Development of Thermal and Photochemical Strategies for Thiol−Ene Click Polymer Functionalization

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ABSTRACT: A series of alkene-functional polymers were synthesized by controlled polymerization techniques in order to investigate and compare the efficiency and orthogonality of both photochemically and thermally initiated thiol−ene click coupling reactions. The copolymers were designed to have single or multiple alkene-functional groups along the backbone, and to evaluate the robustness of these procedures, functionalization reactions with a library of mercaptans were studied. In comparing the photoinitiated reaction to its thermal counterpart, the thiol−ene photocoupling was found to proceed with higher efficiency, require shorter reaction times for complete conversion, and displayed a higher tolerance to various backbones and functional groups. To examine the orthogonality of the thiol−ene click reaction, an asymmetric telechelic polymer based on PS was designed with alkene functionality at one end and an azide at the other. The thermally initiated thiol−ene coupling was found to be completely orthogonal with the traditional azide/alkyne click reaction allowing the individual chain ends to be quantitatively functionalized without the need for protection/deprotection strategies. From these studies, the demonstrated efficiency and orthogonality of thiol−ene chemistry shows it to be a practical addition to the family of click reactions that are suitable for polymer functionalization.

Introduction

A recent achievement in synthetic chemistry is the preparation of large, well-defined polymeric systems which carry tailored functional groups and have been shown to be critical for a range of potential applications in microelectronics and biomedical systems. The advent of facile controlled polymerization techniques,[1−5] such as living radical/ring-opening procedures, is one of the main drivers and principal accomplishments in this area. Such reactions have allowed well-defined, functional materials to become ubiquitous in both academic and industrial settings. However, the range of monomers that are both synthetically available and compatible[6] with these controlled polymerization techniques can limit versatility, and employing postpolymerization modifications to target a specific function is a viable option to extend the usefulness of these systems.[7] The concept of postpolymerization functionalization strategies introduces a number of major challenges, such as efficiency and orthogonality, which must be overcome in order to allow well-defined materials to be prepared. An excellent example of the power of postpolymerization strategies when combined with controlled polymerization techniques is the wide range of functional materials that have been prepared using Cu-catalyzed azide/alkyne click (CuAAC) chemistry.[8−10] By significantly decreasing the barrier to polymer functionalization, CuAAC chemistry[11] has allowed for a stunning diversity of functional materials with tailored physical, chemical, and mechanical properties to be prepared.[12,13] For example, Haddleton and co-workers have employed CuAAC chemistry to construct glycopolymers from alkyne-backbone-functional polymers,[14,15] while Bertozzi and Tirrell have further enlarged the field by developing bioconjugation strategies that employ a strained alkyne moiety and do not require the use of copper.[16] The orthogonality of traditional CuAAC chemistry has also allowed the reaction to be combined with other efficient chemistries such as Diels−Alder cycloadditions,[17,18] while Francis and co-workers have elegantly demonstrated the efficiency of coupling between aldehydes and hydroxylamines (oxime bond formation) for the chemical modification of proteins and viral capsids.[19] Furthermore, Maynard and co-workers have modified block copolymers by oxime bond formation,[20] and amino−oxy functional telechelic polymers have been used for conjugation with biomolecules.[20,21] These examples clearly illustrate the opportunity for building and expanding the repertoire of chemical transformations that fall within the realm of "click" chemistry.

In analogy with the CuAAC and oxime reactions described above, thiol−ene chemistry is an emerging synthetic tool that has the potential to fall within the realm of click chemistry.[22] Previously, the reaction between a thiol and nonactivated double bond has been used for the fabrication of cross-linked polymeric matrices that span applications ranging from dental resins[23] and hydrogels[24,25] to materials for imprint lithography,[26,27] including systems with novel physical and mechanical properties, such as photoinduced plasticity.[28] In order to rigorously test the robustness and efficiency of thiol−ene coupling as a click reaction to build and functionalize macromolecules,[29] we have recently reported the synthesis of dendrimers via solvent-free, UV-initiated thiol−ene chemistry that was shown to proceed quantitatively and with a high degree of specificity in a matter of minutes.[27] Moreover, thiol−ene reactions have also been employed for the end-group modification of alkene-functional poly(ethylene glycol) (PEG),[30] and more recently, Schlaad and co-workers have shown that poly(oxazolines) can be photochemically clicked with thiols having diverse functionalities,[31] although the lack of a radical initiator prolongs the reaction time (12−24 h).[32] In a related study with poly(butadiene), David and Kornfield have shown that thiols can be coupled to the polymer

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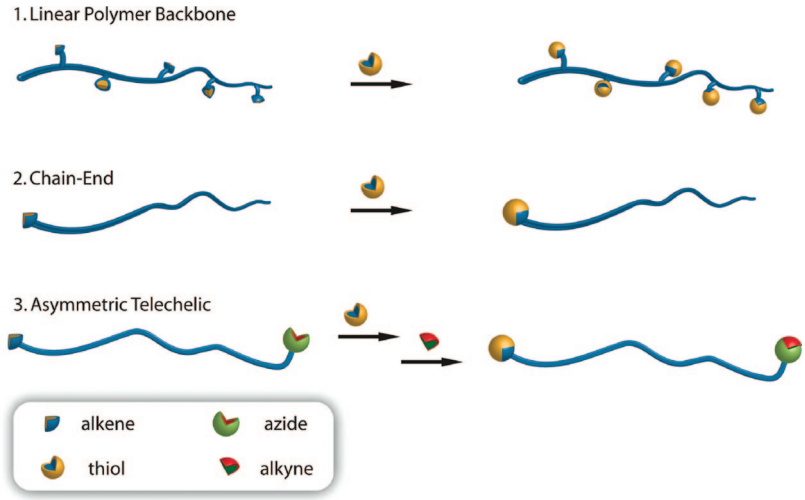


Figure 1. Schematic representation of polymer functionalization reactions examined using thiol−ene click chemistry.

backbone under thermal conditions within 2−6 h, using a thermal radical initiator.[33]

In a similar vein to the classic click reaction between azides and alkynes where the starting materials can be easily prepared (facile conversion of alkyl halides to azides by displacement using NaN_3[34]), the wide availability and associated stability of the thiol and alkene starting materials offers a number of advantages when designing synthetic strategies. In addition to the range of commercially available thiols including cysteine-containing peptides,[24,35] alkyl halides,[33] alcohols,[33] reversible addition−fragmentation chain transfer (RAFT) agents,[36,37] and even alkenes can be readily converted to thiols.[33] In addition, the thiol−ene reaction can be carried out under solvent-free conditions that do not yield any harmful byproducts.[22,27] Finally, purification of the macromolecules can be done by simple precipitation techniques to remove any excess mercaptans. In order to investigate the efficiency and orthogonality of both photochemically and thermally initiated thiol−ene click coupling reactions, this paper explores the general philosophy of click reactions through the mercaptan functionalization of a series of alkene-functional polymers (Figure 1).

Experimental Section

Materials and Instrumentation. All materials were obtained from Aldrich and used as received, unless otherwise noted. Styrene (99%), 4-vinylbenzyl chloride (99%), and cysteamine (98%) were purchased from Fluka. 3-Buten-1-ol (96%) was purchased from Acros. Fmoc-protected cysteine (99.6%) was purchased from Chem-Impex International. Methacryloyl chloride, benzyl alcohol, and ε-caprolactone were distilled before use. Prior to polymerization, styrene was filtered over basic alumina to remove the radical inhibitor. Fmoc-protected cysteine was purchased from Chem-Impex International. Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. The radical initiator 2,2′-azobis(2-methylpropionitrile) (AIBN) was recrystallized from ethanol. Column chromatography was performed on a Biotage SP1 flash purification system using FLASH 25+M cartridges and FLASH 25+ samplet cartridges. Ultraviolet (UV) light irradiation of the samples was carried out with a 15 W UVP Black Ray UV bench lamp XX-15 L, which emits around 365 nm wavelength (intensity ca. 4.6 mW cm^{-2}). Nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were recorded on a Bruker DMX-500 MHz spectrometer, a Varian Unity Inova 400 MHz spectrometer, and a Varian Mercury Vx 200 MHz spectrometer at room temperature. Chemical shifts are reported in parts per million (δ) relative to $CHCl_3$ (7.24 ppm for ^1H and 77.2 ppm for ^{13}C) or DMSO (2.50 ppm for ^1H and 39.5 ppm for ^{13}C) as internal reference. Gel permeation chromatography (GPC) was carried out on a Waters 2695 separation module equipped with a Waters 2414 refractive index detector and a Waters 2996 photodiode array detector, using THF as the eluent. Molecular weights (MWs) and polydispersity indices (PDIs) are reported relative to PS, PMMA, and PEG. Infrared spectra were recorded on a Perkin-Elmer Spectrum 100 with a Universal ATR sampling accessory.

1-[(3-Butenyloxy)methyl]-4-vinylbenzene (**1**). Compound **1** was synthesized by the previously published procedure of Husseman et al.[40] Briefly, to a solution of 3-buten-1-ol (6.00 g, 83.2 mmol) in dry THF (100 mL) was added sodium hydride (60% dispersion in oil, 4.01 g, 100 mmol), and the reaction was stirred for 20 min at room temperature. A solution of 4-vinylbenzyl chloride (9.55 g, 62.6 mmol) in dry THF (15 mL) was added dropwise through an addition funnel. The reaction mixture was brought to reflux and stirred overnight. The solvent was evaporated, and the reaction mixture was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic fractions were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure. The product was purified by column chromatography using a 9:1 ratio of hexanes to CH_2Cl_2 to yield the monomer, **1**, as a colorless oil (8.63 g, 73%). δ_H (500 MHz, $CDCl_3$): 7.45−7.30 (complex m, 4H, aromatic), 6.77 (m, 1H, CH_2=CHPh), 5.89 (m, 1H, OCH_2-CH_2CH=CH_2), 5.80 (dd, 1H, CH_2=CHPh), 5.27 (dd, 1H, CH_2=CH−Ph), 5.12 (m, 2H, OCH_2CH_2CH=CH_2), 4.53 (s, 2H, $PhCH_2O$), 3.55 (t, 2H, OCH_2CH_2CH=CH_2), 2.39 (m, 2H, OCH_2CH_2CH=CH_2).

S-Methoxycarbonylphenylmethyl Dithiobenzoate (MCPDB, RAFT Agent, **2***).* Compound **2** was synthesized by the previously published procedure of Perrier et al.[41]

*P(***1***-co-Styrene).* Styrene (4.69 g, 45 mmol), **1** (0.941 g, 5 mmol), **2** (0.0315 g, 0.104 mmol), and AIBN (1.1 mg, 0.007 mmol) were added to an ampule, subjected to three freeze−pump−thaw cycles, and then sealed. The ampule was heated in an oil bath at 75 °C for 16 h, and the contents were diluted with CH_2Cl_2 before precipitating into cold MeOH. The resulting polymer was dried in vacuo. The polymer contained 10% of the ene-functional monomer **1**, characterized by ^1H NMR (see Figure 2, top). M_n = 14.5 kg/mol, PDI = 1.07. δ_H (500 MHz, $CDCl_3$): 7.20−6.30 (b, aromatic of PSt), 5.94 (b, 1H, CH=CH_2), 5.15 (b, 2H, CH=CH_2), 4.47 (b, 2H, St−CH_2−O−CH_2−), 3.55 (b, 2H, St−CH_2−O−CH_2−), 2.43 (b, 2H, −O−CH_2−CH_2−CH=CH_2), 2.30−1.30 (b, n × 3H, CH−CH_2). δ_C (500 MHz, $CDCl_3$): 147.4, 138.5, 137.5, 130.0, 129.8, 129.6, 129.4, 129.3, 128.1, 127.6127.7, 127.4, 118.1, 74.7, 71.6, 42.4, 36.3. IR: 3060, 3026, 2921, 2850, 1944, 1874, 1804, 1738, 1642, 1602, 1584, 1513, 1493, 1452, 1359, 1181, 1155, 1095, 1028, 994, 909, 820, 756, 713 cm^{-1}.

But-3-enyl Methacrylate (**3**). Compound **3** was synthesized according to the literature procedure of D'Annibale et al.[42] Briefly,

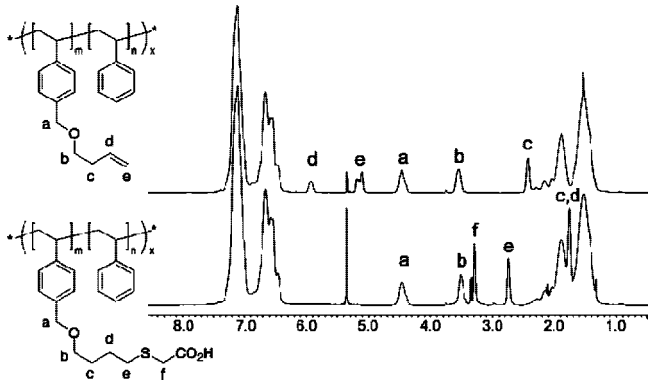


Figure 2. ^{1}H NMR spectra of P(**1**-*co*-S) (top) and its product after the thiol−ene coupling with **7** (bottom).

to a flask under nitrogen was added 3-butenol (5.00 g, 69.3 mmol), triethylamine (9.13 g, 90.2 mmol), and 75 mL of CH_2Cl_2. The solution was allowed to stir for 10 min before cooling to 0 °C and adding methacryloyl chloride dropwise. The solution was stirred at 0 °C for 45 min, followed by stirring overnight at room temperature. The reaction mixture was diluted with 250 mL of CH_2Cl_2 and extracted with water (2 × 200 mL). The organic fraction was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The product was purified by column chromatography using 50:50 hexanes to CH_2Cl_2 to afford **3** as a colorless oil (6.1 g, 73%).

*P(**3**-co-MMA).* Methyl methacrylate (6.0 g, 60 mmol), **3** (1.68 g, 12 mmol), ethyl-2-bromo isobutyrate (42 mg, 0.215 mmol), and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA, 77 mg, 0.445 mmol) were added to a flask and sparged with nitrogen for 15 min. Copper(I) bromide (32 mg, 0.223 mmol) was placed in a Schlenk flask with a stir bar and evacuated for 15 min. The reagents were transferred to the Schlenk flask through a cannula and the mixture heated to 75 °C, with stirring, for 2 h. The solution was then diluted with CH_2Cl_2 and passed through neutral alumina to remove the excess copper. The solution was concentrated, and the polymer was precipitated into hexanes. The resulting polymer contained 17% of the ene-functional monomer **3** by ^{1}H NMR. M_n = 17 kg/mol, PDI = 1.23. δ_H (500 MHz, $CDCl_3$): 5.82 (m, 1H, CH═CH_2), 5.17 (m, 2H, CH═CH_2), 4.03 (b, 2H, −O−CH_2−), 3.62 (s, n × 3H, −$OCHH_3$), 2.42 (b, 2H, −$OCHH_2CH_2$), 2.10−0.80 (b, n × 5H, backbone). δ_C (500 MHz, $CDCl_3$): 178.1, 177.8, 177.0, 134.0, 117. 5, 64.1, 54.5, 51.8, 44.9, 44.6, 32.6, 18.7, 16.5. IR: 2951, 1723, 1480, 1435, 1387, 1239, 1143, 987, 915, 841, 749 cm^{-1}.

9-Decenyl 2-Bromo-2-methylpropanoate (**5**). The alkene-functional ATRP initiator was synthesized by the previously published procedure of Ohno et al.[43]

6-Allyl-ε-caprolactone (ACL, 7-Allyl-1-oxacycloheptan-2-one) and Poly(6-Allyl-ε-caprolactone-co-ε-caprolactone) P(ACL-co-CL). ACL and P(ACL-*co*-CL) were synthesized using the previously published procedure by Mecerreyes et al.[44] The initiator used was freshly distilled benzyl alcohol, and the polymerization was carried out with stannous 2-ethylhexanoate ($Sn(Oct)_2$) as a catalyst using a monomer feed ratio of 1:9 ACL:CL. The resulting polymer contained 10% of the ene-functional monomer ACL by ^{1}H NMR. The molecular weight of the polymer was determined to be 9 kg/mol by ^{1}H NMR (GPC: M_n = 21.0 kg/mol, PDI = 1.43).

Alkene Chain-End-Functionalized-PS, e-PS. A 50 mL flask was charged with **5** (0.575 g, 1.80 mmol), PMDETA (312 mg, 1.80 mmol), styrene (18.0 g, 0.173 mol), and chlorobenzene (6.00 g, 65.1 mmol). The solution was purged with argon for 10 min and subsequently added, via cannula, to a 25 mL Schlenk flask, loaded with copper(I) bromide (258 mg, 1.80 mmol). The mixture was heated to 90 °C for 1.5 h. The viscous liquid was dissolved in dichloromethane (50 mL) and washed with water (3 × 50 mL) in order to remove all copper. The organics were dried with $MgSO_4$ and filtered. Solvent was removed in vacuo. The resulting viscous liquid was dissolved in dichloromethane, and the polymer was precipitated in methanol. The precipitate was filtered and dried in vacuo to yield the polymer as a white powder (7.14 g, 40%, GPC: M_n = 6.0 kg/mol, PDI = 1.08). δ_H (200 MHz, $CDCl_3$): 7.26−6.31 (br, n × 5H, aromatics), 5.77 (m, 1H, −C*H*CH_2), 4.89 (m, 2H, −CHC*H*$_2$), 4.46 (b, 1H, −CH_2Br), 2.41−0.76 (b, n × 3H). δ_C (100 MHz): 145.5, 139.4, 128.1, 127.6, 125.7, 114.4, 64.3, 44.0, 41.9, 40.5, 34.0, 29.6, 28.5, 26.1. FT-IR, *ν*: 3026, 2923, 1725, 1601, 1493, 1452, 1028, 907, 756, 697.

Alkene Chain-End-Functionalized-PMMA, e-PMMA. A 50 mL flask was charged with **5** (255 mg, 0.80 mmol), PMDETA (139 mg, 0.80 mmol), methyl methacrylate (10.0 g, 0.10 mol), and chlorobenzene (8.00 g, 86.8 mmol). The solution was purged with nitrogen for 10 min and subsequently added, via cannula, to a 25 mL Schlenk flask, loaded with copper(I) bromide (115 mg, 0.80 mmol). The mixture was heated to 70 °C for 1 h. The viscous liquid was dissolved in dichloromethane (50 mL) and extracted with water (3 × 50 mL) in order to remove all copper. The organics were dried with $MgSO_4$ and filtered. Solvent was removed in vacuo. The resulting viscous liquid was dissolved in dichloromethane (30 mL), and the polymer was precipitated in hexanes (400 mL). The precipitate was filtered and dried in vacuo, yielding the polymer as a white powder (4.06 g, SEC: M_n = 7.9 kg/mol, PDI = 1.20). δ_H (400 MHz, $CDCl_3$): 5.76 (m, 1H), 4.92 (m, 2H), 3.56 (b, n × 3H), 2.10−0.80 (b, n × 5H). δ_C (100 MHz, $CDCl_3$): 178.38, 177.24, 114.44, 64.70, 54.53, 52.08, 45.14, 44.79, 29.67, 18.99, 16.62. FT-IR,*ν*: 2994, 2950, 1725, 1480, 1435, 1388, 1269, 1240, 1191, 1145, 988, 841, 749 cm^{-1}.

Alkene Chain-End-Functionalized-PEG, e-PEG. Allyl bromide (1.74 mL, 20 mmol, 20 equiv) was added with a syringe to a mixture of poly(ethylene glycol) monomethyl ether (HO-PEG, 5.0 kg/mol, 5.00 g, 1.00 mmol), potassium *tert*-butoxide (*t*BuOK) (0.45 g, 4.00 mmol, 4 equiv), and dry THF (15 mL). The mixture was stirred at room temperature for 2 days and then poured into 100 mL of saturated NH_4Cl, aqueous. The organics were extracted with chloroform (4 × 50 mL) and then dried with $MgSO_4$. The solvent was removed in vacuo to yield a white solid (4.96 g, 99%). δ_H (200 MHz, $CDCl_3$): 5.85 (m, 1H, C*H*═CH_2), 5.19 (m, 2H, CH═C*H*$_2$), 3.98 (m, 2H, methylene next to ene), 3.62 (b, n × 4H, methylene of PEG), 3.34 (s, 3H, −OMe). δ_C (100 MHz): 134.7, 117.0, 72.1, 71.9, 70.5, 70.0, 69.4, 61.5, 59.0. FT-IR, *ν*: 2882, 1963, 1725, 1466, 1455, 1360, 1341, 1279, 1241, 1147, 1098, 1060, 958, 841 cm^{-1}.

Azide/Alkene Chain-End-Functionalized-PS, e-PS−N$_3$. The alkene chain end functionalized polystyrene (2.40 g, M_n = 6.0 kg/mol, 0.40 mmol) and sodium azide (260 mg, 4.00 mmol, 10 equiv) were dissolved in DMF (10 mL) and heated to 70 °C for 24 h. DCM (50 mL) was added, and the mixture was washed with water (3 × 50 mL). The organics were dried with $MgSO_4$ and filtered. Solvent was partially removed in vacuo, and the polymer was precipitated in methanol. The precipitate was filtered off and dried in vacuo, yielding the polymer as a white powder (2.20 g, 92%). δ_H (200 MHz, $CDCl_3$): 7.37−6.38 (br, n × 5H, aromatics), 5.88 (m, 1H, C*H*═ CH_2), 5.03 (m, 2H, CH═C*H*$_2$), 3.99 (b, 1H, CHN_3), 2.41−0.88 (b, n × 3H). δ_C (100 MHz): 145.2, 139.6, 127.9, 127.5, 125.6, 114.1, 64.1, 45.9, 43.7, 40.2, 29.4, 28.8, 28.2, 25.7. FT-IR, *ν*: 3028, 2923, 2094, 1728, 1602, 1492, 1452, 1031, 753, 696 cm^{-1}.

General Procedures for Thiol−Ene Photoreactions. *Ene-Functional Polymer + Thiol.* In a vial, the polymer, 5−10 equiv of thiol (with respect to the alkene), and 0.2 equiv of DMPA were dissolved in the minimal amount of the solvent required to solubilize all components. The solvents for each system are specified in Tables 1 and 2. The vial was sealed with a screw cap fitted with a PTFE septum, and the mixture was purged with argon for 5−10 min. Irradiation with a 365 nm UV lamp was carried out at specified time intervals (see Tables 1 and 2). The polymers were purified by precipitation. For the reaction details of each thiol−ene coupling, please see the Supporting Information.

General Procedures for Thiol−Ene Thermal Reactions. *Ene-Functional Polymer + Thiol.* In an ampule, the polymer, 5−10 equiv of thiol (with respect to the alkene), and 0.5 equiv of AIBN

Table 1. Summary of the Reaction Conditions and Product Conversion for the Thiol Coupling (Using Compounds 7−11) to Alkene End-Functional Polymers Based on PS, PMMA, and PCL

thiol	solvent[a]	reaction time (h) [$h\nu/\Delta$][b]	conversion (%)[c]
	P(**1**-*co*-S)		
7	PhH	0.5/3	100/100
8	PhCl	0.25/3	100/100
9	PhCl	2/15	100/100
10	DMF/PhCl (1/1 mixture)	0.5/8	100/45
11	DMF	0.5/6	100/86
	P(**3**-*co*-MMA)		
7	PhCl	0.5/24	100/100
8	PhCl	0.5/−	100/−
9	PhCl	2/24	46/37
10	DMF/PhCl (1/1 mixture)	0.5/−	98/−
11	DMF	0.5/6	72/57
	P(ACL-*co*-CL)		
7	PhCl	0.5/3	100/100
8	PhCl	0.5/3	100/100
9	PhCl	0.5/15	98/39
10	DMF	0.5/8	100/17
11	PhCl	0.5/15	100/50

[a] Solvent abbreviations: PhH = benzene, PhCl = chlorobenzene, DMF = *N,N*′-dimethylformamide. [b] Photochemical reaction ($h\nu$) at room temperature included DMPA as a radical initiator, $\lambda = 365$ nm, and the thermal reaction (Δ) included AIBN and was heated to 80 °C. [c] Percent conversion was obtained from the disappearance of the alkene peaks by ^{1}H NMR and the appearance of peaks corresponding to the product.

were dissolved in the minimal amount of solvent required to solubilize all components. The mixture was degassed via three freeze−pump−thaw cycles and subsequently flame-sealed. The ampule was heated at 80 °C at specified time intervals (see Tables 1 and 2). The polymers were purified by precipitation. For the reaction details of each thiol−ene coupling, please see the Supporting Information.

HO_2C−PS−N_3. e-PS−N_3 (480 mg, 0.08 mmol), thioglycolic acid (74 mg, 0.80 mmol, 10 equiv), and AIBN (6.6 mg, 0.04 mmol, 0.5 equiv) were dissolved in benzene (2 mL). The mixture was degassed via three freeze−pump−thaw cycles and subsequently flame-sealed. The ampule was heated at 80 °C for 4 h. The mixture was poured into methanol, yielding a white powder (397 mg, 83%). δ_H (200 MHz, $CDCl_3$): 7.41−6.30 (b, n × 5H, aromatics), 3.97 (b, 1H, CHN_3), 3.28 (s, 2H, CH_2COOH), 2.69 (t, 2H, CH_2SCH_2COOH), 2.42−0.86 (b, n × 3H, CH-CH_2). FT-IR, ν: 3025, 2921, 2850, 1724, 1601, 1493, 1452, 1260, 1094, 1026, 906, 798, 755, 696 cm^{-1}.

HO_2C−PS−OH (from HO_2C−PS−N_3). A 10 mL flask was charged with propargyl alcohol (11.2 mg, 0.20 mmol, 10 equiv), PMDETA (10.4 mg, 0.06 mmol, 3 equiv), and dry THF (1 mL). The solution was purged with argon for 5 min and subsequently added, via cannula, to a 10 mL Schlenk flask, loaded with HO_2C−PS−N_3 (120 mg, 0.02 mmol) and copper(I) bromide (8.6 mg, 0.06 mmol, 3 equiv). The mixture was stirred at room temperature for 24 h. The THF was removed under reduced pressure. The residue was redissolved in dichloromethane (10 mL) and washed with water (3 × 10 mL) in order to remove all copper. The organics were dried with $MgSO_4$ and filtered. Again, the solvent was removed under reduced pressure, the residue was dissolved in dichloromethane, and the polymer was precipitated into methanol. The precipitate was filtered and dried in vacuo to yield the polymer as a white powder (53.1 mg, 44%). δ_H (200 MHz, $CDCl_3$): 7.33−6.29 (b, n × 5H, aromatic of PSt), 5.10 (b, 1H, −CH−N), 4.68 (b, 2H, CH_2OH), 3.27 (s, 2H, CH_2COOH), 2.68 (t, 2H, CH_2SCH_2COOH), 2.32−0.68 (b, n × 3H, CH−CH_2).

e-PS−OH. A 10 mL flask was charged with propargyl alcohol (22.4 mg, 0.40 mmol, 10 equiv), PMDETA (20.8 mg, 0.12 mmol, 3 equiv), and dry THF (2 mL). The solution was purged with argon for 5 min and subsequently added, via cannula, to a 10 mL Schlenk flask, loaded with e-PS−N_3 (240 mg, 0.04 mmol) and copper(I) bromide (17.2 mg, 0.12 mmol, 3 equiv). The mixture was stirred at room temperature for 24 h. The THF was then removed under reduced pressure, and the residue was dissolved in dichloromethane (20 mL) and washed with water (3 × 10 mL) in order to remove all copper. The organics were dried with $MgSO_4$ and filtered. Again, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, and the polymer was precipitated into methanol. The precipitate was filtered and dried in vacuo to yield the polymer as a white powder (185 mg, 77%). δ_H (200 MHz, $CDCl_3$): 7.37−6.36 (br, n × 5H, aromatics), 5.89 (m, 1H, CH=CH_2), 5.25−4.70 (m, 2H of CH=CH_2 + 1H CHN), 4.71 (b, 2H, CH_2OH), 2.39−0.87 (b, n × 3H, CH−CH_2).

Table 2. Summary of the Reaction Conditions and Product Conversion Yields of the Thiol Coupling (Using Compounds 7−11) to Alkene End-Functional Polymers Based on PS, PMMA, and PEG

thiol	solvent	reaction time (h) [$h\nu/\Delta$]	conversion (%)
	e-PS		
7	PhH	1/4	100/100
8	PhCl	1/4	100/100
9	PhCl	1/4	100/74
10	PhCl	1/4	100/60
11	DMF	1/48	100/98
	e-PMMA		
7	PhH	1/4	100/100
8	PhCl	1/4	100/76
9	PhCl	1/24	79/48
10	PhCl	1/4	53/13
11	PhH	1/4	93/100
	e-PEG		
7	PhH	1/4	100/100
8	PhCl	1/4	100/100
9	PhCl	1/4	94/56
10	DMF/PhCl (1/1 mixture)	1/4	100/33
11	DMF/PhCl (1/1 mixture)	1/4	100/83

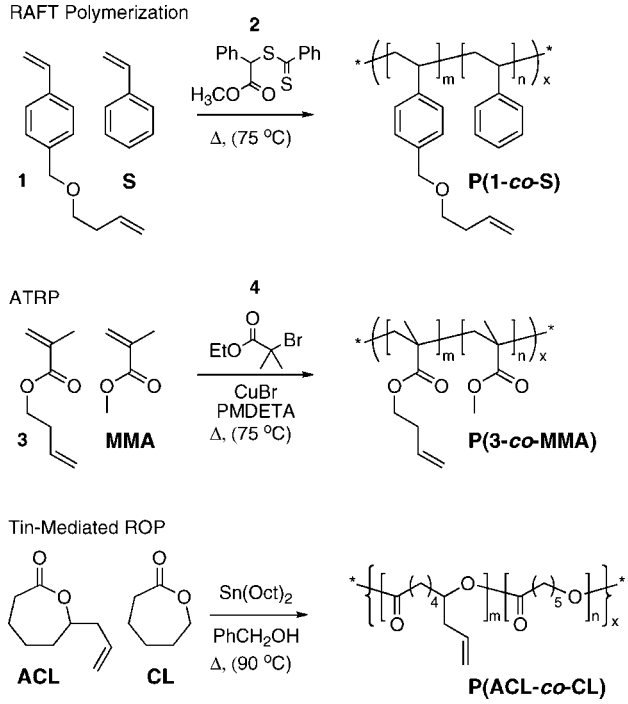
HO_2C−PS−OH (from e-PS−OH). e-PS−OH (90 mg, 0.015 mmol), thioglycolic acid (13.8 mg, 0.15 mmol, 10 equiv), and DMPA (1.1 mg, 0.0043 mmol, 0.3 equiv) were dissolved in chlorobenzene (0.4 mL). The vial was sealed with a rubber septum, and the mixture was purged with argon for 5−10 min. Irradiation with UV light (365 nm) was carried out for 1 h at room temperature. The mixture was poured into methanol, yielding a white powder (87 mg, 96%). δ_H (200 MHz, $CDCl_3$): 7.33−6.29 (b, n × 5H, aromatic of PSt), 5.10 (b, 1H, methyne adjacent to triazole), 4.69 (b, 2H, methylene adjacent to −OH), 3.31 (s, 2H, −CH_2−COOH), 2.73 (t, 2H, −CH_2−SCH_2COOH), 2.43−0.86 (b, n × 3H, main chain).

Results and Discussion

Synthesis of Ene-Functional Polymers. In designing suitable macromolecular substrates for evaluating the potential of thiol−ene chemistry for polymer functionalization, both RAFT and ATRP techniques were examined as polymerization techniques suitable for vinyl systems while the synthesis of biodegradable polymers based on ε-caprolactone was conducted through tin-mediated ROP (Scheme 1).[44,45] For the backbone functionalized derivatives, a wide range of monomeric structures are possible with monomers **1** and **3** designed to bear an additional unconjugated alkene unit having a low rate of polymerization to avoid cross-linking during polymerization. The synthesis of monomer **1** was accomplished by chloride displacement, from 4-vinylbenzyl chloride, using 3-butene-1-ol.[40] Similarly, **3** was obtained via the nucleophilic acyl substitution of methacryloyl chloride with 3-butene-1-ol.[42] Finally, 6-allyl-ε-caprolactone (ACL) was prepared by the oxidation of allylcyclohexanone using *m*-chloroperoxybenzoic acid (MCPBA).

In order to have multiple alkene groups along the backbone, the level of comonomer incorporation was ca. 10% alkene in P[**3**-*co*-S] and P[ACL-*co*-CL] and ca. 17% in P[**3**-*co*-MMA].

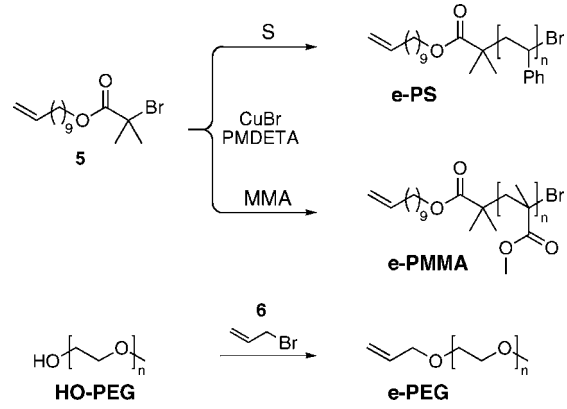
Scheme 1. Synthetic Strategies for Preparation of Backbone-Functionalized Copolymers



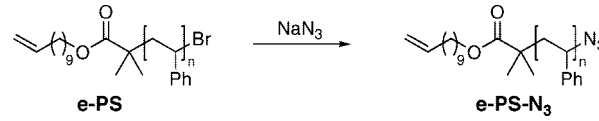
Synthetically, the alkene-functional styrene monomer **1** was copolymerized at 75 °C with styrene S using the RAFT agent, **2**, to afford P(**1**-*co*-S) with a monomer feed ratio of 1:9 (**1** to S, respectively), leading to ca. 10% incorporation of **1** (14.5 kg/mol with a PDI of 1.07). Similarly, the MMA-based polymer was synthesized by copper-mediated ATRP using the initiator **4** and PMDETA as the copper ligand with heating to 75 °C. In this case, a feed ratio of 1:5 (**3** to MMA, respectively) yielded 17% incorporation of **3** having a molecular weight of ca. 17 kg/mol and a PDI of 1.23. We note that copolymerization of allyl methacrylate and methyl methacrylate under the same conditions resulted in an insoluble cross-linked material, demonstrating the importance of having a two-carbon spacer in the design of these materials. For both PS and PMMA systems, the highest molecular weight attempted was at 20 kg/mol, yielding a PDI ca. 1.1 in the PS-based material and PDI ca. 1.2 for the PMMA-based system, though it should be noted that higher molecular weight materials can be obtained. The copolymerization of ACL with CL was performed using stannous 2-ethylhexanoate ($Sn(Oct)_2$) under dry conditions, as previously reported by Mecerreyes et al.[44] Benzyl alcohol was chosen as the initiator to allow accurate determination of molecular weight of the copolymer by ^1H NMR and to provide quantification of the level of functionalization. The feed ratio of 1:9 ACL:CL led to a 1:9 ratio of incorporation in the final copolymer, which was determined to have a molecular weight of ca. 9 kg/mol by ^1H NMR (GPC: $M_n = 21.0$ kg/mol, PDI = 1.23, PS standards).

The syntheses of single, end-group functionalized polymers are shown in Scheme 2 with both PS and PMMA polymers being synthesized by living free-radical polymerization, namely ATRP,[39] starting from the ene-functional initiator **5**. Given that the thiol−ene coupling reactions were characterized by ^1H NMR, the polymers were designed to have moderate molecular weights (ca. 5−8 kg/mol) in order to be able to clearly observe and quantify structural changes to the single reactive chain end after the thiol−ene reactions. The ATRP of **5** with styrene afforded the ene-functional poly(styrene) (e-PS), having a molecular weight of 6.0 kg/mol (PDI of 1.08). Similarly, the

Scheme 2. Synthetic Strategies for Preparation of Chain-End-Functionalized Copolymers



Scheme 3. Synthesis of Asymmetrically Chain-End-Functionalized Polymer, e-PS−N_3



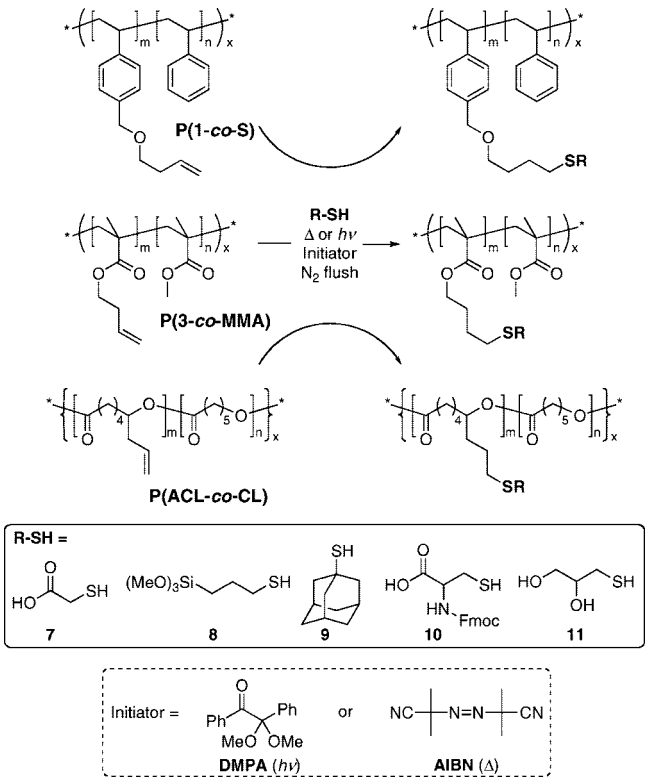
ene-functional methyl methacrylate polymer (e-PMMA) was prepared having a molecular weight of 7.5 kg/mol (PDI of 1.20). Finally, the well-defined, commercially available monomethyl ether-terminated PEG derivative (HO-PEG, 5 kg/mol, PDI of 1.04) was reacted with allyl bromide, in the presence of potassium *tert*-butoxide, to afford the ene-functional poly(ethylene glycol) (e-PEG) in essentially quantitative yield.

In order to test the orthogonality of the thiol−ene click reaction, an asymmetrically functional telechelic polymer was also prepared. The starting material for this synthesis was the end-functionalized polystyrene derivative, e-PS, bearing bromine as a terminal group, which was displaced by NaN_3 to yield the desired telechelic e-PS−N_3 (Scheme 3).[46] The resulting asymmetrically functionalized polymer e-PS−N_3 is conveniently set up to carry out two sequential click reactions: thiol−ene coupling to the double bond and CuAAC cycloaddition to the azide.

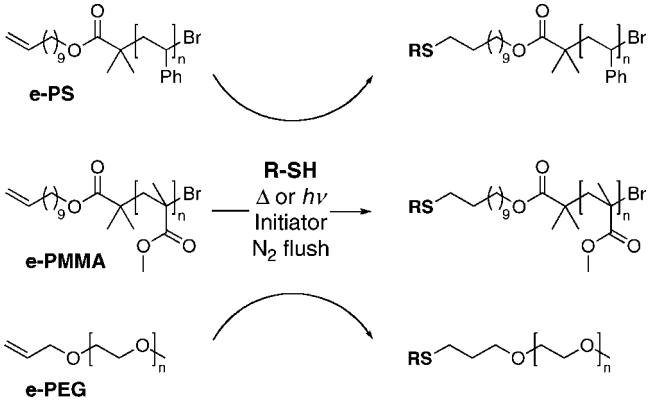
Thiol−Ene Coupling to Backbone-Functional Polymers. The thiol−ene coupling reaction to ene-functionalized polymers has been carried out thermally using AIBN as the radical initiator[33] and photochemically without any initiator over an extended period of time.[31] In order to study the coupling differences between the thermal and photochemical processes using radical initiators, both AIBN and 2,2-dimethoxy-2-phenylacetophenone (DMPA) were employed. The capability of varying the reaction conditions through the use of either a thermal or photochemical radical initiator is an important feature of the thiol−ene coupling chemistry, as this allows the use of thermally sensitive groups with the room temperature photochemical reaction. Conversely, compounds having photosensitive groups can be prepared by exploiting the thermal coupling reaction. The selected array of functional thiols (R−SH) that were used in this study is shown in Scheme 4 along with the range of thiol−ene coupling reactions to the polymer backbone that were explored.

All reactions were carried out in the minimal amount of solvent required to solubilize the polymer, mercaptan, and radical initiator (see Supporting Information). Although we and others have showed that thiol−ene coupling reactions do not require deoxygenation when performed under solvent-free conditions, the requirement for solubilization of the polymers

Scheme 4. Library of Thiol Starting Materials and Range of Polymer Functionalization Reactions



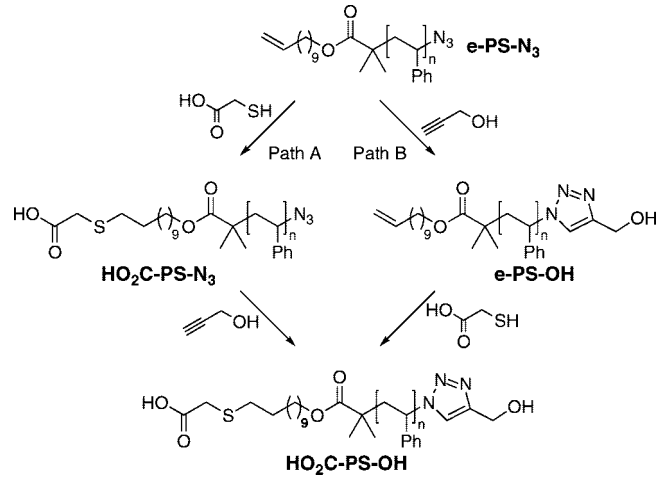
Scheme 5. Polymer Functionalization Reactions for Representative Monofunctional, Chain End Derivatives



in an appropriate solvent necessitated the purging of the reaction mixtures to prevent oxygen inhibition of the radical initiator.[27] When the polymer coupling reactions were carried out in solvent, without deoxygenation, the thiol−ene reaction did not occur as efficiently or failed to react at all. We postulate that quenching of the thiol−ene reactions in solvent occurs due to the presence of oxygen.

To demonstrate the compatibility and efficiency of the thiol−ene reaction with different functional groups, the thiols **7**−**11** were selected and their coupling reaction studied for a molar ratio of 5:1 (thiol:alkene) in order to avoid large excesses of reagents that may be expensive or lead to complicated purification procedures (Scheme 4). For example, thioglycolic acid, **7**, was chosen for its ability to add carboxylic acid functionality in lieu of double bonds, which results in a significant change in solubility and associated increase in ability to bind to the surface of nanoparticles, etc.[47] Similarly, the 3-mercaptopropyltrimethoxysilane, **8**, contains the trimethoxysilane group that can allow for coupling to ceramic surfaces, such as silica, and to form cross-linked networks via acid/base-catalyzed condensation reactions,[48] while the protected amino acid, *N*-(9-fluorenylmethoxycarbonyl)cysteine (Fmoc-C, **10**), is a building block/model for the attachment of peptide fragments to synthetic materials. We note that the Fmoc-protected analogue of cysteine was used for its solubility in *N,N′*-dimethylformamide (DMF) and solvent mixtures with chlorobenzene (PhCl), which are required for the hydrophobic polystyrene and PMMA derivatives.

Scheme 6. Orthogonal Strategies for Combined Thiol−Ene and CuAAC Click Functionalization of e-PS−N_3



As can be seen in Table 1, for a standard set of conditions (5.0 equiv of thiol) a marked difference is observed when the thermal and photochemical reactions are compared and when different backbones are examined. As monitored by the disappearance of the protons associated with the double bonds, and the appearance of proton signals corresponding to the thioether product, the conversion efficiencies were found to be essentially quantitative for the photochemical reactions. On the other hand, lower yields were observed in most cases for the thermal processes after significantly longer reaction times, typically hours, compared to minutes for the photochemical series. The low yields associated with the PMMA derivative or thiols, **9**−**11**, under thermal conditions could be improved by the addition of a larger excess of thiol but did not approach quantitative conversion. Interestingly, the photochemical coupling between **9** and P(**3**-*co*-MMA) yielded the lowest conversion efficiency both thermally and photochemically, possibly due to the poor miscibility between the polymer and small molecule. In addition, the thermal reaction of P(**3**-*co*-MMA) with **8** resulted in an insoluble product that could not be analyzed by ^{1}H NMR. Furthermore, the thermal reaction between P(**3**-*co*-MMA) and **10** yielded an insoluble mixture after prolonged exposure to heat, potentially due to thermal cleavage of the Fmoc protecting group.

Purification of the products was done by simple precipitation techniques, and Figure 2 shows the ^{1}H NMR of P(**1**-*co*-S) before and after reaction with **7**. The disappearance of the vinyl protons (*d* and *e*) is clear, as is the appearance of the proton peaks from the α-carbon (*f*) and the shift of *e* from ca. 5.2 ppm in the reactant to ca. 2.8 ppm in the product. These results demonstrate both the efficiency of the reaction and the high degree of anti-Markovnikov selectivity in formation of a range of addition products functionalized through a stable thioether linkage.

Thiol−Ene Coupling to End-Functional Polymers. Compared to backbone functionalized polymers, the synthesis of end-functional polymers presents a number of additional challenges

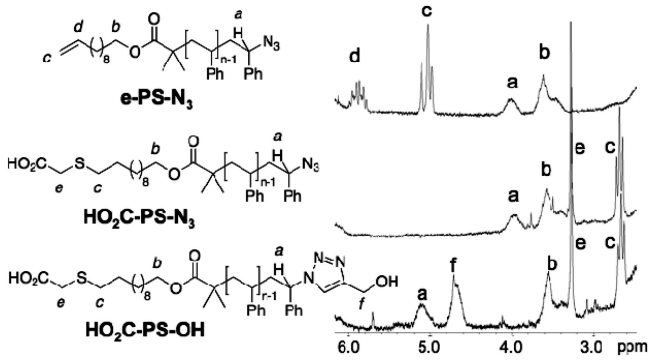


Figure 3. ^{1}H NMR spectra of e-PS−N_3 (top), the product after the initial thiol−ene coupling with thioglycolic acid (HO_2C−PS−N_3, middle), and the product after the subsequent CuAAC reaction with propargyl alcohol (HO_2C−PS−OH, bottom).

with efficiency and orthogonally being foremost. However, if successful, the ability to fabricate polymers with a single type of chain end functional group that can be modified with any thiol-containing moiety leads to a powerful synthetic tool for a variety of applications, especially in surface and interfacial engineering.[30] As with the backbone-functionalized materials described above, the thiol−ene coupling reactions using the PS-, PMMA-, and PEG-based polymers were examined under similar photochemical and thermal conditions (Scheme 5). In all cases, the minimal amount of solvent was used, and the reaction mixtures were deoxygenated by bubbling with nitrogen for 10 min. The major difference was that 10 equiv of thiol per alkene were used for the coupling reactions to compensate for the reduced concentration of alkene units, though it should be noted that for many of the quantitative conversions, the number of equivalents of thiol could be significantly reduced without decreasing the overall efficiency of the reaction.

The reaction efficiencies are summarized in Table 2 for the thiol−ene reactions between the three types of polymers and the mercaptans shown in Scheme 4. Similar to the backbone functionalization, we observed differences between the photochemical and thermal reactions, where the photochemical reaction led to higher efficiencies in terms of reaction time, with essentially quantitative reactions being observed for the polystyrene and poly(ethylene glycol) derivatives. Lower yields were associated between the PMMA derivative and thiols **9**−**11** under thermal conditions, and as mentioned, these yields can be improved by the addition of a larger excess of thiol.

Orthogonality of Thiol−Ene and CuAAC Click Reactions. In order to test the orthogonality of the thiol−ene coupling reaction with the copper-catalyzed azide/alkyne cycloaddition chemistry, the asymmetric telechelic polymer, e-PS-N_3, having a single alkene at one chain end and a single azide unit at the other chain end, was prepared by chain end modification of the corresponding ATRP derivative (Scheme 3). Two synthetic pathways are possible starting from e-PS-N_3: initial thiol−ene coupling followed by CuAAC of the azide group (path A) or the reverse strategy where the cycloaddition reaction is followed by thiol−ene addition across the double bond (path B) (Scheme 6). Given that the efficiency of chain end functionalization reactions was being evaluated, thioglycolic acid and propargyl alcohol were chosen as coupling agents due to the unique resonances afforded by these units in the ^{1}H NMR spectra of the products involved. In conjunction with the choice of thioglycolic acid and propargyl alcohol, polystyrene was selected as the backbone since its ^{1}H NMR resonances are in the region between 1.2−2.1 ppm (aliphatic backbone protons) and 6.2−7.5 ppm (aromatic protons). Thus, the region between 2.1 and 6.2 ppm is free from overlapping peaks, which allows minor changes to the functional end-groups of e-PS-N_3 to be detected.

In path A, the thermally initiated thiol−ene coupling between thioglycolic acid and e-PS−N_3 gives HO_2C−PS−N_3 in quantitative yield with Figure 3 showing the ^{1}H NMR spectra of e-PS-N_3 (Figure 3, top), HO_2C-PS-N_3 (Figure 3, middle), and the final product, HO_2C−PS−OH, (Figure 3, bottom). Comparison of the spectra clearly shows the disappearance of the signals corresponding to the vinyl protons at 5.0 and 5.8 ppm (peaks c and d) after the initial thiol−ene reaction coincident with the appearance of a peak at 3.2 ppm (peak e, Figure 3, middle) from the protons attached to the α-carbon of the terminal carboxylic acid. In the final product, HO_2C−PS−OH, the appearance of a signal for the $-CH_2-$OH protons at 4.6 ppm (peak f, Figure 3, bottom) demonstrates the successful CuAAC coupling reaction and the shift of signal **a** to 5.1 ppm (from 4.0 ppm) is fully consistent with the reaction of the azide group to form a triazole heterocycle in the product HO_2C−PS−N_3. Similar spectral changes were observed in the ^{13}C and IR data which supports both the efficiency of the thiol−ene and CuAAC reaction coupled with the compatibility of the azide group and initial thiol−ene addition step.

In examining path B, initial CuAAC coupling with propargyl alcohol followed by thiol−ene addition of thioglycolic acid across the terminal double bond of e-PS-N_3 proved to have analogous efficiency and compatibility with quantitative functionalization of both chain ends being observed. It should be noted that in both cases the thermal thiol−ene reaction was preferred over the photochemical process due to the potential sensitivity of azides under UV illumination for an extended period of time.[49]

Conclusions

In conclusion, we have demonstrated a range of synthetic opportunities through the development of robust, efficient, and orthogonal organic transformations, such as thiol−ene reactions. A library of alkene-functionalized backbone and chain-end-functionalized linear polymers were prepared by controlled polymerization techniques and shown to undergo essentially quantitative conversions when reacted with thiols via thiol−ene click chemistry using radical initiators. Stark differences were observed when using photochemical and thermal radical initiators, where the use of a thermal initiator led to lower yields and longer reactions times. The compatibility with functional groups was demonstrated by the efficient addition of a wide range of thiols across the double bonds while a high degree of orthogonality was evident from stepwise functionalization of telechelic macromolecules using thiol−ene and CuAAC click reactions. This ability to routinely prepare functionalized linear polymers represents a significant advance compared to traditional approaches and is further evidence of the synthetic utility of click reactions in both biological systems and materials chemistry.

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Supporting Information Available: Synthetic details on the thiol−ene coupling reactions and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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