from chilled methanol. The precipitation was repeated two times to give 457 mg (91% yield) of polymer **20** as a white powder. GPC:

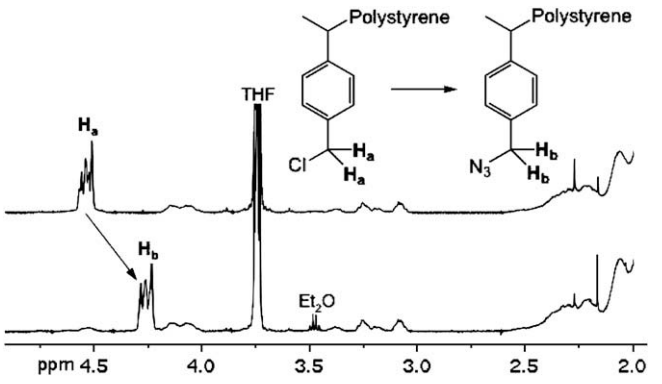
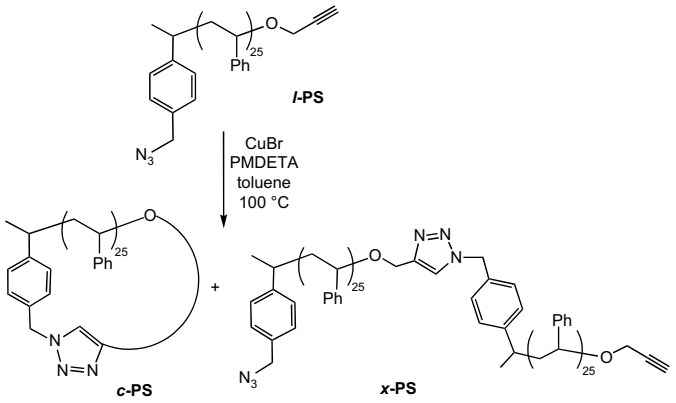


Fig. 3. Expansion of an overlay of the ^1H NMR spectra ($CDCl_3$) of polystyrenes **19** and **20** showing a distinct upfield shift in the benzylic methylene chain endgroup following conversion of chloro to azide.



Scheme 7. Macrocyclization of ***l*-PS** via copper-catalyzed "click" chemistry.

$M_n = 3058$, PDI = 1.25. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.26 (m, 2H, polymer α-chain end –ArCH_2N_3) ppm. IR (film): 3029, 2925, 2089 (N_3), 1729, 1454, 1372, 1153 cm^{-1}.

*2.2.13. Azide-alkyne α, ω heterotelechelic polystyrene (**l-PS**)*

According to the general oxidation procedure described above, azide α-chain end functionalized polystyrene **20** (438 mg, 0.15 mmol), CAN (806 mg, 1.47 mmol), dichloromethane (5 mL), acetonitrile (5 mL), and freshly distilled propargyl alcohol (1.5 mL) were employed. Repeated precipitation into chilled methanol gave 339 mg (82% yield) of linear heterotelechelic polystyrene as a white powder. GPC: $M_n = 3{,}291$, PDI = 1.21. IR (film): 3434 (C≡C), 3031, 2934, 2097 (N_3), 1729, 1453, 1372, 1153 cm^{-1}.

*2.2.14. Macrocyclization of azide-alkyne α, ω heterotelechelic polystyrene (**c-PS**)*

A solution of heterotelechelic polystyrene ***l*-PS** ($M_n = 3291$, PDI = 1.21, 134 mg, 0.007 mmol) in toluene (50 mL) was deoxygenated by three freeze–pump–thaw cycles. The polymer solution was added via syringe pump, at a flow rate of 0.035 mL/min, to a deoxygenated solution of copper(I) bromide (20 mg, 0.14 mmol) and PMDETA (29 μL, 0.14 mmol) in toluene (100 mL) heated to 100 °C. The addition of the polymer solution was complete after 24 h. The reaction was stirred at 100 °C for an additional hour and then cooled to RT. The copper catalyst was removed by filtration through neutral alumina followed by filtration through silica gel. The solvent was removed in vacuo and the residue dissolved in THF and precipitated into methanol. The precipitation process was repeated two more times to give 67 mg (50% yield) of an amorphous solid. Multi-peak fitting analysis of the raw GPC data indicated 67% ***c*-PS** ($M_n = 3172$, PDI = 1.15), 19% unreacted ***l*-PS** ($M_n = 4295$, PDI = 1.06), and 14% ***x*-PS** ($M_n = 8617$, PDI = 1.14).

3. Results and discussion

3.1. Post-polymerization introduction of a terminal alkyne via oxidative cleavage of the alkoxyamine endcap

We have previously shown that secondary benzylic *N*-alkoxyamines (found in polystyrene prepared by NMRP) are oxidatively cleaved upon treatment with CAN [52]. Benzyl cations are formed; trapping by various nucleophiles provides a method of polymer chain end functionalization. Oxidative cleavage of polystyrene prepared by NMRP with CAN and trapping of the terminal cation with propargyl alcohol was developed as a method to incorporate terminal alkynes onto polystyrene chain ends. Polystyrene **1** was prepared by NMRP and treated with CAN in a mixed solvent system of 1.0:1.0:0.3 dichloromethane:acetonitrile:propargyl alcohol to effect oxidative cleavage of the terminal alkoxyamine. A large excess of propargyl alcohol was used relative to the polystyrene chain ends to ensure efficient chain end functionalization providing predominately propargyl ether **2** (Scheme 1).

Quantification of terminal alkyne incorporation onto polystyrene **2** was carried out by labeling the polymer chain end with UV-active azide-substituted anthracene **4** via copper-catalyzed Huisgen 1,3-dipolar cycloaddition. Small molecule model compound **6** was prepared from the *N*-alkoxyamine initiator for spectroscopic comparison of the molar extinction coefficients (ε). Following repeated precipitation of **5** to remove any excess azide reagent **4**, samples of identical concentrations of **5** and **6** were prepared in chloroform and measured by UV–visible analysis (Fig. 1). From the ratio of the molar extinction coefficients of **5** to **6**, the amount of polystyrene chain ends labeled with anthracene was determined to be 64%. This amount of chain end functionalization was considered adequate for further chemical modification at the polymer terminus.

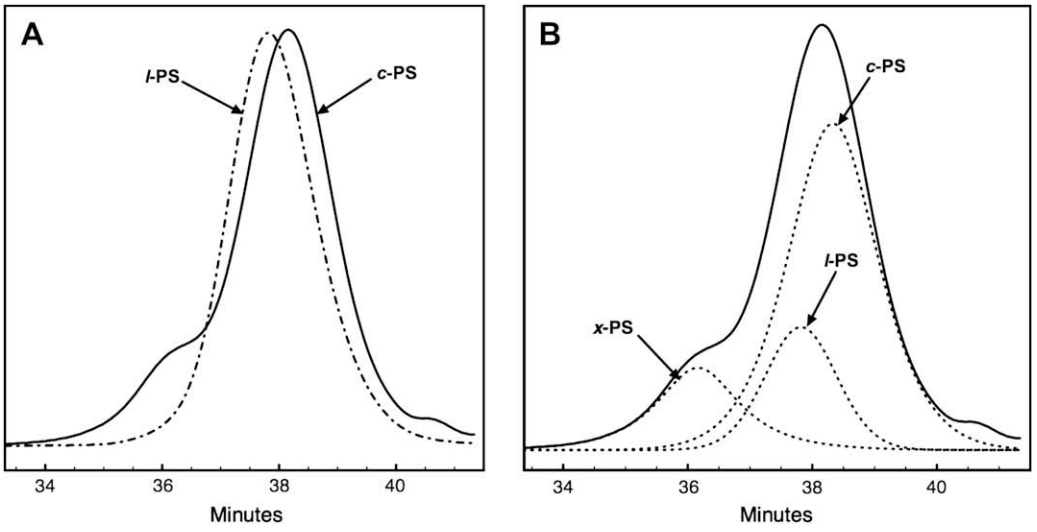


Fig. 4. (A) Overlay of GPC chromatographs for linear ***l*-PS** and cyclic polymer ***c*-PS**. (B) GPC chromatograph of ***c*-PS** with computationally derived Gaussian curves labeled with their corresponding components.

3.2. Post-polymerization introduction of a terminal azide by radical exchange of the dormant nitroxide

A complimentary post-polymerization method for exchanging nitroxide for azide was investigated. Ethanesulfonyl azide **7**, introduced and developed by Renaud and Ollivier [56,58] as an azidation method for carbon radicals, should react as shown in Scheme 2. It was envisioned that the polymeric radical would add to the azido group with loss of ethanesulfonyl radical. After rapid loss of SO_2, the resulting ethyl radical would be trapped irreversibly by the nitroxide radical to form azide-terminated polymer **8** and *N*-ethoxyamine **9**. As a model reaction, the initiator *N*-alkoxyamine **3** was heated at 120 °C in the presence of 5–10 equivalents of ethanesulfonyl azide **7** (Scheme 3). The appearance of both the benzyl azide **10** and the *N*-ethoxyamine **9** was monitored by ^{1}H NMR spectroscopy of the crude reaction mixtures. Only traces of the benzyl azide **10** were produced in aromatic solvents, whereas the polar solvents *N*,*N*-dimethylacetamide and *N*-methyl-2-pyrrolidinone [59] showed larger amounts of product formation. Isolation of the products from the *N*-methyl-2-pyrrolidinone reaction yielded 27% of the benzyl azide **10** and 23% of the *N*-ethoxyamine **9**. Subjecting the ester-substituted alkoxyamine **11** (a polyacrylate mimic) to the same conditions (Scheme 4) did not give any of the desired azide **12**, although some *N*-ethoxyamine **9** was isolated. Authentic benzyl azide **10** and α-carbonyl azide **12** (both prepared by nucleophilic displacement of the corresponding bromides) were thermally stable at 120 °C as determined by NMR. The failure of this ester-substituted radical to react is in accord with the work of Renaud et al.: they have shown that only *electron rich* radicals add effectively to ethanesulfonyl azide **7**, and have capitalized on this selectivity to carry out tandem sequences of carboazidation [60].

This radical azidation reaction was then applied to a sample of polystyrene **13** prepared by NMRP: heating with 9 equiv of ethanesulfonyl azide **7** for 4 h at 120 °C in *N*-methyl-2-pyrrolidinone resulted in polymer **14**. In order to confirm that a terminal azide group had been introduced, a "click" reaction with an acetylene attached to a pyrene dye **15** was carried out to form **16** (Scheme 5). The polymer product was precipitated three times from dichloromethane/methanol to remove any contamination by unreacted starting material. The analogous reaction was carried out with the small molecule model compound **10** to provide triazole product **17** that was rigorously characterized. Comparison of the UV–vis spectra shown in Fig. 2 provides compelling evidence that some of the polystyrene chains **13** were successfully converted to the azide **14**, and subsequently to the pyrene-labeled triazole **16**. Fluorescence was clearly seen upon exposure of a sample of **16** to a hand-held UV lamp at 366 nm. However, the fluorescence for polymer **16** (at 1.7×10^{-4} M) was weaker than the signal for model compound **15** at a more dilute concentration (1.1×10^{-5} M), indicating that azidation was incomplete (Fig. 2).

3.3. Macrocyclization of α, ω heterotelechelic polystyrene

To prepare azide-alkyne α, ω heterotelechelic polymers for macrocyclization, an *N*-alkoxyamine initiator **18** was utilized bearing a benzylic chloride chain end. Addition of azide as a post-polymerization nucleophilic substitution reaction introduces the "click" partner to the terminal acetylene. Attempts to carry an azide group through the radical polymerization were unsuccessful, presumably due to the addition of the active polymer radicals to the azide functionality [61,62]. Benzyl chloride functionalized *N*-alkoxyamine **18** was prepared according to a literature procedure [54] and used in the polymerization to form **19** (Scheme 6). Nucleophilic displacement of the terminal chloride with sodium azide gave **20**, which was conveniently monitored by ^{1}H NMR (Fig. 3). An upfield shift of the benzylic methylene protons ($\mathbf{H_a}$) from 4.54 to 4.26 ppm was observed following substitution of the chloro group by the azide. Oxidative cleavage of the terminal *N*-alkoxyamine with CAN in the presence of a large excess of propargyl alcohol afforded the desired azide-alkyne α, ω heterotelechelic polystyrene ***l*-PS** (linear polystyrene).

Table 1
Composition and molecular weight data calculated from multi-peak curve fitting analysis of raw data obtained from GPC analysis of cyclic polystyrene ***c*-PS**.

Entry	Polymer	M_n[a]	M_w[b]	PDI[c]	%Comp	M_n[d]	M_w[d]	PDI[d]
1	***x*-PS**	8 617	9 807	1.14	14			
2	***l*-PS**	4 295	4 556	1.06	19	3988	4671	1.17
3	***c*-PS**	3 172	3 658	1.15	67			

[a] Number average molecular weight.
[b] Weight average molecular weight.
[c] Polydispersity index (M_w/M_n).
[d] Values obtained from GPC analysis (GPC analysis utilized refractive index detection, not corrected for differential mass response).

Macrocyclization of the heterotelechelic polymer was achieved by syringe pump addition of a dilute deoxygenated solution containing ***l*-PS** in toluene to a deoxygenated solution containing copper(I) bromide and *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA) in toluene (Scheme 7). The temperature of the reaction was maintained at 100 °C during addition of the polymer substrate to enhance the rate of cycloaddition. The elevated temperature aids in the formation of cyclic polymers as opposed to inter-polymer coupling. Analysis of the resulting polymer sample by GPC revealed a slight shift in the elution time of the cyclic product compared to the starting polymer ***l*-PS** (linear polystyrene) (Fig. 4A). The shoulder to the left of the chromatograph of ***c*-PS** (cyclic polystyrene) is attributed to disfavored inter-polymer coupling ***x*-PS** (cross-coupled polystyrene). The GPC data obtained for this polymeric mixture was analyzed by applying a Gaussian curve fit to elucidate the composition and determine the amount of cyclization. This curve fitting technique has been shown to be useful in the analysis of similar systems where complex chromatographic data arises from overlapping signals [24,63,64]. The Gaussian curves are defined by the height, position, and width of the peak at half the maximum. These values were computationally optimized through a series of iterations to minimize deviation of the summation curve to the experimentally observed data set (Fig. 4B) [65]. From the curve fit, the number and weight average molecular weights, polydispersity index, and percent composition of each component in the mixture were determined (Table 1). The data analysis indicates that 67% of cyclization took place with only 14% of polymer cross coupling competing. In addition, 19% of polymer chains remained unreacted, from either a lack of chain end functionalization or a need for an increased reaction time or catalyst amount. The unreacted linear polymer data obtained from the curve fit is consistent with the values from GPC analysis of pure ***l*-PS**, corroborating the accuracy of the curve fitting protocol. A decrease in the PDI was observed; this may be an artifact of the curve fit method.

4. Conclusion

Use of CAN-mediated oxidation of the ω-chain end of polystyrene prepared by NMRP converted an *N*-alkoxyamine to a propargyl ether to set the stage for "click" functionalization. Quantification of terminal alkyne incorporation was performed by labeling the polymer chain end with UV-active anthracene via "click" chemistry. A complimentary exchange of nitroxide for azide provided polystyrene with partial incorporation of azide. An α, ω heterotelechelic polystyrene polymer was prepared from a benzyl chloride functionalized *N*-alkoxyamine initiator. Conversion to the azide-alkyne α, ω heterotelechelic polymer followed by treatment

with copper(I) bromide and PMDETA in toluene under high dilution and elevated temperature effected predominately intramolecular cycloaddition to form macrocyclic polystyrene.

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